Development of Cascade Reactions and Strategies for Carbon Centred Nucleophilic Additions to Blocked Isocyanates

By

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Abstract

Isocyanates are invaluable bulk chemicals that play a central role in the synthesis of various polymers and provide a key platform for the synthesis of nitrogen-containing molecules such as carbamates and ureas. Unfortunately, isocyanates suffer from high toxicity, low functional group tolerance, and a propensity to undergo deleterious side-reactions. Consequently, blocked (masked) isocyanate derivatives have been the subject of increased interest resulting from their reduced toxicity and exceptional control over isocyanate reactivity. This strategy has largely been relegated to the polymerization literature, although its use in the synthesis of complex urea and carbamate derivatives is well established in synthetic organic chemistry.

However, prominent gaps in the blocked isocyanate literature were clear at the outset of this research project. First and foremost, the development of heteroatom-substituted isocyanates, such as *N*- and *O*-substituted derivatives, remained relatively scarce despite their potential for the synthesis of important nitrogen-containing derivatives. Furthermore, the additions of carbon-centred nucleophiles on blocked *N*-, *O*-, and even *C*-substituted blocked isocyanates were exceedingly rare. Finally, the use of a blocking group strategy in catalytic transformations of isocyanates remained largely absent from the literature. This was particularly striking given the widespread development of catalytic transformations of isocyanates.

As such research efforts began focusing on furthering the development of blocked *N*-isocyanates as a vital platform for heterocyclic synthesis (chapter 2). Initially, the cascade reactivity of blocked *N*-iso(thio)cyanates was expanded to incorporate electrophiles such as alkynes (section 2.2). This readily provided access to imidazolone and thiazolidine products. Subsequently, the development of a cascade reaction providing access to 1,2,4-triazin-3(*2H*)-ones was explored (section 2.3). This provided the first examples of an *N*-isocyanate cascade which hinged on the use of acid catalysis. Moreover, insight into hydrazone isomerization was gained. Finally, these efforts culminated in the development of cascade reactions providing access to a rare class of 1,2,4-triazinones as well as 5-aminopyridazinones (section 2.4). This provided the first example of a cascade reaction involving a C-C bond formation onto a blocked *N*-isocyanate derivatives. Furthermore, this development was pivotal in re-focusing attention on the development of general strategies to achieve addition of carbon nucleophiles onto blocked isocyanate derivatives.

Towards this end, the development of two strategies to achieve carbon-centred nucleophilic additions on both blocked *N*- And *O*-isocyanates were developed (chapter 3). Inspiration from the

isocyanate literature led to the development of carboxylic acids as formal carbon nucleophiles (section 3.2). This strategy was found to be quite general for the synthesis of hydroxamates from blocked *O*-isocyanates. Furthermore, encouraging results were generated on the ability of Grignard reagents to form similar products (section 3.3). Particularly important is the paradigm shift this allows from C-N bond formation to C-C bond formation for the synthesis of hydroxamate derivatives. Furthermore, lead results suggest the potential of this reactivity to translate to blocked *N*-substituted derivatives, a transformation which had failed with carboxylic acids.

Finally, the development of a catalytic amide synthesis from blocked isocyanate precursors was targeted (chapter 4). The use of a blocking group strategy was able to address the current major limitation of isocyanates as amide precursors, that is functional group tolerance (section 4.2). Indeed, a commercially available rhodium catalyst was found to allow efficient amidation of various ambiphilic blocked isocyanate derivatives using arylboroxines as nucleophiles. Mechanistic studies including the use of variable time normalization analysis supported the presence of two alternative kinetic regimes contingent on the reaction conditions employed. Furthermore, these data suggested the success of this transformation, in the case of ambiphilic derivatives, hinged on a rate determining isocyanate release (chapter 4). Finally, initial results strongly support the potential for Boc-carbamates to provide a general platform for amidation in the presence of strong nucleophiles such as primary amines.

The potential of a blocking group strategy in catalytic reaction development was further displayed with the development of a palladium catalyzed amidation of blocked derivatives with arylboroxine nucleophiles (section 4.3). Indeed, the use of blocked isocyanates was found to be absolutely key in achieving efficient reactivity with the palladium catalyst. This result, coupled with the sparse reports on blocked isocyanates in catalysis, strongly suggest that the use of such a strategy could allow the development of reactivity otherwise unattainable when using free isocyanates.

Acknowledgements

To the delight of both myself, and likely all the individuals who've been a part of my life over the past 5 years, I'm leaving graduate school a much different person than the individual that joined the Beauchemin group 5 years ago. As a result, I have a long list of people I'll forever be indebted to for their guidance and influence over the years. First and foremost, I must thank André for allowing me to join the group. André has been an exceptionally supportive supervisor and I hope to be half as patient as he is if I'm ever granted the responsibility of overseeing a team.

I also need to thank Jean-François Vincent-Rocan. JF was a huge influence on my development during the early years in the Beauchemin lab. I not only significantly expanded my knowledge of chemistry, but also seriously transformed my work ethic as a result of the example set by JF, who was a notorious workaholic and quite efficient.

I must furthermore extend my gratitude to all the fellow Beauchemin members I've had the pleasure of collaborating with on various projects including Sampada Chitale, Mohammed Dahab, Erica Barbera, Kwame Agyei, Nième Séguin, and David Brzezinski. Without your help, many of the developments made throughout my time in the Beauchemin lab would not have been possible. More broadly, I want to thank all the individuals both inside and outside the Beauchemin lab that I've built friendships with over my time here. You guys are largely what motivated me to come into work day in day out!

I must extent my gratitude to several faculty members at the University of Ottawa and funding agencies. First and foremost, both Professor Jeffrey W. Keillor and Stephen Newman have allotted me significant amounts of their time to discuss my research project. This was particular helpful in providing guidance on aspects of my research which was well outside my zone of expertise. Furthermore, I'd like to thank both Dr. Sharon Curtis and Glenn A. Facey for their help over the years. Specifically, Glenn played an essential role in allowing me to develop a protocol to run kinetic NMR experiments. Finally, I'm also indebted to both NSERC and OGS for their funding of my research during my graduate studies.

I would be remiss if I didn't thank my family. I'm forever indebted to both my parents and my in-laws for the support they've provided me. Attending graduate school would have been largely unmanageable without them. Finally, my wife has been an indispensable stabilizing force in my life since we met 3 years ago, remaining supportive throughout my time at UOttawa.

“Chance favours the prepared mind” -Louis Pasteur

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List of Abbreviations

Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BG	Blocking group
°C	Degree Celsius
Cbz	carboxybenzyl
CDI	carbonylimidazole
cis	On the same side
cod	Cyclooctadiene
δ	Chemical shift in parts per million
Δ	Thermolysis
d	Deuterium (in NMR solvent)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	Dichloroethane
DIPEA	Diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
ee	Enantiomeric excess
EI	Electron impact
Equiv	Equivalent
Et	Ethyl
Et_3N	Triethylamine
FLU	Fluorenone
FT	Fourier transform
g	Gram
h	Hour
hv	Light

HRMS	High-resolution mass spectroscopy
Hz	Hertz
HAT	Hydrogen atom transfer
IR	Infrared
J	Coupling constant
L	Litre
LG	Leaving group
m	meta
M	Molar
Me	Methyl
MeCN	Acetonitrile
mg	milligram
mL	millilitre
mmol	millimole
NHC	*N*-heterocyclic carbene
Nuc	Nucleophile
NMR	Nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
NOE	Nuclear Overhauser effect
o	Ortho
p	Para
PNA	*p*-nitroaniline
PTSA	*p*-toluenesulfonic acid
Ph	Phenyl
Ppm	Parts per million
rt	Room temperature
s	Second
S_N2	Biomolecular nucleophilic substitution
syn	Together, same side
t	Tertiary
TFA	Trifluoroacetic acid
TGA	Thermogravimetric analysis

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TOF	Time of flight
T3P	Propylphosphonic anhydride
UV	Ultra-violet
μW	Microwave

Statement of Contributions

Over the course of my time as a graduate student in the Beauchemin lab, I had the opportunity to collaborate with many fellow graduate students and undergraduate students alike. Herein I will layout my contributions to the projects described in this thesis.

Early on in my studies I collaborated with Jean-François Vincent-Rocan, who served as my immediate supervisor during our developments of various *N*-isocyanate cascade reactions. Jean-François developed the 1,2,4-triazinone cascade and optimized it (section 2.4), while I obtained the initial hits and subsequent optimization of the 5-aminopyridazinone (section 2.4) cascade and the imidazolone (section 2.2) cascade. The scale up and scope of these cascades were largely divided in half, as were the mechanistic experiments.

Following this work, I was given the role of immediate supervisor to Mohammed A. Dahab, a visiting PhD student, during our development of the 1,2,4-triazin-3(*2H*)-one cascade (section 2.3). I played a central role in the development/optimization of the cascade reaction as well as the mechanistic experiments while Mohammed played a central role in the scale up and scope of the reaction.

The development of stoichiometric amidation reactions of blocked *N*- and *O*-isocyanates were developed with several undergraduate students where I served as project supervisor (chapter 3). The first hit was achieved with Nièvе Séguin on carboxylic acid nucleophiles with blocked *O*-isocyanates. Nièvе performed most of the optimization reactions while I directed the reaction optimization process. The scale up and isolation, performed to establish the applicability of this transformation was primarily conducted by Erica Barbera, an honours student I mentored. I played a primary role in shaping the scope of the reaction, helping troubleshoot problematic substrates, and targeting the pharmaceutical derivatives. I subsequently obtained the first hit for carboxylic acid addition to *N*-isocyanates which was given to a fellow colleagues for optimization.

The first hit on the development of organomagnesium addition to blocked *O*-isocyanates was achieved with Kwame Agyei, an undergraduate honours student I supervised. Kwame played a central role in running optimization reactions for this transformation while I governed the direction of the optimization. Both Kwame and I have contributed to the scale up and isolation of this transformation. I also played a central role in designing control reactions to address reproducibility issues which were largely carried out by Alshimaa Mohamed, a fellow graduate student. I was then able to achieve the first hit of similar reactivity on blocked *N*-isocyanate derivatives.

Finally, I was the sole contributor to the development of the rhodium-catalyzed amidation involving blocked isocyanates. Nearing the conclusion of this project, I obtained the first hit on the palladium-catalyzed transformation, at which point I subsequently supervised David Brzezinski, a beginning MSc student, over the course of the project development. The optimization of this reactionwas largely a collaborative effort. David has played a central role in the scale-up and survey of the applicability of this transformation while I focused on developing and carrying out control experiments to better understand the mechanism of this transformation.

Chapter 1: Introduction

1.1 Isocyanates

Isocyanates are a highly reactive heterocumulenes reported in 1849 by Wurtz.[1] It was not until 1937 where their polymerization to form polyurethanes was discovered by Bayer[2] leading to an eruption in research interest regarding these intermediates.[3] Since then, isocyanates have become a vital organic building block with several industrial scale application ranging from coatings, paints, adhesives, and etc. Moreover, their value to fine chemical production such as agrochemical and pharmaceutical development can hardly be overstated due to their importance in urea, carbamate, and heterocyclic synthesis.

The high reactivity of isocyanates with various nucleophilic motifs may come as no surprise when their allenic nature is taken together with the major resonance contributors depicted in figure 1.1. The high electronegativities of both the oxygen and nitrogen atoms result in a highly polarized heterocumulene with the majority of the electron density located on the heteroatoms, leaving a significant partial positive charge the carbon atom. In fact, the distribution of charge densities is to date one of the sole points of agreement from theoretical chemists on the fundamental isocyanate structure. Other seemingly straightforward electronic and geometrical features of isocyanates such as whether the oxygen or the nitrogen bears more charge, the linearity (or lack thereof) of the N=C=O motif, and the ground state structure of aryl isocyanates remain unsettled areas of isocyanate chemistry due to a number of conflicting reports.[4]

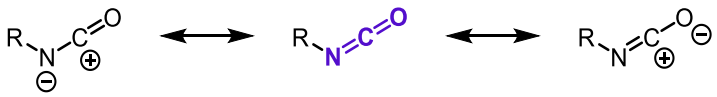


Figure 1.1: Major resonance contributors of isocyanates

Nevertheless, basic reactivity trends for isocyanates are well documented.[5] The more electron withdrawing the R substituent of the isocyanate, the higher the electrophilicity of the isocyanate, resulting in the reactivity trend depicted in figure 1.2. The reaction rates of isocyanates with various protic nucleophiles have also been reported depicted in figure 1.2 with the associated relative reaction rate.

---

[1] Wurtz, A. *Justus Liebigs Ann. Chem.* **1849**, *71*, 326.
[2] Bayer, O. *Angew. Chem.* **1947**, *59*, 257.
[3] Six, C.; Richter, F. *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, **2012**, vol. 20, pp. 63-82.
[4] For a review of theoretical calculations of isocyanates, see: Caraculacu, A. A.; Coseri, S. *Prog. Polym. Sci.* **2001**, *26*, 799.
[5] Delebecq, E.; Pascault, J.-P.; Boutevin, B.; Ganachaud, F. *Chem. Rev.* **2013**, *113*, 80.

Moreover, the addition of catalysts and the choice of solvent can profoundly impact the observed reactivity.

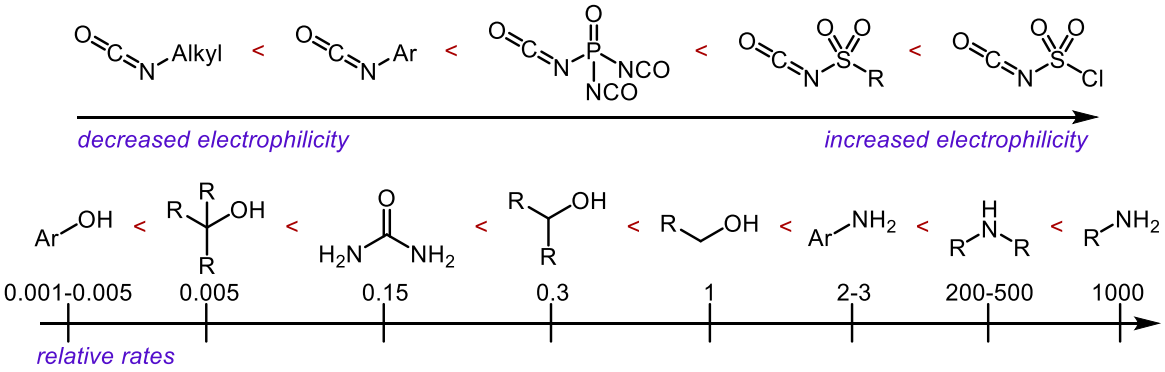


Figure 1.2: Relative reactivity trends of isocyanates and their nucleophilic partners.

1.2 Stoichiometric Carbon Centred Nucleophilic Addition to Isocyanates

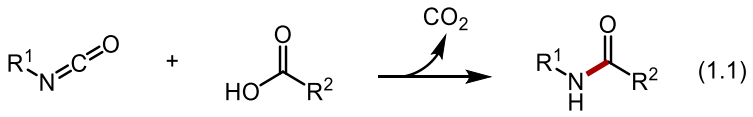
The addition of various protic nucleophiles to isocyanates for the synthesis carbamates, ureas and their polymeric variants is the most common use of isocyanates and has been extensively studied. However, given their low cost and broad commercial availability, isocyanates have attracted interest as a potential platform for amide synthesis through the addition of various carbon centred nucleophiles.

1.2.1 Carboxylic acids as formal carbon nucleophiles

Although the use of isocyanates as a platform for amide synthesis is comparatively less well studied, examples of such reactivity date back to the inception of isocyanates themselves where Wurtz detected the formation of amide products when reacting isocyanates with carboxylic acids (eq. 1.1).[6] Since this initial report, sparse examples of this reactivity have been described in the literature. Early reports generally employed higher temperatures and non-polar solvents to produce the desired amide.[7] More recently the use of DMAP as a catalyst in non-polar solvents was found to allow room temperature reactivity.[8] Moreover dipeptides were readily synthesized with minimal to no epimerization of stereochemical configuration.[8b] Recently, Crich described a procedure making use of a polar aprotic solvent (DMF) with DIPEA as a mild base which allowed room temperature reactivity. Interestingly, this

[6] Wurtz, A. *Annalen* **1849**, *71*, 326.
[7] (a) Agre, C. L.; Dinga, G.; Pflaum, R. *J. Org. Chem.* **1955**, *20*, 695. (b) Blagbrough, I. S.; Mackenzie, N. E.; Ortiz, C.; Scott, I. *Tetrahedron Lett.* **1986**, *27*, 1251.
[8] (a) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569. (b) Schuemacher, A. C.; Hoffmann, R. W. *Synthesis* **2001**, 243.

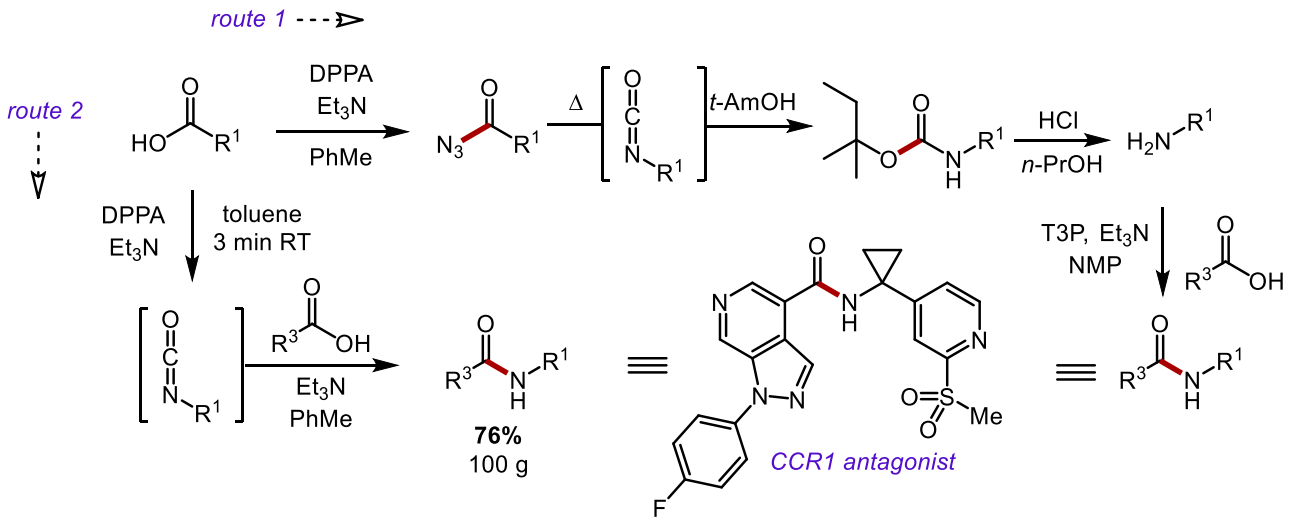
reaction was limited to aromatic isocyanates, where even phenyl isocyanate was found to result in sluggish reactivity compared to its electron poor counterparts.[9] Nevertheless, complex carboxylic acids bearing free alcohols were tolerated under the reaction conditions with no sign of undesired carbamate formation.



(1.1)

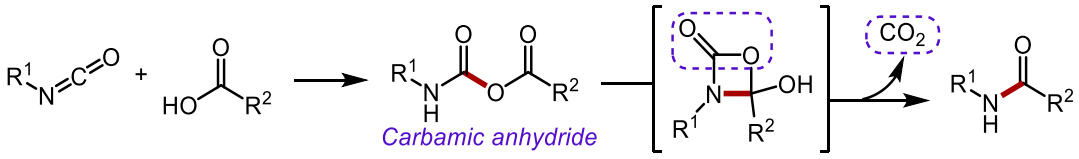
A recent application of this unusual amide bond synthesis was developed by Senanayake and coworkers[10] during their scale up of a CCR1 antagonist entering clinical trials for treatment of rheumatoid arthritis. The general synthetic scheme involved the transformation of a carboxylic acid to an isocyanate via Curtius rearrangement, nucleophilic attack providing a protected amine, deprotection, and acylation forming the desired amide product (scheme 1.1, route 1). Remarkably, they were able to develop a semi-continuous process which circumvented 2 of these steps (scheme 1.1, route 2). Flow chemistry was employed for the Curtius rearrangement. This allowed control over acyl azide concentration, vital due to safety concerns, as well as mitigating by-product formation observed in batch operations. The isocyanate product was then fed into a batch reactor containing the carboxylic acid forming the desired amide with a 76% yield on 100 g scale. Remarkably, this remains the sole report of the direct amidation of isocyanates derived from a Curtius rearrangement with carboxylic acids, despite the prevalence of its 4-step counterpart (scheme 1.1, route 1).[11]

[9] Sasaki, K.; Crich, D. *Org. Lett.* **2011**, *13*, 2256.
[10] Marsini, M. A.; Buono, F. G.; Lorenz, J. C.; Yang, B.-S.; Reeves, J. T.; Sidhu, K.; Sarvestani, M.; Tan, Z.; Zhang, Y.; Li, N.; Lee, H.; Brazzillo, J.; Nummy, L. J.; Chung, J. C.; Luvaga, I. K.; Narayanan, B. A.; Wei, X.; Song, J. J.; Roschangar, F.; Yee, N. K.; Senanayake, C. H. *Green Chem.* **2017**, *19*, 1454.
[11] Ghosh, A. K.; Brindisi, M.; Sarkar, A. *ChemMedChem* **2018**, *13*, 2351.



Scheme 1.1: Application of isocyanate/carboxylic acid amide synthesis to CCR1 antagonist scale up.

The mechanism of this intriguing amide bond synthesis remains to be fully elucidated. A simplified overview of the mechanism begins with the formation of a mixed carbamic anhydride from the isocyanate and carboxylic acid starting material (scheme 1.2). In some cases, this intermediate can be isolated and characterized.[12] This intermediate is then presumed to undergo an intramolecular 1,3-acyl transfer reaction with the extrusion of CO_2. ^{14}C- and ^{13}C- labeling studies have concluded that the carbonyl present in the amide product derives from the carboxylic acid starting material.[13,7b] Recent theoretical calculations have further supported the feasibility of an intramolecular acyl transfer via a 4 membered ring intermediate.[14] Moreover, similar strained 1,3-acyltransfer pathways have also been proposed in alternative amide syntheses.[15]



Scheme 1.2: A simplified mechanism for amide synthesis from isocyanates and carboxylic acids.

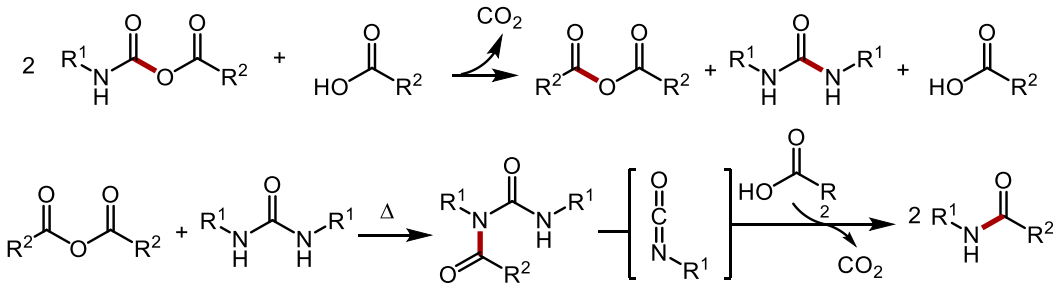
[12] Naegeli, C.; Tyabji, A.; *Helv. Chim. Acta* **1934**, *17*, 931. b) Naegeli, C.; Tyabji, A. *Helv. Chim. Acta* **1935**, *18*, 142. c) Motoki, S.; Saito, T.; Kagami, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 775.

[13] Fry, A. *J. Org. Chem.* **1953**, *75*, 2686.

[14] Jiang, Y.-Y.; Liu, T.-T.; Zhang, R.-X.; Xu, Z.Y.; Sun, X.; Bi, S. *J. Org. Chem.* **2018**, *83*, 2676.

[15] a) Restorp, P.; Rebek Jr., J. *J. Am. Chem. Soc.* **2008**, *130*, 11850. b) Santo, E. D.; Alberto, M. E.; Russo, N.; Toscano, M. *ChemCatChem* **2015**, *7*, 2309.

Notably, early reports on amide synthesis from isocyanates and carboxylic acids observed substantial formation of symmetrical urea and anhydride by-products. Unexpectedly, upon heating the urea and anhydride mixture above 135 °C, formation of the desired amide product was formed. No mechanism was proposed for this transformation. The interception of the carbamic anhydride intermediate by a carboxylate could explain the formation of the symmetrical anhydride (scheme 1.3). At increased temperature, the acylation of the parent urea would lead to a blocked isocyanate (see section 1.4), which upon deblocking would release a molecule of product, along with a molecule of isocyanate which could be further converted to the desired amide product.



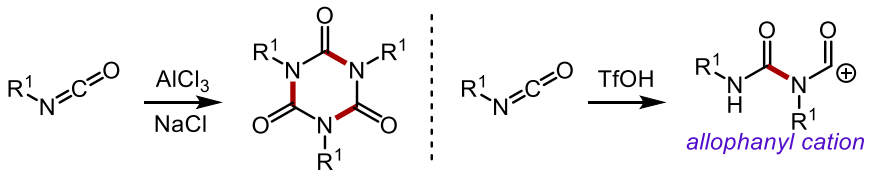
Scheme 1.3: Potential mechanism for anhydride formation and subsequent amide formation from symmetrical urea.

1.2.2 Electrophilic aromatic substitution with isocyanates

Given the high electrophilicity intrinsic to isocyanates, one may assume they provide an ideal platform for direct C-H amidation through electrophilic aromatic substitution chemistry. Surprisingly, few reports of isocyanates undergoing this type of transformation in an intermolecular setting have been disseminated.[16] These reports make use of acidic conditions to promote the transformation by increasing the electrophilicity of the isocyanate species. Interestingly, isocyanates have been observed to oligomerize in the presence of $AlCl_3$ with even weak Lewis bases (scheme 1.4). [16a] Moreover, studies by Olah and coworkers attempting to identify protonated isocyanate species in super acidic media (TfOH) instead discovered the existence of dimeric allophanyl cations.[17] Thus, the limited reports of intermolecular reactivity of this sort may be a result of the propensity of isocyanates to oligomerize under the reaction conditions. Though perhaps the lack of reports can more easily be attributed to the lack of

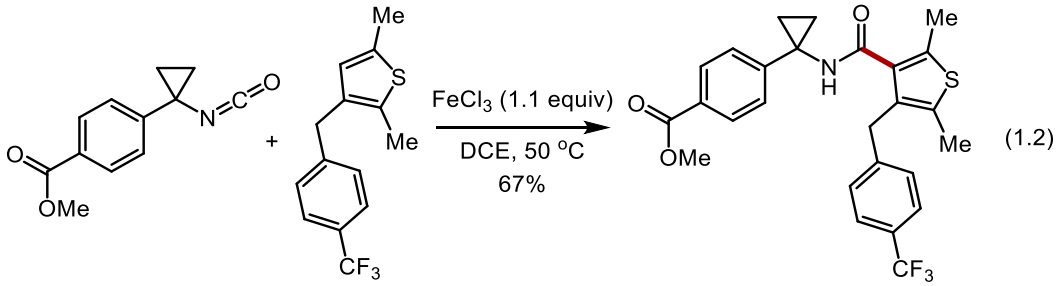
[16] (a) Effenberger, F.; Gleiter, R. *Chem. Ber.* **1964**, *97*, 472. (b) Varun, B. V.; Sood, A.; Prabhu, K. R. *RSC Adv.* **2014**, *4*, 60798. (c) Qarah, A. F.; Schaeff, M. N.; Klumpp, D. A. *J. Org. Chem.* **2017**, *82*, 10623.
[17] Olah, G. A.; Nishimura, J.; Kreienbühl, P. *J. Am. Chem. Soc.* **1973**, *95*, 7672.

practicality of the current methodologies employing concentrated super acids or super stoichiometric aluminum.



Scheme 1.4: Reported reactivity of isocyanates in the presence of acidic catalyst

Nevertheless, this chemistry has found some applications in the synthesis of medicinally relevant compounds. In their development of prostaglandin EP4 receptor antagonist, Davies and coworkers from Merck Frosst chose a direct C-H amidation strategy to access a highly substituted thiophene ring over the original medicinal chemistry route employing a HATU mediated amide bond synthesis (eq. 1.2).[18] A similar strategy was also employed by Franck and coworkers in their synthesis of Epicocconone derivatives.[19]

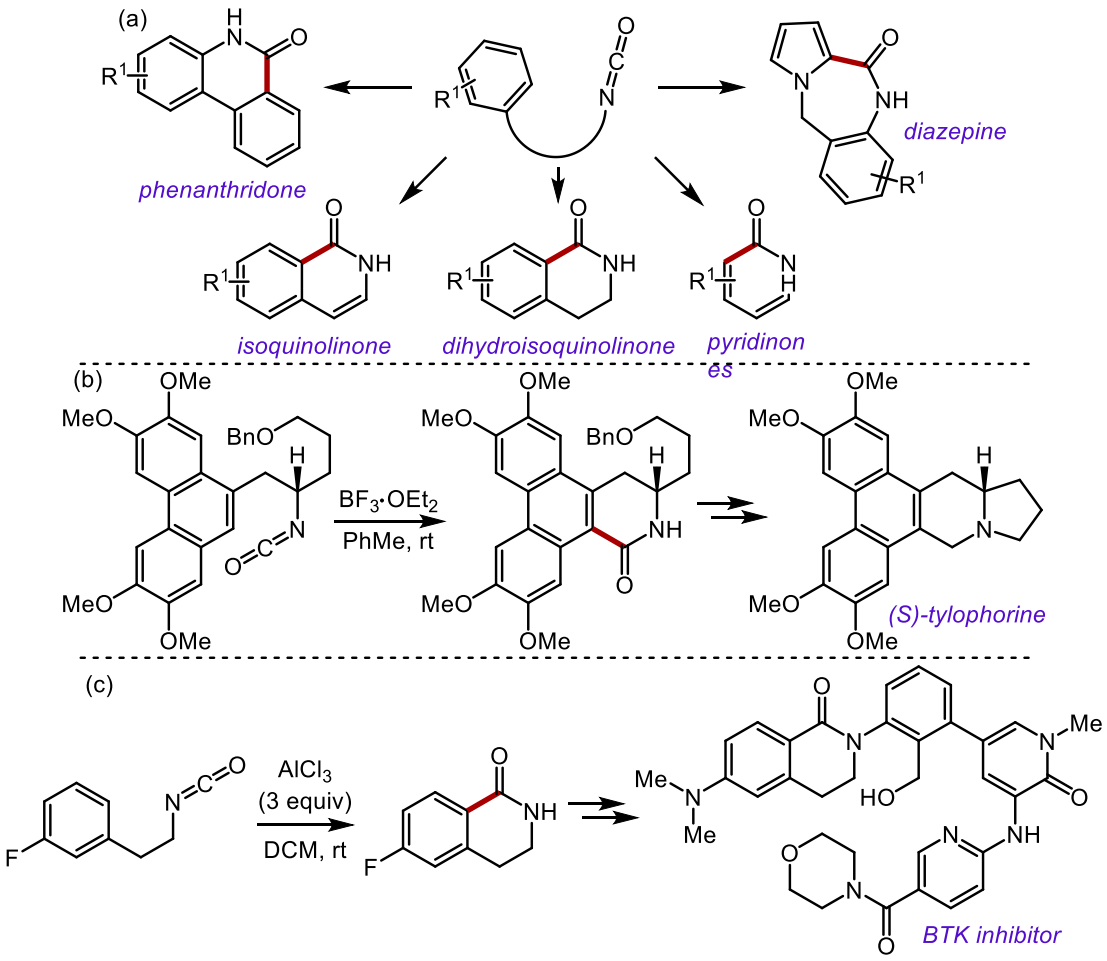


The intramolecular variant of the above described reactivity of isocyanates has provided a fruitful platform for heterocyclic synthesis. Such a strategy has been employed to access a variety of heterocycles including phenanthridone,[20] medium ringed lactams,[21] diazepines,[22] dihydroisoquinolinone,[23] isoquinolinones,[24] and pyridinones (scheme 1.5a).[25] Moreover, application in the total synthesis of natural

[18] Gauvreau, D.; Dolman, S. J.; Hughes, G.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2010**, *75*, 4078.
[19] Peixoto, P. A.; Boulangé, A.; Ball, M.; Naudin, B.; Alle, T.; Cosette, P.; Karuso, P.; Franck, X. *J. Am. Chem. Soc.* **2014**, *136*, 15248.
[20] (a) Butler, J. M. *J. Am. Chem. Soc.* **1949**, *71*, 2578. (b) Afarinkia, K.; Ndibwami, A. *Synlett* **2007**, 1940.
[21] Butler, D. E.; Alexander, S. M. *J. Heterocyclic Chem.* **1982**, *19*, 1173.
[22] Daich, A.; Povazanec, F.; Decroix, B. *J. Heterocyclic Chem.* **1991**, *28*, 1911.
[23] (a) Hanessian, S.; Demont, E.; van Otterlo, W. A. L. *Tetrahedron Lett.* **2000**, *41*, 4999. (b) Judd, K. E.; Mahon, M. F.; Caggiano, L. *Synthesis*, **2009**, 2809. (c) Dou, D.; Viwanathan, P.; Li, Y.; He, G.; Alliston, K. R.; Lushington, G. H.; Brown-Clay, J. D.; Padmanabhan, R.; Groutas, W. *J. Comb. Chem.* **2010**, *12*, 836. (c) Murashige, R.; Ohtsuka, Y.; Sagisawa, K.; Shiraishi, M. *Tetrahedron Lett.* **2015**, *56*, 3410
[24] Chuang, T.-H.; Wu, P.-L. *J. Chin. Chem. Soc.* **2006**, *53*, 413.
[25] Chuang, T.-H.; Chang, W.-Y.; Li, C.-F.; Wen, Y.-C.; Tsai, C.-C. *J. Org. Chem.* **2011**, *76*, 9678

products has also be reported. In 2006, Wu and coworkers described a racemic route to tylophorine, a natural product exhibiting interesting cytotoxic activity.[26] The isoquinolinone intermediate was successfully prepared using a tandem Curtius rearrangement of a cinnamic acid derivative followed by cyclization. This transformation was catalyzed by $Hg(OAc)_2$ and required 180 °C. These harsh conditions were necessary to achieve isomerization of the olefin to the required (*Z*)-orientation necessary for intramolecular cyclization.[24,27] An enantioselective route to (*S*)-tylophorine was subsequently reported in 2014 by Wang and coworkers (scheme 1.5b).[28] An unusually mild Curtius rearrangement was described, occurring at 0 °C, forming the desired isocyanate followed by a Lewis acid mediated electrophilic aromatic substitution producing the desired dihydroisoquinolinone. A similar strategy was also employed in the synthesis of haemanthidine,[29] and dievodiamine.[30] Finally, Hong and coworkers were able to circumvent a problematic Schmidt rearrangement using phosgenation followed by intramolecular trapping (scheme 1.5c). This provided scalable strategy to access the dihydroisoquinolinone ring system during their development of a BTK inhibitor.[31]

[26] Chuang, T.-H.; Lee, S.-J.; Yang, C.-W.; Wu, P.-L. *Org. Biomol. Chem.* **2006**, *4*, 860.
[27] For a similar approach see: Cheng, X.; Waters, S. P. *Org. Lett.* **2013**, *15*, 4226.
[28] Chen, F.; Su, B.; Wang, Q. *Org. Chem. Front.* **2014**, *1*, 674.
[29] Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781.
[30] Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 3302.
[31] Hong, J.-B.; Davidson, J. P.; Jin, Q.; Lee, G. R.; Matchett, M.; O'Brien, E.; Welch, M.; Bingenheimer, B.; Sarma, K. *Org. Process Res. Dev.* **2014**, *18*, 228.



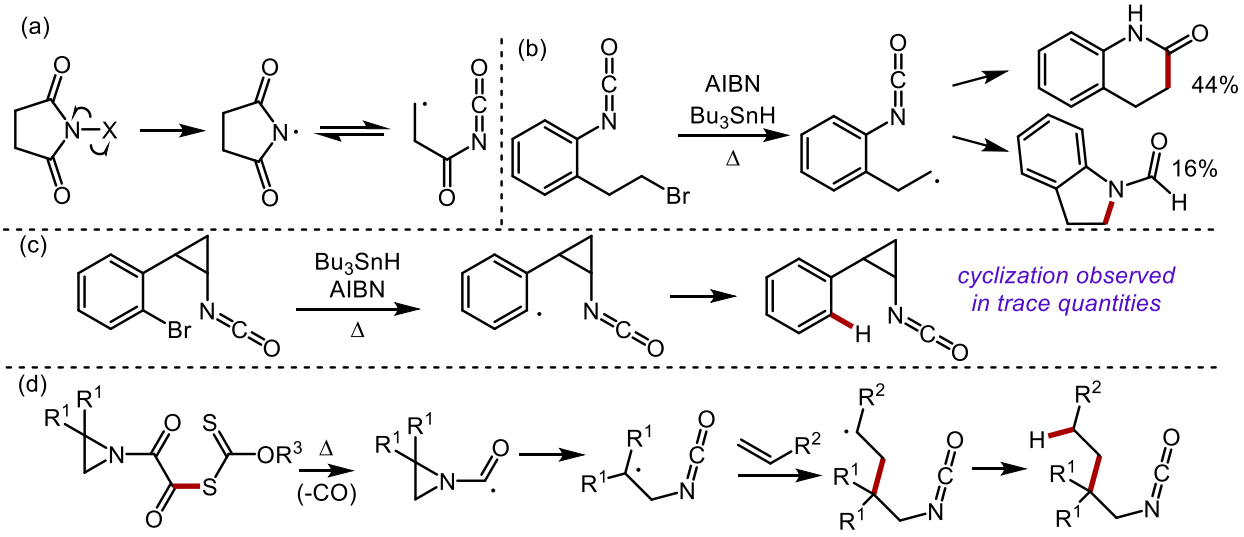
Scheme 1.5: (a) Intramolecular Friedel-Crafts amidation of isocyanates. (b) Application in tylophorine synthesis. (c) Application in scale-up of BTK inhibitor.

1.2.3 Carbon-centred radical addition to isocyanates

In contrast to the high reactivity isocyanates exhibit in the presence of various nucleophiles, their susceptibility to radical addition is rather low. This is most convincingly demonstrated by their stability during polymerization reactions and subsequent post-polymerization modification.[32] Nevertheless, some examples of radical addition to isocyanates have been reported. Early reports on the reactivity of isocyanates and radicals focused on the reversibility of succinimidyl radical opening from N-halogenated

[32] For selected examples see: (a) Beck, J. B.; Killops, K. L.; Kang, T.; Sivanandan, K.; Bayles, A.; Mackay, M. E.; Wooley, K. L.; Hawker, C. J. *Macromolecules* **2009**, *42*, 5629. (b) Flores J. D.; Shin, J.; Hoyle, C. E.; McCormick, C. L. *Polym. Chem.* **2010**, *1*, 213. (c) Gody, G.; Rossner, C.; Moraes, J.; Vana, P.; Maschmeyer, T.; Perrier, S. *J. Am. Chem. Soc.* **2012**, *134*, 12596.

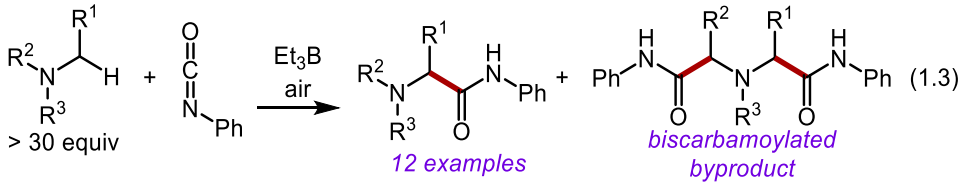
succinimide precursors (scheme 1.6a).[33] The first report of radical addition onto isocyanates as a preparative method was reported by Walton, where a dihydroquinolinone was obtained from an intramolecular *6-endo-dig* radical cyclization onto an isocyanate (scheme 1.6b).[34] Interestingly, a competitive *5-endo-trig* cyclization onto the nitrogen of the isocyanate forming an acyl radical was observed to lead to various deleterious by-products highlighting the intrinsic difficulties of isocyanate based reactivity in radical reactions. While the methodology was low yielding and plagued with many by-products, this work provided the first example of the potential synthetic use of isocyanates in radical reactions. Unfortunately, follow up work by both Walton[35] and Zard[36] displayed the reluctance of intramolecular radical cyclization to occur on similar systems (scheme 1.6c and d). These results are explained by invoking a rapid ring opening process which competes with the rate of cyclization. Thus, the stabilizing effect of aryl substituted isocyanates on the resulting amidyl radical make them virtually a prerequisite for competent addition onto isocyanates.



Scheme 1.6: (a) *N*-Halogenated succinimide derivatives radical ring opening. (b) Walton synthesis of dihydroquinolinone. (c) Walton's work showing reluctant cyclization on alkyl isocyanates. (d) Zard's work showing reluctant cyclization on alkyl isocyanates

[33] (a) Koenig, T.; Wielesek, R. R. *Tetrahedron Lett.* **1975**, 2007. (b) Tlumak, R. L.; Day, J. C.; Slanga, J. P.; Skell, P. S. *J. Am. Chem. Soc.* **1982**, *104*, 7257. (c) Kaushal, P.; Roberts, B. P. *J. Chem. Soc. Perkin Trans. II* **1989**, 1559.
[34] Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2003**, *68*, 2960.
[35] Minin, P. L.; Walton, J. C. *Org. Biomol. Chem.* **2004**, *2*, 2471.
[36] Heinrich, M. R.; Pérez-Martín, I.; Zard, S. Z. *Chem. Commun.* **2005**, 5928.

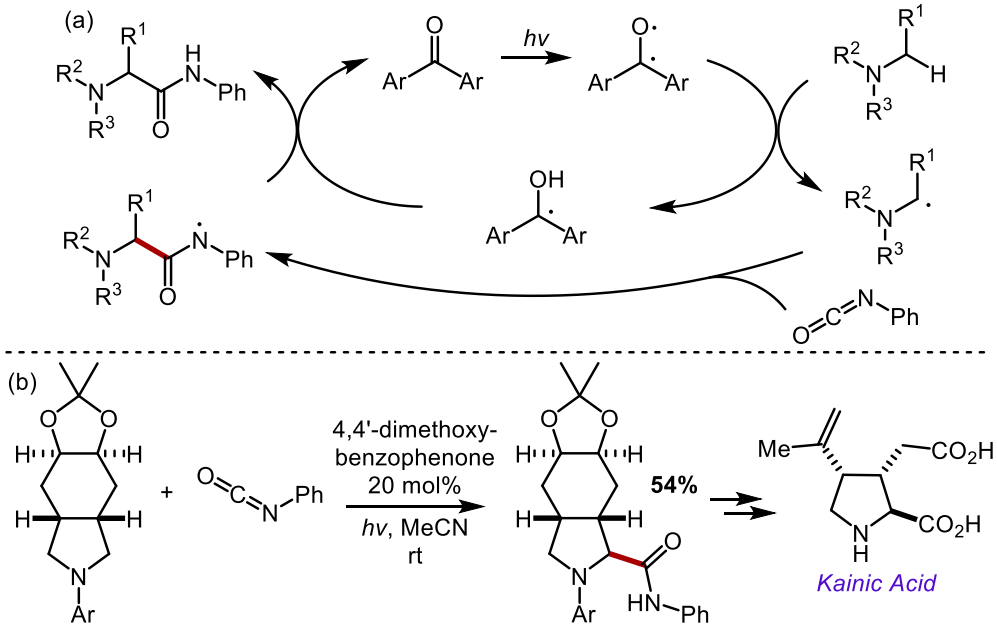
The first example of intermolecular radical addition to isocyanates was reported by Yoshimitsu and coworkers (eq. 1.3).[37] Et_3B/O_2 was used as a radical initiator producing α-amino radicals which subsequently underwent addition onto the parent isocyanate. Limitations of this method include the formation of ethyl carbamate by-product, approaching yields of 30% in some cases, arising from the production of ethanol or ethoxyl radical under the reaction conditions. The unwanted formation of biscarbamoylated by-products arising from intramolecular 5-HAT reactivity was also observed. Moreover, upwards of 30 equivalents of tertiary amine were required to achieve satisfactory yields. The scope of this reaction was also only explored with phenyl isocyanate.



(1.3)

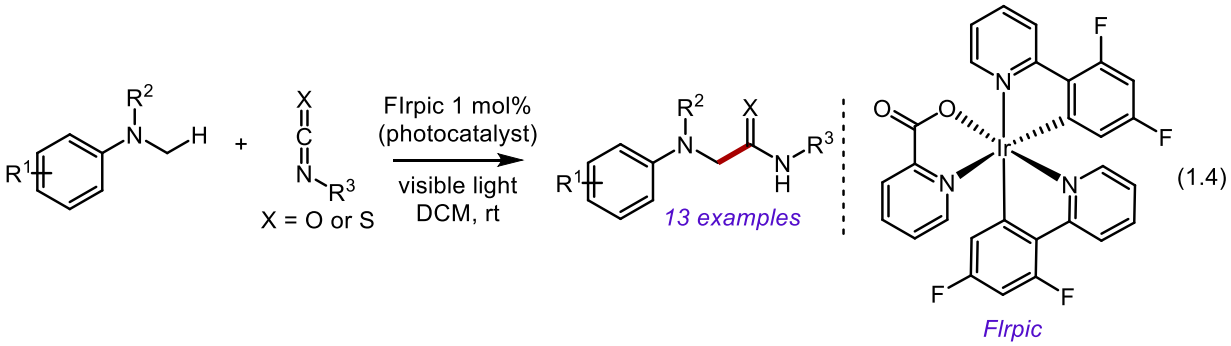
Following this report, Yoshimitsu and coworkers developed a catalytic variant using benzophenone derivatives as triplet photosensitizers (scheme 1.7).[38] Remarkably, this methodology allowed the use of the amine as the limiting reagent with slight excess of the phenyl isocyanate providing a 54% yield. This methodology was employed in the synthesis of kainic acid and its scope was not further explored. A similar methodology was reported at approximately the same time activating ethereal C-H bonds.[39] They found that this methodology was limited to electron poor aryl isocyanates. Moreover, high loadings of the isocyanate were necessary, which may result from the undesired photoexcitation of the species under the reaction conditions. Isocyanates are known to absorb at wavelengths below 300 nm, resulting in their degradation to highly reactive nitrenes.[40] This would be far from surprising when employing a mercury lamp and could explain the use of wavelength filters employed by Yoshimitsu and coworkers.

[37] Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115.
[38] Kamon, T.; Irifune, Y.; Tanaka, T.; Yoshimitsu, T. *Org. Lett.* **2011**, *13*, 2674.
[39] Kamijo, S.; Hoshikawa, T.; Inoue, M. *Tetrahedron Lett.* **2011**, *52*, 2885.
[40] Waddell, W. H.; Feilchenfeld, N. B. *J. Am. Chem. Soc.* **1983**, *105*, 5499.



Scheme 1.7: (a) Proposed mechanism for triplet photosensitizer catalyzed synthesis of α-aminoamides. (b) Application in the synthesis of kainic acid precursor.

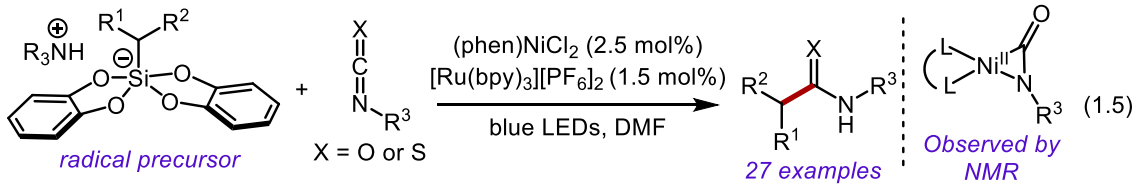
Photoredox catalysis has also been explored as an alternative to triplet photosensitization by Li and coworkers (eq 1.4).[41] Photoexcitation of the catalyst allows amine oxidation giving rise to a radical cation. This intermediate is easily deprotonated providing access to α-amino radicals. Addition onto an aryl isocyanate generates an amidyl radical which upon reduction closes the catalytic cycle and regenerates the catalyst. The reduction was proposed to be difficult (E_{red} calculated @ 0.94-1.48 V) and was used to explain the use of a novel, highly reducing photocatalyst (E_{red} = 1.91 V vs SCE). This procedure was successfully extended to the use isothiocyanate derivatives. Interestingly, formation of biscarbamoylated by-products were not observed though a facile 1,5 HAT could still be expected.



(1.4)

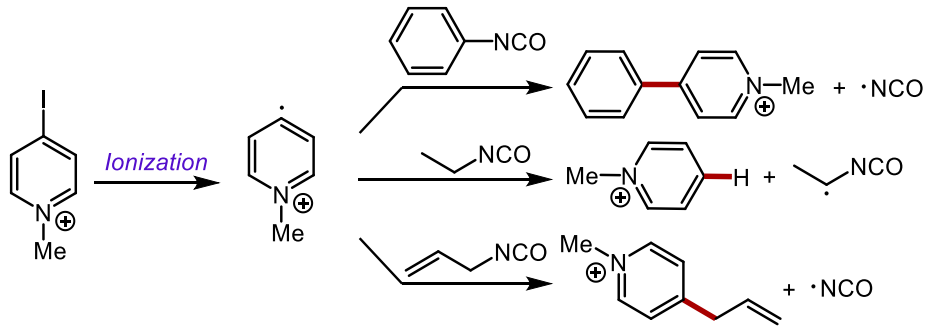
[41] Zhou, H.; Lu, P.; Gu, X.; Li, P. *Org. Lett.* **2013**, *15*, 5646.

Thus far, all procedures describing the intermolecular addition of radicals to isocyanates have been limited to aryl derivates. This limitation was recently tackled by Molander and coworkers through an innovative methodology employing dual metallaphotoredox catalysis (eq. 1.5).[42] Silicates were employed as carbon centred radical precursors as they are easily oxidized by most standard photocatalysts. This radical is intercepted by a nickel species, proposed to be bound to an isocyanate in η^2-fashion. The *in situ* formation of an organometallic species to mediate the addition of the carbon centred radical to the isocyanate provided the key to expanding the scope of this transformation. Although urea by-products were observed under the reaction conditions, the lack of isocyanate oligomerization is surprising given the ability of low valent nickel species to catalyze this reaction.[43]



An in-depth mechanistic analysis was recently performed by O'Hair and coworkers on the reactivity of aryl radicals with iso(thio)cyanates by mass spectroscopy (scheme 1.8).[44] Interestingly, they found electrophilic aromatic radicals preferred *ipso* addition on a variety of substituted aryl isocyanates, extruding cyanate radical. Moreover, alkyl and allyl isocyanate were found to predominately undergo C-H abstraction and olefin addition respectively. This is contrasted by the reactivity of isothiocyanates which were observed to preferentially undergo addition at sulfur generating the corresponding imidoyl radicals in line with previously reported cascade reactivity of these species.[45] Theoretical gas phase calculations supported the observed reactivity in the mass spectrometer. Attempts were then made to translate these results into solution phase chemistry. Diazonium salts were employed as aryl radical precursors. Reactions with isocyanates were found to yield predominately aryl radical homocoupling. Isothiocyanates were observed to undergo the predicted reactivity although in an uncontrolled fashion. Taken together, these results highlight the difficulties associated with radical reactions of isocyanates.

[42] Zheng, S.; Primer, D. N.; Molander, G. A. *ACS catal.* **2017**, *7*, 7957.
[43] Kashiwagi, T.; Hidai, M.; Uchida, Y.; Misono, A. *J. Polym. Sci. Part C, Polym. Lett.* **1970**, *8*, 173.
[44] Weragoda, G. K.; Pilkington, R. L.; Polyzos, A.; O'Hair, R. A. J. *Org. Biomol. Chem.* **2018**, *16*, 9011.
[45] Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *J. Org. Chem.* **2003**, *68*, 3454.



Scheme 1.8: O'Hair's study of radical addition to isocyanates.

1.2.4 Stoichiometric organometallic addition to isocyanates

The stoichiometric addition of various organometallic reagents onto isocyanates generating amide products dates to the beginning of the 20th century. Sporadic reports of such reactivity are found throughout the scientific literature over the course of the 20th century with a notable increase in rate in the 21st century. These reports span the use of organozinc, organoaluminum, organomagnesium, organolithium, organoboron, and organocuprates.[46] The following paragraphs will detail recent trends in the stoichiometric organometallic addition to isocyanates.

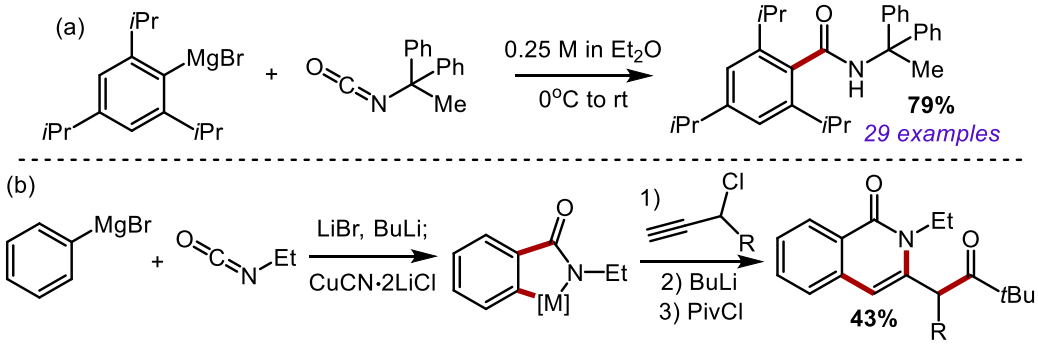
In recent years, reports of high yielding stoichiometric organometallic addition to isocyanates have transformed this chemistry from academic curiosity, to a powerful alternative amide bond synthesis. In 2012, Bode and coworkers reported the synthesis of sterically hindered/electronically deactivated amides by reacting isocyanates with Grignard reagents (scheme 1.9a).[47] These amides are typically difficult to access via traditional amide bond synthesis. That same year, Ready and coworkers reported a remarkable one-pot four-component coupling to access isoquinolones (scheme 1.9b).[48] Grignard addition

[46] For selected examples see: (a) Blaise *Compt. Rend.* **1901**, *132*, 38. (b) Gilman, H.; Furry, M. *J. Am. Chem. Soc.* **1928**, *50*, 1214. (c) Gilman, H.; Marple, K. E. *J. Org. Chem.* **1936**, *1*, 315. (d) Singleton, H. M.; Edwards Jr., W. R. *J. Am. Chem. Soc.* **1938**, *60*, 540. (e) Gilman, H.; Hofferth, B.; Melvin, H. W. *J. Am. Chem. Soc.* **1950**, *72*, 3045. (f) Field, L.; Lawson, J. E.; McFarland, J. W. *J. Am. Chem. Soc.* **1956**, *78*, 4390. (g) Parker, K. A.; Gibbons, E. G. *Tetrahedron Lett.* **1975**, *12*, 981. (h) Hendi, S. B.; Hendi, M. S.; Wolfe, J. F. *Synth. Commun.* **1987**, *17*, 13. (i) Tordeux, M.; Francese, C.; Wakselman, C. *J. Fluor. Chem.* **1989**, *43*, 27. (j) Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609. (k) Chorell, E.; Das, P.; Almqvist, F. *J. Org. Chem.* **2007**, *72*, 4917 (l) de Meijere, A.; Lygin, A. V. *Org. Lett.* **2009**, *11*, 389. (m) Schade, M. A.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2010**, *12*, 3648. (n) Hill, M. S.; Liptrot, D. J.; Mahon, M. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 5364. (o) Chawner, S. J.; Cases-Thomas, M. J.; Bull, J. A. *Eur. J. Org. Chem.* **2017**, 5015. (p) Hampton, C. S.; Harmata, M. *Tetrahedron Lett.* **2017**, *58*, 2530. (q) Geri, J. B.; Wolfe, M. M. W.; Szymczak, N. K. *Angew. Chem. Int. Ed.* **2018**, *57*, 1381. (r) Yamane, Y.; Sunahara, K.; Okano, K.; Mori, A. *Org. Lett.* **2018**, *20*, 1688.

[47] Schafer, G.; Matthey, C.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 9173.

[48] Antezak, M. I.; Ready, J. M. *Chem. Sci.* **2012**, *3*, 1450.

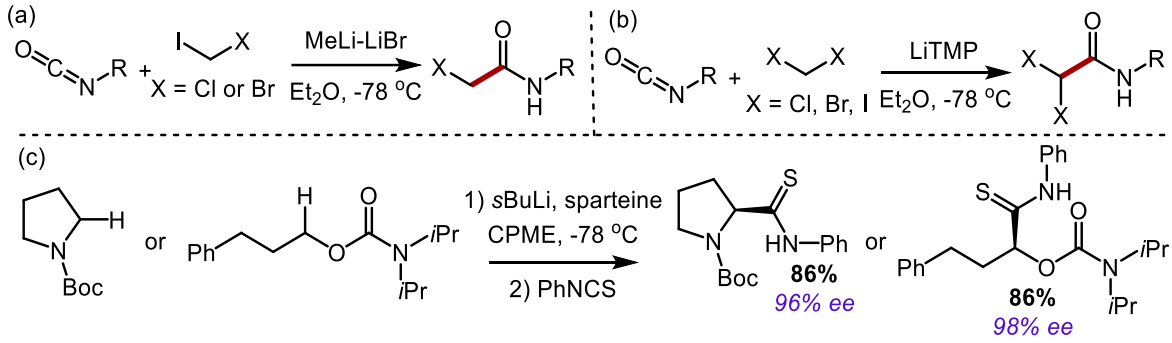
to the isocyanate produces an amide anion which directs an ortho metalation event, subsequently harnessed for further derivatization.



Scheme 1.9: (a) Bode's synthesis of sterically hindered/electronically deactivated amides. (b) Ready's 4-component 1-pot synthesis of isoquinolones.

Pace and coworkers have made numerous contributions to the addition of organometallic reagents onto isocyanates and isothiocyanates.[49] They first reported the addition of lithium carbenoids to isocyanates providing access to α-halogenated (scheme 1.10a) and dihalogenated amides (scheme 1.10b).[50] Particularly impressive was the use of Barbier type conditions in the latter where LiTMP forms lithium carbenoids selectively from dihalomethane precursors while avoiding direct addition onto the isocyanate. The use of less bulky amide bases such as LDA were observed to form the undesired urea in high yield. They then provided a facile procedure to access various thioamides through the reaction of isothiocyanates with various organolithium reagents building from Bode's work (scheme 1.10c).[51] Noteworthy was the ability to employ chiral lithiated species using sparteine and *s*-BuLi, forming products with high enantioselectivity. Interestingly, such a procedure has yet to be reported on isocyanate derivatives; however, a stereoretentive process was recently reported by Aggarwal and coworkers.[52] Finally, in 2016 Pace reported a chemoselective reduction of isocyanates to the desired formamide using the Schwartz reagent, which allowed them to avoid the unwanted overreduction.[53]

[49] Pace, V.; Monticelli, S.; de la Vega-Hernández, K.; Castoldi, L. *Org. Biomol. Chem.* **2016**, *14*, 7848.
[50] (a) Pace, V.; Castoldi, L.; Holzer, W. *Chem. Commun.* **2013**, *49*, 8383. (b) Pace, V.; Castoldi, L.; Mamuye, A. D.; Holzer, W. *Synthesis* **2014**, 2897.
[51] Pace, V.; Castoldi, L.; Monticelli, S.; Safranek, S.; Roller, A.; Langer, T.; Holzer, W. *Chem. Eur. J.* **2015**, *21*, 18966.
[52] Pulis, A. P.; Varela, A.; Citti, C.; Songara, P.; Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 10835.
[53] Pace, V.; de la Vega-Hernández, K.; Urban, E.; Langer, T. *Org. Lett.* **2016**, *18*, 2750.



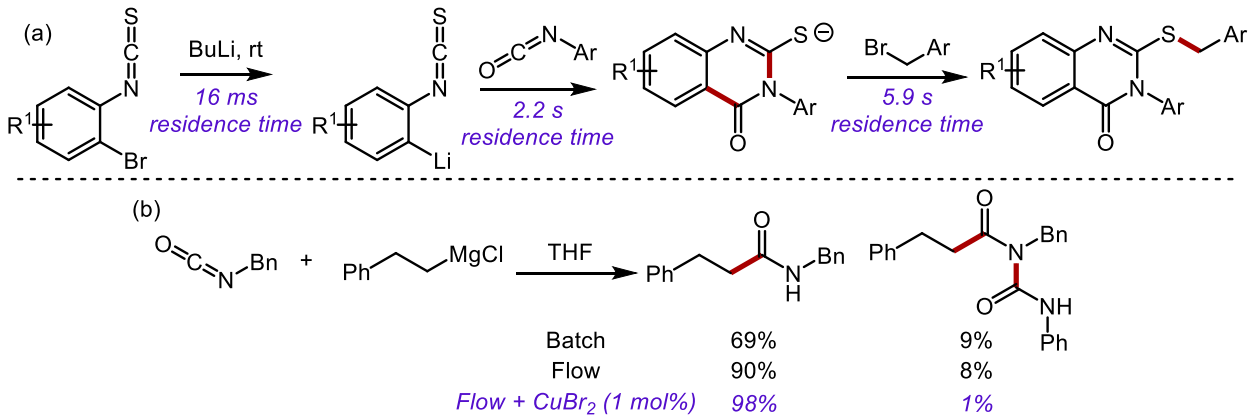
Scheme 1.10: (a) Pace synthesis of α-halogenated amides. (b) Pace synthesis of α-dihalogenated amides. (c) Pace synthesis of chiral thioamides

The application of flow chemistry has recently been employed to expand the scope of organometallic addition to isocyanates.[54] This concept was first applied by Kim and coworkers with their novel synthesis of thioquinazolinones (scheme 1.11a).[55] *o*-Bromophenylisothiocyanates selectively underwent a lithium halogen exchange reaction followed by trapping with an isocyan ate. This heterocycle can then undergo a substitution reaction to form the desired thioquinazolinones. Lindsay and coworkers also made use of flow chemistry to expand upon the work of Bode (scheme 1.11b).[56] Addition to non-sterically encumbered isocyanates were observed to undergo rapid oligomerization, forming unwanted acylurea by-products. The use of flow chemistry readily diminished the formation of this unwanted by-product through careful control of the residence time providing a general amide synthesis with a much broader scope than previously reported with batch type conditions.

[54] For examples not centred on isocyanate reactivity see: (a) Kim, H.; Min, K.-I.; Inoue, K.; Im, D. J.; Kim, D.-P.; Yoshida, J.-I. *Science* **2016**, *352*, 691. (b) Ganiek, M. A.; Becker, M. R.; Berionni, G.; Zipse, H.; Knochel, P. *Chem. Eur. J.* **2017**, *23*, 10280. (c) Huck, L.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. *Org. Lett.* **2017**, *19*, 3747. (d) Weidmann, N.; Ketels, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2018**, *57*, 10748.

[55] Kim, H.; Lee, H.-J.; Kim, D.-P. *Angew. Chem. Int. Ed.* **2015**, *54*, 1877.

[56] Williams, J. D.; Kerr, W. J.; Leach, S. G.; Lindsay, D. M. *Angew. Chem. Int. Ed.* **2018**, *57*, 12126.

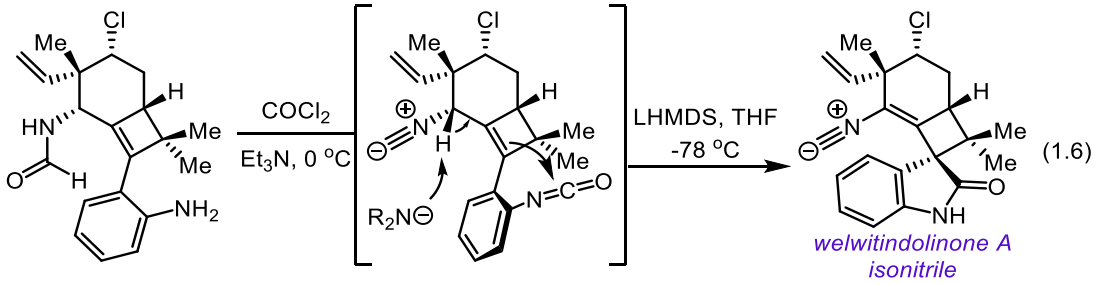


Scheme 1.11: (a) Kim flow synthesis of thioquinazolinones. (b) Flow synthesis of amide from isocyanates and Grignard reagents

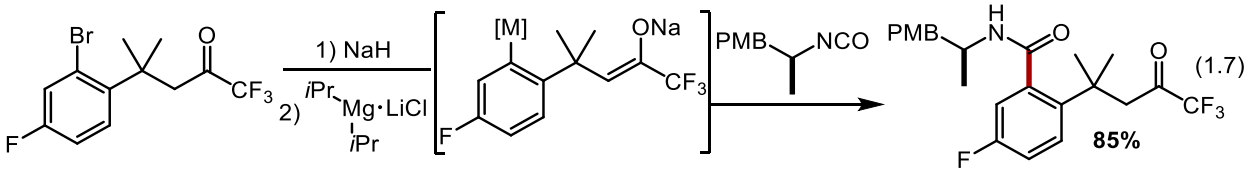
The direct addition of organometallic reagents to isocyanates has also been applied in several applications. Taylor and coworkers employed the addition of vinyl organomagnesium reagents to cinnamic acid derived isocyanates during their synthesis of lansamide-I and lansiumamides A-C.[57] Vinyl organolithium reagents were used in a similar vein by De Brabander and coworkers during their synthesis of salicylihalamide A. The presence of significant amounts of acylurea by-product was also observed.[58] A similar approach was explored by Sarpong and coworkers during their unified synthesis of a family of diterpenoid alkaloids, although a subsequent cycloaddition displaying poor selectivity forced them to abandon the original route.[59] Lombardo and coworkers at BMS generated their desired organolithium via direct lithiation of chlorothiazole which readily added onto the isocyanate during their development of a potent kinase inhibitor.[60] Wood and coworkers employed a LiHMDS mediated lithiation followed by intramolecular cyclization for the final step in the synthesis of welwitindolinone A isonitrile (eq. 1.6).[61] Impressively, the lithiation occurs without interference from the isocyanate. A similar intramolecular

[57] Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735.
[58] (a) Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *2*, 4241. (b) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245.
[59] Kou, K. G. M.; Kulyk, S.; Marth, C. J.; Lee, J. C.; Doering, N. A.; Li, B. X.; Gallego, G. M.; Lebold, T. P.; Sarpong, R. *J. Am. Chem. Soc.* **2017**, *139*, 13882.
[60] Lombardo, L. J.; Lee, F. Y.; Chen, P.; Norris, D.; Barrish, J. C.; Behnia, K.; Castaneda, S. Cornelius, L. A. M.; Das, J.; Doweyko, A. M.; Fairchild, C.; Hunt, J. T.; Inigo, I.; Johnston, K.; Kamath, A.; Kan, D.; Klei, H.; Marathe, P.; Pang, S.; Peterson, R.; Pitt, S.; Schieven, G. L.; Schmidt, R. J.; Tokarski, J.; Wen, M.-L.; Wityak, J.; Borzilleri, R. M. *J. Med. Chem.* **2004**, *47*, 6658.
[61] Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448.

cyclization making use of lithium halogen exchange has also been reported during the synthesis of *(+)*-pancratistatin.[62]



Senanayake and coworkers reported an impressive example of Grignard addition to isocyanates during the development of the large-scale synthesis of a glucocorticoid agonist (eq. 1.7).[63] This key step involved magnesium halogen exchange while in the presence of a trifluoromethyl ketone. To circumvent protection/deprotection of the reactive ketone, this motif was 'protected' via enolate formation, which would remove its electrophilic character while remaining less nucleophilic than the subsequently formed aryl Grignard species thus avoiding competitive addition to the isocyanate. NaH was the reagent of choice for enolization to avoid the formation of a protic conjugate acid species. Standard lithium and magnesium halogen exchange reagents proved low yielding when coupled with the addition onto the isocyanate. The use of highly activated dialkylmagnesium turbo Grignard reagents developed in the Knochel lab was found to dramatically increase the rate of magnesium halogen exchange and allowed an 85% yield of the desired amide product.



1.3 Catalytic Amidation of Isocyanates

The importance of the amide functional group in a variety of fields has stimulated the development of novel syntheses of this key functional group.[64] Nevertheless, many methodologies, including classical

[62] Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
[63] Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Rodriguez, S.; Qu, B.; Kim, S.; Niemeier, O.; Li, Z.; Byrne, D.; Campbell, S.; Chitroda, A.; DeCroos, P.; Fachinger, T.; Fuchs, V.; Gonnella, N. C.; Grinberg, N.; Haddad, N.; Jäger, B.; Lee, H.; Lorenz, J. C.; Ma, S.; Narayanan, B. A.; Nummy, L. J.; Premasiri, A.; Roschangar, F.; Sarvestani, M.; Shen ,S.; Spinelli, E.; Sun, X.; Varsolona, R. J.; Yee, N.; Brenner, M.; Senanayake, C. H. *J. Org. Chem.* **2013**, *78*, 3616.
[64] De Figueiredo, R. M.; Suppo, J.-S.; Campagne, J.-M. *Chem. Rev.* **2016**, *116*, 12029.

acylation procedures, continue to rely on stoichiometric activating agents, sparking research on the development of greener catalytic processes.[65] Towards this end, isocyanates provide a fruitful platform for the development of catalytic amide synthesis for several reasons: 1) the numerous strategies for catalytic generation of nucleophilic organometallic species can readily be exploited for amide synthesis when coupled with isocyanates, 2) the activated π-bonds of isocyanates are readily amenable to alternative activation modes such as metal-mediated oxidative cycloadditions, broadening the scope of applicability, 3) the intrinsically high reactivity of isocyanates can help overcome limitations typically observed within classical amidation methods when using sterically hindered/electronically deactivated substrates, 4) isocyanates are most commonly formed through phosgenation which, although hazardous, is considered a green, environmentally benign procedure.[66]

1.3.1 Isocyanate coordination modes to transition metals

Isocyanates are isoelectronic structures to carbon dioxide and as such, share similar coordination modes to various metal species.[67] The most common of such binding motifs is the η^2-C,N coordination complex (figure 1.3). Paradoxically, characterization of these complexes has proven challenging given their intrinsic instability which will be expanded upon below. η^2-C,O bound coordination complexes have also been identified and are proposed as the second most prevalent binding motif. Finally, μ^2-C,N complexes where isocyanates serve as a bridge between different metal centres have also been characterized, although are generally rarer. Notably, the existence of isocyanates bound to metal centers via dative bonds undoubtably plays an important role in various metal catalyzed transformations of isocyanates, however, the characterization of such interactions has as of yet eluded chemist.

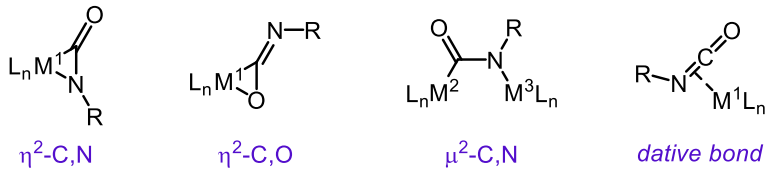
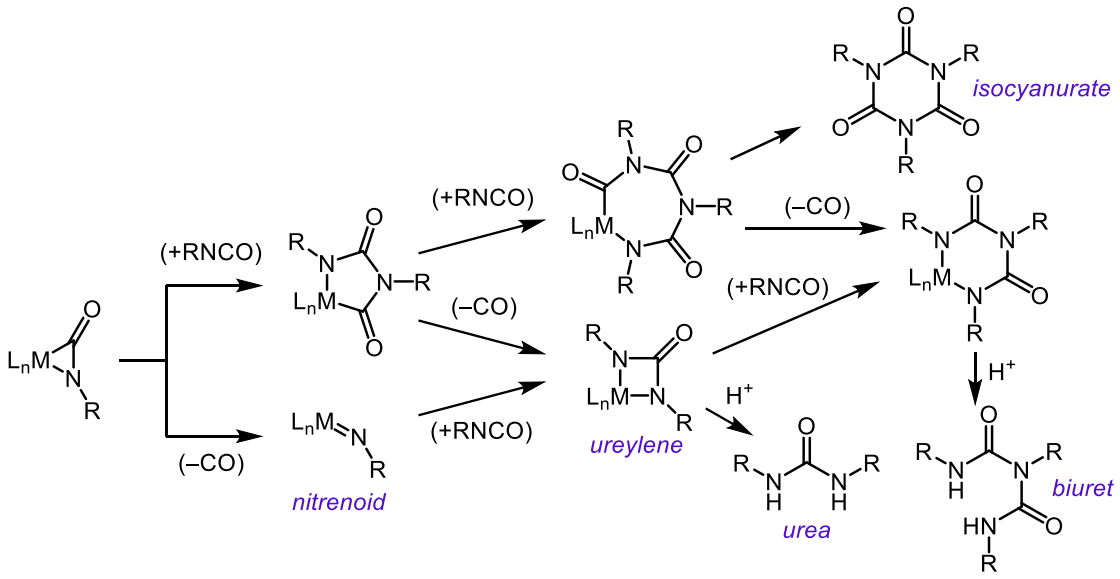


Figure 1.3: Various coordination modes of isocyanates to metals

[65] Sabatini, M. T.; Boulton, L. T.; Sneddon, H. F.; Sheppard, T. D. *Nat. Catal.* **2019**, *2*, 10.
[66] Andraos, J. *Pure Appl. Chem.* **2012**, *84*, 827.
[67] For a review of isocyanate coordination to metal centres, see: Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927.

As mentioned above, the instability of a variety of low valent metal complexes including, but not limited to, Pt, Pd, Ni, Rh, Ir, and Ti complexes with isocyanates is well documented.[68] The most common degradation products are the ureylene/urea derivatives. These by-products are proposed to arise through two potential mechanisms; 1) nitrene formation via decarbonylation followed by addition to a second isocyanate molecule, or head to tail oxidative cycloaddition followed by decarbonylation (scheme 1.12). Oxidative cycloaddition processes have also been proposed to account for the formation of biuret by-products. This intrinsic reactivity has been harnessed for the catalytic generation of 1,3,5-isocyanurates, an important additive to numerous urethane-based polymers. More specifically, both low valent nickel[68d] and palladium[69] complexes have been reported as efficient trimerization catalysts. While these highlight the potential difficulties in developing metal-catalyzed isocyanate transformations, numerous reports have nevertheless been disseminated on the topic. These reports will be covered in the following section with a focus on achieving C-C bond formation with isocyanates.[70]



Scheme 1.12: Low valent metal reactivity with isocyanates

1.3.2 Catalytic amide synthesis through redox neutral couplings of isocyanate

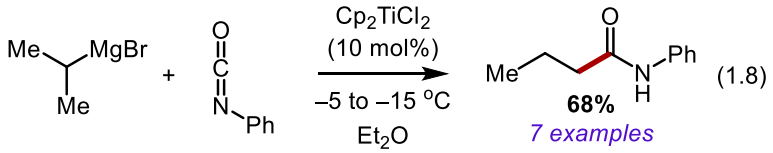
[68] (a) Beck, W.; Rieber, W.; Cenini, S.; Porta, F.; La Monica, G. *J. Chem. Soc. Dalton Trans.* **1974**, 298. (b) Cenini, S.; La Monica, G. *Inorganica Chimi. Acta* **1976**, *18*, 279. (c) Gaal, H. L. M.; Verlaan, J. P. J. *J. Organomet. Chem.* **1977**, *133*, 93. (d) Hoberg, H.; Oster, B. W.; Kruger, C.; Tsay, Y. H. *J. Organomet. Chem.* **1983**, *252*, 365.

[69] (a) Paul, F.; Moulin, S.; Piechaczyk, O.; Le Floch, P.; Osborn, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 7294. (b) Lee, G. S.; Choi, K.-Y.; Kim, Y.-J.; Park, S.; Lee, S. W. *Dalton Trans.* **2015**, *44*, 6537. (c) Choi, J.-H.; Jung, K.-Y.; Kim, Y.-J.; Im, H. J.; Lee, S. W. *Polyhedron* **2016**, *117*, 283.

[70] For a recent review, see: Serrano, E.; Martin, R. *Eur. J. Org. Chem.* **2018**, 3051.

Much of the early reports of transition metal catalyzed C-C bond formation of isocyanates made use of stoichiometric nucleophiles where transmetallation with a metal catalyst formed the necessary organometallic intermediate to achieve addition onto the isocyanate. These methodologies are perhaps most straightforward given the absence of changes in oxidation state at the metal center and could explain their early developments in the field. The following section will highlight selected examples of these developments.

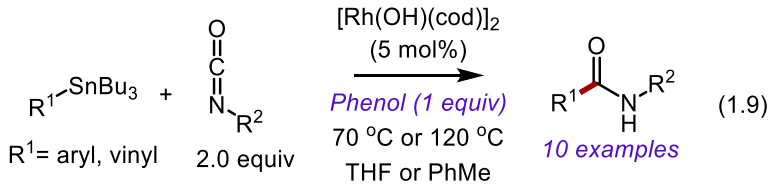
Early work on metal catalyzed amidation of isocyanates was reported by Zhang and coworkers where Cp_2TiCl_2 was observed to mediate the addition of alkyl Grignard species to isocyanates (eq. 1.8).[71] Interestingly, linear aliphatic amides were invariably generated whether branched or linear Grignard reagents were employed. This was explained by formation of an alkyl titanium species upon initial transmetallation, followed by β-hydride elimination and subsequent migratory insertion leading to the formation of the most stable titanium species. Higher temperatures (ie: room temperature) led to the competitive insertion of the titanium hydride intermediate into the isocyanate.[72]



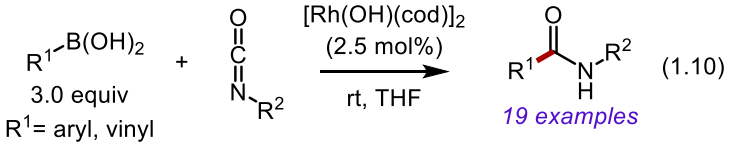
(1.8)

To avoid the use of highly reactive Grignard reagents, Mori and coworkers developed a similar transformation by making use of much less reactive organostannanes with a rhodium catalyst (eq. 1.9).[73] Sluggish catalytic activity was observed initially, hypothesized to result from the lack of protons present to free the amide product and promote catalyst turnover. Phenol was chosen as an additive and resulted in high yields though 2.0 equivalents of the isocyanate were necessary due to the propensity of phenol to form the undesired carbamate. Moreover, the organostannane scope was limited to electron rich aromatic systems while a notable decline in yield was also observed when employing alkyl isocyanates.

[71] Zhang, Y.; Jiang, J.; Chen, Y. *Tetrahedron Lett.* **1987**, *28*, 3815.
[72] Zhang, Y.; Jiang, J.; Zhang, Z. *Tetrahedron Lett.* **1988**, *29*, 651.
[73] Koike, T.; Takahashi, M.; Arai, N.; Mori, A. *Chem. Lett.* **2004**, *33*, 1364.

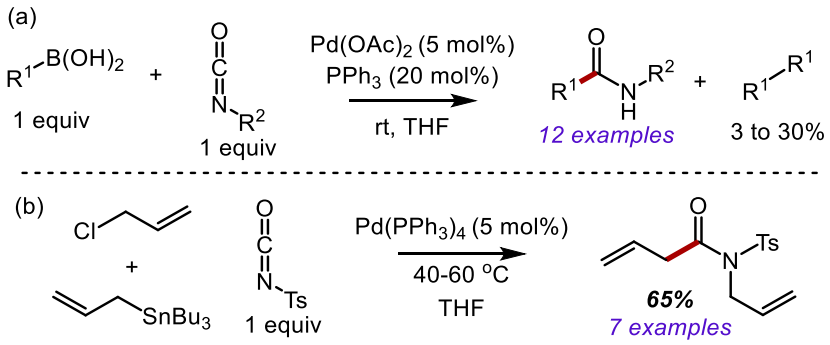


Murakami and coworkers were then able to employ organoboron reagents in this rhodium catalyzed amidation which are much less toxic and broadly commercially available (eq. 1.10).[74] Moreover, lower rhodium loadings, lower temperatures, and broader functional group tolerance was observed under their conditions. Nevertheless, 3.0 equivalents of the organoboron reagent was necessary for efficient reactivity which may be attributed to a competitive protodemetallation pathway.



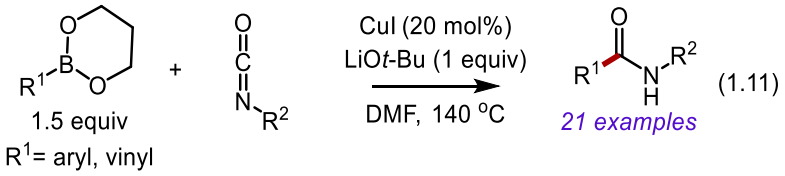
Alternative catalytic systems have also been explored by Kianmehr making use of palladium catalysis. Unlike the previously described rhodium catalysis, the palladium variant was plagued by the formation of homocoupling by-products due to the ability of Pd(II) species to undergo a second transmetallation event, followed by reductive elimination (scheme 1.13a).[75] Up to 30% yield of this by-product was observed under standard reaction conditions, much greater than the 5 mol% palladium employed. Surprisingly, the authors proposed a Pd(0)/Pd(II) catalytic cycle involving oxidative addition into the aryl boron bond. This proposal would allow catalyst turnover in the absence of a competent oxidant, however it is unprecedented in the literature. Palladium catalysis has also been employed in the bis-allylation of isocyanates in both an intra- and intermolecular fashion (scheme 1.13b) though this chemistry suffers from similar homocoupling issues as well as monoallylation and regioselectivity issues.[76]

[74] Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 3577.
[75] Kianmehr, E.; Rajabi, A.; Ghanbari, M. *Tetrahedron Lett.* **2009**, *50*, 1687.
[76] (a) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (b) Solin, N.; Narayan, S.; Szabó, K. J. *Org. Lett.* **2001**, *3*, 909.



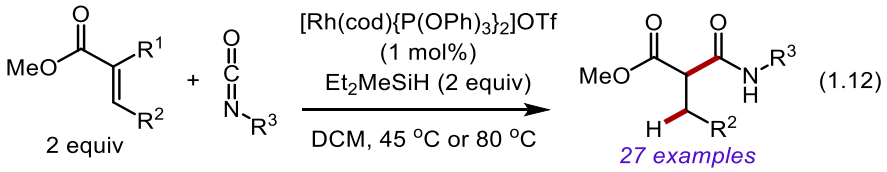
Scheme 1.13: (a) Palladium catalyzed amidation of isocyanates. (b) Palladium catalyzed bis allylation of isocyanates.

Zhang and coworkers were able to develop the copper catalyzed amidation of isocyanates with organoboron reagents although highly forcing conditions (i.e. high temperature, strong base) were necessary (eq. 1.11).[77] Mitigation of the detrimental homocoupling reaction observed in the palladium system was overcome by employing copper (I) salts. However, in the case of highly electron poor organoboron reagents such as 3-nitrophenylboronic acid, homocoupling by-products dominated the reaction mixture. Interestingly, previous reports have highlighted the ability of *tert*-butoxide bases to promote addition of organoboron reagents onto isocyanates though no background reaction was observed in the absence of the copper catalyst in this case.[78]



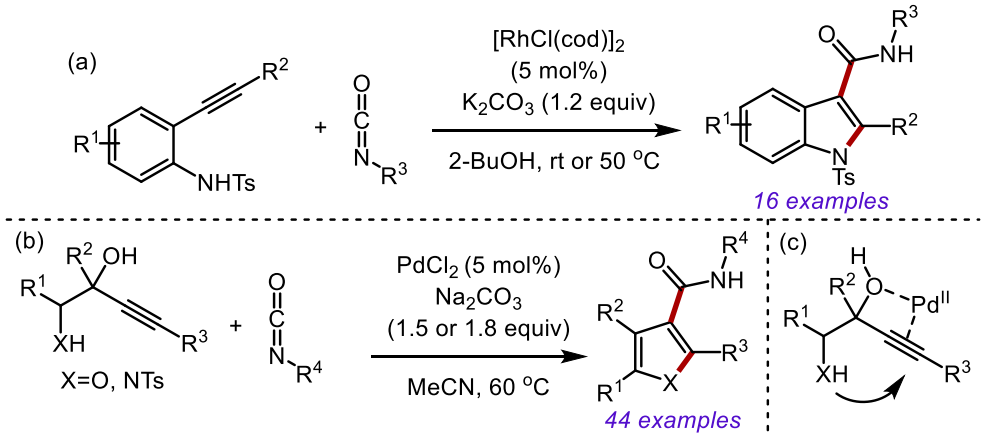
Similar amidation methods have also been developed making use of unsaturated C-C bonds to generate the desired organometallic nucleophile *in situ*. This was first demonstrated by Itoh and coworkers where an initial hydrometallation of activated olefins generates a rhodium enolate followed by a subsequent insertion into the isocyanate (eq. 1.12).[79] The initial insertion showed exquisite selectivity for the olefin even with increased substitution, though α-substitution was poorly tolerated suggestive of difficult addition onto the isocyanate. Moreover, the highly reduced yields observed when using alkyl isocyanates support this latter point.

[77] Lew, T. T. S.; Lim, D. S. W.; Zhang, Y. *Green Chem.* **2015**, *17*, 5140.
[78] Grigg, R. D.; Rigoli, J. W.; Hoveln, R. V.; Neale, S.; Schomaker, J. M. *Chem. Eur. J.* **2012**, *18*, 9391.
[79] Muraoka, T.; Matsuda, I.; Itoh, K.; *Organometallics* **2001**, *20*, 4676.



(1.12)

Inamoto and coworkers developed a rhodium catalyzed intramolecular amino rhodation of aniline derivatives which were subsequently intercepted with isocyanates producing 3-indolecarboxamides (scheme 1.14a).[80] Noteworthy is the use of 2-BuOH as the solvent which provided the best results even in the presence of highly electrophilic isocyanates. Interestingly, a recent publication has reported the catalyst free variation of this cascade.[81] Shortly after the work of Inamoto, Reddy and coworkers described a similar palladium catalyzed variant where oxy- or aminopalladation results in the formation of furanyl- and pyrrolyl-3-carboxamides (scheme 1.14b).[82] Analogous to Inamoto's work, alkyl isocyanates were reported to be better reaction partners. Moreover, mechanistic probes revealed the propargylic alcohol motif to be a necessary feature of the reaction, leading the authors to propose its involvement in directing the palladation event (scheme 1.14c).

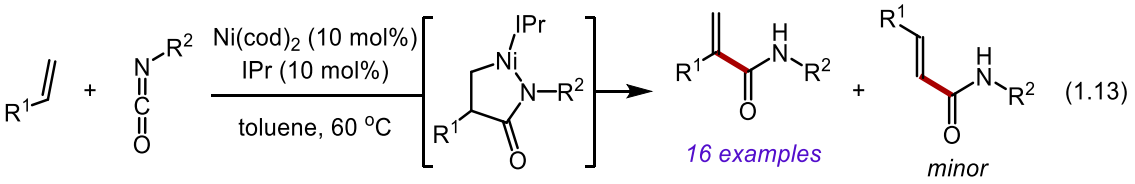


Scheme 1.14: (a) Inamato's cascade synthesis of 3-indolecarboxamides. (b) Reddy's cascade synthesis of 3-pyrrolyl and 3-furanyl carboxamides. (c) Proposed directed palladation event.

Inspiration garnered from Hoberg's original work[83] on nickel catalyzed cycloadditions of isocyanates led Jamison and coworkers to develop a nickel catalyzed acrylamide synthesis from olefins

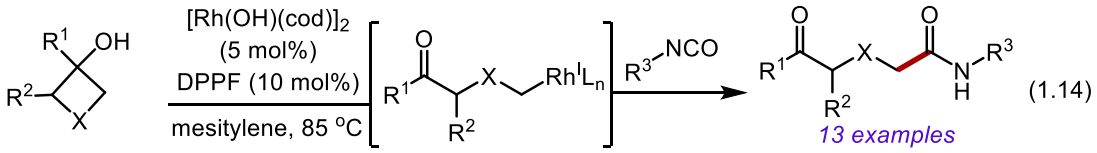
[80] Mizukami, A.; Ise, Y.; Kimachi, T.; Inamoto, K. *Org. Lett.* **2016**, *18*, 748.
[81] Rode, N. D.; Aschi, M.; Chiarini, M.; Vecchio, L. D.; Marinelli, F.; Arcadi, A. *Adv. Synth. Cat.* **2018**, *360*, 3672.
[82] Rajesh, M.; Puri, S.; Kant, R.; Reddy, M. S. *Org. Lett.* **2016**, *18*, 4332.
[83] Hoberg, H.; Hernandez, E. *J. Chem. Soc., Chem. Commun.* **1986**, 544.

and isocyanates (eq. 1.13).[84] The five membered metallacycle, formed from an oxidative cycloaddition, can undergo β-hydride elimination followed by a reductive elimination to provide α-substituted acrylamides. Selectivity in the cycloaddition was opposite to that observed in Hoberg's work, proposed to arise from the use of bulky NHC ligands. Unfortunately, the reaction was largely limited to sterically hindered alkyl isocyanates with minimal product observed with primary alkyl substituents. This was attributed to the unwanted oligomerization of isocyanates which was a competitive process under the reaction conditions. Louie and coworkers have further developed this reactivity to the synthesis of dienamides employing enyne precursors.[85]



(1.13)

Murakami and coworkers developed an innovative strategy for alkyl rhodium formation using C-C σ-bond cleavage (eq. 1.14).[86] The traditional reactivity of alcohols with isocyanates was largely evaded through a rhodium induced ring opening of cyclobutanols, proposed to be promoted through strain release. This is supported by the required use of tertiary cyclobutanols as well as a bulky diphosphine ligand. Dropwise addition of the isocyanate/alcohol solution to the reaction mixture was necessary to avoid undesired carbamate formation.



(1.14)

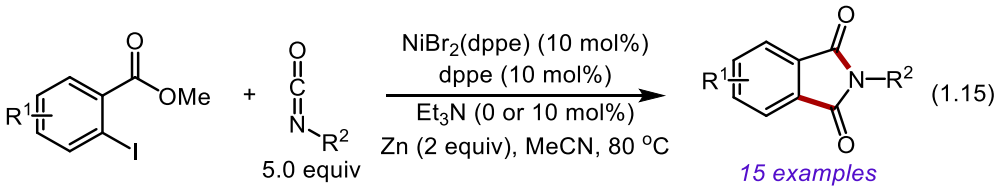
1.3.3 Catalytic amide synthesis through reductive cross-couplings

In recent years, the reductive cross-coupling of organic halides in C-C bond formation has garnered much attention due to its avoidance of stoichiometric organometallic reagents allowing the use

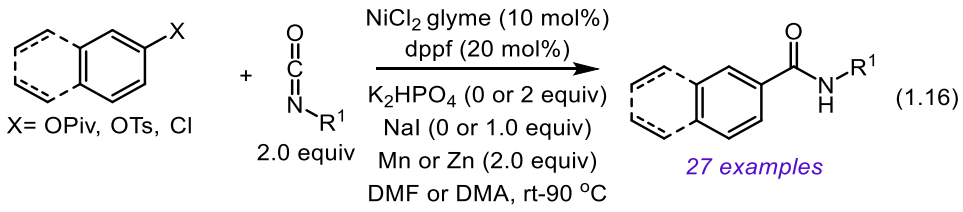
[84] Schleicher, K. D.; Jamison, T. F. *Org. Lett.* **2007**, *9*, 875.
[85] D'Souza, B. R.; Louie, J. *Org. Lett.* **2009**, *11*, 4168.
[86] Ishida, N.; Nakanishi, Y.; Murakami, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11878.

of easy to handle electrophiles.[87] This strategy has been adopted in the synthesis of amides from isocyanates and organic halides which will be covered in the following section.

Cheng and coworkers provided the first example of such reductive couplings with the ir synthesis of phthalimides (eq. 1.15).[88] Unfortunately this reaction was afflicted by both unwanted homocoupling of the aryl halide and isocyanate oligomerization to the isocyanurate, leading to high loadings of the latter.



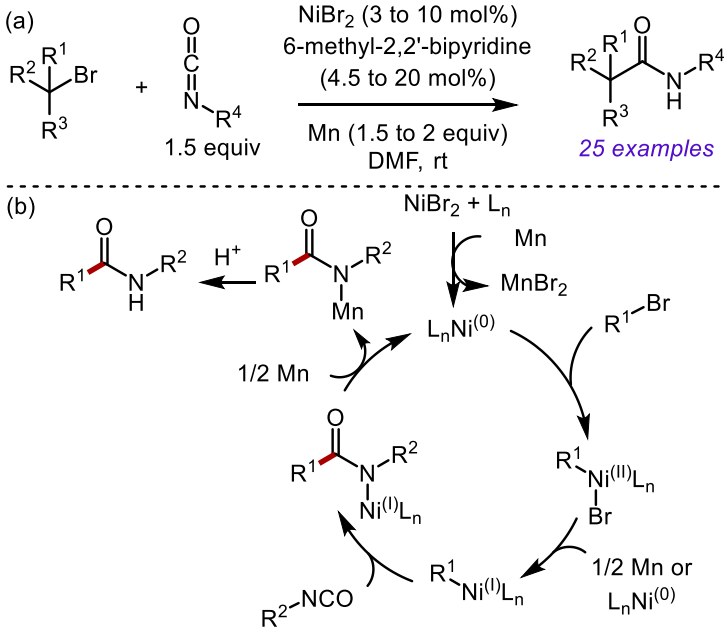
Building from this initial report, Martin and coworkers provided several reports of reductive cross-couplings of isocyanates, the first of which made use of aryl and benzylic pseudohalides (eq. 1.16).[89] Unsurprisingly, homocoupling, isocyanurate formation, and carbamate by-products were all observed over the course of the optimization. Homocoupling was suppressed by the inclusion of NaI while the addition of K_2HPO_4 was found to reduce the latter by-products. The C-O bond cleavage of pivalates was limited to naphthalene derivatives, while both aryl chlorides and aryl tosylates were able to overcome this limitation. Unfortunately, the scope of the isocyanate partner was limited to alkyl isocyanates due to the propensity of oligomerization exhibited by their aryl counterparts.



Martin and coworkers followed up this report with a methodology allowing the use of alkyl bromides as coupling partners, an impressive feat given their propensity to undergo β-hydride elimination (scheme 1.15a).[90] Nevertheless, aryl isocyanates continue to prove problematic substrates with sterically hindered derivatives required to avoid the formation of acylurea by-products. Mechanistic investigations of the reaction support the formation of an alkyl Ni(II) species which undergoes a manganese mediated

[87] Knappke, C. E. I; Grupe, S.; Gartner, D.; Corpet, M.; Gosmini, C.; von Wangelin, A. J. *Chem. Eur. J.* **2014**, *20*, 6828.
[88] Hsieh, J.-C.; Cheng, C.-H. *Chem. Commun*. **2005**, 4554.
[89] Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 7253.
[90] Serrano, E.; Martin, R. *Angew. Chem. Int. Ed.* **2016**, *55*, 11207.

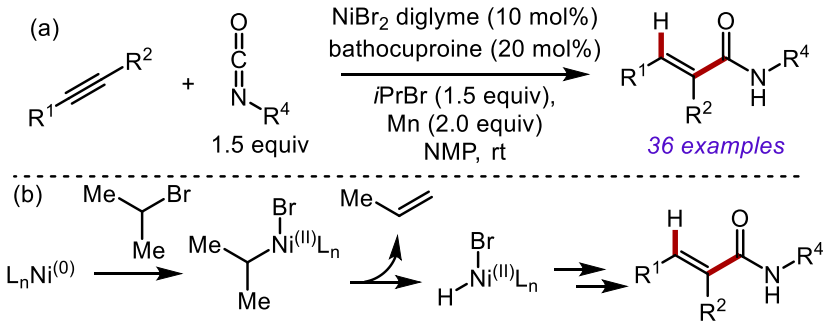
reduction (alternatively comproportionation with a Ni(0) species) to Ni(I) which inserts into the isocyanate A final manganese mediated reduction regenerates the Ni(0) catalyst and the amide product (scheme 1.15b). Notably, the direct insertion of an alkyl Ni(II) species into the isocyanate can not be ruled out.



Scheme 1.15: (a) Nickel catalyzed reductive coupling of isocyanates with alkyl bromides. (b) Proposed catalytic cycle.

Finally, Martin and coworkers reported an innovative reductive variant of Itoh's work generating the desired organometallic *in situ* via hydrofunctionalization of alkynes (scheme 1.16a).[91] Screening of various hydride donors led to trace product formation as a result of the sensitivity of the isocyanate functional group. To overcome this limitation, alkyl bromides were employed as hydride sources due to their propensity to undergo β-hydride elimination, an *a priori* parasitic reaction (scheme 1.16b). The nickel hydride was selectively intercepted by the alkyne followed by insertion into the isocyanate generating the acrylamide product. Unfortunately, the use of aryl isocyanates was again limited to a single electron-rich, sterically hindered example.

[91] Wang, X.; Nakajima, M.; Serrano, E.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 15531.



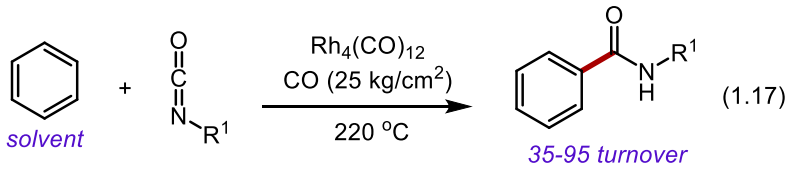
Scheme 1.16: (a) Nickel catalyzed hydroamidation of alkynes. (b) Proposed formation of nickel hydride species

1.3.4 Catalytic amidation of isocyanate through C-H activation

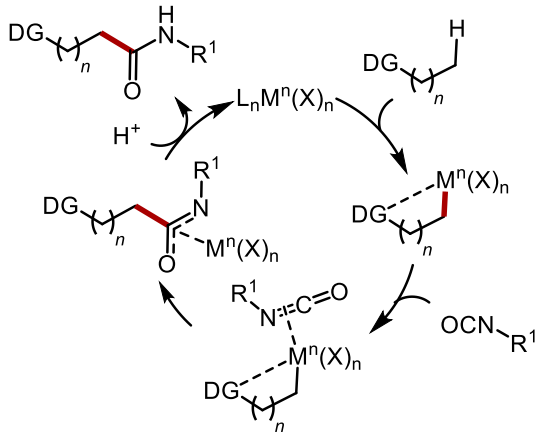
The direct catalytic amidation of C-H bonds using isocyanates has garnered much interest due to its ability to overcome potential regioselectivity issues when compared to Friedel-Crafts type reactivity, as well as avoiding the use of stoichiometric metalation reagents which hamper functional group tolerance (ie: lithiation/magnesiation). Moreover, the direct activation of C-H bonds results in a reduction in overall step count, removing the otherwise necessary transformation of the C-H bond to the required electrophilic/nucleophilic functional group. Selected developments towards this end will be covered in the following section.

Seminal work by Sonogashira and Hagihara on direct catalytic C-H amidation using isocyanates can be traced back to 1978 where a rhodium catalyst was found to amidate benzene employing the latter as a solvent at 225 °C (eq. 1.17).[92] Numerous reports have since been published employing milder conditions, spanning a variety of alternative metal catalyst including Re, Ir, Ru, Co, and Mn, though generally requiring the use of directing groups. A comprehensive review has recently summarized these works.[93-94]

[92] Hong, P.; Yamazaki, H.; Sonogashira, K.; Hagihara, N. *Chem. Lett.* **1978**, 535.
[93] Hummel, J. R.; Boerth, J. A.; Ellman, J. A. *Chem. Rev.* **2017**, *117*, 9163.
[94] For recent examples see: (a) Han, J.; Wang, N.; Huang, Z.-B.; Zhao, Y.; Shi, D.-Q. *J. Org. Chem.* **2017**, *82*, 6831. (b) Reddy, K. N.; Subhadra, U.; Sridhar, B.; Reddy, B. V. S. *Org. Biomol. Chem.* **2018**, *16*, 2522. (c) Jeong, T.; Lee, S. H.; Chun, R.; Han, S.; Han, S. H.; Jeon, Y. U.; Park, J.; Yoshimitsu, T.; Mishra, N. K.; Kim, I. S. *J. Org. Chem.* **2018**, *83*, 4641. (d) Zhao, H.; Zhou, X.; Li, B.; Liu, X.; Guo, N.; Lu, Z.; Wang, S. *J. Org. Chem.* **2018**, *83*, 4153.



A general catalytic cycle for such transformations can be seen below (scheme 1.17).[95] The C-H activation event is generally proposed to derive from electrophilic activation, in line with the many reports making use of cationic metal catalyst (i.e. employing additives such as $AgSbF_6$) as well as competition experiments where more electron rich C-H activation partners outcompete their electron poor counterparts. Moreover, many reports, though not all, make use of acetate additives (ie: KOAc, NaOAc, etc.), bringing forth the possibility of carboxylate assisted C-H activation mechanism. Coordination of the isocyanate is followed by insertion to form the desired C-C bond. This insertion event has been observed to be reversible in some cases.[96] Protodemetallation releases the desired product and regenerates the catalyst.

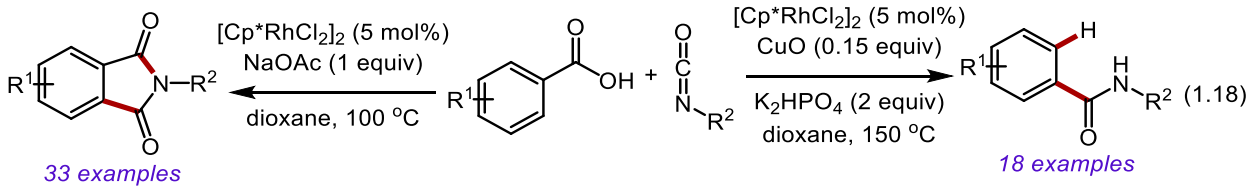


Scheme 1.17: A general catalytic mechanism of directed C-H amidation with isocyanates.

To overcome the directing group limitation of these transformations, decarboxylative methodologies have been explored as alternatives. Li and coworkers initially reported that aryl carboxylic acids could direct a rhodium catalyzed ortho C-H amidation which gives rise to phthalimides upon cyclization (eq. 1.18).[97] They subsequently showed that aryl carboxylates could be employed as traceless

[95] For mechanistic studies on C-H activation see: (a) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492. (b) Davies, D. L.; Macgregor, S. A.; McMullin, C. L. *Chem. Rev.* **2017**, *117*, 8649.
[96] (a) Jeong, T.; Han, S.; Mishra, N. K.; Sharma, S.; Lee, S.-Y.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 7243. (b) Moselage, M.; Li, J.; Kramm, F.; Ackermann, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 5341.
[97] Shi, X-Y.; Renzetti, A.; Kundu, S.; Li, C.-J. *Adv. Synth. Cat.* **2014**, *356*, 723.

directing groups with both rhodium or ruthenium catalysts.[98] Noteworthy is the lack of observed uncatalyzed amide bond synthesis between the carboxylate and the isocyanate under such harsh reaction conditions (refer to section 1.2.1). Recently, a palladium variation of this reactivity has been reported.[99] Interestingly, the authors employed isothiocyanates in an effort to form thioamide derivatives, yet were surprised to find the formation of amide products. This unusual result was attributed to an oxygen mediated C=S to C=O transformation, however little mechanistic evidence was provided to support this claim. Furthermore, the use of isocyanates directly produced trace amounts of the desired product, highlighting the intrinsic differences in reactivity of these isoelectronic species.



Unusual isocyanate reactivity was observed by Hiyama and coworkers during their study of electron rich alkynes as directing groups for palladium catalyzed benzoxazinone synthesis (scheme 1.18a).[100] This requires a formal C-H bond amination event to occur, which stands in stark contrast to selectivity observed under standard directed C-H amidation techniques using isocyanates. To explain the otherwise abnormal C-N bond formation, the authors propose that an initial ortho palladation event is followed by C-N bond formation via reductive elimination (scheme 1.18b). Given the necessity of $Zn(OAc)_2$ to achieve high yields, its role was proposed to be the activation of the isocyanate via the formation of a mixed carbamic anhydride providing a nucleophilic amide anion which could rationalize the C-N bond forming event. Subsequent oxidative addition to form the acyl palladium species inserts across the alkyne and releases the desired product upon protodemetallation. Such a mechanism had little experimental support save for a handful of deuterium labelling experiments.[101] Nevertheless this work does provide an eccentric example of isocyanates in C-H amidation and could provide a useful starting point for further development of unorthodox reactivity.

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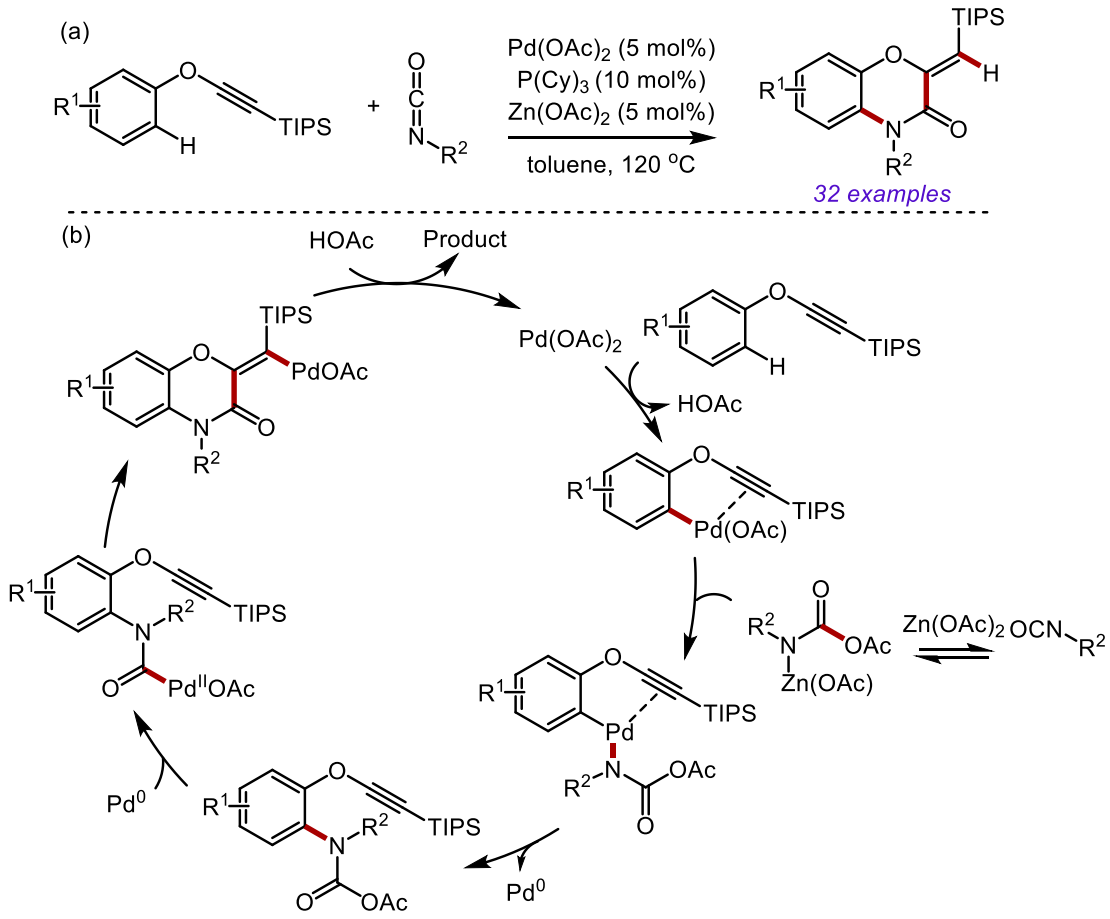
[98] (a) Shi, X.-Y.; Liu, K.-Y.; Fan, J.; Dong, X.-F.; Wei, J.-F.; Li, C.-J. *Chem. Eur. J.* **2015**, *21*, 1900. (b) Shi, X.-Y.; Dong, X.-F.; Fan, J.; Liu, K.-Y.; Wei, J.-F.; Li, C.-J. *Sci. China Chem.* **2015**, *58*, 1286.

[99] Tulichala, R. N. P.; Shankar, M.; Swamy, K. C. K. *J. Org. Chem.* **2018**, *83*, 4375.

[100] (a) Minami, Y.; Kanda, M.; Hiyama, T. *Chem. Lett.* **2014**, *43,* 1408. (b) Minami, Y.; Kanda, M.; Sakai, M.; Hiyama, T. *Tetrahedron* **2015**, *71*, 4522.

[101] Given their more recent work (Minami, Y.; Noguchi, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2017**, *139*, 14013), an alternative mechanism based on Pd-H species could be proposed which would account for the unorthodox insertion.



Scheme 1.18: (a) Hiyama and coworkers synthesis of benzoxazinone derivatives. (b) Proposed catalytic mechanism.

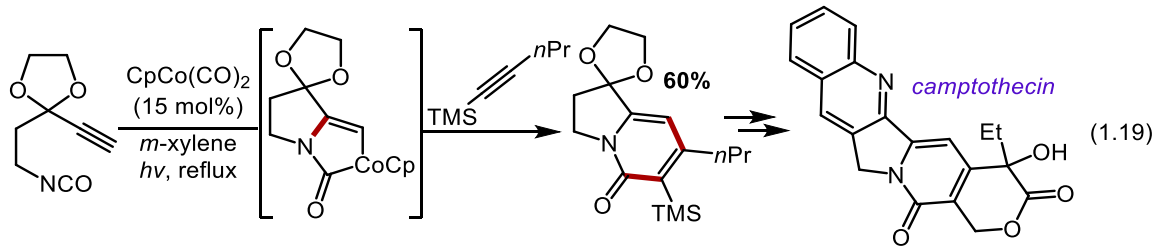
1.3.5 Transition metal catalyzed cycloadditions of isocyanates involving C-C bond formation

Isocyanates have long since been used in heterocyclic synthesis and are highly amenable to cascade type reactivity. They have also garnered much attention in their use as 2π components in various cycloadditions, most notably [2+2] providing access to the privileged β-lactam structure. The incorporation of metal catalysis has greatly expanded the scope of reactivity observed in cycloadditions of isocyanates which will be covered in the following section.

[2+2+2] Cycloadditions have been most heavily studied allowing access to a variety of 6-membered ring systems.[102] Seminal work can be traced back to Hong[103] and Vollhardt.[104] A cobalt catalyst

[102] For an example of [4+2] reactivity see: Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem. Int.* **2006**, *45*, 2734.
[103] Hong, P.; Yamazaki, H.; *Tetrahedron Lett.* **1977**, 1333.
[104] Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49,* 4786.

was able to cyclotrimerize isocyanates with alkynes resulting in the synthesis of pyridones and indolizinones. Vollhardt provided an indepth study of this cyclotrimerization with different catalysts, and tethered substrates, ultimately resulting in a highly regioselective transformation which allowed the formal total synthesis of camptothecin (eq. 1.19). Noteworthy was the detrimental formation of oligomeric isocyanate by-products in both these early reports.

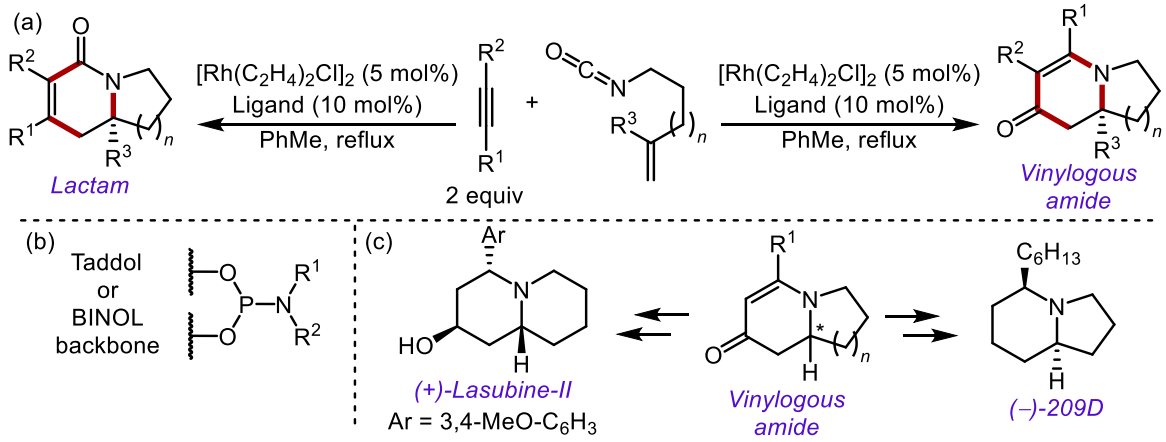


A plethora of variations of this initial reactivity have since been reported with alternative reaction partners as well as catalysts.[105] Noteworthy is the work of Rovis and coworkers where alkenes were successfully employed in these [2+2+2] cycloadditions allowing access to chiral lactams and vinylogous amides (scheme 1.19a).[106] The selectivity observed under the reaction conditions arose from a complex interplay between stereoelectronic effects of the phosphoramidite ligand and that of the alkyne. This methodology was successfully applied in the enantioselective synthesis of (+)-lasubine II and (-)-209D (scheme 1.19c). Moreover, access to medium sized heterocycles was achieved by extending this methodology to the use of dienes resulting in a [4+2+2].[107] Interestingly, the major by-product observed under the reaction conditions was the symmetrical urea. This is in contrast to similar work on metal catalyzed cycloadditions of isocyanates which generally compete against cyclotrimerization of either the isocyanate or the alkyne.

[105] For selected examples see: (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117. (b) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (c) Bonage, L. V. R.; Zhang, H.-C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473. (d) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737. (e) Miura, T.; Morimoto, M.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 15836. (f) Alvarez, S.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2013**, *78*, 9995.

[106] For reviews of this work, see: (a) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. (b) Friedman, R. F.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *Pure Appl. Chem.* **2010**, *82*, 1353.

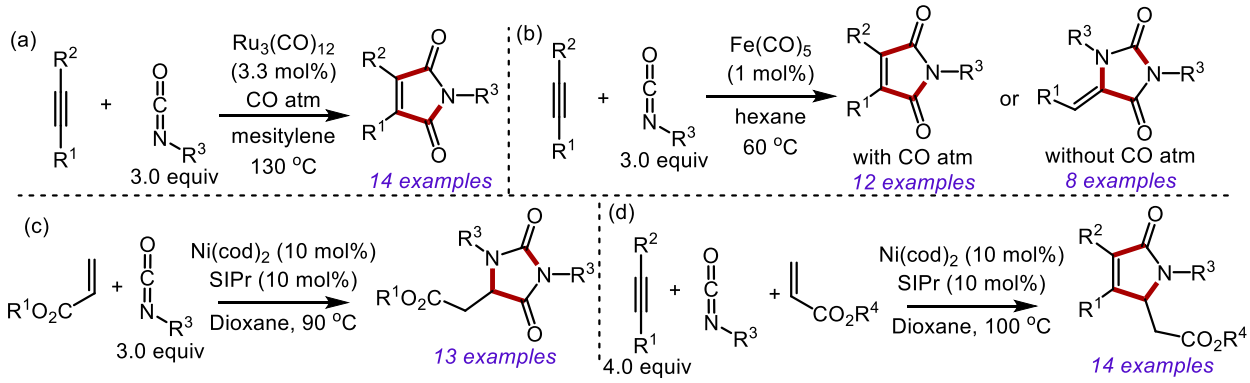
[107] Yu, R. T.; Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13250.



Scheme 1.19: (a) Rovis and coworkers rhodium catalyzed cyclotrimerization of isocyanates, alkynes, and alkenes. (b) Ligand system employed in cyclotrimerization. (c) Application of vinylogous amides in total synthesis.

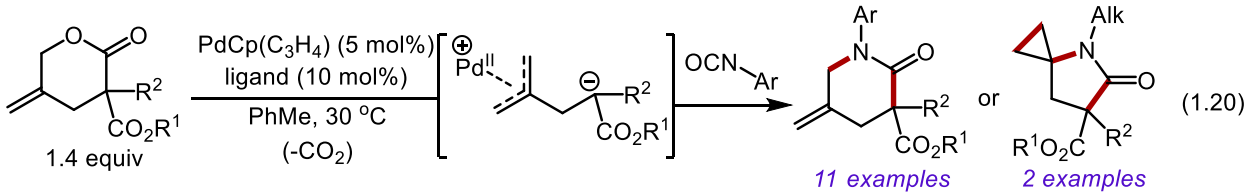
Synthesis of 5-membered heterocycles have also been explored through variation of the Pauson-Khand [2+2+1] cycloaddition incorporating isocyanates as reaction partners.[108] Kondo and coworkers were able to develop the first highly efficient ruthenium catalyzed maleimide synthesis from isocyanates, alkynes, and carbon monoxide (scheme 1.20a).[109] Building upon this work, Mathur and coworkers developed the iron catalyzed variation of this transformation (scheme 1.20b).[110] Moreover, in the absence of a CO atmosphere, efficient hydantoin production was observed through the incorporation of 2 equivalents of isocyanate. A slight variation of this hydantoin synthesis was then reported by Murakami and coworkers using activated olefins as opposed to alkynes as reaction partners (scheme 1.20c).[111] Noteworthy was the observation of isocyanate oligomerization when moving from aryl isocyanates to the alkyl derivatives. Finally, Matsubara and coworkers developed a [2+2+1] cycloaddition between isocyanates, alkynes, and activated olefins as opposed to carbon monoxide giving rise to γ-butyrolactones (scheme 1.19d).[112]

[108] For an example of [4+1] reactivity see: Meloche, J. L.; Ashfeld, B. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 6604.
[109] Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **2006**, *128*, 14816.
[110] Mathur, P.; Joshi, R. K.; Rai, D. K.; Jha, B.; Mobin, S. M. *Dalton Trans.* **2012**, *41*, 5045.
[111] Miura, T.; Mikano, Y.; Murakami, M. *Org. Lett.* **2011**, *13*, 3560.
[112] Ozawa, T.; Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2010**, *46*, 8055.



Scheme 1.20: (a) Kondo's maleimide synthesis. (b) Mathur's maleimide/hydantoin synthesis. (c) Murakami's hydantoin synthesis. (d) Matsubara's synthesis of γ-butyrolactones

π-Allyl species have been exploited extensively in cycloadditions with isocyanates for the synthesis of various cyclic carbamates and ureas.[113] An interesting example of employing π-allyl chemistry for the synthesis of cyclic amides was reported by Hayashi and coworkers (eq. 1.20). Methylidene valerolactone precursors were found to undergo palladium catalyzed decarboxylation forming the desired π-allyl ester enolate species which reacts readily with aryl isocyanates providing access to 2-piperidones. The introduction of chiral phosphoramidate ligands resulted in reliably high levels of enantioselectivity. Remarkably, the use of alkyl isocyanates resulted in a [3+2] cycloaddition forming a strained spirocydic compound. This reactivity was further explored in a follow up article where product distribution was observed to be easily controlled through variations in the ligand system.[114] Noteworthy is the use of the isocyanate as the limiting reagent, as well as the lack of trimerization observed, regardless of the rate determining π-allyl formation.

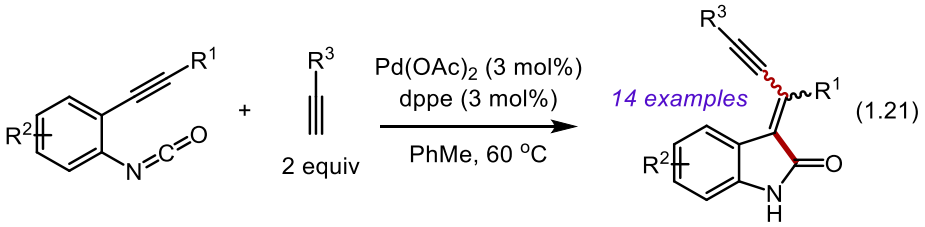


The oxindole scaffold has garnered much interest from the synthetic community given its broad biological importance and has proven an ideal platform for metal catalyzed heterocyclic synthesis with

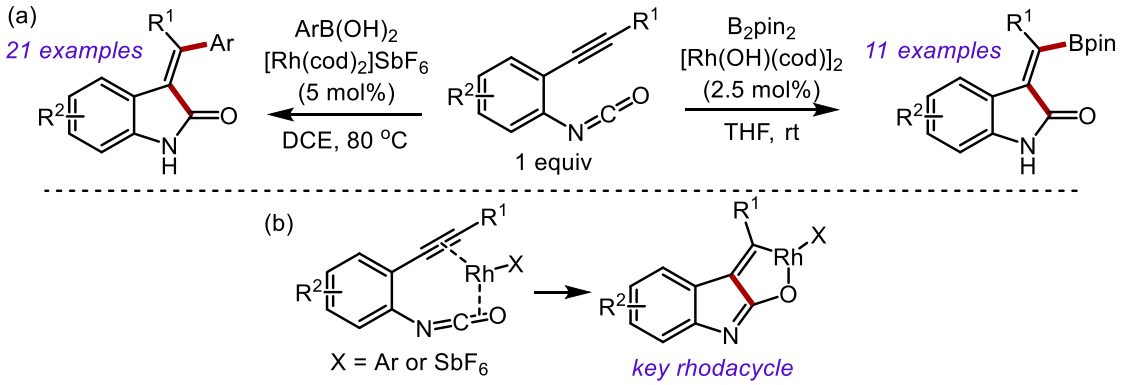
[113] For selected examples see: (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. (b) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (c) Zhou, H.-B.; Alper, H. *J. Org. Chem.* **2003**, *68*, 3439. (d) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836.

[114] Shintani, R.; Tsuji, T.; Park, S.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7508.

isocyanates. The first such example was reported by Yamamoto and coworkers in 2004 (eq. 1.21).[115] The palladium catalyzed addition of alkynes to 2-(alkynyl)phenyl isocyanate derivatives resulted in the formation of the desired oxindole existing almost exclusively as the (*E*)-isomer. Interestingly, milder conditions led to a mixture of *E* and *Z* isomers and control reactions revealed the role of the phosphine ligand in olefin isomerization.



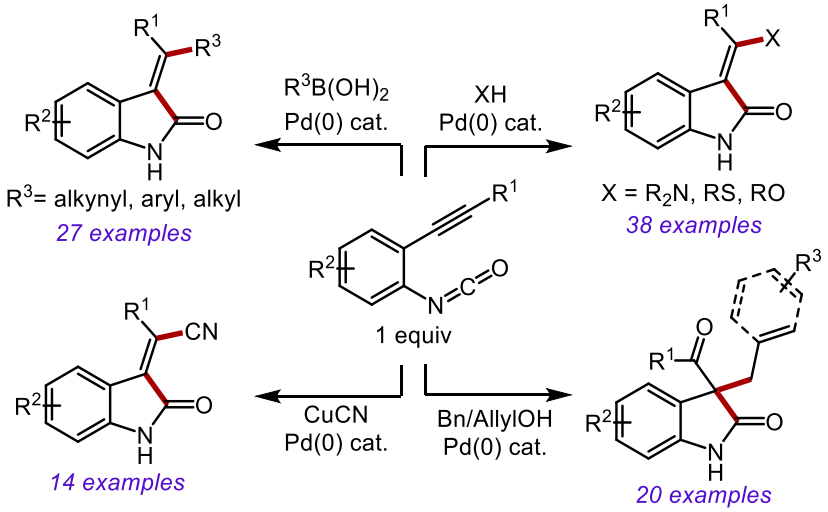
This seminal work was followed by several examples from Murakami and coworkers using 2-(alkynyl)phenyl isocyanates as a platform to access a variety of oxindole derivatives. Their first of such reports came in 2007, where a rhodium catalyst underwent a similar cascade as described above using arylboronic acids as nucleophilic coupling partners (scheme 1.21a).[116] This was followed up by a similar borylation cascade making use of bis(pinacolato)diboron species (scheme 1.21a).[117] Although multiple alternative pathways for product formation are conceivable, the authors favoured a rhodium mediated oxidative cycloaddition for the formation of the oxindole ring (scheme 1.21b).



Scheme 1.21: (a) Murakami's rhodium catalyzed synthesis of substituted oxindoles. (b) Proposed key rhodacycle intermediate.

[115] Kamijo, S.; Sasaki, Y.; Kanazawa, C.; Shubeler, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 7718.
[116] Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, *9*, 5075.
[117] Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 1743.

They then focused their attention towards the development of the palladium catalyzed variant of these cascades.[118] Gratifyingly, the palladium catalyst proved to have a much broader scope with respect to organoboron nucleophiles allowing the use of sp, sp^2, and sp^3 substituted derivatives (scheme 1.22). In contrast to Yamamoto's work, Pd(0) precatalysts were highly active while Pd(II) showed almost no reactivity, leading the authors to propose an oxidative cycloaddition based mechanism as opposed to a stepwise addition suggested in Yamamoto's work. This was followed by several reports varying the nucleophile employed under the reaction conditions.[119] During their synthesis of amido substituted oxindoles, the use of various nitrogen nucleophiles was probed under the reaction conditions. Non-nucleophilic amines (amides, tosylamines, carbamates, etc.) provided the desired products in high yields while aniline derivatives were simply too nucleophilic, providing predominantly the formation of the undesired urea.[119a]



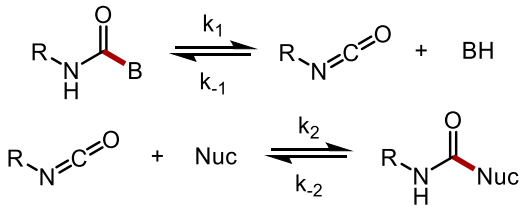
Scheme 1.22: Murakami's work on palladium catalyzed synthesis of substituted oxindoles.

1.4 Blocked Isocyanates

As described in section 1.1, isocyanates experienced an eruption in research interest after the discovery of their polymerization. However, drawbacks were quickly apparent including the sensitivity of isocyanates to hydrolysis, difficulties in controlling reactivity, and high toxicity. This led to the development of blocked isocyanates, described by Wicks in an early review as "an isocyanate which has

[118] Miura, T.; Toyoshima, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10,* 4887.
[119] (a) Miura, T.; Toyoshima, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2009**, *11*, 2141. (b) Miura, T.; Toyoshima, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2009**, *38*, 1174. (c) Miura, T.; Toyoshima, T.; Kozawa, O.; Murakami, M. *Org. Lett.* **2010**, *39*, 1132. (d) Toyoshima, T.; Mikano, Y.; Miura, T.; Murakami, M. *Org. Lett.* **2010**, *12*, 4584.

been reacted with material which will prevent its reaction at room temperature with compounds that conventionally react with isocyanates but will permit that reaction to occur at higher temperatures."[120] This development largely eliminated the toxicity associated with isocyanates and endowed its users with a high degree of control over reactivity increasing the breadth of applications attainable within isocyanate polymerization.[121] Consequently, considerable attention has been paid to studying the kinetics of nucleophilic exchange reactions with a variety of blocked isocyanates.[5,122] A simplified overview of such systems can be seen in scheme 1.23 where elimination of the blocking group releases the isocyanate which subsequently undergoes addition with the desired nucleophile. Control over the reactivity of the isocyanate in such systems is achieved by manipulating factors which effect the equilibrium between the free isocyanate and the blocked isocyanate. These factors include temperature, solvent, catalyst, isocyanate structure, and blocking group structure described below. The presence of addition elimination pathways (ie: tetrahedral intermediates) have also been observed and should be kept in mind when discussing blocked isocyanate reactivity.



Scheme 1.23: General reaction scheme of blocked isocyanate undergoing nucleophilic exchange.

Temperature exerts significant control over the position of the equilibrium between blocked and unblocked isocyanates where increased temperatures shift the equilibrium towards the latter. It is common to attribute specific "deblocking temperatures" to particular blocking groups though it is important to mention how such temperatures are measured. Deblocking temperatures are measured and reported using a variety of different instruments (ie: IR, FTIR, TGA, UV-VIS, etc.) and thus are limited to the detection limits of the instrument employed.[5] Moreover, one must keep in mind that this is in fact an equilibrium and thus there is no exact temperature where the isocyanate exists solely in its blocked form, and beyond such temperature, in its unblocked form. Moreover, "deblocking temperatures" do not necessarily translate into reactivity due to the importance of the rate of the forward reaction (ie: k_2).

[120] Wicks Jr., Z. W. *Prog. Org. Coat.* **1975**, *3*, 73.
[121] Wicks, D. A.; Wicks Jr., Z. W. *Prog. Org. Coat.* **2001**, *41*, 1.
[122] For reviews of blocked isocyanate reactivity see: (a) Wicks, D. A.; Wicks Jr., Z. W. *Prog. Org. Coat.* **1999**, *36*, 148. (b) Wicks, D. A.; Wicks Jr., Z. W. W. *Prog. Org. Coat.* **2001**, *43*, 131. (c) Rolph, M. S.; Markowska, A. L. J.; Warriner, C. N.; O'Reilly, R. K. *Polym. Chem.* **2016**, *7*, 7351. (d) ref 5.

Consequently, a primary amine may exhibit high reactivity at a specific temperature while similar reactivity would require a significant increase in temperature when employing primary alcohol nucleophiles. With this in mind, figure 1.4 provides the reader with a list of blocking groups with a range of reported deblocking temperatures.[122b] Such data could nevertheless be useful in providing prospective users of blocked isocyanates a general idea of temperature ranges one could expect reactivity with particular blocked derivatives.

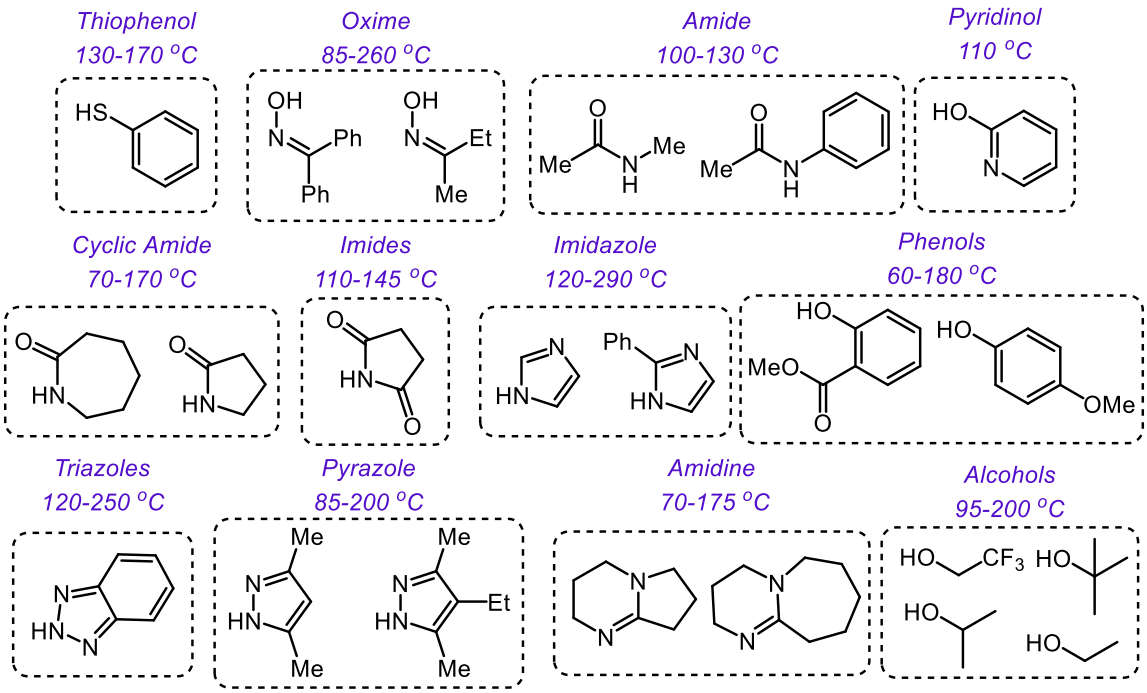


Figure 1.4: Various blocking group categories with a range of deblocking temperatures reported within such categories, along with representative examples of blocking groups.

The solvent employed in a reaction has a significant impact on the position of the deblocking equilibrium. Generally, non-polar solvents shift the equilibrium towards the blocked isocyanate while polar aprotic solvents favour the opposite (figure 1.5).[122] This is attributed to the ability of polar aprotic solvents to hydrogen bond with the blocking group, reducing k_{-1} resulting in a shift in the equilibrium.[123] Noteworthy is under systems where the kinetics are dominated by the subsequent addition of the

[123] (a) Gnanarajan, T. P.; Nasar, A. S.; Iyer, N. P.; Radhakrishnan, G. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 4032. (b) Nasar, A. S.; Raghavan, A.; Kumar, V. S. *J. Macromol. Sci., Part A: Pure Appl. Chem.* **2005**, *42*, 309.

nucleophile onto the free isocyanate, non-polar solvents may be favoured by promoting the formation of nucleophile/isocyanate complexes.[124]

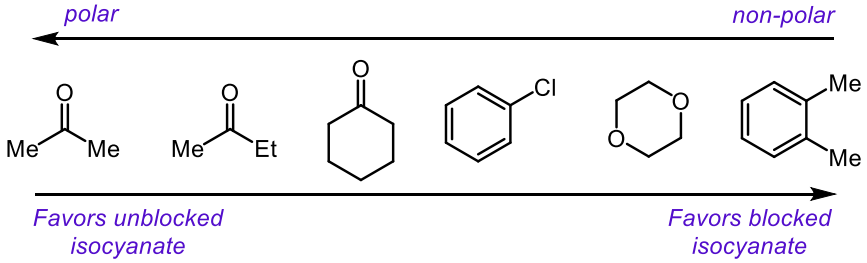
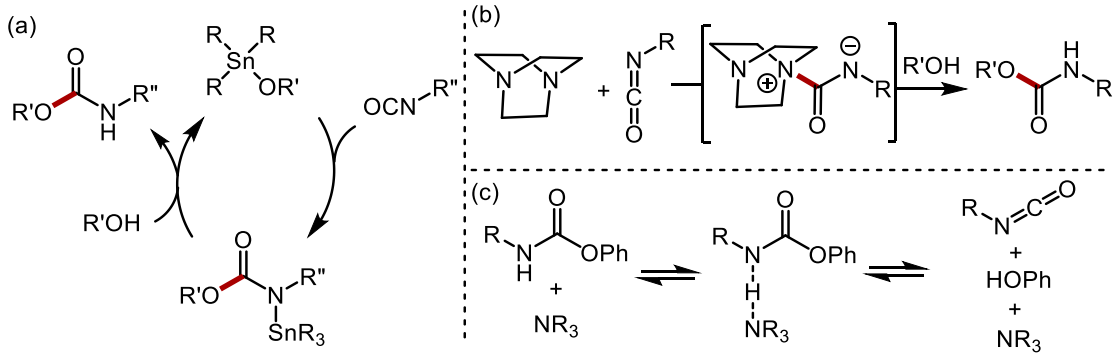


Figure 1.5: Solvent effects on blocked isocyanate equilibrium.

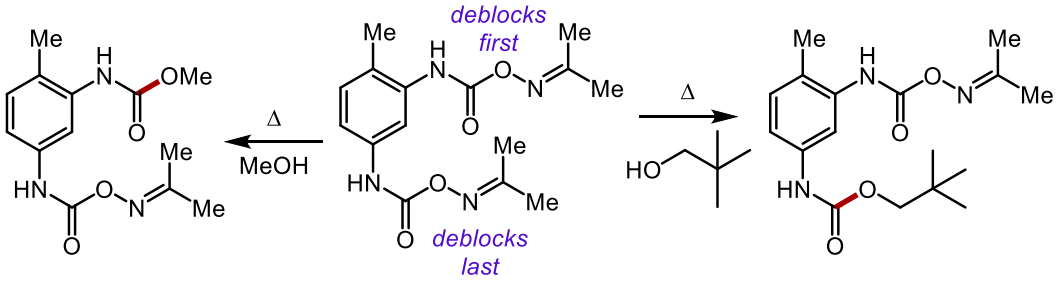
Catalyst have significant impacts on the observed reactivity of blocked isocyanates. The effects of catalyst on the addition of nucleophiles to isocyanates is well understood, while reports on their effect on deblocking remain limited. Moreover, the effect of catalyst is further complicated by the potential to affect both deblocking and addition, promote addition elimination pathways, and promote side reactions. Organotin catalysts are the most common class of catalyst employed. These species catalyze the addition of alcohols to isocyanates and have been shown to have no effect on the deblocking (scheme 1.24a).[125] Nucleophilic amines are also broadly used to catalyze the addition of alcohols onto isocyanates, DABCO being most common (scheme 1.24b). Moreover, basic amines have been observed to catalyze deblocking although this effect is strongly blocking group dependent. Specifically, systems where transfer of a proton to nitrogen is necessary (ie: oxime, amine, pyrazole) are either unaffected or inhibited by basic additives[126] while base mediated isocyanate release of phenol blocked derivatives is well documented (scheme 1.24c).[127]

[124] Baker, J. W.; Gaunt, J. *J. Chem. Soc.* **1949**, 27.
[125] Carlson, G. M.; Neag, C. M.; Kuo, C.; Provder, T. *Polym. Sci. Technol.* **1987**, *36*, 197.
[126] (a) Levine, A. W.; Fech, J., Jr. *J. Org. Chem.* **1972**, *37*, 1500. (b) Levine, A. W.; Fech, J. *J. Org. Chem.* **1972**, *37*, 2455. (c) Vandenabeele-Trambouze, O.; Mion, L.; Garrelly, L.; Commeyras, A. *Adv. Environ. Res.* **2001**, *6*, 45. (d) Cai, K.; Ying, H.; Cheng, J. *Chem. Eur. J.* **2018**, *24*, 1.
[127] (a) Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 808. (b) Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1244. (c) Kothandaraman, H.; Nasar, A. S.; Suresh, K. R. *J.M.S.-Pure Appl. Chem.* **1996**, *A33*, 833. (d) Ilieva, S.; Nalbantova, D.; Hadjieva, B.; Galabov, B. *J. Org. Chem.* **2013**, *78*, 6440.



Scheme 1.24: (a) Proposed catalytic cycle for organotin catalyst. (b) Proposed mechanism of action for nucleophilic amine catalyst. (c) Proposed mechanism of action for base mediated phenyl carbamate deblocking.

The structure of the isocyanate motif itself plays a role in the reactivity observed. It is widely accepted that alkyl isocyanates deblock at lower temperatures than their aryl counterparts.[122] This has been attributed to the increased thermodynamic stability of aromatic isocyanates resulting from the conjugation of the π-system. Correspondingly, aryl isocyanates containing electron donating substituents shift the equilibrium towards the blocked form relative to their electron poor counterparts. Steric effects also play a role where more sterically demanding isocyanates shift the equilibrium towards the unblocked isocyanate. Importantly, lower deblocking temperatures do not always translate into increased reaction rates where large dependence on the nucleophile employed under the reaction conditions can be observed. This is most convincingly demonstrated by a report from Pappas and coworkers where increasing the steric demand of the nucleophile from methanol to neopentyl alcohol results in a reversal in selective substitution reactivity (scheme 1.25).[128]



Scheme 1.25: Interplay between deblocking rates and steric hindrance.

[128] Pappas, S. P.; Urruti, E. H.; Proceedings of the Water-borne Higher-Solids Coating Symposium, New Orleans, 1986, p. 146

The strength of the blocking group strategy largely resides in the wide variety of blocking groups reported, coupled with the ability to fine tune the equilibrium between blocked and free isocyanate through blocking group manipulation. Phenol is a commonly employed blocking group as a result of its relatively low deblocking temperature. The electronics of the phenolic motif are easily manipulated and play a crucial role on isocyanate deblocking (figure 1.6). Electron donating substituents favour the blocked form, while the reverse is true of electron withdrawing substituents. This trend is proposed to arise due to variations in the C-O bond strength of the resulting blocked isocyanate. Moreover, electronic effects overshadow steric effects with blocking groups such as *o*-cresol and 2,6-dimethylphenol exhibiting higher deblocking temperatures than their phenol counterpart.[129]

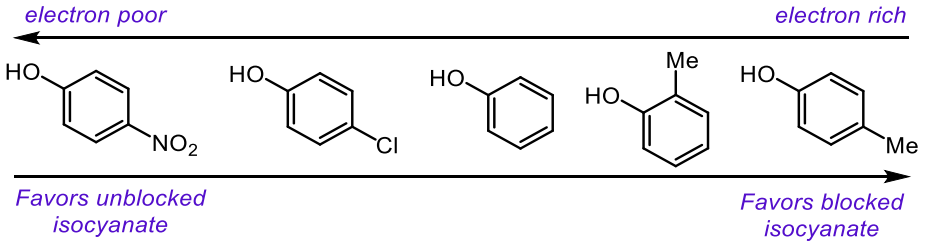
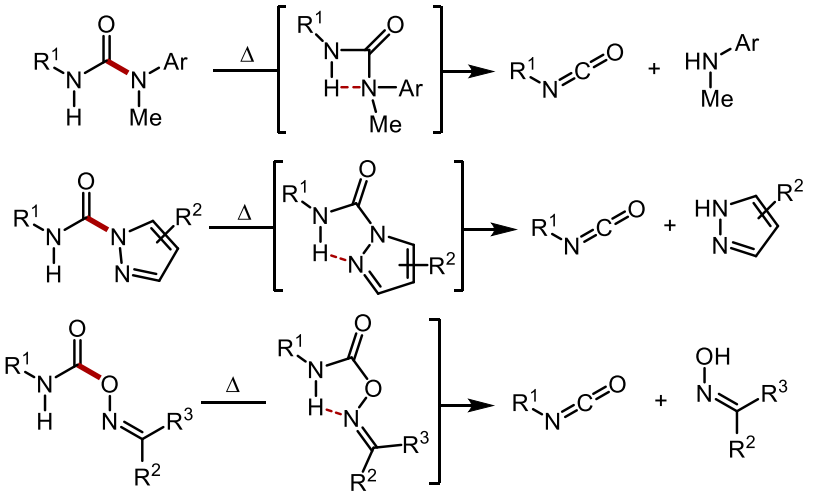


Figure 1.6: Effect of temperature of the equilibrium using phenol blocked isocyanate

Importantly, the electronic trends observed in phenol blocked isocyanates do not always hold true as observed in the case of aniline blocked isocyanates where electron rich derivatives were observed to deblock at lower temperatures.[130] These electronic effects were also observed with oxime and pyrazole blocked isocyanates. These phenomena can be explained by invoking an intramolecular hydrogen bond between the N-H and the lone pair of the nitrogen on the leaving group (scheme 1.26). Consequently, electron donating substituents increase the strength of this interaction resulting in decreased deblocking temperatures.

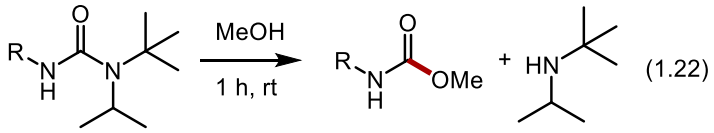
[129] (a) Kothandaraman, H.; Nasar, A. S. *Polymer* **1993**, *34*, 610. (b) Muhlebach, A. *J. Polym. Sci. A* **1994**, *32*, 753. (c) Nasar, A. S.; Kalaimani, S. *RSC Adv.* **2016**, *6*, 76802. (d) Kalaimani, S.; Ali, B. M.; Nasar, A. S. *RSC Adv.* **2016**, *6*, 106990.

[130] Sankar, G.; Nasar, A. S. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1557.



Scheme 1.26: Various deblocking transition states depicting the importance of the intramolecular hydrogen bond strength.

Though steric effects are minimal for phenol blocked isocyanates, they play a significant role controlling the position of the equilibrium in most other systems. In general, the more sterically demanding a blocking group, the smaller k_{-1} becomes and thus shifting the equilibrium towards the free isocyanate. Moreover, k_1 would be expected to benefit through favorable steric decompression. This trend is observed in the case of alcohols where lower deblocking temperatures result moving from primary to tertiary alcohols. Aliphatic amines have typically been avoided as blocked derivatives. This likely results from their large k_{-1} making it difficult to achieve substitution with competing nucleophiles without using large excess. Recently, the use of highly sterically hindered amines as blocking groups have been reported to undergo facile solvolysis (eq. 1.22).[131] This was subsequently applied to the development of polyureas which are amenable to degradation under exceptionally mild conditions.[132]



(1.22)

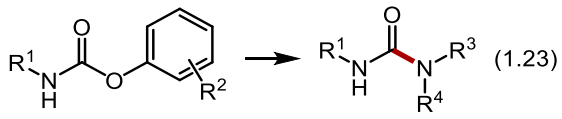
[131] (a) Houlden, C. E.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2010**, *12*, 3090. (b) Cai, K.; Ying, H.; Cheng, J. *Chem. Eur. J.* **2018**, *24*, 7345.

[132] Ying, H.; Cheng, J. *J. Am. Chem. Soc.* **2014**, *136*, 16974.

1.5 Non-polyurethane Based Applications of Blocked Isocyanates

1.5.1 Reactions with heteroatom nucleophiles

The widespread application of a blocking group strategy within the polymerization of isocyanates should come as no surprise given the effect on toxicity, the diverse range of blocking groups to choose from, and the ability to fine tune deblocking parameters through blocking group manipulation and reaction parameters. As such, this strategy has not remained relegated to polymerizations, where medicinal chemists have seemingly embraced blocked isocyanates wholeheartedly for the synthesis of ureas. Although isocyanates provide a dominant platform for the synthesis of ureas, the need to access highly functionalized derivatives typically targeted by medicinal chemist has seemingly led the field to adopt blocked isocyanate chemistry. A simple Reaxys search, as seen in equation 1.23, revealed over 700 publications using phenol blocked isocyanates to synthesize ureas with over 50% of these publications originating from 5 medicinal chemistry journals. Furthermore, over 1,200 patents were found using the same search, largely used for the synthesis of medicinal chemistry libraries.



(1.23)

To illustrate the value of blocked isocyanates to the pursuit of complex bioactive ureas, several representative examples can be seen in figure 1.7.[133] Notably, these blocked isocyanates are readily accessed through the reaction of the parent amine, with phenyl chloroformate providing access to stable, isolable precursors. In fact, accessing the parent isocyanate in these cases could prove problematic given the high reactivity of phosgene. The reduced reactivity of phenyl chloroformate allows for controlled and selective formation of the blocked isocyanate derivative.

[133] (a) Bajji, A. C.; Sundaram, M.; Myszka, D. G.; Davis, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14302. (b) Wang, W.; Xu, S.; Duan, Y.; Liu, X.; Li, X.; Wang, C.; Zhao, B.; Zheng, P.; Zhu, W. *Eur. J. Med. Chem.* **2018**, *145*, 315. (c) Qi, B.; Yang, Y.; Gong, G.; He, H.; Yue, X.; Xu, X.; Hu, Y.; Li, J.; Chen, T.; Wan, X.; Zhang, A.; Zhou, G. *Eur. J. Med. Chem.* **2019**, *163*, 10. (d) Wang, C.; Xu, S.; Peng, L.; Zhang, B.; Zhang, H.; Hu, Y.; Zheng, P.; Zhu, W. *J. Enzyme Inhib. Med. Chem.* **2019**, *34*, 203.

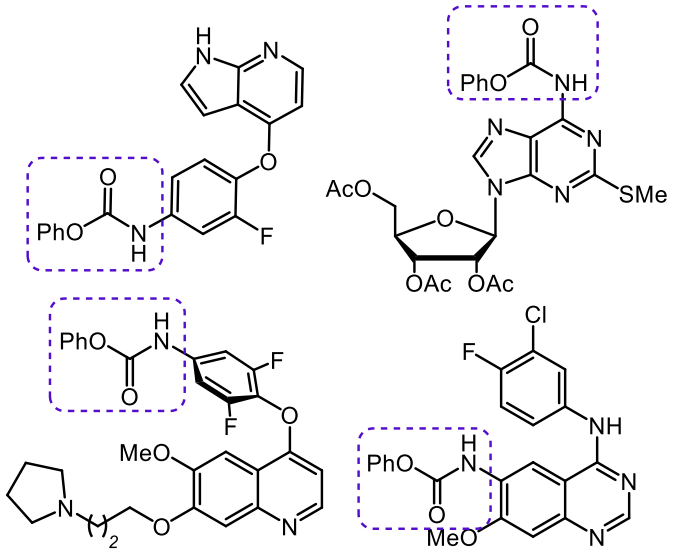


Figure 1.7: Representative examples of complex blocked isocyanates used in the synthesis of ureas.

Advancements in the use of blocked isocyanates undergoing addition reactions with heteroatom nucleophiles has remained largely stagnant[134] though a few notable exceptions will be covered in the following sections. Increases in reaction complexity have recently been pursued through the development of cascade type reactions for the rapid synthesis of various heterocyclic derivatives (see section 1.5.3 and 1.5.4).[135] Notable examples were the development of Lewis acid catalyzed synthesis of oxazolidinones developed by Jacobsen[136] and expanded upon by Kleij (eq. 1.24).[137] In this case, the normal reactivity of isocyanates with epoxides was reversed where the epoxide undergoes ring opening nucleophilic attack using the blocked isocyanate as a nucleophile, followed by intramolecular cyclization. Although the

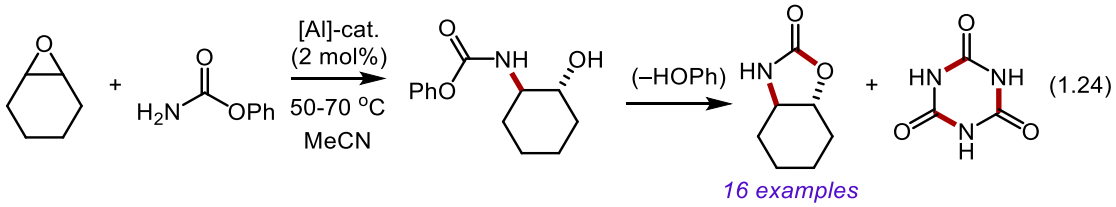
[134] Selected examples of blocked isocyanates in synthesis: (a) Guichard, G.; Semetey, V.; Didierjean, C.; Aubry, A.; Briand, J.-P.; Rodriguez, M. *J. Org. Chem.* **1999**, *64*, 7702. (b) Thavonekham, B. *Synthesis* **1997**, 1189. (c) Kitteringham, J.; Shipton, M. R.; Voyle, M. *Synth. Commun.* **2000**, *30*, 1937. (d) Bridgeman, E.; Tomkinson, N. C. O. *Synlett* **2006**, 243. (e) Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 5717. (f) Wei, Y.; Liu, J.; Lin, S.; Ding, H.; Liang, F.; Zhao, B. *Org. Lett.* **2010**, *12*, 4220. (g) Moon, S.-Y.; Kim, U. B.; Sung, D.-B.; Kim, W.-S. *J. Org. Chem.* **2015**, *80*, 1856. (h) Senadi, G. C.; Mutra, M. R.; Lu, M. R.; Lu, T.-Y.; Wang, J.-J. *Green Chem.* **2017**, *19*, 4272. (i) Tanwar, D. K.; Ratan, A.; Gill, M. S. *Org. Biomol. Chem.* **2017**, *15*, 4992. (j) Wang, M.; Han, J.; Si, X.; Hu, Y.; Zhu, J.; Sun, X. *Tetrahedron Lett.* **2018**, *59*, 1614.

[135] For selected examples see: (a) Zavialov, I. A.; Dahanukar, V. H.; Nguyen, H.; Orr, C.; Andrews, D. R. *Org. Lett.* **2004**, *6*, 2237. (b) Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E. *RSC Adv.* **2016**, *6*, 36978. (c) Tanwar, D. K.; Ratan, A.; Gill, M. S. *Synlett* **2017**, *28*, 2285.

[136] Birrell, J. A.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 2895.

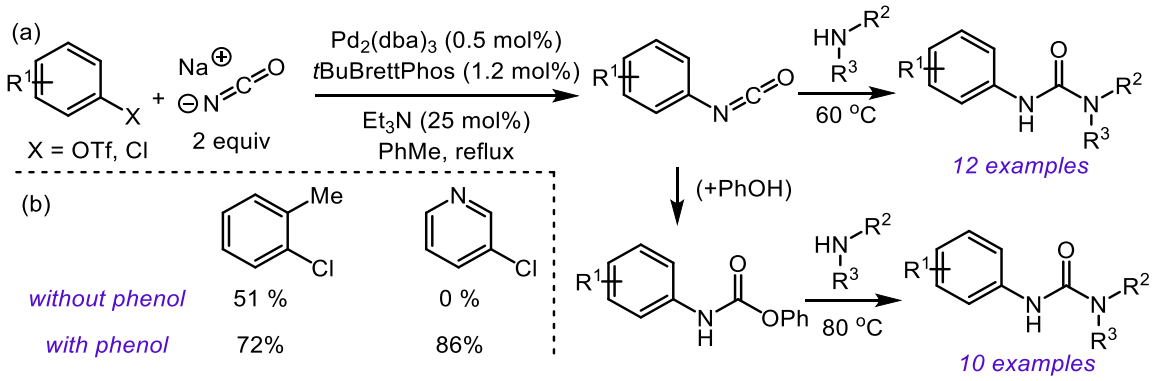
[137] Laserna, V.; Guo, W.; Kleij, A. W. *Adv. Synth. Catal.* **2015**, *357*, 2849.

formation of an isocyanate intermediate was not proposed, the formation of isocyanurate trimers under the reaction conditions is highly suggestive.[138]



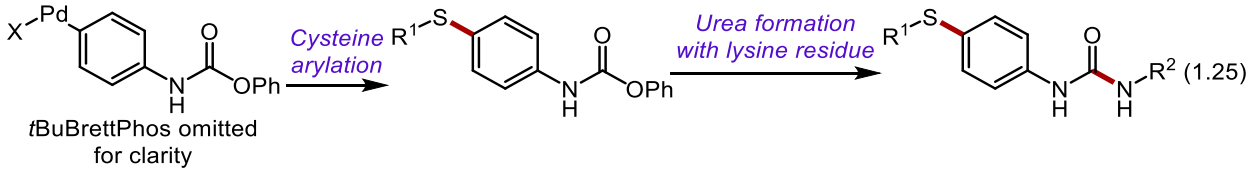
Buchwald and coworkers developed an innovative approach to urea synthesis by forming isocyanates using a palladium catalyzed cross-coupling of sodium cyanate with aryl chlorides/triflates (scheme 1.27a).[139] The use of a highly sterically hindered *t*-BuBrettPhos ligand proved necessary and is believed to diminish the ability of the Pd(0) species to undergo unwanted isocyanurate formation as well as minimize the potential formation of inactive palladacycles.[69] The synthesis of a variety of isocyanates occurred readily forming the desired urea products upon the addition of an amine nucleophile following the completion of the cross coupling. Notably, chemoselective formation of the isocyanate C-N bond was observed when the amine nucleophile was introduced at the beginning of the reaction, however diminished yields were observed. This was suspected to arise as a consequence of catalyst deactivation through the coordination of the Lewis basic amine. Notably, 2 classes of substrates proved problematic for this methodology; sterically hindered aryl electrophiles, and substrates bearing unhindered Lewis basic motifs. The addition of phenol to the reaction mixture mitigated unwanted degradation/catalyst deactivation by blocking the isocyanate *in situ* (scheme 1.27b). This is most convincingly highlighted through the successful implementation of 3-chloropyridine, which had previously yielded no desired product. Expanding this work to incorporate the synthesis of carbamates was then explored although the blocking group strategy was not employed due to the difficulties of adding poorly nucleophilic alcohols to phenol blocked isocyanates.[140]

[138] For an example of free isocyanate trimerization using a similar catalyst see: Wu, W.; Mason, J.; North, M. *Chem. Eur. J.* **2017**, *23*, 12937.
[139] Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 11132.
[140] Vinogradova, E. V.; Park, N. H.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 1394.



Scheme 1.27: (a) Buchwald's palladium catalyzed synthesis of unsymmetrical ureas. (b) Effect of phenol additive on difficult substrates.

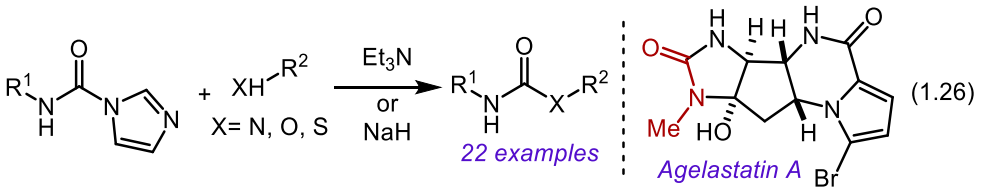
A further innovative use of blocked isocyanates was reported by Buchwald and Pentelute with their use of bifunctional palladium oxidative addition complexes as peptide/protein cross-linkers (eq. 1.25).[141] *p*-Bromo-*O*-phenyl carbamate readily forms organopalladium complexes upon the oxidative addition of Pd(0) precursors. This material was stable for several months and readily undergoes arylation selectively at cysteine residues. Cross-linking is achieved upon the addition of lysine containing peptides/proteins where the primary amine reacts with the phenol blocked isocyanate motif. This methodology was amenable to both intra- and intermolecular cross-linking reactions.



The use of imidazole blocked isocyanates have also found use in substitution reactions with various protic nucleophiles. Analogous to phenol blocked isocyanates, imidazole blocked derivates are readily accessed through the reaction of an amine with CDI. In contrast to phenol blocked derivates, imidazole blocked isocyanates have increased lability under acidic conditions.[142] Recently, Batey and coworkers reported a simple prep for the synthesis of imidazole blocked methyl isocyanate from CDI and methyl amine.[143] This precursor readily reacted with a variety of amines providing access to urea products

[141] Kubota, K.; Dai, P.; Pentelute, B. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2018**, *140*, 3128.
[142] (a) Raspoet, G.; Nguyen, M. T. *J. Org. Chem.* **1998**, *63*, 6867. (b) Rawling, T.; McDonagh, A. M.; Tattam, B.; Murray, M. *Tetrahedron* **2012**, *68*, 6065.
[143] Duspara, P. A.; Islam, M. S.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2012**, *77*, 10362.

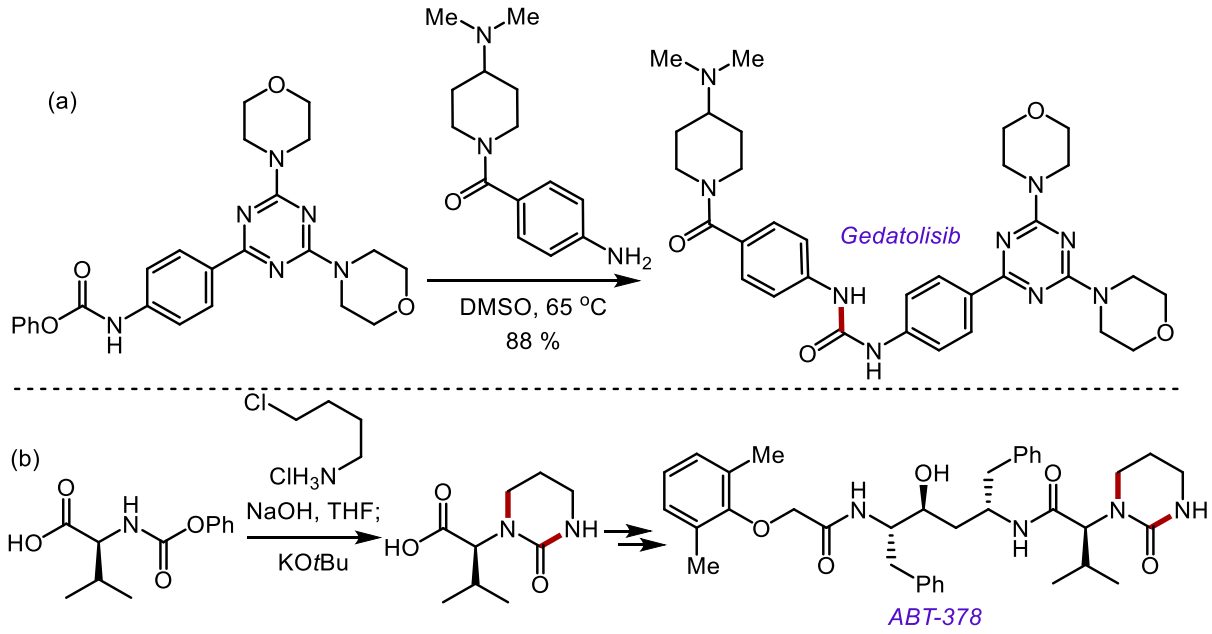
(eq. 1.26). Moreover, reactivity with various alcohols and thiols was observed though, similar to phenol blocked isocyanates, NaH was necessary in the case of weak nucleophiles such as alcohols and deactivated amines. Batey and coworkers made use of this development shortly thereafter during their total synthesis of agelastatin A.[144-145]



(1.26)

The application of blocked isocyanates in the scaled synthesis of various biologically active targets has also been described by several pharmaceutical companies including Merck, BMS, Abbott, Pfizer, Novartis, and Boehringer Ingelheim.[146] Worthy of note, is in most cases the authors were drawn to the use of a blocking group strategy to avoid the use of phosgene, for its ease of operation, reduced cost, and mild reaction conditions. Importantly, in some cases the desired isocyanate failed to form using typical phosgenation chemistry (scheme 1.28a), [146i] while in other cases, its instability resulted in cumbersome scale-up operations (scheme 1.28b).[146a]

[144] Duspara, P. A.; Batey, R. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 10862.
[145] For an example of phenol blocked methyl isocyanate see: Gauthier Jr., D. R.; Sherry, B. D.; Cao, Y.; Journet, M.; Humphrey, G.; Itoh, T.; Mangion, I.; Tschaen, D. M. *Org. Lett.* **2015**, *17*, 1353.
[146] For selected examples see: (a) Stoner, E. J.; Cooper, A. J.; Dickman, D. A.; Kolaczkowski, L.; Lallaman, J. E.; Liu, J.-H.; Oliver-Shaffer, P. A.; Patel, K. M.; Paterson Jr., J. B.; Plata, D. J.; Riley, D. A.; Sham, H. L.; Stengel, P. J.; Tien, J.-H. J. *Org. Proccess Res. Dev.* **2000**, *4*, 264. (b) Yue, T.-T.; McLeaod, D. D.; Albertson, K. B.; Beck, S. R.; Deerberg, J.; Fortunak, J. M.; Nugent, W. A.; Radesca, L. A.; Tang, L.; Xiang, C. D. *Org. Process Res. Dev.* **2006**, *10*, 262. (c) Itoh, T.; Kato, S.; Nonoyama, N.; Wada, T.; Maeda, K.; Mase, T.; Zhao, M. M.; Song, J. Z.; Tschaen, D. M.; McNamara, J. M. *Org. Process Res. Dev.* **2006**, *10*, 822. (d) Shieh, W.-C.; McKenna, J.; Sclafani, J. A.; Xue, S.; Girgis, M.; Vivelo, J.; Radetich, B.; Prasad, K. *Org. Process Res. Dev.* **2008**, *12*, 1146. (e) Wang, X.-J.; Xu, Y.; Zhang, L.; Krishnamurthy, D.; Wirth, T.; Nicola, T.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 4412. (f) Ashcroft, C. P.; Dessi, Y.; Entwistle, D. A.; Hesmondahalgh, L. C.; Longstaff, A.; Smith, J. D. *Org. Process Res. Dev.* **2012**, *16*, 470. (g) Bhalerao, D. S.; Arkala, A. K. R.; Madhavi, Y. V.; Nagaraju, M.; Gade, S. R.; Kumar, U. K. S.; Bandichor, R.; Dahanukar, V. H. *Org. Process Res. Dev.* **2015**, *19*, 1559. (h) Humphrey, G. R.; Dalby, S. M.; Andreani, T.; Xiang, B.; Luzung, M. R.; Song, Z. J.; Shevlin, M.; Christensen, M.; Belyk, K. M.; Tschaen, D. M. *Org. Process Res. Dev.* **2016**, *20*, 1097. (i) Liu, X.; Zhu, G.; Li, L.; Liu, Y.; Wang, F.; Song, X.; Mao, Y. *Org. Process Res. Dev.* **2018**, *22*, 62.



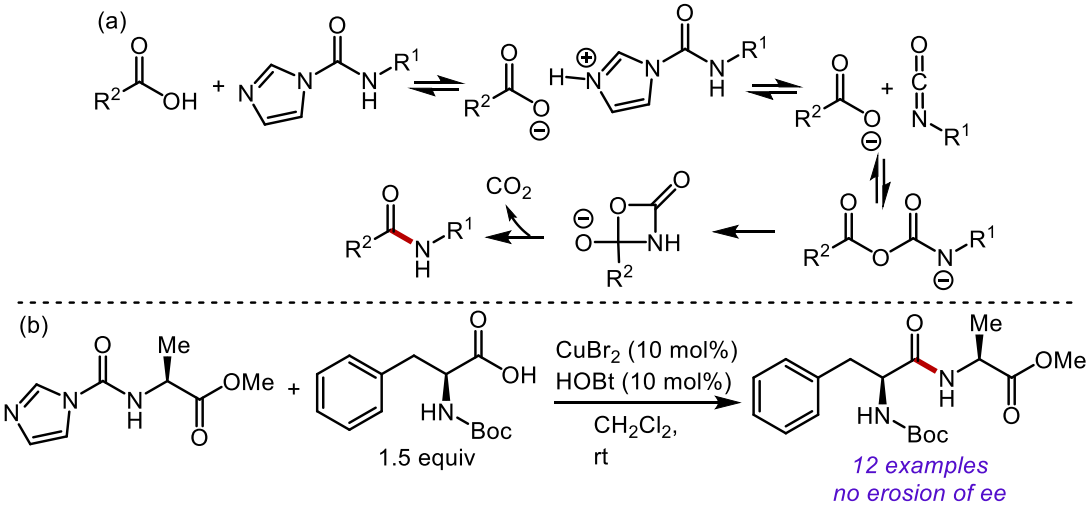
Scheme 1.28: (a) Mao and coworkers synthesis of Gedatolisib. (b) Stoner and coworkers synthesis of ABT-378

1.5.2 Stoichiometric amidation of blocked isocyanates.

The use of blocked isocyanates as precursors to amide bonds has seen much less attention compared to the synthesis of carbamate and urea derivatives. An early example was reported by Gante using imidazole and 3,5-dimethylpyrazole blocked isocyanates in peptide coupling with protected amino acids.[147] They noted a clear difference in reactivity between both blocking groups where imidazole readily provided the desired product while pyrazole blocked derivatives were limited to nucleophilic substitution with hydrazides. A potential mechanism for this transformation is shown in scheme 1.29a. Alternatively, the presence of an addition elimination pathway could also be operative in such a system. In contrast, Gürtler and Gertzmann achieved amide bond formation with pyrazole blocked isocyanates though the addition of bidentate Lewis acid catalyst were necessary for high yields.[148] Ehler and Orgel reported the formation of oligopeptides upon allowing an imidazole blocked isocyanate to sit in a buffered solution at room temperature.[149] Though the hydrolysis of the starting material was a significant by-product, this highlighted the potential for such a technique to be harnessed for exceptionally mild amide bond

[147] Gante, J. *Chem. Ber.* **1966**, *99*, 2521.
[148] Gertzmann, R.; Gürtler, C. *Tetrahedron Lett.* **2005**, *46*, 6659.
[149] Ehler, K. W.; Orgel, L. E. *Biochim. Biophys. Acta* **1976**, *434*, 233.

synthesis. This was exploited by Campagne and coworkers, though no reference to this preceding work was cited in their manuscript (scheme 1.29b). Catalytic $CuBr_2$ and HOBt allowed for room temperature reactivity in organic solvent, mitigating the detrimental hydrolysis observed in Ehler and Orgel's work.[150] The use of basic reaction conditions (ie: Et_3N) resulted in no desired reaction, highlighting the importance of acid activation with these imidazole blocked derivatives. Notably, racemization studies showed no detected epimerization of stereochemical information under the reaction conditions. This was in stark contrast to other standard peptide coupling strategies tested where between 2-35% epimerization was observed.

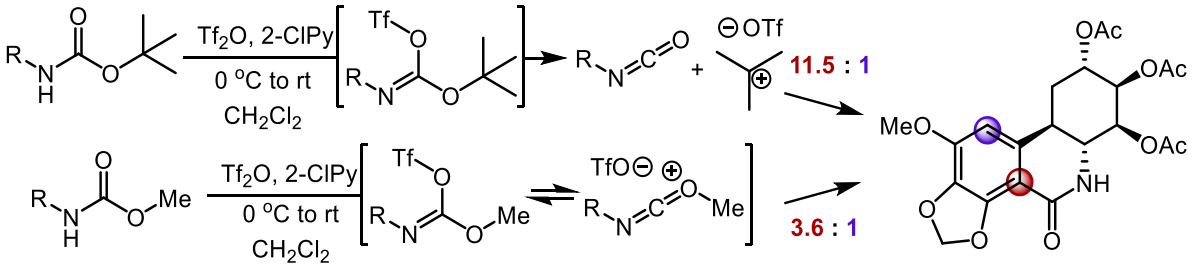


Scheme 1.29: (a) Proposed mechanism for imidazole blocked isocyanate amidation. (b) Campagne and coworkers peptide synthesis using imidazole blocked isocyanates.

Intramolecular Friedel-Crafts type amidation reactions have also been explored from carbamate precursors. Kim and coworkers discovered an increased regioselectivity when using Boc protected amines relative to methyl carbamate derivatives as electrophilic precursors during their synthesis of dihydronarciclasine (scheme 1.30).[151] They hypothesized that this difference in regioselectivity must arise due to the formation of different precursors to cyclization. Upon further study, they were indeed able to identify the formation of an isocyanate *in situ* from Boc-protected amines upon triflic anhydride activation. This work was further elaborated in a subsequent publication probing the scope of applicability

[150] (a) Suppo, J.-S.; Subra, G.; Bergès, M.; de Figueiredo, R. M.; Campagne, J.-M. *Angew. Chem. Int. Ed.* **2014**, *53*, 5389. (b) de Figueiredo, R. M.; Suppo, J.-S.; Midrier, C.; Campagne, J.-M. *Adv. Synth. Cat.* **2017**, *359*, 1963.
[151] Hwang, S.; Kim, D.; Kim, S. *Chem. Eur. J.* **2012**, *18*, 9977.

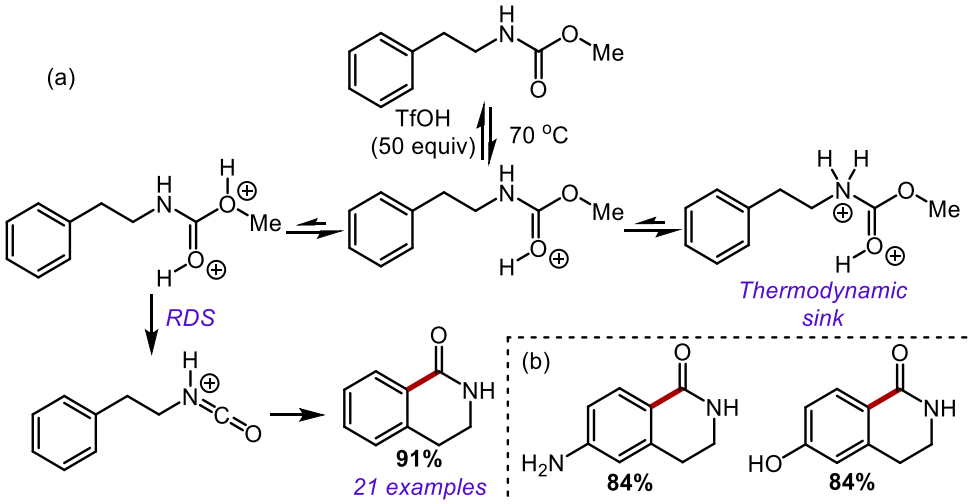
of this finding. [152] Worthy of note is the stark conceptual difference between this approach to blocked isocyanate precursors and those previously discussed. Specifically, triflic anhydride activation results in the degradation of the blocking group thus removing the presence of a controlled equilibrium. Finally, a modification of their earlier work was recently reported using Hendrickson POP reagent.[153] Notably, this strategy was recently adopted by Sarlah and coworkers during early studies of pancratistatin.[154]



Scheme 1.30: Proposed pathways for *t*Bu vs methyl carbamate during Tf_2O promoted intramolecular Friedel-Crafts.

An alternative approach to this type of intramolecular Friedel-Crafts acylation was explored by Ohwada and coworkers (scheme 1.31a).[155] They set out to study the ability to form diprotonated carbamates in super acidic medium. Kinetic studies were consistent with the formation of a protonated isocyanate intermediate, where the rate determining step was the scission of the carbamate C-O bond. Computational studies revealed an initial protonation of the carbonyl oxygen, followed by a second protonation on the carbamate nitrogen. Unfortunately, this protonation inhibits the formation of the isocyanate, resulting in an unfavourable equilibrium with oxygen protonation where the rate determining isocyanate formation can then occur. Notably, the presence of protic nucleophiles, typically beyond the reach of standard isocyanate chemistry, were readily tolerated under the reaction conditions, highlighting the potential of the blocking group strategy (scheme 1.31b).

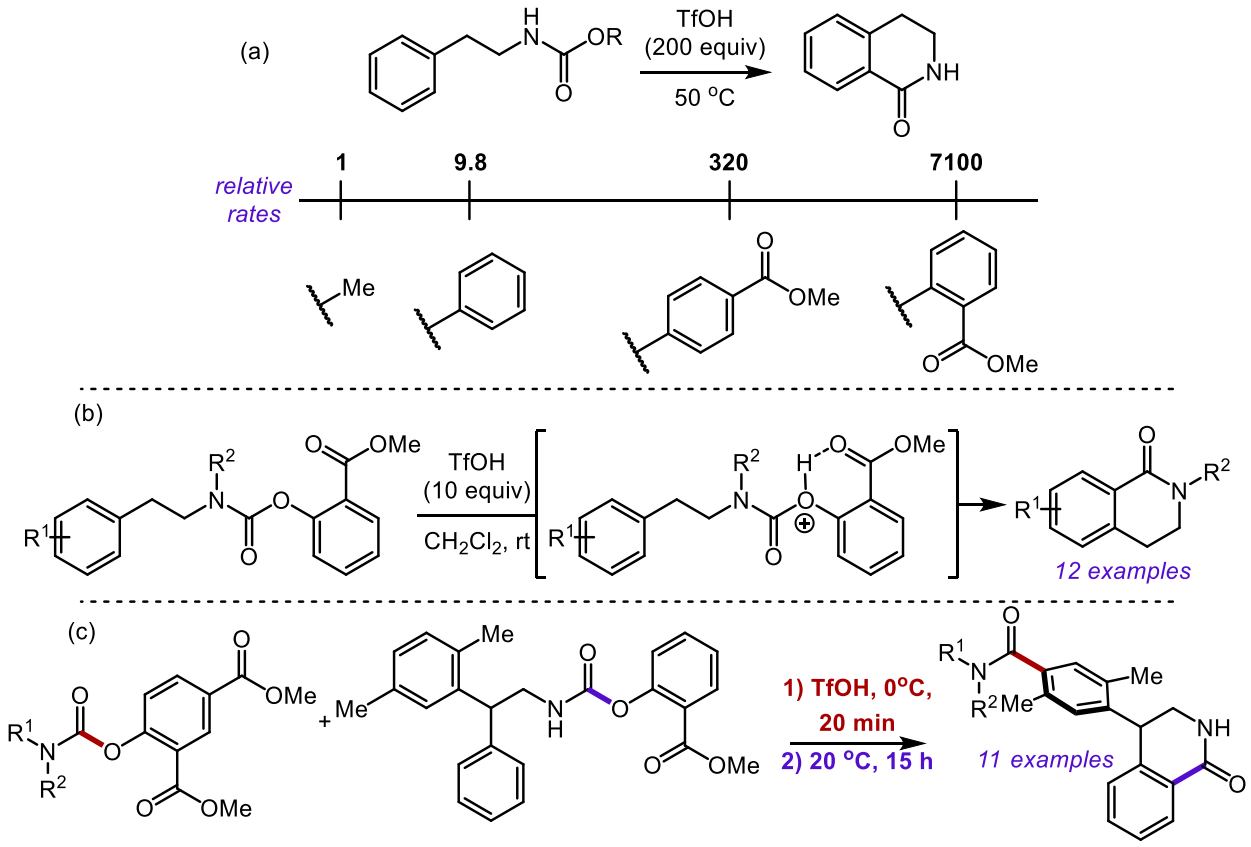
[152] In, J.; Hwang, S.; Kim, C.; Seo, J. H.; Kim, S. *Eur. J. Org. Chem.* **2013**, 965.
[153] Cho, H.; Lee, J. O.; Hwang, S.; Seo, J. H.; Kim, S. *Asian, J. Org. Chem.* **2016**, *5*, 287.
[154] (a) Bingham, T. W.; Hernandez, L. W.; Olson, D. G.; Svec, R. L.; Hergenrother, P. J.; Sarlah, D. *J. Am. Chem. Soc.* **2019**, *141*, 657. For similar applications in pancratistatin synthesis see: (b) Jung, Y.-G.; Kang, H.-U.; Cho, H.-K.; Cho, C.-G. *Org. Lett.* **2011**, *13*, 21.
[155] Kurouchi, H.; Kawamoto, K.; Sugimoto, H.; Nakamura, S.; Otani, Y.; Ohwada, T. *J. Org. Chem.* **2012**, *77*, 9313.



Scheme 1.31: (a) Ohwada and coworkers study the formation of tetrahydroisoquinolone formation in super acidic media. (b) Tolerance of protic nucleophiles under the reaction conditions.

To overcome the harsh reaction conditions necessary for product formation, Ohwada and coworkers studied a variety of alternative blocking groups to allow milder reaction conditions. Moving from OMe to OPh resulted in a slight increase in reaction rate while *o*-methyl salicylate increased reaction rates dramatically (scheme 1.32a).[156] This rate increase was attributed to the now favourable protonation of the phenolic leaving group due to the presence of an intramolecular hydrogen bond supported by both experimental and computational studies (scheme 1.32b). Notably, this allowed the reduction of temperature, TfOH loading, and reaction time. Moreover, α-amino acids bearing stereochemical information were amenable to the transformation with no observed epimerization. Ohwada and coworkers were then able to develop the intermolecular variation of this transformation[157] followed by the development of a cascade reaction (scheme 1.32c).[158] This latter reactivity is a perfect example of the control a blocking group strategy endows on its user, where o,*p*-methyl salicylate allows the initial intermolecular Friedel-Crafts to occur rapidly at 0 °C, followed by a pendant intramolecular cyclization then occurs upon reaching room temperature.

[156] Kurouchi, H.; Sumita, A.; Otani, Y.; Ohwada, T. *Chem. Eur. J.* **2014**, *20*, 8682.
[157] Sumita, A.; Kurouchi, H.; Otani, Y.; Ohwada, T. *Chem. Asian J.* **2014**, *9*, 2995.
[158] Sumita, A.; Otani, Y.; Ohwada, T. *Org. Biomol. Chem.* **2016**, *14*, 1680.

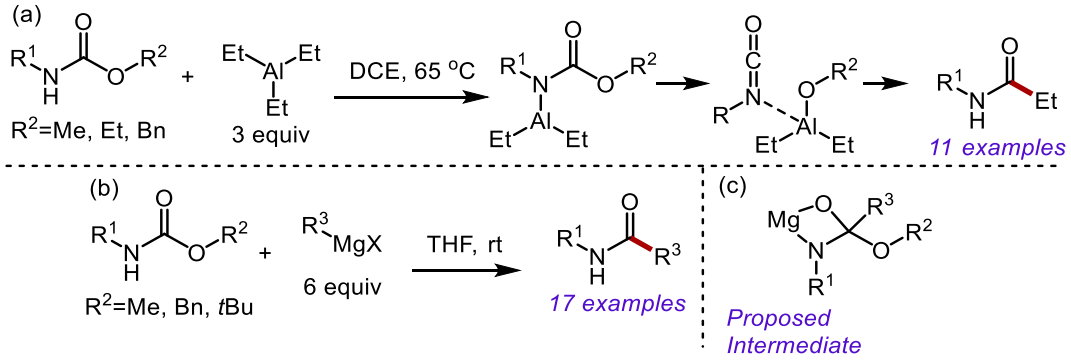


Scheme 1.32: (a) Relative rates of tetrahydroisoquinolone formation with different blocking groups. (b) New system for tetrahydroisoquinolone formation with key protonated intermediate shown. (c) Cascade reaction exploiting different deblocking rates.

Examples of stoichiometric organometallic addition to carbamate derivates have also been reported. Early examples made use of α-lithiated species such as phosphonates or sulfoxides which form stable chelates upon product formation.[159] The use of tertiary carbamates were amenable to these transformations, thus implicating the feasibility of addition elimination pathways in such systems. Kaim and coworkers reported an interesting example making use of stoichiometric trialkylaluminum reagents (scheme 1.33a).[160] Upon heating a mixture of trialkylaluminum in the presence of secondary carbamates for over two days, acceptable yields of the desired alkyl amide were observed. The formation of an isocyanate intermediate was proposed as a consequence of chemoselective amide formation in the presence of an ester functionality, as well as the lack of reactivity exhibited by tertiary carbamate

[159] For early examples see: (a) Tay, M. K.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Org. Lett.* **1989**, *45*, 4430. (b) White, J. D.; Blakemore, P. R.; Milicevic, S. *Org. Lett.* **2002**, *4*, 1803.
[160] Kaim, L. E.; Grimaud, L.; Lee, A.; Perroux, Y.; Tirla, C. *Org. Lett.* **2004**, *6*, 381.

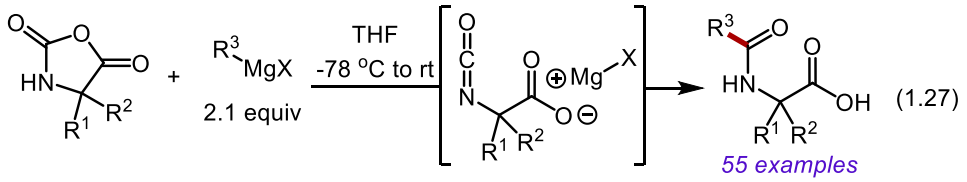
derivatives under the reaction conditions. González and coworkers then reported similar reactivity with Grignard reagents (scheme 1.33b). The intermediacy of an isocyanate species was not entertained, instead the existence of a tetrahedral intermediate was proposed (scheme 1.33c).[161,162]



Scheme 1.33: (a) Kaim's addition of trialkylaluminum reagents to carbamates. (b) Grignard addition to carbamates developed by González. (c) Proposed intermediate in Grignard work.

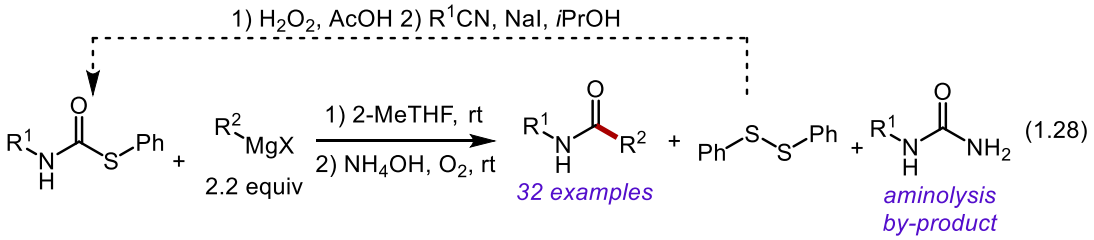
Bode and coworkers reported an interesting application of Grignard addition onto sterically hindered isocyanates building from their earlier work (eq. 1.27).[163] They hypothesized that using excess equivalents of Grignard reagent in the presence of *N*-carboxyanhydrides (NCA), deprotonation would occur first, followed by the release of the isocyanate which would undergo nucleophilic attack with the remaining Grignard reagent. This strategy was amenable to a variety of aryl Grignard reagents, however alkyl Grignard reagents led to complex mixtures. This latter result was mitigated by implementing the use of a sterically hindered sacrificial base. Moreover, various organolithium reagents were amenable to the transformation as well. The use of chiral NCA precursors were tolerated with no observed epimerization. Finally, the intermediacy of an isocyanate was observed using *in situ* IR, supporting its potential involvement in the transformation. Impressively, the isocyanate motif remained untouched in the reaction media in the presence of mesityl Grignard at -78 °C, only upon warming was the addition observed.

[161] Latorre, A.; Rodríguez, S.; Izquierdo, J.; González, F. V. *Tetrahedron Lett.* **2009**, *50*, 2653.
[162] For a similar observation of Grignard reactivity see: Garcia, J.; Mata, E. G.; Tice, C. M.; Hormann, R. E.; Nicolas, E.; Albericio, F.; Michelotti, E. L. *J. Comb. Chem.* **2005**, *7*, 843.
[163] Schafer, G.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1526.



(1.27)

Finally, Maes and coworkers reported a similar transformation making use of thiophenol blocked isocyanates (eq. 1.28).[164] A variety of hindered Grignard reagents provided the desired product in good yield. Workup with ammonium hydroxide under an oxygen atmosphere provided the oxidized diphenyl disulfide which could be readily recycled. Noteworthy is the absence of oligomeric by-products reported by Lindsay and coworkers even with non-sterically demanding thiocarbamate partners.[56] Interestingly, when alkyl, or less hindered aryl Grignard reagents were employed, urea by-products resulting from the aminolysis of the thiocarbamate starting material during work up was observed. This was readily mitigated through the use of more reactive organolithium reagents.



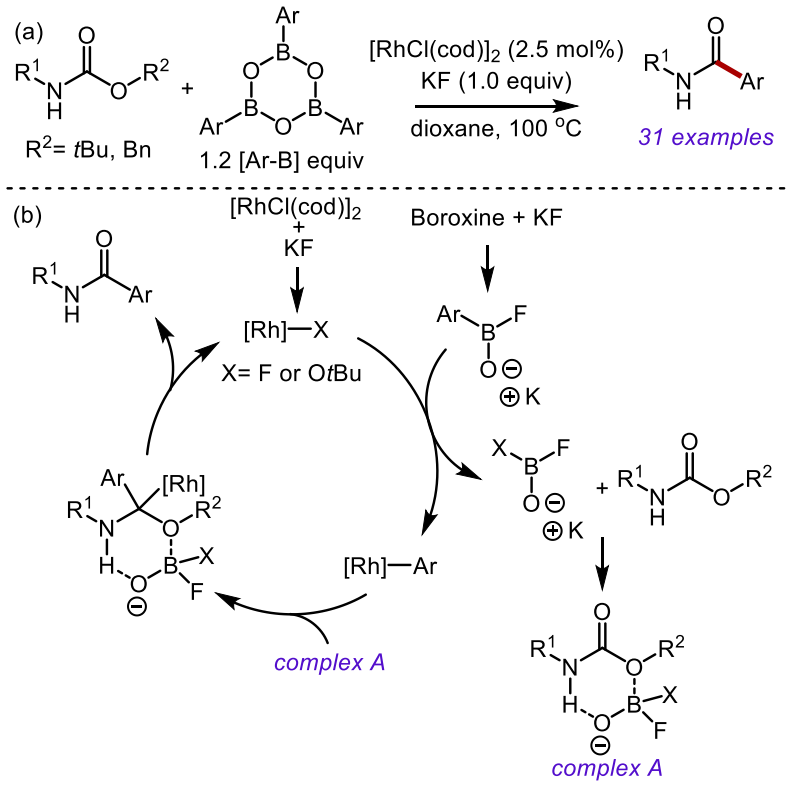
(1.28)

1.5.3 Catalytic amidation of blocked isocyanates.

During their study of copper catalyzed amidation of isocyanates with organoboronic esters, Zhang and coworkers observed the competitive addition of the alkoxide base onto the isocyanate under the reaction conditions.[77] Notably, this species could be converted to the desired product using prolonged reaction time under forcing conditions. They then embarked on a study of direct amidation of common amine protecting groups where a rhodium catalyst, and boroxine derivatives were observed to provide superior results (scheme 1.34a).[165] A variety of *N*-Boc and Cbz carbamates were readily transformed to the desired amides. Zhang and coworkers proposed a mechanism involving direct addition of arylrhodium species to the carbamate largely based of the lack of observable isocyanate species when monitored by NMR spectroscopy (scheme 1.34b). However, though the reaction is run at 100 °C, the NMR spectra were

[164] Mampuys, P.; Ruijter, E.; Orru, R. V. A.; Maes, B. U. W. *Org. Lett.* **2018**, *20*, 4235.
[165] Lim, D. S. W.; Lew, T. T. S.; Zhang, Y. *Org. Lett.* **2015**, *17*, 6054.

taken at room temperature. Thus, any equilibrium between the blocked and the free isocyanate of largely vanished under such conditions.

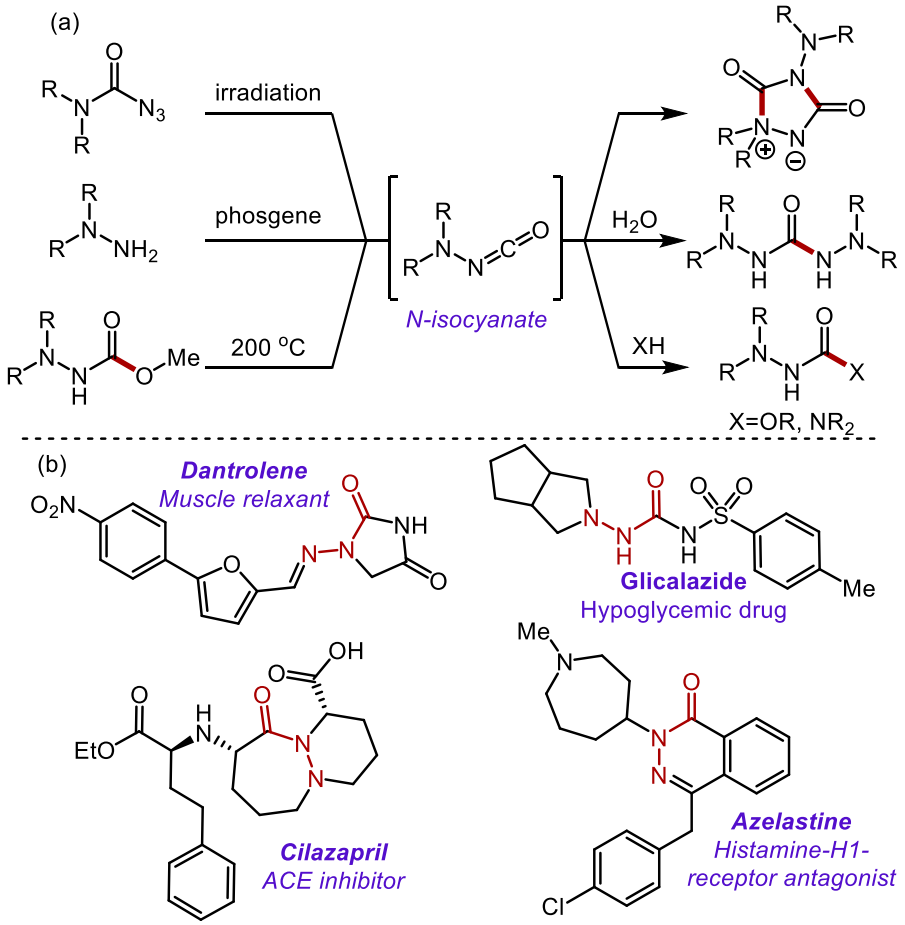


Scheme 1.34: (a) Direct amidation of *N*-Boc and Cbz carbamates. (b) Proposed mechanism.

1.5.4 Development of N-substituted isocyanates using a blocking group strategy.

In contrast to the broad applications of carbon substituted isocyanates, heteroatom substituted derivates have received much less attention. The synthesis and study of *N*-substituted isocyanates have been reported sporadically throughout the 20th century. The majority of these studies concerned themselves with solvolysis based reactivity with limited reports of synthetic developments using such species. This was largely due to difficulties in generating the *N*-isocyanate, compounded by their highly unstable nature as they are known to dimerize at temperatures as low as −40 °C (scheme 1.35a).[166] Nevertheless, the N-N-C=O motif is broadly present within both pharmaceuticals and agrochemicals and thus, harnessing the chemistry of *N*-substituted isocyanates could prove a fruitful platform for their synthesis (scheme 1.35b).

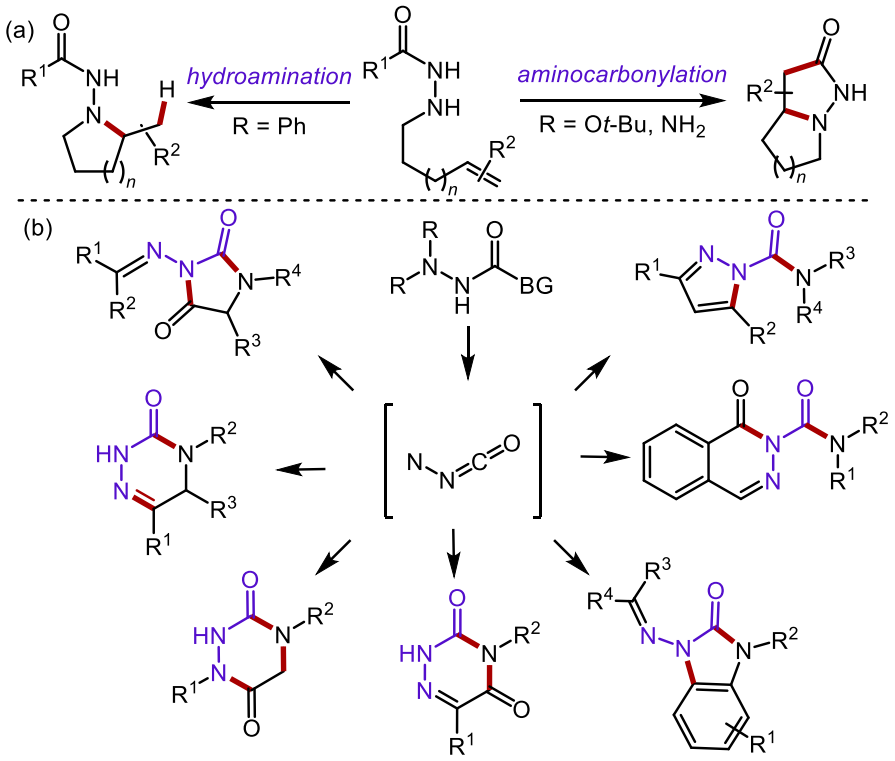
[166] For a review of *N*-isocyanate chemistry see: (a) Reichen, W. *Chem. Rev.* **1978**, *78*, 569. (b) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, *15*, 1745. (c) Vincent-Rocan, J.-F.; Beauchemin, A. M. *Synthesis* **2016**, *48*, 3625.



Scheme 1.35: (a) Selected examples of *N*-isocyanate generation and reactivity. (b) Selected examples of bioactive compounds bearing the N-N-C=O motif.

In 2009, during a study of hydroamination reactivity of various hydrazine derivatives, the discovery of a fascinating by-product arising from the apparent [3+2] cycloaddition of an *N*-isocyanate intermediate with a pendant olefin was made (scheme 1.36a).[167] This reactivity was further explored and computational experiments were found to support the possibility of a cycloaddition, though the barrier to reactivity was much lower than that observed experimentally. This led to the study of alternative blocking groups where eventually room temperature reactivity was in fact achieved. Since this initial discovery, much effort has been devoted in the Beauchemin lab towards developing the reactivity of these blocked *N*-isocyanate precursors to undergo intramolecular cycloadditions, various substitution reactions, and cascade reactivity (scheme 1.36b).

[167] Rovedo, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.



Scheme 1.36: (a) Initial discovery of aminocarbonylation reactivity. (b) Selected examples of blocked *N*-isocyanate developments.

1.5.5 Development of O-substituted isocyanates using a blocking group strategy.

Recently, it became apparent that *O*-substituted isocyanates were suitable candidates for the use of blocking group chemistry for reasons similar to that of *N*-substituted derivates. They were exceptionally rare in the literature and largely relegated to academic curiosities[168] as well as exhibiting poor stability where rapid oligomerization to trimeric isocyanurate derivatives was well documented.[169] Moreover, taming the reactive nature of *O*-isocyanates promised to be a fruitful venture due to the importance of hydroxamic acid derivatives in bioactive compounds, synthetic intermediates, and chiral ligand backbones (Figure 1.8).

[168] For selected examples *O*-substituted isocyanates see: (a) Nef, J. U. *Liebigs Ann. Chem.* **1894**, *280*, 263. (b) Jones, L. W. *J. Am. Chem. Soc.* **1898**, *20*, 1. (c) Jones, L. W.; Neuffer, L. *J. Am. Chem. Soc.* **1917**, *39*, 652. (d) Teles, J. H.; Maier, G. *Chem. Ber.* **1989**, *122,* 745. (e) Jamieson, C. S.; Mebel, A. M.; Kaiser, R. I. *Phys. Chem. Chem. Phys.* **2005**, *7*, 4089.

[169] (a) McKay, A. F.; Garmaise, D. L.; Paris, G. Y.; Gelblum, S. *Can. J. Chem.* **1960**, *38*, 343. (b) Staab, H. A. *Angew. Chem. Int. Ed.* **1962**, *1*, 351. (c) Randolph, M .T.; Hendrick T. J. *J. Org. Chem.* **1965**, *30*, 1268. (d) Heep, U. *Tetrahedron* **1975**, *31*, 77.

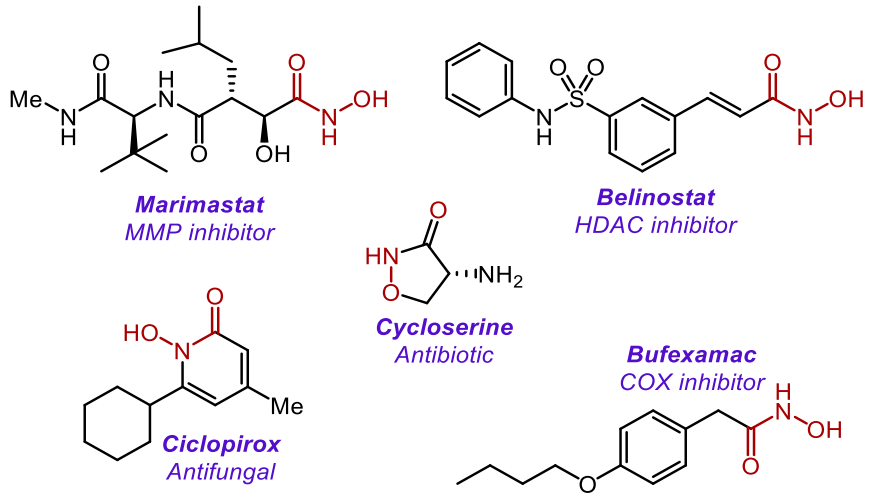
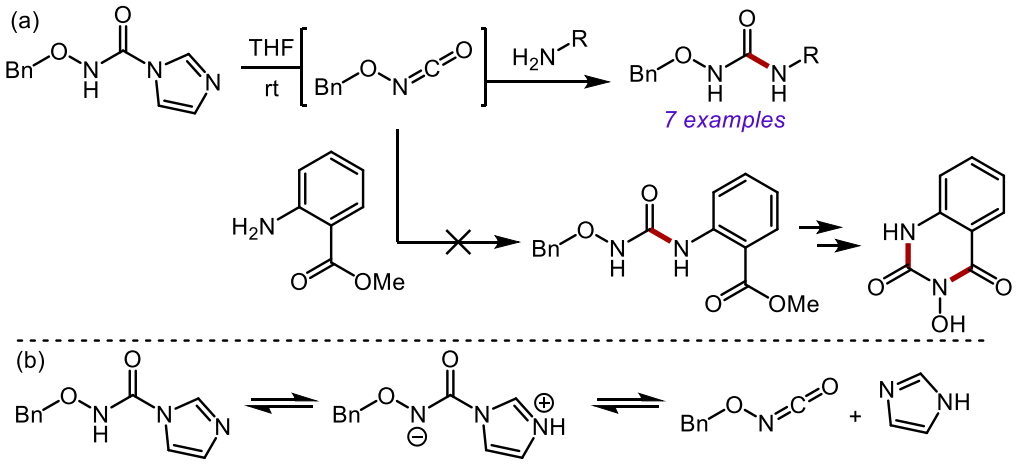


Figure 1.8: Selected examples of biologically active compounds bearing O-N-C=O motif.

Intimations of the potential strength of such a strategy were garnered from a report from Romine and coworkers at BMS.[170] The development of a novel route to *N*-hydroxyquinazolinedione derivatives was envisioned making use of *O*-isocyanate precursors, though their intrinsic instability led them to explore imidazole protected derivates generated *in situ* from the parent hydroxylamine and CDI (scheme 1.37a). Hydroxyureas are readily obtained upon the addition of amines to the reaction flask. However, cascade reactivity eluded them when employing *o*-ester aniline derivatives, necessary to achieve the formation of the desired heterocycle. Moreover, the acid labile nature of the imidazole protecting group coupled with the highly acidic *N*-H of *O*-substituted blocked derivatives make these compounds difficult to handle and thus do not alleviate the underlying problem with *O*-isocyanates (scheme 1.37b). Nevertheless, this work provide foundational knowledge supporting further development of blocked *O*-isocyanate reagents.

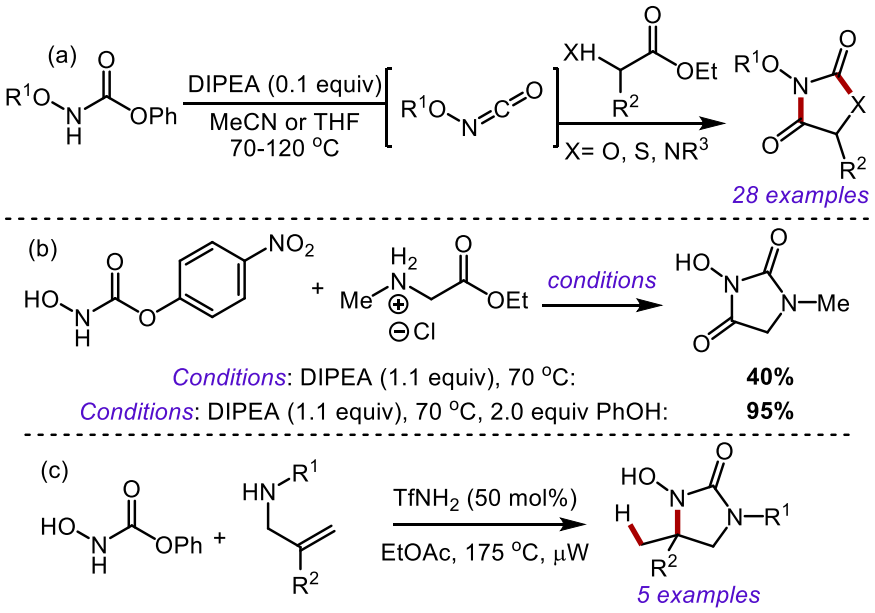
[170] Romine, J. L.; Martin, S. W.; Meanwell, N. A.; Epperson, J. R. *Synthesis* **1994**, 846.



Scheme 1.37: (a) Urea synthesis from imidazole blocked *O*-isocyanate precursor. (b) Stability issues of CDI blocked *O*-substituted isocyanate.

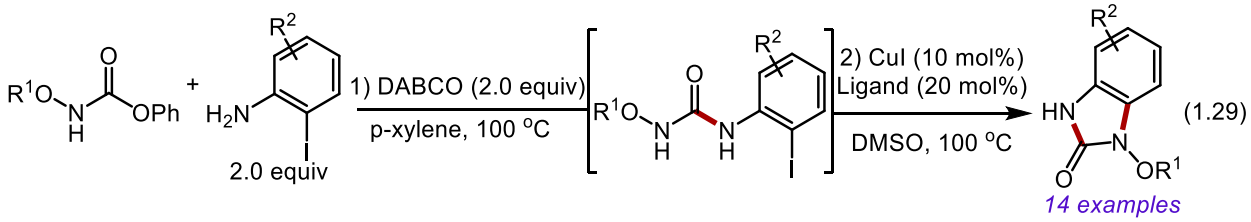
Recent studies in the Beauchemin group building upon this seminal work has focused on the use of phenol blocked derivatives which are bench stable compounds amenable to room temperature substitution/cascade reactivity under suitable conditions. These derivatives were readily employed in the synthesis of alkoxy-hydantoins and dihydrouracil derivates exhibiting broad functional group tolerance (scheme 1.38a).[171] Moreover, direct access to substrates bearing the free OH was readily achieved, removing the need for subsequent deprotection. The importance of the specific blocking group employed was also displayed when moving to a *p*-nitrophenol derivative where a precipitous drop in yield was observed due to its increased lability (scheme 1.38b). The addition of 2 equivalents of phenol to the reaction was able to salvage the yield to its original optimized levels. Probing the effect of leaving groups was further explored in a subsequent publication for simple nucleophilic exchange with morpholine on a variety of blocked *O*-isocyanate precursors.[172] Profound differences were observed between the reactivity of substrates bearing the free OH, *O*-alkyl, and *O*-acyl derivatives. Moreover, a Cope-type hydroamination cascade was reported with allylic amines (scheme 1.38c).

[171] Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. *Adv. Synth. Catal.* **2017**, *359*.
[172] Allen, M. A.; Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. *Org. Lett.* **2017**, *19*, 6574.



Scheme 1.38: (a) Cascade reaction with blocked *O*-iscocyanates and α-aminoesters. (b) Effect of blocking group on reaction efficiency. (c) Cope-type hydroamination cascade with allylic amines.

Finally, a cascade synthesis of alkoxybenzimidazolones and dihydroquinazolinones was developed making use of blocked *O*-isocyanate precursors (eq. 1.29).[173] *o*-Iodoanilines readily added to the blocked precursors and subsequently C-N bond formation using a copper catalyst provided the desired products in good yield. Remarkably, the use of primary aniline/benzylamine derivates were well tolerated under the reaction conditions in stark contrast to previously described cascade which are generally limited to the use of secondary amines.



1.6 Project Goals

Although the use of isocyanates as a platform for amide synthesis has been extensively studied, many limitations remain hindering the widespread adoption of these strategies. As documented in sections 1.2 and 1.3, many procedures suffer from the formation of unwanted by-products,

[173] Wang, Q.; An, J.; Alper, H.; Xiao, X-J.; Beauchemin, A. M. *Chem. Commun.* **2017**, *53*, 13055.

oligomerization of the isocyanate, harsh reaction conditions, or catalyst deactivation. This latter occurrence could prove particularly problematic in impeding the developments of further catalytic reactivity. Most importantly, functional group tolerance using current methodologies remains severely limited with examples of isocyanates bearing Lewis basic motifs (ie: tertiary amines, *N*-heterocycles) seldomly encountered while protic motifs are altogether absent.[174]

The use of blocked isocyanates provides a promising platform for the development of controlled isocyanate reactivity, as displayed in section 1.5. This strategy is particularly attractive to address issues such as unwanted oligomerization, catalyst deactivation, and most importantly, functional group limitations. However, examples in which a blocking group strategy was necessary to overcome inherent limitations of isocyanate reactivity are limited to systems where protic nucleophiles are employed such as the synthesis of ureas, semicarbazides, or oxyureas. In contrast, its use to broaden the scope of isocyanate amidations is almost absent from the literature with the sole exception of Ohwada's work; however, high loadings of triflic acid present their own limitations.

As such, the focus of my graduate work has been the development of new C-C bond forming reactions from blocked isocyanate derivatives with an emphasis on the use of species where a blocking group strategy is a prerequisite for success. The potential of this approach emerged during the development of reaction cascades involving masked isocyanates (chapter 2). The main objective for this part was to exploit and demonstrate the ability of blocked *N*-isocyanates to undergo highly controlled cascade reactions providing access to a variety of heterocyclic derivatives. Throughout the course of these studies, it became apparent that a major limitation of both blocked *N*- and *O*-isocyanate chemistry, was the inability to achieve broadly applicable C-C bond formation from these precursors. This led to the development of the first examples of carbon-based nucleophilic additions on *N*- and *O*-substituted isocyanates (chapter 3). Finally, given the limited use of blocked *C*-substituted isocyanates in amide bond synthesis, coupled with the intrinsic functional group limitations which currently plague amide synthesis from isocyanates, a catalytic amide bond synthesis using ambiphilic *C*-substituted isocyanates was developed (chapter 4).

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[174] For examples of pyridyl isocyanates employed in stoichiometric amidations, see: (a) Maryanoff, B. E.; McComsey, D. F.; Ho, W.; Shank, R. P.; Dubinsky, B. *Bioorg Med. Chem. Lett.* **1996**, *6*, 333. (b) Oberhoff, M.; Duda, L.; Karl, J.; Mohr, Erker, G.; Frohlich, R.; Grehl, M. *Organometallics* **1996**, *15*, 4005. (c) Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel. W.; Meier, H.; Trummlitz, G. *J. Med. Chem.* **1997**, *40*, 980. (d) Chenniappan, V. K.; Rahaim, R. J. *Org. Lett.* **2016**, *18*, 5090.

Chapter 2: Development of *N*-Isocyanate Cascade Reactions

2.1 Introduction

When I joined the Beauchemin lab in 2014, the development of blocked *N*-isocyanate derivatives as powerful organic building blocks was well underway. Historically, the use of *N*-isocyanates had largely been limited to academic curiosity with only approximately 60 publications on the topic since their discovery at the beginning of the 20th century.[175] This was largely attributed to the cumbersome methodologies accessing such motifs coupled with their high propensity to oligomerize, even at temperatures as low as -40 °C.[176] Nevertheless, harnessing such could provide access to a general platform for the synthesis of compounds bearing the N-N-C=O motif, present in a wide variety of pharmaceuticals and agrochemicals (figure 2.1).

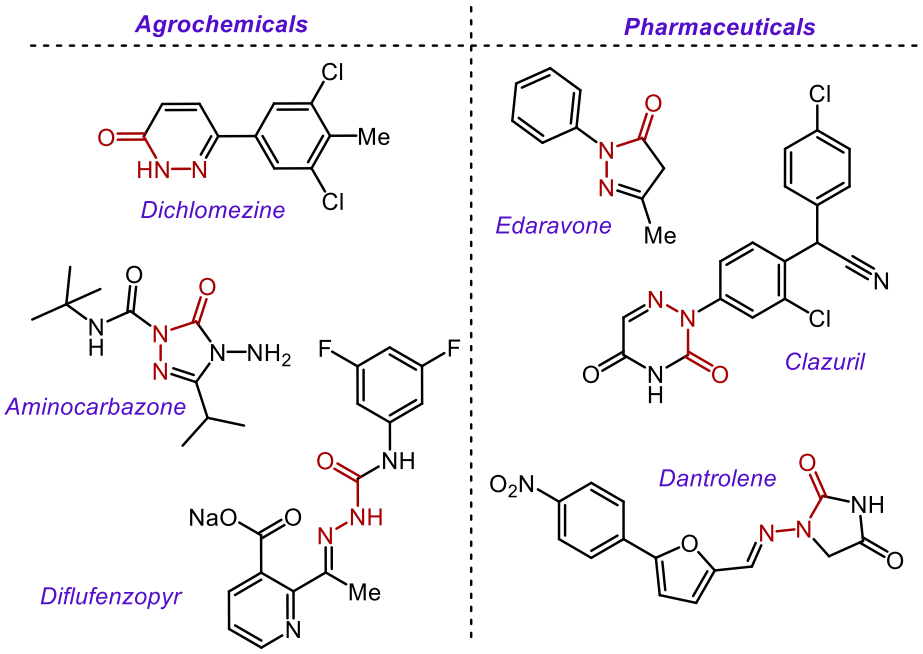
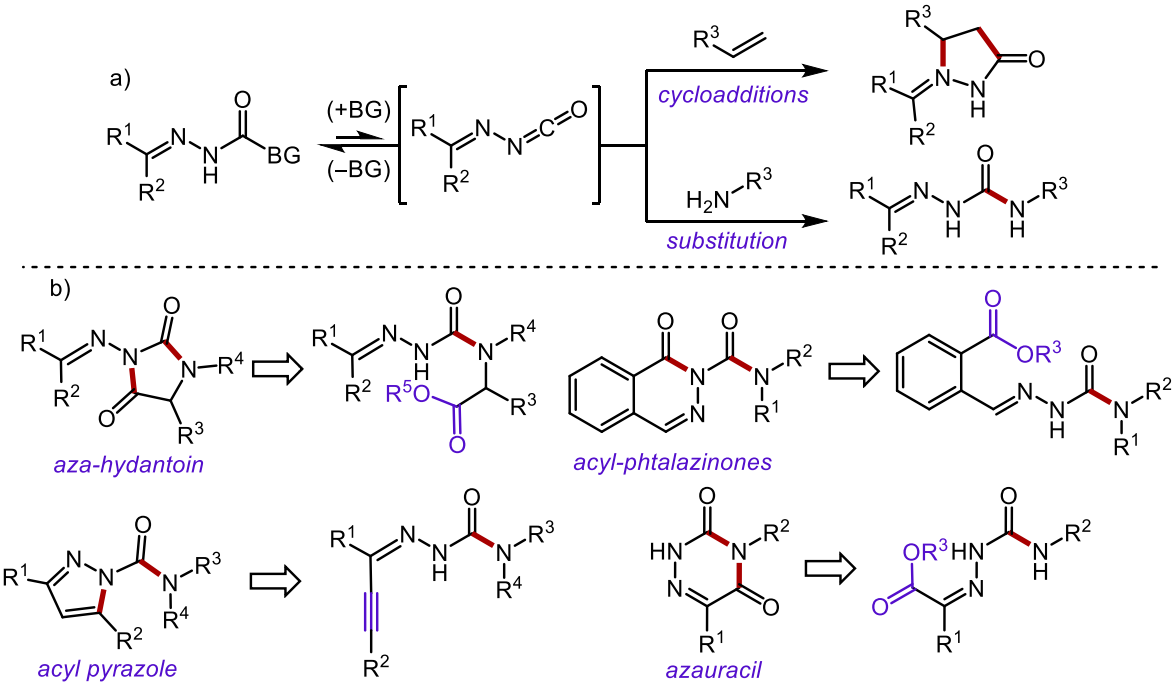


Figure 2.1: Various agrochemicals and pharmaceuticals bearing the N-N-C=O

Indeed, the Beauchemin group successfully applied a blocking group strategy which allowed a high degree of control over the reactivity of these reactive intermediates. This had proven a particularly fruitful platform for the synthesis of various heterocyclic motifs using two major reaction manifolds which

[175] (a) Busch, M. *Chem. Cent. J.* **1901**, *i,* 933. (b) Acree, S. F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3154.
[176] Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, *15*, 1745.

harnessed the amphoteric nature of *N*-isocyanates: 1) cycloaddition reactivity forming pyrazolones[177] and cyclic-azomethine imines,[178] 2) substitution cascades forming aza-hydantoins,[179] acyl-phtalazinones, acyl pyrazoles, azauracil,[180] and saturated heterocyclic derivatives (scheme 2.1a).[181] This latter class of cascade reactions had proven particularly adept in the synthesis of various bioactive heterocycles however, conceptually, these cascades all rely on the substitution of an amine nucleophile onto a blocked *N*-isocyanate derivative, followed by an intramolecular cyclization onto an activated electrophile (scheme 2.1b). Thus, targeting expanding the reactivity of this reaction manifold was of the utmost interest.



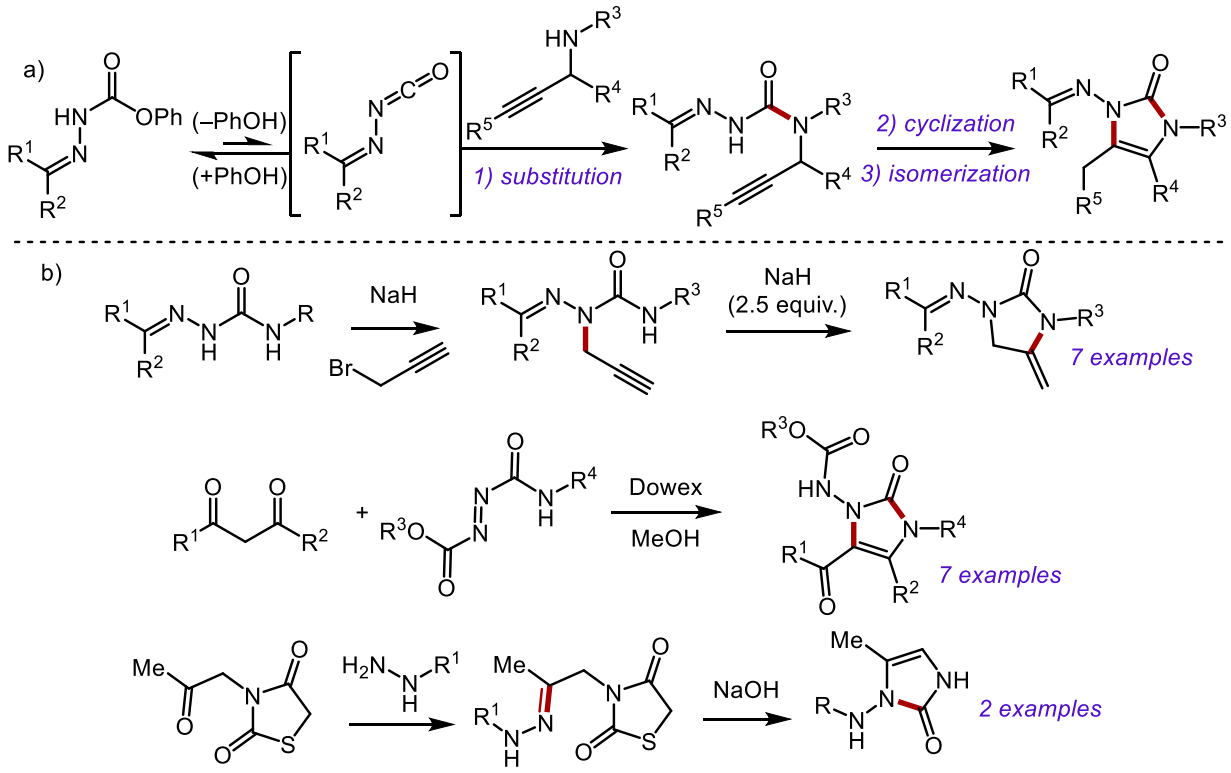
Scheme 2.1: a) Alternative reaction manifolds developed in blocked *N*-isocyanate transformations. b) Cascade synthesis of various heterocycles relying on pendant electrophile

[177] Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 3612.
[178] (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A. M.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111. (b) Gan, W.; Moon, P. J.; Clavette, C.; Neves, N. D.; Markiewicz, T.; Toderian, A. B.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 1890.
[179] Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *Chem. Eur. J.* **2015**, *21*, 3886.
[180] Vincent-Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjiani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, *7*, 315.
[181] (a) Clavette, C.; Vincent-Rocan, J.-F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12705. (b) Ivanovich, R. A.; Vincent-Rocan, J.-F.; Elkaeed, E. B.; Beauchemin, A. M. *Org. Lett.* **2015**, *17*, 4898.

2.2 Divergent Reactivity of *N*-Substituted Iso(thio)cyanates

As described above, the cascade reactivity developed thus far had largely been relegated to activated electrophilic systems such as esters or conjugated π-systems, often benefiting from aromatization as driving force for cyclization step (scheme 2.1b).[182] It was speculated that less activated systems such as alkynes would be amenable to cascade type reactivity given the precedence within the isocyanate literature.[183] Towards this end, the use of propargylic amines was envisioned as an ideal platform to test this hypothesis (scheme 2.2a). Substitution with blocked *N*-isocyanate derivates is expected to occur readily followed by an intramolecular hydroamination/isomerization providing rapid access to aza-imidazolone derivatives. These derivatives are relatively rare in the literature and have limited synthetic reports (scheme 2.2b),[184] in stark contrast to their carbon substituted analogue which represent a privileged bioactive heterocycle.[185]

[182] See ref 171b for examples of unactivated systems using Cope-type hydroaminations.
[183] Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. *Chem. Rev.* **2017**, *117*, 14091.
[184] a) Bezensek, J.; Groselj, U.; Stare, K.; Svete, J.; Stanovnik, B. *Arkivoc* **2014**, 294. b) Proulx, C.; Lubell, W. D. *Org. Lett.* **2012**, *14*, 4552. c) Bezensek J.; Groselj, U.; Stare, K.; Svete, J.; Stanovnik, B. *Tetrahedron* **2012**, *68*, 516. d) Bombek, S.; Pozgan, F.; Kocevar, M.; Polanc, S. *New J. Chem.* **2005**, *29*, 948. e) Korotkikh, N. I.; Shvaika, O. P. *Chem. Heterocycl. Compd.* **1993**, *29*, 349.
[185] For selected examples of imidazolone bioactivity see: (a) Congiu, C.; Cocco, M. T.; Onnis, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 989. (b) Lu, X.; Hu, Y. *Bioorg. Med. Chem.* **2008**, *16*, 2550. (c) Bronson, J. J.; DenBleyker, F. L.; Falk, P. J. Mate, R. A.; Ho, H.-T.; Pucci, M. J.; Snyder, L. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 873.

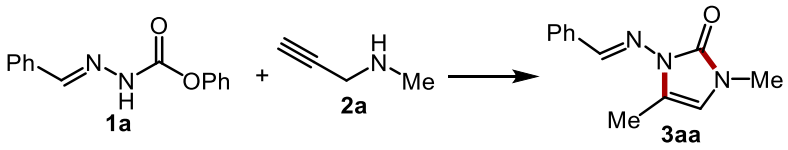


Scheme 2.2: a) Proposed synthetic cascade using blocked N-isocyanates with propargyl amines. b) Recent developments on the synthesis of aza-imidazolones.

The reaction of *N*-methyl propargyl amine (**2a**) with phenol blocked *N*-isocyanate precursor **1a** was chosen as the model system. The substitution of the parent amine onto the *N*-isocyanate occurred readily under microwave irradiation at 100 °C; however, cyclization to the desired imidazolone product **3aa** was only observed in trace quantities (table 2.1, entry 1). Pleasingly, upon the addition of catalytic Et_3N, the desired product was readily formed in 79% yield (entry 2). This facile cyclization using mild catalytic base is in stark contrast to related systems which employed superstoichiometric NaH,[186] NaOEt,[187] or precious metal salts.[188] Increasing the reaction time to two hours resulted in an 87% yield (entry 3), while subsequent time or temperature increases had negligible effects on the reaction efficiency (entry 4-5). Importantly, conditions making use of conventional heating in $PhCF_3$ were also developed although longer reaction times were required (entry 6).

[186] Prouix, C.; Lubell, W. D. *Org. Lett.* **2012**, *14*, 4552.
[187] Easton, N. R.; Cassady, D. R.; Dillard, R. *J. Org. Chem.* **1964**, *29*, 1851.
[188] For selected examples see: (a) Lei, A.; Lu, X. *Org. Lett.* **2000**, *2*, 2699. (b) Verniest, G.; Padwa, A. *Org. Lett.* **2008**, *10*, 4379. (c) Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2011**, *76*, 5867.

Table 2.1: Optimization of *N*-Isocyanate Cascade for Imidazolone synthesis[a]



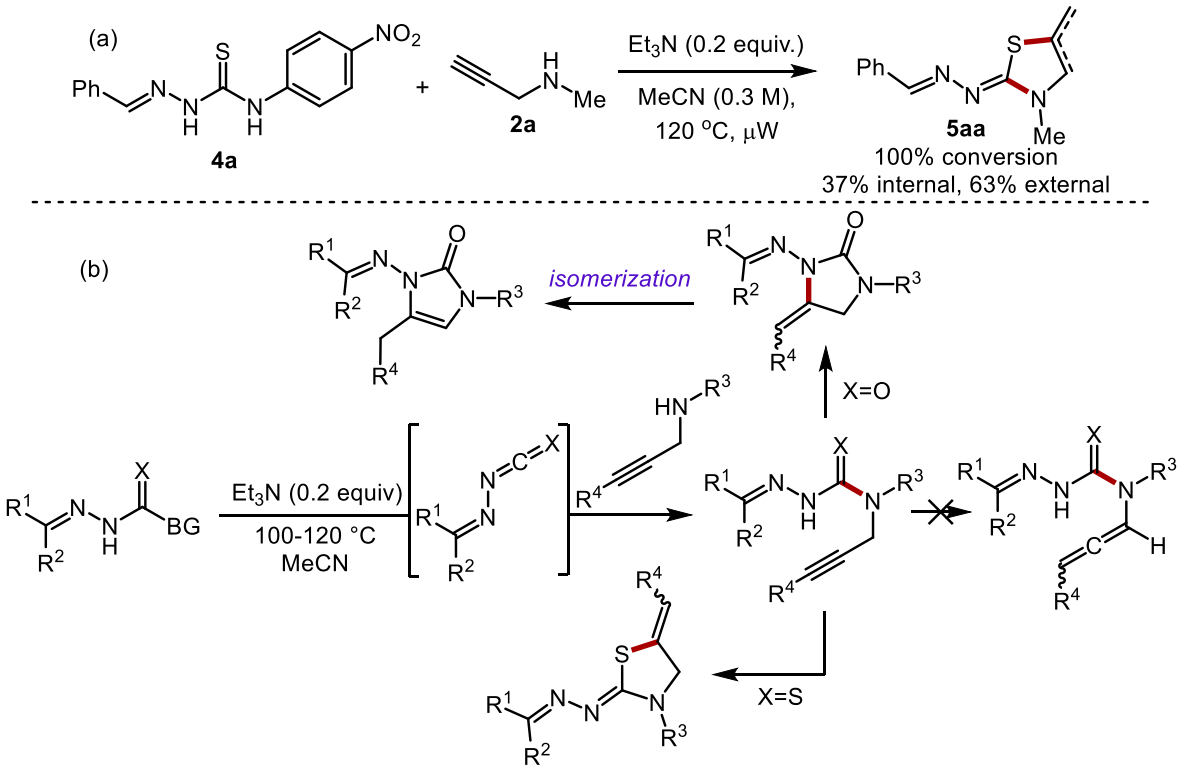
Entry	Source	Temperature (°C)	Base	Time (h)	Solvent (0.3 M)	Yield (%)
1	μW	100	None	3	MeCN	5
2	μW	100	Et_3N	1	MeCN	79
3	μW	100	Et_3N	2	MeCN	87 (86)
4	μW	100	Et_3N	3	MeCN	90
5	μW	150	Et_3N	2	MeCN	86
6	Oil Bath	100	Et_3N	14	$PhCF_3$	68

[a]Conditions: hydrazone **1a** (1.0 equiv.), *N*-methylpropargylamine **2a** (1.1 equiv.), Et_3N (0.2 equiv.), and MeCN (0.3 M) were added to an oven-dried microwave vial and heated in an oil bath or microwave reactor (μW) at the indicated temperature. ^1H NMR yield based on 1,3,5-trimethoxybenzene internal standard, isolated yield in parentheses.

The application of *N*-isothiocyanates in the current cascade reaction was studied in parallel, where prior work in the Beauchemin lab suggested these derivates react similarly to their *N*-isocyanate counterparts.[179] Notably, a *p*-nitroaniline blocked *N*-isothiocyanate was employed given the ease of access of these blocked derivatives. In contrast to *N*-isocyanates, the sulfur atom was observed to cyclize on the alkyne as opposed to the nitrogen, akin to previous reports of similar cyclizations (scheme 2.3a). Interestingly, only partial isomerization of the exocyclic olefin to the aromatic compound was observed where no significant change in ratio resulted irrespective of reaction condition modifications (**5aa**). This may arise due to reduced ability of the alkenyl sulfide as compared to the enamine to isomerize to the aromatic imidazolone products. Moreover, the presence of the exocyclic olefin strongly suggests a mechanism involving the direct cyclization onto the alkyne as opposed to isomerization to the allene which was recently proposed for similar cyclizations by computational experiments[189] under similar

[189] Casnati, A.; Perrone, A.; Mazzeo, P. P.; Bacchi, A.; Mancuso, R.; Gabriele, B.; Maggi, R.; Maestri, G.; Motti, E.; Stirling, A.; Della Ca', N. *J. Org. Chem.* **2019**, *84*, 3477.

conditions (scheme 2.3b). Nevertheless, this divergent reactivity provides ready access to thiazolidine motifs which are broadly biologically active.[190]



Scheme 2.3: a) Thiazolidine synthesis using blocked *N*-isothiocyanate cascade. b) Proposed mechanism for imidazolone and thiazolidine synthesis.

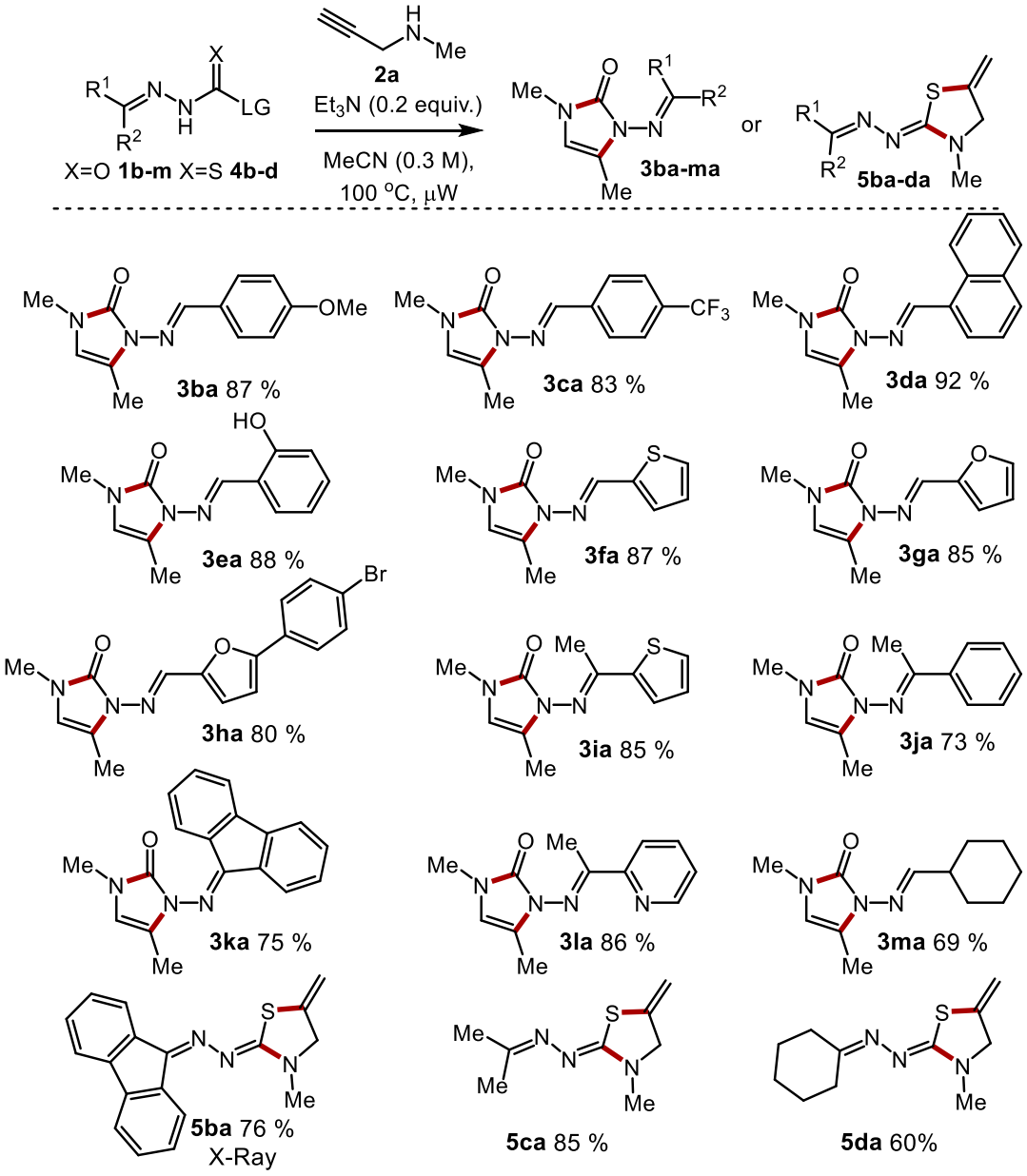
With these optimized conditions in hand, the scope of these cascades was explored with the help of Jean-François Vincent-Rocan. Gratifyingly, a variety of *N*-isocyanate precursors reacted efficiently with *N*-methylpropargylamine to form the aza-imidazolones (table 2.2). Several hydrazone derivatives derived from aromatic aldehyde were probed first. Electron-rich, electron poor, and heteroaromatic *N*-isocyanate precursors were all well tolerated, yielding the desired imidazolones in 83-92% yield (**3ba**-**3ga**). More complex hydrazones can also be used, such as a *N*-isocyanate precursor possessing the azumolene bicydic core which rapidly formed the drug analog **3ha**. Ketohydrazones were also surveyed and similarly provided high yields (73-86%) tolerating a range of substituents including heterocyclic and aliphatic derivatives (**3ia**-**3ma**). In contrast, when *N*-isothiocyanate precursors were tested, effects on

[190] For selected examples of bioactivity see: (a) Mohamed, A. M.; Abdel-Hafez, N. A.; Kassem, A. F.; Abbas, E. M. H.; Mounier, M. M. *Russ. J. Gen. Chem.* **2017**, *87*, 2391. (b) Tageldin, G. N.; Fahmy, S. M.; Ashour, H. M.; Khalil, M. A.; Nassra, R. A.; Labouta, I. M. *Bioorg. Chem.* **2018**, *80*, 164. (c) Abdellatif, K. R. A.; Fadaly, W. A. A.; Kamel, G. M.; Elshaier, Y. A. M. M.; El-Magd, M. A. *Bioorg. Chem.* **2019**, *82*, 86.

isomerization of the cyclized product was observed. Indeed, using a fluorenone-derived *N*-isothiocyanate precursors led to cyclization via the sulfur atom, but no isomerization occurred resulting in the selective formation of product **5ba**, for which an X-ray structure was obtained to support its formation.[191] Similar reactivity was also observed with other thiosemicarbazones (**5ca**-**5da**).

[191] See supporting information for more information

Table 2.2: Scope of hydrazone precursors for *N*-iso(thio)cyanate cascade[a]

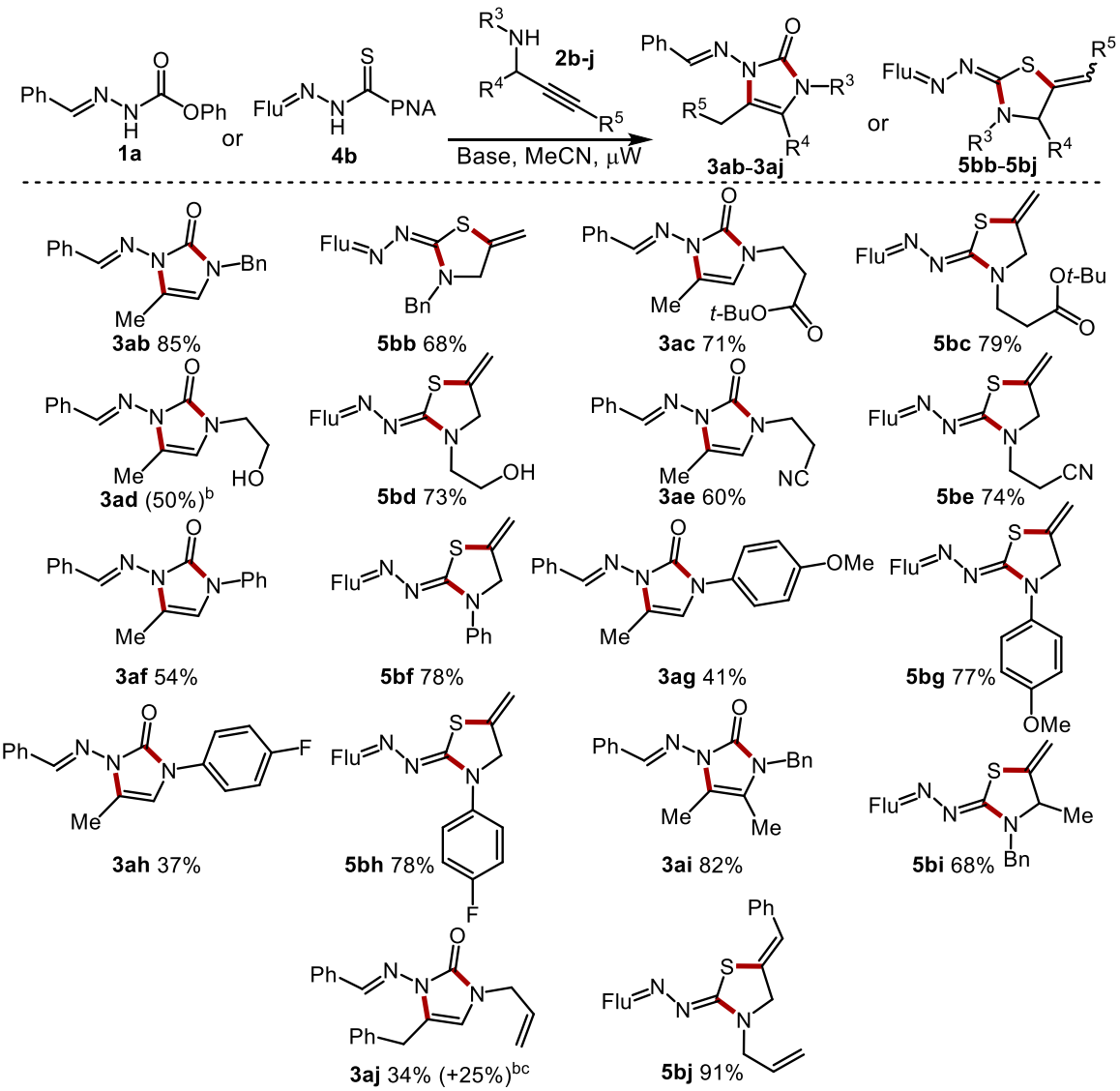


[a]Conditions: **1b**-**m** or **4b**-**d** (0.6 mmol), *N*-methylpropargylamine **2a** (1.1 equiv.), Et_3N (0.2 equiv.), and MeCN (0.3 M) were added to an oven-dried microwave vial and heated in a microwave reactor at 100 °C (120 °C for *N*-isothiocyanate precursors **4b**-**d**).

The scope of the propargylic amine on both *N*-iso(thio)cyanate precursors was then probed (Table 2.3). A variety of propargylic amine derivatives can be readily accessed through simple substitution reactions of primary amines and propargyl bromide. This was performed using benzaldehyde-derived *N*-isocyanate precursor **1a** and fluorenone-derived *N*-isothiocyanate **4b**. Importantly, both precursors are readily obtained on multigram scale without the need for purification by column chromatography.

Interestingly, the cascade reactions with *N*-isothiocyanate precursor **4b** proved more efficient (68-91%), and significantly less sensitive to variations in the structure of the propargylic amine than its *N*-isocyanate counterpart (37-85%). Nevertheless, reaction with propargylic amines possessing *N*-benzyl group, *N*-alkyl chains with esters, a nitrile or a free hydroxyl group, *N*-aryl groups, and also an internal phenyl-substituted alkyne all delivered the desired thiazolidines or imidazolones. Notably, cyclization on the alkyne occurred selectively in the presence of pendant esters which were previously observed to react readily under similar conditions (**3ac**-**5bc**).[179] The largest contrast in reactivity was observed when employing *N*-aryl derivatives where differences of up to 41% yield were observed (**3ah**-**5bh**). Interestingly, the use of the internal alkyne to form thiazolidine **5bj** appeared to be beneficial to the cascade reaction (91%). However, the *N*-isocyanate cascade using the internal alkyne led to a modest 34% yield of the desired imidazolone **3aj**, as substitution partially prevented the isomerization (25% of the exocyclic imidazolinone **3i** was also formed). Overall, a comparison of the reactivity shows that cascade reactions of *N*-isothiocyanates are more robust likely due to a more facile cyclization.

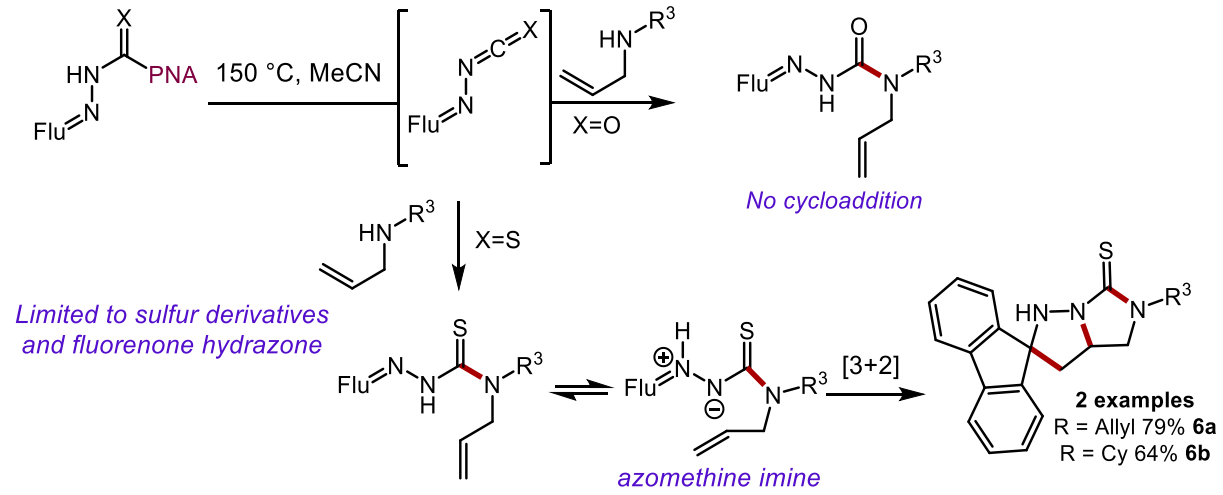
Table 2.3: Scope of propargylic amine precursor for *N*-iso(thio)cyanate cascade[a]



[a]Conditions: **1a** or **4b** (0.6 mmol), propargylamine **2b-j** (1.1 equiv.), Et_3N (0.2 equiv.), MeCN (0.3 M), and heated at 100-150 ℃. [b]Based on ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c]Yield for product with an exocyclic alkene.

The potential incorporation of alkene derivatives in this cascade reaction was then tested by Jean-François Vincent-Rocan. This was easily probed through the use of readily available allylic amines, where diallylamine proved an obvious choice. Surprisingly, cascade reactivity was observed with *N*-isothiocyanate derivatives, however the product was not a result of the envisioned substitution/cyclization cascade. Instead, the formation of a pentacyclic spirocycle derivative was observed under the reaction conditions. This product was proposed to arise from the *in situ* formation of an azomethine imine followed by an intramolecular [3+2] cycloaddition (scheme 2.4). In contrast to the

pioneering work of Overman and coworkers who formed related dipoles under acidic conditions,[192] our mildly basic conditions proved sufficient to promote the formation of the key azomethine imine intermediate. Unfortunately, this reactivity was specific to fluorenyl derived *N*-isothiocyanate derivatives, likely a result of the increased stabilization of the azomethine imine intermediate.



Scheme 2.4: Cascade cycloaddition with allylic amines

2.3 A Cascade Synthesis of 1,2,4-Triazin-3(2*H*)-ones

1,2,4-Triazinones are an important class of heterocycles which display a broad range of biological activities arising from its structural similarities to pyrimidine bases.[193] Their saturated analogue has also attracted interest from medicinal[194] and agricultural chemists alike, most notably highlighted by the development of pymetrozine (scheme 2.5b), an antifeedant insecticide currently being employed in the United States and Europe.[195] Despite the value of these heterocycles, current synthetic approaches

[192] For cycloadditions of related azomethine imines, see: (a) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. (b) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880. (c) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559. (d) Gergely, J.; Morgan, J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144.

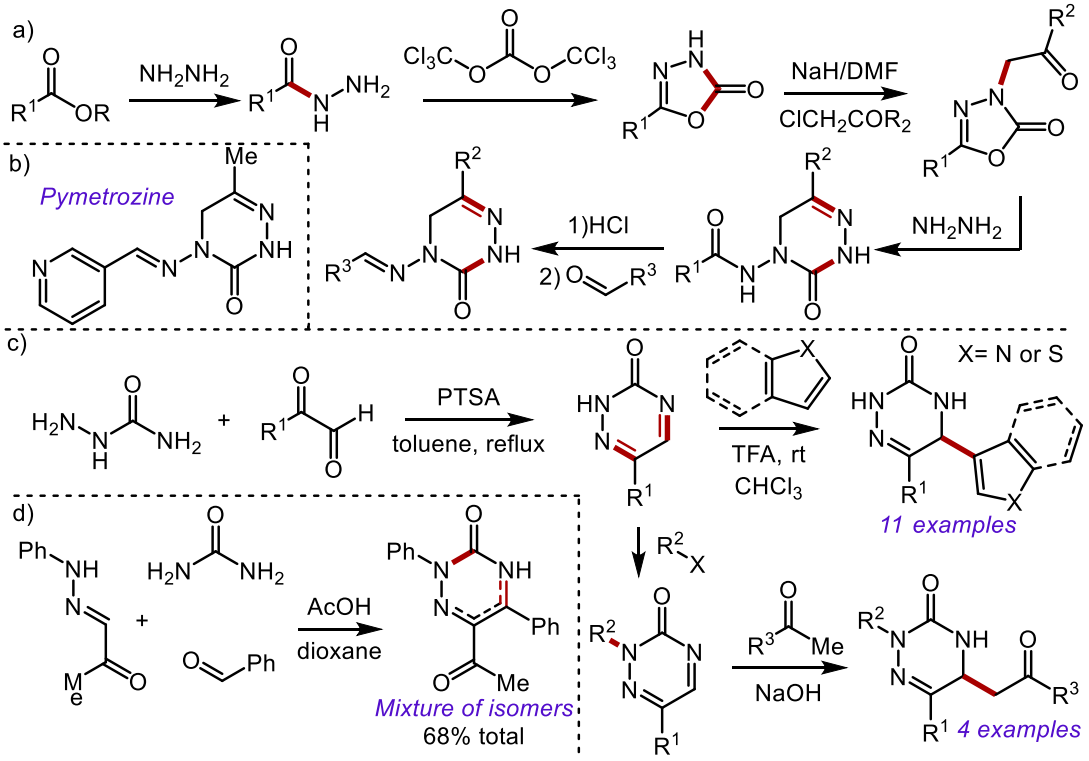
[193] For selected examples of 1,2,4-triazinone bioactivity, see: (a) Schmitz, W. D.; Brenner, A. B.; Bronson, J. J.; Ditta, J. L.; Griffin, C. R.; Li, Y.-W.; Lodge, N. J.; Molski, T. F.; Olson, R. E.; Zhuo, X.; Macor. J. E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3579. (b) Sztanke, K.; Tuzimski, T.; Sztanke, M.; Rzymowska, J.; Pasternak, K. *Bioorg. Med. Chem.* **2011**, *19*, 5103. (c) Saad, H. A.; Moustafa, A. H. *Molecules* **2011**, *16*, 5682.

[194] For selected examples of 1,2,4-triazin-3(2*H*)-one bioactivity, see: (a) Kristinsson, H. US 4931439, **1990**. (b) Martin, M.; Nadler, G.; Zimmermann, R. US 4933336, **1990**. (c) Oi, N.; Tokunaga, M.; Suzuki, M.; Nagai, Y.; Nakatani, Y.; Yamamoto, N.; Maeda, J.; Minamimoto, T.; Zhang, M.-R.; Suhara, T.; Higuchi, M. *J. Med. Chem.* **2015**, *58*, 8444. (d) Yang, Y.; Liu, Y.; Song, H.; Li, Y.; Wang, Q. *Bioorg. Med. Chem.* **2016**, *24*, 391.

[195] European Food Safety Authority *EFSA Journal* **2014**, *12*, 3817.

providing access to these compounds and derivative thereof have remained rudimentary, typically requiring multistep synthesis or generally displaying low yields (scheme 2.5a,c,d).[196]

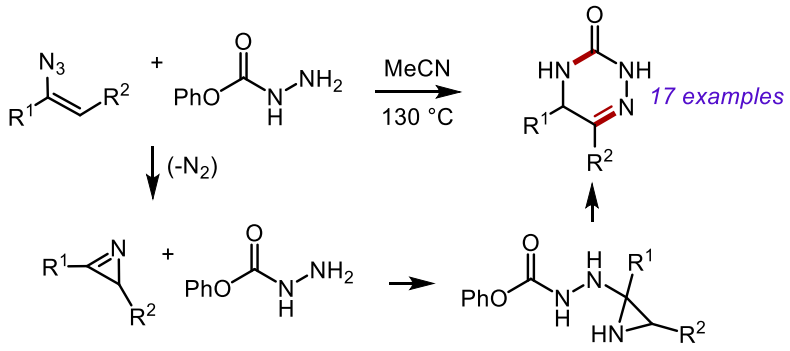
[196] For selected publications on 1,2,4-triazin-3(2H)-one syntheses,see: (a) Biltz, V. H. *Justus Liebigs Ann. Chem.* **1905**, *339*, 243. (b) Busch, M.; Kuspert, K. *J. Prakt. Chem.* **1936**, *144*, 273. (c) Polonovski, M.; Pesson, M.; Rajzman, P. C. R. *Hebd. Seances Acad. Sci.* **1954**, *238*, 695. (d) Mustafa, A.; Asker, W.; Mansour, A.K.; Zaher, H. A. A.; Eloui, A. R. *J. Org. Chem.* **1963**, *28*, 3519. (e) Holland, D. G.; Amstutz, E. D. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1047. (f) M'Packo, J. P.; Vinot, N. C. R. *Seances Acad. Sci., Ser. C* **1970**, 1201. (g) Paudler, W. W.; Lee, J. *J. Org. Chem.* **1971**, *36*, 3921. (h) Vinot, N.; M'Packo, J. P. *Bull. Soc. Chim. Fr.* **1972**, 4637. (i) Daunis, J.; Pigiere, C. *Bull. Soc. Chim. Fr.* **1973**, 2818. (j) Daunis, J.; Djouai-Hifdi, L.; Lopez, H. *J. Heterocycl. Chem.* **1979**, *16*, 427. (k) Nakayama, Y.; Sanemitsu, Y.; Mizutani, M.; Yoshioka, H. *J. Heterocycl. Chem.* **1981**, *18*, 631. (l) Teraji, T.; Shiokawa, Y.;Okumura, K.; Sato, Y. US 4616014, **1986**. (m) Lozanova, K.; Simov, D.; Kalcheva, V. *Chem. Heterocycl. Compd.* **1987**, *23*,1024. (n) Milcent, R.; Yver, B.; Barbier, G. *J. Heterocycl. Chem.* **1992**, *29*, 959. (o) Miki, H.; Iwanaga, K.; Matsuno, T.; Aoki, I. US5994355, **1999**. (p) Nagato, S.; Kawano, K.; Ito, K.; Norimine, Y.; Ueno, K.; Hanada, T.; Amino, H.; Ogo, M.; Hatakeyama, S.; Ueno, M.; Groom, A. J.; Rivers, L.; Smith, T. WO 200222587, **2001**. (q) Kelly, M. J.; Jacobson, R. M. US 2004019209, **2004**. (r) Verardo, G.; Geatti, P.; Merli, M.; Strazzolini, P. *Eur. J. Org.Chem.* **2006**, 2638. (s) Darwish, E. S.; Abdelhamid, I. A.; Nasra, M. A.; Abdel-Gallil, F. M.; Fleita, D. H. *Helv. Chim. Acta* **2010**, *93*,1204. (t) Egorov, I. N.; Tseitler, T. A.; Zyryanov, G. V.; Rusinov, V.L.; Chupakhin, O. N. *ARKIVOC* **2011**, 323. (u) Wang, B.; Ke, S.; Kishore, B.; Xu, X.; Zou, Z.; Li, Z. *Synth. Commun.* **2012**, *42*, 2327. (v) Egorov, I. N. Z. *Naturforsch., B: J. Chem. Sci.* **2014**, *69*, 899.



Scheme 2.5: a) General reaction scheme for the synthesis of pymetrozine derivatives. b) Structure of the insecticide pymetrozine. c) Recent advances in the synthesis of 1,2,4-triazin-3(*2H*)-ones. d) Recent report of Biginelli reaction applied for the synthesis of 1,2,4-triazin-3(*2H*)-one.

Recently, Yu and coworkers reported a novel cascade synthesis of these heterocycles using phenyl carbazate and vinyl azides (scheme 2.6).[197] This methodology provided a variety of 1,2,4-triazin-3(*2H*)-ones in good yield. Interestingly in this approach, vinyl azides serve as precursors for 2*H*-azirines, which are equivalent to dehydrated α-aminoketones. Consequently, the reaction does not allow access to products substituted at the 4-position. Moreover, the applicability of such a reaction is limited due to the use of organic azides under a closed reaction system at high temperatures.

[197] Shao, J.; Xingyu, L.; Shu, K.; Tang, P.; Luo, J.; Chen, W.; Yu, Y. *Org. Lett.* **2015**, *17*, 4502.

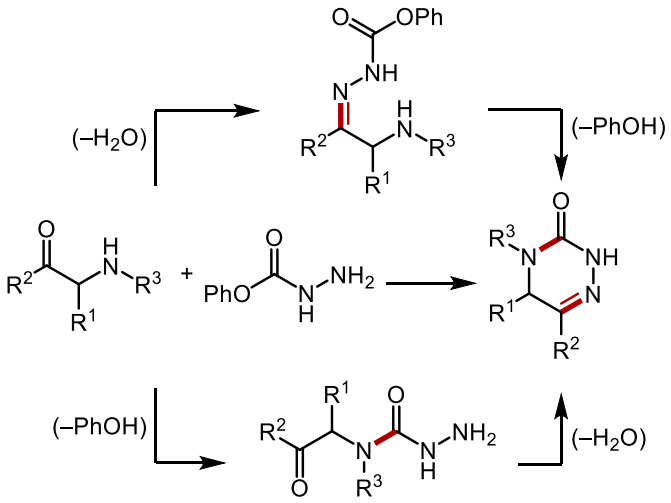


Scheme 2.6: Yu's synthesis of 1,2,4-dihydrotriazinones using vinyl azides

Given the Beauchemin lab's expertise in heterocyclic synthesis using *N*-isocyanates as reactive intermediates, milder, more broadly applicable conditions were believed to be within reach. Making use of α-amino ketone starting materials, initial substitution followed by intramolecular condensation would provide the desired product, however competitive oligomerization of the *N*-isocyanate starting material could prove particularly problematic under such a kinetic regime (Scheme 2.7).[179] Alternatively, initial condensation (hydrazone formation) followed by intramolecular cyclization appears more promising. However, such condensations can be difficult, especially with hindered ketones as substrates,[198] thus necessitating a high degree of control over *N*-isocyanate deblocking for efficient reactivity. Additional difficulties present within this system is the added ability of α-amino ketones to oligomerize under the reaction conditions.[199]

[198] (a) Dirksen, A.; Dawson, P. E. *Bioconjugate Chem.* **2008**, *19*, 2543. (b) Kool, E. T.; Park, D.-H.; Crisalli, P. *J. Am. Chem. Soc.* **2013**, *135*, 17663. (c) Crisalli, P.; Kool, E. T. *Org. Lett.* **2013**, *15*, 1646.

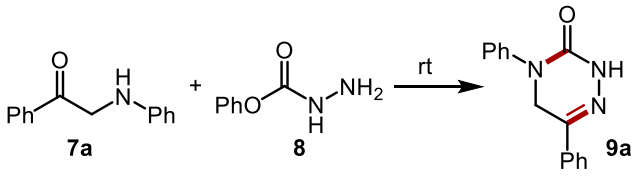
[199] For an entry into stable α-amino carbonyl compounds, see:(a) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772. (b) He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029.



Scheme 2.7: Potential pathways to 1,2,4-triazin-3(*2H*)-ones from α-aminoketones

Bearing this in mind, investigations were initiated with the help of Mohammed Dahab, probing conditions to form the desired 1,2,4-triazin-3(2*H*)-one using phenyl carbazate and 2-anilinoacetophenone as model system (table 2.4). This particular α-amino ketone was chosen due to its ease of access and reduced tendency to dimerize. Initially, basic conditions were tested using DBU which had previously been reported as a competent catalyst for simple substitution reactions of phenyl carbazate.[179] Unfortunately, these conditions did not provide the desired semicarbazide or product, instead resulting in the degradation of the α-amino ketone and dimerization of the carbazate (entry 1). Thermal conditions were also tested yielding no reaction (entry 2), while the addition of a mild base produced similar results to that observed with DBU (entry 3). Taken together, these initial experiments suggested that the nucleophilicity of the aniline is not sufficient to outcompete phenyl carbazate oligomerization. Thus, conditions which would promote the condensation reaction were then surveyed. This proved fruitful with stoichiometric amounts of citric acid providing the desired product in 73% NMR yield after stirring for 12 hours at room temperature (entry 4). A solvent scan was performed where THF was the optimal solvent for this cascade reaction (entries 5-7). The concentration of the reaction was observed to have significant effect on the overall reaction with a 0.1 M reaction resulting in a 27% yield (entry 8) while increasing the reaction concentration from 0.50 to 1.0 M resulted in no change in yield (entry 9). A control reaction performed in the absence of citric acid stressed its importance in this cascade with neither the condensation product (hydrazone) or the desired product detected by NMR spectroscopy (entry 10). With optimized conditions in hand, the scope of this novel cascade was probed largely carried out by Mohammed Dahab.

Table 2.4: Optimization of 1,2,4-dihydrotriazin-3(*2H*)-one cascade[a]



Entry	Additive (equiv.)	Solvent (M)	Time (h)	Yield (%)
1	DBU (0.2)	THF (0.3)	16	Degradation
2[b]	None	THF (0.3)	16	No reaction
3[b]	Et_3N (0.2)	THF (0.3)	16	Degradation
4	Citric acid (1.0)	THF (0.5)	12	73
5	Citric acid (1.0)	MeCN (0.5)	12	60
6	Citric acid (1.0)	$PhCF_3$ (0.5)	12	11
7	Citric acid (1.0)	MeOH (0.5)	12	62
8	Citric acid (1.0)	THF (0.1)	12	27
9	Citric acid (1.0)	THF (1.0)	12	73
10	none	THF (1.0)	12	No reaction

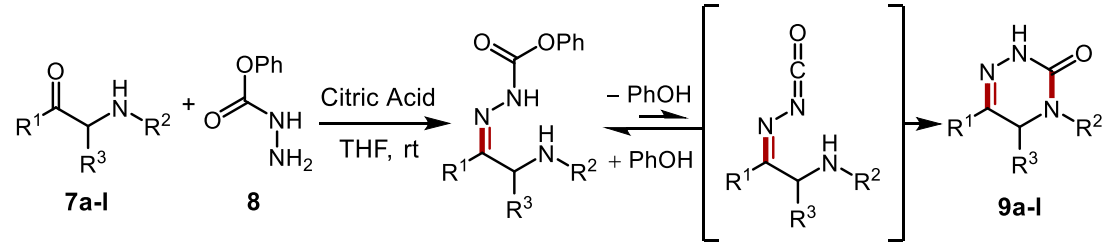
[a]Conditions: phenyl carbazate **8** (0.2 mmol)), α-aminoketone **7a** (1.05 equiv.), and citric acid (1.0 equiv.) in THF (0.5 M) at r.t. ^1H NMR yield based on 1,3,5 trimethoxybenzene as internal standard. [b]Reflux.

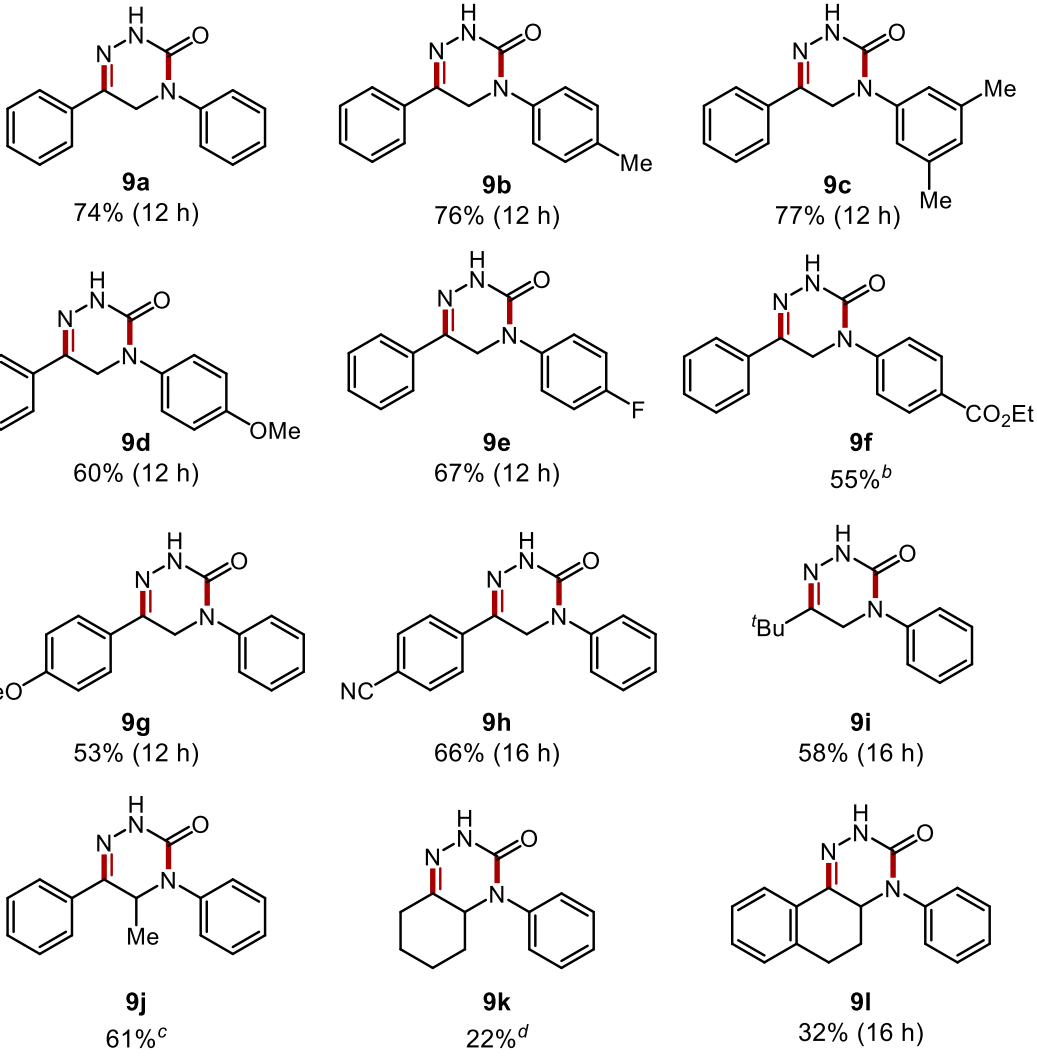
The substituent effects on the aniline moiety was evaluated first (table 2.5). Electron-donating substituents on the aniline ring were well tolerated under the reaction conditions with *p*-methyl (**9b**), 3,5-dimethyl (**9c**), and *p*-methoxy (**9d**) all providing the 1,2,4-triazin-3(2H)-one in good yields. Electron-withdrawing groups also afforded the desired product as illustrated with *p*-fluoro-substituted product **9e**, and even the strongly electron-withdrawing ester yielded product although heating was necessary to achieve cyclization (**9f**). A variety of different substituents on the ketone motif of the starting material was then surveyed. Both electron-rich (**9g**) and electron-poor (**9h**) aromatic ketones provided the product in moderate to good yield. An alkyl substituted α-amine ketone was also a competent reaction partner under the reaction conditions, despite the increased steric bulk (**9i**). Finally, the impact of substitution at the α-position was probed. As expected, the presence of a methyl group at this position had a substantial effect on the reaction: heating was required to achieve efficient cyclization to form product **9j** in good yield. Cyclic derivatives also proved amenable to the cascade although these were found to be low-yielding (**9k** and **9i**). Importantly, strongly deactivated substrates such as ortho chloro, *p*-nitro, or tosylamine were not

observed to form the desired product under a variety of reaction conditions. Overall, this methodology provides mild access to an array of 1,2,4-triazin-3(2H)-ones. Moreover, the applicability of this procedure to large-scale synthesis was demonstrated with the gram scale formation of 1,2,4-triazin-3(2H)-one **9a** in 88% yield.[200]

[200] See supporting information for a detailed procedure.

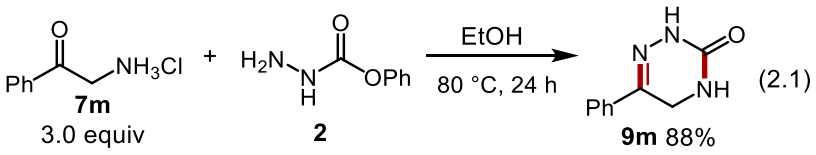
Table 2.5: Scope of 1,2,4-dihydrotriazin-3(*2H*)-one cascade[a]



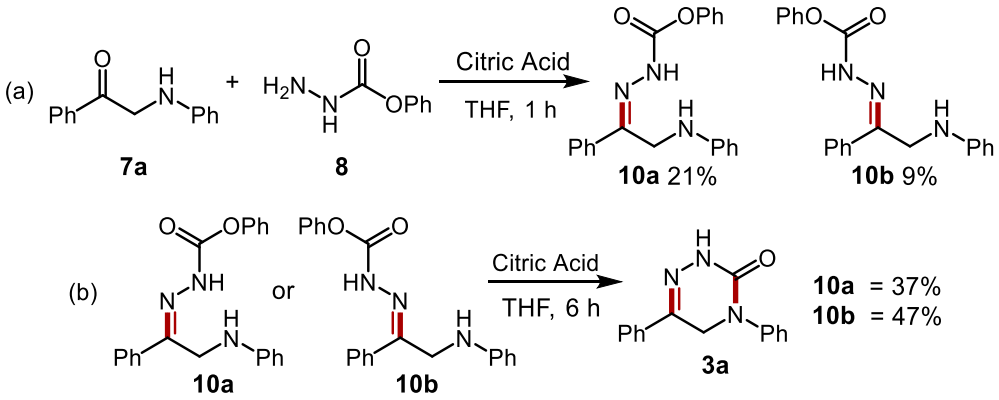


[a]Conditions: phenyl carbazate **8** (0.6 mmol), α-aminoketone **7a-i** (1.05 equiv.), and citric acid (1.0 equiv.) in THF (1.0 M) at r.t. [b] Stirred at r.t. for 7h, followed by reflux for 20 h. [c]Stirred at r.t. for 12 h, followed by reflux for 24 h. [d]Stirred at r.t. for 12 h, followed by reflux for 20 h.

The applicability of this protocol was then explored with a primary α-aminoketone (eq. 2.1), using commercially available 2-aminoacetophenone hydrochloride (**7m**) as the test substrate. This substrate was not amenable to room temperature reactivity, in fact, reflux in ethanol in the presence of excess of carbazate was required to obtain a high yield of **9m**. This preliminary data suggests the scope of this protocol could be expanded to include other α-aminoketones.



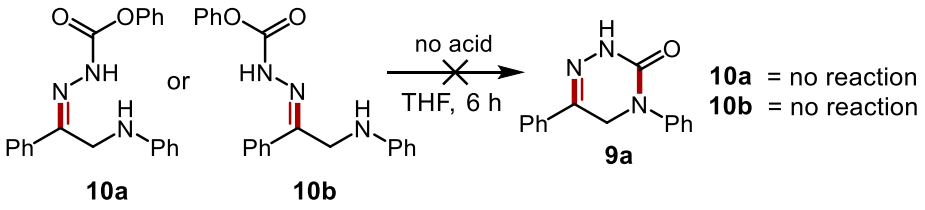
Finally, attempts at probing the mechanism of this cascade reaction were undertaken. In order to support the proposed mechanism, that is, intermolecular condensation followed by *N*-isocyanate formation and intramolecular cyclization, isolation of the α-aminocarbazone intermediate was sought. The reaction substrate **7a** was interrupted after one hour (scheme 2.8a). This resulted in the formation and isolation of both the *Z* (**10a**) and the *E* (**10b**) isomers of the desired α-aminocarbazone. These intermediates were separately submitted to the standard reaction conditions to probe their capacity to form product. Gratifyingly, both isomers were observed to form the desired 1,2,4-triazin-3(2H)-one, albeit in modest yield, supporting their role as intermediates in the reaction cascade (scheme 2.8b). Moreover, this demonstrates the ease with which *E*/*Z* isomerization occurs under the reaction conditions, as reaction monitoring indicated that both reactions looked identical by TLC shortly after the addition of citric acid.



Scheme 2.8: (a) Isolation of hydrazone intermediate. (b) Control experiments with hydrazone intermediate.

The effect of citric acid on the cyclization was also investigated. It was initially assumed that acid only benefited the initial condensation given the lack of formation of **10a** and **10b** in the absence of acid.

Moreover, given previous work using base catalysis to achieve *N*-isocyanate formation, it would be possible that acid impedes *N*-isocyanate formation. Unexpectedly, submitting both **10a** and **10b** to the standard reaction conditions without citric acid yielded starting material with no detectable product formed (scheme 2.9). This represents the first evidence of acid-promoted cyclization of blocked (masked) *N*-isocyanates. Moreover, the ease with which cyclization occurs is in sharp contrast to Ohwada's work presented in Chapter 1 where strong acids were necessary to achieve isocyanate formation.[155-158]



Scheme 2.9: Probing the effect of citric acid on the reaction

2.4 A Cascade Synthesis of Pyridazinones and Triazinones.

The incorporation of a pendant electrophilic motif as part of the *N*-isocyanate precursor had proven a powerful strategy for the synthesis of heterocycles such as azauracil, acyl pyrazole, and phthalazinones.[179] Expansion of this reactivity to incorporate ketone electrophiles was of interest, specifically with *N*-isocyanate precursors containing an α-ketohydrazone (scheme 2.10). Upon substitution with simple primary amines, such as system would allow for a subsequent intramolecular condensation, providing access to rare 1,2,4-triazinones bearing an exocyclic olefin. 1,2,4-Triazinones represent an important class of nitrogen containing heterocycles, epitomized by azauracils, which possess a broad range of biological activities.[201] In contrast, 1,2,4-triazinone targeted by this synthetic sequence are scarcely found in the literature, likely a consequence of their difficult syntheses.[202] Consequently, a novel cascade sequence accessing such derivates may prove highly valuable.

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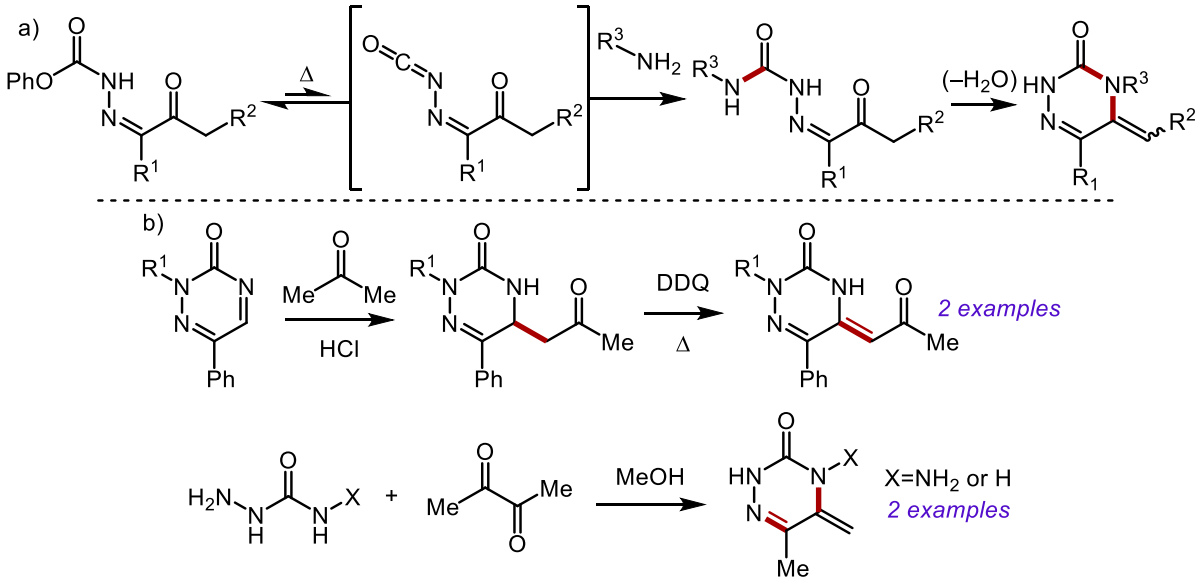
[201] For selected examples of azauracil bioactivity, see: (a) Majo, V. J.; Milak, M. S.; Prabhakaran, J.; Mali, P.; Savenkova, L.; Simpson, N. R.; Mann, J. J.; Parsey, R. V.; Dileep Kumar, J. S. *Bioorg. Med. Chem.* **2013**, *21*, 5598. (b) Dow, L. R.; Schneider, S. R.; Paight, E. S.; Hank, R. F.; Chiang, P.; Cornelius, P.; Lee, E.; Newsome, W. P.; Swick, A. G.; Spitzer, J.; Hargrove, D. M.; Patterson, T. A.; Pandit, J.; Chrunyk, B. A.; LeMotto, P. K.; Danley, D. E.; Rosner, M. H.; Ammirati, M. J.; Simons, S. P.; Schulte, G. K.; Tate, B. F.; DaSilva-Jardine, P. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 379. (c) Pontillo, J.; Guo, Z.; Wu, D.; Struthers, R. S.; Chen, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4363. (d) Rankovic, Z.; Cai, J.; Fradera, X.; Dempster, M.; Mistry, A.; Mitchell, A.; Long, C.; Hamilton, E.; King, A.; Boucharens, S.; Jamieson, C.; Gilespie, J.; Cumming, I.; Uitdehaag, J.; Van Zeeland, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1488.

[202] a) Paudler, W. W.; Lee, J*J. Org. Chem.* **1971**, *36*, 3921. (b) Rasmussen, A.; Rise, F.; Undheim, K. *Acta Chem. Scand.* **1985**, *39b*, 235. (c) Stanovnik, B.; Tisler, M.; Copar, A. *J. Heterocycl. Chem.* **1995**, *32*, 425. (d) Alekseyev, V. V.; Saminskaya, A. G.; Yakimovich, S. I. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2012**, *48*, 476.

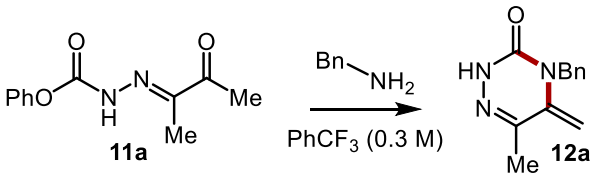


Scheme 2.10: Design of cascade synthesis of rare 1,2,4-triazinones.

Towards this end, Jean-François Vincent-Rocan began an optimimization with α-ketocarbazone **11a**, derived from *O*-phenyl carbazate and 2,3-butanedione (table 2.6). Encouraging results were observed early on, where benzyl amine readily reacted with the model substrate at 150 °C under microwave irradiation for 2 hours (entry 1). However, the desired product was only obtained in 34% yield with the remaining mass balance attributed to uncyclized semicarbazone. A higher yield was observed upon heating at 175 °C though severe degradation was observed upon heating at 200 °C with minimal uncyclized product remaining; thus 175 °C was chosen as the optimal temperature (entry 2-3). Both $MgSO_4$ and Et_3N proved to be beneficial additives (entry 4-5), while acetic acid resulted in near quantitative product formation (entry 6). Alternatively, the use of $MgSO_4$ for longer reaction times also provided the 1,2,4-triazinone in high yield (entry 7).[203]

[203] The use of microwave heating proved optimal. In contrast, conventional heating yielded product **12a** in 31% under conditions similar to entry 7, at reflux in 1,2-dichlorobenzene for 14 h.

Table 2.6: Optimization of 1,2,4-triazinone cascade[a]



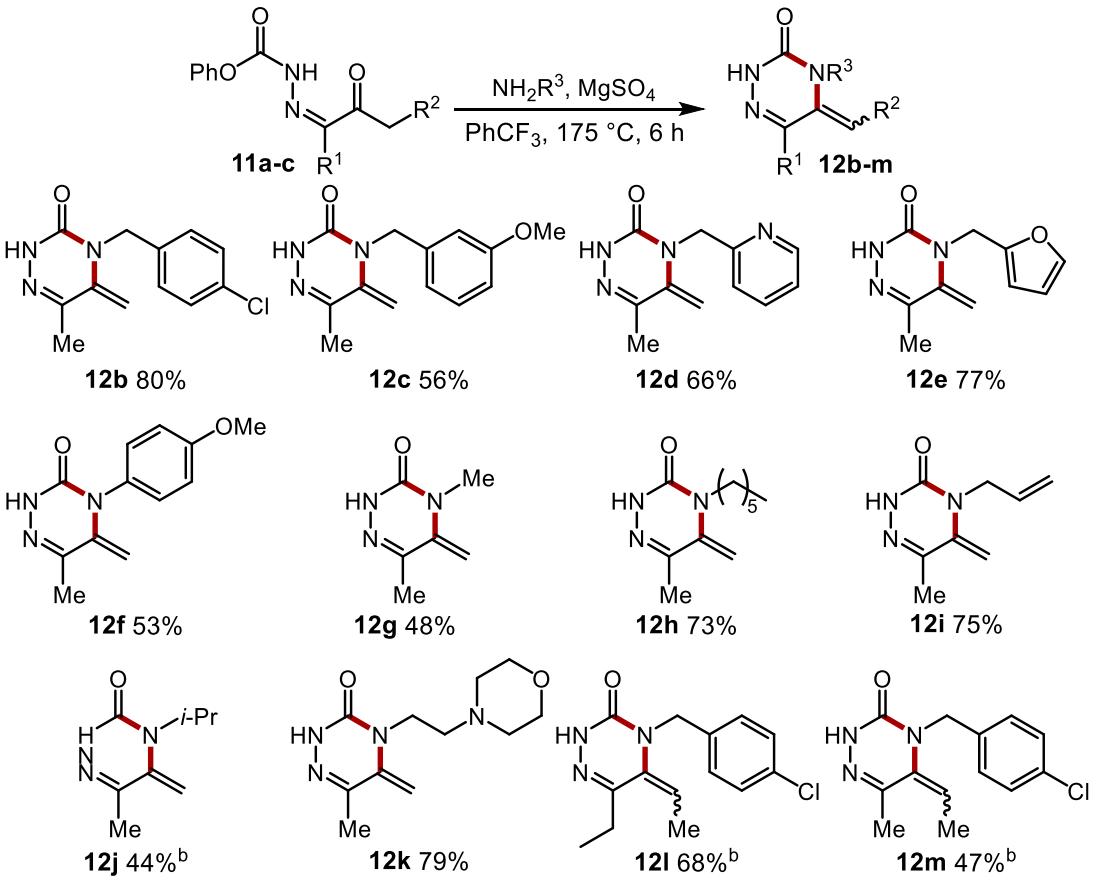
Entry	Temp (°C), time (h)	Additive	Yield (%)
1	150, 2	None	34
2	175, 2	None	44
3	200, 2	none	37
4	175, 2	$MgSO_4$[b]	56
5	175, 2	Et_3N[c]	64
6	175, 2	AcOH[c]	94
7	175, 2	$MgSO_4$[b]	87 (75)[d]

[a]Conditions: carbazone **11a** (0.2 mmol), $BnNH_2$ (1.1 equiv.), in $PhCF_3$ (0.3 M), heated in a microwave reactor and the indicated temperature. ^1H NMR yield based on 1,3,5-trimethoxybenzene internal standard. [b]1 equiv. [c]0.2 equiv. [d]Isolated yield.

With these conditions in hand, the scope of this new approach to form rare heterocycles was probed by Jean-François Vincent-Rocan. Unfortunately, it rapidly became apparent that conditions employing acetic acid led to functional group tolerance issues and reduced efficiency for the cascade. This likely results from the sensitive nature of the exocyclic alkene under acidic conditions. Thus, evaluation of the reaction scope relied on conditions using $MgSO_4$. A variety of primary amines were found to produce the desired triazinones, typically ranging from modest to good yields (table 2.7). The benzylamine- derived triazinone was isolated in 75% yield. Both electron-poor and electron-rich benzylic amines formed the desired product with moderate to good yield (**12b** and **12c**). The reaction conditions also allowed for heterocycle incorporation with both pyridinyl- (**12d**) and furanyl- containing triazinones (**12e**) being isolated in good yields. Despite reduced nucleophilicity, aniline could also be incorporated in this cascade though providing only modest yield (**12f**). Both short-chain (**12g**) and long-chain (**12h**) aliphatic amines afforded the desired products. In addition, allylamine was found to be a competent reaction partner (**12i**). Sterically demanding branched aliphatic amine (**12j**) also resulted in the desired triazinone product despite the necessity of higher reaction temperature. Basic moieties were also well tolerated, where a pendant morphline motif formed the desired product in good yield (**12k**). Reaction with α-ketocarbazones derived from different diones was also of interest. Fortunately, 3,4-hexanedione and 2,3-pentanedione

derived carbazones resulted in modest to good yields of the desired products **12l** and **12m**, albeit in a *E*/*Z* ratio of approximately 1:2.[204] Overall this report provides an efficient methodology to access a diverse library of rare 1,2,4-triazinones.

Table 2.7: Scope of 1,2,4-triazinone[a]



[a]Conditions: carbazone **11a-c** (0.6 mmol), amine (1.1 equiv.), $MgSO_4$ (1.0 equiv.), in $PhCF_3$ (0.3 M), heated in a microwave reactor for 6h at 175 °C. Isolated yields show. [b]Performed at 200 °C.

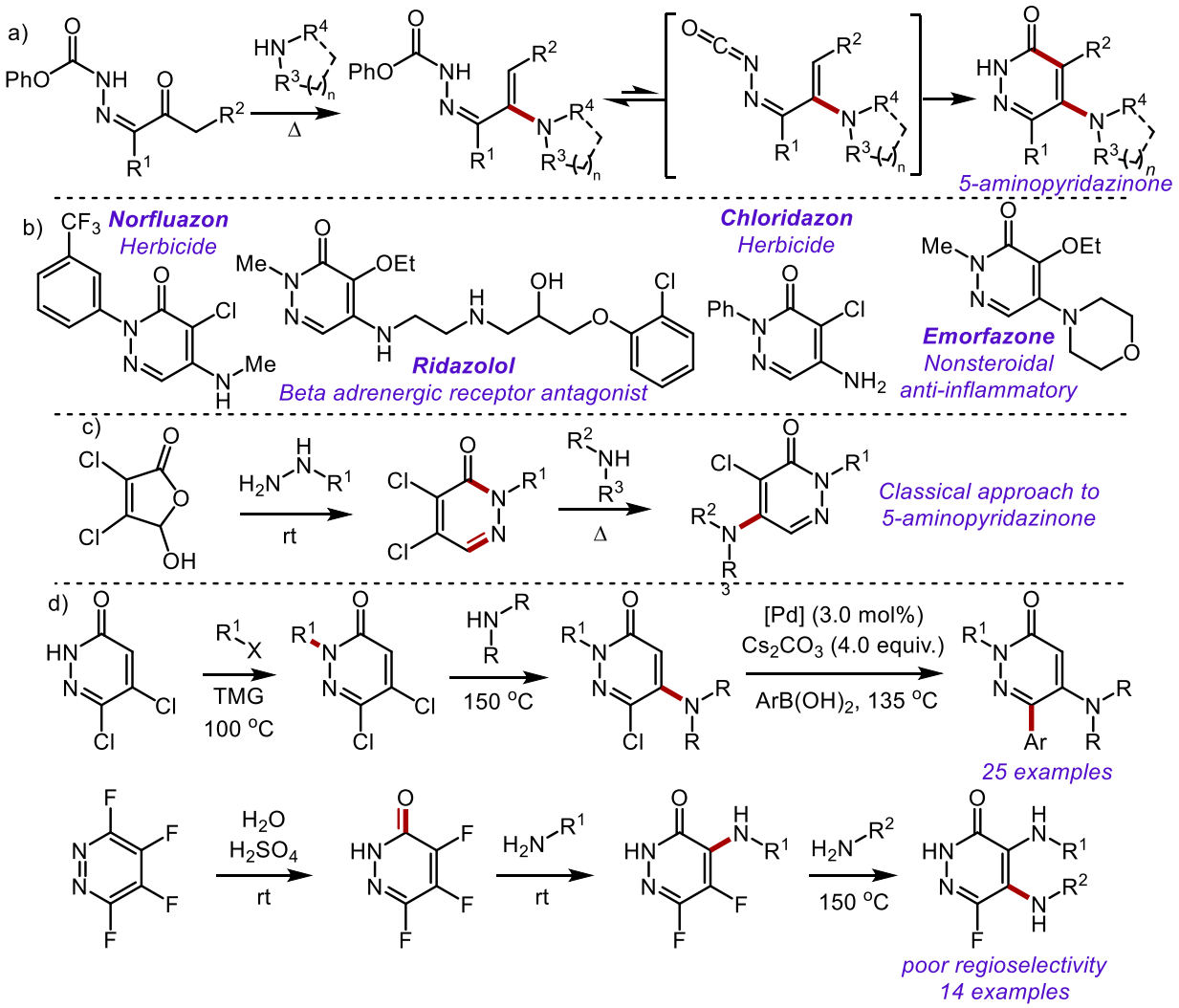
At this stage, the ability to harness this pendant electrophilic ketone, and transform it into a nucleophilic motif was appealing (scheme 2.11a). Specifically, the condensation of a secondary amine on the ketone would give rise to a nucleophilic enamine. Upon deblocking, cyclization of the enamine onto the *N*-isocyanate would provide access to highly valuable 5-aminopyridazinones. These heterocycles possess broad biological activities and are present in agrochemicals (e.g., norflurazon) as well as

[204] See supporting information for further details.

pharmaceuticals (e.g., emorfazone) (scheme 2.10b).[205] Novel pathways accessing these derivatives could prove highly valuable given the limited methodologies currently reported (scheme 2.11c, d).[206] Moreover, this work would provide the first example of carbon centred nucleophilic addition onto blocked *N*-isocyanate which have otherwise been limited to the addition of heteroatom nucleophiles.

[205] For selected publications on aminopyridazinone bioactivity, see: (a) Sotelo, E.; Fraiz, N.; Yanez, M.; Terrades, V.; Laguna, R.; Cano, E.; Ravina, E. *Bioorg. Med. Chem.* **2002**, *10*, 2873. (h) Kaminski, J.; Moo-Puc, R.; Cedillo-Rivera, R.; Kazimierczuk, Z. *Synth. Commun.* **2006**, *36*, 2719. (i) Wroblowski, B.; Wigglesworth, M. J.; Szekeres, P. G.; Smith, G. D.; Rahman, S. S.; Nicholson, N. H.; Muir, A. I.; Hall, A.; Heer, J. P.; Garland, S. L.; Coates, W. J. *J. Med. Chem.* **2009**, *52*, 818.

[206] For publications on aminopyridazinone synthesis, see: (a) Cao, P.; Qu, J.; Burton, G.; Rivero, R. A. *J. Org. Chem.* **2008**, *73*, 7204.(b) Pattison, G.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. *J. Org. Chem.* **2009**, *74*, 5533. (c) Estevez, I.; Ravina, E.; Sotelo, E. *J. Heterocyclic Chem.* **1998**, *35*, 1421. (d) Schober, B. D.; Megyeri, G.; Kappe, T. *J. Heterocycl. Chem.* **1990**, *27*, 471. (e) Karldury, D. *Angew. Chem.* **1960**, *72*, 864. (f) Pollak, A.; Tisler, M. *Tetrahedron* **1965**, *21*, 1323. (g) Landquist, J. K.; Thornber, C. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1114. (h) Fahmy, S. M.; Abed, N. M.; Mohareb, R. M.; Elnagdi, M. H. *Synthesis* **1982**, *1982*, 490. (i) Homer, R. F.; Gregory, H.; Wiggins, L. F. *J. Chem. Soc.* **1948**, 2191. (j) Marlow, A. L.; Wallace, E.; Seo, J.; Lyssikatos, J. P.; Yang, H. W.; Blake, J. US Patent 7,517,994 B2, Apr 14, 2009.



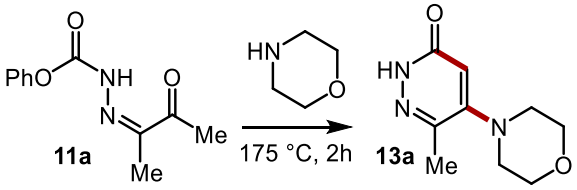
Scheme 2.11: a) Cascade synthesis of 5-aminopyridazinone using blocked *N*-isocyanate derivatives. b) Various bioactive 5-aminopyridazinone. c) Classical approach to 5-aminopyridazinone. d) Recent advancements in the accessing 5-aminopyridazinone.

Investigations towards the synthesis of 5-aminopyridazinones began using α-ketohydrazone **11a** (table 2.8). A potential impediment to the development of this synthetic sequence is the rapid addition of amine nucleophiles onto *N*-isocyanates, potentially sequestering the amine necessary for generating the enamine nucleophile and competing against the subsequent cyclization. Morpholine was chosen as model substrate given previous reports on morpholine derived semicarbazones undergoing substitution reactions at 100 °C.[207] Pleasingly, the desired aminopyridazinone was generated in 64% yield under microwave irradiation at 175 °C for 2.0 hours (entry 1). Notably, 3.0 equivalents of morpholine were

[207] Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074.

necessary to achieve efficient product formation. Furthermore, $MgSO_4$ and pivalic acid had minimal beneficial effects on the yield of the cascade individually (entry 2-3), though together they led to a high-yielding cascade for the formation of pyridazinone **13a** (entry 4).[208]

Table 2.8: Optimization of 5-aminopyridazinone cascade[a]



Entry	Additive	Yield (%)
1	None	64
2	$MgSO_4$[b]	66
3	PivOH[c]	73
4	PivOH[c] + $MgSO_4$[b]	83 (71)[d]

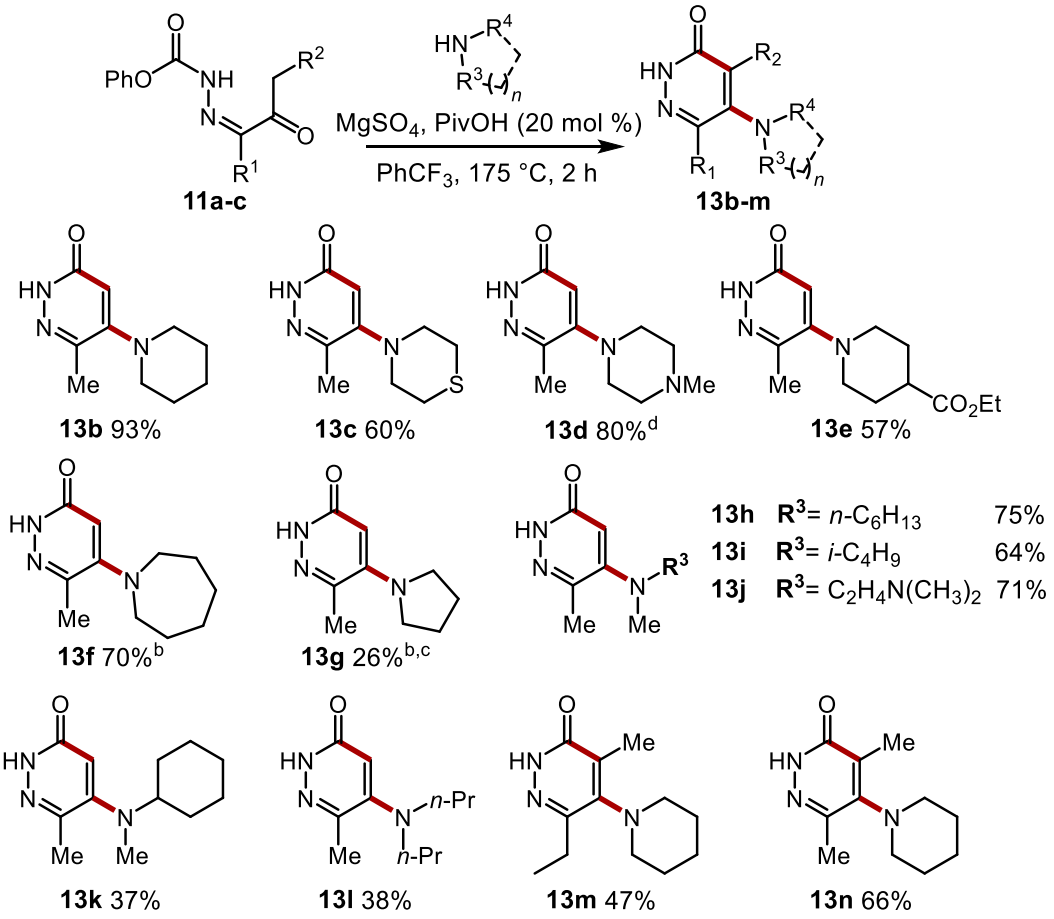
[a]Conditions: carbazone **11a** (0.2 mmol), morpholine (3.0 equiv.), in $PhCF_3$ (0.3 M), heated in microwave reactor at 175 °C. ^{1}H NMR yield based on 1,3,5-trimethoxybenzene internal standard. [b]1 equiv. [c]0.2 equiv. [d]Isolated yield.

The scope of this novel cascade was then explored with a variety of secondary amines (table 2.9). Cyclic amines, particularly 6-membered derivatives, proved optimal for this reaction. Morpholine (**13a**), piperidine (**13b**), and thiomorpholine (**13c**) proved to be competent reaction partners. *N*-Methylpiperazine (**13d**) was also well tolerated under the reaction conditions though required a slight increase in reaction time. Pleasingly, an ester functional group was compatible with the reaction conditions despite the presence of acid and excess amine (**13e**). The 7-membered heterocycle azepane also provided the desired product, although longer reaction time was again necessary (**13f**). In contrast, pyrrolidine-derived aminopyridazinone was only formed in modest yield even at increased temperature and reaction time (**13g**). Acyclic amines were also competent reaction partners with *N*-methylhexylamine (**13h**), *N*-methylisobutylamine (**13i**), and *N*,*N*,*N*'-trimethylethylenediamine (**13j**), affording the desired products in good yields. A decrease in reaction efficiency was observed upon increasing the steric bulk of the acyclic amine with both dipropylamine (**13k**) and *N*-methylcyclohexylamine (**13l**). Finally, the effect of masked *N*-isocyanates derived from alternative diones was also examined. Surprisingly, the 3,4-hexanedione derivative (**13m**) resulted in a significantly lower yield than the 2,3-pentanedione derivative

[208] The use of microwave heating proved optimal. In contrast, conventional heating yielded product **13a** in 23% under conditions similar to entry 4, at reflux in 1,2-dichlorobenzene for 14 h.

(**13n**). This was unexpected given the steric bulk at the nucleophilic carbon of the enamine remaining constant in both cases. Overall, this methodology was compatible with a broad scope of different amines and allowed access to alkyl-substituted 5-aminopyridazinones at the 4- and 6-positions.[206h,i] These are difficult to access with currently reported literature methods, which require lengthy multistep reaction sequences.

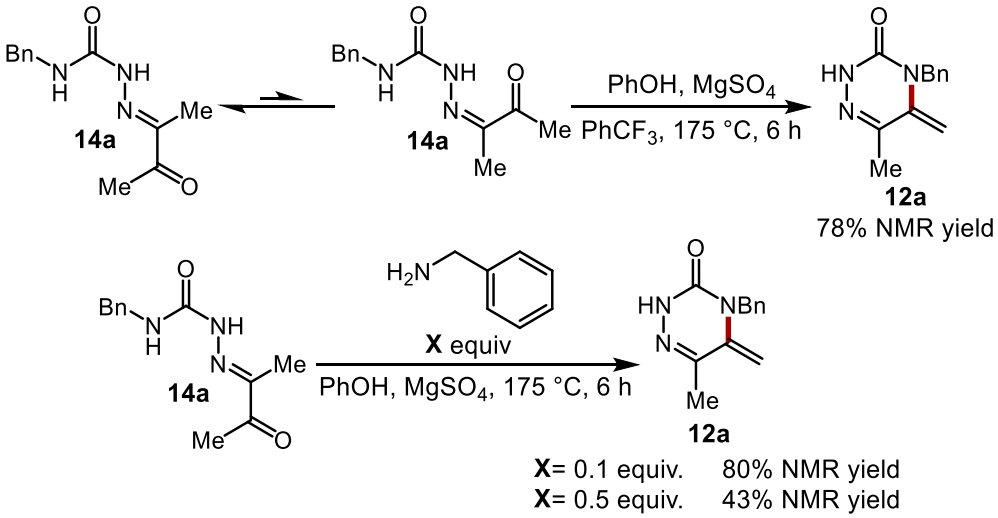
Table 2.9: Scope of 5-aminopyridazinone[a]



[a]Conditions: carbazone **11a-c** (0.6 mmol), amine (3.0 equiv.), $MgSO_4$ (1.0 equiv.), pivalic acid (0.2 equiv.), in $PhCF_3$ (0.3 M), heated in a microwave reactor for 2 h at 175 °C. Isolated yields are shown. [b]Performed at 200 °C for 6 h without acid. [c]NMR yield. [d]4 h, without $MgSO_4$.

Mechanistic investigations of this novel cascade reactivity were then undertaken. Toward this end, a likely intermediate in the triazinone forming cascade is semicarbazone **14a**, formed as a result of *N*-isocyanate deblocking followed by addition of benzylamine. Such intermediates have previously been reported to form at room temperature in related systems.[179] Semicarbazone **14a** was then subjected to

the conditions of the cascade reaction, and as expected, triazinone formation proceeded smoothly to form triazinone **12a**, in a similar yield to that of the direct reaction from carbazone **11a** (scheme 2.12). It is also noteworthy that semicarbazone **14a** exists exclusively as the *E*-isomer in solution, thus efficient cyclization implies isomerization to the *Z*-isomer occurs under the reaction conditions.[209] While this result supports the formation of **12a** through direct condensation of **14a** on the carbonyl, an alternative involving cyclization of an enamine onto the *N*-isocyanate is also plausible. To probe this possibility, cyclization of intermediate **14a** was attempted in the presence of excess benzylamine, which would be required for enamine formation. Interestingly, the addition of benzylamine was observed to inhibit product formation. Overall, these results support the feasibility of initial substitution with the primary amine forming the semicarbazone, followed by intramolecular condensation on the pendant ketone [179] These mechanistic experiments were carried out by Jean-François Vincent-Rocan.



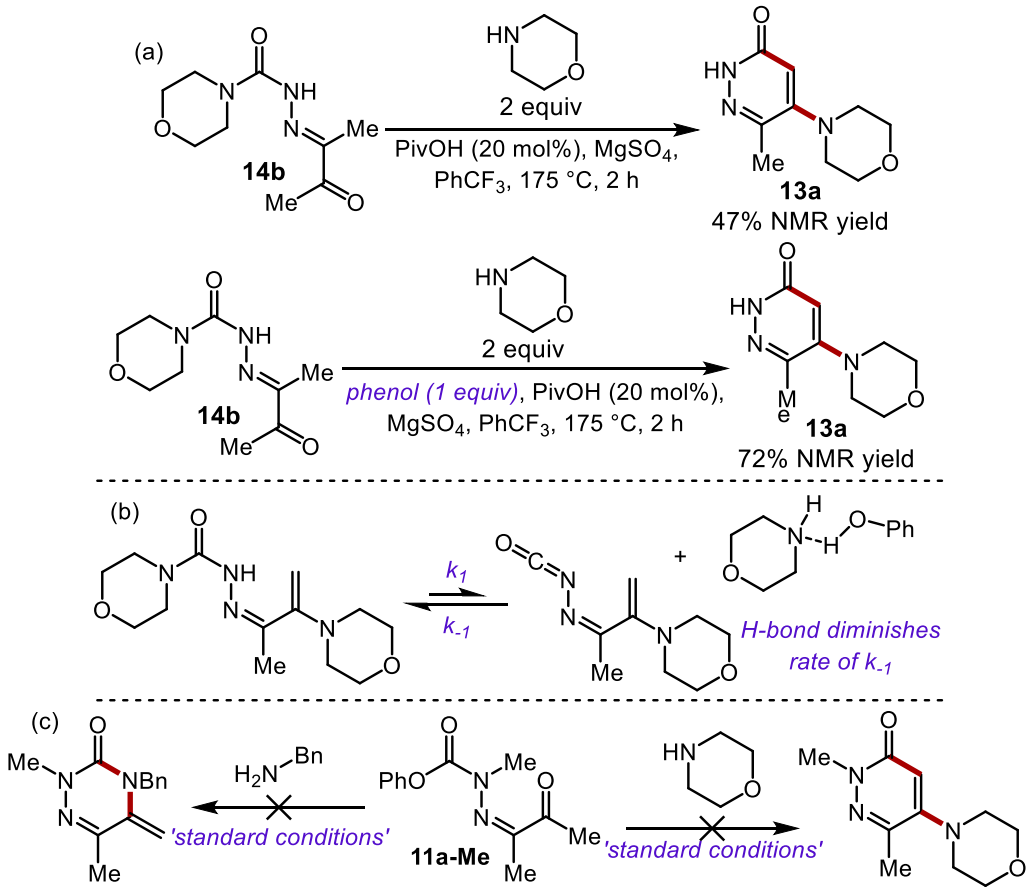
Scheme 2.12: Mechanistic investigation of 1,2,4-triazinone cascade.

To probe the intermediacy of the related morpholine derived semicarbazone **14b** in the cascade synthesis of 5-aminopyridazinone derivatives, semicarbazone **14b** was synthesized and subjected to the reaction conditions (scheme 2.13a). In this case, a lower yield was obtained in contrast to the standard reaction conditions on carbazone **11a**. This may suggest that condensation to form the enamine occurs directly on carbazone **11a**, prior to morpholine substitution forming **14b**; however, this is highly unlikely given the high loadings of amine required and the ability of morpholine to form **14b** at room temperature. Therefore, a control reaction with the addition of phenol was carried out to replicate the standard reaction

[209] See supporting information for more details.

conditions more closely. Interestingly, a significant increase in yield (72%) was observed, showing that efficient product formation can occur from intermediate **14b**. Furthermore, this provides the first evidence of a blocking group playing a dual role in controlling the reactivity of blocked *N*-isocyanates. The beneficial effect of phenol on reaction efficiency is not yet understood. Its ability to shift the equilibrium towards the unblocked *N*-isocyanate is one potential explanation where its ability to hydrogen bond the basic amine would be expected to slow the rate of k_{-1} (scheme 2.13b). Moreover, this hypothesis also takes into account the lack of effect phenol had on the triazinone cascsade, where deblocking from a semicarbazone intermediate was found to be unlikely. Finally, control experiments carried out by Jean-François Vincent-Rocan employing *N*-methylated precursors support the involvement of a *N*-isocyanate intermediate (scheme 2.13c).[210] This methylated derivative would lose the ability to form the requisite *N*-isocyanate intermediate while having minimal impact on the ability to undergo addition elimination pathway, especially at such high temperatures.

[210] See supporting information for details on the synthesis of these precursors and the various reactions run which support the involvement of an *N*-isocyanate intermediate.



Scheme 2.13: a) Mechanistic investigation of 5-aminopyridazinone cascade. b) Proposal for beneficial effect of phenol. c) Supporting the involvement of an *N*-isocyanate intermediate.

2.5 Conclusion and Perspective

In conclusion, several novel cascade reactions of *N*-isocyanates were developed from simple precursors. The main conceptual advancements drawn from these works include: 1) the ability to expand cascade reaction of *N*-iso(thio)cyanate derivatives to incorporate unactivated electrophiles observed in the synthesis of imidazolones and thiazolidines, 2) expansion of the reactivity manifold to incorporate the *in situ* formation of complex azomethine imine species from *N*-isothiocyanate derivates, 3) the first cascade where successful product formation did not hinge on an initial substitution reaction with an amine nucleophile in the case of 1,2,4-triazin-3(*2H*)-ones, 4) the first example of an *N*-isocyanate cascade reaction relying on acid-catalysis, in stark contrast to previous work which generally relied on base-catalysis, 5) initial insights on the presence of *E*/*Z* isomerization events as a prerequisite for successful product formation, 6) the first cascade reaction of blocked *N*-isocyanates relying on the addition of a carbon nucleophile, 7) the first evidence of the blocking group playing an beneficial secondary role under

the reaction conditions. Moreover, these novel synthetic methodologies provide access to heterocydes which are rarely found in the literature (e.g. 1,2,4-triazinones) and/or are characterized by limited synthetic reports providing access to them (e.g. 5-aminopyridazinone, 1,2,4-triazinone, 1,2,4-triazin-3(*2H*)-one).

Chapter 3: Development of Carbon-Based Nucleophilic Addition to Blocked *N*- and *O*-Isocyanates

3.1 Introduction

The development of bench stable blocked *N*- and *O*- isocyanate derivatives has proven a fruitful platform for the synthesis of a variety of important compounds bearing the N-N-C=O or O-N-C=O motifs. However, a major limitation remains the inability to utilize these precursors as a general platform to access hydrazide and hydroxamate derivatives through the addition of carbon nucleophiles. Such reactivity of blocked *N*-isocyanates has remained strictly limited to the generation of specific heterocycles, namely arising from cycloaddition reactions[177-178] or the formation of 5-aminopyridazinone.[211] Moreover, the reactivity of blocked *O*-isocyanates is currently fully restricted to heteroatom nucleophiles. Given the broad biological activities exhibited by both hydrazides[212] and hydroxamic acid/hydroxamate derivatives,[213] the development of general procedures providing access to these functional groups from blocked precursors could prove highly valuable to the synthetic community (figure 3.1).

[211] Derasp, J. S.; Vincent-Rocan, J.-F.; Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 658.
[212] Le Goff, G.; Ouazzani, J. *Bioorg. Med. Chem.* **2014**, *22*, 6529.
[213] (a) Pal, D.; Saha, S. *J. Adv. Pharm. Techol. Res.* **2012**, *3*, 92. (b) Bertrand, S.; Helesbeux, J.-J.; Larcher, G.; Duval, O. *Mini Rev. Med. Chem.* **2013**, *13*, 1311.

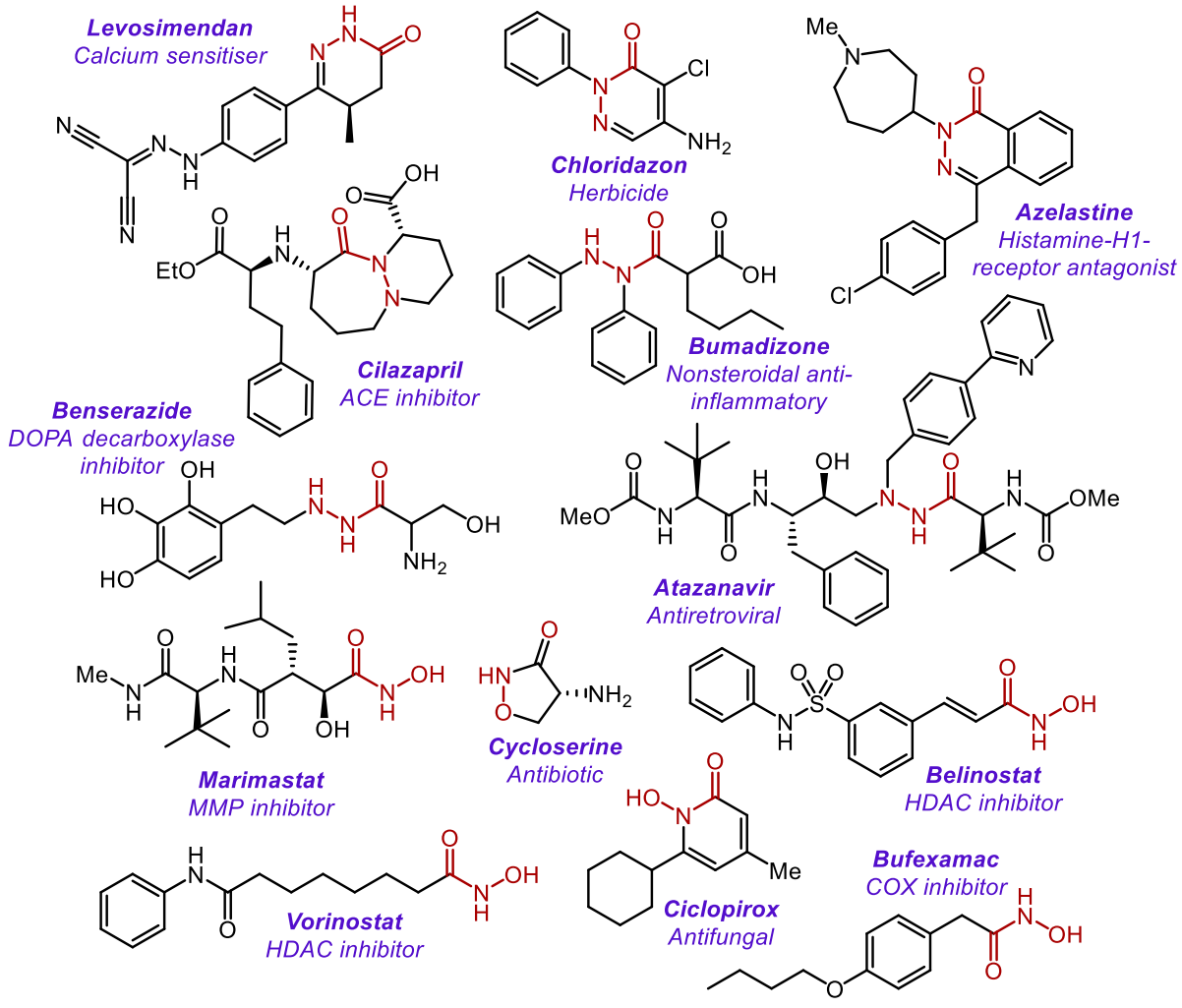
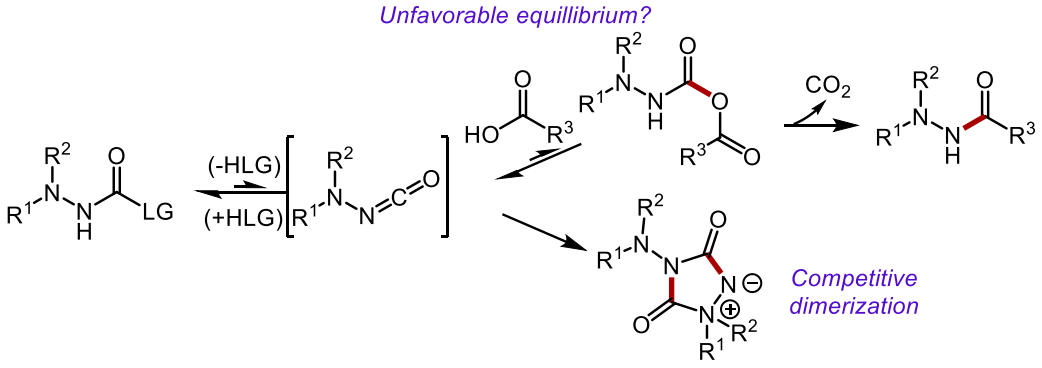


Figure 3.1: Various biologically active hydrazide and hydroxamic acid derivatives

3.2 Carboxylic Acids as Formal Carbon Nucleophiles

To achieve such a goal, inspiration was garnered from the isocyanate amidation literature. The use of carboxylic acids as formal carbon nucleophiles (see section 1.2.1) was an attractive methodology for 2 main reasons; 1) the successful developments of *N*- and *O*-isocyanates have largely relied on protic nucleophiles, thus remaining within the expertise of the Beauchemin lab, 2) the mild reaction conditions reported to achieve amide bond formation from blocked[150] and unblocked[8,9] derivatives. However, the propensity of *N*- and *O*-isocyanates to undergo oligomerization reactions in the absence of strong nucleophiles was of particular concern for the success of such a strategy (scheme 3.1). This is most starkly illustrated in intermolecular cycloadditions of *N*-isocyanates, where olefins are generally employed in large excess to achieve high yields of the desired cycloadduct.[178] Consequently, the wide-ranging success

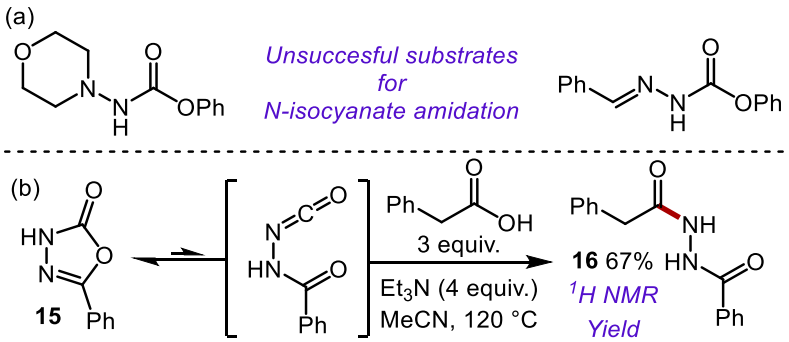
of various substitutions/cascades using blocked *N*- and *O*-isocyanate have relied on the use of strong nucleophiles such as amines, which largely mitigate any undesired oligomerization.



Scheme 3.1: Carboxylic acids as formal carbon nucleophiles with blocked *N*-Isocyanates

Nevertheless, investigations began by probing the ability of blocked *N*-isocyanates to form hydrazides using carboxylic acids. Initially, both hydrazide and hydrazone derived blocked *N*-isocyanate precursors were targeted(scheme 3.2a). A variety of reaction conditions were tested with variations in temperature, base loading, substrate equivalency, with no desired product formation observed. Attention was then focused on oxadiazolones as a potential platform to form hydrazide derivatives. Recent studies in the Beauchemin group have suggested these precursors are in fact heterocyclic blocked *N*-isocyanate precursors.[214] However, unlike their non-heterocyclic counterpart, these derivatives are highly stable to oligomerization as a result of their aromatic character. Pleasingly, upon heating oxadiazolone **15** at 120 °C in MeCN in the presence of excess Et_3N, the desired product **16** was formed with an NMR yield of 67% (scheme 3.2b). However, isolation of this species from the reaction mixture proved problematic resulting in only 33% isolated yield. The optimization of this reaction is currently being conducted by William Monfette, a fellow graduate student, and Owen Lutes, an undergraduate student.

[214] Manuscript currently in preparation.



Scheme 3.2: (a) Initial attempts to amidate amino- and imino-substituted isocyanate derivatives. (b) Successful application of oxadiazolone precursors in *N*-isocyanate amidation.

Attention was then focused on achieving similar reactivity on *O*-substituted isocyanates. Analogous to their *N*-substituted counterparts, *O*-isocyanates exhibit an intrinsic propensity for oligomerization (especially trimerization) and have thus far been limited to cascades making use of strong protic nucleophiles (see section 1.5.5). However, the use of *O*-isocyanates as a platform for hydroxamate/hydroxamic acid synthesis is highly attractive. As described above, these functional groups display potent biological activity, along with applications ranging from synthetic intermediates[215] to chiral ligand backbone.[216] However, advancements in the synthesis of these potent functional groups remain lacking (scheme 3.3). Recent developments have focused on oxidative strategies, converting alcohols,[217] aldehydes,[218] or oximes[219] to the corresponding hydroxamate/ hydroxamic acid. Although innovative, these strategies are characterized by limited functional group tolerance. The direct transformation of unactivated esters to hydroxamates/hydroxamic acids has also been explored although generally require either strong bases, protic conditions, or large excess of the hydroxyl amine nucleophile which typically limit functional group tolerance.[220] Consequently, the most common methodology employed to access hydroxamates/ hydroxamic acids remains stoichiometric activation of carboxylic acids.

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[215] For a recent review on hydroxamate directing groups, see: Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578. For a recent review of hydroxamates as synthetic intermediates, see: Pirnot, M.; Wang, Y.-M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 48.

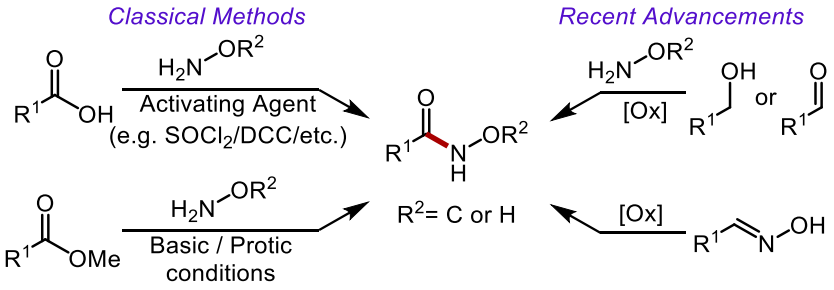
[216] (a) Li, Z.; Yamamoto, H. *Acc. Chem. Res.* **2013**, *46*, 506. (b) Xioa, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138.

[217] Dettori, G.; Gaspa, S.; Porcheddu, A.; De Luca, L. *Org. Biomol. Chem.* **2014**, *4582*.

[218] (a) De Luca, L.; Porcheddu, A.; Gaspa, S.; Dettori, G. *Adv. Synth. Catal*. **2014**, 356, 2709. (b) Papadopoulos, G. N.; Kokotos, C. G. *Chem. Eur. J.* **2016**, *22*, 6964.

[219] Ghosh, H.; Patel, B. K. *Org. Biomol. Chem.* **2010**, *8*, 384.

[220] (a) Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Galemmo Jr., R. A. *J. Org. Chem.* **2005**, *70*, 4873. (b) Gissot, A.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 6925. (c) Riva, E.; Gagliardi, S.; Mazzoni, C.; Passarella, D.; Rencurosi, A.; Vigo,

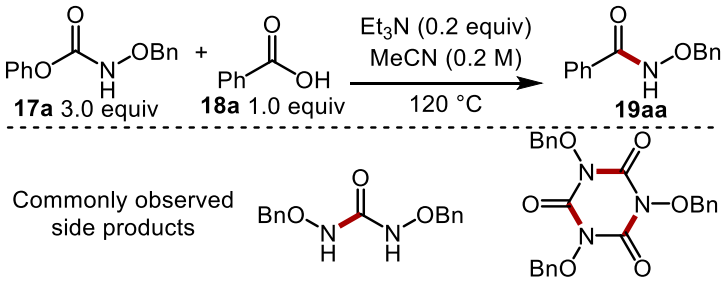


Scheme 3.3: Prior art in synthesis of hydroxamates/hydroxamic acids.

Towards this end, blocked *O*-isocyanate precursors provide a promising platform for the synthesis of hydroxamates which circumvents the need for stoichiometric activation of the carboxylic acid. The optimization of this reaction was largely conducted by Nièv e Séguin an undergraduate student under my supervision. Phenol blocked *O*-isocyanate **17a** with benzoic acid **18a** was chosen as the model reaction (table 3.1). Near quantitative yield of **19aa** was obtained using 3.0 equivalents of **18a** with 0.2 equivalents of Et_3N in acetonitrile at 120 °C (entry 1). Reducing the loading of **17a** to 2.0 equivalents had no effect on the reaction (entry 2), but a further reduction to 1.5 equivalents resulted in a lower yield (entry 3). This is attributed to the competitive oligomerization of the *O*-isocyanate forming isocyanurate trimers compounded by the formation of urea by-products, arising from hydrolysis. Both the absence of base or the use of excess base was detrimental to the reaction (entry 4-5) highlighting the importance of controlled *O*-isocyanate release. Moreover, employing acidic conditions also proved ineffective providing no desired product (entry 6). Reducing the temperature to 82 °C resulted in a much more sluggish reaction (~5 h to 48 h) although little effect on the yield was observed (entry 7). In cases where the blocked derivative is of greater value than the carboxylic acid partner, using the blocke d derivative as the limiting reagent would be highly desirable. Reversing the equivalency of **17a** and **18a** did form the desired product, although a significant reduction in yield was observed (entry 8). Notably, a 75% yield was attainable when employing 1.5 equivalents of carboxylic acid and 0.5 equivalents of Et_3N.

D.; Martinelli, M. *J. Org. Chem.* **2009,** *74*, 3540. (d) Beillard, A.; Bhurruth-Alcor, Y.; Bouix-Peter, C.; Bouquet, K.; Chambon, S.; Clary, L.; Harris, C. S.; Millois, C.; Mouis, G.; Ouvry, G.; Pierre, R.; Reitz, A.; Tomas, L. *Tetrahedron Lett.* **2016**, *57*, 2165.

Table 3.1: Optimization of *O*-isocyanate amidation[a]

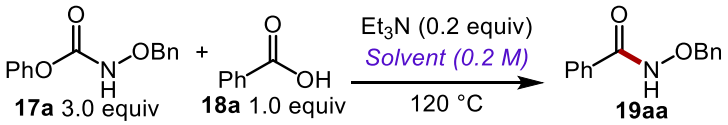


Entry	Deviation from optimized conditions	Yield (%)
1	None	>99
2	2.0 equivalents of **17a**	>99
3	1.5 equivalents of **17a**	85
4	No base	9
5	1.2 equivalents of Et_3N	87
6	No Et_3N, 0.2 equivalent of PTSA	0
7	Reflux instead of 120 °C	>99
8	1.0 equivalent of **17a**/ 3.0 equivalent of **18a**	63

[a]Conditions: **17a** (0.6 mmol), **18a** (0.2 mmol), Et_3N (0.04 mmol), MeCN (0.2 M), 120 °C unless otherwise noted. ^1H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.

Different solvents were then probed for their ability to promote the desired transformation (table 3.2). Non-polar solvents such as THF and toluene (entry 2-3) were observed to significantly hinder the desired reaction while polar aprotic solvent such as DMSO and MeCN (entry 3-4) proved much more efficient, with the latter being the best. The favorable reactivity observed in polar aprotic solvent could result from 2 main factors: 1) the ability of polar aprotic solvents to promote isocyanate release, 2) the ability of polar aprotic solvents to stabilize the 4-membered transition state leading to product. This latter point is supported by the fact that in early reports using non-polar solvent generally high temperature were required, while Crich's most recent procedure achieved room temperature activity in DMF.[9]

Table 3.2: Solvent scan[a]



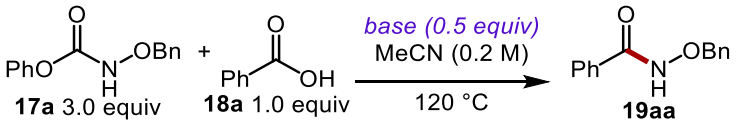
Entry	Solvent	Yield (%)
1	THF	42
2	Toluene	58
3	DMSO-d_6	81
4	MeCN	>99

[a]Conditions: **17a** (0.6 mmol), **18a** (0.2 mmol), Et_3N (0.04 mmol), solvent (0.2 M), 120 °C. ^1H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.

The effect of different bases on the reaction efficiency was then probed (table 3.3). These reactions were carried out using 0.5 equivalents of the base to simplify reaction setup. A range of alternative tertiary amine bases were found to be largely competent for the transformation including Et_3N (entry 1), DIPEA (entry 2), TMEDA (entry 3), and *N*-methylmorpholine (entry 4). In contrast, DBU proved a poor choice for the transformation (entry 5), however given the reasonable performance of K_2CO_3 (entry 6), its increased basicity is unlikely the cause of this poor reactivity, which may in fact result from unwanted reactivity with the isocyanate species.[221]

[221] Polenz, I.; Laue, A.; Uhrin, T.; Ruffer, T.; Lang, H.; Schmidt, F. G.; Spange, S. *Polym. Chem.* **2014**, *5*, 6678.

Table 3.3: Base scan[a]

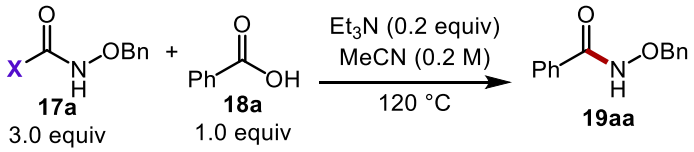


Entry	Base	Yield (%)
1	Et_3N	>99
2	DIPEA	>99
3	TMEDA	98
4	*N*-methylmorpholine	93
5	DBU	48
6	K_2CO_3	88

[a]Conditions: **17a** (0.6 mmol), **18a** (0.2 mmol), base (0.1 mmol), MeCN (0.2 M), 120 °C. ^{1}H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.

Finally, the effect of the blocking group was probed (table 3.4). It was hypothesized that the kinetic regime governing the reactivity in this system may be characterized by a highly dynamic pre-equilibrium, largely favoring the phenol blocked starting material. Consequently, varying the blocking group could significantly impact the position of this equilibrium and its dynamic nature, in turn affecting the rate of by-product formation under the reaction conditions. Prior work in the Beauchemin lab has shown the potential for simple alcohols to act as blocking groups on *O*-isocyanates.[172] Unfortunately, both *O*-tert butyl (entry 1) and *O*-ethyl blocked derivates (entry 2) were found to be completely inert under the reaction conditions. Alternatively, *p*-nitro phenol (entry 3) was also tested as a leaving group in hopes of achieving more efficient reactivity under milder reaction conditions. However reaction efficiency was found to dramatically decrease with significant amounts of by-product formation observed.

Table 3.4: Blocking group scan[a]



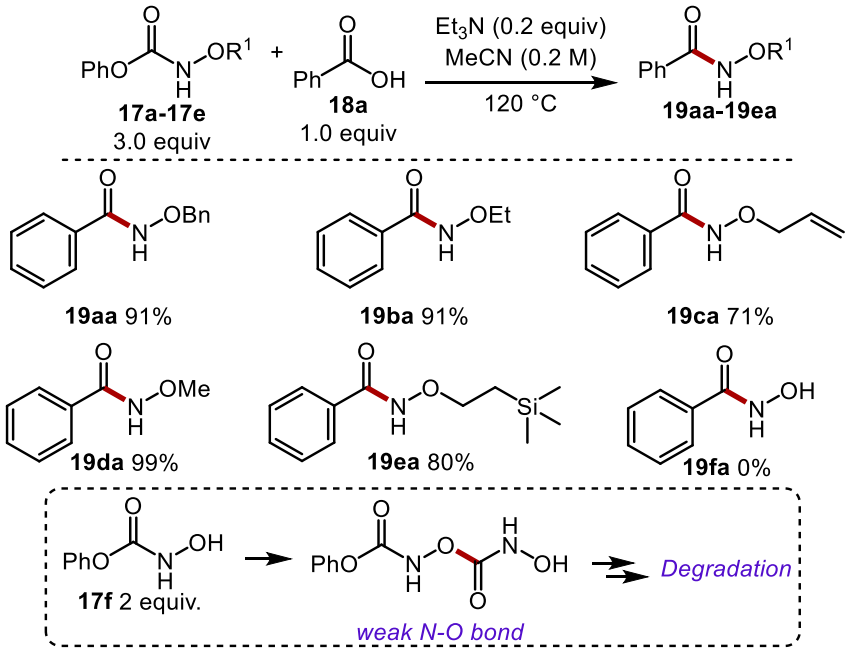
Entry	Blocking group (X)	Yield (%)
1[b]	O*t*-Bu	0
2[b]	OEt	0
3[c]	$OC_6H_4(4\text{-}NO_2)$	46
4	OPh	>99

[a]Conditions: **17a** (0.6 mmol), **18a** (0.2 mmol), Et_3N (0.04 mmol), MeCN (0.2 M), 120 °C. ^1H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard. [b]O-Ethyl hydroxylamine derived starting material. [c]Reaction run at 80 °C with O-methyl hydroxylamine derived starting material.

With these optimized conditions in hand, attention was focused towards the scope of this novel transformation (table 3.5). The scope of this transformation was largely conducted by Erica Barbera, an undergraduate honours student under my supervision. The optimized substrate was readily isolated on 0.6 mmol scale in 91% yield (**19aa**). A variety of substituted *O*-isocyanates were found to form the desired hydroxamates in good yield (**19ba**-**19ea**). Unfortunately, blocked derivatives bearing the free OH proved unsuccessful under a variety of reaction conditions (**19fa**). Prior work probing substitution on these derivates revealed the importance of using strong nucleophiles.[171-172] Competitive addition of the free OH onto the *O*-isocyanate forms a hydroxamate derivative with an exceptionally weak N-O bond, inevitably undergoing Lossen type degradation pathway (table 3.5).[222]

[222] For examples of Lossen rearrangement of hydroxamic acids, see: (a) Hoshino, Y.; Okuno ,M.; Kawamura, E.; Honda, K.; Inoue, S. *Chem. Commun.* **2009**, *2281.* (b) Jasikova, L.; Hanikyrova, E.; Skriba, A.; Jasik, J.; Roithová, J. *J. Org. Chem.* **2012**, *77*, 2829. (c) AbdelHafez, E.-S. M. N.; Aly, O. M.; Abuo-Rahma, G. E.-D. A. A.; King, S. B. *Adv. Synth. Catal.* **2014**, *356,* 3456. (d) Strotman, N. A.; Ortiz, A.; Savage, S. A.; Wilbert, C. R.; Ayers, S.; Kiau, S. *J. Org. Chem.* **2017**, *82*, 4044.

Table 3.5: Scope of *O*-isocyanate partner[a]

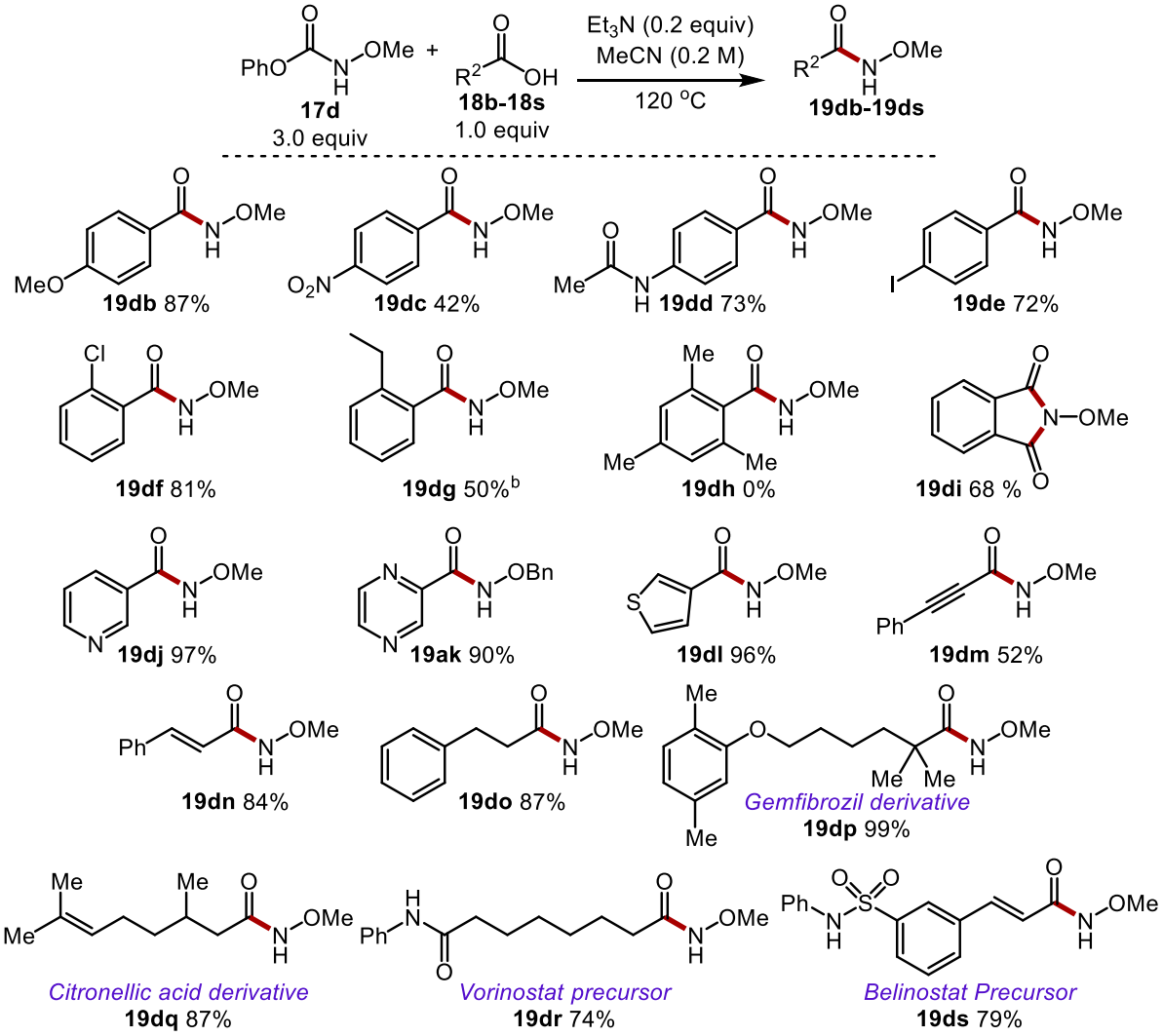


[a]Conditions: **17a-e** (1.8 mmol), **18a** (0.6 mmol), Et_3N (0.12 mmol), MeCN (0.2 M), 120 °C. Isolated yields are shown.

The scope of the carboxylic acid coupling partner was then explored with the *O*-methyl blocked precursor (table 3.6). Both electron-rich (**19db**) and electron-poor (**19dc**) benzoic acid derivatives were amenable to the transformation, though the latter proved lower yielding. A benzoic acid derivative bearing a protic acetamide motif was a competent reaction partner (**19dd**). Pleasingly, derivatives bearing halides were readily accessed providing a functional group handle for further derivatization (**19de**-**19df**). Substrates bearing increased steric hinderance at the ortho position were also probed where a precipitous decline in reactivity was observed with *o*-ethyl (**19dg**) and the complete loss of reactivity when employing mesityl derived carboxylic acid (**19dh**). Interestingly, the use of phthalic acid was amenable to the transformation where subsequent cyclization to the alkoxy substituted phthalimide was observed (**19di**). A variety of heterocyclic derivatives were competent reaction partners under the conditions despite the potential liability that Lewis basic motifs introduce with respect to isocyanate oligomerization (**19dj**-**19dl**). Surprisingly, both phenyl propiolic acid (**19dm**) and cinnamic acid (**19dn**) provided access to the desired products, while Michael addition type by-products arising from hydroxylamine release were not detected under the reaction conditions. The use of alkyl carboxylic acids was also explored. Phenylpropionic acid (**19do**) and Gemfibrozil (**19dp**) were competent reaction partners, in spite of the increased steric demand of the latter. Citronellic acid was readily employed providing the hydroxamate derivative in good yield (**19dq**). Finally, the applicability of this strategy was displayed by targeting the synthesis of

pharmaceutically relevant compounds where precursors to both Vorinostat (**19dr**) and Belinostat (**19ds**) were formed in high yields.

Table 3.6: Scope of the carboxylic acid partner[a]



[a]Conditions: **17d** (1.8 mmol), **18b-18s** (0.6 mmol), Et_3N (0.12 mmol), MeCN (0.2 M), 120 °C. Isolated yields are shown. [b] Compound isolated with urea by-product. Yield calculated by ^1H NMR.

Unfortunately, a variety of substrates were not amenable to this novel hydroxamate synthesis (figure 3.2). Several substrates bearing protic motifs proved problematic reaction partners. Surprisingly, benzoic acid derivates bearing free phenolic OH were not amenable to the transformation. Electron poor aromatic rings bearing halides failed to provide the desired product; however, no by-products arising from unwanted S_NAr type reactivity was observed. Finally, substrates bearing ketone functionality readily formed oximes by reacting with hydroxylamine released from unwanted hydrolysis.

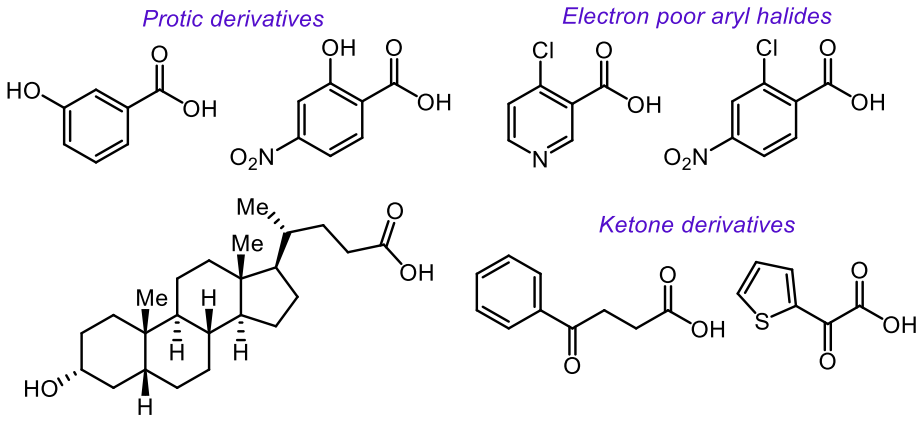
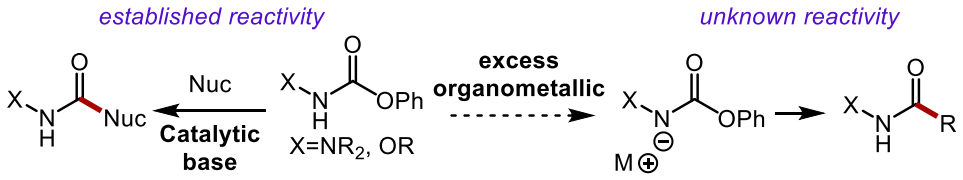


Figure 3.2: Failed substrates

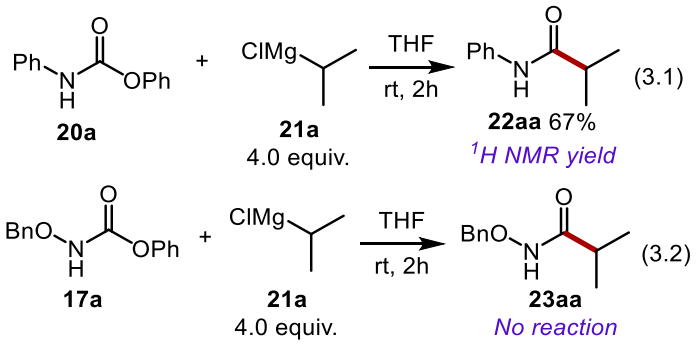
3.3 Grignard Reagents as Carbon Nucleophiles.

As described in the introduction of this document, the direct addition of various organometallic reagents onto isocyanates readily provide amide products (see section 1.2.4). Conceptually, such a methodology could be extended to encompass both the synthesis of hydrazides and hydroxamates using blocked *N*- and *O*-isocyanate precursors (scheme 3.4). However, a major concern introduced through the use of highly reactive organometallics is their basicity. Thus far, both *N*- and *O*- substituted isocyanates have been observed to undergo base-mediated deblocking, generally requiring only catalytic amounts of the base. In contrast, achieving C-C bond formation using organometallic reagents such as Grignard reagents would necessitate superstoichiometric amounts of such compounds, resulting in full deprotonation of the blocked precursor, which may subsequently result in uncontrolled reactivity.



Scheme 3.4: Development of stoichiometric organometallic addition to blocked *O*- or *N*-substituted isocyanates

Indeed, a control reaction on phenol blocked derivative **20a** derived from phenyl isocyanate suggests deblocking under such conditions is exceptionally facile, where the complete consumption of the starting material was observed in 2 hours, providing an unoptimized 67% yield of the amide product **22aa** (eq. 3.1). In stark contrast, submitting blocked *O*-isocyanate precursor **17a** to these same reaction conditions reveals no product formation with mostly unreacted starting material (eq. 3.2).

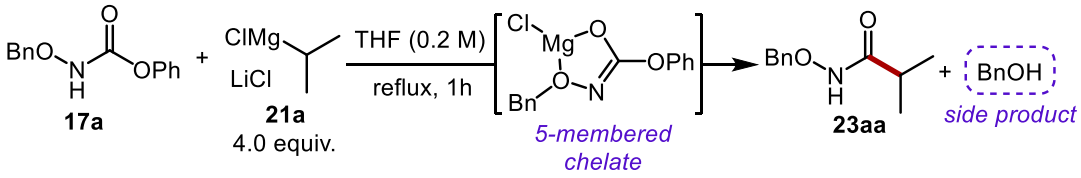


Given these above results, it was hypothesized that *O*-isocyanate generation from blocked precursor **17a** is fundamentally different than its *C*-substituted counterpart (**20a**), possibly due to the formation of a stable 5-membered chelate upon deprotonation (table 3.7). This stable chelate could explain the reluctance of such a species to generate the desired *O*-isocyanate species. Pleasingly, after extensive optimization, largely conducted by Kwame Agyei, an undergraduate honors student under my supervision, the desired product (**23aa**) was obtained in 85% yield while refluxing in the presence of excess turbo Grignard reagent (table 3.7, entry 1). Notably, the formation of benzyl alcohol under the reaction conditions was observed and confirmed by spiking the reaction with benzyl alcohol. The generation of benzyl alcohol strongly suggest the presence of a deleterious Lossen rearrangement, although reports of non-activated substrates undergoing this rearrangement are limited to hydroxamic acid derivatives.[222] Alternatively, an S_N2 type pathway, similar to that reported in recent amination studies, could be envisioned.[223] However, the high kinetic acidity of these blocked derivatives is expected to hinder such a pathway. Increasing the reaction time to 2 hours led to a slight decrease in yield (entry 2) while a dramatic loss of product formation was observed upon refluxing the reaction overnight (entry 3). These results strongly suggest the degradation of the product under the reaction conditions. Notably, increased degradation also resulted in decreased formation of benzyl alcohol. This counterintuitive result suggests that the formation of the benzyl alcohol under the reaction conditions does not play a benign role, and could subsequently undergo further nucleophilic reactivity; however, no such by-products were identified throughout the course of the optimization. The role of the lithium chloride was then probed where a significant reduction in yield was observed upon employing the non-turbo Grignard (entry 4). The increased reactivity associated with turbo Grignard reagents may be vital in outcompeting undesired

[223] (a) Gao, H.; Zhou, Z.; Kwon, D.-H.; Coombs, J.; Jones, S.; Behnke, N. E.; Ess, D. H.; Kürti, L. *Nat. Chem.* **2017**, *9*, 681. (b) Behnke, N. E.; Kielawa, R.; Kwon, D.-H.; Ess, D. H.; Kürti, L. *Org. Lett.* **2018**, *20*, 8064.

degradation of the starting material or product.[224] Finally, reducing the Grignard loading to 2.5 equivalents produced the desired product in a slightly lower yield (entry 5).

Table 3.7: Optimization of Grignard addition to blocked *O*-isocyanates[a]



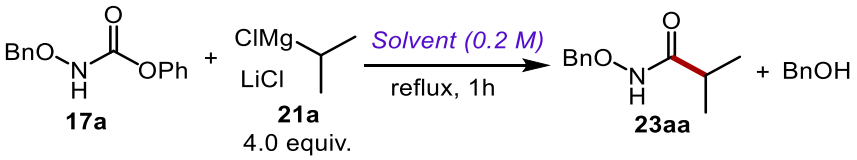
Entry	Deviation from optimized conditions	Yield of 23aa (%)	Yield of BnOH (%)
1	None	85	10
2	2 h reaction time	78	20
3	16 h reaction time	42	15
4	No LiCl/2 h reaction time	49	33
5	2.5 equivalents of **21a**	78	21

[a]Conditions: **17a** (0.2 mmol), **21a** (0.8 mmol), THF (0.2 M), at 66 °C in a sealed microwave vial unless otherwise noted. ^{1}H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.

Various solvents were then scanned for their ability to promote the desired transformation (table 3.8). Concentrated solutions of the Grignard reagent in THF were used and diluted to 0.2 M with the desired solvent. Various ethers as well as toluene were found to have no substantial effect on the reaction outcome (entry 1-3). In contrast, the use of CH_2Cl_2 resulted in significant formation of the benzyl alcohol by-product with minimal product formation (entry 4).

[224] Bao, R. L.-Y.; Zhao, R.; Shi, L. *Chem. Commun.* **2015**, *51*, 6884.

Table 3.8: Solvent scan[a]



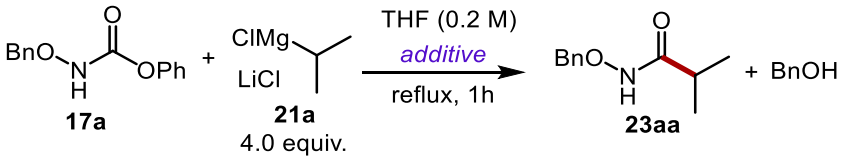
Entry	Solvent	Yield of 23aa (%)	Yield of BnOH (%)
1	Ether	85	15
2	Dioxane	86	10
3	Toluene	84	15
4	CH_2Cl_2	15	85
5	THF	85	10

[a]Conditions: **17a** (0.2 mmol), **21a** (0.8 mmol), diluted to 0.2 M with indicated solvent, at 66 °C in a sealed microwave vial. ^{1}H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.

Finally, a variety of additives were then tested for their ability to promote the desired reaction (table 3.9). Copper (I) and (II) salts in both catalytic amounts and stoichiometric were found to increase the production of benzyl alcohol with reduced product yield. Both TMSCl and zinc chloride were found to reduce product formation although no increase in benzyl alcohol production was observed. Moreover, this latter result suggests milder organozinc reagents may be amenable to the transformation, as formation of the organozinc halide likely occurred under the reaction conditions.[225]

[225] Knochel, P.; Millot, N.; Rodriguez, A. L. Tucker, C. E. *Org. React. (N.Y.)* **2001**, *58*, pp 417-731

Table 3.9: Additive scan[a]

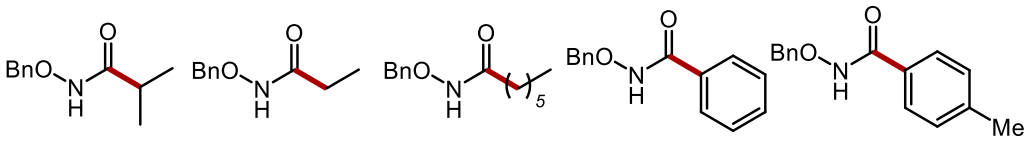


Entry	Additive (equiv.)	Yield 23aa (%)	Yield of BnOH (%)
1	$CuBr_2$ (1.0)	46	48
2	$CuBr_2$ (0.1)	72	28
3	CuBr (1.0)	48	42
4	TMSCl (1.0)	67	16
5	$ZnCl_2$ (1.0)	50	18
6	none	85	10

[a]Conditions: **17a** (0.2 mmol), **21a** (0.8 mmol), THF (0.2 M) at 66 °C in a sealed microwave vial with the indicated additive. ^{1}H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard.

With optimized conditions in hand, attention was focused on the scope of this novel hydroxamate synthesis (table 3.10). Unfortunately, significant hurdles were met early on. Upon scale-up of the optimization substrate (**23aa**), the desired product was only isolated in 66% yield, suggesting some optimization of the isolation procedure may be necessary. Moreover, the use of ethyl turbo Grignard reagent formed only trace amounts of the desired product (**23ab**). Comparatively, the use of its non-turbo variant proved slightly superior. In contrast, the opposite was true for the *n*-hexyl derived substrate where much greater yields were observed with the use of the turbo Grignard (**23ac**). The use of aromatic nucleophiles was then probed through the use of phenyl Grignard, where the turbo Grignard failed to provide the desired product while its non-turbo variant produced a respectable 65% yield (**23ac**). Finally, the tolyl Grignard provided the desired product in an 81% isolated yield.

Table 3.10: Scope of Grignard reagent with comparison turbo vs non-turbo Grignard comparison[a]

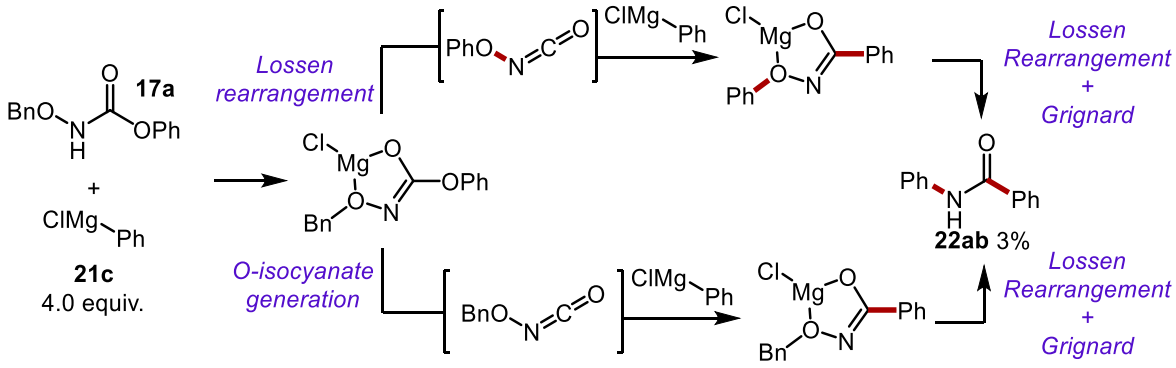


	23aa Yield (%)	**23ab** Yield (%)	**23ac** Yield (%)	**23ac** Yield (%)	**23ad** Yield (%)
Turbo Grignard	85 (66)	7	70	0	N/A
Non-turbo Grignard	49	20	17	65 (55)	(81)

[a]Conditions: **17a** (0.2 mmol), **21a-d** (0.8 mmol), THF (0.2 M) at 66 °C in a sealed microwave vial for 1 hour. ^{1}H NMR yield determined by using 1,3,5-trimethoxybenzene as internal standard. Yields in parenthesis indicated isolated yield from 0.6 mmol reaction scale.

The lack of clear reactivity trends between the use of turbo and non-turbo Grignards coupled with the large variance in yields arising from seemingly benign electronic changes strongly suggest a fundamental part of this reactivity is not yet understood. Currently, efforts to understand the reactivity within this system are focused on dissecting the intricacies of the Grignard reagent. During the optimization differences in efficiency were observed when employing purchased Grignard reagents in comparison to reagents synthesized from Mg(0). Moreover, sporadic precipitate formation in the latter raises concern over the nature of the species introduced to the reaction system. The presence of diorganomagnesium reagents could have drastically different reactivity in this system compared to its RMgX counterpart.[226] Control reactions probing these effects on the desired reaction are ongoing. Variance in product stability could also play a role in explaining these sporadic results. Control reactions investigating the stability of the hydroxamate products are also on-going. Noteworthy, was the isolation of an anilide side product derived from phenyl Grignard reaction on substrate **17a** (scheme 3.5). This result strongly supports the presence of a competitive Lossen rearrangement, likely arising from one of two possible pathways outlined in scheme 3.5. Unfortunately, the lack of identification of other by-products suggest the mass balance is currently being lost through uncontrolled degradation pathways.

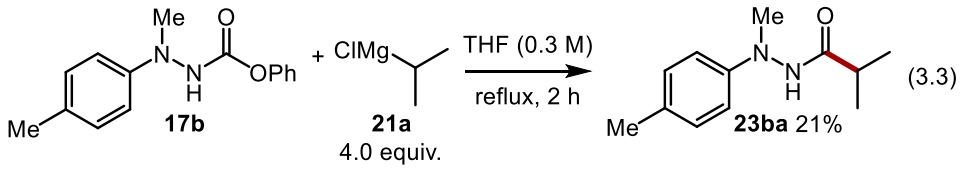
[226] Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 159.



Scheme 3.5: Proposed mechanisms for formation of anilide by-product **22ab**

3.4 Conclusion and Perspective

Overall, two strategies have been successfully developed to achieve a general platform for the synthesis of hydrazides and hydroxamate derivatives. Carboxylic acids were observed to provide the desired product when employing oxadiazolone blocked *N*-isocyanate precursors as well as blocked O-isocyanates derivatives. Alternatively, Grignard reagents were also observed to provide access to hydroxamate products when reacted with blocked *O*-isocyanate derivatives. Furthermore, preliminary results suggest the potential of this latter strategy to achieve hydrazide formation from amino-substituted derivatives (eq. 3.3), a strategy that was met with failure in the case of the carboxylic acids.

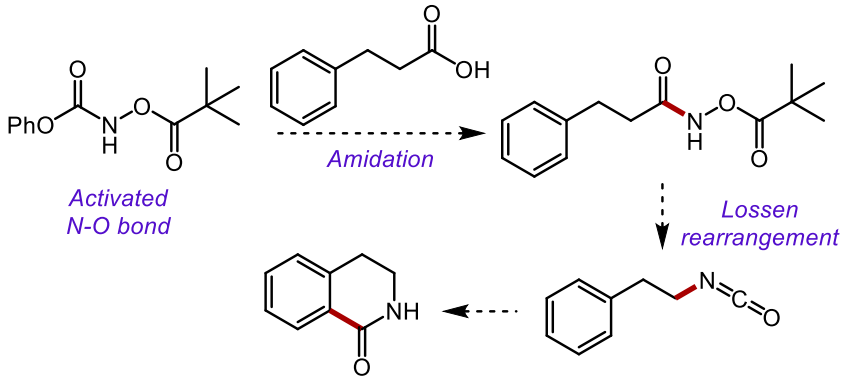


Although the development of this Grignard reactivity is currently in its infancy, its exploration holds great promise for future developments. First and foremost, this reactivity provides a novel disconnection to both hydroxamate and hydrazide derivatives which are currently relegated to C-N bond forming reactions. Moreover, with the advent of reliable magnesiation chemistry utilizing turbo Hauser bases, a better understanding of Grignard reagents on these blocked derivatives could pave the way toward the direct transformation of C-H bonds into hydrazides or hydroxamates.[227] However, reproducibility issues will need to be addressed. This will be targeted by gaining a broader understanding of the effect of lithium chloride on different substrates, the effect of diorganomagnesium species on the

[227] Klatt, T.; Markiewicz, J.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253.

reaction outcome, and probing the stability of various products under the reaction conditions. This project will be carried forward by Alshimaa Mohamed during her PhD in the Beauchemin lab.

The use of carboxylic acids as formal carbon nucleophiles for the synthesis of hydroxamates resulted in a broad reaction scope and generally provided the desired products in good yields. Future work will be geared towards understanding the necessity for high temperatures to achieve efficient reactivity. Given the mild reaction conditions reported for analogous reactivity on *C*-isocyanates,[150] this must result from a fundamental difference between the reactivity of *C*- and *O*-isocyanate derivatives, or the blocking group employed. Finally, the development of this reactivity provides the foundation for the development of more complex cascade reactivity. Indeed, targeting derivatives bearing highly activated N-O bonds is attractive for the rapid assembly of valuable heterocyclic derivatives (scheme 3.6).



Scheme 3.6: Future work harnessing activated *O*-isocyanate precursors for cascade reactions

Chapter 4: Catalytic Amidation of Ambiphilic Isocyanates

4.1 Introduction

As described in the introduction, metal catalyzed reactions of isocyanates for the synthesis of amides as well as various heterocyclic derivatives have generated much interest (see section 1.3). However, a closer look at many of these innovative reports reveals repeated examples of undesired reactivity such as the formation of isocyanurate trimers, urea and acyl urea by-products arising from the uncontrolled reactivity of the isocyanate (figure 4.1). In the gravest of cases, catalyst deactivation has been observed as a result of unwanted isocyanate reactivity,[69] which could stifle further advancements in catalytic transformations of isocyanates. Moreover, all methodologies suffer from limited functional group tolerance, intrinsic to the use of isocyanates. Specifically, the presence of protic motifs as well as Lewis basic functional groups such as *N*-heterocycles or tertiary amines are exceedingly rare.

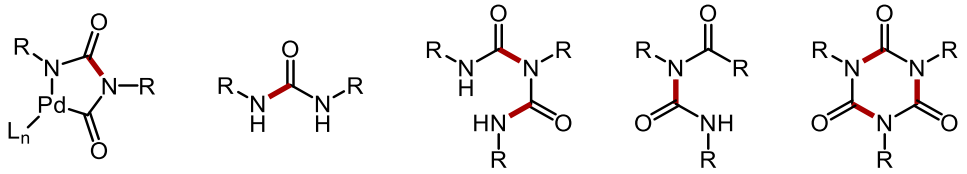
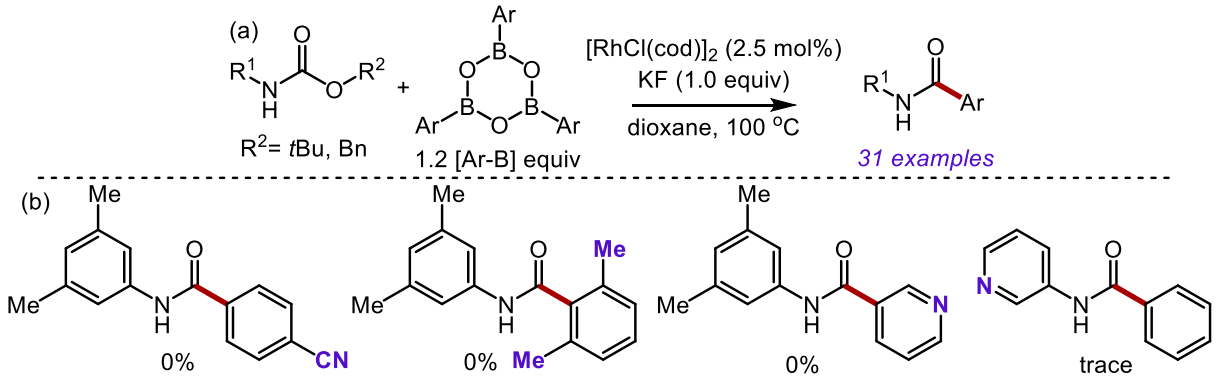


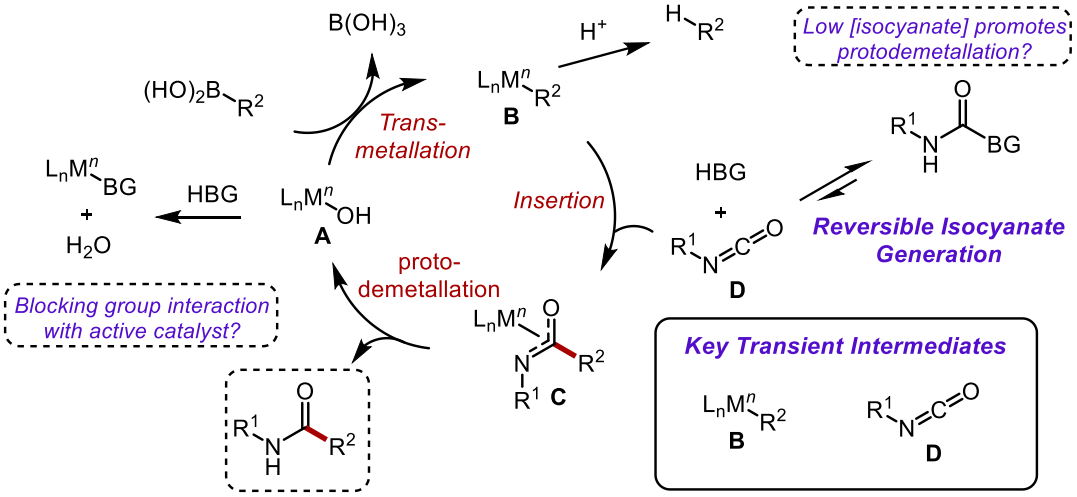
Figure 4.1: Isocyanate derived side products observed throughout their catalytic transformations.

The application of a blocking group strategy holds great promise for overcoming these severe limitations. Oligomerization and other unwanted by-product formation would be limited when isocyanate concentration in solution is controlled. Surprisingly, the use of blocked isocyanates in catalytic transformations is almost altogether absent from the literature apart from the 4 examples highlighted in the introduction.[139,141,165,173] However, 3 of these examples rely on the stoichiometric addition of amine nucleophiles to blocked derivatives. Zhang and coworkers provide the sole report of catalytic amidation of these species with the direct amidation of Cbz- and Boc-carbamates (scheme 1.34).[165] However, the release of isocyanates *in situ* was explicitly excluded as a mechanistic pathway by the authors. Moreover, a severely limited scope was observed where the entirety of the scope could conceivably have been performed on free isocyanates (scheme 4.1). Consequently, broadly applicable amidation reactions of blocked isocyanates remain unexplored.



Scheme 4.1: a) Rhodium catalyzed amidation of Cbz- Boc-carbamates. b) Representative examples of failed substrates in the amidation of Cbz- and Boc- carbamates.

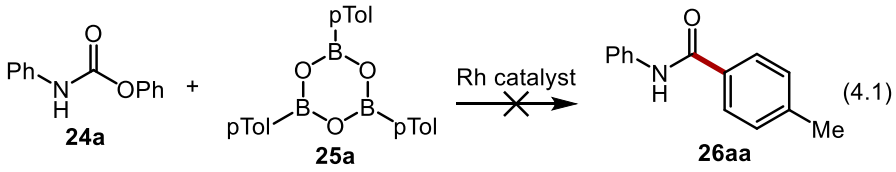
Towards this end, the development of a mild, catalytic amidation of blocked isocyanates with an explicit interest in the use of substrates which would be problematic, if not impossible without the implementation of a blocking group strategy was targeted. The challenges envisioned with the development of this methodology are severalfold (scheme 4.2). First and foremost, a catalytic amide synthesis from blocked isocyanate precursors demands the chemoselective reaction of two transiently formed species present in low concentrations while avoiding common side reactions, such as protodemetallation, homocoupling, etc. Moreover, the blocking group employed must be chosen judiciously as to avoid interference with the catalytic cycle. Finally, the incorporation of otherwise problematic functional groups such as Lewis basic motifs or protic nucleophiles demands a robust, and rapid catalytic cycle.



Scheme 4.2: Proposed catalytic cycle for the catalytic amidation of blocked isocyanates.

4.2 Rhodium Catalyzed Amidation of Blocked Isocyanates.

Inspiration was garnered from several examples of catalytic amide synthesis from isocyanates and organoboron reagents.[75,75,77,165] Organoboron species are ideal for the development at hand due to their low toxicity, broad commercial availability, and functional group compatibility. A commercially available rhodium catalyst was targeted as a result of the exceptionally mild conditions it allowed in a related system.[74] The use of masked isocyanate **24a** with arylboroxine **25a** was employed as the model reaction. Phenol was chosen as the ideal blocking group due to its susceptibility to base mediated deblocking which would provide access to exceptionally mild conditions. Moreover, the release of phenol into the reaction system is expected to have minimal impact on the catalytic cycle.[228] Unfortunately, the formation of the desired product was not observed using Murakami's reported conditions (eq. 4.1), who had reported a similar transformation on free isocyanate derivatives (eq. 1.10).[74] Moreover, conditions reported by Zhang and coworkers for the amidation of Cbz- and Boc-carbamates (scheme 1.34) also failed to provide the desired product from masked isocyanate precursor **24a**.



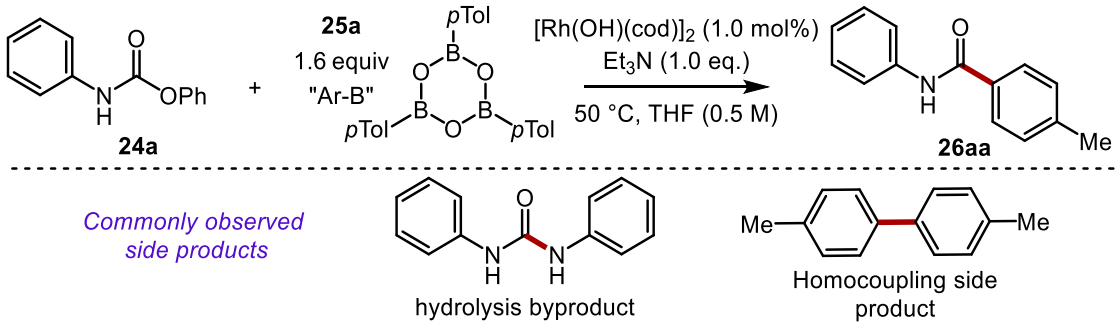
Murakami's conditions: 1.0 equiv. **25a**, $[RhOH(cod)]_2$ (2.5 mol%), THF, rt.
Zhang's conditions: 0.4 equiv. **25a**, $[RhCl(cod)]_2$ (2.5 mol%), KF (1.0 equiv), dioxane, 100 °C

Gratifyingly, after extensive optimization, mild conditions using 1.0 mol% of commercially available $[Rh(OH)(cod)]_2$, 1.0 equivalent of Et_3N, at 50 °C provided the desired amide product **26aa** in high yield in only 8 hours (Table 4.1, entry 1). These conditions allowed the reduction of both the catalyst and organoboron reagent relative to Murakami's work on 'free' isocyanates.[74] Moreover, this increase in efficiency is in stark contrast to Mori's work where stoichiometric phenol inhibited a related reaction of 'free' isocyanates.[73] Increasing the catalyst loading resulted in only a slight increase in yield (entry 2), while the reaction does not reach completion upon decreasing the loading to 0.5 mol% (entry 3). Increasing the base loading led to a lower yield, with more urea side product (entry 4). In contrast, a reaction without Et_3N yielded mostly starting material (entry 5). These results suggest precise control over base-promoted isocyanate generation is necessary to form amide **26aa** efficiently. The formation of **26aa** also occurred in

[228] Related systems where phenol was a beneficial additive: (a) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem. Int. Ed.* **2004**, *43*, 719. (b) Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159. Related work where phenol resulted in catalyst inhibition: (c) Chen, F.-X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341.

the absence of base at 120 °C (thermal deblocking conditions, entry 6). In contrast, sluggish reactivity was observed at room temperature even with increased catalyst loading and longer reaction time (entry 7). A cationic rhodium catalyst displayed similar reactivity (entry 9) though $[Rh(OH)(cod)]_2$ proved optimal due to its shorter reaction time and bench stability. Both copper and palladium catalysts yielded no detectable product (entry 10). Finally, control reactions lacking the rhodium catalyst yielded no detectable product (entries 11-12).

Table 4.1: Optimization of rhodium catalyzed amidation of blocked isocyanate[a,b]

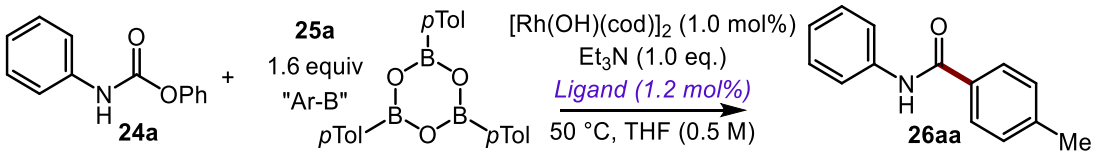


Entry	Deviation from optimized conditions	Yield (%)
1	None	89
2	2.5 mol% catalyst	95
3	0.5 mol% catalyst	69
4	3.0 equivalents of Et_3N	79
5	No Et_3N	0
6	No Et_3N @ 120 °C	70
7	Room temperature[c]	44
8	$[Rh(Cl)(cod)]_2$	0
9	$[Rh(MeCN)_2(cod)]BF_4$[d]	89%
10	$Cu(OAc)_2$[e] or $Pd(OAc)_2/PPh_3$[f]	0
11	No catalyst, no Et_3N @ 120 °C	0
12	No catalyst	0

[a]Conditions: **24a** (0.2 mmol), **25a** (1.6 equiv. 'Ar-B'), $[Rh]_2$ (1.0 mol%), Et_3N (0.2 mmol), THF (0.5 M), 50 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]$[RBO]_3$:$RB(OH)_2$ = 1:2.1 see supporting information for more details. [c]2.5 mol% catalyst. [d]2.0 mol% catalyst. [e]0.2 and 2.0 equivalents tested. [f]$Pd(OAc)_2$ (5.0 mol%), PPh_3 (0.2 equiv.).

Although the cyclooactadiene ligands inherent to the commercially available catalyst were effective, a screen of various ligands was conducted to observe potential ligand effects (table 4.2). Notably, Buchwald type ligands such as SPhos and BrettPhos provided the desired product in similar yields to that observed using the cyclooctadiene ligands (entry 1-2). RuPhos and DavePhos provided the desired product although in lower yields (entry 3-4). Finally, bidentate ligand systems were observed to be particularly inefficient under this catalytic regime where BINAP, DPPP, and DPPE formed the desired product in low yields (entry 5-7). Notably, presence of large quantities of starting material (**20a**) accounts for the low yields observed in entry 3 to 7.

Table 4.2: Ligand screen[a]

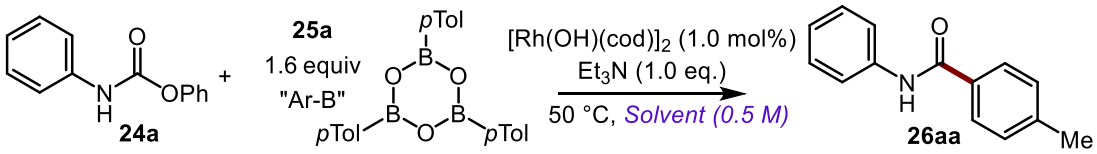


Entry	Ligand	Yield (%)
1	SPhos	84
2	BrettPhos	86
3	RuPhos	52
4	DavePhos	51
5	BINAP[b]	30
6	DPPP[b]	36
7	DPPE[b]	39

[a]Conditions: **24a** (0.2 mmol), **25a** (1.6 equiv. 'Ar-B' see foonote b, table 4.1), $[RhOH(cod)]_2$ (1.0 mol%), Et_3N (0.2 mmol), ligand (1.2 mol%), THF (0.5 M), 50 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]1.0 mol% ligand.

The effect of different solvents on the reaction was also probed (table 4.3). Interestingly, THF was by far the best candidate for the desired transformation (entry 1). Solvents which have very low polarity, such as $PhCF_3$ and CH_2Cl_2 (entry 2-3), as well as highly polar solvents such as DMSO, MeCN, and MeOH displayed quite poor reactivity overall (entry 4-6). It should be noted that the use of MeOH resulted in the predominant formation of the methyl carbamate.

Table 4.3: Solvent scan[a]

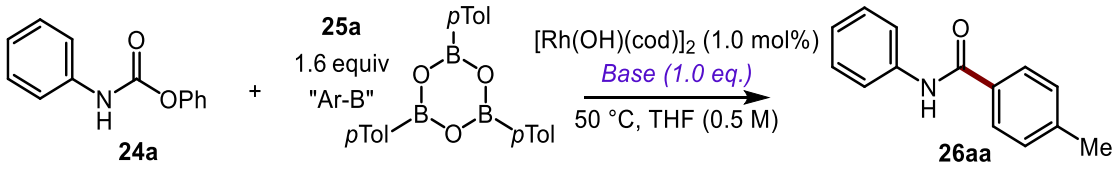


Entry	Solvent	Yield (%)
1	THF	89
2	$PhCF_3$	16
3	CH_2Cl_2	15
4	DMSO	8
5	MeCN	43
6	MeOH[b]	10

[a]Conditions: **24a** (0.2 mmol), **25a** (1.6 equiv. 'Ar-B' see footnote b, table 4.1), $[RhOH(cod)]_2$ (1.0 mol%), Et_3N (0.2 mmol), solvent (0.5 M), 50 °C. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]90% formation of methanol derived carbamate.

The use of triethylamine as the base of choice also proved singularly competent for the desired transformation (table 4.4). Various organic and inorganic bases showed little or no activity for the desired transformation (entry 2-6). Notably, reducing the Et_3N loading to catalytic amounts was detrimental to the reaction largely resulting in unreacted starting material (entry 7). Given the fundamental link between base loading and isocyanate concentration,[127] this result can be rationalized through off cycle catalytic degradation of the aryl boroxine coupling partner as a result of the dramatic decrease in available isocyanate.

Table 4.4: Base scan[a]

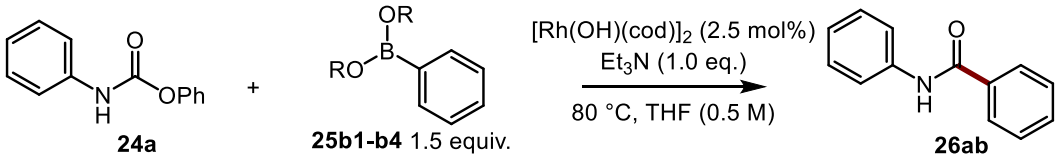


Entry	Base	Yield (%)
1	Et_3N	89
2	DBU	0
3	DIPEA	26
4	*N*-methylmorpholine	0
5	K_2CO_3	0
6	Cs_2CO_3	24
7	Et_3N (0.2 equiv.)	5>

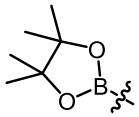
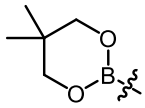
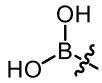
[a]Conditions: **24a** (0.2 mmol), **25a** (1.6 equiv. 'Ar-B' see footnote b, table 4.1), $[RhOH(cod)]_2$ (1.0 mol%), base (0.2 mmol), THF (0.5 M), 50 °C. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

The use of alternative organoboron reagents was also probed for their ability to provide the desired product (table 4.5). The use of boroxines proved particularly efficient to achieve the desired transformation with both arylboronic acid pinacol ester (**25b1**) and trifluoroborate salts (**25b2**) providing the desired product in under 5% yield even with increased temperature and catalyst loading (entry 1-2). Notably, arylboronic acid neopentyl ester (**25b3**) did provide the desired product, however in a significantly reduced yield compared to the use of boroxines (entry 3). In stark contrast to its dehydrated counterpart, freshly recrystallized aryl boronic acid (**25b4**) formed the desired product in only trace quantities (entry 4).

Table 4.5: Application of alternative organoboron reagent[a]



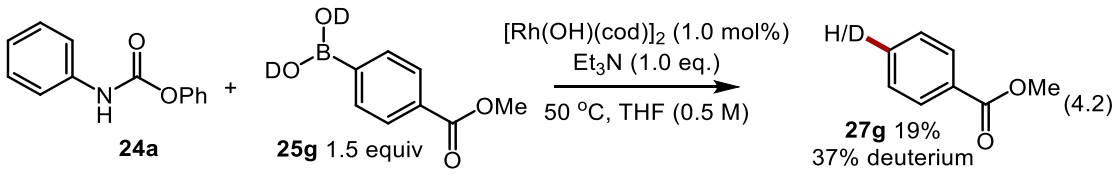
24a **25b1-b4** 1.5 equiv. **26ab**

Entry	Organoboron	Yield (%)
1		< 5
2		< 5
3		53
4[b]		< 5

[a]Conditions: **24a** (0.2 mmol), **25b1-b4** (1.5 equiv.), $[RhOH(cod)]_2$ (2.5 mol%), Et_3N (0.2 mmol), THF (0.5 M), 80 °C. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]Freshly recrystallized from water.

The poor reactivity exhibited by various alternative organoboron reagents is likely attributable to their diminished propensity to undergo transmetallation. However, this does not explain the lack of product formation observed when employing boronic acid species. Indeed, monitoring the parent reaction by TLC when employing freshly recrystallized *p*-tolylboronic acid revealed the absence of the organoboron species in approximately 1 hour. It was hypothesized that oligomerization of the boronic acid *in situ*, promoted by the presence of basic amines and low polarity solvents,[229] was releasing water and promoting a rapid protodemetallation pathway. To test this hypothesis, 4-methoxycarbonylphenylboronic acid (**25g**) was recrystallized in D_2O and submitted to the reaction conditions (eq. 4.2). Isolation of the protodemetallated by-product (**27g**) revealed partial deuteration at the *ipso*-position. The low yield of the compound is attributed to volatility. These results provide evidence to support a kinetically fast protodemetallation when boronic acids are employed directly. Notably, this side reaction is exacerbated by the use of blocked derivatives given the stark contrast with prior work by Murakami,[74] where high yields of product were obtained employing arylboronic acids with free isocyanates.

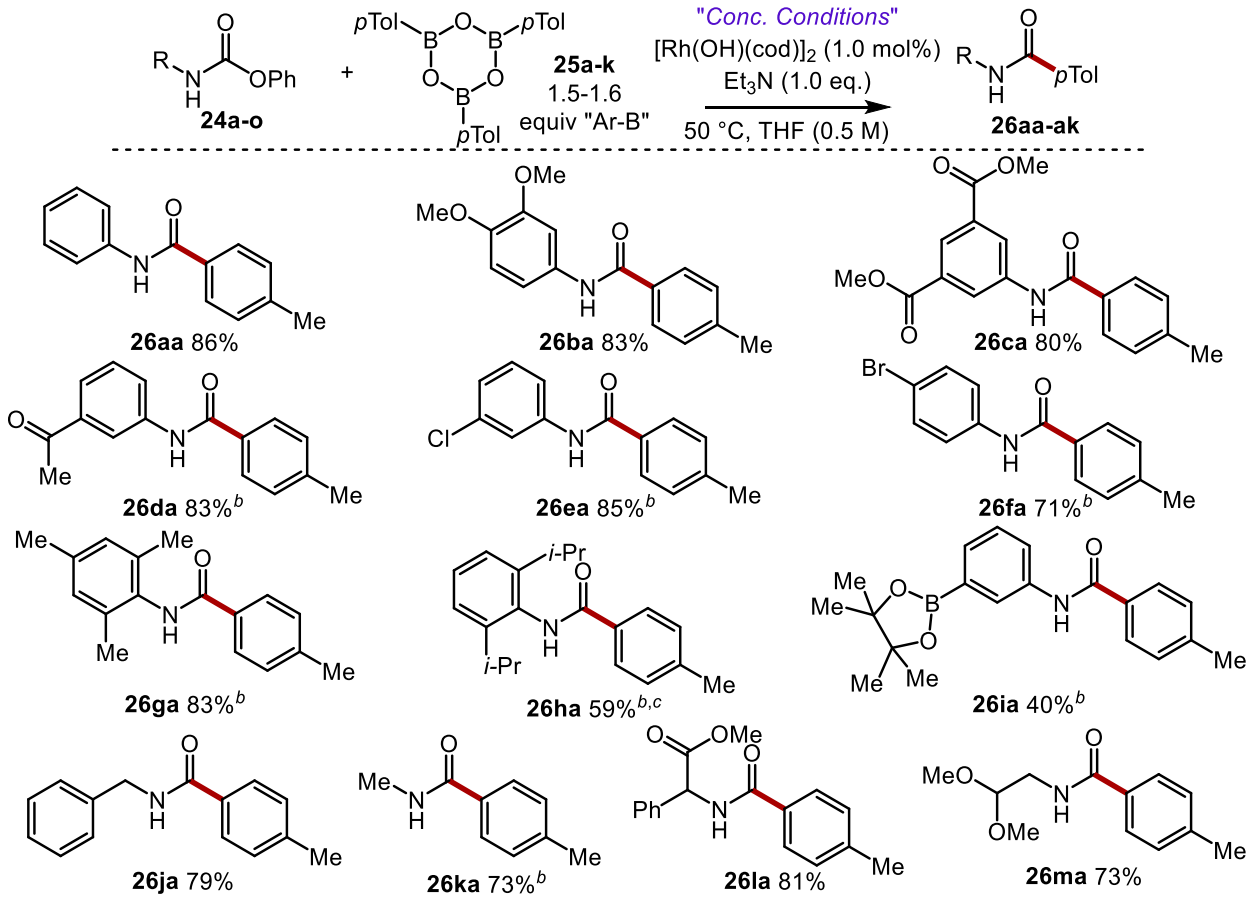
[229] (a) A. L. Korich, P. M. Iovine, *Dalt. Trans.* **2010**, *39*, 1423; (b) Y. Tonkunaga, Heterocycles **2013**, *87*, 991.



With optimized conditions, the scope of blocked isocyanate reagents was investigated (Table 4.6). The model reaction provided the desired product **26aa** in 86% isolated yield on 0.6 mmol scale. Both electron-donating (**26ba**) and electron-withdrawing (**26ca**) groups were tolerated on the isocyanate precursor. Gratifyingly, ketones (**26da**) and aryl halides (**26ea-fa**) were compatible with the reaction. Sterically hindered substrates also provided the desired products in excellent to moderate yields (**26ga-ha**). Conceptually this provides a catalytic alternative to Bode's synthesis of sterically hindered/electronically deactivated amides from isocyanates using Grignard nucleophiles. Despite the tendency for boron species to equilibrate *in situ*,[230] a boronic acid pinacol ester bearing starting material provided the desired product **26ia**, albeit in modest yield. Pleasingly, a benzylamine-derived blocked isocyanate was a competent reaction partner despite the decreased deblocking rate of aliphatic masked isocyanates compared to their aromatic counterparts (**26ja**). Methyl amide **26ka** was also formed in good yield, thus providing a safe alternative to the use of methyl isocyanate. An amino acid derivative and a precursor containing an acetal also formed the desired products efficiently (**26la**-**26ma**). Unfortunately, the readily epimerizable stereocentre in the former was not conserved under the reaction conditions

[230] (a) Fyfe, J. W. B.; Seath, C. P.; Watson, A. J. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 12077. (b) Seath, C. P.; Fyfe, J. W. B.; Molloy, J. J.; Watson, A. J. B. *Angew. Chem. Int. Ed.* **2015**, *54*, 9976.

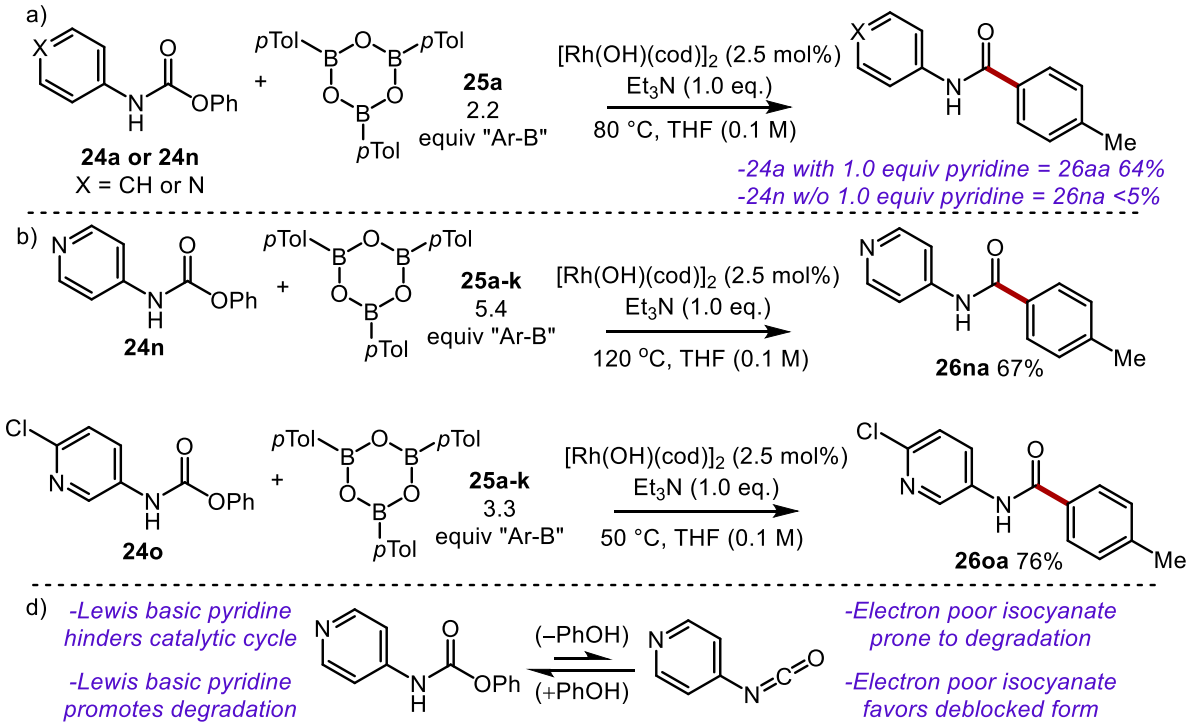
Table 4.6: Masked isocyanate scope[a]



[a]Conditions: **24a-o** (0.6 mmol), **25a** (1.6 equiv "Ar-B", see footnote b, Table 4.1), $[Rh]_2$ (1.0 mol%), Et_3N (0.6 mmol), THF (0.5 M), 50 °C unless otherwise noted; isolated yields. [b]$[Rh]_2$ 2.5 mol%. [c]0.3 mmol $[RBO]_3$.

As mentioned in the introduction, isocyanates bearing Lewis basic heterocycles are rarely observed as substrates during the amidation of isocyanates. As such, the ability to tolerate such motifs in the described system was of utmost importance. A blocked isocyanate derived from 4-aminopyridine (**24n**) was subjected to the reaction conditions however, only trace amounts of product was observed even when employing increased reaction temperatures (scheme 4.3a). A control reaction was run using model substrate **24a** under identical conditions with the addition of an equivalent of pyridine to remove its electronic effect from the isocyanate motif, while probing its influence as a Lewis base. Interestingly, the desired product was observed although in lower yield, with increased urea by-product formation. Gratifyingly, the desired product (**26na**) was obtained in acceptable yields upon increasing both the temperature and the organoboron reagent loading (scheme 4.3b). In contrast, the use of a similar substrate with attenuated Lewis basicity provided the desired product under milder reaction conditions

(**26oa**). Taken together, the difficulties encountered with blocked isocyanate **24n** is believed to arise from its intrinsic Lewis basicity, combined with its electronic effect on the isocyanate. This is supported by the control reactions where product formation is only observed when using pyridine as an additive. More specifically, the electron withdrawing nature of the pyridyl motif increases the susceptibility of the isocyanate to degradation[231] while also shifting the equilibrium towards the unblocked form (scheme 4.3c). Furthermore, the Lewis basic pyridyl motif can itself promote degradation, while also hindering catalytic turnover.[232] These latter two effects are attenuated by the incorporation of an *o*-chloro substituent which is believed to be the key in achieving milder reaction conditions for substrate **24o**.



Scheme 4.3: a) Control reactions. b) Amidation of pyridyl containing substrates. c) Synergistic effect of pyridyl substrates.

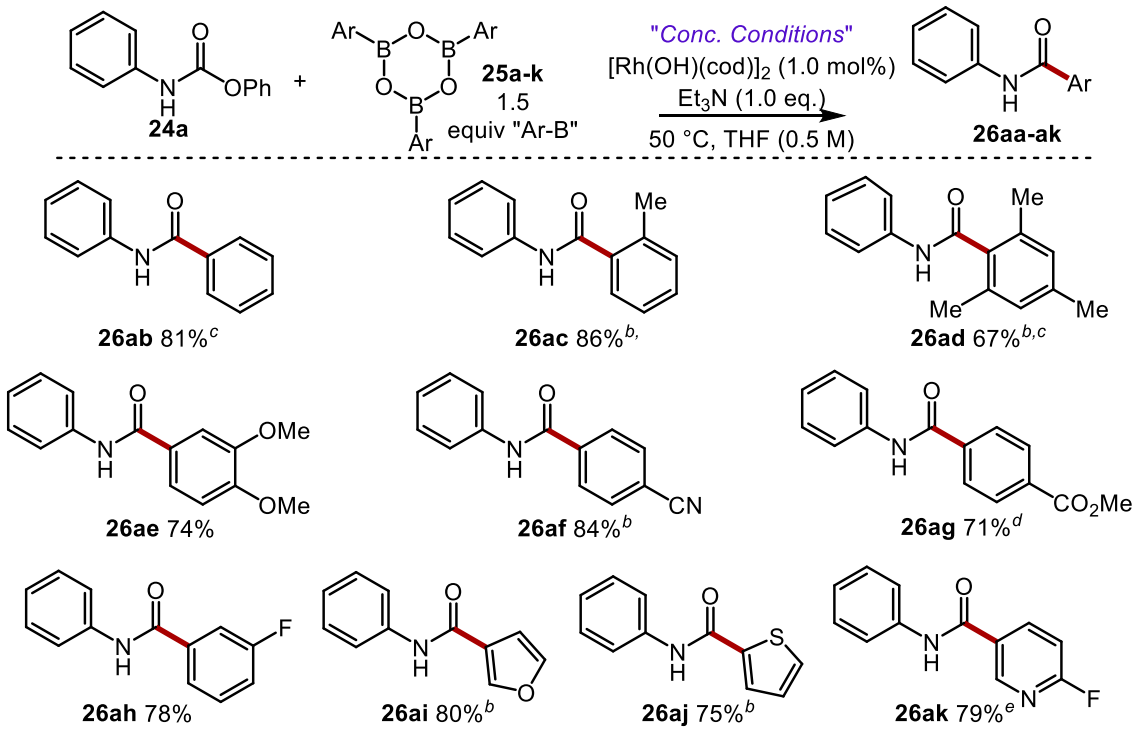
The effect of different boroxine derivatives on the transformation was then surveyed (Table 4.7). A variety of boroxines were competent reaction partners including sterically hindered (**26ac-3ad**), electron-rich (**26ae**), electron-deficient (**26af-3ag**), halide-containing (**26ah**), and heterocyclic reagents

[231] (a) Holt, J.; Andreassen, T.; Bakke, J. M.; Fiksdahl, A. *J. Heterocycl. Chem.* **2005**, *42*, 259. (b) Holt, J.; Fiksdahl, A. *J. Heterocycl. Chem.* **2007**, *44*, 375.

[232] Albrecht, F.; Sowada, O.; Fistikci, M.; Boysen, M. M. K. *Org. Lett.* **2014**, *16*, 5212. (b) Chen, Y.-J.; Cui, Z.; Feng, C.-G.; Lin, G.-Q. *Adv. Synth. Catal.* **2015**, *357*, 2815. (c) Schafer, P.; Palacin, T.; Sidera, M.; Fletcher, S. P. *Nat. Commun.* **2017**, *8*, 15762.

(**26ai-3aj**). Remarkably, a pyridyl boroxine was compatible with the reaction, though modified conditions were necessary (**26ak**). These substrates are typically problematic given their increased propensity for protodeboronation and ability to influence catalytic turnover.[232] Finally, catalyst loadings as low as 0.5 mol% were possible although recrystallization of the boronic acid before dehydration was essential to achieve such efficiency (**26ag**).

Table 4.7: Scope of arylboroxine reagent[a]



[a]Conditions: 24a (0.6 mmol), 25a-k (0.3 mmol $[RBO]_3$), $[Rh]_2$ (1.0 mol%), Et_3N (0.6 mmol), THF (0.5 M), 50 °C unless otherwise noted; isolated yields. [b]$[Rh]_2$ 2.5 mol%. [c]0.9 mmol $RB(OH)_2$. [d]$[Rh]_2$ 0.5 mol%. [e]0.6 mmol $[RBO]_3$, $[Rh]_2$ 2.5 mol%, 80 °C.

Throughout the course of the scope of organoboron reagents coupling partner, a few substrates proved particularly problematic for the desired amide bond synthesis (figure 4.2). Boroxines containing amide functionality failed to provide the desired product. These results were unexpected given the presence of the amide functionality in the product of the standard reaction. Attempts at including organoboron reagents containing nucleophilic motifs were also made. The presence of an aniline motif and a benzylic alcohol both failed to provide the desired product. The former resulted in predominant urea formation while the latter is believed to suffer from exceptionally poor solubility leading to poor reactivity. Notably, the dehydration of these highly polar derivatives was particularly difficult to monitor by ^{1}H-NMR, thus poor reactivity could be due to the formation of alternative organoboron species. Indeed

the reactivity observed with boroxine **25g** indicates the composition of the boroxine can have drastic effects on reactivity.

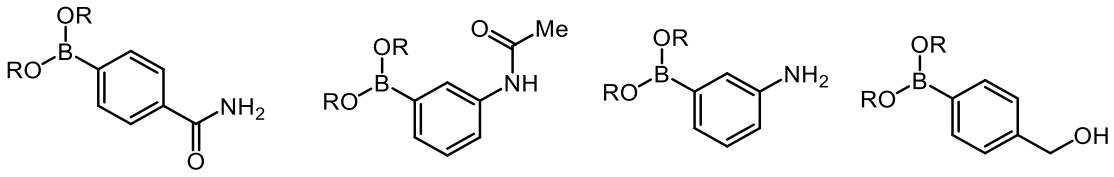
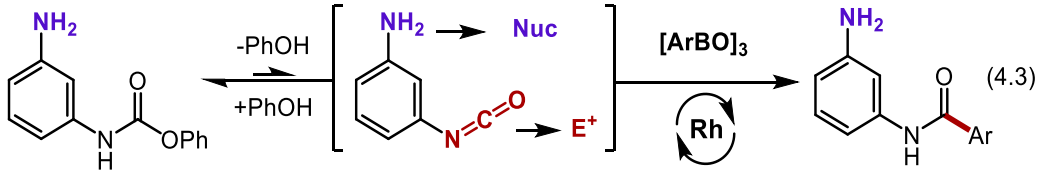


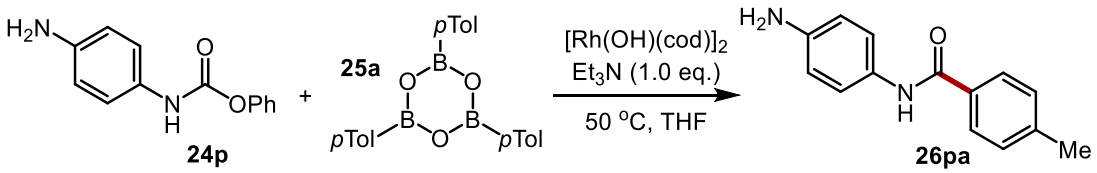
Figure 4.2: Various failed organoboron substrates.

Attention was then focused on the use of blocked isocyanates containing protic nucleophiles which are fundamentally beyond the reach of typical isocyanate amidations (eq. 4.3). We hypothesized that stringent control over the isocyanate concentration imparted by the blocking group would allow the high degree of chemoselectivity necessary for the transient formation of the organometallic nucleophile to outcompete stoichiometric protic motifs present in the reaction system.



Studies began using blocked isocyanate **24p**, containing a free aniline nucleophilic motif, and boroxine **25a** as the model system (table 4.8). Unfortunately, optimized reaction conditions only provided the product in 29% yield even when employing 5 times the catalyst loading (entry 1). Pleasingly, by decreasing the concentration of the reaction and increasing the organoboron loading, efficient formation of the desired product was observed in approximately 18 hours (entry 2). Decreasing the catalyst loading to 2.5 mol% had minimal effect on product formation while further reduction led to a precipitous fall in yield (entry 3-4). Interestingly, a slight reduction in organoboron loading was highly detrimental to overall efficiency (entry 5). The importance of controlling the deblocking equilibrium can be seen explicitly upon exclusion of the base and varying reaction temperatures. A temperature of 100 °C proved optimal, while both increasing and decreasing the temperature resulted in a precipitous reduction in yield (entry 6-8). These results are a consequence of the influence of temperature on deblocking, where increased temperatures results in an increased rate of deblocking upon which catalytic turnover cannot compete, while at lower temperature deblocking becomes deblocking much slower resulting in sluggish reactivity. Thus with optimized conditions in hand (entry 3), the scope of applicability of ambiphilic isocyanates was explored

Table 4.8: Optimization of ambiphilic blocked isocyanate amidation[a]

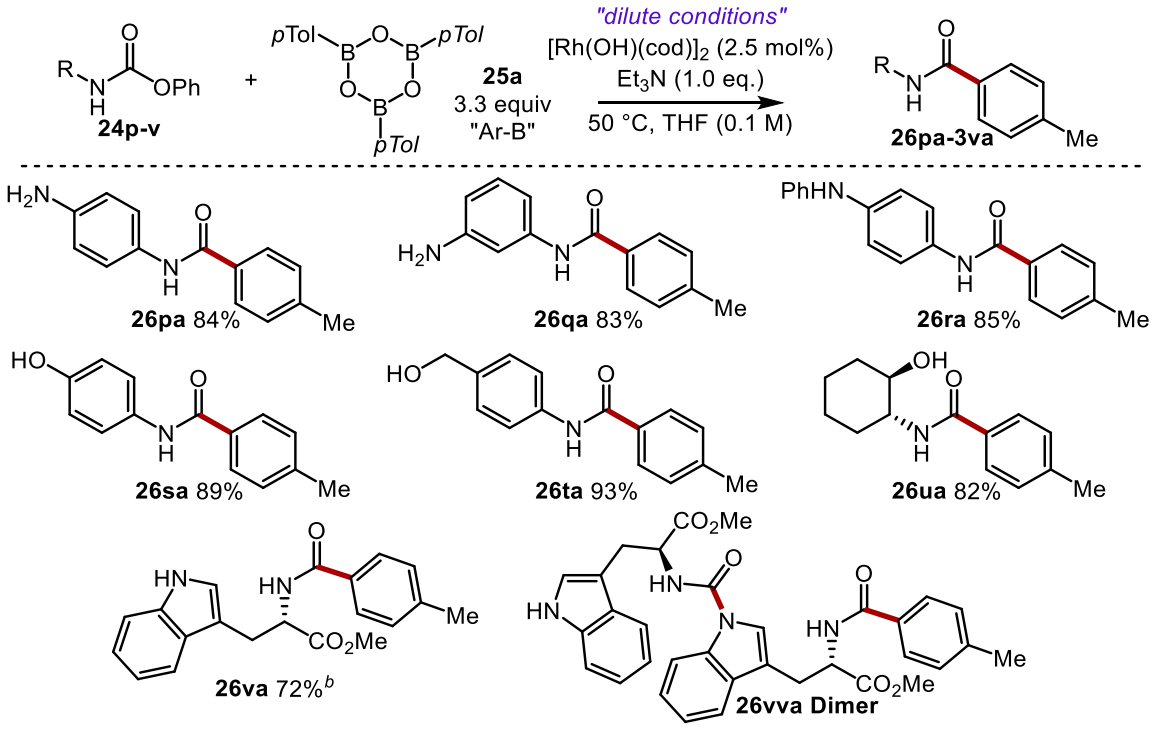


Entry	Catalyst	25a (equiv)	Concentration (M)	Temperature (°C)	Yield (%)
1	5.0 mol%	1.6	0.5	50	29
2	5.0 mol%	3.3	0.1	50	92
3	2.5 mol%	3.3	0.1	50	85
4	1.0 mol%	3.3	0.1	50	35
5	2.5 mol%	2.4	0.1	50	36
6[b]	5.0 mol%	1.6	0.1	80	34
7[b]	5.0 mol%	1.6	0.1	100	75
8[b]	5.0 mol%	1.6	0.1	120	25

[a]Conditions: **24p** (0.2 mmol), **25a** (1.6 equiv. 'Ar-B' see table 4.1 footnote b for details), $[Rh]_2$ (1.0 mol%), Et_3N (0.2 mmol), THF (0.5 M), 50 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]No Et_3N.

Pleasingly, these optimized conditions proved broadly applicable to a variety of ambiphilic blocked isocyanates (table 4.9). Aniline derivatives produced the desired products in high yields (**26pa-26ra**). A phenolic motif was also tolerated. Alcohols (**26ta**) were compatible, even in cases where a rapid intramolecular cyclization may be expected (**26ua**). Finally, the reaction could also be achieved with an unprotected (N-H) tryptophan derivative with minimal loss of the stereochemical information. Interestingly, when the reaction was performed at 50 °C, competitive dimer formation occurred (**26vva**). This was alleviated by increasing the reaction temperature to 80 °C (**26va**). Control reactions suggest the formation of this dimer was not reversible under the reaction conditions.

Table 4.9: Scope of amphoteric blocked isocyanates[a]



[a]Conditions: **24p-v** (0.6 mmol), **25a** (3.3 equiv "Ar-B", see table 4.1 footnote b), $[Rh]_2$ (2.5 mol%), Et_3N (0.6 mmol), THF (0.1 M), 50 °C unless otherwise noted; isolated yields. [b]At 80 °C.

A variety of ambiphilic substrates failed to provide the desired amide product over the course of the optimization (figure 4.3). In contrast to **25ua**, ethanol amine and threonine derived blocked isocyanates were observed to undergo cyclization as opposed to the desired amidation. Similarly, intramolecular cyclization was observed to outcompete the desired amidation in the presence of amide substrates as well. Finally, dopamine derived blocked isocyanate also failed to provide the desired product. Interestingly, control reactions of **24a** in the presence of stoichiometric catechol were found to provide the desired product **26aa**, although temperatures as high as 120 °C were necessary. However, this reactivity failed to translate to the substrate in question.

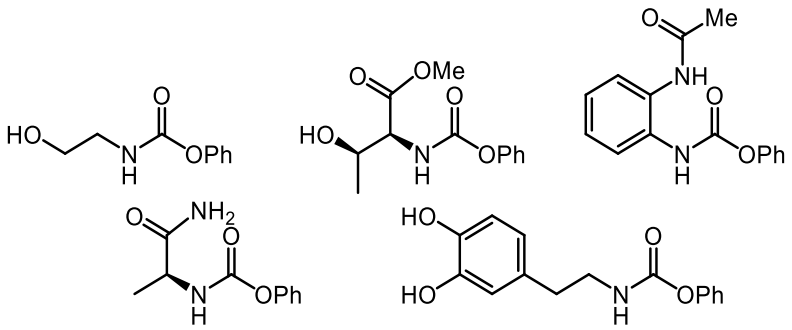
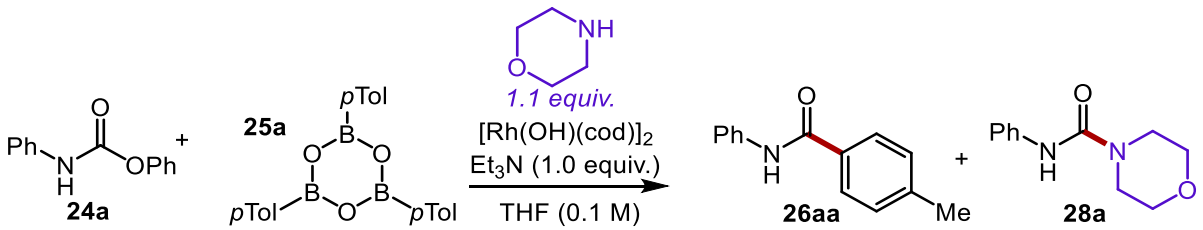


Figure 4.3: Failed ambiphilic blocked isocyanate substrates.

Pushing the limits of nucleophilicity amenable to this novel methodology was then probed. Primary and secondary amines are reported to add to isocyanates at rates approximately 100 to 500 times greater than their aniline counterparts (figure 1.2). The ability to achieve chemoselective amidations in the presence of these highly nucleophilic motifs was tested through the addition of stoichiometric amounts of morpholine to the optimized reaction (table 4.10). No desired product was observed under the 'concentrated conditions' employed in table 4.6 (entry 1), while the desired product was observed in 39% yield upon utilizing the 'dilute conditions' from table 4.9 (entry 2). Unfortunately, the urea by-product was formed in 46% yield (**28a**), with no improvement in yield upon varying the catalyst loading, organoboron loading, base loading and temperature (entries 3-7).

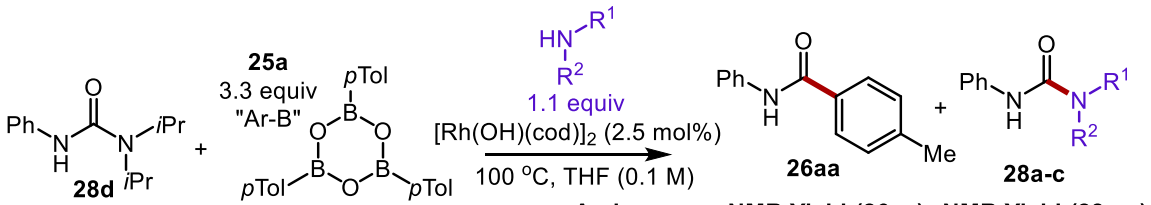
Table 4.10: Optimization of the reaction forming **26aa** in the presence of morpholine[a]



Entry	Catalyst (mol %)	25a ("Ar-B" equiv)	Temperature (°C)	26aa (%)	28a (%)
1[b]	2.5	1.6	50	0	98
2	2.5	3.3	50	39	46
3	5.0	3.3	50	27	71
4	5.0	5.4	50	26	61
5	2.5	3.3	70	9	90
6	2.5	3.3	35	0	66
7[c]	2.5	3.3	50	6	89

[a]Conditions: **24a** (0.2 mmol), **25a** (1.6 equiv "Ar-B", see footnote b, Table 4.1), $[Rh]_2$ (2.5 mol%), Et_3N (0.2 mmol), morpholine (0.22 mmol), THF (0.1 M), 50 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]0.5 M THF. [c]0.2 equiv Et_3N.

The high reactivity of phenol blocked isocyanates with aliphatic amine nucleophiles prompted us to turn our attention towards more robust alternatives (scheme 4.4). The use of diisopropylamine blocked derivatives was chosen (**28d**).[131] Pleasingly, the desired product was now formed as the dominant product in 72% yield, with minimal urea by-product observed (**28a**). This result was not specific to morpholine where the presence of stoichiometric dibenzylamine was readily outcompeted by the desired catalytic transformation. A primary amine was also tolerated under reaction conditions although significant amounts of urea by-product was observed (**28c**), likely resulting from their increased rate of addition onto the isocyanates.

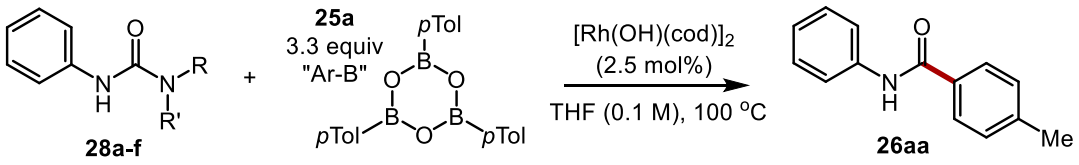


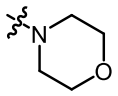
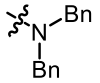
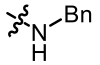
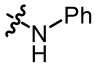
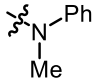
	Amine	NMR Yield (26aa)	NMR Yield (28a-c)
(a)	morpholine	72%	15%
(b)	dibenzylamine	94%	<5%
(c)	benzylamine	43%	46%

Scheme 4.4: Successful amidation of diisopropylamine blocked isocyanate in the presence of aliphatic amines.

To confirm the ability of the catalytic system to outcompete such strong nucleophiles, the reversibility of various urea derivatives was probed (table 4.11). Surprisingly, morpholine blocked derivative **28a** readily provided the product under the reaction conditions while both dibenzyl (**28b**) and benzyl amine (**28c**) blocked derivatives proved inert under the reaction conditions. Diphenyl urea (**28e**), and its methylated analogue (**28f**) were also observed to be inert under the reaction conditions. Although the reversibility of **28a** under the reaction conditions was unexpected, these latter results unambiguously demonstrate the chemoselectivity of the rhodium catalyzed amidation in the presence of aliphatic amines.

Table 4.11: Probing the lability of various urea derivatives[a]



Entry	28a-f		yield of 26aa (%)
1		**28a**	99
2		**28b**	< 5
3		**28c**	< 5
4		**28e**	< 5
5		**28f**	< 5

[a]Conditions: **28a-f** (0.2 mmol), **25a** (3.3 equiv "Ar-B", see footnote b, Table 4.1), $[Rh]_2$ (2.5 mol%), THF (0.1 M), 100 °C. ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

Efforts were then directed at gaining insight on the reaction mechanism using the variable time normalization analysis developed by Burés.[233] This methodology provides a simple procedure to probe the order of various reagents under the reaction conditions using few experiments, saving time and resources. Thus, the order in catalyst was probed initially under the reported 'concentrated conditions' from table 4.6, using a fluorinated precursor (**24w**) amenable to monitoring by fluorine NMR (figure 4.4). Varying the catalyst loading, while holding all other reagent concentrations constant allowed the generation of 3 datasets which are plotted together. The y-axis represents the product concentration while the x-axis is the time, multiplied by the concentration of the catalyst, to the power of X. The order of the catalyst corresponds to the power of X which provides the best overlap. As can be seen in the plot in figure 4.4, good overlap is observed using 0.75 suggesting the catalyst is in fact involved in the rate determining step.[234] Moreover, the less than unit order suggests the existence of an equilibrium between the active catalyst and a dimeric resting state, a phenomenon which has been observed in the similar reaction of

[233] (a) Burés, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2028. (b) Burés, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 16084.
[234] See supporting info for experimental set-up, raw data, and plots at alternative power values.

aryl boronic acids and enone electrophiles.[235] Conversely, a 0th order dependence in blocked isocyanate **24w** was observed suggesting the isocyanate species is not part of the rate determining step. Taken together, these data are consistent with a rate determining transmetallation, as this is the sole step which involves the catalyst and excludes the isocyanate species (refer to scheme 4.1).

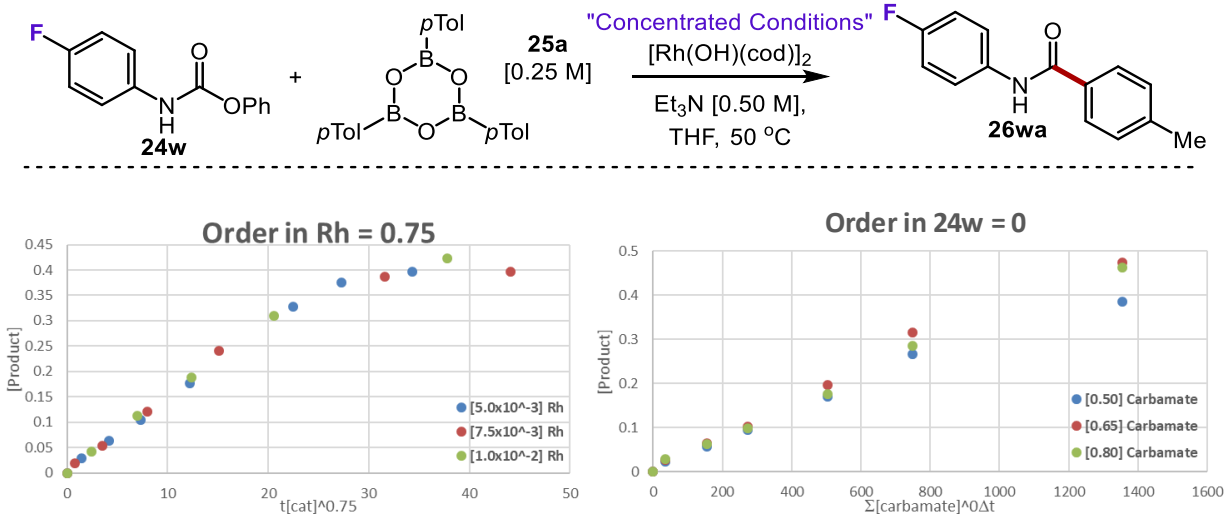


Figure 4.4: Determination of order in catalyst and **24w** under 'concentrated conditions'

The need for alternative reaction conditions to achieve efficient amidation of ambiphilic isocyanates prompted the study of the mechanism under the reported 'dilute conditions' (table 4.9). In direct contrast to the 'concentrated conditions', a 0th order dependence in catalyst was observed while a 0.75 order dependence in the carbamate was found (figure 4.5). Taken together, these results strongly suggest a change in rate determining step where isocyanate release becomes rate limiting. Moreover, Et_3N displayed a 1st order dependence under these conditions,[236] strongly supporting its role in deblocking. Although the 0.75 order in **26wa** was surprising, precedence for the existence of carbamates as dimeric species has been reported.[237] The presence of dimeric resting states for blocked isocyanates holds interesting implications for *N*- and *O*-substituted derivatives where the increased acidity of the latter would be expected to exacerbate this effect.

[235] Kina, A.; Iwamura, H.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 3904.
[236] See supporting information for plots probing the order of Et_3N at various concentrations.
[237] For precedence on dimeric carbamate, see: Ghosh, A. K.; Brindisi, M. J. *Med. Chem.* **2015**, *58*, 2895.

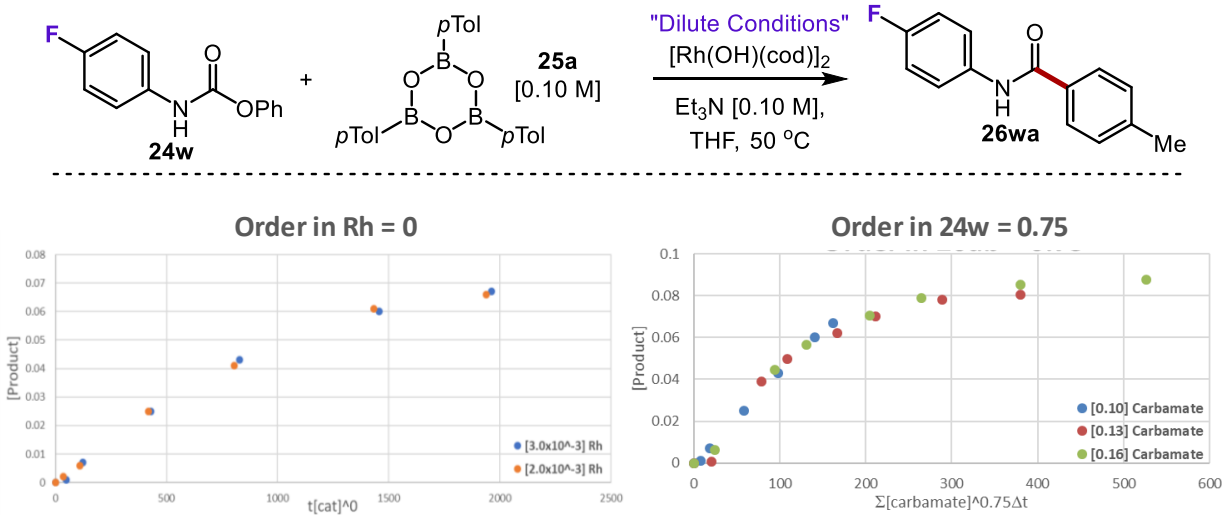
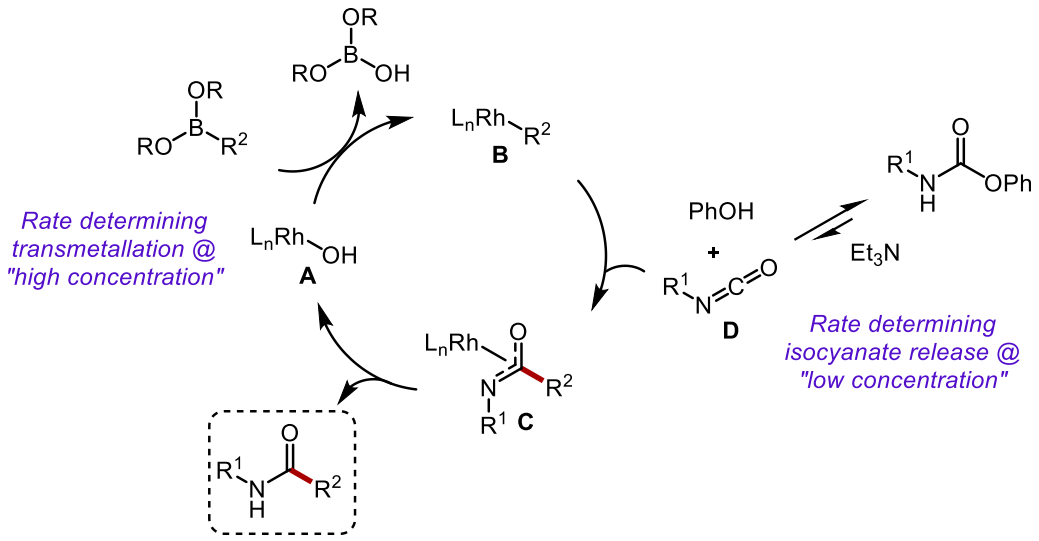


Figure 4.5: Determination of order in catalyst and **24w** under 'dilute conditions'

The major changes in conditions employed for efficient amidation of ambiphilic blocked isocyanates were the dilution of the reaction medium, increasing the catalyst loading, and increasing the equivalents of organoboron reagent. However, the concentration of the catalyst and the organoboron reagent remain at slightly lower levels under 'dilute conditions' despite their increased loading. This suggests the rate of catalytic turnover remains similar under both conditions and thus does not explain the efficiency of the 'dilute conditions' for ambiphilic isocyanate derivatives. Indeed, a diminished rate of deblocking as a consequence of the 5-fold dilution of the Et_3N base is believed to be responsible for the change in rate determining step and consequently, the reaction efficiency (scheme 4.5). This is supported by the 1st order dependence in base under such conditions. These data coupled with the lack of product formation when using *N*-methylated phenyl carbamate precursors strongly support the intermediacy of an isocyanate species.[238] Taken together, this strongly suggest the success of this catalytic amidation relied on a rate limiting isocyanate release to achieve high chemoselectivity in the presence of stoichiometric nucleophiles.

[238] See supporting information for corresponding control experiments.



Scheme 4.5: Simplified mechanistic overview.

At this stage the prospects of synthesizing blocked isocyanate derivatives containing pendant nucleophilic aliphatic amines to employ in this amidation was targeted. Unfortunately, all attempts to synthesize these species using phenol as a blocking group were unsuccessful due to the highly labile nature of the blocking group in the presence of amines (figure 4.6). Not only would the presence of the basic amines introduce the potential for base mediated deblocking leading to oligomerization, the viability of addition elimination pathways with strong nucleophiles and phenol blocked derivatives is strongly suspected. Moreover, diisopropylamine blocked isocyanates were similarly observed to undergo unwanted oligomerization, albeit less severely. Consequently, attention was focused on the potential of Boc-protected amines. The high stability of these species coupled with the precedence set by Zhang and coworkers[165] suggest a promising platform for the direct amidation of functionally group dense blocked isocyanates.

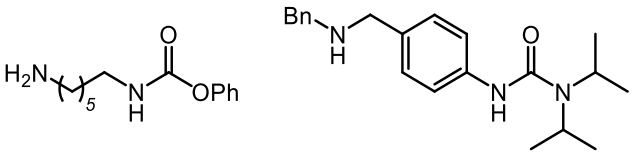
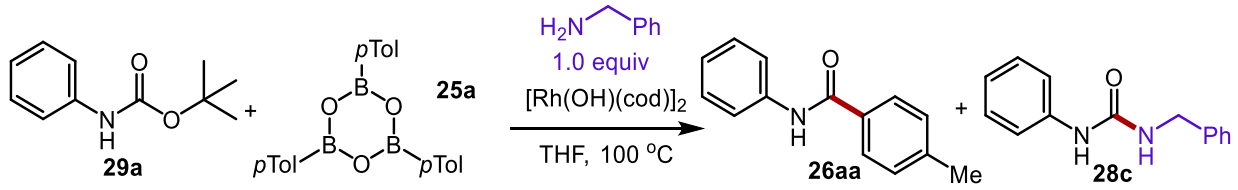


Figure 4.6: Failed attempts at blocked isocyanates containing aliphatic amines.

To probe the potential of this amidation, Boc-amine **29a** was prepared and subjected to a variety of amidation conditions in the presence of an aliphatic amine additive (table 4.12). Benzyl amine was chosen as the model amine as it proved most problematic when using diisopropylamine blocked

derivatives. Unfortunately, upon employing the 'dilute conditions' from table 4.9, no product was detected even in the presence of increased catalyst loading (entry 1). Notably, only small amounts of urea by-product observed suggesting Boc-amines do in fact display greater stability as compared to their diisopropylamine counterpart. Increasing the reaction concentration 5-fold resulted in the production of the desired product in 71% yield (entry 2). Diminishing the catalyst loading proved detrimental to the reaction (entry 3). The addition of Et_3N resulted in a dramatic increase in urea formation (entry 4). Finally, diminishing the temperature to 70 °C in THF had minimal effect on the yield (entry 5). Surprisingly, a reduction in boroxine loading was observed to inhibit the transformation entirely (entry 6). Taken together, these initial results strongly support the potential of Boc-carbamates in chemoselective amidation. However, the strong dependence on boroxine loading and increased reaction concentration stands in stark contrast to the development of 'dilute conditions' necessary for efficient amidation of phenol blocked ambiphilic isocyanates. A mechanistic study will be necessary to probe the underlying kinetic regime in this system.

Table 4.12: Optimization of Boc-amidation in the presence of benzyl amine.[a]



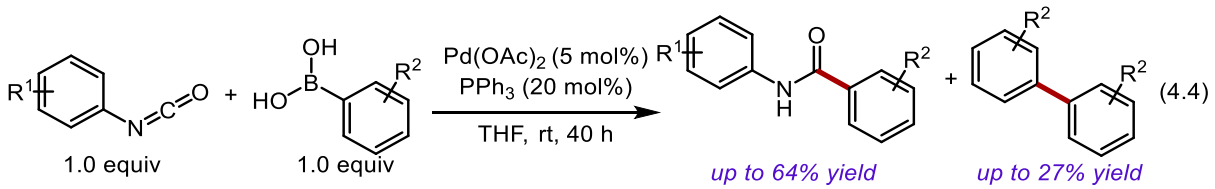
Entry	Concentration (M)	Catalyst (mol %)	25a ("Ar-B" equiv)	26aa yield (%)	28c yield (%)
1	0.1	5.0	3.0	0	8
2	0.5	5.0	3.0	71	9
3	0.5	2.5	3.0	57	8
4[b]	0.5	5.0	3.0	39	31
5[c]	0.5	5.0	3.0	67	8
6[c]	0.5	5.0	1.5	0	3

[a]Conditions: **29a** (0.2 mmol), **25a** (0.2 equiv), $[Rh]_2$ (5.0 mol%), $BnNH_2$ (0.2 mmol), THF (0.1 M), 100 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]Et_3N (0.2 mmol). [c]70 °C.

4.3 Palladium Catalyzed Amidation of Blocked Isocyanates

With the successful application of a rhodium catalyst for the amidation of blocked isocyanates, the prospects of employing alternative metal catalysts were targeted. Palladium is an attractive alternative given its lower cost and higher availability. Remarkably, the development of palladium

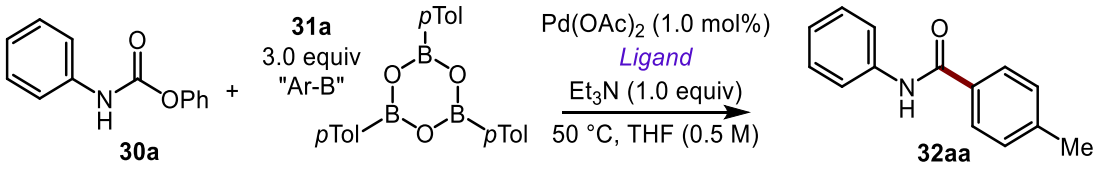
catalyzed transformations of isocyanates remain rather limited[76,100,114-115,119-119] when contrasted to its dominant role in the development of cross coupling reactions,[239] C-H activations,[240] and Buchwald-Hartwig aminations.[241] This may be the result of an increased tendency of palladium to undergo deleterious side reactions in the presence of isocyanates.[69] This unwanted activity is hinted at in the palladium catalyzed synthesis of urea derivatives developed by Buchwald and coworkers, where blocking the isocyanate in situ was found to increase yields for problematic substrates.[139] Nevertheless, precedence for the palladium catalyzed addition of arylboronic acids to isocyanates suggested the feasibility of such a transformation on blocked derivatives (eq. 4.4).[75] Unfortunately, this prior work is characterized by low yields and suffered from a detrimental homocoupling side reaction. The implementation of a blocking strategy in such a system would seemingly exacerbate this undesired homocoupling side reaction however, the ability to modulate catalytic activity through the use of ligands was thought to hold the key to overcome this limitation.



Studies began using the catalyst system reported by Kianmehr and coworkers on the model system studied for the rhodium catalysis with the help of David Brzezinski (table 4.13).[75] Unfortunately, this catalyst system failed to provide the desired product (entry 1-2). A variety of ligands were subsequently screened including bidentate phosphines (entry 3-5), bypyridine (entry 6), and Buchwald type ligands (entry 7-11). Interestingly, SPhos proved almost singularly effective at promoting the desired reaction (entry 11). No significant difference in reactivity was observed when using SPhos in either 1.2 or 2.0 equivalents relative to Pd (entry 12-13) while a decrease in reactivity was observed upon using 3.0 equivalents (entry 14). Notably, the organoboron reagent loading could be dropped to 1.5 equivalents with no significant impact on the overall efficiency (entry 15).

[239] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177.
[240] (a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754. (b) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787.
[241] Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.

Table 4.13: Ligand screen[a]

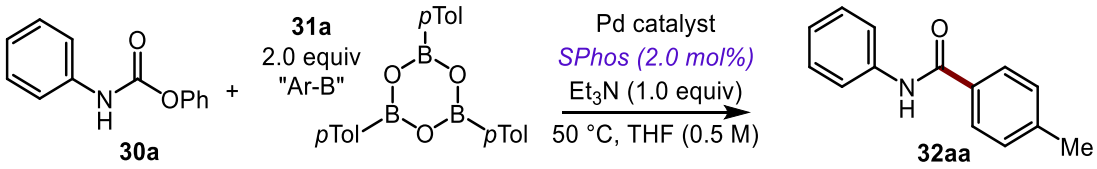


Entry	Ligand	Yield (%)
1	PPh_3 (4.0 mol%)	0
2	PPh_3 (2.0 mol%)	0
3	Binap (1.0 mol%)	6
4	DPPE (1.0 mol%)	8
5	DPPP (1.0 mol%)	15
6	Bipyridine (1.0 mol%)	0
7	DavePhos (2.0 mol%)	16
8	*t*-BuXPhos (2.0 mol%)	5
9	BrettPhos (2.0 mol%)	4
10	RuPhos (2.0 mol%)	19
11	SPhos (2.0 mol%)	81
12[b]	SPhos (2.0 mol%)	92
13[b]	SPhos (1.2 mol%)	91
14[b]	SPhos (3.0 mol%)	49
15[c]	SPhos (1.2 mol%)	89

[a]Conditions: **30a** (0.2 mmol), **31a** (0.2 mmol, 3.0 'Ar-B' equiv), $Pd(OAc)_2$ (1.0 mol%), ligand (2.0 mol%) Et_3N (0.2 mmol), THF (0.5 M), 50 °C, unless indicated otherwise. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]**31a** (0.13 mmol, 2.0 'Ar-B' equiv). [c]**31a** (0.10 mmol, 1.5 'Ar-B' equiv).

A variety of palladium precatalysts were then screened for their ability to promote the desired reaction (table 4.14). Interestingly, the next most competent precatalyst was $Pd_2(dba)_3$ (entry 4). This was unexpected given the presumed catalytic cycle which remains in a Pd(II) oxidation state. Furthermore increasing the loading of $Pd(OAc)_2$ was found to be detrimental to the reaction (entry 5-6), especially in the case of 3.0 mol%, where significant amounts of starting material remained.

Table 4.14: Palladium precatalyst screen[a]

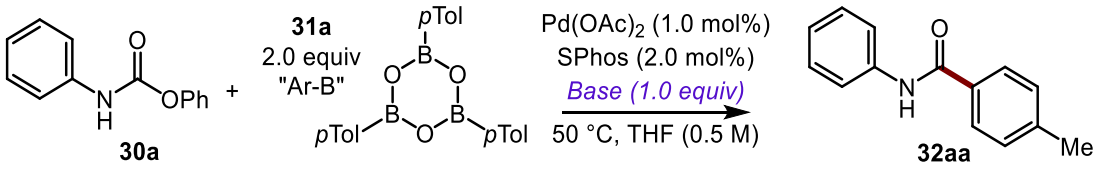


Entry	Pd catalyst	Yield (%)
1	$Pd(acac)_2$ (1.0 mol%)	10
2	$Pd(Cl)_2$ (1.0 mol%)	4
3	$Pd(TFA)_2$ (1.0 mol%)	16
4	$Pd_2(dba)_3$ (0.5 mol%)	21
5[b]	$Pd(OAc)_2$ (2.0 mol%)	72
6[b]	$Pd(OAc)_2$ (3.0 mol%)	40 >[c]

[a]Conditions: **30a** (0.2 mmol), **31a** (0.13 mmol, 2.0 'Ar-B' equiv), Pd precatalyst (1.0 mol%), SPhos (2.0 mol%) Et_3N (0.2 mmol), THF (0.5 M), 50 °C unless indicated otherwise. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]**21a** (0.10 mmol, 1.5 'Ar-B' equiv), 1:2 ratio Pd:SPhos. [c]Overlapping NMR peaks hampered yield. Starting material dominated mass balance.

The ability of various bases to promote the desired transformation was then probed (table 4.15). Analogous to the rhodium catalyzed reaction, Et_3N proved almost singularly effective at providing the desired product (entry 1). DBU, *N*-MeMorph, and K_2CO_3 failed to provide the desired product in even trace amounts (entry 2-4). The desired product was observed when using DIPEA however in reduced yield (entry 5). Unsurprisingly, the exclusion of base in the reaction resulted in the absence of product formation with predominately **30a** remaining (entry 6).

Table 4.15: Base screen[a]

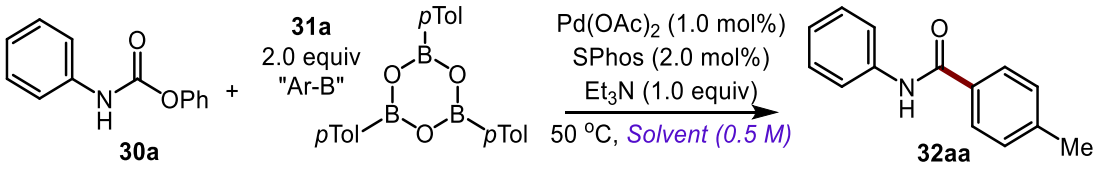


Entry	Base	Yield (%)
1	Et_3N	92
2	DBU	0
3	*N*-methylmorpholine	0
4	K_2CO_3	0
5	DIPEA	47
6	none	0

[a]Conditions: **30a** (0.2 mmol), **31a** (0.13 mmol, 2.0 'Ar-B' equiv), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), Base (0.2 mmol), THF (0.5 M), 50 °C. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

The effect of solvents on the palladium catalyzed amidation were then probed (table 4.16). DMF, MeCN and DCM performed particularly poorly in the desired transformation (entry 1-3). Interestingly, toluene provided the desired product in 62% yield (entry 4). This was unexpected given the likely decrease in isocyanate concentration due to the reduced polarity of toluene relative to THF. Nevertheless, ethereal solvents such as dioxane (entry 5) and THF (entry 6) proved ideal for the transformation at hand.

Table 4.16: Solvent screen[a]

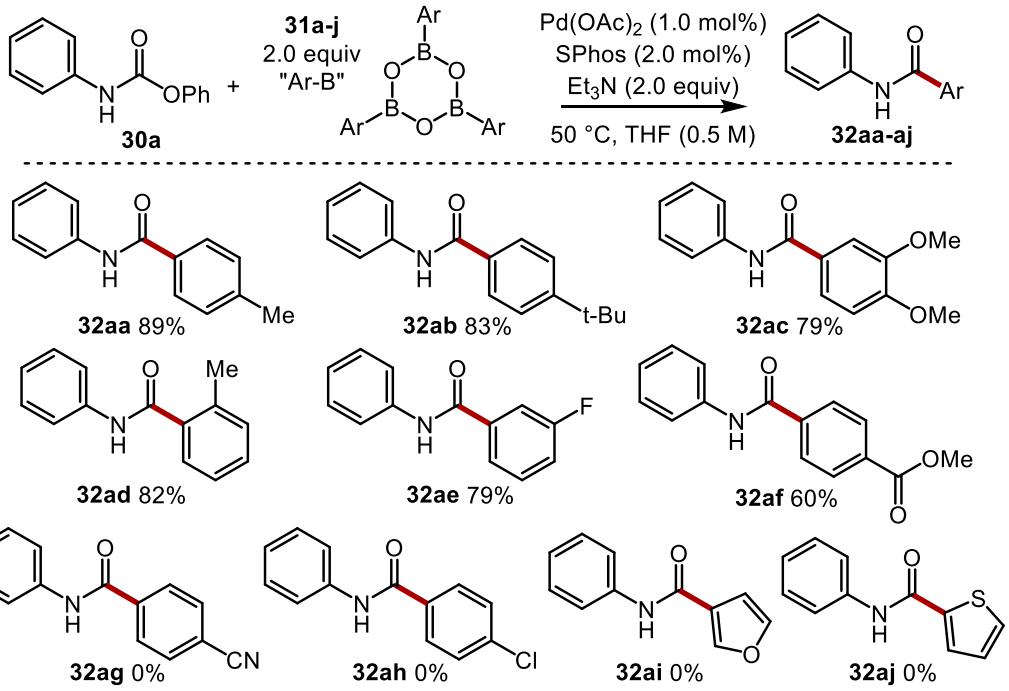


Entry	Solvent	Yield (%)
1	DMF	10
2	MeCN	4
3	CH_2Cl_2	11
4	Toluene	62
5	Dioxane	82
6	THF	92

[a]Conditions: **30a** (0.2 mmol), **31a** (0.13 mmol, 2.0 'Ar-B' equiv), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), Et_3N (0.2 mmol), solvent (0.5 M), 50 °C. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

The optimized conditions obtained in the end are seen in table 4.13 entry 15. Unfortunately, reproducibility issues with respect to the reaction reaching completion were observed upon scale-up. This was largely mitigated by varying the reaction conditions slightly with an increase in both the SPhos (2:1 ratio to Pd) and Et_3N (2.0 equivalents). With these conditions in hand, the scope of the aryl boroxine reagent on the reaction was then probed (table 4.17). The optimized substrate was successfully isolated providing the desired product in 89% yield (**32aa**). Various electron rich arylboroxine derivatives were competent reaction partners under the optimized conditions (**32ab**-**ac**). A substrate bearing increased steric hinderance formed the desired product with little effect on reaction efficiency (**32ad**). A mild electron withdrawing group was tolerated with no issues (**32ae**). However, upon increasing the deactivating nature of the substituents, a decrease in reactivity was observed, where *p*-methylester required 48 hours to reach completion (**32af**), while *p*-cyano proved incompetent for the desired amidation (**32ag**). Unfortunately, a halide bearing motif (**32ah**), and heterocyclic derivatives also proved problematic reaction partners (**32ai-aj**).

Table 4.17: Arylboroxine substrate scope for palladium catalyzed amidation[a]

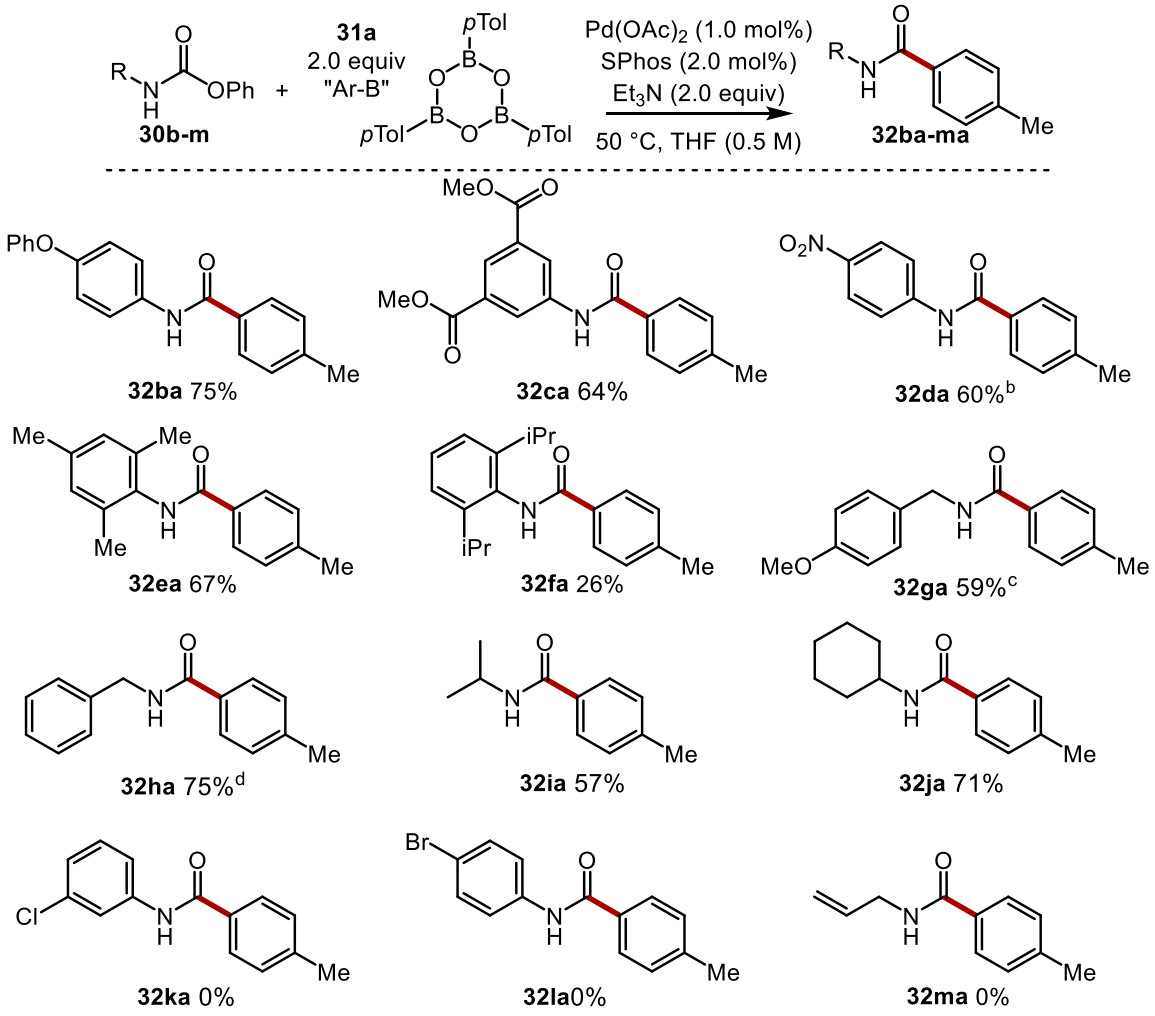


[a]Conditions: **30a** (0.6 mmol), **31a-q** (0.4 mmol, 2.0 'Ar-B' equiv), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), Et_3N (1.2 mmol), solvent (0.5 M), 50 °C.

Attention was then focused on the scope of the blocked isocyanate derivative, largely conducted by David Brzezinski (table 4.18). The use of both electron-rich aryl isocyanates and electron-poor derivatives were amenable to the transformation (**32ba-ca**). The presence of a *p*-nitro motif was tolerated under the reaction conditions although higher temperatures were necessary to achieve a respectable yield (**32da**). A mesityl derived blocked aryl isocyanate precursor was a competent reaction partner in spite of its steric bulk (**32ea**), however a particularly low yield was achieved upon increasing the steric bulk (**32fa**). The applicability of alkyl derivates were then tested for the desired transformation. A variety of benzylic substrates (**32ga-ha**) and secondary amine derived substrates (**32ia-ja**) were amenable to the transformation. However, overall alkyl derivatives were less well behaved than their aryl counterparts, where lower yields were generally observed and, in some cases, increase in temperature was necessary. This phenomenon likely results from a more demanding insertion of the Pd-aryl species and/or a shift in the deblocking equilibrium diminishing the concentration of isocyanate under the reaction conditions. Both of these effects are expected to exacerbate a competitive homocoupling side-reaction. Analogous to the arylchloride boroxine **31h**, blocked isocyanate derivatives that could undergo oxidative addition failed to provide the desired product under the reaction conditions (**32ka-ma**). Taken together, these

results support the formation Pd(0) under the reaction conditions where subsequent oxidative addition into aryl halides or π-allyl formation deactivates the catalyst.

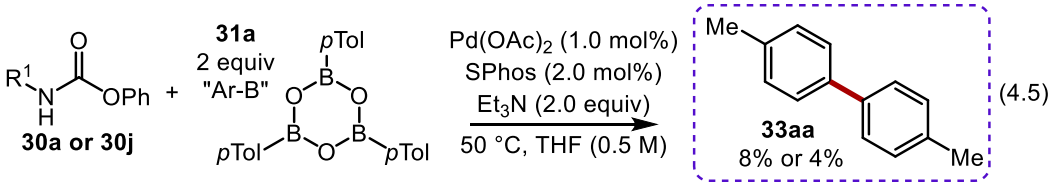
Table 4.18: Blocked isocyanate scope for palladium catalyzed amidation.[a]



[a]Conditions: **30ba-na** (0.6 mmol), **31a** (0.4 mmol, 2.0 'Ar-B' equiv), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), Et_3N (1.2 mmol), THF (0.5 M), 50 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]100 °C in dioxane. [c]70 °C. [d]80 °C.

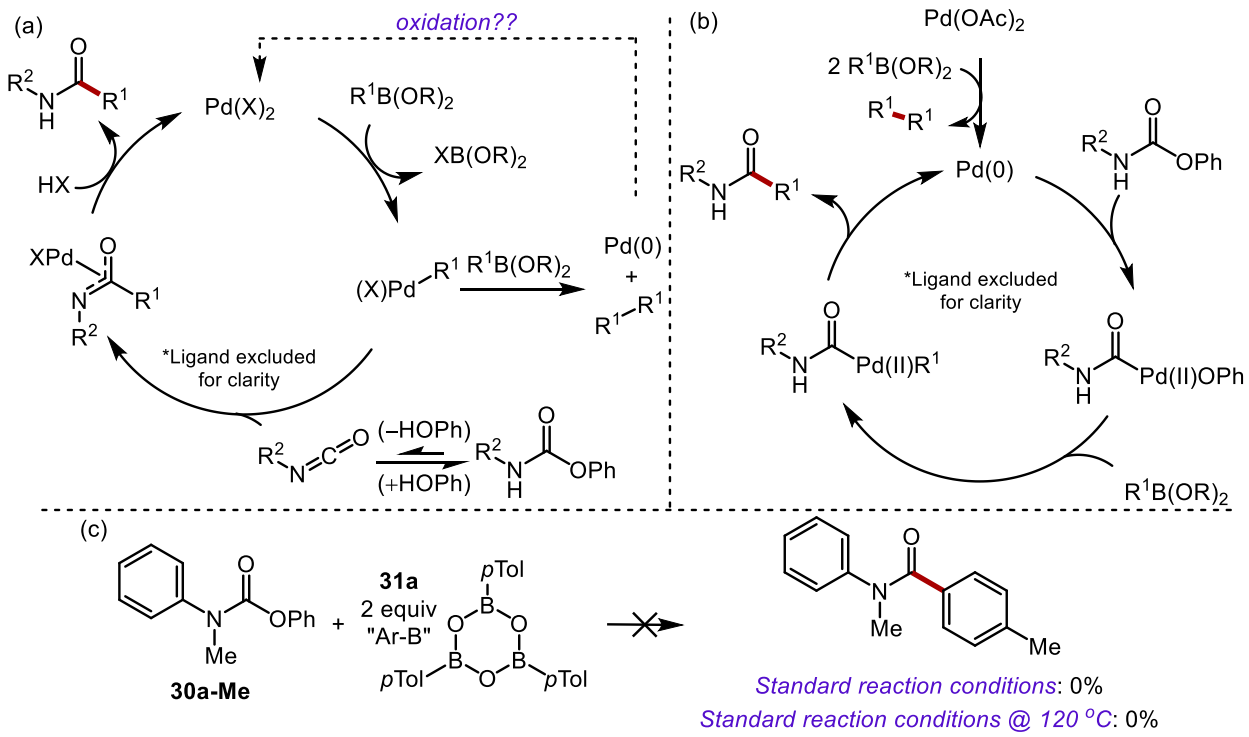
Overall, trends in reactivity are difficult to discern although it is clear that currently the palladium-catalyzed process exhibits a marked decrease in robustness as compared to its rhodium counterpart. A number of by-products were isolated over the course of the reaction scope which could provide insight towards this end. First and foremost, the formation of homocoupling by-products are consistently formed in greater yield than the loading of the palladium catalyst (eq. 4.5). This, along with the above mentioned inhibitory effect of substrates amenable to oxidative addition, strongly support the formation of Pd(0)

under the reaction conditions. However, if a redox neutral Pd(II) catalytic cycle is operative, a competent oxidant capable of re-oxidizing the inactive Pd(0) species is necessary to explain this result (scheme 4.6a). Trace quantities of oxygen could explain this result however, the presence of oxidized arylboron by-products were not detected under the reaction conditions. Moreover, the strict anhydrous set-up employed coupled with the use of basic conditions bring into question the ability to reform the active catalyst through protodemetallation. Phenol could conceivably play such a role; however, no evidence towards this end has been obtain as of yet.



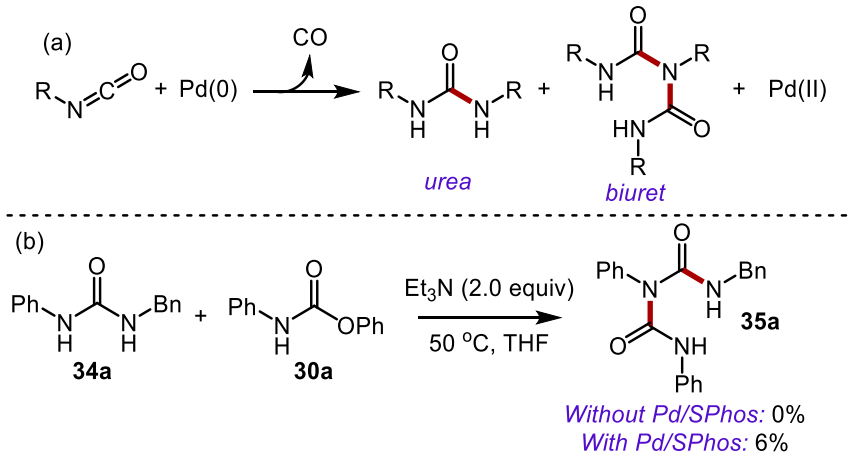
Given these inconsistencies, the potential for a Pd(0)-Pd(II) catalytic cycle was posited, with oxidative addition into the C-O bond as the key step (scheme 4.6b).[242] To test this hypothesis, control reactions on a methylated blocked isocyanate derivate (**30a-Me**) were employed (scheme 4.6c). This inhibits the ability to form isocyanates under the reaction conditions, while minimally effecting any pathway involving oxidative addition into the C-O bond. No product was formed under standard reaction conditions, or upon heating at 120 °C. This supports the necessary formation of an isocyanate intermediate for productive product formation.

[242] For representative examples of Pd(0) oxidative addition into similar C-O bonds, see: (a) Halima, T. B; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. *J. Am. Chem. Soc.* **2017**, *139*, 1311. (b) Halima, T. B.; Vandavasi, J. K.; Shkoor, M.; Newman, S. G. *ACS Catal.* **2017**, *7*, 2176. (c) Shi, S.; Lei, P.; Szostak, M. *Organometallics* **2017**, *36*, 3784. (d) Shi, S.; Nolan, S. P.; Szostak, M. *Acc. Chem. Res.* **2018**, *51*, 10, 2589. (e) Masson-Makdissi, J.; Vandavasi, J. K.; Newman, S. G. *Org. Lett.* **2018**, *20*, 4094.



Scheme 4.6: (a) Redox neutral Pd(II) catalytic cycle. (b) Pd(II)-Pd(0) catalytic cycle. (c) Control reaction with methylated derivative.

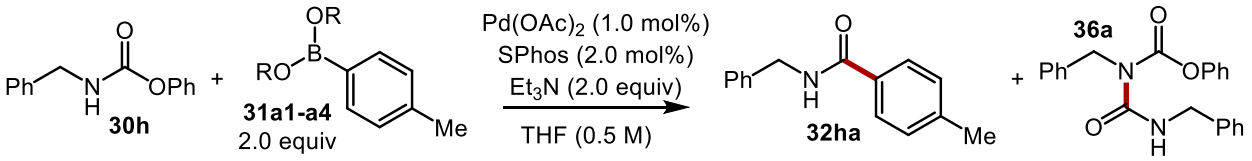
Alternatively, the palladium mediated oligomerization of isocyanates could serve as an *in situ* oxidation technique (scheme 4.7a).[69] The presence of biuret and urea by-products detected during studies undertaken to establish the scope of this reaction support this hypothesis. However, control reactions reveal a palladium mediated addition of urea nitrogen onto the blocked isocyanate **30a** (scheme 4.7b). This reactivity was not observed in the absence of palladium suggesting the formation of the biuret by-product does not required a Pd(0) species. The formation of urea itself could be mediated via a Pd(0)-Pd(II) pathway, although the presence of urea throughout experiments even in the absence of palladium make it difficult to draw conclusions towards this end. Consequently, the oligomerization of the isocyanate species is an attractive explanation for *in situ* oxidation, however no direct evidence has been generated thus far in support of this pathway.

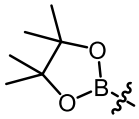
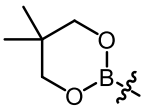
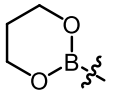
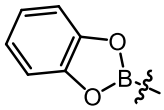


Scheme 4.7: (a) Oxidation of Pd(0) catalyst via isocyanate oligomerization. (b) Control reaction showing the involvement of Pd(II) in biuret formation.

The ability to avoid the formation of a low valent palladium species altogether was hypothesized to be possible through manipulation of the organoboron reagent (table 4.19). Employing boronic acid ester reagents were expected to reduce the rate of transmetallation allowing to circumvent the detrimental homocoupling reaction. However, these derivatives were nearly completely inert at both 50 °C and 70 °C. A catechol derived arylboron reagent was the sole example where product was observed, however only at increased temperature. Interestingly, the oligomerization was observed to occur competitively in all reactions (**36a**), with increase in formation at higher temperature.

Table 4.19: Probing the reactivity of various organoboron reagents[a]

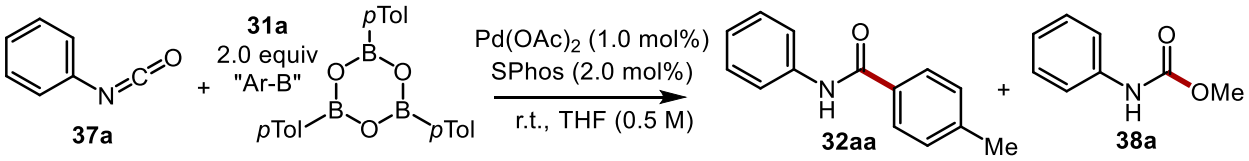


		conducted @ 50 °C		*conducted @ 70 °C*	
Entry	**Organoboron**	**Yield 32ha (%)**	**Yield 36a (%)**	**Yield 32ha (%)**	**Yield 36a (%)**
1		0	3	0	3
2		0	17	0	32
3		0	7	0	20
4		0	4	13	6

[a]Conditions: **30h** (0.2 mmol), **31a1-a4** (0.4 mmol), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), Et_3N (0.4 mmol), THF (0.5 M), 50 °C unless otherwise indicated. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

The effect of the blocking group on the reaction was then probed. As alluded to above, the implementation of the blocking group strategy in such a system was believed to have deleterious effects on the overall reactivity by exacerbating the homocoupling side reaction. As such, its removal was expected to result in highly efficient isocyanate amidation. Surprisingly, the catalytic system was almost completely inactive when employing free phenyl isocyanate at both room temperature or 50 °C (table 4.22, entry 1-2). The addition of Et_3N was observed to boost the yield slightly, however significant degradation of the isocyanate was observed (entry 3). In fact, control reactions revealed the formation of trimeric isocyanurate by-product in the presence of Et_3N. Interestingly, Kianmehr's catalytic system, which was completely inactive on blocked isocyanate **30a**, did provide the desired product using their reported reaction conditions (entry 5). Furthermore, employing the commercially available boronic acid **31a** without further manipulation was observed to boost the yield slightly (entry 6). Nevertheless, the 64% yield reported in their communication was not able to be reproduced.

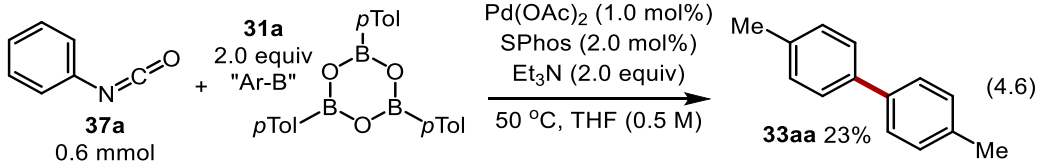
Table 4.20: Control reactions on free isocyanate[a]



Entry	Deviation from conditions	32aa Yield (%)	38a yield (%)[b]
1	None	6	79
2	50 °C	6	74
3	2.0 equiv Et_3N @ 50 °C	17	21
4[c]	2.0 equiv Et_3N @ 50 °C, No Pd/SPhos/Boroxine	0	5%
5	[Pd] 5.0 mol%, PPh_3 (20 mol%), 0.33 equiv $[RBO]_3$	14	42%
6[d]	[Pd] 5.0 mol%, PPh_3 (20 mol%), 1.0 equiv $RB(OH)_2$	28	68%

[a]Conditions: **37a** (0.2 mmol), **31a** (0.13 mmol), $Pd(OAc)_2$ (1.0 mol%), SPhos (2.0 mol%), Et_3N (0.4 mmol), THF (0.5 M), 50 °C unless otherwise noted. ^1H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]Reactions were quenched with MeOH and stirred at room temperature for 1 h. Presence of **38a** is assumed to represent remaining starting material. [c]Crude NMR matched literature reports of phenyl isocyanurate. [d]Commercially available boronic acid used directly.

To gain further insight on the role of the blocking group under the reaction conditions, entry 3 from table 4.20 was run on large scale in hopes of isolating telling by-products (eq. 4.6). Unfortunately, no such by-products were isolated during column chromatography. However, the homocoupling by-product **33aa** was isolated in 23% yield. This is almost three times the amount formed when employing the blocked isocyanate starting material **30a**. Moreover, this result is almost identical to that observed by Kianmehr in their work using $Pd(OAc)_2/PPh_3$.[75] This suggest the fundamental assumption made at the outset of this research project, that is, ligands will allow the mitigation of the undesired homocoupling by-product formation, is likely incorrect.



4.4 Conclusion and Perspective

In conclusion, these results strongly support the use of a blocked isocyanate strategy in catalytic amidation reactions. In the case of rhodium catalysis, an unprecedented scope was achieved overcoming

the severe limitations typically encountered using free isocyanates. Initial mechanistic studies suggest that efficient amidation of ambiphilic derivatives hinged on a rate determining isocyanate release. Moreover, initial results on the amidation of Boc-carbamates holds great promise for the expansion of such reactivity to encompass substrates bearing highly nucleophilic amines. Moreover, the interesting dependence on aryl boroxine loading in such a system suggests the potential dual role of such a species. Conceivably, these Lewis acidic species could play a further role in sequestering the amine nucleophile diminishing the rate of competitive addition. Mechanistic studies probing the intermediacy of an isocyanate and the dependence of the arylboroxine species are of utmost importance in further developing this transformation. Overall, this work provides the first steps on the path to broadly applicable amidation of blocked isocyanates, analogous to that observed in urea synthesis from similar precursors with blocked isocyanates in the synthesis of ureas.

The success of the palladium catalyzed amidation of blocked isocyanates was found to rely on the use of a blocking group strategy where exceptionally poor reactivity was observed on free isocyanates. This result helps crystallize the power of implementing a blocking group strategy, a concept that has been largely overlooked in the development of catalytic transformations of isocyanates. The exact role of the blocking group in this system is currently not well understood, although it is believed to play a role in mitigating undesired reactivity with the isocyanate species. Further mechanistic investigations of this system are necessary to gain an understanding of the role played by the blocking group and the nature of the catalytic cycle. Such investigations will be carried out by David Brzezinski throughout the remainder of his masters. This information holds great promise in promoting the further development of palladium catalyzed transformations of isocyanates which have seen sparse attention in the literature.

Chapter 5: Summary and Outlook

In conclusion, the goals stated at the outset of this thesis, that is, expanding the development of *N*-isocyanate cascades and developing general strategies for the addition of carbon nucleophiles to blocked *N*-, *O*-, and *C*-iscocyanates have either been achieved or have promising initial results. Importantly, ample opportunities remain on many of these novel avenues of research for further developments which in some cases have been alluded to in the text, which will be further elaborated upon here.

The synthesis of hydroxamates from blocked *O*-isocyanates and carboxylic acids has proven versatile. However, a more in-depth study of the mechanism could provide insight into designing a reagent which allows milder reaction conditions. This is of primary importance to help address the excessive formation of by-products formed under the reaction requiring high loadings of the blocked *O*-isocyanate reagent. Furthermore, milder reaction conditions would allow the expansion of applicability to large scale synthesis. Nevertheless, this initial work lays the foundation for understanding such reactivity, an understanding which should allow for the development of reaction cascades of higher complexity.

The synthesis of hydroxamate derivatives using Grignard reagents as nucleophiles also holds excellent potential however, identification of the underlying issues resulting in sporadic results will be key in developing a broadly applicable transformation. This issue is currently being addressed by Alshimaa Mohamed. Moreover, circumventing the need for heating at reflux is highly desirable as this is expected to mitigate the undesired product/starting material degradation. This could be achieved through probing the use of alternative blocking groups, or probing additives which may destabilize the formation of a 5-membered chelate (e.g. glyme, diglyme, TMEDA, etc.). If successful, a significant increase in applicability is expected given the potential for employing functionalized Grignard reagents pioneered by Knochel and coworkers.[243] Such studies could lay the foundation for the eventual development of the direct transformation of C-H bonds into hydroxamate/hydroxamic acid derivatives through the use of turbo Hauser bases.[227] This reactivity is expected to transfer to the synthesis of hydrazides given the initial result on blocked *N*-isocyanates described at the end of chapter 3.

Finally, the successful development of catalytic amidations of blocked *C*-isocyanates is expected to have broad implications for future developments of catalytic transformations of isocyanates. The unprecedent functional group tolerance achieved using such a strategy stands in stark contrast to the near absence of reports using blocked isocyanates in catalysis. Moreover, initial results on the chemoselective amidation of *O*-*t*-butyl carbamates suggest a fruitful platform for amide synthesis in the presence of highly nucleophilic/Lewis basic motifs. The success of such a transformation is expected to have broad implications given the widespread use of Boc-amines as protecting groups, coupled with the widespread application of a deprotection/acylation synthetic sequence. Future work towards this end should focus a study of the mechanism to shed light on whether an isocyanate intermediate is in-fact active under the reaction conditions.

The palladium catalyzed amidation of blocked isocyanate derivatives will also be further pursued by David Brzezinski throughout his graduate studies. Although this reaction has been met with reasonable success, a thorough understanding of the underlying issues plaguing this catalytic system is necessary to increase its scope of applicability. Moreover, identification of these underlying issues could hold the key

[243] Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

as to why so few examples of palladium catalyzed transformations of isocyanates have been reported. Finally, an in-depth understanding of such a transformation could provide the foundation for developing palladium catalyzed C-H amidation. Although the C-H amidation using isocyanates is well developed, such transformations hinge on the presence of a directing group which are typically undesired in the final compound, thus requiring additional steps for their removal. Alternatively, undirected C-H arylation chemistry using palladium catalysis is well developed.[244] Conceivably, such reactivity may be harnessed to develop undirected C-H amidations using blocked isocyanates.

Finally, the successful development of these metal catalyzed transformations of blocked isocyanates holds broader implications for catalysis as a whole. The near absence of precedence for catalytic transformations of isocyanates suggest a thorough study of alternative reactivity manifolds could provide fruitful avenues of research. For instance, the development of organocatalyzed reactions making use of bulky secondary amines has been thoroughly developed,[245] however, their use with isocyanates is largely unknown. Naturally sequestration of the active catalyst through nucleophilic attack of the isocyanate would hamper such development, however a thorough understanding of blocked isocyanate derivatives coupled with the reversible addition of bulky amine onto isocyanate suggest such a strategy holds untapped opportunities.

[244] For selected examples see: (a) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749. (b) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
[245] Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

Chapter 6: Supporting Information

6.1 General Information

Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum, cut to size. Visualization was accomplished with UV light followed by staining with a potassium permanganate solution and heating.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 MHz and 400 MHz spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm or DMSO-d_6 at 2.50 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.43 for ^{13}C NMR). ^{1}H NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextuplet, sept = septuplet, m = multiplet), integration and coupling constant(s) in Hz. Infrared (IR) spectra were obtained on neat samples using an Attenuated Total Reflectance Fourier transform infrared spectrometer (ATR-FTIR). High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV (EI) or Micromass Q-TOF I- Time of Flight Electrospray Ionization mass spectrometer (ESI) at the Ottawa-Carleton Mass Spectrometry Centre. Enantiomeric excess was determined using Agilent technologies 1200 series HPLC. Optical rotations were measured using Anton Paar mcp500 polarimeter.

Unless otherwise noted, all commercially available materials were purchased from commercial sources and used without further purification. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and trifluorotoluene ($PhCF_3$) was passed through an activated alumina column embedded in a solvent purification system provided by LC Technology Solutions.

6.2 Supporting Information for Chapter 2

6.2.1 Divergent reactivity of N-substituted iso(thio)cyanates (section 2.2)

Starting material synthesis

Blocked *N*-iso(thio)cyanates **1a-b,d,f-h,i-j,l,**[178b] **1c**,[207] **1k**,[178a] **1m**,[246] **1h,4b,**[179] and **4a**[247] were prepared by known methods following literature procedures. Propargylic amines **2c,**[248] **2d,**[249] **2e,**[250] **2g-h,**[251] **2i,**[252] and **2j**[253] were prepared by known methods following literature procedures.

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[246] *Int. Pat.*, WO2013067646A1, 2013

[247] Lieber, E.; Ramachandra, J. *Can. J. Chem.* **1959**, *37*, 101

[248] Roy, O.; Faure, S.; Thery, V.; Didierjean, C.; Taillefumier, C. *Org. Lett.* **2008**, *10*, 921

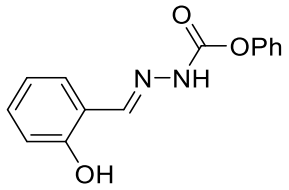
[249] Nieman, J. A.; Nair, S. K.; Heasley, S. E.; Schultz, B. L.; Zerth, H. M.; Nugent, R. A.; Chen, K.; Stephanski, K. J.; Hopkins, T. A.; Knechtel, M. K.; Oien, N. L.; Wieber, J. L; Wathen, M. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3039.

[250] Ya, Z.; Porco Jr., J. A.; Snyder, J. K. *Org. Lett.* **2007**, *9*, 393.

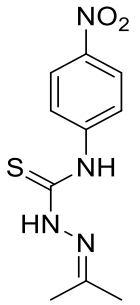
[251] Rajagopal, B.; Chou, C.-H.; Chung, C.-C.; Lin, P.-C. *Org. Lett.* **2014**, *16*, 3752

[252] Wipf, P.; Hopkins, C. R. *J. Org. Chem.* **1999**, *64*, 6881.

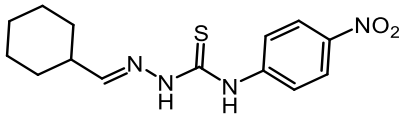
[253] Kwong, F. Y.; Li, Y. M.; Lam, W. H.; Qui, L.; Lee, H. W.; Yeung, C. H.; Chang, K. S.; Chan, A. S. C. *Chem. Eur. J.* **2005**, *11*, 3872.



(*E*)-Phenyl 2-(2-hydroxybenzylidene)hydrazinecarboxylate (1e): Phenyl carbazate (2.53 g, 16.6 mmol) was dissolved in methanol (50.0 mL) completely in a round bottom flask charged with a stir bar. Salicylaldehyde (1.77 mL, 16.7 mmol) was then added to the mixtue. The mixture was stirred at room temperature for 1 hour. The precipitate was then filtered and recrystallized in boiling EtOAc followed by a few drops of hexanes yielding the title compound as thin colorless needles (1.372 g, 32%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 11.81 (br s, 1H), 10.71 (br s, 1H), 8.40 (br s, 1H), 7.56 (dd, *J* = 7.7, 1.6 Hz, 1H) 7.47-7.40 (m, 2H) 7.30-7.21 (m, 4H), 6.93-6.86 (m, 2H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 156.9 (C), 145.5 (C), 131.2 (CH), 139.5 (CH), 128.4 (CH) 125.6 (CH), 121.8 (CH), 119.4 (CH), 119.0 (C), 116.3 (CH). IR (film): 1684, 1675, 1663, 1649, 1514, 1456, 1393, 1307, 1248, 1166 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{12}N_2O_3$ [M]$^+$: 256.0845 Found: 256.0850

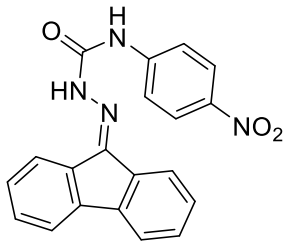


***N*-(4-Nitrophenyl)-2-(propan-2-ylidene)hydrazinecarbothioamide (4c):** To a solution of acetone (0.15 mL, 2.00 mmol) in MeOH (10.0 mL) was added *N*-(4-nitrophenyl)hydrazinecarbothioamide (0.425 g. 2.00 mmol) and the solution was stirred at reflux for 3 hours. Upon cooling, a solid precipitated and was collected by filtration to afford the desired product as a orange solid (0.250 g, 50%). TLC R_f = 0.29 in 10 % EtOAC/CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-d_6): δ 10.75 (br s, 1H), 10.25 (br s, 1H), 8.20 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 2.04 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 175.8 (C), 154.5 (C), 145.5 (C), 143.1 (C), 123.7 (CH), 123.5 (CH), 25.1 (CH_3), 18.1 (CH_3). IR (film):1637, 1596, 1558, 1523, 1330, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{12}N_4O_2S$ [M]$^+$: 252.0681. Found: 252.0694.



***N*-(4-Nitrophenyl)-2-(cyclohexylmethylene)hydrazinecarbothioamide (4d):** To a solution of cyclohexane carboxaldehyde (0.225 g, 2.00 mmol) in MeOH (10.0 mL) was added *N*-(4-nitrophenyl)hydrazinecarbothioamide (0.425 g. 2.00 mmol) and the solution was stirred at reflux for 3 hours. Upon cooling, a solid precipitated and was collected by filtration to afford the desired product as a yellow solid (0.375 g, 61%). TLC R_f = 0.36 in 10% EtOAC/CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-d_6): δ 8.25-8.14 (m, 3H), 8.05-8.02 (m, 2H), 7.45 (d, *J* = 5.7 Hz, 1H), 2.32-2.23 (m, 1H), 1.84-1.61 (m, 5H), 1.34-1.16 (m, 5H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 175.0 (C), 152.8 (CH), 145.4 (C), 143.2 (C), 123.7 (CH). 40.1 (CH), 29.5

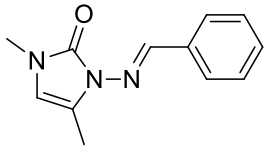
(CH_2), 25.4 (CH_2), 25.0 (CH_2). IR (film): 2941, 1641, 1585, 1552, 1450, 1332, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{18}N_4O_2S$ $[M]^+$: 306.1150. Found: 306.1197.



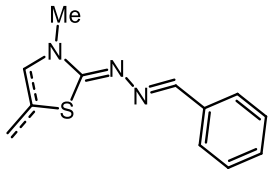
2-(9H-Fluoren-9-ylidene)-N-(4-nitrophenyl)hydrazinecarbamide (1k-PNA): To a solution of 9-fluorenone hydrazone (1.94 g, 10 mmol) in MeCN (50.0 mL) was slowly added 4-nitrophenyl isocyanate (1.62 g, 10 mmol). The solution was stirred at room temperature for 3 hours and the title compound was obtained by filtration as a yellow amorphous solid (3.44 g, 96%). ^{1}H NMR (300 MHz; DMSO-d_6): δ 10.64 (br s, 1H), 10.02 (br s, 1H), 8.06-8.03 (m, 1H), 8.01-7.96 (m, 2H), 7.93-7.90 (m, 1H), 7.85-7.83 (m, 1H), 7.57-7.52 (m, 1H), 7.48-7.36 (m, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 153.2 (C), 145.7 (C), 145.5 (C), 145.3 (C), 141.8 (C), 141.3 (C), 139.0 (C), 136.7 (C), 131.2 (CH), 130.0 (CH), 128.1 (CH), 127.0 (CH), 124.9 (CH), 122.2(CH), 120.7 (CH), 120.2 (CH), 118.9 (CH). IR (film): 1684, 1649, 1541, 1529, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{14}N_4O_3$ $[M]^+$: 358.1060. Found: 358.1060.

Synthesis of imidazolone/thiazolidine products

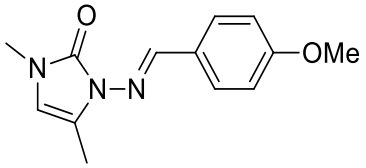
General procedure A: An oven-dried 5 mL microwave tube was charged with a stir bar, a carbazone (1.0 equiv.), a propargylic amine (1.1 equiv.), Et_3N (20 mol %) and MeCN (0.30 M). The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 2-6 hours at 100-150 °C in a microwave (μW) reactor. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



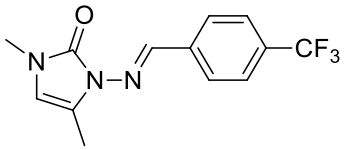
(*E*)-3-(Benzylideneamino)-1,4-dimethyl-1H-imidazol-2(3H)-one (table 2.1, 3aa): Synthesized according to general procedure **A** using carbazone **1a** (0.144 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 35% EtOAc/Hexane and the pure compound was obtained as an off-white solid (0.126 g, 86%). TLC R_f = 0.21 in 35% EtOAc/Hexane. ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.89 (s, 1H), 7.74-7.71 (m, 3H), 7.38-7.34 (m, 3H), 5.87 (q, *J*= 1.37 Hz, 1H), 3.17 (s, 3H), 2.13 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.9 (CH), 150.1 (C), 135.2 (C), 130.2 (CH), 128.6 (CH), 127.4 (CH), 120.0 (C), 106.0 (CH), 30.0 (CH_3), 10.0 (CH_3). IR (film): 2955, 2853, 1653, 1522, 1506, 1394, 903 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O$ $[M]^+$: 215.1059. Found: 215.1056.



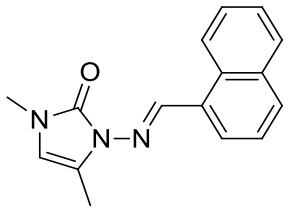
Scheme 2.3, 5aa: Synthesized according to general procedure **A** using thiosemicarbazone **4a** (0.180 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. NMR analysis showed a ratio of 63 / 37 of products with exocyclic and endocyclic double bonds. A 6 hours reaction gave 67% (exo) and 27% and 2 hours at 150 °C gave 70% and 27% while comparing to phenol production.



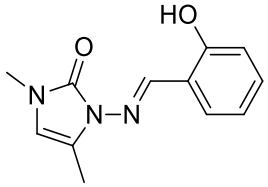
(*E*)-3-((4-Methoxybenzylidene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 2.2, entry 3ba): Synthesized according to general procedure **A** using 4-methoxybenzaldehyde carbazone **1b** (0.162 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as an off-white solid (0.126 g, 87%). TLC R_f = 0.18 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.84 (s, 1H), 7.74-7.69 (m, 2H), 6.96-6.91 (m, 2H), 5.91-5.90 (m, 1H), 3.85 (s, 3H), 3.23 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.3 (C), 151.1 (CH), 129.9 (CH), 127.9 (C), 120.0 (C), 114.0 (CH), 105.6 (CH), 55.3 (CH_3), 29.9 (CH_3), 9.9 (CH_3). IR (film): 1674, 1653, 1609, 1516, 1398, 1263, 1250, 1180, 1169, 1030 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O_2$ $[M]^+$: 245.1164. Found: 245.1123.



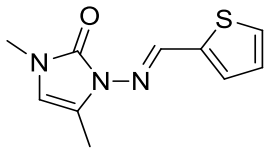
(*E*)-1,4-Dimethyl-3-((4-(trifluoromethyl)benzylidene)amino)-1H-imidazol-2(3H)-one (Table 2.2, entry 3ca): Synthesized according to general procedure **A** using 4-trifluoromethylbenzaldehyde carbazone **1c** ((0.185 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow solid (0.141 g, 83%). TLC R_f = 0.32 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.00 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 5.98-5.92 (m, 1H), 3.24 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 148.8 (CH), 127.3 (CH), 125.5 (CH), 119.9 (C), 106.4 (CH), 29.9 (CH_3), 9.9 (CH_3). IR (film): 1680, 1560, 1429, 1400, 1321, 1255, 1180, 1166 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_3OF_3$ $[M]^+$: 283.0932. Found: 283.0983.



(*E*)-1,4-Dimethyl-3-((naphthalen-1-ylmethylene)amino)-1H-imidazol-2(3H)-one (Table 2.2, entry 3da): Synthesized according to general procedure **A** using naphthalene based carbazone **1d** (0.174 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow solid (0.146 g, 92%). TLC R_f = 0.37 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.71 (s, 1H), 8.67 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.06 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.93-7.88 (m, 2H), 7.61-7.50 (m, 3H), 5.96 (q, *J* = 1.2 Hz, 1H), 3.27 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.6 (CH), 130.7 (CH), 130.7 (C), 128.6 (CH), 127.0 (C), 126.9 (CH), 126.4 (CH), 126.0 (CH), 125.3 (CH), 124.1 (CH), 120.1 (C), 29.9 (CH_3), 10.1 (CH_3). IR (film): 1693, 1564, 1539, 1472, 1420, 1288, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{15}N_3O$ $[M]^+$: 265.1215. Found: 265.1224.

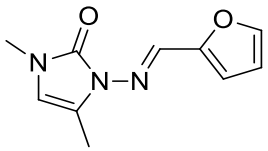


(*E*)-3-((2-Hydroxybenzylidene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 2.2, entry 3ea): Synthesized according to general procedure **A** using (*E*)-phenyl 2-(2-hydroxybenzylidene)hydrazinecarboxylate **1e** (0.154 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a white solid (0.122 g, 92%). TLC R_f = 0.4 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.87 (br s, 1H), 9.99 (s, 1H), 7.35-7.26 (m, 2H), 6.99-6.99 (m, 2H), 5.96 (s, 1H), 3.24 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 158.4 (C), 155.3 (CH), 132.1 (CH), 132.0 (CH), 119.7 (CH), 118.5 (C), 118.0 (C), 116.9 (CH), 106.5 (CH), 30.0 (CH_3), 9.9 (CH_3). IR (film): 1700, 1684, 1556, 1398, 1379, 1255 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$: 231.1008. Found: 231.1007.

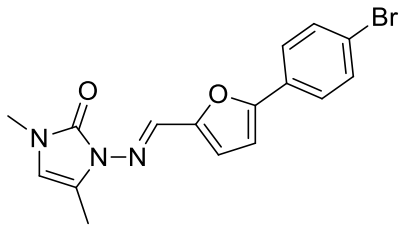


(*E*)-1,4-Dimethyl-3-((thiophen-2-ylmethylene)amino)-1H-imidazol-2(3H)-one (Table 2.2, entry 3fa): Synthesized according to general procedure **A** using thiopehene based carbazone **1f** (0.148 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a white solid (0.116 g, 87%). TLC R_f = 0.29 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 10.06 (s, 1H), 7.36 (dd, *J* = 9.4, 4.3 Hz, 2H), 7.08-7.05 (m, 1H), 5.93-5.89 (m, 1H) 3.22 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 145.7 (CH), 140.4 (C), 130.6

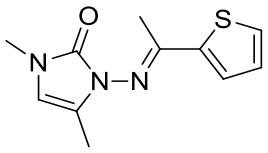
(CH), 128.1 (CH), 127.5 (CH), 119.8 (C), 118.5 (C), 105.9 (CH), 29.9 (CH_3), 9.8 (CH_3). IR (film): 1690, 1431, 1397, 1387, 1310, 1256 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3OS$ $[M]^+$: 221.0623. Found: 221.0599.



(*E*)-3-((Furan-2-ylmethylene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 2.2, entry 3ga): Synthesized according to general procedure **A** using furan based carbazone **1g** (0.138 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 2 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a white solid (0.105 g, 85%). TLC R_f = 0.32 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.83 (s, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 6.76 (dd, *J* = 3.4, 0.5 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.91 (q, *J* = 1.2 Hz, 1H), 3.21 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.1 (C), 145.6 (CH), 140.8 (CH), 119.9 (C), 114.3 (CH), 111.8 (CH), 106.0 (CH), 29.9 (CH_3), 9.9 (CH_3). IR (film): 1695, 1653, 1558, 1433, 1398, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3O_2$ $[M]^+$: 205.0851. Found: 205.0866.

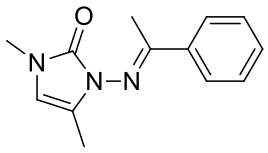


(*E*)-3-(((5-(4-Bromophenyl)furan-2-yl)methylene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 2.2, entry 3ha): Synthesized according to general procedure **A** using carbazone **1h** (0.231 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by filtration and the pure compound was obtained as a light brown solid (0.175 g, 80%). TLC R_f = 0.41 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 9.73 (s, 1H), 7.73-7.62 (m, 4H), 7.20-7.10 (m, 2H), 6.34 (s, 1H), 3.12 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz; DMSO-*d*6): δ 153.8 (C), 149.3 (C), 139.4 (CH), 131.9 (CH), 128.6 (C), 125.8 (CH), 121.3 (C), 118.3 (CH), 117.0 (C), 109.1 (CH), 107.1 (CH), 29.6 (CH_3), 9.6 (CH_3). IR (film): 1657, 1556, 1436, 1251, 1067, 1028 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{14}N_3O_2Br$ $[M]^+$: 359.0269. Found: 359.0244.

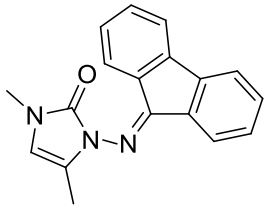


(*E*)-1,4-Dimethyl-3-((1-(thiophen-2-yl)ethylidene)amino)-1H-imidazol-2(3H)-one (Table 2.2, entry 3ia): Synthesized according to general procedure **A** using thiophene based carbazone **1i** (0.156 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 40% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow oil (0.120 g, 85%). TLC R_f = 0.16 in 40% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.51 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.07

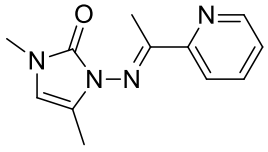
(dd, *J* = 5.1, 3.7 Hz, 1H), 5.97 (q, *J* = 1.3 Hz, 1H), 3.24 (s, 3H), 2.42 (s, 3H), 2.03 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 165.6 (C), 142.2 (C), 129.9 (CH), 129.4 (CH), 127.3 (CH), 119.7 (C), 106.7 (CH), 30.4 (CH_3), 17.6 (CH_3), 10.0 (CH_3). IR (film): 1695, 1670, 1652, 1553, 1431, 1396, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_3OS$ $[M]^+$: 235.0779. Found: 235.0803.



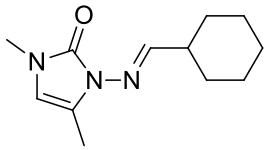
(*E*)-1,4-Dimethyl-3-((1-phenylethylidene)amino)-1H-imidazol-2(3H)-one (Table 2.2, entry 3ja): Synthesized according to general procedure **A** using acetophenone based carbazone **1j** (0.153 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 40% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow oil (0.100 g, 73%). TLC R_f = 0.3 in 40% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.96-7.90 (m, 2H), 7.47-7.34 (m, 3H), 5.98 (q, *J* = 1.3 Hz, 1H), 3.23 (s, 3H), 2.39 (s, 3H), 2.03 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.9 (C), 148.3 (C), 137.1 (C), 130.5 (CH), 128.2 (CH), 127.2 (CH), 119.5 (C), 106.7 (CH), 30.3 (CH_3), 17.6 (CH_3), 10.0 (CH_3). IR (film): 1680, 1558, 1506, 1433, 1398, 1385, 1355, 1265, 1180 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O$ $[M]^+$: 229.1215. Found: 229.1220.



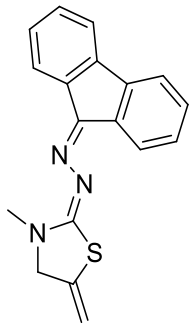
3-((9H-Fluoren-9-ylidene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 2.2, entry 3ka): Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate **1k** (0.189 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 20% EtOAc/CH_2Cl_2 and the pure compound was obtained as an orange solid (0.130 g, 75%). TLC R_f = 0.10 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.51 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.92 (d, *J* = 7.5, 1H), 7.59 (dd, *J* = 7.4, 4.0 Hz, 2H), 7.42 (qd, *J* = 7.7, 1.1 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.32-7.27 (m, 1H), 7.24-7.19 (m, 1H) 6.10 (q, *J* = 1.4 Hz, 1H), 3.31 (s, 3H), 2.08 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 165.6 (C), 143.0 (C), 141.6 (C), 136.4 (C), 132.4 (CH), 131.9 (CH), 131.0 (C), 128.6 (CH), 128.2 (CH), 127.7 (CH), 123.6 (CH), 120.0 (CH), 119.8 (C), 119.7 (CH), 107.5 (CH), 30.6 (CH_3), 17.6 (CH_3), 10.2 (CH_3). IR (film): 1686, 1678, 1605, 1589, 1450, 1431, 1379, 1340, 1180 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{15}N_3O$ $[M]^+$: 289.1215. Found: 289.1252.



(*E*)-1,4-Dimethyl-3-((1-(pyridin-2-yl)ethylidene)amino)-1H-imidazol-2(3H)-one (Table 2.2, entry 3la): Synthesized according to general procedure **A** using pyridine based carbazone **1l** (0.153 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 20% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow oil (0.119 g, 86%). TLC R_f = 0.08 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.65 (d, *J* = 4.2 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.72 (td, *J* = 7.7, 1.6 Hz, 1H), 7.33 (dd, *J* = 6.4, 5.0 Hz, 1H) 6.00 (d, *J* = 1.2 Hz, 1H), 3.25 (s, 3H), 2.53 (s, 3H), 2.03 (d, *J* = 0.9 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.7 (C), 148.6 (CH), 136.2 (CH), 124.8 (CH), 122.0 (CH), 119.6 (C), 107.0 (CH), 30.4 (CH_3), 16.6 (CH_3), 10.0 (CH_3). IR (film): 1701, 1690, 1670, 1636, 1560, 1543, 1499, 1472, 1263, 1082 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{14}N_4O$ $[M]^+$: 230.1168. Found: 230.1158.



(*E*)-3-((Cyclohexylmethylene)amino)-1,4-dimethyl-1H-imidazol-2(3H)-one (Table 2.2, entry 3ma): Synthesized according to general procedure **A** using cyclohexyl based carbazone **1m** (0.148 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 10% EtOAc/CH_2Cl_2 and the pure compound was obtained as a white solid (0.0900 g, 68%). TLC R_f = 0.31 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.98 (d, *J* = 5.5 Hz, 1H), 5.82 (q, *J* = 1.2 Hz, 1H), 3.16 (s, 3H), 2.33-2.22 (m, 1H), 2.05 (d, *J* = 1.4 Hz, 1H), 1.87-1.62 (m, 5H), 1.38-1.17 (m, 5H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.3 (CH), 150.0 (C), 119.7 (C), 105.1 (CH), 41.8 (CH_3), 29.9 (CH_2), 29.7 (CH), 25.9 (CH_2), 25.4 (CH_2), 9.8 (CH_3). IR (film): 1684, 1664, 1345, 1265, 1248 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3O$ $[M]^+$: 221.1528. Found: 221.1527.



(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-methyl-5-methylenethiazolidine (Table 2.2, entry 5ba): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), *N*-methylpropargylamine **2a** (0.0460 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a yellow solid (0.139 g, 76%). TLC R_f = 0.12 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.75-8.67 (m, 1H), 7.97-7.88 (m, 1H), 7.74-7.62 (m, 2H),

7.44-7.27 (m, 4H), 5.30-5.22 (m, 2H), 4.47-4.40 (m, 2H), 3.31-3.24 (m, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 141.3 (C), 140.1 (C), 137.7 (C), 132.0 (C), 129.7 (CH), 129.1 (CH), 129.0 (C), 127.6 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.5 (CH), 105.4 (CH_2), 59.2 (CH_2), 33.7 (CH_3). IR (film):1690, 1607, 1566, 1537, 1456, 1408, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{15}N_3S$ $[M]^+$: 305.0987. Found: 305.1005. The X-Ray information is available from the Cambridge Crystallographic Data Center: CCDC 1420524.

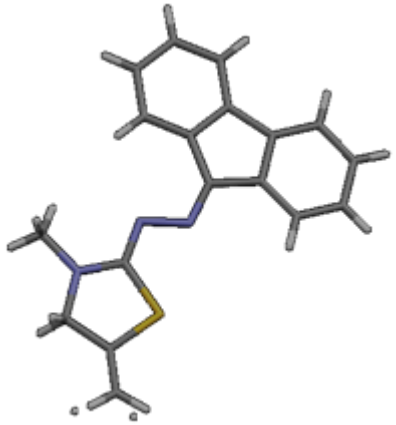
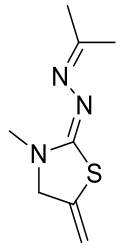
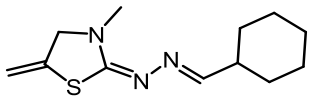


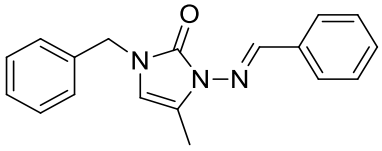
Figure 6.1: X-ray crystal structure for entry **5ba**



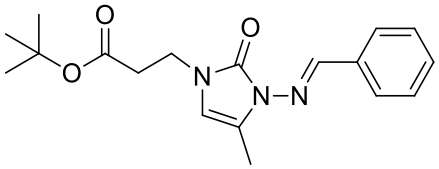
(*E*)-3-Methyl-5-methylene-2-(propan-2-ylidenehydrazono)thiazolidine (Table 2.2, entry 5ca): Synthesized according to general procedure **A** using *N*-(4-nitrophenyl)-2-(propan-2-ylidene)hydrazinecarbothioamide **4c** (0.0760 g, 0.300 mmol), *N*-methylpropargylamine **2a** (0.0230 g, 0.330 mmol), Et_3N (0.00600 g, 0.120 mmol) and MeCN (1.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a yellow solid (0.0470 g, 85%). TLC R_f = 0.24 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.18-5.13 (m, 2H), 4.23 (t, *J* = 2.3 Hz, 2H), 3.02 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 164.4 (C), 159.8 (C), 138.7 (C), 104.6 (CH_2), 58.7 (CH_2), 33.3 (CH_3), 24.7 (CH_3), 18.1 (CH_3). IR (film):1679, 1638, 1593, 1466, 1389, 1263, 1068 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_{13}N_3S$ $[M]^+$: 183.0830. Found: 183.0835.



(*E*)-2-((*Z*)-(Cyclohexylmethylene)hydrazono)-3-methyl-5-methylenethiazolidine (Table 2.2, entry 5da): Synthesized according to general procedure **A** using N-(4-nitrophenyl)-2-(cyclohexylmethylene)hydrazinecarbothioamide **4d** (0.0920 g, 0.300 mmol), *N*-methylpropargylamine **2a** (0.0230 g, 0.330 mmol), Et_3N (0.0060 g, 0.060 mmol) and MeCN (1.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a yellow oil (0.0430 g, 60%). TLC R_f = 0.30 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.59 (d, *J* = 5.8 Hz, 1H), 5.20-5.14 (m, 2H), 4.27 (t, *J* = 2.3 Hz, 2H), 3.02 (s, 3H), 2.33-2.22 (m, 1H), 1.89-1.63 (m, 5H), 1.38-1.17 (m, 5H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 166.5 (C), 160.7 (CH), 138.3 (C), 104.7 (CH_2), 58.9 (CH_2), 40.7 (CH), 33.3 (CH_3), 30.2 (CH_2), 26.0 (CH_2), 25.4 (CH_2). IR (film): 2910, 1639, 1585, 1423, 1392, 1265, 951 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3S$ $[M]^+$: 237.1300. Found: 237.1329.

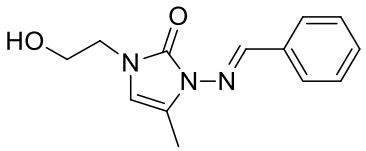


(*E*)-1-Benzyl-3-(benzylideneamino)-4-methyl-1H-imidazol-2(3H)-one (Table 2.3, entry 3ab): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), *n*-benzylpropargylamine **2b** (0.960 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as an off white solide (0.148 g, 85%). TLC R_f = 0.3 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.98 (s, 1H), 7.81-7.78 (m, 2H), 7.45-7.30 (m, 8H), 5.90 (d, *J* = 1.2 Hz, 1H), 4.79 (s, 2H), 2.18 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 151.2 (CH), 149.8 (C), 136.7 (C), 135.1 (C), 130.2 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.8 (CH), 120.4 (C), 104.6 (CH), 46.7 (CH_2), 10.0 (CH_3). IR (film): 2953, 2853, 1679, 1647, 1456, 1398, 1362, 1327, 1258 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O$ $[M]^+$: 291.1372. Found: 291.1387.

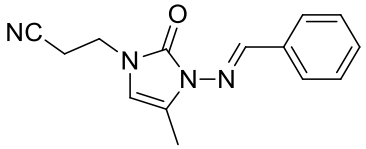


(*E*)-*tert*-Butyl 3-(3-(benzylideneamino)-4-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)propanoate (Table 2.3, entry 3ac): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), the propargylic amine **2c** (0.121 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by column chromatography using a gradient of CH_2Cl_2 to 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as a yellow oil (0.140 g, 71%). TLC R_f = 0.47 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.91 (s, 1H), 7.79-7.73 (m, 2H), 7.42-7.37 (m, 3H), 6.02 (d, *J* = 1.2 Hz, 1H), 3.85 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.17 (d, *J* = 1.2 Hz, 3H), 1.45 (s, 9H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.6 (C), 151.2 (CH), 135.1 (C), 130.2 (CH), 128.6 (CH), 127.3 (CH),

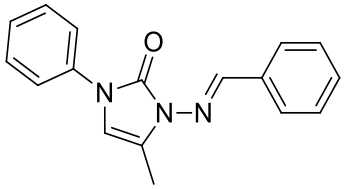
119.9 (C), 105.4 (CH), 81.1 (CH), 39.2 (CH_2), 35.2 (CH_2), 28.0 (CH_3), 9.9 (CH_3). IR (film): 1718, 1687, 1555, 1506, 1418, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{23}N_3O_3$ $[M]^+$: 329.1739. Found: 329.1710.



(*E*)-3-(Benzylideneamino)-1-(2-hydroxyethyl)-4-methyl-1H-imidazol-2(3H)-one (Table 2.3, entry 3ad): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), ethanolpropargylamine **2d** (0.0650 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 6 hours. After trying multiple purification methods and different reaction conditions that did not increase the yield or the purity of the obtained compound, a NMR yield was determined using ratio of phenol to the desired compound : 49-51%.



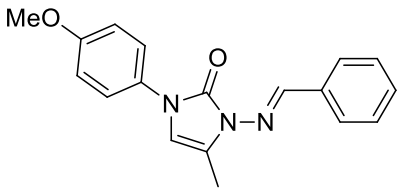
(*E*)-3-(3-(Benzylideneamino)-4-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)propanenitrile (Table 2.3, entry 3ae): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), the propargylic amine **2e** (0.0710 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 6 hours. The crude mixture was purified by column chromatography using 6% EtOAc/CH_2Cl_2 and the pure compound was obtained as a white solid (0.0920 g, 60%). TLC R_f = 0.40 in 6% EtOAc/CH_2Cl_2. ^1H NMR (300 MHz; $CDCl_3$): δ 9.84 (s, 1H), 7.79-7.73 (m, 2H), 7.44-7.39 (m, 3H), 6.07 (d, *J* = 1.4 Hz, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.18 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 151.8 (CH), 149.3 (C), 134.7 (C), 130.4 (CH), 128.6 (CH), 127.4 (CH), 121.0 (C), 117.4 (C), 104.7 (CH), 39.4 (CH_2), 18.0 (CH_2), 9.9 (CH_3). IR (film): 2360, 1730, 1701, 1553, 1433, 1398, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{14}N_4O$ $[M]^+$: 254.1168. Found: 254.1155.



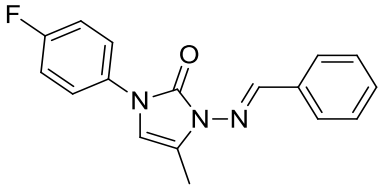
(*E*)-3-(Benzylideneamino)-4-methyl-1-phenyl-1H-imidazol-2(3H)-one (Table 2.3, entry 3af): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), *n*-phenylpropargylamine **2f** (0.0870 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by Et_3N treated[254] column chromatography using 25% hexanes/CH_2Cl_2 and

[254] Et_3N is crucial for separating product from phenol. Every solvent system without the use of Et_3N resulted in poor to no separation of the two compounds.

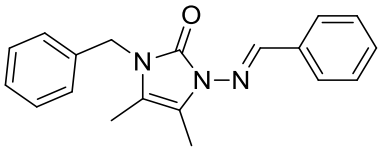
the pure compound was obtained as a yellow solid (0.0900 g, 54%). TLC R_f = 0.25 in 25% hexanes/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.98 (s, 1H), 7.84-7.77 (m, 2H), 7.63-7.58 (m, 2H), 7.48-7.40 (m, 5H), 7.29-7.23 (m, 1H), 6.37 (q, *J* = 1.3 Hz, 1H), 2.18 (d, *J* = 1.4 Hz, 3H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 151.8 (C), 135.0 (C), 130.4 (C), 129.2 (CH), 128.6 (CH), 127.5 (CH), 125.8 (CH), 121.7 (C), 121.6 (CH), 104.2 (CH), 10.1 (CH_3). IR (film): 1693, 1684, 1506, 1398, 1376, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{15}N_3O$ $[M]^+$: 277.1215. Found: 227.1228.



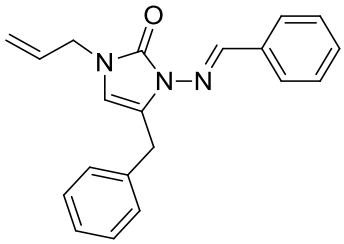
(*E*)-3-(Benzylideneamino)-1-(4-methoxyphenyl)-4-methyl-1H-imidazol-2(3H)-one (Table 2.3, entry 3ag): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), 4-methoxy-*n*-propargylaniline **2g** (0.106 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by filtration and the pure compound was obtained as an off-white solid (0.0760 g, 41%). TLC R_f = 0.20 in 50% hexanes/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.98 (s, 1H), 7.81-7.78 (m, 2H), 7.50-7.46 (m, 1H), 7.44-7.41 (m, 3H), 6.98-6.94 (m, 2H), 6.28 (q, *J* = 1.4 Hz, 1H), 3.83 (s, 3H), 2.26 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 157.6 (C), 151.6 (CH), 148.7 (C), 135.0 (C), 130.3 (CH), 130.0 (C), 128.6 (CH), 127.4 (CH), 123.5 (CH), 121.1 (C), 114.3 (CH), 104.7 (CH), 55.5 (CH_3), 10.0 (CH_3). IR (film): 2960, 2849, 1684, 1653, 1555, 1520, 1506, 1397, 1255, 1251 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}N_3O_2$ $[M]^+$: 307.13208. Found: 307.13229.



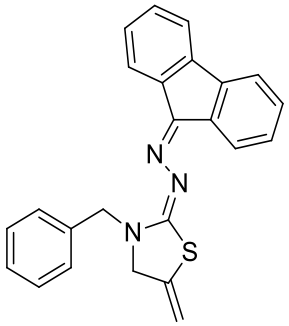
(*E*)-3-(Benzylideneamino)-1-(4-fluorophenyl)-4-methyl-1H-imidazol-2(3H)-one (Table 2.3, entry 3ah): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), 4-fluoro-*n*-propargylaniline **2h** (0.0980 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified column chromatography using 6% EtOAc/Hexane and the pure compound was obtained as a yellow solid (0.0660 g, 37%). TLC R_f = 0.25 in 6% EtOAc/Hexane. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.95 (s, 1H), 7.81-7.78 (m, 2H), 7.57-7.53 (m, 2H), 7.44-7.41 (m, 3H), 7.15-7.09 (m, 2H), 6.29 (q, *J* = 1.2 Hz, 1H), 2.26 (d, *J* = 1.6 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 161.7 (C), 159.3 (C), 152.0 (CH), 148.6 (C), 135.0 (C), 133.0 (133.0 fluorine coupling) (C), 130.5 (CH), 128.7 (CH), 127.5 (CH), 123.6 (CH), 123.5 (CH), 121.8 (C), 116.1 (CH), 115.9 (CH), 10.1 (CH_3). IR (film): 2954, 2841, 1690, 1678, 1558, 1512, 1400, 1377, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{14}N_3O$ $[M]^+$: 295.1121. Found: 295.1164.



(*E*)-1-Benzyl-3-(benzylideneamino)-4,5-dimethyl-1H-imidazol-2(3H)-one (Table 2.3, entry 3ai): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), the propargylic amine **2i** (0.105 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. The crude mixture was purified by Et_3N treated silica gel column chromatography using 2% hexanes/CH_2Cl_2 and the pure compound was obtained as a white solid (0.150 g, 82%). TLC R_f = 0.12 in 2% hexanes/CH_2Cl_2. ^{1}H NMR (300 MHz; $CDCl_3$): δ 9.96 (s, 1H), 7.80-7.75 (m, 2H), 7.46-7.39 (m, 3H), 7.37-7.31 (m, 2H), 7.30-7.25 (m, 3H), 4.87 (s, 2H), 2.16 (d, *J* = 1.1 Hz, 3H), 1.94 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 150.7 (CH), 150.0 (C), 137.5 (C), 135.4 (C), 130.0 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 115.2 (C), 112.0 (C), 44.1 (CH_2), 8.8 (CH_3), 8.3 (CH_3). IR (film): 1701, 1664, 1653, 1558, 1387, 1265 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{19}N_3O$ [M]$^+$: 305.1528. Found: 305.1522.

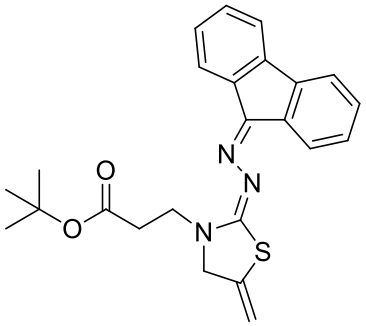


(*E*)-1-Allyl-4-benzyl-3-(benzylideneamino)-1H-imidazol-2(3H)-one (Table 2.3, entry 3aj): Synthesized according to general procedure **A** using carbazone **1a** (0.146 g, 0.600 mmol), the propargylic amine **2j** (0.113 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 100 °C for 6 hours. Purifications were unsuccessful (product seems to degrade and equilibrate threw isomerization), therefore another reaction was performed and 0.0114 g of 1,3,5-trimethoxybenzene was added as NMR internal standard. 35 % of desired product (endocyclic alkene) was observed with 14 % of the exocydic present.

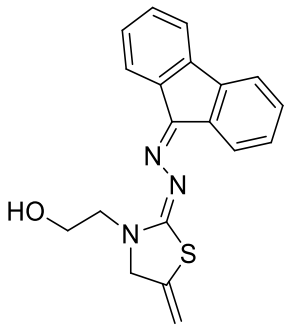


(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-benzyl-5-methylenethiazolidine (Table 2.3, entry 5bb): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), *n*-benzyl propargylamine **2b** (0.0960 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by filtration and the pure compound was

obtained as a yellow solid (0.155g, 68%). TLC R_f = 0.27 in 40% CH_2Cl_2/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.64 (dt, *J* = 7.6, 0.6 Hz, 1H), 7.91-7.88 (m, 1H), 7.69-7.61 (m, 2H), 7.42-7.27 (m, 4H), 5.25-5.22 (m, 2H), 4.54 (t, *J* = 2.3 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H), 1.48 (s, 9H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.0 (C), 169.9 (C), 153.1 (C), 141.4 (C), 140.1 (C), 137.7 (C), 131.9 (C), 129.7 (CH), 129.2 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.4 (CH), 105.4 ($CH_{2)}$, 81.1 (C), 58.0 (CH_2), 43.0 (CH_2), 33.0 (CH_2), 28.0 (CH_3) . IR (film): 1684, 1647, 1554, 1506, 1107, 903 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{19}N_3S$ [M]$^+$: 381.1300. Found: 381.1321.

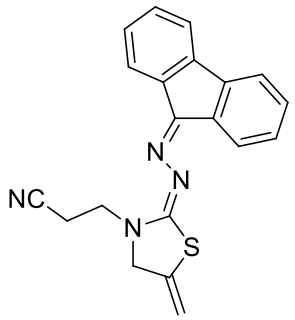


(*E*)- *tert*-Butyl 3-(2-((9H-fluoren-9-ylidene)hydrazono)-5-methylenethiazolidin-3-yl)propanoate (Table 2.3, entry 5bc): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), the propargylic amine **2c** (0.121 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a orange foam (0.200 g, 79%). TLC R_f = 0.27 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.64 (dt, *J* = 7.6, 0.6 Hz, 1H), 7.91-7.88 (m, 1H), 7.69-7.61 (m, 2H), 7.42-7.27 (m, 4H), 5.25-5.22 (m, 2H), 4.54 (t, *J* = 2.3 Hz, 2H), 3.93 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H), 1.48 (s, 9H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.0 (C), 169.9 (C), 153.1 (C), 141.4 (C), 140.1 (C), 137.7 (C), 131.9 (C), 129.7 (CH), 129.2 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.4 (CH), 105.4 ($CH_{2)}$, 81.1 (C), 58.0 (CH_2), 43.0 (CH_2), 33.0 (CH_2), 28.0 (CH_3) . IR (film): 1676, 1601, 1558, 1526, 1501, 1431, 1420, 1398, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{25}N_3O_2S$ [M]$^+$: 419.1667. Found: 419.1666.



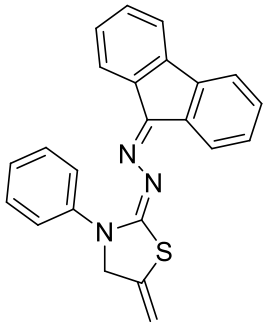
(*E*)-2-(2-((9H-fluoren-9-ylidene)hydrazono)-5-methylenethiazolidin-3-yl)ethanol (Table 2.3, entry 5bd): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), ethanolpropargylamine **2d** (0.0650 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and

heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 100% EtOAc and the pure compound was obtained as a yellow solid (0.147 g, 73%). TLC R_f = 0.20 in 100% EtOAc. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.55 (d, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.40-7.29 (m, 4H), 5.25-5.20 (m, 2H), 4.55 (t, *J* = 2.2 Hz, 2H), 4.00 (t, *J* = 4.9 Hz, 2H), 3.84-3.82 (m, 2H) . ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.8 (C), 153.0 (C), 153.1 (C), 141.5 (C), 140.1 (C), 137.6 (C), 137.5 (C), 131.7 (C), 129.9 (CH), 129.3 (CH), 128.5 (CH), 127.8 (CH), 127.5 (CH), 121.7 (CH), 119.6 (CH), 119.5 (CH), 106.4 (CH_2), 61.3 (CH_2), 58.8 (CH_2), 49.8 (CH_2). IR (film): 2960, 2853, 1535, 1495, 1416, 1265, 1141 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{17}N_3OS$ [M]$^+$: 335.1092. Found: 335.1100.

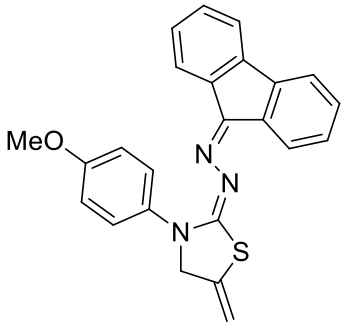


(*E*)-3-(2-((9H-Fluoren-9-ylidene)hydrazono)-5-methylenethiazolidin-3-yl)propanenitrile (Table 2.3, entry 5be): Synthesized according to general procedure **A** using a derivative of thiosemicarbazone **4b**[255] (0.225 g, 0.600 mmol), the propargylic amine **2e** (0.0710 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography using 20% EtOAc/Hexanes and the pure compound was obtained as a orange solid (0.152 g, 74%). TLC R_f = 0.27 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.59 (d, *J* = 7.2 Hz,1H), 7.84 (dd, *J* = 12.6, 7.3 Hz, 2H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.49-7.30 (m, 4H), 5.39 (d, *J* = 12.3 Hz, 2H), 4.69-4.68 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (100 MHz; DMSO- d_6): δ 170.2 (C), 151.8 (C), 140.6 (C), 139.5 (C), 136.7 (C), 136.6 (C), 131.0 (CH), 130.4 (CH), 129.7 (C), 128.6 (CH), 128.1 (CH), 127.8 (CH), 121.0 (CH), 120.2 (CH), 120.2 (CH), 119.1 (C), 106.6 (CH_2), 60.0 (CH_2), 42.4 (CH_2), 33.0 (CH_2), 15.1 (CH_2). IR (film): 2314, 1684, 1601, 1458, 1420, 1398 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{16}N_4S$ [M]$^+$: 344.1096. Found: 384.1126.

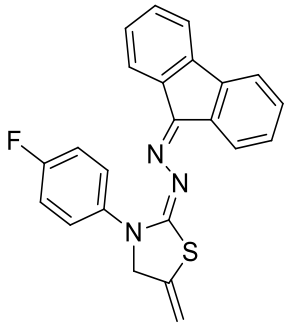
[255] *o*-Nitroaniline was used as leaving group to ensure good separation for the flash chromatography. For synthesis see: Lavergne, K.; MSc thesis, University of Ottawa, 2015



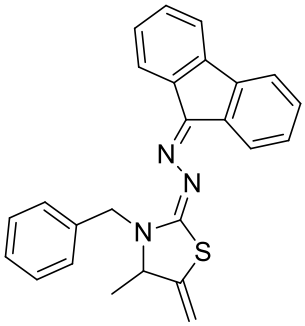
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-5-methylene-3-phenylthiazolidine (Table 2.3, entry 5bf): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), *n*-phenylpropargylamine **2f** (0.0870 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as a orange solid (0.170 g, 78%). TLC R_f = 0.12 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.34 (d, *J* = 7.6, 1H), 7.84-7.72 (m, 5H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.45-7.30 (m, 4H), 7.22-7.19 (m, 1H), 5.43 (d, *J* = 15.1 Hz, 2H), 5.11 (s, 2H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 169.0 (C), 152.8 (C), 140.6 (C), 139.7 (C), 136.5 (C), 135.8 (C), 130.6 (CH), 130.6 (C), 129.9 (CH), 128.9 (CH), 127.9 (CH), 125.7 (CH), 123.3 (CH), 121.2 (CH), 120.3 ($CH_)$, 120.3 (CH), 106.4 (CH_2), 58.8 (CH_2). IR (film): 1684, 1647, 1555, 1506, 1107 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{23}H_{17}N_3S$ [M]$^+$: 367.1143. Found: 367.1438.



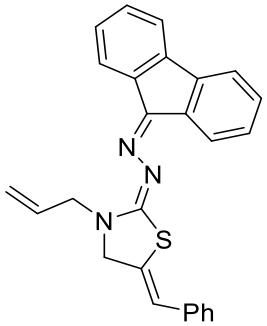
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-(4-methoxyphenyl)-5-methylenethiazolidine (Table 2.3, entry 5bg): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), 4-methoxy-*n*-propargylaniline **2g** (0.106 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as a brown solid (0.170 g, 78%). TLC R_f = 0.3 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.38 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.90 (dq, *J* = 7.4, 0.7 Hz, 1H), 7.63-7.57 (m, 4H), 7.38-7.27 (m, 3H), 7.15 (td, *J* = 7.6, 1.1 Hz, 1H), 7.03-6.99 (m, 2H), 5.31 (dq, *J* = 11.1, 2.1 Hz, 2H), 4.87 (t, *J* = 2.3 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 168.9 (C), 157.3 (C), 154.2 (C), 144.3 (C), 140.4 (C), 137.5 (C), 136.8 (C), 133.2 (C), 131.7 (C), 130.0 (CH), 129.4 (CH), 128.7 (CH), 127.7 (CH), 127.5 (CH), 125.0 ($CH_)$, 121.9 (CH), 119.5 (CH), 119.5 (CH), 114.1 (C), 105.6 (CH_2), 59.4 (CH_2), 55.6 (CH_3). IR (film): 2968, 2854, 1734, 1555, 1497, 1246, 1022 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{24}H_{19}N_3OS$ [M]$^+$: 397.1249. Found: 397.1224.



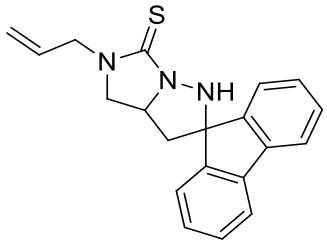
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-(4-fluorophenyl)-5-methylenethiazolidine (Table 2.3, entry 5bh): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), 4-fluoro-*n*-propargylaniline **2h** (0.0980 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as an orange solid (0.180 g, 78%). TLC R_f = 0.11 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; DMSO-d_6): δ 8.26 (d, *J* = 7.6, 1H), 7.83-7.71 (m, 5H), 7.45-7.31 (m, 5H), 7.24-7.19 (m, 1H), 5.42 (d, *J* = 12.2 Hz, 2H), 5.08 (s, 2H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 168.6 (C), 152.8 (C), 140.3 (C), 139.4 (C), 136.3 (C), 135.7 (C), 130.4 (CH), 130.0 (CH), 129.4 (CH), 127.7 (CH), 127.4 (CH) 127.3 (CH), 125.5 (CH), 125.4 (CH), 120.8 (CH), 119.6 ($CH_)$, 119.6 (CH), 115.3 (CH), 115.0 (CH), 105.8 (CH_2), 58.6 (CH_2). IR (film): 1690, 1670, 1609, 1595, 1526, 1506, 1477, 1433, 1398 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{23}H_{16}N_3SF$ [M]$^+$: 385.1049. Found: 385.1015.



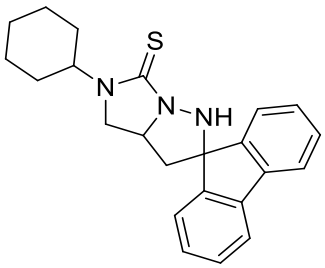
(*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-benzyl-4-methyl-5-methylenethiazolidine (Table 2.3, entry 5bi): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), the propargylic amine **2i** (0.105 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified by column chromatography and the pure compound was obtained as an orange foam (0.161 g, 68%). TLC R_f = 0.26 in 25% CH_2Cl_2/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.55-8.52 (m, 1H), 7.93-7.89 (m, 1H), 7.66-7.60 (m, 2H), 7.44-7.16 (m, 9H), 5.41 (d, *J* = 15.3, 1H), 5.23 (t, *J* = 1.97, 1H), 5.14 (t, *J* = 1.85, 1H), 4.53-4.43 (m, 2H), 1.45 (d, *J* = 6.40, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.2 (C), 153.2 (C), 143.7 (C), 141.4 (C), 140.2 (C), 137.8 (C), 136.3 (C), 131.9 (C), 129.8 (CH), 129.2 (CH), 128.9 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 121.7 (CH), 119.5 (CH), 119.5 (CH), 105.3 (CH_2), 62.5 (CH), 48.8 (CH_2), 20.3 (CH_3). IR (film): 2854, 1599, 1521, 1506, 1423, 1398, 1244 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{25}H_{21}N_3S$ [M]$^+$: 395.1456. Found: 395.1432.



(2*E*,5*E*)-2-((9H-Fluoren-9-ylidene)hydrazono)-3-allyl-5-benzylidenethiazolidine (Table 2.3, entry 5bj): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), the propargylic amine **2j** (0.113 g, 0.660 mmol), Et_3N (0.0120 g, 0.120 mmol) and MeCN (2.0 mL) and heated at 120 °C for 2 hours. The crude mixture was purified filtration and the pure compound was obtained as an orange solid (0.223 g, 91%). TLC R_f = 0.13 in 20% EtOAc/hexanes. ^{1}H NMR (300 MHz; $CDCl_3$): δ 8.69 (d, *J* = 7.3, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.66 (dd, *J* = 11.8, 7.3 Hz, 2H), 7.46-7.27 (m, 9H), 7.22-7.19 (m, 1H), 6.55 (s, 1H), 6.00 (ddt, *J* = 16.9, 10.4, 6.2 Hz, 1H), 5.41-5.32 (m, 2H), 4.58 (d, *J* = 1.7 Hz, 2H), 4.35 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 169.3 (C), 141.4 (C), 140.2 (C), 137.6 (C), 135.9 (C), 131.9 (C), 131.5 (CH), 129.9 (CH), 129.3 (CH), 129.1 (C), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 121.9 (CH_2), 120.2 (CH), 119.5 (CH), 119.5 (CH), 119.0 (CH_2), 58.4 (CH_2), 49.5 (CH_2). IR (film): 1602, 1533, 1522, 1460, 1263 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{26}H_{21}N_3S$ $[M]^+$: 407.1456. Found: 407.1665.



5'-Allyl-3',3a',4',5'-tetrahydrospiro[fluorene-9,2'-imidazo[1,5-b]pyrazole]-6'(1'H)-thione (Scheme 2.4, 6a): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), diallylamine (0.0640 g, 0.660 mmol),) and MeCN (2.0 mL) and heated at 150 °C for 2 hours. The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as yellow solid (0.158 g, 79%). TLC R_f = 0.4 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.73 (dd, *J* = 13.7, 7.2 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.43-7.23 (m, 5H), 5.94-5.82 (m, 2H), 5.31-5.26 (m, 2H), 4.58-4.50 (m, 1H), 4.45-4.25 (m, 2H), 3.87 (dd, *J* = 10.7, 7.9 Hz, 1H), 3.68 (d, *J* = 10.6 Hz, 1H), 2.50-2.43 (m, 1H), 2.20-2.12 (m, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 188.5 (C), 150.7 (C), 139.2 (C), 138.5 (C), 131.8 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 124.6 (CH), 123.8 (CH), 119.9 (CH), 119.6 (CH), 118.1 (CH_2), 74.7 (C), 60.6 (CH), 49.7 (CH_2), 49.6 (CH_2), 45.4 (CH_2). IR (film): 1680, 1610, 1553, 1379, 1360, 1310, 1255 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{19}N_3S$ $[M]^+$: 333.1300. Found: 333.1292.



5'-Cyclohexyl-3',3a',4',5'-tetrahydrospiro[fluorene-9,2'-imidazo[1,5-b]pyrazole]-6'(1'H)-thione (Scheme 2.4, 6a): Synthesized according to general procedure **A** using thiosemicarbazone **4b** (0.225 g, 0.600 mmol), allylcyclohexylamine (0.0920 g, 0.660 mmol),) and MeCN (2.0 mL) and heated at 150 °C for 4 hours. The crude mixture was purified by column chromatography using 5% EtOAc/CH_2Cl_2 and the pure compound was obtained as a orange was obtained as a yellow solid (0.145 g, 64%). TLC R_f = 0.26 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.74 (dd, *J* = 14.4, 7.0 Hz, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.42-7.22 (m, 5H), 5.85 (s, 1H), 4.51-4.41 (m, 2H), 3.85-3.79 (m, 1H), 3.70-3.67 (m, 1H), 2.42 (dd, *J* = 12.6, 6.7 Hz, 1H), 2.11-2.04 (m, 1H), 1.88-1.75 (m, 4H), 1.65 (d, *J* = 10.8 Hz, 1H), 1.55-1.28 (m, 4H), 1.19-1.08 (m, 1H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 187.6 (C), 150.7 (C), 148.4 (C), 139.2 (C), 128.7 (CH), 128.0 (CH), 127.8 (CH), 124.6 (CH), 123.8 (CH), 119.9 (CH), 119.6 (CH), 74.6 (C), 60.5 ($CH_)$, 55.3 (CH), 46.2 (CH_2), 45.4 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.9 (CH_2). IR (film): 1680, 1653, 1556, 1456, 1263, 1226, 1032 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{23}H_{25}N_3S$ [M]$^+$: 375.1769. Found: 375.1797.

6.2.2 A cascade synthesis of 1,2,4-Triazin-3(2H)-ones (section 2.3)

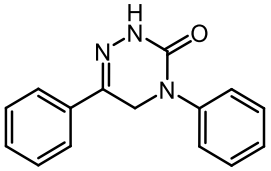
Starting material synthesis

α-Amino ketones **7a-c,e-g,k,**[256] **d,h,i,**[257] **j,**[258] **k,**[259] were prepared by known methods following literature procedures.

Synthesis of 1,2,4-triazin-3(2*H*)-ones products

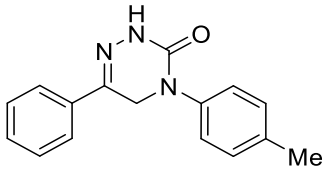
General Procedure B: In a dry microwave vial equipped with a stir bar, α-amino ketone (1.05 eq.) was added to phenyl carbazate (1.00 eq.) and citric acid (1.00 eq.). The vial was then sealed and purged with argon followed by the addition of purified THF (1.0 M). The resulting solution was left stirring at room temperature for 12-16 hours. The reaction mixture was concentrated under reduced pressure, diluted with a saturated $NaHCO_3$ solution, (20 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried with $NaSO_4$, filtered, and concentrated under reduced pressure. The crude products were purified by column chromatography or through recrystallization in MeOH.

[256] Li, X.; Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y. *Org. Lett.* **2015**, *17*, 2984.
[257] Mohamed, M. S.; Hussein, W. M.; McGeary, R. P.; Vella, P.; Schenk, G.; Abd El-hameed, R. H. *Eur. J. Med. Chem.* **2011**, *46*, 6075.
[258] Barton, D. H. R.; Chern, C.; Tachdjian, C. *Heterocycles* **1994**, *37*, 793.
[259] Vanhoof, P. M.; US3970650, **1976.**



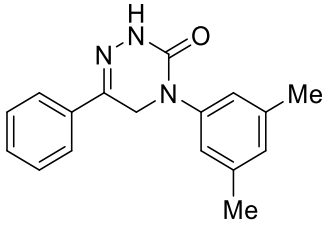
4,6-Diphenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9a)

Synthesized according to general procedure **B** using α-amino ketone **7a** (0.133 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.60 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.186 g, 74%). TLC Rf = 0.23 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.68 (ddd, *J* = 4.4, 2.5, 1.4 Hz, 2H), 7.44 (t, *J* = 2.7 Hz, 2H), 7.42 (dd, *J* = 2.7, 1.6 Hz, 4H), 7.40 (d, *J* = 3.1 Hz, 1H), 7.31 – 7.26 (m, 1H), 4.74 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 143.3, 140.4, 133.4, 130.0, 129.2, 128.8, 126.6, 125.3, 124.5, 47.7. IR (ATR diamond): 3216, 3097, 1662, 1625, 1593, 1195, 772 cm^{-1}. HRMS(EI): Exact mass calcd for $C_{15}H_{13}N_3O$ $[M]^+$: 251.1053. Found: 251.1056.



6-Phenyl-4-(p-tolyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9b)

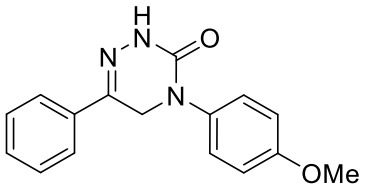
Synthesized according to general procedure **B** using α-amino ketone **7b** (0.142 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.202 g, 76%). TLC Rf = 0.27 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.72 – 7.63 (m, 2H), 7.44 – 7.39 (m, 3H), 7.32 – 7.27 (m, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 4.70 (s, 2H), 2.39 – 2.34 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 143.0, 137.9, 136.6, 133.5, 129.9, 129.8, 128.7, 125.3, 124.6, 47.9, 21.0. IR (ATR diamond): 3234, 3107, 1677, 1594, 1496, 1181, 714 cm^{-1}. HRMS(EI): Exact mass calcd for $C_{16}H_{15}N_3O$ $[M]^+$: 265.1210. Found: 265.1201.



4-(3,5-Dimethylphenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9c)

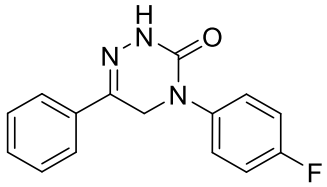
Synthesized according to general procedure **B** using α-amino ketone **7c** (0.151 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The

title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.215 g, 77%). TLC Rf = 0.23 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.68 (ddd, *J* = 4.5, 2.4, 1.4 Hz, 2H), 7.44 – 7.40 (m, 3H), 7.02 (s, 2H), 6.94 (d, *J* = 0.7 Hz, 1H), 4.70 (s, 2H), 2.35 (d, *J* = 0.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 143.2, 140.3, 139.0, 133.5, 129.9, 128.7, 128.6, 125.3, 122.6, 48.0, 21.3. IR (ATR diamond): 3217, 3099, 2945, 1594, 1477, 1175, 745 cm^{-1}**.** HRMS(EI): Exact mass calcd for $C_{17}H_{17}N_3O$ [M]$^+$: 279.1366. Found: 279.1394.



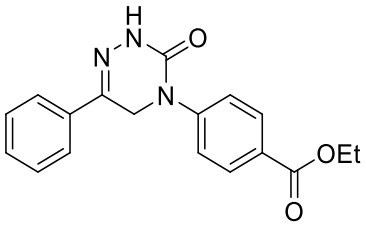
4-(4-Methoxyphenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9d)

Synthesized according to general procedure **B** using α-amino ketone **7d** (0.152 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.169 g, 60%). TLC Rf = 0.14 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.66 (ddd, *J* = 4.4, 2.5, 1.4 Hz, 2H), 7.45 – 7.39 (m, 3H), 7.34 – 7.29 (m, 2H), 6.99 – 6.91 (m, 2H), 4.69 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 151.7, 142.9, 133.5, 133.3, 129.9, 128.7, 126.3, 125.2, 114.5, 55.5, 48.4. IR (ATR diamond): 3209, 3090, 2946, 1587, 1461, 1179, 736 cm^{-1}**.** HRMS(EI): Exact mass calcd for $C_{16}H_{15}N_3O_2$ [M]$^+$: 281.1159. Found: 281.1164.



4-(4-Fluorophenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9e)

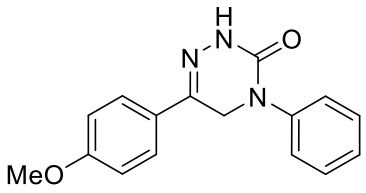
Synthesized according to general procedure **B** using α-amino ketone **7e** (0.144 g, 0.630 mmol), phenylcarbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The title compound was purified by recrystallization from MeOH to yield a white solid (0.180 g, 67%). TLC Rf = 0.23 5% in EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.69 – 7.64 (m, 2H), 7.42 (dd, *J* = 6.8, 3.5 Hz, 3H), 7.38 (dd, *J* = 8.9, 4.8 Hz, 2H), 7.11 (t, *J* = 8.5 Hz, 2H), 4.70 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, $J_{C\text{-}F}$ = -247.5 Hz), 151.6, 143.0, 136.5 (d, $J_{C\text{-}F}$ = 3.1 Hz), 133.4, 130.1, 128.8, 126.6 (d, $J_{C\text{-}F}$ = 8.5 Hz), 125.3 (s), 116.0 (d, $J_{C\text{-}F}$ = 22.2 Hz) , 48.1 (s). IR (ATR diamond): 3213, 3062, 2943, 1629, 1483, 1185, 759 cm^{-1}**.** HRMS (EI): Exact mass calcd for $C_{15}H_{12}FN_3O$ [M]$^+$: 269.0959. Found: 269.0950.



Ethyl 4-(3-oxo-6-phenyl-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)benzoate (table 2.5, 9f)

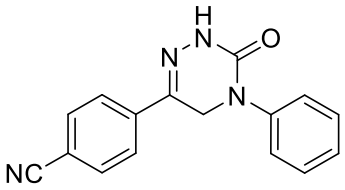
Synthesized according to general procedure **B** using α-amino ketone **7f** (0.178 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 7 hours then reflux for 20 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.178 g, 55%). TLC Rf = 0.17 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.21 (m, 1H), 8.12 – 8.10 (m, 1H), 8.09 (s, 1H), 7.71 – 7.66 (m, 2H), 7.52 (s, 1H), 7.50 – 7.48 (m, 1H), 7.45 – 7.41 (m, 3H), 4.76 (s, 2H), 4.38 (d, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 151.0, 144.2, 143.5, 133.2, 130.4, 130.2, 128.8, 127.9, 125.3, 123.2, 61.1, 46.9, 14.3. IR (ATR diamond): 3230, 3103, 2247, 1668, 160, 1472, 1164, 759 cm^{-1}

HRMS(EI): Exact mass calcd for $C_{18}H_{17}N_3O_3$ [M]$^+$: 323.1264. Found: 323.1259.

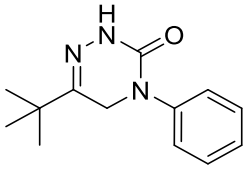


6-(4-Methoxyphenyl)-4-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9g)

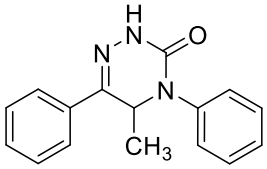
Synthesized according to general procedure **B** using α-amino ketone **7g** (0.152 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.149 g, 53%). TLC Rf = 0.14 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.65 – 7.59 (m, 2H), 7.47 – 7.38 (m, 4H), 7.32 – 7.26 (m, 1H), 6.95 – 6.90 (m, 2H), 4.70 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 151.6, 143.2, 140.5, 129.1, 126.8, 126.5, 126.0, 124.5, 114.1, 55.4, 47.6. IR (ATR diamond): 3191, 3110, 2922, 1692, 1451, 1190, 826 cm^{-1}**.** HRMS (EI): Exact mass calcd for $C_{16}H_{15}N_3O_2$ [M]$^+$: 281.1159. Found: 281.1165.



4-(3-Oxo-4-phenyl-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)benzonitrile(table 2.5, 9h)
Synthesized according to general procedure **A** using α-amino ketone **7h** (0.149 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature overnight. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white-orange solid (0.0970 g, 66%). TLC Rf = 0.17 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.81 – 7.76 (m, 2H), 7.73 – 7.67 (m, 2H), 7.48 – 7.38 (m, 4H), 7.31 (s, 1H), 4.75 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 140.8, 140.1, 137.5, 132.5, 129.3, 127.0, 125.7, 124.6, 118.2, 113.2, 47.5. IR (ATR diamond): 3202, 3096, 2935, 2225, 1670, 1434, 1161, 771 cm^{-1}**.** HRMS (EI): Exact mass calcd for $C_{16}H_{12}N_4O$ [M]$^+$: 276.1006. Found: 276.0969.

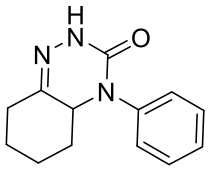


6-(*tert*-Butyl)-4-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9i)
Synthesized according to general procedure **B** using α-amino ketone **7i** (0.120 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 16 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.134 g, 58%). TLC Rf = 0.16 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.40 (ddd, *J* = 9.2, 5.5, 1.9 Hz, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.23 (m, 2H), 4.25 (s, 2H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 152.8, 140.5, 129.1, 126.3, 124.4, 46.0, 36.4, 27.1. IR (ATR diamond): 3203, 3101, 2954, 2225, 1639, 1427, 1196, 772 cm^{-1}**.** HRMS (EI): Exact mass calcd for $C_{13}H_{17}N_3O$ [M]$^+$: 231.1366. Found: 231.1387.



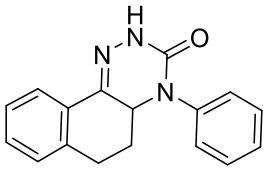
5-Methyl-4,6-diphenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.5, 9j)
Synthesized according to general procedure **B** using α-amino ketone **7j** (0.135 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours then reflux at 100 °C for 20 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.186 g, 74%). TLC Rf = 0.16 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.50 (s, 1H), 7.77 – 7.63 (m, 2H), 7.46 – 7.35 (m, 7H), 7.32 – 7.25 (m, 1H), 4.94 (q, J = 6.8 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 147.2, 139.9, 132.8, 129.9, 129.4, 128.8, 127.1, 126.2, 125.5, 54.5,15.9. IR (ATR diamond): 3204, 3094, 2929, 1621, 1433, 1180, 764 cm^{-1}. HRMS(EI): Exact mass calcd for $C_{16}H_{15}N_3O$ $[M]^+$: 265.1210. Found: 265.1231.



4-Phenyl-4,4a,5,6,7,8-hexahydrobenzo[e][1,2,4]triazin-3(2*H*)-one (table 2.5, 9k)

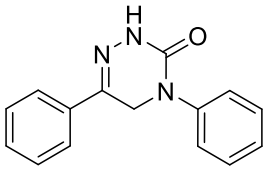
Synthesized according to general procedure **B** using α-amino ketone **7k** (0.119 g, 0.630 mmol), phenyl carbazate (0.0912 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours, then reflux at 100 °C for 24 hours. The title compound was purified by column chromatography (20% EtOAc/CH_2Cl_2) to yield a brownish white solid (0.0970 g, 23%). TLC Rf = 0.30 in 20% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.42 – 7.34 (m, 2H), 7.32 – 7.23 (m, 3H), 4.34 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.49 (dd, *J* = 9.0, 6.9 Hz, 1H), 2.13 – 2.00 (m, 1H), 1.93 – 1.78 (m, 3H), 1.55 – 1.27 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 148.8, 138.3, 129.4, 127.8, 127.6, 59.9, 33.6, 33.5, 26.7, 24.0. IR (ATR diamond): 3210, 3094, 2942, 2860, 1675, 1441, 1169, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O$ $[M]^+$: 229.1210. Found: 229.1219.



4-Phenyl-4,4a,5,6-tetrahydronaphtho[2,1-e][1,2,4]triazin-3(2*H*)-one (table 2.5, 9l)

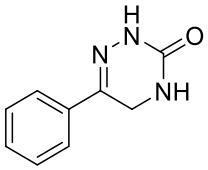
Synthesized according to general procedure **B** using α-amino ketone **7l** (0.149 g, 0.630 mmol), phenyl carbazate (0.091 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 16 hours. The title compound was purified by column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0. 050 g, 31%). TLC Rf = 0.18 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.14 – 8.06 (m, 1H), 7.52 – 7.43 (m, 2H), 7.40 (dt, *J* = 9.7, 4.4 Hz, 1H), 7.30 (ddd, *J* = 4.9, 3.5, 2.1 Hz, 4H), 7.15 (dd, *J* = 6.7, 1.8 Hz, 1H), 4.60 (dd, *J* = 12.6, 4.7 Hz, 1H), 2.83 (dd, *J* = 8.7, 3.5 Hz, 2H), 2.01 – 1.94 (m, 1H), 1.85 – 1.71 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 143.4, 137.6, 137.5, 129.8, 129.7, 129.5, 128.5, 128.4, 128.1, 126.9, 124.6, 55.3, 28.2, 27.5. IR (ATR diamond): 3217, 3097, 2924, 1626, 1486, 1127, 773 cm^{-1}. HRMS(EI): Exact mass calcd for $C_{17}H_{15}N_3O$ [M]+: 277.1210. Found: 277. 1221

Gram Scale Reaction



4,6-Diphenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (9a)

Synthesized according to general procedure **B** using α-amino ketone **7a** (1.05 g, 4.99 mmol), phenyl carbazate (0.722 g, 4.75 mmol) and citric acid (0.912 g, 4.75 mmol), then purified THF (4.75 mL, 1.00 M) was added under argon. The resulting solution was left stirring at room temperature for 12 hours. The title compound was purified by crystallization using methanol to yield a white solid (0.716 g, 60%). The remaining part was purified again using column chromatography (5% EtOAc/CH_2Cl_2) to yield a white solid (0.335 g, 28%). TLC Rf = 0.23 in 5% EtOAc/CH_2Cl_2.

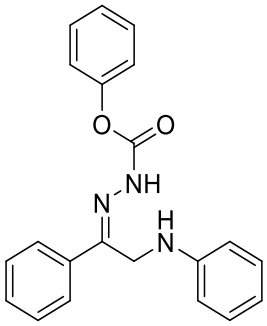


6-Phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (eq. 2.1, 9m):

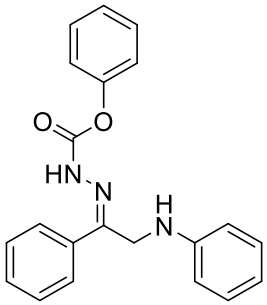
In a dry microwave vial equipped with a stir bar, 2-aminoacetophenone HCl (0.103 g, 0.600 mmol) was added to a solution of phenyl carbazate (0.273 g, 1.80 mmol) in ethanol (1.20 mL, 0.50 M) and refluxed under argon for 24 hours. The reaction mixture was concentrated under reduced pressure, and dry loaded onto silica gel. The title compound was purified by column chromatography (100% EtOAc to 5% MeOH/CH_2Cl_2) to yield a white solid (0.0813 g, 77%). TLC Rf = 0.27 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (d, *J* = 1.76, 1H), 7.63 – 7.61 (m, 2H), 7.40 – 7.34 (m, 3H), 7.22 (s, 1H), 4.60 (d, *J* = 1.76, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.4, 141.9, 134.6, 129.7, 129.0, 125.5, 40.5. Spectra were consistent with literature reports.[260]

[260] Shao, J.; Liu, X.; Shu, K.; Tang, P.; Luo, J.; Chen, W.; Yu, Y. *Org. Lett.* **2015**, *17*, 4502.

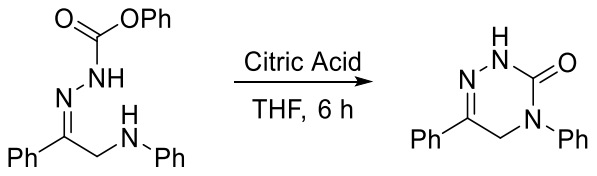
Mechanistic Study



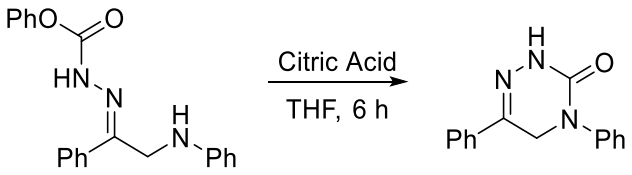
Phenyl (*Z*)-2-(1-phenyl-2-(phenylamino)ethylidene)hydrazine-1-carboxylate (scheme 2.8a, 10a)
Synthesized according to general procedure **B** using α-amino ketone **7a** (0.133 g, 0.630 mmol), phenyl carbazate (0.091 g, 0.600 mmol) and citric acid (0.115 g, 0.600 mmol), then purified THF (0.6 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 1 hour. The reaction was concentrated, diluted with $NaHCO_3$, extracted with EtOAc (3x). The organic layers were combined, dried over Na_2SO_4, filtered, concentrated under reduced pressure and the title compound was purified by column chromatography (CH_2Cl_2) to yield a white solid (0.0433 g, 21%). TLC Rf = 0.21 in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.81 – 7.74 (m, 2H), 7.41 – 7.31 (m, 5H), 7.28 – 7.16 (m, 5H), 6.90 (dd, *J* = 10.6, 4.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 4.33 (d, *J* = 5.1 Hz, 2H), 4.07 (t, *J* = 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 146.8, 136.5, 129.6, 129.4, 129.3, 128.6, 126.5, 125.6, 121.5, 120.3, 114.9, 44.2.



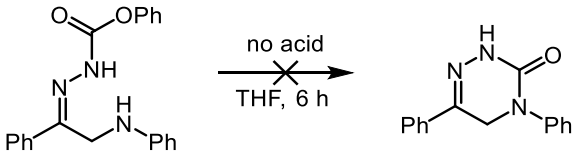
Phenyl (*E*)-2-(1-phenyl-2-(phenylamino)ethylidene)hydrazine-1-carboxylate (scheme 2.8a, 10b)
From the same experiment, another white solid corresponding to the *E* isomer could be isolated (0.0194 g, 9 %). TLC Rf = 0.08 in CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.56 – 7.45 (m, 3H), 7.35 (d, *J* = 7.1 Hz, 2H), 7.29 – 7.23 (m, 3H), 7.22 – 7.13 (m, 4H), 6.75 – 6.64 (m, 3H), 4.55 (s, 1H), 4.22 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 147.2, 131.6, 130.2, 129.8, 129.4, 129.2, 127.02, 125.7, 121.4, 117.8, 113.2, 49.8.



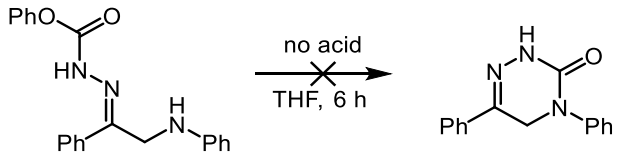
Scheme 2.8b: Synthesized according to general procedure **B** using carbazone **10a** (0.0507 g, 0.147 mmol) and citric acid (0.0283 g, 0.147 mmol), then purified THF (0.15 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 6 hours. The solution was subsequently diluted with a saturated $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. 1,3,5-Trimethoxybenzene was added and ^1H NMR was used to determine a 37% NMR with no detectable remaining starting material.



Scheme 2.8b: Synthesized according to general procedure **B** using carbazone **10b** (0.0458 g, 0.133 mmol) and citric acid (0.0262 g, 0.133 mmol), then purified THF (0.14 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 6 hours. The solution was subsequently diluted with a saturated $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. 1,3,5-Trimethoxybenzene was added and ^1H NMR was used to determine a 47% NMR with no detectable remaining starting material.



Scheme 2.9: Synthesized according to general procedure **B** using carbazone **10a** (0.0503 g, 0.146 mmol) in purified THF (0.15 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 6 hours. The solution was subsequently diluted with a saturated $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. 1,3,5-Trimethoxybenzene was added and ^1H NMR was used to determine 83% remaining starting material with no detectable product present.

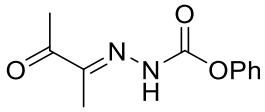


Scheme 2.9: Synthesized according to general procedure **B** using carbazone **10b** (0.0406 g, 0.118 mmol) in purified THF (0.12 mL, 1.0 M) was added under argon. The resulting solution was left stirring at room temperature for 6 hours. The solution was subsequently diluted with a saturated $NaHCO_3$ solution (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. 1,3,5-Trimethoxybenzene was added and ^1H NMR was used to determine 79% remaining starting material, 6% of the *Z*-isomer, and no detectable product present.

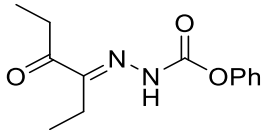
6.2.3 A cascade synthesis of Pyridazinones and Triazinones. (section 2.4)

Starting material synthesis

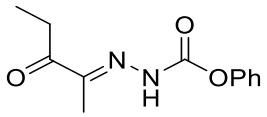
General Procedure C: *O*-Phenylcarbazate (1.0 equiv), 1,2 dione (1.1 equiv), and methanol (0.30 M) were added to a dry round bottom flask. The flask was capped with a septum and stirred overnight at room temperature. The reaction was then concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



(*E*)-Phenyl 2-(3-oxobutan-2-ylidene)hydrazinecarboxylate (11a): Synthesized according to general procedure **C** using *O*-phenylcarbazate (3.44 g, 20.0 mmol) and 2,3-butanedione (1.89 g, 22.0 mmol). The title compound was concentrated under reduced pressure to yield a pure white solid (4.01 g, 91%). TLC Rf = 0.08 in 30: 20: 50 CH_2Cl_2: Et_2O: Hexane. ^1H NMR (300 MHz, DMSO-d_6): δ 7.42-7.39 (m, 2H), 7.26-7.20 (m, 3H), 2.30 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.7 (C), 130.0 (CH), 126.3 (CH), 122.2 (CH), 24.7 (CH_3), 10.5 (CH_3). IR (film): 1266, 1145, 730, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{13}N_2O_3$ $[M+H]^+$: 221.0882 Found: 221.0904.



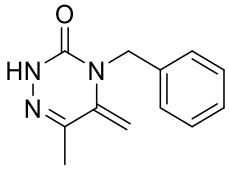
(*E*)-Phenyl 2-(4-oxohexan-3-ylidene)hydrazinecarboxylate (11b): Synthesized according to general procedure **C** using *O*-phenylcarbazate (0.456 g, 3.00 mmol) and 3,4-hexanedione (0.376 g, 3.00mmol). The title compound was concentrated under reduced pressure, recrystallized in methanol, filtered and dried under reduced pressure to yield a pure white solid (0.574 g, 77%). TLC Rf = 0.14 in 30: 20: 50 CH_2Cl_2: Et_2O: Hexane. ^1H NMR (300 MHz, DMSO-d_6): δ 11.25-11.22 (m, 1H), 7.44-7.39 (m, 2H), 7.28-7.21 (m, 3H), 2.79 (q, *J* = 7.4 Hz, 2H), 2.54 (q, *J* = 7.5 Hz, 2H), 0.91 (dt, *J* = 20.7, 7.4 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 200.2 (C), 130.0 (CH), 126.2 (CH), 122.2 (CH), 29.7 (CH_2), 17.0 (CH_2), 10.6 (CH_3), 8.7 (CH_3). IR (film): 1741, 1685, 1487, 1265, 1190, 1130, 736 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$: 249.1195 Found: 249.1226.



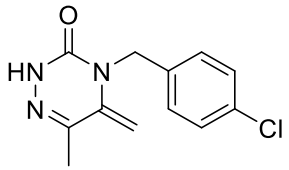
(*E*)-Phenyl 2-(3-oxopentan-2-ylidene)hydrazinecarboxylate (11c): Synthesized according to general procedure **C** using *O*-phenylcarbazate (0.305 g, 2.00 mmol) and 2,3-pentanedione (0.220 g, 2.20 mmol) stirring at 0 °C for 6 hours. The title compound was concentrated under reduced pressure, dry loaded unto silica and purified by column chromatography (30% CH_2Cl_2/20% Ether/ 50% Hexane) to yield a pure white solid (0.291 g, 62%). TLC Rf = 0.18 in 30: 20: 50 CH_2Cl_2: Et_2O: Hexane. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.48-7.42 (m, 2H), 7.31-7.23 (m, 3H), 2.83 (q, *J* = 7.3 Hz, 2H), 1.98 (s, 3H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz; DMSO-d_6): δ 200.3 (C), 130.0 (CH), 126.3 (CH), 122.2 (CH), 29.5 (CH_2), 10.8 (CH_3), 8.7 (CH_3). IR (film): 1770, 1681, 1487, 1265, 1156, 1124, 736 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{15}N_2O_3$ $[M+H]^+$: 235.1038 Found: 235.1076.

Synthesis of 1,2,4-triazinones:

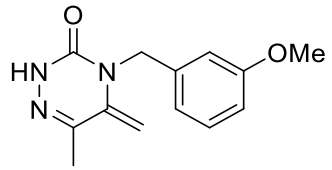
General Procedure D: An oven dried microwave tube was charged with the keto-carbazaone (1.0 equiv), $MgSO_4$ (1.0 equiv), primary amines (1.1 equiv) and α,α,α-trifluorotoluene (0.30 M). The tube was sealed with a microwave cap and heated for six hours 175 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



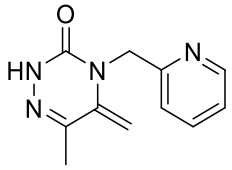
4-Benzyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.6, 12a): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), benzylamine (0.0710 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol).The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.0970 g, 75%). TLC Rf = 0.29 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (br s, 1H), 7.37-7.24 (m, 5H), 4.94 (s, 2H), 4.32 (d, *J* = 2.8 Hz, 1H), 4.24 (d, *J* = 2.8 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 143.4 (C), 136.6 (C), 135.2 (C), 128.7 (CH), 127.4 (CH), 126.7 (CH), 90.6 (CH_2), 45.9 (CH_2), 19.0 (CH_3). IR (film): 1699, 1558, 1506, 1266, 736 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O$ $[M]^+$: 215.1059. Found: 215.1066.



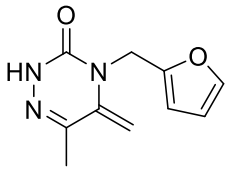
4-(4-Chlorobenzyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12b): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 4-chlorobenzylamine (0.0930 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a beige solid (0.120 g, 80%). TLC Rf = 0.30 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (br s, 1H), 7.33-7.28 (m, 2H), 7.23-7.18 (m, 2H), 4.90 (s, 2H), 4.33 (d, *J* = 2.8 Hz, 1H), 4.18 (d, *J* = 2.7 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4 (C), 143.3 (C), 136.7 (C), 133.2 (C), 128.9 (CH), 128.2 (CH), 90.5 (CH_2), 55.2, 45.3 (CH_2), 19.0 (CH_3). IR (film): 1652, 1510, 1259, 771 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{12}N_3OCl$ $[M]^+$: 249.0669. Found: 249.0677.



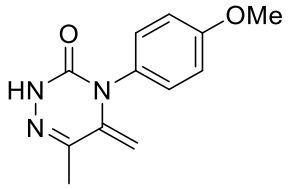
4-(3-Methoxybenzyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12c): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 3-methoxybenzylamine (0.0910 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.0820 g, 56%). TLC Rf = 0.24 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (br s, 1H), 7.28-7.22 (m, 1H), 6.87-6.78 (m, 3H), 4.91 (s, 2H), 4.33 (d, *J* = 2.8 Hz, 1H), 4.24 (d, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9 (C), 149.3 (C), 143.3 (C), 136.9 (C), 136.6 (C), 129.7 (CH), 118.9 (CH), 112.5 (CH), 112.5 (CH), 90.6 (CH_2), 55.2 (CH_3), 45.8 (CH_2), 19.0 (CH_3). IR (film): 1683, 1506, 1271, 781 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_3O_2$ $[M]^+$: 245.1164. Found: 245.1136.



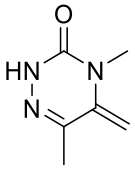
6-Methyl-5-methylene-4-(pyridin-2-ylmethyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12d): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 2-picolylamine (0.0710 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (40% EtOAc/CH_2Cl_2) to yield a beige solid (0.0860 g, 66%). TLC Rf = 0.14 40% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (br s, 1H), 8.58-8.55 (m, 1H), 7.65 (td, *J* = 7.7, 1.7 Hz, 1H), 7.28-7.25 (m, 1H), 7.21-7.17 (m, 1H), 5.06 (s, 2H), 4.33 (q, *J* = 3.0 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7 (C), 149.3 (CH), 149.3 (C), 143.4 (C), 136.9 (CH), 136.7 (C), 122.4 (CH), 121.0 (CH), 91.0 (CH_2), 48.0 (CH_2), 19.0 (CH_3). IR (film): 1683, 1265, 730, 700 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{12}N_4O$ $[M]^+$: 216.1011. Found: 216.0996.



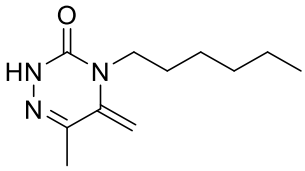
4-(Furan-2-ylmethyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12e): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 4-furfurylamine (0.0640 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a beige solid (0.0950 g, 77%). TLC Rf = 0.31 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 7.35 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.34-6.30 (m, 2H), 4.89 (s, 2H), 4.54 (d, *J* = 2.8 Hz, 1H), 4.40 (d, *J* = 3.0 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1 (C), 148.9 (C), 143.3 (C), 142.0 (CH), 136.6 (C), 110.4 (CH), 108.6 (CH), 89.9 (CH_2), 38.9 (CH_2), 19.0 (CH_3). IR (film): 1687, 1506, 1266, 730 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_3O_2$ $[M]^+$: 205.0851. Found: 205.0884.



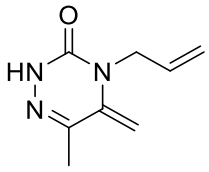
4-(4-Methoxyphenyl)-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 2f): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 4-methoxyaniline (0.0810 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (25% EtOAc/CH_2Cl_2) to yield a brown solid (0.0730 g, 53%). TLC Rf = 0.27 25% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.19-7.13 (m, 3H), 7.05-7.00 (m, 2H), 4.31 (d, *J* = 2.2 Hz, 1H), 3.87 (d, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6 (C), 148.5 (C), 143.3 (C), 139.8 (C), 129.5 (CH), 128.6 (C), 115.4 (CH), 91.5 (CH_2), 55.4 (CH_3), 19.0 (CH_3). IR (film): 1695, 1513, 1265, 750, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_3O_2$ $[M]^+$: 231.1008. Found: 231.0997.



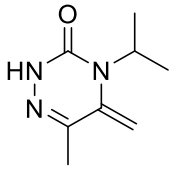
4,6-Dimethyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12g): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 2.0 M methylamine in THF (0.033 mL, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a brown solid (0.0400 g, 48%). TLC Rf = 0.18 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 4.35 (d, *J* = 2.3 Hz, 1H), 4.22 (d, *J* = 2.2 Hz, 1H), 3.11 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0 (C), 142.7 (C), 138.0 (C), 88.4 (CH_2), 28.8 (CH_3), 18.9 (CH_3). IR (film): 1652, 1265, 743, 705 cm^{-1}. HRMS (EI): Exact mass calcd for $C_6H_9N_3O$ $[M]^+$: 139.0746. Found: 139.0763.



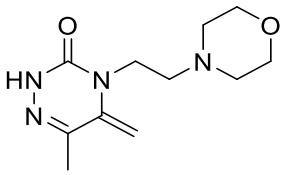
4-Hexyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12h): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), hexylamine (0.0670 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a beige solid (0.0920 g, 73%). TLC Rf = 0.31 in 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (br s, 1H), 4.39-4.24 (m, 1H), 4.31-4.26 (m, 1H), 3.74-3.64 (m, 2H), 2.07 (s, 3H), 1.64-1.55 (m, 2H), 1.39-1.26 (m, 6H), 0.91-0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8 (C), 143.0 (C), 136.7 (C), 88.4 (CH_2), 42.1 (CH_2), 31.5 (CH_2), 26.5 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 19.1 (CH_3), 14.0 (CH_3). IR (film): 1652, 1506, 1266, 732, 688 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{19}N_3O$ $[M]^+$: 209.1528. Found: 209.1524.



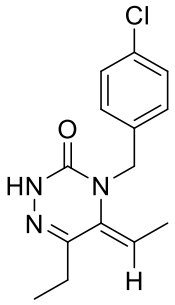
4-Allyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12i): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), allyl amine (0.0380 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.0700 g, 71%). TLC Rf = 0.26 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (br s, 1H), 5.83-5.70 (m, 1H), 5.27-5.19 (s, 2H), 4.38-4.29 (m, 4H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9 (C), 143.1 (C), 136.7 (C), 130.4 (CH), 117.3 (CH_2), 89.7 (CH_2), 44.5 (CH_2), 19.0 (CH_3). IR (film): 1683, 1583, 1266, 732, 688 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{11}N_3O$ $[M]^+$: 165.0902. Found: 165.0908.



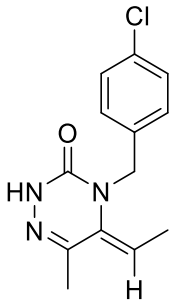
4-Isopropyl-6-methyl-5-methylene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12j): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), isopropylamine (0.0390 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 200 °C. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a light brown solid (0.0440 g, 44%). TLC Rf = 0.19 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (br s, 1H), 4.51-4.41 (m, 3H), 2.05 (s, 3H), 1.46 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (C), 143.6 (C), 136.8 (C), 90.3 (CH_2), 47.5 (CH), 19.1 (CH_3), 18.5 (CH_3). IR (film): 1683, 1265, 738, 706 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_{13}N_3O$ $[M]^+$: 167.1059. Found: 167.1015.



6-Methyl-5-methylene-4-(2-morpholinoethyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12k): Synthesized according to general procedure **D** using keto-carbazone **11a** (0.132 g, 0.600 mmol), 4-(2-aminoethyl)morpholine (0.0860 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 175 °C. The title compound was purified by column chromatography (10% MeOH/CH_2Cl_2) to yield a light brown solid (0.113 g, 79%). TLC Rf = 0.37 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 4.36 (s, 2H), 3.88-3.83 (m, 2H) 3.72-3.69 (m, 4H), 2.59-2.52 (m, 6H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3 (C), 143.6 (C), 137.6 (C), 90.4 (CH_2), 57.1 (CH), 28.2 (CH_2), 26.3 (CH_2), 25.3 (CH_2), 19.2 (CH_3). IR (film): 1695, 1563, 1266, 730 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{17}N_3O$ [M]$^+$: 207.1372. Found: 207.1392.



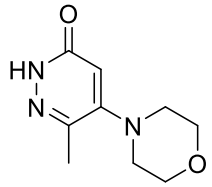
(*Z*)-4-Benzyl-6-ethyl-5-ethylidene-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12l): Synthesized according to general procedure **D** using keto-carbazone **11b** (0.149 g, 0.600 mmol), 4-chlorobenzylamine (0.0930 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 200 °C. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid as a 2:1 mixture favoring the Z isomer (0.113 g, 68%). TLC Rf = 0.30 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (br s, 0.30H), 8.03 (br s, 0.60H) 7.31-7.26 (m, 2H), 7.17-7.10 (m, 2H), 5.18 (q, *J* = 7.5 Hz, 0.70H), 4.93-4.85 (m, 2.30H), 2.61 (q, *J* = 7.4 Hz, 0.6H), 2.39 (q, *J* = 7.4 Hz, 1.40H) 1.79 (d, *J* = 7.8 Hz, 1H), 1.75 (d, *J* = 7.6 Hz, 2H) 1.11 (t, *J* = 7,4 Hz, 1H), 1.02 (t, *J* = 7.4 Hz, 2H) . ^{13}C NMR (75 MHz, $CDCl_3$): * denotes minor isomer δ 152.9 (C), 149.9 (C), 135.8 (C), 133.1 (C), 131.3 (C), 128.8* (CH), 128.7 (CH), 128.1 (CH), 127.9* (CH), 109.1 (CH), 107.3* (CH), 48.3 (CH_2), 46.5* (CH_2), 28.3* (CH_2), 25.0 (CH_2), 13.6 (CH_3), 13.2* (CH_3), 11.3* (CH_3), 10.9 (CH_3). IR (film): 1695, 1265, 734, 705 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{16}N_3OCl$ [M]$^+$: 277.0982. Found: 277.0988.



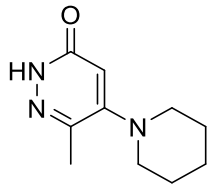
(*Z*)-4-Benzyl-5-ethylidene-6-methyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (table 2.7, 12m): Synthesized according to general procedure **D** using keto-carbazone **11c** (0.141 g, 0.600 mmol), 4-chlorobenzylamine (0.0930 g, 0.660 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol) at 200 °C. The title compound was purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid as a 2:1 mixture favoring the Z isomer (0.0750 g, 47%). TLC Rf = 0.18 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.59 (br s, 0.30H), 10.44 (br s, 0.60H) 7.41-7.35 (m, 2H), 7.27-7.15 (m, 2H), 5.05 (q, *J* = 7.5 Hz, 0.70H), 4.88-4.72 (m, 2.30H), 2.19 (s, 1.10H), 1.96 (s, 1.90H) 1.76 (d, *J* = 7.6 Hz, 1.10H), 1.62 (d, *J* = 7.6 Hz, 1.90H). ^{13}C NMR (75 MHz, DMSO-d_6): * denotes minor isomer δ 151.3 (C), 149.8 (C), 144.1* (C), 137.4 (C), 132.1 (C), 131.4* (CH), 131.3 (C), 130.6* (C), 128.5* (CH), 128.4 (CH), 128.2* (CH), 127.8 (CH), 105.7 (CH), 104.1* (CH), 47.3 (CH_2), 44.7* (CH_2), 22.7* (CH_3), 18.7 (CH_3), 13.0 (CH_3), 12.9* (CH_3). IR (film): 1651, 1558, 1263, 730, 703 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{14}N_3OCl$ [M]$^+$: 263.0825. Found: 263.0821.

Synthesis of 5-aminopyridazinone

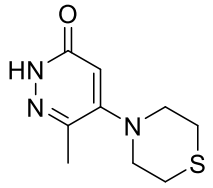
General Procedure E: An oven dried microwave tube was charged with the keto-carbazaone (1.0 equiv), $MgSO_4$ (1.0 equiv), pivalic acid (0.20 equiv), secondary amine (3.0 equiv) and α,α,α-trifluorotoluene (0.30 M). The tube was sealed with a microwave cap and heated for two hours 175 °C. The tube was cooled to ambient temperature, filtered, concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding products.



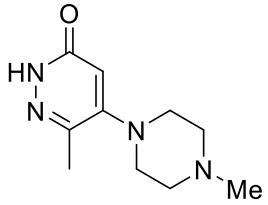
6-Methyl-5-morpholinopyridazin-3(2*H*)-one (table 2.8, 13a): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), morpholine (0.156 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.012o g, 0.12o mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a light brown solid (0.0834 g, 71%). TLC Rf = 0.28 in 5% MeOH/EtOAc. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.40 (br s, 1H), 6.03 (s, 1H), 3.72-3.69 (m, 4H), 2.96-2.93 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8 (C), 154.7 (C), 141.1 (C), 110.7 (CH), 65.8 (CH_2), 50.0 (CH_2), 18.7 (CH_3). IR (film): 1708, 1363, 1220, 910, 727 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{13}N_3O_2$ [M]$^+$: 195.1008. Found: 195.1034.



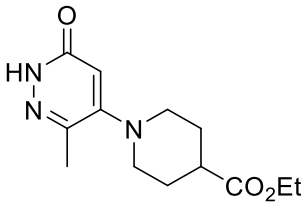
6-Methyl-5-(piperidin-1-yl)pyridazin-3(2*H*)-one (table 2.9, 13b): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), piperidine (0.1530 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.107 g, 93%). TLC Rf = 0.34 in 5% MeOH/EtOAc. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.30 (br s, 1H), 5.96 (s, 1H), 2.90-2.87 (m, 4H), 2.20 (s, 3H) 1.65-1.50 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.9 (C), 155.7 (C), 141.4 (C), 110.1 (CH), 50.8 (CH_2), 25.3 (CH_2), 23.4 (CH_2) 18.4 (CH_3). IR (film): 1662, 1633, 904, 723 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{15}N_3O$ [M]$^+$: 193.1215. Found: 193.1211.



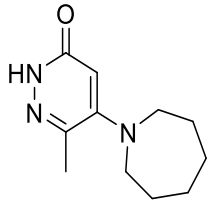
6-Methyl-5-thiomorpholinopyridazin-3(2*H*)-one (table 2.9, 13c): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), thiomorpholine (0.186 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0912 g, 57%). TLC Rf = 0.13 in 100% EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.89 (s, 1H), 6.18 (s, 1H), 3.24-3.20 (m, 4H), 2.77-2.74 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 156.5 (C), 142.9 (C), 112.2 (CH), 52.5 (CH_2), 27.5 (CH_2), 18.7 (CH_3). IR (film): 1647, 1266, 730, 706 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{13}N_3OS$ [M]$^+$: 211.0779. Found: 211.0758.



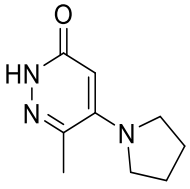
6-Methyl-5-(4-methylpiperazin-1-yl)pyridazin-3(2*H*)-one (table 2.9, 13d): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), *N*-methylpiperazine (0.0930 g, 1.80 mmol), pivalic acid (0.0120 g, 0.120 mmol) for 4 h without the addition of $MgSO_4$. The title compound was purified by column chromatography (50% MeOH/EtOAc) to yield a light brown solid (0.100 g, 80%). TLC Rf = 0.13 in 50% MeOH/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.33 (s, 1H), 6.13 (s, 1H), 2.98 (t, *J* = 4.7 Hz, 4H), 2.51 (t, *J* = 4.3 Hz, 4H), 2.29 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7 (C), 155.6 (C), 142.5 (C), 111.0 (CH), 54.5 (CH_2), 49.9 (CH_2), 45.9 (CH_3), 19.1 (CH_3). IR (film): 2945, 1635, 1431, 1367, 1232, 1126, 852 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{16}N_4O$ [M]$^+$: 208.1324. Found: 208.1343.



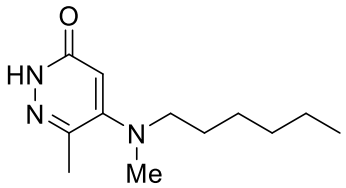
Ethyl-1-(3-methyl-6-oxo-1,6-dihydropyridazin-4-yl)piperidine-4-carboxylate (table 2.9, 13e): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), ethyl-4-piperidinecarboxylate (0.283 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0912 g, 57%). TLC Rf = 0.18 in 100% EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.25 (s, 1H), 6.13 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.25 (d, *J* = 12.7 Hz, 2H), 2.68-2.61 (m, 2H), 2.42 (ddd, *J* = 14.2, 6.7, 3.3 Hz, 1H), 2.23 (s, 3H), 1.98 (dd, *J* = 13.5, 3.2 Hz, 2H), 1.81 (qd, *J* = 12.3, 3.4 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (101 MHz, CDCl3): δ 174.3 (C), 163.8 (C), 156.1 (C), 142.9 (C), 111.1 (CH), 60.7 (CH_2), 49.8 (CH_2), 40.4 (CH), 27.9 (CH_2), 18.8 (CH_3), 14.2 (CH_3). IR (film): 2960, 1724, 1633, 1429, 1377, 1265, 1172, 1042, 730 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{19}N_3O_3$ $[M]^+$: 265.1426. Found: 265.1456.



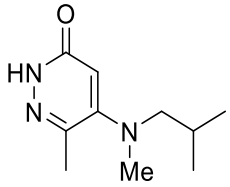
5-(Azepan-1-yl)-6-methylpyridazin-3(2*H*)-one (table 2.9, 13f): Synthesized according to general procedure **E** keto-carbazone **11a** (0.132 g, 0.600 mmol), azepane (0.178 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol) at 200 °C. The title compound was analyze by ^{1}H and a NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (s, 1H), 3.28 (t, *J* = 5.8 Hz, 4H), 2.33 (s, 3H), 1.74 (t, *J* = 1.6 Hz, 4H), 1.58 (dt, *J* = 6.0, 2.9 Hz, 4H).



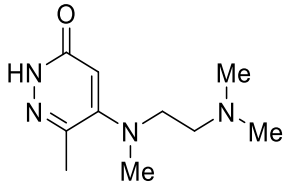
6-Methyl-5-(pyrrolidin-1-yl)pyridazin-3(2*H*)-one (table 2.9, 13g): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), azepane (0.178 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), no acid at 200 °C. The title compound was analyze by ^{1}H and a NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard (26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 1H), 3.47-3.41 (m, 4H), 2.46 (s, 3H), 2.01-1.97 (m, 4H).



5-(Hexyl(methyl)amino)-6-methylpyridazin-3(2*H*)-one (table 2.9, 13h): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), *N*-methylhexylamine (0.208 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a light brown solid (0.100 g, 75%). TLC Rf = 0.15 EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.59 (br s, 1H), 6.04 (s, 1H), 3.09-3.04 (m, 2H), 2.79 (s, 3H) 2.33 (s, 3H), 1.68-1.58 (m, 2H), 1.34-1.23 (m, 6H), 0.90-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (C), 155.5 (C), 141.6 (C), 108.0 (CH), 53.9 (CH_2), 39.3 (CH_3), 31.5 (CH_2), 27.1 (CH_2), 26.5 (CH_2), 22.5 (CH_2), 20.6 (CH_3), 13.9 (CH_3). IR (film): 1635, 1506, 1265, 734 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{21}N_3O$ [M]$^+$: 223.1685. Found: 223.1701.

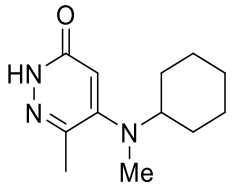


5-(Isobutyl(methyl)amino)-6-methylpyridazin-3(2*H*)-one (table 2.9, 13i): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), *N*-methylisobutylamine (0.157 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0750 g, 64%). TLC Rf = 0.12 EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.79 (br s, 1H), 6.05 (s, 1H), 2.95-2.90 (m, 2H), 2.82 (s, 3H) 2.33 (s, 3H), 1.95 (dt, *J* = 13.5, 6.8 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 155.5 (C), 141.6 (C), 108.2 (CH), 61.1 (CH_2), 40.5 (CH_3), 31.5 (CH_2), 26.6 (CH), 20.9 (CH_3), 20.2 (CH_3). IR (film): 1635, 1265, 736, 699 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{17}N_3O$ [M]$^+$: 195.1372. Found: 195.1351.

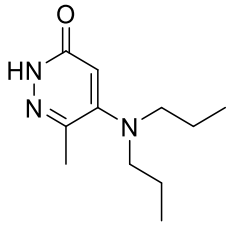


5-((2-(Dimethylamino)ethyl)(methyl)amino)-6-methylpyridazin-3(2*H*)-one (table 2.9, 13j): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), *N,N,N'*-trimethylethylenediamine (0.184 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 100% MeOH) to yield a light brown solid (0.0900 g, 71%). TLC Rf = 0.15 in MeOH. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.97 (br s, 1H), 6.08 (s, 1H), 3.24-3.20 (m, 2H), 2.82 (s, 3H) 2.51-2.46 (m, 2H), 2.33 (s, 3H), 2.23 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 155.3 (C), 141.4 (C), 108.4 (CH), 58.6 (CH_2), 51.9 (CH_2), 45.7 (CH_3),

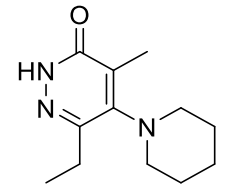
39.7 (CH_3), 20.5 (CH_3). IR (film): 1683, 1561, 1265, 742 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{18}N_4O$ (-C_3H_8N) $[M]^+$: 152.0824. Found: 152.0792.



5-(Cyclohexyl(methyl)amino)-6-methylpyridazin-3(2*H*)-one (table 2.9, 13k): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), *N*-methylcyclohexylamine (0.202 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield an off white/brown solid (0.049 g, 37%). TLC Rf = 0.15 in 100% EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.69 (d, *J* = 0.2 Hz, 1H), 6.05 (s, 1H), 3.15 (tt, *J* = 11.5, 3.5 Hz, 1H), 2.64 (s, 3H), 2.30 (s, 3H), 1.84 (s, 2H), 1.73-1.63 (m, 3H), 1.50 (dd, *J* = 36.4, 3.1 Hz, 2H), 1.33-1.18 (m, 2H), 1.10 (tt, *J* = 12.5, 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C), 155.7 (C), 142.2 (C), 108.9 (CH), 60.6 (CH), 32.5 (CH_3), 29.5 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 20.2 (CH_3). IR (film): 2898, 1726, 1639, 1438, 727 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3O$ $[M]^+$: 221.1528. Found: 221.1524.

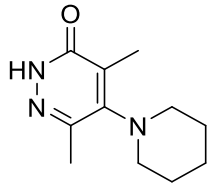


5-(Dipropylamino)-6-methylpyridazin-3(2*H*)-one (table 2.9, 13l): Synthesized according to general procedure **E** using keto-carbazone **11a** (0.132 g, 0.600 mmol), dipropylamine (0.182 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a brown solid (0.0630 g, 47%). TLC Rf = 0.14 in 60% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (s, 1H), 3.04-3.01 (m, 4H), 2.28 (s, 3H), 1.52 (sextet, *J* = 7.5 Hz, 4H), 0.84 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (C), 154.2 (C), 142.5 (C), 109.6 (CH), 53.1 (CH_2), 20.4 (CH_3), 20.1 (CH_2), 11.4 (CH_3). IR (film): 1647, 1108, 904, 717 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{19}N_3O$ $[M]^+$: 209.1528. Found: 209.1525.



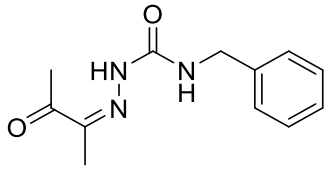
6-Ethyl-4-methyl-5-(piperidin-1-yl)pyridazin-3(2*H*)-one (table 2.9, 13m): Synthesized according to general procedure **E** using keto-carbazone **11b** (0.148 g, 0.600 mmol), piperidine (0.153 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by

column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield a yellow solid (0.0630 g, 47%). TLC Rf = 0.46 in 100% EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.27 (br s, 1H), 3.01 (m, 4H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 1.58 (m, 6H), 1.16 (q, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9 (C), 151.7 (C), 151.0 (C), 130.7 (C), 51.3 (CH_2), 26.6 (CH_2), 25.4 (CH_2), 24.2 (CH_2), 12.30 (CH_3), 12.27 (CH_3). IR (film): 2956, 1635, 1442, 1266, 725 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{19}N_3O$ $[M]^+$: 221.1528. Found: 221.1526.

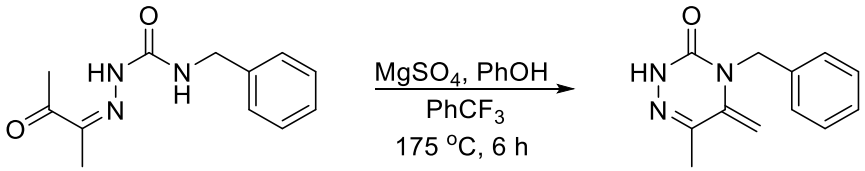


4,6-Dimethyl-5-(piperidin-1-yl)pyridazin-3(2*H*)-one (table 2.9, 13n): Synthesized according to general procedure **E** using keto-carbazone **11c** (0.149 g, 0.600 mmol), piperidine (0.153 g, 1.80 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The title compound was purified by column chromatography (gradient: 100% EtOAc to 5% MeOH/EtOAc) to yield an off-white solid (0.0815 g, 66%). TLC Rf = 0.27 in 100% EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.46 (s, 1H), 3.00 (d, *J* = 5.3 Hz, 4H), 2.22 (s, 3H), 2.09 (s, 3H), 1.57 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.1 (C), 152.0 (C), 146.6 (C), 129.3 (C), 51.2 (CH_2), 26.6 (CH_2), 24.2 (CH_2), 19.6 (CH_3), 12.2 (CH_3). IR (film): 1637, 1266, 730, 706 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{17}N_3O$ $[M]^+$: 207.1372. Found: 207.1379.

Mechanistic Study

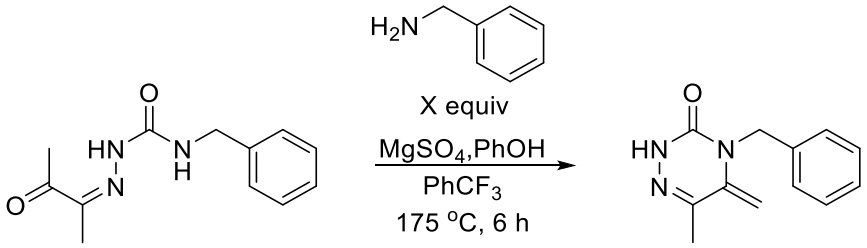


(*E*)-*N*-Benzyl-2-(3-oxobutan-2-ylidene)hydrazinecarboxamide (14a): To a solution of keto-carbazone **11a** (0.220 g, 1.00 mmol) and benzylamine (0.118 g, 1.10 mmol) in THF (3.3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0300 g, 0.200 mmol) and the solution was stirred at room temperature for 16 h. The solution was concentrated and purified by column chromatography (10% EtOAc/CH_2Cl_2) to yield a white solid (0.200 g, 86%). TLC Rf = 0.25 10% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.05 (br s, 1H), 7.70 (t, *J* = 6.2 Hz, 1H), 7.36-7.28 (m, 4H), 7.26-7.20 (m, 1H), 4.39 (d, *J* = 6.2 Hz, 2H), 2.39 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2 (C), 155.2 (C), 144.3 (C), 140.3 (C), 128.2 (CH), 126.9 (CH), 126.6 (CH), 42.7 (CH_2), 24.4 (CH_3), 9.4 (CH_3). IR (film): 1695, 1652, 1263, 732, 705 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{15}N_3O_2$ –(C_2H_3O) $[M]^+$: 190.0936. Found: 190.0979.

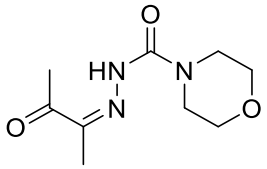


Scheme 2.12: Performed according to general procedure **D** using keto semi-carbazone **14a** (0.140 g, 0.600 mmol), phenol (0.0540 g, 0.600 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The solution was concentrated

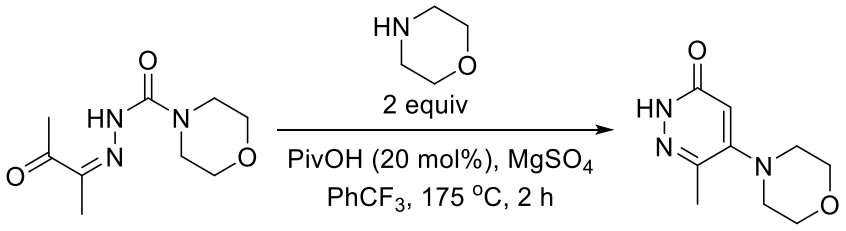
under reduced pressure. 1,3,5-trimethoxybenzene was added and ^{1}H NMR was used to determine a 78% NMR yield.



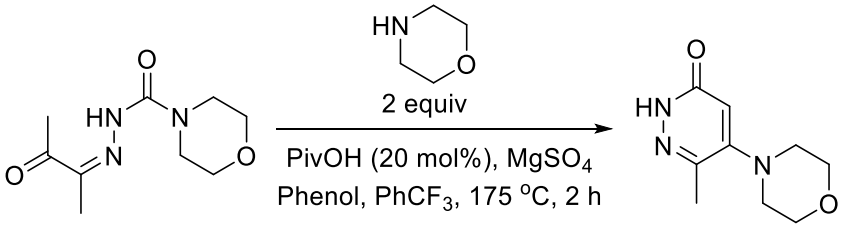
Scheme 2.12: Performed according to general procedure **D** using keto semi-carbazone **14a** (0.140 g, 0.600 mmol), benzylamine (0.1 and 0.5 equiv), phenol (0.0540 g, 0.600 mmol) and $MgSO_4$ (0.0720 g, 0.600 mmol). The solution was concentrated under reduced pressure. 1,3,5-trimethoxybenzene was added and ^{1}H NMR was used to determine a 80% (with 0.1 equiv) and 43% (0.5 equiv) NMR yield.



(*E*)-*N*'-(3-Oxobutan-2-ylidene)morpholine-4-carbohydrazide (14b): To a solution of keto-carbazone **11a** (0.220 g, 1.00 mmol) and morpholine (0.0960 g, 1.10 mmol) in THF (3.0 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0300 g, 0.200 mmol) and the solution was stirred at room temperature for 16 h. The solution was concentrated and purified by column chromatography (50% EtOAc/CH_2Cl_2) to yield a white solid (0.169 g, 79%). TLC Rf = 0.13 50% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 3.70-3.59 (m, 8H), 2.29 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.0 (C), 156.1 (C), 145.8 (C), 66.6 (CH_2), 46.1 (CH_2), 24.3 (CH_3), 8.4 (CH_3). IR (film): 1654, 1265, 1114, 981, 727, 698 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{16}N_3O_3$ $[M+H]^+$: 214.1147 Found: 214.1174.

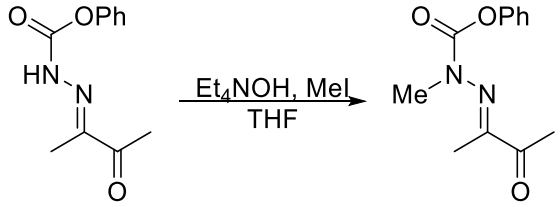


Scheme 2.13: Performed according to general procedure **E** using keto semi-carbazone **14b** (0.128 g, 0.600 mmol), morpholine (0.103 g, 1.20 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol). The solution was concentrated under reduced pressure. 1,3,5-trimethoxybenzene was added and ^{1}H NMR was used to determine a 47 % NMR yield

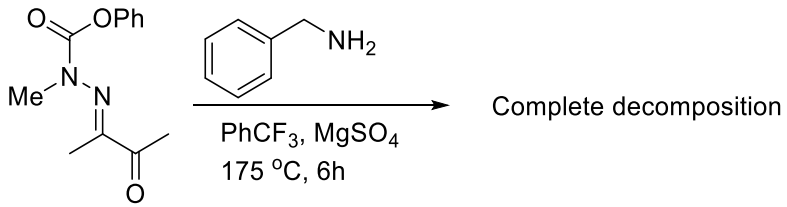


Scheme 2.13: Performed according to general procedure **E** using keto semi-carbazone **14b** (0.128 g, 0.600 mmol), morpholine (0.103 g, 1.20 mmol), $MgSO_4$ (0.0720 g, 0.600 mmol), pivalic acid (0.0120 g, 0.120 mmol) and phenol (0.0570 g, 0.600 mmol). The solution was concentrated under reduced pressure. 1,3,5-trimethoxybenzene was added and ^{1}H NMR was used to determine a 72 % NMR yield.

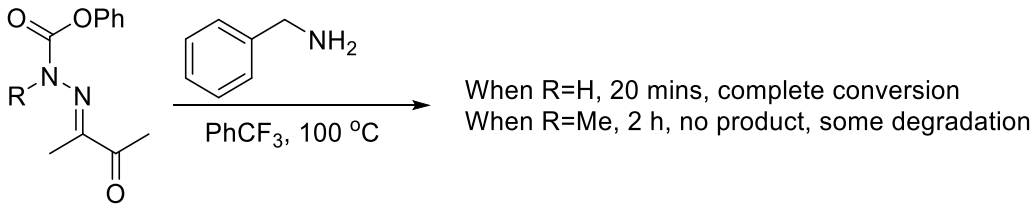
***N*-Methyl control experiments:**



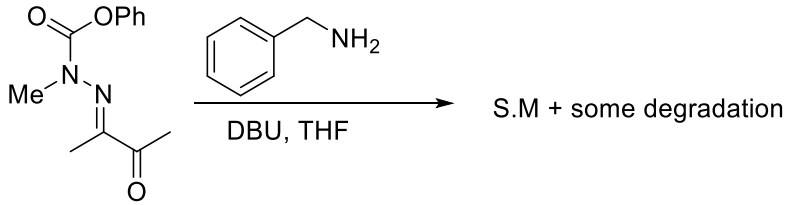
Phenyl (*Z*)-1-methyl-2-(3-oxobutan-2-ylidene)hydrazine-1-carboxylate (11a-*N*-methyl): To a solution of **11a** (0.660 g, 3.00 mmol) in THF (15.0 mL) was added MeI (0.56 mL, 9.0 mmol). The solution was cooled to 0 °C and a solution of 25% tetraethylammonium hydroxide in water (1.77 g, 3.30 mmol) was added dropwise. The reaction was allowed to stir at room temperature for 1 hour. Water and CH_2Cl_2 was added and the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2 and the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was purified by column chromatography (100% CH_2Cl_2 to 5% EtOAc/CH_2Cl_2) to afford the pure compound as a clear oil (0.170 g, 24%). TLC Rf = 0.72 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.37 (m, 2H), 7.27-7.21 (m, 1H), 7.18-7.13 (m, 2H), 3.49 (d, *J* = 1.1 Hz, 3H), 2.49 (d, *J* = 0.8 Hz, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6 (C), 150.9 (C), 129.4 (CH), 125.8 (CH), 121.4 (CH), 39.0 (CH_3), 25.2 (CH_3), 14.3 (CH_3). IR (film): 1722, 1701, 1420, 1368, 1267, 1111 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{10}H_{11}N_2O_2$ (-C_2H_3O) $[M]^+$: 191.0821 Found: 191.0815



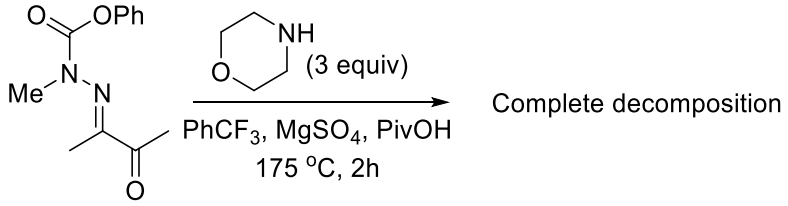
When **11a-*N*-methyl** was subjected to the reaction conditions (table 2.7), no product was detected. Instead a complete decomposition was apparent by crude ^{1}H NMR.



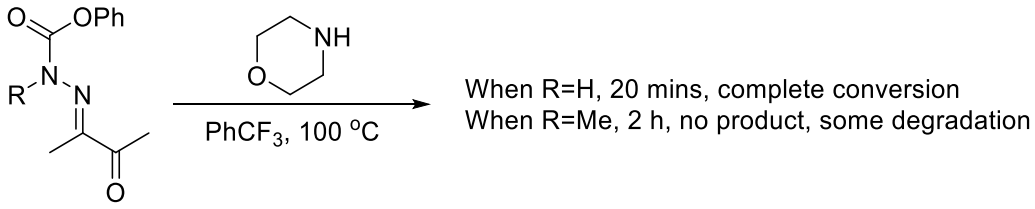
When an exchange reaction was attempted at 100 °C, **11a** was completely converted to **14a** in 20 minutes at 100 °C in the microwave. However, no sign of product was observed after 2 hours under the same reaction conditions while using **11a-*N*-methyl**.



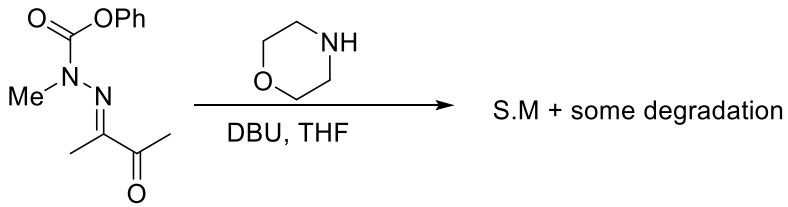
Using the same conditions to form **14a** from **11a**, **11a-*N*-methyl** was observed with some degradation.



When **11a-*N*-methyl** was subjected to the reaction conditions (table 2.9), no product was detected. Instead a complete decomposition was apparent by crude ^{1}H NMR.



When an exchange reaction was attempted at 100 °C, **11a** was completely converted to **14b** in 20 minutes at 100 °C in the microwave. However, no sign of product was observed after 2 hours under the same reaction conditions while using **11a-*N*-methyl**.



Using the same conditions to form **14b** from **11a**, **11a-*N*-methyl** was observed with some degradation.

6.3 Supporting Information for Chapter 3

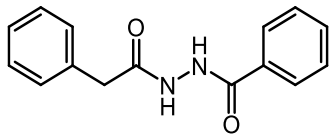
6.3.1 Carboxylic acids as formal carbon nucleophiles (section 3.2)

Starting material synthesis

Blocked *N*-isocyanate **15**[261] was prepared by known methods following literature procedures. Blocked *O*-isocyanates **17a,c-d,**[173] **b, e-f**[172] were prepared by known methods following literature procedures. Carboxylic acid **18r**[262] and **18s**[263] were prepared by known methods following literature procedures. Urea[264] and isocyanurate[265] formation were monitored by ^{1}H NMR based on previous literature reports.

Synthesis of hydrazide/hydroxamate product

General Procedure F: An oven dried round-bottom flask was charged with a stir bar, carboxylic acid (1.0 equiv.), blocked *O*-isocyanate (3.0 equiv.), Et_3N (0.2 equiv.) and MeCN (0.2 M). The vial was sealed under an inert atmosphere of argon with a microwave cap. The vial was immersed in a oil bath at 120˚C while stirring and monitored by TLC. Upon completion, the crude mixture was concentrated under reduced pressure and purified by silica gel chromatography using an appropriate solvent system to obtain the corresponding hydroxamate.



***N'*-Benzoyl-2-phenylmethylhydrazide (scheme 3.2, 16):** Synthesized according to general procedure **F** using phenyl acetic acid (0.245 g, 1.80 mmol), blocked *N*-isocyanate **15** (0.0973 g, 0.600 mmol), Et_3N (0.33 mL, 2.40 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 20 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure, diluted with EtOAc (100 mL), and extracted with saturated bicarb (2x40 mL), and brine (1 x 40 mL). The organic layer was concentrated under reduced pressure, dry loaded onto silica (MeOH), and purified by silica gel column chromatography using 20 % EtOAc/CH_2Cl_2 to generate the pure compound as a white solid (36.1 mg, 24 %). TLC Rf = 0.21 in 20 % EtOAc/CH_2Cl_2. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 10.17 (s, 1H), 7.93 – 7.77 (m, 2H), 7.61 – 7.38 (m, 3H), 7.38 – 7.11 (m, 5H), 3.52 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9 (C), 165.9 (C), 136.1 (C), 132.9 (C), 132.2 (CH), 129.5 (CH), 128.9 (CH), 128.7 (CH), 127.8 (CH), 126.9 (CH), 40.8 (CH_3). Spectral data was consistent with literature reports.[266]

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[261] Levins, C. G.; Wan, Z.-K. *Org. Lett.* **2008**, *10*, 1755.

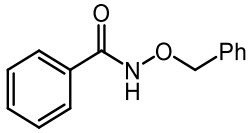
[262] Mai, A.; Esposito, M.; Sbardella, G.; Massa, S. *Org. Prep. Proced. Int.* **2001**, *33*, 391.

[263] Reisch, H. A.; Leeming, P.; Raje, P. S. US Patent 8,642,809, February 4, 2014.

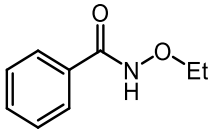
[264] Anumandla, D.; Littlefield, R.; Jeffrey, C. S. *Org. Lett.* **2014**, *16*, 5112

[265] Naruhisa, H.; Hyogo, H.-S. E.P. 1,666,470, July 6, 2006.

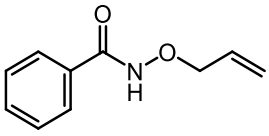
[266] Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988.



***N*-(Benzyloxy)benzamide (table 3.5, 19aa):** Synthesized according to general procedure **F** using benzoic acid (0.0733 g, 0.600 mmol), blocked *O*-isocyanate **17a** (0.384 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 5 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (124.1 mg, 91 %). TLC Rf = 0.21 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.62 (br s, 1H), 7.68-7.66 (m, 2H), 7.52-7.48 (m, 1H), 7.45-7.35 (m, 7H), 5.04 (s, 2H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 164.4 (C), 135.9 (C), 132.3 (C), 131.5 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.3 (CH), 127.0 (CH), 76.9 (CH_2). Spectral data was consistent with literature reports.[267]

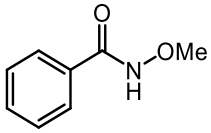


***N*-Ethoxybenzamide (table 3.5, 19ba):** Synthesized according to general procedure **F** using benzoic acid (0.0733 g, 0.600 mmol), blocked *O*-isocyanate **17b** (0.326 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 24 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (90.2 mg, 91 %). TLC Rf = 0.28 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.95 (br s, 1H), 7.77-7.74 (m, 2H), 7.47-7.42 (m, 1H), 7.37-7.32 (m, 2H), 4.01 (q, 2H), 1.23 (t, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.6 (C), 132.1 (C), 131.9 (CH), 128.6 (CH), 127.3 (CH), 72.3 (CH_2), 13.6 (CH_3). IR (film): 3193, 2979, 1643, 1577, 1513, 1483, 1383, 1305, 1152 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 165.07898. Found: 165.07904.

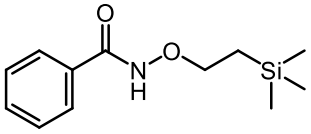


***N*-(Allyloxy)benzamide (table 3.5, 19ca):** Synthesized according to general procedure **F** using benzoic acid (0.0733 g, 0.600 mmol), blocked *O*-isocyanate **17c** (0.348 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 22 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as an amorphous white solid (75.5 mg, 71 %). TLC Rf = 0.36 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.51 (br s, 1H), 7.75-7.72 (m, 2H), 7.50-7.45 (m, 1H), 7.40-7.35 (m, 2H), 6.00 (ddt, J = 16.9, 10.3, 6.4 Hz, 1H), 5.33 (dq, J = 17.2, 1.4 Hz, 1H), 5.28 (ddt, J = 10.3, 1.7, 0.9 Hz, 1H), 4.47 (d, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.4 (C), 132.4 (C), 132.0 (CH), 128.7 (CH), 127.3 (CH), 120.7 (CH_2), 77.5 (CH), 77.3 (CH_2). IR (film): 3196, 3061, 3022, 2990, 1643, 1516, 1481, 1307, 1154 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 177.07898. Found: 177.08050.

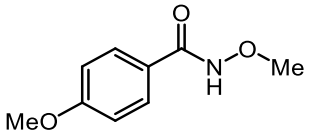
[267] Dev, D.; Palakurthy, N. B.; Thalluri, K.; Chandra, T. J.; Mandal, B. *J. Org. Chem.* **2014**, *79*, 5420.



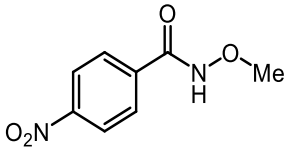
***N*-Methoxybenzamide (table 3.5, 19da)**: Synthesized according to general procedure **F** using benzoic acid (0.0733 g, 0.600 mmol), blocked *O*- isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 5 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (89.8 mg , 99 %). TLC Rf = 0.54 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.91 (br s, 1H), 7.75 (dd, J = 8.32, 1.35 Hz, 2H), 7.49-7.44 (m, 1H), 7.39-7.34 (m, 2H), 3.80 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 167.0 (C), 132.1 (C), 131.9 (CH), 128.7 (CH), 127.3 (CH), 64.4 (CH_3). IR (film): 3188, 3180, 2979, 2935, 1638, 1511, 1470, 1307, 1151 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 151.16500. Found: 151.06507.



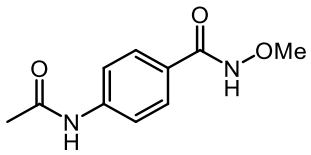
***N*-(2-(Trimethylsilyl)ethoxy)benzamide: (table 3.5, 19ea)**: Synthesized according to general procedure **F** using benzoic acid (0.0733 g, 0.600 mmol), blocked *O*-isocyanate **17e** (0.456 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 22 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 10 % EtOAc/Hexanes to generate the pure compound as a yellow oil (113.9 mg, 80 %). TLC Rf = 0.23 in 10% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.44 (br s, 1H), 7.77-7.74 (m, 2H), 7.49-7.44 (m, 1H), 7.39-7.35 (m, 2H), 4.04 (t, J = 8.4 Hz, 2H), 1.04 (m, 2H), 0.00 (s, 9H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.5 (C), 132.3 (C), 132.0 (CH), 128.7 (CH), 127.3 (CH), 74.6 (CH_2), 16.9 (CH_2), -1.3 (CH_3). IR (film): 3043, 2953, 2825, 1687, 1593, 1543, 1452, 1369, 1204, 1068 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 237.11851. Found: 237.11724.



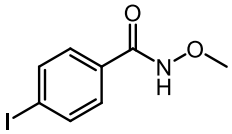
***N*,4-Dimethoxybenzamide (table 3.6, 19db)**: Synthesized according to General Procedure **F** using 4-methoxybenzoic acid (0.0913 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 16 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 55% EtOAc/Hexanes to generate the pure compound as a yellow solid (94.6 mg, 87 %). TLC Rf = 0.27 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.56 (br s, 1H), 7.74-7.71 (m, 2H), 6.88-6.84 (m, 2H), 3.81 (s, 6H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.5 (C), 162.7 (C), 129.1 (CH), 124.2 (C), 114.0 (CH), 64.5 (CH_3), 55.5 (CH_3). IR (film): 3166, 2927, 1643, 1487, 1255, 1152, 1015cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 181.07389. Found: 181.07121.



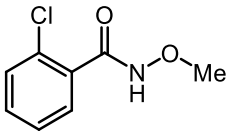
***N*-Methoxy-4-nitrobenzamide (table 3.6, 19dc)**: Synthesized according to general procedure **F** using 4-nitrobenzoic acid (0.100 g, 0.6000 mmol), blocked *O*-isocyanate **17d** (0.3009 g, 1.800 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 24 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 50% EtOAc/Hexanes to generate the pure compound as a white powder (49.4 mg, 42 %). TLC Rf = 0.26 in 50 % EtOAc/Hexanes. ^{1}H NMR (400 MHz; DMSO-d_6): δ 12.07 (br s, 1H), 8.33-8.30 (m, 2H), 8.00-7.96 (m, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 162.0 (C), 149.1 (C), 138.0 (C), 128.5 (CH), 123.6 (CH), 63.3 (CH_3). IR (film): 3157, 2988, 2941, 1650, 1598, 1513, 1307, 1295, 1145, 1042 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 196.04841. Found: 196.04553.



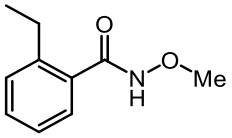
4-Acetamido-*N*-methoxybenzamide (table 3.6, 19dd): Synthesized according to general procedure **F** using *p*-(acetylamino)benzoic acid (0.108 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 6 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 10% MeOH/CH_2Cl_2 to generate the pure compound as a yellow solid (91.2 mg, 73 %). TLC Rf = 0.44 in 10 % MeOH/CH_2Cl_2. ^{1}H NMR (400 MHz; DMSO-d_6): δ 11.60 (br s, 1H), 10.17 (br s, 1H), 7.71-7.63 (m, 4H), 3.68 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 168.7 (C), 142.2 (C), 127.9 (C), 126.4 (CH), 118.2 (CH), 63.2 (CH_3), 24.1 (CH_3). IR (film): 3197, 1653, 1596, 1538, 1498, 1297, 1038 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 208.08479. Found: 208.08364.



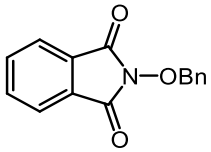
4-Iodo-*N*-methoxybenzamide (table 3.6, 19de): Synthesized according to general procedure **F** using *p*-iodobenzoic acid (0.149 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 23 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (119.7 mg, 72%). TLC Rf = 0.20 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.8 (C), 137.8 (CH), 132.1 (C), 129.5 (CH), 99.8 (C), 63.7 (CH_3) .HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 276.95997. Found: 276.95919.



2-Chloro-*N*-methoxybenzamide (table 3.6, 19df): Synthesized according to general procedure **F** using *o*-chlorobenzoic acid (0.0939 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.3009 g, 1.800 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 23 hours at 120 ˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (90.2 mg, 81 %). TLC Rf = 0.28 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.77 (br s, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.43-7.39 (m, 2H), 7.38-7.31 (m, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 164.5 (C), 132.3 (C), 132.1 (C), 131.3 (CH), 130.6 (CH), 130.4 (CH), 127.3 (CH), 64.9 (CH_3). IR (film): 3125, 2932, 2808, 1635, 1530, 1432, 1310, 1031 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 185.02436. Found: 185.02051.

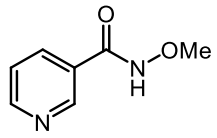


2-Chloro-*N*-methoxybenzamide (table 3.6, 19dg): Synthesized according to general procedure **F** using *o*-ethylbenzoic acid (0.0901 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 10 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (92.5 mg, 50 %[268]). TLC Rf = 0.25 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.95 (br s, 1H), 7.35-7.11 (m, 4H), 3.99 (s, 3H), 2.72 (q, J = 7.6 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.0 (C), 144.1 (C), 132.5 (C), 130.7 (CH), 129.5 (CH), 127.3 (CH), 125.7 (CH), 65.5 (CH_3), 26.3 (CH_2), 15.8 (CH_3). IR (film): 3127, 2929, 2880, 1634, 1524, 1443, 1393, 1314 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 179.09463. Found: 179.09237.

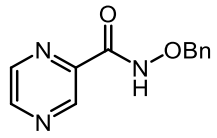


2-(Benzyloxy)isoindoline-1,3-dione (table 3.6, 19ai): Synthesized according to general procedure **F** using phtalic acid (0.0997 g, 0.600 mmol), blocked *O*-isocyanate **17a** (0.3838 g, 1.800 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 18 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 20 % EtOAc/Hexanes to generate the pure compound as a white powder (91.2 mg, 60 %). TLC Rf = 0.47 in 30% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.84-7.71 (m, 4H), 7.55-7.53 (m, 2H), 7.41-7.36 (m, 3H), 5.22 (s, 2H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 163.7 (C), 134.6 (C), 133.9 (CH), 130.1 (CH), 129.5 (C), 129.1 (CH), 128.7 (CH), 123.7 (CH), 80.1 (CH_2). IR (film): 2884 1724, 1460, 1378, 1129, cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 253.07389 Found: 253.07267.

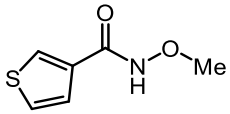
[268] Yield calculated taking into account urea by-product



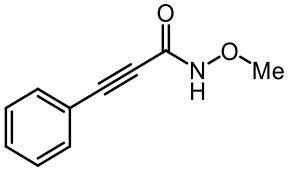
***N*-Methoxynicotinamide (table 3.6, 19dj)**: Synthesized according to general procedure **F** using nicotinic acid (0.0739 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 23 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 60% EtOAc/Hexanes to generate the pure compound as a green oil (88.6 mg, 97 %). TLC Rf = 0.47 in 10% MeOH/CH_2Cl_2. ^{1}H NMR (400 MHz; $CDCl_3$): δ 9.94 (br s, 1H), 8.95 (s, 1H), 8.71 (dd, J = 5.0, 1.7 Hz, 1H), 8.15 (dt, J = 8.0, 1.9 Hz, 1H), 7.40 (ddd, J = 8.0, 4.9, 0.9 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 162.4 (C), 152.2 (C), 148.0 (CH), 134.9 (CH), 128.0 (CH), 124.0 (CH), 63.4 (CH). IR (film): 3161, 2935, 2816, 1648, 1591, 1416, 1304, 1050 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 152.05858. Found: 152.05692.



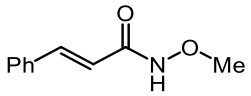
***N*-(Benzyloxy)pyrazine-2-carboxamide (table 3.6, 19ak)**: Synthesized according to general procedure **F** using 2-pyrazylcarboxylic acid (0.0745 g, 0.600 mmol), blocked *O*-isocyanate **17a** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 2 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 20% MeOH/EtOAc to generate the pure compound as a white solid (123.8 mg, 90 %). TLC Rf = 0.35 in 20% MeOH/EtOAc. ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.25 (br s, 1H), 9.33 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.42-7.39 (m, 2H), 7.35-7.30 (m, 3H), 5.03 (s, 2H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.4 (C), 147.8 (C), 144.2 (CH), 143.8 (CH), 142.7 (CH), 135.0 (C), 129.3 (CH), 128.9 (CH), 128.7 (CH), 78.7 (CH_2). IR (film): 3154, 2923, 1686, 1482, 1396, 1286, 1016 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 229.08513. Found: 229.06318.



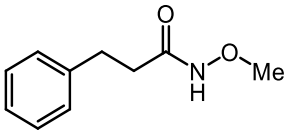
***N*-Methoxythiophene-3-carboxamide (table 3.6, 19dl)**: Synthesized according to general procedure **F** using 3-thiophene carboxylic acid (0.0769 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 15 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 5% EtOAc/CH_2Cl_2 to generate the pure compound as clear crystals (90.5 mg, 96 %). TLC Rf = 0.25 in 5% EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz; $CDCl_3$): δ 8.85 (br s, 1H), 7.94 (dd, J = 3.0, 1.3 Hz, 1H), 7.40 (dd, J = 5.1, 1.3 Hz, 1H), 7.35 (dd, J = 5.1, 3.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (400 MHz; $CDCl_3$) δ 164.2 (C), 134.1 (C), 129.4 (CH), 126.9 (CH), 126.2 (CH), 64.9 (CH_3). IR (film): 3231, 3087, 2923, 1642, 1524, 1419, 1289, 1026 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 157.01975. Found: 157.02189.



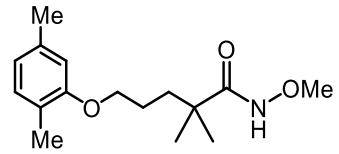
***N*-Methoxy-3-phenylpropiolamide (table 3.6, 19dm)**: Synthesized according to general procedure **F** using phenylpropiolic acid (0.0877 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), triethylamine (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 24 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 30 % EtOAc/Hexanes to generate the pure compound as a yellow oil (54.7 mg, 52 %). TLC Rf = 0.22 in 30% EtOAc/Hexanes. ^{1}H NMR (400 MHz; DMSO-d_6): δ 11.04 (br s, 1H), 7.43-7.38 (m, 2H), 7.26-7.22 (m, 1H), 7.16-7.12 (m, 2H), 3.65 (s, 3H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 163.7 (C), 134.6 (C), 133.9 (C), 130.1 (C), 129.5 (CH), 128.7 (CH), 123.7 (CH), 80.1 (CH_3). IR (film): 3407, 2922, 2852, 2116, 1741, 1458, 1376, 1062 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 175.06333. Found: 175.06198.



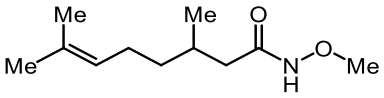
***N*-Methoxycinnamamide (table 3.6, 19dn)**: Synthesized according to general procedure **F** using (*E*)-3-phenylacrylic acid (0.0889 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 16 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 25 % EtOAc/Hexanes to generate the pure compound as a white solid (89.3 mg, 84 %). TLC Rf = 0.30 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; DMSO-d_6): δ 11.30 (br s, 1H), 7.58 (d, J = 7.1Hz, 2H), 7.51 (d, J = 15.8 Hz, 1H), 7.44-7.36 (m, 3H), 6.42 (d, J = 15.9 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 162.7 (C), 139.6 (C), 134.6 (CH), 129.7 (CH), 128.9 (CH), 127.6 (CH), 118.5 (CH), 63.4 (CH_3).IR (film): 3130, 2981, 2941, 1615, 1519, 1448, 1339, 1217, 1057 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 177.07898. Found: 177.07819.



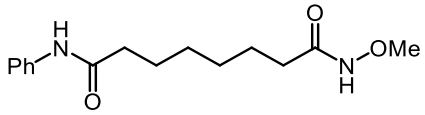
***N*-Methoxy-3-phenylpropanamide (table 3.6, 19do)**: Synthesized according to general procedure **F** using 3-phenylpropionic acid (0.0901 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 16 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 40% EtOAc/Hexanes to generate the pure compound as a yellow oil (93.6 mg, 87 %). TLC Rf = 0.24 in 40% EtOAc/Hexanes. ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.10 (br s, 1H), 7.26-7.22 (m, 2H), 7.19-7.15 (m, 3H), 3.62 (s, 3H), 2.94 (t, J = 8.7 Hz, 2H), 2.41 (t, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.3 (C), 140.5 (C), 128.5 (CH), 128.4 (CH), 126.3 (CH), 64.0 (CH_3), 34.8 (CH_2), 31.5 (CH_2). IR (film): 3173, 2969, 1649, 1490, 1438, 1149, 1065 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 179.09463. Found: 179.09263.



5-(2,5-Dimethylphenoxy)-*N*-methoxy-2,2-dimethylpentanamide (table 3.6, 19dp): Synthesized according to general procedure **F** using gemfibrozil (0.150 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 23 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 20 % EtOAc/Hexanes to generate the pure compound as a yellow oil (166.0 mg, 99 %). TLC Rf = 0.28 in 20% EtOAc/Hexanes. ^{1}H NMR (400 MHz; DMSO-d_6): δ 10.86 (br s, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.69 (s, 1H), 6.61 (d, J = 7.3 Hz, 1H), 3.88 (t, J = 5.8 Hz, 2H), 3.55 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H), 1.58 (m, 4H), 1.08 (s, 6H). ^{13}C NMR (100 MHz; DMSO-d_6) δ 173.5 (C), 156.4 (C), 136.0 (C), 130.0 (C), 122.5 (CH), 120.5 (CH), 112.0 (CH), 67.6 (CH_3), 62.7 (CH_3), 40.2 (CH_2), 36.8 (C), 24.8 (CH_2), 24.5 (CH_2), 21.0 (CH_3), 15.5 (CH_3). IR (film): 3215, 2924, 2867, 2815, 1646, 1507, 1262, 1128, 1039 cm^{-1}. HRMS (EI): Exact mass calcd for $C_8H_9NO_2$ [M]+: 279.18344. Found: 279.18274.

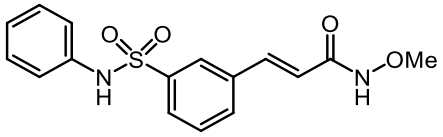


***N*-Methoxy-3,7-dimethyloct-6-enamide (table 3.6, 19dq)**: Synthesized according to general procedure **F** using citronellic acid (0.102 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 5 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 20% EtOAc/CH_2Cl_2 to generate the pure compound as a colourless oil (104.2 mg, 87 %). TLC Rf = 0.20 in 20% EtOAc/CH_2Cl_2 ^{1}H NMR (400 MHz; $CDCl_3$): δ 8 10.11 (br s, 1H), 5.01 (t, J = 6.9 Hz, 1H), 3.69 (s, 3H), 2.09 (dd, J = 13.3, 5.5 Hz, 1H), 1.92 (tdd, J = 21.2, 9.8, 5.5 Hz, 4H), 1.61 (s, 3H), 1.53 (s, 3H), 1.37-1.28 (m, 1H), 1.21-1.11 (m, 1H), 0.89 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.6 (C), 131.5 (C), 124.3 (CH), 64.0 (CH_3), 40.5 (CH_3), 36.9 (CH_3), 30.3 (CH_3), 25.7 (CH_2), 25.5 (CH), 19.3 (CH_2), 17.7 (CH_2). IR (film): 3172, 2962, 2916, 1651, 1510, 1439, 1377, 1052 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_{21}NO_2$ [M+Na]+: 222.14700. Found: 222.14690.



***N*^{1}-Methoxy-*N*^{8}-phenyloctanediamide (table 3.6, 19dr)**: Synthesized according to general procedure **F** using 8-oxo-8-(phenylamino)octanoic acid (0.0733 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.80 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 2 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 100 % EtOAc/Hexanes to generate the pure compound as a white solid (123.6 Mg, 74 %). TLC Rf = 0.25 in 100 % EtOAc/Hexanes. ^{1}H NMR (400 MHz; DMSO-d_6): δ 8 10.93 (br s, 1H), 9.83 (br s, 1H), 7.60-7.57 (m, 2H), 7.29-7.25 (m, 2H), 7.03-6.99 (m, 1H), 3.56 (s, 3H), 2.29 (t, J = 7.4 Hz, 2H), 1.93 (t, J = 7.4 Hz, 2H), 1.61-1.46 (m, 4H), 1.28-1.27 (m, 4H). ^{13}C NMR (400 MHz; DMSO-d_6) δ 171.1 (C), 169.0 (C), 139.3 (C), 128.6 (CH), 122.8 (CH), 119.0 (CH), 63.0 (CH_3), 36.3 (CH_2), 32.2 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 24.9 (CH_2), 24.8 (CH_2). IR (film): 3297, 3253, 3197, 2923, 2849,

1695, 1655, 1597, 1540, 1439, 1382, 1247, 1190, 1060 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{22}N_2O_3$ [M+Na]+: 301.15281. Found: 301.15210.

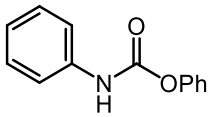


(*E*)-*N*-Methoxy-3-(3-(*N*-phenylsulfamoyl)phenyl)acrylamide (table 3.6, 19ds): Synthesized according to general procedure **F** using (*E*)-3-(3-(*N*-phenylsulfamoyl)phenyl)acrylic acid (0.0733 g, 0.600 mmol), blocked *O*-isocyanate **17d** (0.301 g, 1.800 mmol), Et_3N (17 µL, 0.20 mmol) and MeCN (3.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 19 hours at 120˚C in an oil bath. The crude mixture was concentrated under reduced pressure and purified by silica gel column chromatography using 100 % EtOAc to generate the pure compound as a white solid (157.5 mg, 79 %). TLC Rf = 0.35 in 100 % EtOAc. ^{1}H NMR (400 MHz; DMSO-d_6): δ 8 11.36 (br s, 1H), 10.35 (br s, 1H) 7.93 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 15.9 Hz, 1H), 7.25-7.20 (m, 2H), 7.10 (dd, J = 8.6, 1.3 Hz, 2H), 7.05-7.00 (m, 1H), 6.46 (d, J = 15.9 Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (400 MHz; DMSO-d_6) δ 162.0 (C), 140.3 (C), 137.7 (C), 137.5 (C), 135.6 (CH), 132.0 (CH), 130.0 (CH), 129.2 (CH), 127.4 (CH), 125.1 (CH), 124.4 (CH), 120.8 (CH), 120.4 (CH), 63.4 (CH_3). IR (film): 3557, 3074, 2890, 1664, 1627, 1493, 1338, 1306, 1150, 1063 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{16}N_2O_4S$ [M]+: 332.08308. Found: 332.08394.

6.3.2 Grignard reagents as carbon nucleophiles (section 3.3)

Starting material synthesis

Blocked *O*-isocyanate **17a**[173] and **17b**[269] were prepared by known methods following literature procedures. Non-commercially available Grignard reagents were prepared following literature procedures.[270]



Phenyl phenylcarbamate (20a): $NaHCO_3$ (0.924 g, 11.0 mmol) was added to a round bottom flask containing THF:water (0.30 M, 3:1 mixture) followed by the addition of the amine (0.913 mL, 10.0 equiv.). The temperature of the solution was brought to 0 °C upon which the phenyl chloroformate (1.32 mL, 10.5 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 30 min (note: Degradation to urea by-product detected when left for 2 hours). The desired product was extracted pure from the reaction mixture yielding an amorphous white solid (1.91 g, 90% yield). TLC R_F = 0.53 in 60% CH_2Cl_2/hexanes. ^{1}H-NMR (DMSO-d_6) δ 7.01 (1H, t, *J*=7.4 Hz), 7.17-7.24 (3H, m), 7.29 (2H, t, *J*=8.0 Hz), 7.39 (2H, t, *J*=5.3 Hz), 7.48 (1H, d, *J*=7.7 Hz), 10.19 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 118.9 (CH), 121.8 (CH), 123.9 (CH), 125.8 (CH), 129.2 (CH), 129.5 (CH), 137.5 (C), 150.6 (C), 151.9 (C). Data is consistent with literature.[271]

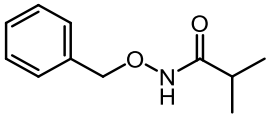
Hydroxamate product synthesis

[269] Elkaeed, E. B.; An, J.; Beauchemin, A. M. *J. Org. Chem.* **2017**, *82*, 9890.

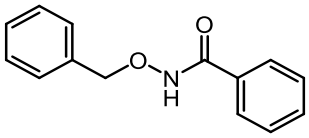
[270] Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802.

[271] U. Jacquemard, V. Beneteau, M. Lefoix, S. Routier, J.-Y. Merour, G. Coudert, *Tetrahedron*, **2004**, *60*, 10039.

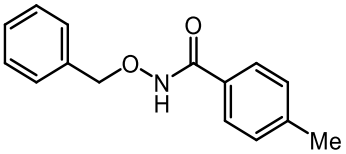
General Procedure G: An oven dried microwave vial was charged with a stir bar and cooled under a stream of argon. The blocked O-isocyanate precursor (1.0 equiv.) was added to the vial, sealed with a microwave cap, and purged under a stream of argon. The starting material was dissolved in THF (total reaction concentration 0.20M), cooled to 0 °C, upon which the Grignard reagent was added dropwise (4.0 equiv., sol'n in THF). The microwave vial was then transferred to an oil bath and stirred at reflux for 1.0 hour. Upon completion, the reaction is cooled to 0 °C and quenched with a saturated NH_4Cl solution (40 mL) and extracted with EtOAc (3x40 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography providing the desired product.



***N*-(Benzyloxy)isobutyramide (table 3.10, 23aa):** Synthesized according to general procedure **G** using isopropyl magnesium chloride lithium chloride (2.40 mmol), blocked *O*-isocyanate **17a** (0.145 g, 0.600 mmol), and THF (3.0 mL, 0.20 M). The crude mixture was purified by silica gel column chromatography using 10 % EtOAc/CH_2Cl_2 to generate the pure compound as an amorphous white solid (77.1 mg, 66 %). TLC Rf = 0.25 in 10 % EtOAc/CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.95 (s, 1H), 7.39 – 7.31 (m, 5H), 4.77 (m, 2H), 2.20 (m, J = 6.8 Hz, 1H), 0.98 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.2 (C), 136.1 (C), 128.8 (CH), 128.3 (CH), 128.2 (CH), 76.6 (CH_2), 31.1 (CH), 19.2 (CH_3). IR (film): 3157, 2968, 1646, 1511 cm^{-1}. HRMS (ESI): Exact mass calculated for $C_{11}H_{15}NO_2$ $[M+Na]^+$: 216.1000. Found: 216.1000.

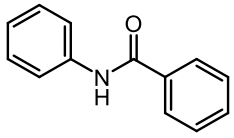


***N*-(Benzyloxy)benzamide (table 3.10, 23ac):** Synthesized according to general procedure **G** using isopropyl magnesium chloride lithium chloride (2.40 mmol), blocked *O*-isocyanate **17a** (0.145 g, 0.600 mmol), and THF (3.0 mL, 0.20 M). The crude mixture was purified by silica gel column chromatography using 100% CH_2Cl_2 to 10 % EtOAc/CH_2Cl_2 to generate the pure compound as an amorphous white solid (74.5 mg, 66 %). TLC Rf = 0.11 in 100 % CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.76 – 7.73 (m, 2H), 7.57 – 7.33 (m, 8H), 4.93 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 136.0 (C), 132.3 (C), 131.6 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 76.9 (CH_2). Spectral data was consistent with literature reports.[267]

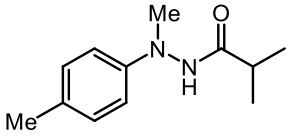


***N*-benzyloxy-4-methylbenzamide (table 3.10, 23ad):** Synthesized according to general procedure **G** using isopropyl magnesium chloride lithium chloride (2.40 mmol), blocked *O*-isocyanate **17a** (0.145 g, 0.600 mmol), and THF (3.0 mL, 0.20 M). The crude mixture was purified by silica gel column chromatography using 20 % EtOAc/Hexanes to generate the pure compound as an amorphous white solid (117.3 mg, 81

%). TLC Rf = 0.28 in 20 % EtOAc/Hexanes. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.46 – 7.33 (m, 5H), 7.26 (d, J = 8.0 Hz, 2H), 4.92 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.35 (C), 141.5 (C), 135.9 (C), 129.5 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 76.9 (CH_2), 21.0 (CH_3). Spectral data was consistent with literature reports.[272]



***N*-phenylbenzamide (scheme 3.5, 22ab):** This by-product was isolated during the purification of **23ac** as as a white solid (0.0054 mg, 66 %). TLC Rf = 0.16 in 100 % CH_2Cl_2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.01 – 7.93 (m, 2H), 7.82 – 7.74 (m, 1H), 7.63 – 7.57 (m, 1H), 7.57 – 7.51 (m, 2H), 7.40 – 7.32 (m, 2H), 7.11 (tt, *J* = 7.4, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.01, 139.63, 135.45, 132.00, 129.06, 128.84, 128.10, 124.11, 120.81. HRMS (EI): Exact mass calcd for $C_{13}H_{11}NO$ [M]+: 197.0841. Found: 197.0819. Spectral data was consistent with literature reports.[273]



***N*'-methyl-*N'*-(*p*-tolyl)isobutyrohydrazide (eq. 3.3, 23ba):** Synthesized according to general procedure **G** using isopropyl magnesium chloride (2.40 mmol), blocked *O*-isocyanate **17b** (0.154 g, 0.600 mmol), and THF (2.0 mL, 0.30 M). The crude mixture was purified by silica gel column chromatography using 40 % EtOAc/Hexanes to generate the pure compound as a white solid (25.9 mg, 21 %). TLC Rf = 0.35 in 40 % EtOAc/Hexanes. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 0.79H), 7.02 (d, *J* = 8.1 Hz, 1.28H), 6.75 (d, *J* = 8.6 Hz, 0.88H), 6.69 (d, *J* = 8.6 Hz, 1.59H), 3.10 (overlapping singlets, 3H), 2.97 (dt, *J* = 13.7, 6.9 Hz, 0.45H), 2.37 (p, *J* = 6.9 Hz, 0.65H), 2.27 (s, 1.23H), 2.23 (s, 1.96H), 1.19 (d, *J* = 6.9 Hz, 3.71H), 1.14 (d, *J* = 6.9 Hz, 1.31H), 1.05 (d, *J* = 6.9 Hz, 1.26H) (rotamers present). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 182.1 (C), 175.5 (C), 147.7 (C), 147.4 (C), 130.2 (C), 129.8 (CH), 129.6 (CH), 129.0 (C), 113.7 (CH), 113.3 (CH), 43.3 (CH_3), 41.0 (CH_3), 33.7 (CH_3), 29.1 (CH_3), 20.4 (CH), 20.4 (CH), 19.5 (CH_3), 19.3 (CH_3), 19.2 (CH_3). IR (film): 3224, 3019, 2960, 2922, 2870, 1658, 1612, 1509 cm^{-1}.

6.4 Supporting Information for Chapter 4

6.4.1 Rhodium catalyzed addition of boroxines to blocked isocyanate (section 4.2)

Preparation of aryl boroxines: Arylboroxines were readily prepared using literature procedures.[274] Arylboronic acids were heated to 110 °C overnight under reduced pressure and the corresponding boroxines were stored in a desiccator. Recrystallization of the boronic acid in water before dehydration resulted in a profound increase in reaction efficiency in some cases (**26ag**). This allowed the catalyst loading to diminish from 2.5 mol% $[Rh]_2$ before without prior recrystallization (61% yield) to 0.5 mol% $[Rh]_2$ (71% yield). The generality of this observation was not established.

[272] Kim, J.-J.; Park, Y.-D.; Kim, H.-K.; Cho, S.-D.; Kim, J.-K.; Lee, S.-G.; Yoon, Y.-J. *Synth. Commun.* **2005**, *35*, 731.
[273] Y. Rao, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2009**, *131*, 12924.
[274] H. H. Jung, A. W. Buesking, J. A. Ellman, *Org. Lett.* **2011**, *13*, 3912.

Aryl boronic esters (**25b3**, **31a2**, **31a3**, **31a4**) were synthesized according to literature procedures.[77]

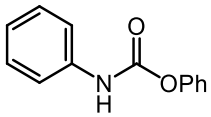
Urea synthesis

Urea **28a,**[275] **b,**[276] **c,**[277] **d,**[278] **e,**[279] **and f**[280] were prepared by known methods following literature procedures.

Blocked isocyanate synthesis

General procedure H: $NaHCO_3$ (3.30 mmol, 1.10 equiv.) was added to a round bottom flask containing THF:water (10.0 mL, 3:1) followed by the addition of the amine (3.00 mmol, 1.00 equiv.). The temperature of the solution was brought to 0 °C upon which the phenyl chloroformate (3.15 mmol, 1.05 equiv.) was added dropwise. The solution was allowed to warm to room temperature and subsequently monitored for the disappearance of starting material (generally 0.5 to 2 hours). Upon completion, the reaction was diluted with EtOAc (40 mL), then extracted with water (1 x 30 mL) and brine (1 x 30 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude extract was purified by silica gel chromatography to give the corresponding products.

General procedure I: An amine (3.00 mmol, 1.00 equiv.), CH_2Cl_2 (0.3 M), and Et_3N (3.30 mmol, 1.10 equiv.) were added to a dry round bottom flask. The temperature of the solution was brought to 0 °C upon which phenyl chloroformate (3.15 mmol, 1.05 equiv.) was added dropwise. The solution was warmed to room temperature and subsequently monitored for the disappearance of starting material. The reaction was concentrated under reduced pressure, resuspended in EtOAc (40 mL) and extracted with water (1 x 30 mL) and brine (1 x 30 mL). The organic layer was collected, dried over sodium sulfate, and concentrated under reduced pressure. The crude extract was purified by silica gel chromatography to give the corresponding products.



Phenyl phenylcarbamate (24a): Synthesized according to general procedure **H** using aniline (0.913 mL, 10.0 mmol), phenyl chloroformate (1.32 mL, 10.5 mmol), and $NaHCO_3$ (0.924 g, 11.0 mmol). The reaction reached completion within 0.5 hours (note: Degradation to urea by-product detected when left for 2 hours). The desired product was extracted pure from the reaction mixture yielding an amorphous white solid (1.91 g, 90% yield). TLC R_F = 0.53 in 60% CH_2Cl_2/hexanes. ^{1}H-NMR (DMSO-d_6) δ 7.01 (1H, t, *J*=7.4 Hz),

[275] Houlde, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 100066

[276] Gutschow, M. *J. Org. Chem.* **1999**, *64*, 5109.

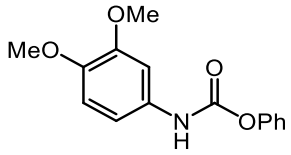
[277] Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q. *J. Org. Chem.* **1991**, *56*, 820.

[278] Synthesis: Figlus, M.; Tarruella, A. C.; Messer, A.; Sollis, S. L.; Hartley, R. C. *Chem. Commun.* **2010**, *46*, 4405. Characterization: Gately, D. A.; Norton, J. R.; Goodson, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 986.

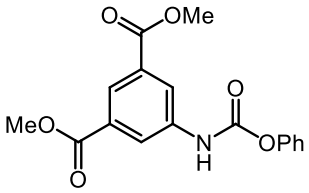
[279] Busschaert, N.; Kirby, I. L.; Young, S.; Coles, S. J.; Horton, P. N.; Light, M. E.; Gale, P. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 4426.

[280] Yamauchi, D.; Nishimura, T.; Yorimitsu, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 7200.

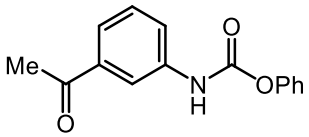
7.17-7.24 (3H, m), 7.29 (2H, t, *J*=8.0 Hz), 7.39 (2H, t, *J*=5.3 Hz), 7.48 (1H, d, *J*=7.7 Hz), 10.19 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 118.9 (CH), 121.8 (CH), 123.9 (CH), 125.8 (CH), 129.2 (CH), 129.5 (CH), 137.5 (C), 150.6 (C), 151.9 (C). Data is consistent with literature.[271]



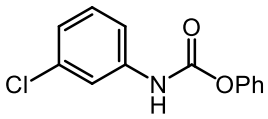
Phenyl (3-phenyl (3,4-dimethoxyphenyl)carbamate (24b): Synthesized according to general procedure **H** using 3,4-dimethoxyaniline (0.766 g, 5.00 mmol), phenyl chloroformate (0.569 mL, 5.25 mmol), and $NaHCO_3$ (0.462 g, 5.50 mmol). The reaction reached completion within 0.5 hours. The desired product was extracted pure from the reaction mixture yielding an amorphous purple/brown solid (1.17 g, 86% yield). TLC R_F = 0.26 in CH_2Cl_2. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.82 (6H, s), 6.78 (2H, m), 7.02 (1H, s), 7.14-7.25 (4H, m), 7.36 (2H, t, *J*=6.9 Hz). ^{13}C-NMR (75 MHz, Acetone-d_6): δ 55.1 (CH_3), 55.6 (CH_3), 104.2 (CH), 110.6 (CH), 112.6 (CH), 121.8 (CH), 125.1 (CH), 129.1 (CH), 132.4 (C), 145.7 (C), 149.7 (C), 151.2 (C), 151.8 (C). IR (film): 3339, 1741, 1191 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{15}NO_4$ [M]$^+$: 273.1001. Found: 273.1011.



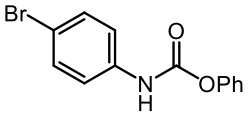
Dimethyl 5-((phenoxycarbonyl)amino)isophthalate (24c): Synthesized according to general procedure **H** using dimethyl 5-aminoisophthalate (0.628 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 2 hours. The desired product was dry loaded onto silica gel (MeOH) and purified by column chromatography (80% CH_2Cl_2/hexanes) yielding an amorphous white solid (0.750 g, 76% yield). TLC R_F = 0.24 in 80% CH_2Cl_2/hexanes. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.82 (6H, s), 7.21-7.25 (3H, m), 7.40 (2H, t, *J*=7.9 Hz), 8.01 (1H, s), 8.29 (2H, s), 10.58 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): 52.8 (CH_3), 122.3 (CH), 123.1 (CH), 124.2 (CH), 126.1 (CH), 129.9 (CH), 131.1 (C), 140.1 (C), 150.8 (C), 152.1 (C), 165.6 (C). IR (film): 3268, 1702, 1217 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{15}NO_6$ [M]$^+$: 329.0899. Found: 329.0916.



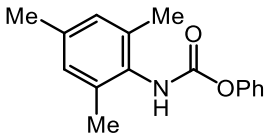
Phenyl (3-acetylphenyl)carbamate (24d): Synthesized according to general procedure **H** using 1-(3-aminophenyl)ethanone (0.676 g, 5.00 mmol), phenyl chloroformate (0.569 mL, 5.25 mmol), and $NaHCO_3$ (0.462 g, 5.50 mmol). The reaction reached completion within 0.5 hours. The desired product was extracted pure from the reaction mixture yielding an amorphous white solid (0.948 g, 74 % yield). TLC R_F = 0.18 in 5% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.59 (3H, s), 7.12-7.19 (3H, m), 7.24 (1H, m), 7.37-7.44 (3H, m), 7.66-7.73 (2H, m), 8.03 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 26.7 (CH_3), 118.6 (CH), 121.7 (CH), 123.4 (CH), 123.7 (CH), 125.9 (CH), 129.4 (CH), 129.5 (CH), 137.8 (C), 138.2 (C), 150.4 (C), 152.0 (C), 198.3 (C). IR (film): 3311, 1735, 1670, 1189 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{13}NO_3$ $[M]^+$: 255.0895. Found: 255.0873.



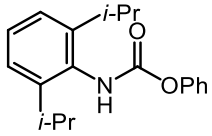
Phenyl (3-chlorophenyl)carbamate (24e): Synthesized according to general procedure **H** using 3-chloroaniline (0.317 mL, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 2 hours. The desired product was dry loaded onto silica gel (MeOH) and purified by column chromatography (50% CH_2Cl_2/hexanes) yielding an amorphous white solid (0.533 g, 72% yield) TLC R_F = 0.45 in 50% CH_2Cl_2/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.05 (1H, d, *J*=7.1 Hz), 7.14-7.26 (6H, m), 7.37 (2H, t, *J*=8.4 Hz), 7.49 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 117.0 (CH), 119.0 (CH), 121.7 (CH), 124.0 (CH), 126.0 (CH), 129.5 (CH), 130.1 (CH), 134.8 (C), 138.7 (C), 150.4 (C), 151.8 (C). IR (film): 3389, 1758, 1192, 784 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{10}ClNO_2$ $[M]^+$: 247.0400. Found: 247.0406.



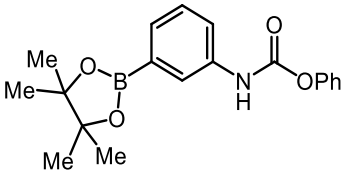
Phenyl (4-bromophenyl)carbamate (24f): Synthesized according to general procedure **H** using 4-bromoaniline (0.516 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 2 hours. The desired product was dry loaded onto silica gel (MeOH) and purified by column chromatography (50% CH_2Cl_2/hexanes) yielding an amorphous white solid (0.707 g, 81% yield). TLC R_F = 0.45 in 50% CH_2Cl_2/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.12-7.16 (3H, m), 7.21-7.30 (3H, m), 7.35-7.41 (6H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 116.5 (C), 120.4 (CH), 121.7 (CH), 125.9 (CH), 129.5 (CH), 132.1 (CH), 136.5 (C), 150.4 (C), 151.7 (C). IR (film): 3304, 1711, 1218, 687 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{10}NO_2Br$ $[M]^+$: 290.9895. Found: 290.9895.



Phenyl mesitylcarbamate (24g): Synthesized according to general procedure **I** using 2,4,6-trimethylaniline (0.421 mL, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and Et_3N (0.460 mL, 3.30 mmol). The reaction reached completion within 16 h. The crude mixture was purified using column chromatography (80% CH_2Cl_2/hexanes) providing the pure product as an amorphous white solid (0.688 g, 90% yield). TLC R_F = 0.36 in 80% CH_2Cl_2/hexanes ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.30 (7.1H, s), 2.37 (1.9H, s), 6.48 (1H, s, br), 6.92-6.96 (2H, m, br), 7.09 (0.6H, m, br), 7.20-7.24 (2.4H, m, br), 7.32-7.41 (2H, m) (note: rotamers present). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.4 (CH_3), 21.0 (CH_3), 121.5 (CH), 121.7 (CH), 125.3 (CH), 125.5 (CH), 129.1 (CH), 129.4 (CH), 130.6 (C), 131.4 (CH), 135.6 (C), 135.9 (C), 137.4 (C), 137.1 (C), 151.0 (C), 151.2 (C), 152.7 (C), 154.6 (C) (note: rotamers present). IR (film): 3275, 1704, 1238 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{17}NO_2$ $[M]^+$: 255.1259. Found: 255.1273.

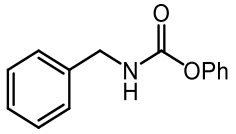


Phenyl (2,6-diisopropylphenyl)carbamate (24h): Synthesized according to general procedure **I** using 2,6-diisopropylaniline (0.566 mL, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and Et_3N (0.459 mL, 3.30 mmol). The reaction time was for 16 h. The crude mixture was purified using column chromatography (50% CH_2Cl_2/hexanes) providing the pure product as an amorphous white solid (0.325 g, 36% yield). TLC R_F = 0.23 in 50% CH_2Cl_2/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.33 (12H, m), 3.25 (1H, m, *J*=6.9 Hz), 3.38 (1H, m, *J*=6.9 Hz), 6.08 (0.4H, s, br), 6.27 (0.5H, s, br), 7.01 (1H, d, *J*=7.8 Hz), 7.16-7.22 (4H, m), 7.34-7.39 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.5 (CH_3), 23.7 (CH_3), 24.0 (CH_3), 28.7 (CH), 28.8 (CH), 121.4 (CH), 121.6 (CH), 123.7 (CH), 125.3 (CH), 125.6 (CH), 128.6 (CH), 128.8 (CH), 129.3 (CH), 129.4 (CH),130.3 (C), 130.8 (C), 146.8 (CH), 151.0 (C), 151.2(C), 153.4 (C), 154.8 (C). IR (film): 1801, 1173 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{23}NO_2$ $[M]^+$: 297.1729. Found: 297.1754.

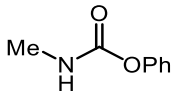


Phenyl (3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (24i): Synthesized according to general procedure **H** using 3-aminophenylboronic acid pinacolate (0.657 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 1 hour. The desired product was dry loaded on to silica gel (MeOH:CH_2Cl_2) and purified by column chromatography (20% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.628 g, 62% yield). TLC R_F = 0.53 in 20% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.32 (12H, s), 6.91 (1H, s, br), 7.15-7.24 (3H, m), 7.32-7.40 (3H, m), 7.53 (1H, d, *J*=7.3 Hz), 7.69-7.71 (2H, m, br). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 25.1 (CH_3), 84.1 (C), 122.0 (CH), 122.4 (CH), 124.8 (CH), 125.9 (CH), 128.9 (CH), 129.5 (C), 129.8 (CH), 138.6

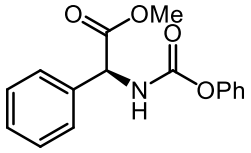
(C), 150.9 (C), 152.2 (C). IR (film): 3276, 1715, 1195 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{22}BNO_4$ $[M]^+$: 339.1642. Found: 339.1658.



Phenyl benzylcarbamate (24j): Synthesized according to general procedure **H** benzylamine (0.328 mL, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 0.3 hours. The desired product was dry loaded onto silica gel (MeOH) and purified by column chromatography (60% CH_2Cl_2/hexanes) yielding an amorphous white solid (0.565 g, 83% yield). TLC R_F = 0.21 in 60% CH_2Cl_2/hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.42 (1.8H, d, *J*=6.0 Hz), 4.47 (0.20H, s, br), 5.26 (0.11H, s, br), 5.53 (0.85H, s, br), 7.08-7.24 (3H, m), 7.28-7.40 (7H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 45.3 (CH_2), 121.7 (CH), 125.4 (CH), 127.7 (CH), 127.8 (CH), 128.8 (CH), 129.4 (CH), 138.2 (C), 151.1 (C), 154.8 (C). Data is consistent with literature.[281]

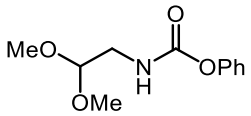


Phenyl methylcarbamate (24k): Synthesized following a previously reported literature procedure. Data is consistent with literature.[145]

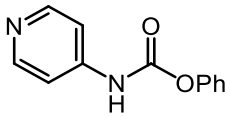


(*S*)-Methyl 2-((phenoxycarbonyl)amino)-2-phenylacetate (24l): Synthesized according to general procedure **H** (*S*)-2-phenylglycine methyl ester hydrochloride (0.605 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.554 g, 0.660 mmol). The reaction reached completion within 0.3 hours. The desired product was dry loaded onto silica gel (MeOH) and purified by column chromatography (60% CH_2Cl_2/hexanes) yielding an amorphous white solid (0.659 g, 77% yield). TLC R_F = 0.33 in 60% CH_2Cl_2/hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.72 (3H, s), 5.48 (1H, d, *J*=7.5 Hz), 6.37 (1H, d, *J*=7.4 Hz), 7.11-7.20 (3H, m), 7.29-7.46 (7H, m). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 52.9 (CH_3), 58.1 (CH), 121.6 (CH), 125.5 (CH), 127.3 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 136.4 (C), 150.9 (C), 153.8 (C), 171.2 (C). IR (film): 3330, 1737, 1705, 1211 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{15}NO_4$ $[M]^+$: 285.1001. Found: 285.1066. $[\alpha]^{20}_D$ -104° (*c* 0.87, MeCN).

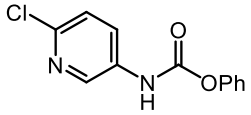
[281] R. Martinez, D. J. Ramon, M. Yus, *Adv. Synth. Catal.* **2008**, *350*, 1235.



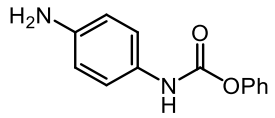
Phenyl (2,2-dimethoxyethyl)carbamate (24m): Synthesized according to general procedure **H** using aminoacetaldehyde dimethyl acetal (0.327 mL, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 3.30mmol). The reaction reached completion within 0.3 hours. The desired product was purified by column chromatography yielding a colorless oil (0.503 g, 74% yield). TLC R_F = 0.36 in 10% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.33-3.41 (8H, m), 4.42 (1H, t, *J*=5.3 Hz), 5.56 (1H, s, br), 7.07-7.19 (3H, m), 7.31 (2H, t, *J*=7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 42.6 (1C, s), 54.3 (1C, s), 102.6 (1C, s), 121.6 (1C, s), 125.3 (1C, s), 129.2 (1C, s), 151.0 (1C, s), 154.8 (1C, s). IR (film): 3318, 1719, 1198 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{11}H_{15}NO_4Na$ [M+Na]$^+$:248.0899. Found: 248.0907.



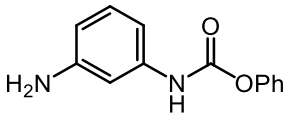
Phenyl pyridin-4-ylcarbamate (24n): Synthesized according to general procedure **I** using 4-aminopyridine(0.188 g, 2.00 mmol), phenyl chloroformate (0.276 mL, 2.20 mmol), and Et_3N (0.334 mL, 2.40 mmol). The reaction was stirred for 16 hours. The crude extract was dry loaded onto silica gel using MeOH and purified by column chromatography (EtOAc) yielding an amorphous white solid (0.300 g, 70 % yield). TLC R_F = 0.29 in EtOAc. ^{1}H-NMR (300 MHz, methanol-d_4): δ 8.32 (2H, d, *J*=6.5 Hz), 7.52 (2H, d, *J*=6.5 Hz), 7.36 (2H, m), 7.19 (3H, m). ^{13}C-NMR (400 MHz, Acetone-d_6): δ 113.7 (CH), 122.8 (CH), 126.7 (CH), 130.4 (CH), 147.0 (C), 151.5 (CH), 151.8 (C), 152.5 (C). IR (film): 1751, 1188 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{11}N_2O_2$ [M+H]$^+$: 215.0821. Found: 215.0826.



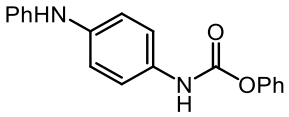
Phenyl (6-chloropyridin-3-yl)carbamate (24o): Synthesized according to general procedure **I** using 6-chloro-pyridin-3-ylamine (0.385 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and Et_3N (0.460 mL, 3.30 mmol). The reaction reached completion within 2 hours. The crude mixture was dry loaded onto silica gel (acetone) and purified using column chromatography (5% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.297 g, 40% yield). TLC R_F = 0.33 in 5% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, Acetone-d_6): δ 7.21-7.28 (3H, m), 7.39-7.44 (3H, m), 8.10 (1H, dd, *J*=2.8 Hz, 8.7 Hz), 8.59 (1H, d, *J*=2.7 Hz), 9.52 (1H, s). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 121.7 (CH), 124.1 (CH), 125.6 (CH), 128.9 (CH), 129.3 (CH), 135.2 (C), 140.0 (CH), 144.5 (C), 150.9 (C), 151.9 (C). IR (film): 1741, 1193 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_9N_2O_2Cl$ [M]$^+$: 248.0353. Found: 248.0334.



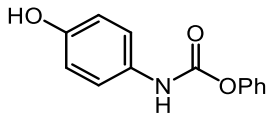
Phenyl (4-aminophenyl)carbamate (24p): Synthesized according to general procedure **I** using with p-phenylenediamine (1.85 g, 11.0 mmol), phenyl chloroformate (1.25 mL, 10.0 mmol), and Et_3N (1.53 mL, 11.0 mmol) and CH_2Cl_2 (100 mL). The reaction time was for 16 hours. The crude reaction mixture was dry loaded onto silica (MeOH) and purified by column chromatography (80% CH_2Cl_2/EtOAc) yielding a pure white/yellow amorphous solid (1.27 g, 56 % yield). TLC R_F = 0.53 in 80% CH_2Cl_2/EtOAc. 1H-NMR (400 MHz, Acetone-d_6): δ 3.58 (1H, s), 6.62 (1H, q, *J*=2.9 Hz), 6.86 (1H, s), 7.19 (1H, m, *J*=5.4 Hz), 7.36 (1H, t, *J*=7.9 Hz). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 114.5 (CH), 120.5 (CH), 121.8 (CH), 124.9 (CH), 128.4 (C) 129.1 (CH), 144.6 (C), 151.4 (C), 151.9 (C). IR (film): 3450, 3367, 3308, 1706, 1196 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_2O_2$ [M]$^+$: 228.0898. Found: 228.0901.



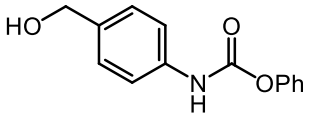
Phenyl (3-aminophenyl)carbamate (24q): Synthesized according to general procedure **I** using with m-phenylenediamine (0.324 g, 3.00 mmol), phenyl chloroformate (0.376 g, 3.00 mmol), and Et_3N (0.460 mL, 3.30 mmol). The reaction was complete within 16 hours. The crude mixture was dry loaded onto silica gel (MeOH) and purified by column chromatography (10% EtOAc/ CH_2Cl_2) yielding an amorphous yellow/white solid (0.393 g, 57% yield). TLC R_F = 0.25 in 10% EtOAc/ CH_2Cl_2. ^{1}H-NMR (400 MHz, Acetone-d_6): δ 4.66 (1H, s, br), 6.38 (1H, d, *J*= 7.1 Hz), 6.79 (1H, d, *J*=8.0 Hz), 6.96-7.01 (2H, m), 7.16-7.23 (3H, m), 7.39 (2, t, *J*=2.6 Hz), 8.95 (1H, s, br). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 104.5 (CH), 107.2 (CH), 109.5 (CH), 121.8 (CH), 125.1 (CH), 129.1 (CH), 129.2 (CH), 139.5 (C), 149.1 (C), 151.2 (C), 151.5 (C). IR (film): 3403, 3314, 1724, 1196 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_2O_2$ [M]$^+$: 228.0899. Found: 228.0898.



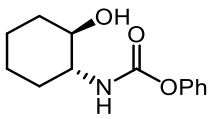
Phenyl (4-(phenylamino)phenyl)carbamate (24r): Synthesized according to general procedure **I** using with *N*-phenyl-p-phenylenediamine (0.368 g, 2.00 mmol), phenyl chloroformate (0.260 mL, 2.10 mmol), and Et_3N (0.306 mL, 2.20 mmol). The reaction was stirred for 16 hours. The crude mixture was dried loaded onto silica (CH_2Cl_2/MeOH) and purified by column chromatography (100% CH_2Cl_2) yielding an amorphous yellow solid (0.447 g, 73 % yield). TLC R_F = 0.39 in CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.64 (1H, s, br), 6.87-6.91 (2H, m), 6.98-7.04 (4H, m), 7.17-7.26 (6H, m), 7.29-7.34 (2H, m), 7.36-7.41 (2H, t, *J*=7.4 Hz). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 117.2 (CH), 119.4 (CH), 120.6 (CH), 120.7 (CH), 121.7 (CH), 125.7 (CH), 129.4 (CH), 129.4 (CH), 131.1 (C), 139.4 (C), 143.7 (C), 150.7 (C), 152.0 (C). IR (film): 3410, 3315, 1726, 1193 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{16}N_2O_2$ [M]$^+$: 304.1212. Found: 304.1188.



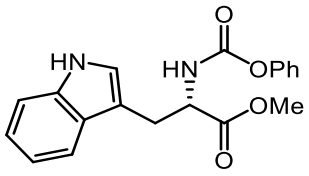
Phenyl (4-hydroxyphenyl)carbamate (24s): Synthesized according to general procedure **H** using 4-aminophenol (0.327 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 mL, 3.30 mmol). The reaction reached completion within 0.5 hours. The crude mixture was purified using column chromatography (10% EtOAc/ CH_2Cl_2) yielding an amorphous white solid (0.579 g, 84% yield). TLC R_F = 0.34 in 10% EtOAc/ CH_2Cl_2. ^{1}H-NMR (300 MHz, Acetone-d_6): δ 6.82 (2H, d, *J*=8.9 Hz), 7.16-7.21 (3H, m), 7.33-7.43 (4H, m), 8.19 (1H, s), 8.87 (1H, s). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 115.7 (CH), 120.9 (CH), 122.1 (CH), 125.4 (CH), 129.5 (CH), 131.0 (C), 151.5 (C), 152.3 (C), 153.8 (C). IR (film): 3350, 1719, 1196 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{11}NO_3$ $[M]^+$: 229.0739. Found: 229.0743.



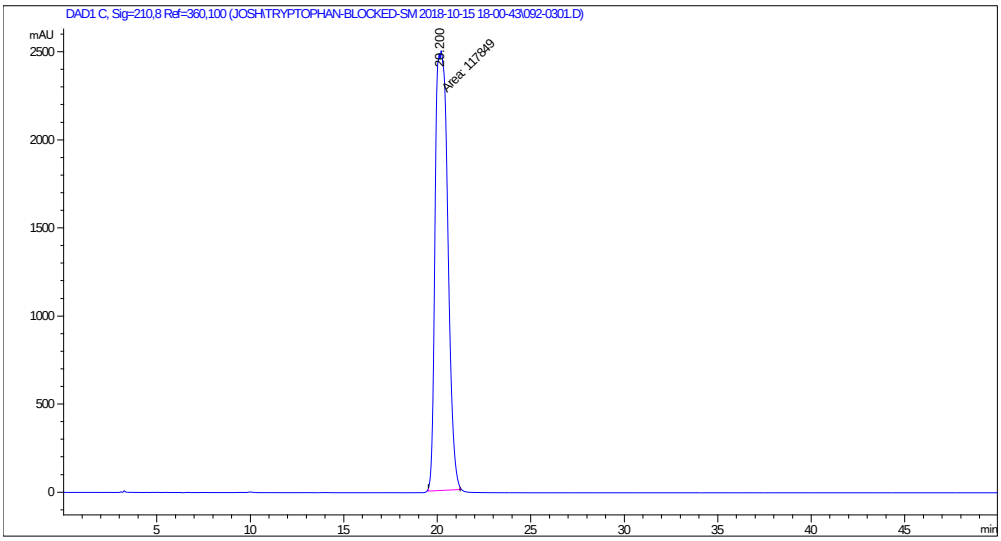
Phenyl (4-(hydroxymethyl)phenyl)carbamate (24t): Synthesized according to general procedure **H** using 4-aminobenzenemethanol (0.369 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 3.30 mmol). The reaction reached completion within 0.3 hours. The product was recrystallized twice (50% EtOAc/ hexanes) yielding a white solid (0.547 g, 75% yield). TLC R_F = 0.63 in 50% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, CDCl3): δ 1.79 (1H, s, br), 4.62 (2H, d, *J*=4.4 Hz), 7.06 (1H, s, br), 7.17 (2H, d, *J*=7.6 Hz), 7.22 (1H, t, *J*=7.3 Hz), 7.30 (2H, d, *J*=8.5 Hz), 7.35-7.42 (4H, m). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 64.8 (CH_2), 118.9 (CH), 121.7 (CH), 125.8 (CH), 128.0 (CH), 129.4 (CH), 136.5 (C), 136.9 (C), 150.6 (C), 151.7 (C). IR (film): 3364, 1725, 1195 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{13}NO_3$ $[M]^+$: 243.0895. Found: 243.0912.



Phenyl ((1*R*,2*R*)-2-hydroxycyclohexyl)carbamate (24u): Synthesized according to general procedure **H** using (1*S*,2*S*)-trans-2-aminocyclohexanol (0.346 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 3.3 mmol). The reaction reached completion within 0.3 hours. The reaction was diluted with EtOAc (50 mL) and extracted with water (1 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over sodium sulfate, concentrated under reduced pressure. The crude mixture was purified by column chromatography (25% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.523 g, 74% yield). TLC R_F = 0.31 in 25% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13-1.36 (4H, m), 1.66-1.73 (1H, m), 2.01-2.08 (1H, m), 2.80 (1H, s), 3.30-3.45 (2H, m), 5.18 (1H, d, *J*=4.6 Hz), 7.11 (2H, d, *J*=7.5 Hz), 7.17 (1H, t, *J*=7.4 Hz), 7.33 (1H, t, *J*=8.3 Hz). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 24.1 (CH_2), 24.6 (CH_2), 31.6 (CH_2), 34.3 (CH_2), 57.3 (CH), 74.7 (CH), 121.6 (CH), 125.4 (CH), 129.3 (CH), 150.9 (C), 155.6 (C). IR (film): 3425, 3243, 1700, 1198 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$: 235.1208. Found: 235.1193. $[\alpha]^{20}_D$ +16.2° (*c* 1.51, MeOH).

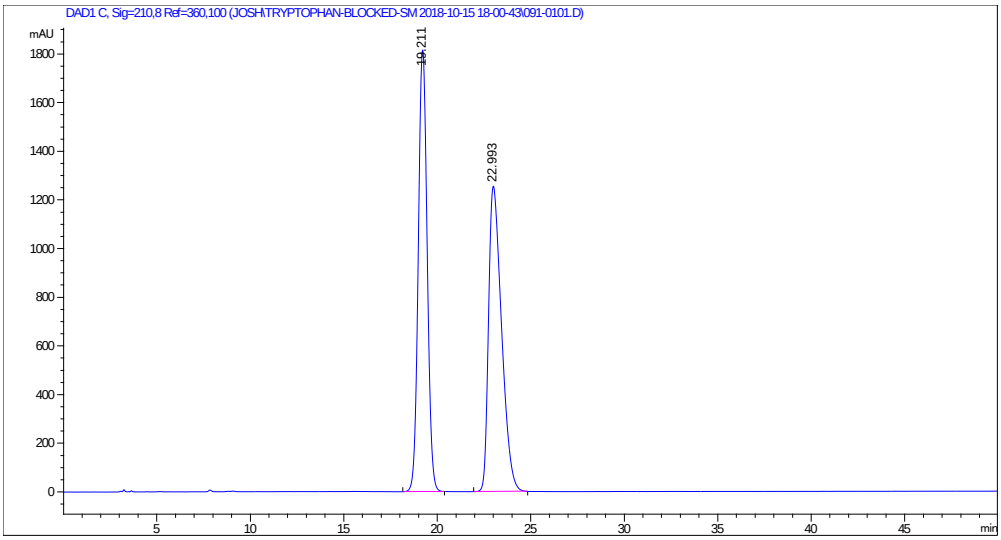


(*S*)-Methyl 3-(1*H*-indol-3-yl)-2-((phenoxycarbonyl)amino)propanoate (24v): Synthesized according to general procedure **H** using (L)-tryptophan methyl ester hydrochloride (0.764 mL, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.529 g, 6.3 mmol). The reaction reached completion within 0.5 hours. The desired product was purified by column chromatography (30% EtOAc/ hexanes) yielding an amorphous white solid (0.783 g, 77%). TLC R_F = 0.23 in 30% EtOAc/ hexanes. ^{1}H-NMR (400 MHz, Acetone-d_6): δ 3.25-3.45 (2H, m), 3.70 (3H, s), 4.62-4.69 (1H, m), 6.99 (1H, d, *J*=8.1 Hz), 7.05-7.19 (5H, m), 7.27-7.35 (3H, m), 7.41 (1H, d, *J*=8.0 Hz), 7.65 (1H, d, *J*=7.8 Hz), 10.08 (1H, s). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 27.5 (CH_2), 51.7 (CH_3), 55.3 (CH), 109.9 (C), 111.5 (CH), 118.3 (CH), 119.0 (CH), 121.5 (CH), 121.7 (CH), 123.8 (CH), 125.1 (CH), 127.7 (C), 129.2 (CH), 136.8 (C), 151.5 (C), 154.3 (C), 172.3 (C). IR (film): 3405, 3328, 1734, 1709, 1214, 1182 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{18}N_2O_4$ [M]$^+$: 338.1267. Found: 338.1258. $[\alpha]^{20}_D$ +18.9° (*c* 1.20, MeCN). Chiral HPLC: ChiralPak column AD-H *i*-PrOH/Hexane = 15:85, 1.0 mL/min, 230 nm, *t* = 20.2 min.



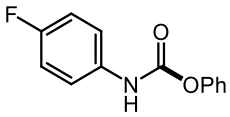
#	Time	Area	Height	Width	Area%	Symmetry
1	20.2	117849.5	2498	0.7863	100.000	0.856

Figure 6.2: HPLC trace and data of **24v** showing presence of single enantiomer.



#	Time	Area	Height	Width	Area%	Symmetry
1	19.211	59954.9	1815.3	0.5153	49.743	0.924
2	22.993	60575.4	1255.1	0.7131	50.257	0.556

Figure 6.3: HPLC trace and data of racemic **24v.**



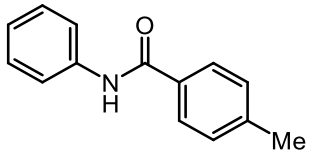
Phenyl (4-fluorophenyl)carbamate (24w): Synthesized according to general procedure **H** using 4-fluoroaniline (0.947 mL, 10.0 mmol), phenyl chloroformate (1.32 mL, 10.5 mmol), and $NaHCO_3$ (0.924 g, 10.5 mmol). The reaction reached completion within 1 hour. The desired product was recrystallized (20% EtOAc/ hexanes) 3 times yielding a white solid (2.02 g, 87 % yield). TLC R_F = 0.73 in CH_2Cl_2. ^{1}H-NMR (400 MHz, Acetone-d_6): δ 7.11 (2H, m, *J*=8.8 Hz), 7.18-7.25 (3H, m), 7.40 (2H, t, *J*=7.5), 7.60-7.64 (2H, m), 9.22 (1H, s, br). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 115.4 (CH, d, *J*=22.6 Hz), 120.3 (CH), 121.8 (CH), 125.3 (CH), 129.3 (CH), 135.2 (C), 151.5 (C, d, *J*=80.6 Hz), 157.5 (C), 159.9 (C). Data is consistent with literature.[282]

Synthesis of Amide products

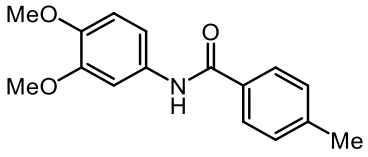
General procedure J (low [Rh], low [RBO]$_3$, high [THF]): An oven-dried microwave vial equipped with a stir bar was cooled under a stream of argon followed by the addition of $[Rh(OH)(cod)]_2$ (6.00x10^3 mmol, 0.0100 equiv.), organoboron reagent (1.6 equiv "Ar-B"), and THF (1.20 mL). Argon was bubbled through the solution for 2 minutes upon which the blocked isocyanate (0.600 mmol, 1.00 equiv.) and Et_3N (0.600 mmol, 1.00 equiv.) were added. The microwave vial was sealed, purged with argon, and placed in a 50 °C oil bath. The reaction was monitored for the disappearance of starting material. Upon completion, the reaction was concentrated under reduced pressure, diluted with EtOAc (40 mL) and extracted 1M NaOH (1 x 30mL), saturated $NaHCO_3$ (1 x 30 mL), and brine (1 x 30 mL). The organic layer was collected, dried

[282] Treventis Corporation. *WO2014039526 A2*, March 13th, 2014.

over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography providing the desired product.



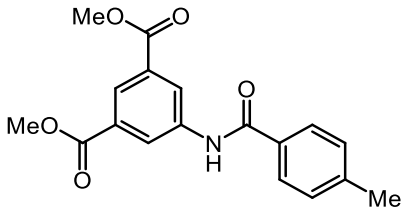
4-Methyl-*N*-phenylbenzamide (table 4.6, 26aa): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), organoboron reagent[283] **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.084 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, $6.00x10^3$ mmol). The reaction reached completion within 8 hours. The desired product was purified by column chromatography (99% CH_2Cl_2/Et_3N) yielding an amorphous white solid (0.109 g, 86 % yield). TLC R_F = 0.42 in 99% CH_2Cl_2/Et_3N. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.34 (3H, s), 7.06 (1H, t, *J*=7.4 Hz), 7.27-7.34 (3H, m), 7.79 (1H, q, *J*=7.5 Hz), 7.87 (1H, d, *J*=8.2 Hz), 10.15 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.4 (CH_3), 120.8 (CH), 123.9 (CH), 128.1 (CH), 129.0 (CH), 129.3 (CH), 132.6 (C), 139.7 (C), 142.0 (C), 165.8 (C). Data is consistent with literature.[284]



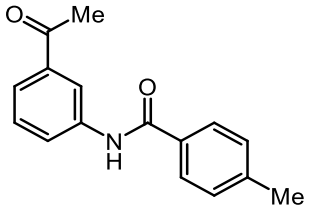
***N*-(3,4-Dimethoxyphenyl)-4-methylbenzamide (table 4.6, 26ba):** Synthesized according to general procedure **J** using masked isocyanate **24b** (0.164 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.084 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, $6.00x10^3$ mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (95% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.135 g, 83 % yield). TLC R_F = 0.13 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.34 (3H, s), 3.70 (3H, s), 3.71 (3H, s), 6.88 (2H, d, *J*=8.8 Hz), 7.27-7.31 (3H, m), 7.44 (1H, d, *J*=2.4 Hz), 7.83 (2H, d, *J*=8.2 Hz), 9.98 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH_3), 55.8 (CH_3), 56.2 (CH_3), 105.9 (CH), 112.3 (CH), 112.7 (CH), 128.0 (CH), 129.3 (CH), 132.6 (C), 133.3 (C), 141.8 (C), 145.5 (C), 148.9 (C), 165.4 (C). IR (film): 3307, 1642, 1231 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{17}NO_3$ $[M]^+$: 271.1208. Found: 271.1189.

[283] Organoboron compound **25a** was used as received from the commercial supplier (Combi-blocks). It was determined that a 2.1:1 mixture of $RB(OH)_2$:$[RBO]_3$ was present. Equivalents based on the number of "Ar-B" presented in the communication to simplify comparisons. The mmol amount of **25a** is reported with reference to the boroxine taking into account the presence of this mixture. It is noteworthy that fully dehydrating the parent mixture resulted in not change in yield with the optimized conditions reported in general procedure **J**.

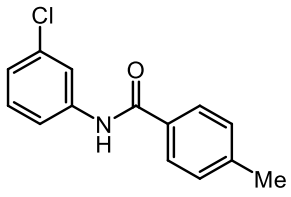
[284] R. Sharma, R. A. Vishwakarma, S. B. Bharate, *Adv. Synth. Catal.* **2016**, *358*, 3027



Dimethyl 5-(4-methylbenzamido)isophthalate (table 4.6, 26ca): Synthesized according to general procedure **J** using masked isocyanate **24c** (0.198 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.084 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, $6.00x10^3$ mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (CH_2Cl_2) yielding an amorphous white solid (0.157 g, 80 % yield). TLC R_F = 0.30 in CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 3.84 (6H, s), 7.20 (2H, d, *J*=7.9 Hz), 7.77 (2H, d, *J*=8.2 Hz), 8.35 (1H, t, *J*=1.5 Hz), 8.50 (2H, d, *J*=1.5 Hz), 8.55 (1H, s, br). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 20.6 (CH_3), 51.9 (CH_3), 124.6 (CH), 124.7 (CH), 124.9 (CH), 127.7 (CH), 129.1 (CH), 131.2 (C), 140.4 (C), 142.4 (C), 165.5 (C), 165.6 (C). IR (film): 3275, 1720, 1236 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{17}NO_5$ $[M]^+$: 327.1107. Found: 327.1113.

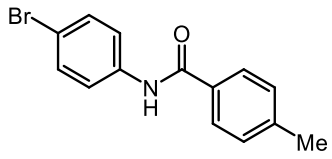


***N*-(3-Acetylphenyl)-4-methylbenzamide (table 4.6, 26da):** Synthesized according to general procedure **J** using masked isocyanate **24d** (0.153 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.084 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$(6.84 mg, 0.0150 mmol). The reaction reached completion within 6 hours (note: yield was significantly reduced when reaction was left overnight). The desired product was purified by column chromatography (90% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.126 g, 80 % yield). TLC R_F = 0.18 in 90% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s), 2.57 (3H, s), 7.33 (2H, d, *J*=7.9 Hz), 7.49 (1H, t, *J*=7.9 Hz), 7.69 (1H, d, *J*=7.5 Hz), 7.90 (2H, d, *J*=7.9 Hz), 8.08 (1H, d, *J*=7.9 Hz), 8.38 (1H, s), 10.35 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH_3), 26.6 (CH_3), 120.0 (CH), 124.2 (CH), 125.2 (CH), 127.4 (CH), 129.3 (CH), 129.3 (CH), 131.7 (C), 137.6 (C), 139.0 (C), 142.5 (C), 166.4 (C), 198.5 (C). IR (film): 3333, 1667, 1304 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{15}NO_2$ $[M]^+$: 253.1103. Found: 253.1119.

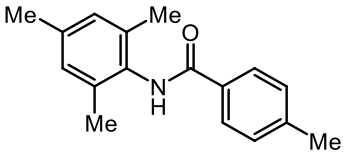


***N*-(3-Chlorophenyl)-4-methylbenzamide (table 4.6, 26ea):** Synthesized according to general procedure **J** using masked isocyanate **24e** (0.149 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6

equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 13 hours. The desired product was purified by column chromatography (75% CH_2Cl_2/ hexanes) yielding an amorphous white solid (0.125 g, 85% yield). TLC R_F = 0.69 CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.35 (3H, s), 7.09-7.12 (1H, m), 7.29-7.35 (3H, m), 7.67-7.70 (1H, m), 7.84 (2H, d, *J*=8.2 Hz), 7.95 (1H, t, *J*=2.0 Hz), 10.28 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH_3), 119.1 (CH), 120.2 (CH), 123.7 (CH), 128.2 (CH), 129.4 (CH), 130.7 (CH), 132.1 (C), 133.4 (C), 141.2 (C), 142.4 (C), 166.1 (C). Data is consistent with literature.[285]

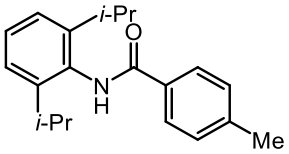


***N*-(4-Bromophenyl)-4-methylbenzamide (table 4.6, 26fa):** Synthesized according to general procedure **J** using masked isocyanate **24f** (0.175 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 13 hours. The desired product was purified by column chromatography (70% CH_2Cl_2/ hexanes) yielding an amorphous white solid (0.124 g, 71 % yield). TLC R_F = 0.69 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.34 (3H, s), 7.30 (2H, d, *J*=8.0 Hz), 7.49 (2H, d, *J*=8.9 Hz), 7.74 (2H, d, *J*=8.9 Hz), 7.83 (2H, d, *J*=8.2 Hz), 10.24 (1H, s).^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH_3), 115.7 (C), 122.7 (CH), 128.2 (CH), 129.4 (CH), 131.9 (CH), 132.3 (C), 139.1 (C), 142.2 (C), 165.9 (C). Data is consistent with literature.[284]

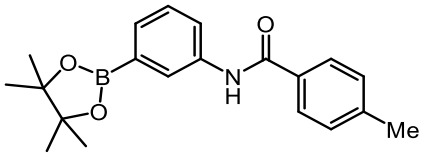


***N*-Mesityl-4-methylbenzamide (table 4.6, 26ga):** Synthesized according to general procedure **C** using masked isocyanate **24g** (0.153 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (CH_2Cl_2 to 5% EtOAc/CH_2Cl_2) yielding an amorphous white solid (125.7 g, 83% yield). TLC R_F = 0.16 in CH_2Cl_2. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.13 (6H, s), 2.25 (3H, s), 2.38 (3H, s), 6.92 (2H, s), 7.31 (2H, d, *J*=8.0 Hz), 7.91 (2H, d, *J*=8.2 Hz), 9.59 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 18.4 (CH_3), 21.0 (CH_3), 21.4 (CH_3), 127.9 (CH), 128.7 (CH), 129.3 (CH), 132.1 (C), 133.2 (C), 135.7 (C), 135.9 (C), 141.7 (C), 165.4 (C). IR (film): 3278, 3252, 1652, 1321 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{19}NO$ $[M]^+$: 253.1467. Found: 253.1446.

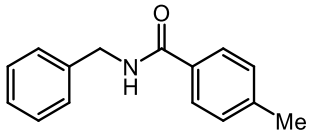
[285] M. L. P. R. Alapati, S. R. Abburu, K. R. Mutyala, S. B. Mukkamala, *Synth. Comm.* **2016**, *46*, 1242.



***N*-(2,6-Diisopropylphenyl)-4-methylbenzamide (table 4.6, 26ha):** Synthesized according to general procedure **J** using masked isocyanate **24h** (0.178 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (20% EtOAc/ hexanes) yielding an amorphous white solid (0.104 g, 59% yield). TLC R_F = 0.27 in 15% EtOAc/ hexanes. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.18 (12H, d, *J*=6.9 Hz), 2.42 (3H, s), 3.13 (2H, m, *J*=6.9 Hz), 7.21 (2H, d, *J*=7.7 Hz), 7.34 (1H, t, *J*=7.7 Hz), 7.58 (1H, s), 7.77 (2H, d, *J*=8.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 23.7 (CH_3), 28.9 (CH), 123.5 (CH), 127.3 (CH), 128.4 (CH), 129.4 (CH), 131.5 (C), 131.6 (C),142.1 (C), 146.5 (C), 166.9 (C). Data is consistent with literature.[286]



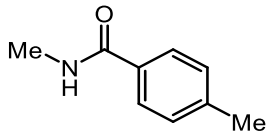
4-Methyl-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide (table 4.6, 26ia): Synthesized according to general procedure **J** using masked isocyanate **24i** (0.204 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 6 hours. The desired product was extracted pure from the reaction mixture yielding an amorphous white solid (0.0808 g, 40% yield). TLC R_F = 0.27 in 20% EtOAc/ hexanes. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.31 (12H, s), 2.36 (3, s), 7.20 (2H, d, *J*=8.0 Hz), 7.34 (1H, t, *J*=7.7 Hz), 7.55 (1H, d, *J*=7.3 Hz), 7.72 (2H, d, *J*=8.1 Hz), 7.78 (1H, s), 8.01 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 24.9 (CH_3), 83.9 (C), 123.4 (CH), 126.2 (CH), 127.1 (CH), 128.6 (CH), 129.4 (CH), 130.7 (CH), 132.1 (C), 137.7 (C), 142.3 (C), 165.7 (C). IR (film): 3230, 1646, 1352 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{24}BNO_3$ $[M]^+$: 337.1849. Found: 337.1863.



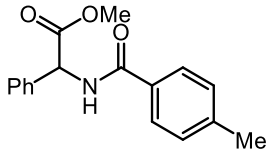
***N*-Benzyl-4-methylbenzamide (table 4.6, 26ja):** Synthesized according to general procedure **J** using masked isocyanate **24j** (0.136 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 6.00 x 10^{-3} mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (CH_2Cl_2) yielding an amorphous white solid (0.107 g, 79% yield). TLC R_F = 0.17 in CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.36 (3H, s), 4.59 (2H, d, *J*=5.7 Hz), 6.63 (1H, s, br), 7.18 (2H, d, *J*=7.9 Hz), 7.24-7.34 (5H, m), 7.67

[286] Y. Wu, S. Wang, L. Zhang, G. Yang, X. Zhu, Z. Zhou, H. Zhu, S. Wu, *Eur. J. Org. Chem.* **2010**, 326.

(2H, t, *J*=4.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 44.0 (CH_2), 127.0 (CH), 127.5 (CH), 127.9 (CH), 128.7 (CH), 129.2 (CH), 131.5 (C), 138.4 (C), 141.9 (C), 167.4 (C). Data is consistent with literature.[287]

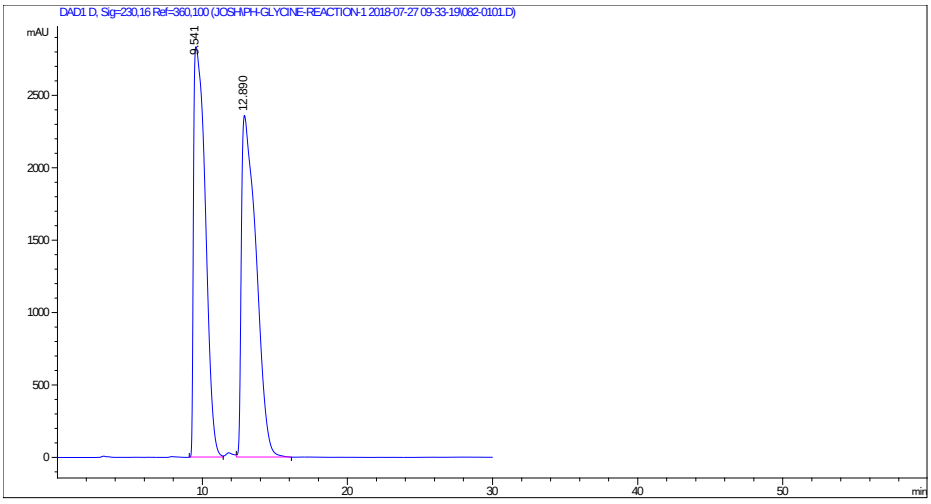


***N*,4-Dimethylbenzamide (table 4.6, 26ka):** Synthesized according to general procedure **J** using masked isocyanate **24k** (0.0906 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 14 hours. The desired product was purified by column chromatography (25% EtOAc/ hexanes) yielding an amorphous white solid (0.0651 g, 73% yield). TLC R_F = 0.26 in 25% EtOAc/ hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, s), 2.91 (3H, d, *J*=4.7 Hz), 6.73 (1H, s, br), 7.13 (2H, d, *J*=7.9 Hz), 7.64 (2H, d, *J*=8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3), 26.7 (CH_3), 126.9 (CH), 129.1 (CH), 131.7 (C), 141.6 (C), 168.4 (C). Data is consistent with literature.[288]



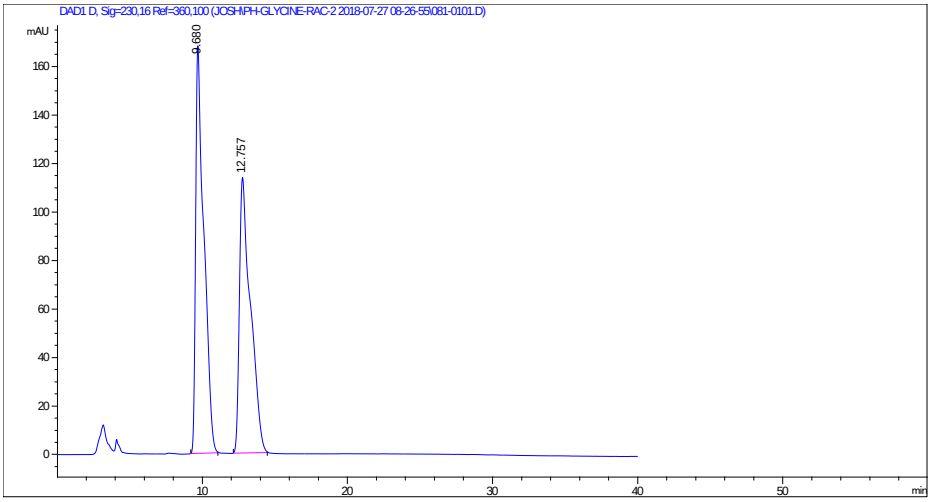
Methyl 2-(4-methylbenzamido)-2-phenylacetate (table 4.6, 26la): Synthesized according to general procedure **J** using masked isocyanate **24l** (0.171 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 6.00 x 10^{-3} mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (CH_2Cl_2) yielding an amorphous white solid (0.131 g, 81% yield). TLC R_F = 0.33 in CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.35 (3H, s), 3.71 (3H, s), 5.76 (1H, d, *J*=7.1 Hz), 7.18 (2H, d, *J*=7.9 Hz), 7.24-7.36 (4H, m), 7.40-7.44 (2H, m), 7.70 (2H, d, *J*=8.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 52.8 (CH_3), 56.8 (CH), 127.2 (CH), 127.3 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 130.8 (C), 136.7 (C), 142.3 (C), 166.6 (C), 171.6 (C). IR (film): 3348, 1738, 1637, 1322, 1175 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{17}H_{17}NO_3$ $[M]^+$: 283.1208. Found: 283.1223. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/Hexane = 10:90, 1.0 mL/min, 230 nm, *t* = 9.54 min and 12.89 min

[287] E. L. Howard, N. Guzzardi, V. G. Tsanova, A. Stika, B. Patel, *Eur. J. Org. Chem.* **2018**, 794.
[288] Y. Jo, J. Ju, J. Choe, K. W. Song, S. Lee, *J. Org. Chem.* **2009**, *74*, 6358.



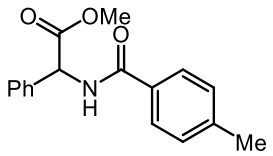
#	Time	Area	Height	Width	Area%	Symmetry
1	9.541	160126.1	2836.6	0.7206	49.043	0.229
2	12.89	166375.2	2361.9	0.9378	50.957	0.25

Figure 6.4. HPLC trace and data of **26la** showing complete racemization

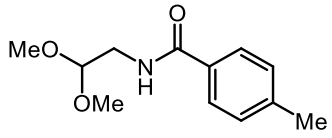


#	Time	Area	Height	Width	Area%	Symmetry
1	9.68	6631.2	168.2	0.54	52.391	0.344
2	12.757	6025.9	113.7	0.7302	47.609	0.362

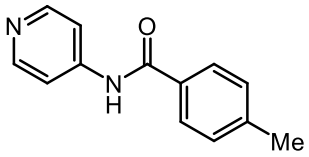
Figure 6.5: HPLC trace and data of racemic **26la**



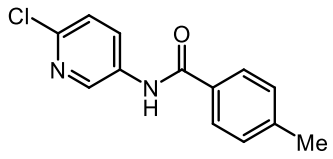
Methyl 2-(4-methylbenzamido)-2-phenylacetate (rac-26la): Synthesized according to general procedure **I** using 2-phenylglycine methyl ester hydrochloride (0.101 g, 0.500 mmol), Et_3N (0.168 mL, 1.20 mmol), and p-toluoyl chloride(0.0730 mL, 0.550 mmol), and CH_2Cl_2 (1.60 mL). The reaction reached completion within 1 hour. The desired product was purified by column chromatography (100% CH_2Cl_2) yielding an amorphous white solid (0.0831 g, 59% yield). Chiral HPLC: ChiralPak column OD-H *i*-PrOH/Hexane = 10:90, 1.0 mL/min, 230 nm, t = 9.5 min, 12.9 min.



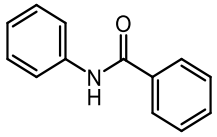
***N*-(2,2-Dimethoxyethyl)-4-methylbenzamide (table 4.6, 26ma):** Synthesized according to general procedure **J** using masked isocyanate **24m** (0.135 g, 0.600 mmol), organoboron reagent **25a** (0.122 g, 0.976 mmol, 1.6 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 5 hours. The desired product was purified by column chromatography (45% EtOAc/ hexanes) yielding an amorphous white solid (0.0977 g, 73% yield). TLC R_F = 0.31 in 45% EtOAc/ hexanes. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, s), 3.36 (6H, s), 3.53 (2H, t, *J*=5.6 Hz), 4.44 (1H, t, *J*=5.3 Hz), 6.51 (1H, s, br), 7.15 (2H, d, *J*=8.0 Hz), 7.63 (2H, d, *J*=8.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3), 41.5 (CH_2), 54.5 (CH_3), 102.8 (CH), 127.0 (CH), 129.1 (CH), 131.5 (C), 141.9 (C), 167.5 (C). IR (film): 3264, 1631, 1111 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_{17}NO_3Na$ $[M+Na]^+$: 246.1106. Found: 246.1114.



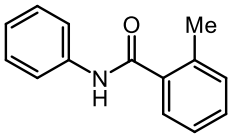
4-Methyl-*N*-(pyridin-4-yl)benzamide (scheme 4.3, 26na): Synthesized according to general procedure **K** using masked isocyanate **24n** (0.128 g, 0.600 mmol), organoboron reagent **25a** (0.408 g, 3.25 mmol, 5.4 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol) at 120 °C. The reaction reached completion within 2 hours. The desired product was purified by column chromatography (5% MeOH/EtOAc) yielding an amorphous white solid (0.0840 g, 66% yield). TLC R_F = 0.19 in 5% MeOH/EtOAc. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.38 (3H, s), 7.35 (2H, d, *J*=8.0 Hz), 7.79 (2H, q, *J*=6.3 Hz), 7.89 (2H, d, *J*=8.1 Hz), 8.47 (2H, d, *J*=6.1 Hz), 10.50 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.5 (CH_3), 114.4 (CH), 128.3 (CH), 129.4 (CH), 131.8 (C), 142.7 (C), 146.4 (C), 150.7 (CH), 166.7 (C). IR (film): 3337, 1651, 1332 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{12}N_2O$ $[M]^+$: 212.0950. Found: 212.0957.



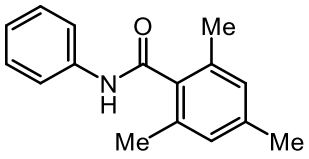
***N*-(6-Chloropyridin-3-yl)-4-methylbenzamide (scheme 4.3, 26oa):** Synthesized according to general procedure **K** using masked isocyanate **24o** (0.149, 0.600 mmol), organoboron reagent **25a** (0.245 g, 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 20 hours. The crude mixture was dry loaded onto silica gel (MeOH) and purified by column chromatography (5% to 10% EtOAc/CH_2Cl_2) yielding and amorphous white solid (0.113 g, 76% yield). TLC R_F = 0.17 in 5% EtOAc/CH_2Cl_2. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.38 (3H, s), 7.35 (2H, d, *J*=8.0 Hz), 7.50 (1H, d, *J*=8.7 Hz), 7.88 (2H, d, *J*=8.1 Hz), 8.25 (1H, dd, *J*=2.8 Hz, 8.7 Hz), 8.79 (1H, d, *J*=2.5 Hz), 10.48 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.5 (CH_3), 124.5 (CH), 128.2 (CH), 129.4 (CH), 131.23 (CH), 131.6 (C), 136.0 (C), 141.9 (CH), 142.6 (C), 144.3 (C), 166.1 (C). IR (film): 3332, 1652, 1289, 825 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{11}N_2OCl$ $[M]^+$: 246.0560. Found: 246.0564.



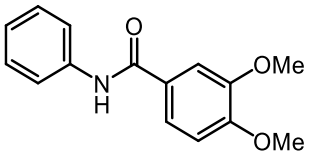
***N*-Phenylbenzamide (table 4.7, 26ab):** Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), organoboron reagent **25b** (0.110 g, 0.900 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 6.00 x 10^{-3} mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (CH_2Cl_2) yielding an amorphous white solid (0.0929 g, 81% yield). TLC R_F = 0.40 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.10 (1H, t, *J*=7.4 Hz), 7.35 (2H, t, *J*=7.5 Hz), 7.50-7.60 (3H, m), 7.80 (2H, d, *J*= 8.7 Hz), 7.95-7.98 (2H, m), 10.26 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 120.8 (CH), 124.1 (CH), 128.1 (CH), 128.8 (CH), 129.1 (CH), 132.0 (CH), 135.5 (C), 139.7 (C), 166.0 (C). Data is consistent with literature.[273]



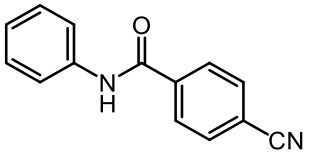
2-Methyl-*N*-phenylbenzamide (table 4.7, 26ac): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25c** (0.107 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (75% $CH_2Cl_2$to 100% CH_2Cl_2) yielding an amorphous white solid (0.109 g, 86% yield). TLC R_F = 0.47 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.40 (3H, s), 7.10 (1H, t, *J*=7.4 Hz), 7.28-7.42 (5H, m), 7.47 (1H, d, *J*=7.4 Hz), 7.78 (2H, d, *J*=7.8 Hz), 10.31 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 19.8 (CH_3), 120.1 (CH), 124.0 (CH), 126.1 (CH), 127.7 (CH), 129.1 (CH), 130.0 (CH), 131.0 (CH), 135.6 (C), 137.8 (C), 139.8 (C), 168.3 (C). Data is consistent with literature.[74]



2,4,6-Trimethyl-*N*-phenylbenzamide (table 4.7, 26ad): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), organoboron reagent **25d** (0.263 g, 0.600 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 20 hours. The desired product was purified by column chromatography (CH_2Cl_2) yielding an amorphous white solid (0.0960 g, 67% yield). TLC R_F = 0.43 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.24-2.27 (9H, m), 6.92 (2H, s), 7.08 (1H, t, *J*=7.4 Hz), 7.33 (2H, t, *J*=8.3 Hz), 7.74 (2H, d, *J*=7.6 Hz), 10.29 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ19.3 (CH_3), 21.1 (CH_3), 120.0 (CH), 123.9 (CH), 128.3 (CH), 129.2 (CH), 134.1 (C), 136.3 (C), 138.1 (C), 139.7 (C), 168.6 (C). Data is consistent with literature.[289]



3,4-Dimethoxy-*N*-phenylbenzamide (table 4.7, 26ae): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25e** (0.148 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 6.00 x 10^{-3} mmol). The reaction reached completion within 8 hours. The desired product was purified by column chromatography (95% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.114 g, 74% yield). TLC R_F = 0.33 in 95% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.80-3.82 (6H, m), 7.03-7.07 (2H, m), 7.29-7.33 (2H, m), 7.51 (1H, d, *J*=2.1 Hz), 7.60 (1H, dd, *J*=2.1, 8.4 Hz), 7.71-7.74 (2H, m), 10.04 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 56.1 (CH_3), 56.1 (CH_3), 111.4 (CH), 111.5 (CH), 121.0 (CH), 121.5 (CH), 123.9 (CH), 127.5 (C), 129.0 (CH), 139.7 (C), 148.8 (C), 152.1 (C), 165.4 (C). Data is consistent with literature.[290]

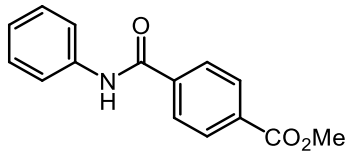


4-Cyano-*N*-phenylbenzamide (table 4.7, 26af): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25f** (0.116 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 6.00 x 10^{-3} mmol). The reaction reached completion within 12 hours. The desired product was purified by column chromatography (CH_2Cl_2 to 96% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.0925 g, 69% yield). TLC R_F = 0.17 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.14 (1H, t, *J*=7.4 Hz), 7.38 (2H, t, *J*=8.5 Hz), 7.78 (2H, d, *J*=8.7 Hz), 8.01-8.04 (2H, m), 8.10-8.12 (2H, m), 10.48 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 114.3 (C), 118.8 (C), 120.9 (CH), 124.6 (CH), 129.0 (CH), 129.2

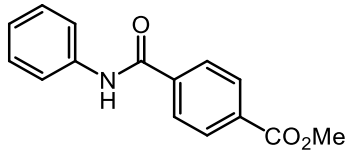
[289] K. Nozawa-Kumada, J. Kadokawa, T. Kameyama, Y. Kondo, *Org. Lett.* **2015**, *17*, 4479.

[290] K. N. Kumar, K. Sreeramamurthy, S. Palle, K. Mukkanti, P. Das, *Tetrahedron Letters*, **2010**, *51*, 899.

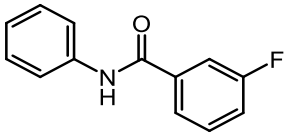
(CH), 132.9 (CH), 139.2 (C), 139.5 (C), 164.6 (C). IR (film): 3353, 2232, 1653 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{10}N_2O$ $[M]^+$: 222.0793. Found: 222.0799.



Methyl 4-(phenylcarbamoyl)benzoate (table 4.7, 26ag): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25g** (0.146 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 5 hours. The desired product was purified by column chromatography (25% EtOAc/ hexanes) yielding an amorphous white solid (0.0933 g, 61% yield). TLC R_F = 0.22 in 25% EtOAc/EtOAc. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.89 (3H, s), 7.12 (1H, t, *J*=6.5 Hz), 7.36 (2H, t, *J*=7.1 Hz), 7.79 (2H, d, *J*=7.4 Hz), 8.08 (4H, s), 10.44 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 52.9 (CH_3), 120.9 (CH), 124.4 (CH), 128.5 (CH), 129.1 (CH), 129.6 (CH), 132.5 (C), 139.4 (C), 139.5 (C), 165.2 (C), 166.2 (C). IR (film): 3366, 1714, 1657, 1276 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{13}NO_3$ $[M]^+$: 255.0895. Found: 255.0891.

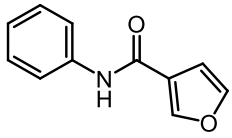


Methyl 4-(phenylcarbamoyl)benzoate (table 4.7, 26ag): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), the organoboron reagent was recrystalized in water before being dehydrated to the boroxine **25g** (0.146 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (1.37 mg, 3.00 x 10^{-3} mmol). The reaction reached completion within 20 hours. The desired product was extracted from the crude reaction mixture and recrystallized twice (50% Acetone/ hexanes) providing a crystalline white solid (0.109 g, 71% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.89 (3H, s), 7.12 (1H, t, *J*=6.5 Hz), 7.36 (2H, t, *J*=7.1 Hz), 7.79 (2H, d, *J*=7.4 Hz), 8.08 (4H, s), 10.44 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 52.9 (CH_3), 120.9 (CH), 124.4 (CH), 128.5 (CH), 129.1 (CH), 129.6 (CH), 132.5 (C), 139.4 (C), 139.5 (C), 165.2 (C), 166.2 (C). IR (film): 3366, 1714, 1657, 1276 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{13}NO_3$ $[M]^+$: 255.0895. Found: 255.0891.

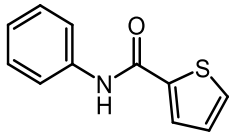


3-Fluoro-*N*-phenylbenzamide (table 4.7, 26ah): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25h** (0.110 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 6.00 x 10^{-3} mmol). The reaction reached completion within 13 hours. The desired product was purified by column chromatography (75% CH_2Cl_2/ hexanes) yielding an amorphous white solid (0.101 g, 78% yield). TLC R_F = 0.22 in 60% CH_2Cl_2/ hexanes. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.11 (1H, t, *J*=7.4 Hz), 7.35 (2H, t, *J*=7.5 Hz), 7.43 (1H, dd, *J*=2.6, 8.3 Hz), 7.54-7.60 (1H, m),

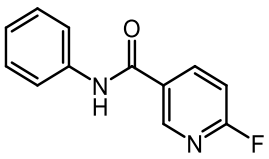
7.75-7.82 (4H, m), 10.31 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 115.0 (CH, d, *J*=22.86 Hz), 118.9 (CH, d, *J*=21.1 Hz), 120.9 (CH), 124.3 (CH), 124.4 (CH), 129.1 (CH), 131.0 (CH, d, *J*=8.0 Hz), 137.7 (C, d, *J*=6.8 Hz), 139.4 (C), 162.4 (C, d, *J*=244.4 Hz), 164.6 (C, d, *J*=2.5 Hz). Data is consistent with literature.[284]



***N*-Phenylfuran-3-carboxamide (table 4.7, 26ai):** Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25i** (0.0844 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 5 hours. The desired product was purified by column chromatography (98:1:1 CH_2Cl_2/EtOAc/AcOH) yielding an amorphous white solid (0.0898 g, 80% yield). TLC R_F = 27 in 60% 98:1:1 CH_2Cl_2/EtOAc/AcOH. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.00 (1H, s), 7.08 (1H, t, *J*=7.4 Hz), 7.34 (2H, t, *J*=7.9 Hz), 7.71 (2H, d, *J*=7.8 Hz), 7.79 (1H, d, *J*=1.4 Hz), 8.38 (1H, s), 9.90 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 109.7 (CH), 120.7 (CH), 123.5 (C), 124.1 (CH), 129.1 (CH), 139.3 (C), 144.7 (CH), 146.3 (CH), 160.9 (C). IR (film): 3329, 1655 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{11}H_9NO_2$ $[M]^+$: 187.0633. Found: 187.0611



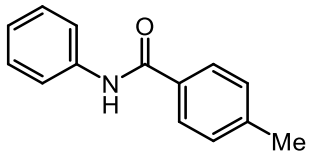
***N*-Phenylthiophene-2-carboxamide (table 4.7, 26aj):** Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25j** (0.0989 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (CH_2Cl_2 to 99% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.0920 g, 75% yield). TLC R_F = 0.18 in CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.08 (1H, t, *J*=7.2 Hz), 7.34 (2H, t, *J*=7.7 Hz), 7.64 (2H, s), 7.76 (2H, d, *J*=7.9 Hz), 8.35 (1H, s), 10.05 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 120.8 (CH), 124.0 (CH), 127.3 (CH), 127.7 (CH), 129.1 (CH), 130.1 (CH), 138.3 (C), 139.5 (C), 161.4 (C). Data is consistent with literature.[290]



6-Fluoro-*N*-phenylnicotinamide (table 4.7, 26ak): Synthesized according to general procedure **J** using masked isocyanate **24a** (0.128 g, 0.600 mmol), boroxine **25k** (0.221 g, 0.600 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 10 hours. The desired product was purified by column chromatography (95% CH_2Cl_2/EtOAc to 90% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.103 g, 79% yield). TLC R_F = 0.16 in 95% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.13 (3H, t, *J*=7.4 Hz), 7.33-7.38 (3H, m), 7.76 (2H, d, *J*=7.7 Hz), 8.50 (1H, dt, *J*=2.5 Hz, 8.2 Hz), 8.82 (1H, d, *J*=2.3 Hz), 10.44 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 109.9 (CH, d, *J*=37.7 Hz), 120.9 (CH), 124.5 (CH), 129.2 (CH), 129.8 (C, d, *J*=4.3 Hz), 139.2 (C), 142.4 (CH, d, *J*=9.1 Hz), 148.2 (CH, d,

J=16.3 Hz), 163.3 (C), 164.8 (C, d, *J*=240.2 Hz). IR (film): 3346, 1651, 1254 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{12}H_9N_2OF$ $[M]^+$: 216.0699. Found: 216.0700.

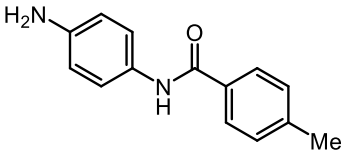
Gram Scale reaction



4-Methyl-*N*-phenylbenzamide (26aa): An oven-dried 50 mL round-bottom flask equipped with a stir bar was cooled under a stream of argon followed by the addition of $[Rh(OH)(cod)]_2$ (21.4 mg, 0.0469 mmol), boroxine **25a** (0.829 g, 7.03 mmol), and THF (9.40 mL). Argon was bubbled through the solution for 2 minutes upon which compound **24a** (1.00 g, 4.69 mmol) and Et_3N (0.653 mL, 4.69 mmol) were added. The flask was sealed with a septum, purged with argon, and placed in a 50 °C oil bath. The reaction was monitored for the disappearance of starting material. The reaction was deemed complete in 24 hours. The reaction was concentrated under reduced pressure, diluted with EtOAc (200 mL) and extracted 1M NaOH (1x 100 mL), saturated $NaHCO_3$ (1 x 100 mL), and brine (1 x 100 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The desired product was purified by column chromatography (99% CH_2Cl_2/Et_3N) yielding an amorphous white solid (0.788 g, 66% yield). TLC R_F = 0.42 in 99% CH_2Cl_2/Et_3N. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.34 (3H, s), 7.06 (1H, t, *J*=7.4 Hz), 7.27-7.34 (3H, m), 7.79 (1H, q, *J*=7.5 Hz), 7.87 (1H, d, *J*=8.2 Hz), 10.15 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.4 (CH_3), 120.8 (CH), 123.9 (CH), 128.1 (CH), 129.0 (CH), 129.3 (CH), 132.6 (C), 139.7 (C), 142.0 (C), 165.8 (C). Data is consistent with literature.

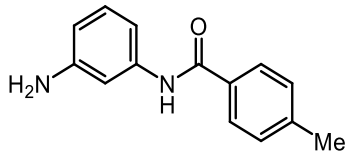
Synthesis of Amide Product from amphoteric reagents

General procedure K (high [Rh], high $[RBO]_3$, low [THF]): An oven-dried microwave vial equipped with a stir bar was cooled under a stream of argon followed by the addition of $[Rh(OH)(cod)]_2$ (0.0150 mmol, 0.0250 equiv.), organoboron reagent (0.600 mmol, 1.00 equiv.), and THF (6.00 mL). Argon was bubbled through the solution for 2 minutes upon which the blocked isocyanate (0.600 mmol, 1.00 equiv.) and Et_3N (0.600 mmol, 1.00 equiv.) were added. The microwave vial was sealed, purged with argon, and placed in a 50 °C oil bath. The reaction was monitored for the disappearance of starting material. Upon completion, the reaction was concentrated under reduced pressure, diluted with EtOAc (40 mL) and extracted 1M NaOH (1x 30mL), saturated $NaHCO_3$ (1 x 30 mL), and brine (1 x 30 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography providing the desired product.

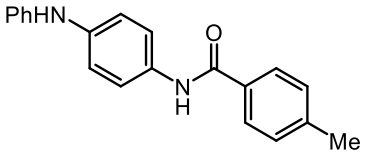


***N*-(4-Aminophenyl)-4-methylbenzamide (table 4.9, 26pa):** Synthesized according to general procedure **K** using masked isocyanate **24p** (0.137 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.95 mmol, 3.3

equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 12 hours. The desired product was purified by column chromatography (75% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.114 g, 84% yield). TLC R_F = 0.36 in 75% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.33 (3H, s), 4.88 (2H, s), 6.51 (1H, d, *J*=8.7 Hz), 7.26 (1H, d, *J*=8.0 Hz), 7.34 (1H, d, *J*=8.7 Hz), 7.80 (1H, d, *J*=8.1 Hz), 9.75 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 169.7 (C), 150.3 (CH_2), 146.2 (CH_2), 137.7 (CH_2), 134.0 (CH), 133.4 (CH_2), 132.7 (CH), 127.5 (CH), 118,9 (CH), 26.2 (CH_3). Data is consistent with literature.[291]



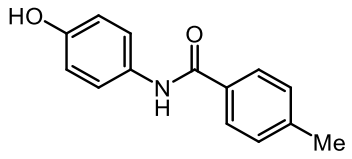
***N*-(3-Aminophenyl)-4-methylbenzamide (table 4.9, 26qa):** Synthesized according to general procedure **K** using masked isocyanate **24q** (0.137 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 12 hours. The desired product was purified by column chromatography (75% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.113 g, 83% yield). TLC R_F = 0.29 in 75% CH_2Cl_2/EtOAc. ^{1}H-NMR (400 MHz, Acetone-d_6): δ 2.35 (3H, s), 4.63 (2H, s, br), 6.42-6.45 (1H, m), 6.98-7.04 (2H, d), 7.25 (2H, d, *J*=8.0 Hz), 7.30 (1H, s), 7.86 (2H, d, *J*=8.2 Hz), 9.29 (1H, s). ^{13}C-NMR (100 MHz, Acetone-d_6): δ 20.6 (CH_3), 106.4 (CH), 109.0 (CH), 110.2 (CH), 127.5 (CH), 129.0 (CH), 129.1 (CH), 132.9 (C), 140.2 (C), 141.7 (C), 148.9 (C), 165.4 (C). Data is consistent with literature.[292]



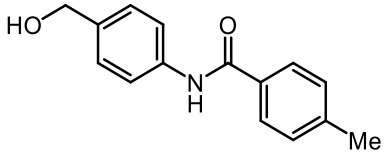
4-Methyl-*N*-(4-(phenylamino)phenyl)benzamide (table 4.9, 26ra): Synthesized according to general procedure **K** using masked isocyanate **24r** (0.183 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (30% EtOAc/ hexanes) yielding an amorphous white solid (0.153 g, 85% yield). TLC R_F = 0.47 in 40% EtOAc/hexanes. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s), 6.77 (1H, t, *J*=7.3 Hz), 7.02-7.09 (4H, m), 7.20 (2H, t, *J*=7.6 Hz), 7.31 (2H, d, *J*=8.0 Hz), 7.65 (2H, d, *J*=8.9 Hz), 7.87 (2H, d, *J*=8.2 Hz), 8.08 (1H, s), 10.03 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH), 116.4 (CH), 118.0 (CH), 119.5 (CH), 122.2 (CH), 128.0 (CH), 129.3 (CH), 129.6 (CH), 132.4 (C), 132.7 (C), 139.6 (C), 141.7 (C), 144.5 (C), 165.3 (C). IR (film): 3403, 3324, 1641, 1304 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{20}H_{18}N_2O$ $[M]^+$: 302.1419. Found: 302.1426.

[291] D.-X. Zhang, S.-K. Xiang, H. Hu, W. Tan, C. Feng, B.-Q. Wang, K.-Q. Zhao, P. Hu, H. Yang, *Tetrahedron,* **2013**, *69*, 10022.

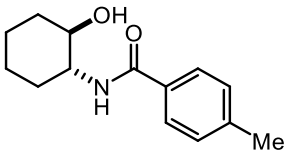
[292] A. Al-Nadaf, G. A. Sheikha, M. O. Taha, *Bioorg. Med. Chem.* **2010**, *18*, 3088.



***N*-(4-Hydroxyphenyl)-4-methylbenzamide (table 4.9, 26sa):** Synthesized according to general procedure **K** using masked isocyanate **24s** (0.138 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 18 hours. The reaction was concentrated under reduced pressure, resuspended in EtOAc (40 mL) and extracted with 1M NaOH (1 x 40 mL). The aqueous phase was quenched with a saturated $NaHCO_3$ (40 mL) and subsequently extracted with EtOAc (3 x 40 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude extract was purified by column chromatography (20% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.121 g, 89% yield). TLC R_F = 0.11 in 10% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s), 6.72-6.74 (2H, m), 7.31 (2H, d, *J*=8.0 Hz), 7.52 (2H, d, *J*=8.9 Hz), 7.85 (2H, d, *J*=8.13 Hz), 9.23 (1H, s), 9.93 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH), 115.4 (CH), 122.7 (CH), 128.0 (CH), 129.3 (CH), 131.22 (C), 132.7 (C), 141.7 (C), 154.1 (C), 165.2 (C). IR (film): 3387, 3326, 1648, 1225 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{13}NO_2$ $[M]^+$: 227.0946. Found: 227.0943.

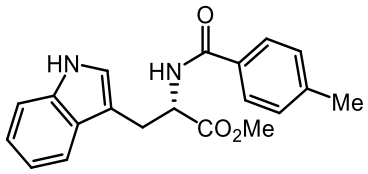


***N*-(4-(Hydroxymethyl)phenyl)-4-methylbenzamide (table 4.9, 26ta):** Synthesized according to general procedure **K** using masked isocyanate **24t** (0.146 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 10 hours. The crude extract was dry loaded onto silica gel (MeOH) and purified by column chromatography (40% EtOAc/CH_2Cl_2 to 50% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.134 g, 93% yield). TLC R_F = 0.45 in 50% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.38 (3H, s), 4.49 (2H, d, *J*=5.6 Hz), 5.15 (1H, t, *J*=5.7 Hz), 7.31 (4H, t, *J*=8.8 Hz), 7.75 (2H, d, *J*=8.5 Hz), 7.89 (2H, d, *J*=8.1 Hz), 10.14 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 21.5 (CH), 63.2 (CH_2), 120.6 (CH), 127.3 (CH), 128.1 (CH), 129.3 (CH), 132.6 (C), 138.2 (C), 138.3 (C), 141.9 (C), 165.7 (C). IR (film): 3325, 1649, 1002 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{15}NO_2$ $[M]^+$: 241.1103. Found: 241.1111.

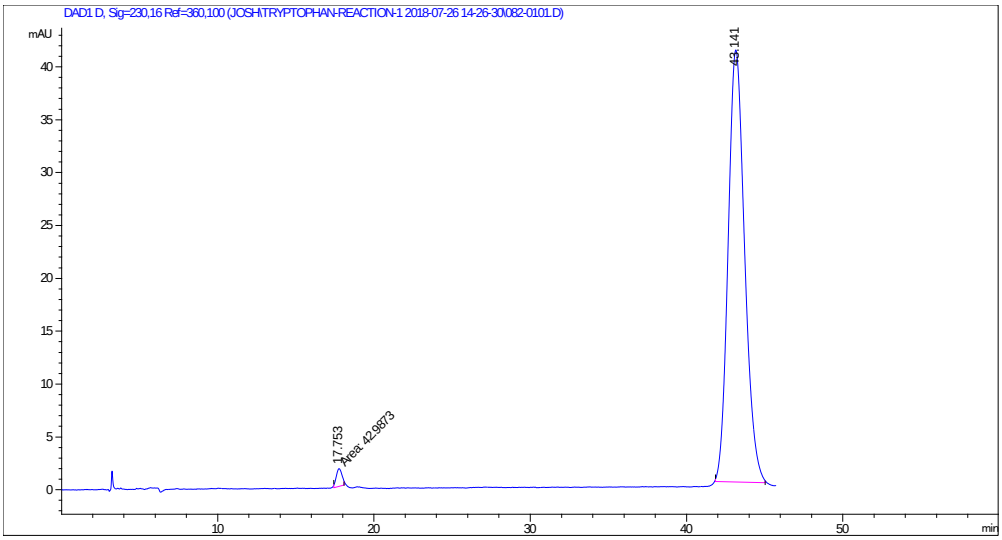


***N*-((1*R*,2*R*)-2-Hydroxycyclohexyl)-4-methylbenzamide (table 4.9, 26ua):** Synthesized according to general procedure **K** using masked isocyanate **24u** (0.141 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 18 hours. The desired product was purified by column

chromatography (25% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.115 g, 82% yield). TLC R_F = 0.16 in 25% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.20-1.28 (4H, m), 1.61-1.66 (2H, m), 1.82-1.91 (2H, m), 2.35 (3H, s), 3.37-3.43 (1H, m), 3.56-3.64 (1H, m), 4.58 (1H, d, *J*=5.2 Hz), 7.25 (2H, d, *J*=8.0 Hz), 7.76 (2H, d, *J*=8.1 Hz), 7.99 (1H, d, *J*=7.9 Hz). ^{13}C-NMR (300 MHz, DMSO-d_6): δ 21.4 (CH_3), 24.6 (CH_2), 24.9 (CH_2), 31.8 (CH_2), 35.0 (CH_2), 55.7 (CH), 71.6 (CH), 127.8 (CH), 129.0 (CH), 132.7 (C), 141.1 (C), 166.4 (C). IR (film): 3470, 3272, 1748, 1614, 1331, 1046 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{14}H_{19}NO_2$ [M]$^+$: 233.1416. Found: 233.1424. $[\alpha]^{20}_D$ +39.4° (*c* 0.80, MeOH).

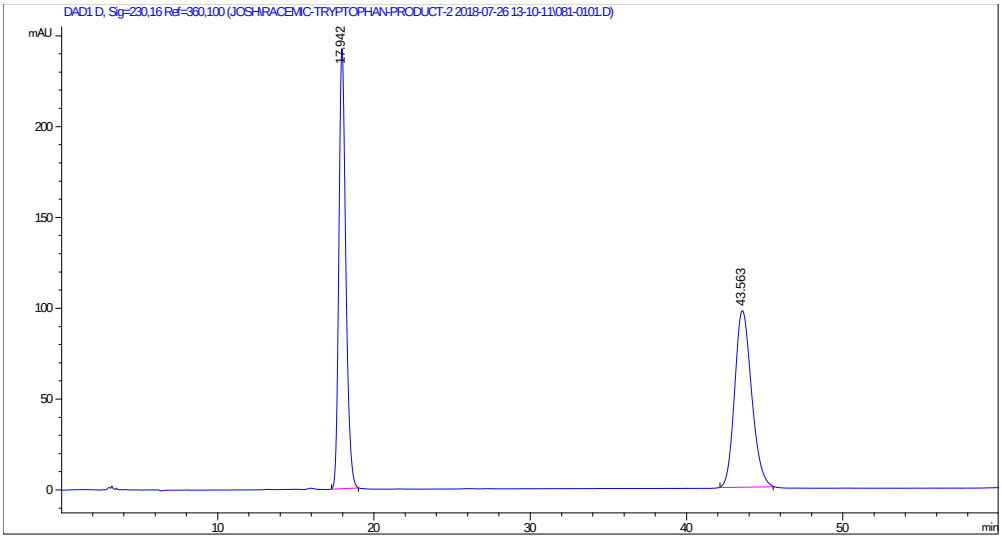


(*S*)-Methyl 3-(1*H*-indol-3-yl)-2-(4-methylbenzamido)propanoate (table 4.9, 26va): Synthesized according to general procedure **K** using masked isocyanate **24v** (0.203 g, 0.600 mmol), organoboron reagent **25a** (0.244 g 1.95 mmol, 3.3 equiv "Ar-B"), Et_3N (0.0836 mL, 0.600 mmol), and [Rh(OH)(cod)]$_2$ (6.84 mg, 0.0150 mmol) at 80 °C. The reaction reached completion within 20 hours. The desired product was purified by column chromatography (5% EtOAc/CH_2Cl_2) yielding a white foam (0.145 g, 72% yield). TLC R_F = 0.24 in 5% EtOAc/CH_2Cl_2. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.34 (3H, s), 3.40-3.45 (2H, m), 3.67 (3H, s), 5.13 (1H, dt, *J*= 5.3, 7.7 Hz), 6.75 (1H, d, *J*=7.7 Hz), 6.93 (1H, d, *J*=2.4 Hz), 7.07 (1H, t, *J*=7.0 Hz), 7.11-7.17 (3H, m), 7.30 (1H, d, *J*=8.1 Hz), 7.53-7.58 (3H, m), 8.71 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 27.7 (CH_2), 52.4 (CH), 53.5 (CH_3), 109.9 (C), 111.4 (CH), 118.6 (CH), 119.7 (CH), 122.2 (CH), 123.0 (CH), 127.1 (CH), 127.7 (C), 129.2 (CH), 131.0 (C), 136.2 (C), 142.2 (C), 167.0 (C), 172.5 (C). IR (film): 3393, 3294, 1732, 1639, 1209 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{20}H_{20}N_2O_3Na$ [M+Na]$^+$: 359.1372. Found: 359.1375. $[\alpha]^{20}_D$ -26.9° (*c* 1.30, MeCN). Chiral HPLC: ChiralPak column AD-H *i*-PrOH/Hexane = 15:85, 1.0 mL/min, 230 nm, *t* = 17.7 min, 43.1 min.



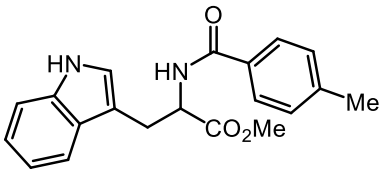
#	Time	Area	Height	Width	Area%	Symmetry
1	17.753	43	1.7	0.4224	1.415	0.938
2	43.141	2994.6	40.9	1.0928	98.585	0.813

Figure 6.6. HPLC trace and data of **26va** showing 97% ee

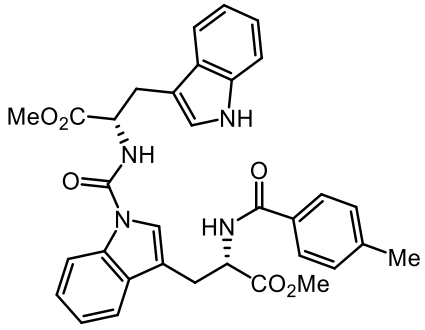


#	Time	Area	Height	Width	Area%	Symmetry
1	17.942	7515.7	242.3	0.4718	50.616	0.764
2	43.563	7332.9	97.2	1.1477	49.384	0.795

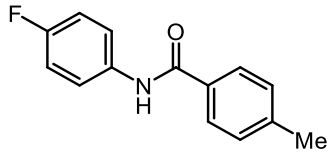
Figure 6.7. HPLC trace and data of racemic **26va**



Methyl (4-methylbenzoyl)tryptophanate (rac-26va): Synthesized according to general procedure **I** using racemic tryptophan methyl ester hydrochloride (0.127 g, 0.500 mmol), Et_3N (0.168 mL, 1.20 mmol), and *p*-toluoyl chloride (0.0730 mL, 0.550 mmol), and CH_2Cl_2 (1.6 mL). The reaction reached completion within 1 hour. The desired product was purified by column chromatography (90% CH_2Cl_2/EtOAc) yielding an amorphous white solid (0.106 g, 63% yield).



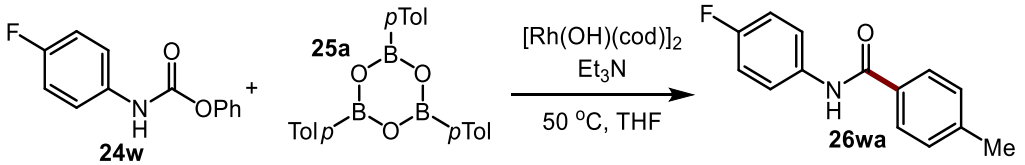
Methyl 3-(1-((3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-1*H*-indol-3-yl)-2-(4-methylbenzamido)propanoate (table 4.9, 26vva): Synthesized according to general procedure **K** using masked isocyanate **24v** (0.203 g, 0.600 mmol), organoboron reagent **25a** (0.244 g, 1.80 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (6.84 mg, 0.0150 mmol). The reaction reached completion within 6 hours. The desired product was purified by column chromatography (20% EtOAc/CH_2Cl_2) yielding an off-white foam (0.0416 g, 24% yield). TLC R_F = 0.39 in 20% EtOAc/CH_2Cl_2. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.34 (3H, s), 3.25-3.45 (4H, m), 3.61 (3H, s), 3.71 (3H, s), 4.93-5.00 (1H, m), 5.05-5.11 (1H, m), 6.09 (1H, d, *J*=7.5 Hz), 6.69 (1H, d, *J*=7.7 Hz), 6.97 (1H, d, *J*=2.4 Hz), 7.03-7.31 (8H, m), 7.44-7.58 (4H, m), 7.89 (1H, d, *J*=7.9 Hz), 8.31 (1H, s, br). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 27.5 (CH_2), 52.5 (CH_3), 52.6 (CH_3), 53.0 (CH), 54.1 (CH), 109.4 (C), 111.5 (CH), 114.4 (CH), 115.2 (CH), 118.4 (C), 119.1 (CH), 119.8 (CH), 122.3 (CH), 122.3 (CH), 122.4 (CH), 123.1 (CH), 124.7 (CH), 127.1 (CH), 127.4 (C), 129.3 (CH), 130.1 (C), 130.8 (C), 135.3 (C), 136.3 (C), 142.4 (C), 151.3 (C), 167.2 (C), 172.3 (C), 172.4 (C). IR (film): 3326, 1735, 1690, 1643 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{33}H_{32}N_4O_6Na$ $[M+Na]^+$: 603.2219. Found: 603.2200. $[\alpha]^{20}_D$ -36.3° (*c* 1.34, MeCN).



***N*-(4-Fluorophenyl)-4-methylbenzamide (figure 4.4, 26wa):** Synthesized according to general procedure **J** using masked isocyanate **24w** (0.138 g, 0.600 mmol), boroxine **25a** (0.106 g, 0.300 mmol), Et_3N (0.0836 mL, 0.600 mmol), and $[Rh(OH)(cod)]_2$ (2.73 mg, 0.0150 mmol). The reaction reached completion within 16 hours. The crude mixture was dry loaded onto silica gel (acetone) and purified by column chromatography (75% CH_2Cl_2/hexanes) white solid (0.107 g, 78% yield). TLC R_F = 0.18 in 75% CH_2Cl_2/ hexanes. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.37 (3H, s), 7.17 (2H, t, *J*=8.9 Hz), 7.32 (2H, d, *J*=8.0 Hz), 7.76-7.82 (1H, m), 7.87 (2H, d, *J*=8.2 Hz), 10.22 (1H, s). ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.4 (CH_3), 115.5 (CH, d, *J*=22.2 Hz), 122.6 (CH, d, *J*=7.82 Hz), 128.1 (CH), 129.3 (CH), 132.3 (C), 136.0 (C, d, *J*=2.57 Hz), 142.0 (C), 158.7 (C, d, *J*=240.0 Hz), 165.7 (C). Data consistent with literature.[284]

Mechanistic Data

The graphical method developed by Burés[233] was used to determine the reaction orders from the concentration profiles. This method uses a variable normalization of the time scale to enable the visual comparison of entire concentration profiles, allowing for the order in each component of the reaction to be determined.



General procedure C and D were followed using an NMR tube in place of a microwave vial on 0.300 mmol scale and 0.0600 mmol scale respectively. Organoboron reagent **25a** was fully dehydrated to the boroxine before use. $PhCF_3$ (0.100 mL, 0.0814 mmol) was used as an internal standard and the reaction was monitored by fluorine NMR at specified time points.

The graphical method developed by Burés was used to plot [Product] against t[cat]$^{\alpha}$ to determine the order in catalyst. When $^{\alpha}$ is the correct order in catalyst the traces will overlay.

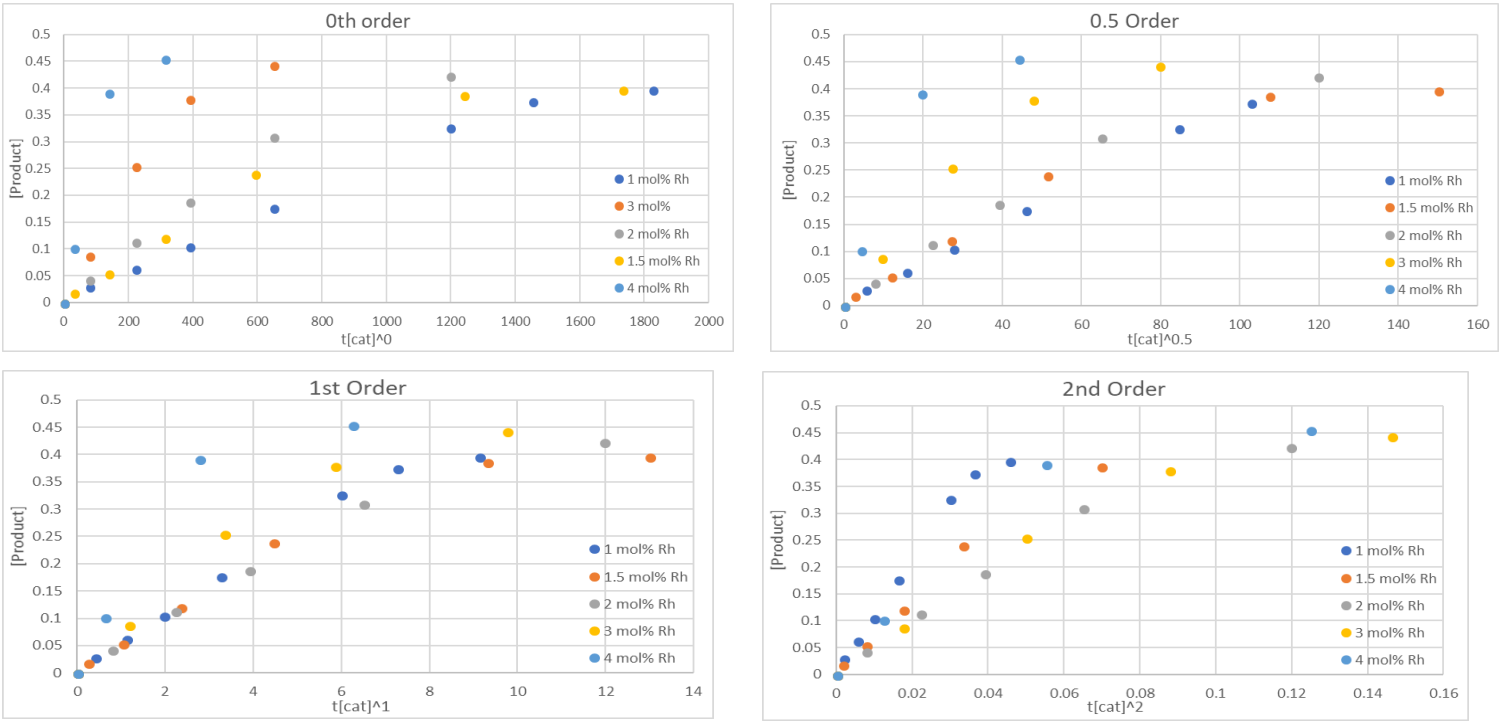


Figure 6.8: Variable time normalization plots for the determination of catalyst order under conditions described in general procedure **J** (low $[RBO]_3$, high [THF])

The lack of overlap in any of the 4 graphs is **Figure 6.8** suggests a possible change in rate determining step at different catalyst loadings under these conditions. This was explored by plotting the catalyst loadings 1-2 mol% and 2-4 mol% separately seen below (**Figures 6.9-6.10**).

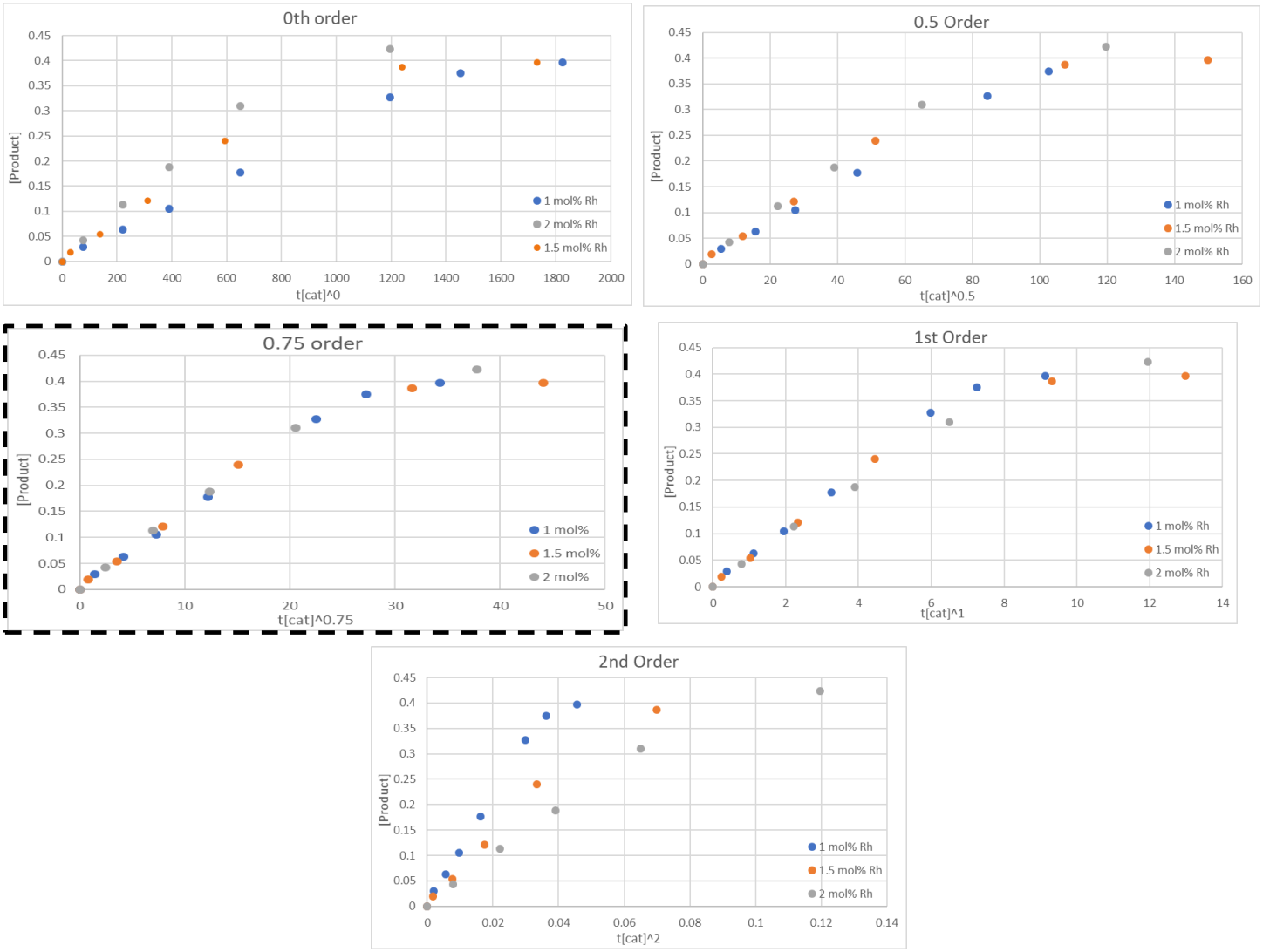


Figure 6.9. Variable time normalization plots for the determination of catalyst order with loadings of 1-2 mol% under conditions described in general procedure **J** (low $[RBO]_3$, high [THF])

The order in catalyst under these conditions was found to be 0.75 by analyzing plots in **Figure 6.9**. This suggests that the catalyst exists partially as a dimeric species under these conditions.

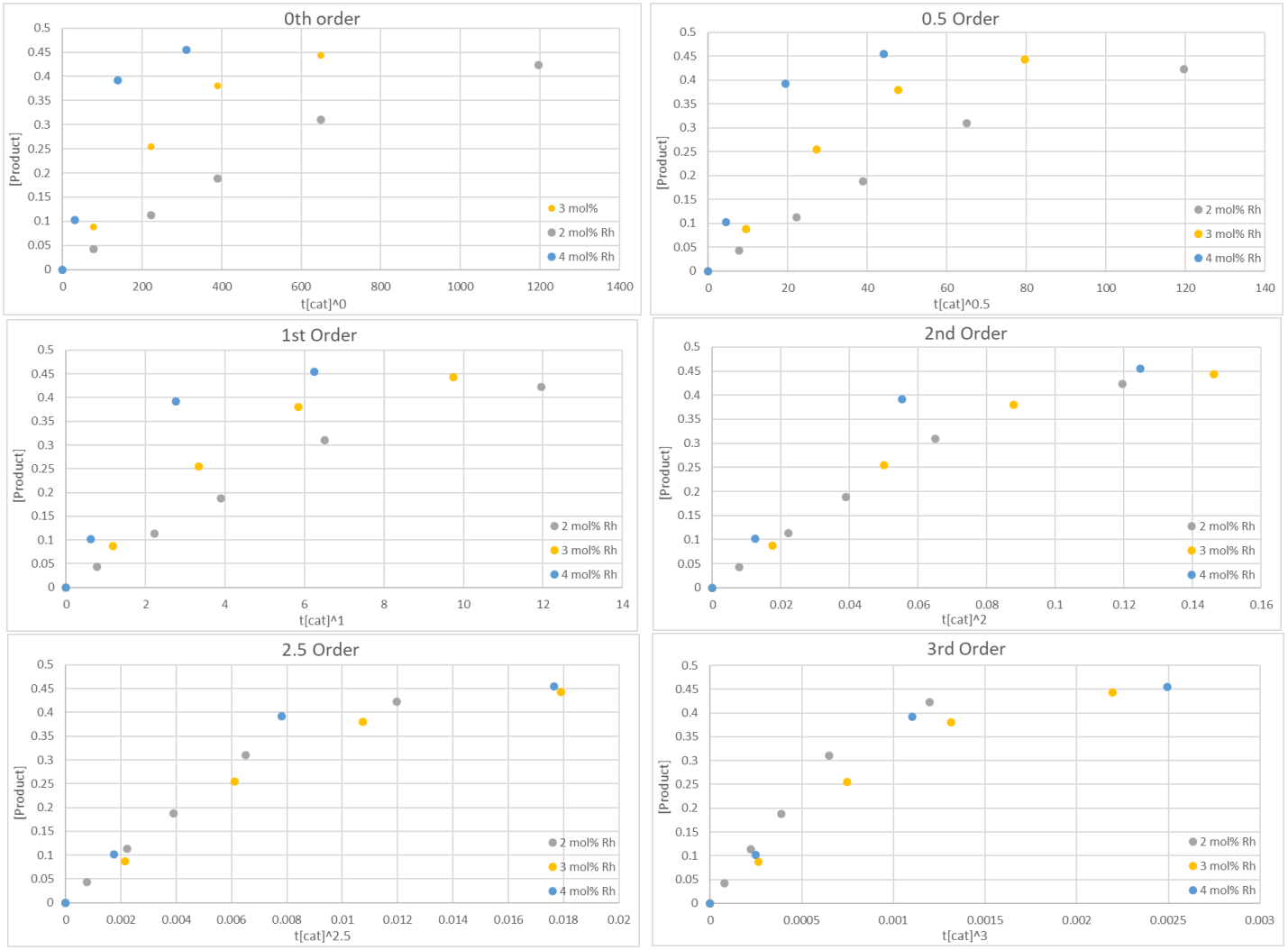


Figure 6.10. Variable time normalization plots for the determination of catalyst order with loadings of 2-4 mol% under conditions described in general procedure **J** (low [RBO]3, high [THF])

The lack of an overlap on all the graphs in **Figure 6.10** led us to graph 2-3/3-4 mol% separately seen in **Figure 6.11-6.12**.

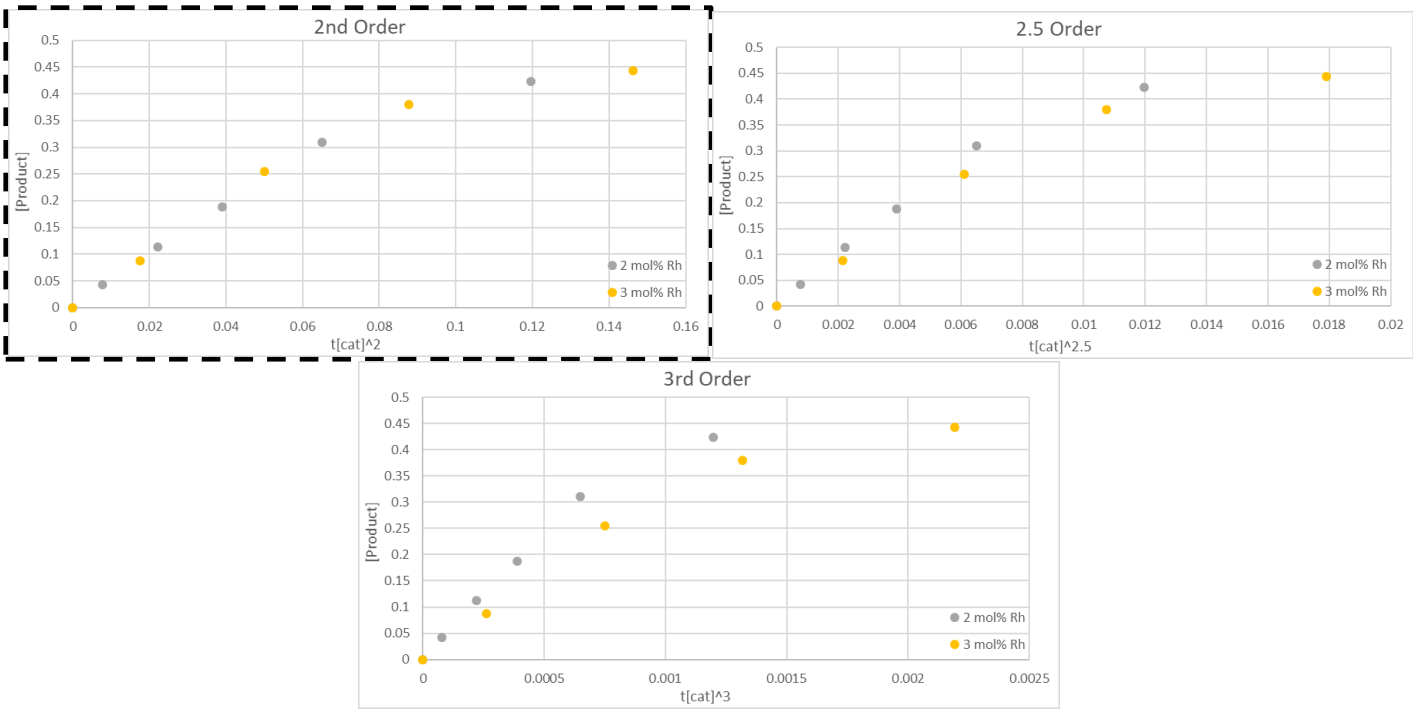


Figure 6.11. Variable time normalization plots for the determination of catalyst order with loadings of 2-3 mol% under conditions described in general procedure **J** (low $[RBO]_3$, high [THF])

See below for discussion of the results seen above in **Figure 6.11**.

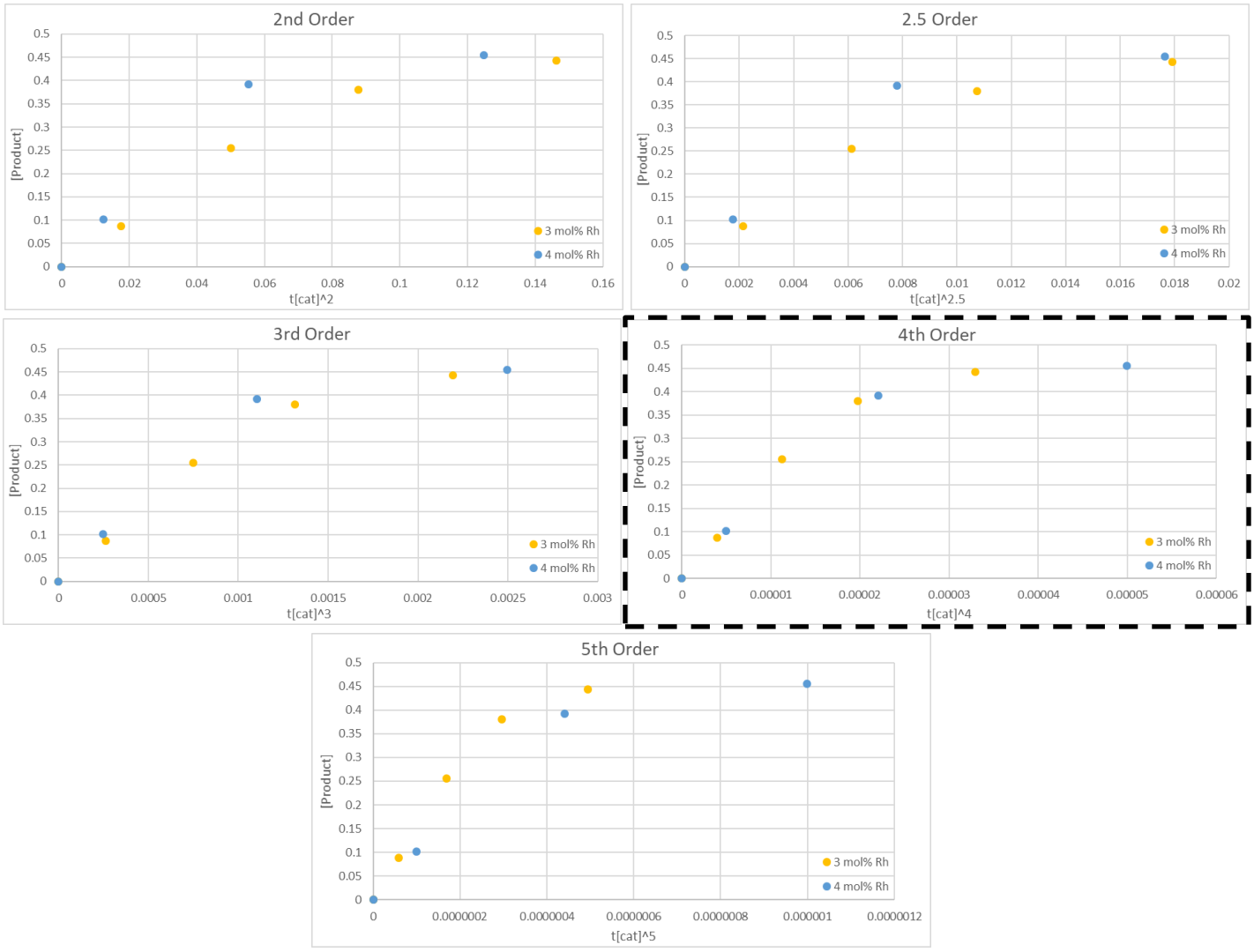


Figure 6.12. Variable time normalization plots for the determination of catalyst order with loadings of 3-4 mol% under conditions described in general procedure **J** (low $[RBO]_3$, high [THF])

The order in catalyst was observed to be 2nd order between 2/3 mol% Rh (**Figure 6.11**), while a 4th order in catalyst is observed between 3/4 mol% Rh (**Figure 6.12**). Rhodium species have been reported to form higher order aggregates in various systems.[293] These preliminary data are currently under further investigation.

[293] W.-L. Duan, H. Iwamura, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2130.

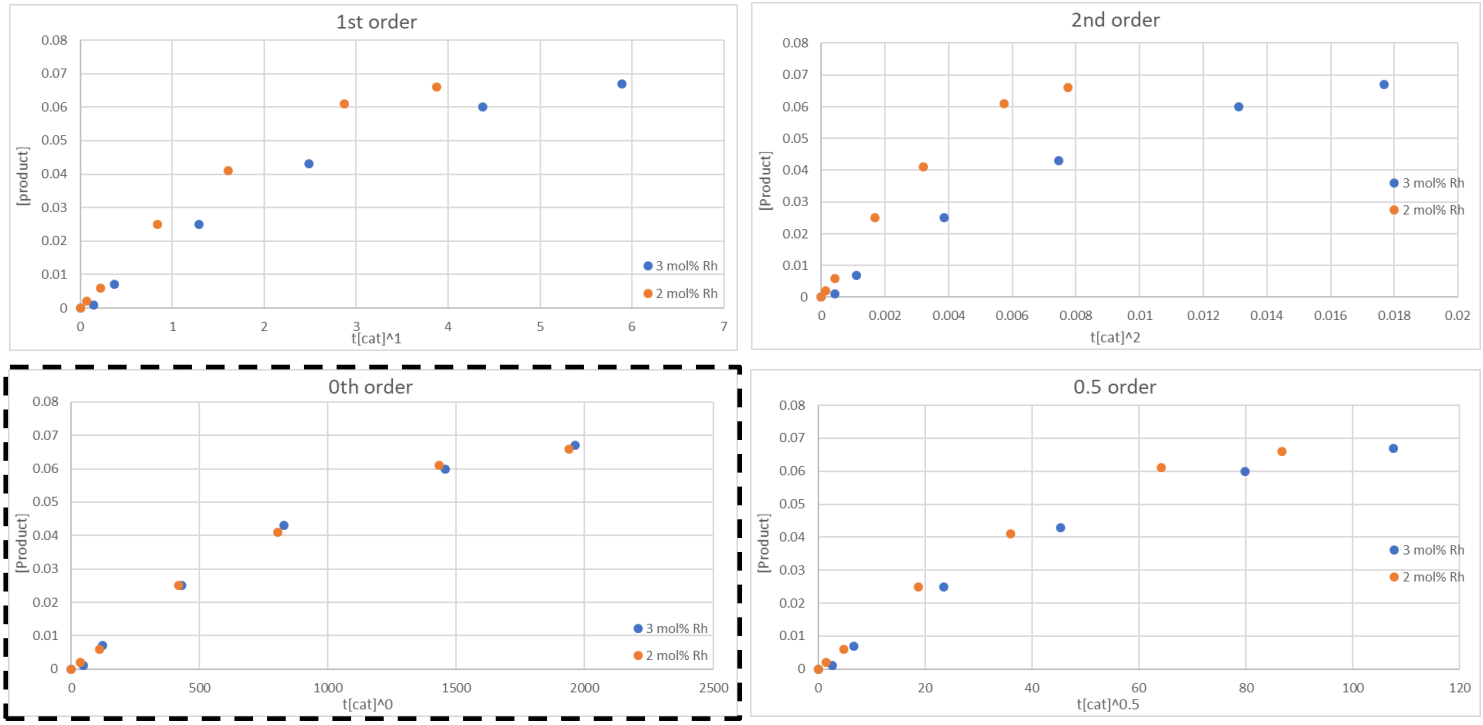


Figure 6.13. Variable time normalization plots for the determination of catalyst order under conditions described in general procedure **K** (high $[RBO]_3$, low [THF])

In contrast to the above cases, the order in catalyst under the conditions optimized for the amphoteric / ambident isocyanate precursors shown in Table 4.9 was found to be 0 by analyzing plots in **Figure 6.13**. This suggest that the catalyst is not involved in the rate determining step at lower concentrations. The lack of involvement of the catalyst in the rate determining step under these conditions supports the existence of an isocyanate intermediate as opposed to direct C-O bond activation[242] or direct addition onto the carbamate[165] where catalyst involvement would be present in all steps of the transformation.

The graphical method developed by Burés was used to plot [Product] against the variable time scale normalized in carbamate **24w** (Σ[carbamate]$^{\alpha}\Delta$t). When α is the correct order in **24w** the traces will overlay.

$$\int_{t=0}^{t=n} [\mathrm{A}]^{\alpha} \mathrm{d}t = \sum_{i=1}^{n} \left(\frac{[\mathrm{A}]_i + [\mathrm{A}]_{i-1}}{2} \right)^{\alpha} (t_i - t_{i-1})$$

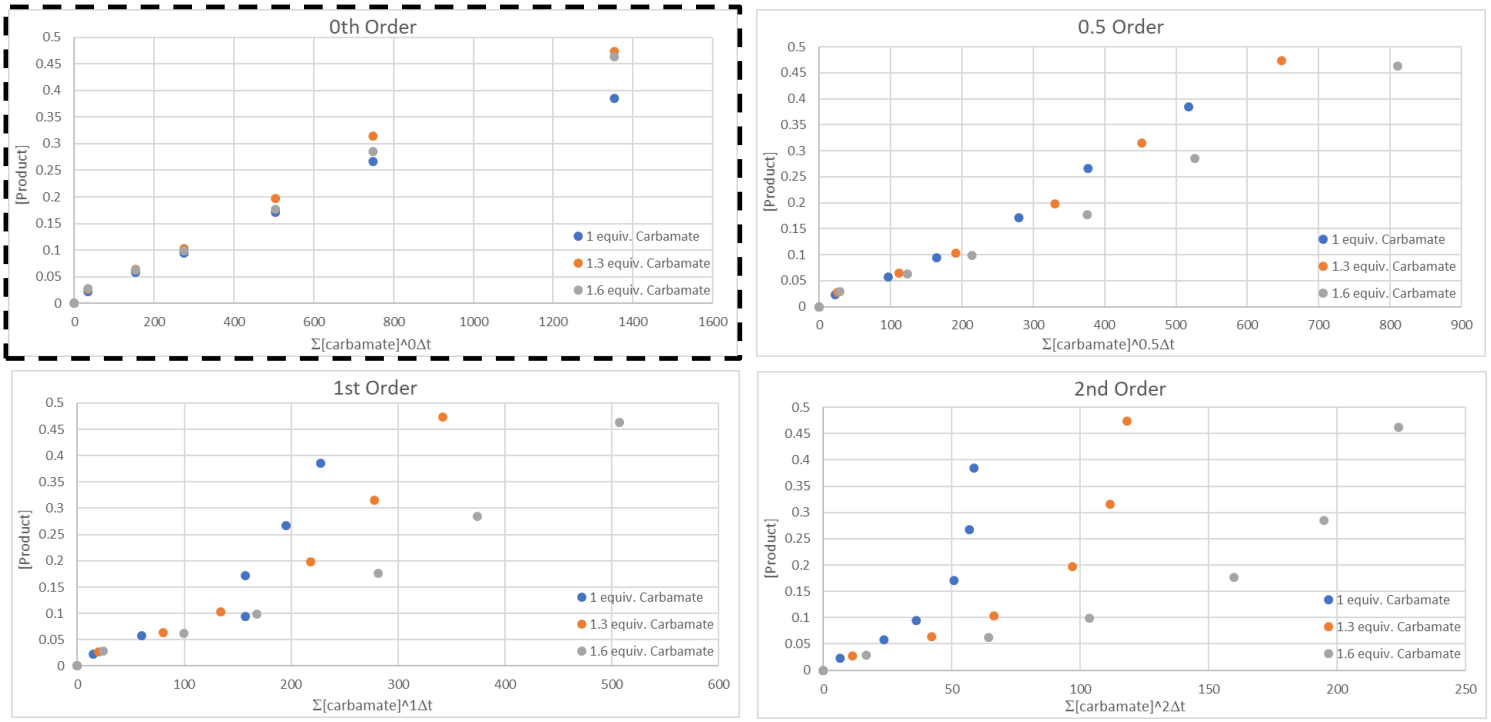


Figure 6.14: Variable time normalization plots for the determination of order in **24w** under conditions described in general procedure **J** (low $[RBO]_3$, high [THF]) with 1 mol% $[Rh(OH)(cod)]_2$

The order in **24w** under the 'concentrated conditions' was found to be 0 by analyzing plots in **Figure 6.14**. This result coupled with the 0.75 order in catalyst (**Figure 6.9**) suggests a rate determining transmetallation, with the existence of a dimeric rhodium specie under such conditions.

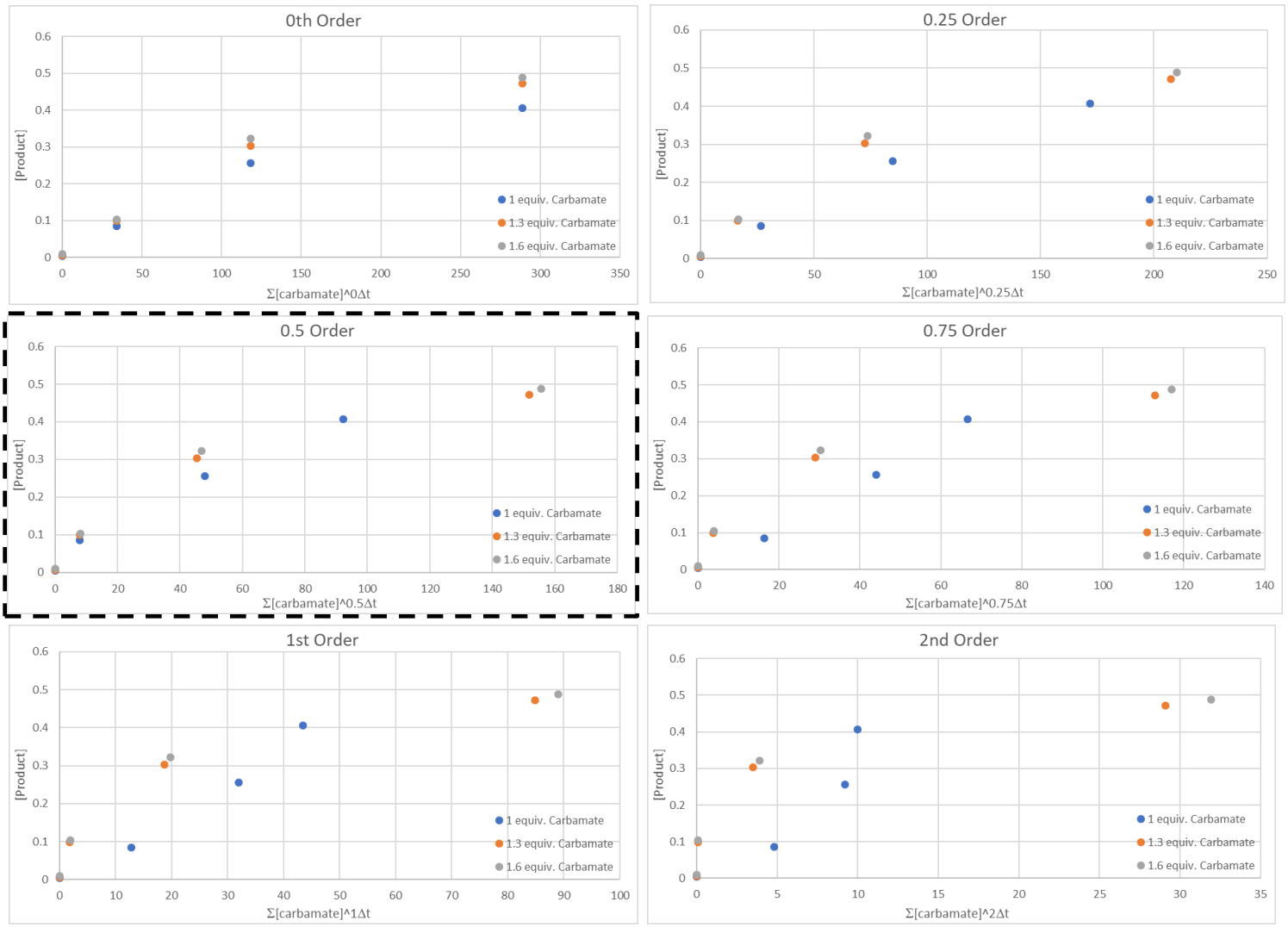


Figure 6.15: Variable time normalization plots for the determination of order in **24w** under conditions described in general procedure **J** (low $[RBO]_3$, high [THF]) with 3 mol% $[Rh(OH)(cod)]_2$

The order in **24w** under 'concentrated conditions' at high catalyst loading was found to be 0.5 by analyzing plots in **Figure 6.15**. This result suggests the existence of a **24w** as a dimer, possibly due to hydrogen-bonding.[237] This result coupled with the higher order in catalyst (**figure 6.11/6.12**) suggests the possibility of a rate determining insertion. The exact mechanistic intricacies of this particular kinetic regime are not yet fully understood and currently under further investigation.

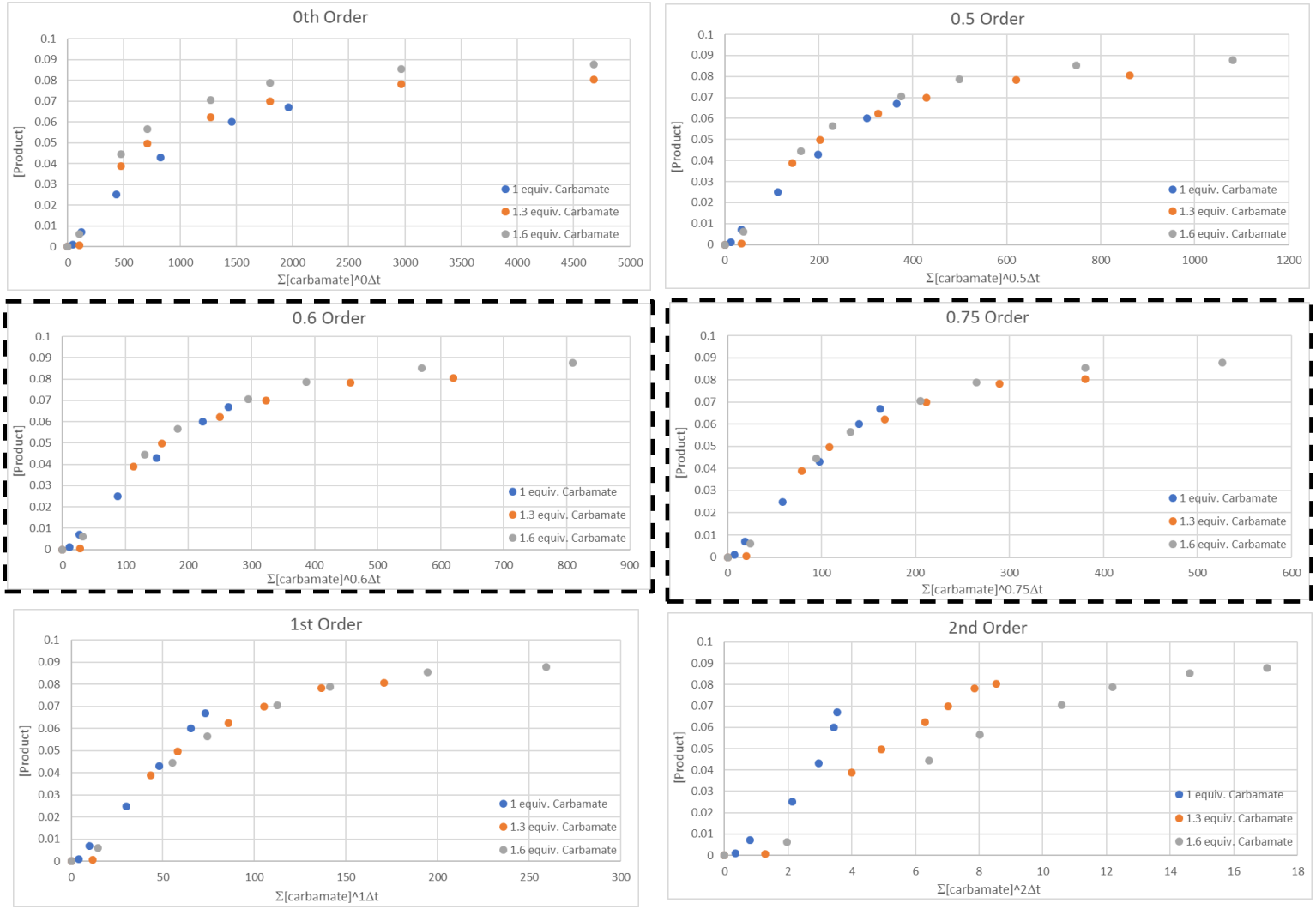


Figure 6.16: Variable time normalization plots for the determination of order in **24w** under conditions described in general procedure **K** (high $[RBO]_3$, low [THF]) with 3 mol% $[Rh(OH)(cod)]_2$

The order of **24w** under the conditions used in Table 4.9 was found to be between 0.6-0.75 order by analyzing plots in **Figure 6.16**. This suggest the existence of **24w** as a dimeric species under these conditions. This coupled with the 0^{th} order in catalyst (**Figure 6.13**) further supports a rate determining isocyanate unmasking under the conditions described in general procedure **K**.

Similarly, the graphical method developed by Burés was used to plot [Product] against t[Base]$^{\alpha}$ to determine the order in Base. When α is the correct order in base the traces will overlay.

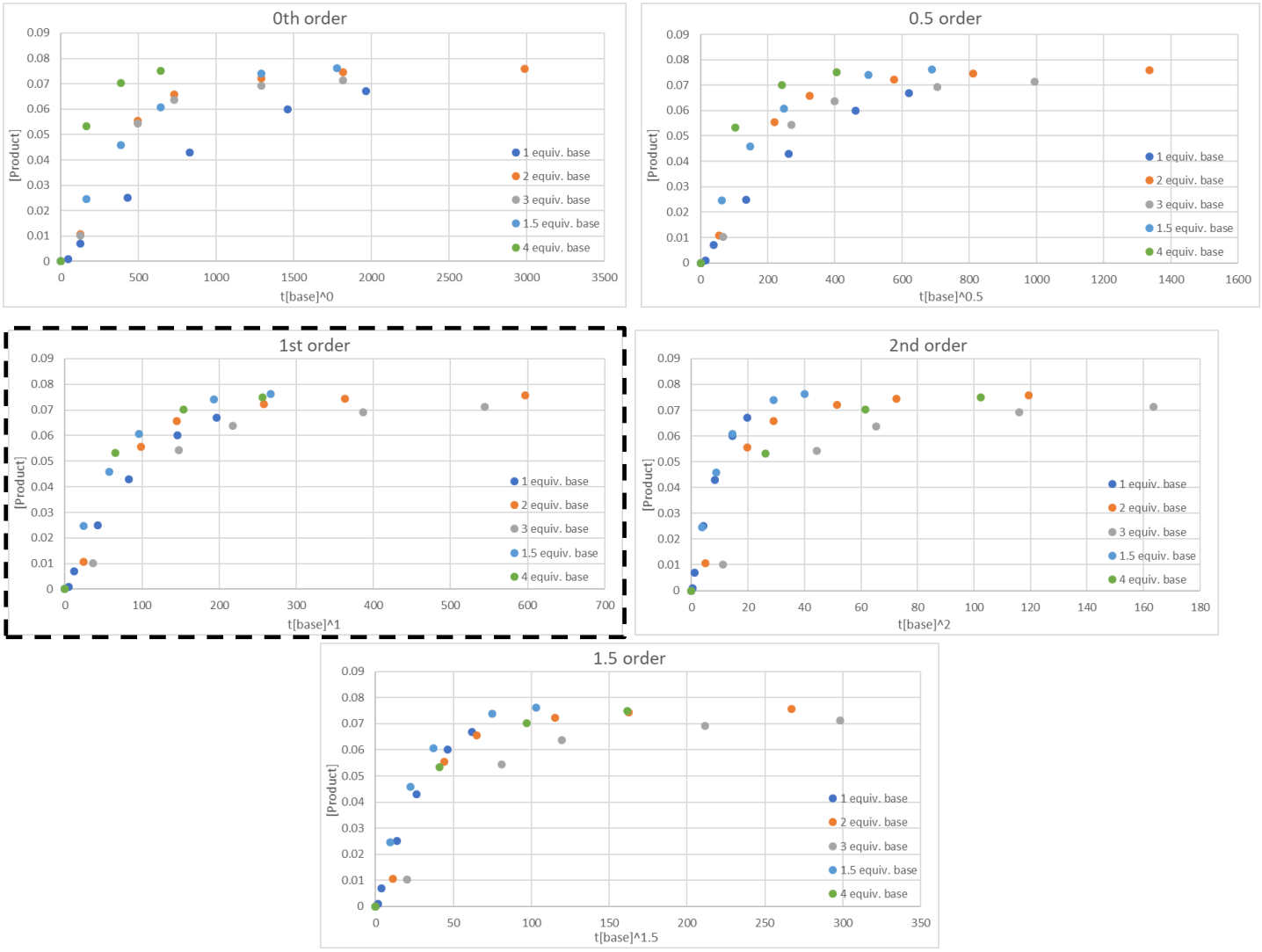
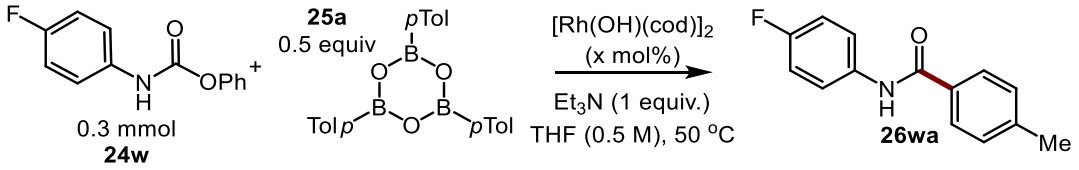


Figure 6.17: Variable time normalization plots for the determination of order in Et_3N under conditions described in general procedure **K** (high $[RBO]_3$, low [THF]) with 3 mol% $[Rh(OH)(cod)]_2$

The order of Et_3N under the conditions used in Table 4.9 was found to be 1 by analyzing plots in **Figure 6.17**. This result further supports deblocking as the rate determining step under the 'dilute conditions', specifically implicating the importance of the base

Raw Data

Table 6.1: Raw data for the determination of order in catalyst under conditions of general procedure **J**. The reaction was run with 1.0 mol%, 1.5 mol%, 2.0 mol%, 3.0 mol%, 4.0 mol% $[Rh(OH)(cod)]_2$



1mol%

time(min)	[prod]
0	0
78	0.0293
222	0.063
390	0.105
650	0.177
1196	0.327
1452	0.375
1825	0.397

1.5 mol%

time(min)	[prod]
0	0
31	0.0188
138	0.054
312	0.121
593	0.24
1241	0.387
1731	0.397

2mol%

time(min)	[prod]
0	0
78	0.0427
222	0.113
390	0.188
650	0.31
1196	0.423

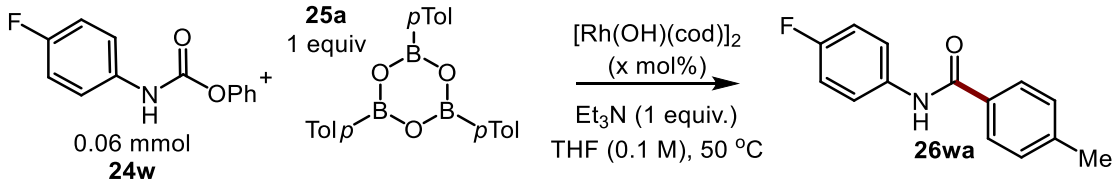
3mol%

time(min)	[prod]
0	0
78	0.0877
222	0.255
390	0.38
650	0.443

4mol%

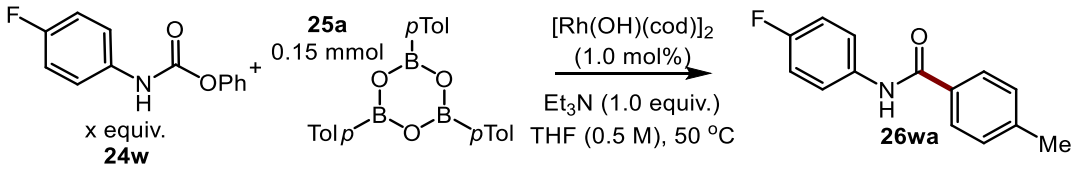
time(min)	[prod]
0	0
31	0.102
138	0.392
312	0.455

Table 6.2: Raw data for the determination of order in catalyst under conditions of general procedure **K**. The reaction was run with 2.0 mol% and 3.0 mol% $[Rh(OH)(cod)]_2$



2mol%		3mol%	
time	[prod]	time(min)	[prod]
0	0	0	0
35	0.002	48	0.001
109	0.006	123	0.007
418	0.025	430	0.025
804	0.041	828	0.043
1434	0.061	1458	0.06
1939	0.066	1963	0.067

Table 6.3: Raw data for the determination of order in **24w** under conditions of general procedure **J** at low catalyst concentration. The reaction was run with 1.0, 1.3, and 1.6 equiv of **24w** where 1.0 equiv = 0.3 mmol



1.0 equiv. 24w

time(min)	[24w]	[prod]
0	0.4688	0
34	0.4066	0.0228
154	0.3485	0.0577
274	0.2998	0.0944
504	0.2036	0.1714
749	0.1082	0.2666
1354	0	0.385

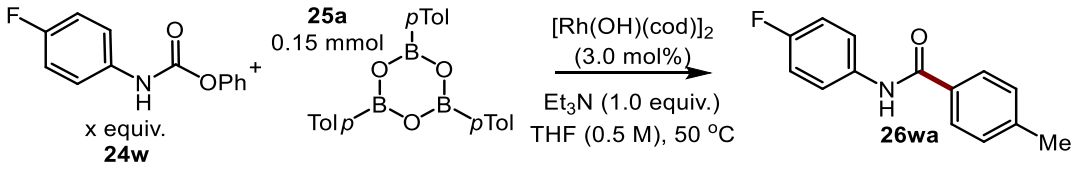
1.3 equiv. 24w

time(min)	[24w]	[prod]
0	0.6177	0
34	0.5394	0.0271
154	0.4747	0.0641
274	0.4211	0.1035
504	0.3084	0.1977
749	0.1811	0.315
1354	0.0292	0.4736

1.6 equiv. 24w

time(min)	[24w]	[prod]
0	0.7391	0
34	0.6629	0.0284
154	0.5974	0.0627
274	0.5445	0.0987
504	0.444	0.1766
749	0.3134	0.2853
1354	0.1263	0.4627

Table 6.4: Raw data for the determination of order in **24w** under conditions of general procedure **J** at high catalyst concentration. The reaction was run with 1.0, 1.3, and 1.6 equiv of **24w** where 1.0 equiv = 0.3 mmol



1.0 equiv. 24w

time(min)	[24w]	[prod]
0	0.4317	0.004
34	0.3219	0.0852
118	0.1346	0.256
289	0	0.4065

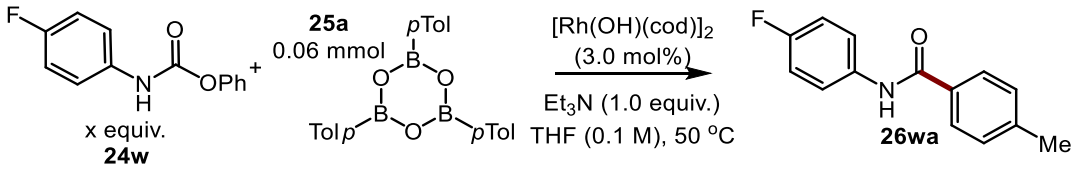
1.3 equiv. 24w

time(min)	[24w]	[prod]
0	0.5689	0.0065
34	0.4332	0.0992
118	0.2075	0.3026
289	0.045	0.4715

1.6 equiv. 24w

time(min)	[24w]	[prod]
0	0.6904	0.0092
34	0.5475	0.1038
118	0.2953	0.3222
289	0.1164	0.4876

Table 6.5: Raw data for the determination of order in **24w** under conditions of general procedure **K** at 3.0 mol% catalyst. The reaction was run with 1.0, 1.3, and 1.6 equiv of **24w** where 1.0 equiv = 0.06 mmol



1.0 equiv. 24w

time(min)	[24w]	[prod]
0	0	0.084
48	0.001	0.083
123	0.007	0.076
430	0.025	0.055
828	0.043	0.036
1458	0.06	0.019
1963	0.067	0.012

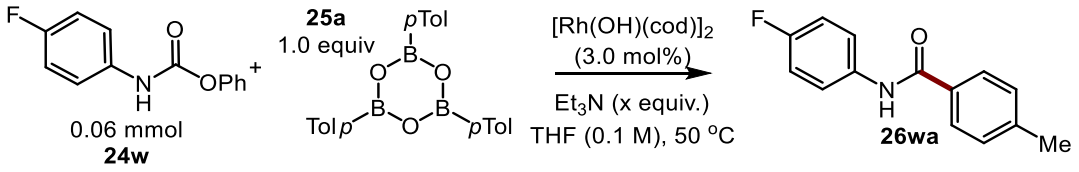
1.3 equiv. 24w

time(min)	[24w]	[prod]
0	0	0.114
107	0.000573	0.104
476	0.0388	0.068
711	0.0497	0.0573
1272	0.0623	0.0415
1800	0.07	0.0325
2970	0.0782	0.0212
4680	0.0805	0.0188

1.6 equiv. 24w

time(min)	[24w]	[prod]
0	0	0.14
107	0.00617	0.131
476	0.0445	0.089
711	0.0565	0.0758
1272	0.0705	0.0595
1800	0.0788	0.0505
2970	0.0853	0.0405
4680	0.0878	0.035

Table 6.6: Raw data for the determination of order in Et_3N under conditions of general procedure **K** at 3.0 mol% catalyst. The reaction was run with 1.0, 1.5, 2.0, 3.0, and 4.0 equiv of Et_3N.



1 equiv.

time(min)	[prod]
0	0
48	0.001
123	0.007
430	0.025
828	0.043
1458	0.06
1963	0.067

1.5 equiv.

time(min)	[prod]
0	0
163	0.0247
384	0.0458
640	0.0607
1288	0.074
1778	0.0762

2 equiv.

time(min)	[prod]
0	0
123	0.0107
492	0.0555
727	0.0657
1288	0.0722
1816	0.0745
2986	0.0758

3 equiv.

time(min)	[prod]
0	0
123	0.0102
492	0.0543
727	0.0637
1288	0.0692
1816	0.0713

4 equiv.

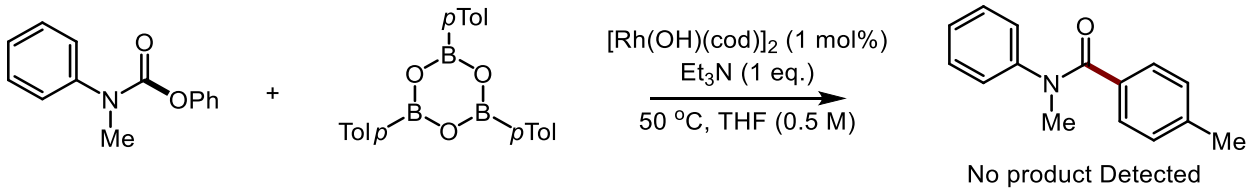
time(min)	[prod]
0	0
163	0.0533
384	0.0702
640	0.075

Evidence for competitive protodemetallation

25g was recrystallized in water and subsequently submitted to the reaction conditions described in general procedure **J**. No boronic acid was detected by TLC 1.0 hour into the reaction. The boronic acid **25g** was then recrystallized in D_2O and submitted to the reaction conditions in general procedure **J** (0.45 mmol of **25g**). The reaction was concentrated under reduced pressure at the 2.0 hour mark. The crude mixture was resuspended in EtOAc (40 mL) and extracted with 1M NaOH (1 x 30 mL), saturated $NaHCO_3$ (1 x 30 mL), and brine (1 x 30 mL). The product was purified by column chromatography (40% CH_2Cl_2/hexanes). Product volatility made it difficult to obtain a yield thus an internal standard was added (1,3,5-trimethoxybenzene, 14.1 mg) resulting in a 19% isolated yield. The low yield can likely be attributed to product lost due to volatility. The ratio of deuterium incorporation was found to be 37%. These results provide evidence for a kinetically fast protodemetallation which outcompetes isocyanate insertion.

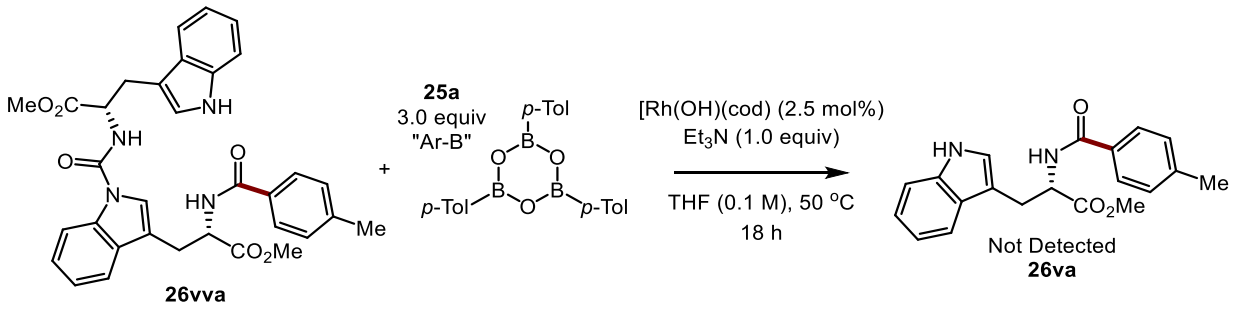
***N*-Methyl control reactions**

The methylated derivative of blocked isocyanate **24a** was prepared to probe the existence of the isocyanate intermediate due to its inability to act as a blocked isocyanate precursor. The carbamate was prepared using a literature procedure.[271]



Under standard conditions, no product formation was detected. This result couple d with the absence of the involvement of the Rh catalyst in the rate determining step under some conditions is highly indicative of an isocyanate as a key reaction intermediate.

Control reaction of tryptophan dimer 26vva



The dimer **26vva** (0.0288 g, 0.0496 mmol) was submitted to the reaction conditions described in general procedure **K** using boroxine **25a** (0.0175 g, 0.0496 mmol, 3 equiv "Ar-B"), Et_3N ($6.9x10^{-3}$ mL, 0.050 mmol), and $[Rh(OH)(cod)]_2$ (0.0056 g, 1.2 $x10^{-3}$ mmol) at 80 °C. The reaction was dried down after 18 hours with no sign of product formation or disappearance of starting material by TLC. The crude reaction mixture was analyzed by NMR and revealed no detectable product formed with 66% starting material remaining. These results suggest the formation of the dimer under the reaction conditions is not reversible.

5.3.2 Rhodium catalyzed addition of boroxines to blocked isocyanate

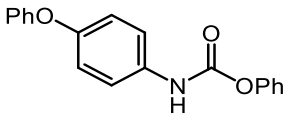
Arylboroxine synthesis: As described in section 6.4.1.

Starting material synthesis: Blocked isocyanate **30c**, **30e**, **30f**, **30h** are described above in section 5.3.1. New blocked isocyanate derivates were synthesized according to general procedure X and are characterized below. **38a** was quantified by ^1H NMR spectroscopy using 1,3,5-trimethoxybenze as internal standard and matched literature reports.[294]

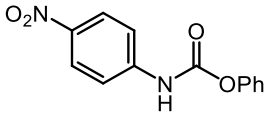
General procedure L: An oven-dried microwave vial equipped with a magnetic stir bar and fitted with a microwave cap was charged with diphenyl carbonate (6.00 mmol, 2.00 equiv.) and heated to 70 °C until the diphenyl carbonate had turned into a liquid. Subsequently, the corresponding amine (3.00 mmol, 1.00 equiv.) was added dropwise to the vial and stirred for an additional 10 minutes at 70 °C. The reaction

[294] Yuan, H.-Y.; Zhang, Q.; Fukaya, N.; Lin, X.-T.; Fujitani, T.; Choi, J.-C. *Bull. Chem. Soc. Jpn.* **2018**, *91*, 10.

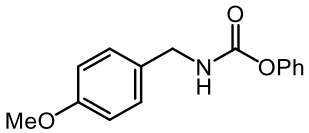
mixture was then cooled to room temperature, diluted with EtOAc (10 mL) and extracted 1M NaOH (1 x 20 mL), saturated $NaHCO_3$ (1 x 20 mL), and brine (1 x 20 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography providing the desired product.



Phenyl(4-phenoxyphenyl)carbamate (30b): Synthesized according to general procedure **H** using 4-phenoxyaniline (0.556 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 2 hours. The crude mixture was recrystallized in ether/hexanes providing the desired product as a crystalline off white solid (0.800 g, 88%). M.P. 156.7-157.0 °C. TLC R_F = 0.5 in 80% hexanes/EtOAc. ^{1}H NMR (500 MHz CDCl3) δ 6.88-6.94 (1H, br s), 6.97-7.02 (4H, m), 7.09 (1H, t, J=7.38 Hz), 7.18-7.21 (2H, m), 7.22-7.25 (1H, m), 7.30-7.35 (2H, m), 7.37-7.44 (4H, m). ^{13}C NMR (125 MHz CDCl3) δ 118.51 (CH), 119.92 (CH), 120.58 (CH), 121.73 (CH), 123.19 (CH), 125.82 (CH), 129.68 (CH), 129.85 (CH), 132.98 (C), 150.67 (C), 151.92 (C), 153.37 (C), 157.66 (C). IR (film): 3392, 3343, 3059, 2112, 1711, 1614, 1589 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{15}NO_3$ [M]$^+$: 305.1052. Found: 305.1065.

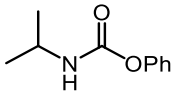


Phenyl(4-nitrophenyl)carbamate (30d): Synthesized according to general procedure **H** using 4-nitroaniline (0.414 g, 3.00 mmol), phenyl chloroformate (0.395 mL, 3.15 mmol), and $NaHCO_3$ (0.277 g, 0.330 mmol). The reaction reached completion within 2 hours. The crude mixture was recrystallized in ether/hexanes providing the desired product as a crystalline off white solid (0.628 g, 81%). M.P. 170.9-171.2 °C. TLC R_F = 0.16 in 80% hexanes/EtOAc. ^{1}H NMR (500MHz CDCl3) δ 7.16-7.21 (1H, m,), 7.26-7.30 (1H, m), 7.34-7.37 (1H br s), 7.39-7.45 (1H, m), 7.58-7.62 (1H, m), 8.19-8.23 (1H, m). ^{13}C NMR (125MHz CDCl3) δ 118.21 (CH), 121.59 (CH), 125.41 (CH), 126.39 (CH), 129.74 (CH), 143.52 (C), 143.56 (C), 150.24 (C), 151.27 (C). IR (film): 3321, 3120, 2113, 1741, 1719, 1614, 1595 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{13}H_{10}N_2O_4$ [M]$^+$: 258.0641 Found: 258.0666. Under 1.0% relative abundance. Exact mass calcd for isocyanate $C_7H_4N_2O_3$ [M]$^+$: 164.0222. Found: 164.0234. Exact mass calcd for phenol C_6H_6O [M]$^+$: 94.0419. Found: 94.0414.

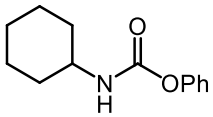


Phenyl(4-methoxybenzyl)carbamate (30g): Synthesized according to general procedure **I** using 4-methoxybenzylamine (0.39 mL, 3.0 mmol), phenyl chloroformate (0.41 mL, 3.3 mmol), and Et_3N (0.47 mL, 0.34 mmol). The reaction reached completion within 2 hours. The desired product was purified by column

chromatography (70% hexanes/EtOAc) yielding an amorphous white solid (0.467 g, 61% yield). TLC R_F = 0.50 in 70% hexanes/EtOAc. ^{1}H NMR (300MHz CDCl3) δ 3.82 (3H, s), 4.39 (2H, d, J=5.83 Hz), 6.86-6.92 (2H, m), 7.10-7.23 (3H, m), 7.26-7.40 (4H, m). ^{13}C NMR (100 MHz CDCl3) δ 44.9 (CH_2), 55.4 (CH_3), 114.3 (CH), 121.7 (CH), 125.4 (CH), 129.3 (CH), 129.4 (CH), 130.3 (C), 151.2 (C), 154.7 (C), 159.3 (C). IR (film): 3287.0, 3059, 2959, 2836, 1699, 1612, 1531 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$: 280.0942. Found: 280.0950.



Phenyl isopropylcarbamate (30i): Synthesized according to general procedure **H** using isopropylamine (0.257 mL, 3.00 mmol), diphenyl carbonate (0.642 g, 3.00 mmol). The desired product was purified by column chromatography (90% hexanes/EtOAc) yielding an amorphous white solid (0.188 g, 35% yield). TLC R_F = 0.40 in 90% hexanes/EtOAc. ^{1}H-NMR (300 MHz, DMSO-d_6): ^{1}H NMR (300 MHz $CDCl_3$) δ 1.24 (1H, d, J=6.55 Hz), 3.89 (1H, m, J=6.92 Hz), 4.75-4.86 (1H, br s), 7.09-7,15 (1H, m), 7.18 (1H, app t, J=7.42 Hz), 7.35 (1H, t, J=7.89 Hz). ^{13}C NMR (125 MHz CDCl3) δ 23.04 (CH_3), 43.56 (CH), 121.76 (CH), 125.29 (CH), 129.37 (CH), 151.19 (C), 153.83 (C). Data consistent with literature.[295]



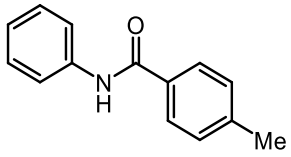
Phenyl isopropylcarbamate (30): Synthesized according to general procedure **L** using cyclohexylamine (0.541 mL, 8.00 mmol) and diphenyl carbonate (1.80 g, 8.40 mmol). The reaction reached completion within 2 hours. The desired product was dry loaded onto silica gel (MeOH) and purified by column chromatography (90% hexanes/EtOAc) yielding an amorphous white solid (1.04 g, 59% yield). TLC R_F = 0.27 in 90% hexanes/EtOAc. ^{1}H NMR (500 MHz $CDCl_3$) δ 1.14-1.27 (1H, m), 1.32-1.42 (1H, m), 1.59-1.65 (1H, m), 1.69-1.78 (1H, m), 1.97-2.07 (1H, m), 3.52-3.61 (1H, m), 4.53-5.00 (1H, br s), 7.13 (1H, d, J=7.90 Hz), 7.18 (1H, t, J=7.33 Hz), 7.35 (1H, t, J=7.75 Hz). ^{13}C NMR (125 MHz $CDCl_3$) δ 24.9 (CH_2), 25.6 (CH_2), 33.4 (CH_2), 50.3 (CH), 121.8 (CH), 125.3 (CH), 129.4 (CH), 151.3 (C), 153.8 (C). Data consistent with literature.[134l,296]

Synthesis of Amide products

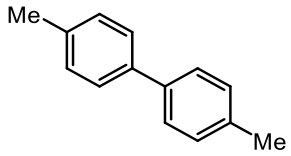
General Procedure M: An oven-dried microwave vial equipped with a magnetic stir bar was cooled under a stream of argon followed by the addition of $Pd(OAc)_2$ ($6.00x10^{-3}$ mmol, 0.0100 equiv.) and SPhos (0.0120 mmol, 0.0200 equiv.). The microwave vial was then sealed and purged under a stre am of argon for a total of 2 minutes and subsequently anhydrous THF (1.2 mL) was added. The resulting mixture was stirred under argon at room temperature for 5 minutes.
A second oven-dried microwave vial equipped with a magnetic stir bar was cooled under a stream of argon followed by the addition of the corresponding carbamate (0.600 mmol, 1.00 equiv.) and arylboroxine (0.400 mmol, 2.00 'Ar-B' equiv.). The microwave vial was then sealed and purged under a stream of argon for a total of 2 minutes. The catalyst solution was then transferred to the vial via syringe and then let stir

[295] Bronner, S. M.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842.
[296] Patonay, T.; Patonay-Peli, E.; Mogyorodi, F. *Synth. Commun.* **1990**, *20*, 2865.

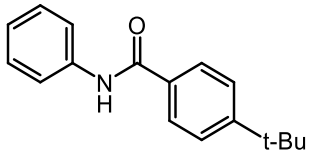
at room temperature for 5 minutes then subsequent addition of Et_3N (1.20 mmol, 2.00 equiv.) via syringe. The microwave vial was then heated to 50 °C for 24 h. Upon completion, the reaction was concentrated under reduced pressure, diluted with EtOAc (40 mL) and extracted 1M NaOH (1 x 30mL), saturated $NaHCO_3$ (1 x 30 mL), and brine (1 x 30 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography providing the desired product.



4-methyl-*N*-phenylbenzamide (table 4.17, 32aa): Synthesized according to general procedure **M** using masked isocyanate **30a** (0.128 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (75% CH_2Cl_2/Hexane to 100% CH_2Cl_2) yielding an amorphous white solid (0.112 g, 89% yield). TLC R_F = 0.42 in 99% CH_2Cl_2/Et_3N. ^1H NMR (500MHz $CDCl_3$) δ 2.42 (3H, s), 7.14 (1H, t, J=7.40 Hz), 7.28 (1H, d, J=7.95 Hz), 7.37 (1H, t, J=7.93 Hz), 7.64 (1H, d, J=7.75 Hz), 7.77 (1H, d, J=8.10 Hz), 7.79-7.84 (1H, br s). ^{13}C NMR (125 MHz $CDCl_3$) δ 21.63 (CH_3), 120.27 (CH), 124.56 (CH), 127.15 (CH), 129.21 (CH), 129.58 (CH), 132.26 (C), 138.17 (C), 142.52 (C), 165.77 (C). Data is consistent with literature.[284]



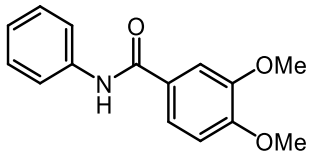
4,4'-dimethyl-1,1'-biphenyl (eq. 4.5, 33aa): Isolated during the isolation of **32aa**. The desired product was purified by column chromatography (60% CH_2Cl_2/Hexane) yielding an amorphous white solid (0.0086 g, 8% yield). TLC R_F = 0.80 in 60% CH_2Cl_2/Hexane. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.2 Hz, 4H), 7.22 (d, *J* = 7.8 Hz, 4H), 2.38 (s, 6zH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (C), 136.7 (C), 129.4 (CH), 126.8 (CH), 21.1 (CH_3). Data consistent with literature.[297]



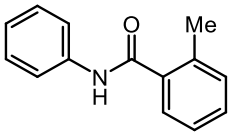
4-(*tert*-butyl)-*N*-phenylbenzamide (table 4.17, 32ab): Synthesized according to general procedure **M** using masked isocyanate **30a** (0.128 g, 0.600 mmol), arylboroxine **31b** (0.192 g, 0.400 mmol, 2.00 equiv

[297] Wang, M.; Tang, B.-C.; Wang, J.-G.; Xiang, J.-C.; Guan, A.-Y.; Huang, P.-P.; Guo, W.-Y.; Wu, Y.-D.; Wu, A.-X. *Chem. Commun.* **2018**, *54*, 7641.

"Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The reaction reached completion within 20 hours. The desired product was purified by column chromatography (40% Hexane/CH_2Cl_2) yielding an amorphous white solid (0.126 g, 83% yield). TLC R_F = 0.33 in 40% Hexane/CH_2Cl_2. ^1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.90 – 7.83 (m, 2H), 7.79 – 7.72 (m, 2H), 7.54 – 7.47 (m, 2H), 7.35 – 7.26 (m, 2H), 7.05 (tt, *J* = 7.3, 1.2 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0 (C), 154.8 (C), 139.8 (C), 132.8 (CH), 129.0 (CH), 128.0 (CH), 125.6 (CH), 124.0 (CH), 120.7 (CH), 35.1 (C), 31.4 (CH_3). Data is consistent with literature.[298]

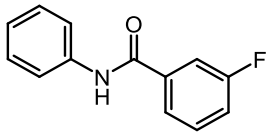


3,4-dimethoxy-*N*-phenylbenzamide (table 4.17, 32ac): Synthesized according to general procedure **M** using masked isocyanate **30a** (0.128 g, 0.600 mmol), arylboroxine **31c** (0.197 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The reaction reached completion within 20 hours. The desired product was purified by column chromatography (100% CH_2Cl_2 to 5% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.122 g, 79% yield). TLC R_F = 0.33 in 95% CH_2Cl_2/EtOAc. ^1H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.76 – 7.70 (m, 2H), 7.60 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.05 (dd, *J* = 7.9, 6.3 Hz, 2H), 3.81 (d, *J* = 4.8 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4 (C), 152.1 (C), 148.8 (C), 139.8 (C), 129.0 (CH), 127.5 (C), 123.9 (CH), 121.5 (CH), 121.0 (CH), 111.5 (CH), 111.4 (CH), 56.1 (CH_3), 56.1 (CH_3). Data is consistent with literature.[290]

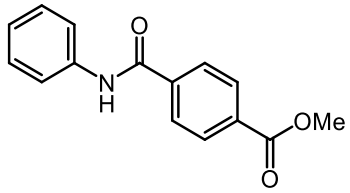


2-methyl-*N*-phenylbenzamide (table 4.17, 32ad): Synthesized according to general procedure **M** using masked isocyanate **30a** (0.128 g, 0.600 mmol), arylboroxine **31d** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (80% Hexane/EtOAc) yielding an amorphous off-white solid (0.104 g, 82% yield). TLC R_F = 0.50 in 80% hexanes/EtOAc. ^1H NMR (300 MHz $CDCl_3$) δ 2.52 (1H, s), 7.16 (1H, t, J=7.41 Hz), 7.23-7.30 (2H, m), 7.33-7.45 (4H, m), 7.49 (2H, d, J=7.30 Hz), 7.62 (2H, d, J=7.78 Hz). ^{13}C NMR (100 MHz CDCl3) δ 19.91 (CH_3), 120.01 (CH), 124.66 (CH), 126.01 (CH), 126.72 (CH), 129.21 (CH), 130.38 (CH), 131.37 (CH), 136.54 (C), 136.58 (C), 138.12 (C), 168.21 (C). Data consistent with literature.[74]

[298] Jo, Y.; Ju, J.; Choe, J.; Song, H.; Lee, S. *J. Org. Chem.* **2009**, *74*, 6358.

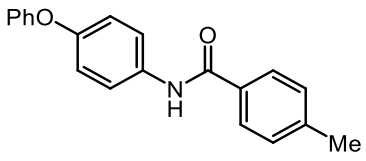


3-fluoro-*N*-phenylbenzamide (table 4.17, 32ae): Synthesized according to general procedure **M** using masked isocyanate **30a** (0.128 g, 0.600 mmol), arylboroxine **31e** (0.146 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The reaction reached completion within 20 hours. The desired product was purified by column chromatography (75% CH_2Cl_2/ hexanes) yielding an amorphous white solid (0.102 g, 79% yield). TLC R_F = 0.22 in 60% CH_2Cl_2/hexanes. ^1H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.82 – 7.71 (m, 4H), 7.55 (td, *J* = 8.0, 5.8 Hz, 1H), 7.40 (tdd, *J* = 8.5, 2.7, 1.0 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.08 (tt, *J* = 7.4, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.6 (C, d, *J* = 2.5 Hz), 162.4 (C, d, *J* = 244.3 Hz), 139.4 (C), 137.7 (C, d, *J* = 6.7 Hz), 131.0 (CH, d, *J* = 8.0 Hz), 129.1 (CH), 124.3 (CH), 120.9 CH, 118.9 (CH, d, *J* = 21.2 Hz), 115.0 (CH, d, *J* = 22.8 Hz). Data consistent with literature.[12]



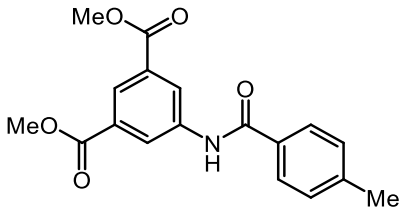
Methyl 4-(phenylcarbamoyl)benzoate (table 4.17, 32af): Synthesized according to general procedure **M** using masked isocyanate **30a** (0.128 g, 0.600 mmol), arylboroxine **31f** (0.192 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The reaction reached completion within 40 hours. The desired product was recrystallized in a 50% EtOAc/Hexane mixture providing the desired compound as a crystalline white solid (0.0914 g, 60% yield). ^1H NMR (500MHz CDCl3) δ 3.96 (3H, s), 7.18 (1H, t, J=7.41 Hz), 7.39 (2H, t, J=7.88 Hz), 7.65 (2H, d, J=7.92 Hz), 7.80-7.87 (1H, br s), 7.93 (2H, d, J=8.27 Hz), 8.15 (2H, d, J=8.30 Hz). ^{13}C NMR (100 MHz $CDCl_3$) δ 52.6 (CH_3), 120.4 (CH), 125.1 (CH), 127.2 (CH), 129.3 (CH), 130.2 (CH), 133.2 (C), 137.7 (C), 139.0 (C), 165.5 (C), 166.3 (C).

Data consistent with **26ag**.

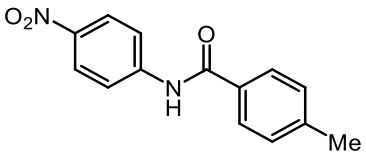


4-methyl-*N*-(4-phenoxyphenyl)benzamide (table 4.18, 32ba): Synthesized according to general procedure **M** using masked isocyanate **30b** (0.1833 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (70% hexanes/EtOAc) yielding an amorphous white solid (0.135 g, 75% yield). TLC R_F = 0.20 in 70% hexanes/EtOAc. ^1H NMR (400MHz, $CDCl_3$) δ 2.43 (3H, s), 6.97-7.12 (5H, m), 7.26-7.36 (4H, m), 7.56-7.63 (2H, m), 7.72-7.76 (1H br

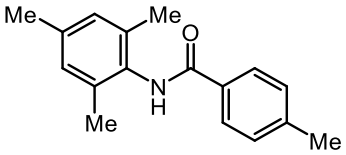
s.), 7.74-7.79 (2H, m). ^{13}C NMR (100MHz CDCl3) δ 21.62 (CH_3), 118.61 (CH), 119.80 (CH), 122.12 (CH), 123.23 (CH), 127.16 (CH), 129.58 (CH), 129.87 (CH), 132.13 (C), 133.66 (C), 142.52 (C), 153.77 (C), 157.69 (C), 165.78 (C). IR (film): 3394, 3358, 3062, 1713, 1651, 1589, 1603 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{20}H_{17}NO_2Na$ $[M+Na]^+$: 326.1157. Found: 326.1157.



Dimethyl 5-(4-methylbenzamido)isophthalate (table 4.18, 32ca): Synthesized according to general procedure **M** using masked isocyanate **30c** (0.214 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (80% Hexane/EtOAc) yielding an amorphous white solid (0.124 g, 64% yield). TLC R_F = 0.24 in 80% Hexane/EtOAc. ^{1}H NMR (500MHz $CDCl_3$) δ 2.44 (3H, s), 3.95 (6H, s), 7.32 (2H, d, J=7.95 Hz), 7.80 (2H, d, J=8.10 Hz), 7.95-7.99 (1H, br s), 8.46-8.47 (1H, m), 8.51-8.53 (2H, m). ^{13}C NMR (125MHz $CDCl_3$) δ 21.68 (CH_3), 52.64 (CH_3), 125.26 (CH), 126.56 (CH), 127.27 (CH), 129.72 (CH), 131.44 (C), 131.58 (C), 138.81 (C), 143.11 (C), 165.87 (C), 166.10 (C). Data is consistent with **26ca**.



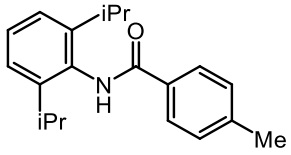
4-methyl-*N*-(4-nitrophenyl)benzamide (table 4.18, 32da): Synthesized according to general procedure **M** using masked isocyanate **30d** (0.154 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (80% Hexane/EtOAc) yielding an amorphous white solid (0.0922 g, 60% yield). TLC R_F = 0.26 in 80% Hexane/EtOAc. ^{1}H NMR (500MHz DMSO-d_6) δ 2.40 (3H, s), 7.37 (2H, d, J=7.98 Hz), 7.90 (2H, d, J=8.11 Hz), 8.06 (2H, d, J=9.23 Hz), 8.26 (2H, d, J=9.18 Hz), 10.67-10.75 (1H, br s). ^{13}C NMR (500MHz DMSO-d_6) δ 21.05 (CH_3), 119.8 (CH), 124.8 (CH), 128.0 (CH), 129.0 (CH), 131.3 (C), 142.4 (C), 145.63 (C), 166.05 (C). Data consistent with literature.[299]



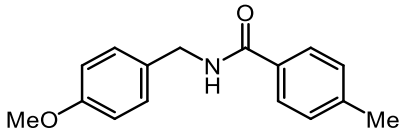
***N*-mesityl-4-methylbenzamide (table 4.18, 32ea):** Synthesized according to general procedure **M** using masked isocyanate **30g** (0.153 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, $6.00x10^{-3}$ mmol), and SPhos (0.0120, 4.93 mg). The

[299] Sharma, N.; Sekar, G. *Adv. Synth. Cat.* **2016**, *358*, 314.

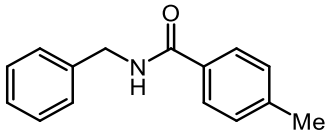
desired product was purified by column chromatography (CH_2Cl_2 to 5% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.102 g, 67% yield). TLC R_F = 0.16 in CH_2Cl_2. ^{1}H NMR (400MHz $CDCl_3$) δ 2.23 (6H, s), 2.29 (3H, s), 2.43 (3H, s), 6.93 (2H, s), 7.29 (2H, d, J=7.95 Hz), 7.81 (2H, d, J=8.08 Hz). ^{13}C NMR (100MHz $CDCl_3$) δ 18.5 (CH_3), 21.1 (CH_3), 21.6 (CH_3), 31.0 (CH_3), 127.3 (CH), 129.1 (CH), 129.5 (CH), 131.4 (C), 131.9 (C), 135.4 (C), 137.1 (C), 142.3 (C), 166.0 (C). Data is consistent with **26ga**.



***N*-(2,6-diisopropylphenyl)-4-methylbenzamide (table 4.18, 32fa):** Synthesized according to general procedure **M** using masked isocyanate **30g** (0.178 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, 6.00x10^{-3} mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (20% EtOAc/ hexanes) yielding an amorphous white solid (0.047 g, 26% yield). TLC R_F = 0.27 in 15% EtOAc/hexanes. ^{1}H NMR (300MHz $CDCl_3$) δ 1.22 (12H, d, J=6.88 Hz), 2.45 (3H, s), 3.14 (2H, m, J=6.92 Hz), 7.19-7.24 (2H, m), 7.29-7.37 (3H, m), 7.82-7.85 (2H, m). ^{13}C NMR (125MHz $CDCl_3$) δ 21.64 (CH_3), 23.79 (CH_3), 29.03 (CH), 123.66 (CH), 127.32 (CH), 128.55 (CH), 129.58 (CH), 131.39 (C), 131.90 (C), 142.39 (C), 146.52 (C), 166.94 (C). Data consistent with literature.[286]



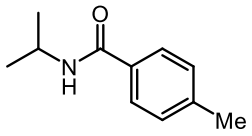
***N*-(4-methoxybenzyl)-4-methylbenzamide (table 4.18, 32ga):** Synthesized according to general procedure **M** using masked isocyanate **30g** (0.154 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, 6.00x10^{-3} mmol), and SPhos (0.0120, 4.93 mg). The reaction reached completion within 16 hours. The desired product was purified by column chromatography (80% Hexane/EtOAc) yielding an amorphous white solid (0.0900 g, 59% yield). TLC R_F = 0.16 80% Hexane/EtOAc. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (3H, s), 3.79 (3H, s), 4.54 (2H, d, J=5.58 Hz), 6.50 (1H, br s.), 6.86 (2H, td, J=2.49, 9.54 Hz), 7.20 (2H, d, J=7.90 Hz), 7.26 (2H, d, J=8.70 Hz), 7.68 (2H, d, J=8.15 Hz). ^{13}C NMR (125 MHz) δ 21.45 (CH_3), 43.55 (CH_2), 55.32 (CH_3), 114.13 (CH), 126.99 (CH), 129.21 (CH), 129.28 (CH) 130.47 (C), 131.61 (C), 141.88 (C), 159.07 (C), 167.25 (C). Data consistent with literature.[300]



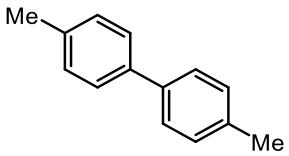
***N*-benzyl-4-methylbenzamide (table 4.18, 32ha):** Synthesized according to general procedure **M** using masked isocyanate **30h** (0.136 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, 6.00x10^{-3} mmol), and SPhos (0.0120, 4.93 mg). The

[300] MacMillan, D. S.; Murray, J.; Sneddon, H. F.; Jamieson, C.; Watson, A. J. B. *Green Chem.* **2013**, *15*, 596.

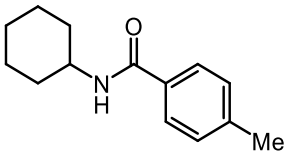
desired product was purified by column chromatography (CH_2Cl_2) yielding an amorphous white solid (0.102 g, 75% yield). TLC R_F = 0.17 in CH_2Cl_2. ^{1}H-NMR (300MHz $CDCl_3$) δ 2.40 (3H, s), 4.65 (2H, d, J=5.71 Hz), 6.26-6.37 (1H, br s), 7.19-7.25 (2H, m), 7.27-7.38 (5H, m), 7.69 (1H, d, J=8.35 Hz). ^{13}C-NMR (125MHz $CDCl_3$) δ 21.6 (CH_3), 44.3 (CH_2), 127.1 (CH), 127.8 (CH), 128.1 (CH), 128.9 (CH), 129.4 (CH), 131.7 (C), 138.5 (C), 142.1 (C), 167.4 (C). Data is consistent with literature.[287]



***N*-isopropyl-4-methylbenzamide (table 4.18, 32ia):** Synthesized according to general procedure **M** using masked isocyanate **30i** (0.107 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, 6.00×10^{-3} mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (80% Hexane/EtOAc) yielding an amorphous white solid (0.0609 g, 57% yield). TLC R_F = 0.32 in 80% Hexane/EtOAc. ^{1}H NMR (500MHz $CDCl_3$) δ 1.25 (6H, d, J=6.55 Hz), 2.38 (3H, s), 4.28 (1H, m, J=6.71 Hz), 5.81-5.94 (1H, br s), 7.21 (2H, d, J=7.90 Hz), 7.64 (2H, d, J=8.03 Hz). ^{13}C NMR (500MHz CDCl3) δ 21.55 (CH_3), 23.05 (CH_3), 41.92 (CH), 126.92 (CH), 129.29 (CH), 132.27 (C), 141.76 (C), 166.73 (C). Data consistent with literature.[301]



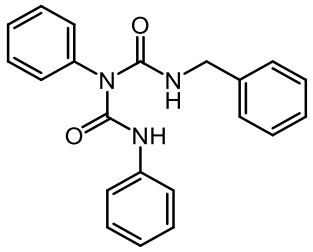
4,4'-dimethyl-1,1'-biphenyl (eq. 4.5, 33aa): Isolated during the isolation of **32ja** yielding an amorphous white solid (0.0037 g, 4% yield). Data was consistent with literature.[297]



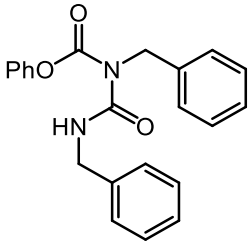
***N*-cyclohexyl-4-methylbenzamide (table 4.18, 32ja):** Synthesized according to general procedure **M** using masked isocyanate **30j** (0.131 g, 0.600 mmol), arylboroxine **31a** (0.141 g, 0.400 mmol, 2.00 equiv "Ar-B"), Et_3N (0.167 mL, 1.20 mmol), $Pd(OAc)_2$ (1.35 mg, 6.00×10^{-3} mmol), and SPhos (0.0120, 4.93 mg). The desired product was purified by column chromatography (20% EtOAc/CH_2Cl_2) yielding an amorphous white solid (0.0927 g, 71% yield). TLC R_F = 0.20 in 20% EtOAc/Hexane. ^{1}H NMR (500MHz $CDCl_3$) δ 1.14-1.27 (3H, m), 1.37-1.48 (2H, m), 1.60-1.69 (1H, m), 1.70-1.79 (2H, m), 1.98-2.06 (2H, m), 2.38 (3H, s), 3.94-4.01 (1H, m), 5.87-5.98 (1H, br s), 7.21 (2H, d, J=7.90), 7.64 (2H, d, J=7.90). ^{13}C NMR (125MHz $CDCl_3$) δ 21.53

[301] (a) Evans, V.; Mahon, M. F.; Webster, R. L. *Tetrahedron* **2014**, *70*, 7593. (b) Rolfe, A.; Probst, D. A.; Volp, K. A.; Omar, I.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2008**, *73*, 8785.

(CH_3), 25.05 (CH_2), 25.73 (CH_2), 33.41 (CH_2), 48.68 (CH), 126.92 (CH), 129.26 (CH), 132.38 (C), 141.69 (C), 166.64 (C). Data consistent with literature.[288]

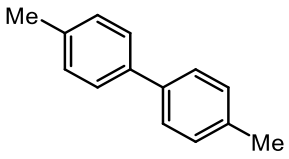


3-Benzyl-1-phenyl-1-(phenylcarbamoyl)urea (scheme 4.6, 35a): Synthesized according to general procedure **M** using urea **34a** (0.0420 g, 0.200 mmol) masked isocyanate **30a** (0.0426 g, 0.200 mmol), Et_3N (0.056 mL, 0.40 mmol), $Pd(OAc)_2$ (0.450 mg, $2.00x10^{-3}$ mmol), and SPhos ($4.00x10^{-3}$ mmol, 1.64 mg). The reaction was concentrated under reduced pressure after 16 hours. The desired product was purified by column chromatography (100 % CH_2Cl_2) yielding an amorphous white solid (3.9 mg, 6% yield). TLC R_F = 0.16 in CH_2Cl_2. ^1H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 7.52 – 7.38 (m, 5H), 7.36 – 7.31 (m, 2H), 7.31 – 7.23 (m, 4H), 7.19 (d, *J* = 7.4 Hz, 3H), 7.10 (t, *J* = 5.9 Hz, 1H), 7.00 (dd, *J* = 7.9, 6.7 Hz, 1H), 4.23 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.0 (C), 152.8 (C), 139.9 (C), 138.7 (C), 137.3 (C), 130.4 (CH), 130.1 (CH), 129.3 (CH), 129.1 (CH), 128.7 (CH), 127.2 (CH), 127.1 (CH), 123.8 (CH), 120.1 (CH), 44.1 (CH_2). IR (film): 2922, 2852, 1707, 1656, 1590, 1497 cm^{-1}. HRMS (EI): Exact mass calcd for $C21H19N_3O_2$ $[M]^+$: 345.14773. Found: 345.14602.



Phenyl benzyl(benzylcarbamoyl)carbamate (table 4.19, 36a): Isolated during small scale reactions probing alternative arylboronic acid ester derivatives. Synthesized according to general procedure **M** using masked isocyanate **30a** (0.0426 g, 0.200 mmol), Et_3N (0.056 mL, 0.40 mmol), $Pd(OAc)_2$ (0.450 mg, $2.00x10^{-3}$ mmol), and SPhos ($4.00x10^{-3}$ mmol, 1.64 mg). The desired product was purified by column chromatography (80% Hexane/EtOAc) yielding an amorphous white solid and used to confirm NMR yields reported in table 4.19. TLC R_F = 0.48 in 80% Hexane/EtOAc. ^1H NMR (300MHz $CDCl_3$) δ 4.53 (2H, d, J=6.21 Hz), 5.19 (2H, s), 6.95 (2H, d, J=7.48 Hz), 7.27-7.45 (13H, m), 8.85-8.94 (1H, br s). ^{13}C NMR (125MHz $CDCl_3$) δ 45.2 (CH_2), 47.4 (CH_2), 121.7 (CH), 126.6 (C), 127.6 (C), 127.6 (C), 127.8 (C), 128.0 (C), 128.7 (C), 128.8 (C), 129.7 (C), 138.1 (C), 138.1 (C), 150.1 (C), 154.3 (C), 155.3 (C).[302] IR (film): 3227, 2968, 2923, 2872, 1657, 1613, 1538, 1510 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{22}H_{20}N_2O_3Na$ [M+Na]: 383.1364. Found: 383.1372.

[302] HMCB experiments revealed overlapping carbon peaks at 138.1.



4,4'-dimethyl-1,1'-biphenyl (eq. 4.6, 33aa): Isolated during the scale up of table 4.22, entry 3 yielding an amorphous white solid (0.0256 g, 23% yield). Data was consistent with literature.[277]

Appendix I

Claims to Original Research

1) Development of a novel azomethine imine reactivity manifold for *N*-isothiocyanate cascade reactions (section 2.2)
2) Development of the first acid catalyzed *N*-isocyanate cascade reaction (section 2.3).
3) Development of the first cascade reaction of *N*-isocyanates undergoing C-C bond formation (section 2.4).
4) Development of novel syntheses of imidazolones, thiazolidines, 1,2,4-triazin-3(2H)-ones, 1,2,4-triazinones, and 5-aminopyridazinones (chapter 2).
5) Development of the first general procedures for the synthesis of hydroxamates/hydrazides from blocked *O*- and *N*-isocyanates using both carboxylic acids and Grignard reagents (chapter 3).
6) Development of the first highly chemoselective catalytic amidation of blocked isocyanates using rhodium catalysis.
7) Development of the first palladium catalyzed amidation of blocked isocyanates.

Publications from this Work

1) Diversity oriented heterocyclic synthesis using divergent reactivity of *N*-substituted iso(thio)cyanates. Vincent-Rocan, J.-F.*; Derasp, J. S.; Beauchemin*, A. M. *Chem. Commun.* **2015**, *51*, 16405.
2) Divergent reactivity of *N*-isocyanates with primary and secondary amines: Access to pyridazinones and triazinones. Derasp, J. S.; Vincent-Rocant, J. F.; Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 658.
3) A cascade synthesis of 1,2,4-Triazin-3(2H)-ones using nitrogen-substituted isocyanates. Dahab, M. A.; Derasp, J. S.; Beauchemin, A. M. *Synlett* **2017**, *28*, 456.
4) Rhodium-catalyzed synthesis of amides from functionalized blocked isocyanates. Derasp, J. S.; Beauchemin, A. M. *submitted.*

Publications from Graduate Studies (Outside this Work)

1) Carbohydrates as efficient catalysts for the hydration of α-amino nitriles. Chitale, S.; Derasp, J. S.; Hussain, B.; Tanveer, K.; Beauchemin, A. M. *Chem. Commun.* **2016**, *52*, 13147.

Presentations from this work

Oral Presentations

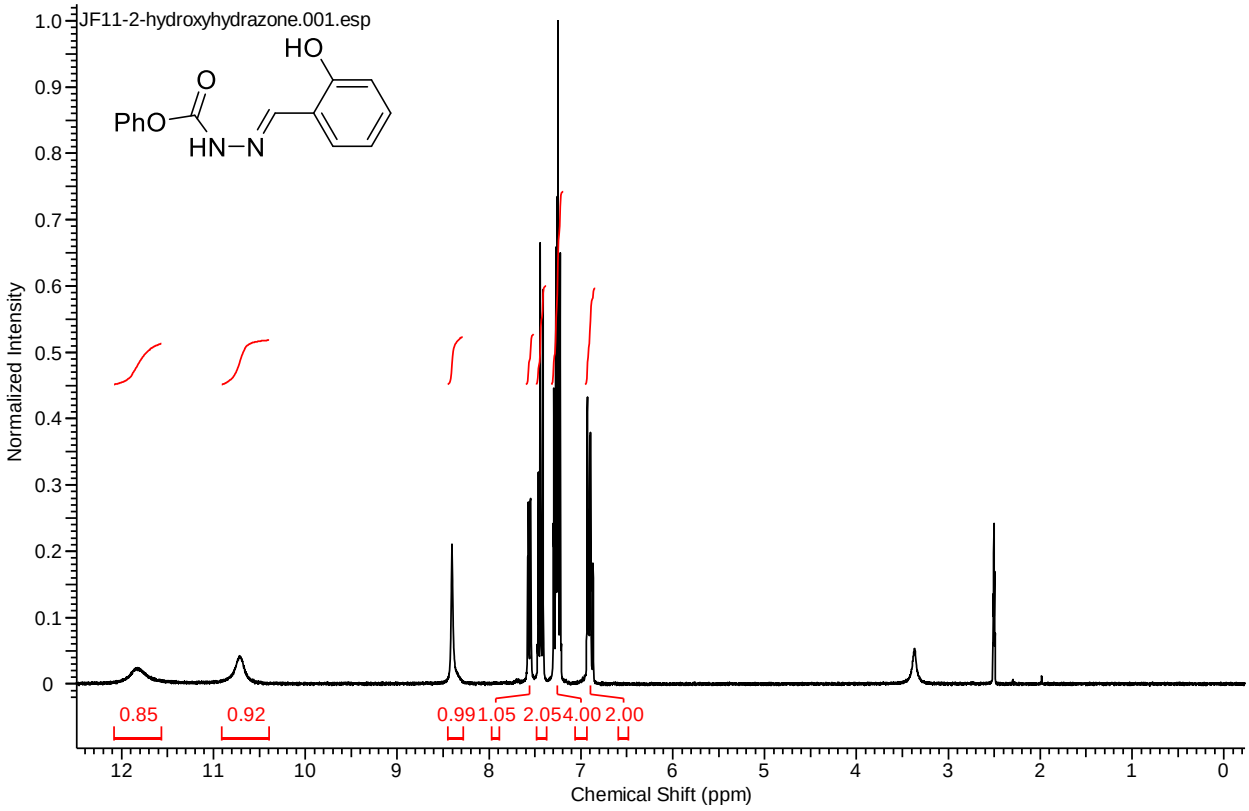
1) Rhodium catalyzed synthesis of Amides from Highly Functionalized Masked Isocyanates. Ottawa Carleton Chemistry Institute Day. June 2018
2) Ambiphilic Isocyanates and their Application in synthesis. QOMSBOC. November 2018.

Poster Presentation

1) Divergent Reactivity of *N*-isocyanates with Primary and Secondary Amines: Access to Pyridazinones and Triazinones. Canadian Chemistry Conference. June 2017
2) Diversity-Oriented Heterocyclic Synthesis using Divergent Reactivity of *N*-substituted Iso(thio)cyanates. QOMSBOC. November 2015.

Appendix II

Spectra


JF11-2-hydroxyhydrazone.001.esp
HO
O
PhO
HN–N
Normalized Intensity
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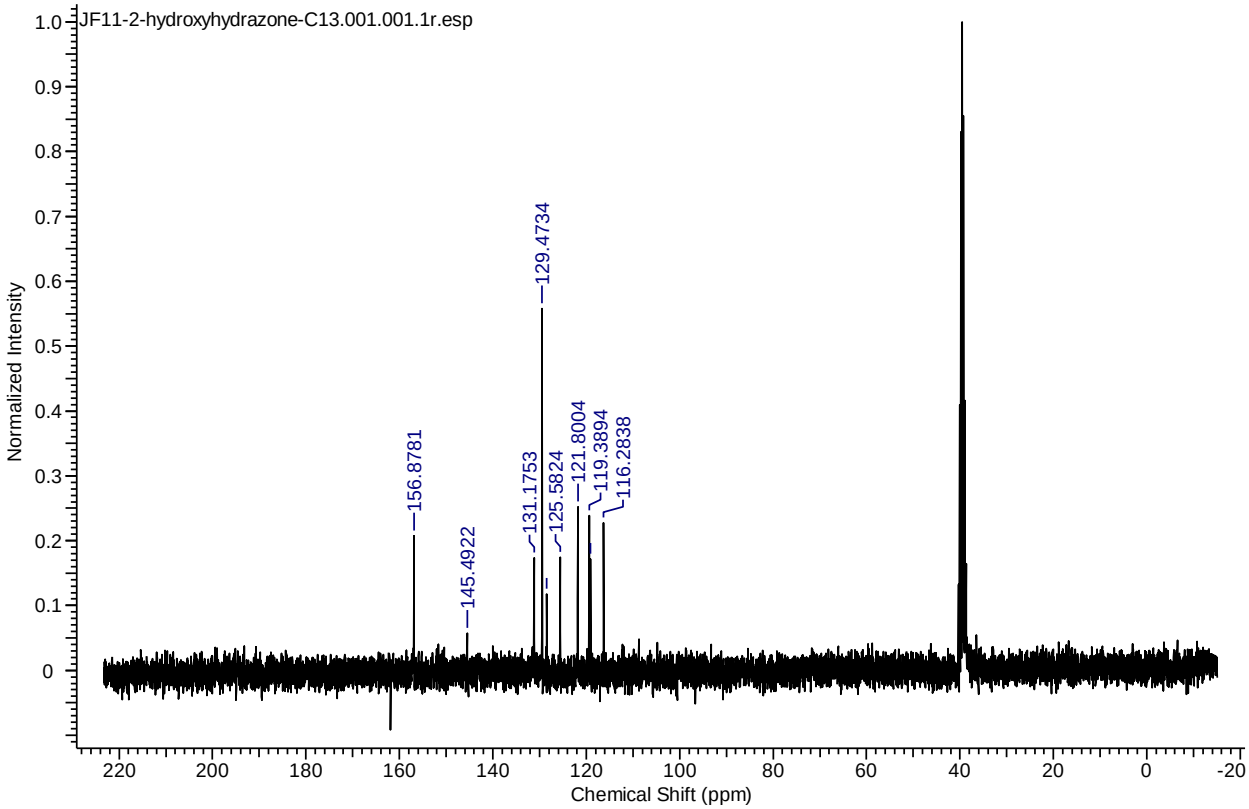
0.92
0.99
1.05
2.05
4.00
2.00
Chemical Shift (ppm)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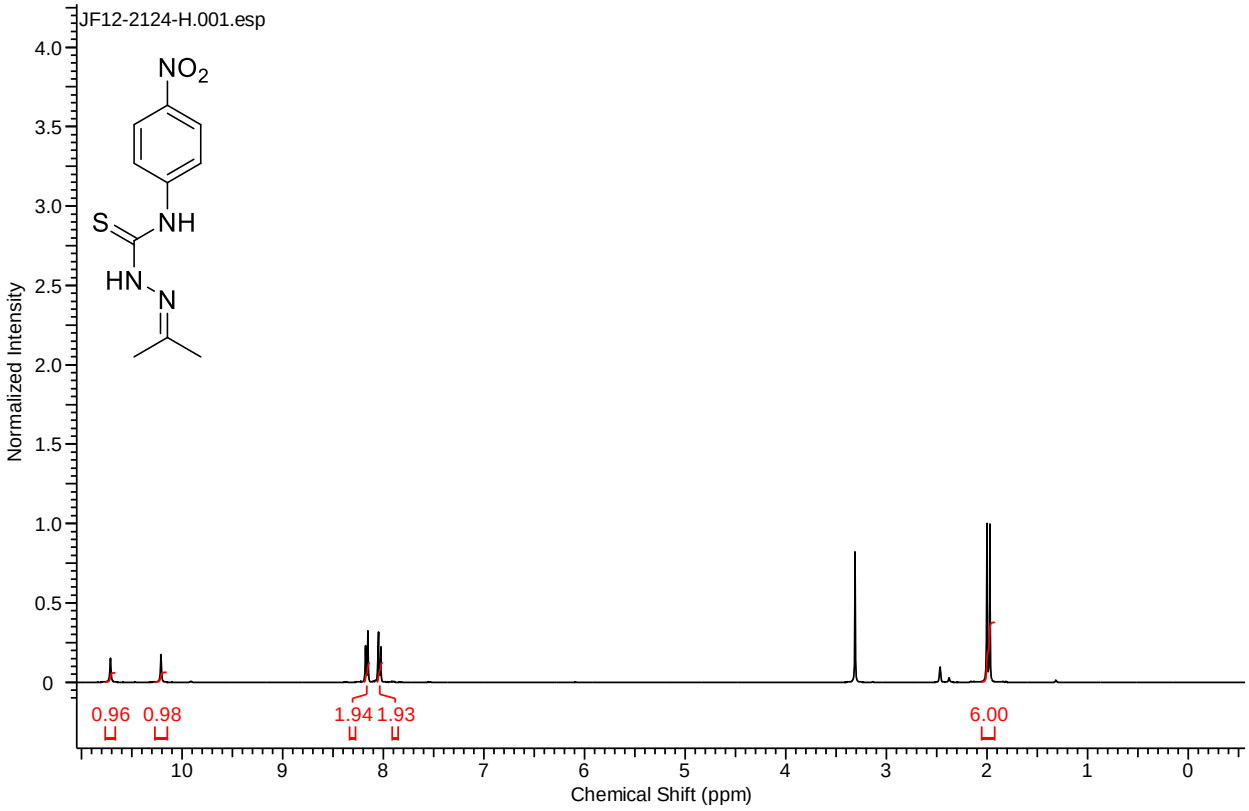
119.3894
116.2838
Chemical Shift (ppm)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NO2
NH
S
HN
N
Normalized Intensity
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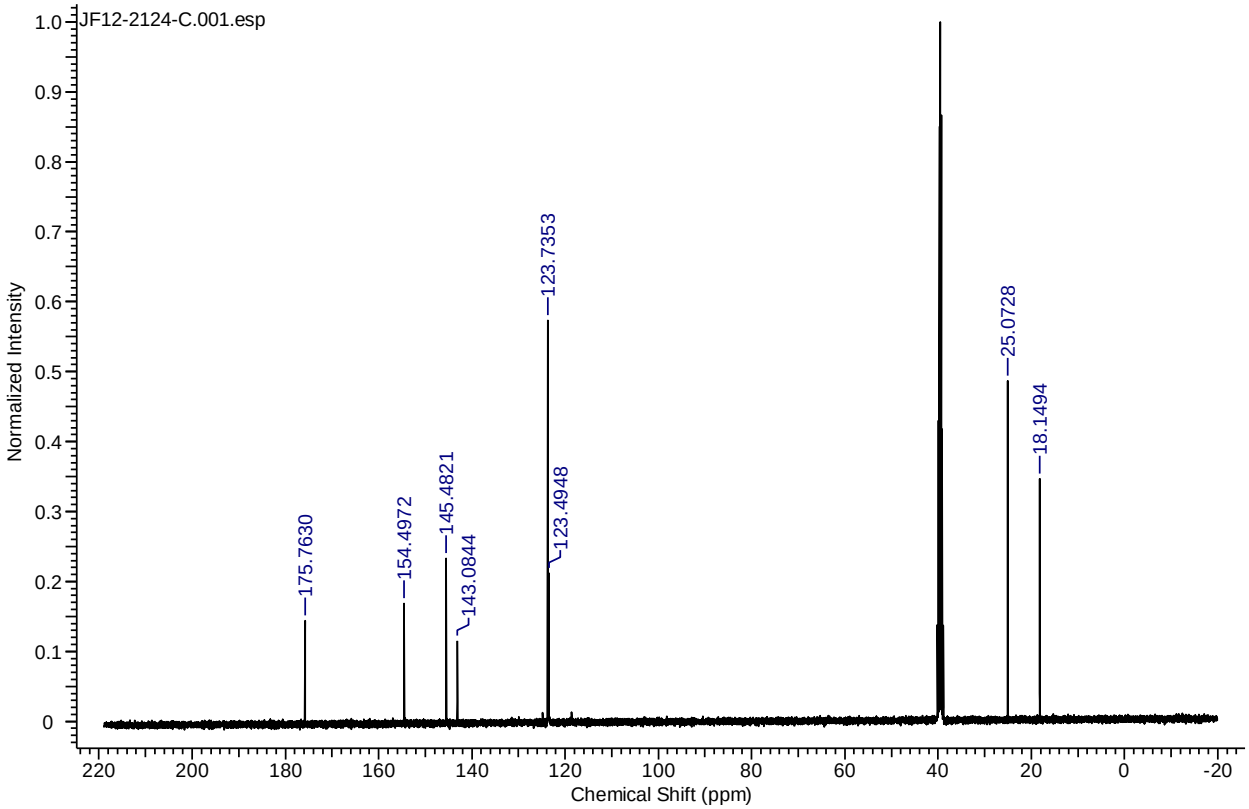
0.98
1.94
1.93
6.00
Chemical Shift (ppm)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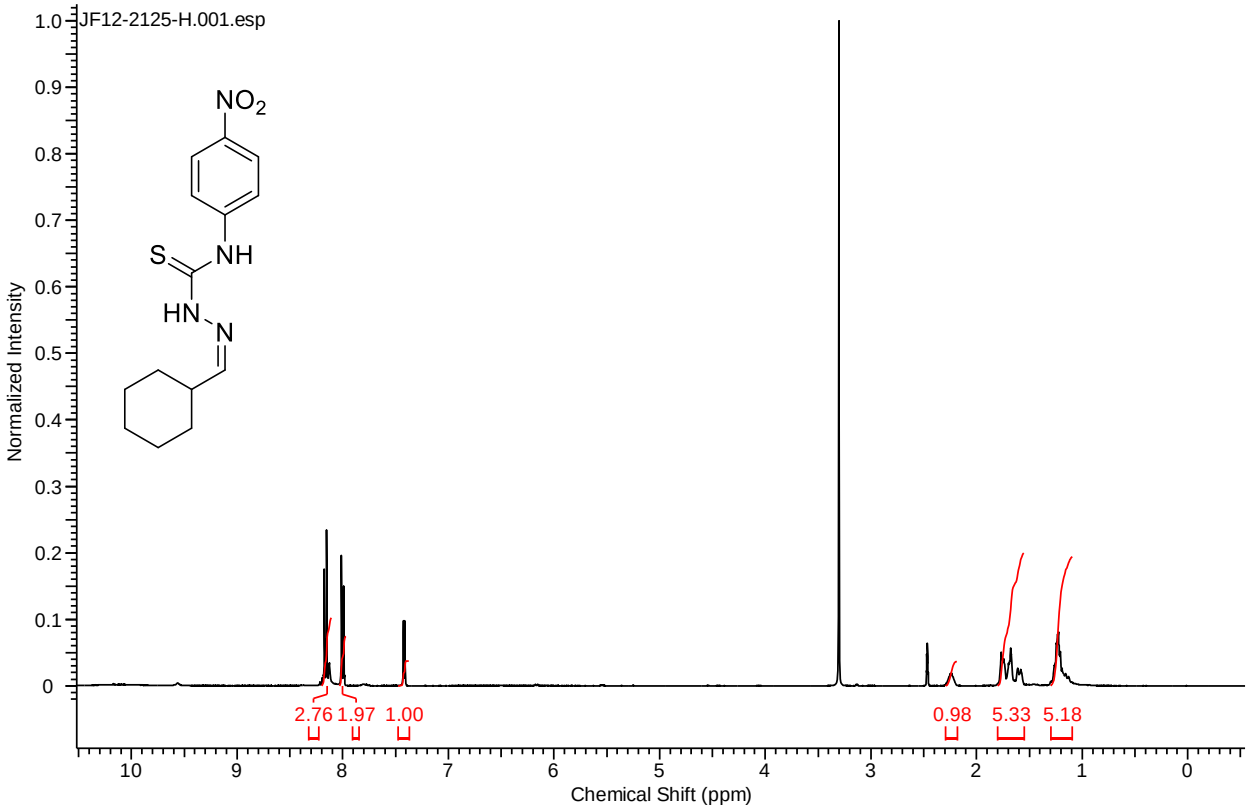
123.7353
123.4948
25.0728
18.1494
Normalized Intensity
Chemical Shift (ppm)


JF12-2125-H.001.esp
NO2
S
NH
HN
N
Normalized Intensity
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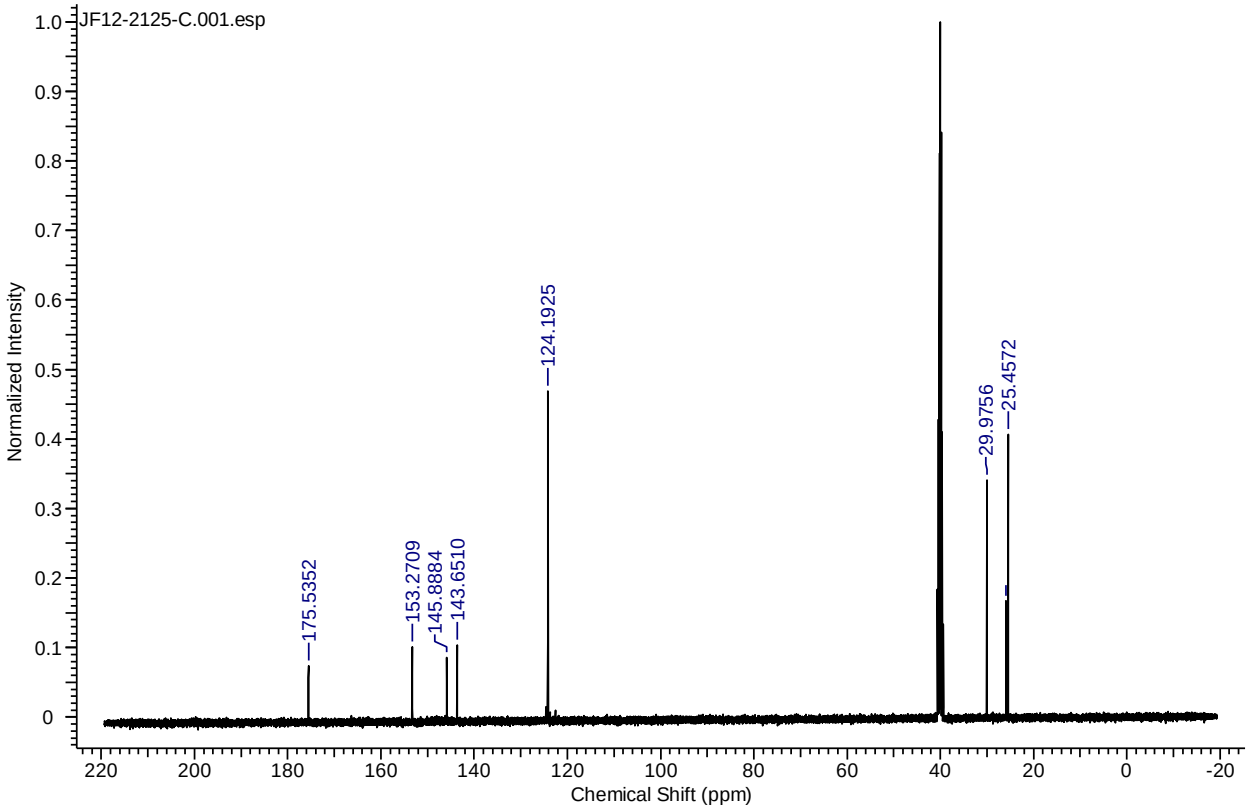
1.00
0.98
5.33
5.18
Chemical Shift (ppm)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Normalized Intensity
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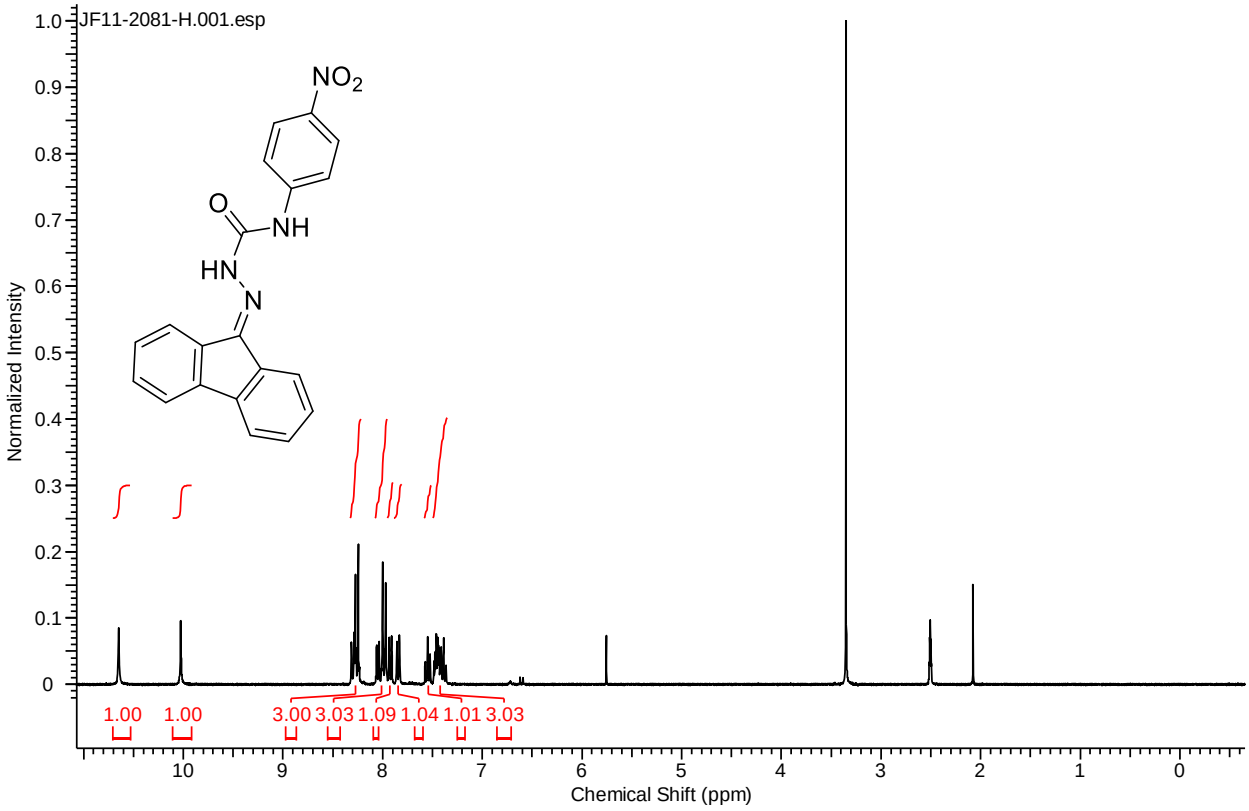
124.1925
29.9756
25.4572
Chemical Shift (ppm)


JF11-2081-H.001.esp
NO2
O
NH
HN
N
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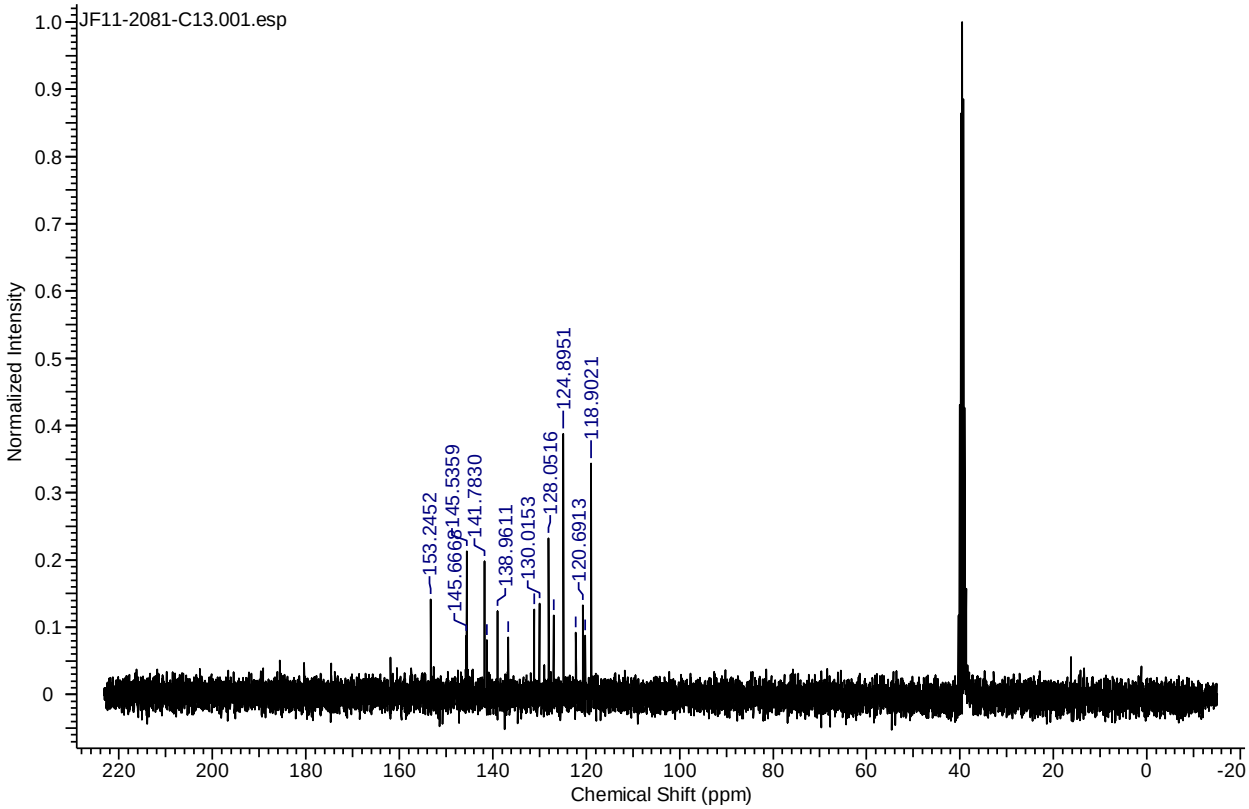
1.00
3.00
3.03
1.09
1.04
1.01
3.03
Chemical Shift (ppm)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Normalized Intensity
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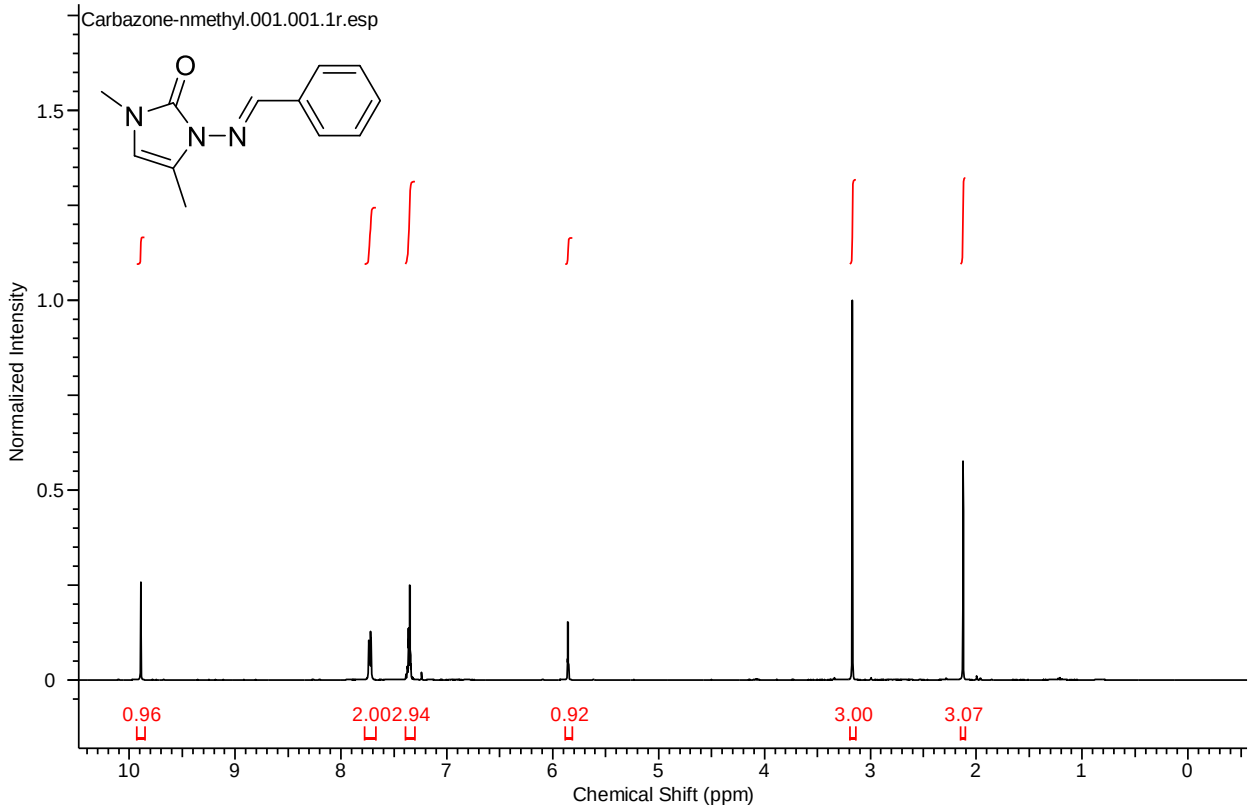
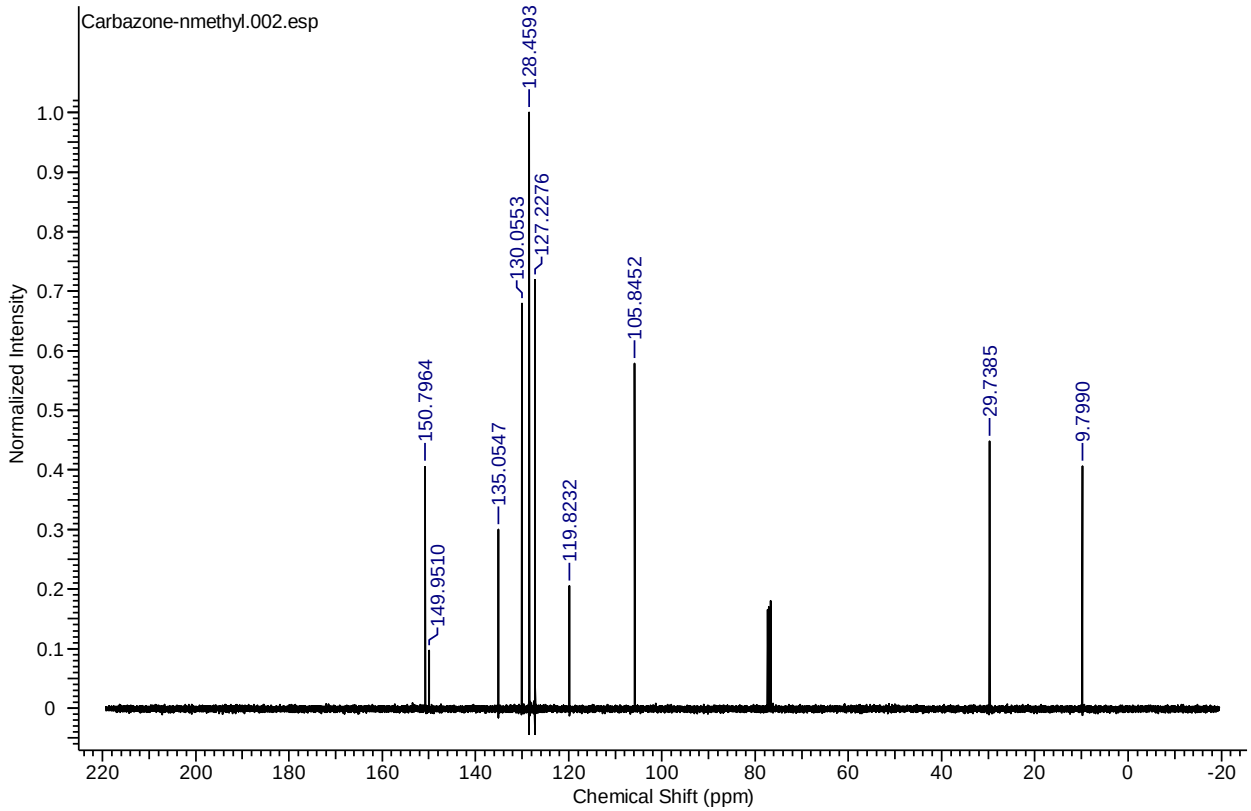
124.8951
120.6913
118.9021
Chemical Shift (ppm)


Carbazone-nmethyl.001.001.1r.esp
O
N
N–N
Normalized Intensity
1.5
1.0
0.5
0
0.96
2.00
2.94
0.92
3.00
3.07
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Carbazone-nmethyl.002.esp
Normalized Intensity
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0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
150.7964
149.9510
135.0547
130.0553
128.4593
127.2276
119.8232
105.8452
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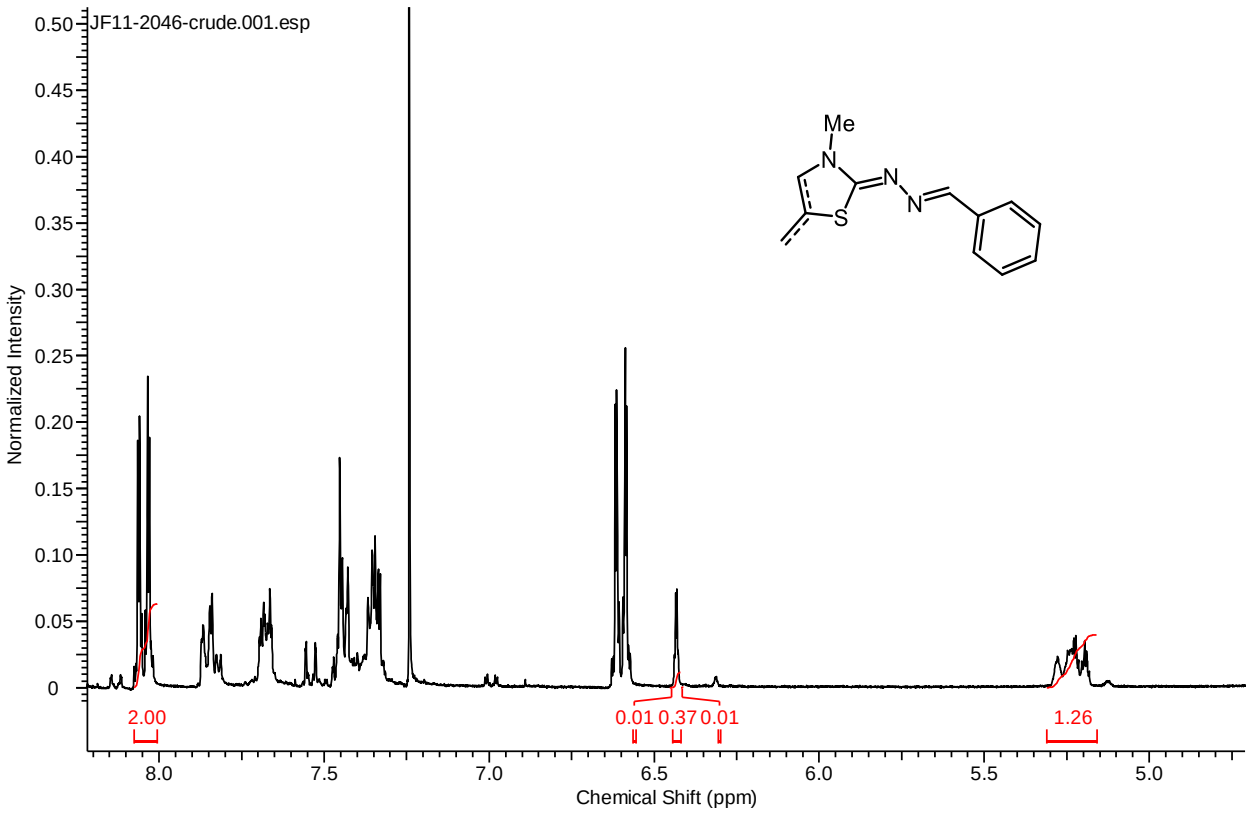
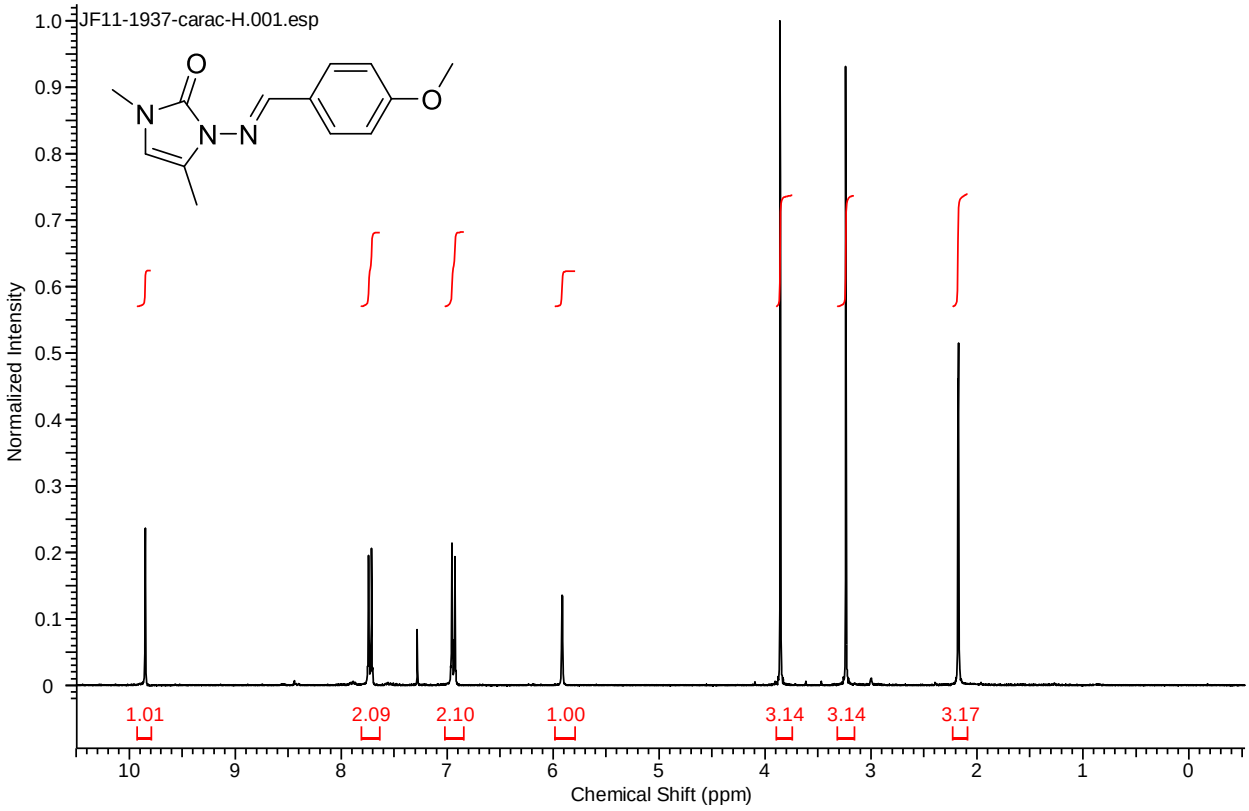
9.7990
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)



According to paranitroaniline production: 37% isomerize and 63 % of desired product.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Normalized Intensity
Chemical Shift (ppm)
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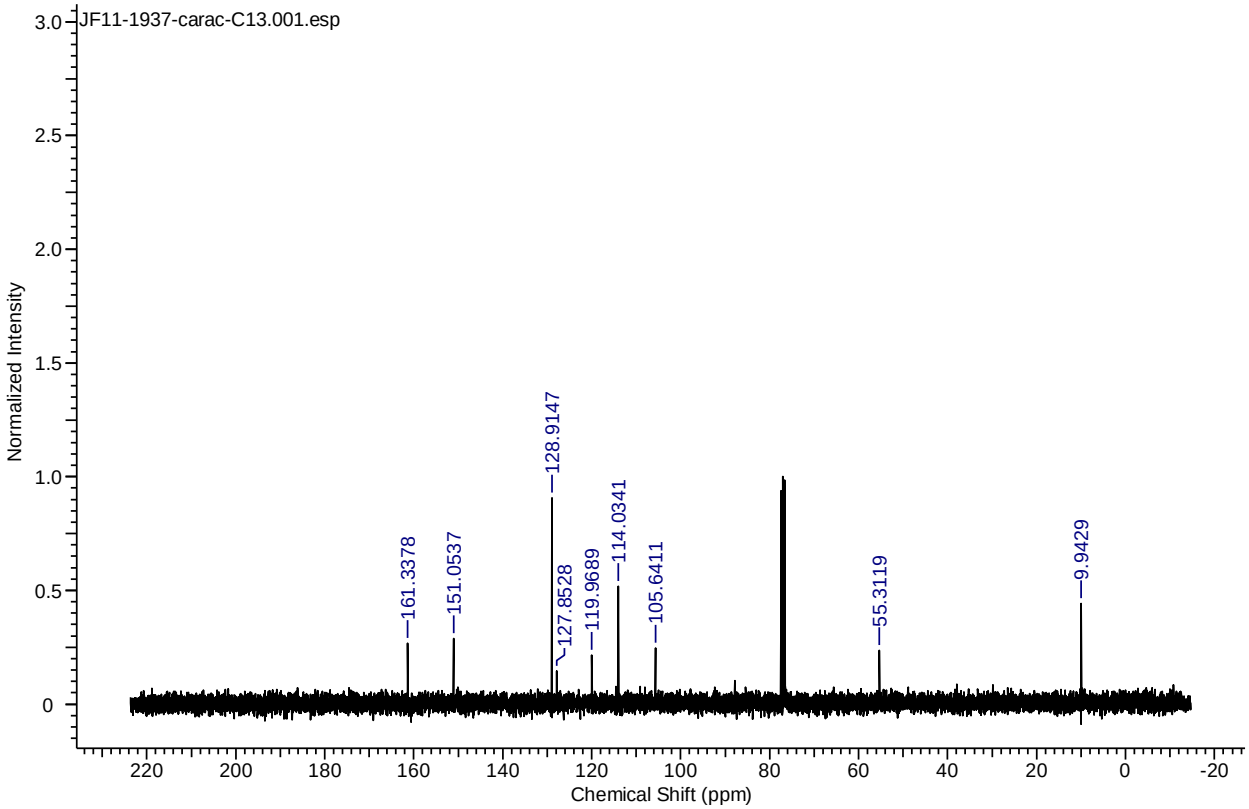
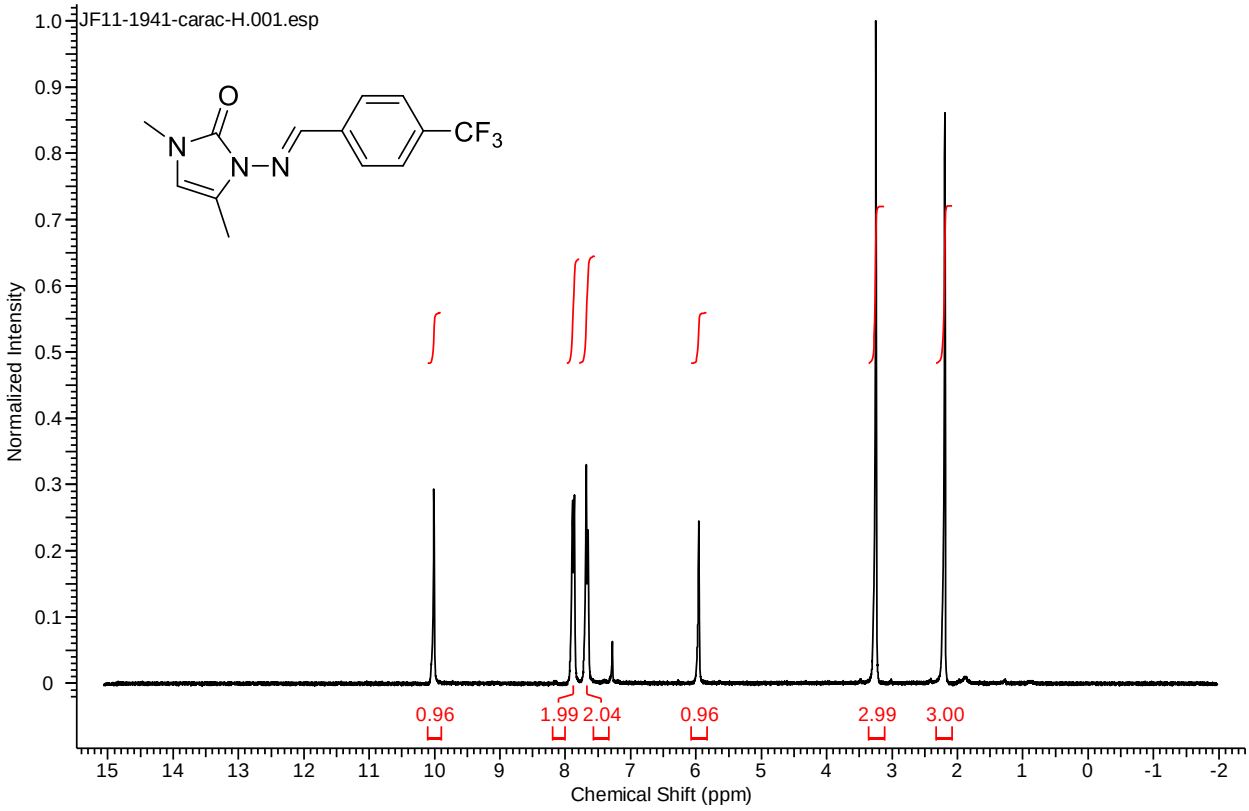
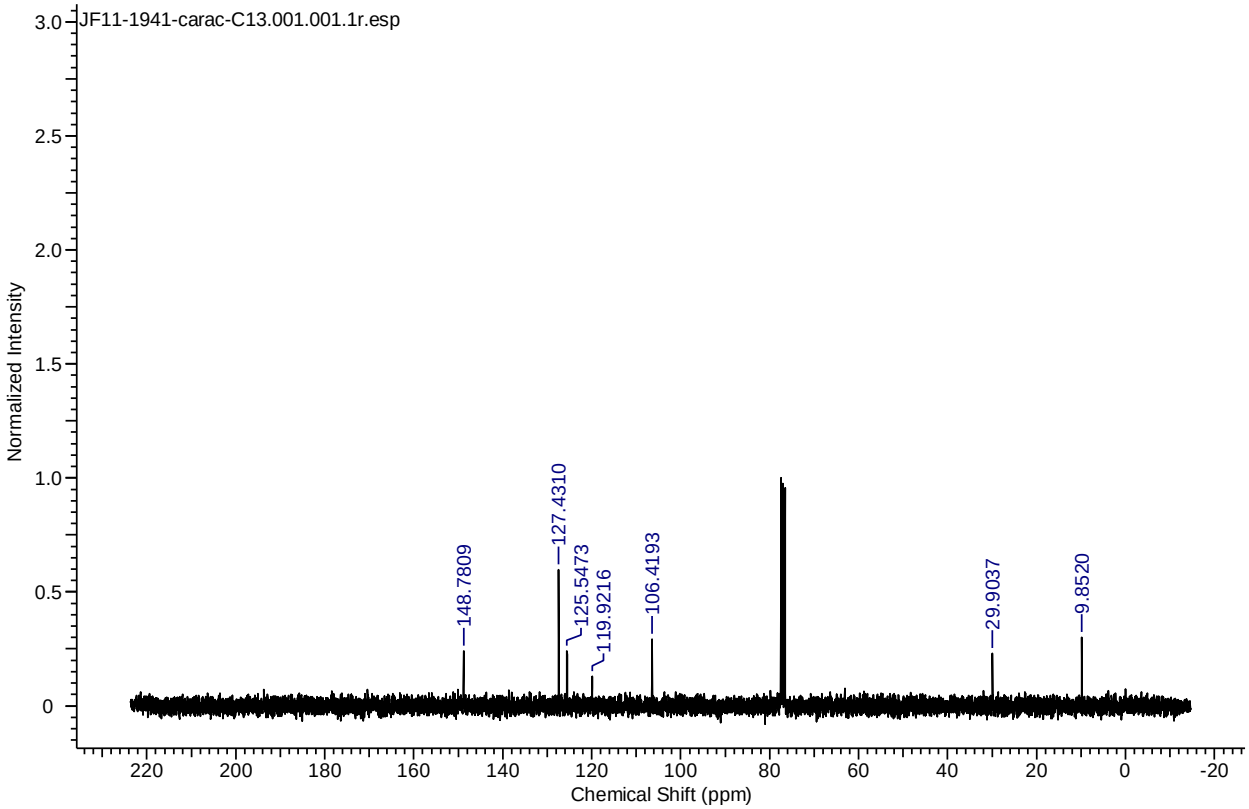
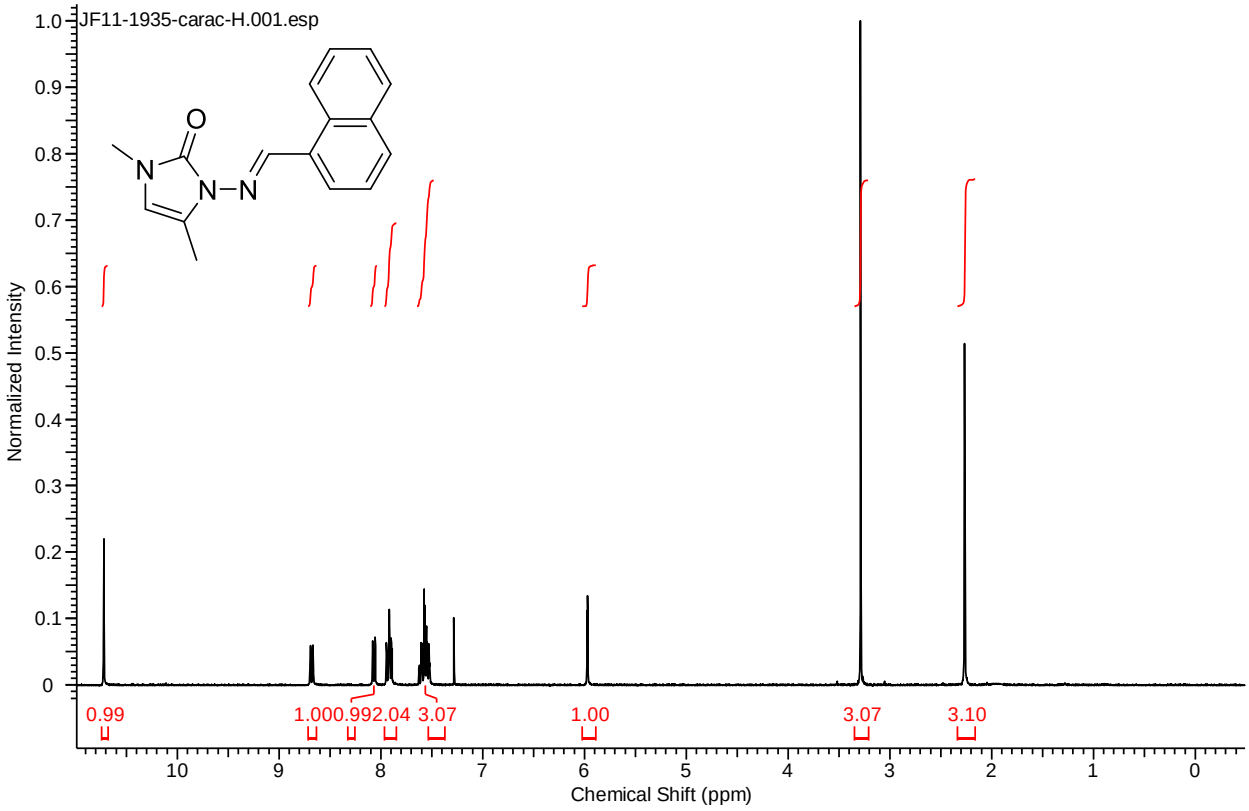
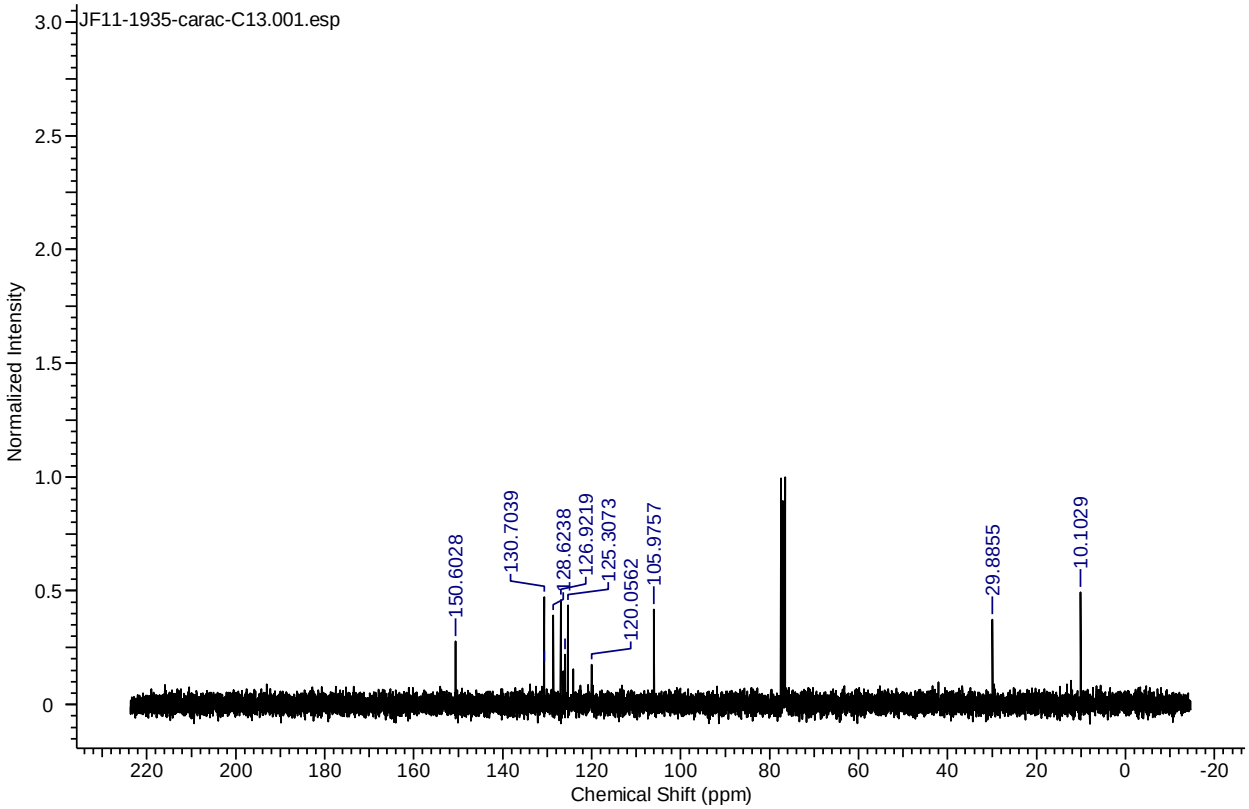
2.09
2.10
1.00
3.14
3.14
3.17

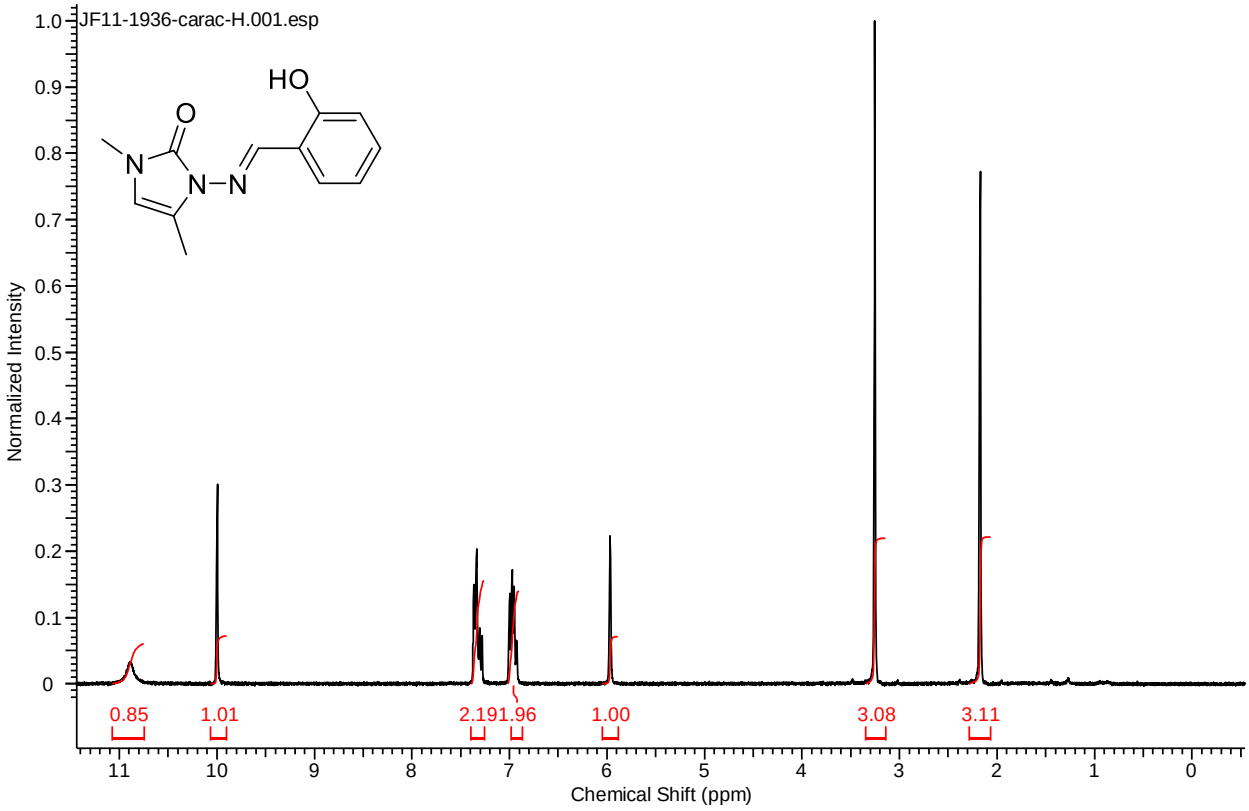

JF11-1937-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
161.3378
151.0537
128.9147
127.8528
119.9689
114.0341
105.6411
55.3119
9.9429

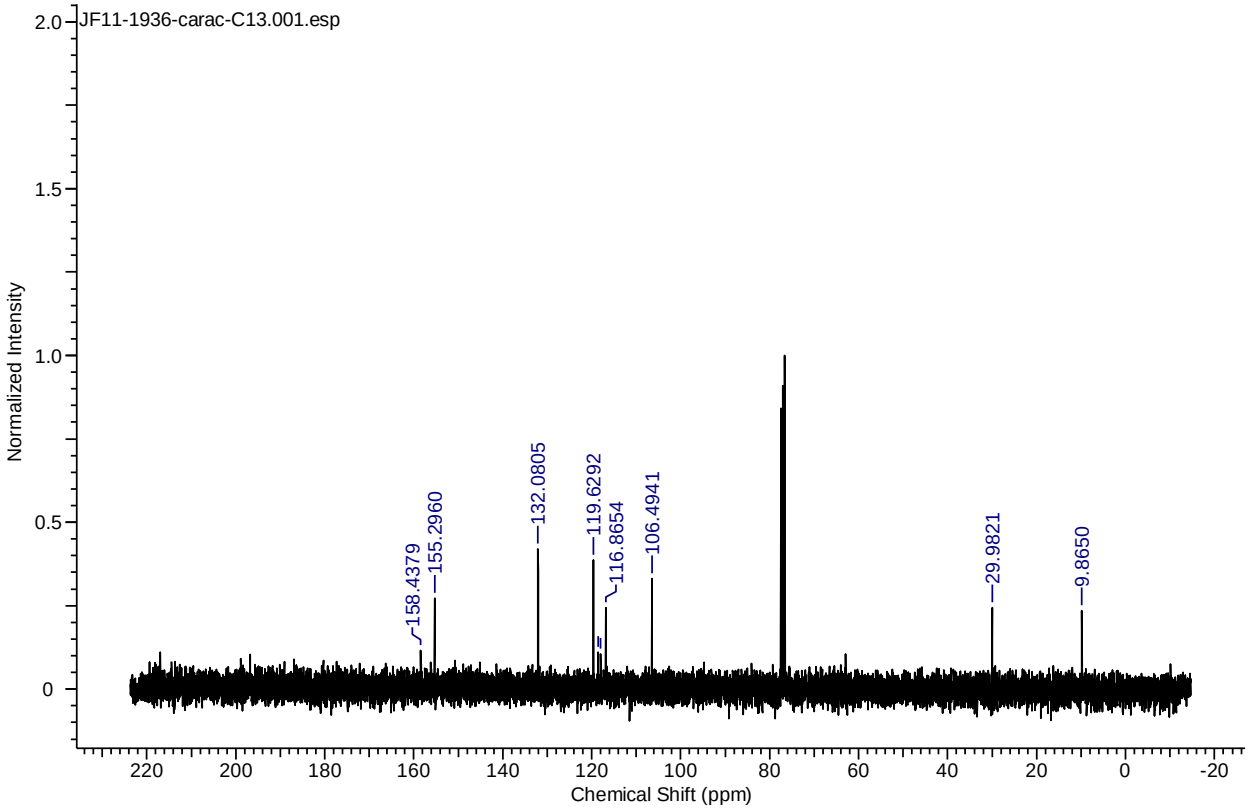

JF11-1941-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.96
1.99
2.04
0.96
2.99
3.00

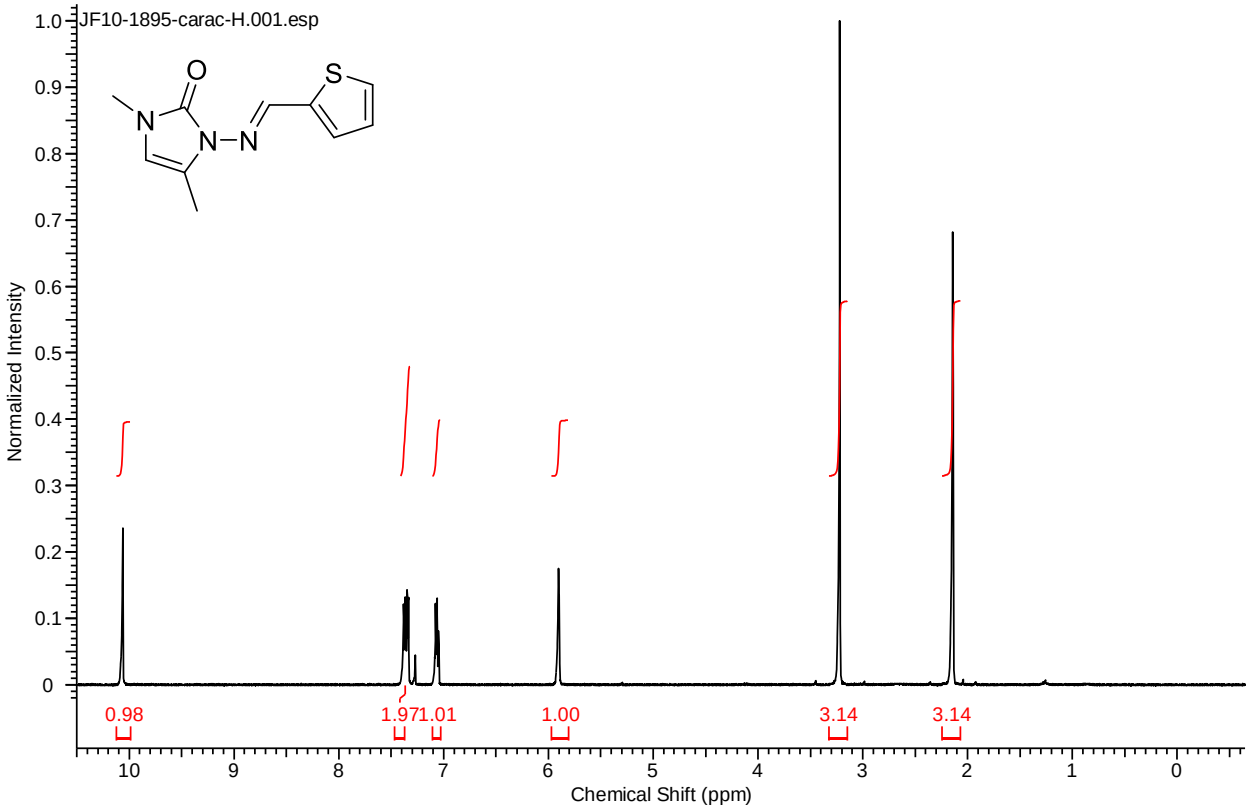

JF11-1941-carac-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
148.7809
127.4310
125.5473
119.9216
106.4193
29.9037
9.8520

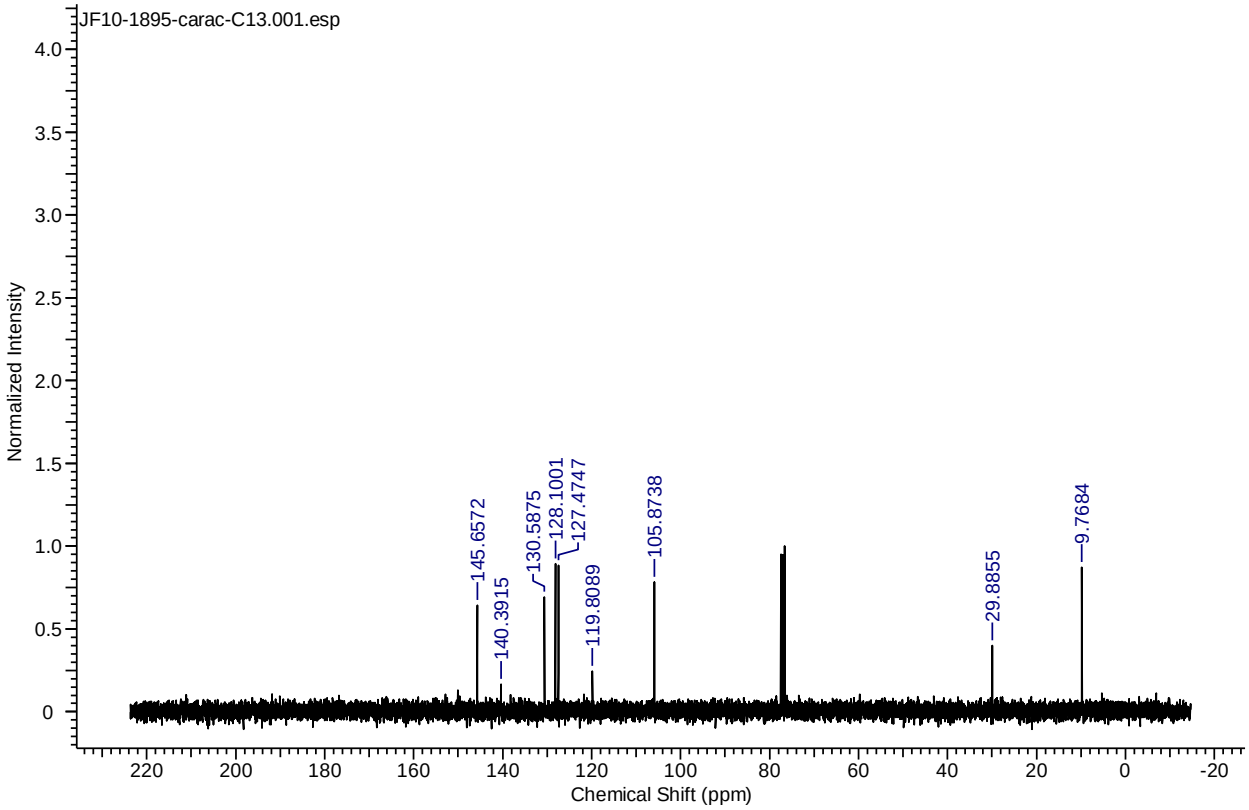

JF11-1935-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.99
1.00
0.99
2.04
3.07
1.00
3.07
3.10

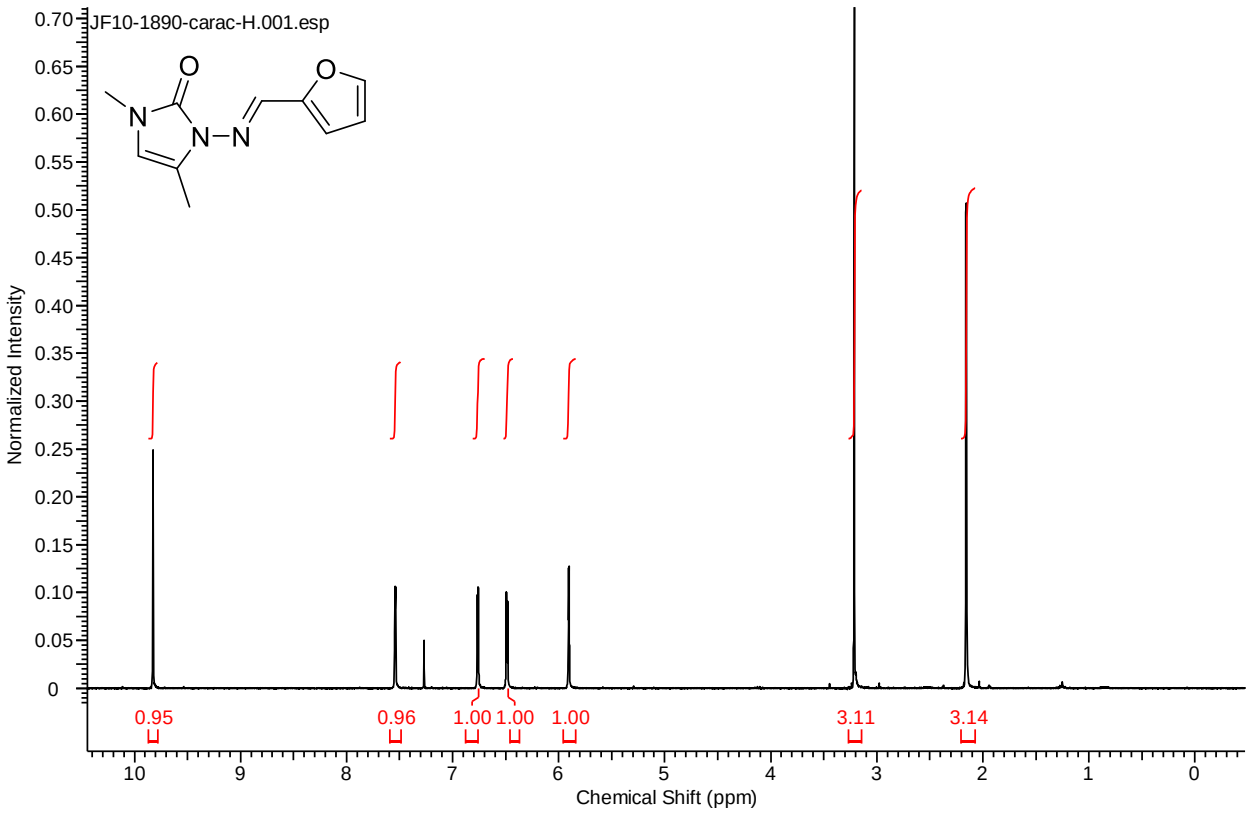

JF11-1935-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
150.6028
130.7039
128.6238
126.9219
125.3073
120.0562
105.9757
29.8855
10.1029

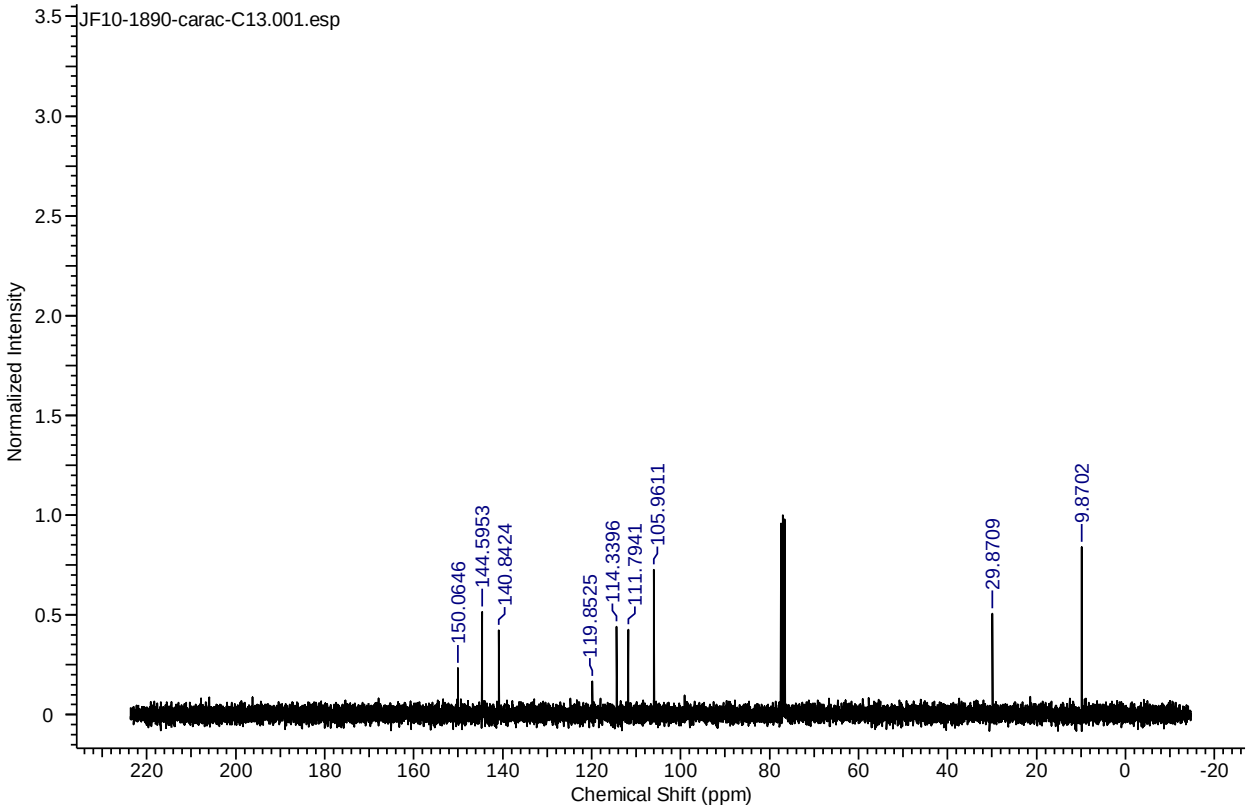

JF11-1936-carac-H.001.esp
HO
O
N
N–N
Normalized Intensity
0.85
1.01
2.19
1.96
1.00
3.08
3.11
Chemical Shift (ppm)

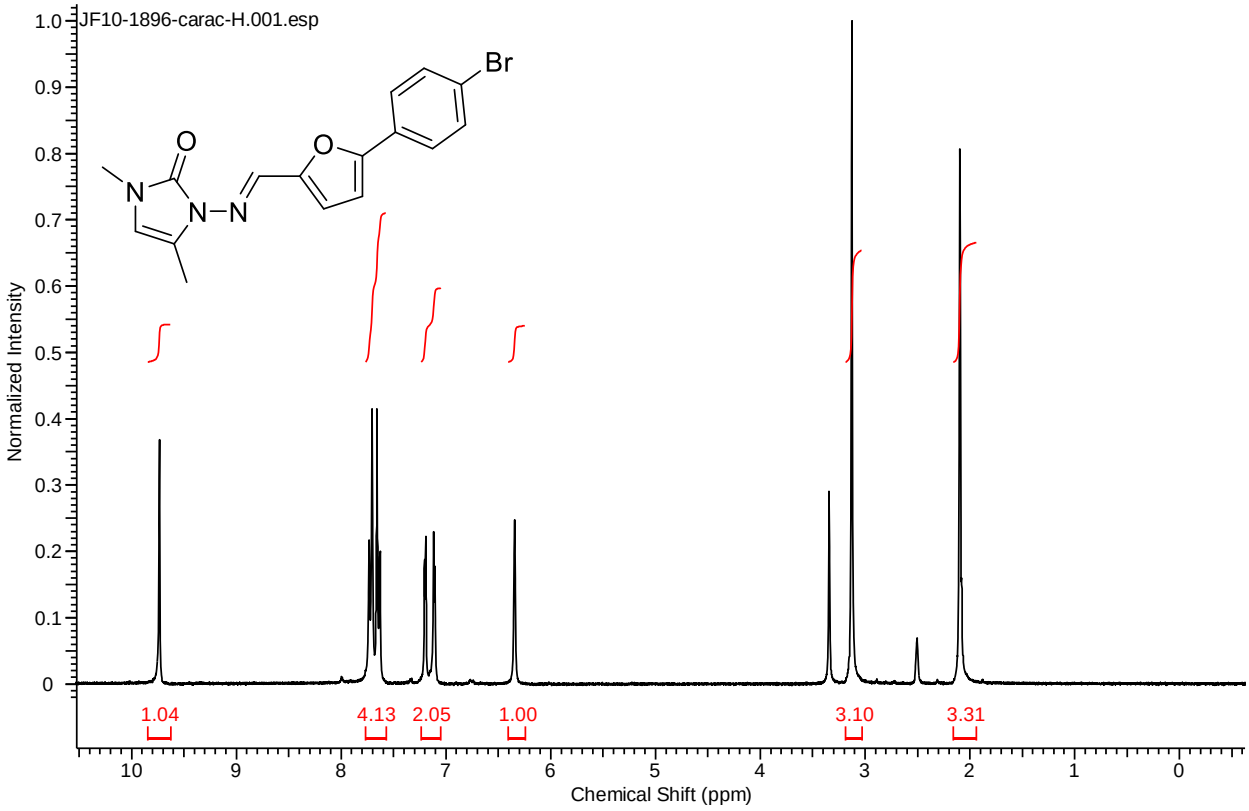

JF11-1936-carac-C13.001.esp
Normalized Intensity
158.4379
155.2960
132.0805
119.6292
116.8654
106.4941
29.9821
9.8650
Chemical Shift (ppm)

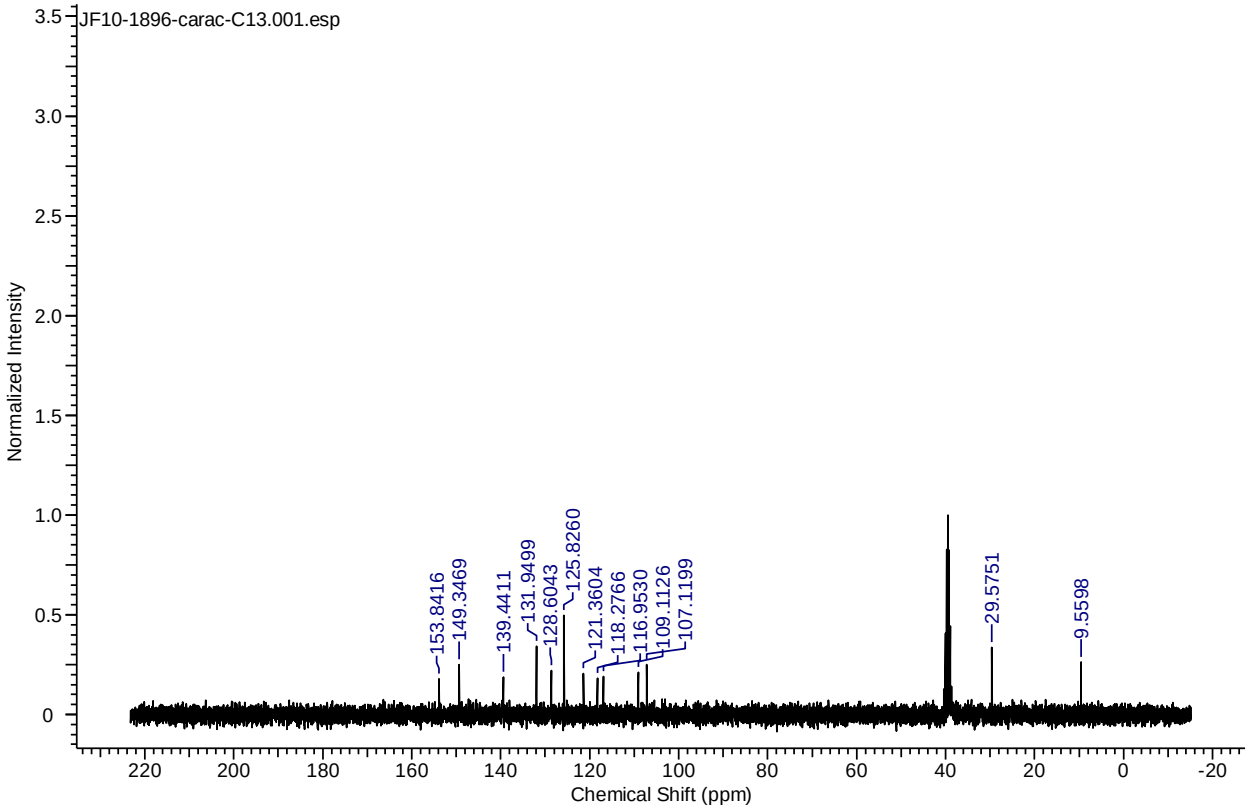

JF10-1895-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98
1.97
1.01
1.00
3.14
3.14

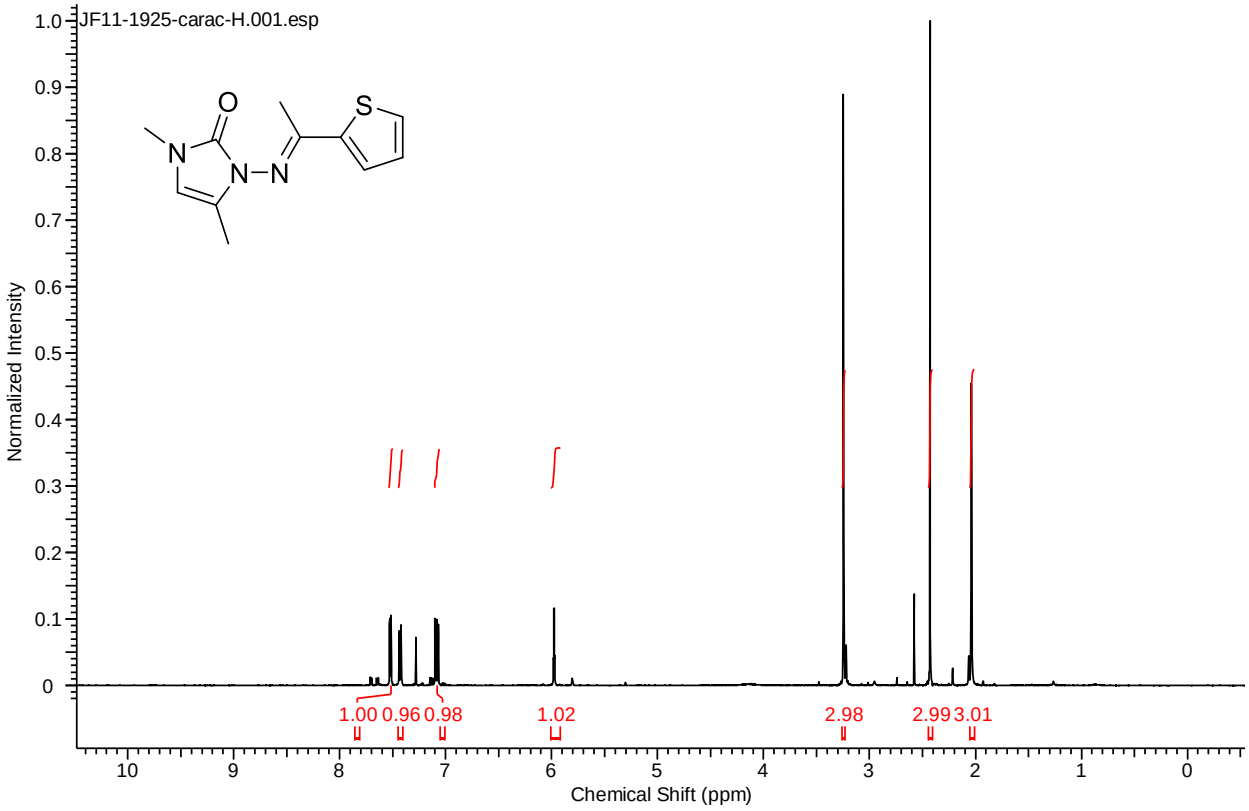

JF10-1895-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
145.6572
140.3915
130.5875
128.1001
127.4747
119.8089
105.8738
29.8855
9.7684

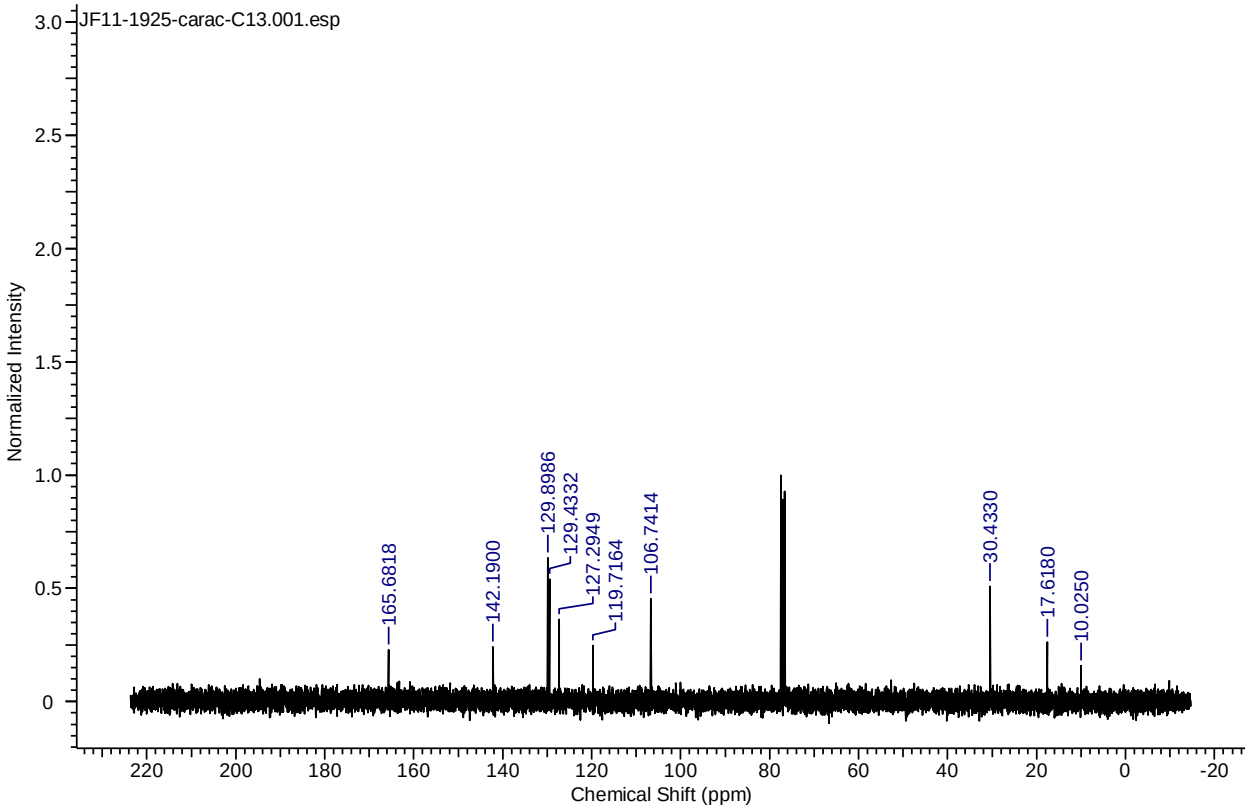

JF10-1890-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.95
0.96
1.00
1.00
1.00
3.11
3.14

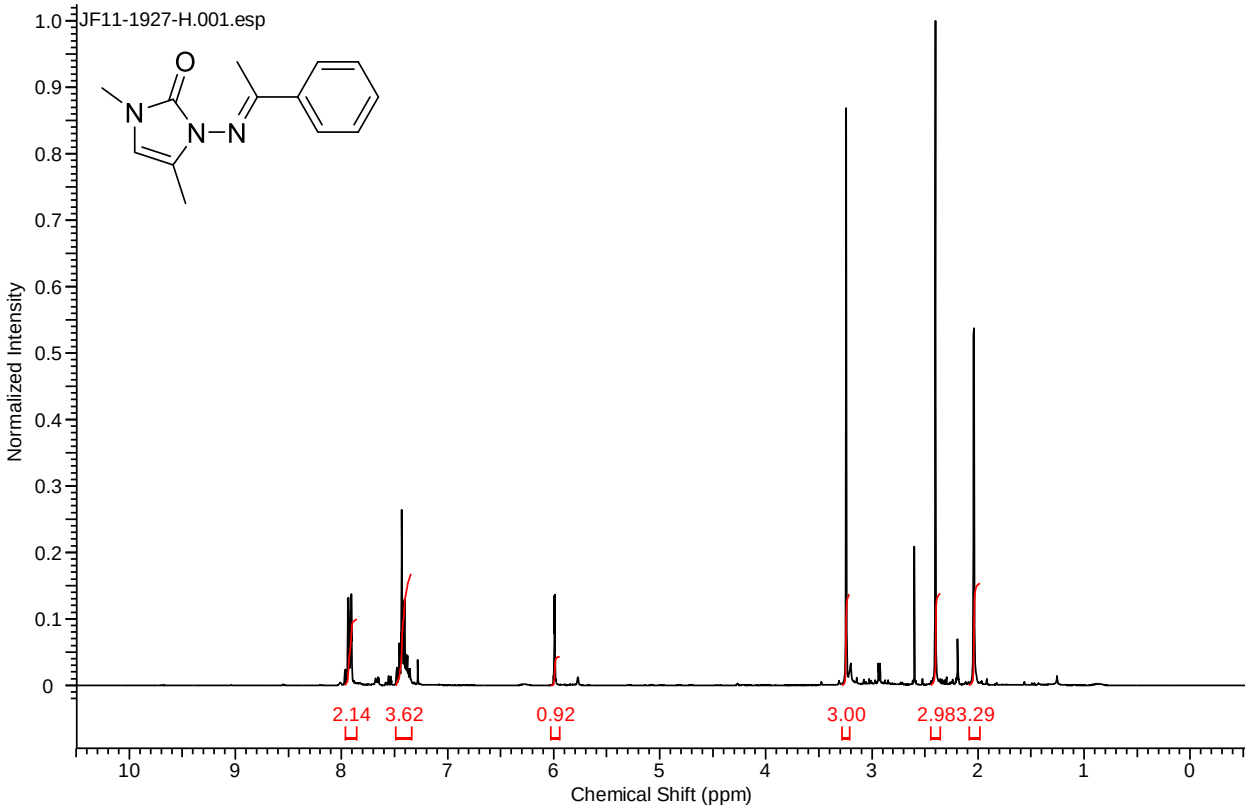

JF10-1890-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
150.0646
144.5953
140.8424
119.8525
114.3396
111.7941
105.9611
29.8709
9.8702

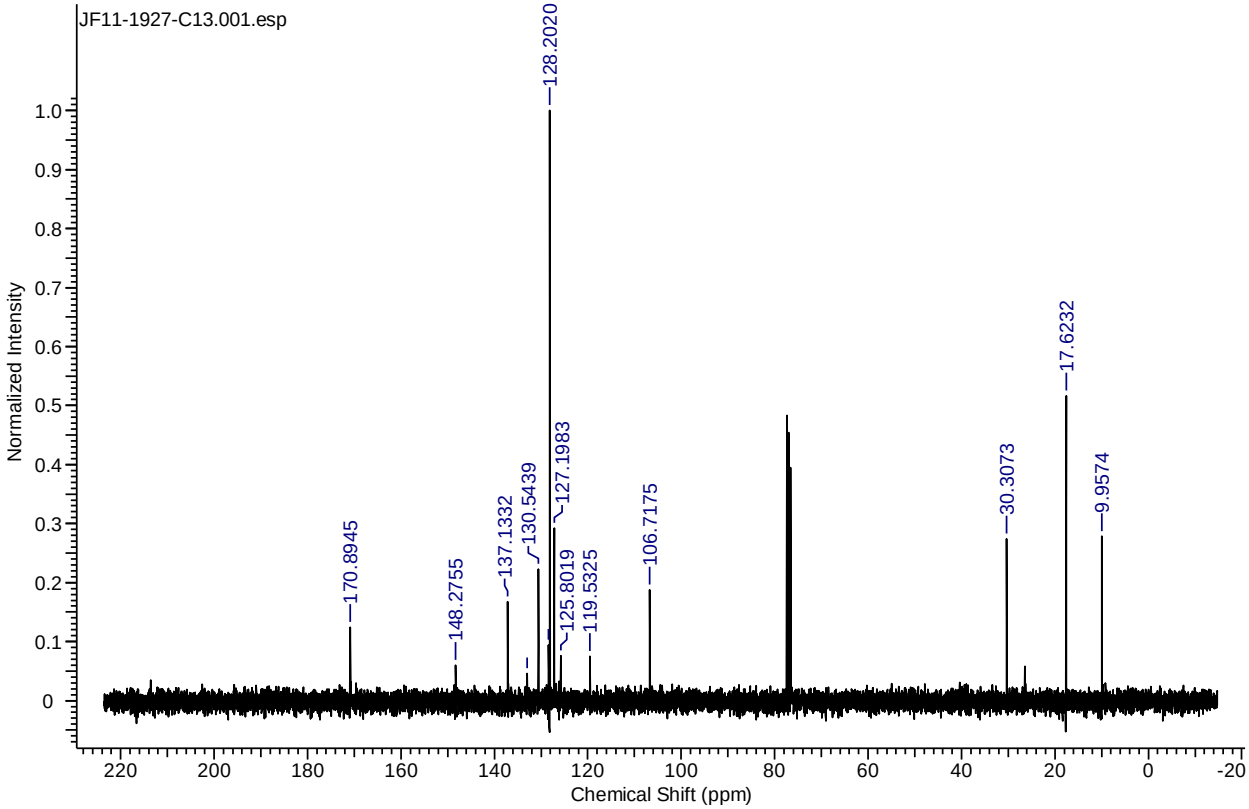

JF10-1896-carac-H.001.esp
Br
O
O
N
N–N
Normalized Intensity
1.04
4.13
2.05
1.00
3.10
3.31
Chemical Shift (ppm)

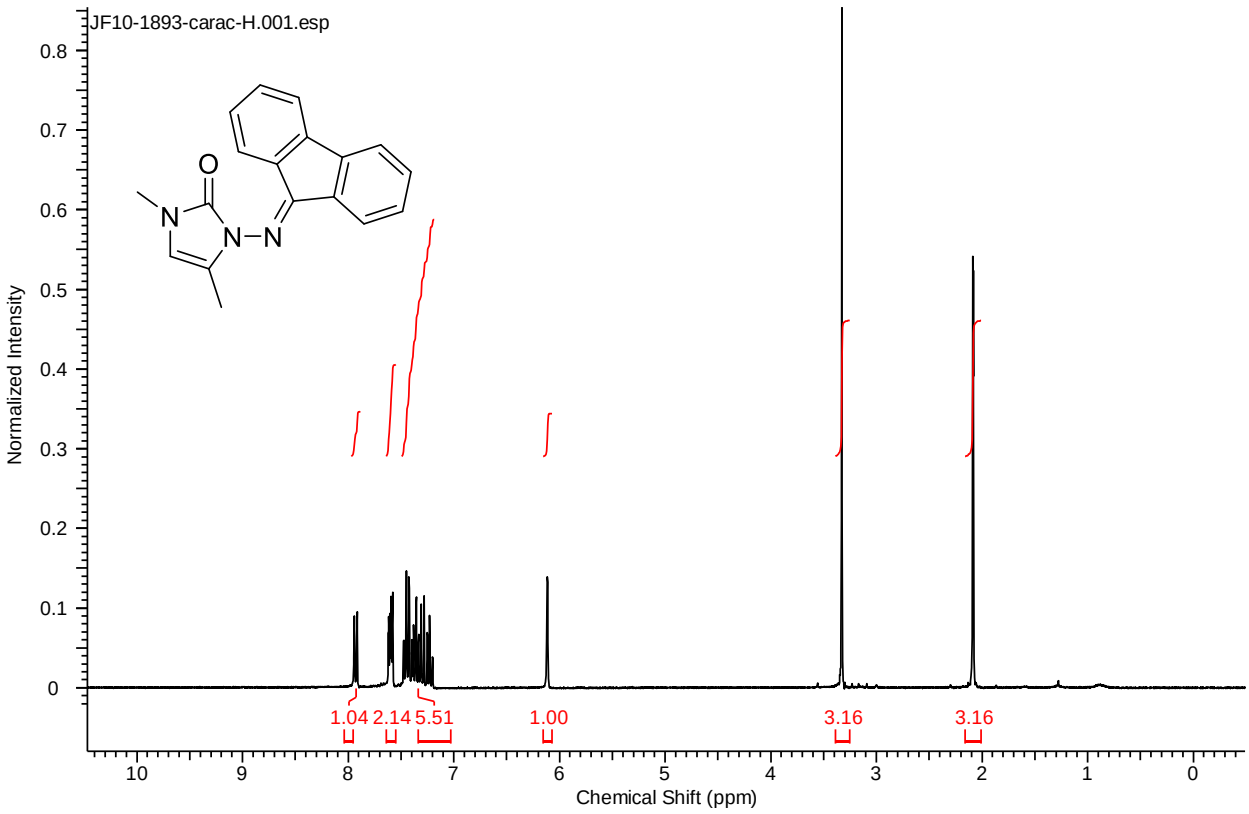

JF10-1896-carac-C13.001.esp
153.8416
149.3469
139.4411
131.9499
128.6043
125.8260
121.3604
118.2766
116.9530
109.1126
107.1199
29.5751
9.5598
Normalized Intensity
Chemical Shift (ppm)

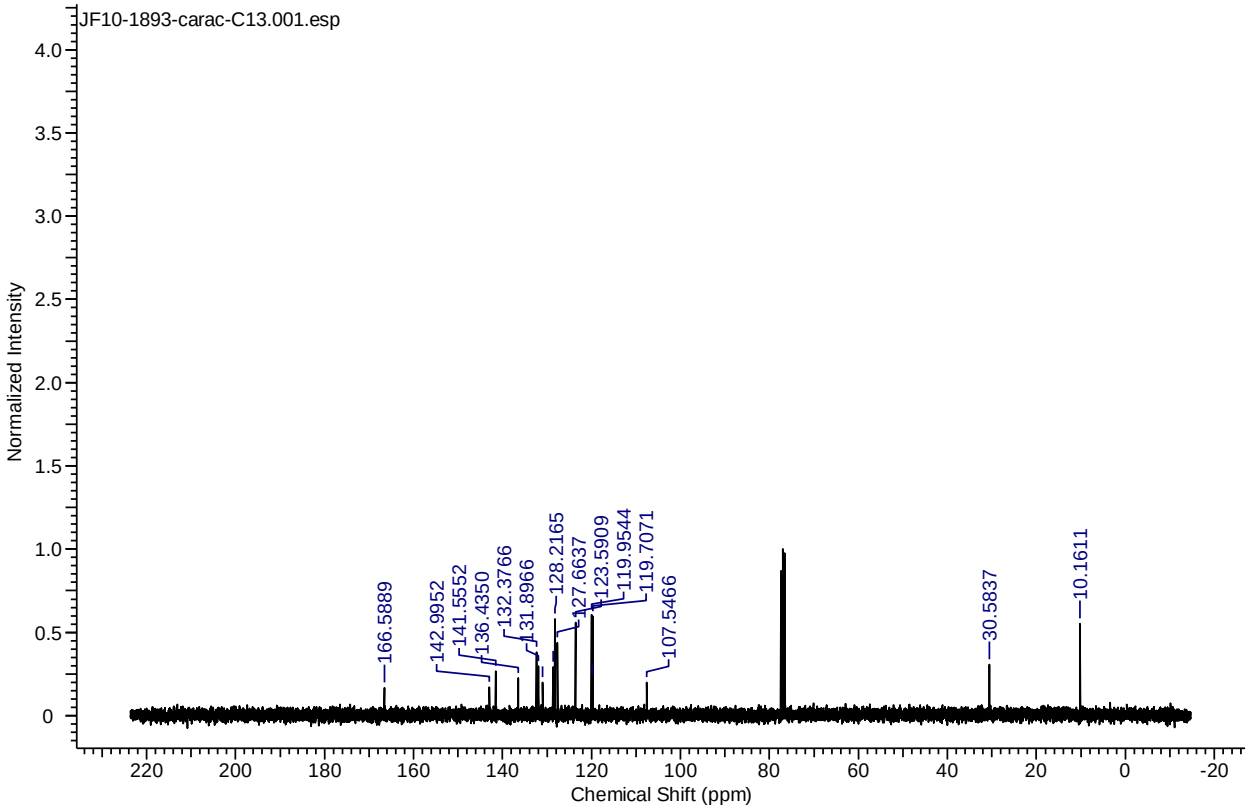

JF11-1925-carac-H.001.esp
O
S
N
N–N
Normalized Intensity
1.00 0.96 0.98
1.02
2.98
2.99 3.01
Chemical Shift (ppm)

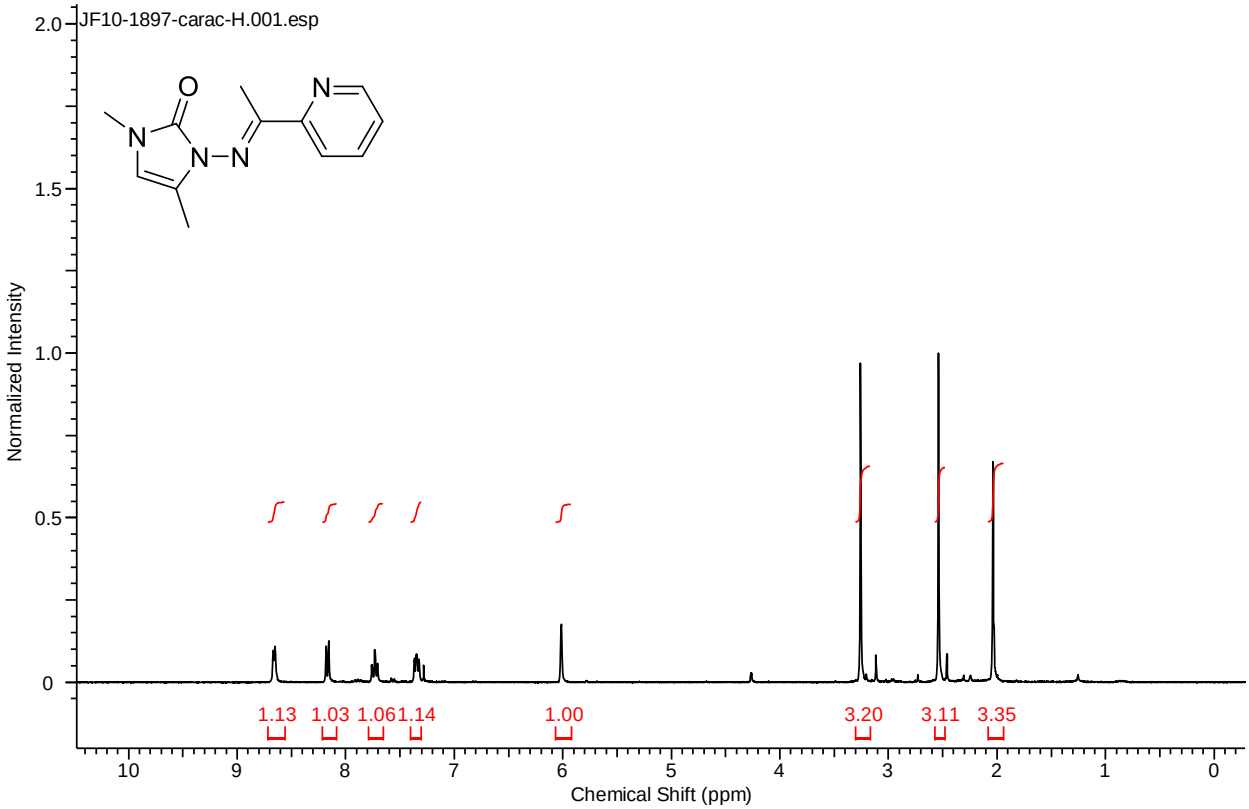

JF11-1925-carac-C13.001.esp
Normalized Intensity
165.6818
142.1900
129.8986
129.4332
127.2949
119.7164
106.7414
30.4330
17.6180
10.0250
Chemical Shift (ppm)

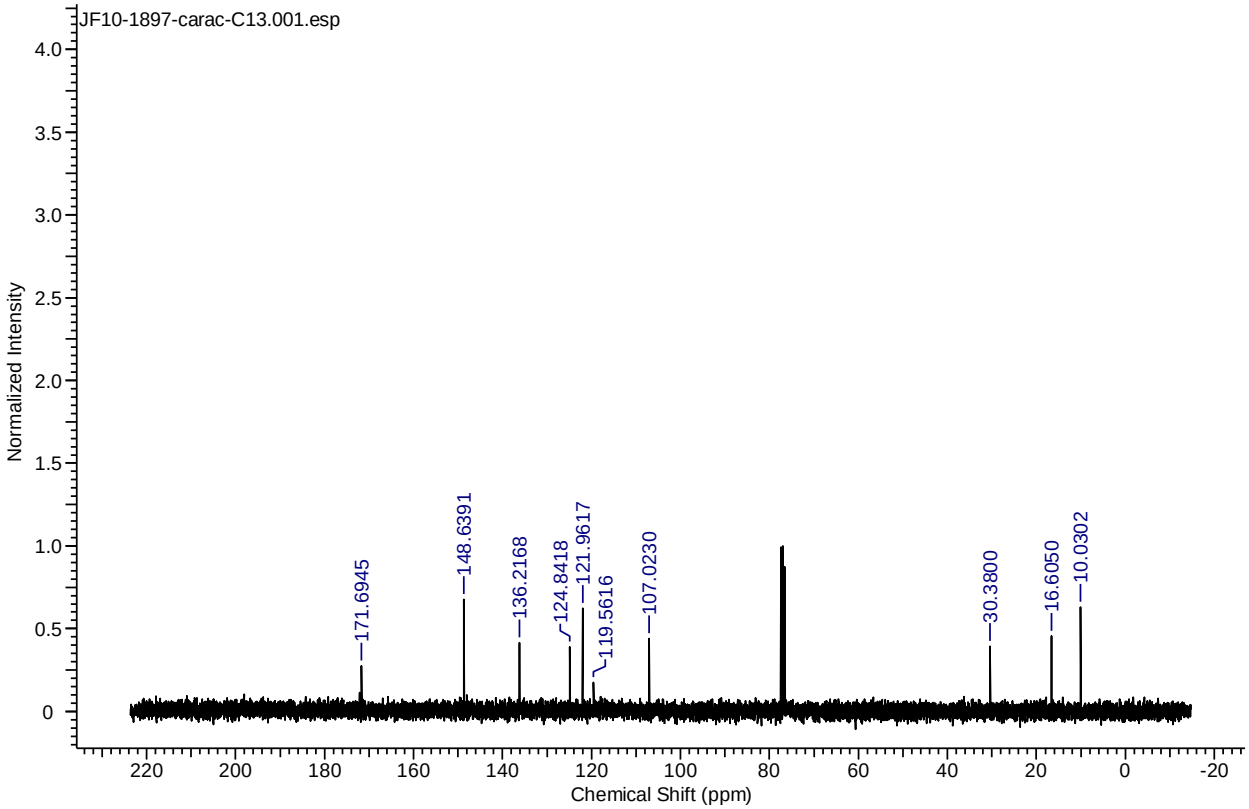

JF11-1927-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
2.14
3.62
0.92
3.00
2.98
3.29

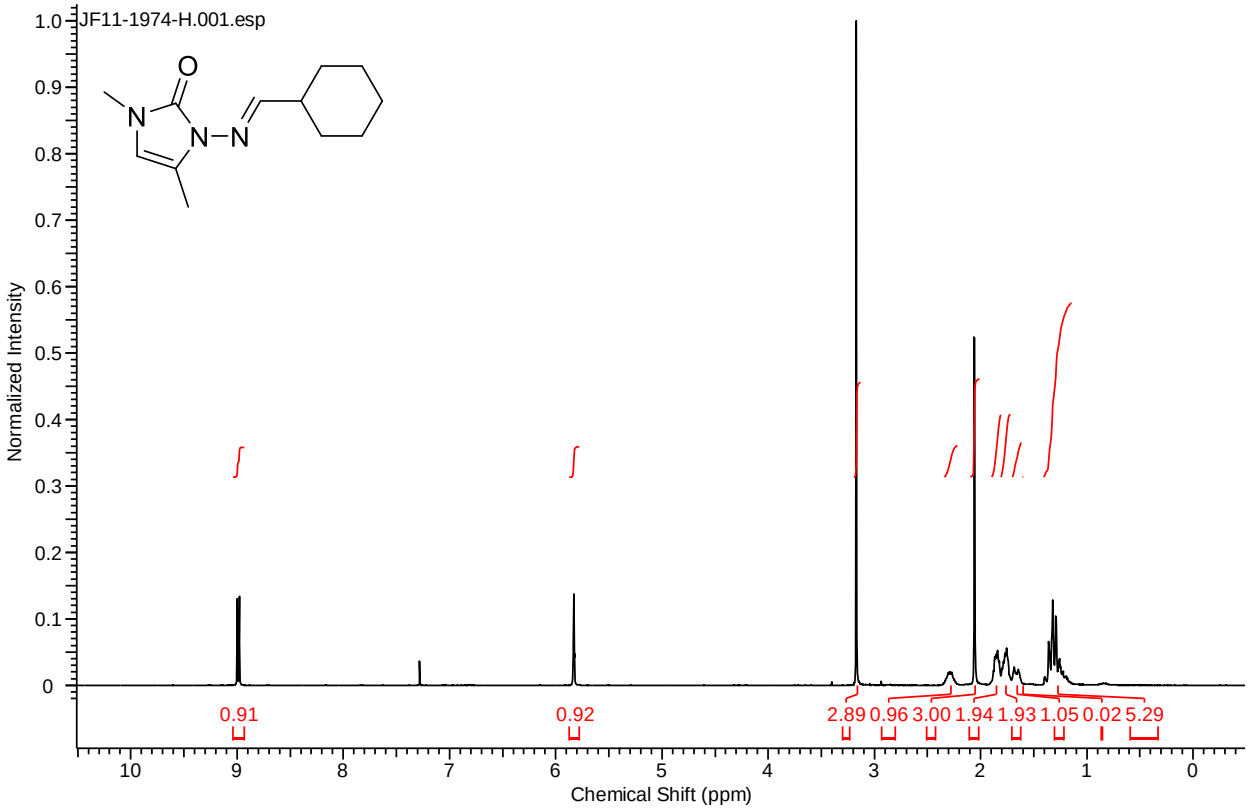

JF11-1927-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
128.2020
127.1983
130.5439
137.1332
170.8945
148.2755
125.8019
119.5325
106.7175
30.3073
17.6232
9.9574

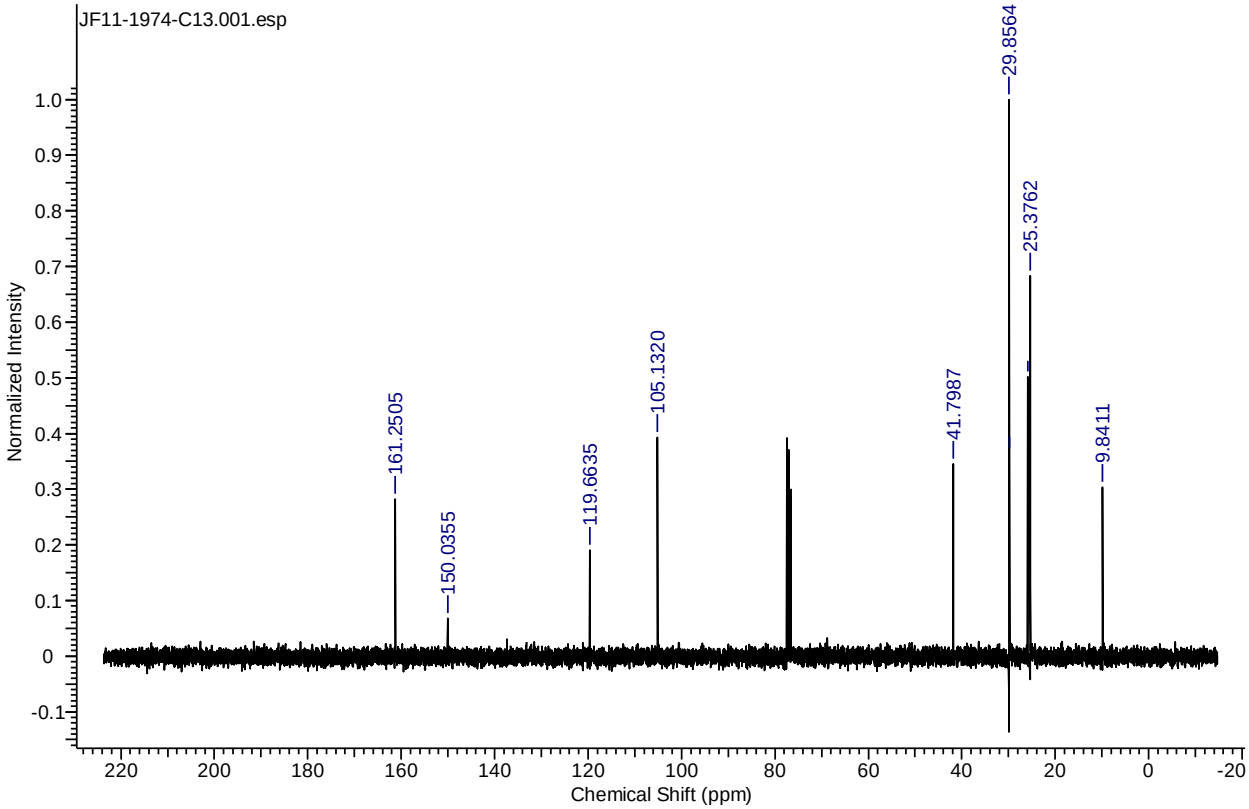

JF10-1893-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.04
2.14
5.51
1.00
3.16
3.16

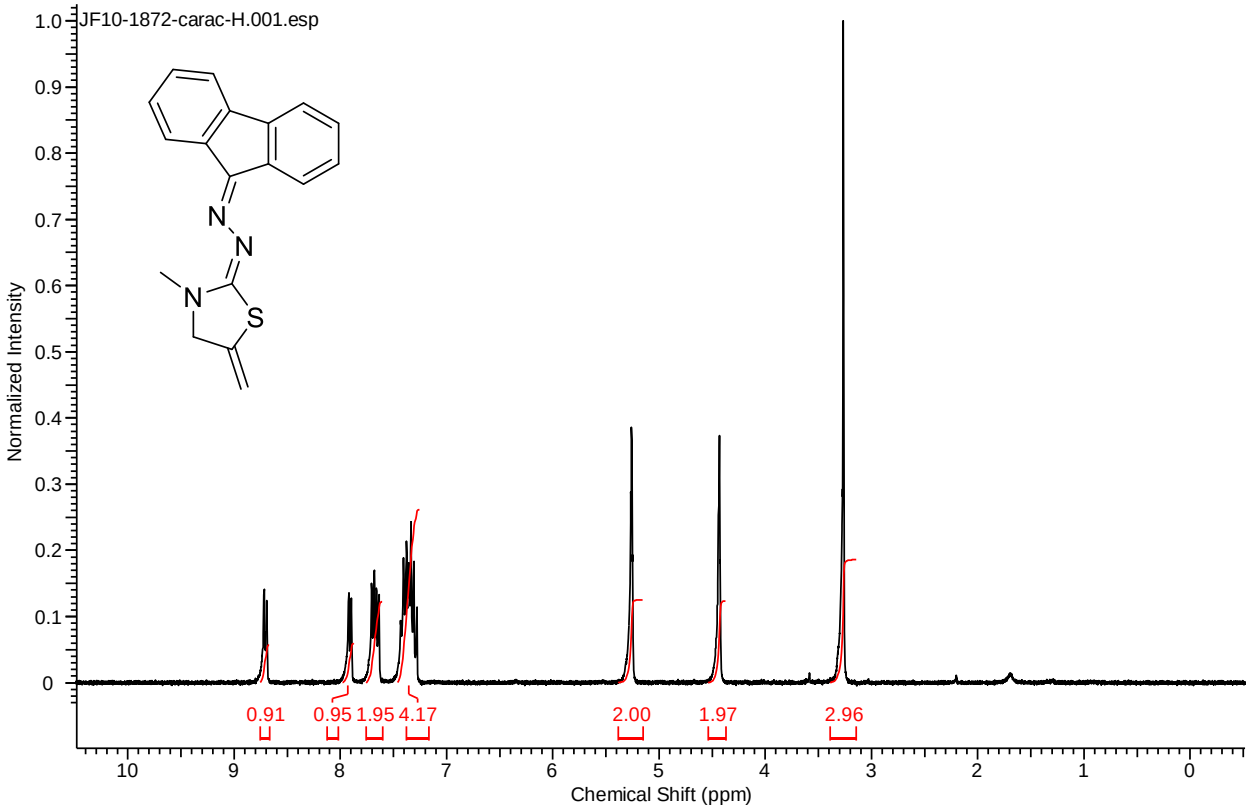

JF10-1893-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
166.5889
142.9952
141.5552
136.4350
132.3766
131.8966
128.2165
127.6637
123.5909
119.9544
119.7071
107.5466
30.5837
10.1611

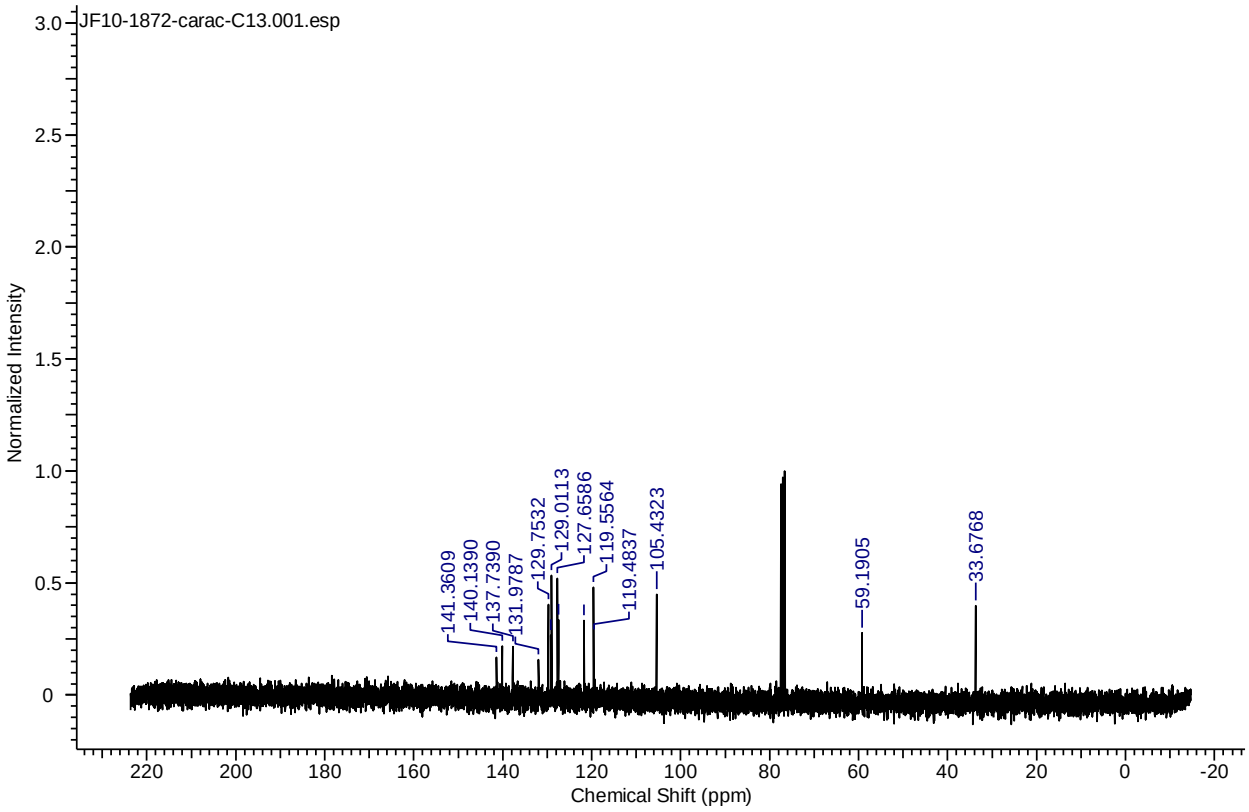

JF10-1897-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.13
1.03
1.06
1.14
1.00
3.20
3.11
3.35

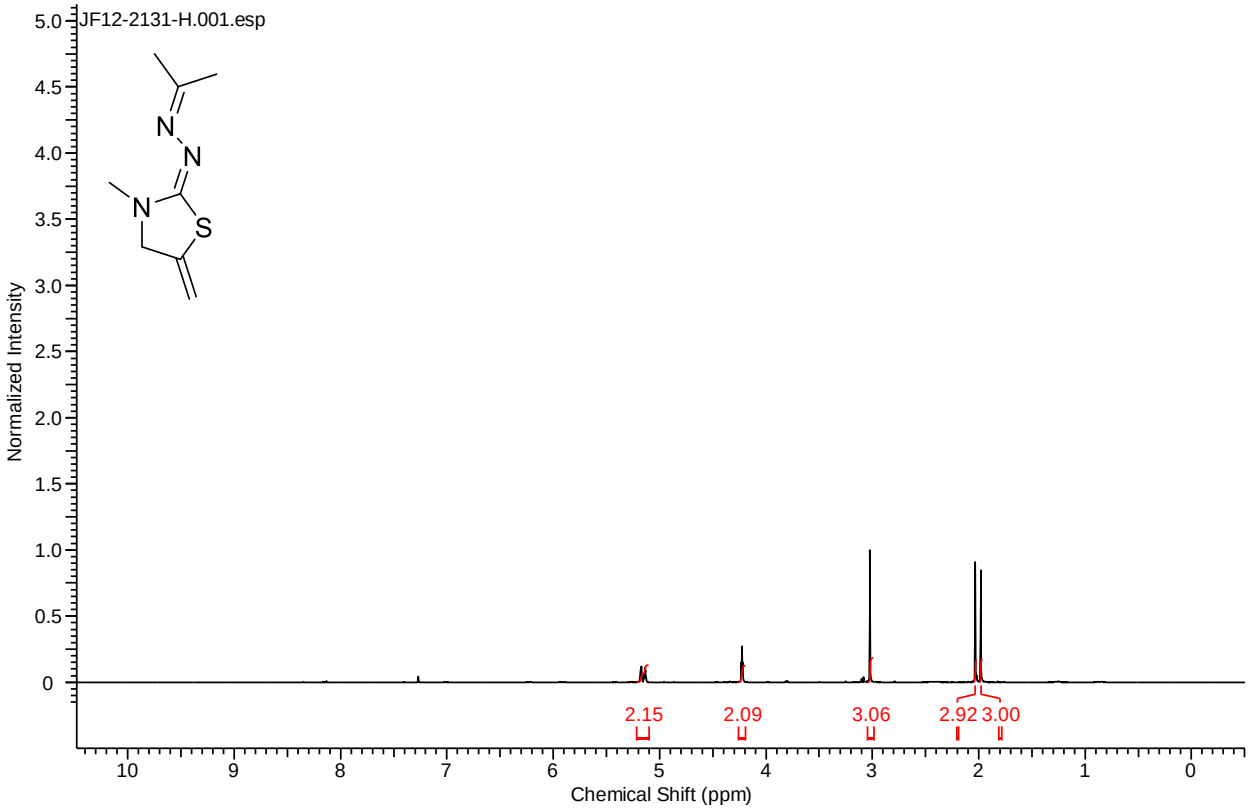

JF10-1897-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
171.6945
148.6391
136.2168
124.8418
121.9617
119.5616
107.0230
30.3800
16.6050
10.0302

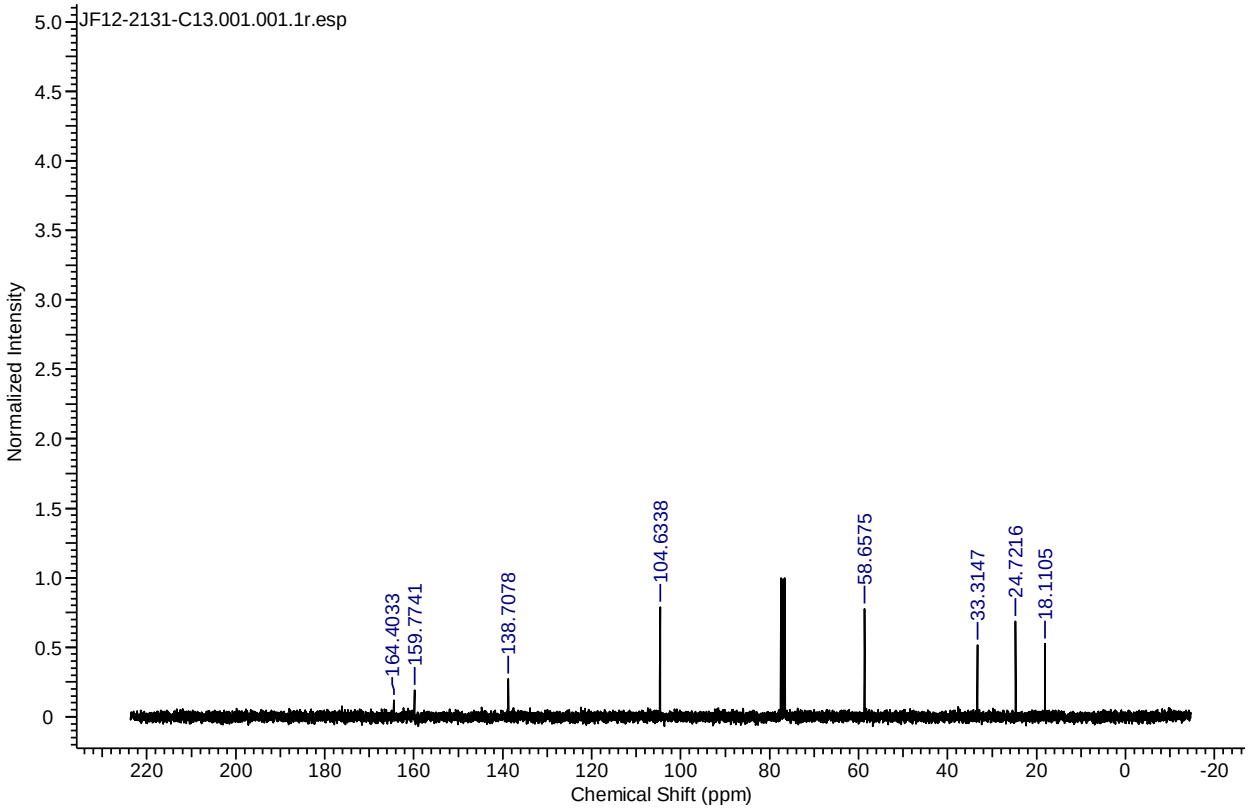

JF11-1974-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.91
0.92
2.89 0.96 3.00 1.94 1.93 1.05 0.02 5.29

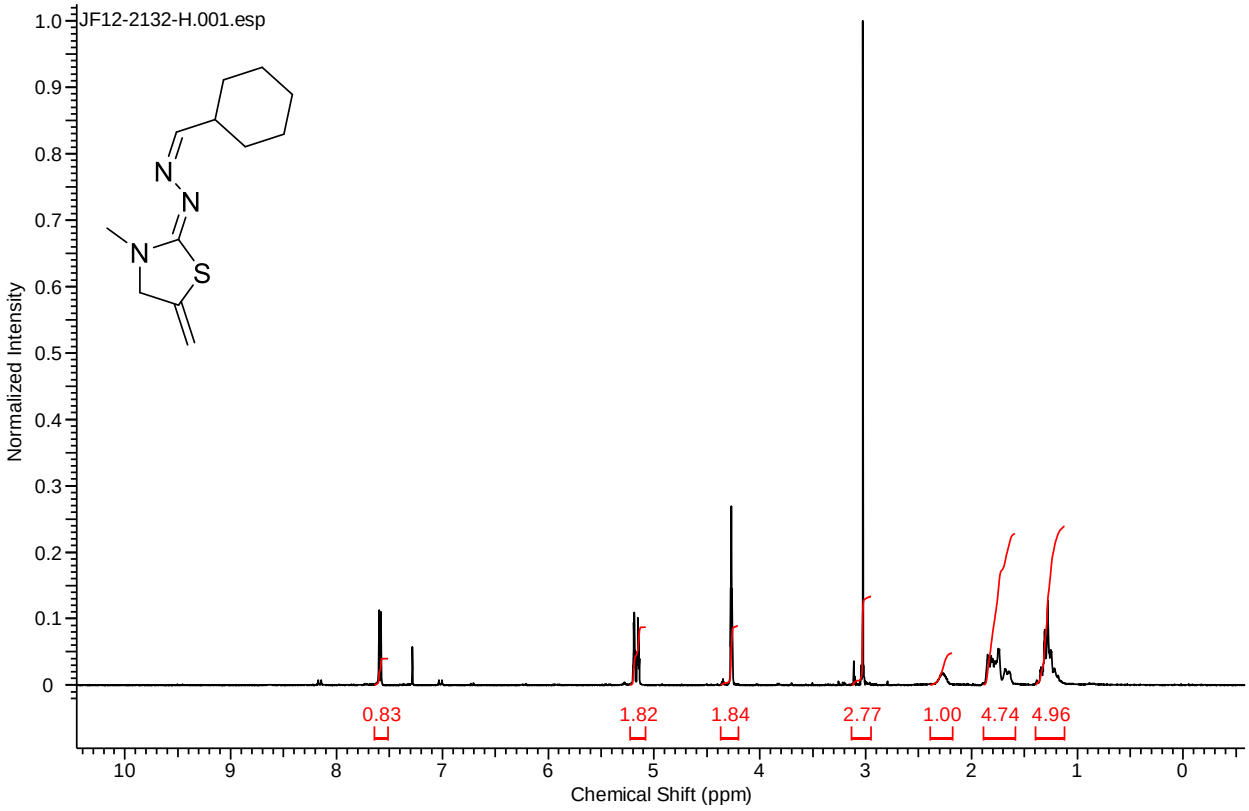

JF11-1974-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
161.2505
150.0355
119.6635
105.1320
41.7987
29.8564
25.3762
9.8411

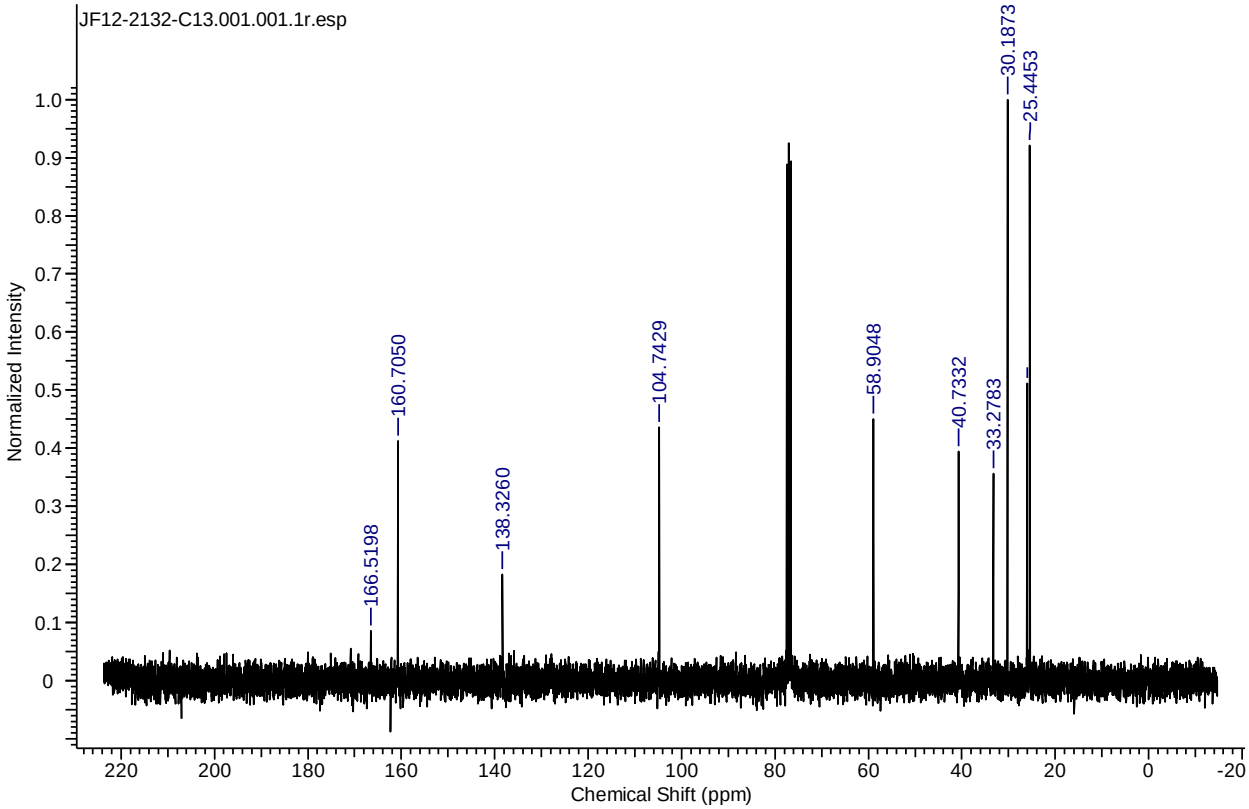

JF10-1872-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.91
0.95
1.95
4.17
2.00
1.97
2.96

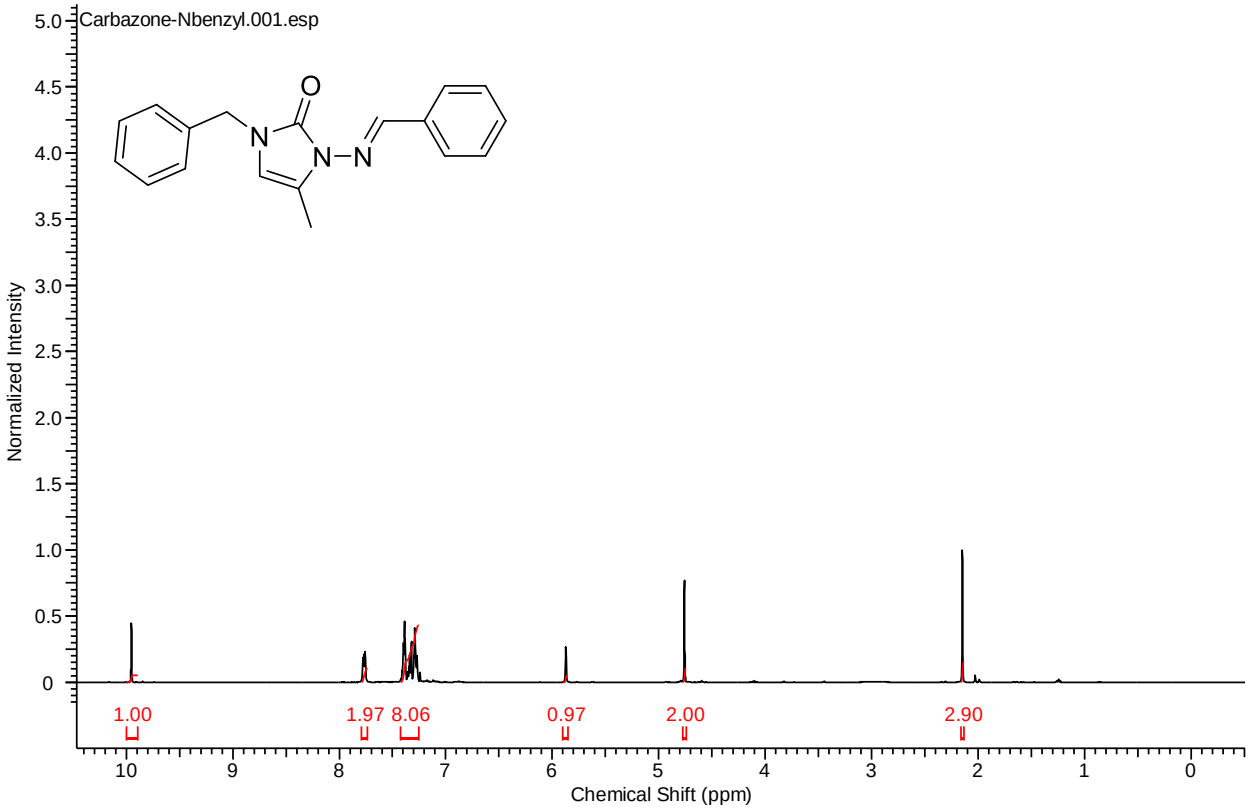

JF10-1872-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
141.3609
140.1390
137.7390
131.9787
129.7532
129.0113
127.6586
119.5564
119.4837
105.4323
59.1905
33.6768

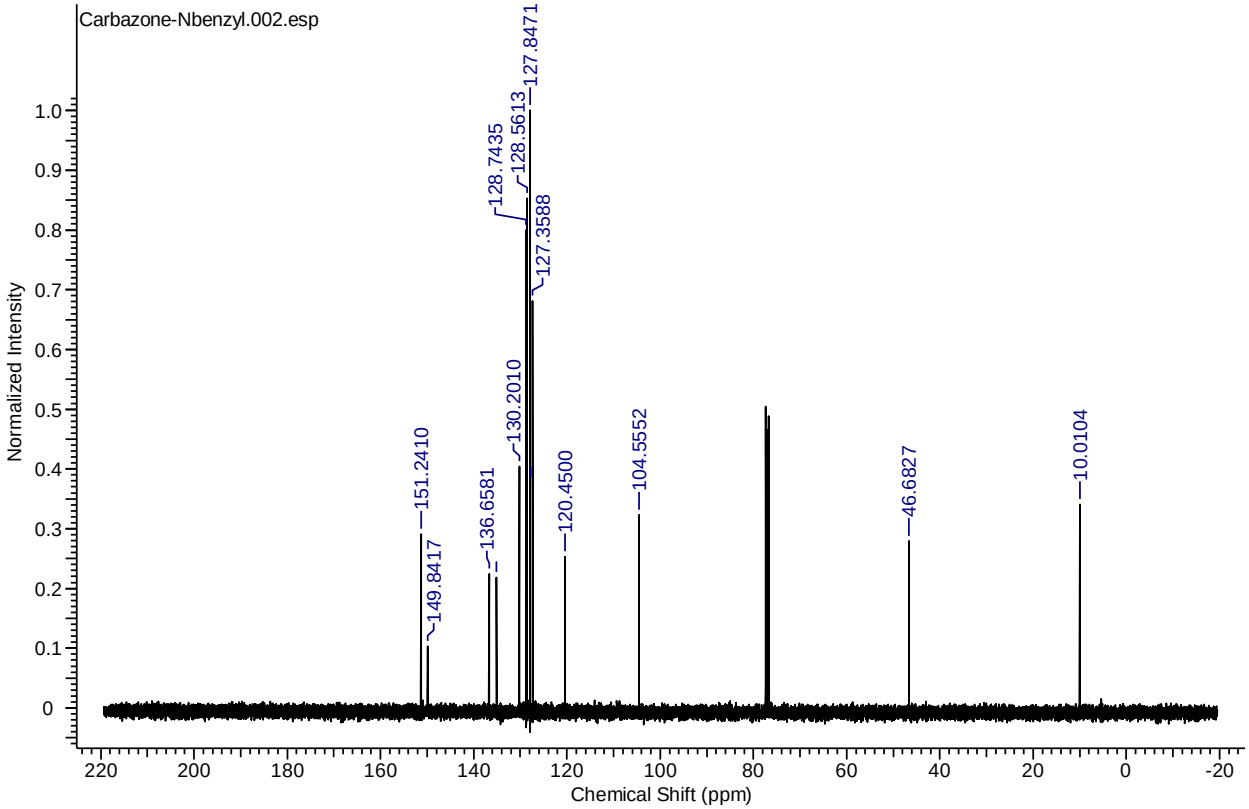

JF12-2131-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
2.15
2.09
3.06
2.92
3.00

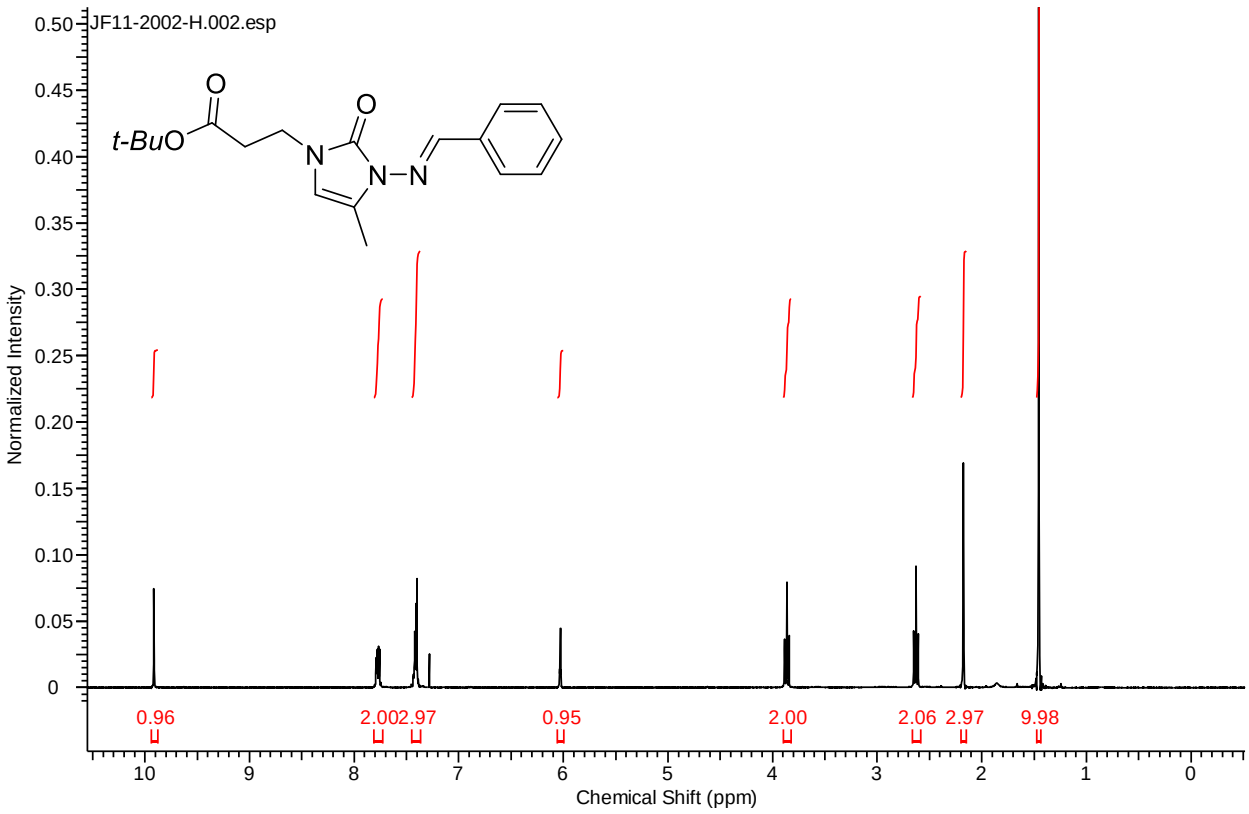

JF12-2131-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
164.4033
159.7741
138.7078
104.6338
58.6575
33.3147
24.7216
18.1105

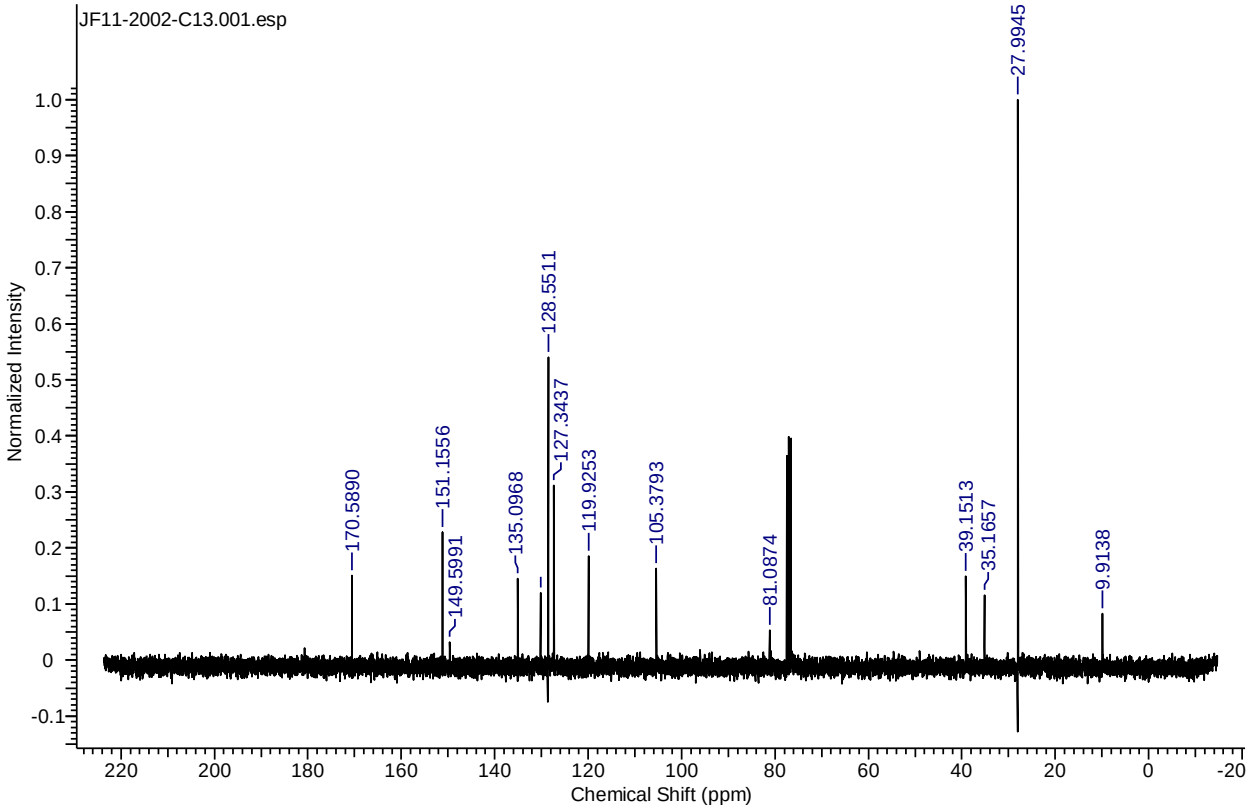

JF12-2132-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.83
1.82
1.84
2.77
1.00
4.74
4.96

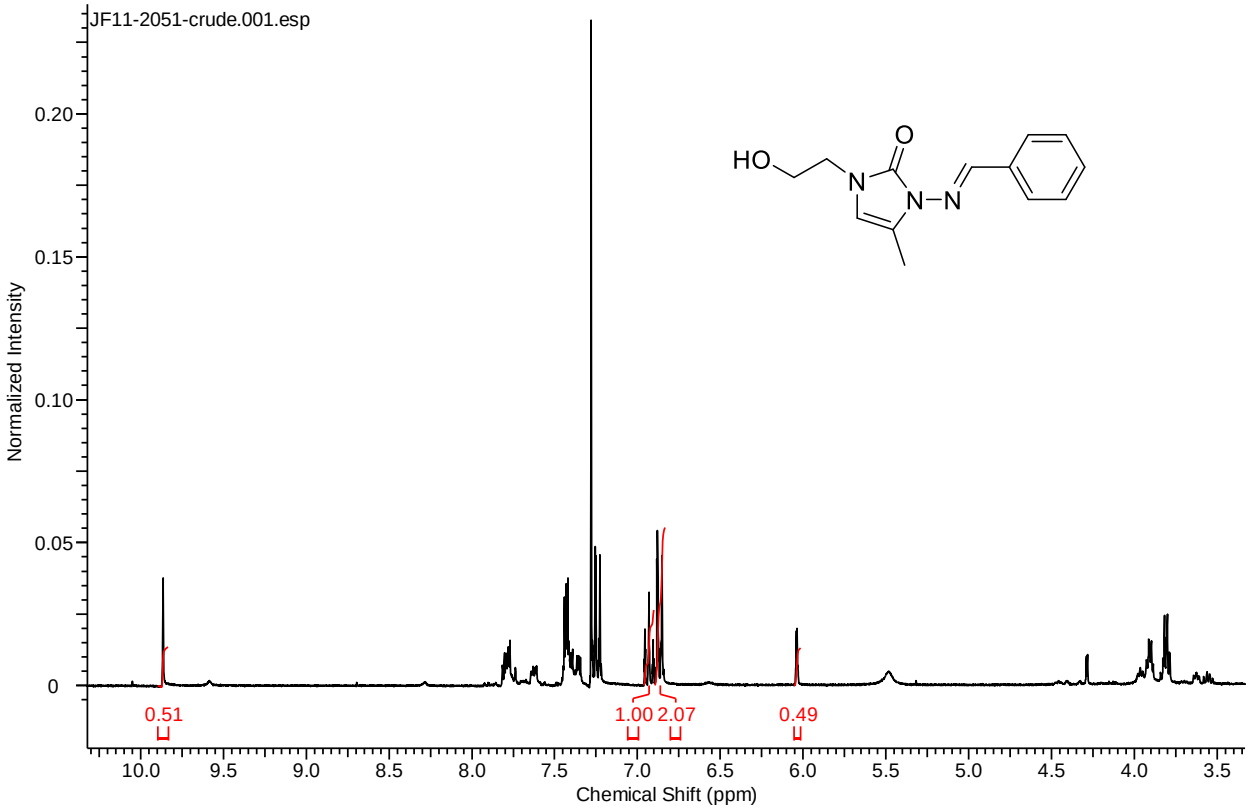

JF12-2132-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
166.5198
160.7050
138.3260
104.7429
58.9048
40.7332
33.2783
30.1873
25.4453

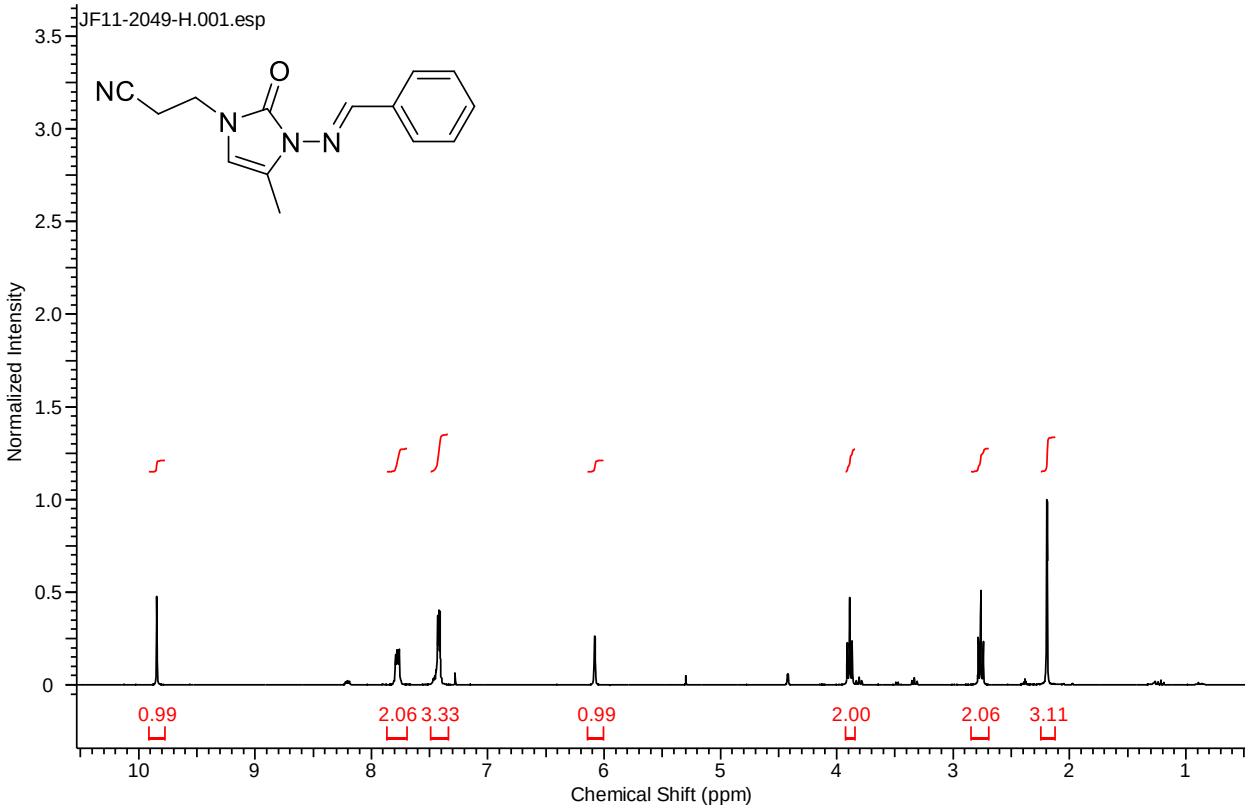

Carbazone-Nbenzyl.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
1.97
8.06
0.97
2.00
2.90

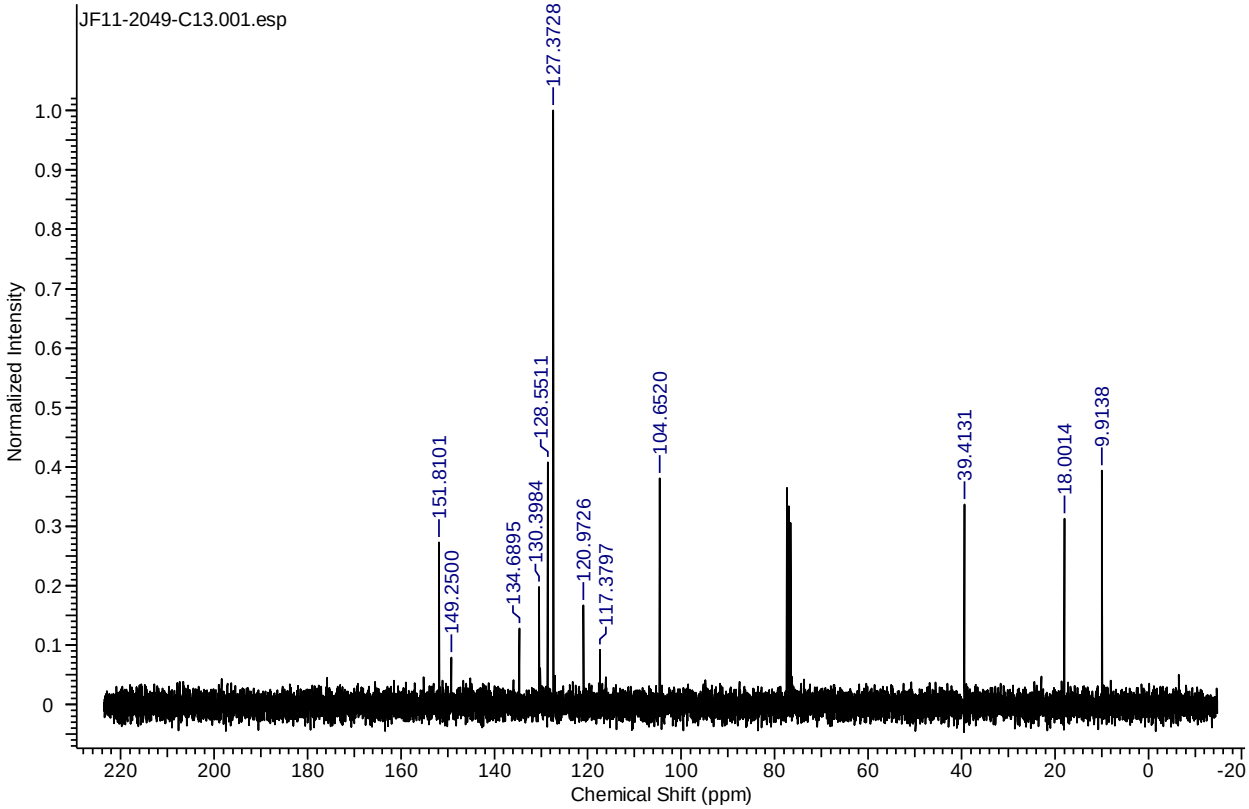

Carbazone-Nbenzyl.002.esp
Normalized Intensity
Chemical Shift (ppm)
151.2410
149.8417
136.6581
130.2010
128.7435
128.5613
127.8471
127.3588
120.4500
104.5552
46.6827
10.0104

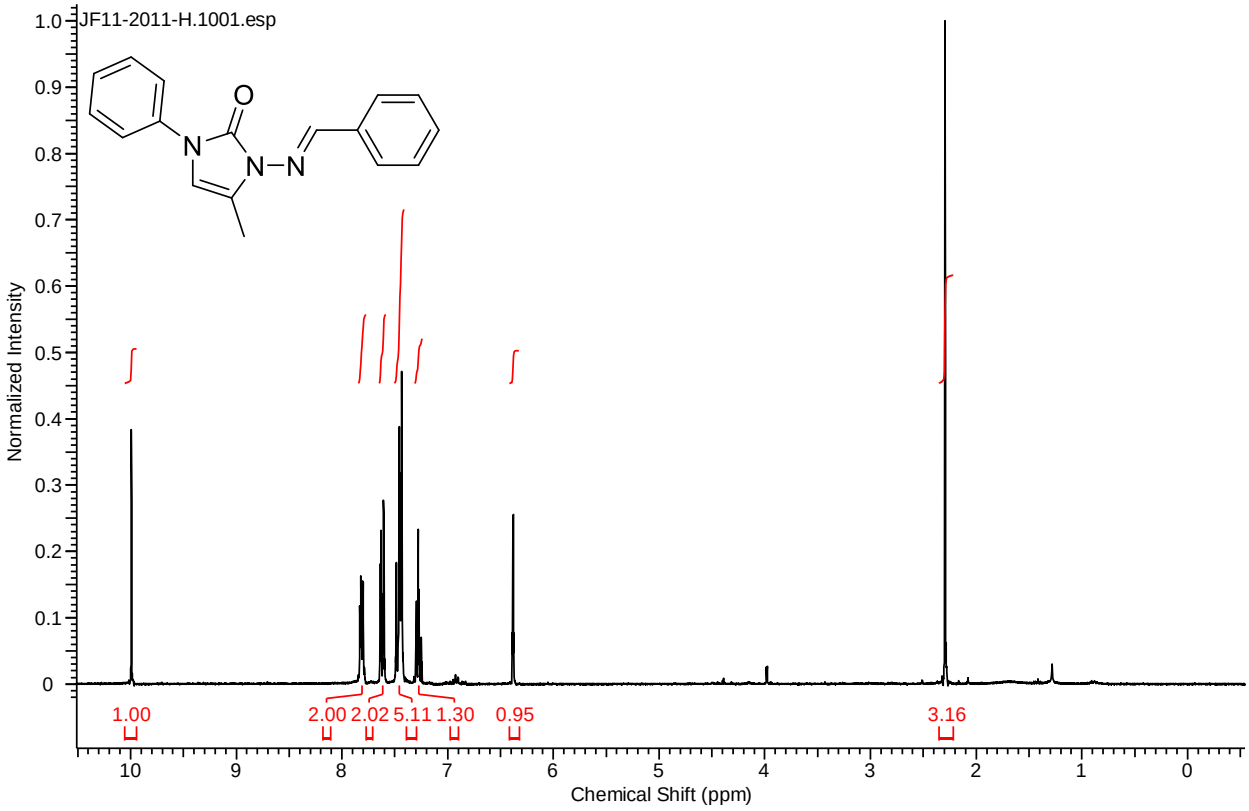

JF11-2002-H.002.esp
t-BuO
O
O
N
N
N
Normalized Intensity
0.96
2.00
2.97
0.95
2.00
2.06
2.97
9.98
Chemical Shift (ppm)

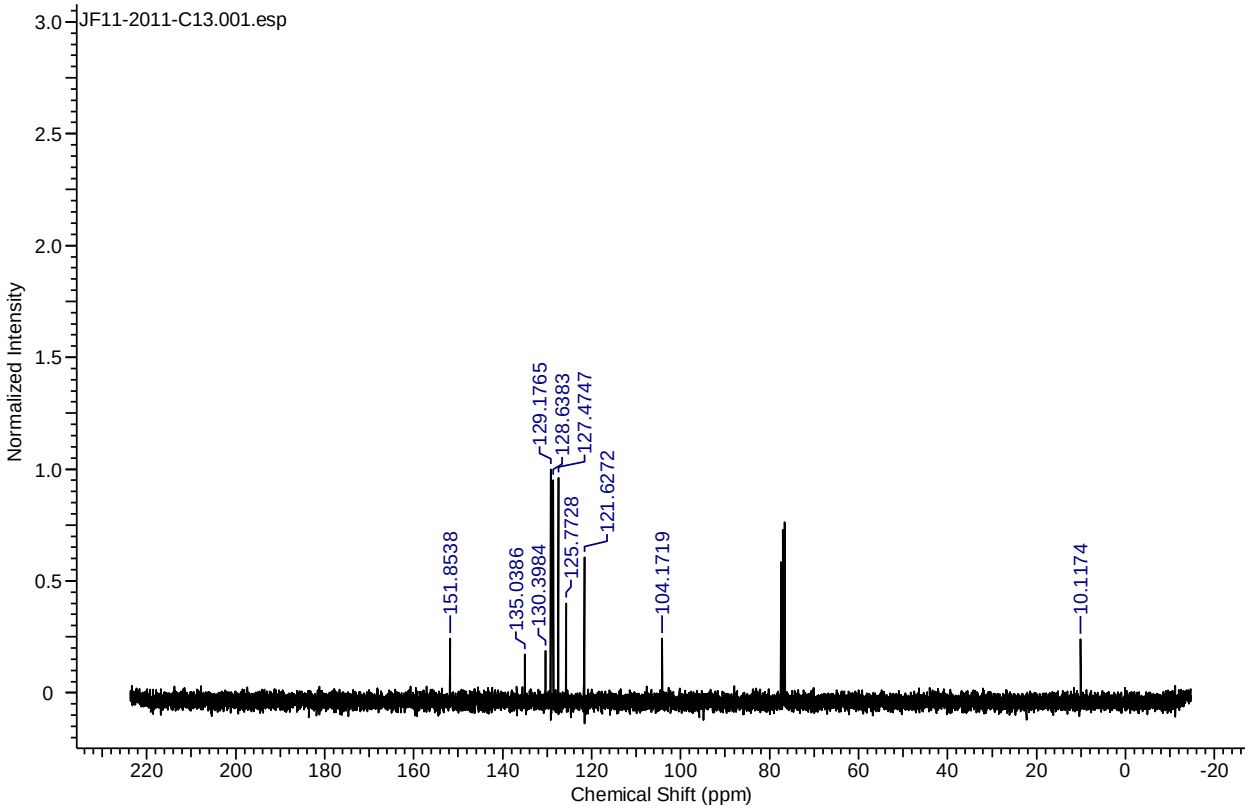

JF11-2002-C13.001.esp
Normalized Intensity
170.5890
151.1556
149.5991
135.0968
128.5511
127.3437
119.9253
105.3793
81.0874
39.1513
35.1657
27.9945
9.9138
Chemical Shift (ppm)

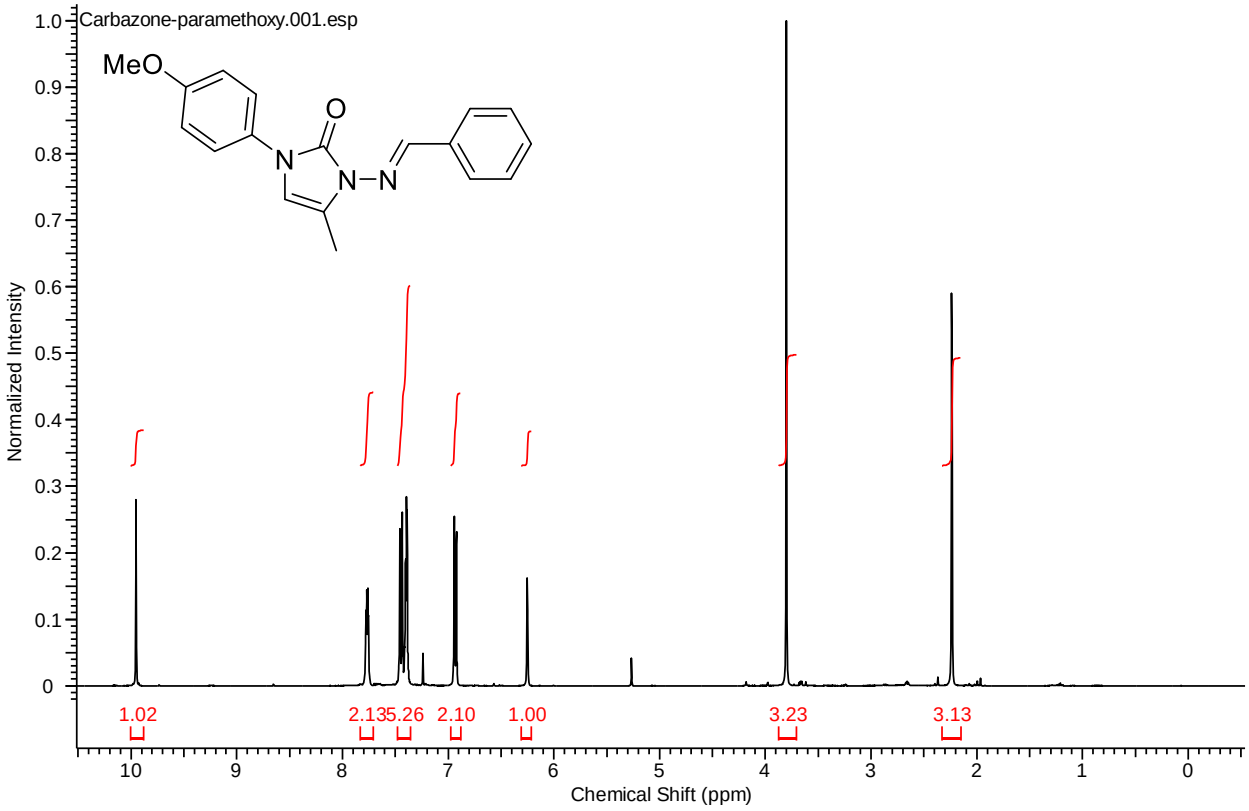

JF11-2051-crude.001.esp
Normalized Intensity
0.20
0.15
0.10
0.05
0
HO
O
N
N
N
0.51
1.00
2.07
0.49
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)

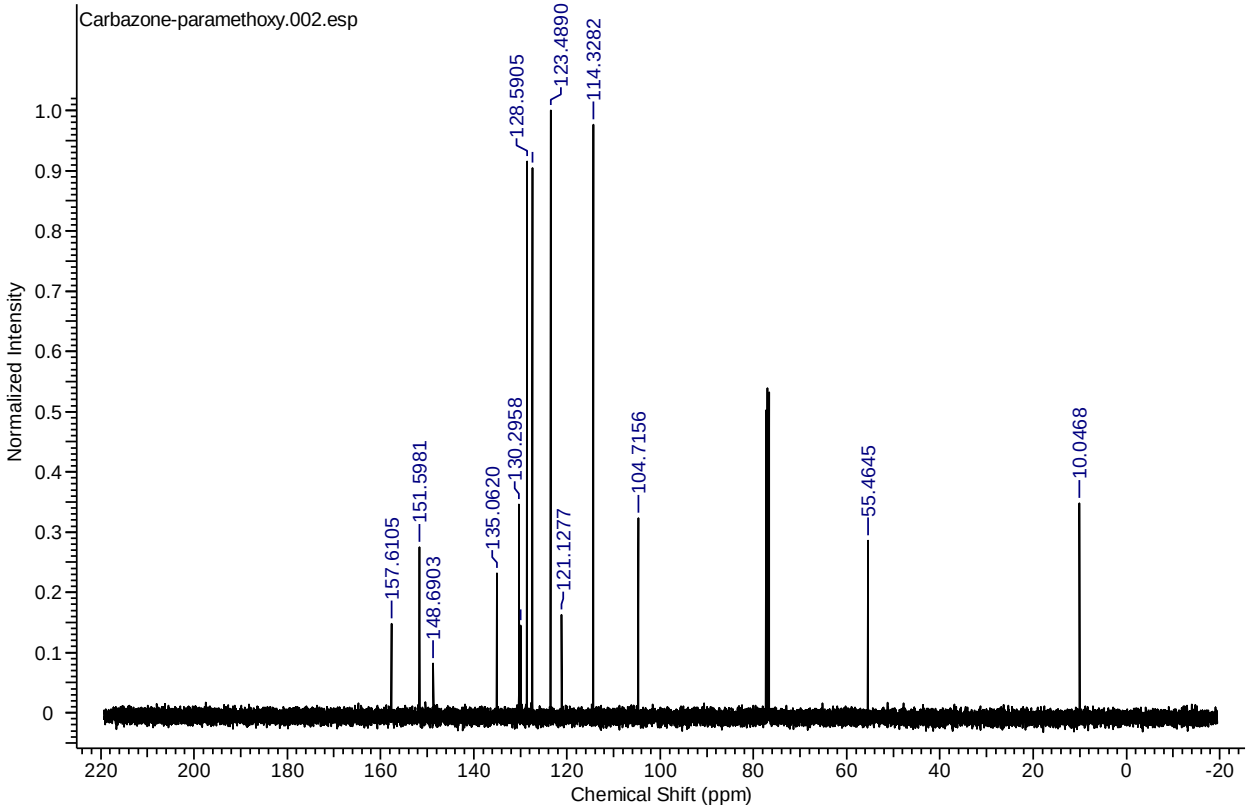

JF11-2049-H.001.esp
NC
O
N
N
N
Normalized Intensity
Chemical Shift (ppm)
0.99
2.06
3.33
0.99
2.00
2.06
3.11

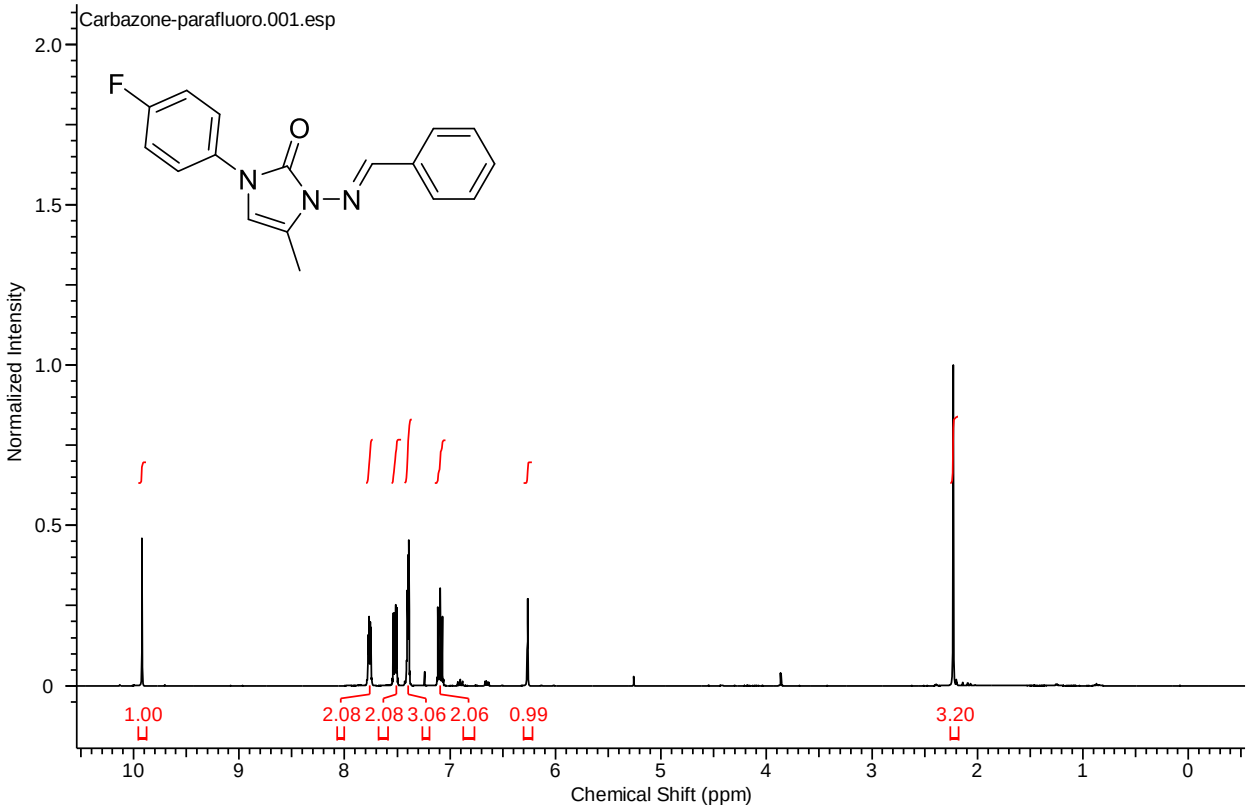

JF11-2049-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
151.8101
149.2500
134.6895
130.3984
128.5511
127.3728
120.9726
117.3797
104.6520
39.4131
18.0014
9.9138

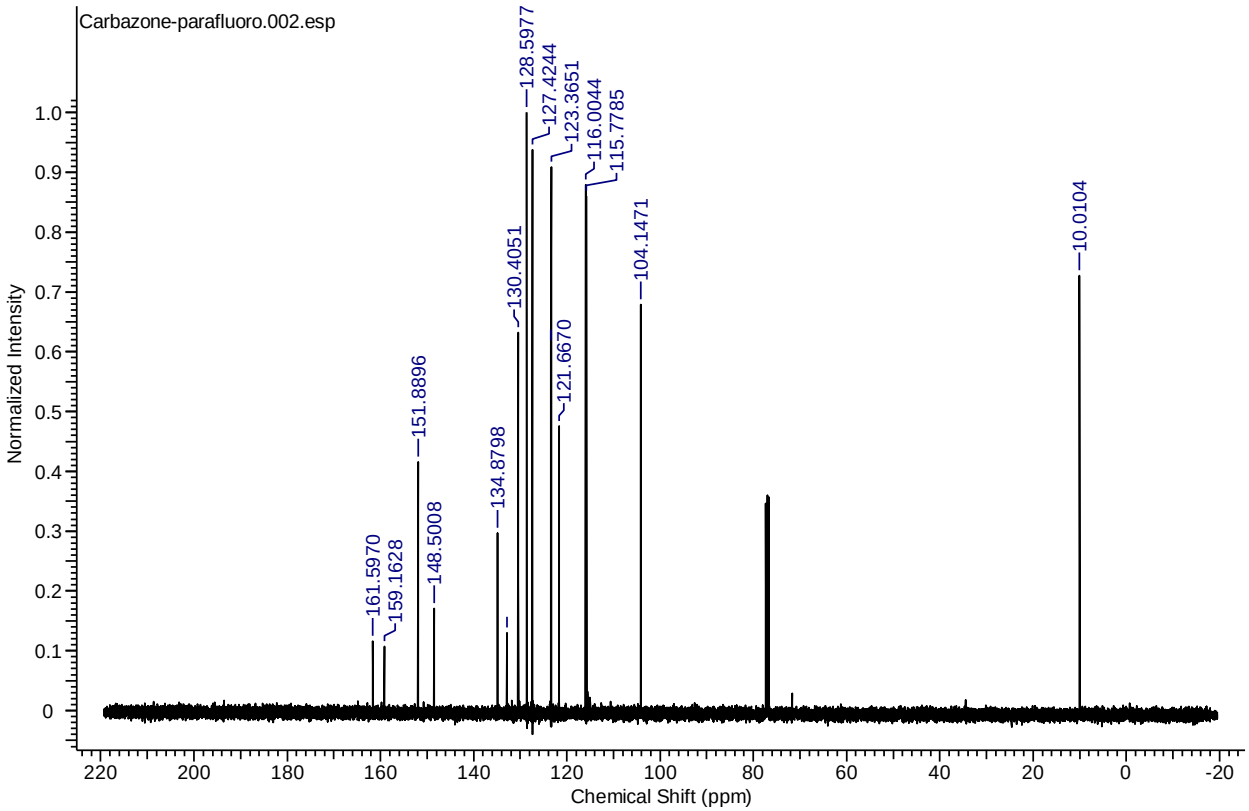

JF11-2011-H.1001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
2.00
2.02
5.11
1.30
0.95
3.16

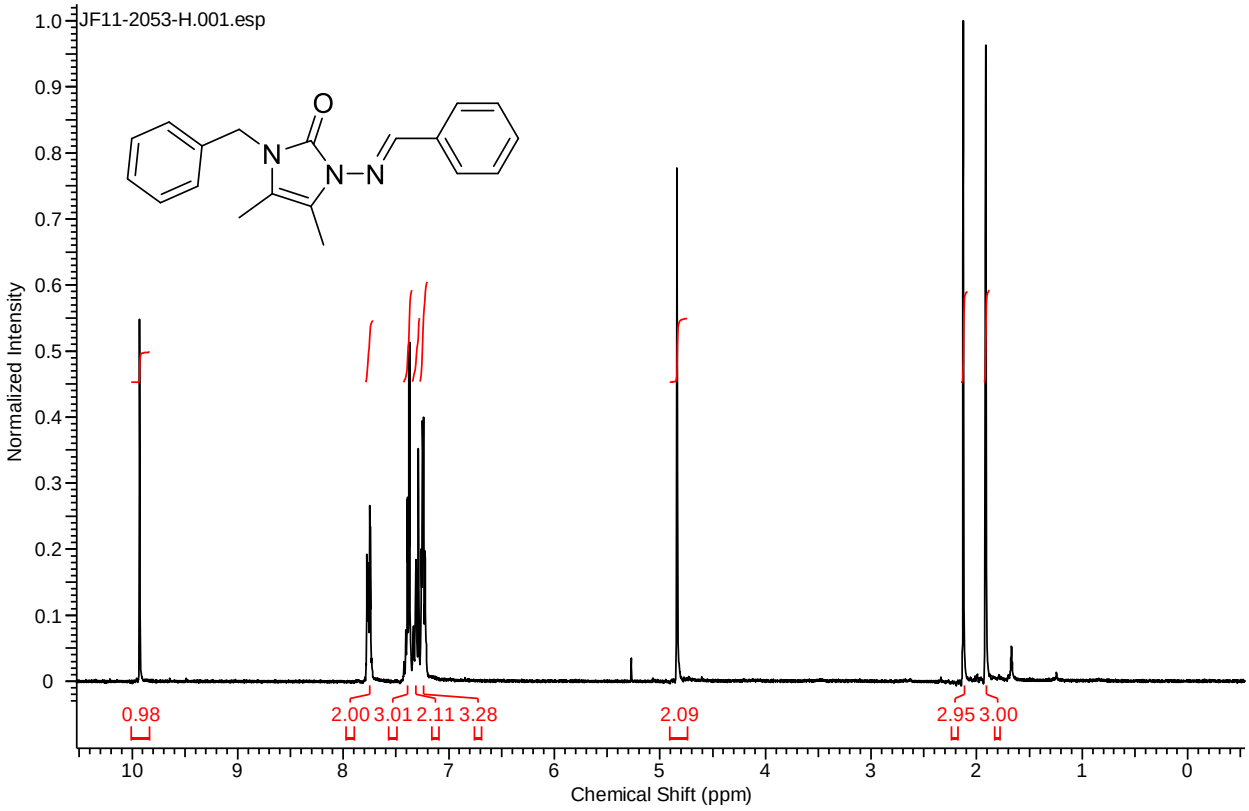

JF11-2011-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
151.8538
135.0386
130.3984
129.1765
128.6383
127.4747
125.7728
121.6272
104.1719
10.1174

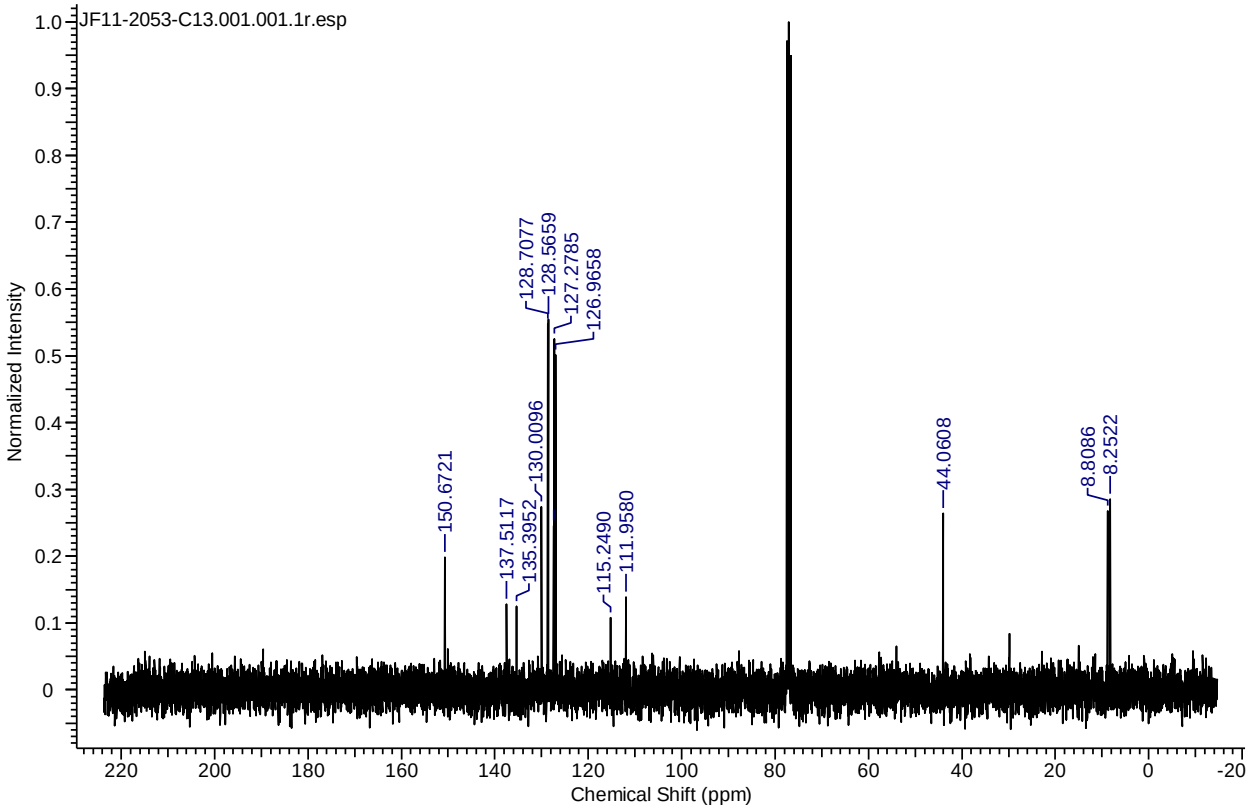

Carbazone-paramethoxy.001.esp
MeO
O
N
N–N
Normalized Intensity
1.02
2.13
5.26
2.10
1.00
3.23
3.13
Chemical Shift (ppm)

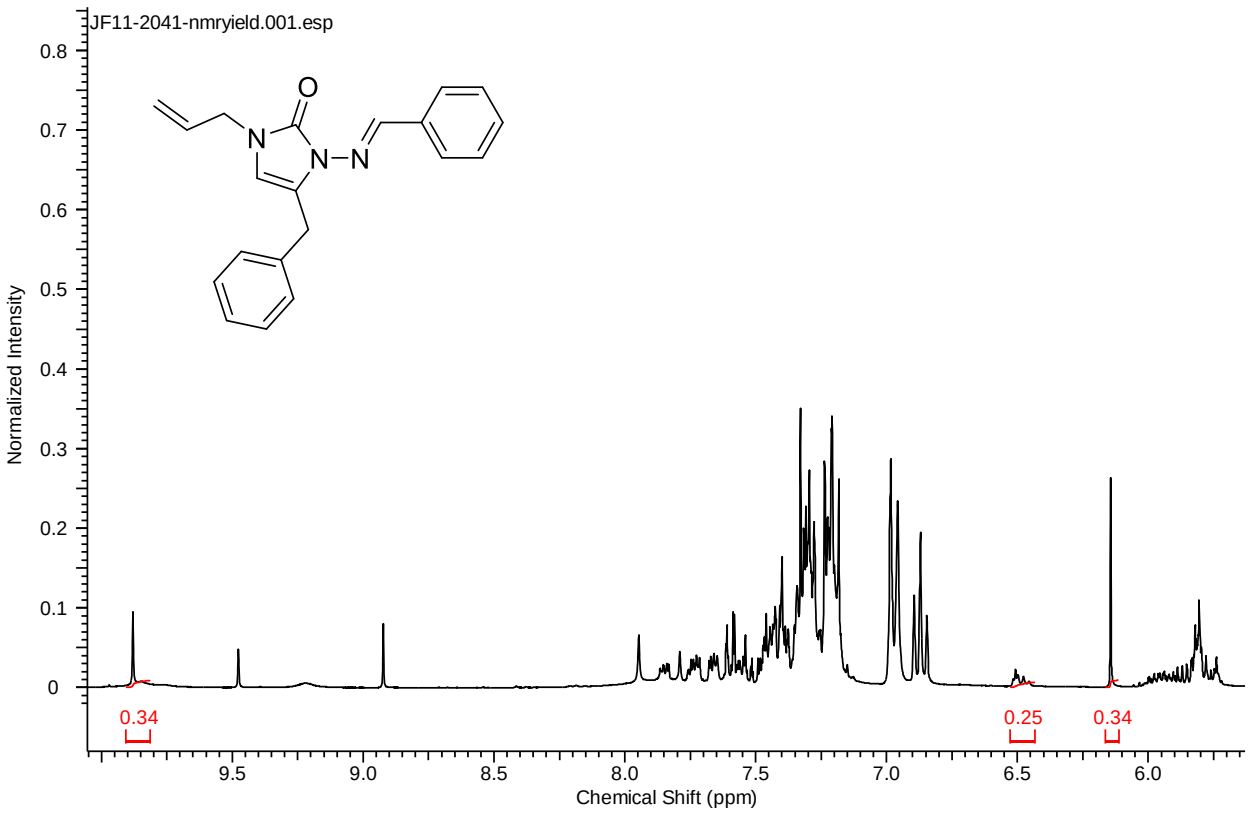

Carbazone-paramethoxy.002.esp
157.6105
151.5981
148.6903
135.0620
130.2958
128.5905
123.4890
121.1277
114.3282
104.7156
55.4645
10.0468
Normalized Intensity
Chemical Shift (ppm)


Carbazone-parafluoro.001.esp
F
O
N
N
N
Normalized Intensity
2.0
1.5
1.0
0.5
0
1.00
2.08
2.08
3.06
2.06
0.99
3.20
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


Carbazone-parafluoro.002.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
161.5970
159.1628
151.8896
148.5008
134.8798
130.4051
128.5977
127.4244
123.3651
121.6670
116.0044
115.7785
104.1471
10.0104
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


JF11-2053-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.98
2.00
3.01
2.11
3.28
2.09
2.95
3.00

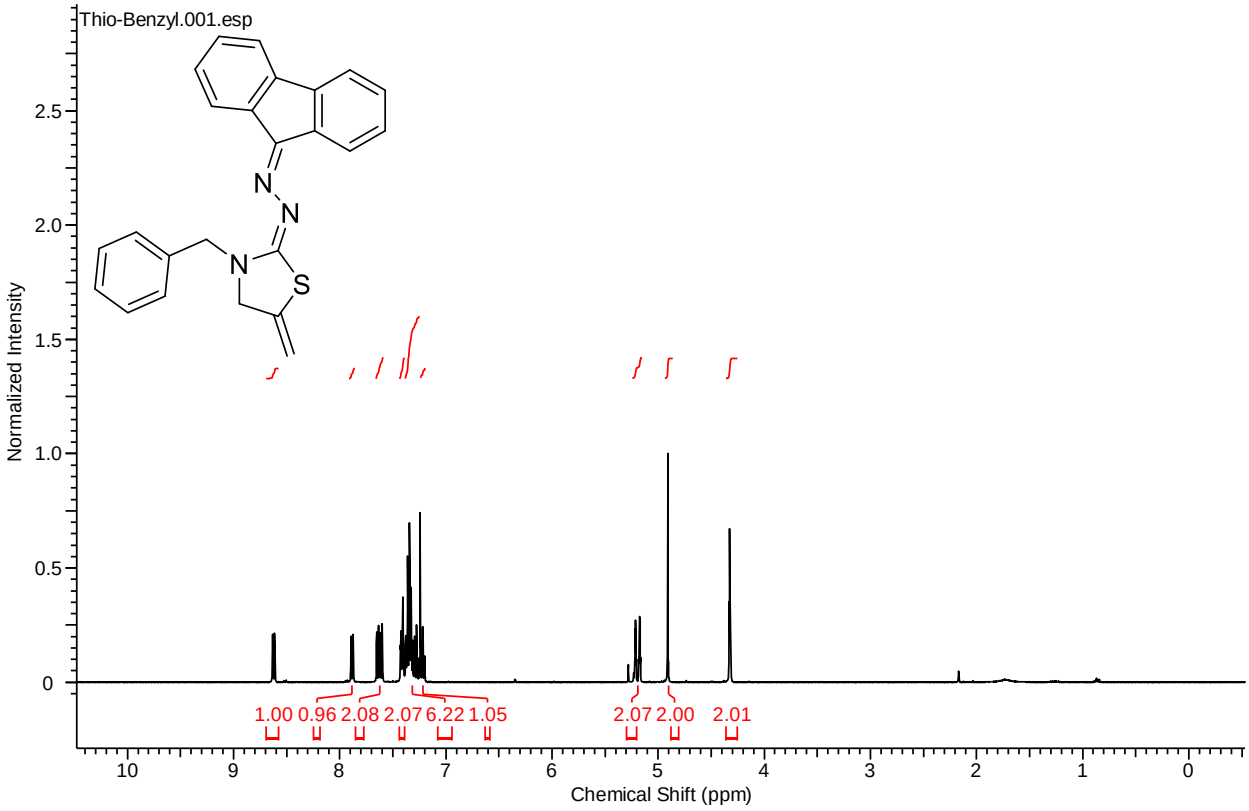

JF11-2053-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
150.6721
137.5117
135.3952
130.0096
128.7077
128.5659
127.2785
126.9658
115.2490
111.9580
44.0608
8.8086
8.2522

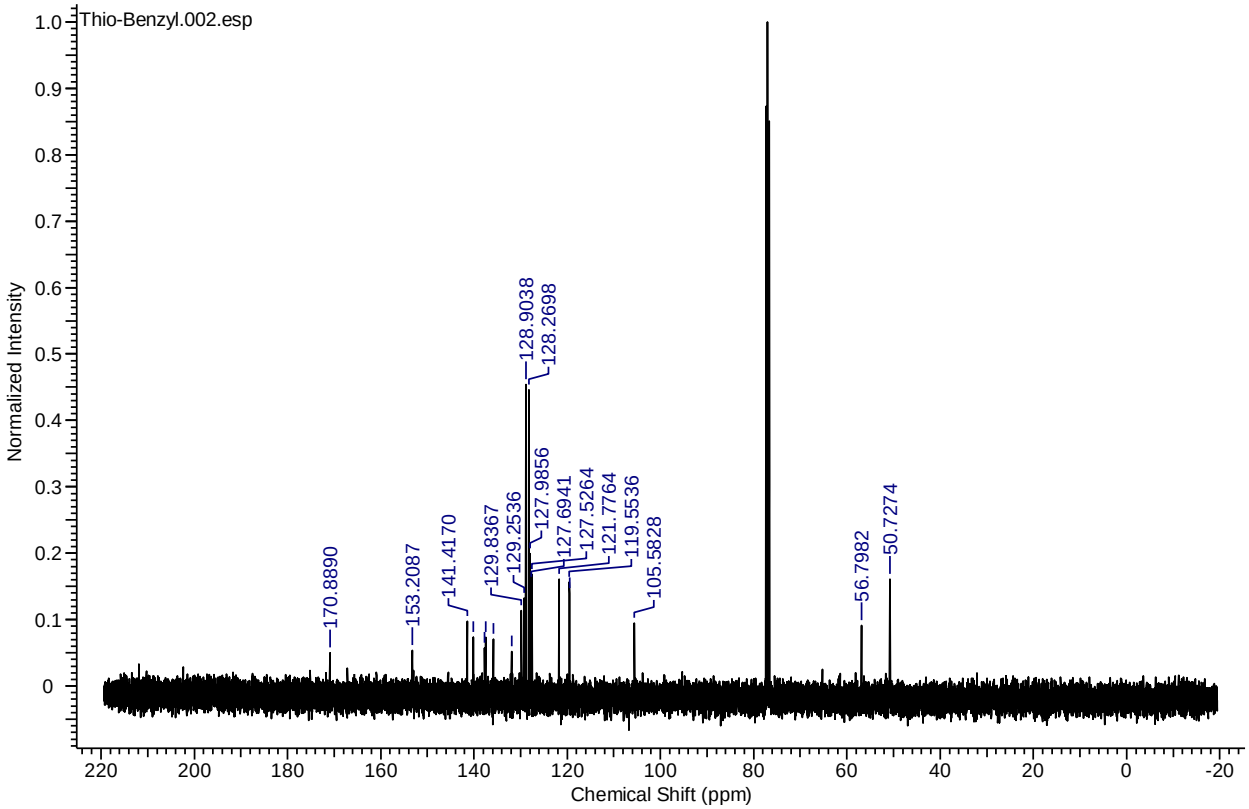


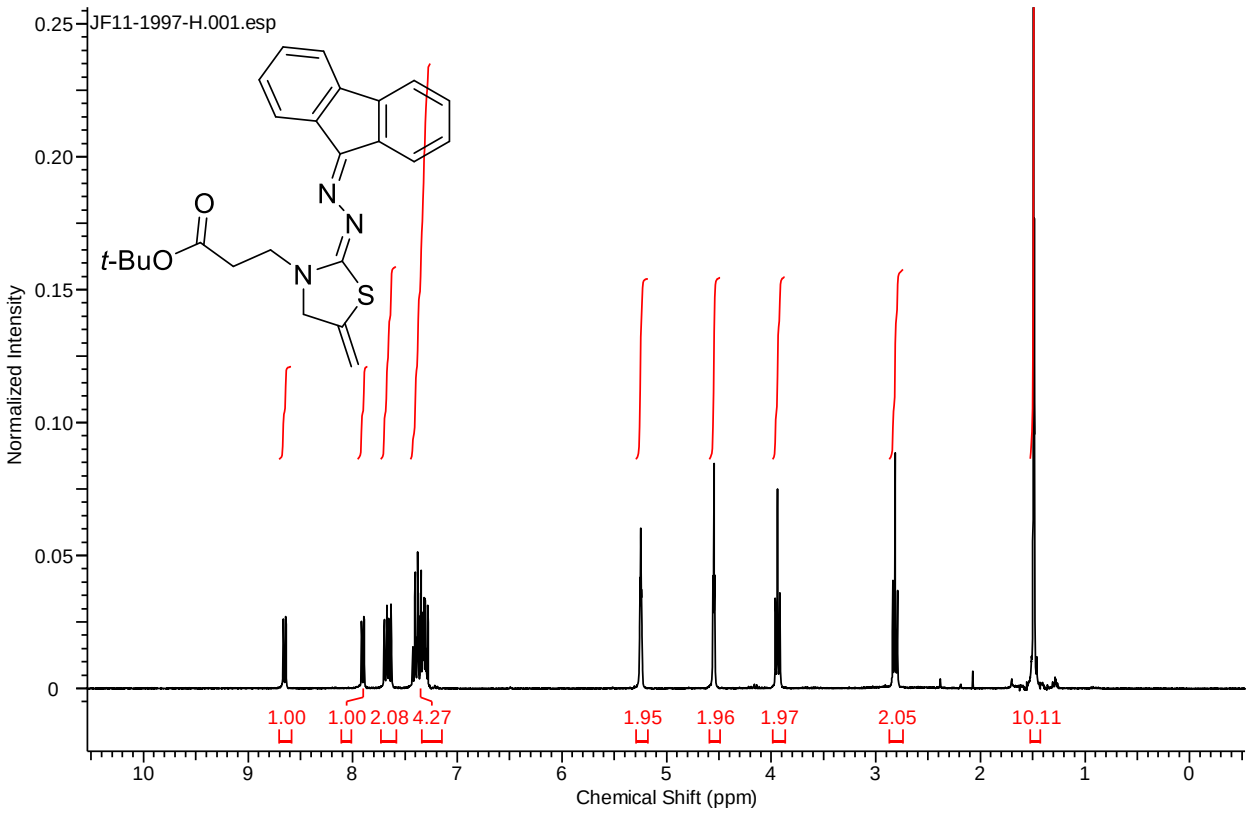
11.4 mg of TMB = 0.0678 mmol

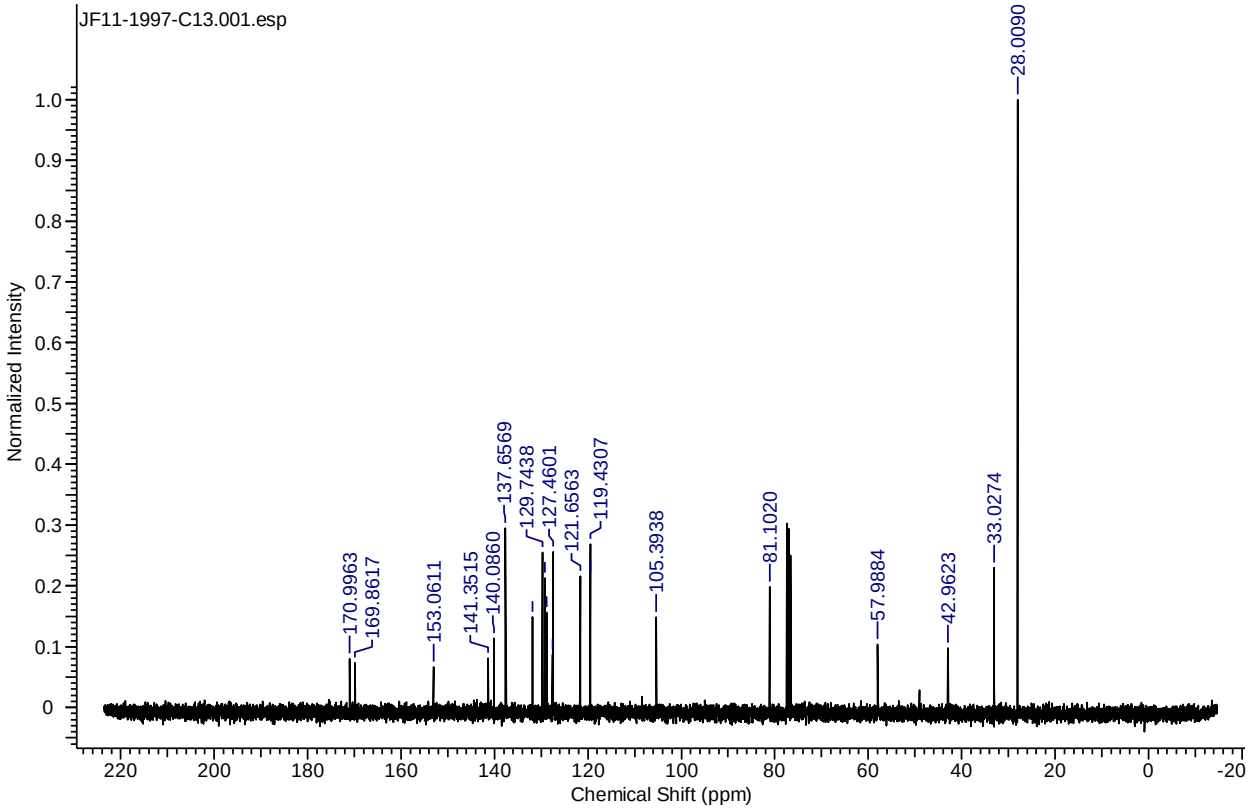
0.600 mmol / 0.0678 mmol = 8.34

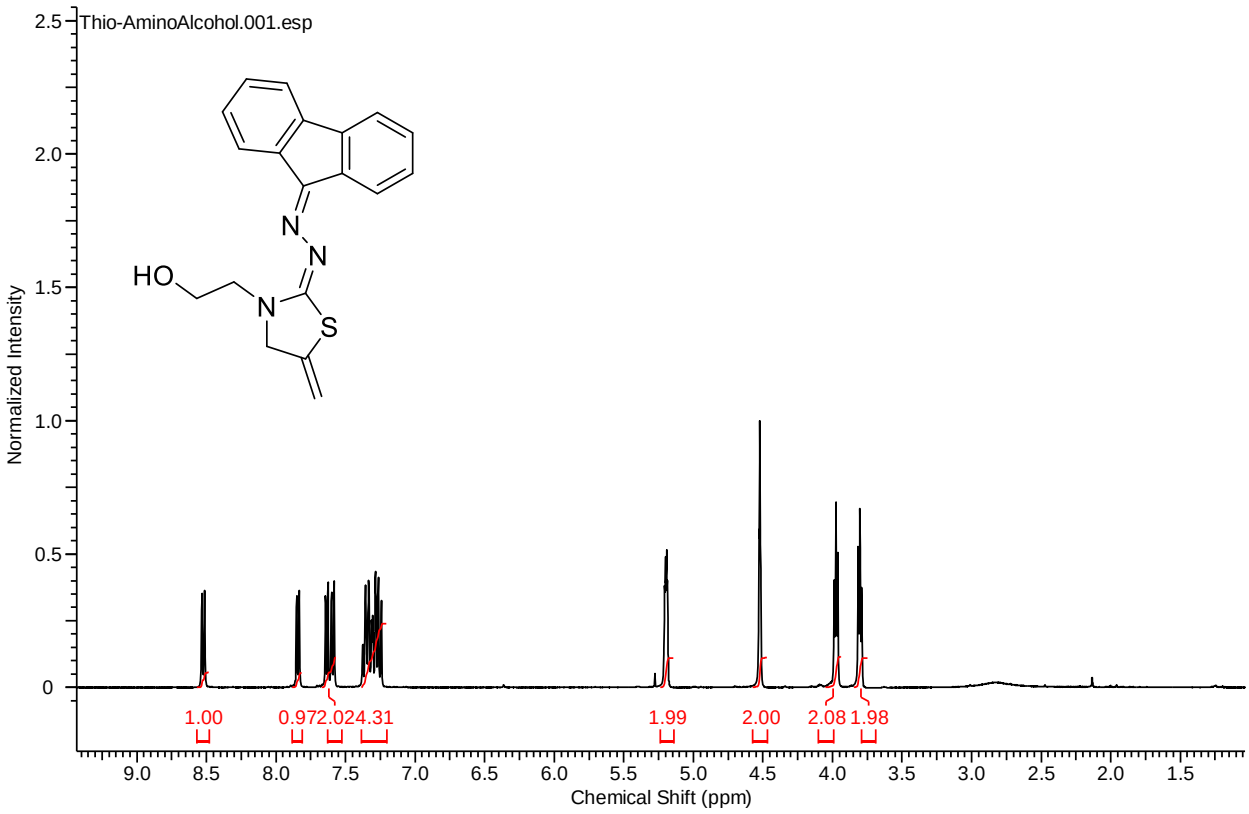
3 proton (tmd signal) / 8.34 = 0.34 proton

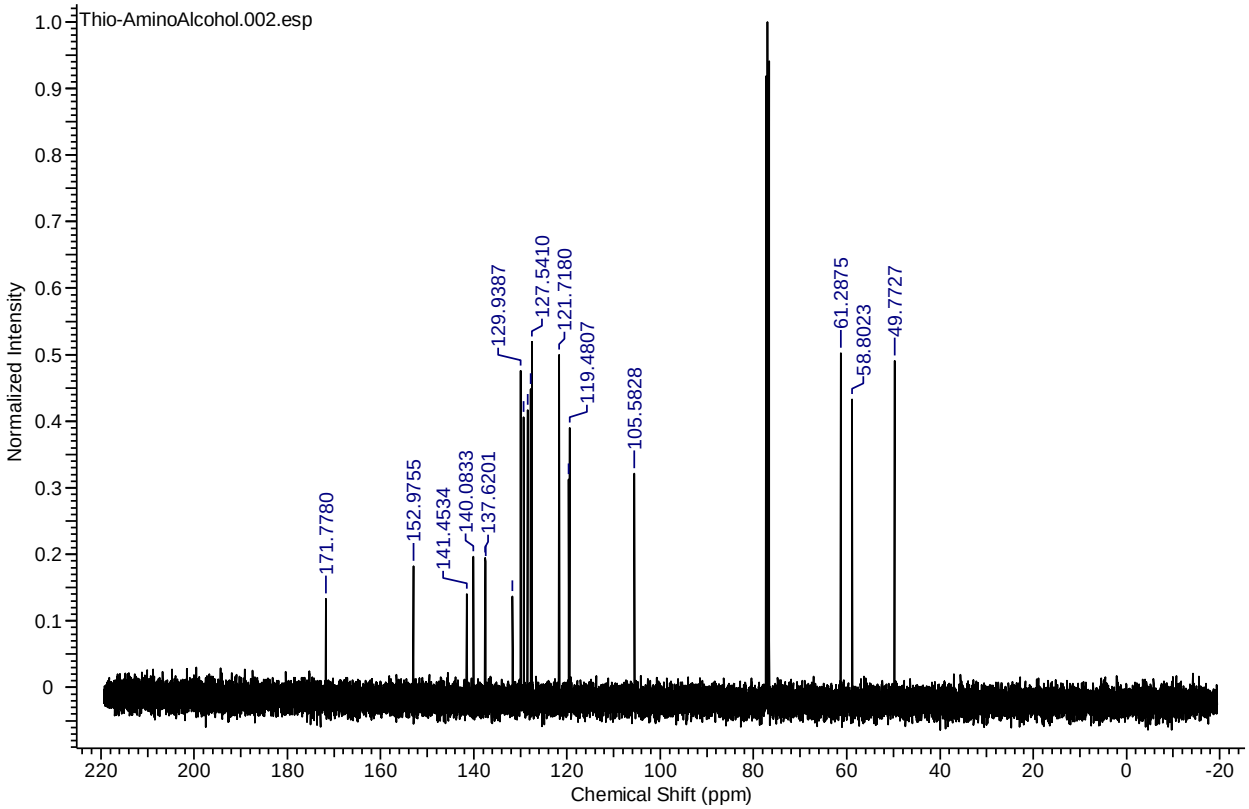

Thio-Benzyl.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00 0.96 2.08 2.07 6.22 1.05
2.07 2.00 2.01

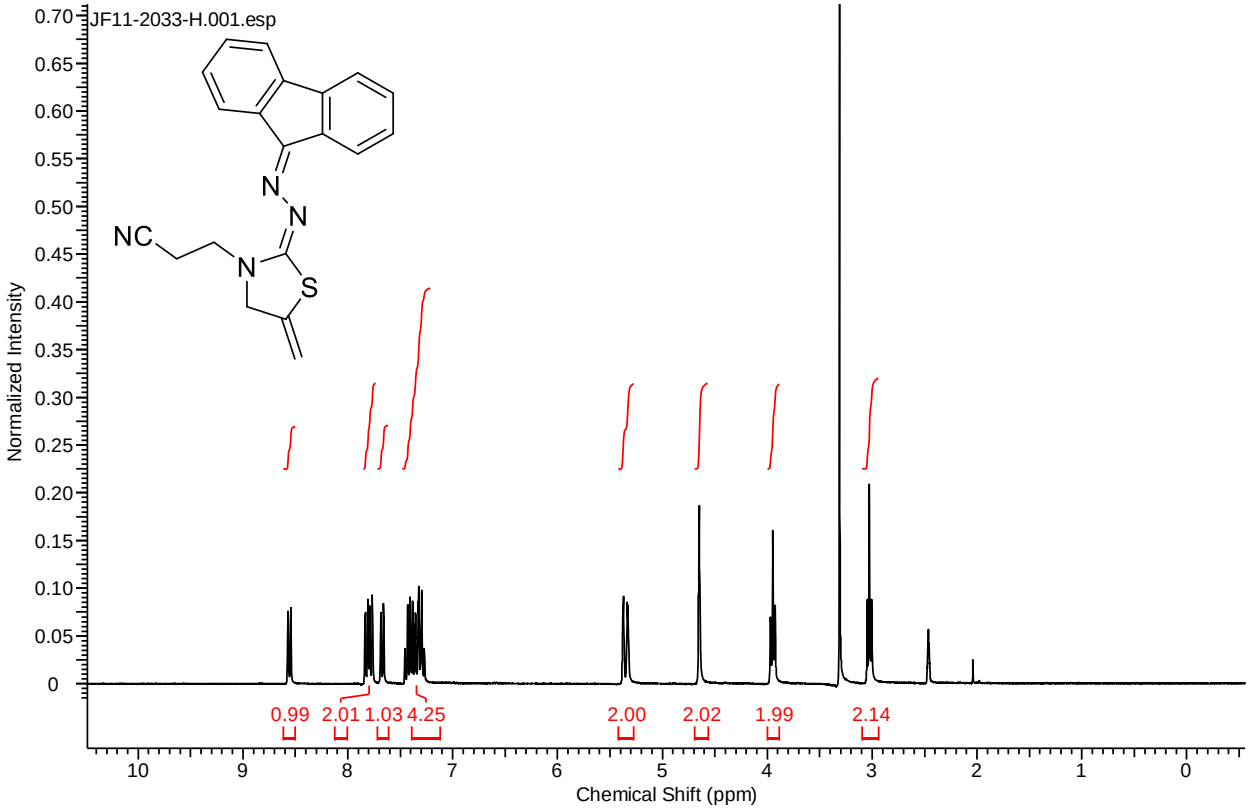

Thio-Benzyl.002.esp
Normalized Intensity
Chemical Shift (ppm)
170.8890
153.2087
141.4170
129.8367
129.2536
128.9038
128.2698
127.9856
127.6941
127.5264
121.7764
119.5536
105.5828
56.7982
50.7274

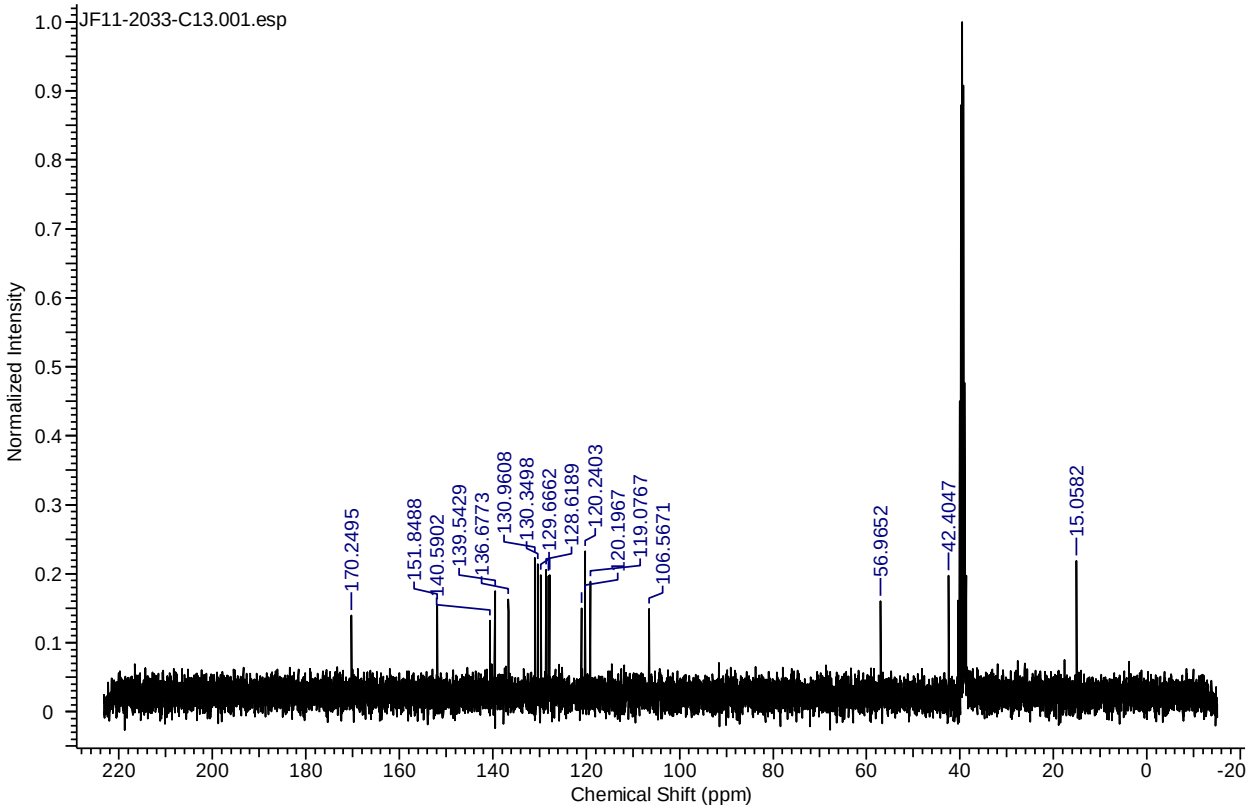

JF11-1997-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
t-BuO
1.00
1.00
2.08
4.27
1.95
1.96
1.97
2.05
10.11

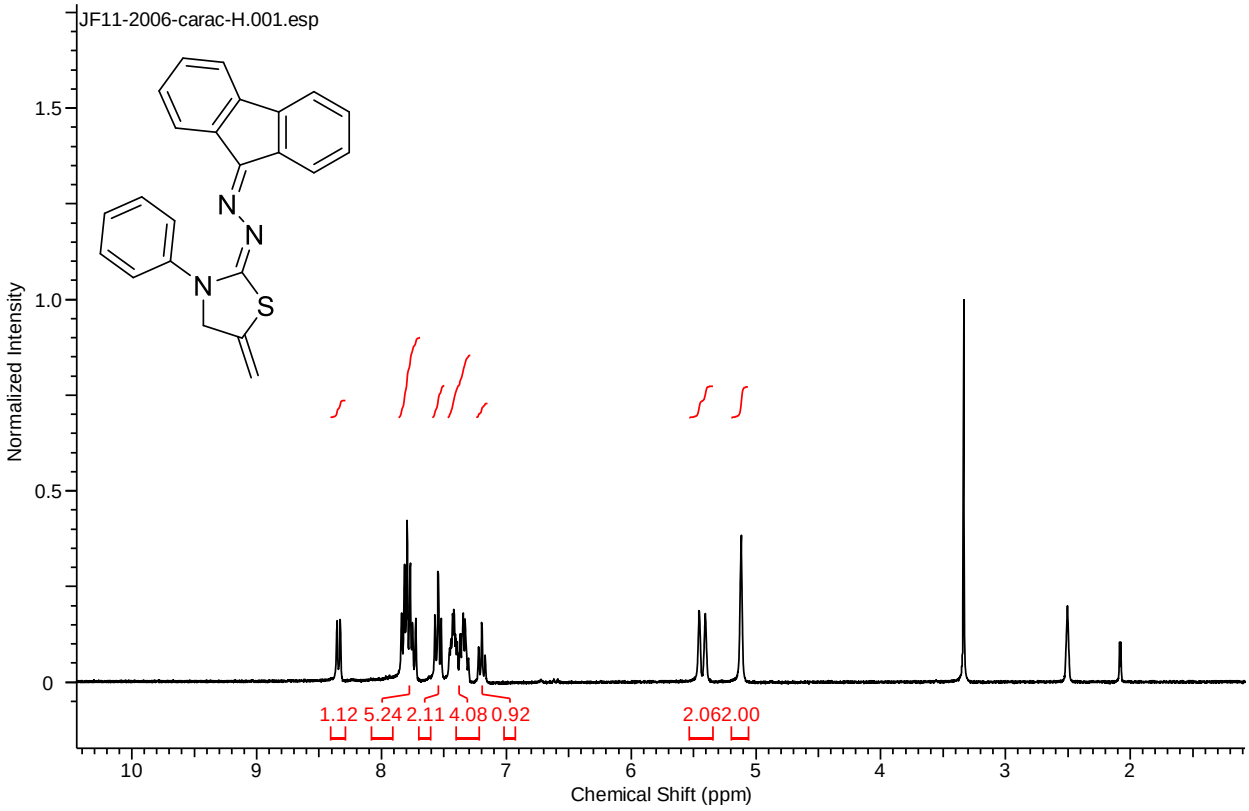

JF11-1997-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
170.9963
169.8617
153.0611
141.3515
140.0860
137.6569
129.7438
127.4601
121.6563
119.4307
105.3938
81.1020
57.9884
42.9623
33.0274
28.0090

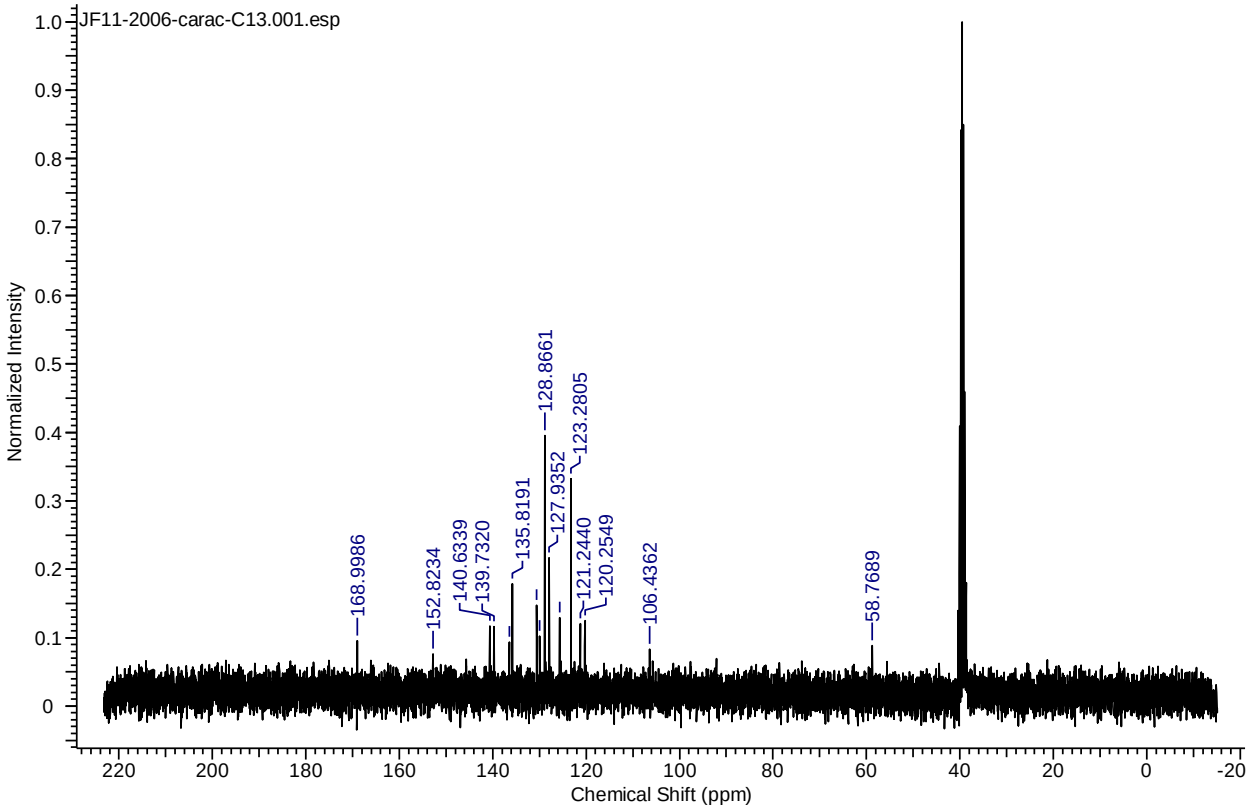

Thio-AminoAlcohol.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.00
0.97
2.02
4.31
1.99
2.00
2.08
1.98
HO
N
N
N
S

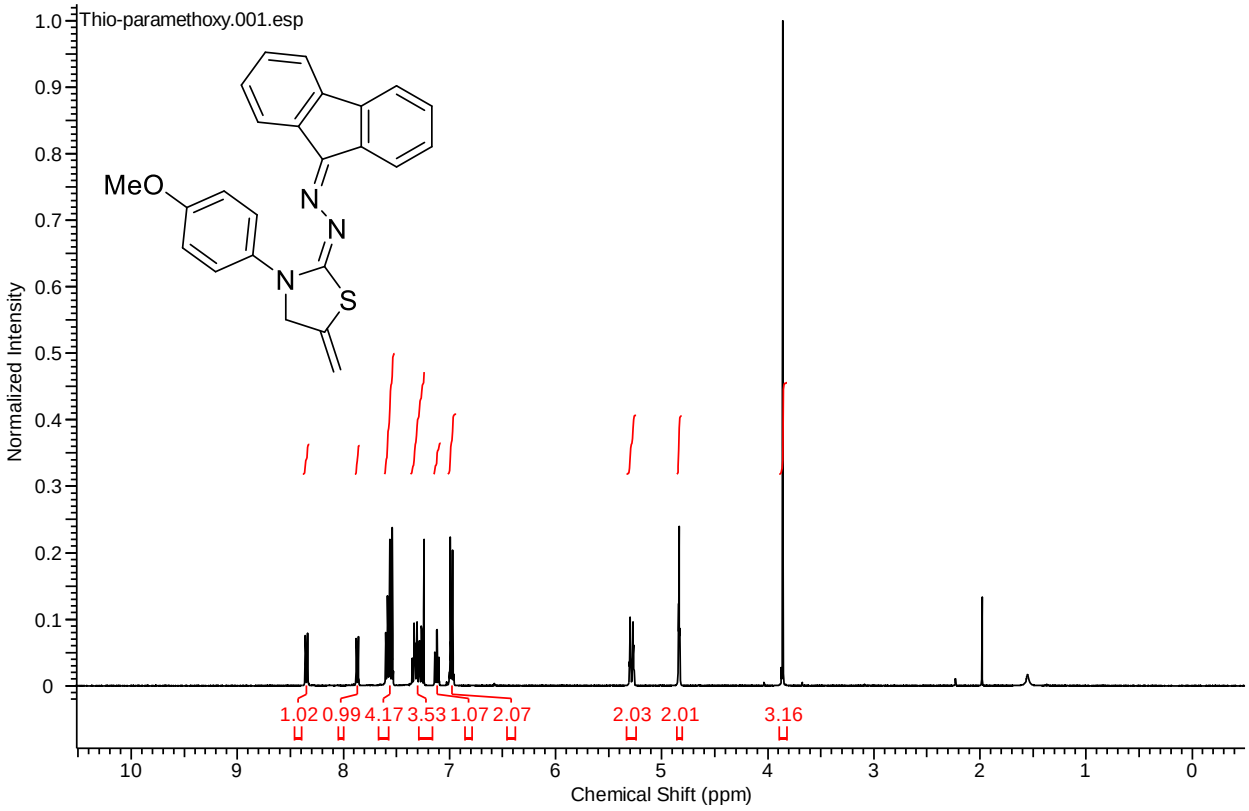

Thio-AminoAlcohol.002.esp
Normalized Intensity
Chemical Shift (ppm)
171.7780
152.9755
141.4534
140.0833
137.6201
129.9387
127.5410
121.7180
119.4807
105.5828
61.2875
58.8023
49.7727

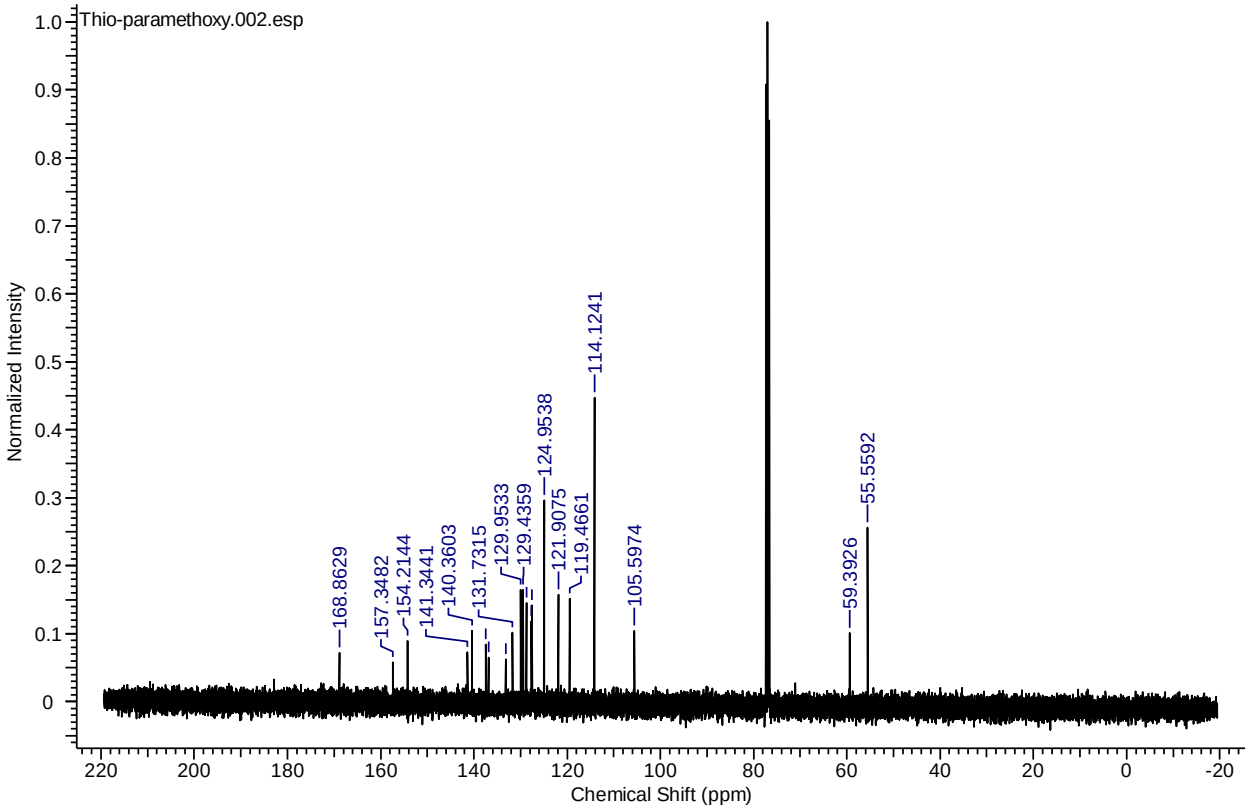

JF11-2033-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.99
2.01
1.03
4.25
2.00
2.02
1.99
2.14
NC
N
N
N
S

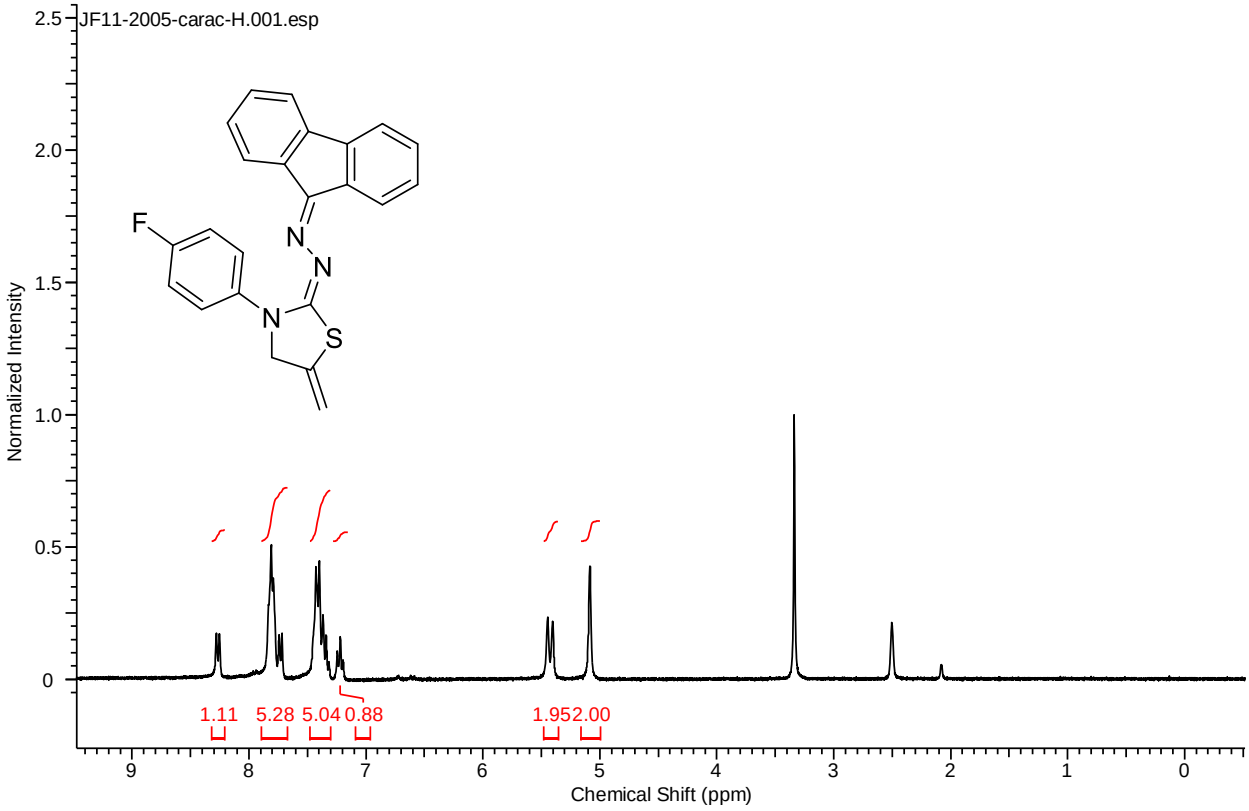

JF11-2033-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
170.2495
151.8488
140.5902
139.5429
136.6773
130.9608
130.3498
129.6662
128.6189
120.2403
120.1967
119.0767
106.5671
56.9652
42.4047
15.0582

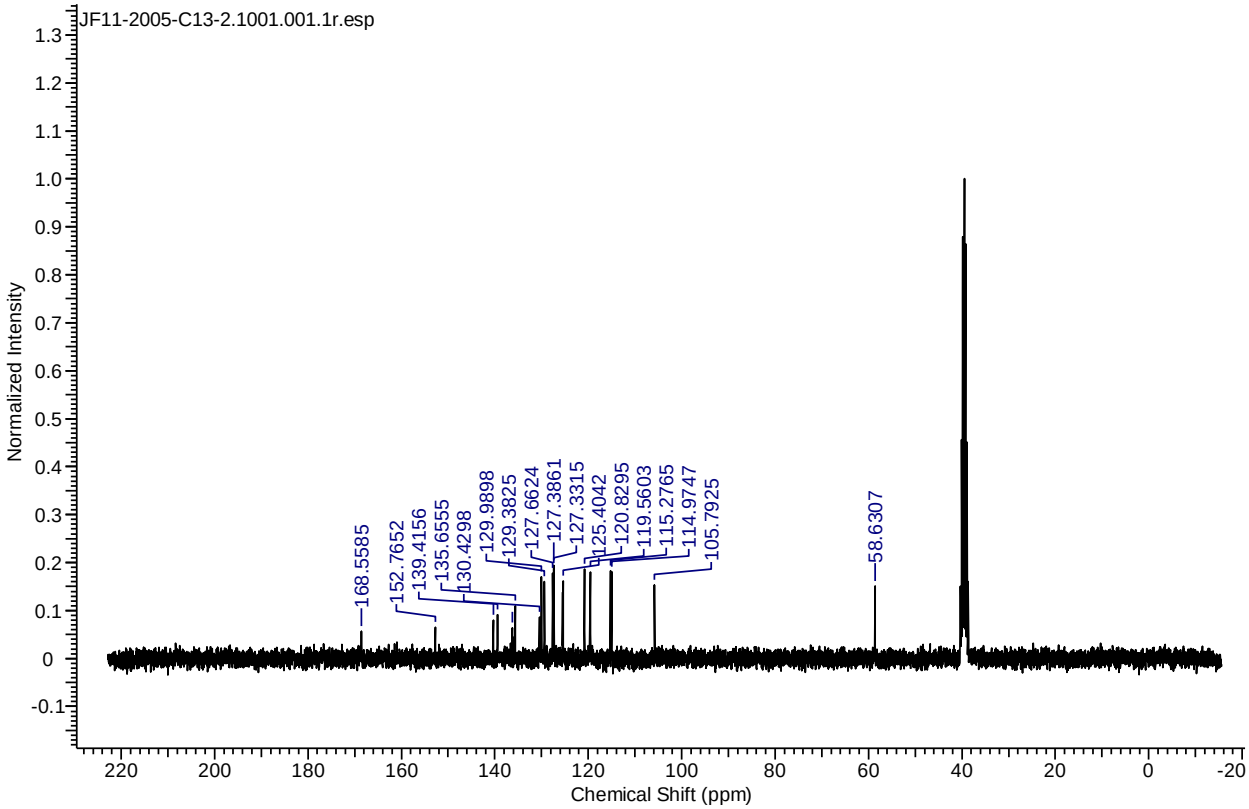

JF11-2006-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.12 5.24 2.11 4.08 0.92
2.062.00

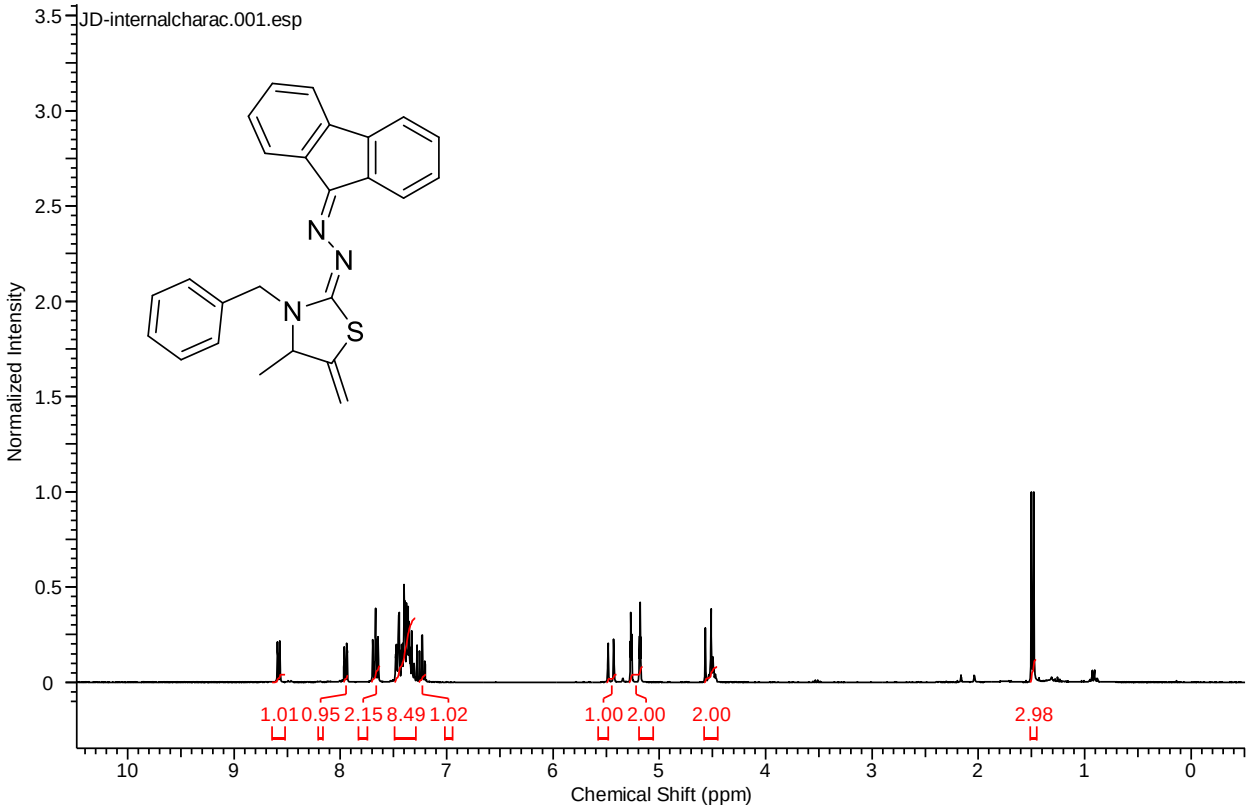

JF11-2006-carac-C13.001.esp
Normalized Intensity
Chemical Shift (ppm)
168.9986
152.8234
140.6339
139.7320
135.8191
128.8661
127.9352
123.2805
121.2440
120.2549
106.4362
58.7689

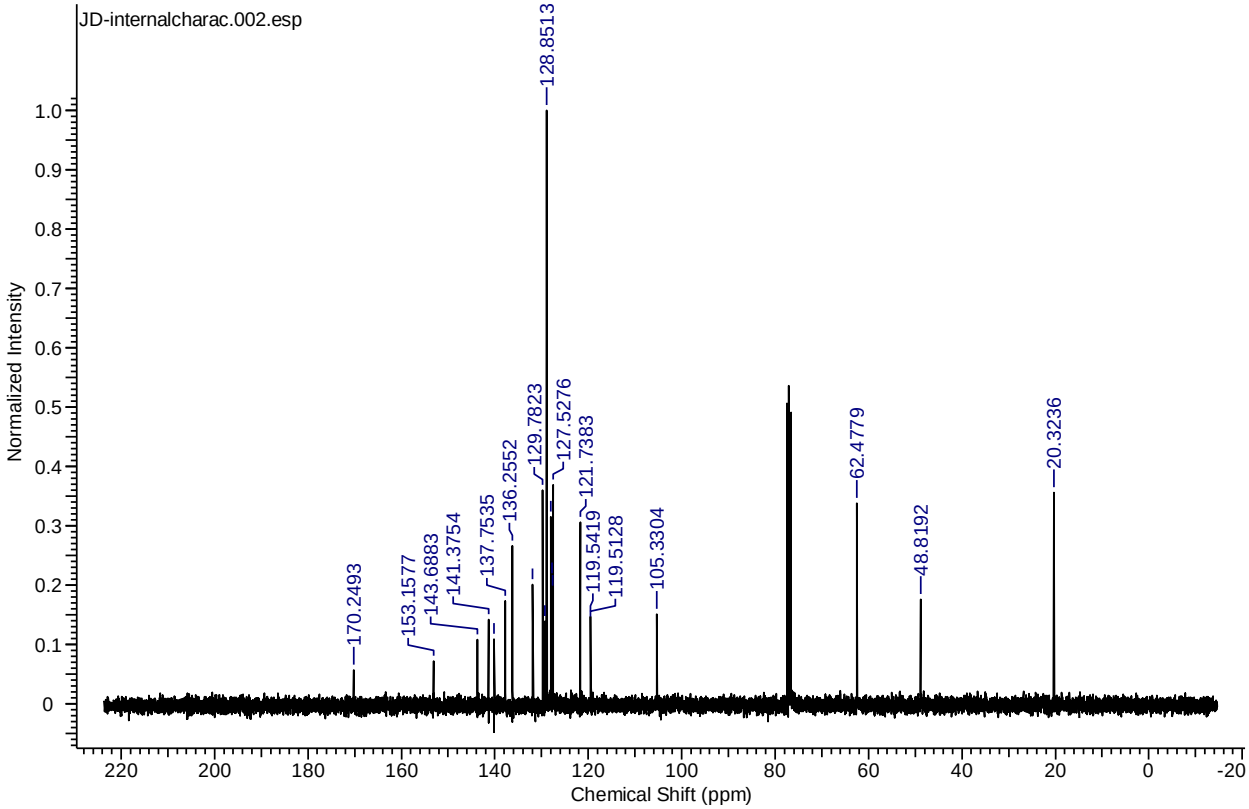

Thio-paramethoxy.001.esp
MeO
N
N
N
S
Normalized Intensity
1.02 0.99 4.17 3.53 1.07 2.07
2.03 2.01
3.16
Chemical Shift (ppm)

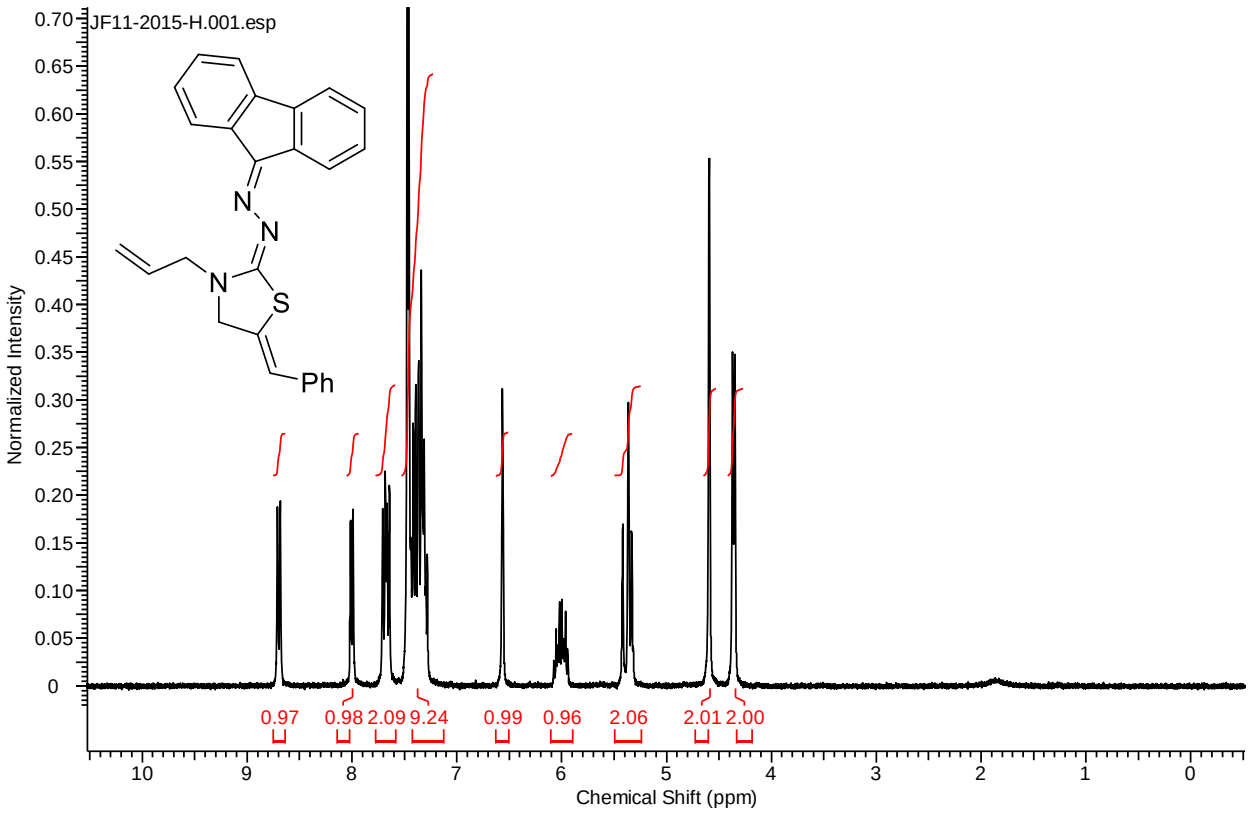

Thio-paramethoxy.002.esp
Normalized Intensity
168.8629
157.3482
154.2144
141.3441
140.3603
131.7315
129.9533
129.4359
124.9538
121.9075
119.4661
114.1241
105.5974
59.3926
55.5592
Chemical Shift (ppm)

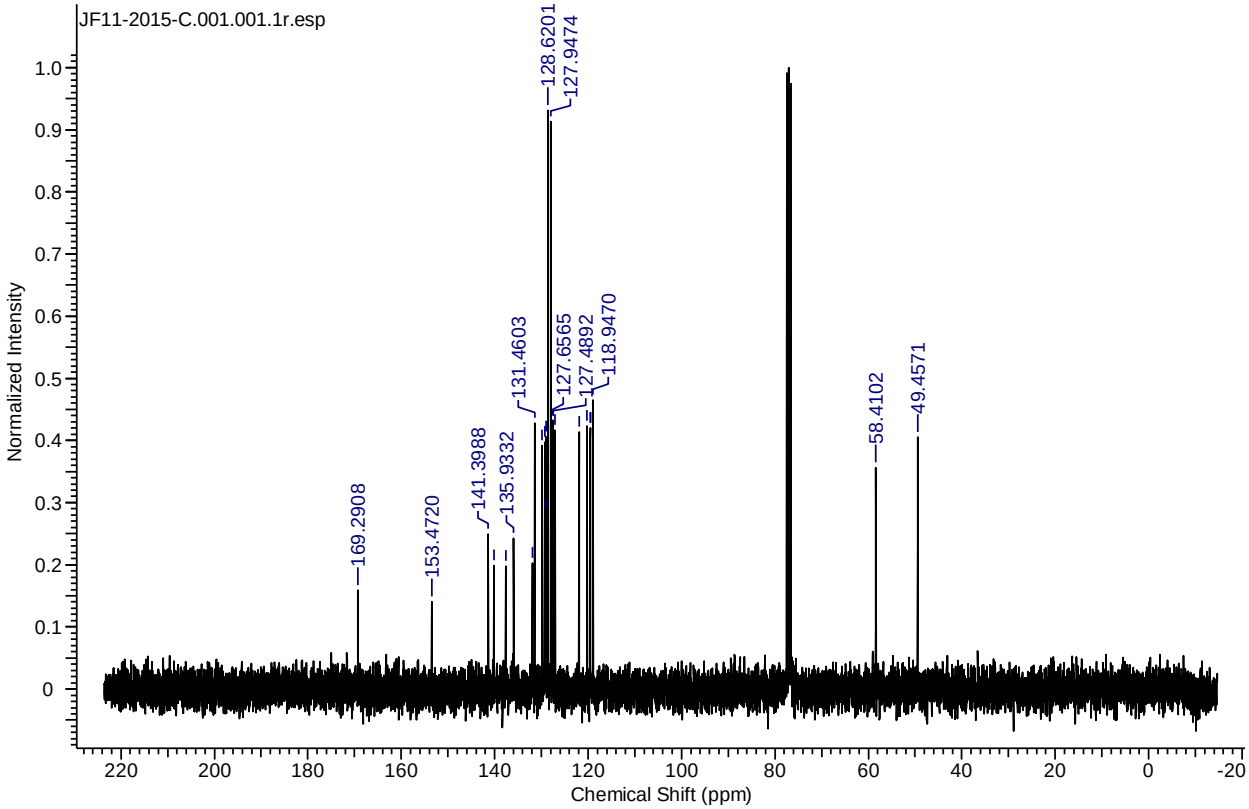

JF11-2005-carac-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.11
5.28
5.04
0.88
1.95
2.00
F
N
N
N
S

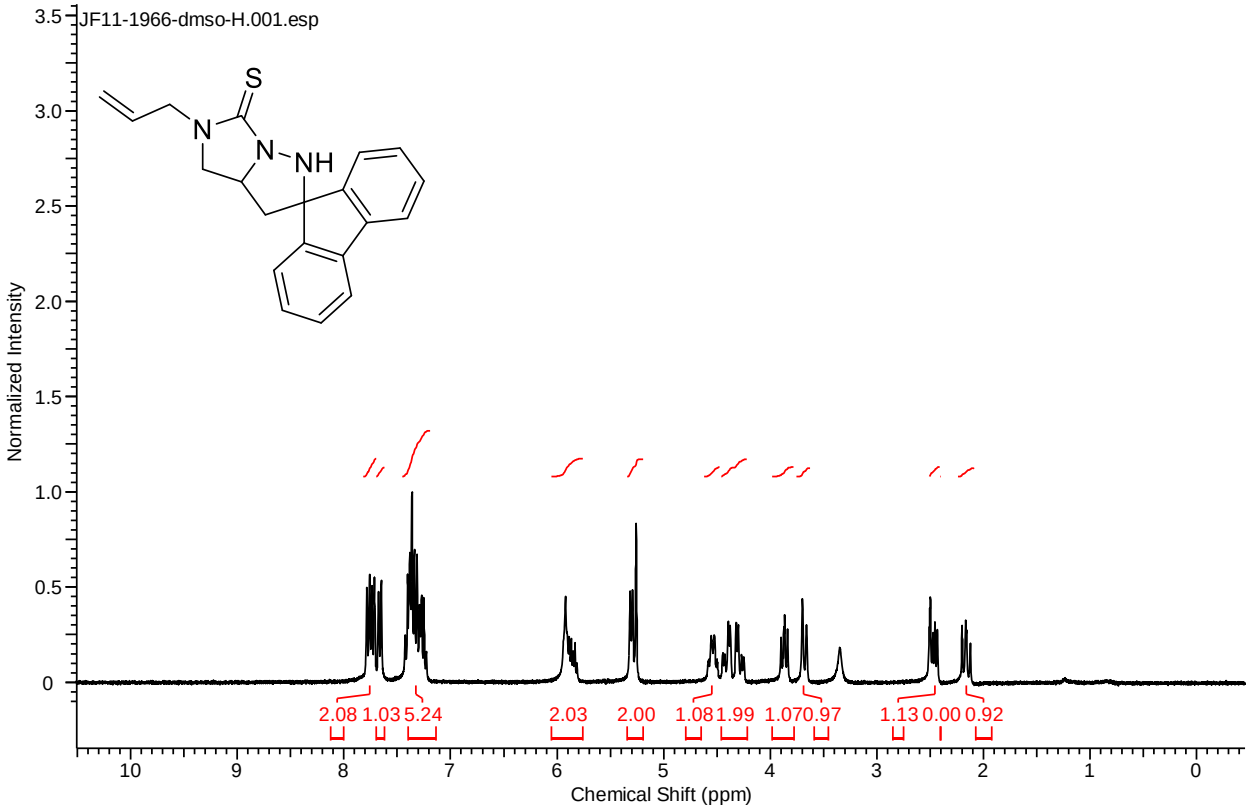

JF11-2005-C13-2.1001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
168.5585
152.7652
139.4156
135.6555
130.4298
129.9898
129.3825
127.6624
127.3861
127.3315
125.4042
120.8295
119.5603
115.2765
114.9747
105.7925
58.6307

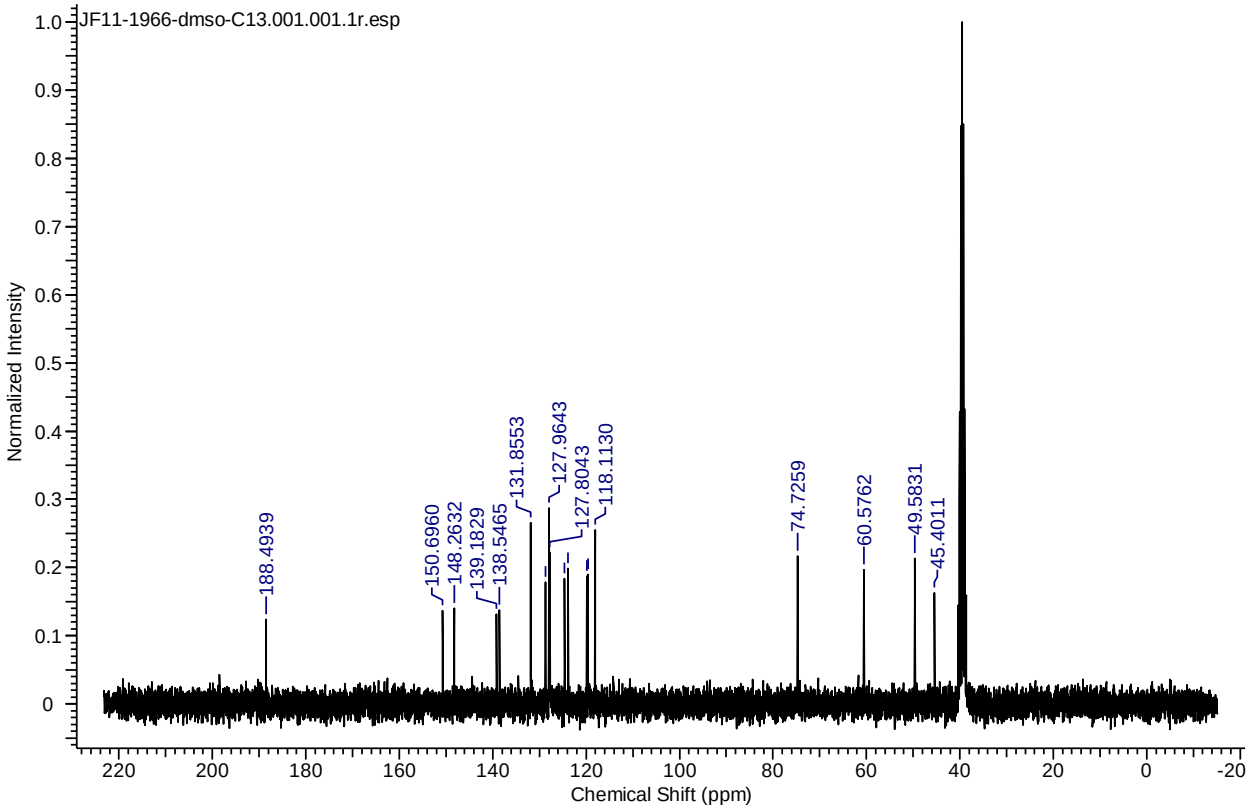

JD-internalcharac.001.esp
Normalized Intensity
Chemical Shift (ppm)
1.01 0.95 2.15 8.49 1.02
1.00 2.00
2.00
2.98
N
N
N
S

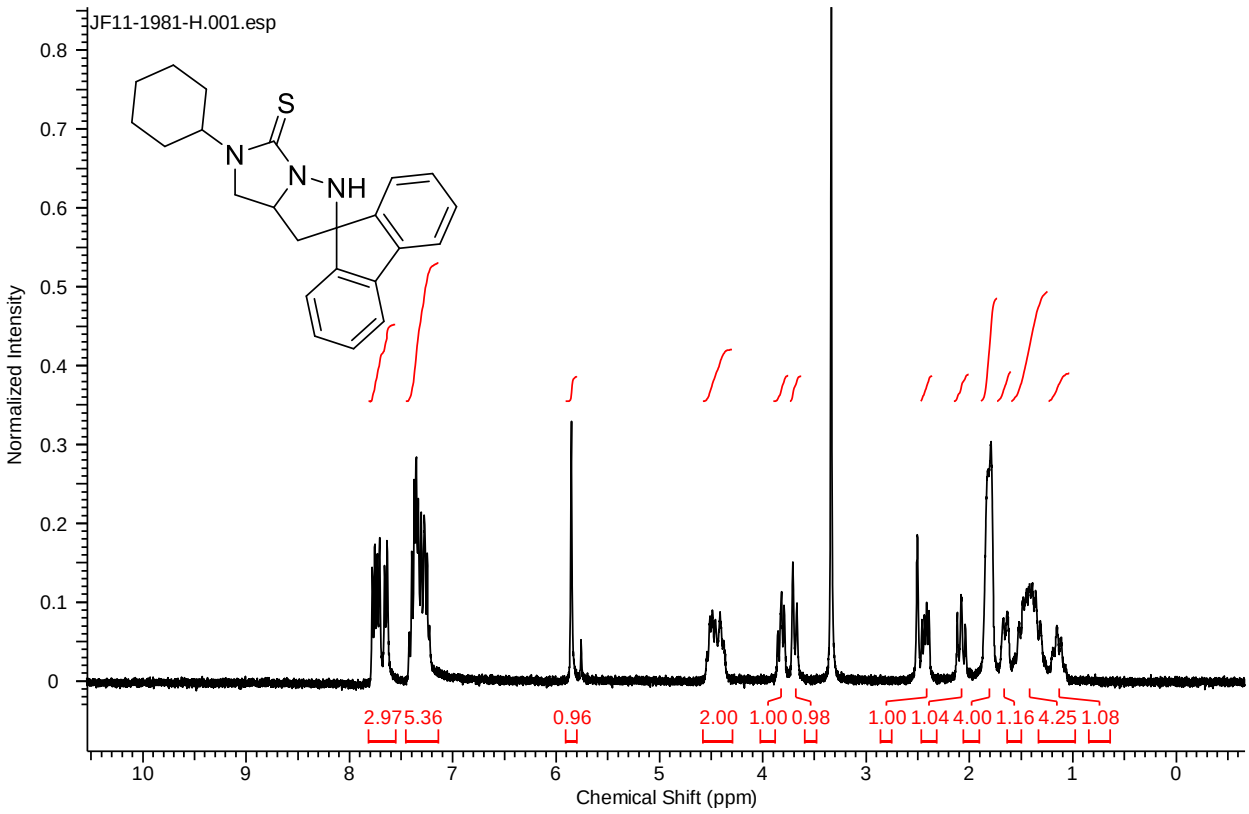

JD-internalcharac.002.esp
Normalized Intensity
Chemical Shift (ppm)
128.8513
129.7823
127.5276
121.7383
119.5419
119.5128
105.3304
62.4779
48.8192
20.3236
170.2493
153.1577
143.6883
141.3754
137.7535
136.2552

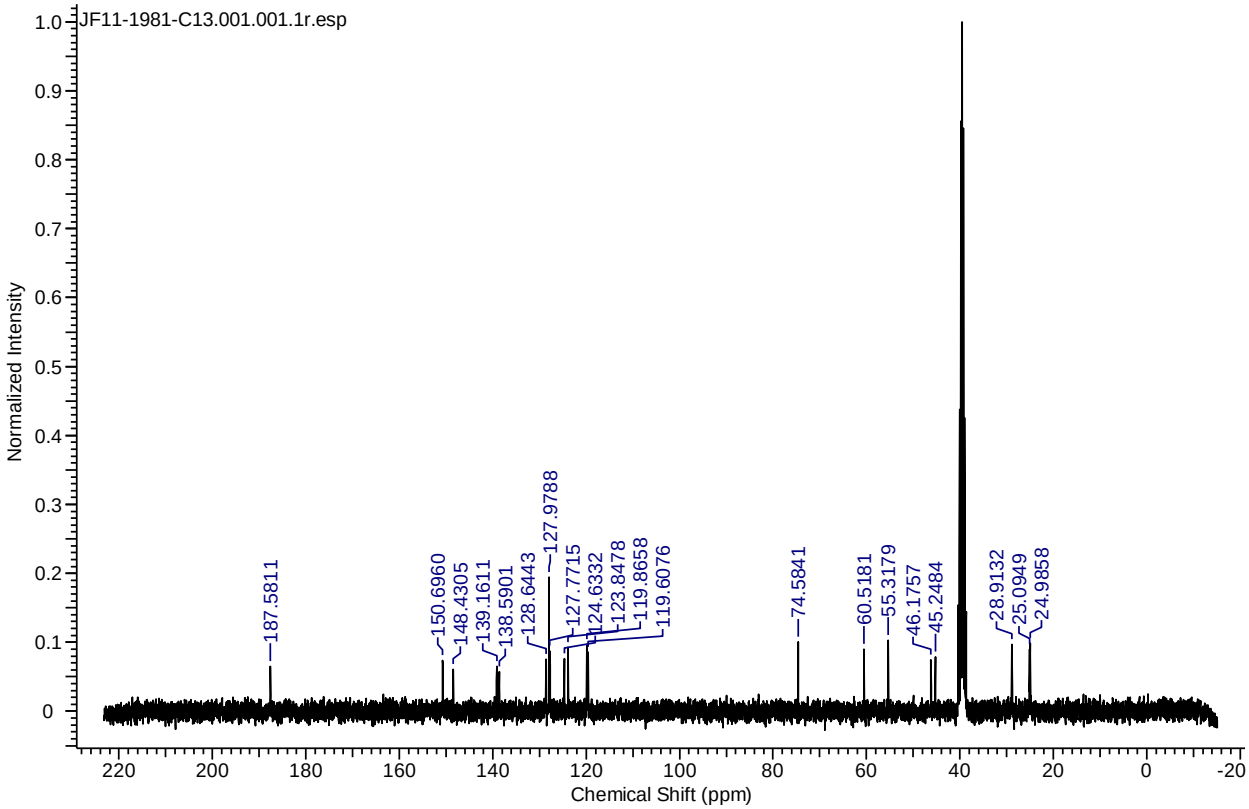

JF11-2015-H.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.97
0.98
2.09
9.24
0.99
0.96
2.06
2.01
2.00
N
N
N
S
Ph


JF11-2015-C.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
169.2908
153.4720
141.3988
135.9332
131.4603
128.6201
127.9474
127.6565
127.4892
118.9470
58.4102
49.4571


JF11-1966-dmso-H.001.esp
S
N
N
NH
Normalized Intensity
2.08 1.03 5.24 2.03 2.00 1.08 1.99 1.07 0.97 1.13 0.00 0.92
Chemical Shift (ppm)


JF11-1966-dmso-C13.001.001.1r.esp
Normalized Intensity
188.4939
150.6960
148.2632
139.1829
138.5465
131.8553
127.9643
127.8043
118.1130
74.7259
60.5762
49.5831
45.4011
Chemical Shift (ppm)


JF11-1981-H.001.esp
S
N
N
NH
Normalized Intensity
Chemical Shift (ppm)
2.97 5.36
0.96
2.00
1.00 0.98
1.00 1.04 4.00 1.16 4.25 1.08


JF11-1981-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
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139.1611
138.5901
128.6443
127.9788
127.7715
124.6332
123.8478
119.8658
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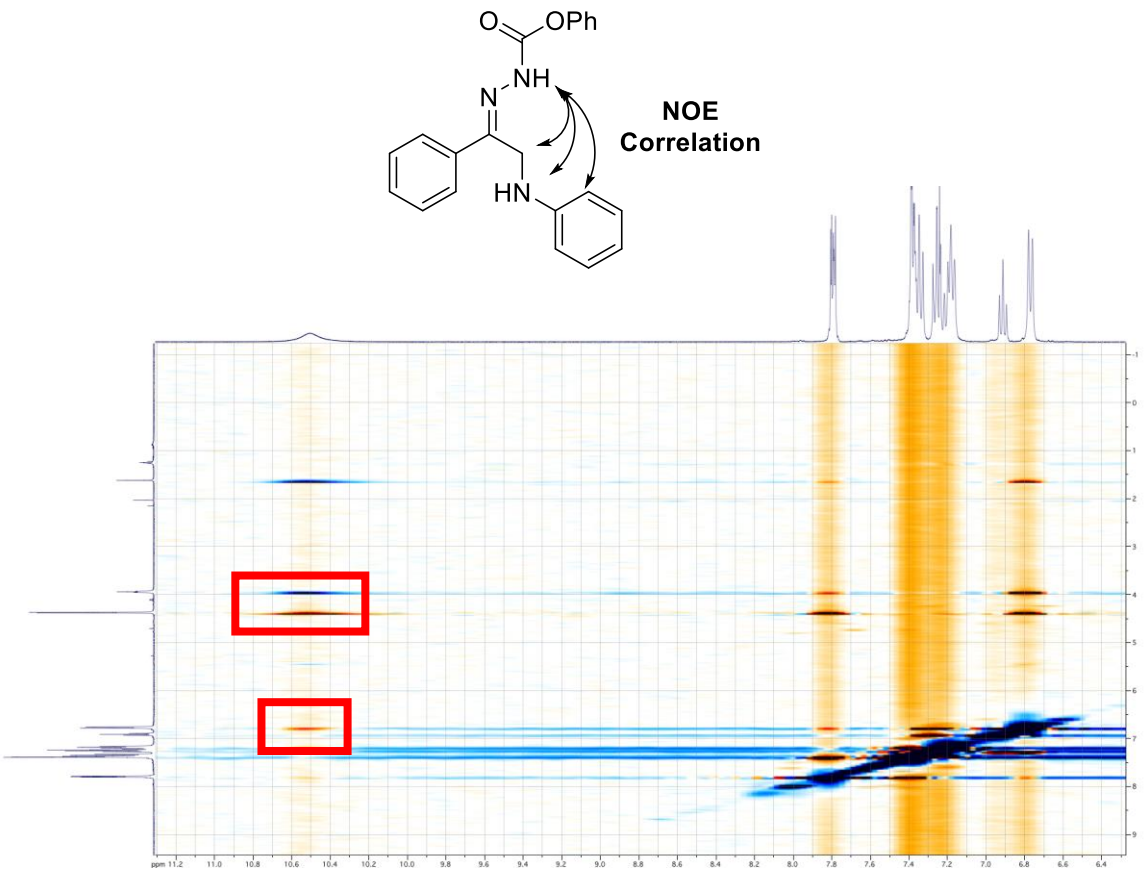
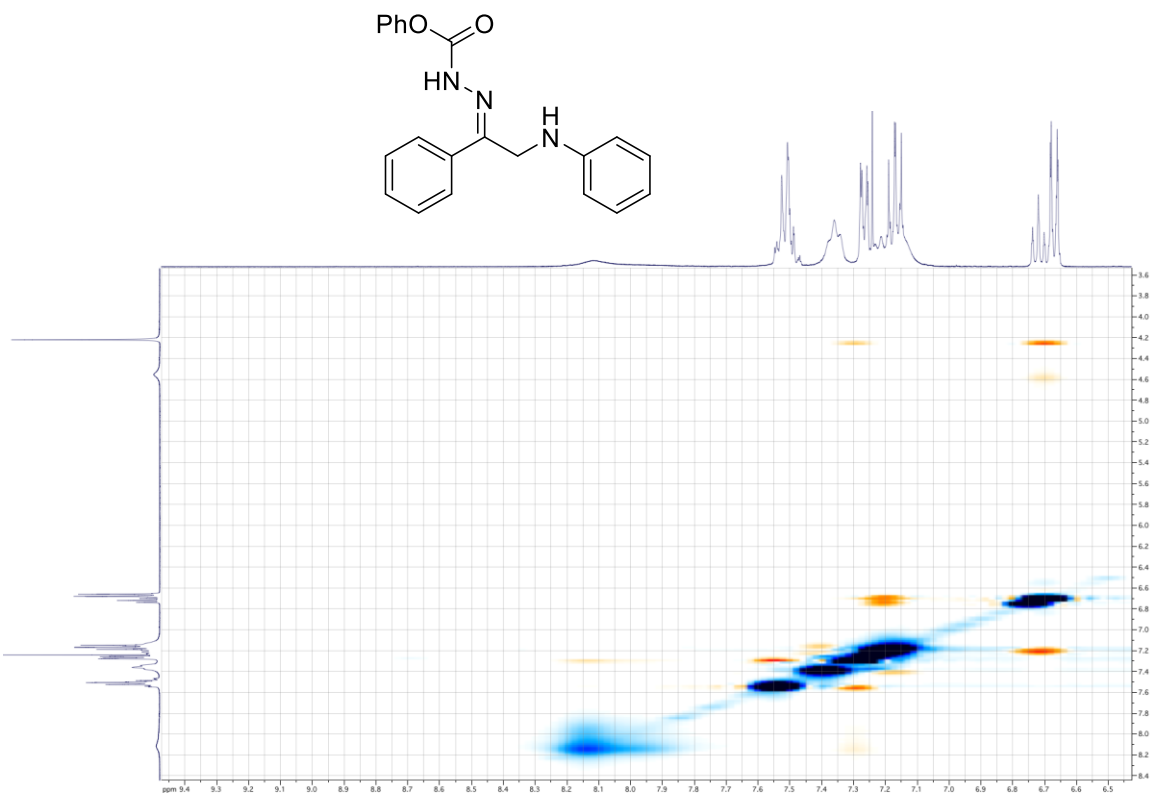
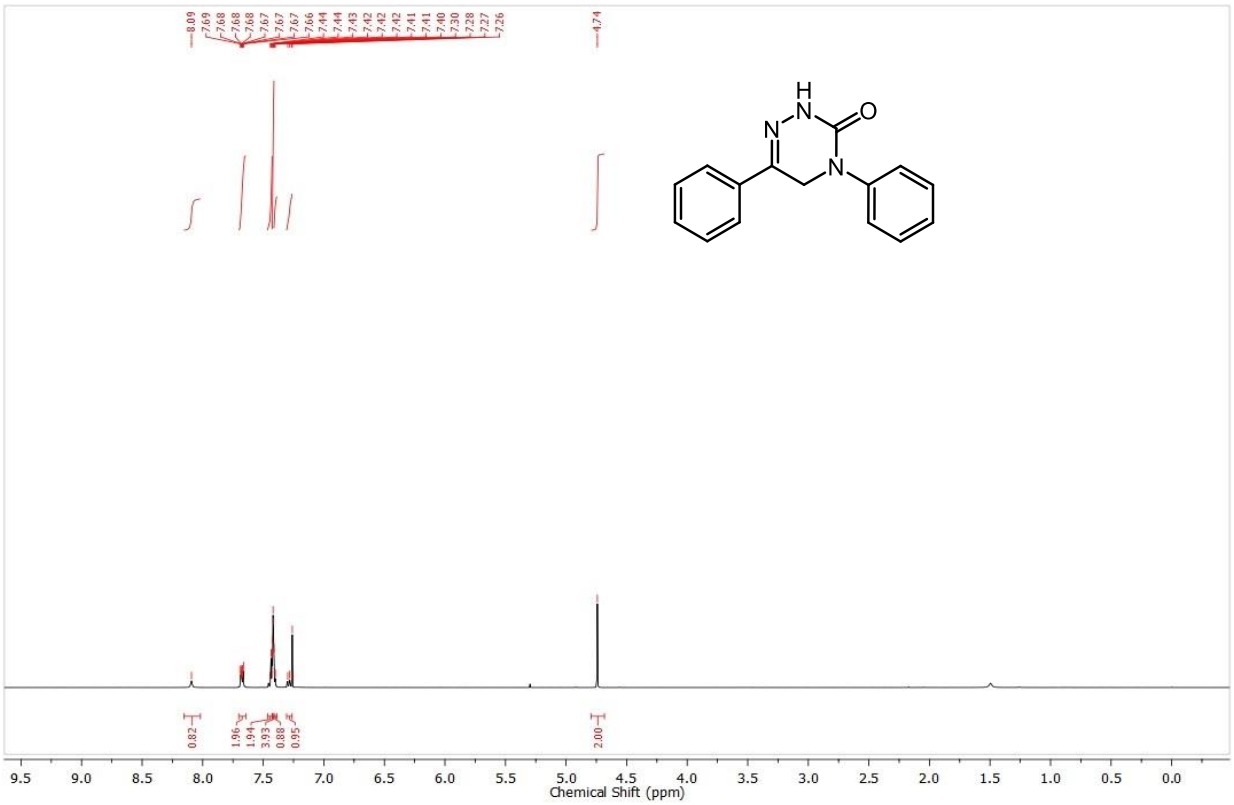
74.5841
60.5181
55.3179
46.1757
45.2484
28.9132
25.0949
24.9858


O
OPh
NH
N
HN
NOE
Correlation


PhO
O
HN
N
H
N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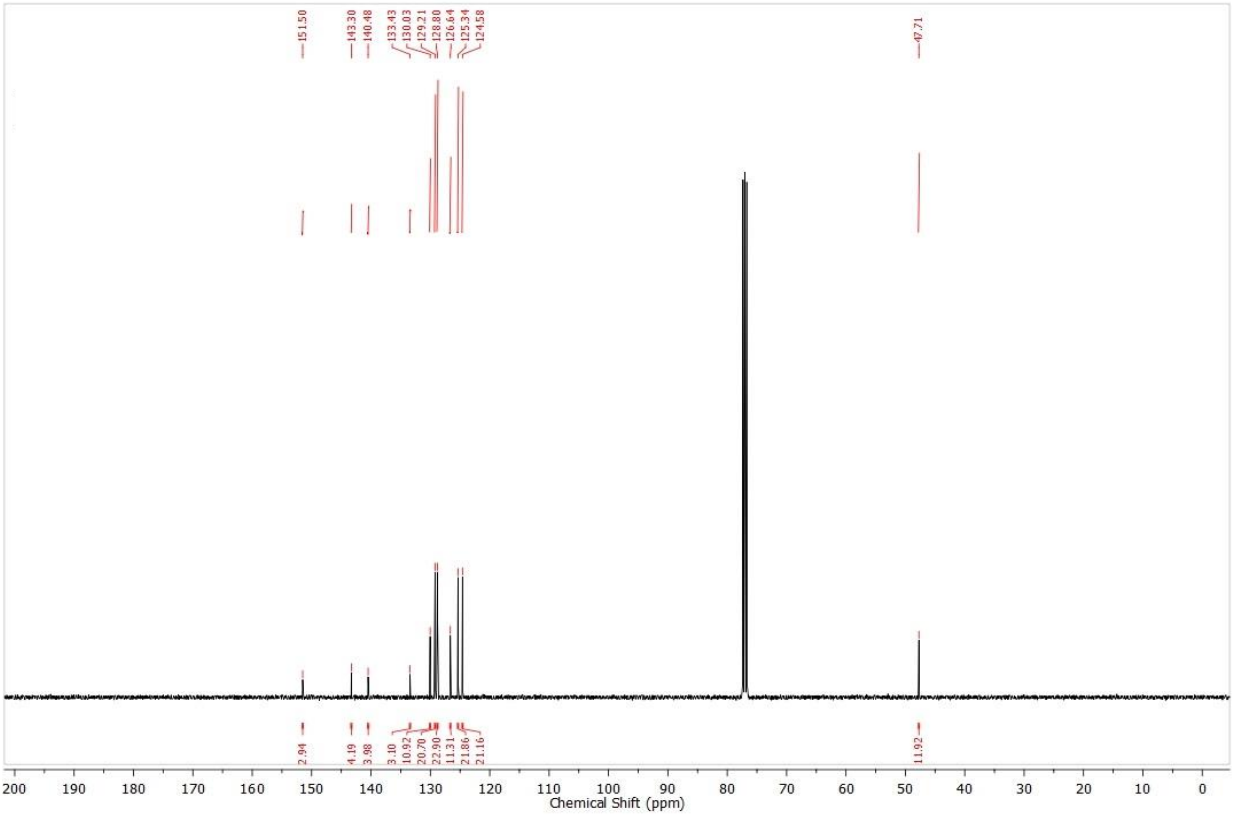
7.68
7.68
7.68
7.68
7.67
7.67
7.67
7.67
7.66
7.44
7.44
7.43
7.42
7.42
7.42
7.41
7.41
7.40
7.30
7.28
7.27
7.26
4.74
H
N
N
O
N
0.82
1.96
1.94
3.93
0.88
0.95
2.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)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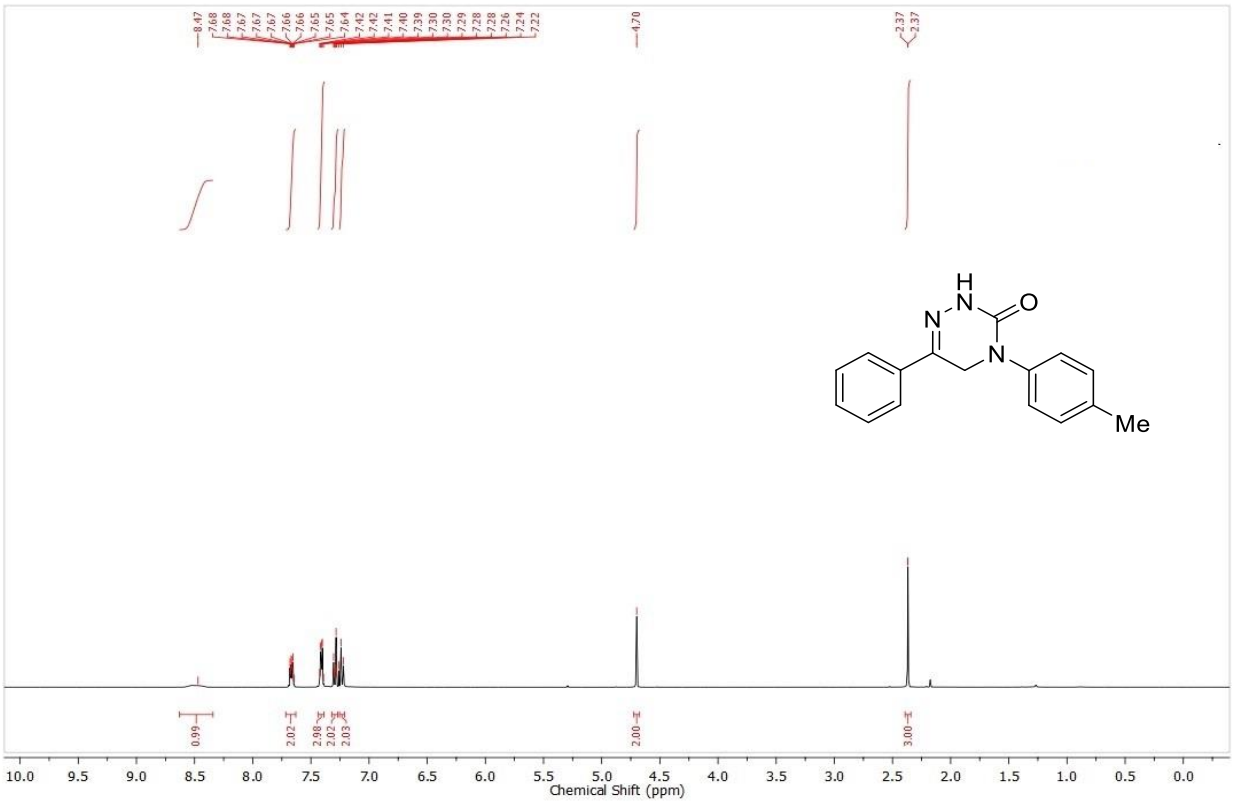
143.30
140.48
133.43
130.03
129.21
128.80
126.64
125.34
124.58
47.71
2.94
4.19
3.98
3.10
10.92
20.70
22.90
11.31
21.86
21.16
11.92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)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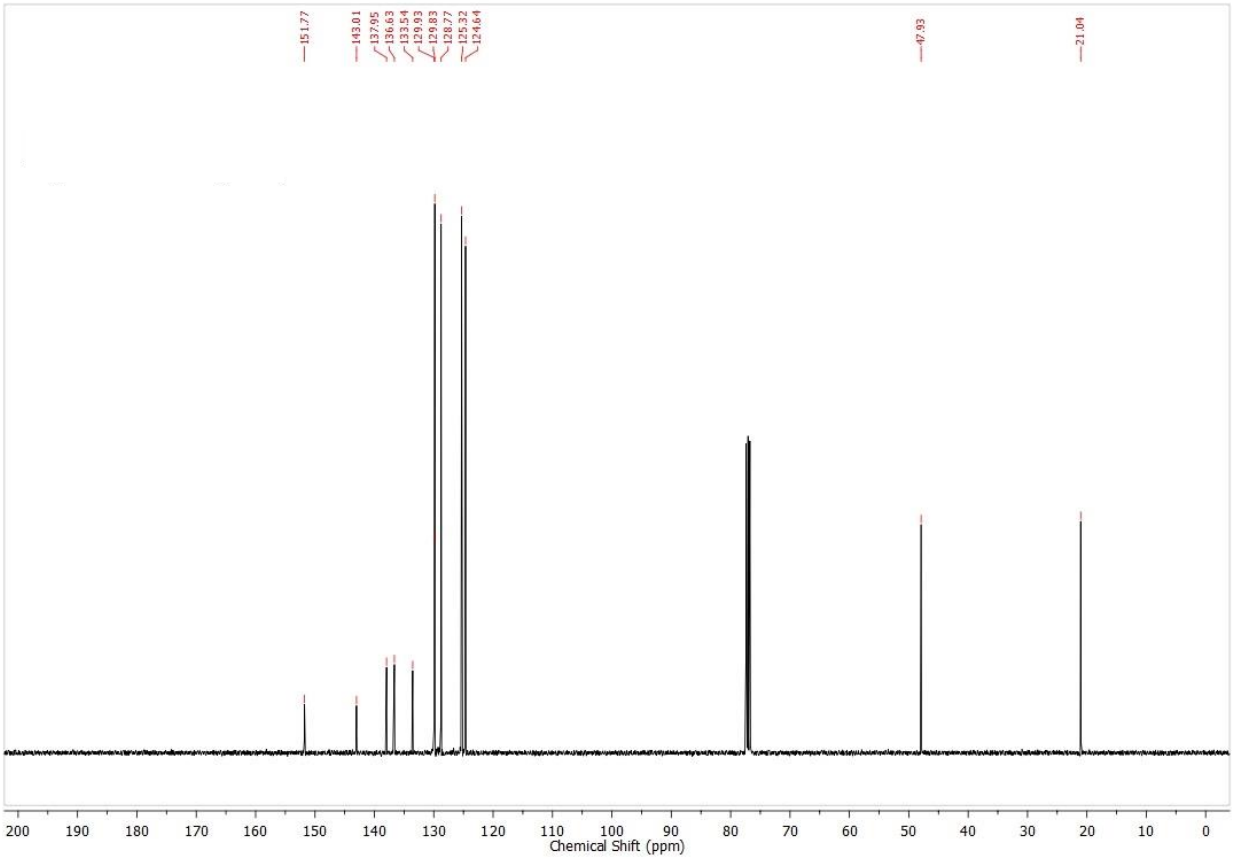
7.68
7.68
7.67
7.67
7.67
7.66
7.66
7.65
7.65
7.64
7.42
7.42
7.41
7.40
7.39
7.30
7.30
7.29
7.28
7.28
7.26
7.24
7.22
4.70
2.37
2.37
H
N
N
O
N
Me
0.99
2.02
2.98
2.02
2.03
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)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143.01
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129.93
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125.32
124.64
47.93
21.04
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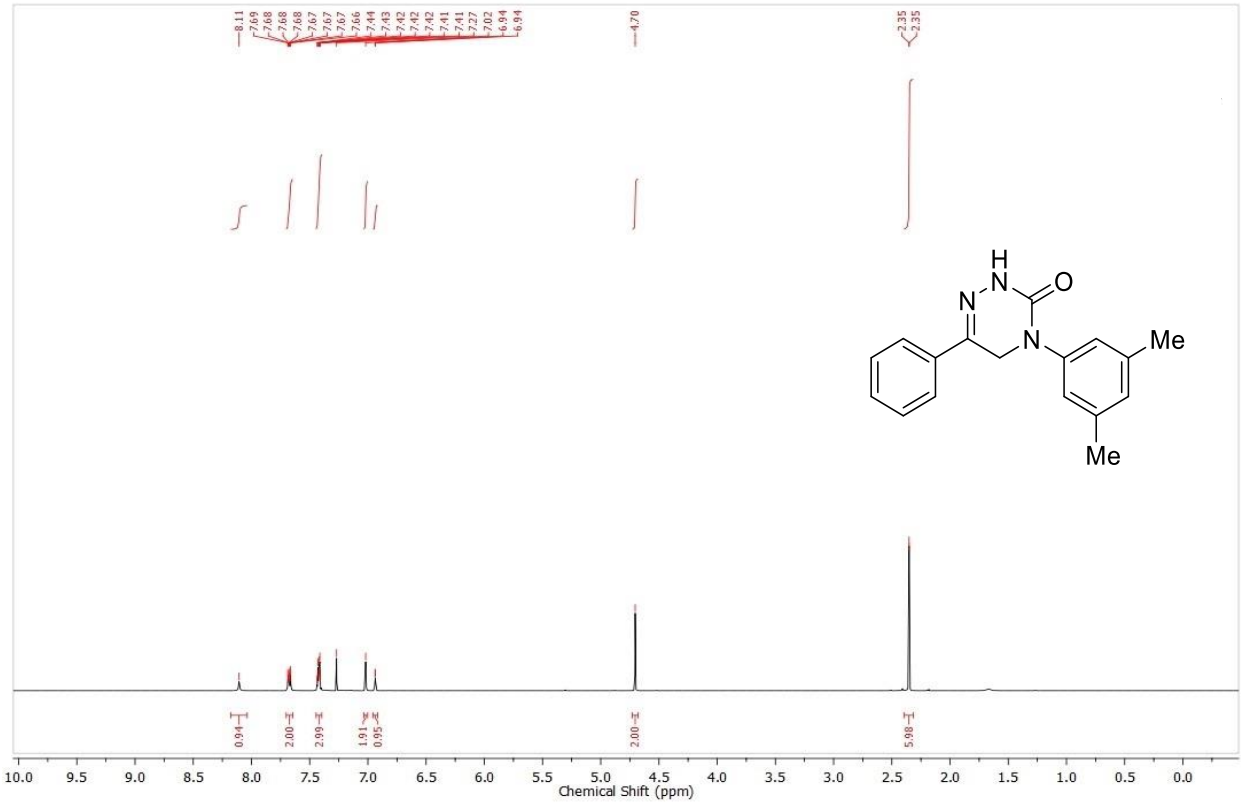
Chemical Shift (ppm)


8.11
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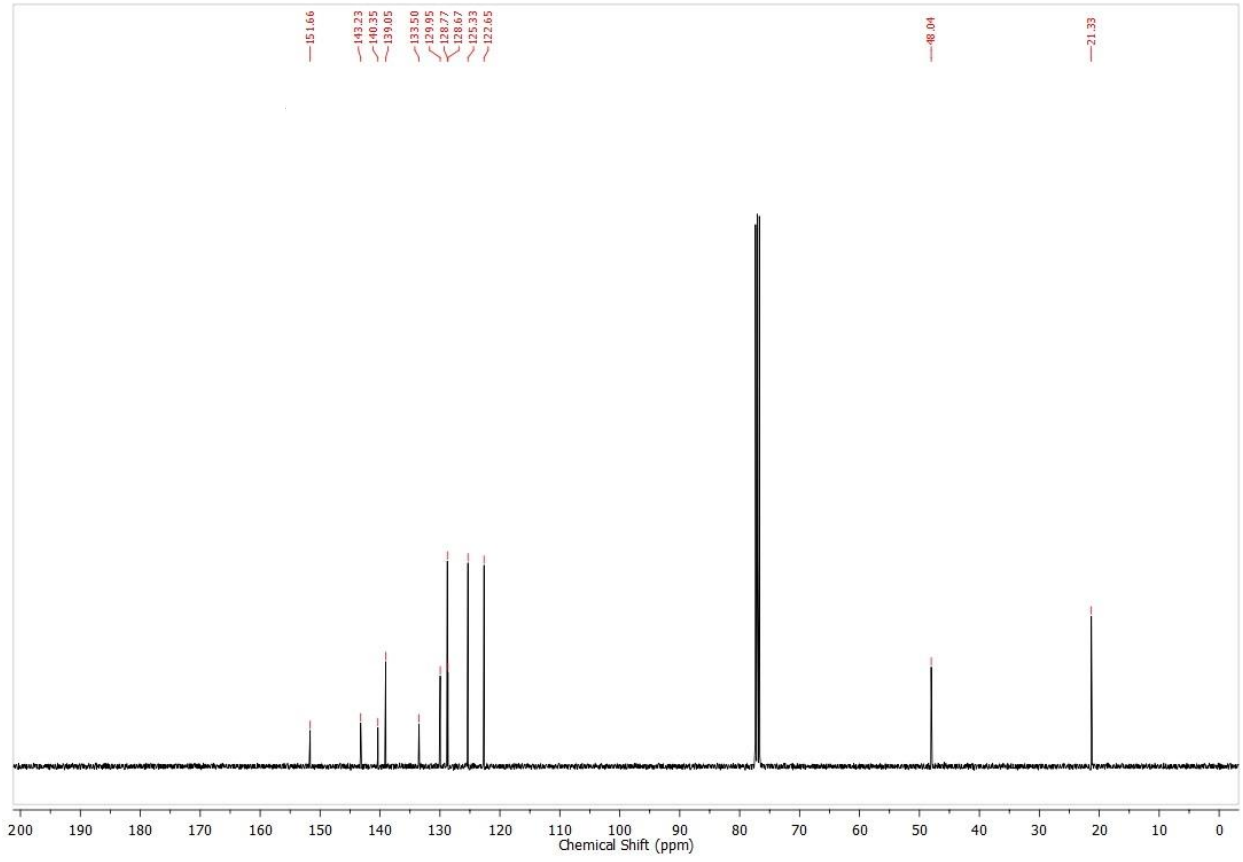
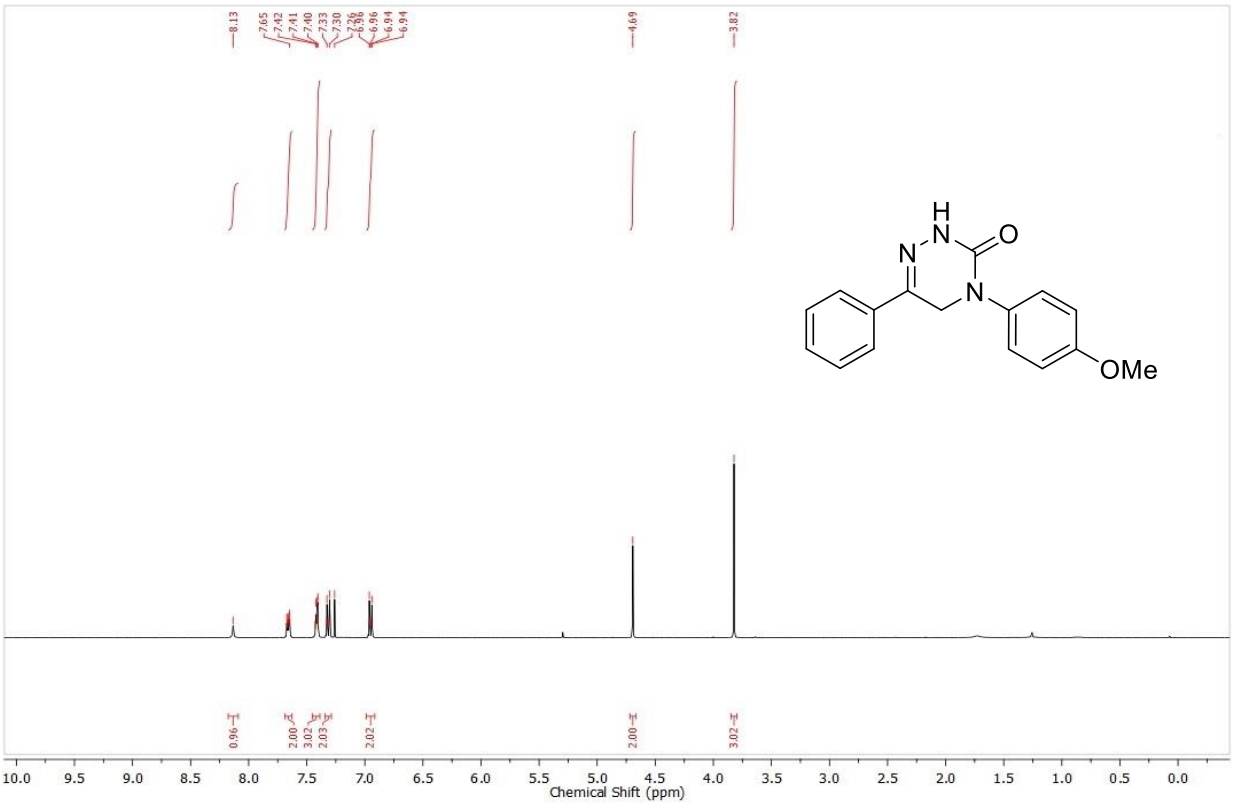
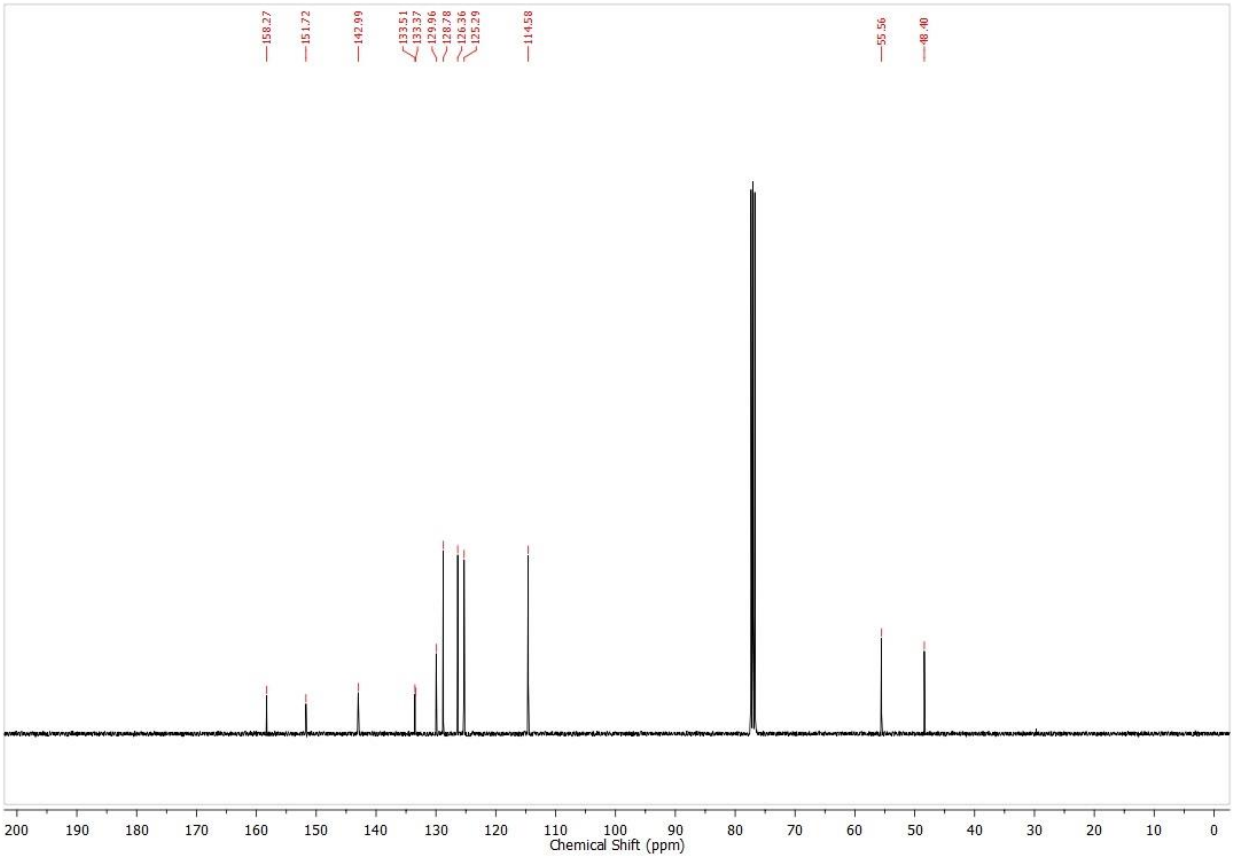
7.68
7.68
7.68
7.67
7.67
7.67
7.66
7.44
7.43
7.42
7.42
7.42
7.41
7.41
7.27
7.02
6.94
6.94
4.70
2.35
2.35
H
N
N
O
N
Me
Me
0.94
2.00
2.99
1.91
0.95
2.00
5.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)


151.66
143.23
140.35
139.05
133.50
129.95
128.77
128.67
125.33
122.65
48.04
21.33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


8.13
7.65
7.42
7.41
7.40
7.33
7.30
6.96
6.94
6.94
4.69
3.82
H
N
N
O
N
OMe
0.96
2.00
3.02
2.03
2.02
2.00
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)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151.72
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133.51
133.37
129.96
128.78
126.36
125.29
114.58
55.56
48.40
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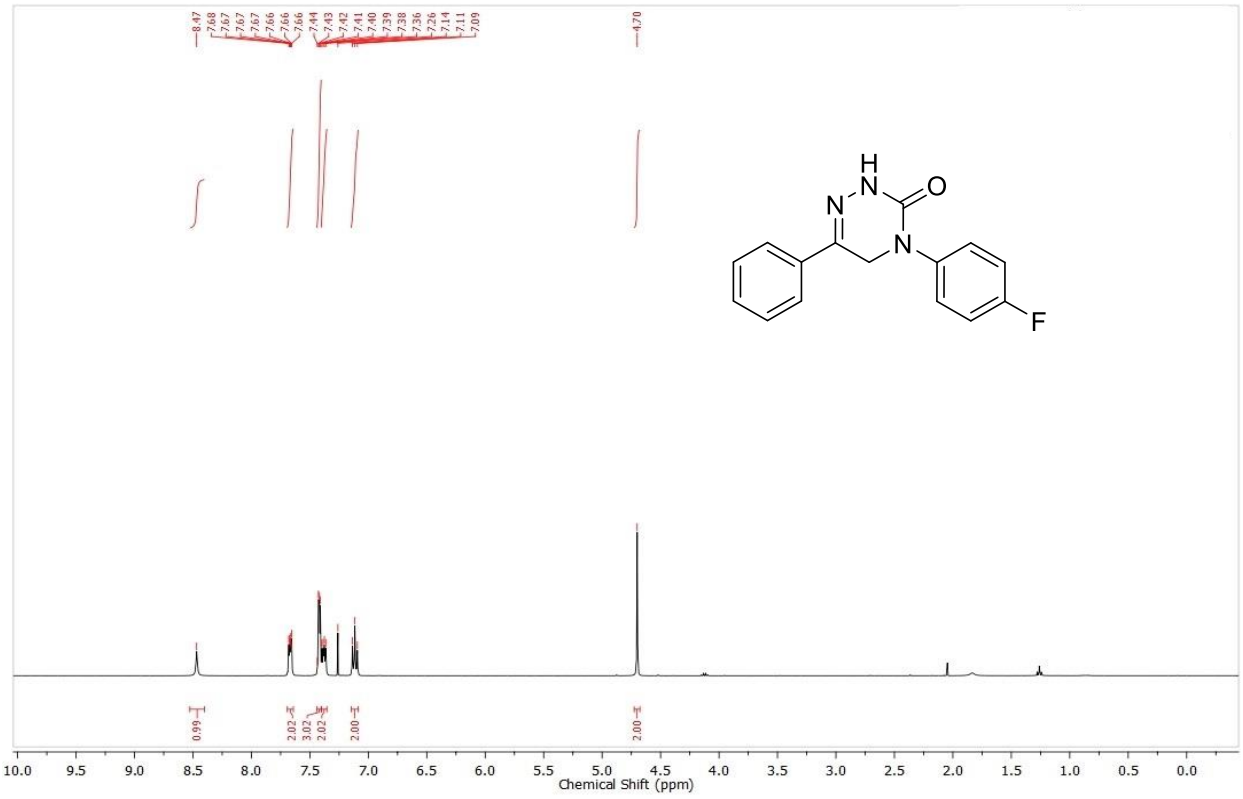
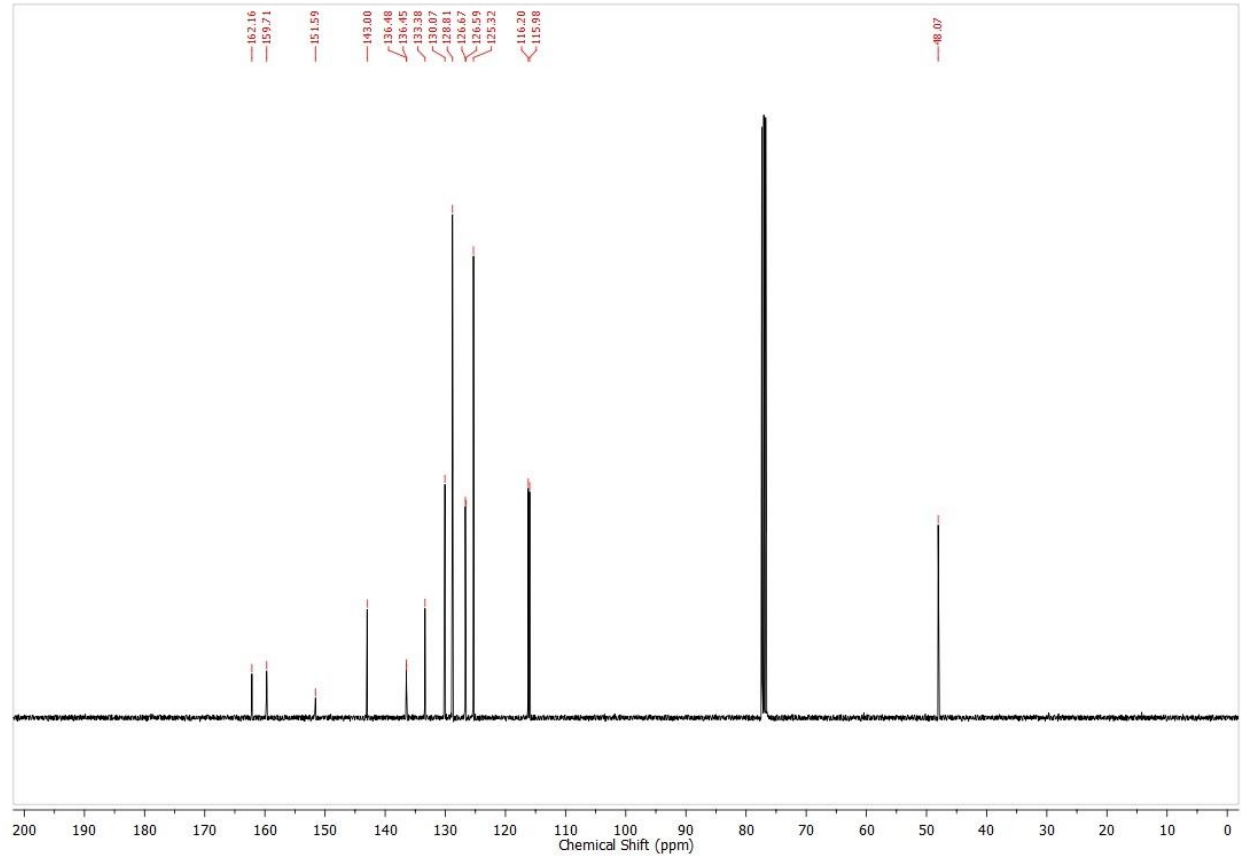
Chemical Shift (ppm)


8.47
7.68
7.67
7.67
7.67
7.66
7.66
7.66
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.36
7.26
7.14
7.11
7.09
4.70
H
N
N
O
N
F
0.99
2.02
3.02
2.02
2.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)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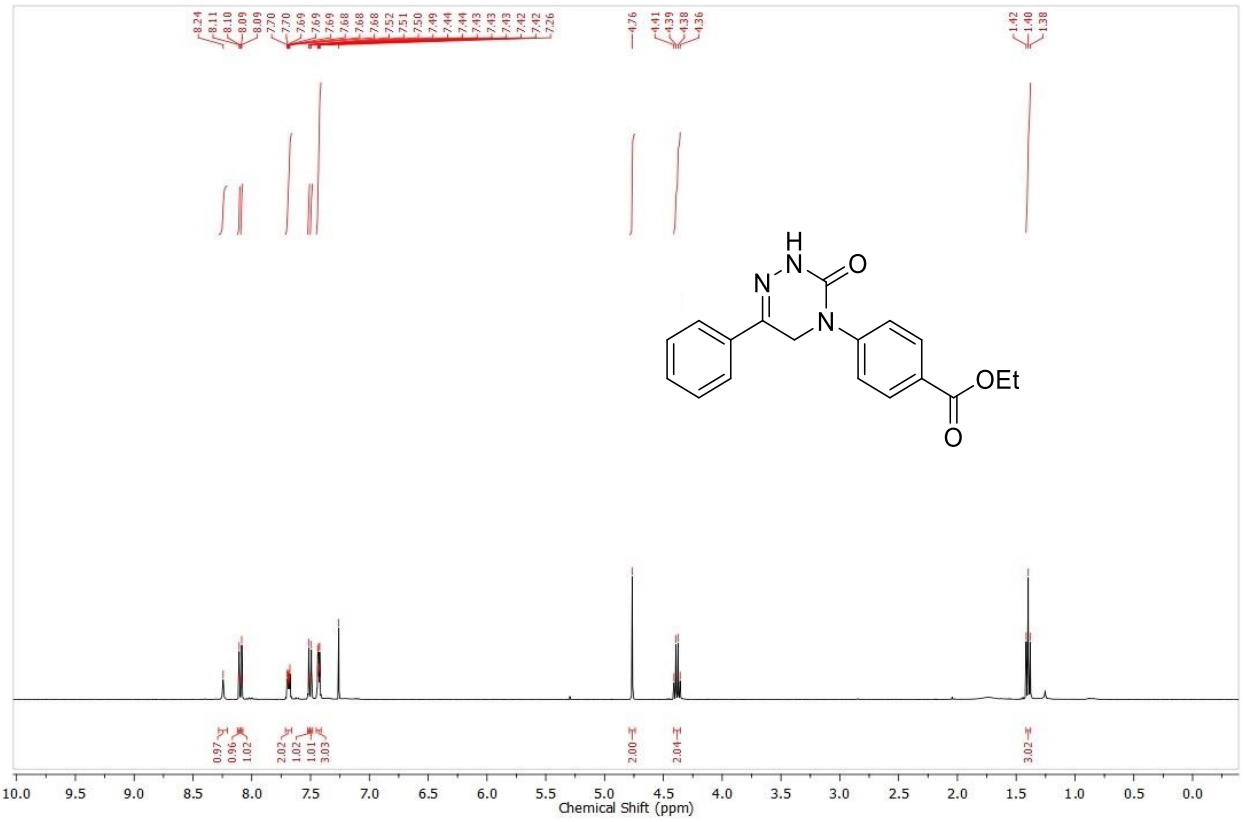
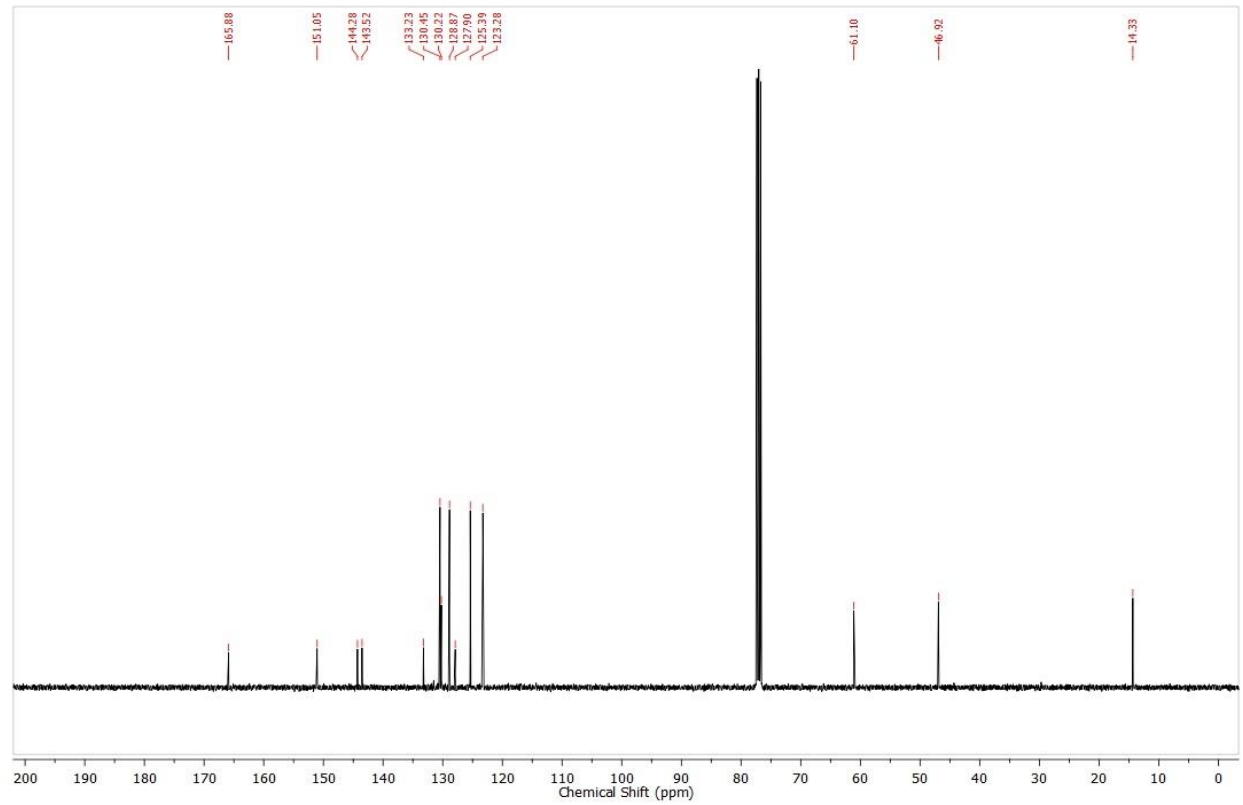
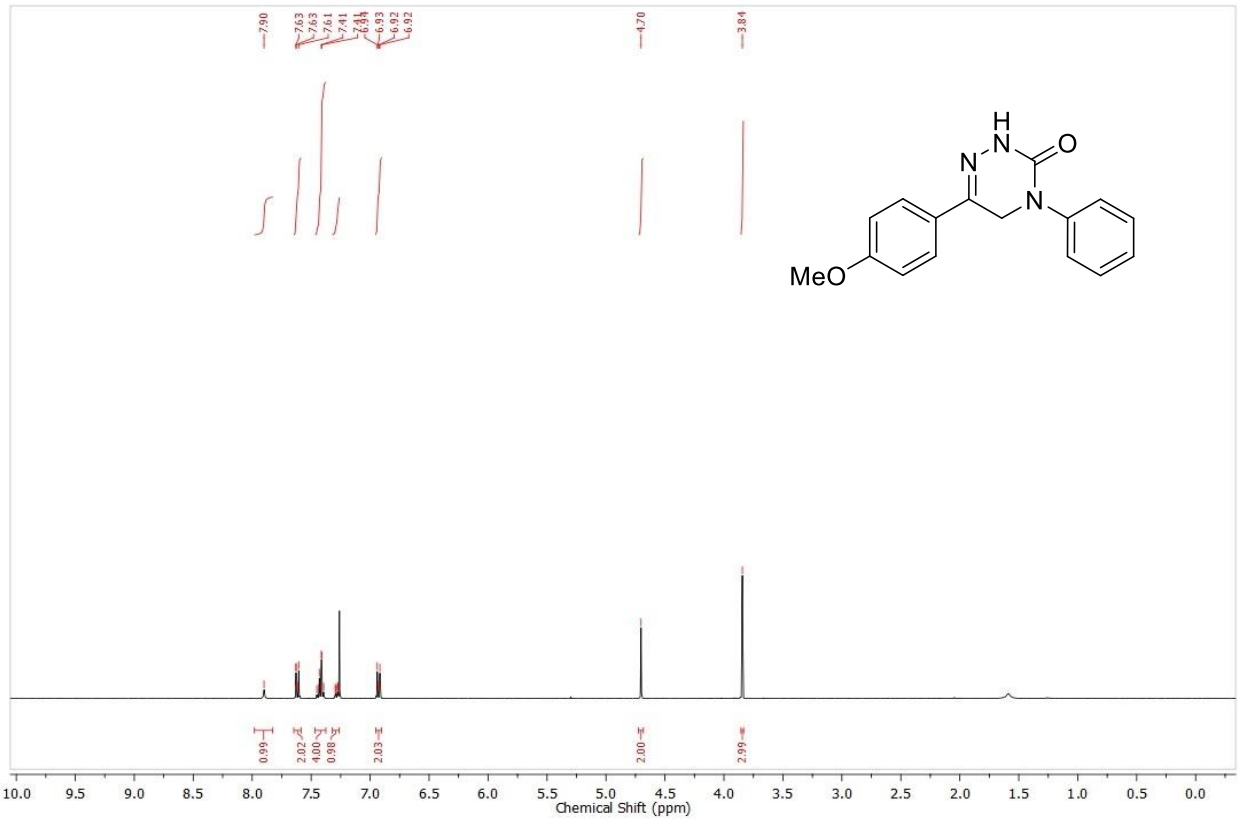
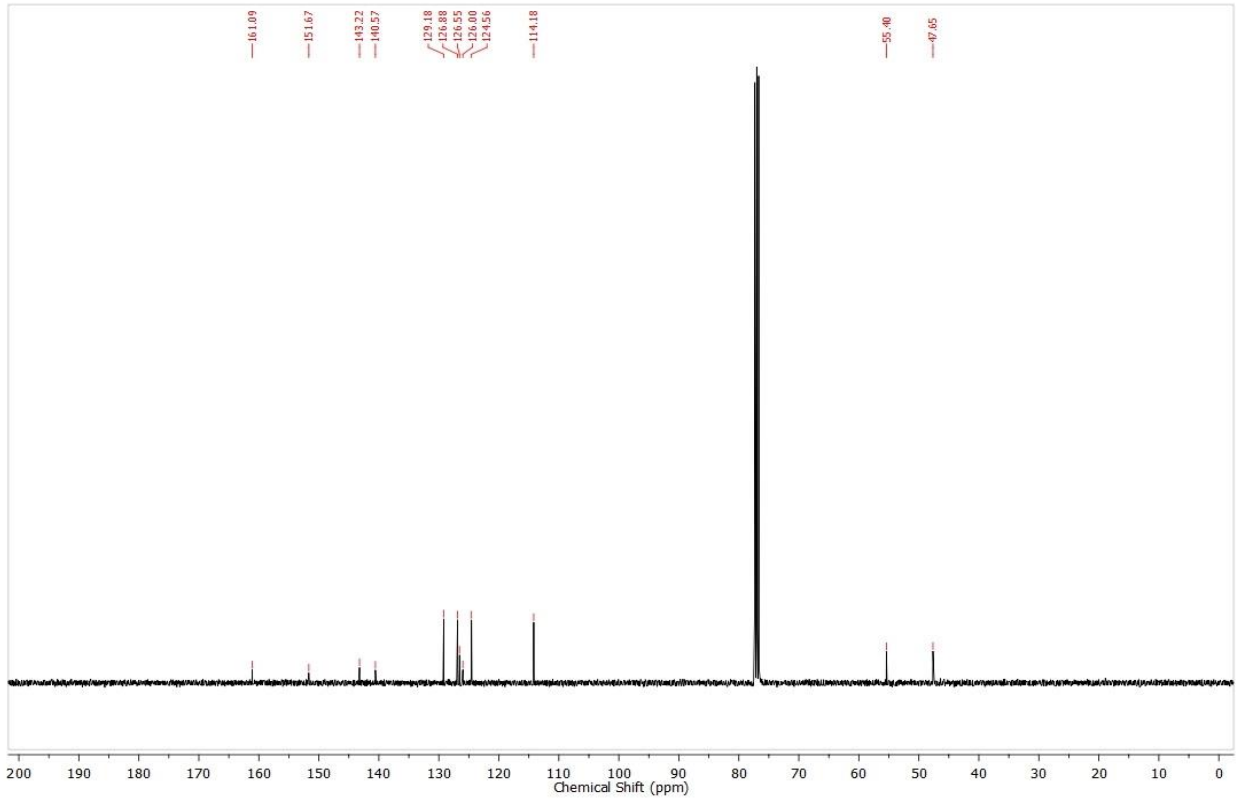
159.71
151.59
143.00
136.48
136.45
133.38
130.07
128.81
126.67
126.59
125.32
116.20
115.98
48.07
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


8.24
8.11
8.10
8.09
8.09
7.70
7.70
7.69
7.69
7.69
7.68
7.68
7.68
7.52
7.51
7.50
7.49
7.44
7.44
7.43
7.43
7.43
7.42
7.42
7.26
4.76
4.41
4.39
4.38
4.36
1.42
1.40
1.38
H
N
N
O
N
OEt
O
0.97
0.96
1.02
2.02
1.02
1.01
3.03
2.00
2.04
3.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)


165.88
151.05
144.28
143.52
133.23
130.45
130.22
128.87
127.90
125.39
123.28
61.10
46.92
14.33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


7.90
7.63
7.63
7.61
7.41
7.41
6.93
6.92
6.92
4.70
3.84
H
N
N
O
N
MeO
0.99
2.02
4.00
0.98
2.03
2.00
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)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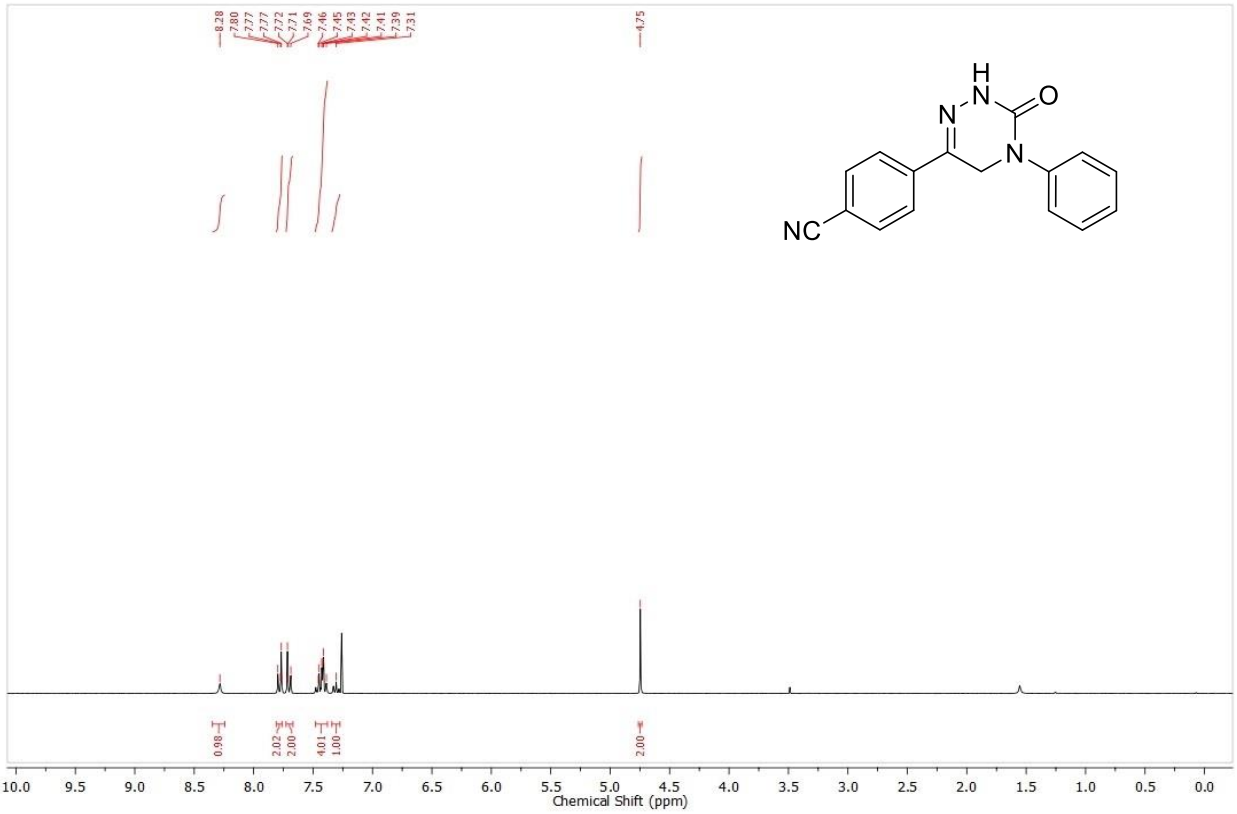
126.88
126.55
126.00
124.56
114.18
55.40
47.65
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)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7.71
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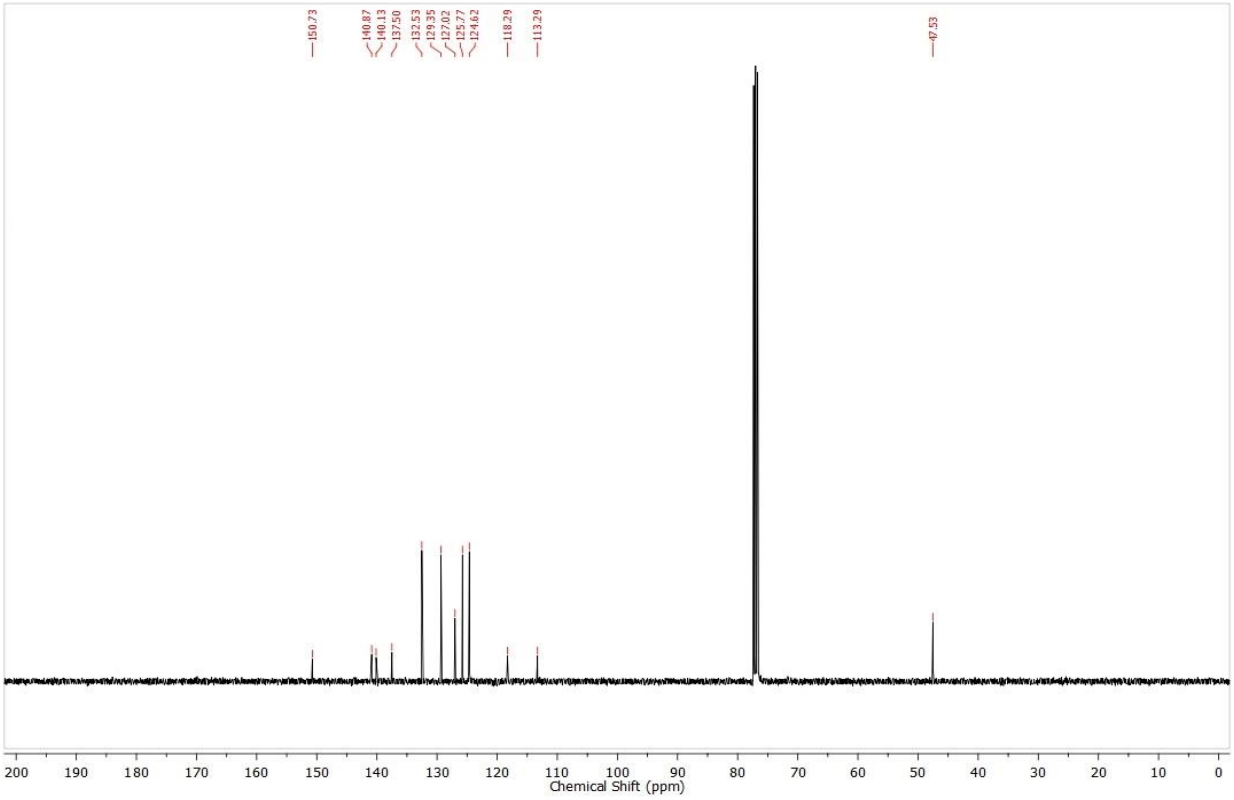
7.46
7.45
7.43
7.42
7.41
7.39
7.31
4.75
H
N
N
O
N
NC
0.98
2.02
2.00
4.01
1.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)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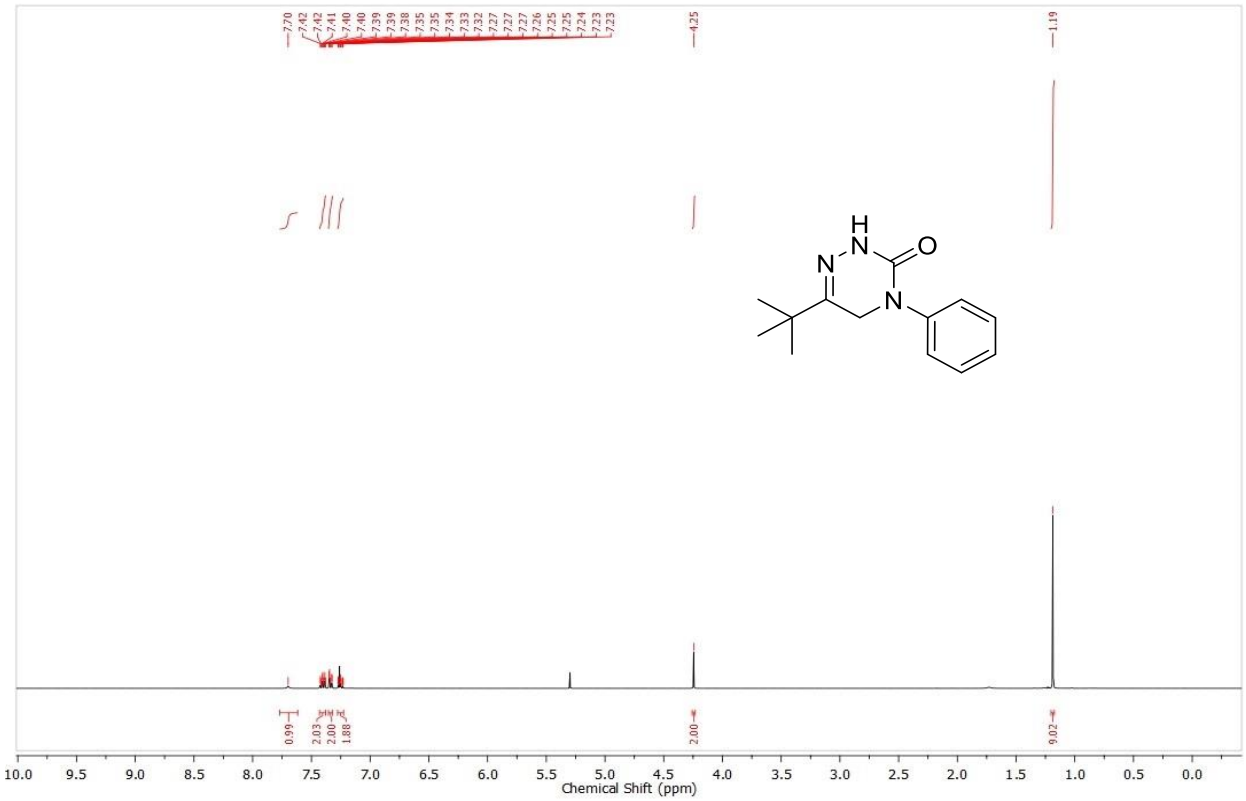
140.87
140.13
137.50
132.53
129.35
127.02
125.77
124.62
118.29
113.29
47.53
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)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7.42
7.41
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7.40
7.39
7.39
7.38
7.35
7.35
7.34
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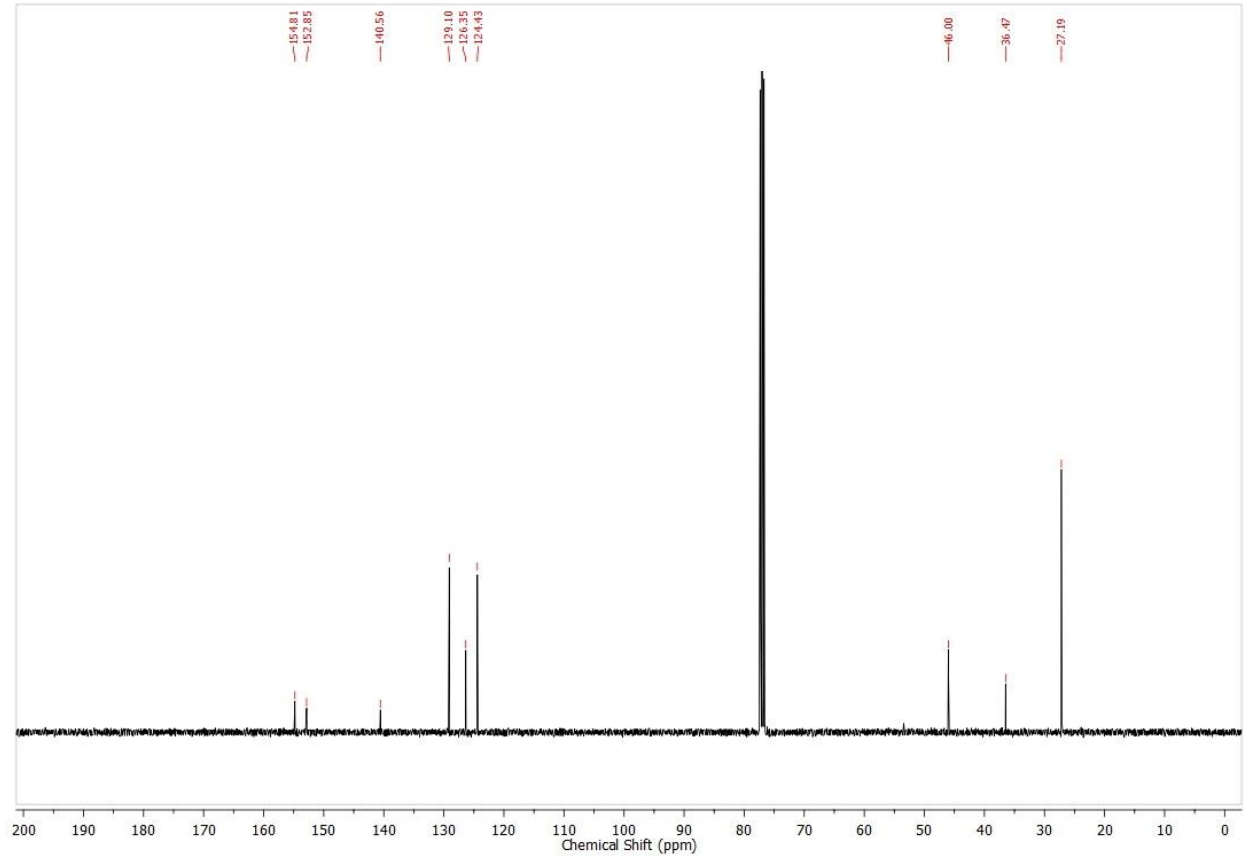
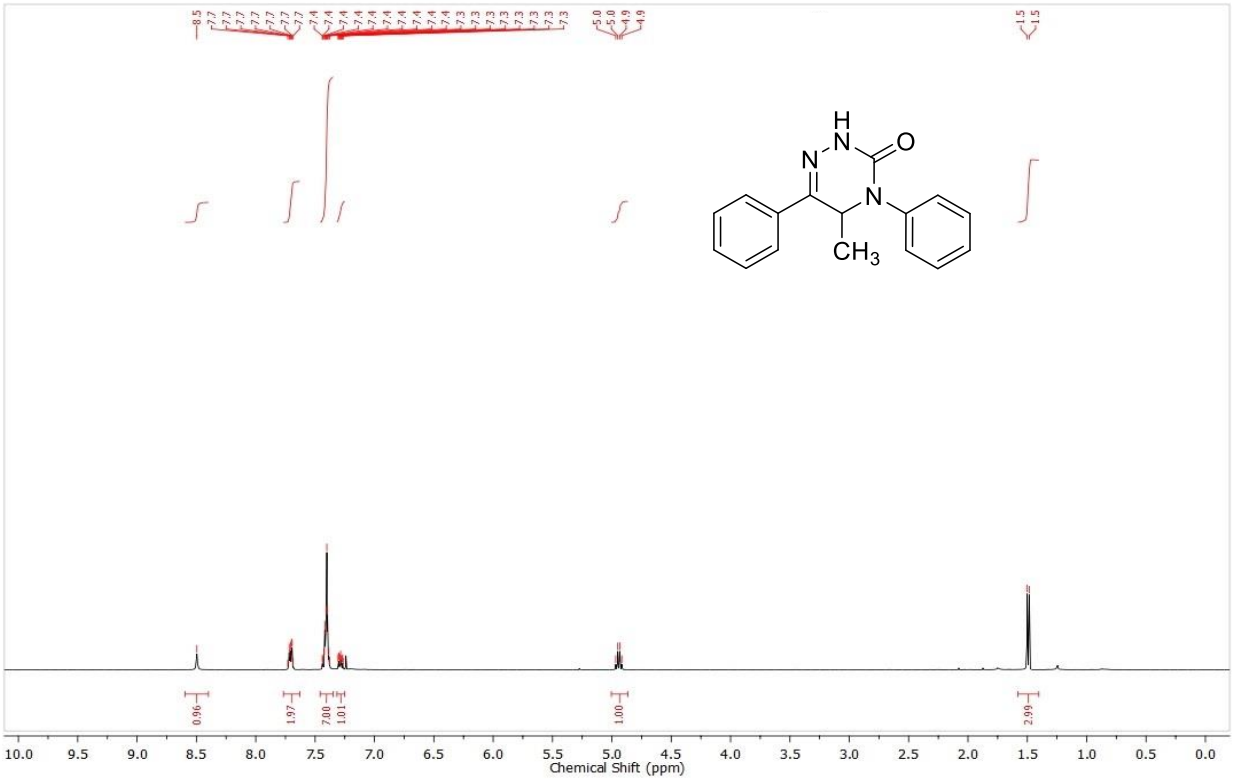
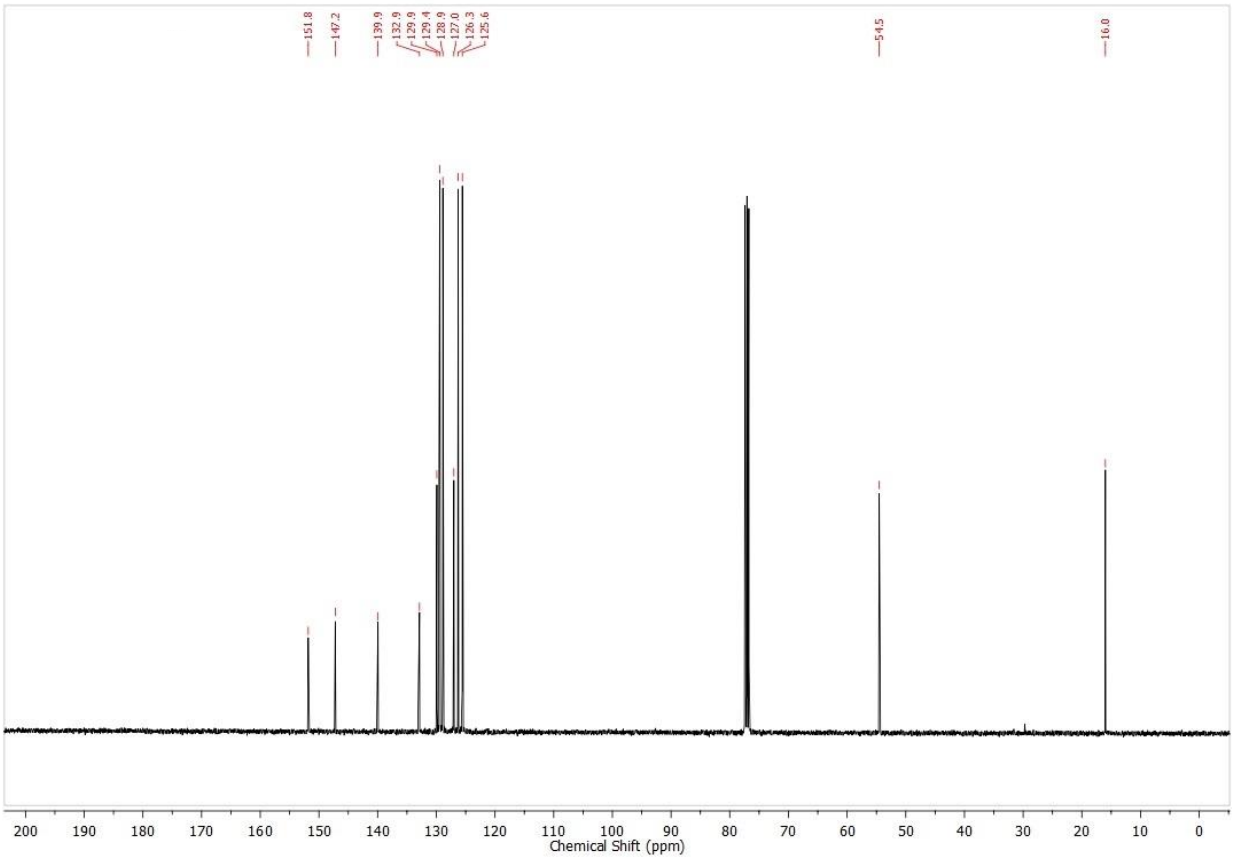
7.32
7.27
7.27
7.27
7.26
7.25
7.25
7.24
7.23
7.23
4.25
1.19
H
N
N
O
N
0.99
2.03
2.00
1.88
2.00
9.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)


154.81
152.85
140.56
129.10
126.35
124.43
46.00
36.47
27.19
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


H
N
N
O
N
CH3
0.96
1.97
7.00
1.01
1.00
2.99
Chemical Shift (ppm)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147.2
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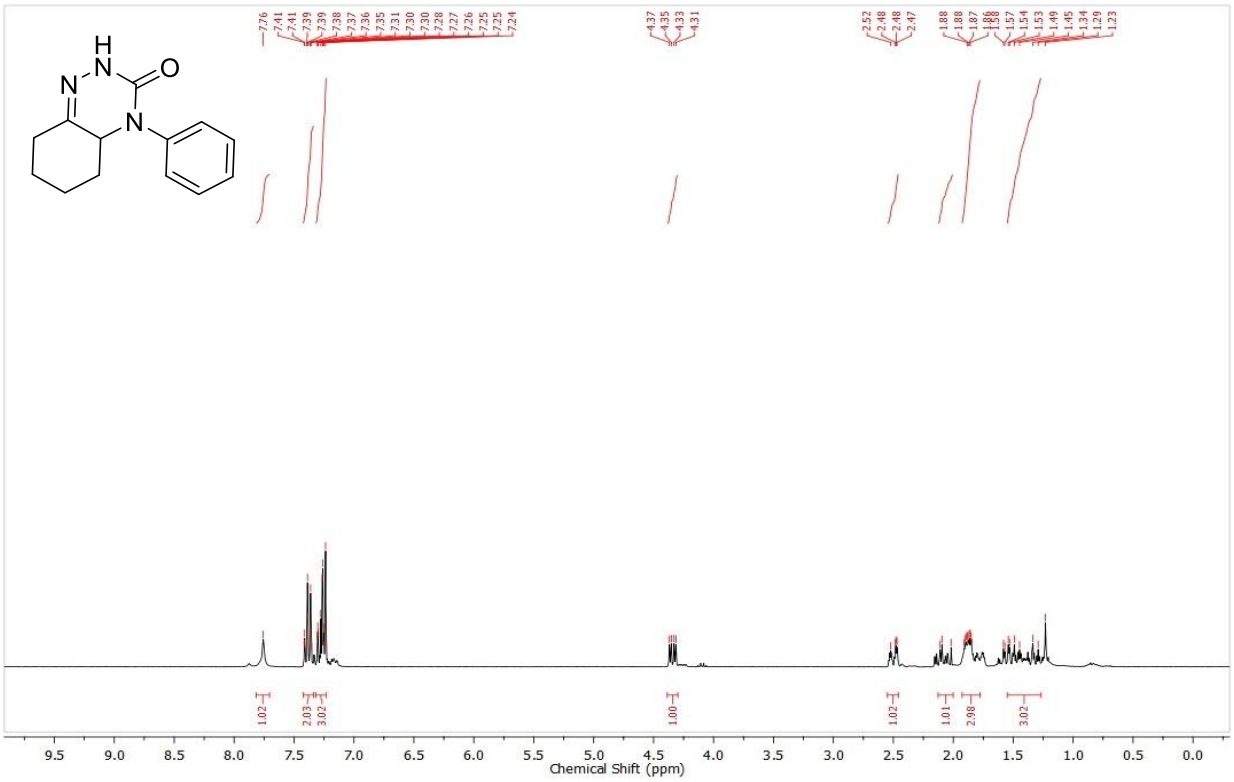
129.4
128.9
127.0
126.3
125.6
54.5
16.0
Chemical Shift (ppm)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7.38
7.37
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7.31
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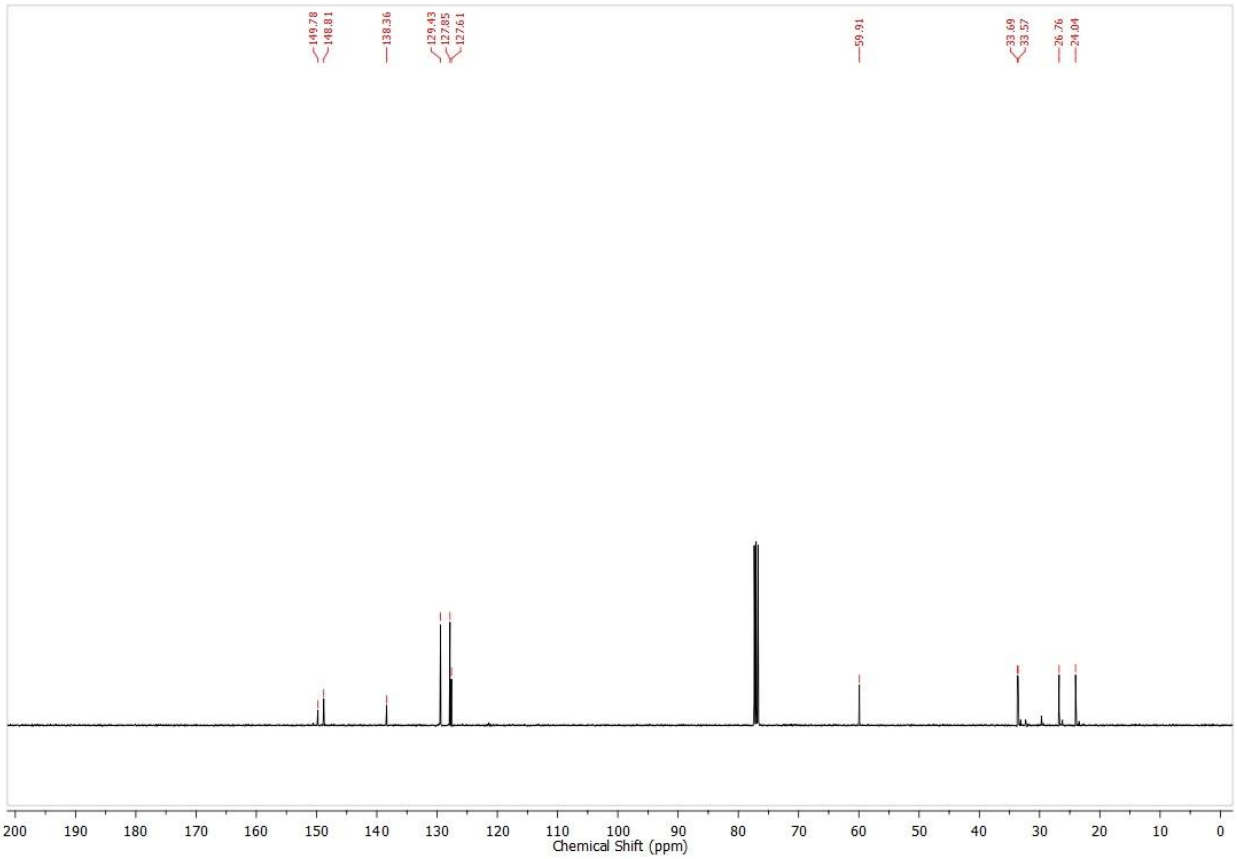
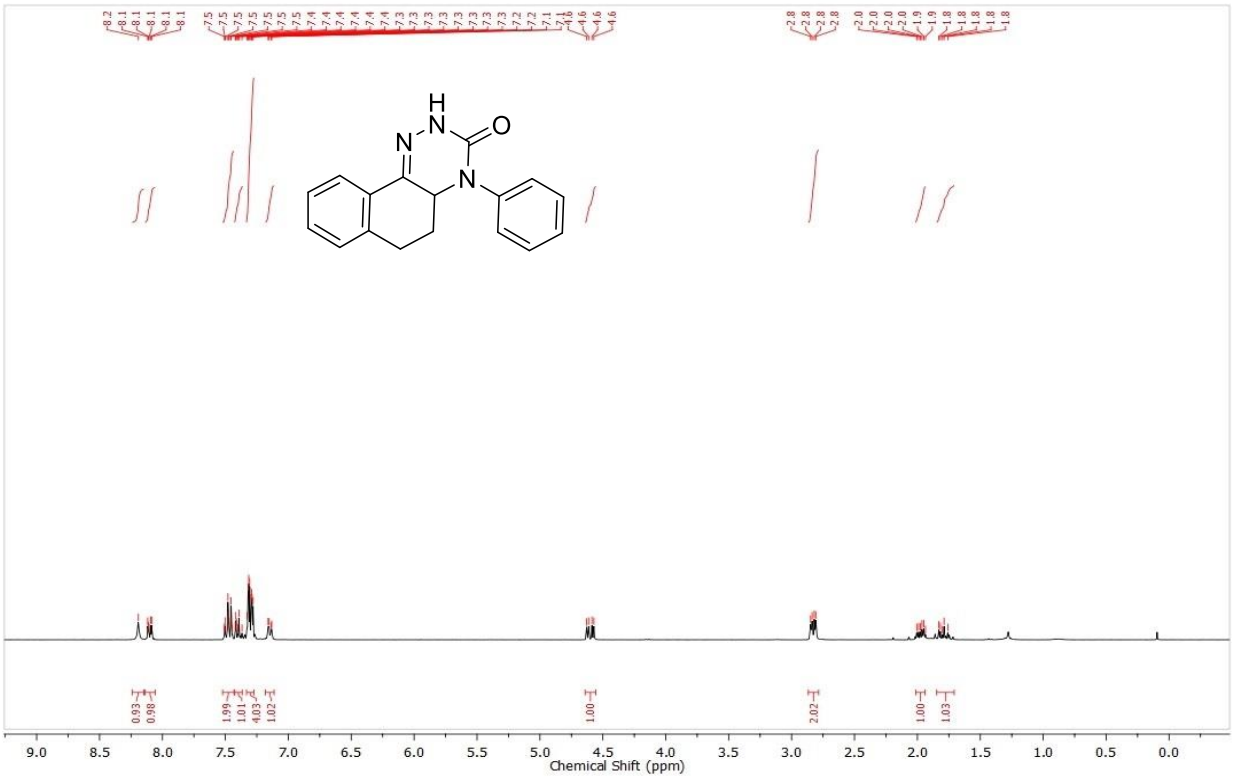
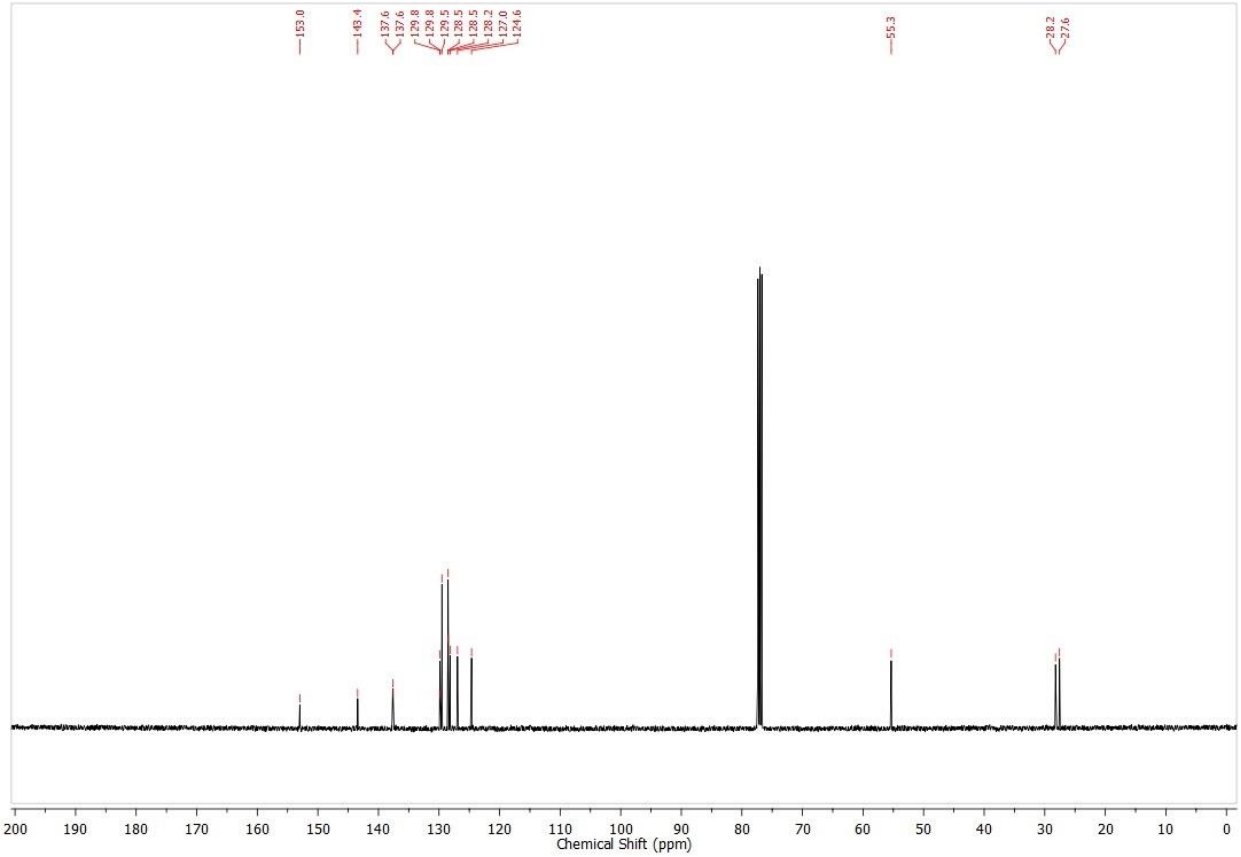
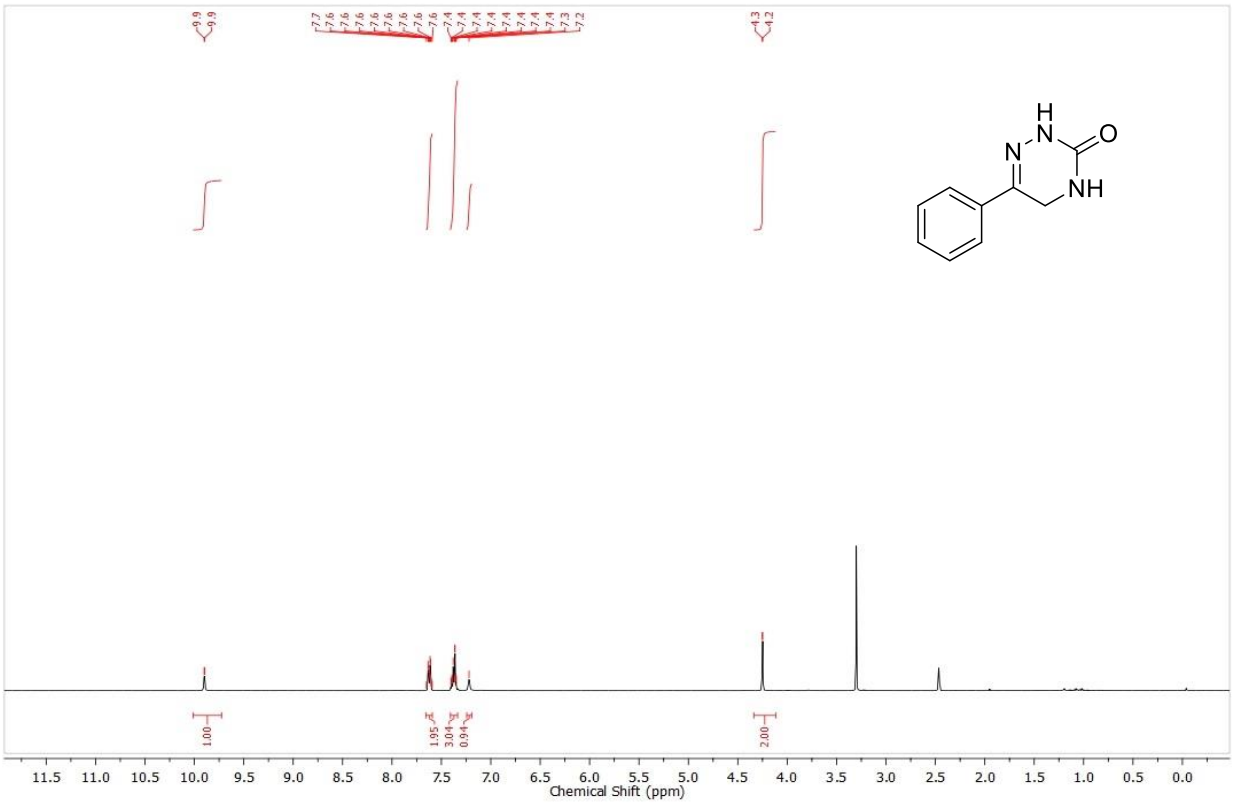
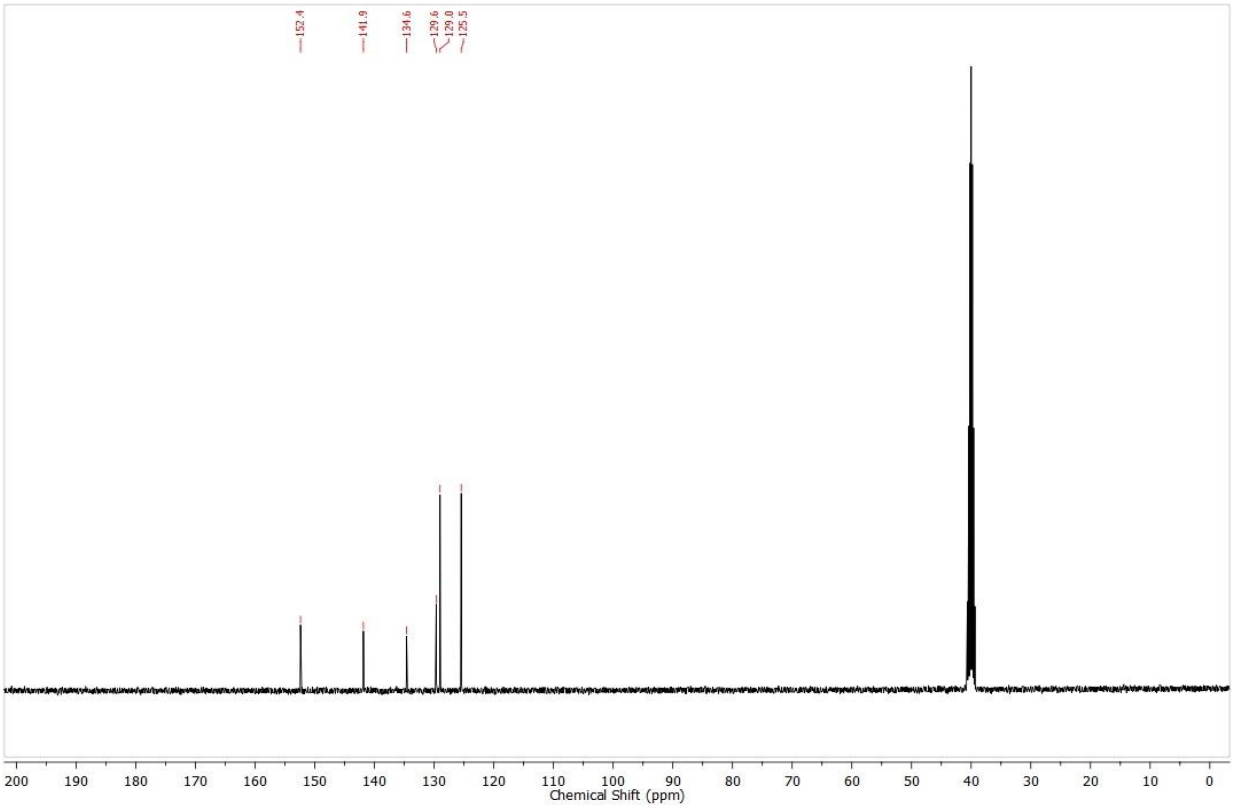
7.30
7.28
7.27
7.26
7.25
7.25
7.24
4.37
4.35
4.33
4.31
2.52
2.48
2.48
2.47
1.88
1.88
1.87
1.86
1.58
1.57
1.54
1.53
1.49
1.45
1.34
1.29
1.23
1.02
2.03
3.02
1.00
1.02
1.01
2.98
3.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)

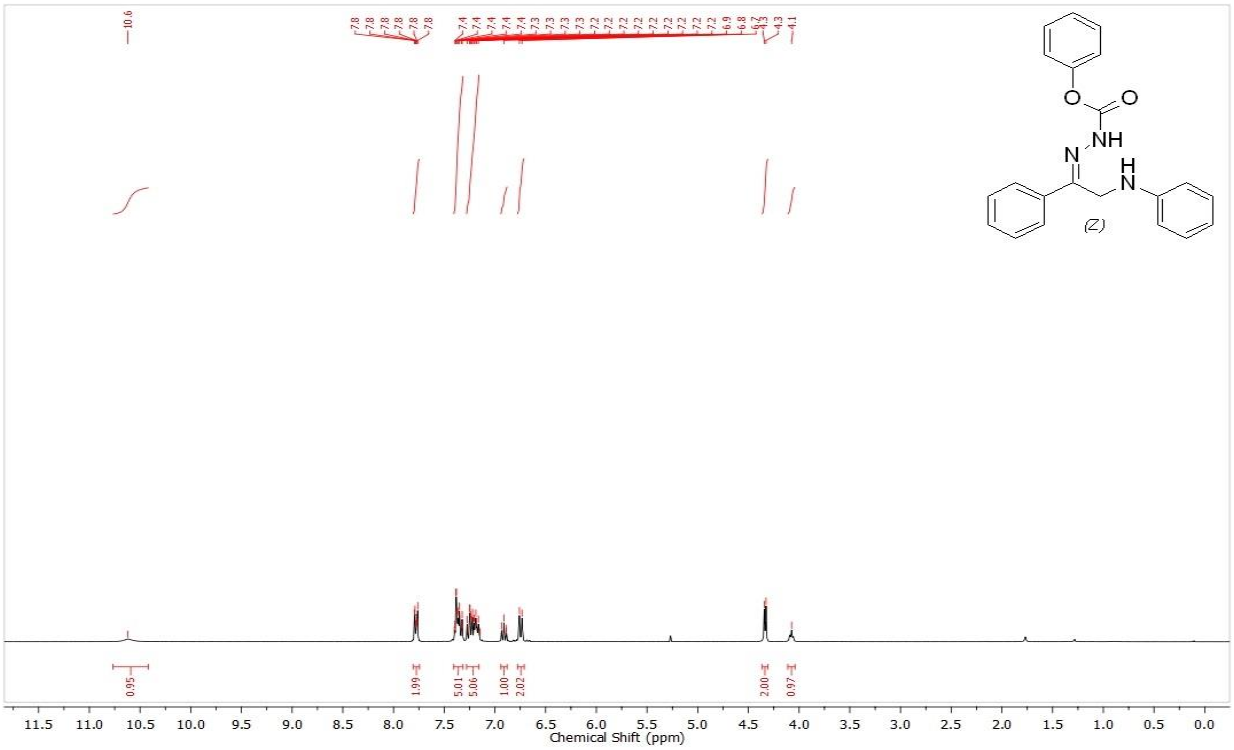

149.78
148.81
138.36
129.43
127.85
127.61
59.91
33.69
33.57
26.76
24.04
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

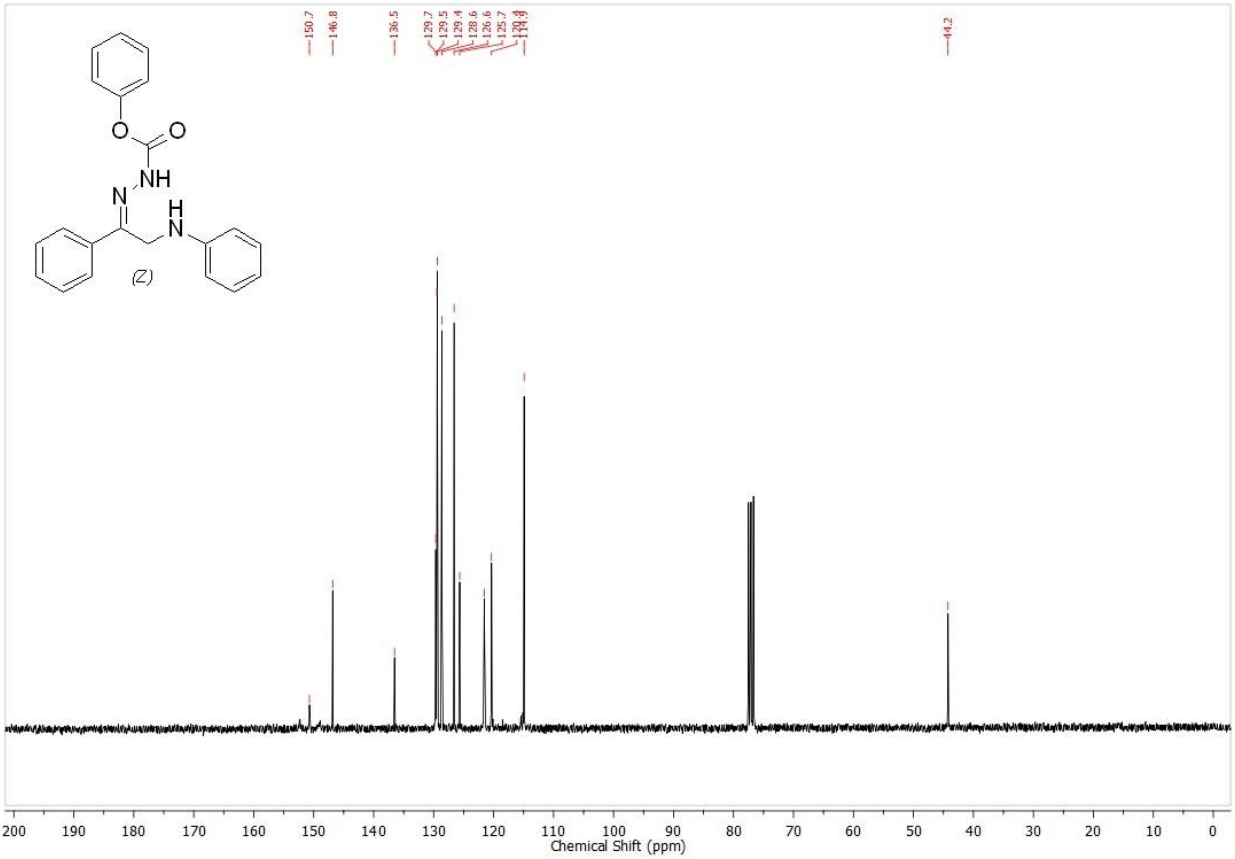

H
N
N
O
N
Chemical Shift (ppm)

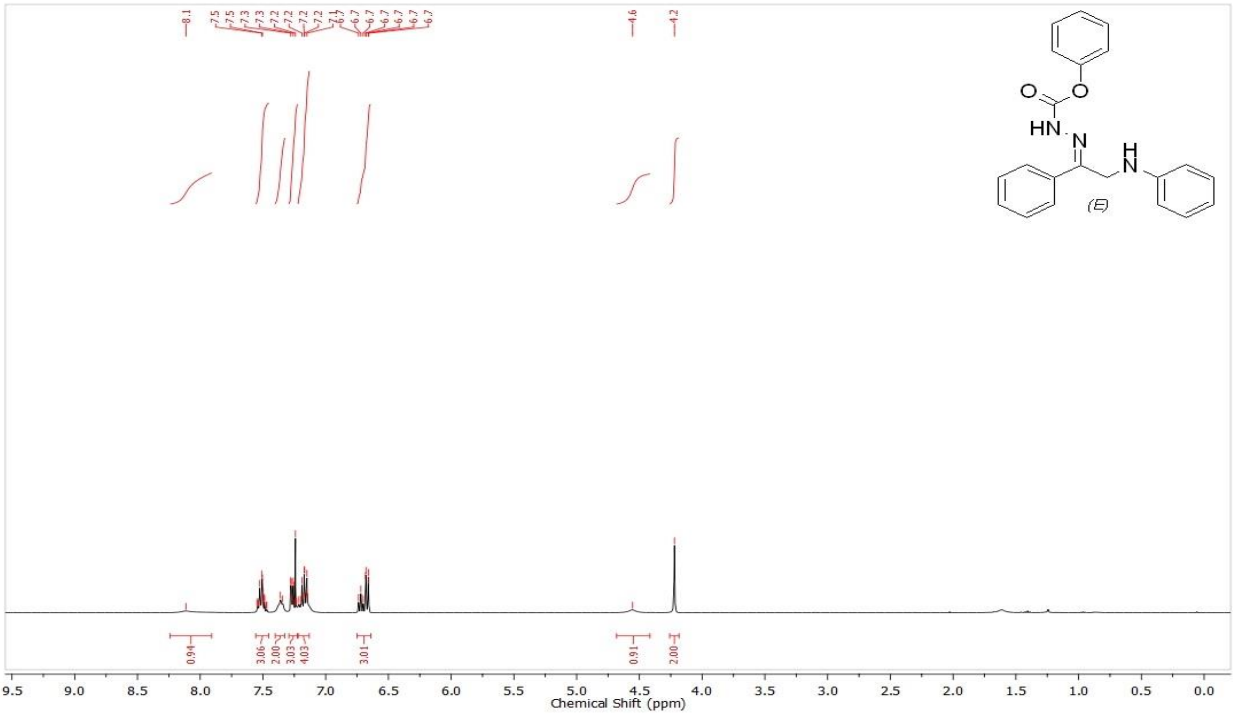

153.0
143.4
137.6
137.6
129.8
129.8
129.5
128.5
128.5
128.2
127.0
124.6
55.3
28.2
27.6
Chemical Shift (ppm)

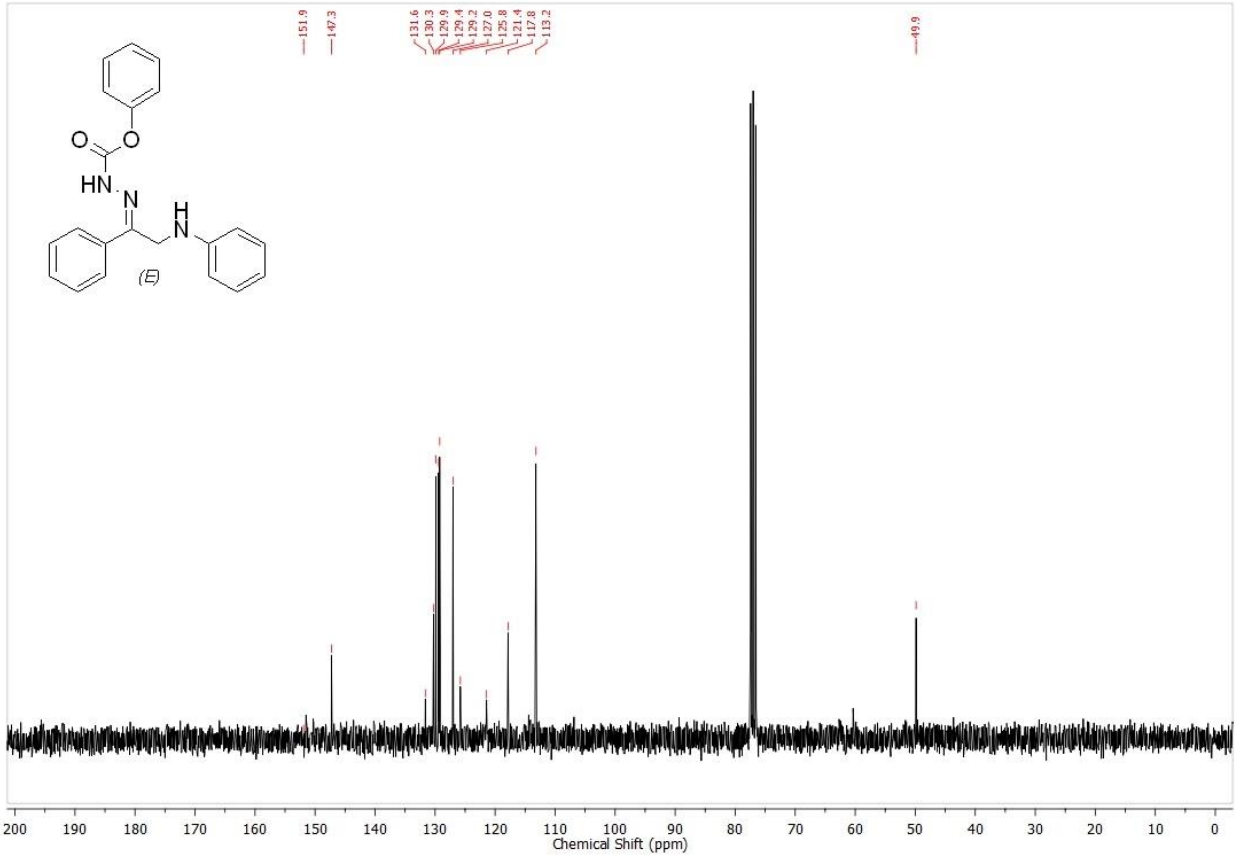

9.9
9.9
7.7
7.6
7.6
7.6
7.6
7.6
7.6
7.6
7.6
7.4
7.4
7.4
7.4
7.4
7.4
7.4
7.4
7.4
7.3
7.2
4.3
4.2
H
N
N
O
NH
1.00
1.95
3.04
0.94
2.00
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chemical Shift (ppm)

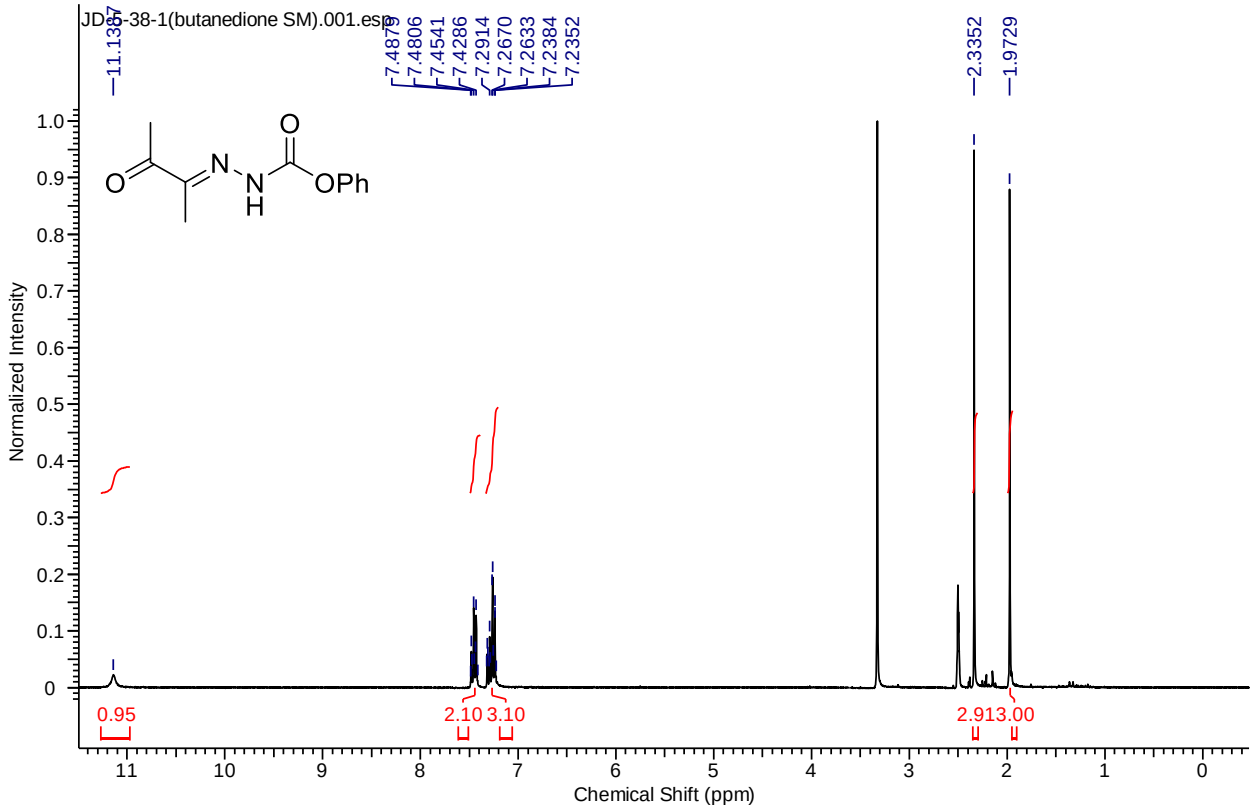

152.4
141.9
134.6
129.6
129.0
125.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

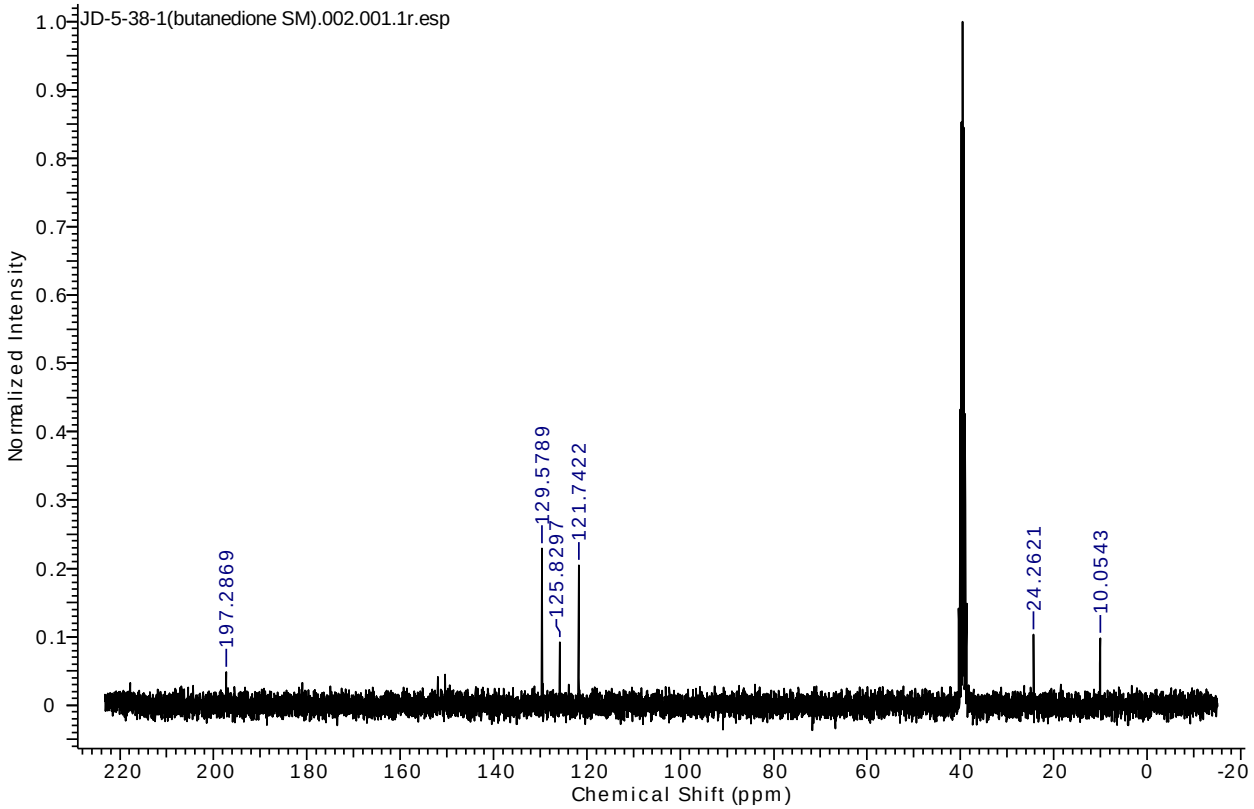

(Z)
Chemical Shift (ppm)

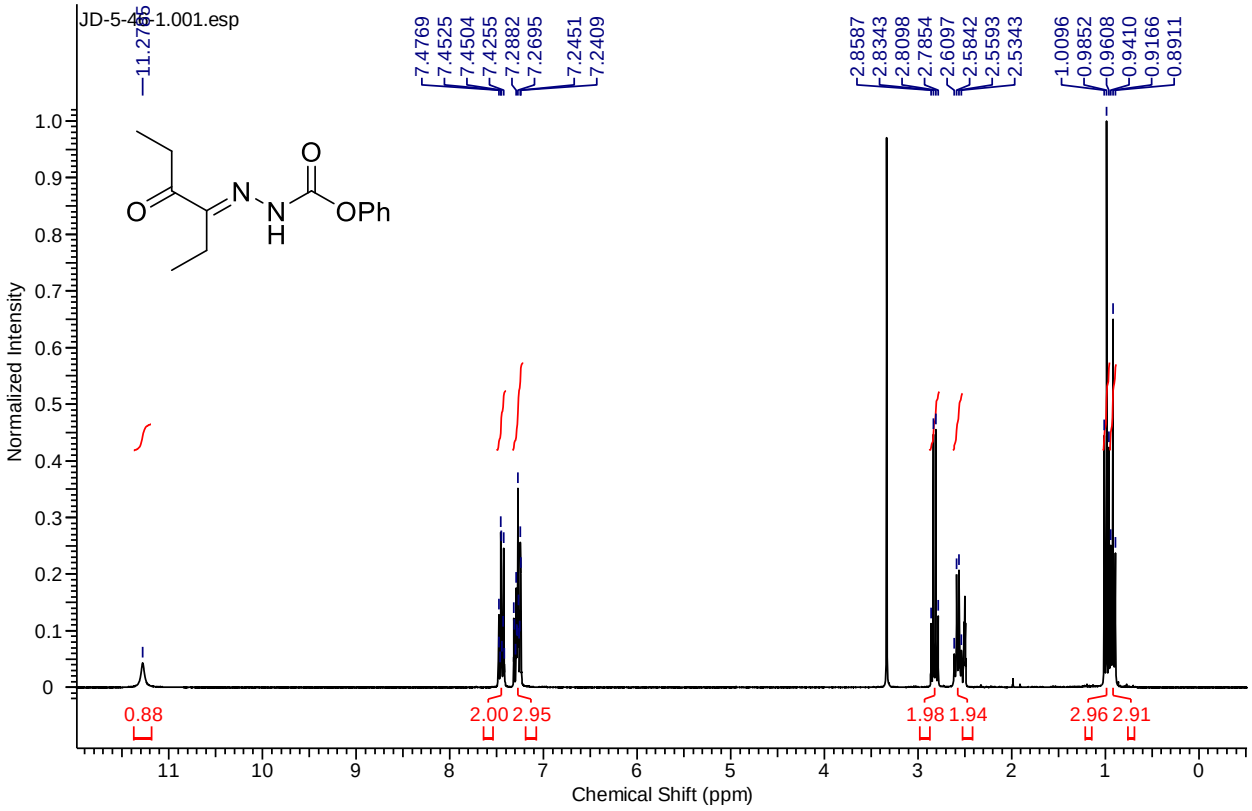

(Z)
Chemical Shift (ppm)

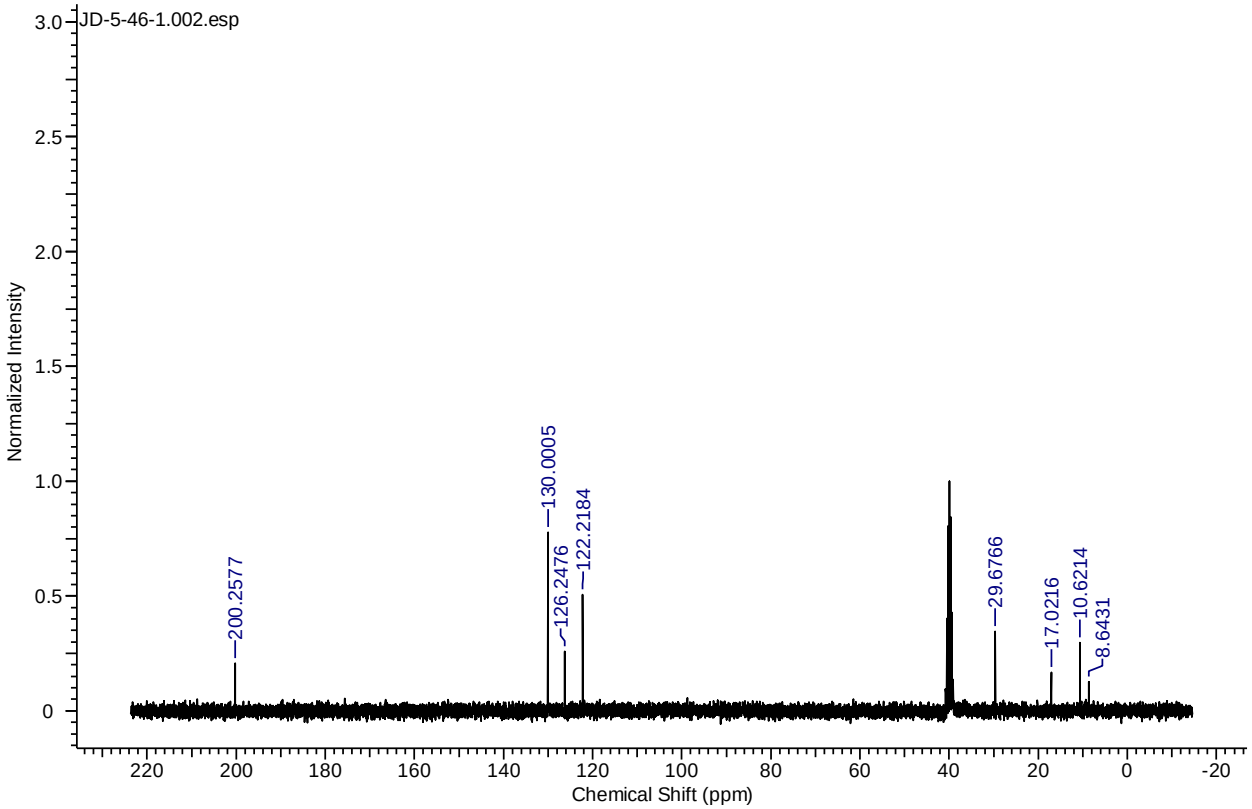

Chemical Shift (ppm)

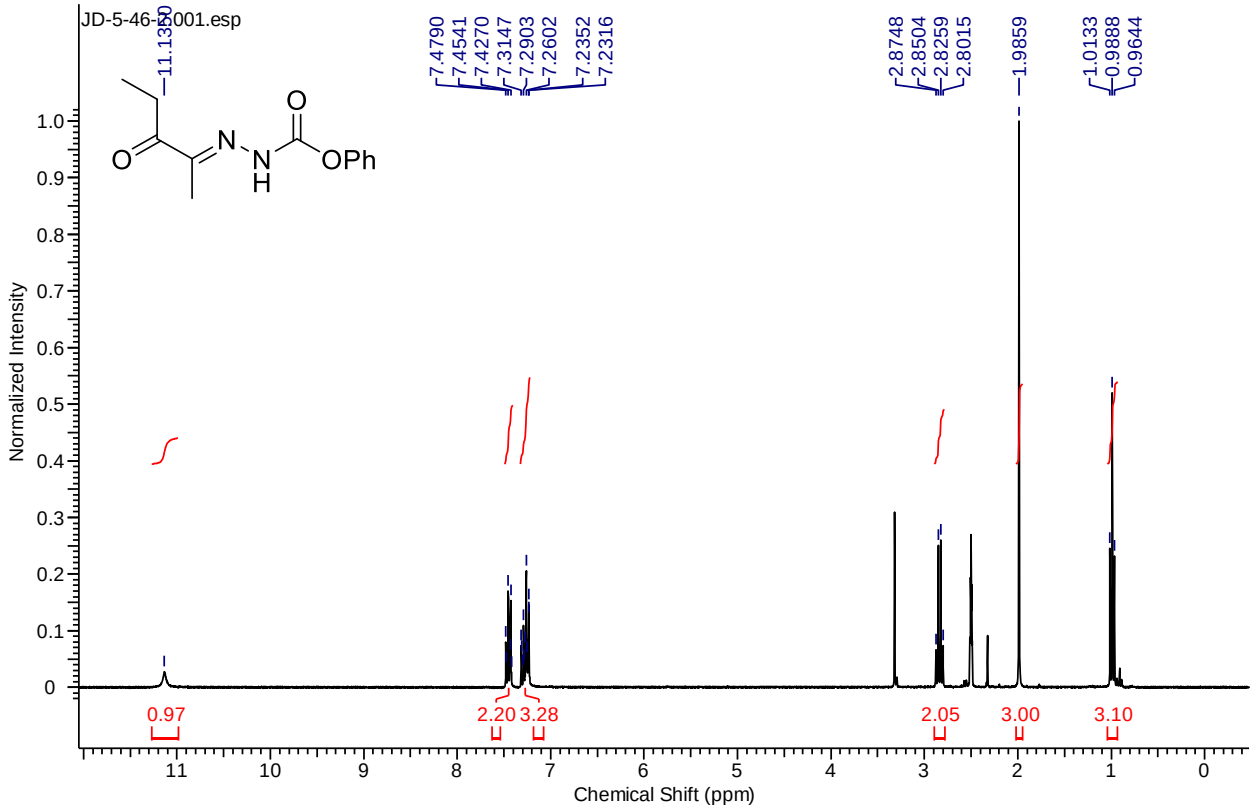

Chemical Shift (ppm)

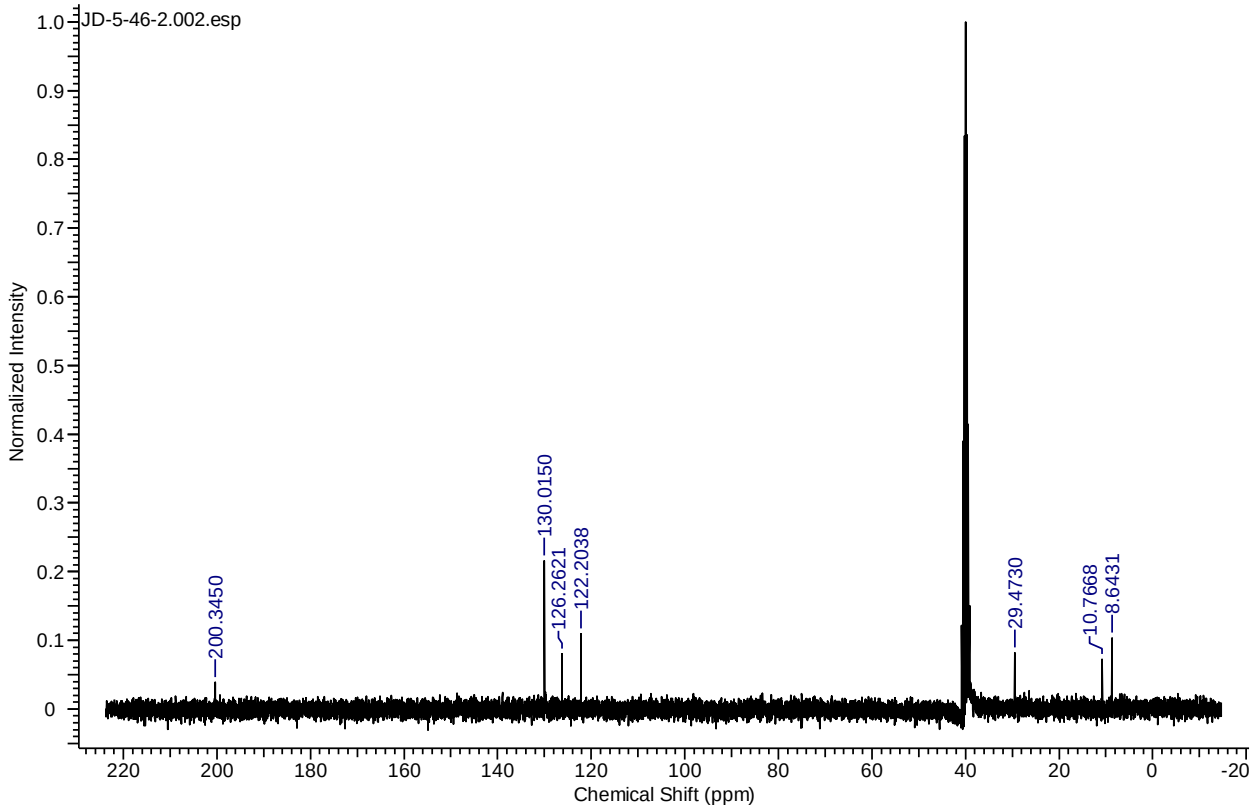

JD-5-38-1(butanedione SM).001.esp
11.1387
7.4879
7.4806
7.4541
7.4286
7.2914
7.2670
7.2633
7.2384
7.2352
2.3352
1.9729
O
N
N
H
O
OPh
Normalized Intensity
0.95
2.10
3.10
2.91
3.00
Chemical Shift (ppm)

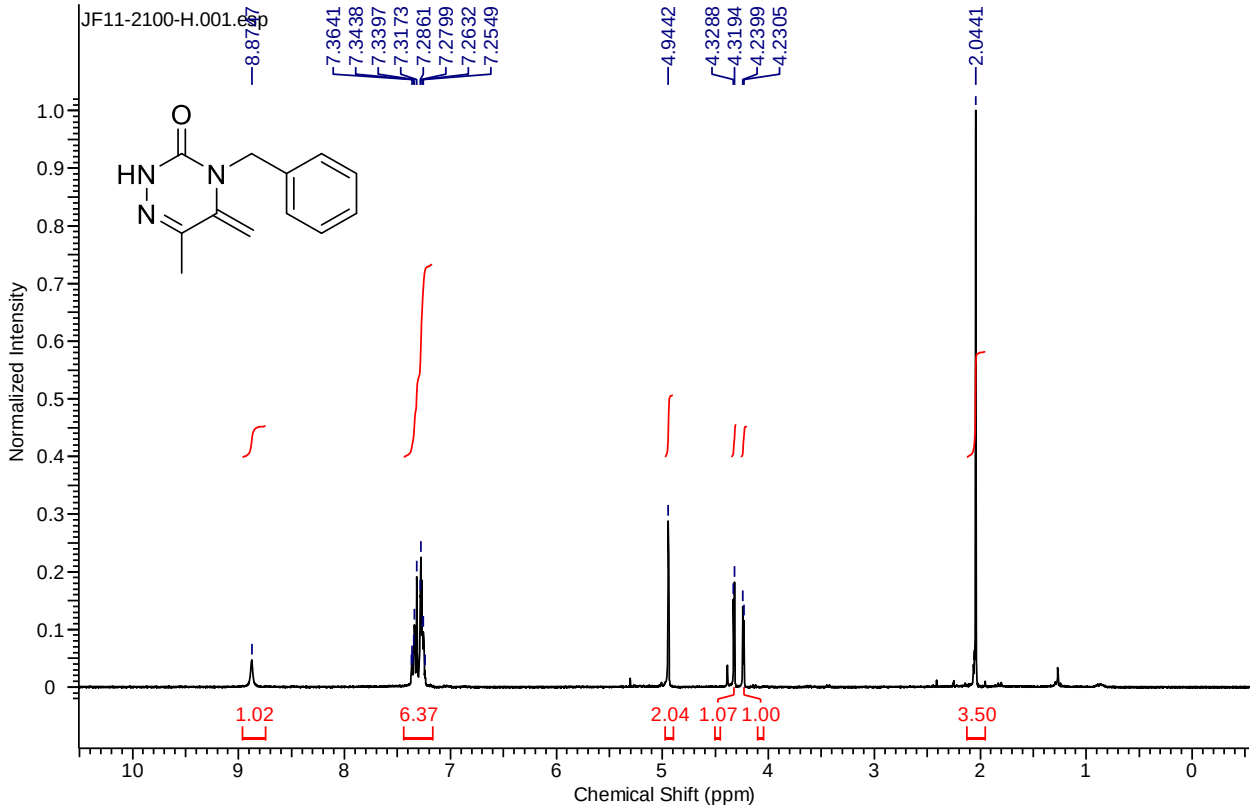

JD-5-38-1(butanedione SM).002.001.1r.esp
197.2869
129.5789
125.8297
121.7422
24.2621
10.0543
Normalized Intensity
Chemical Shift (ppm)

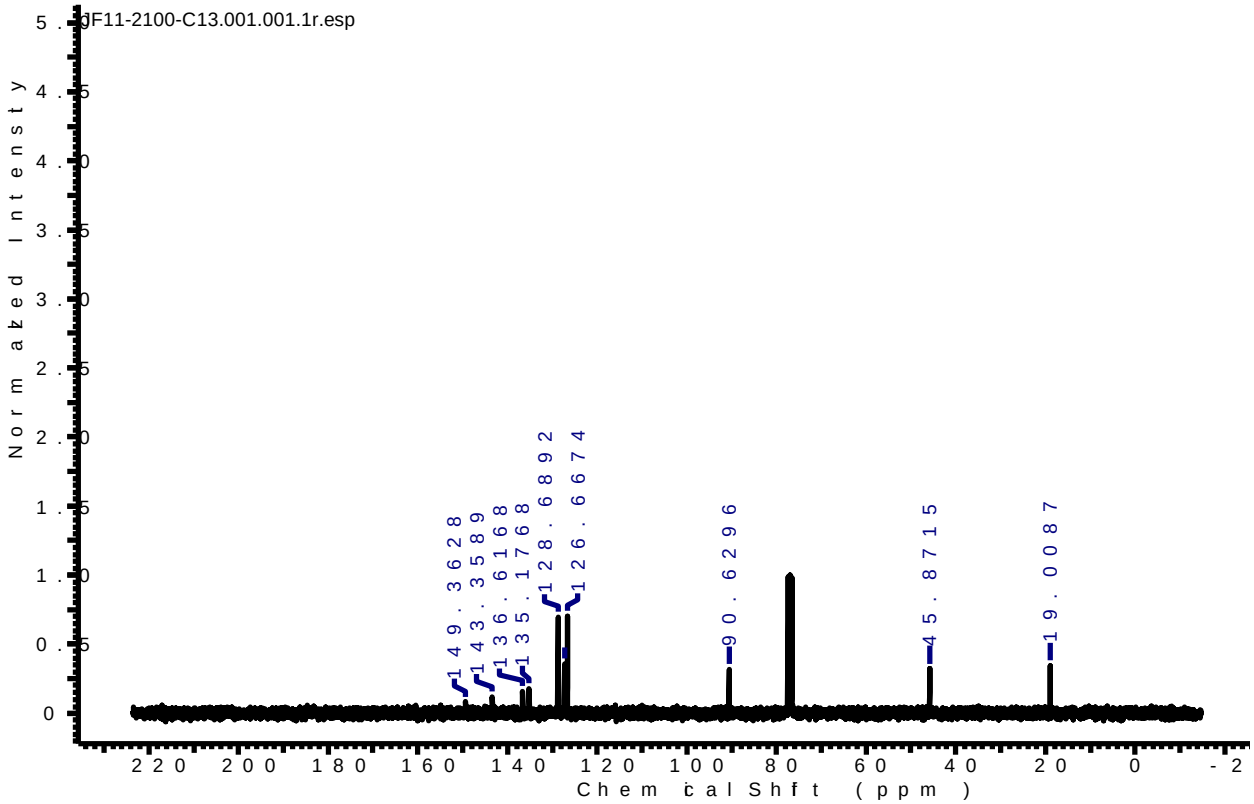

JD-5-46-1.001.esp
11.2756
7.4769
7.4525
7.4504
7.4255
7.2882
7.2695
7.2451
7.2409
2.8587
2.8343
2.8098
2.7854
2.6097
2.5842
2.5593
2.5343
1.0096
0.9852
0.9608
0.9410
0.9166
0.8911
O
N
N
H
O
OPh
Normalized Intensity
0.88
2.00
2.95
1.98
1.94
2.96
2.91
Chemical Shift (ppm)

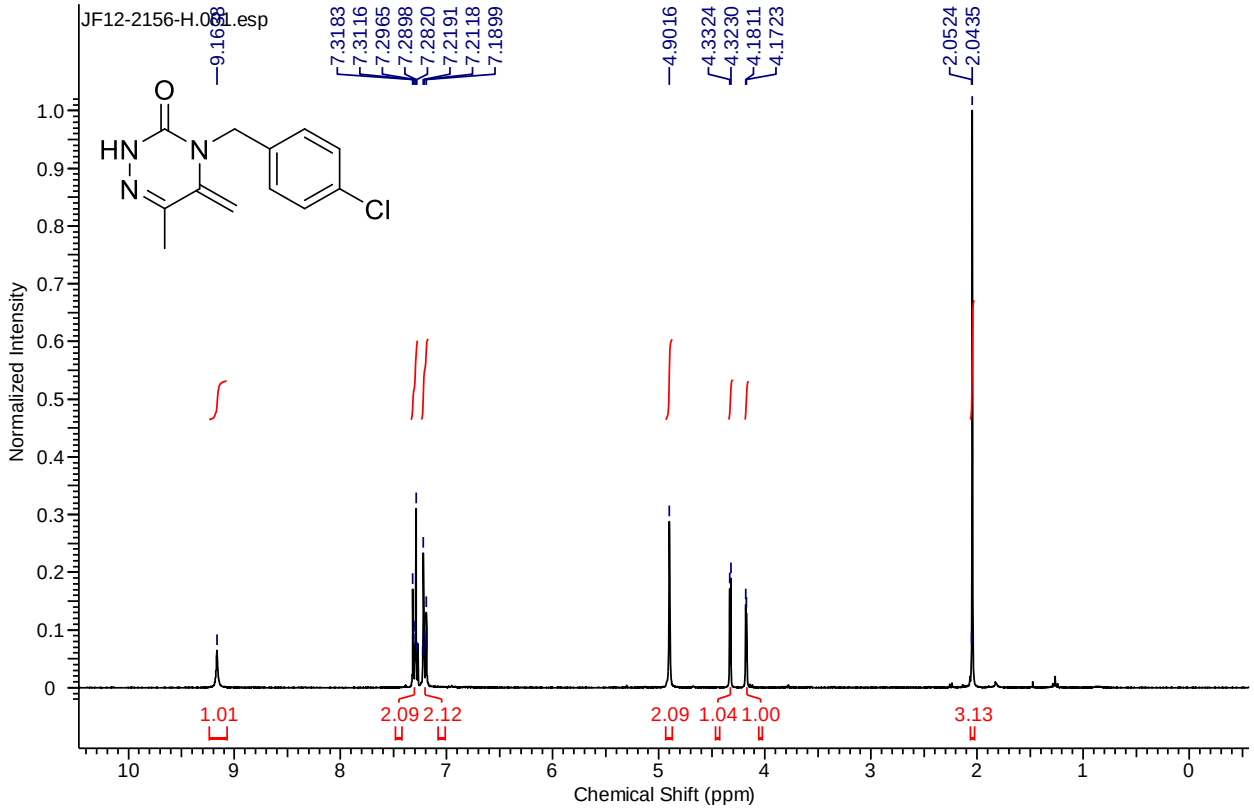

JD-5-46-1.002.esp
200.2577
130.0005
126.2476
122.2184
29.6766
17.0216
10.6214
8.6431
Normalized Intensity
Chemical Shift (ppm)

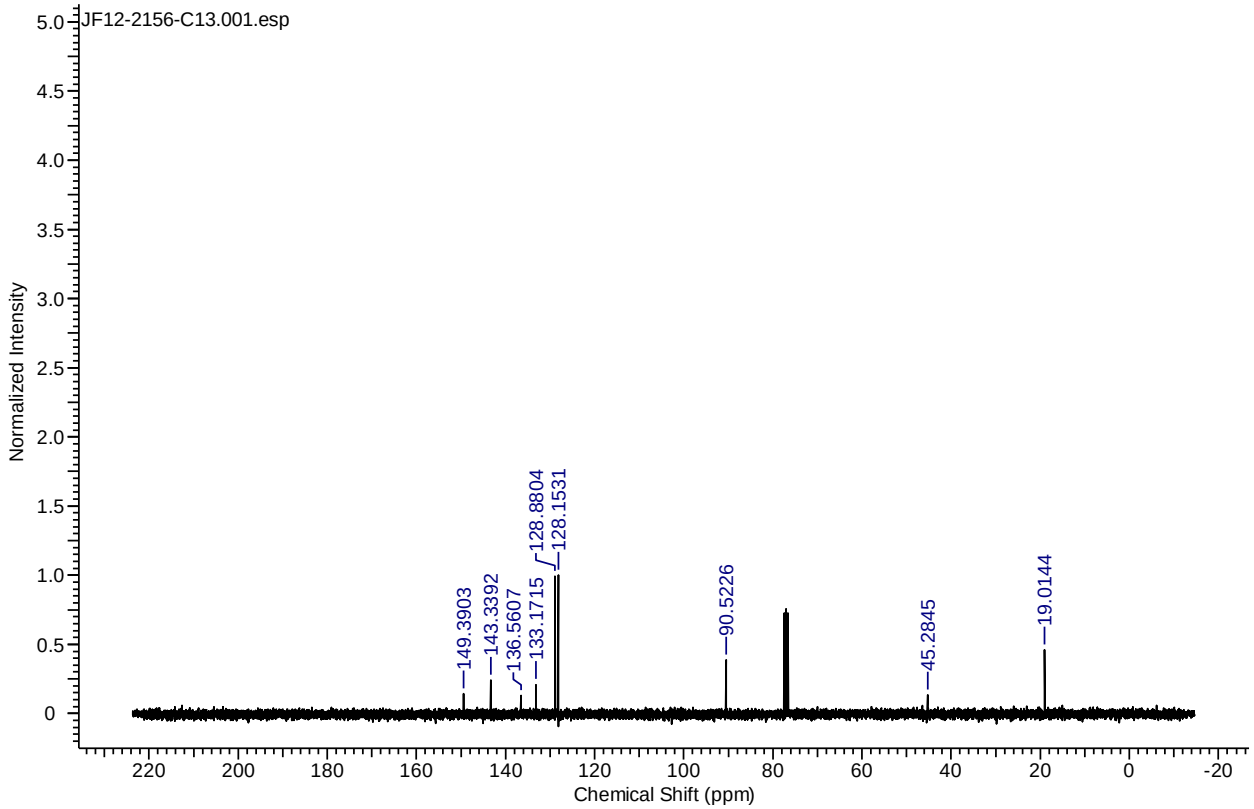

JD-5-46-1.001.esp
11.1350
7.4790
7.4541
7.4270
7.3147
7.2903
7.2602
7.2352
7.2316
2.8748
2.8504
2.8259
2.8015
1.9859
1.0133
0.9888
0.9644
O
N
N
H
O
OPh
Normalized Intensity
0.97
2.20
3.28
2.05
3.00
3.10
Chemical Shift (ppm)

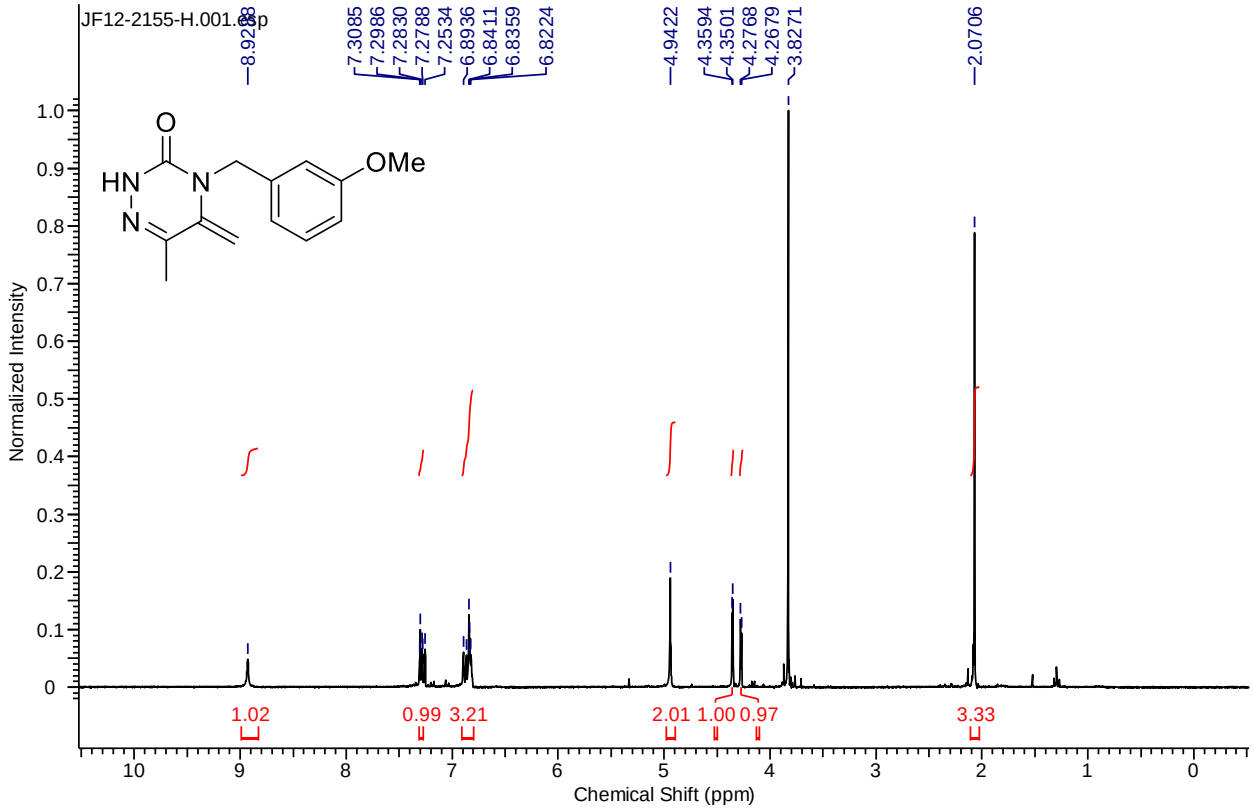

JD-5-46-2.002.esp
200.3450
130.0150
126.2621
122.2038
29.4730
10.7668
8.6431
Normalized Intensity
Chemical Shift (ppm)

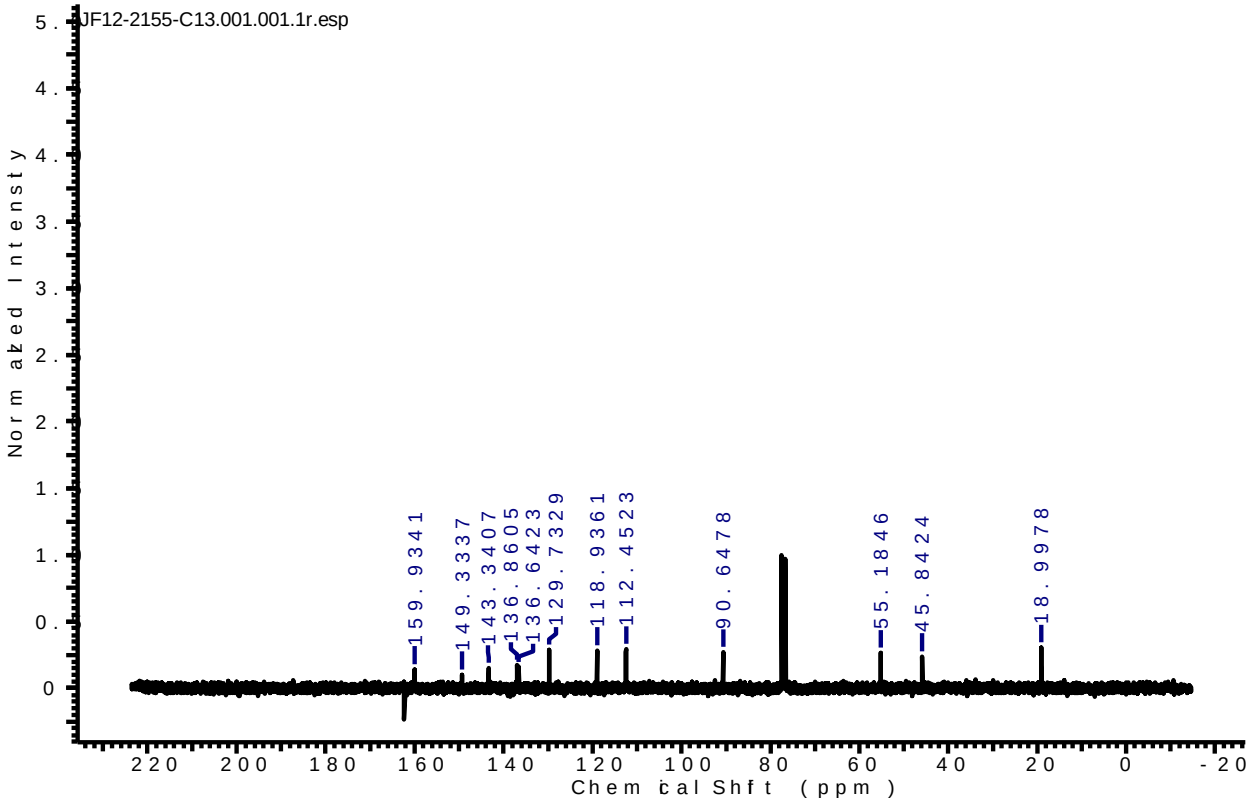

JF11-2100-H.001.esp
8.8747
7.3641
7.3438
7.3397
7.3173
7.2861
7.2799
7.2632
7.2549
4.9442
4.3288
4.3194
4.2399
4.2305
2.0441
Normalized Intensity
1.02
6.37
2.04
1.07
1.00
3.50
Chemical Shift (ppm)

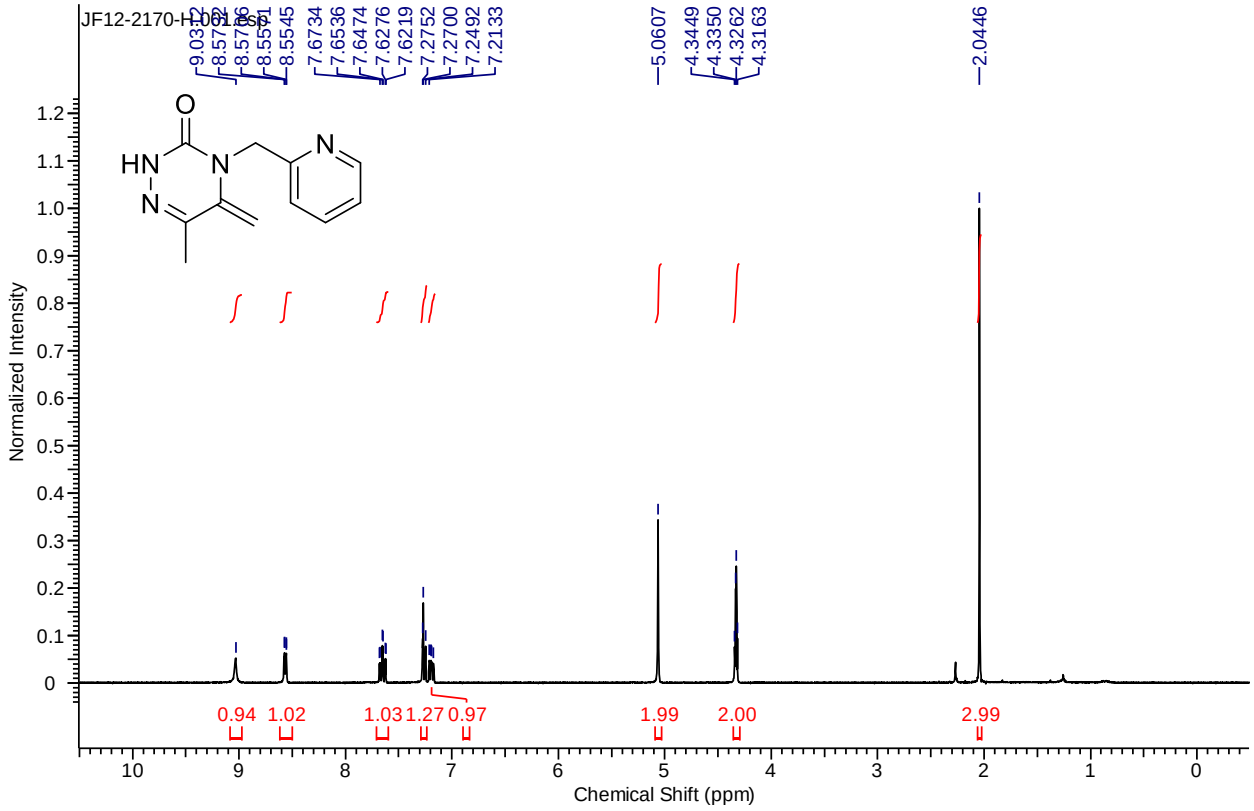

JF11-2100-C13.001.001.1r.esp
149.3628
143.3589
136.6168
135.1768
128.6892
126.6674
90.6296
45.8715
19.0087
Chemical Shift (ppm)

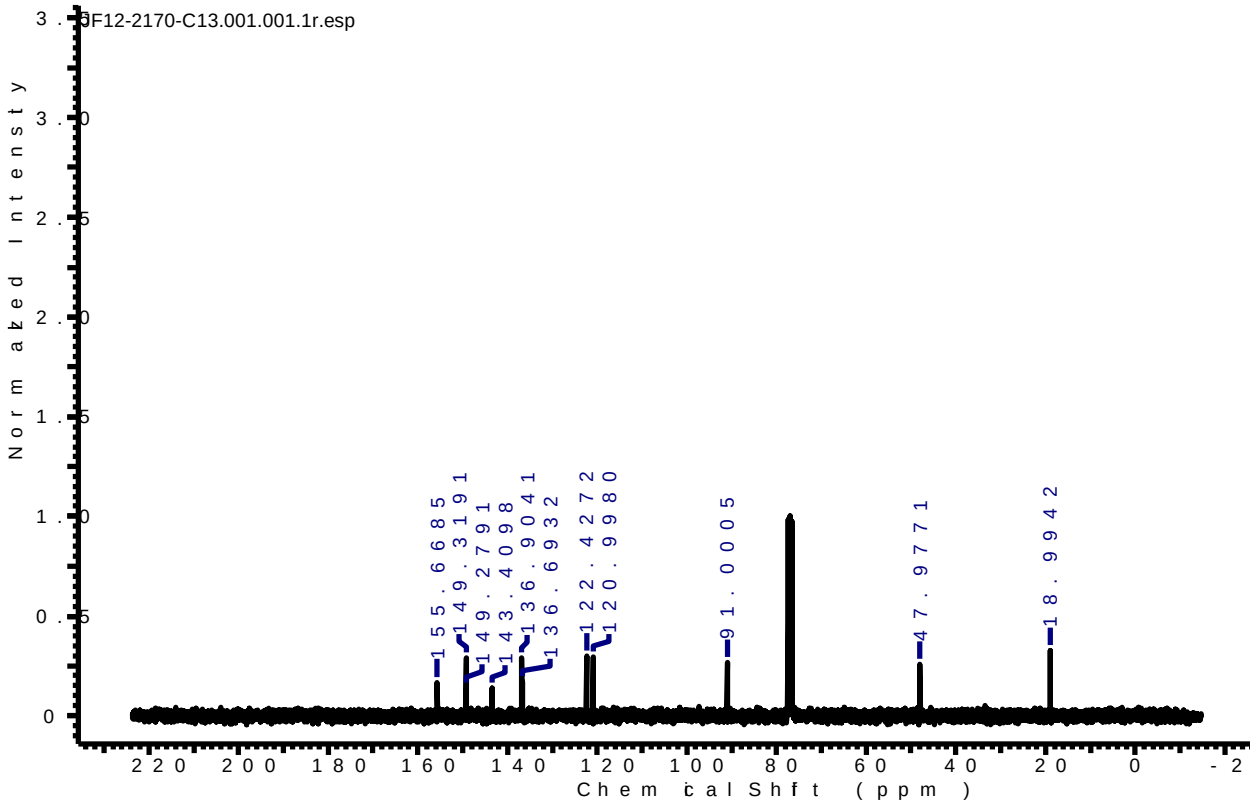

JF12-2156-H.001.esp
9.1693
7.3183
7.3116
7.2965
7.2898
7.2820
7.2191
7.2118
7.1899
4.9016
4.3324
4.3230
4.1811
4.1723
2.0524
2.0435
O
HN
N
N
Cl
1.01
2.09
2.12
2.09
1.04
1.00
3.13
Normalized Intensity
Chemical Shift (ppm)

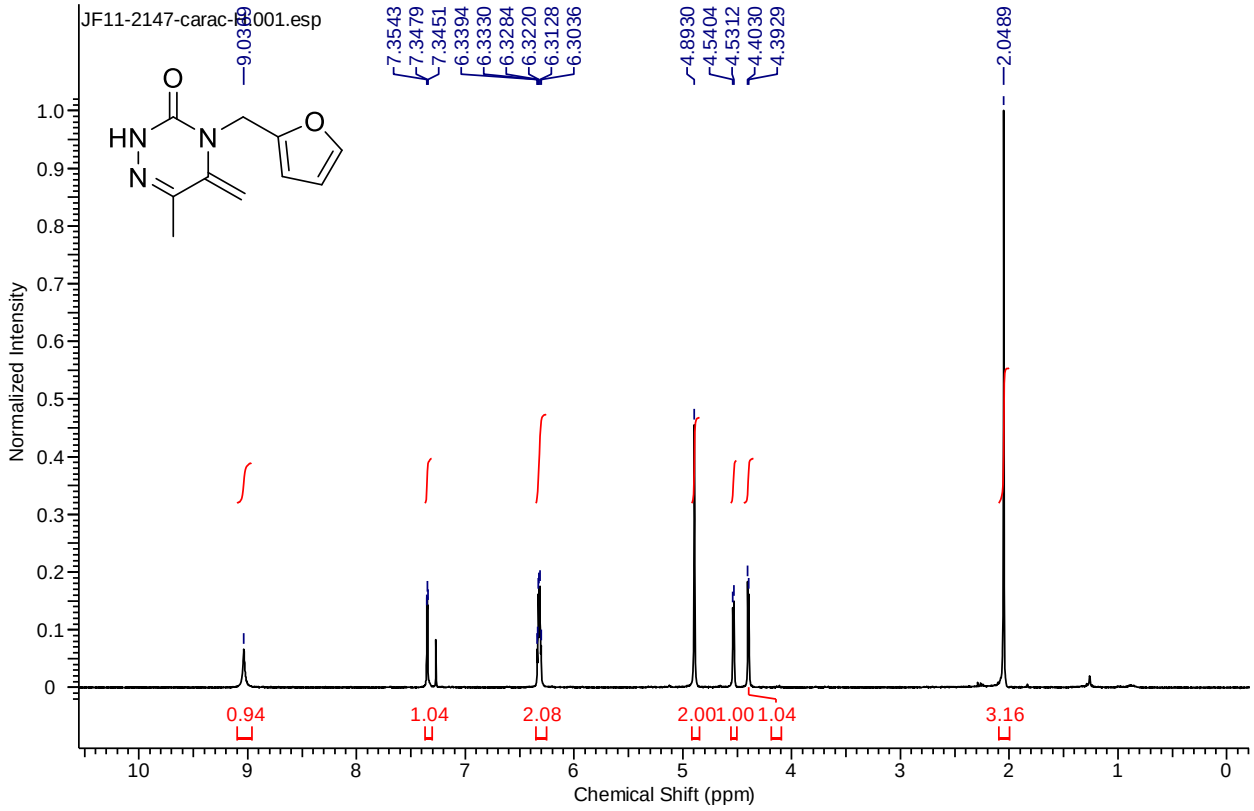

JF12-2156-C13.001.esp
149.3903
143.3392
136.5607
133.1715
128.8804
128.1531
90.5226
45.2845
19.0144
Normalized Intensity
Chemical Shift (ppm)

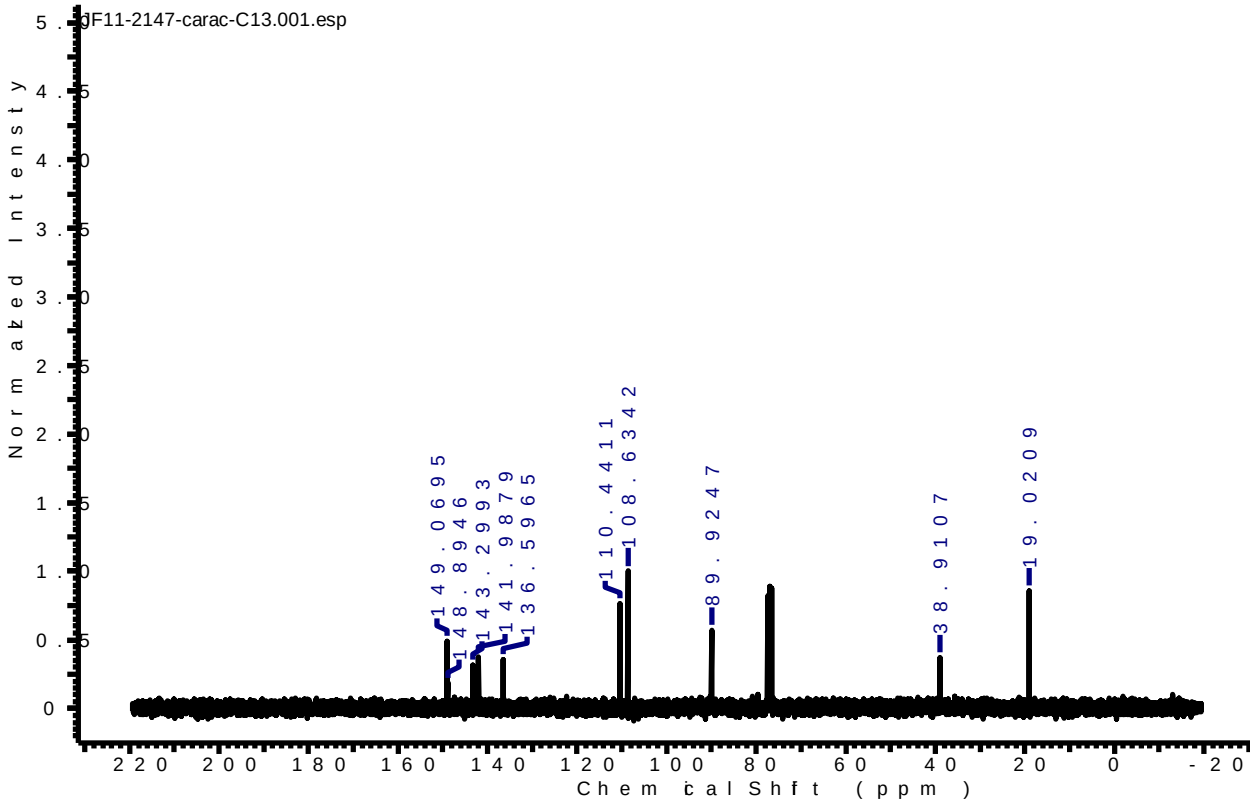

JF12-2155-H.001.esp
8.9288
7.3085
7.2986
7.2830
7.2788
7.2534
6.8936
6.8411
6.8359
6.8224
4.9422
4.3594
4.3501
4.2768
4.2679
3.8271
2.0706
O
HN
N
N
OMe
Normalized Intensity
1.02
0.99
3.21
2.01
1.00
0.97
3.33
Chemical Shift (ppm)

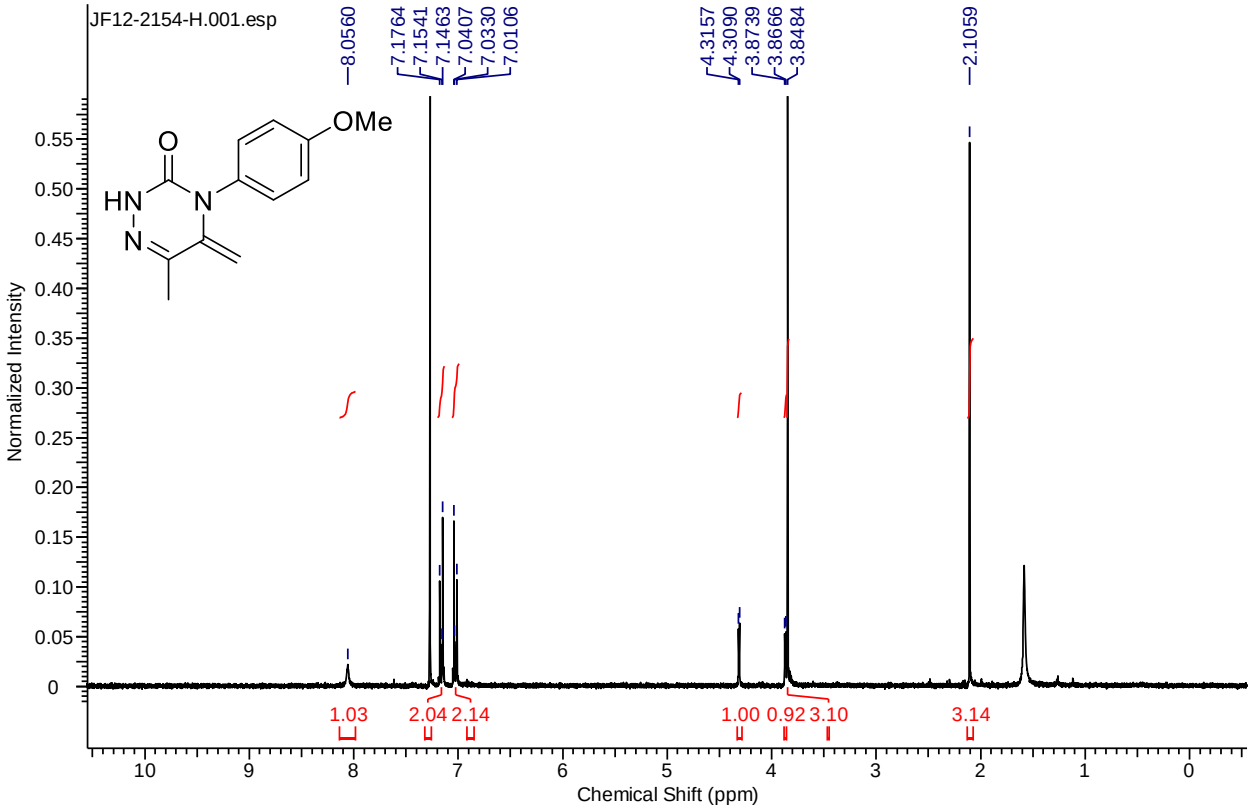

JF12-2155-C13.001.001.1r.esp
159.9341
149.3337
143.3407
136.8605
136.6423
129.7329
118.9361
112.4523
90.6478
55.1846
45.8424
18.9978
Chemical Shift (ppm)

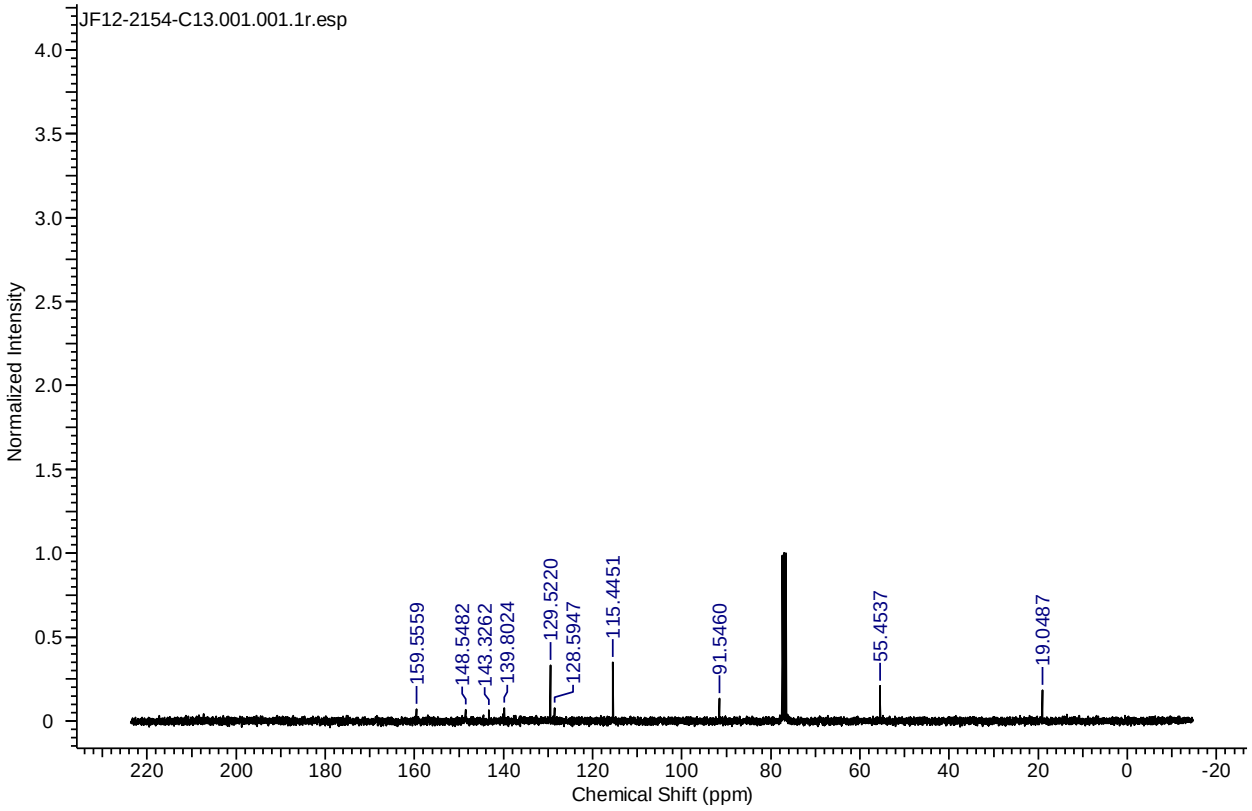

JF12-2170-H.001.esp
9.0312
8.5766
8.5591
8.5545
7.6734
7.6536
7.6474
7.6276
7.6219
7.2752
7.2700
7.2492
7.2133
5.0607
4.3449
4.3350
4.3262
4.3163
2.0446
O
HN
N
N
N
Normalized Intensity
0.94
1.02
1.03
1.27
0.97
1.99
2.00
2.99
Chemical Shift (ppm)

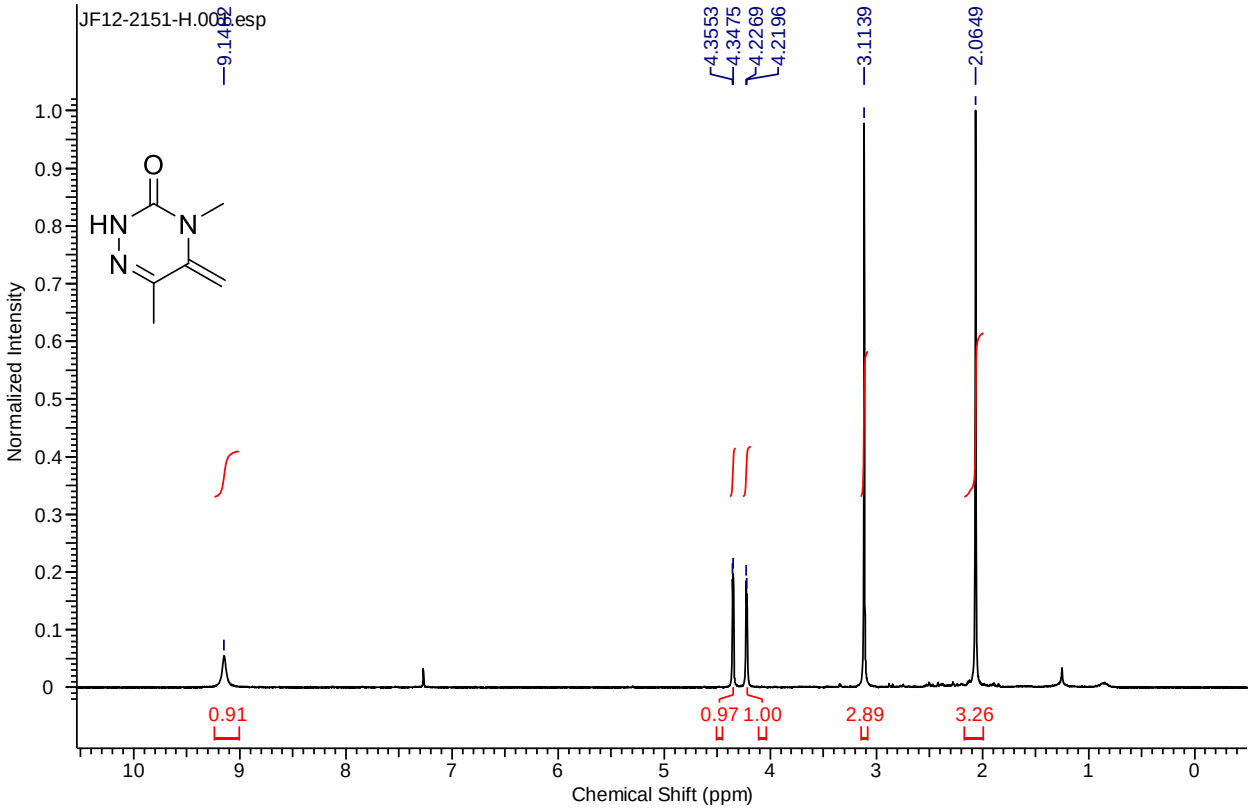

JF12-2170-C13.001.001.1r.esp
Normalized Intensity
155.6685
149.3191
149.2791
143.4098
136.9041
136.6932
122.4272
120.9980
91.0005
47.9771
18.9942
Chemical Shift (ppm)

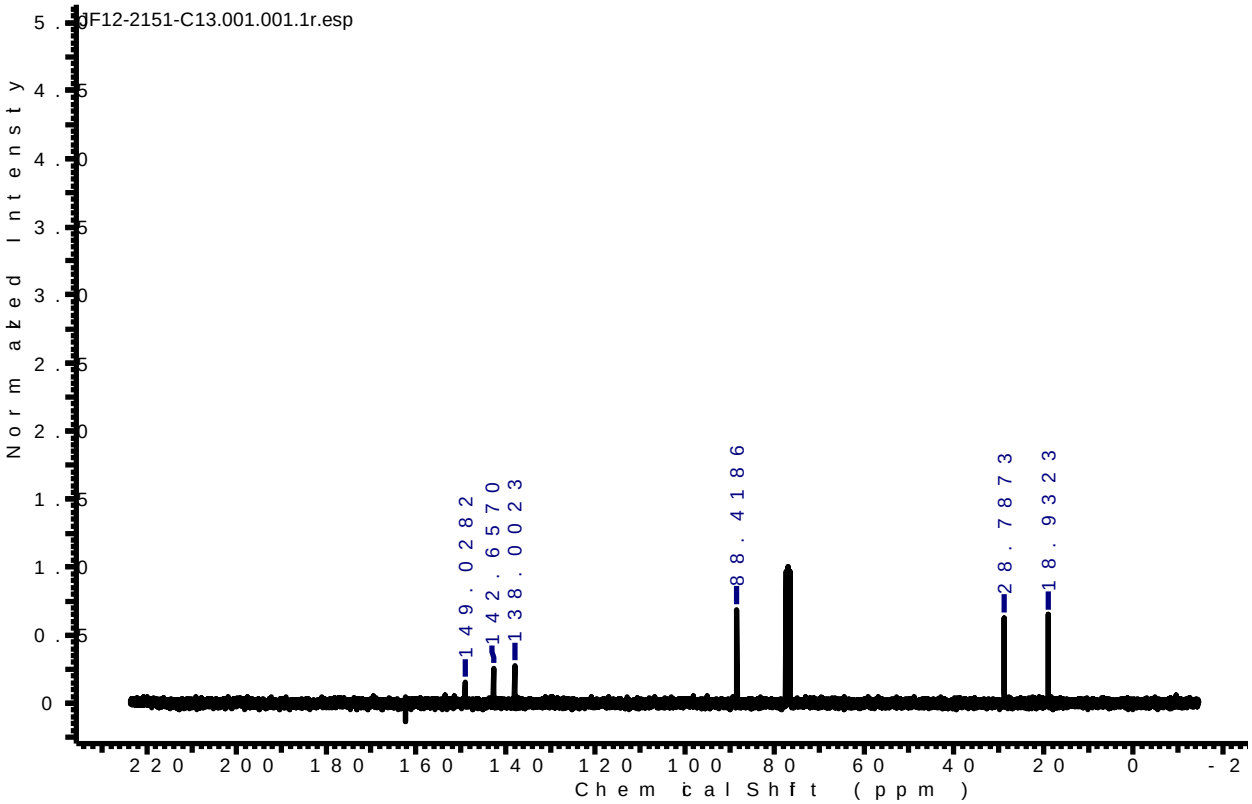

JF11-2147-carac-H1.001.esp
9.0349
7.3543
7.3479
7.3451
6.3394
6.3330
6.3284
6.3220
6.3128
6.3036
4.8930
4.5404
4.5312
4.4030
4.3929
2.0489
Normalized Intensity
0.94
1.04
2.08
2.00
1.00
1.04
3.16
Chemical Shift (ppm)

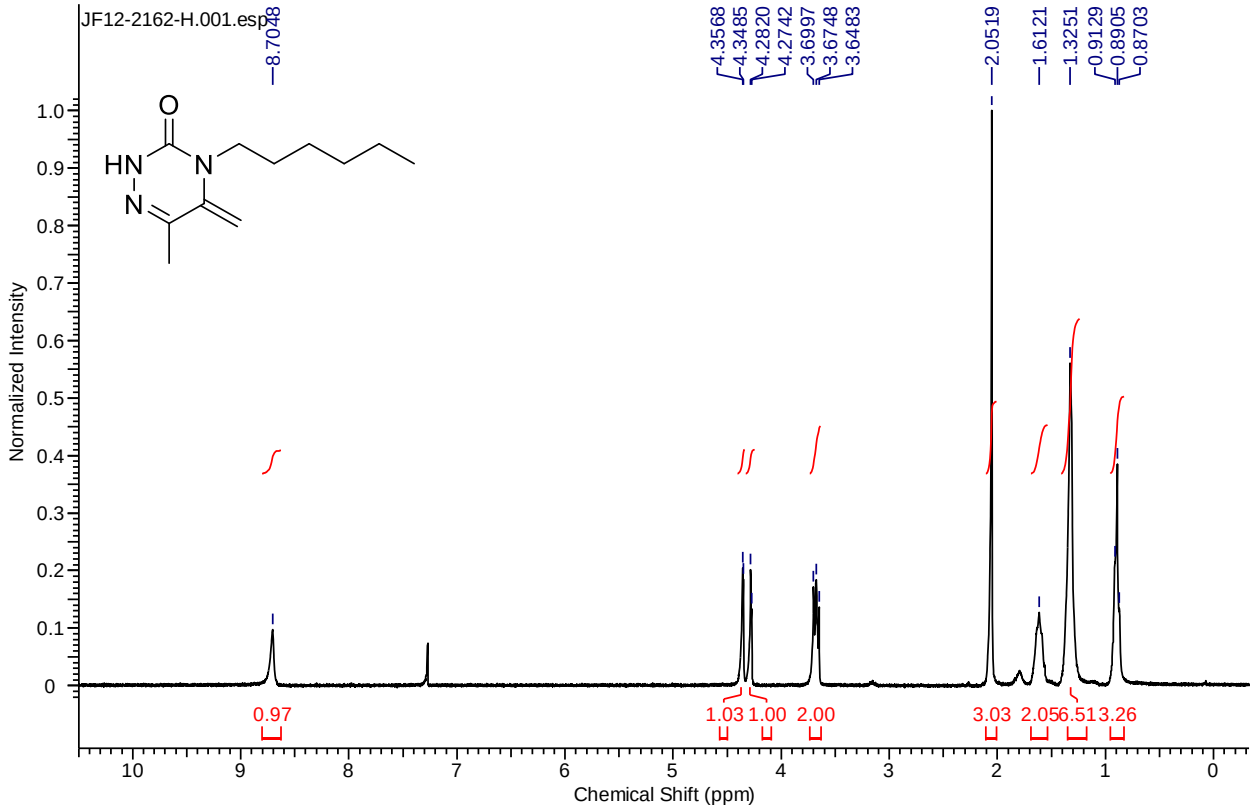

JF11-2147-carac-C13.001.esp
Normalized Intensity
149.0695
148.8946
143.2993
141.9879
136.5965
110.4411
108.6342
89.9247
38.9107
19.0209
Chemical Shift (ppm)

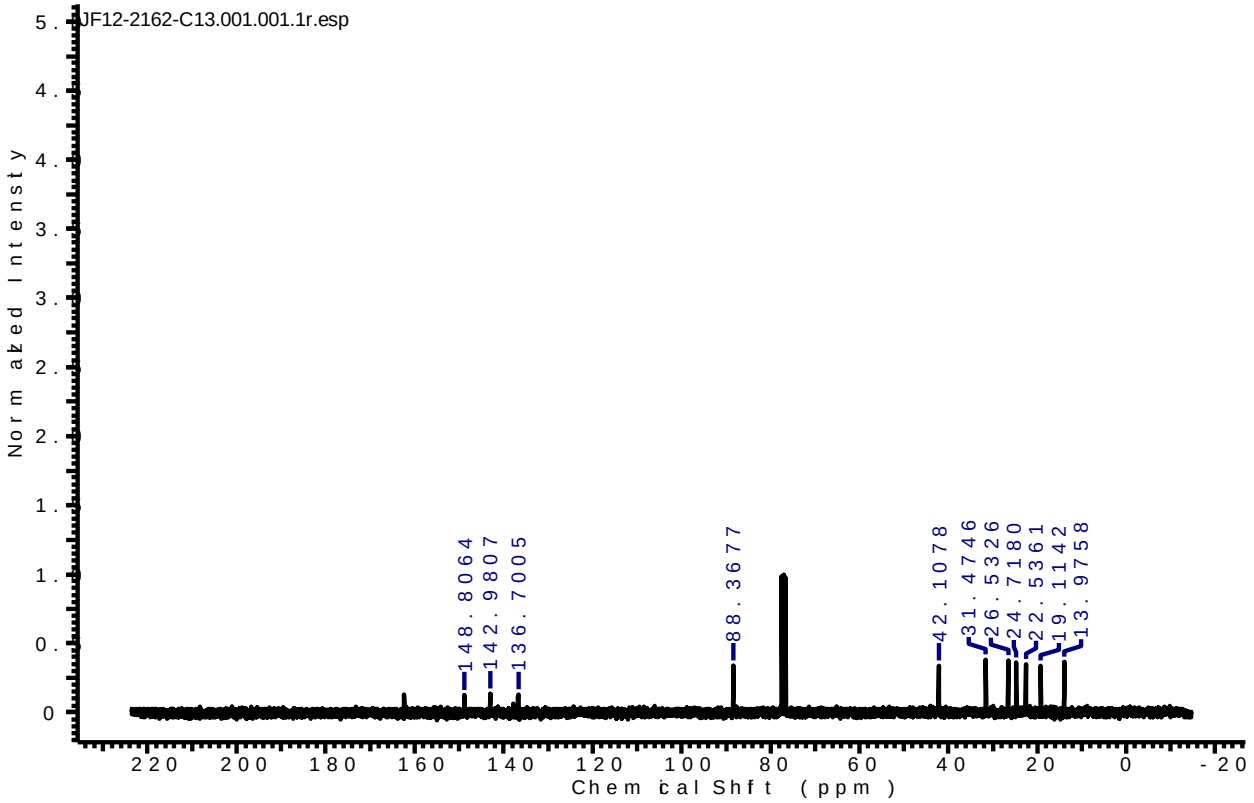

JF12-2154-H.001.esp
8.0560
7.1764
7.1541
7.1463
7.0407
7.0330
7.0106
4.3157
4.3090
3.8739
3.8666
3.8484
2.1059
OMe
O
HN
N
N
Normalized Intensity
1.03
2.04
2.14
1.00
0.92
3.10
3.14
Chemical Shift (ppm)

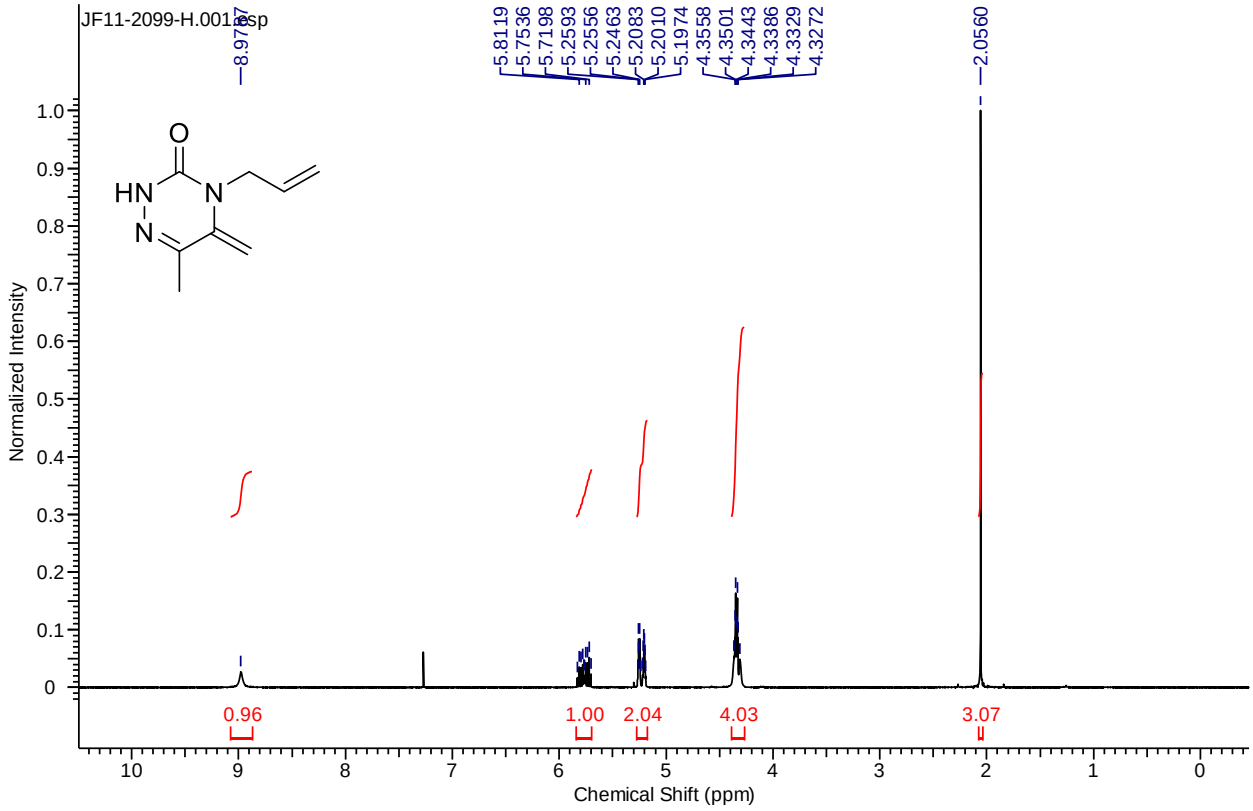

JF12-2154-C13.001.001.1r.esp
Normalized Intensity
159.5559
148.5482
143.3262
139.8024
129.5220
128.5947
115.4451
91.5460
55.4537
19.0487
Chemical Shift (ppm)

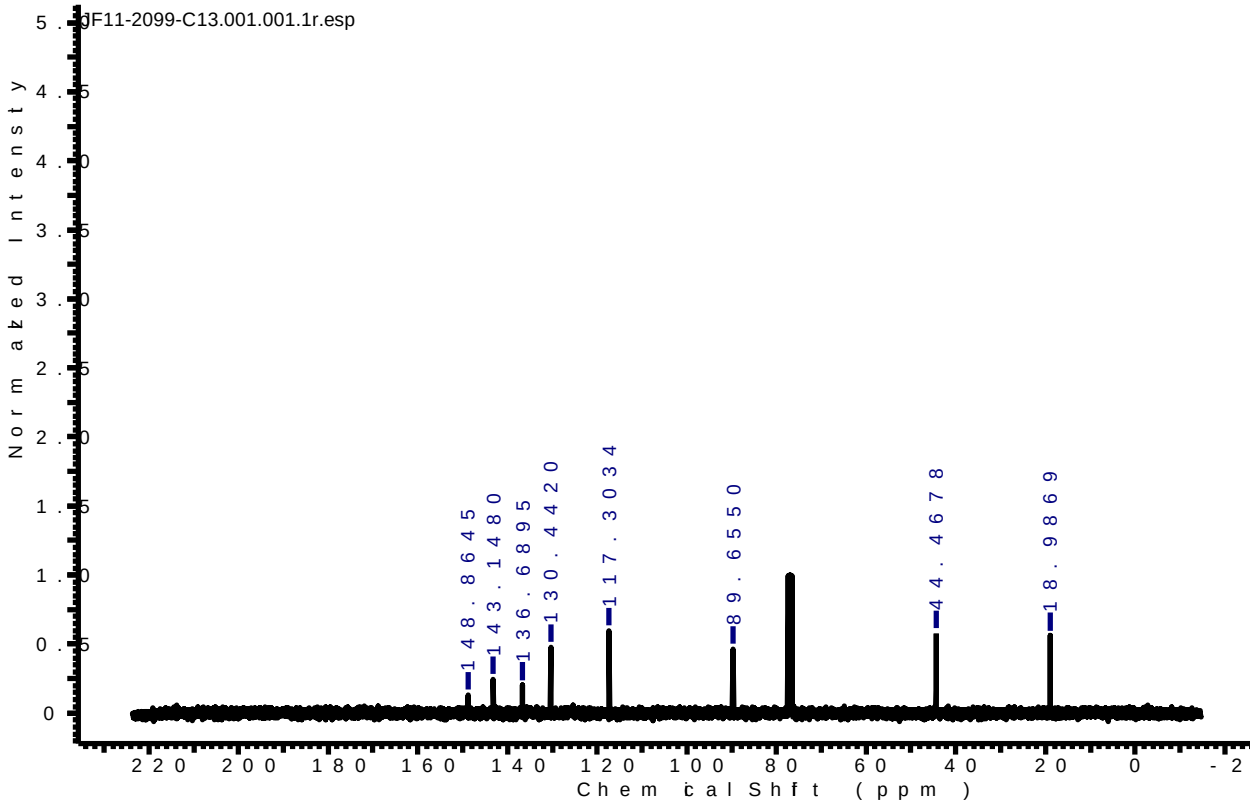

JF12-2151-H.001.esp
9.1482
4.3553
4.3475
4.2269
4.2196
3.1139
2.0649
Normalized Intensity
Chemical Shift (ppm)
0.91
0.97
1.00
2.89
3.26

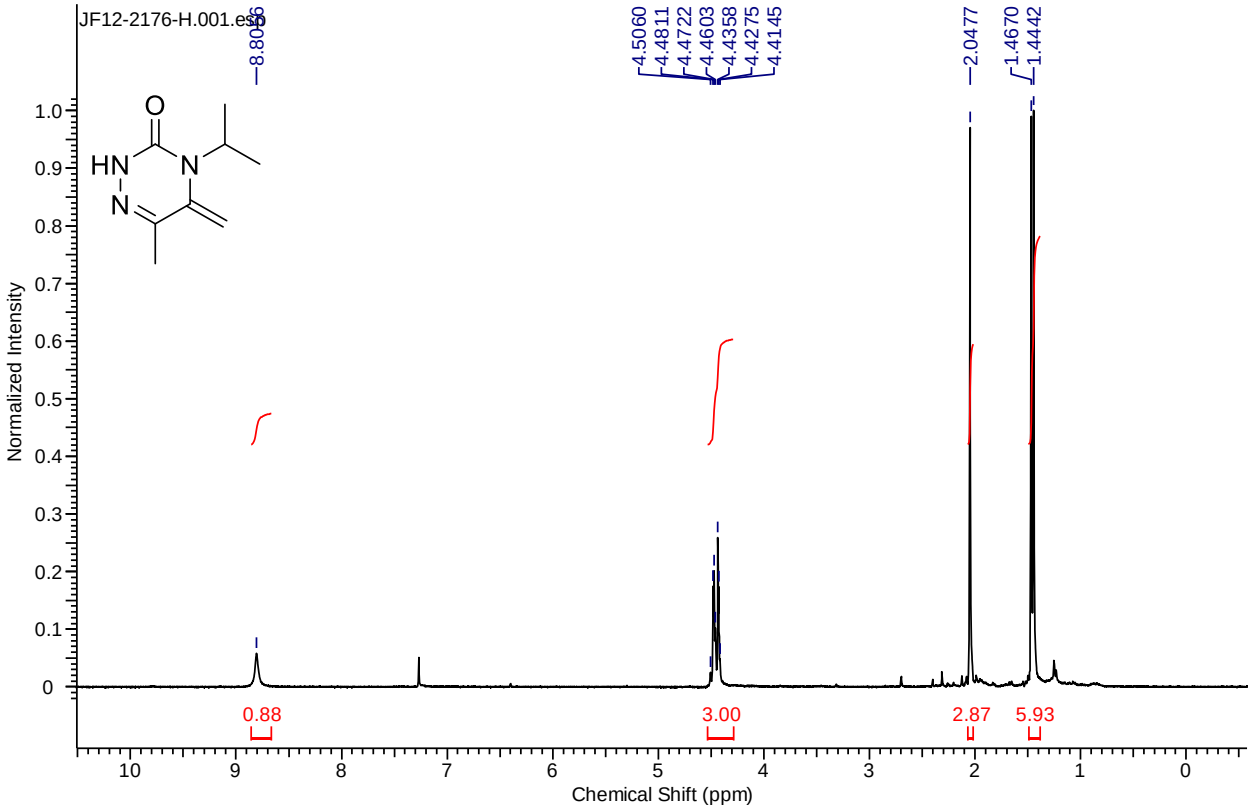

JF12-2151-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
149.0282
142.6570
138.0023
88.4186
28.7873
18.9323

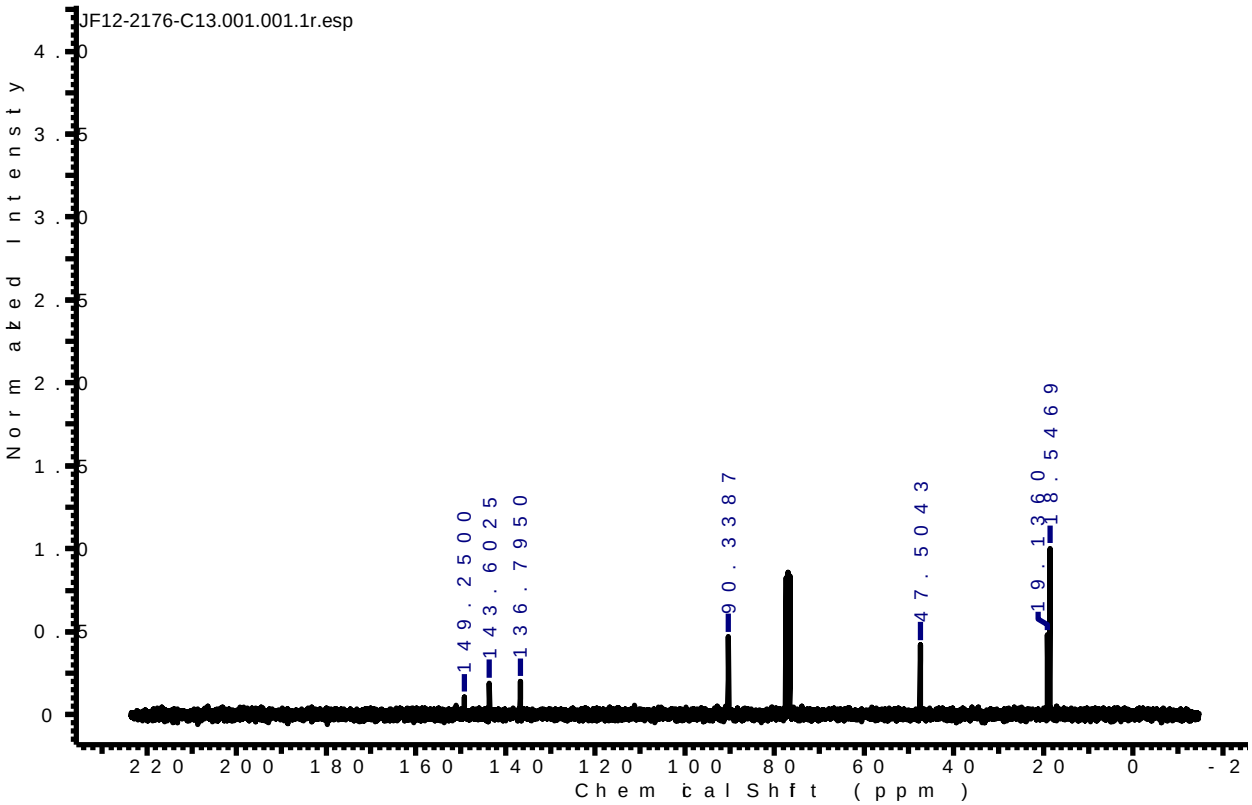

JF12-2162-H.001.esp
8.7048
4.3568
4.3485
4.2820
4.2742
3.6997
3.6748
3.6483
2.0519
1.6121
1.3251
0.9129
0.8905
0.8703
O
HN
N
N
Normalized Intensity
0.97
1.03
1.00
2.00
3.03
2.05
6.51
3.26
Chemical Shift (ppm)

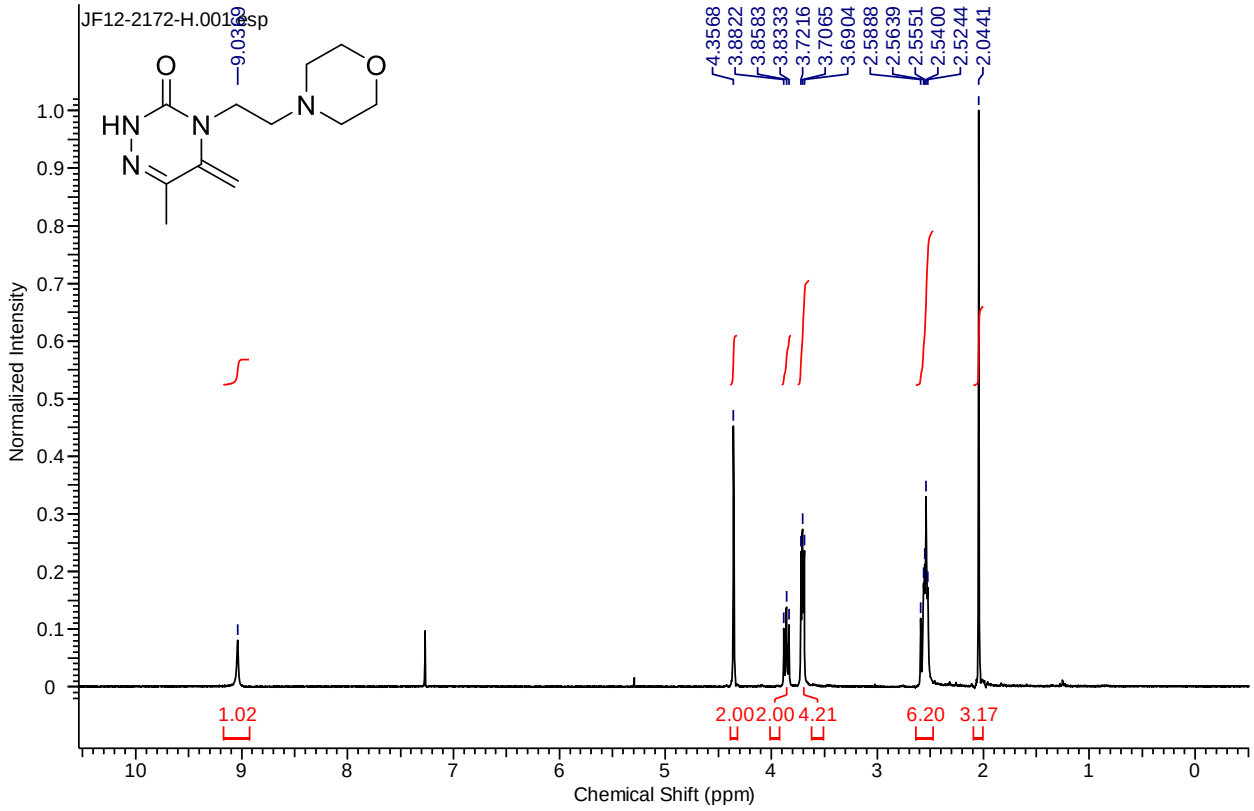

JF12-2162-C13.001.001.1r.esp
Normalized Intensity
148.8064
142.9807
136.7005
88.3677
42.1078
31.4746
26.5326
24.7180
22.5361
19.1142
13.9758
Chemical Shift (ppm)

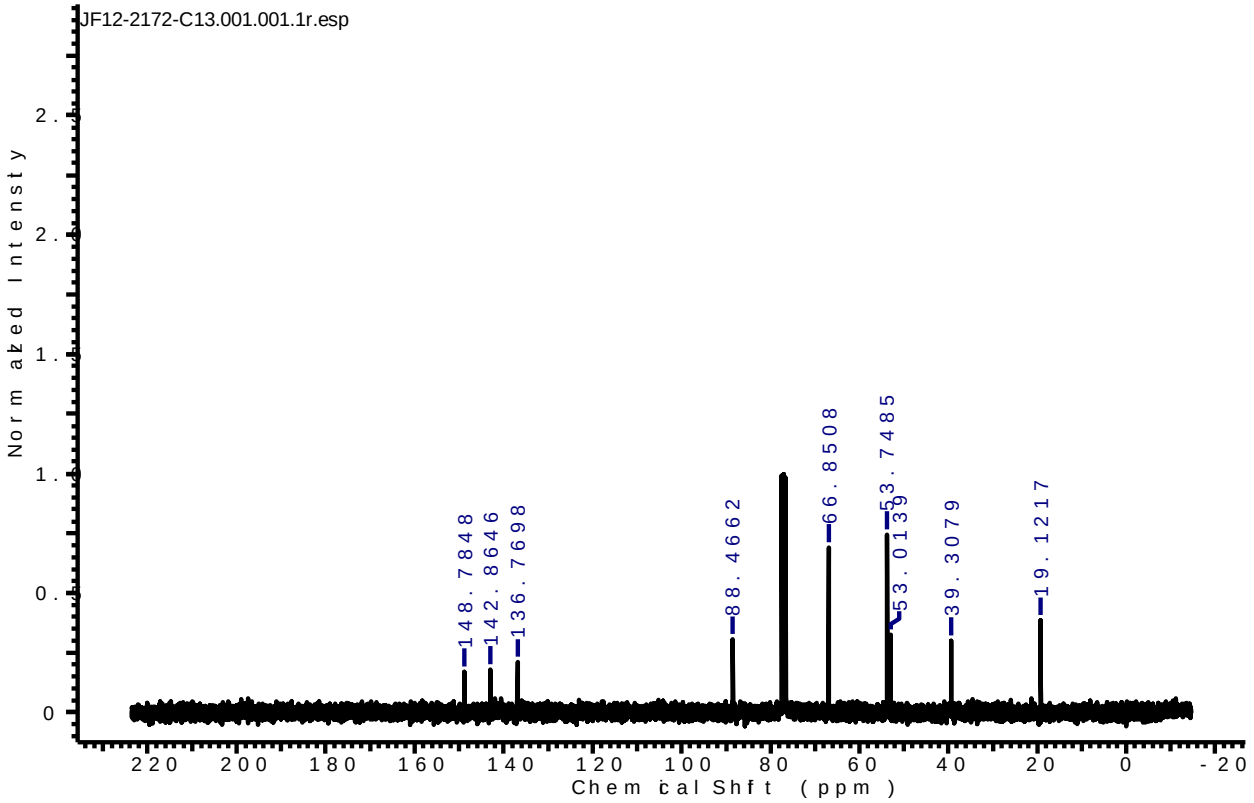

JF11-2099-H.001.esp
8.9767
5.8119
5.7536
5.7198
5.2593
5.2556
5.2463
5.2083
5.2010
5.1974
4.3558
4.3501
4.3443
4.3386
4.3329
4.3272
2.0560
O
HN
N
N
Normalized Intensity
0.96
1.00
2.04
4.03
3.07
Chemical Shift (ppm)

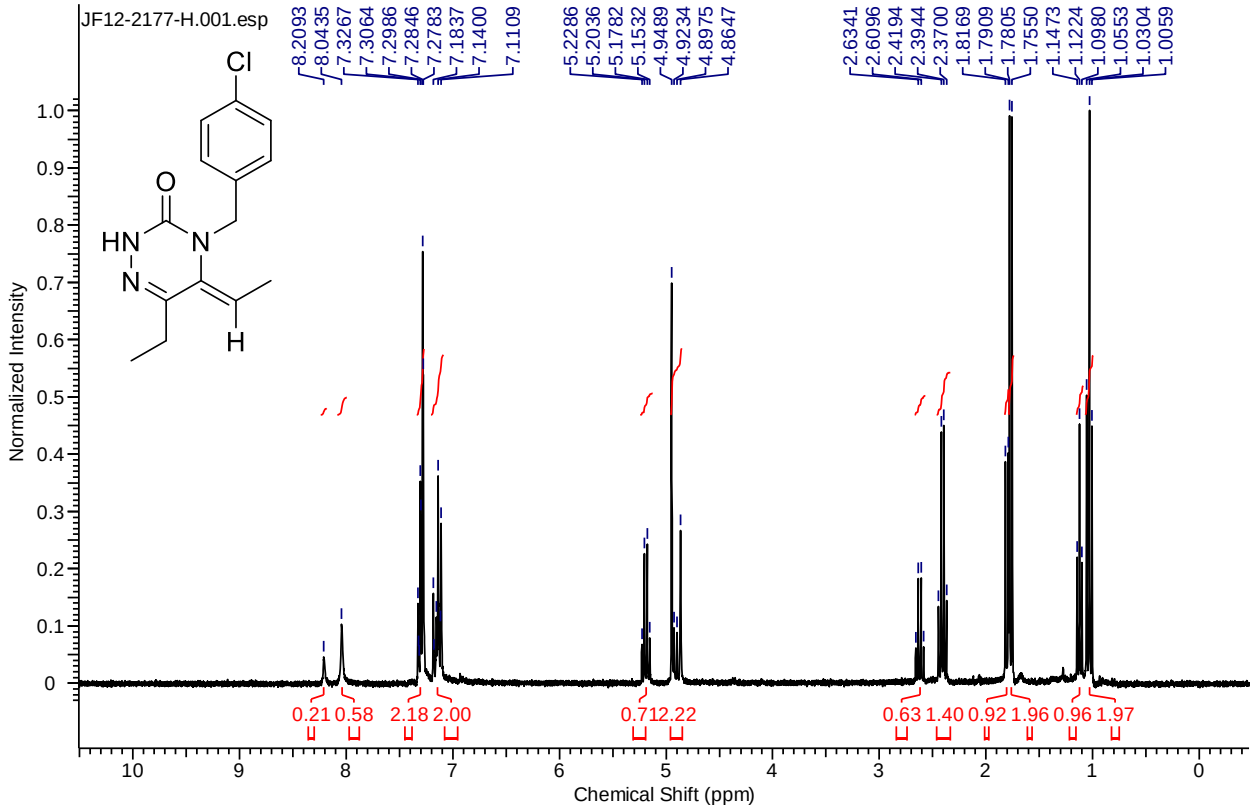

JF11-2099-C13.001.001.1r.esp
148.8645
143.1480
136.6895
130.4420
117.3034
89.6550
44.4678
18.9869
Normalized Intensity
Chemical Shift (ppm)

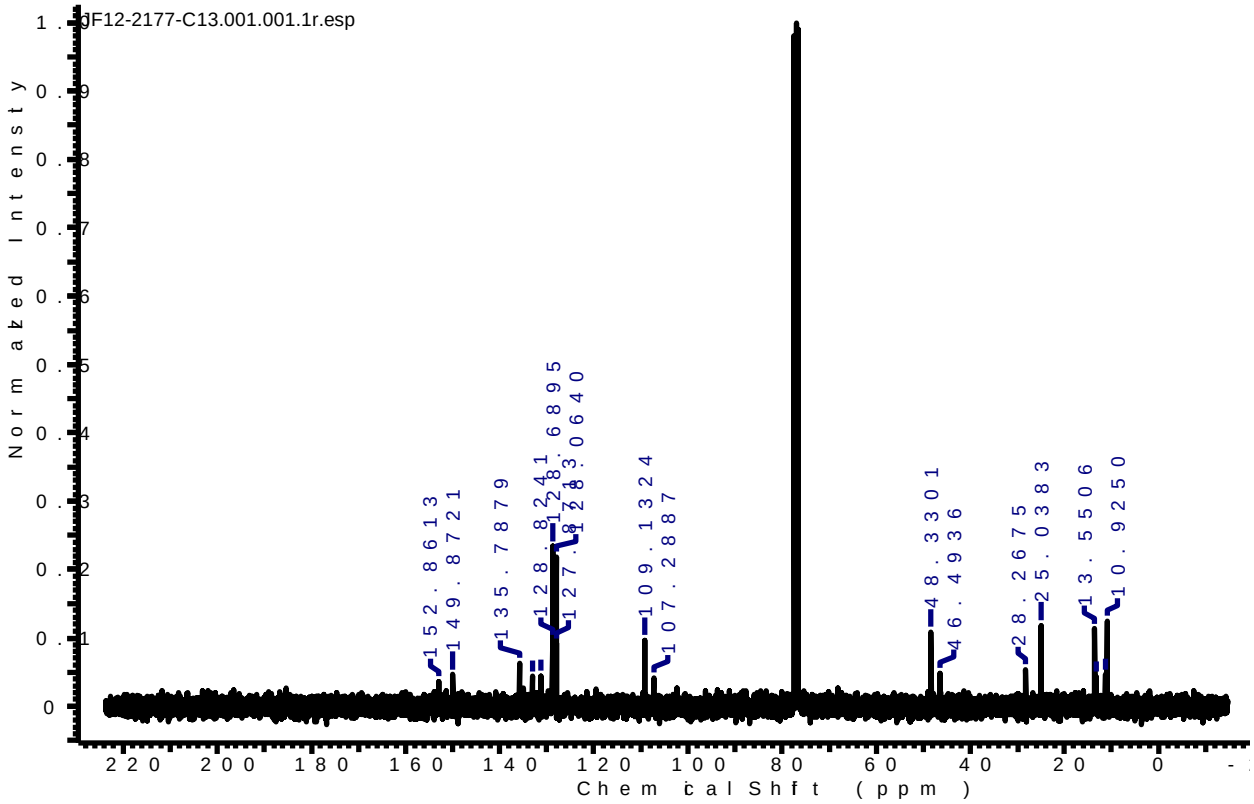

JF12-2176-H.001.esp
8.8056
4.5060
4.4811
4.4722
4.4603
4.4358
4.4275
4.4145
2.0477
1.4670
1.4442
O
HN
N
N
Normalized Intensity
0.88
3.00
2.87
5.93
Chemical Shift (ppm)

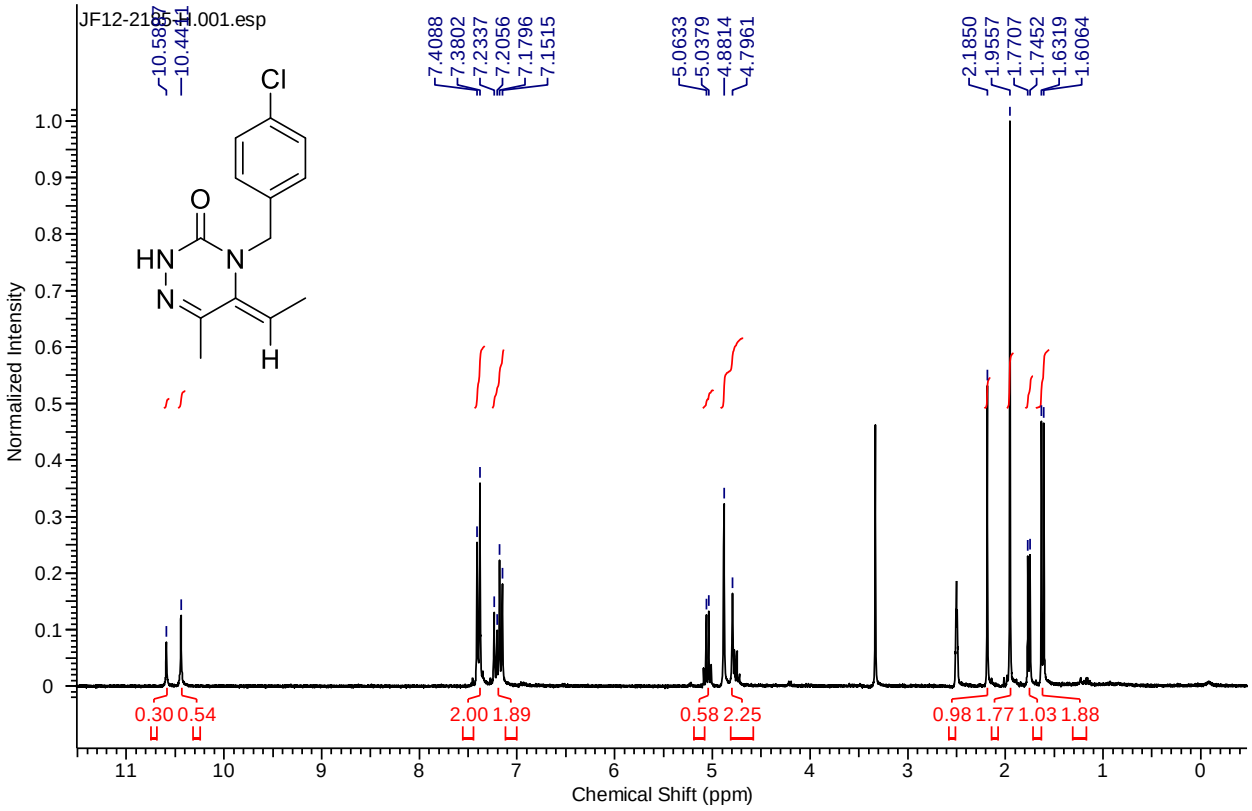

JF12-2176-C13.001.001.1r.esp
149.2500
143.6025
136.7950
90.3387
47.5043
19.1360
18.5469
Chemical Shift (ppm)

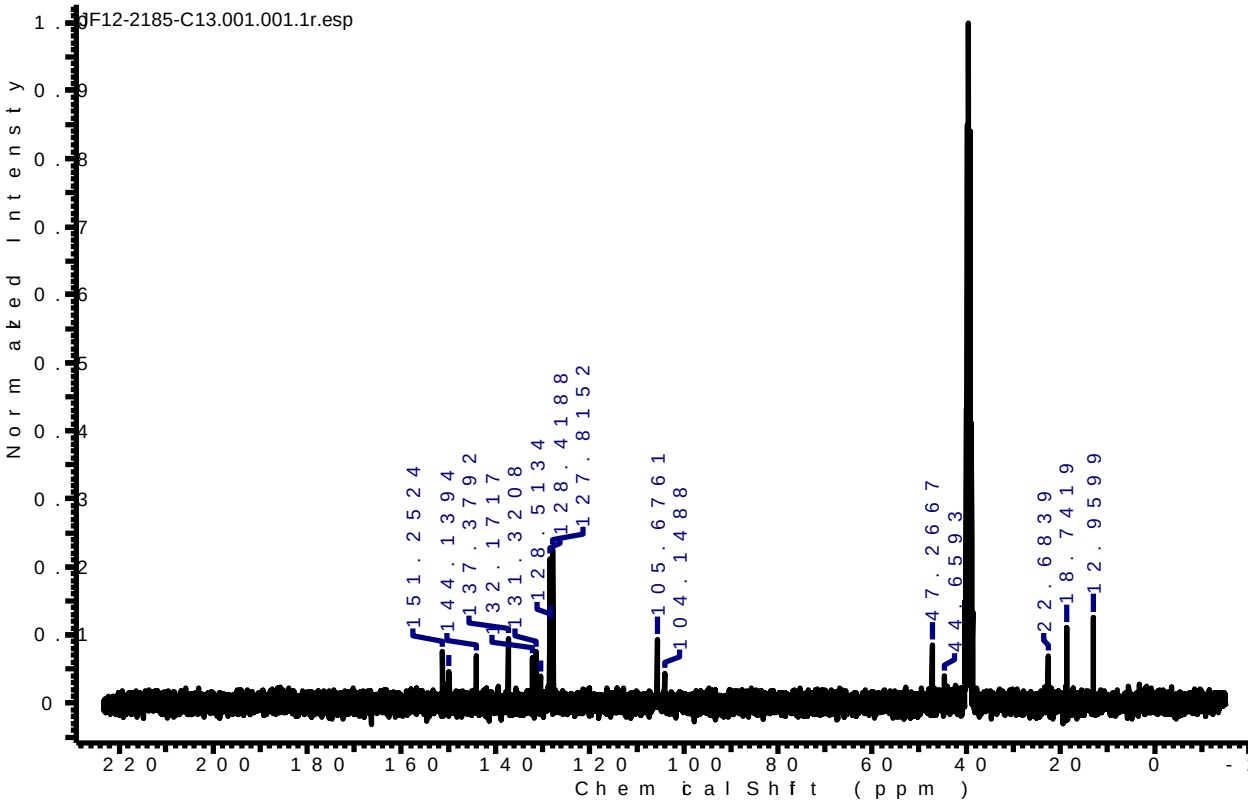

JF12-2172-H.001.esp
9.0369
4.3568
3.8822
3.8583
3.8333
3.7216
3.7065
3.6904
2.5888
2.5639
2.5551
2.5400
2.5244
2.0441
Normalized Intensity
1.02
2.00
2.00
4.21
6.20
3.17
Chemical Shift (ppm)

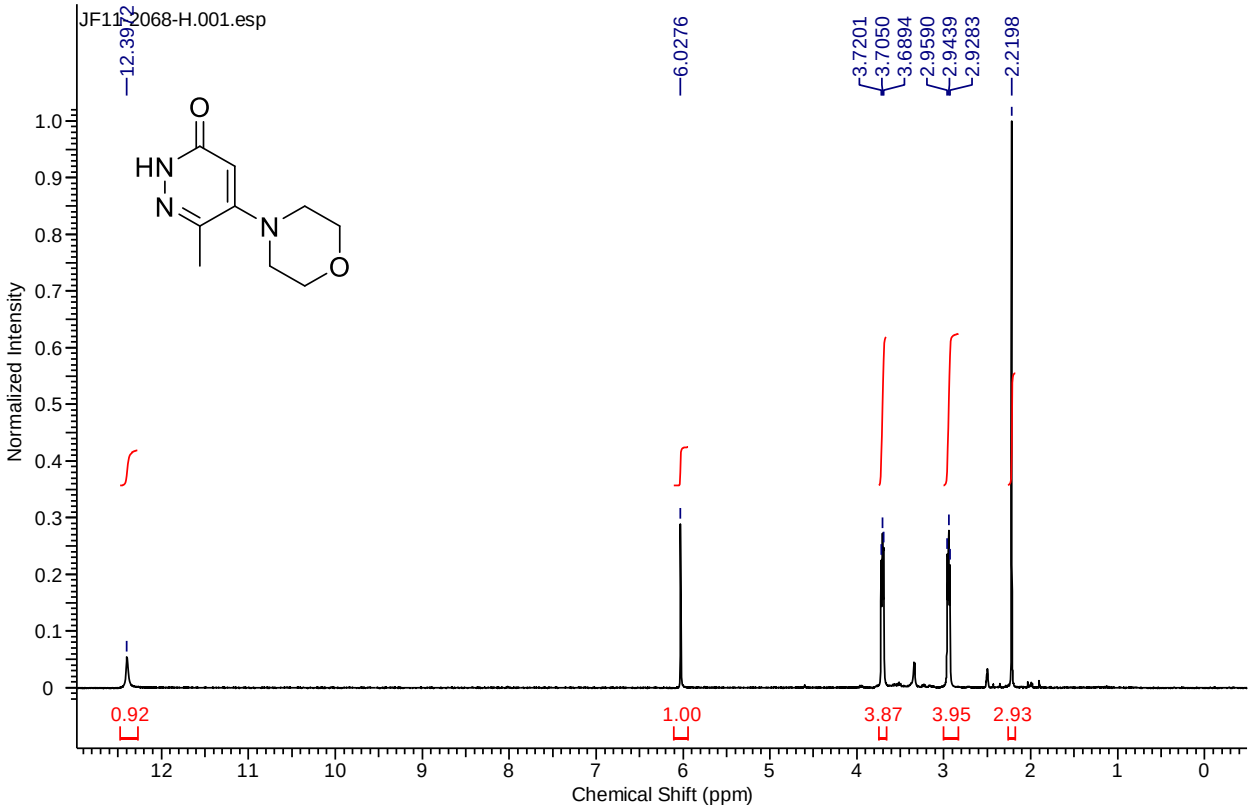

JF12-2172-C13.001.001.1r.esp
148.7848
142.8646
136.7698
88.4662
66.8508
53.7485
53.0139
39.3079
19.1217
Chemical Shift (ppm)

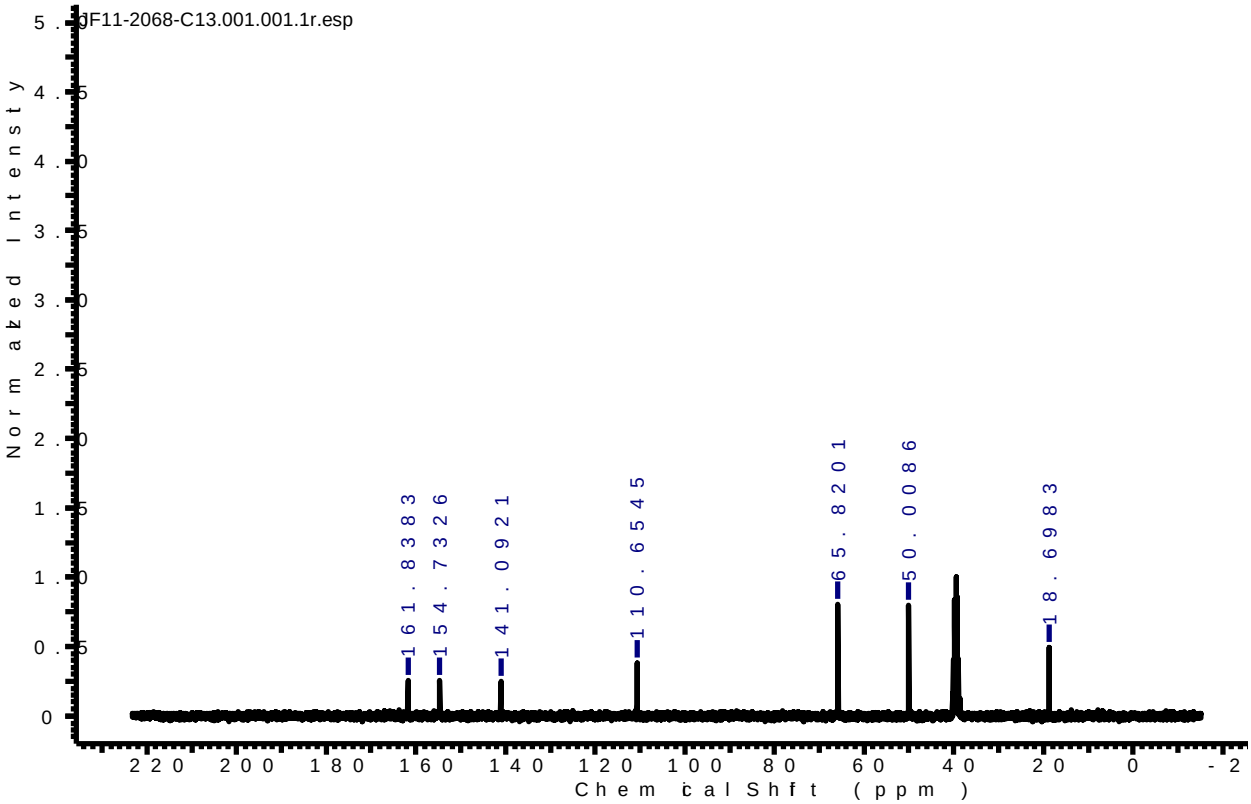

JF12-2177-H.001.esp
Cl
O
HN
N
N
H
8.2093
8.0435
7.3267
7.3064
7.2986
7.2846
7.2783
7.1837
7.1400
7.1109
5.2286
5.2036
5.1782
5.1532
4.9489
4.9234
4.8975
4.8647
2.6341
2.6096
2.4194
2.3944
2.3700
1.8169
1.7909
1.7805
1.7550
1.1473
1.1224
1.0980
1.0553
1.0304
1.0059
0.21 0.58 2.18 2.00
0.71 2.22
0.63 1.40 0.92 1.96 0.96 1.97
Normalized Intensity
Chemical Shift (ppm)

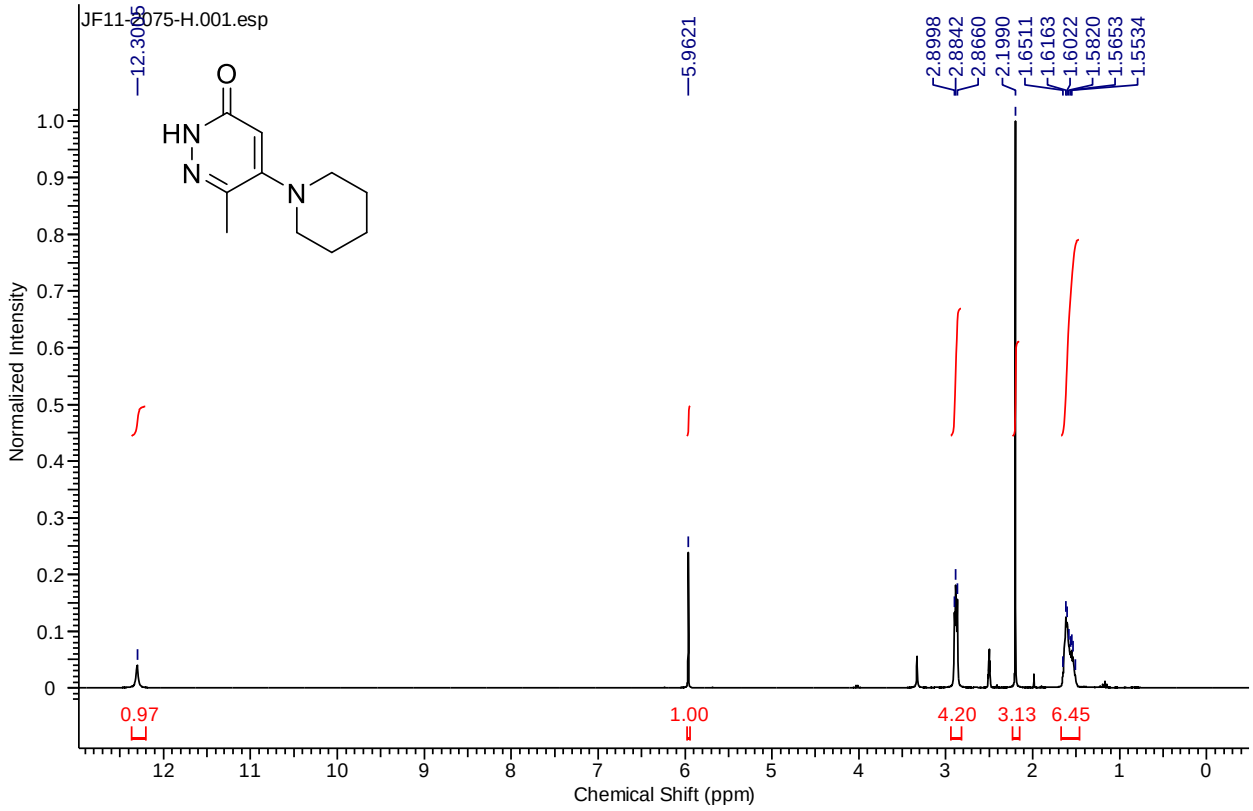

JF12-2177-C13.001.001.1r.esp
Normalized Intensity
152.8613
149.8721
135.7879
128.8241
128.6895
127.8306
127.1640
109.1324
107.2887
48.3301
46.4936
28.2675
25.0383
13.5506
10.9250
Chemical Shift (ppm)

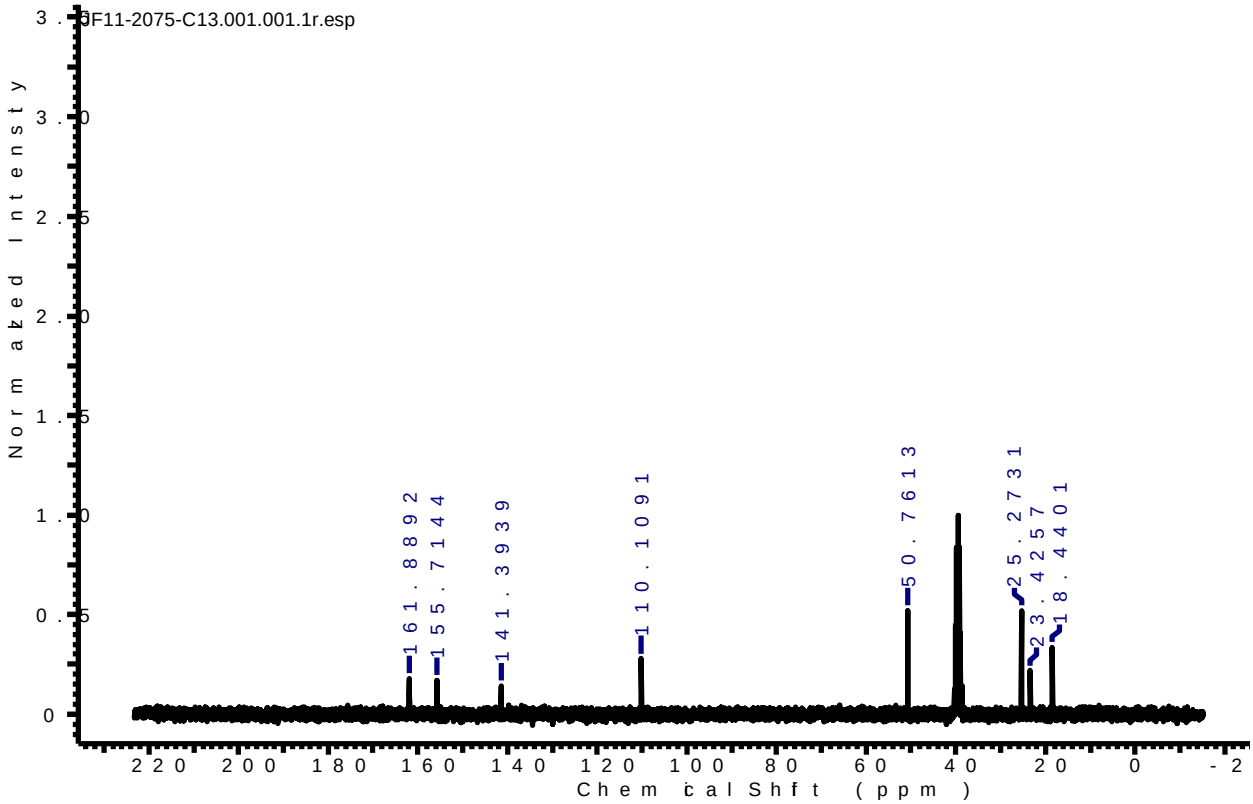

JF12-2185-H1.001.esp
10.5887
10.4411
7.4088
7.3802
7.2337
7.2056
7.1796
7.1515
5.0633
5.0379
4.8814
4.7961
2.1850
1.9557
1.7707
1.7452
1.6319
1.6064
Cl
O
HN
N
N
H
Normalized Intensity
0.30 0.54
2.00 1.89
0.58 2.25
0.98 1.77 1.03 1.88
Chemical Shift (ppm)

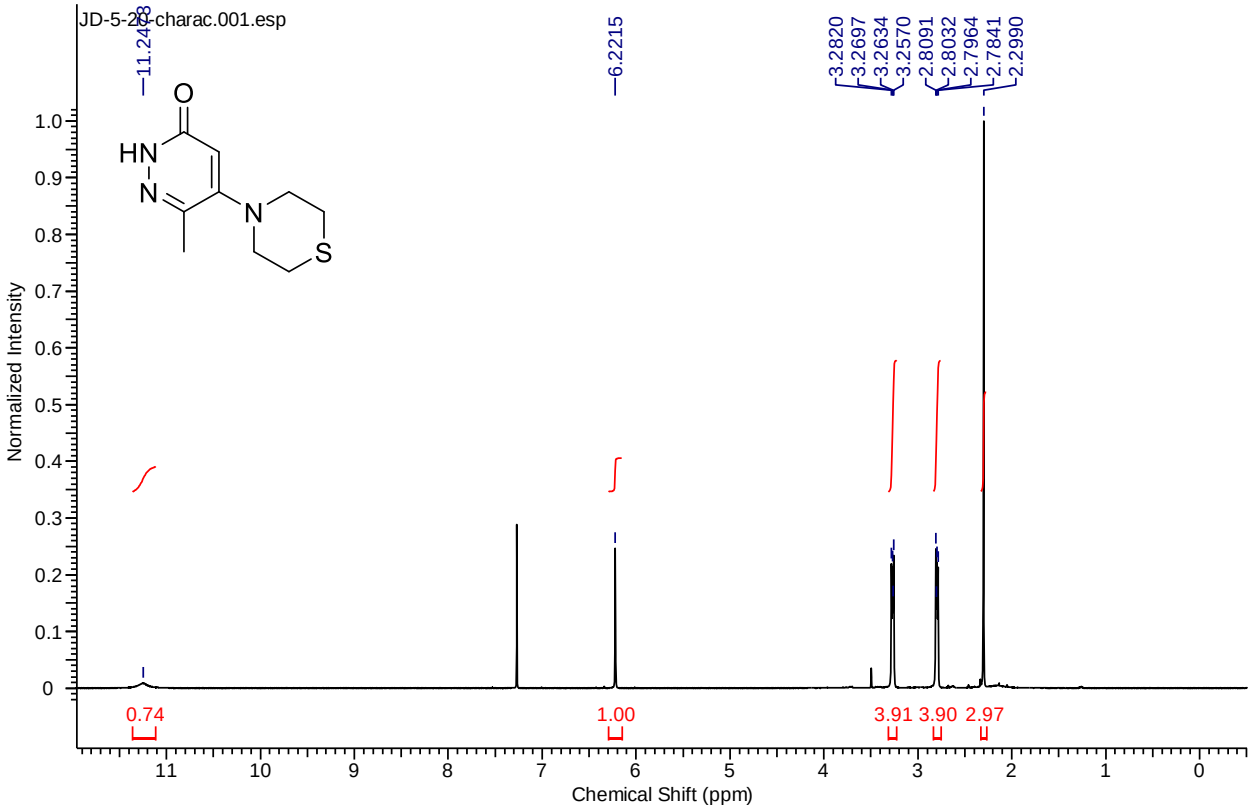

JF12-2185-C13.001.001.1r.esp
Normalized Intensity
151.2524
144.1394
137.3792
132.1717
131.3208
128.5134
128.4188
127.8152
105.6761
104.1488
47.2667
44.6593
22.6839
18.7419
12.9599
Chemical Shift (ppm)

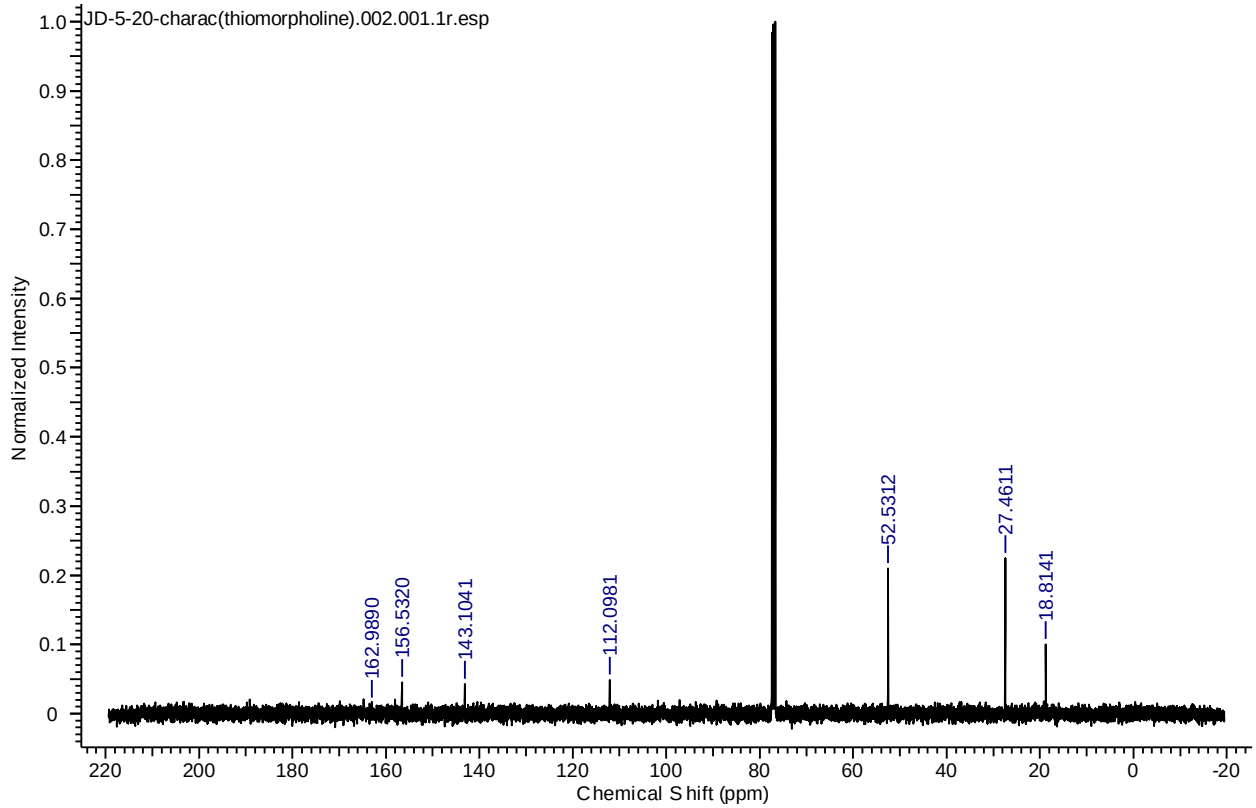

JF11-2068-H.001.esp
12.3972
6.0276
3.7201
3.7050
3.6894
2.9590
2.9439
2.9283
2.2198
HN
N
N
O
O
Normalized Intensity
0.92
1.00
3.87
3.95
2.93
Chemical Shift (ppm)

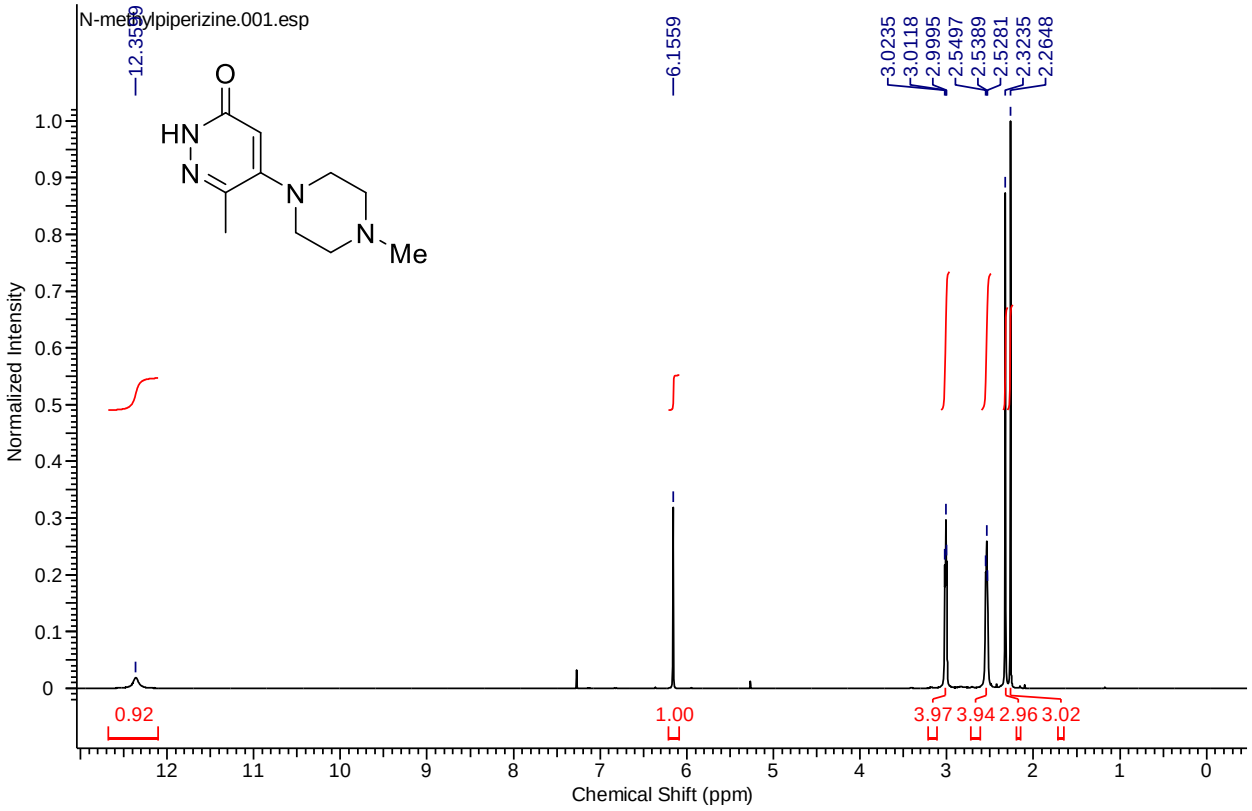

JF11-2068-C13.001.001.1r.esp
161.8383
154.7326
141.0921
110.6545
65.8201
50.0086
18.6983
Normalized Intensity
Chemical Shift (ppm)

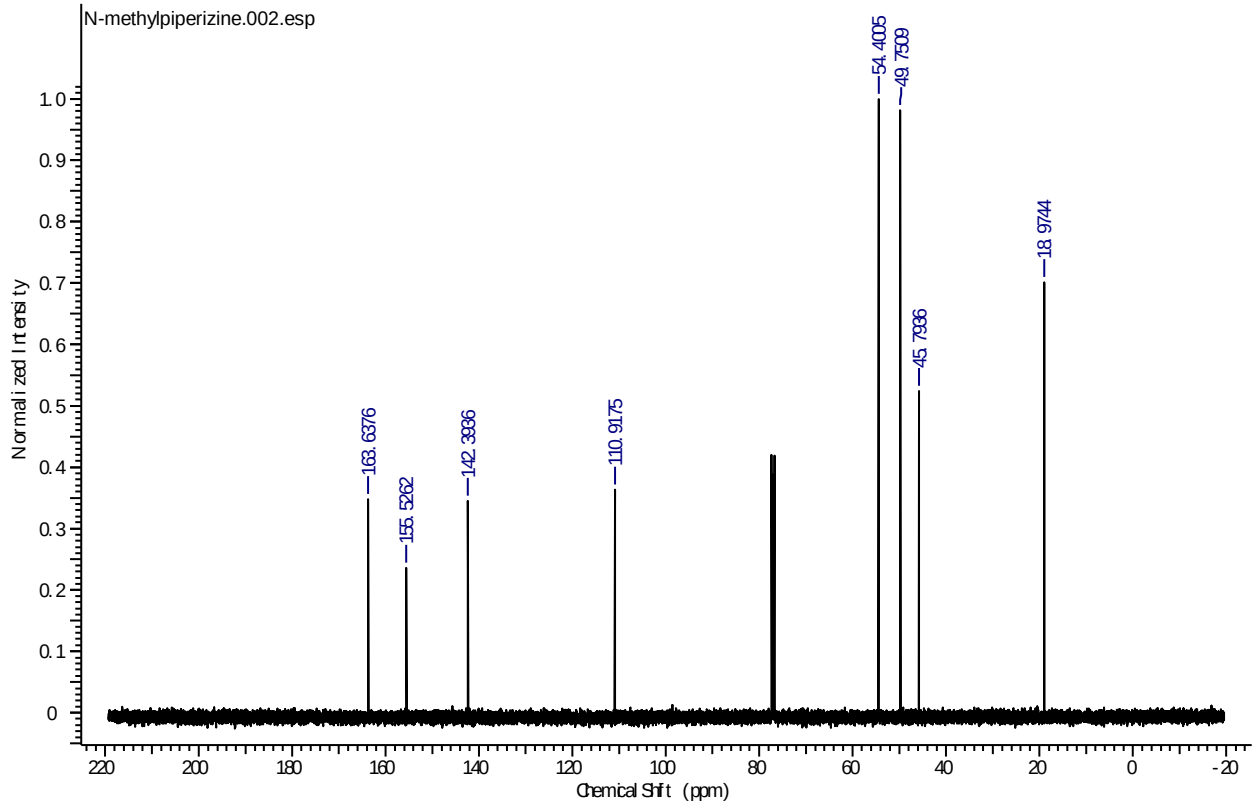

JF11-2075-H.001.esp
12.3005
5.9621
2.8998
2.8842
2.8660
2.1990
1.6511
1.6163
1.6022
1.5820
1.5653
1.5534
O
HN
N
N
Normalized Intensity
0.97
1.00
4.20
3.13
6.45
Chemical Shift (ppm)

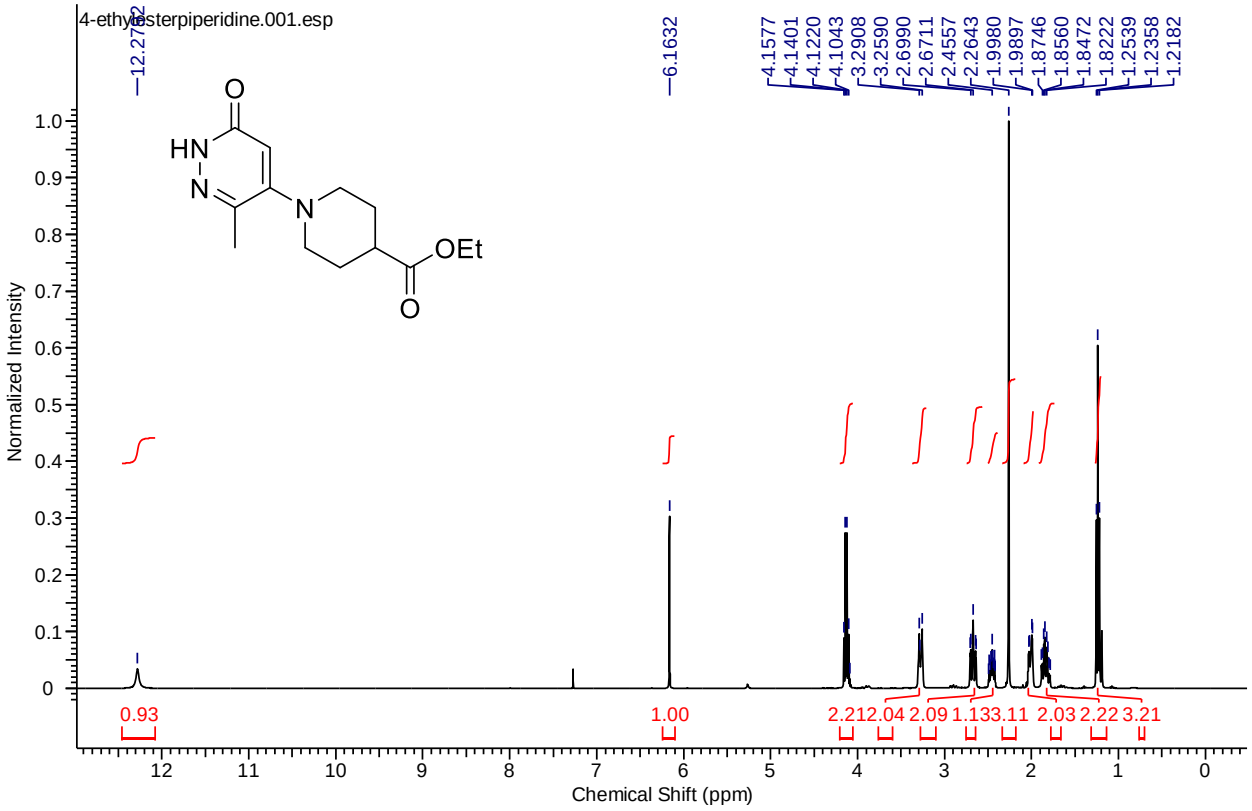

JF11-2075-C13.001.001.1r.esp
161.8892
155.7144
141.3939
110.1091
50.7613
25.2731
23.4257
18.4401
Normalized Intensity
Chemical Shift (ppm)

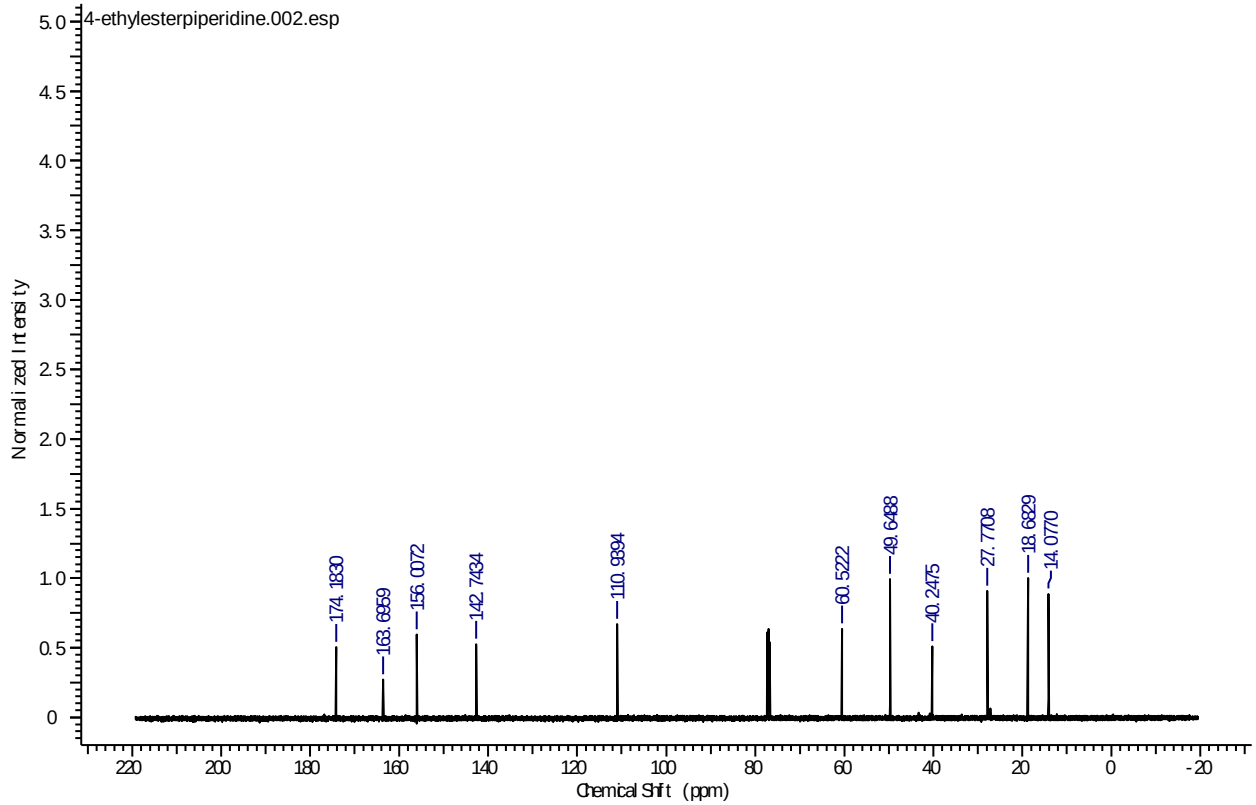

JD-5-20-charac.001.esp
11.2488
6.2215
3.2820
3.2697
3.2634
3.2570
2.8091
2.8032
2.7964
2.7841
2.2990
O
HN
N
N
S
Normalized Intensity
0.74
1.00
3.91
3.90
2.97
Chemical Shift (ppm)

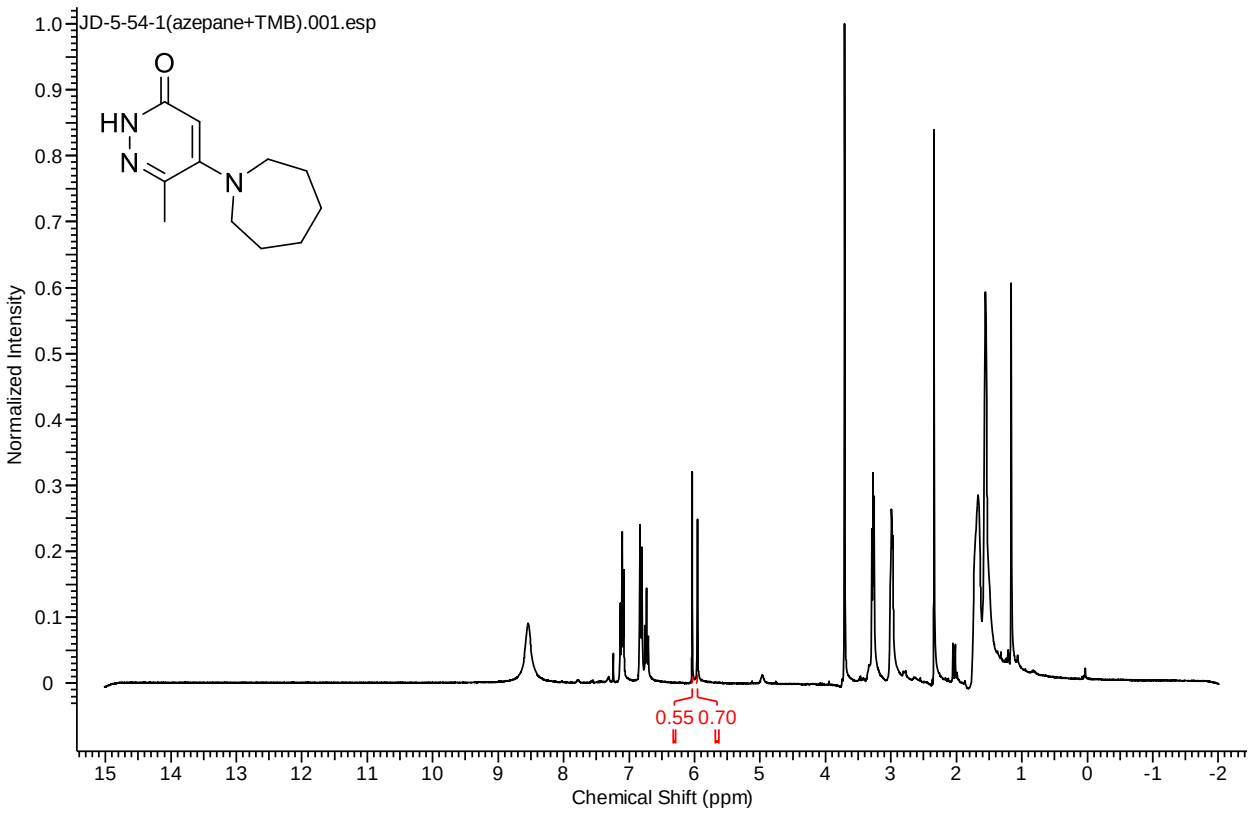

JD-5-20-charac(thiomorpholine).002.001.1r.esp
Normalized Intensity
162.9890
156.5320
143.1041
112.0981
52.5312
27.4611
18.8141
Chemical Shift (ppm)


N-methylpiperizine.001.esp
12.3599
6.1559
3.0235
3.0118
2.9995
2.5497
2.5389
2.5281
2.3235
2.2648
O
HN
N
N
N
Me
Normalized Intensity
0.92
1.00
3.97
3.94
2.96
3.02
Chemical Shift (ppm)

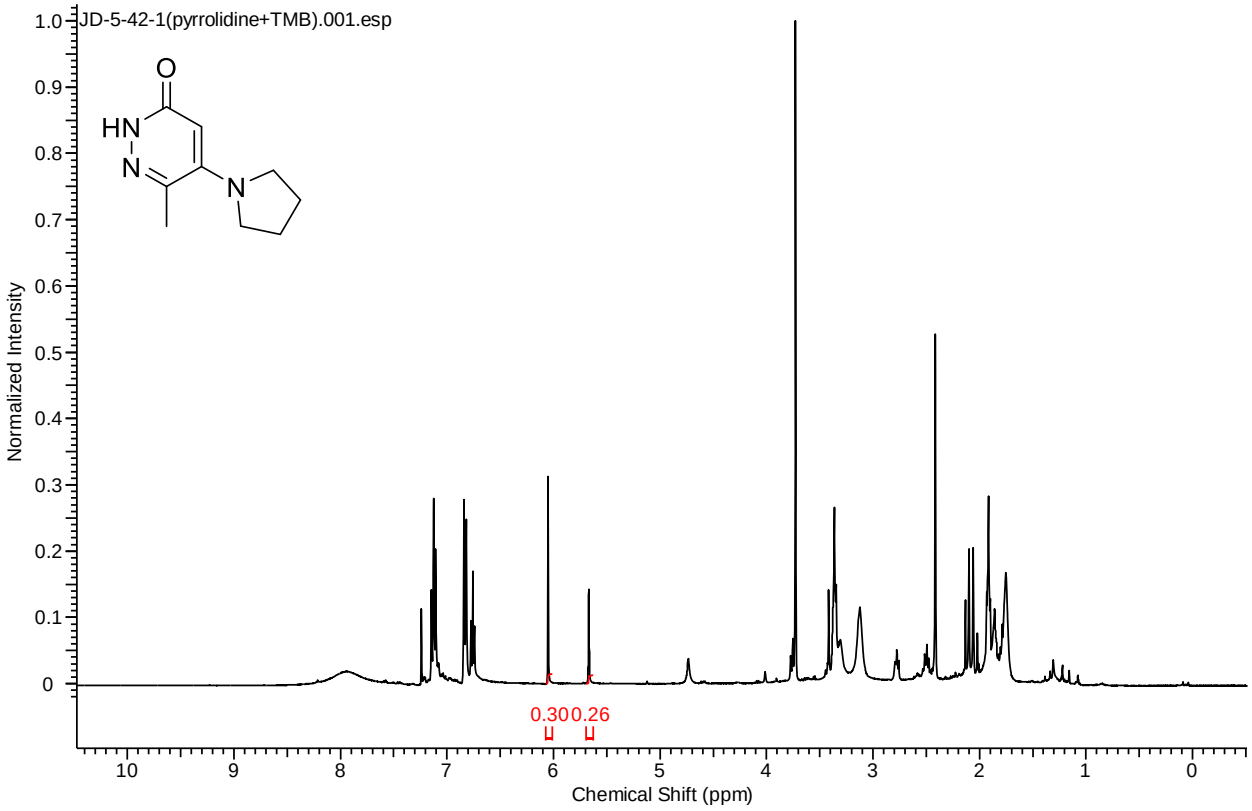

N-methylpiperizine.002.esp
54.4005
49.7509
45.7936
18.9744
163.6376
155.5262
142.3936
110.9175
Normalized Intensity
Chemical Shift (ppm)


4-ethylesterpiperidine.001.esp
12.2762
6.1632
4.1577
4.1401
4.1220
4.1043
3.2908
3.2590
2.6990
2.6711
2.4557
2.2643
1.9980
1.9897
1.8746
1.8560
1.8472
1.8222
1.2539
1.2358
1.2182
HN
N
N
O
O
OEt
Normalized Intensity
Chemical Shift (ppm)
0.93
1.00
2.21
2.04
2.09
1.13
3.11
2.03
2.22
3.21

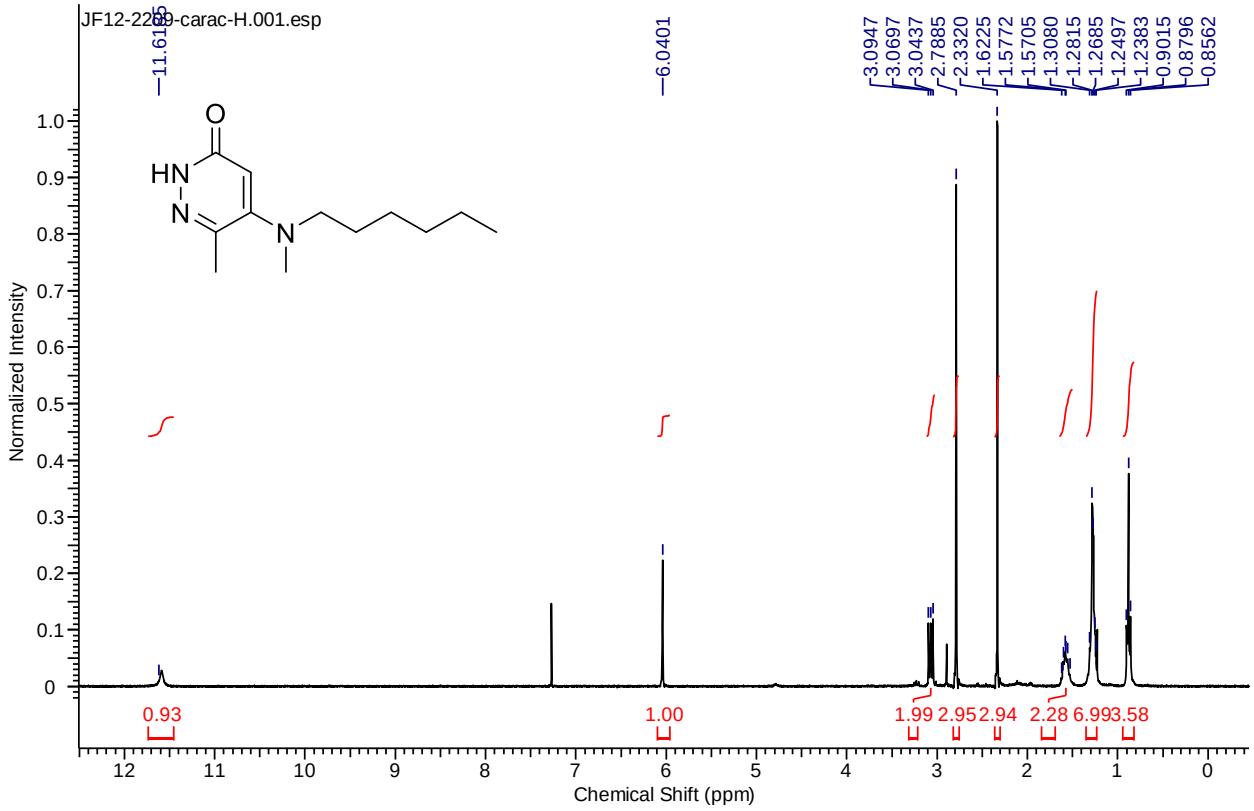

4-ethylesterpiperidine.002.esp
Normalized Intensity
Chemical Shift (ppm)
174.1830
163.6859
156.0072
142.7434
110.9894
60.5222
49.6488
40.2475
27.7708
18.6829
14.0770

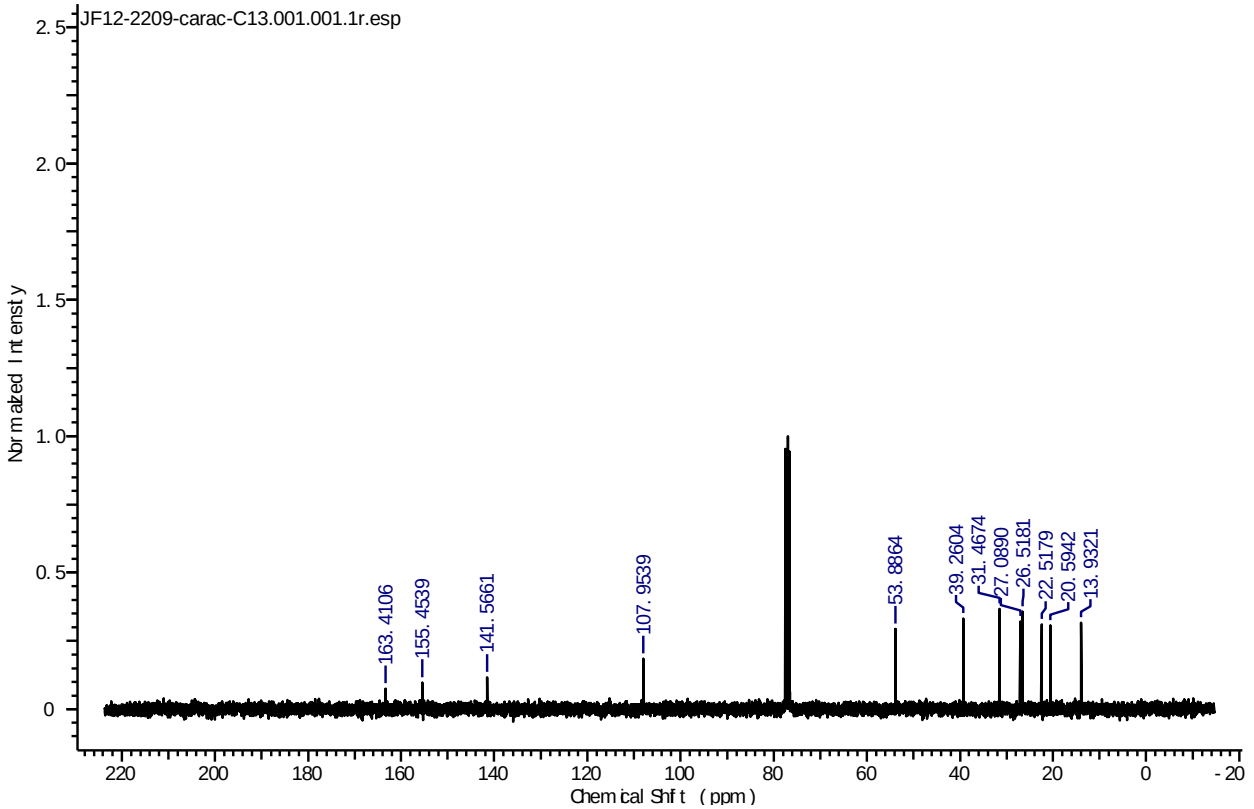


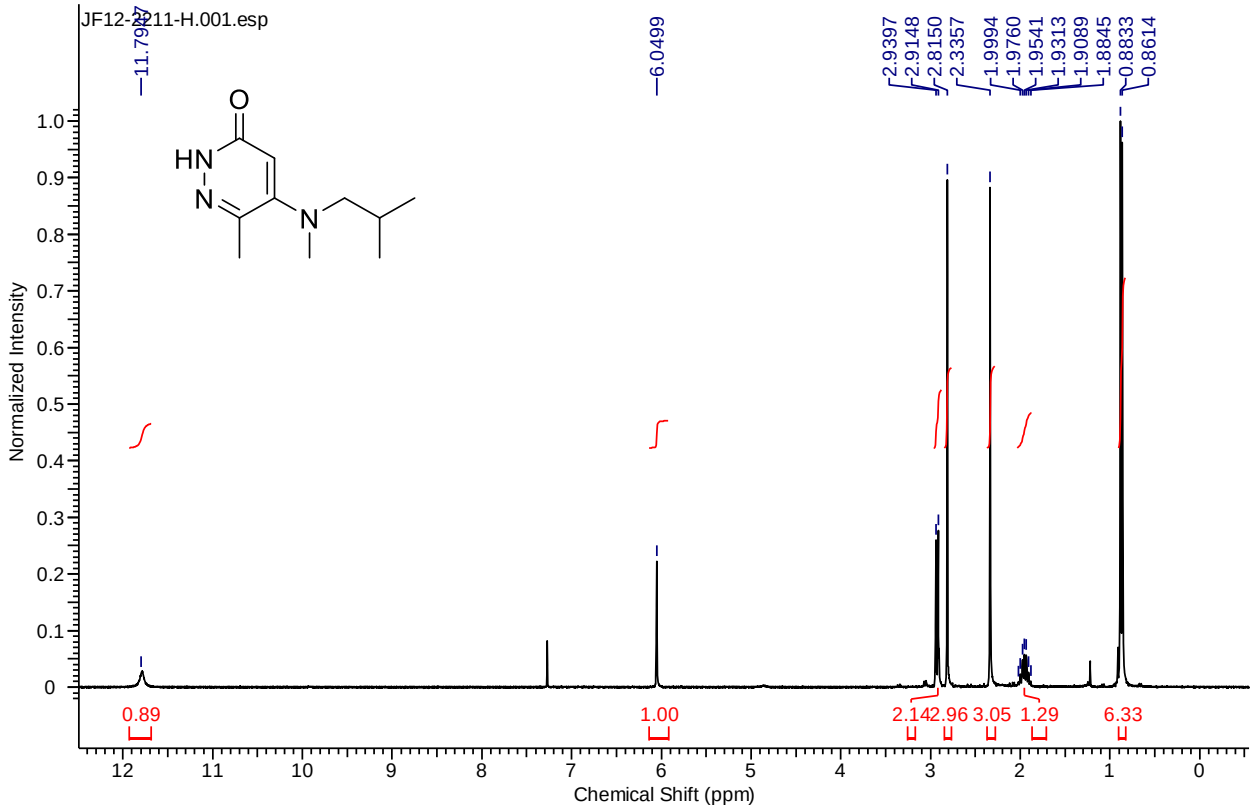
18.0 mg of Trimethoxybenzene (TMB) = 0.11 mmol. We performed a 0.600 mmol scale reaction; therefore we integrated the TMB peak at 0.55 (5.45 times lower than 3 since we added 5.45 times less internal standard.). The alkene peak (equivalent to 1 proton) showed a 70% NMR yield.

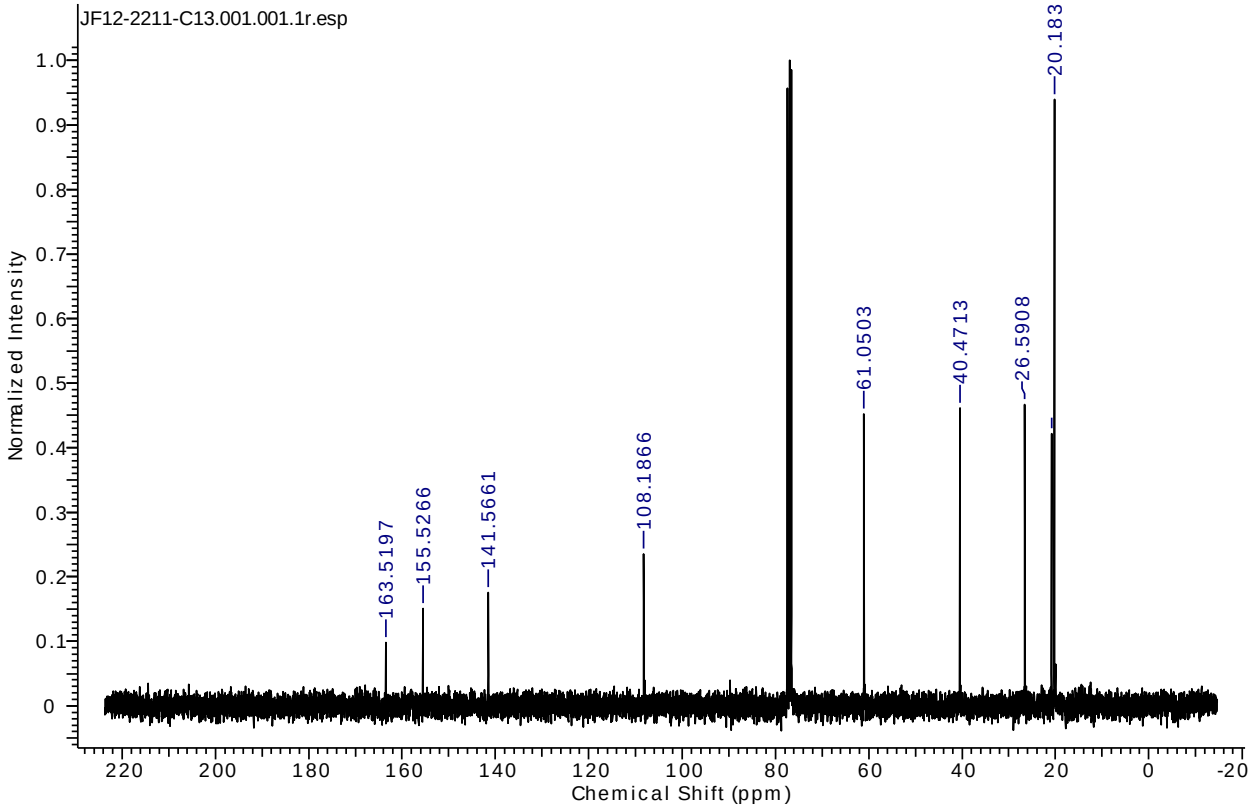


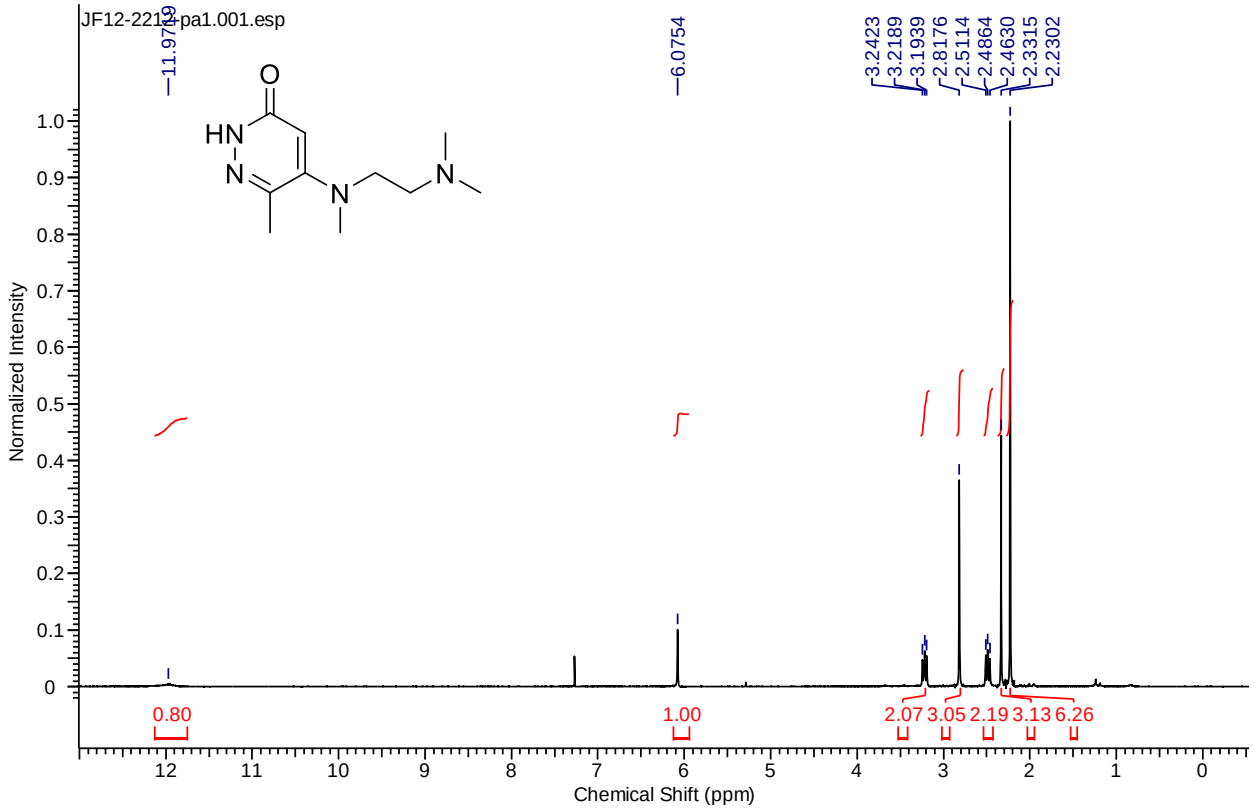
10.0 mg of Trimethoxybenzene (TMB) = 0.06 mmol. We performed a 0.600 mmol scale reaction; therefore we integrated the TMB peak at 0.3 (10% of 3 since we added 10% of internal standard.). The alkene peak (equivalent to 1 proton) showed a 26% NMR yield.

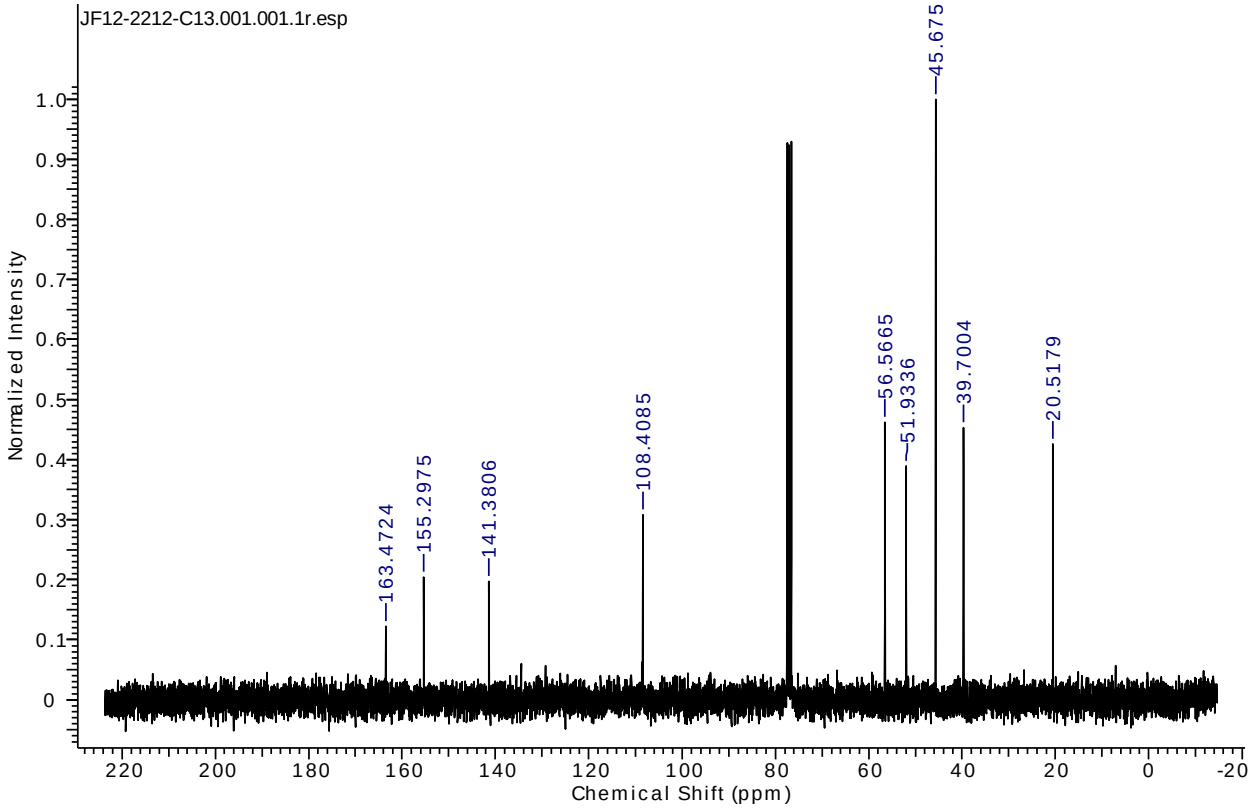

JF12-2209-carac-H.001.esp
11.6190
6.0401
3.0947
3.0697
3.0437
2.7885
2.3320
1.6225
1.5772
1.5705
1.3080
1.2815
1.2685
1.2497
1.2383
0.9015
0.8796
0.8562
O
HN
N
N
Normalized Intensity
Chemical Shift (ppm)
0.93
1.00
1.99
2.95
2.94
2.28
6.99
3.58

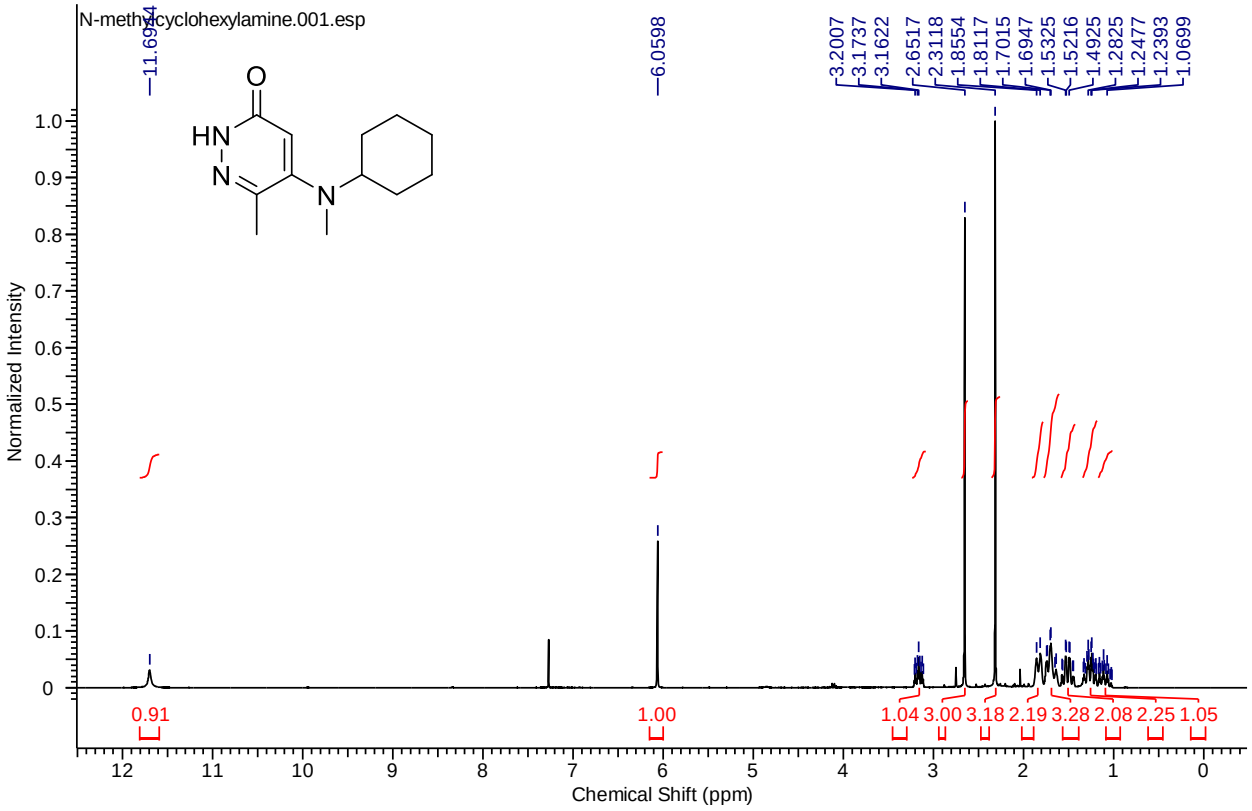

JF12-2209-carac-C13.001.001.1r.esp
Normalized Intensity
Chemical Shift (ppm)
163.4106
155.4539
141.5661
107.9539
53.8864
39.2604
31.4674
27.0890
26.5181
22.5179
20.5942
13.9321

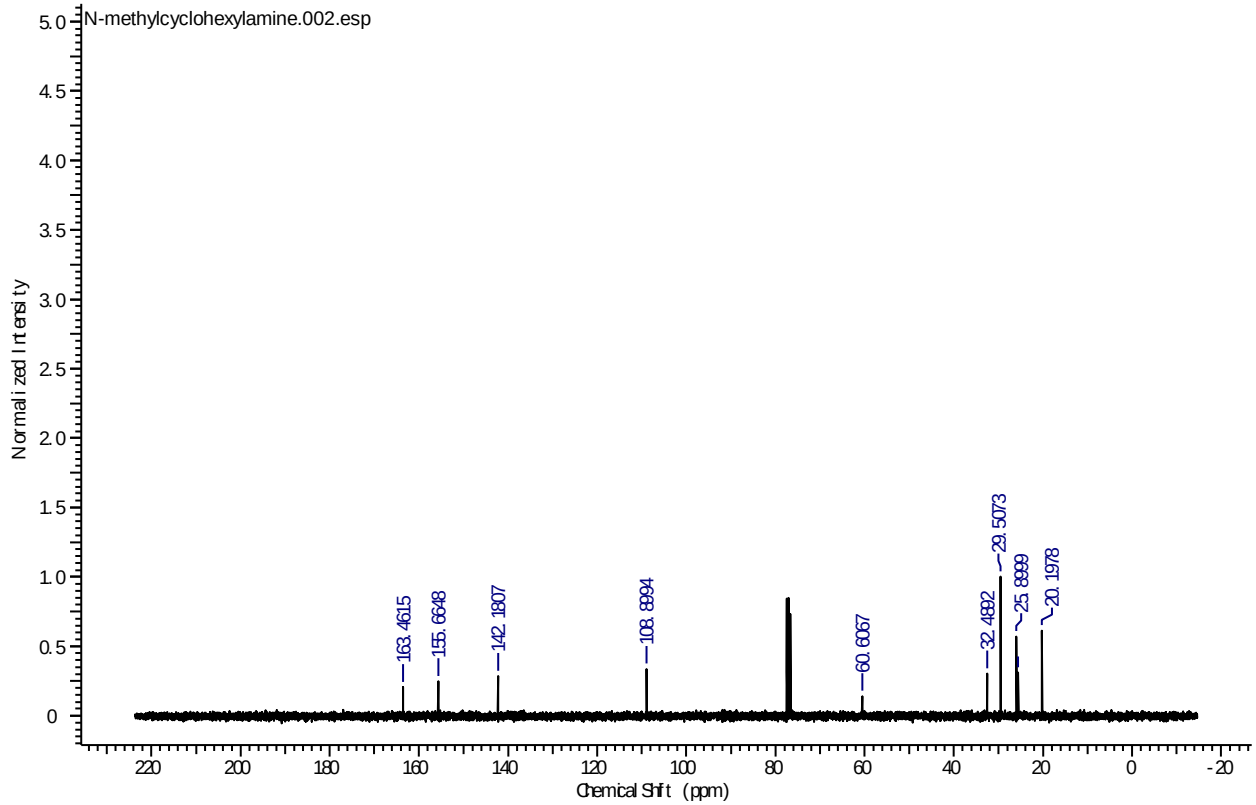

JF12-2211-H.001.esp
11.7927
6.0499
2.9397
2.9148
2.8150
2.3357
1.9994
1.9760
1.9541
1.9313
1.9089
1.8845
0.8833
0.8614
HN
N
O
N
Normalized Intensity
0.89
1.00
2.14
2.96
3.05
1.29
6.33
Chemical Shift (ppm)

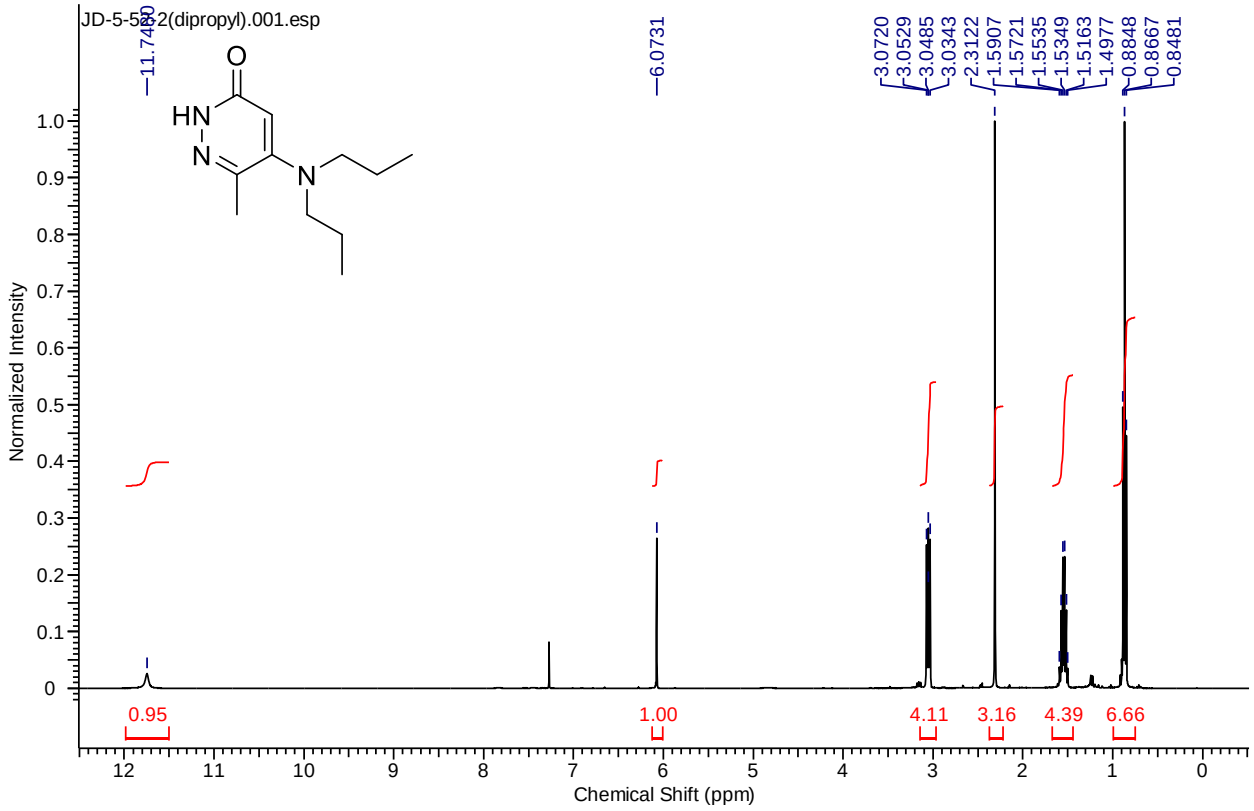

JF12-2211-C13.001.001.1r.esp
20.183
61.0503
40.4713
26.5908
163.5197
155.5266
141.5661
108.1866
Normalized Intensity
Chemical Shift (ppm)

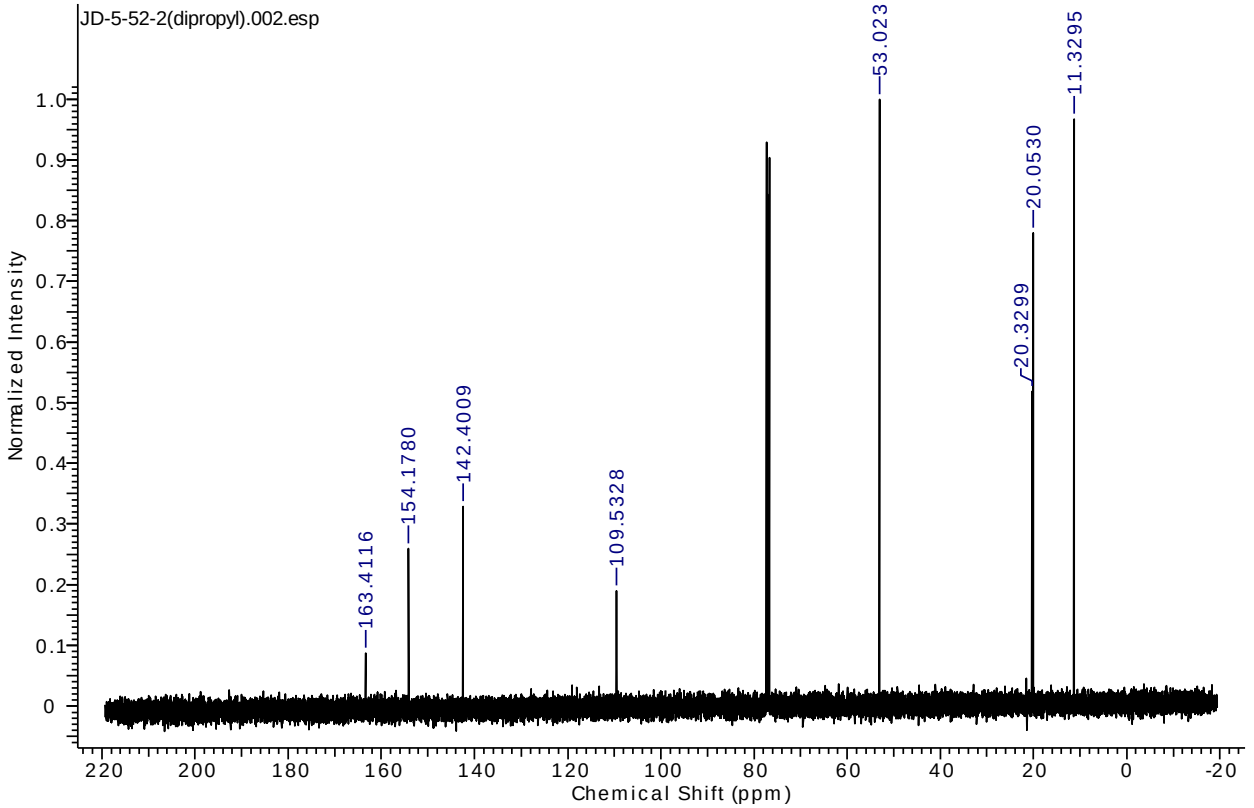

JF12-2212-pa1.001.esp
11.9769
6.0754
3.2423
3.2189
3.1939
2.8176
2.5114
2.4864
2.4630
2.3315
2.2302
HN
N
O
N
N
Normalized Intensity
0.80
1.00
2.07
3.05
2.19
3.13
6.26
Chemical Shift (ppm)

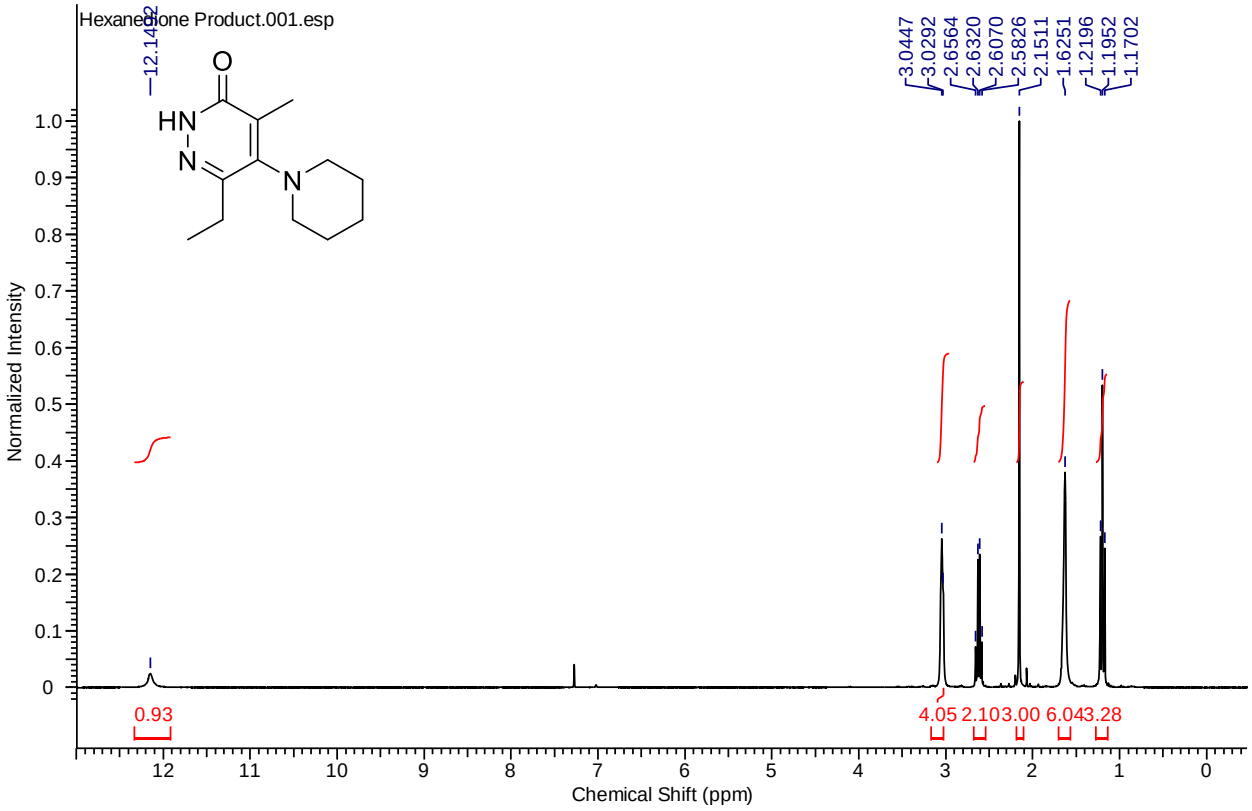

JF12-2212-C13.001.001.1r.esp
45.675
56.5665
51.9336
39.7004
20.5179
163.4724
155.2975
141.3806
108.4085
Normalized Intensity
Chemical Shift (ppm)

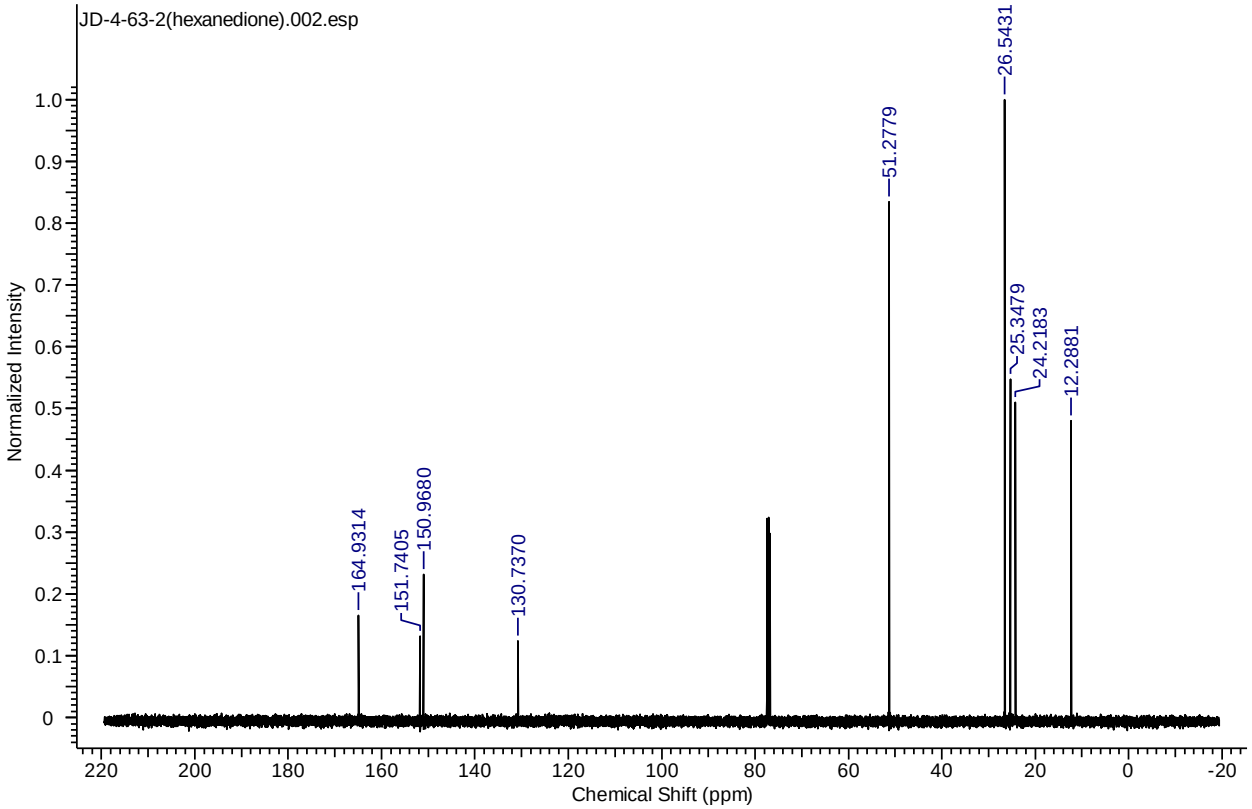

N-methylcyclohexylamine.001.esp
11.6944
6.0598
3.2007
3.1737
3.1622
2.6517
2.3118
1.8554
1.8117
1.7015
1.6947
1.5325
1.5216
1.4925
1.2825
1.2477
1.2393
1.0699
HN
N
O
N
Normalized Intensity
Chemical Shift (ppm)
0.91
1.00
1.04 3.00 3.18 2.19 3.28 2.08 2.25 1.05

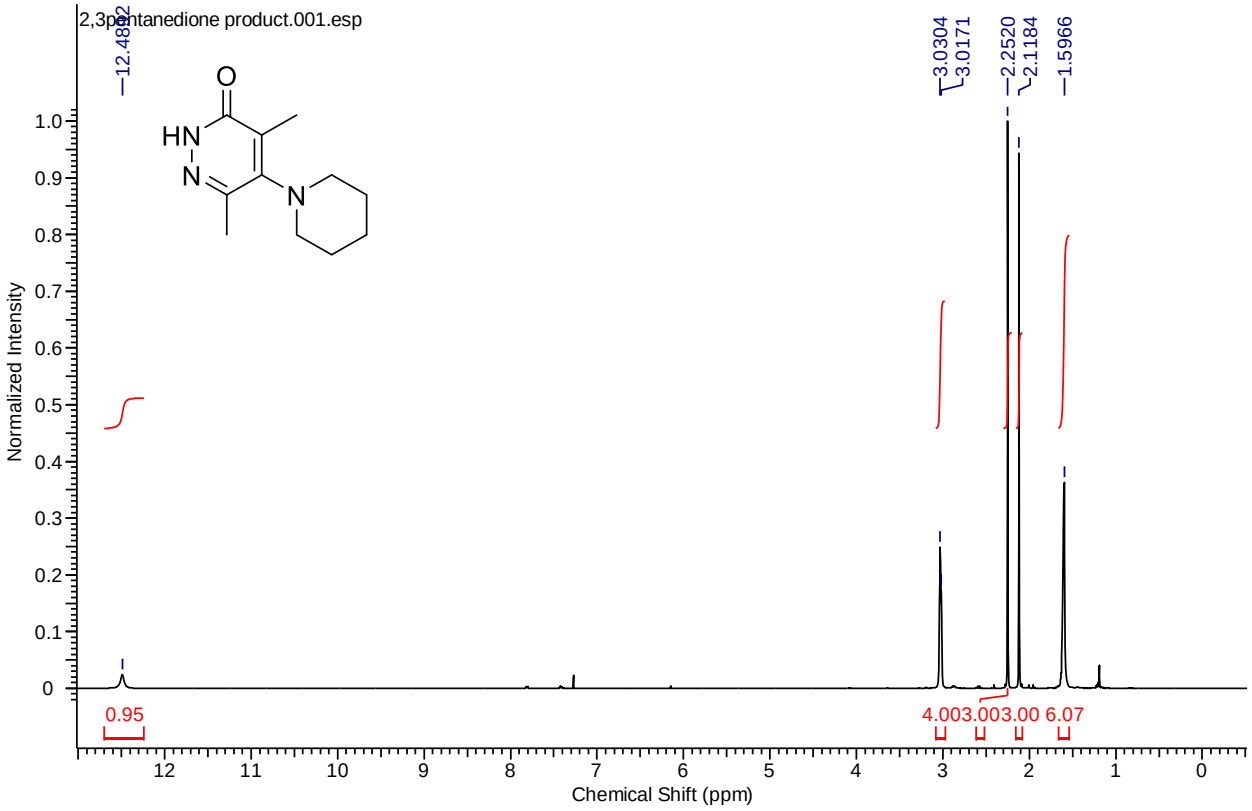

N-methylcyclohexylamine.002.esp
Normalized Intensity
Chemical Shift (ppm)
163.4615
155.6648
142.1807
108.8994
60.6067
32.4892
29.5073
25.8999
20.1978

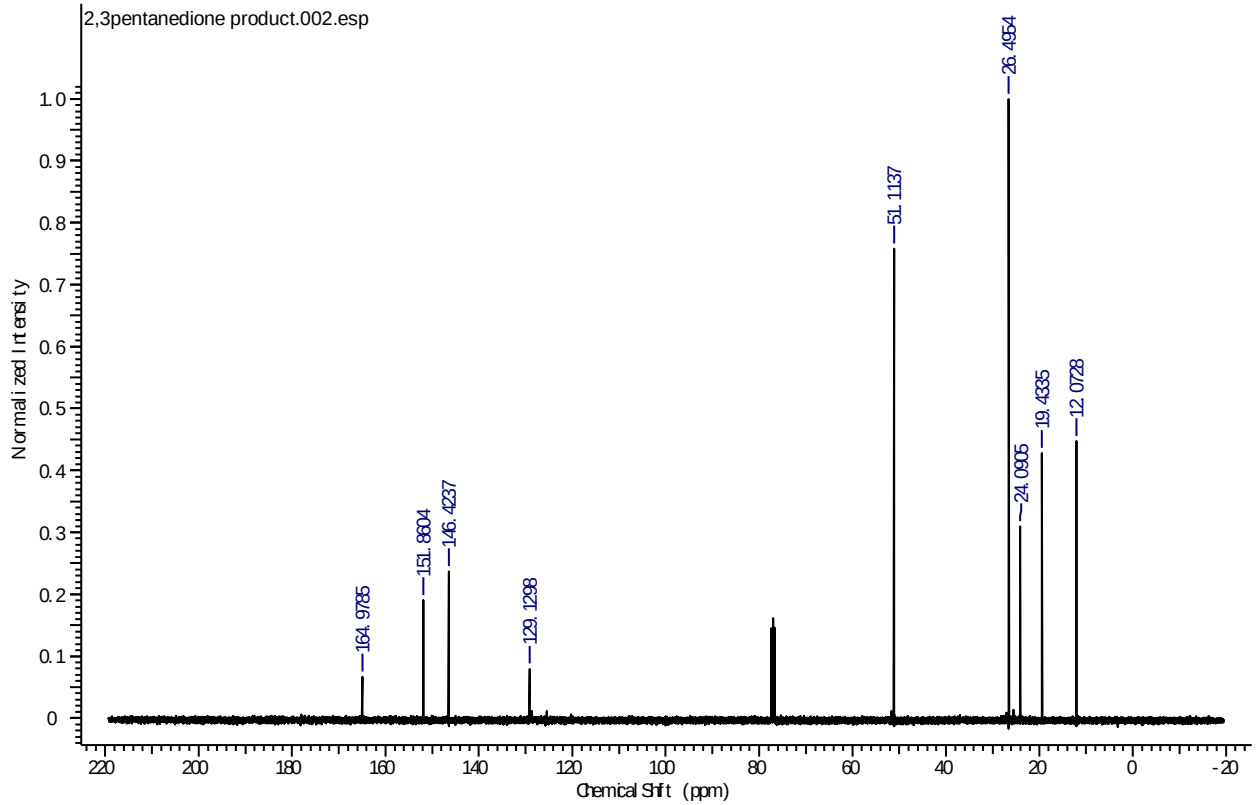

JD-5-52-2(dipropyl).001.esp
11.7480
6.0731
3.0720
3.0529
3.0485
3.0343
2.3122
1.5907
1.5721
1.5535
1.5349
1.5163
1.4977
0.8848
0.8667
0.8481
HN
N
O
N
Normalized Intensity
Chemical Shift (ppm)
0.95
1.00
4.11
3.16
4.39
6.66

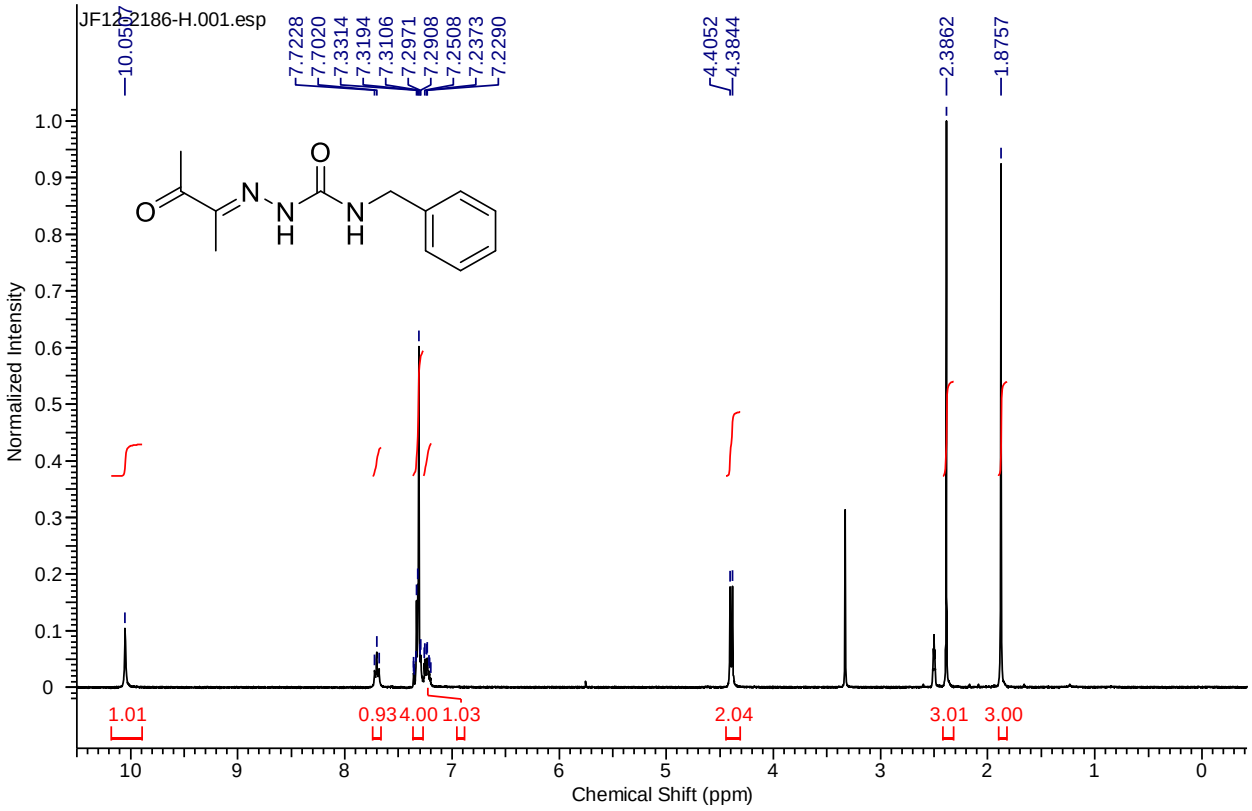

JD-5-52-2(dipropyl).002.esp
163.4116
154.1780
142.4009
109.5328
53.023
20.0530
20.3299
11.3295
Normalized Intensity
Chemical Shift (ppm)

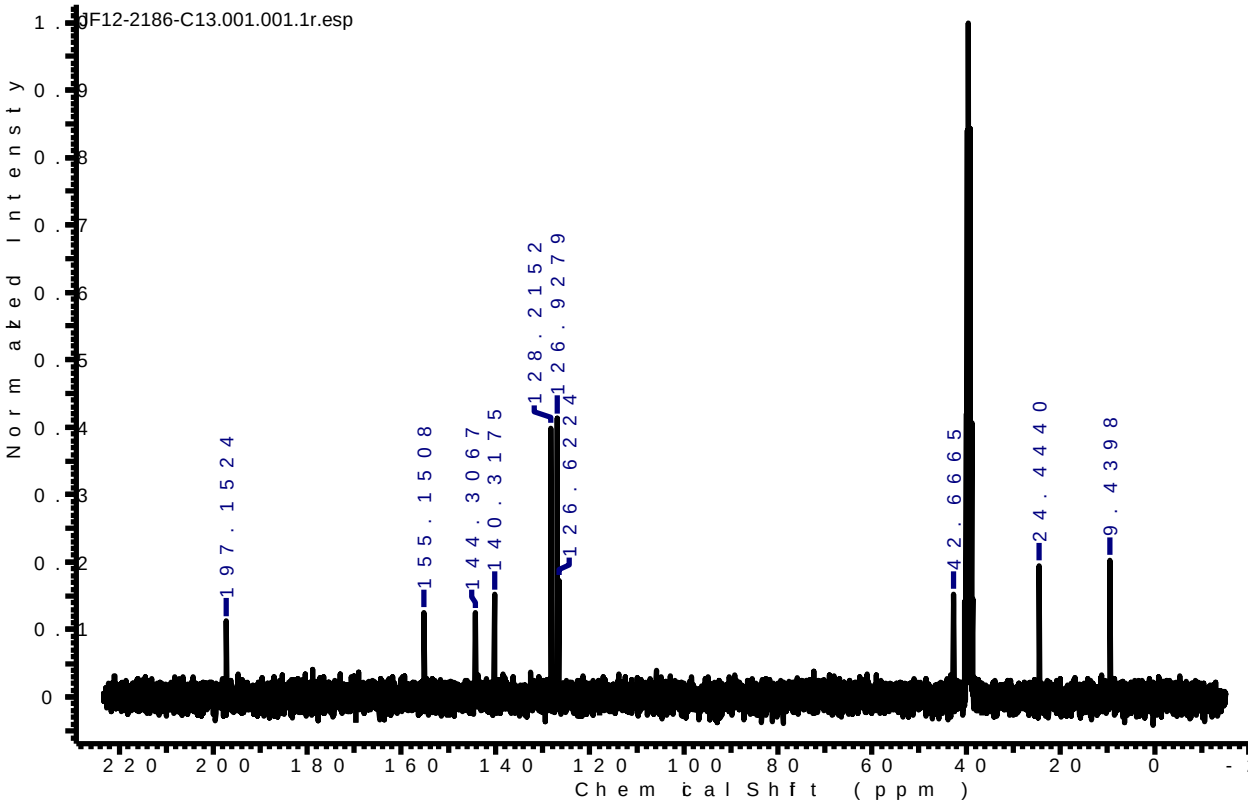

Hexanedione Product.001.esp
12.1442
3.0447
3.0292
2.6564
2.6320
2.6070
2.5826
2.1511
1.6251
1.2196
1.1952
1.1702
O
HN
N
N
Normalized Intensity
Chemical Shift (ppm)
0.93
4.05
2.10
3.00
6.04
3.28

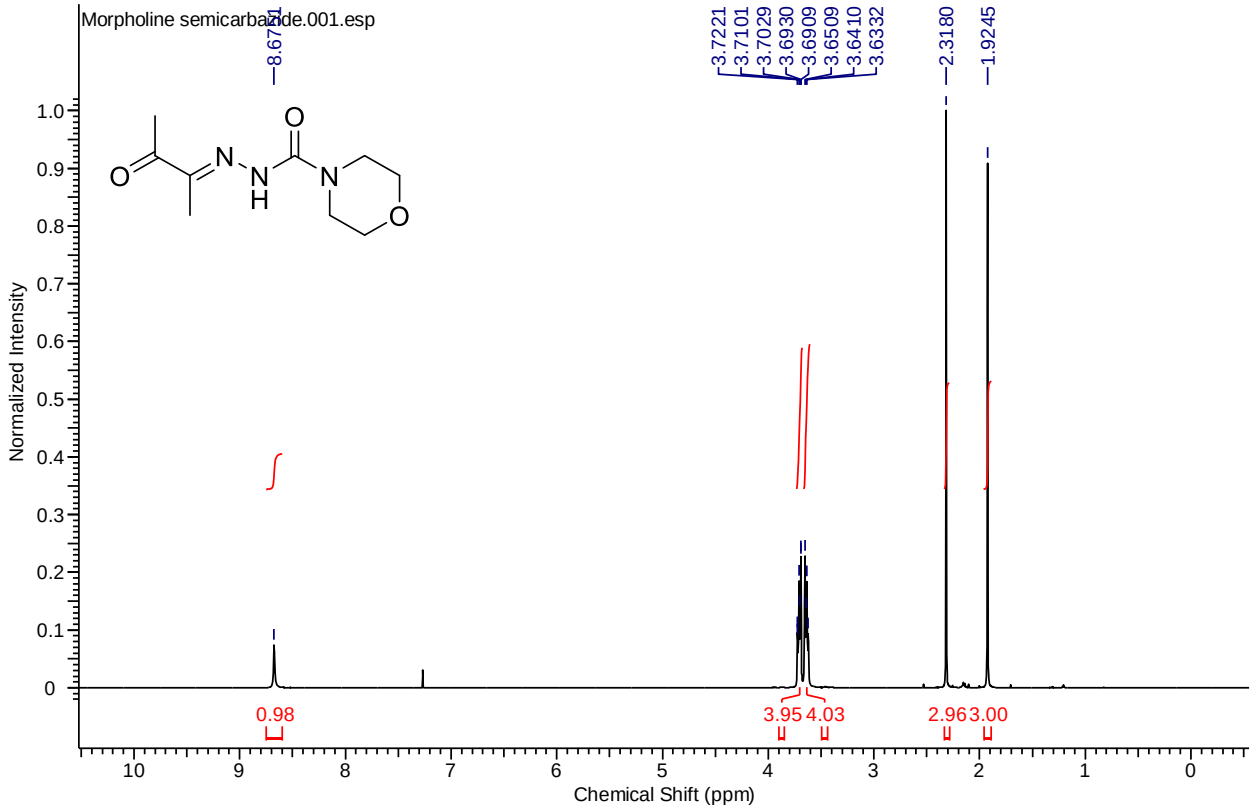

JD-4-63-2(hexanedione).002.esp
26.5431
51.2779
25.3479
24.2183
12.2881
164.9314
151.7405
150.9680
130.7370
Normalized Intensity
Chemical Shift (ppm)

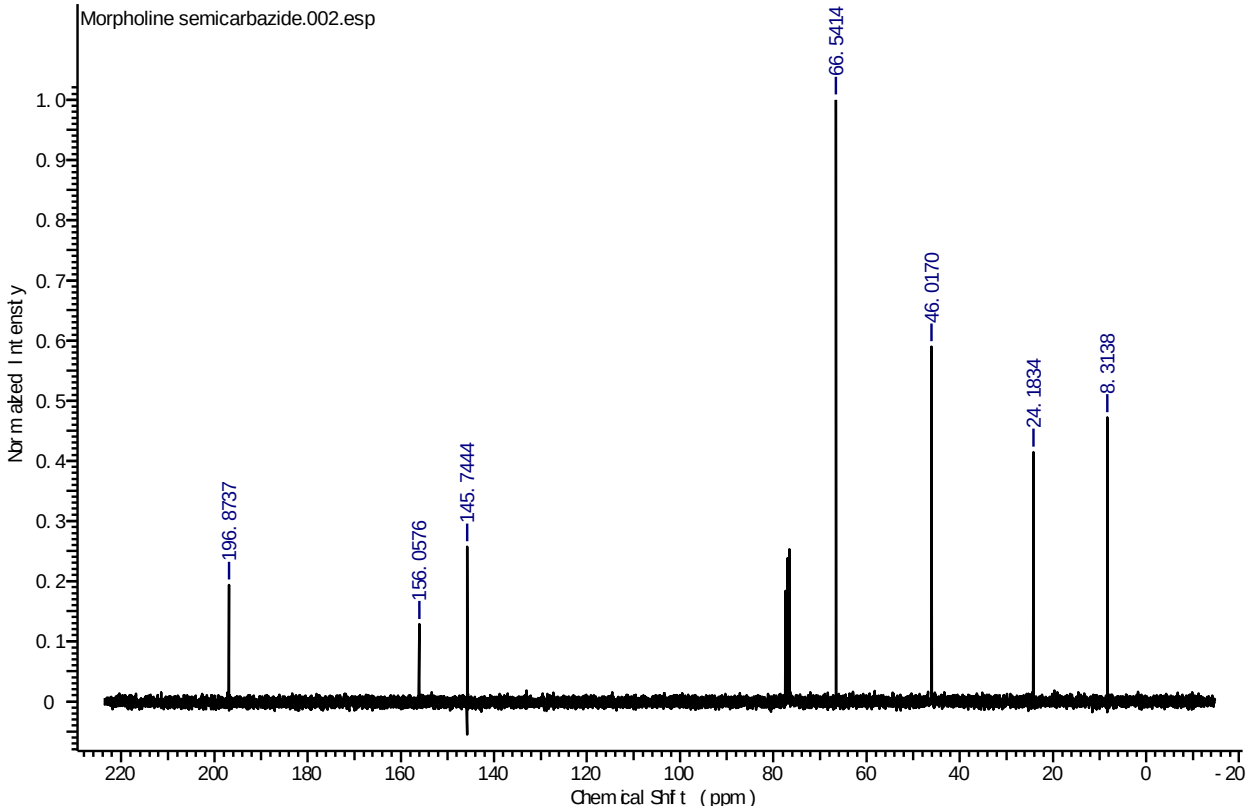

2,3pentanedione product.001.esp
12.4882
3.0304
3.0171
2.2520
2.1184
1.5966
Normalized Intensity
Chemical Shift (ppm)
0.95
4.00
3.00
3.00
6.07

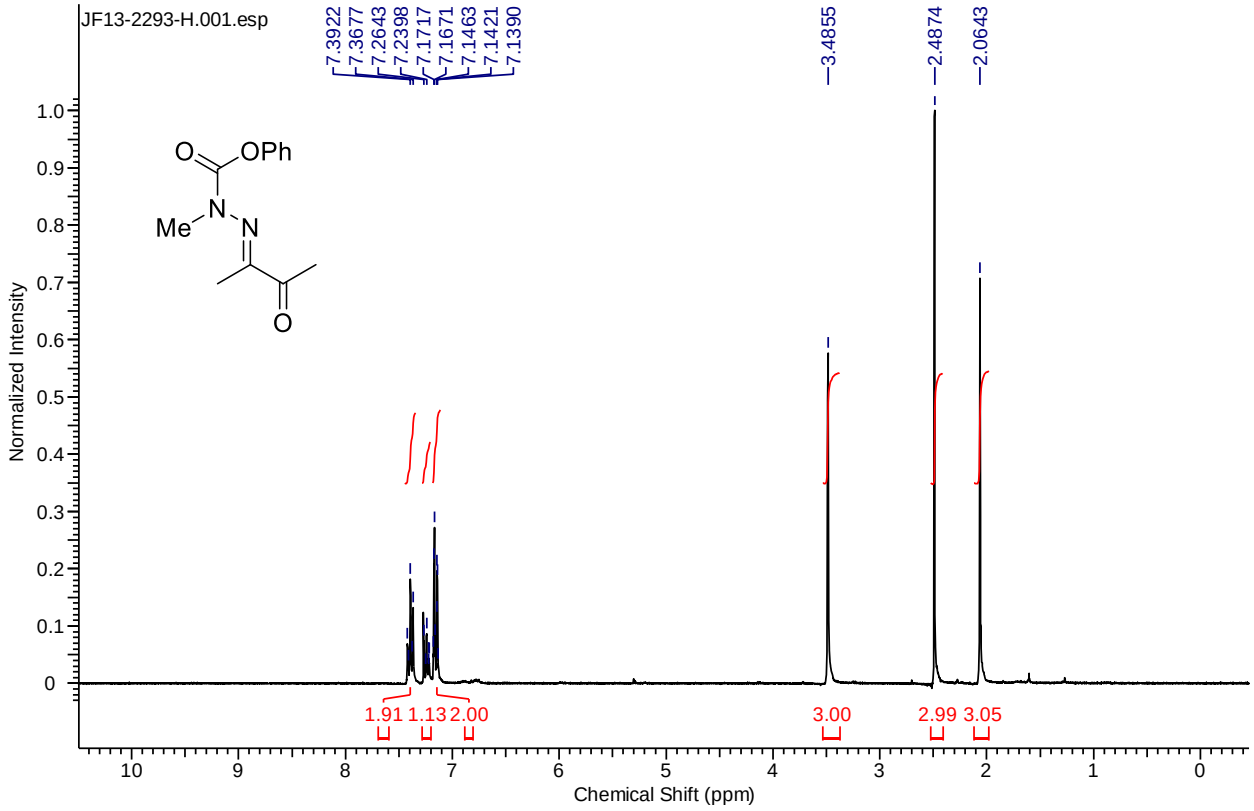

2,3pentanedione product.002.esp
26.4954
51.1137
24.0935
19.4335
12.0728
164.9785
151.8804
146.4237
129.1298
Normalized Intensity
Chemical Shift (ppm)

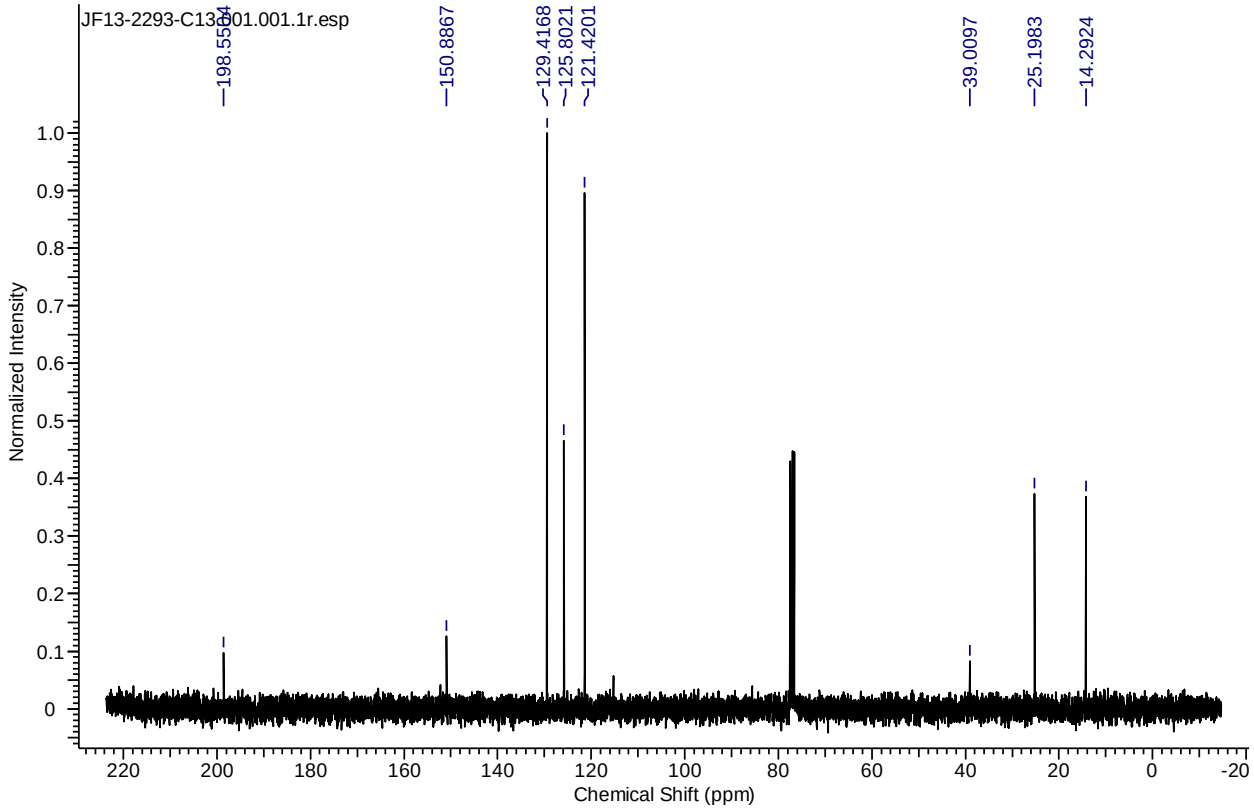

JF12-2186-H.001.esp
10.0507
7.7228
7.7020
7.3314
7.3194
7.3106
7.2971
7.2908
7.2508
7.2373
7.2290
4.4052
4.3844
2.3862
1.8757
Normalized Intensity
1.01
0.93
4.00
1.03
2.04
3.01
3.00
Chemical Shift (ppm)

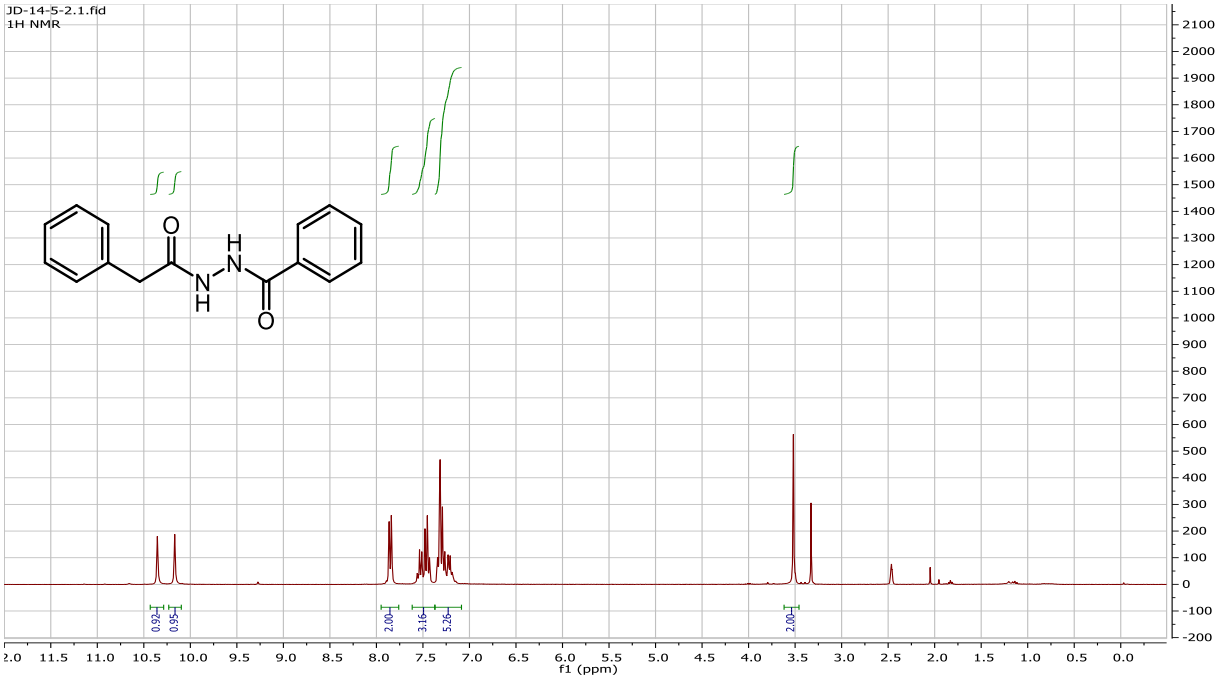

JF12-2186-C13.001.001.1r.esp
Normalized Intensity
197.1524
155.1508
144.3067
140.3175
128.2152
126.9279
126.6224
42.6665
24.4440
9.4398
Chemical Shift (ppm)

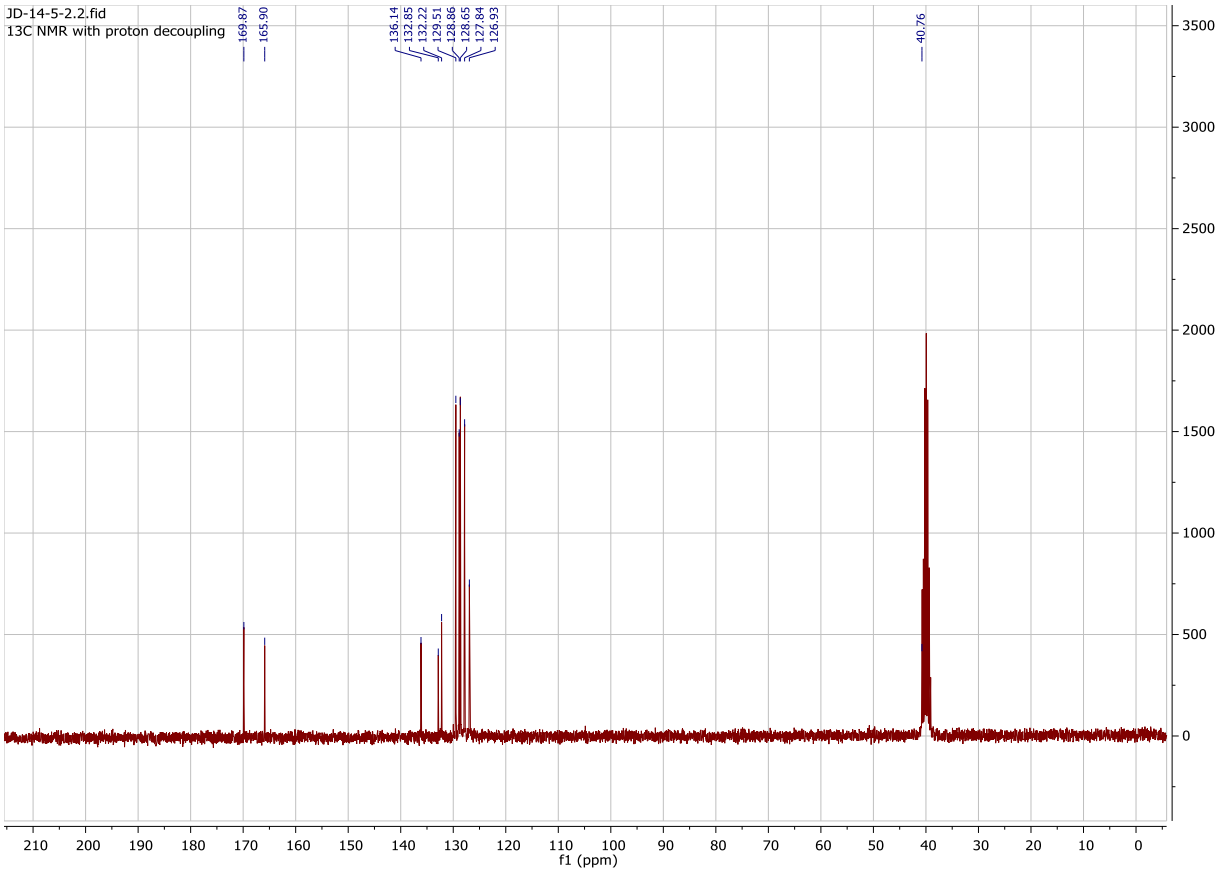

Morpholine semicarbazide.001.esp
8.6751
3.7221
3.7101
3.7029
3.6930
3.6909
3.6509
3.6410
3.6332
2.3180
1.9245
Normalized Intensity
Chemical Shift (ppm)
0.98
3.95
4.03
2.96
3.00

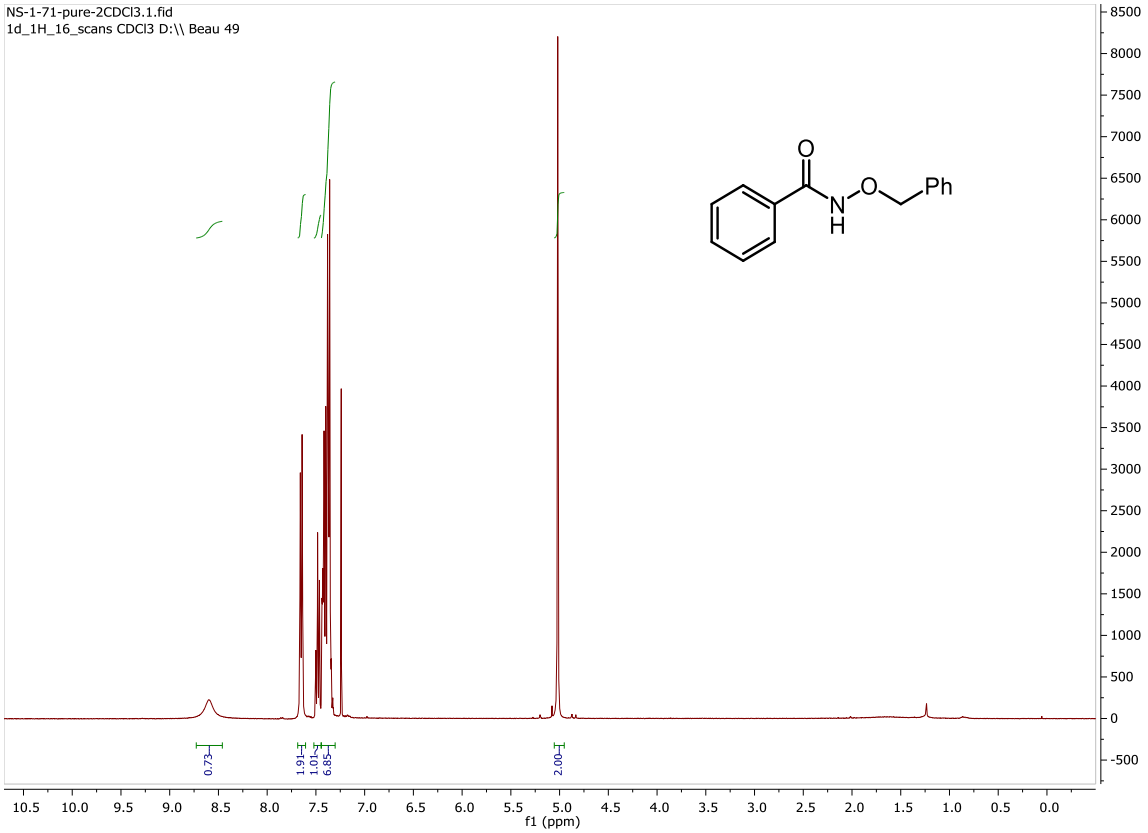

Morpholine semicarbazide.002.esp
66.5414
46.0170
24.1834
8.3138
196.8737
156.0576
145.7444
Chemical Shift (ppm)

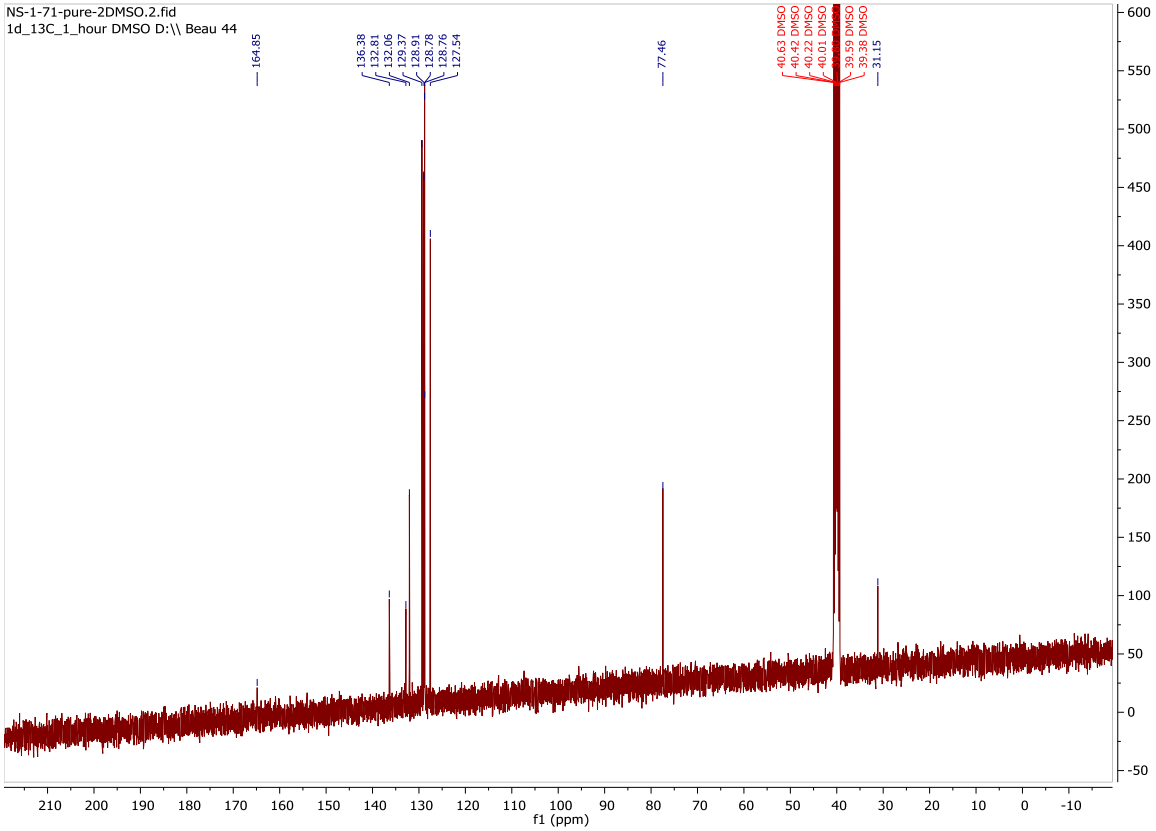

JF13-2293-H.001.esp
7.3922
7.3677
7.2643
7.2398
7.1717
7.1671
7.1463
7.1421
7.1390
3.4855
2.4874
2.0643
O
OPh
Me
N
N
O
1.91 1.13 2.00
3.00
2.99 3.05
Normalized Intensity
Chemical Shift (ppm)

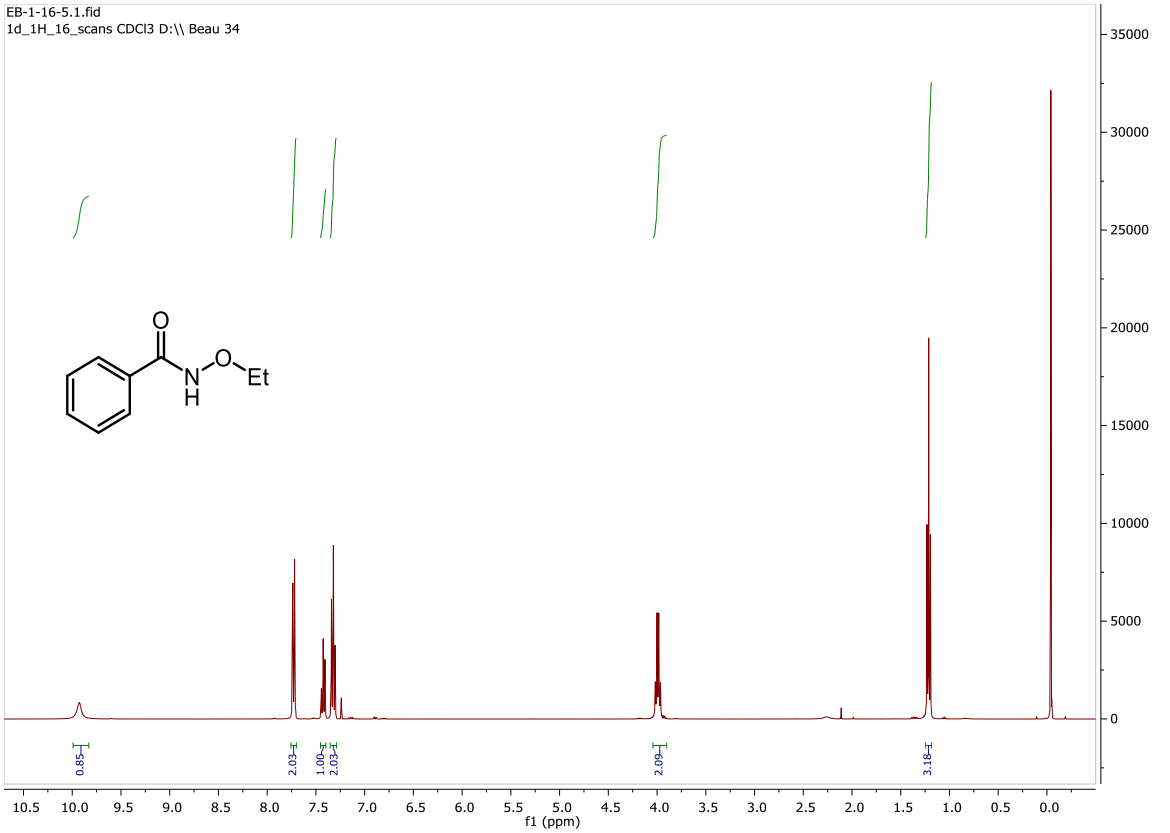

JF13-2293-C13001.001.1r.esp
198.5504
150.8867
129.4168
125.8021
121.4201
39.0097
25.1983
14.2924
Normalized Intensity
Chemical Shift (ppm)

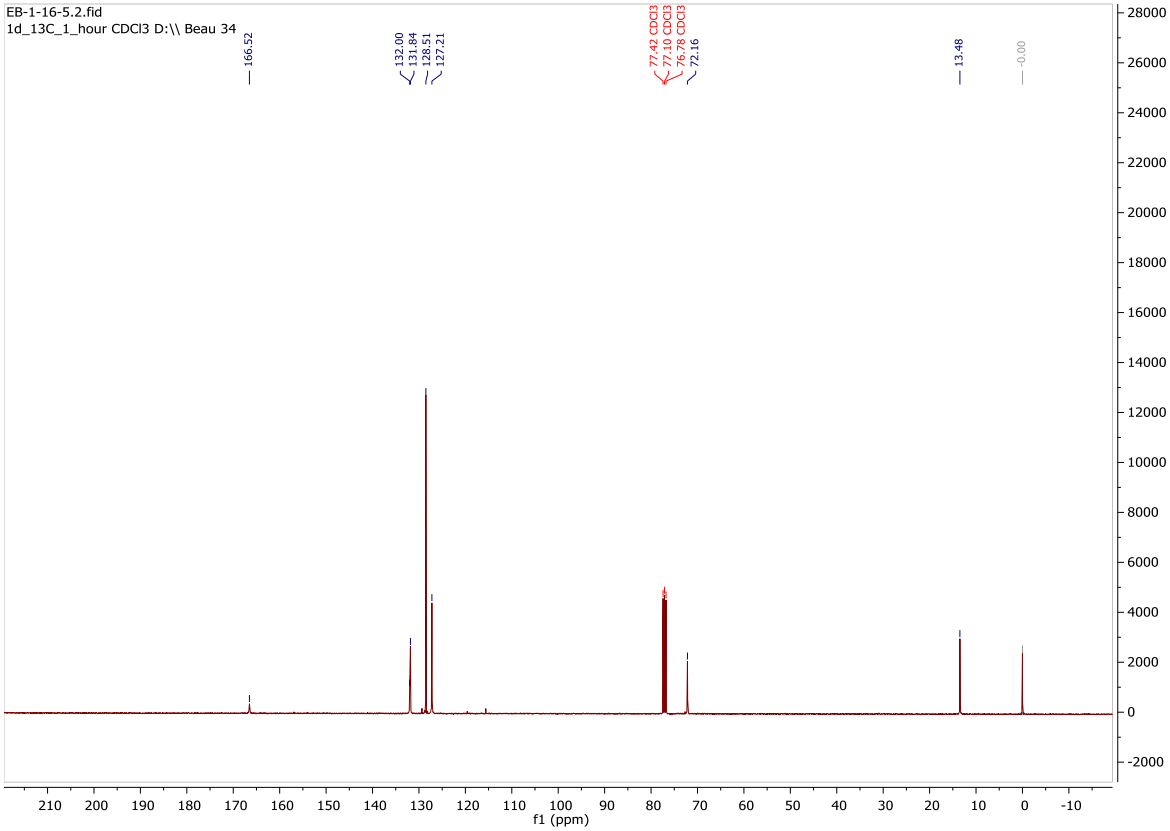

JD-14-5-2.1.fid
1H NMR
0.92
0.95
2.00
3.16
5.26
2.00
f1 (ppm)

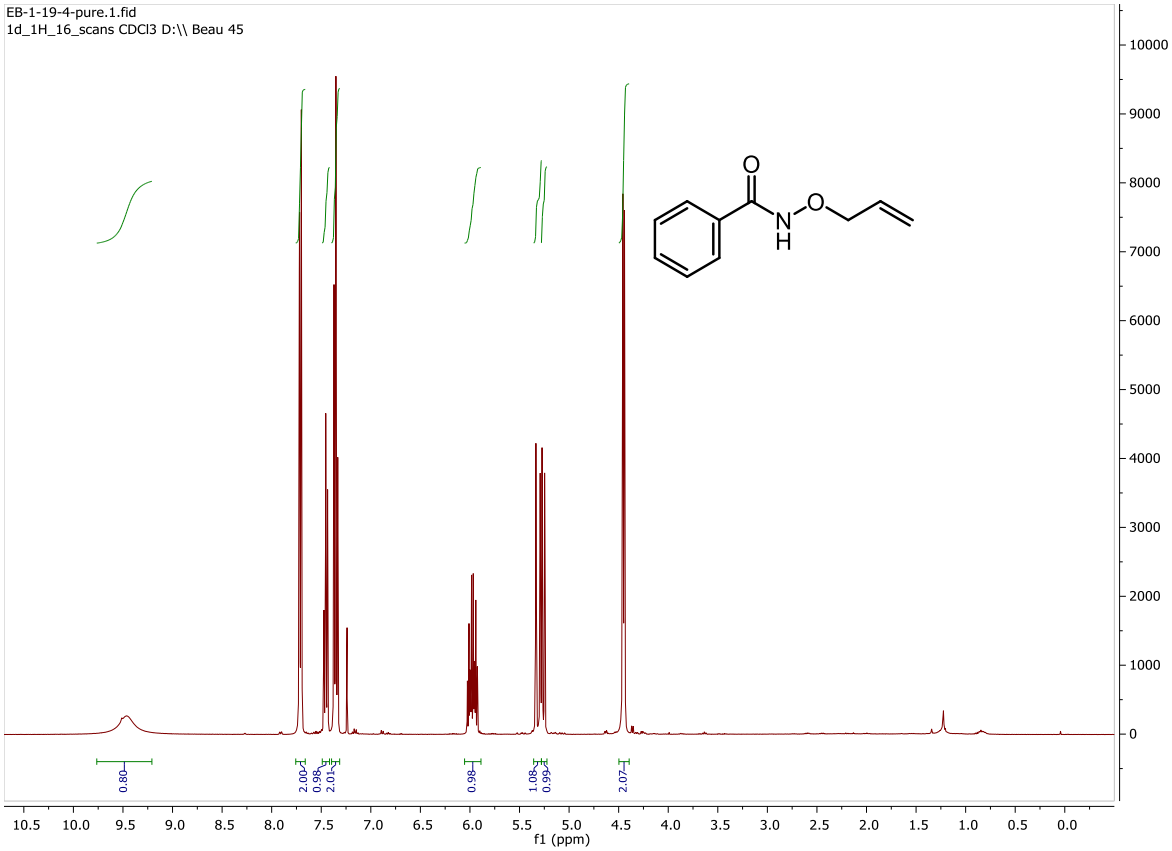

JD-14-5-2.2.fid
13C NMR with proton decoupling
169.87
165.90
136.14
132.85
132.22
129.51
128.86
128.65
127.84
126.93
40.76
f1 (ppm)

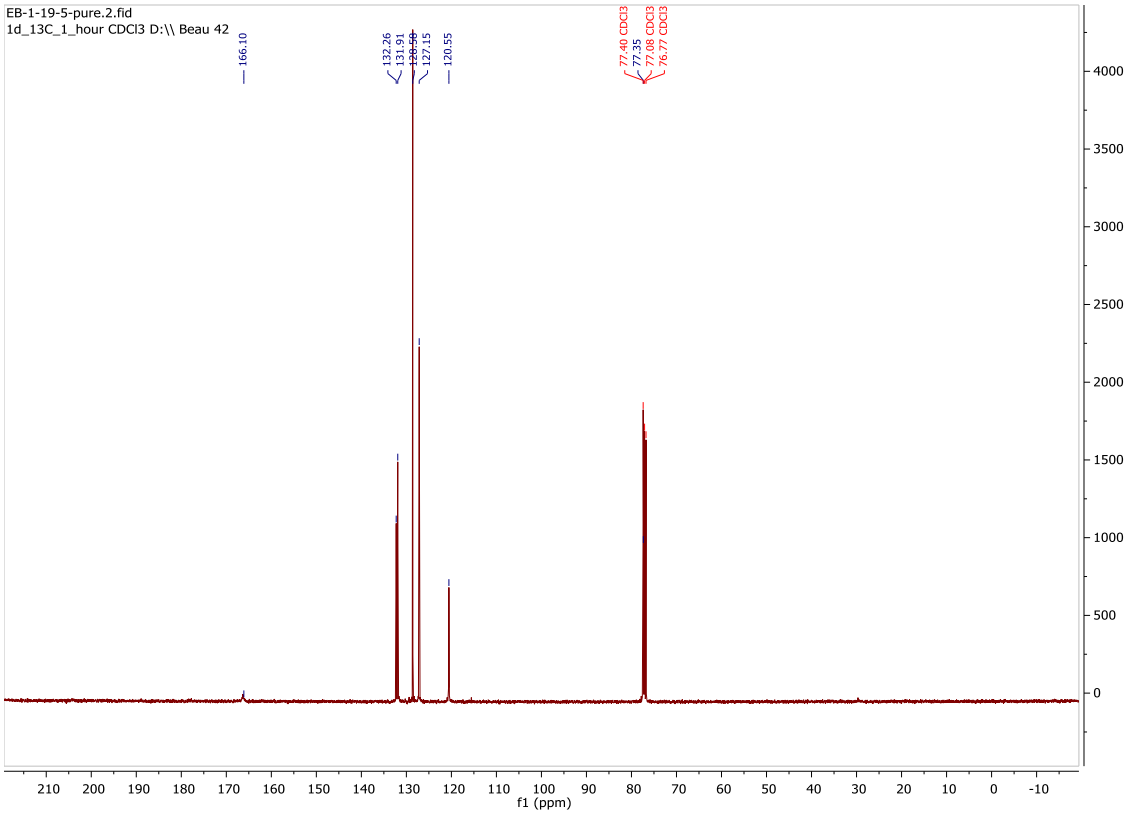

NS-1-71-pure-2CDCl3.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 49
O
N
H
O
Ph
0.73
1.91
1.01
6.85
2.00
f1 (ppm)

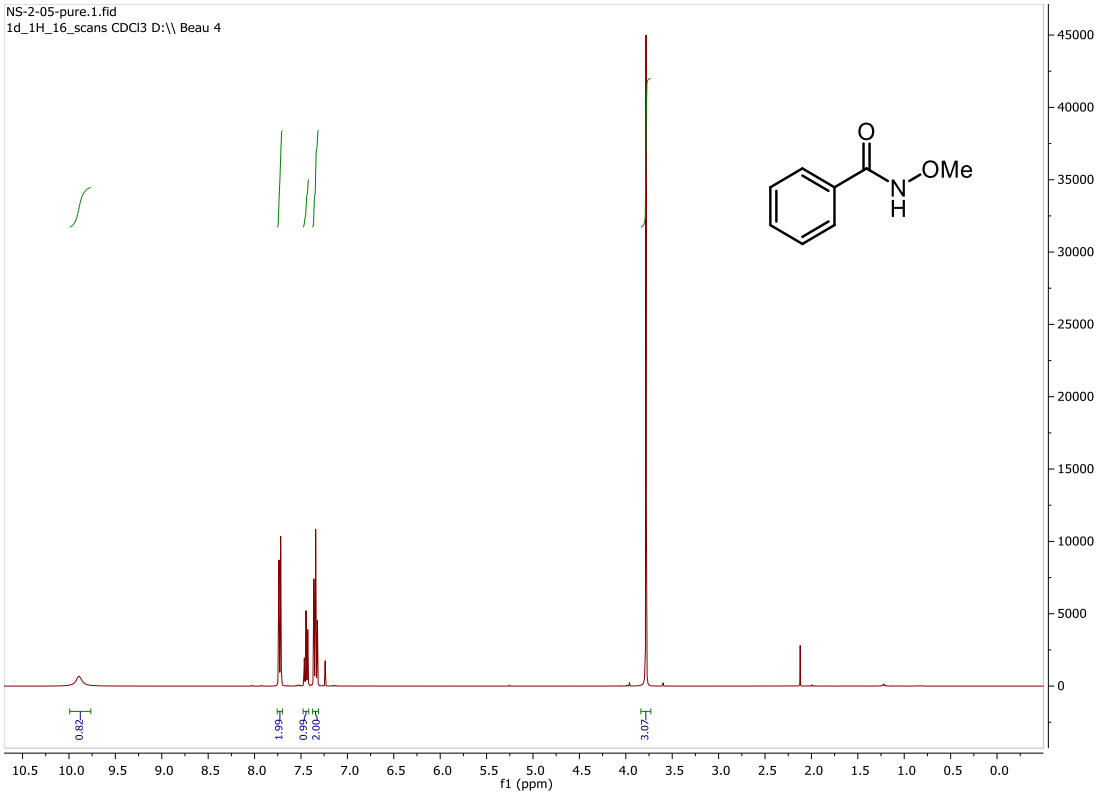

NS-1-71-pure-2DMSO.2.fid
1d_13C_1_hour DMSO D:\\ Beau 44
164.85
136.38
132.81
132.06
129.37
128.91
128.78
128.76
127.54
77.46
40.63 DMSO
40.42 DMSO
40.22 DMSO
40.01 DMSO
39.59 DMSO
39.38 DMSO
31.15
f1 (ppm)

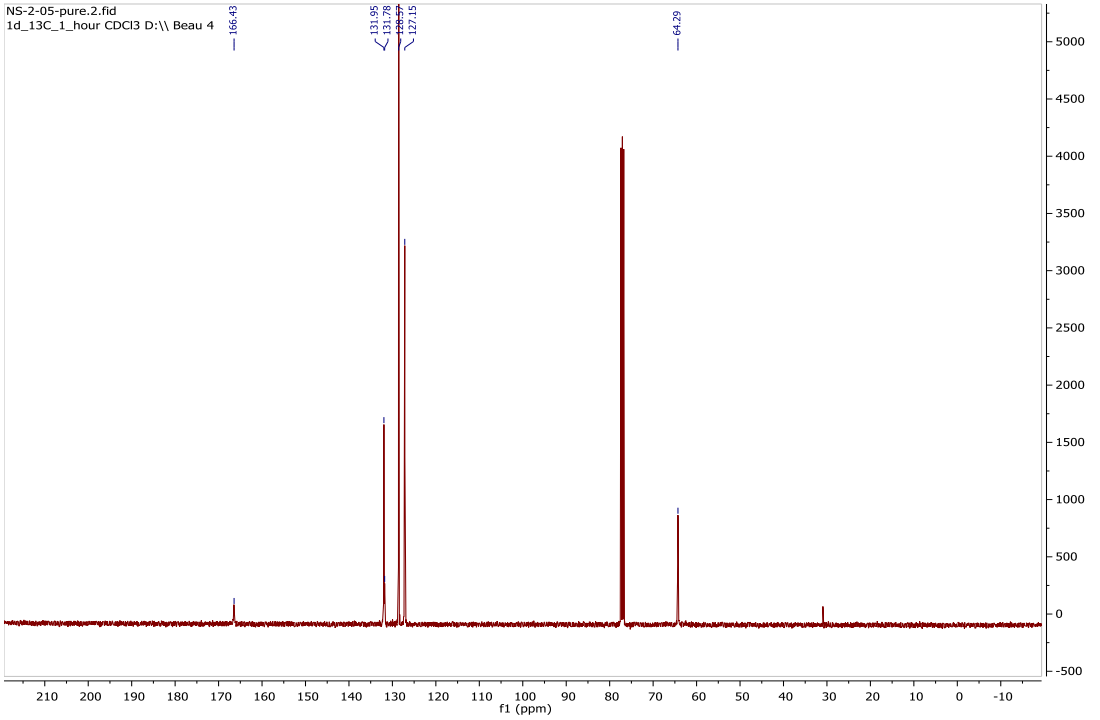

EB-1-16-5.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 34
O
N
H
O
Et
0.85
2.03
1.00
2.03
2.09
3.18
f1 (ppm)

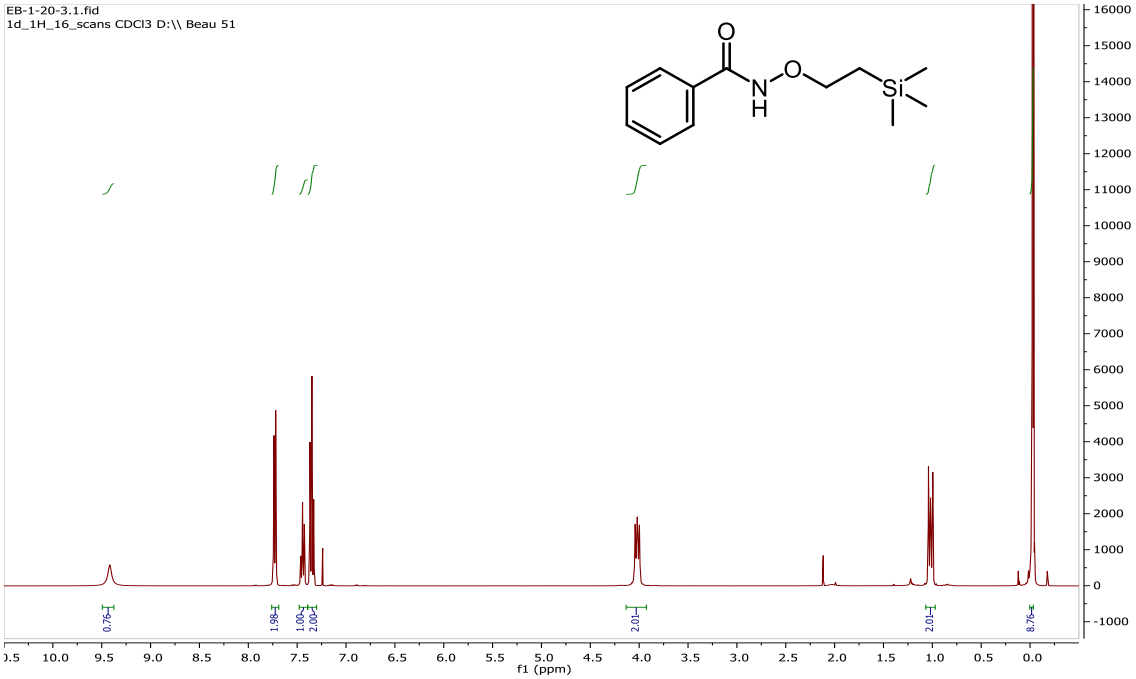

EB-1-16-5.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 34
166.52
132.00
131.64
128.51
127.21
77.42 CDCl3
77.10 CDCl3
76.78 CDCl3
72.16
13.48
-0.00
f1 (ppm)

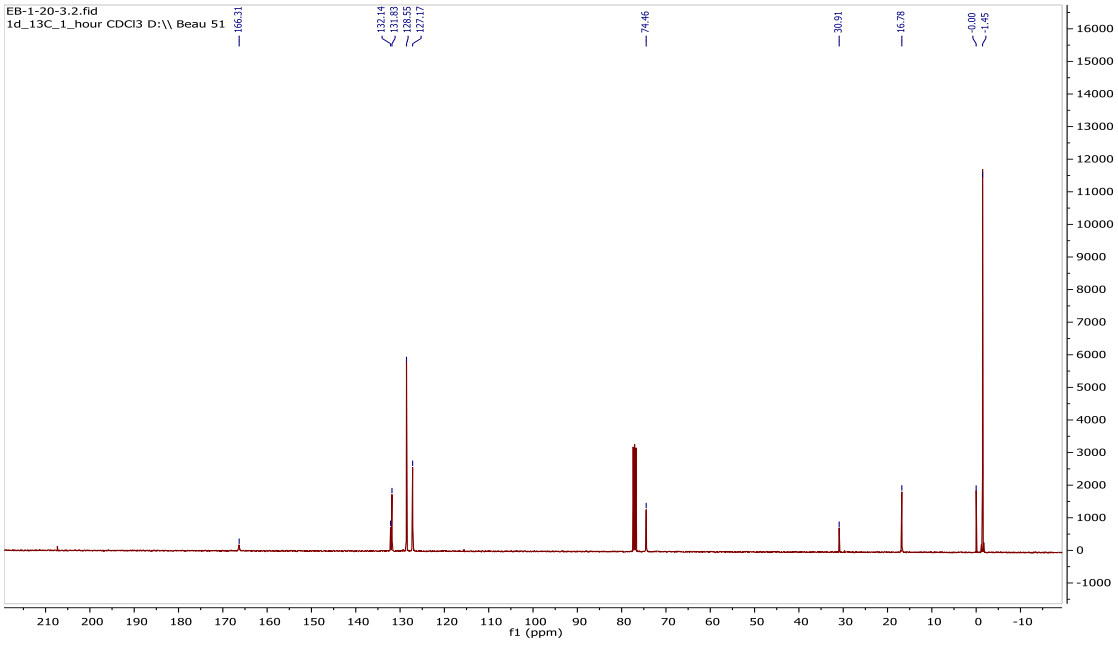

EB-1-19-4-pure.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 45
O
N
H
O
0.80
2.00
0.98
2.01
0.98
1.08
0.99
2.07
f1 (ppm)

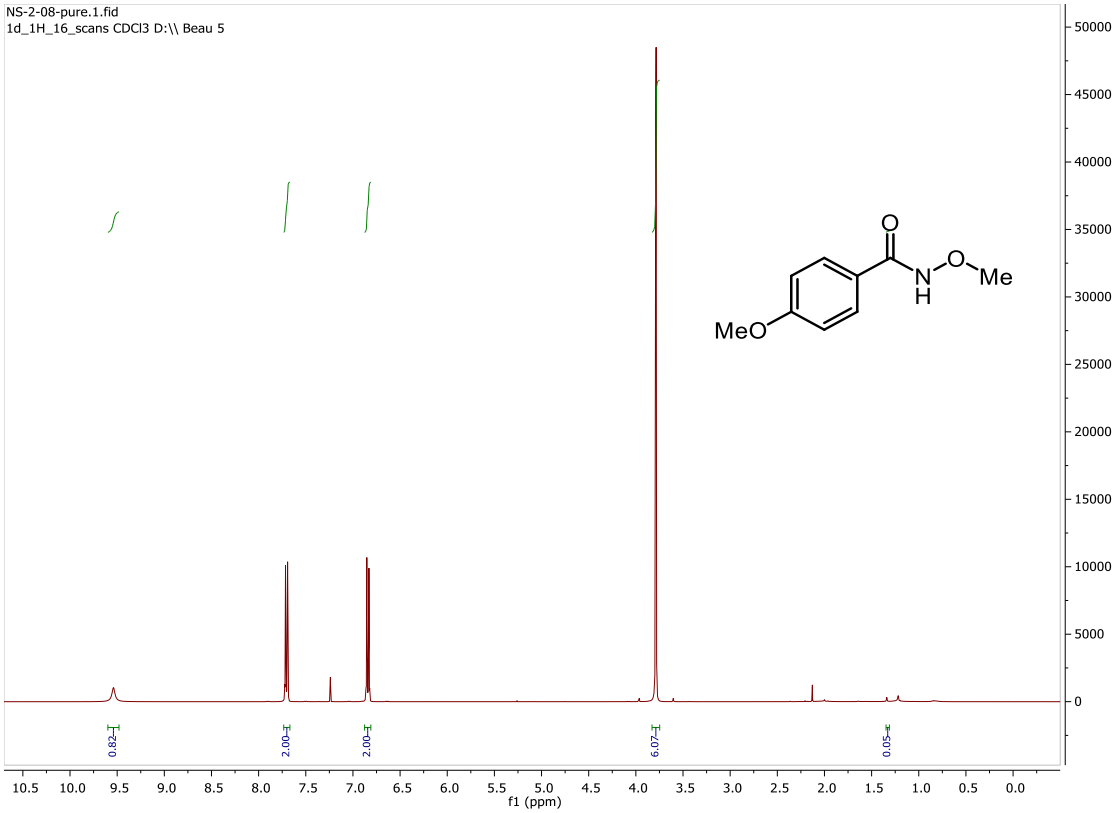

EB-1-19-5-pure.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 42
166.10
132.26
131.91
127.15
120.55
77.40 CDCl3
77.35
77.08 CDCl3
76.77 CDCl3
f1 (ppm)

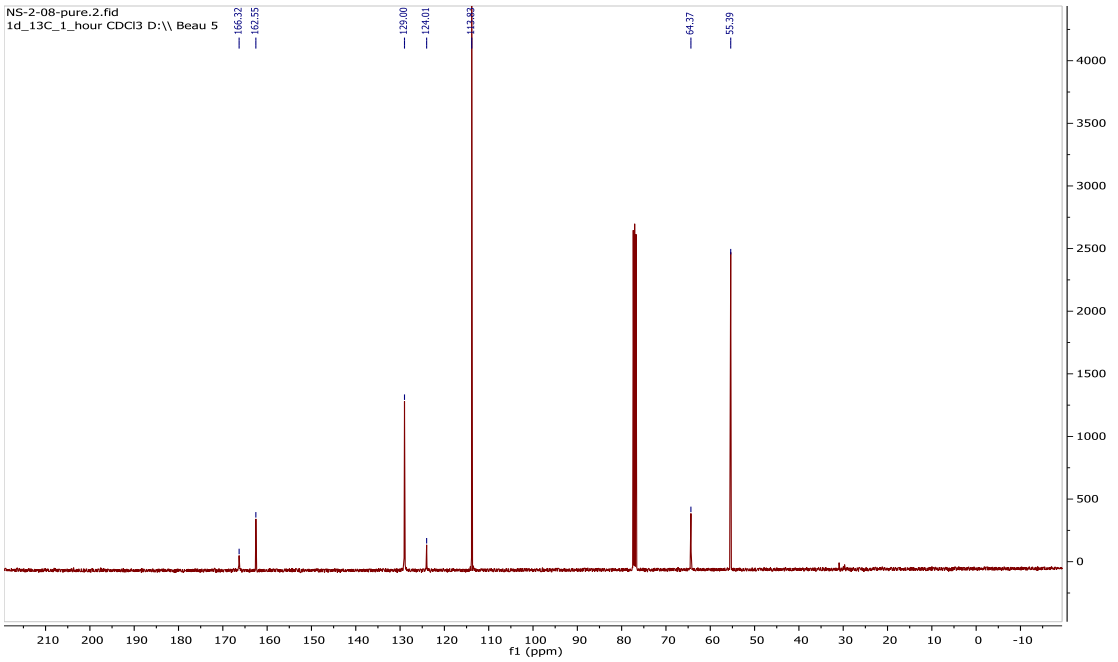

NS-2-05-pure.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 4
O
N
H
OMe
0.82
1.99
0.99
2.00
3.07
f1 (ppm)

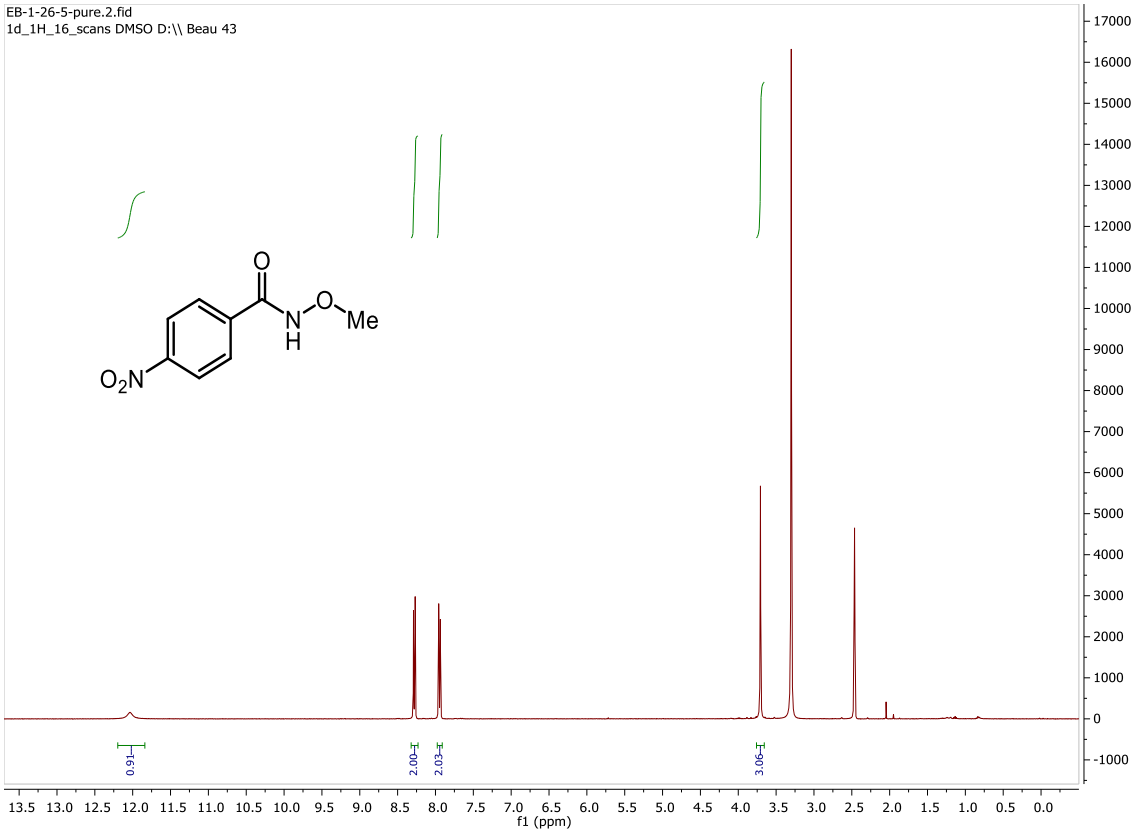

NS-2-05-pure.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 4
166.43
131.95
131.78
128.37
127.15
64.29
f1 (ppm)

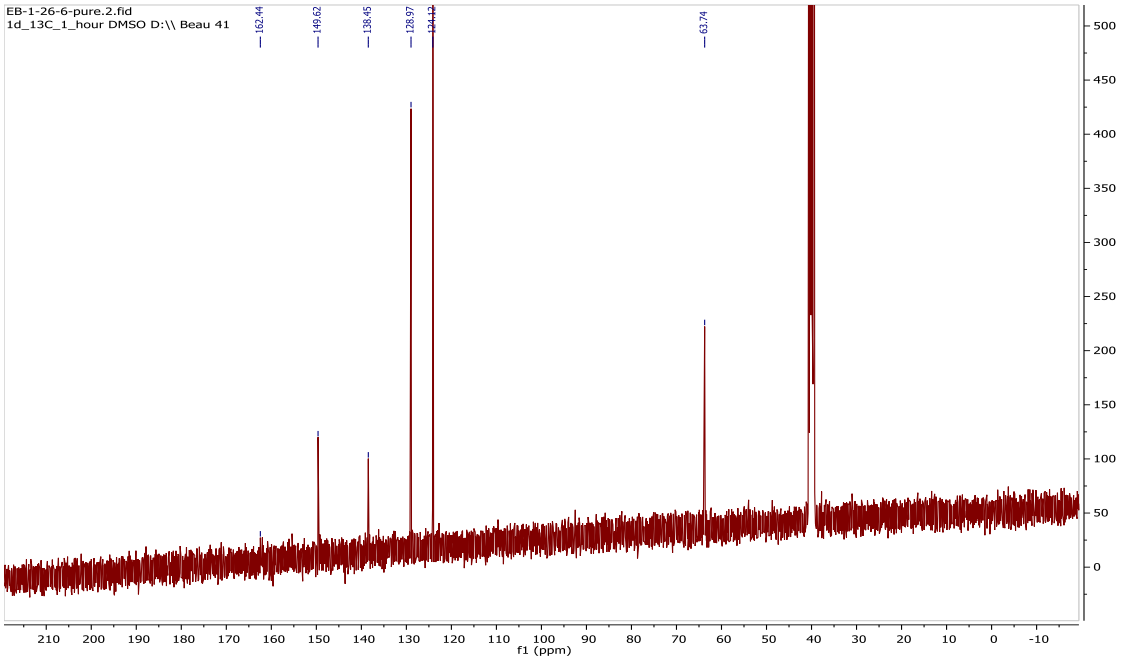

EB-1-20-3.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 51
O
N
H
O
Si
0.76
1.98
1.00
2.00
2.01
2.01
8.76
f1 (ppm)

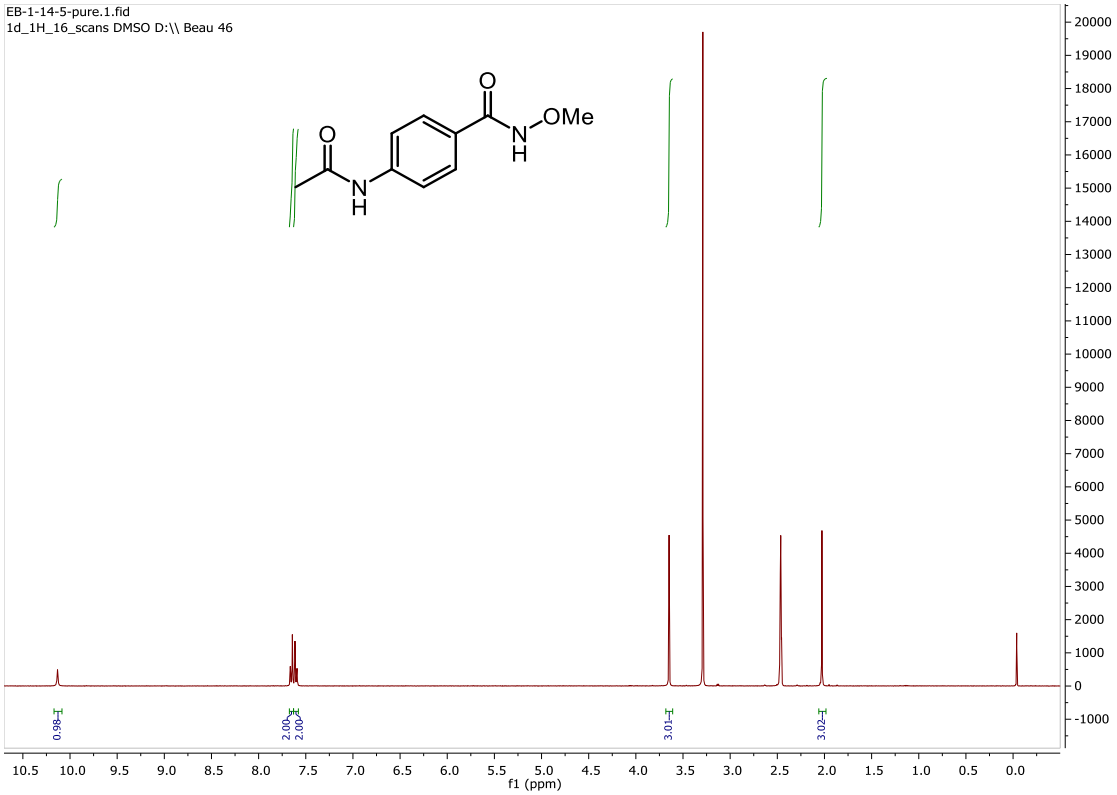

EB-1-20-3.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 51
166.31
132.14
131.83
128.55
127.17
74.46
30.91
16.78
0.00
-1.45
f1 (ppm)

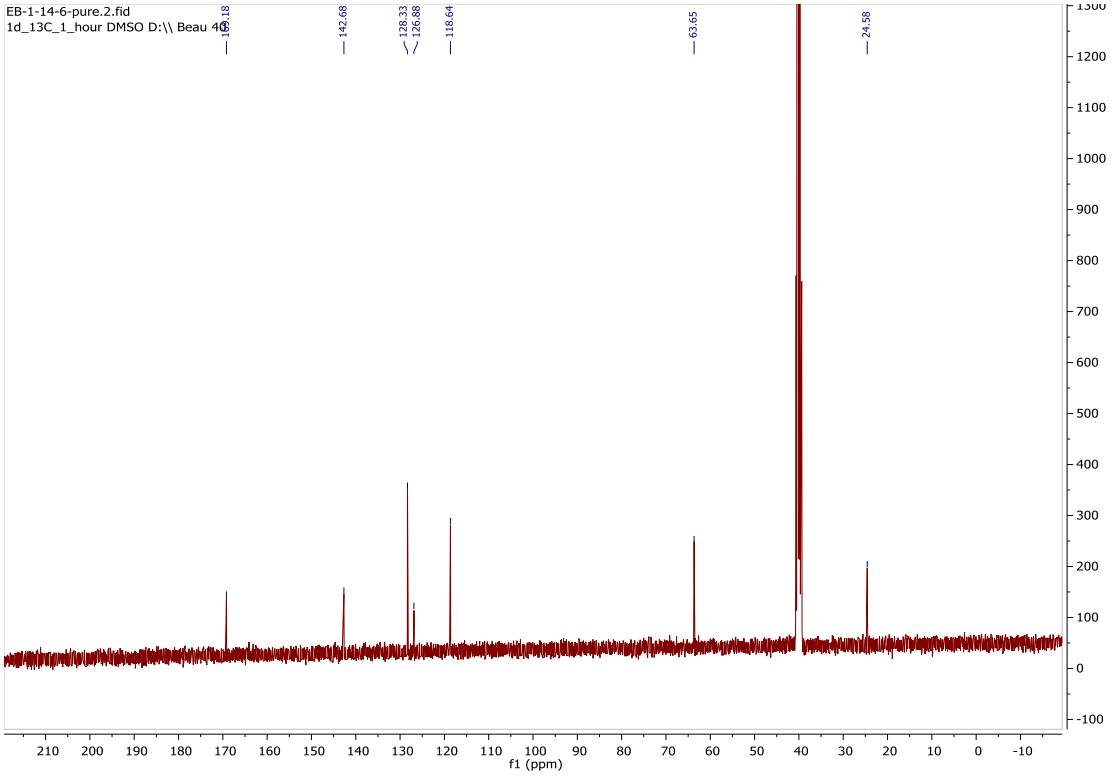

NS-2-08-pure.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 5
O
N
H
O
Me
MeO
0.82
2.00
2.00
6.07
0.05
f1 (ppm)

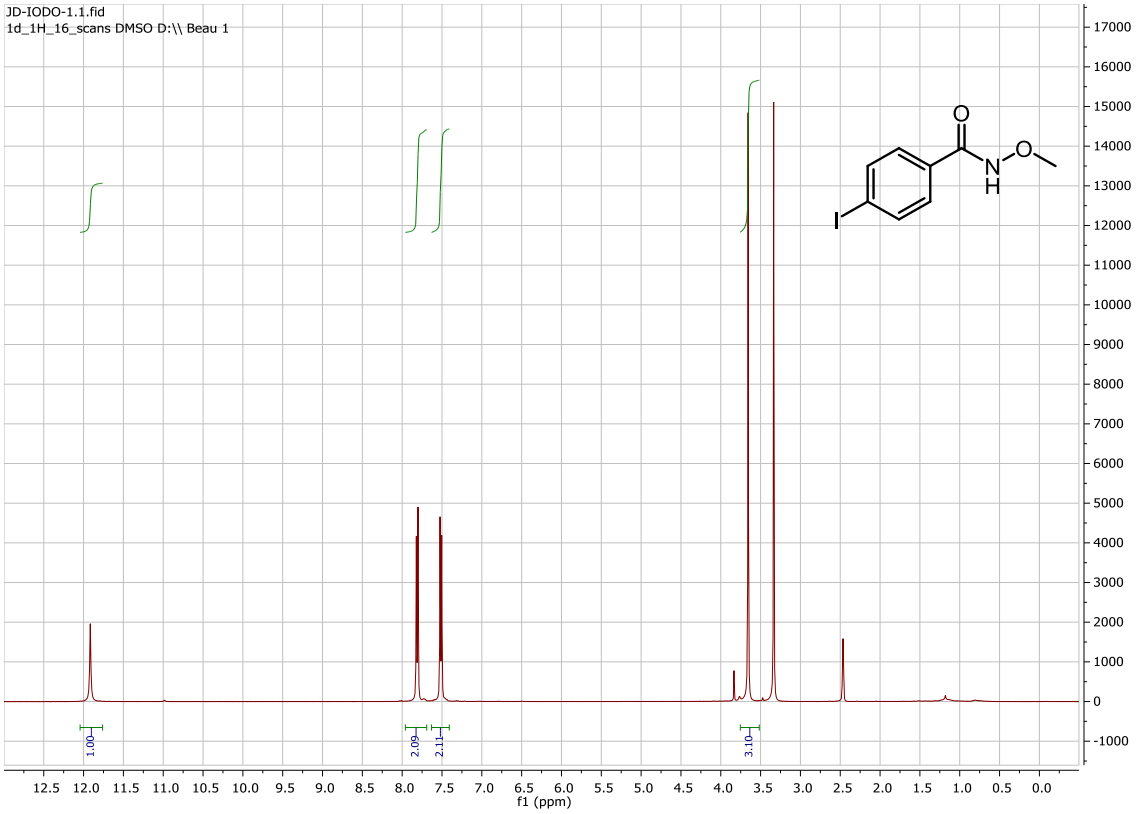

NS-2-08-pure.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 5
166.32
162.55
129.00
124.01
113.82
64.37
55.39
f1 (ppm)

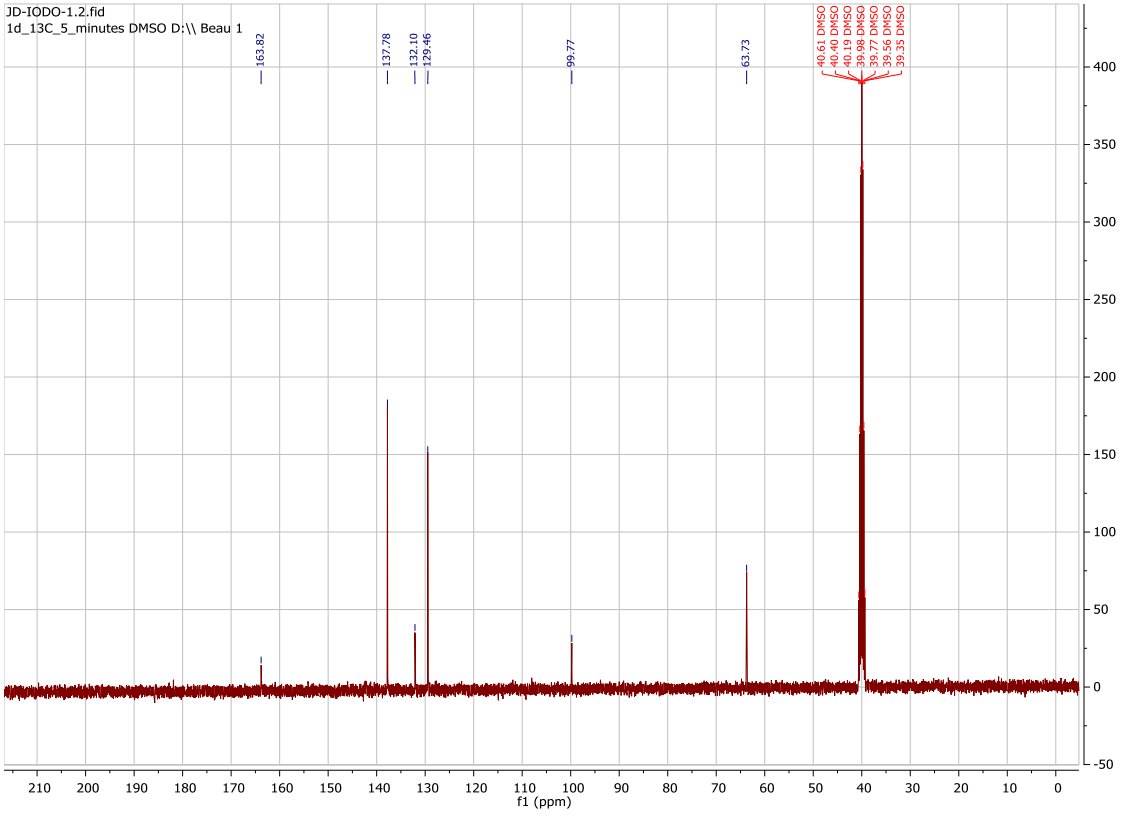

EB-1-26-5-pure.2.fid
1d_1H_16_scans DMSO D:\\ Beau 43
O
N
H
O
Me
O_2N
0.91
2.00
2.03
3.06
f1 (ppm)

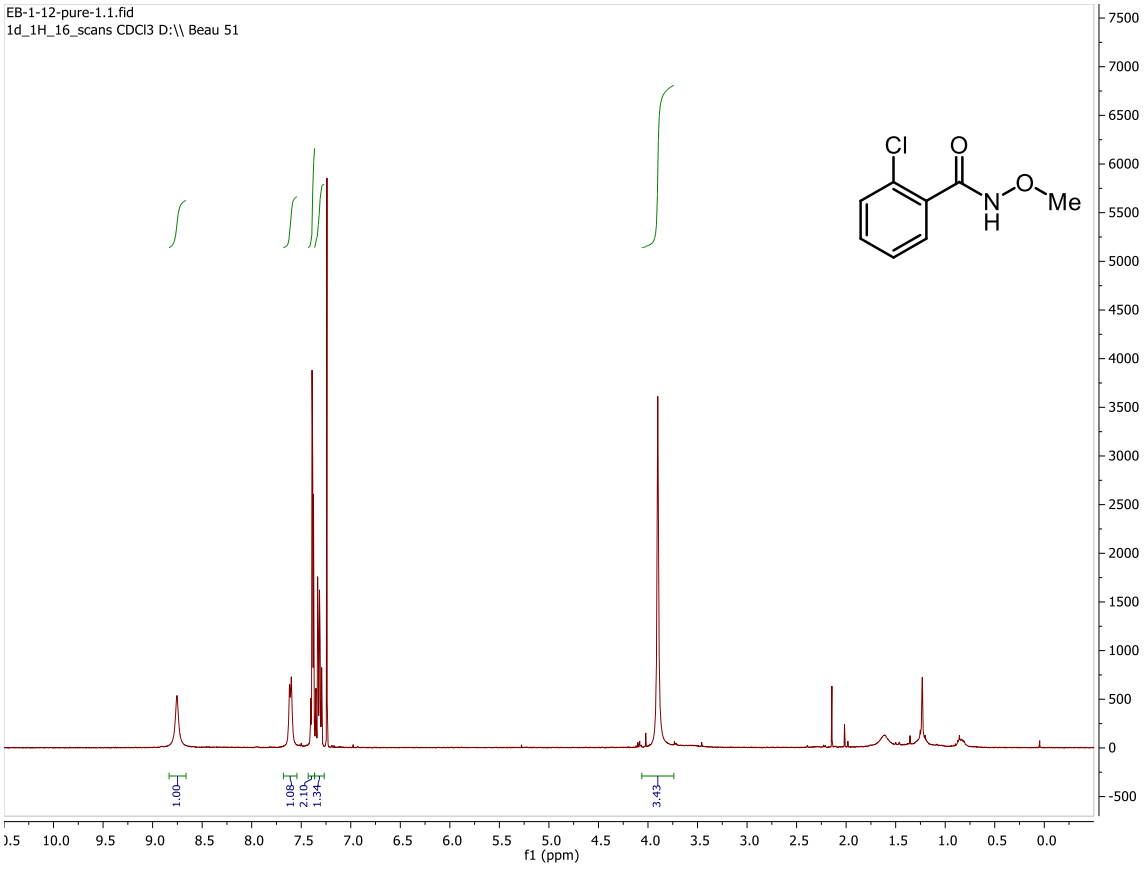

EB-1-26-6-pure.2.fid
1d_13C_1_hour DMSO D:\\ Beau 41
162.44
149.62
138.45
128.97
124.12
63.74
f1 (ppm)

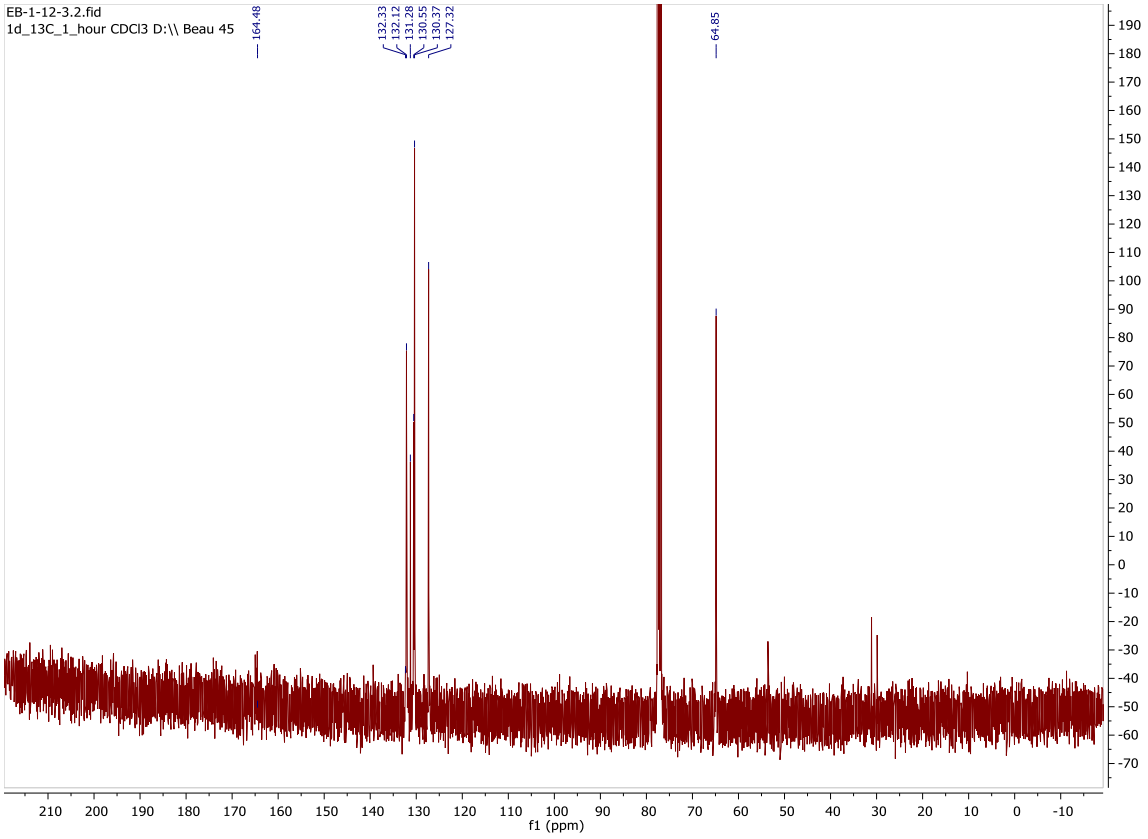

EB-1-14-5-pure.1.fid
1d_1H_16_scans DMSO D:\\ Beau 46
O
N
H
O
N
OMe
0.98
2.00
2.00
3.01
3.02
f1 (ppm)

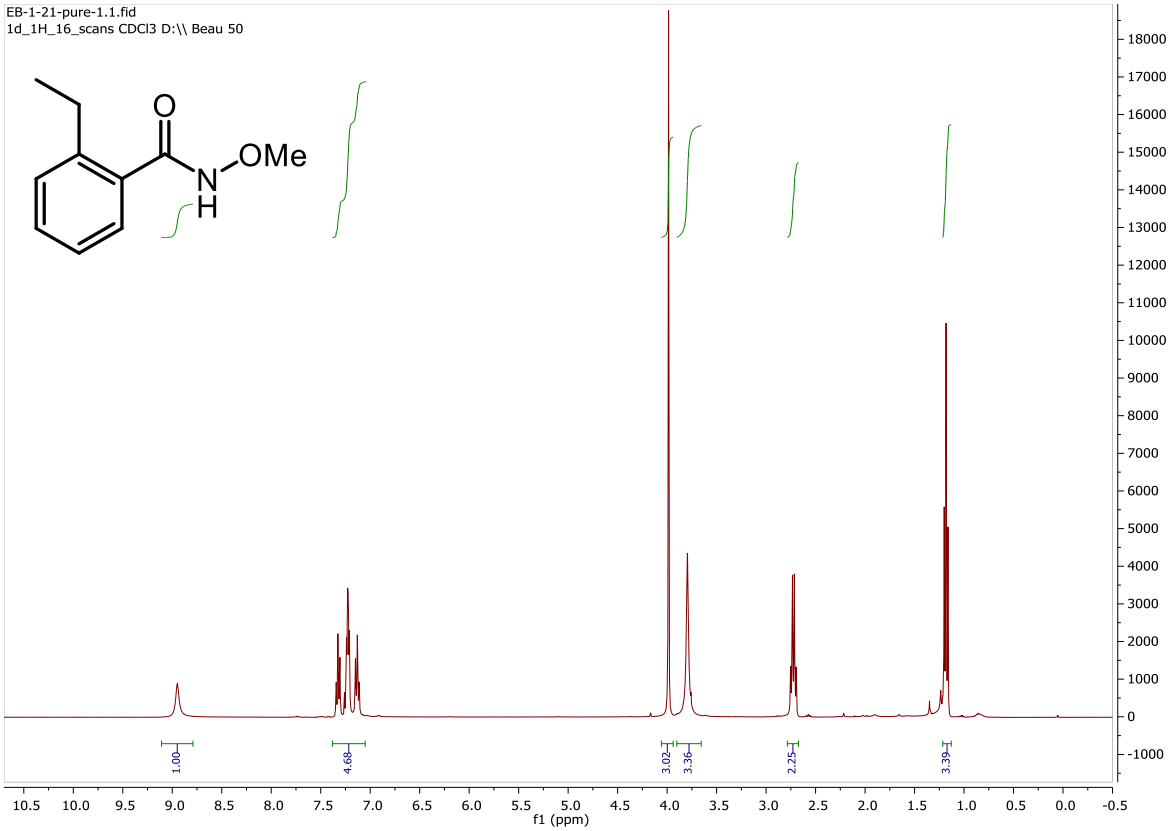

EB-1-14-6-pure.2.fid
1d_13C_1_hour DMSO D:\\ Beau 46
169.18
142.68
128.33
126.88
118.64
63.65
24.58
f1 (ppm)

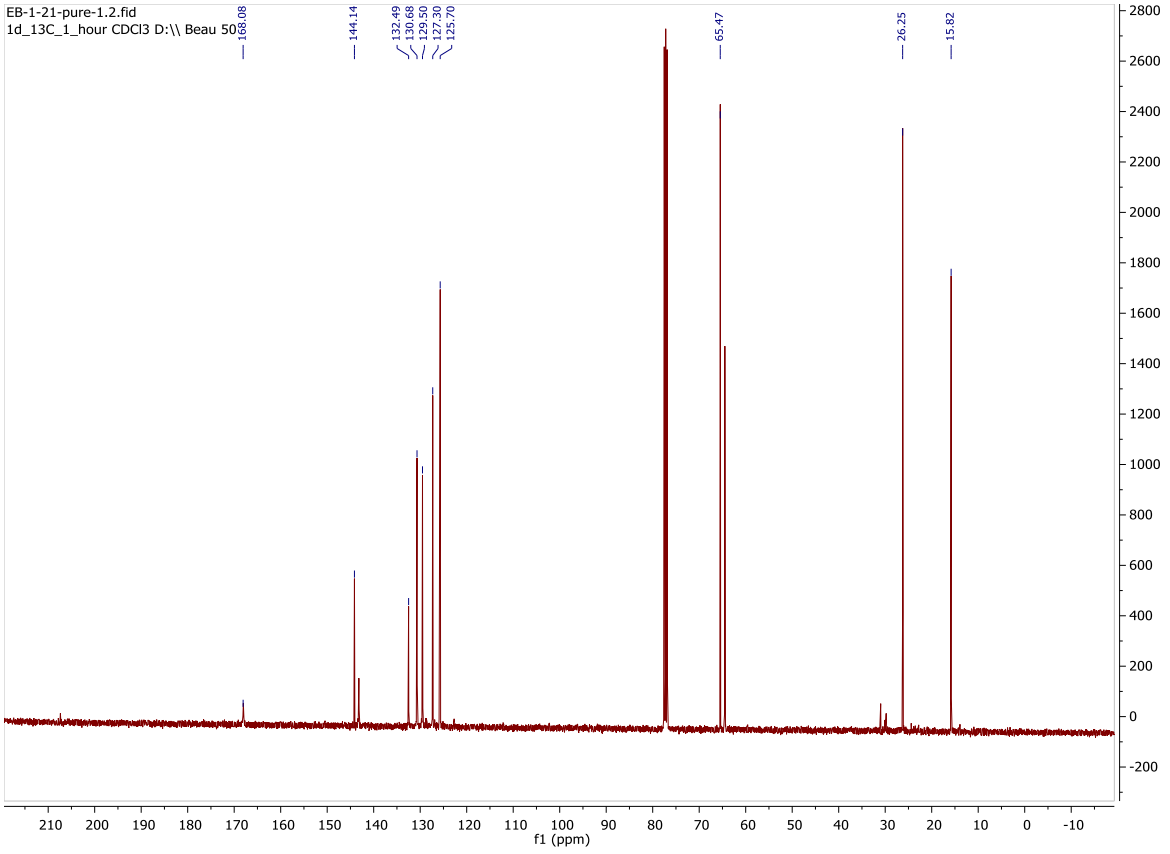

JD-IODO-1.1.fid
1d_1H_16_scans DMSO D:\\ Beau 1
1.00
2.09
2.11
3.10
f1 (ppm)

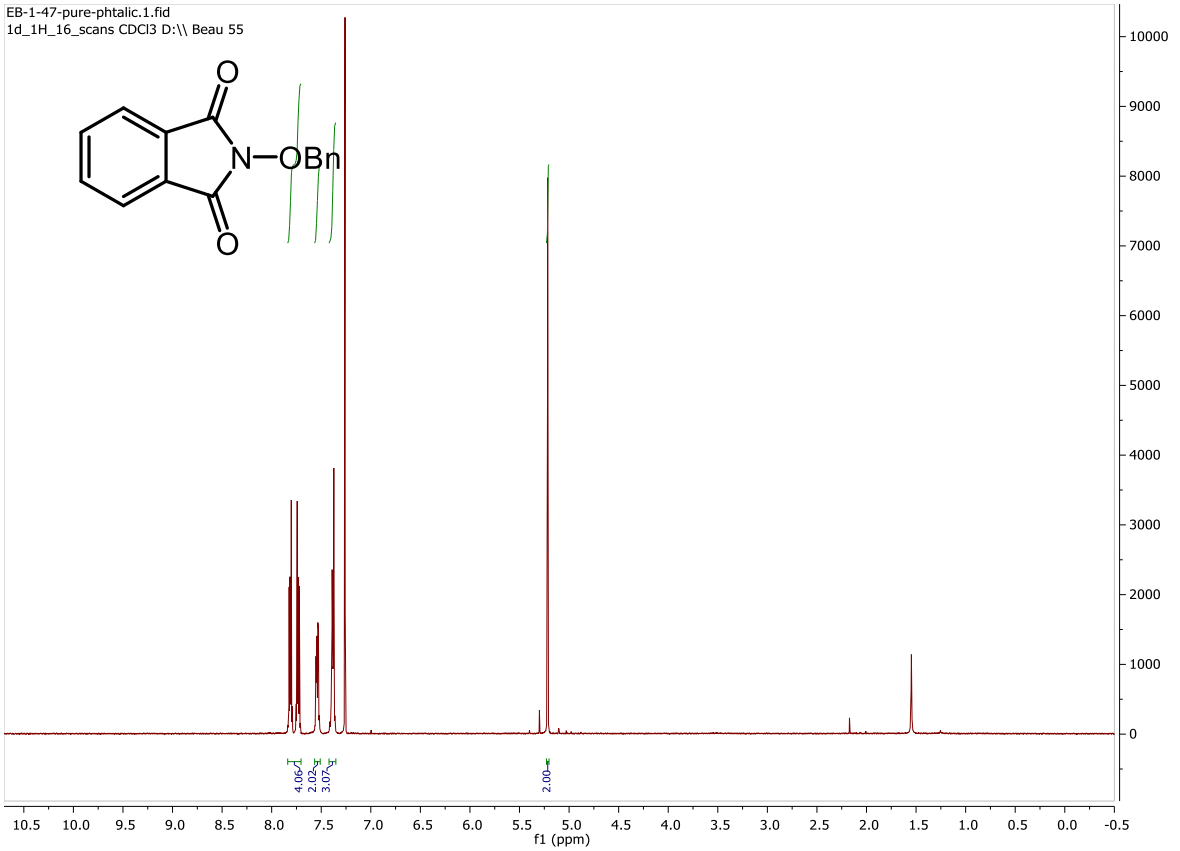

JD-IODO-1.2.fid
1d_13C_5_minutes DMSO D:\\ Beau 1
163.82
137.78
132.10
129.46
99.77
63.73
40.61 DMSO
40.40 DMSO
40.19 DMSO
39.98 DMSO
39.77 DMSO
39.56 DMSO
39.35 DMSO
f1 (ppm)

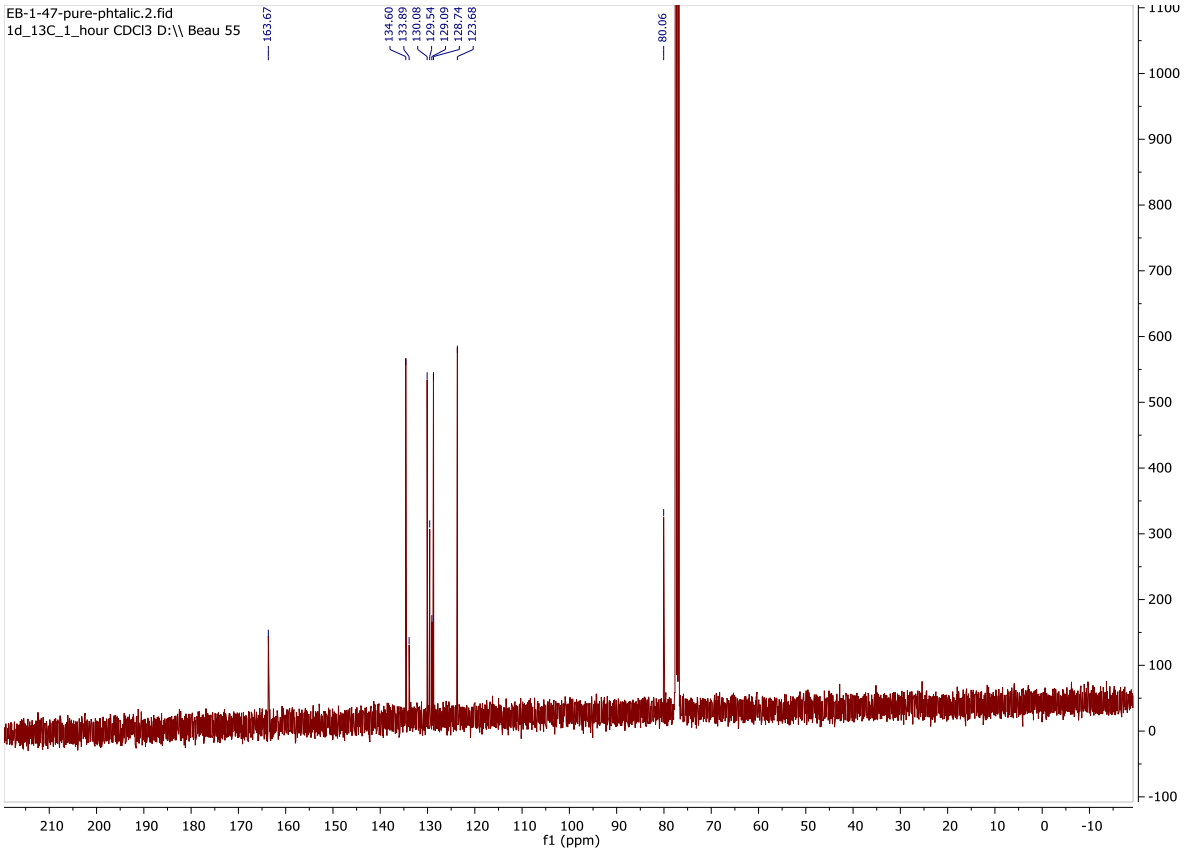

EB-1-12-pure-1.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 51
Cl
O
N
H
O
Me
1.00
1.08
2.10
1.34
3.43
f1 (ppm)

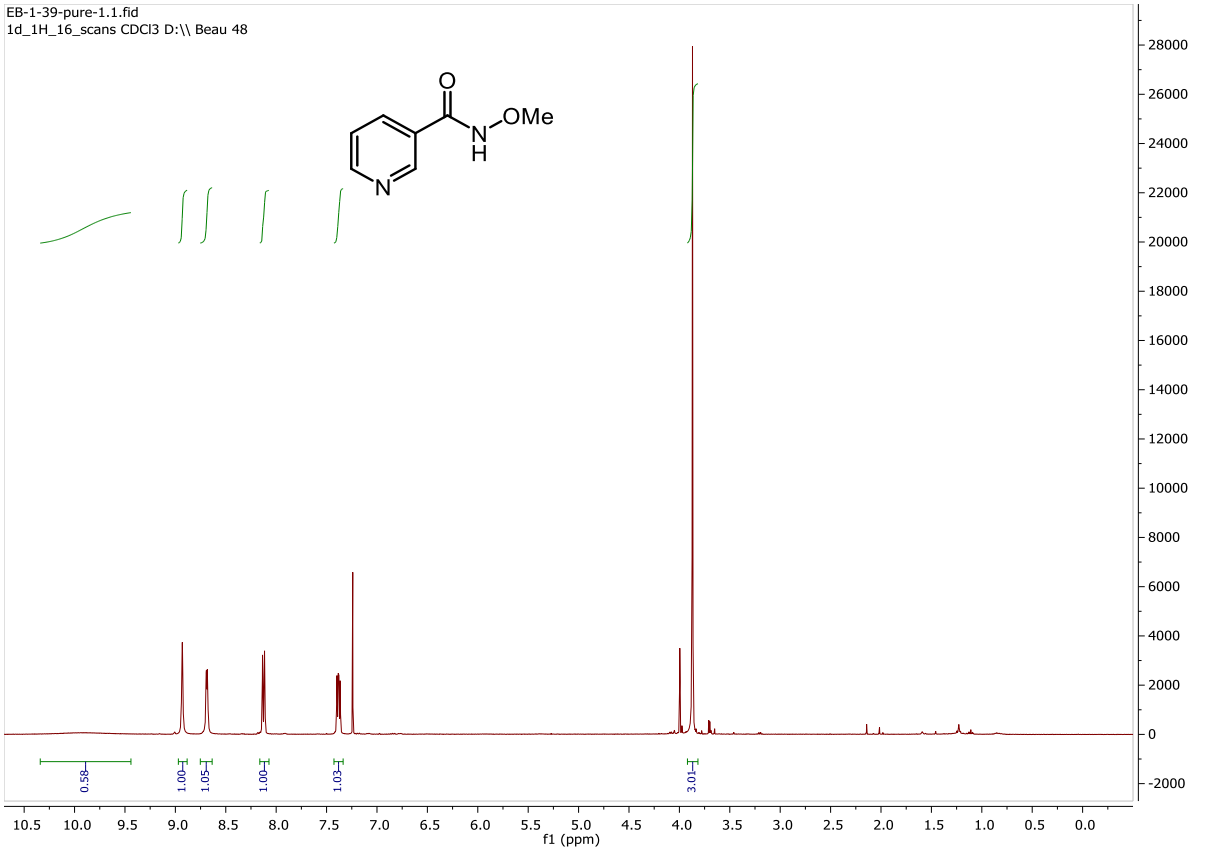

EB-1-12-3.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 45
164.48
132.33
132.12
131.28
130.55
130.37
127.32
64.85
f1 (ppm)

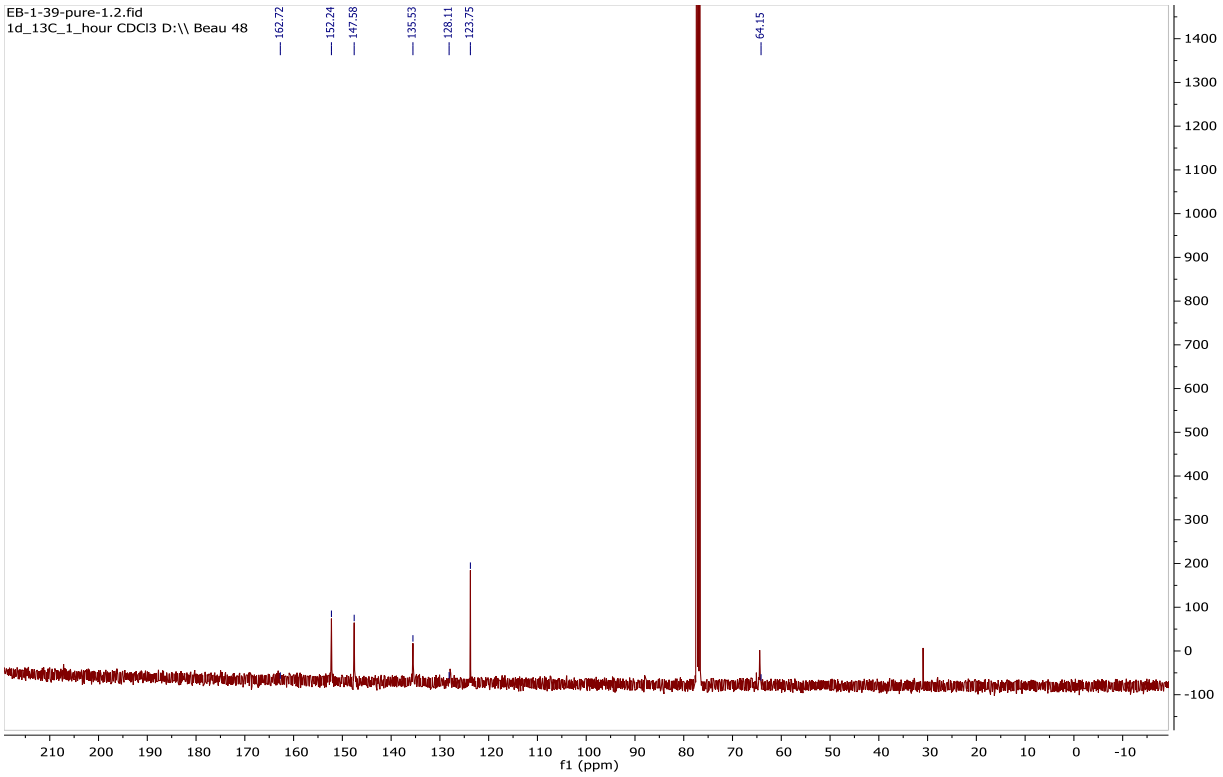

EB-1-21-pure-1.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 50
O
N
H
OMe
1.00
4.68
3.02
3.36
2.25
3.39
f1 (ppm)

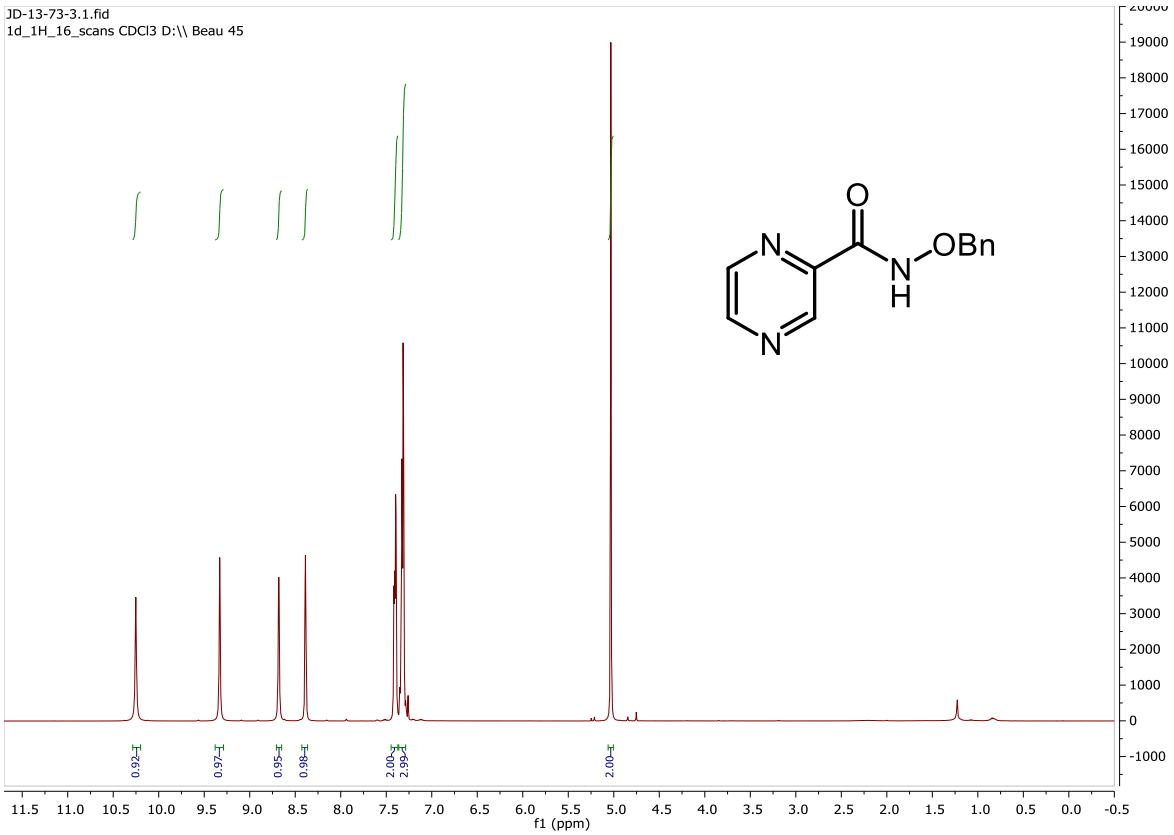

EB-1-21-pure-1.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 50
168.08
144.14
132.49
130.68
129.50
127.30
125.70
65.47
26.25
15.82
f1 (ppm)

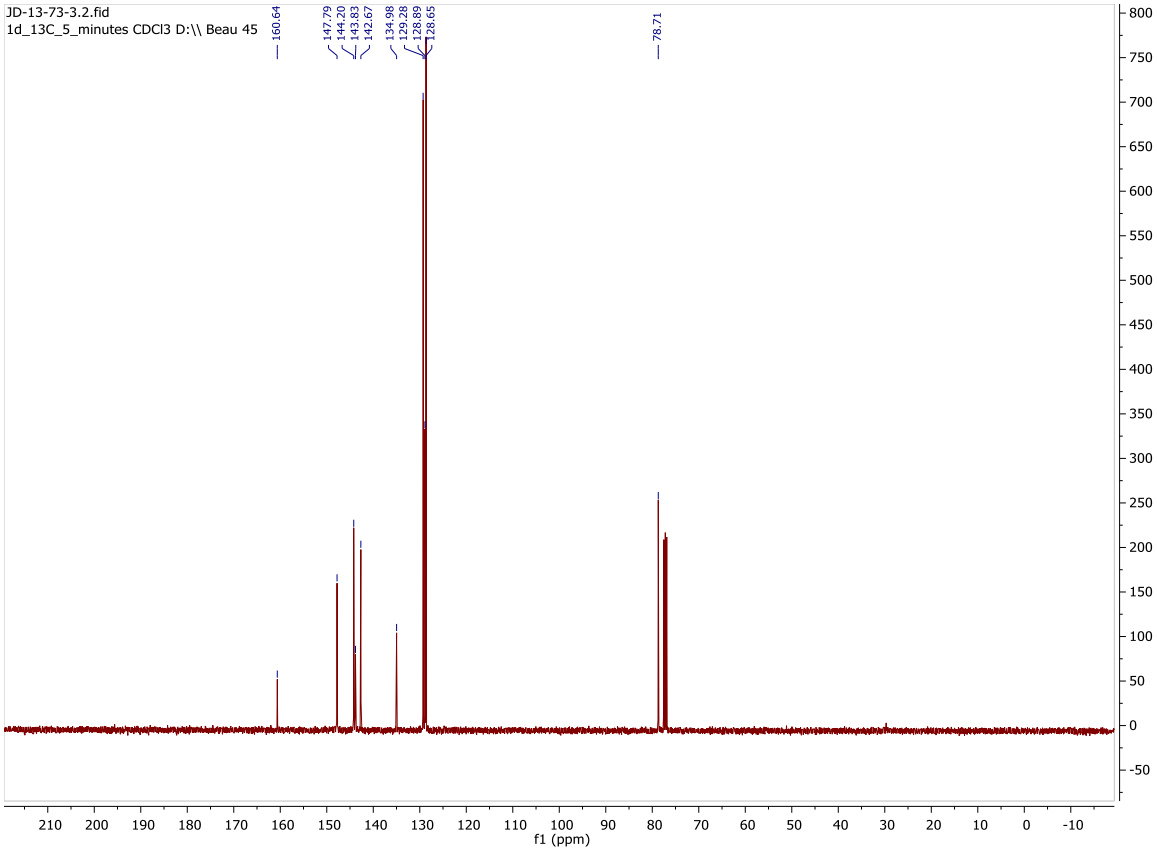

EB-1-47-pure-phtalic.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 55
O
N–OBn
O
4.06
2.02
3.07
2.00
f1 (ppm)

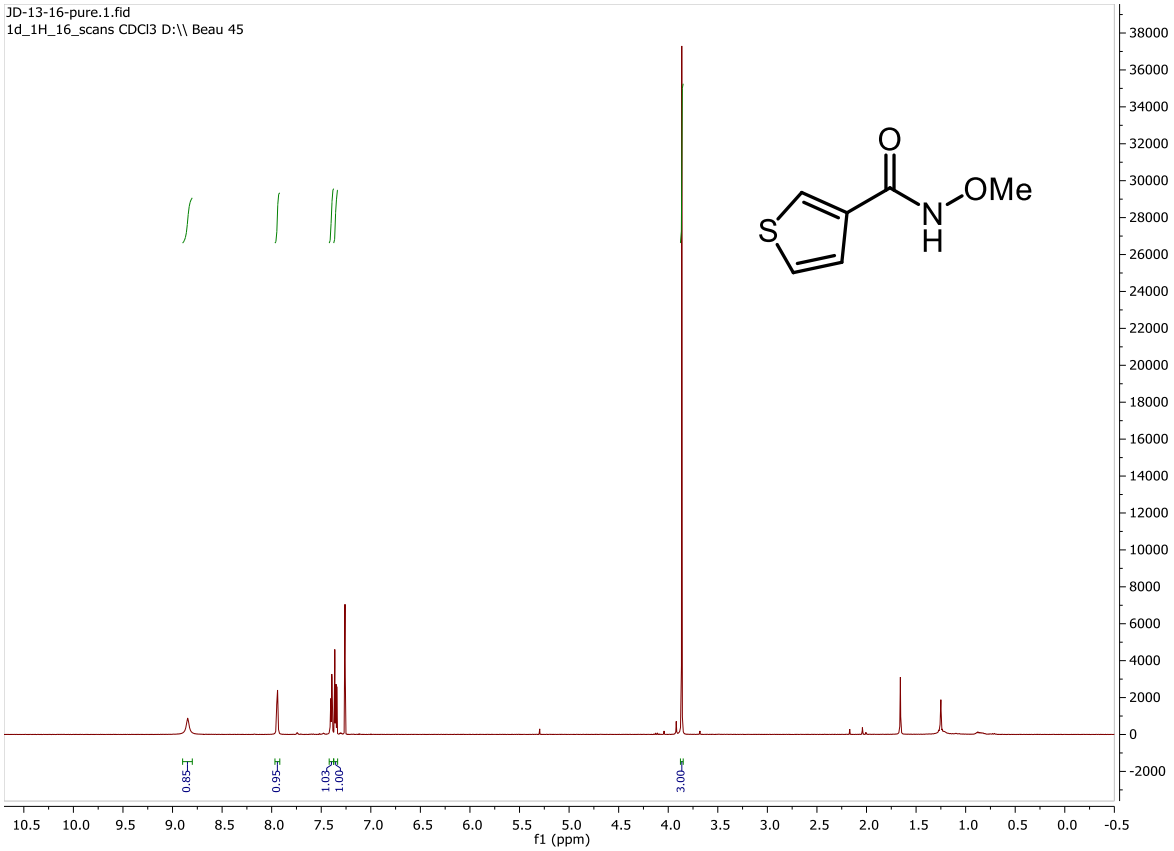

EB-1-47-pure-phtalic.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 55
163.67
134.60
133.89
130.08
129.54
129.09
128.74
123.68
80.06
f1 (ppm)

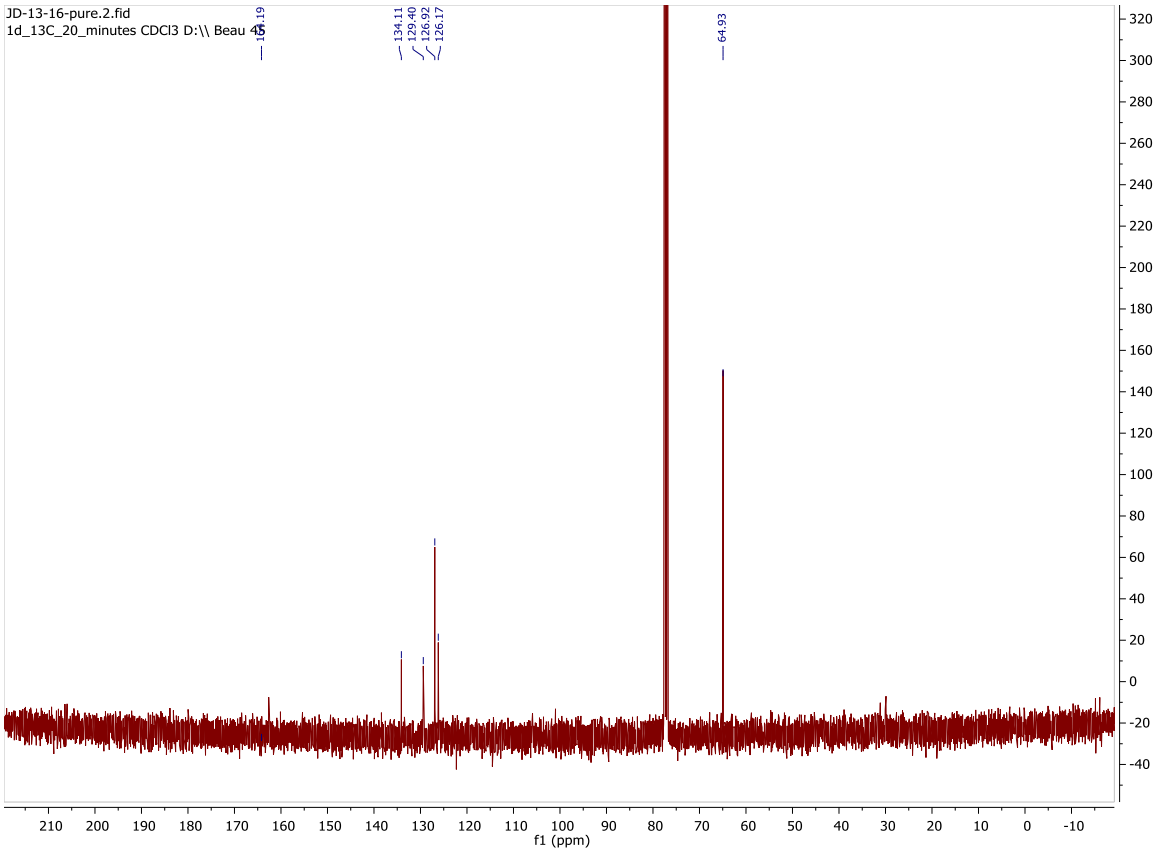

EB-1-39-pure-1.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 48
O
N
H
OMe
N
0.58
1.00
1.05
1.00
1.03
3.01
f1 (ppm)

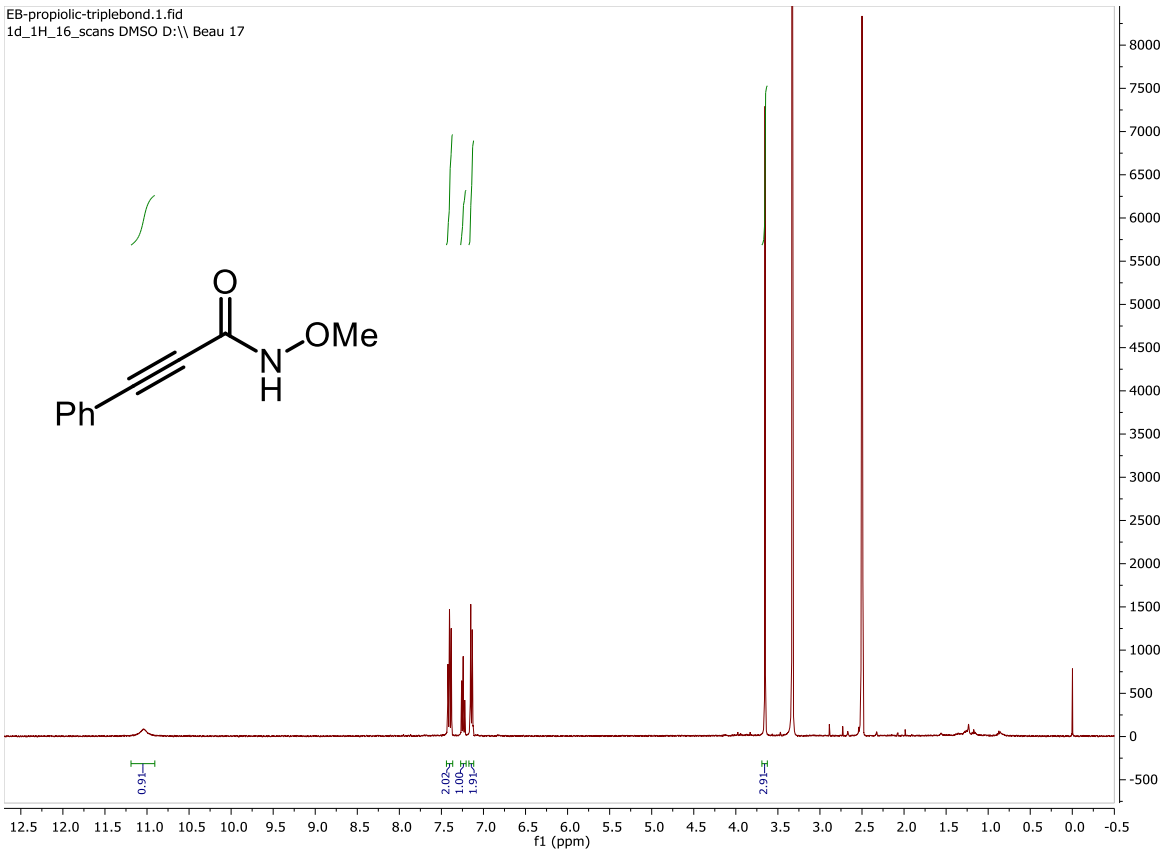

EB-1-39-pure-1.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 48
162.72
152.24
147.58
135.53
128.11
123.75
64.15
f1 (ppm)

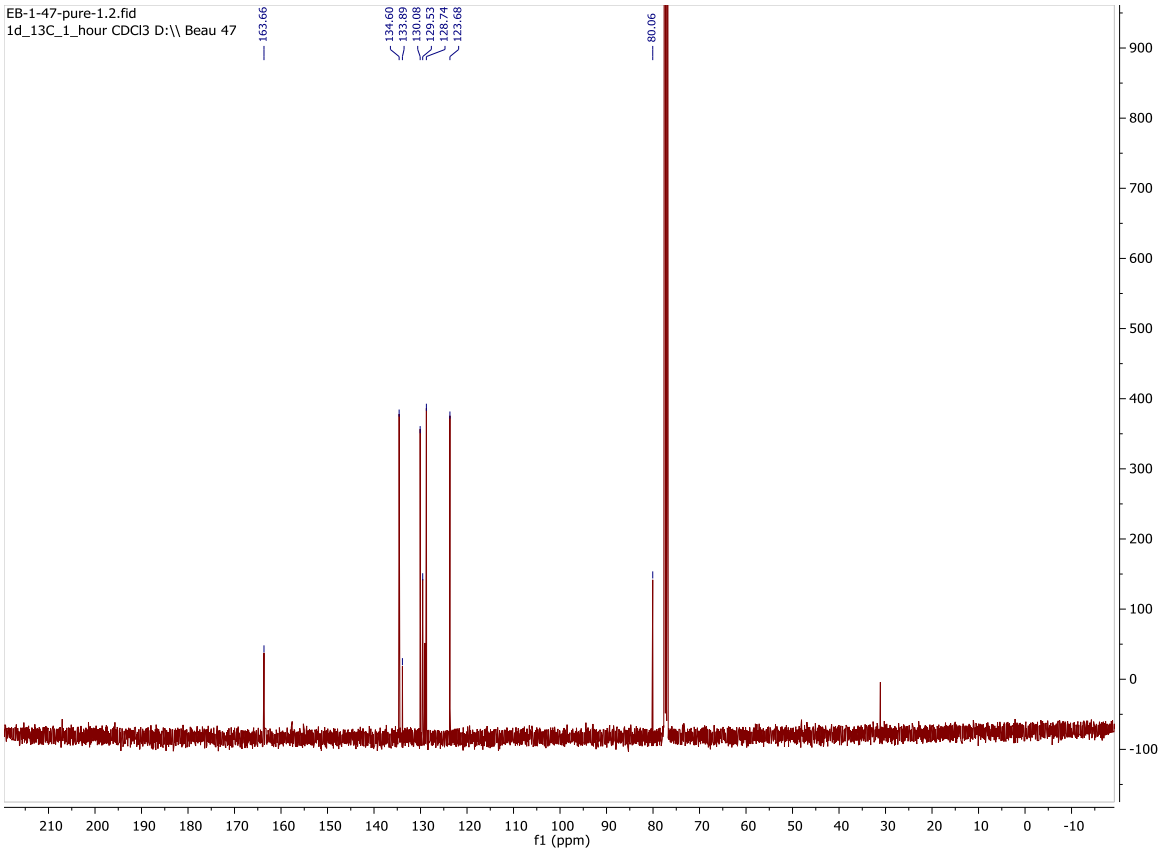

JD-13-73-3.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 45
O
N
OBn
N
H
N
0.92
0.97
0.95
0.98
2.00
2.99
2.00
f1 (ppm)

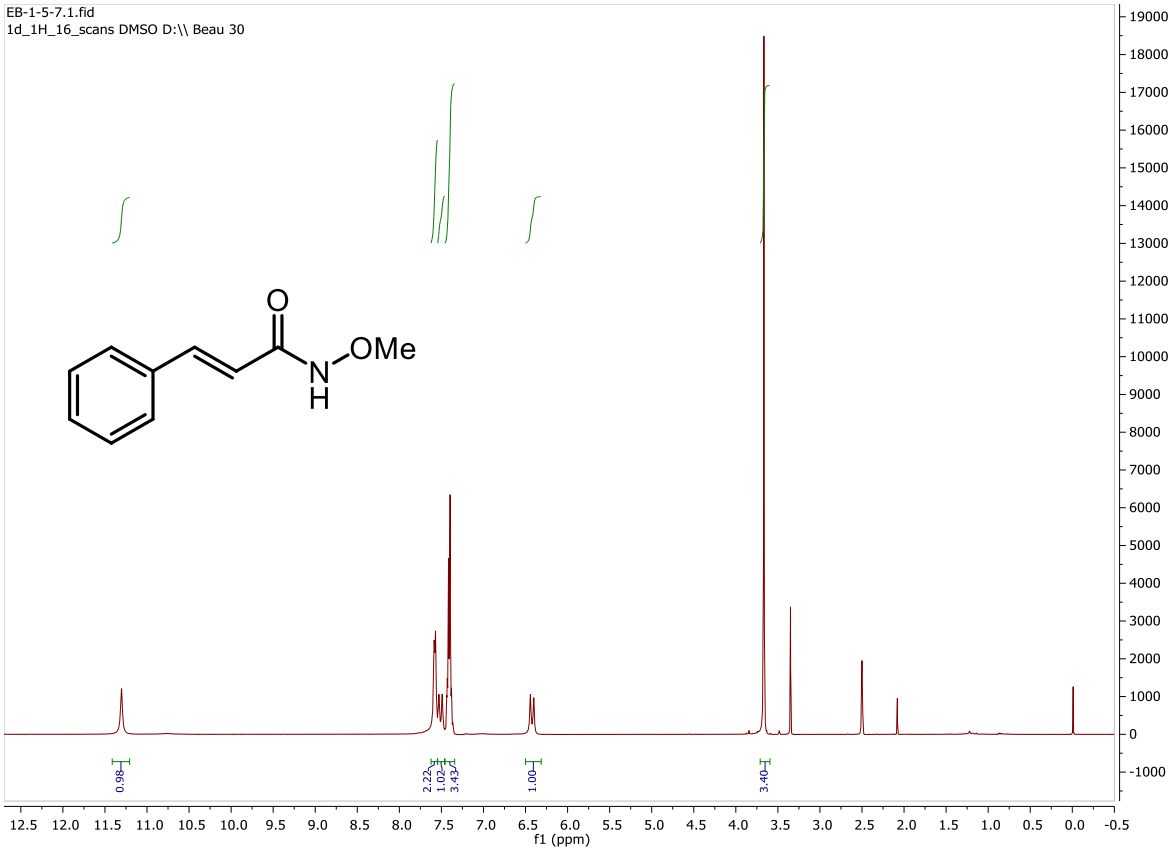

JD-13-73-3.2.fid
1d_13C_5_minutes CDCl3 D:\\ Beau 45
160.64
147.79
144.20
143.83
142.67
134.98
129.28
128.89
128.65
78.71
f1 (ppm)

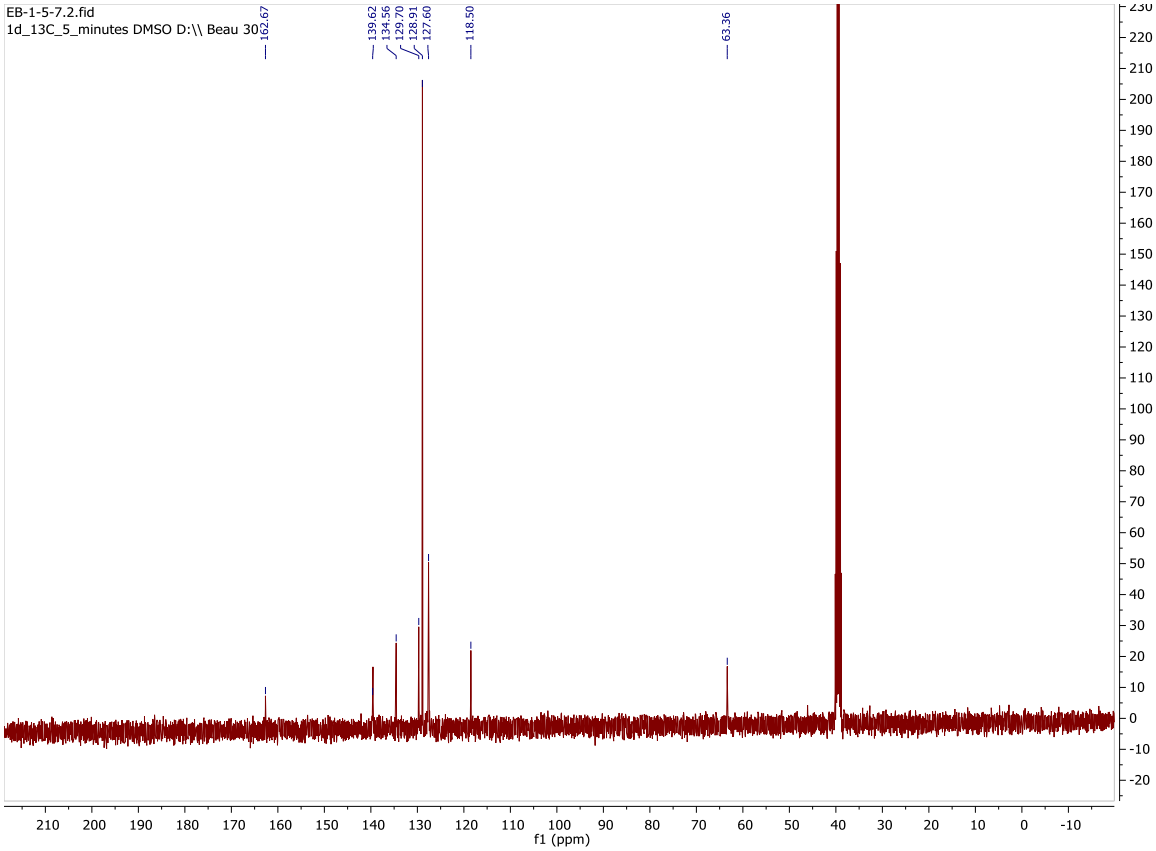

JD-13-16-pure.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 45
O
N
H
OMe
S
0.85
0.95
1.03
1.00
3.00
f1 (ppm)

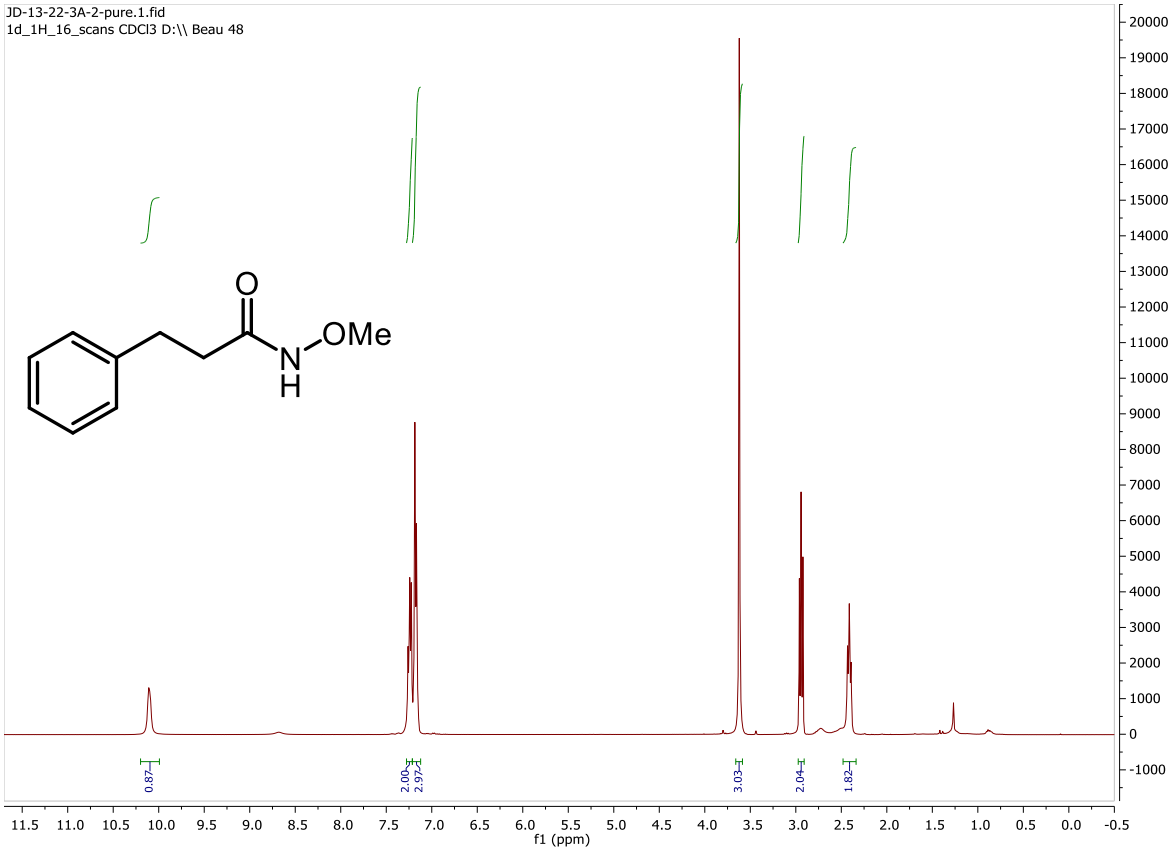

JD-13-16-pure.2.fid
1d_13C_20_minutes CDCl3 D:\\ Beau 45
134.11
129.40
126.92
126.17
64.93
f1 (ppm)

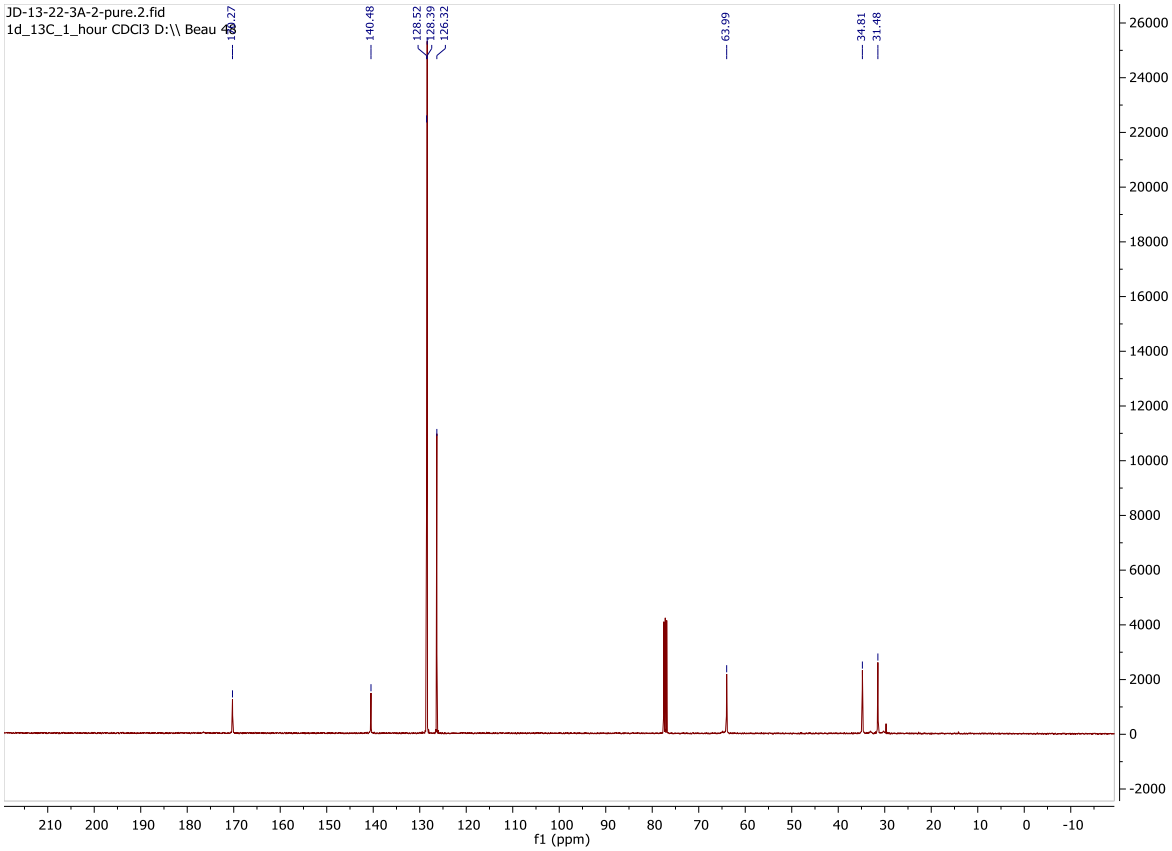

EB-propiolic-triplebond.1.fid
1d_1H_16_scans DMSO D:\\ Beau 17
O
N
H
OMe
Ph
0.91
2.02
1.00
1.91
2.91
f1 (ppm)

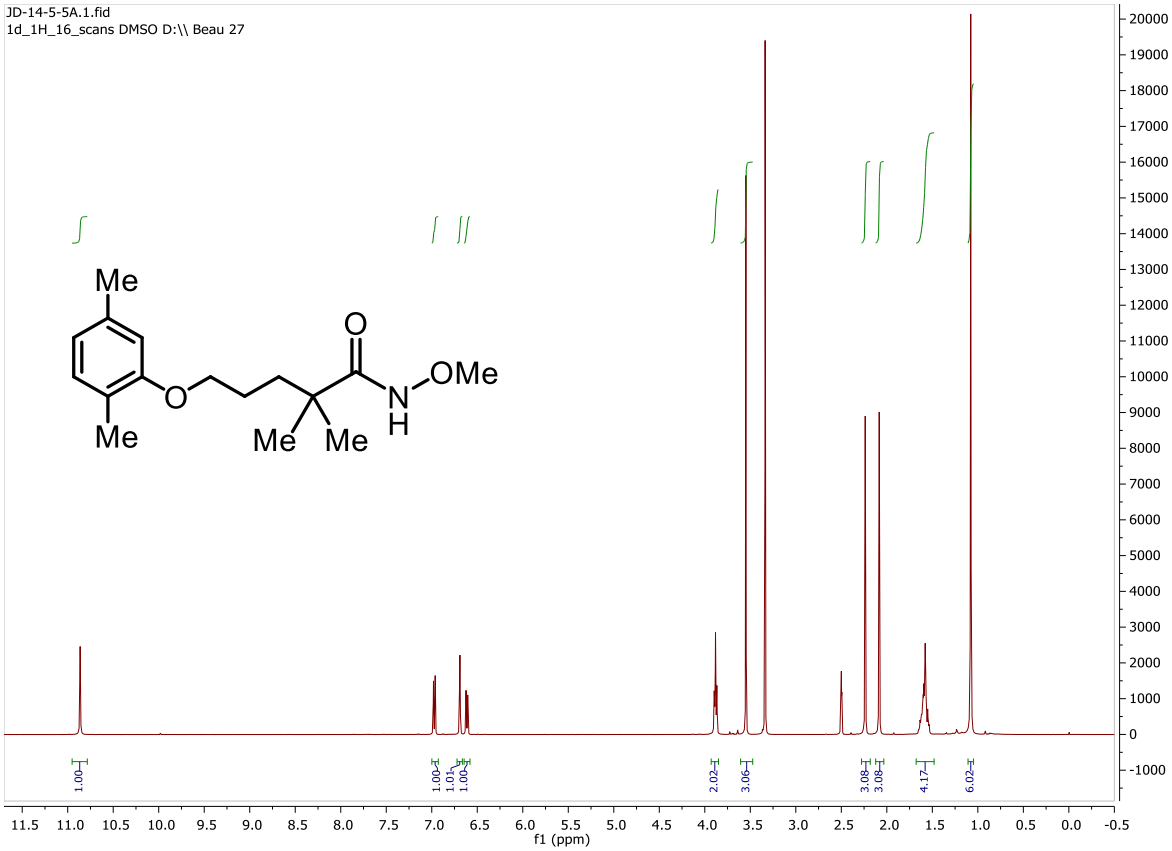

EB-1-47-pure-1.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 47
163.66
134.60
133.89
130.08
129.53
128.74
123.68
80.06
f1 (ppm)

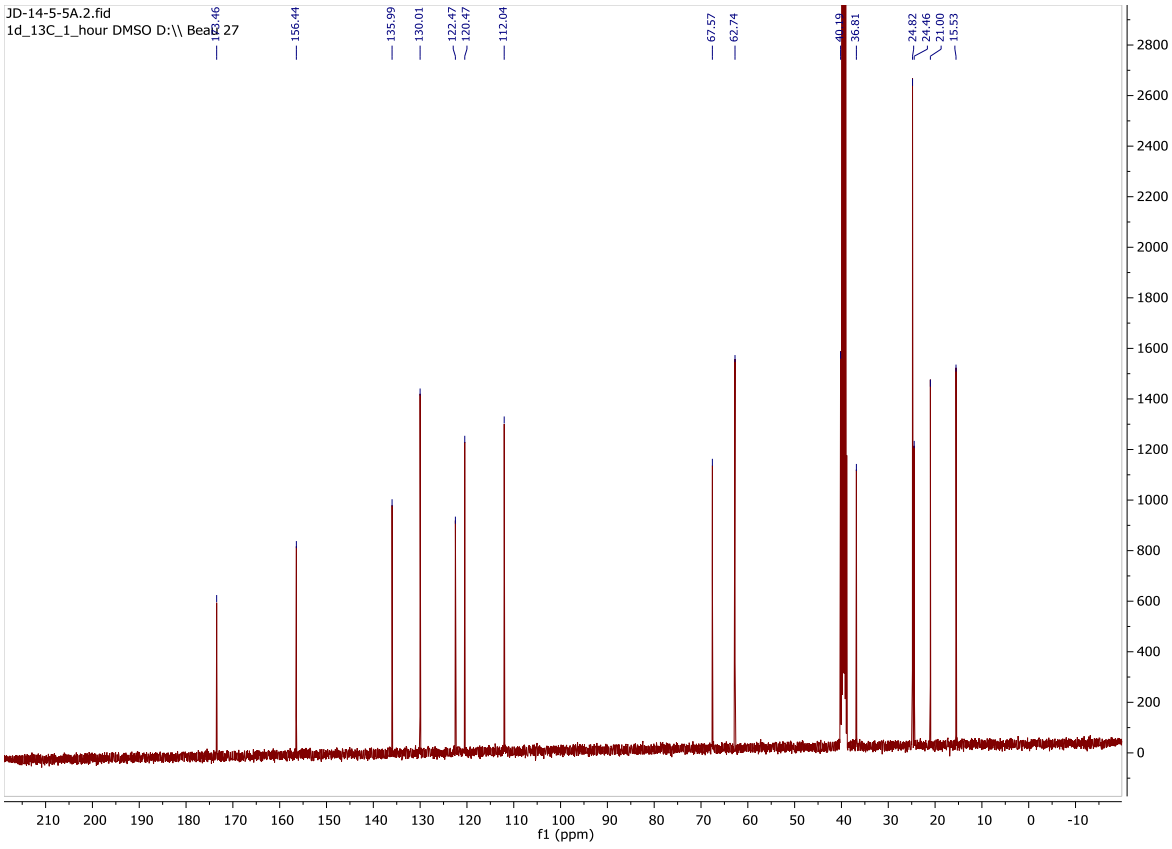

EB-1-5-7.1.fid
1d_1H_16_scans DMSO D:\\ Beau 30
O
N
H
OMe
0.98
2.22
1.02
3.43
1.00
3.40
f1 (ppm)

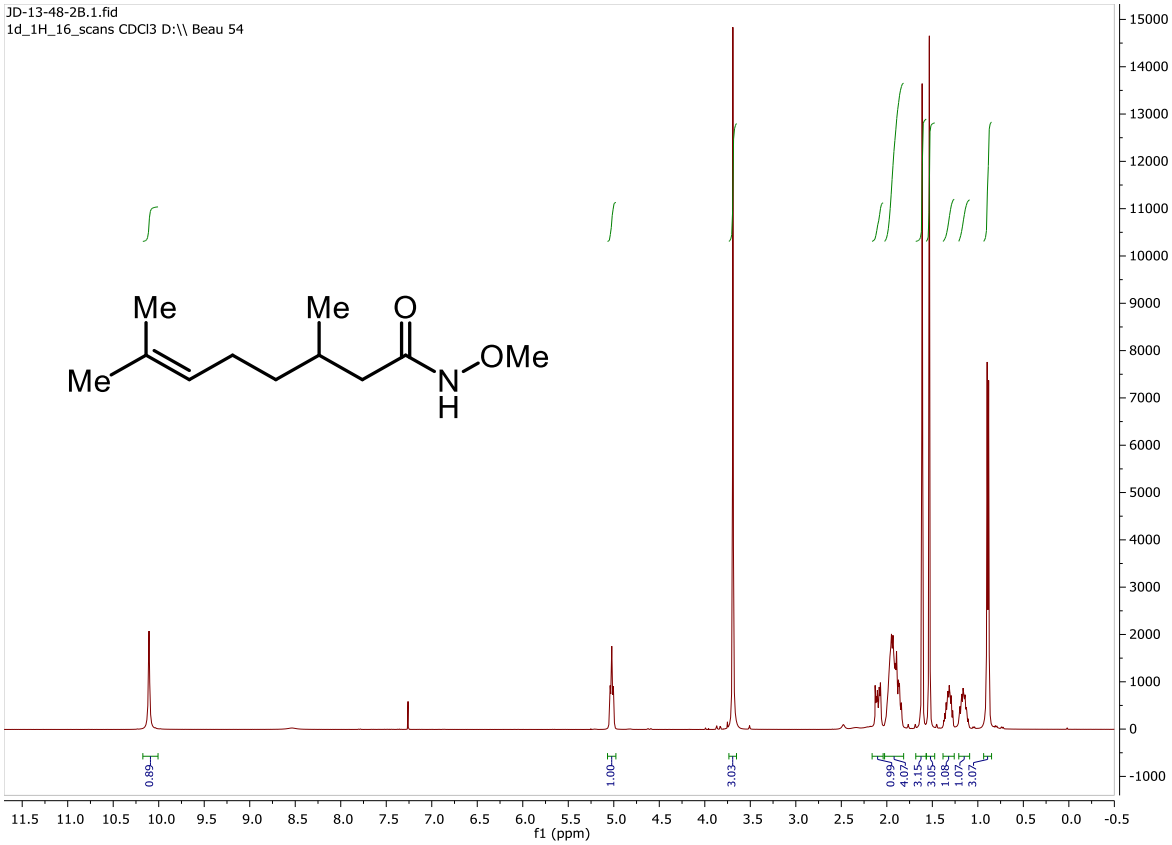

EB-1-5-7.2.fid
1d_13C_5_minutes DMSO D:\\ Beau 30
162.67
139.62
134.56
129.70
129.01
127.60
118.50
63.36
f1 (ppm)

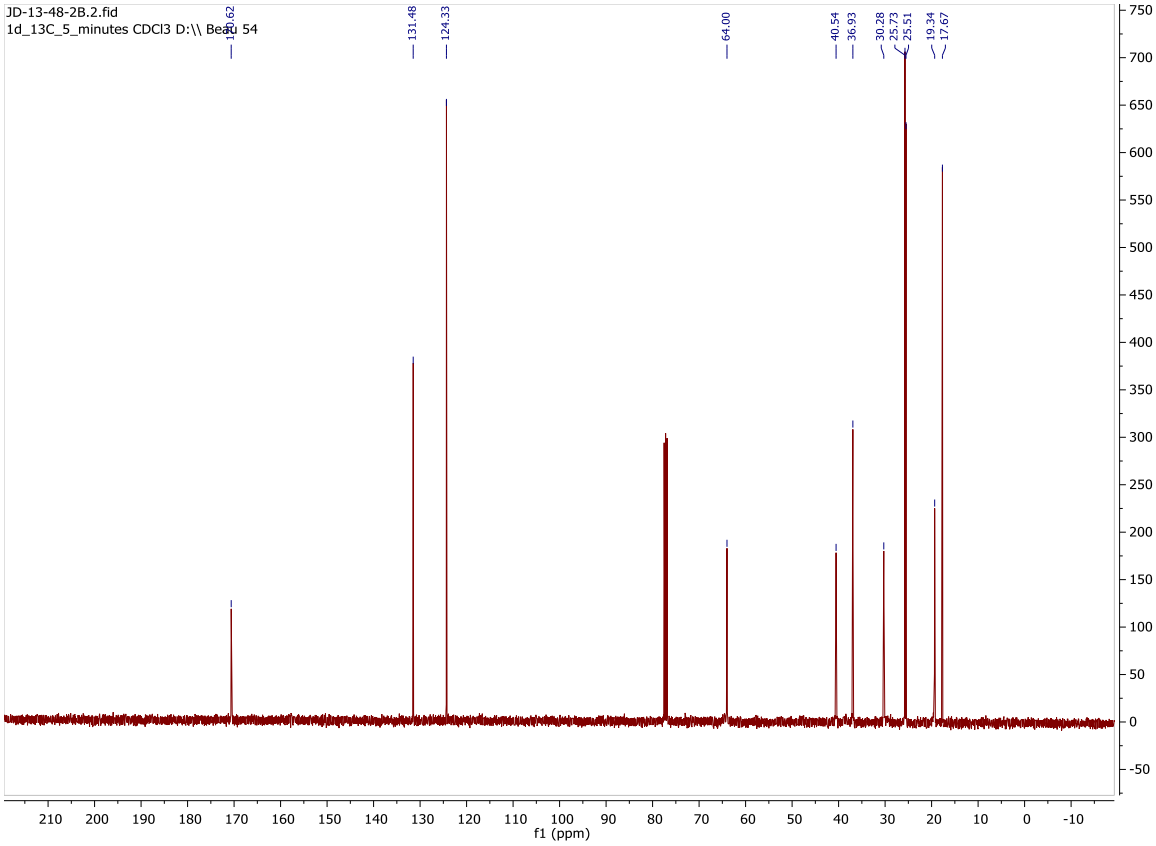

JD-13-22-3A-2-pure.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 48
O
N
H
OMe
0.87
2.00
2.97
3.03
2.04
1.82
f1 (ppm)

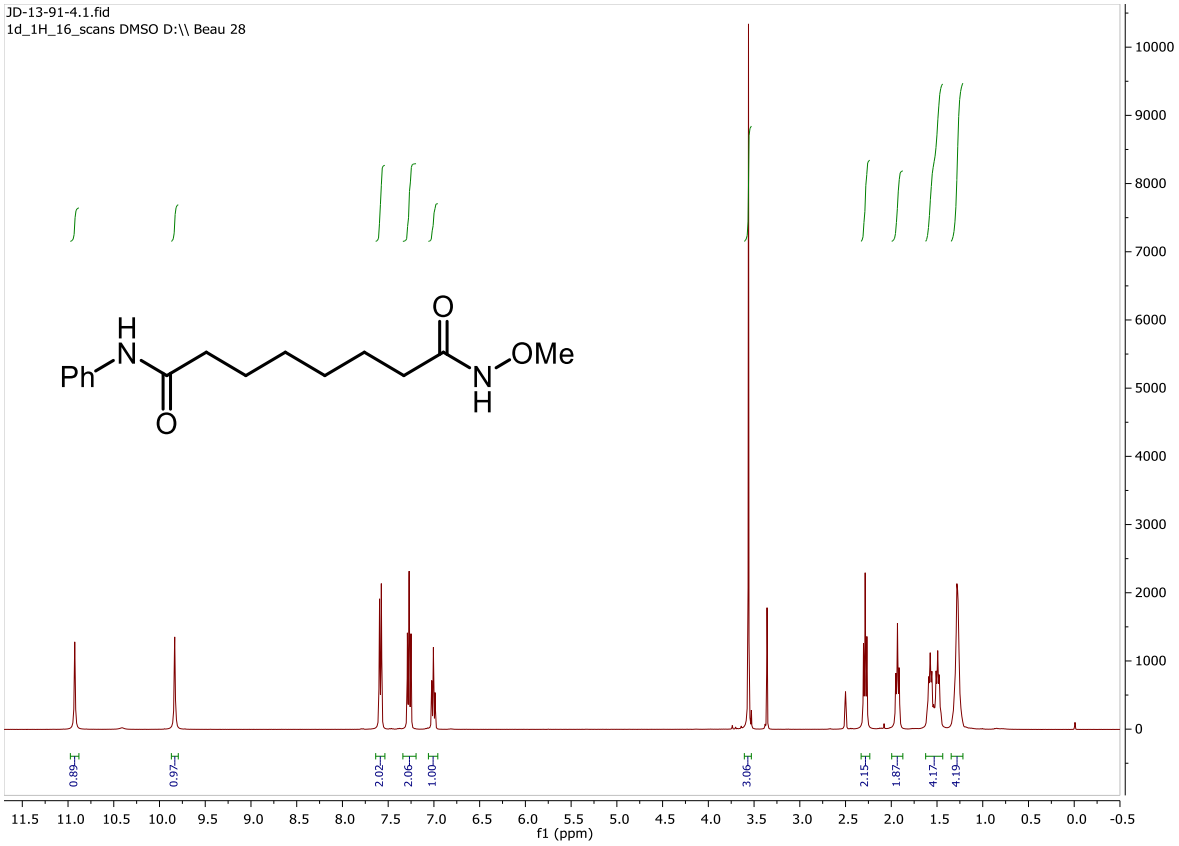

JD-13-22-3A-2-pure.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 48
169.27
140.48
128.52
128.39
126.32
63.99
34.81
31.48
f1 (ppm)

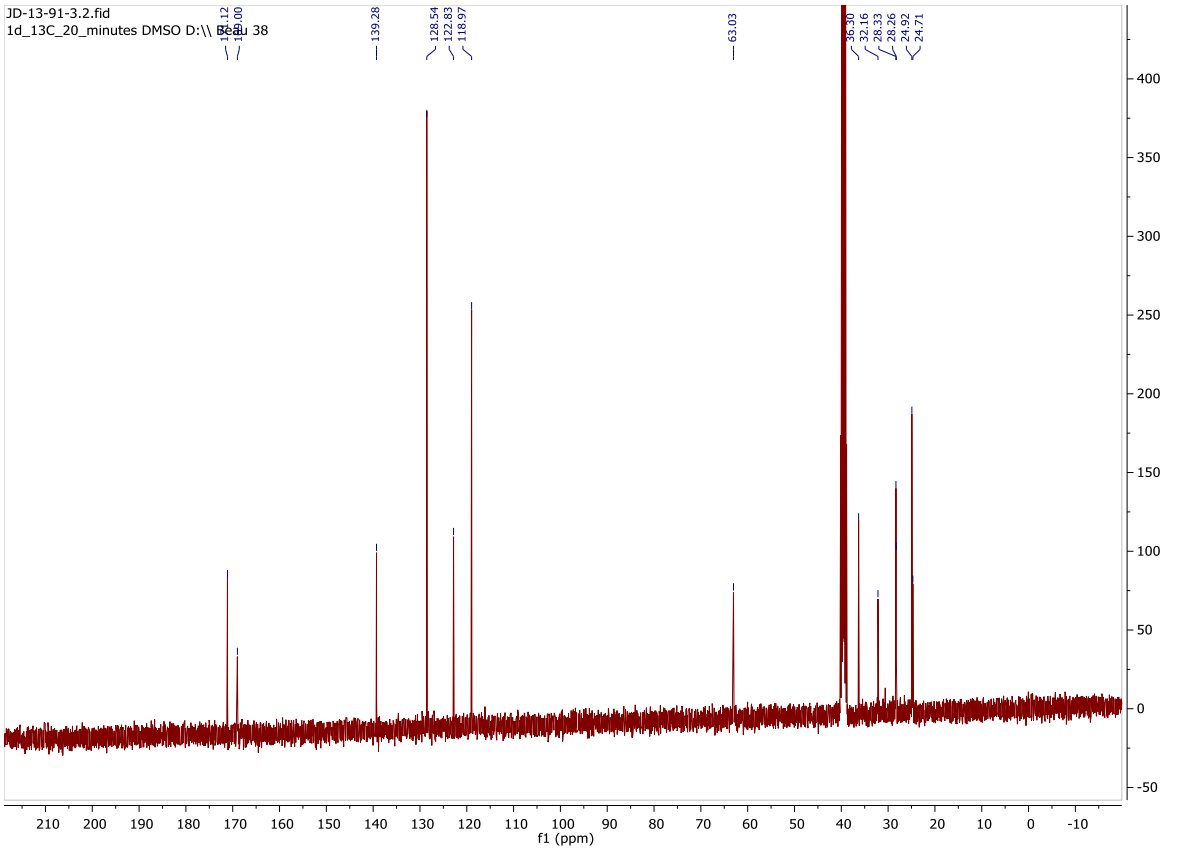

JD-14-5-5A.1.fid
1d_1H_16_scans DMSO D:\\ Beau 27
Me
O
OMe
N
H
O
Me
Me
Me
1.00
1.00
1.01
1.00
2.02
3.06
3.08
3.08
4.17
6.02
f1 (ppm)

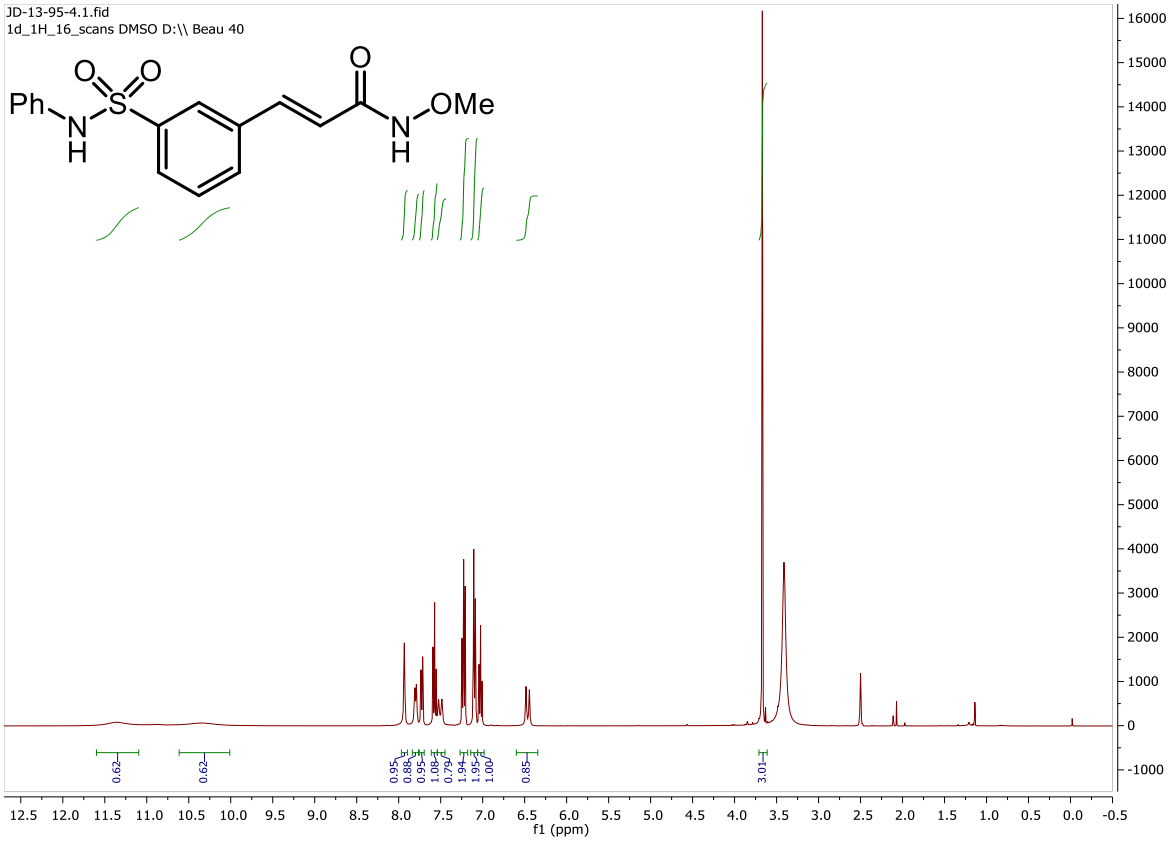

JD-14-5-5A.2.fid
1d_13C_1_hour DMSO D:\\ Beau 27
163.46
156.44
135.99
130.01
122.47
120.47
112.04
67.57
62.74
40.49
36.81
24.82
24.46
21.00
15.53
f1 (ppm)

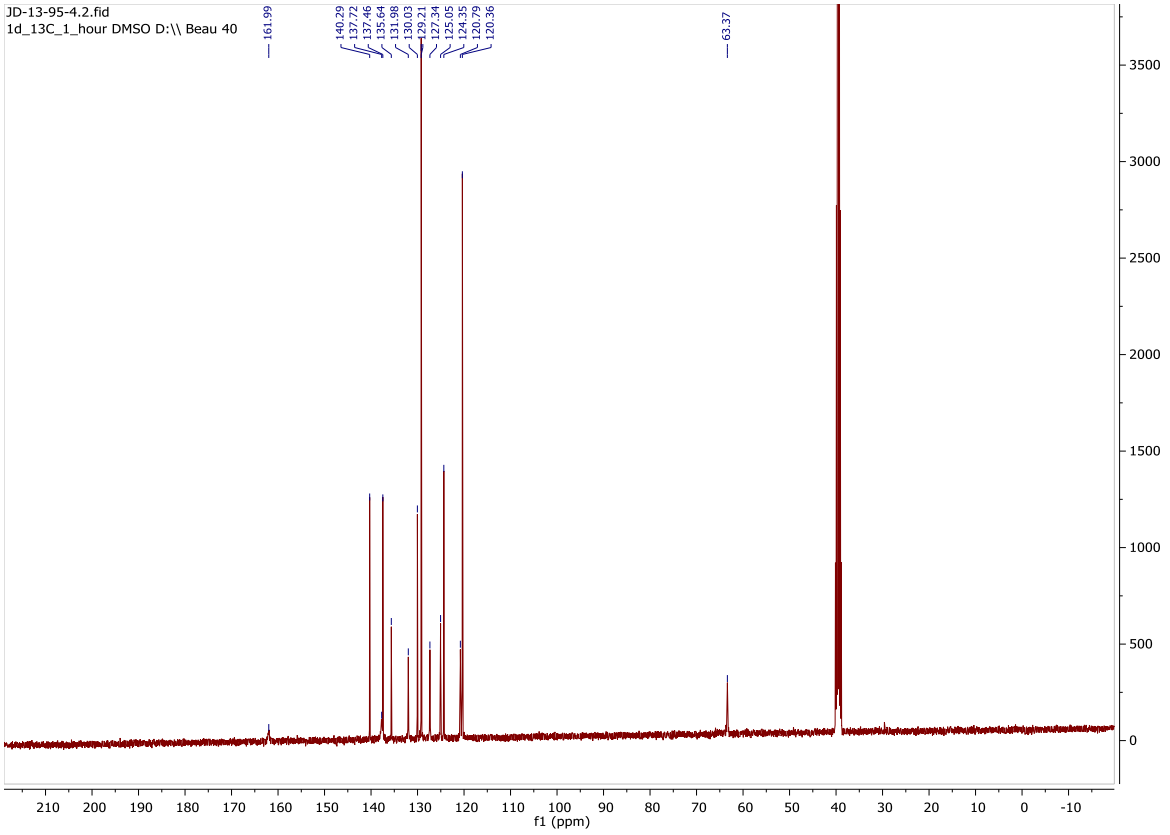

JD-13-48-2B.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 54
Me
Me
O
OMe
N
H
Me
0.89
1.00
3.03
0.99
4.07
3.15
3.05
1.08
1.07
3.07
f1 (ppm)

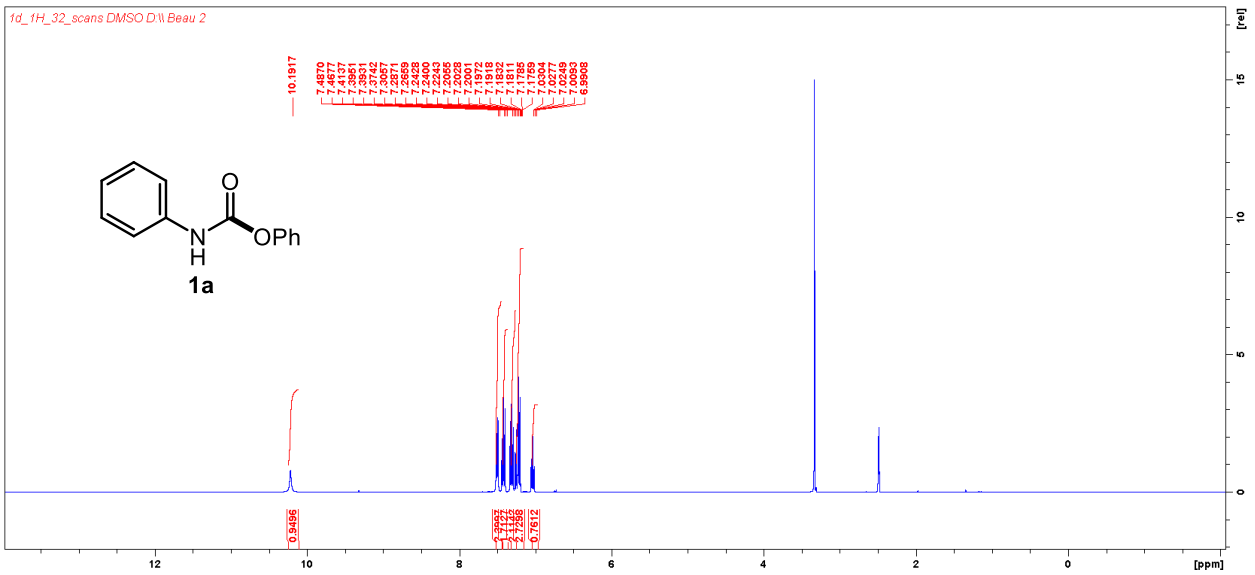

JD-13-48-2B.2.fid
1d_13C_5_minutes CDCl3 D:\\ Beau 54
169.62
131.48
124.33
64.00
40.54
36.93
30.28
25.73
25.51
19.34
17.67
f1 (ppm)

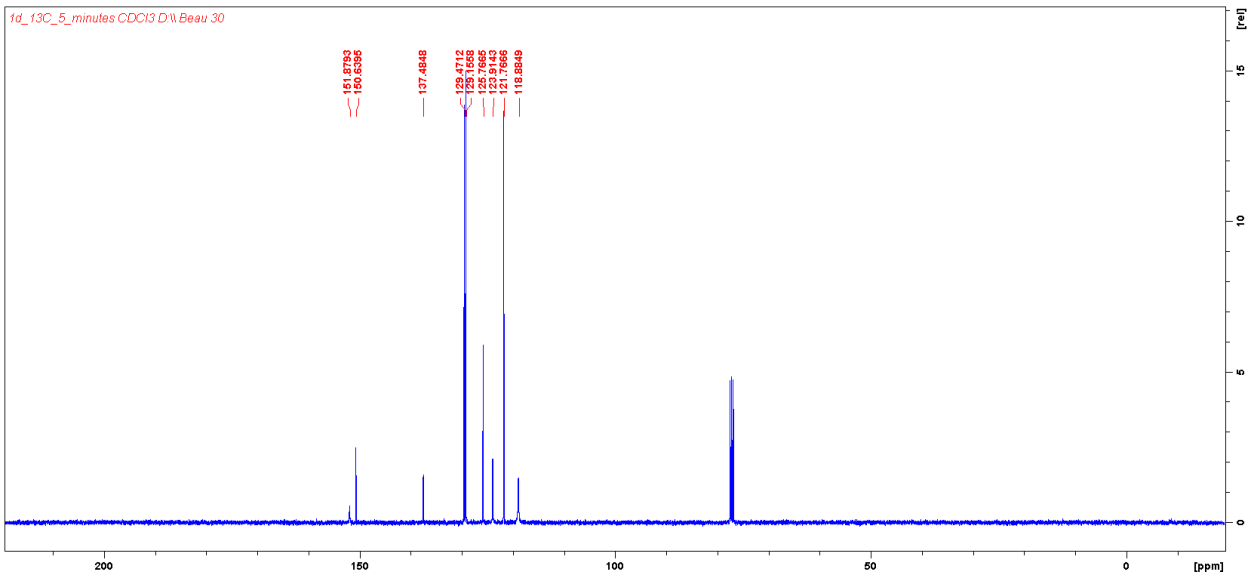

JD-13-91-4.1.fid
1d_1H_16_scans DMSO D:\\ Beau 28
f1 (ppm)

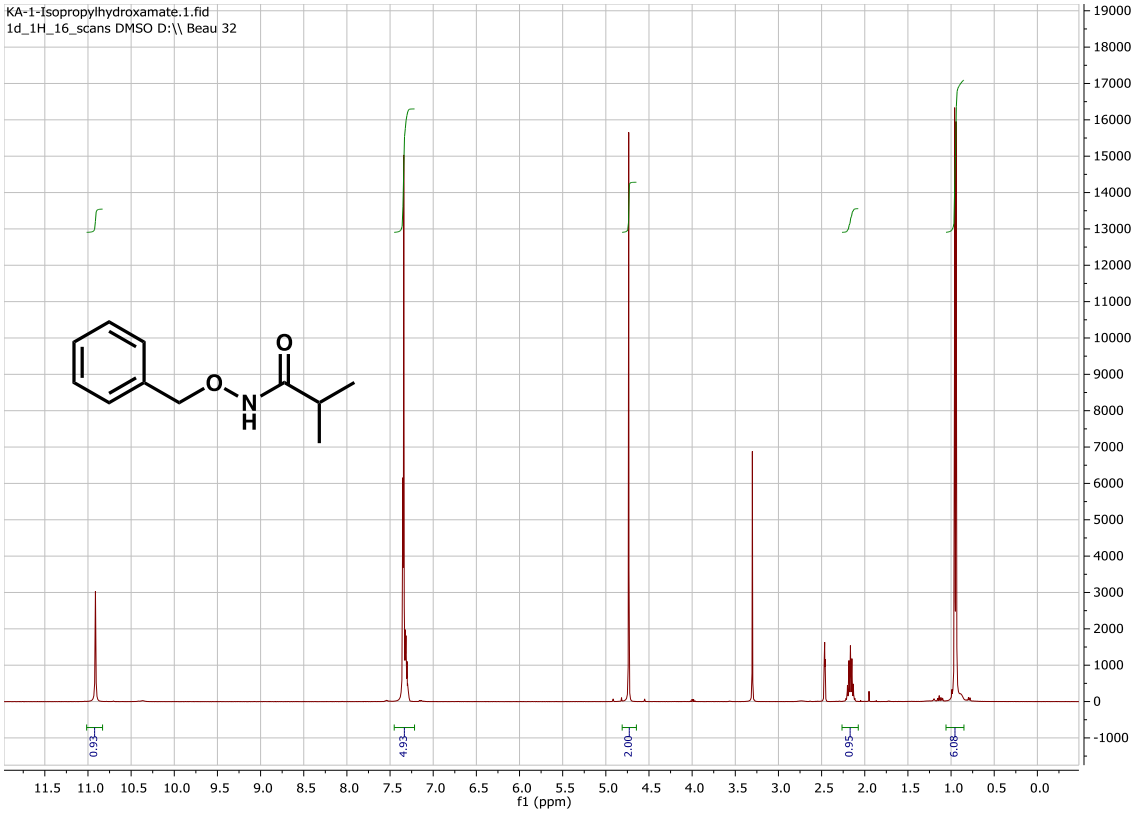

JD-13-91-3.2.fid
1d_13C_20_minutes DMSO D:\\ Beau 38
f1 (ppm)

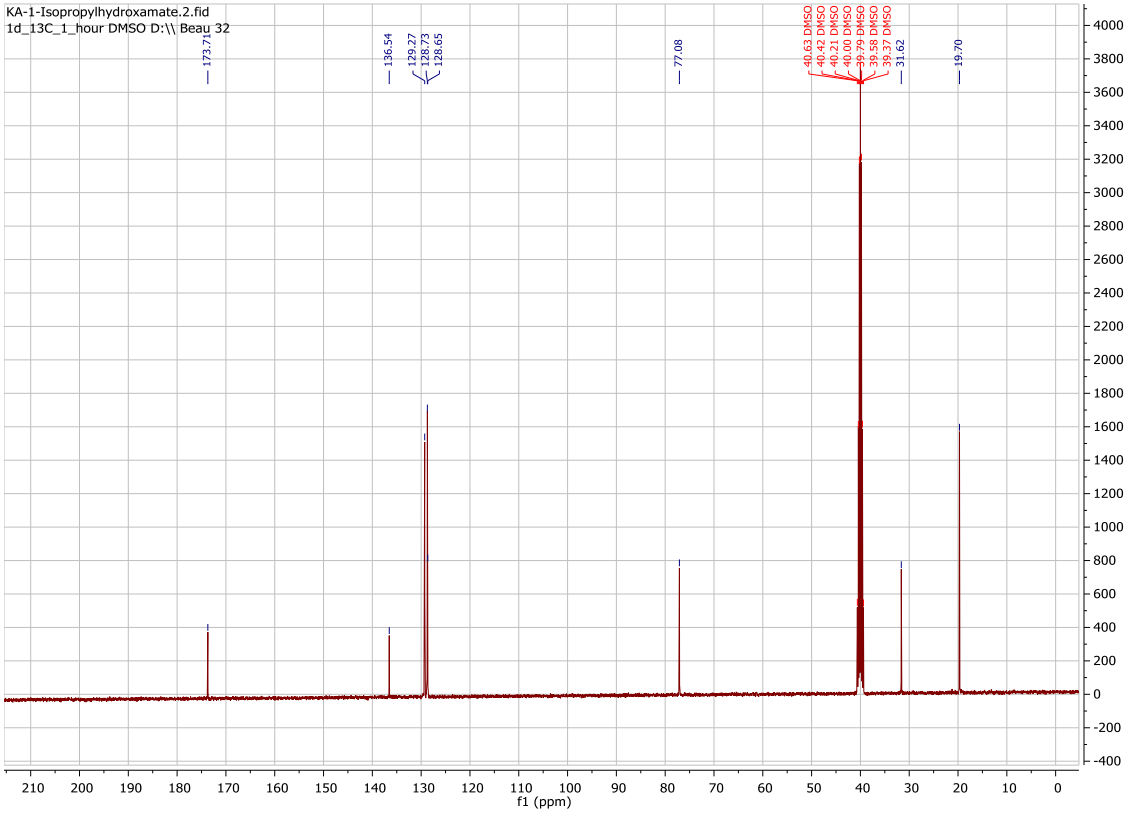

JD-13-95-4.1.fid
1d_1H_16_scans DMSO D:\\ Beau 40
Ph
N
H
S
O
O
O
N
H
OMe
0.62
0.62
0.95
0.88
0.95
1.08
0.79
1.94
1.95
1.00
0.85
3.01
f1 (ppm)

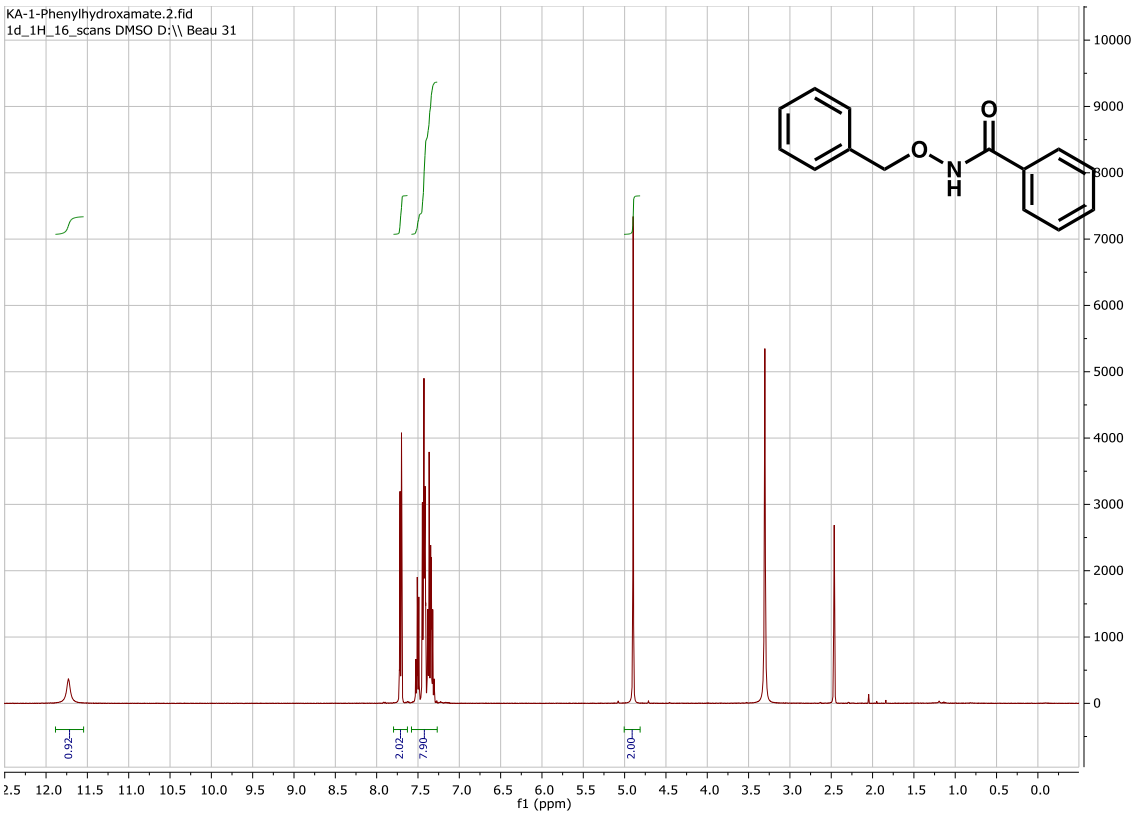

JD-13-95-4.2.fid
1d_13C_1_hour DMSO D:\\ Beau 40
161.99
140.29
137.72
137.46
135.64
131.98
130.03
129.21
127.34
125.05
124.35
120.79
120.36
63.37
f1 (ppm)

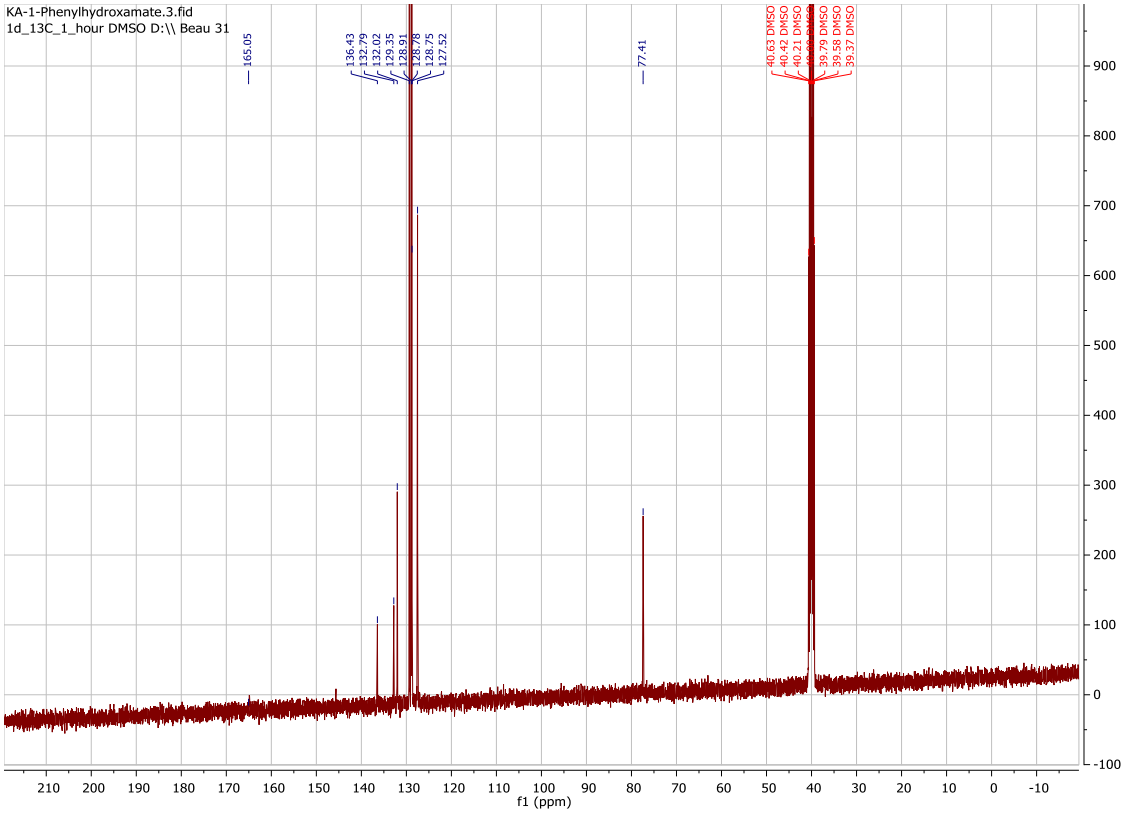

1d_1H_32_scans DMSO D:\\ Beau 2
10.1917
7.4870
7.4677
7.4157
7.3951
7.3931
7.3742
7.3557
7.2871
7.2689
7.2428
7.2240
7.2243
7.2055
7.2028
7.2001
7.1972
7.1918
7.1832
7.1811
7.1785
7.1759
7.0304
7.0277
7.0249
7.0093
6.9908
O
N
H
OPh
1a
0.9496
2.7122
2.7117
2.7296
0.7612
[rel]
[ppm]

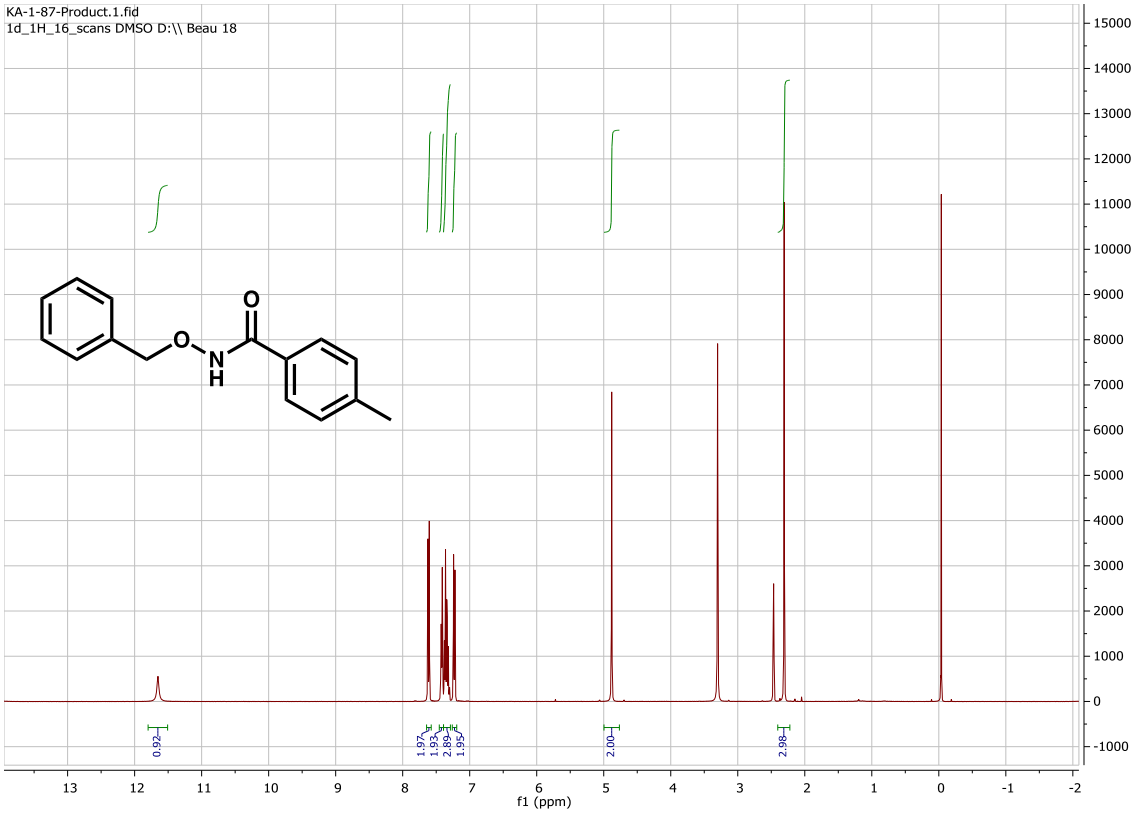

1d_13C_5_minutes CDCl3 D:\\ Beau 30
151.8793
150.6395
137.4848
129.4712
129.1668
129.1565
123.9143
121.7666
118.8849
[rel]
[ppm]

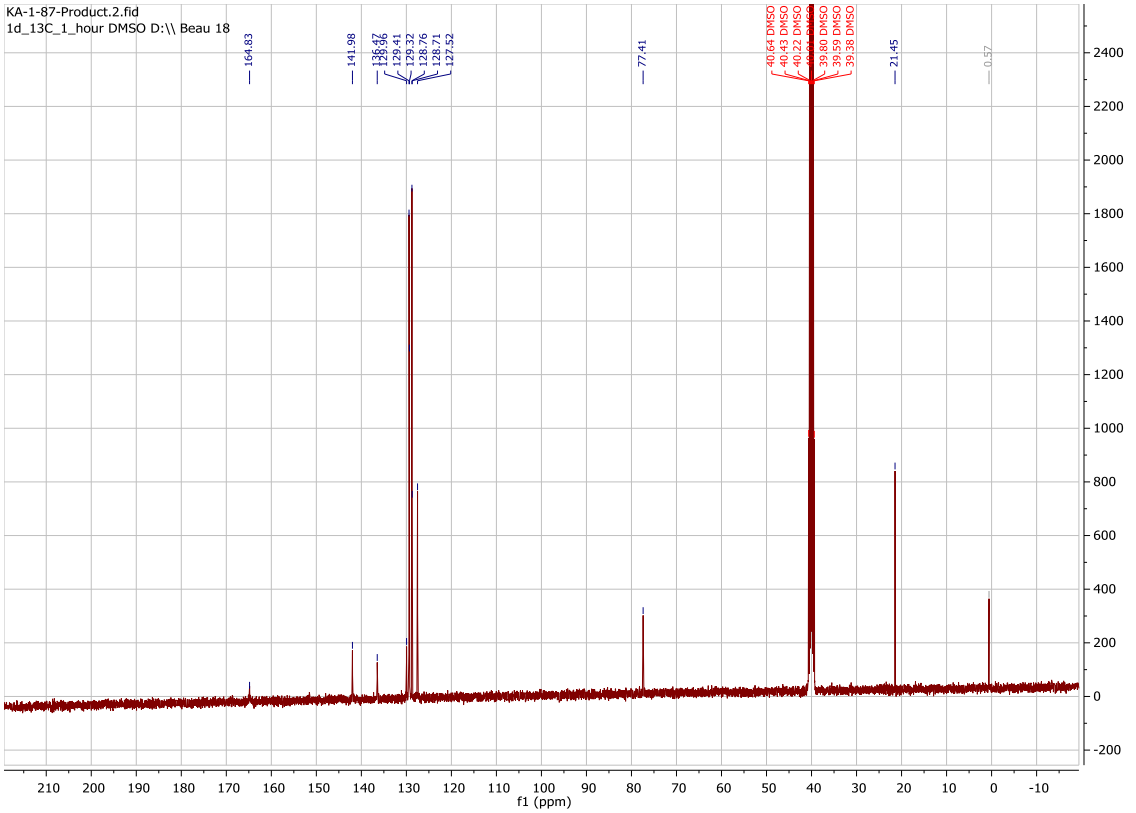

KA-1-Isopropylhydroxamate.1.fid
1d_1H_16_scans DMSO D:\\ Beau 32
O
O
N
H
0.93
4.93
2.00
0.95
6.08
f1 (ppm)

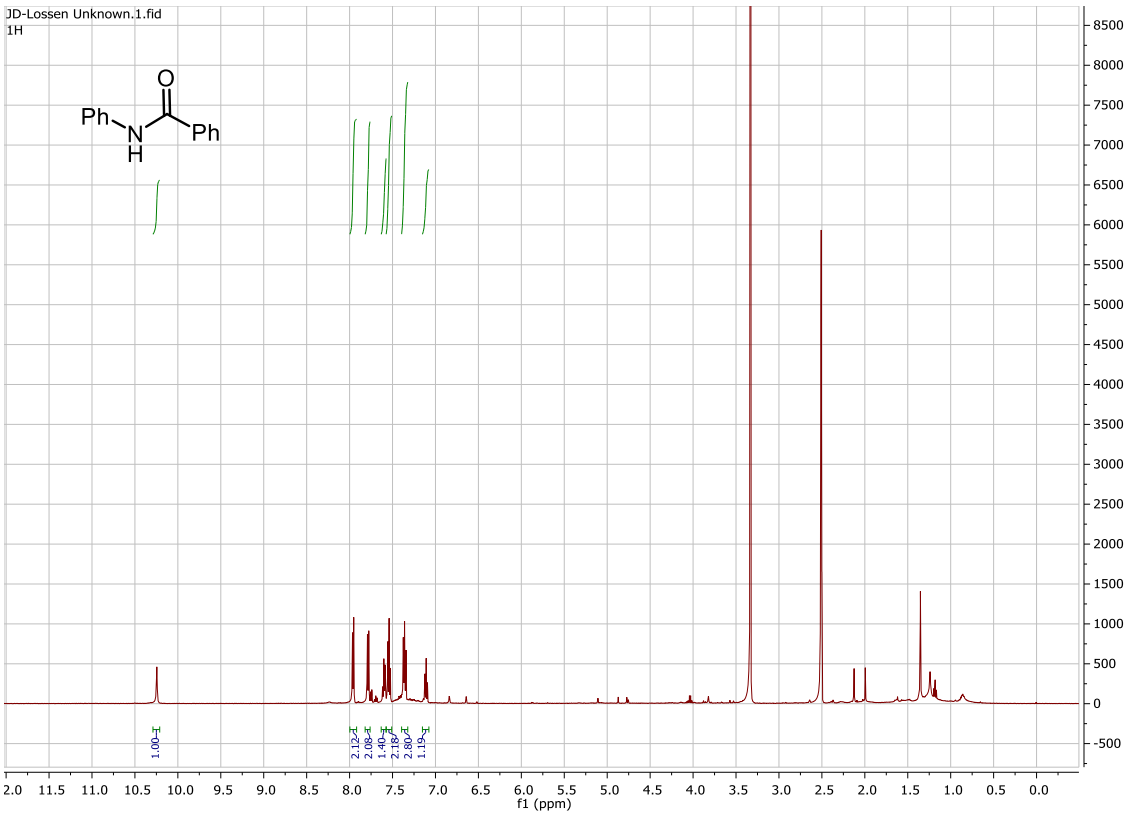

KA-1-Isopropylhydroxamate.2.fid
1d_13C_1_hour DMSO D:\\ Beau 32
173.71
136.54
129.27
128.73
128.65
77.08
40.63 DMSO
40.42 DMSO
40.21 DMSO
40.00 DMSO
39.79 DMSO
39.58 DMSO
39.37 DMSO
31.62
19.70
f1 (ppm)

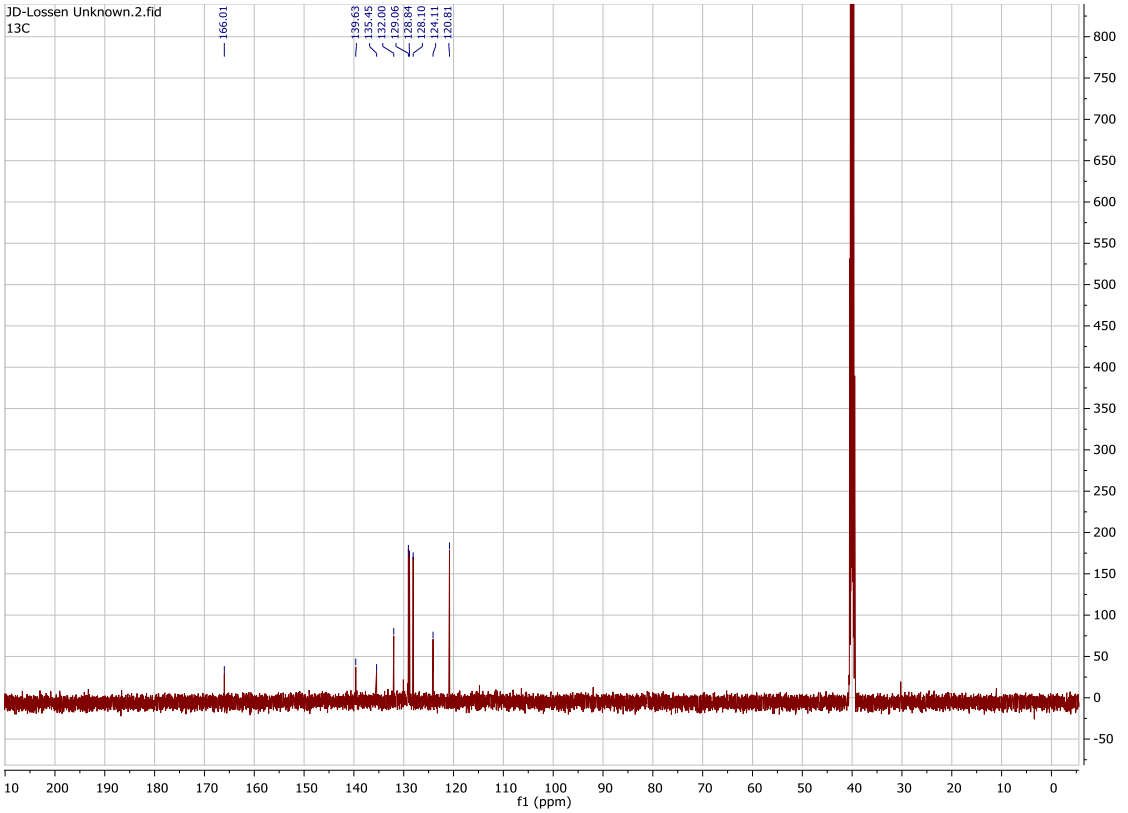

KA-1-Phenylhydroxamate.2.fid
1d_1H_16_scans DMSO D:\\ Beau 31
O
O
N
H
0.92
2.02
7.90
2.00
f1 (ppm)

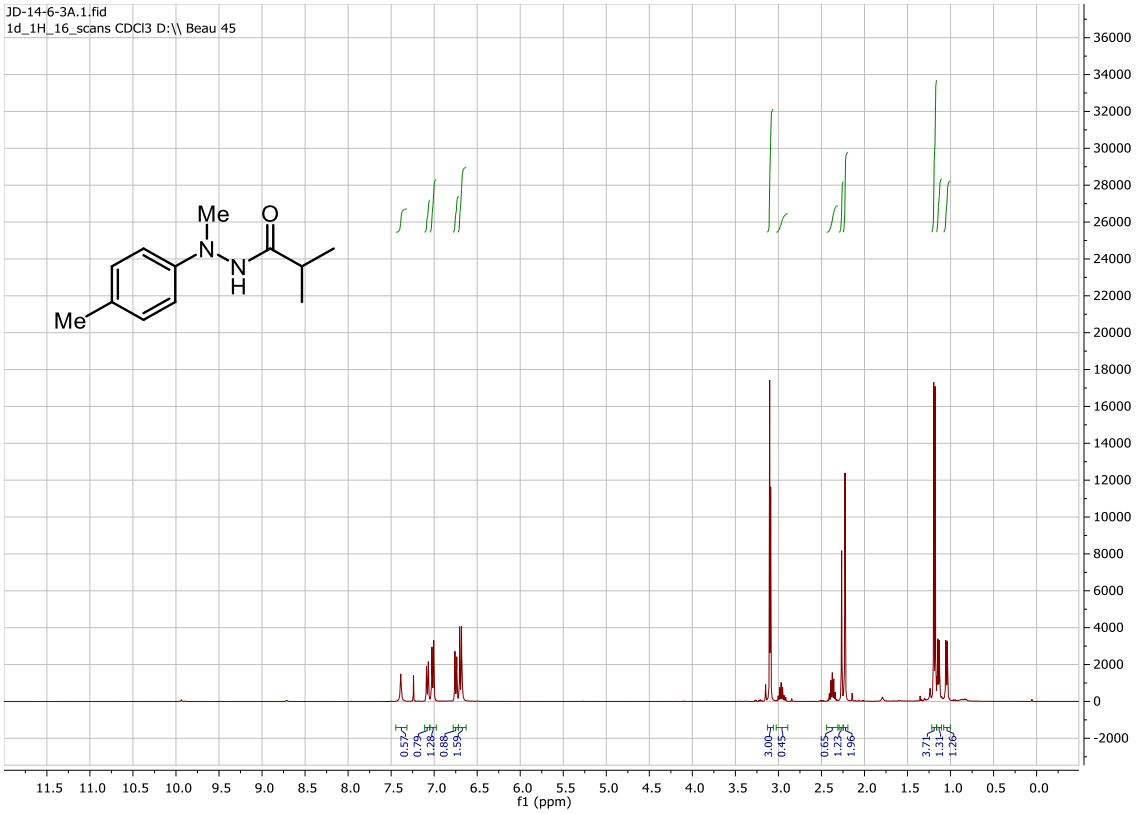

KA-1-Phenylhydroxamate.3.fid
1d_13C_1_hour DMSO D:\\ Beau 31
165.05
136.43
132.79
132.02
129.35
128.91
128.78
128.75
127.52
77.41
40.63 DMSO
40.42 DMSO
40.21 DMSO
39.79 DMSO
39.58 DMSO
39.37 DMSO
f1 (ppm)

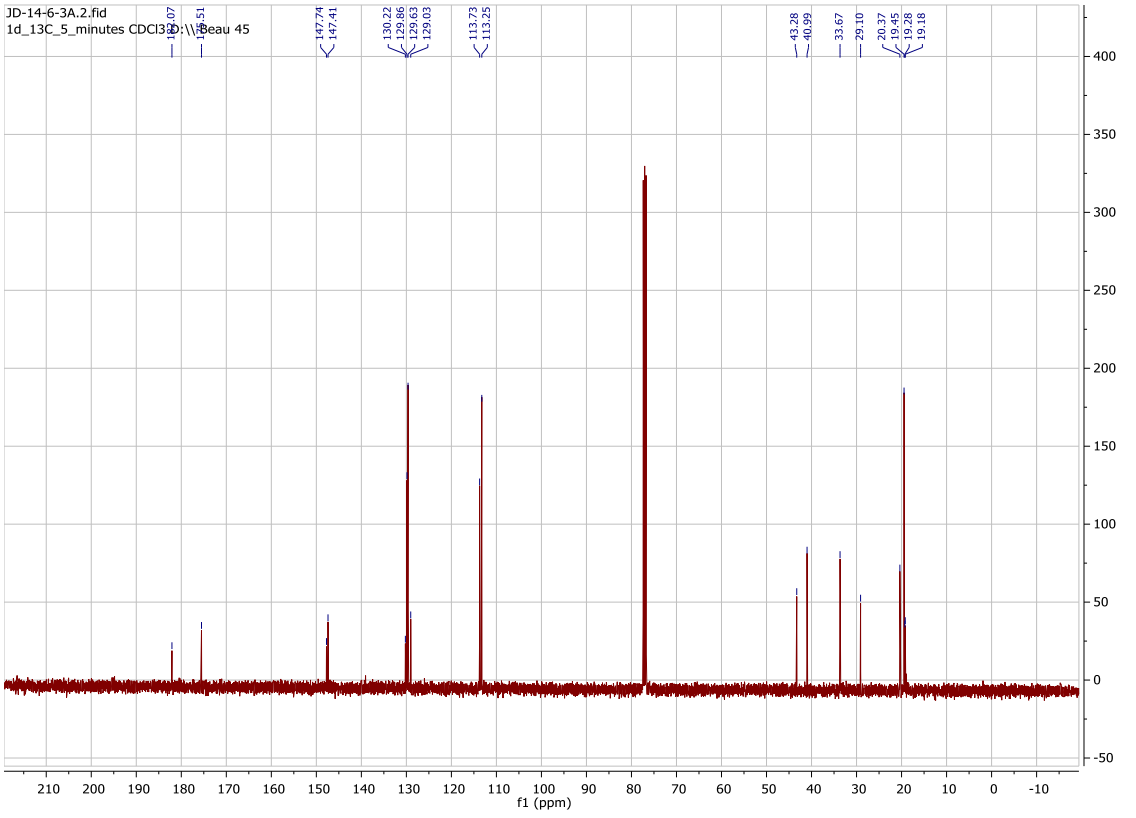

KA-1-87-Product.1.fid
1d_1H_16_scans DMSO D:\\ Beau 18
O
O
N
H
0.92
1.97
1.93
2.89
1.95
2.00
2.98
f1 (ppm)

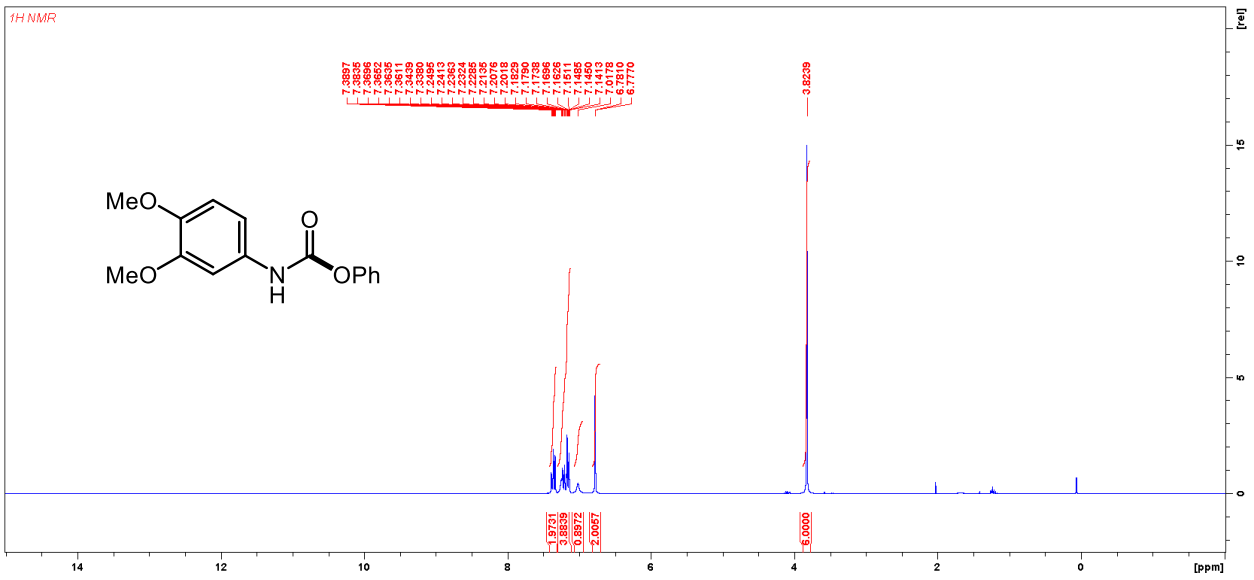

KA-1-87-Product.2.fid
1d_13C_1_hour DMSO D:\\ Beau 18
164.83
141.98
138.47
138.36
129.41
129.32
128.76
128.71
127.52
77.41
40.64 DMSO
40.43 DMSO
40.22 DMSO
39.80 DMSO
39.59 DMSO
39.38 DMSO
21.45
0.57
f1 (ppm)

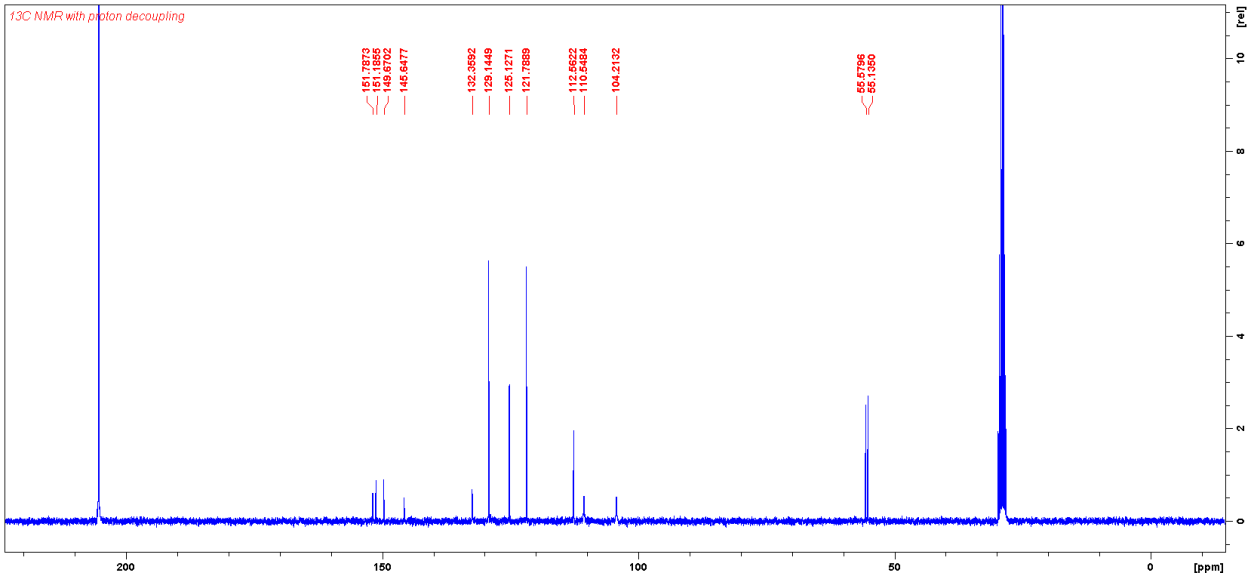

JD-Lossen Unknown.1.fid
1H
Ph
N
H
O
Ph
1.00
2.12
2.08
1.40
2.18
2.80
1.19
f1 (ppm)

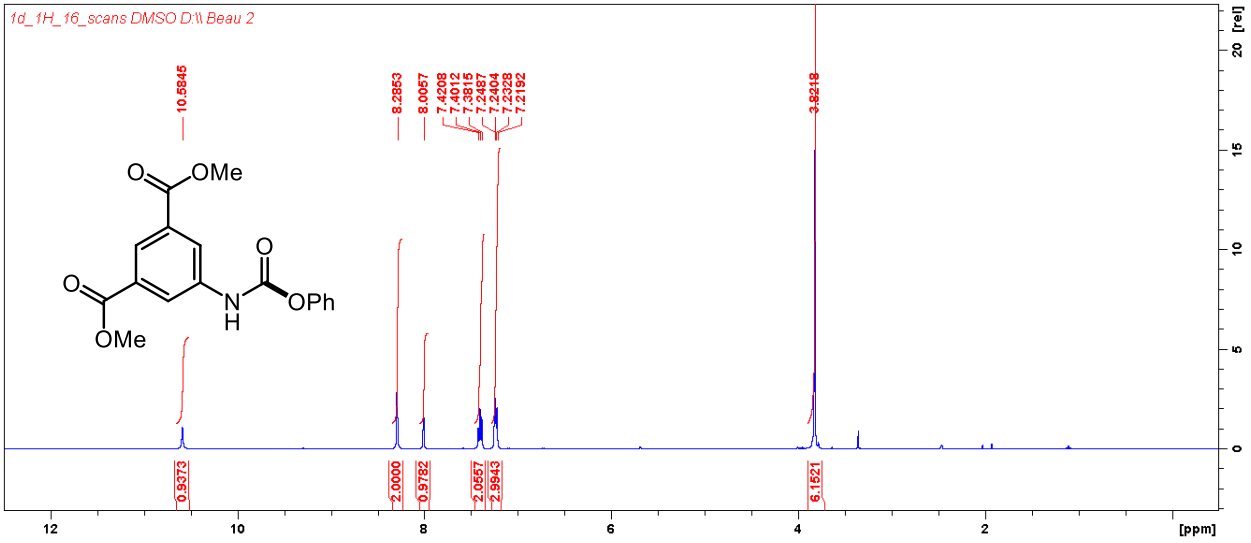

JD-Lossen Unknown.2.fid
13C
166.01
139.63
135.45
132.00
129.06
128.84
128.10
124.11
120.81
f1 (ppm)

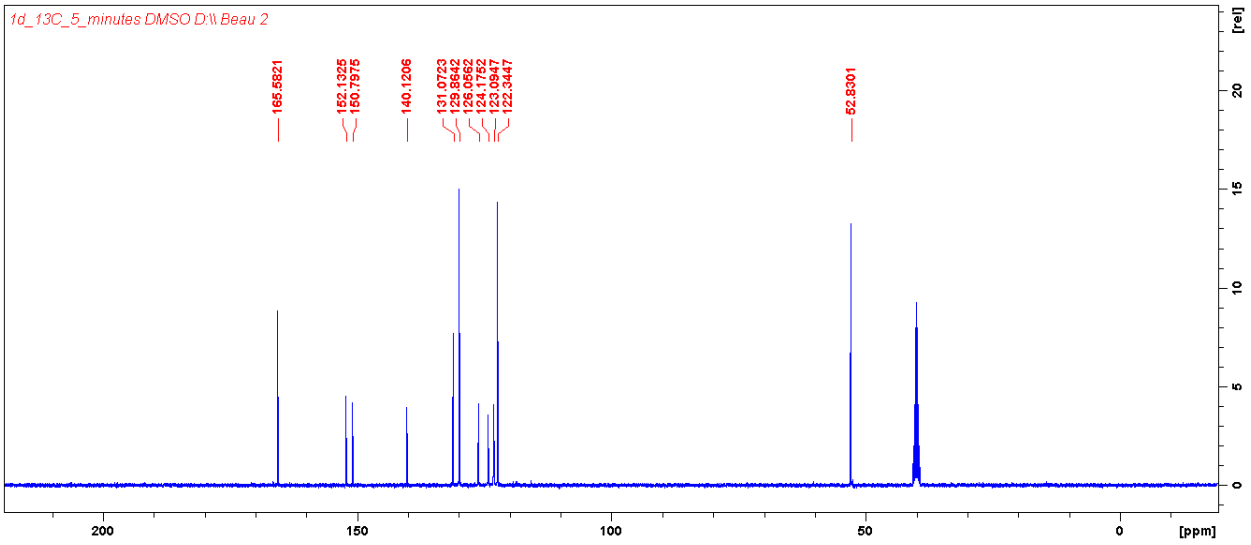

JD-14-6-3A.1.fid
1d_1H_16_scans CDCl3 D:\\ Beau 45
Me
O
N
N
H
Me
0.57
0.79
1.28
0.88
1.59
3.00
0.45
0.65
1.23
1.96
3.71
1.31
1.26
f1 (ppm)

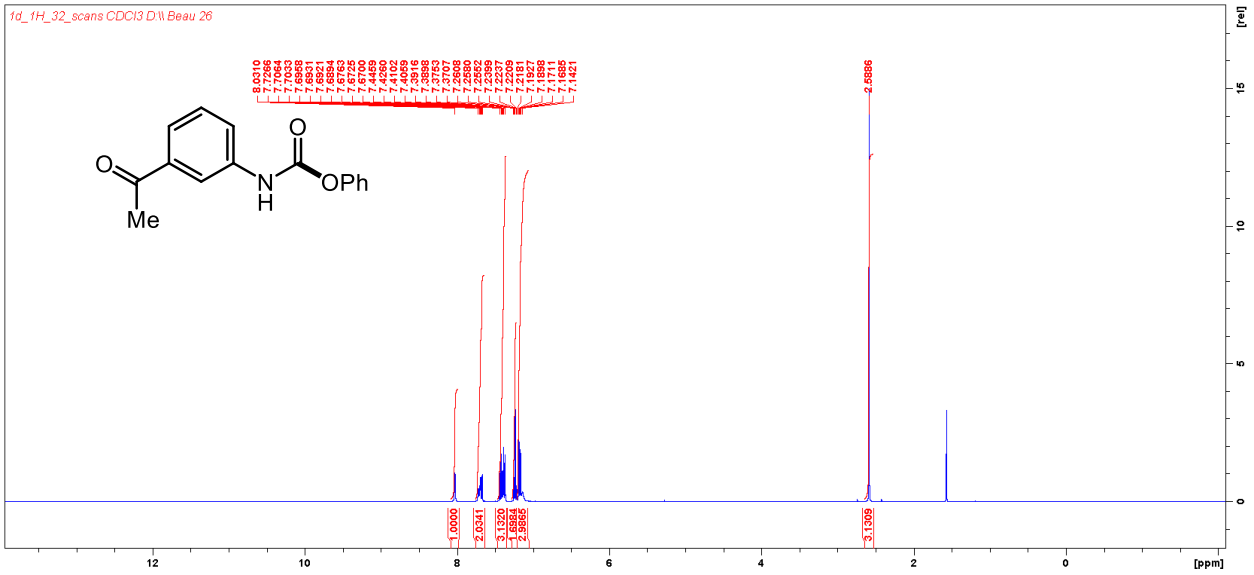

JD-14-6-3A.2.fid
1d_13C_5_minutes CDCl3 D:\\ Beau 45
182.07
176.51
147.74
147.41
130.22
129.86
129.63
129.03
113.73
113.25
43.28
40.99
33.67
29.10
20.37
19.45
19.28
19.18
f1 (ppm)

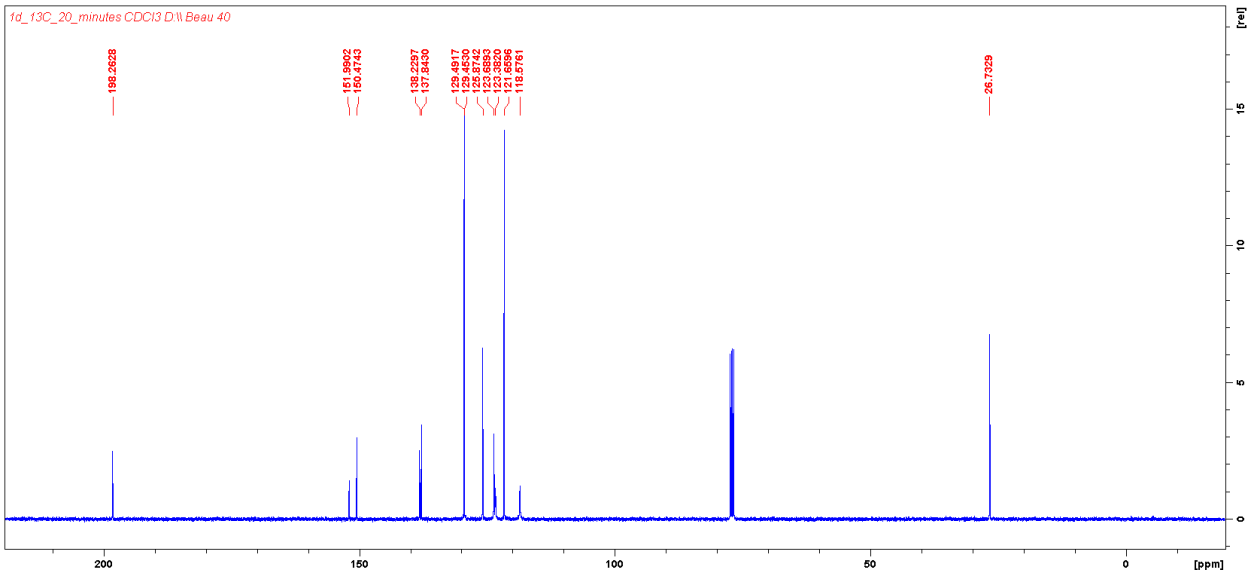

1H NMR
MeO
MeO
N
H
O
OPh
[ppm]

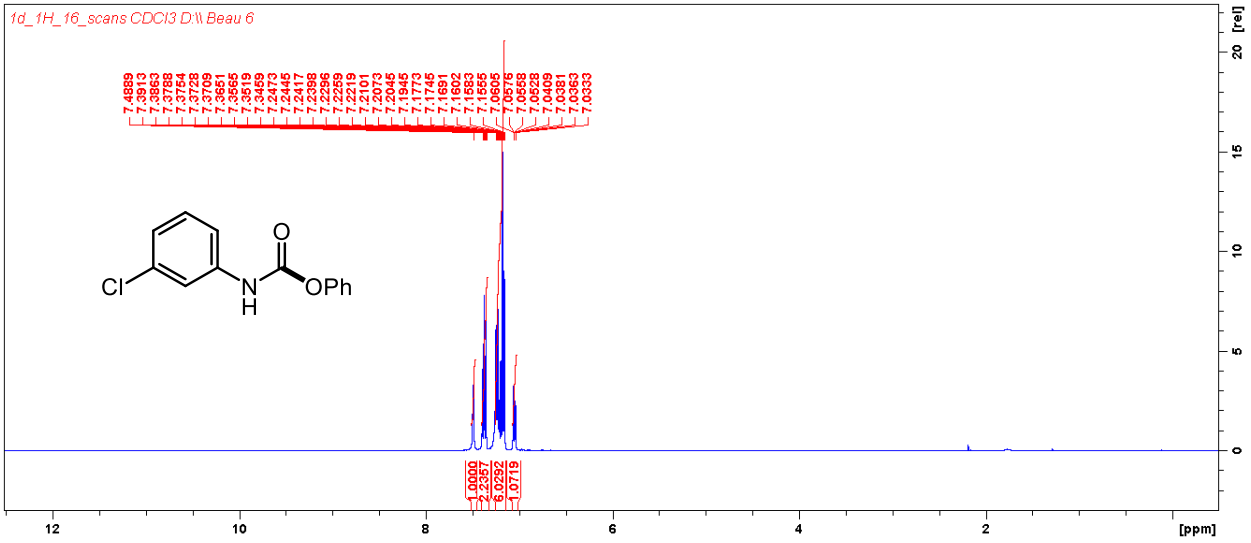

13C NMR with proton decoupling
[ppm]

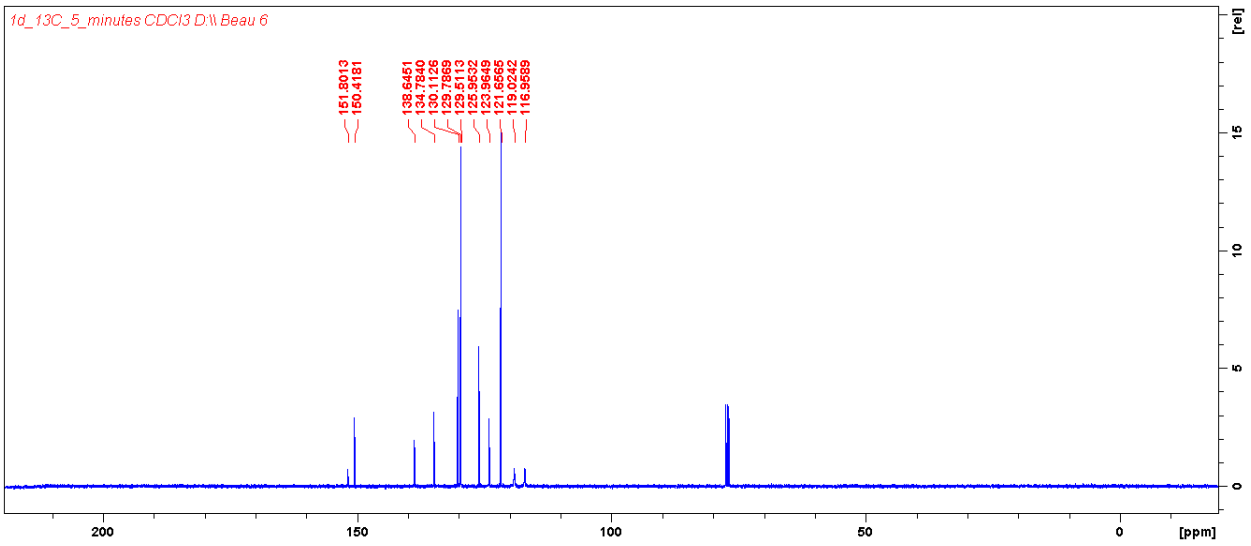

1d_1H_16_scans DMSO D:\\ Beau 2
10.5845
8.2853
8.0057
7.4208
7.4012
7.3815
7.2487
7.2404
7.2328
7.2192
3.8218
O
OMe
O
N
H
O
OPh
OMe
0.9373
2.0000
0.9782
2.0557
2.9943
6.1521
12
10
8
6
4
2
[ppm]
[rel]
20
15
10
5
0

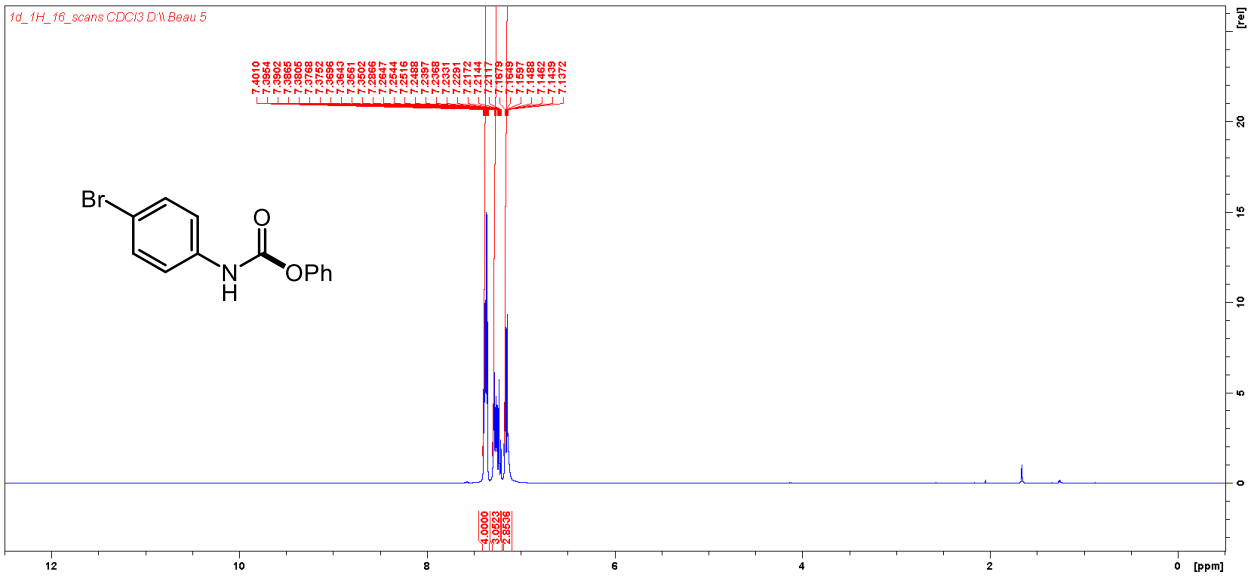

1d_13C_5_minutes DMSO D:\\ Beau 2
166.5821
152.1325
150.7975
140.1206
131.0723
129.8642
129.0552
124.1752
123.0947
122.3447
52.8301
200
150
100
50
0
[ppm]
[rel]
20
15
10
5
0

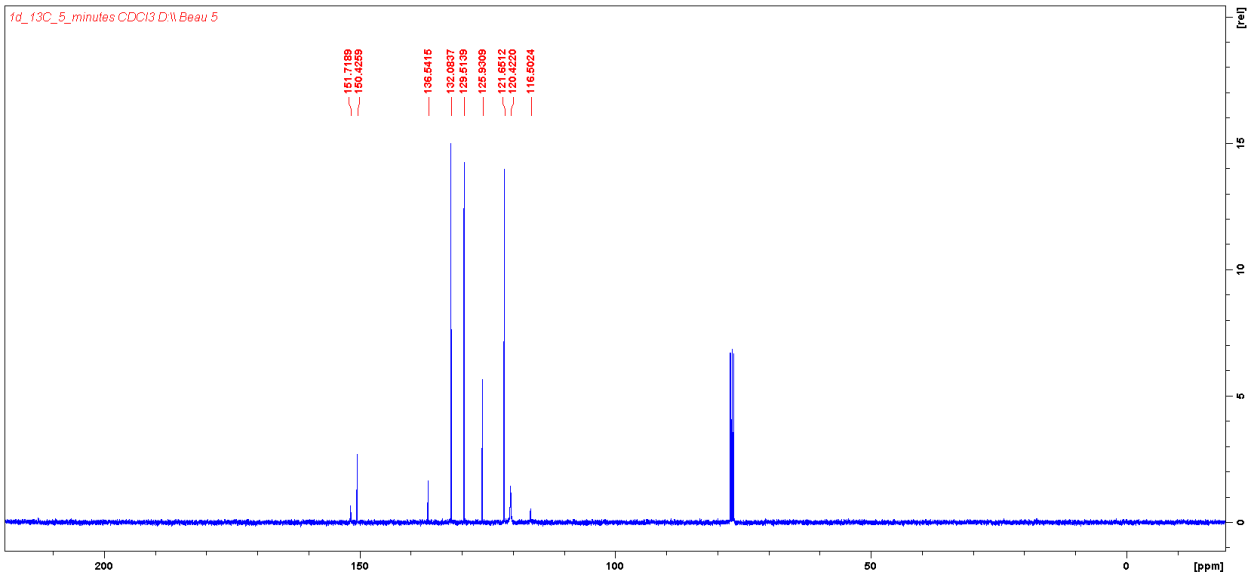

1d_1H_32_scans CDCl3 D:\\ Beau 26
8.0310
7.7266
7.7064
7.6933
7.6838
7.6831
7.6821
7.6684
7.6675
7.6725
7.6700
7.4459
7.4090
7.4102
7.4059
7.3916
7.3898
7.3753
7.3707
7.2808
7.2690
7.2552
7.2399
7.2237
7.2098
7.2181
7.1927
7.1898
7.1711
7.1685
7.1421
2.5886
1.0000
2.0341
3.1320
2.0884
2.9884
3.1309
O
O
N
H
OPh
Me
[rel]
[ppm]

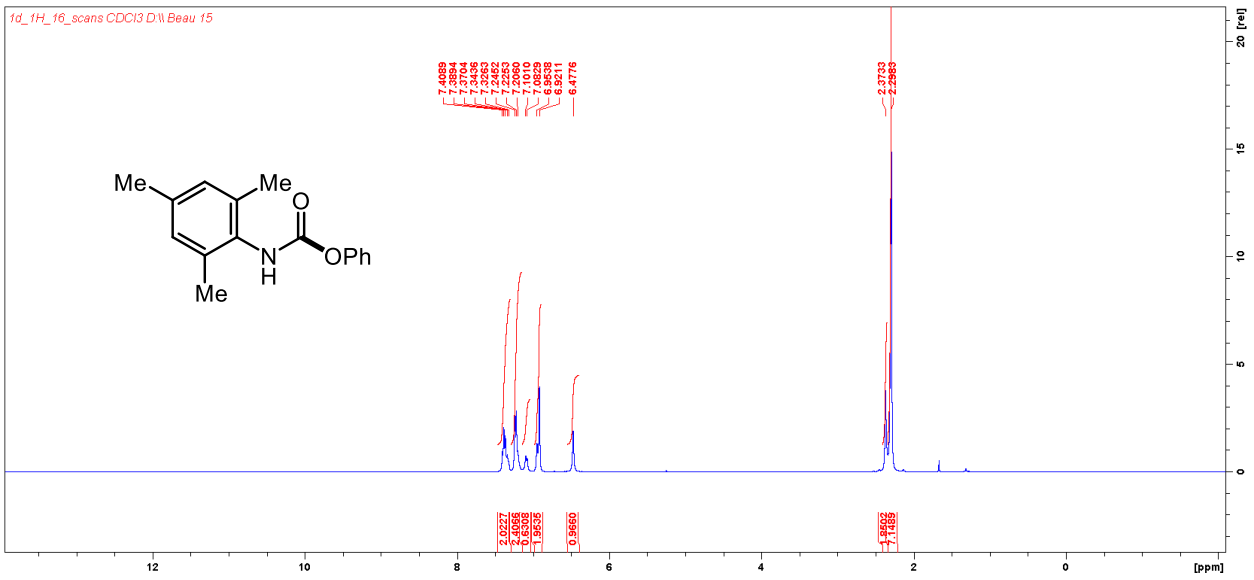

1d_13C_20_minutes CDCl3 D:\\ Beau 40
198.2628
151.9902
150.4743
139.2297
137.9430
129.4917
129.4530
125.8742
123.6893
123.0290
121.6896
118.5761
26.7329
[rel]
[ppm]

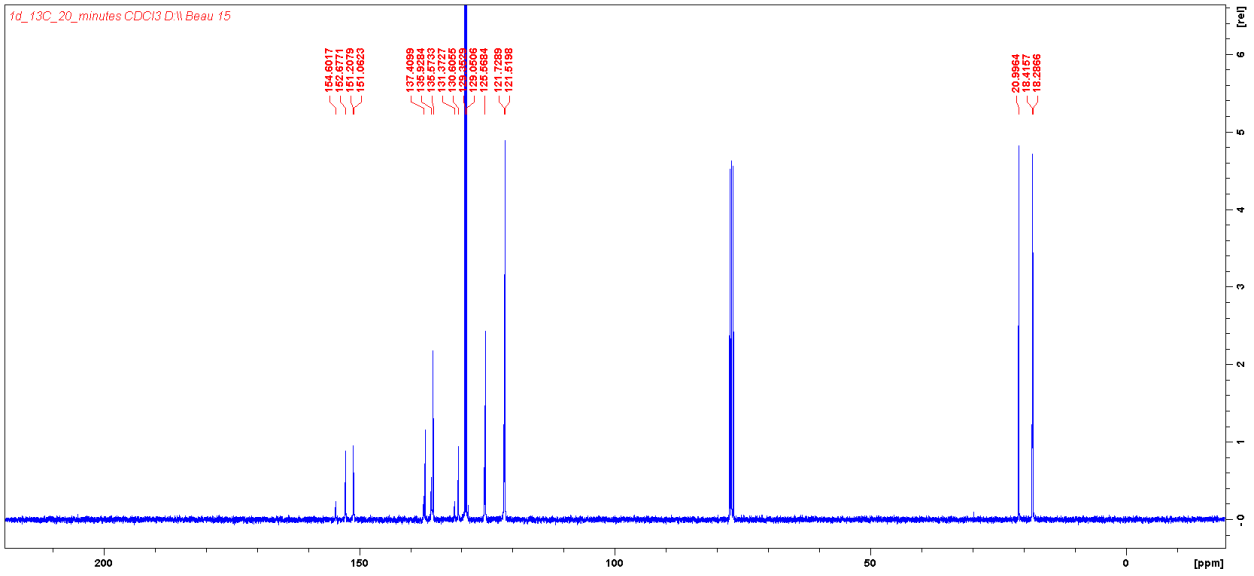

1d_1H_16_scans CDCl3 D:\\ Beau 6
7.4889
7.3913
7.3863
7.3788
7.3754
7.3728
7.3709
7.3651
7.3565
7.3519
7.3459
7.2473
7.2445
7.2417
7.2398
7.2296
7.2259
7.2219
7.2101
7.2073
7.2045
7.1945
7.1773
7.1745
7.1691
7.1602
7.1583
7.1555
7.1505
7.0576
7.0558
7.0528
7.0409
7.0381
7.0363
7.0333
Cl
N
H
O
OPh
1.0000
2.2357
6.0292
1.0719
12
10
8
6
4
2
[ppm]
[rel]

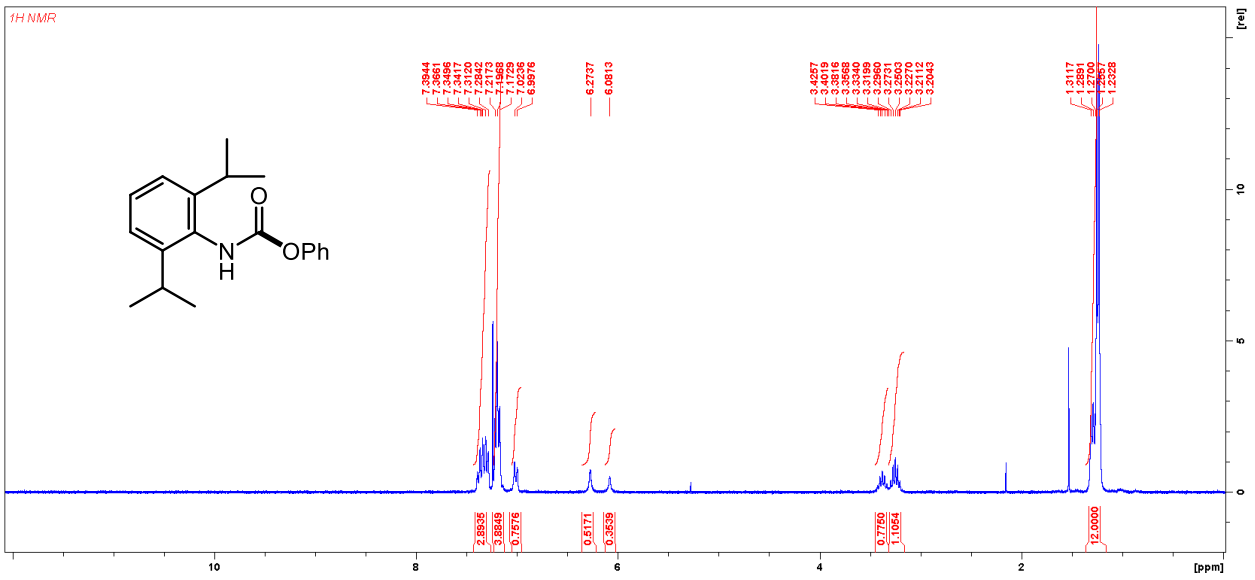

1d_13C_5_minutes CDCl3 D:\\ Beau 6
151.8013
150.4181
138.6451
134.7840
130.1126
129.7869
129.5113
125.9532
123.9649
121.6665
119.0242
116.9589
200
150
100
50
0
[ppm]
[rel]

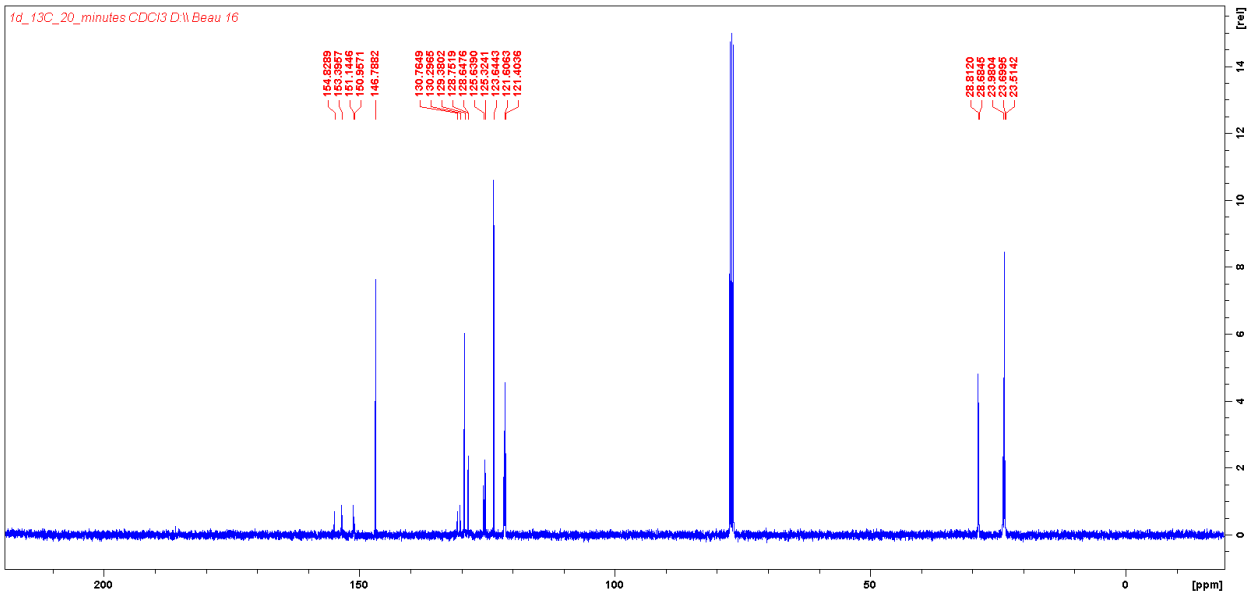

1d_1H_16_scans CDCl3 D:\\Beau 5
Br
O
N
H
OPh
[rel]
[ppm]

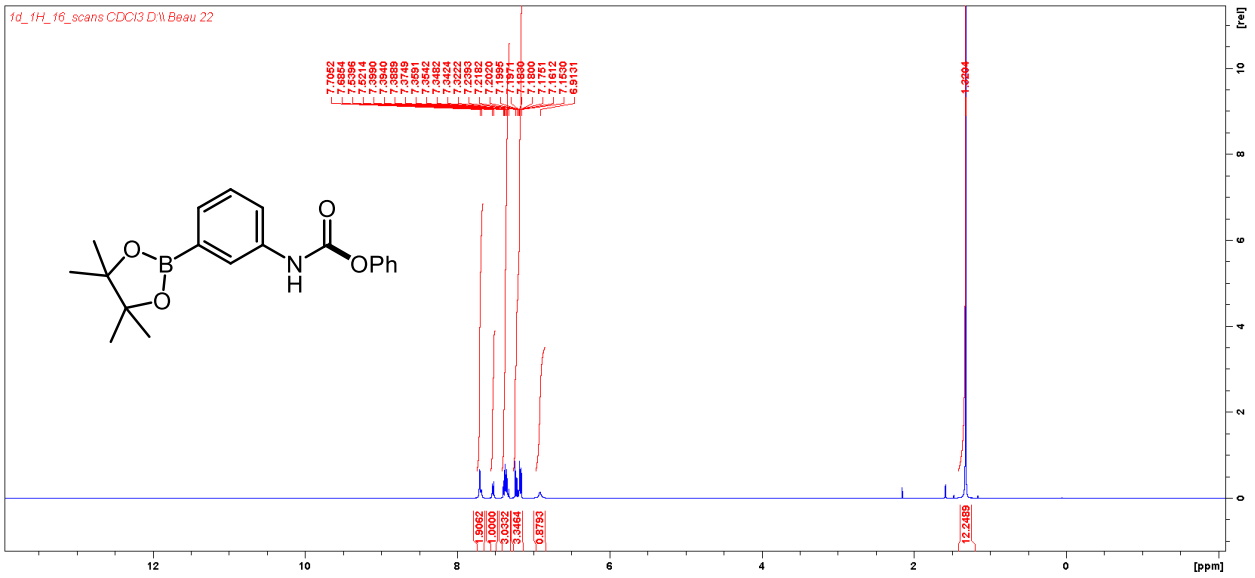

1d_13C_5_minutes CDCl3 D:\\Beau 5
151.7189
150.4259
136.5415
132.0837
129.5139
125.9309
121.6512
120.4220
116.5024
[rel]
[ppm]

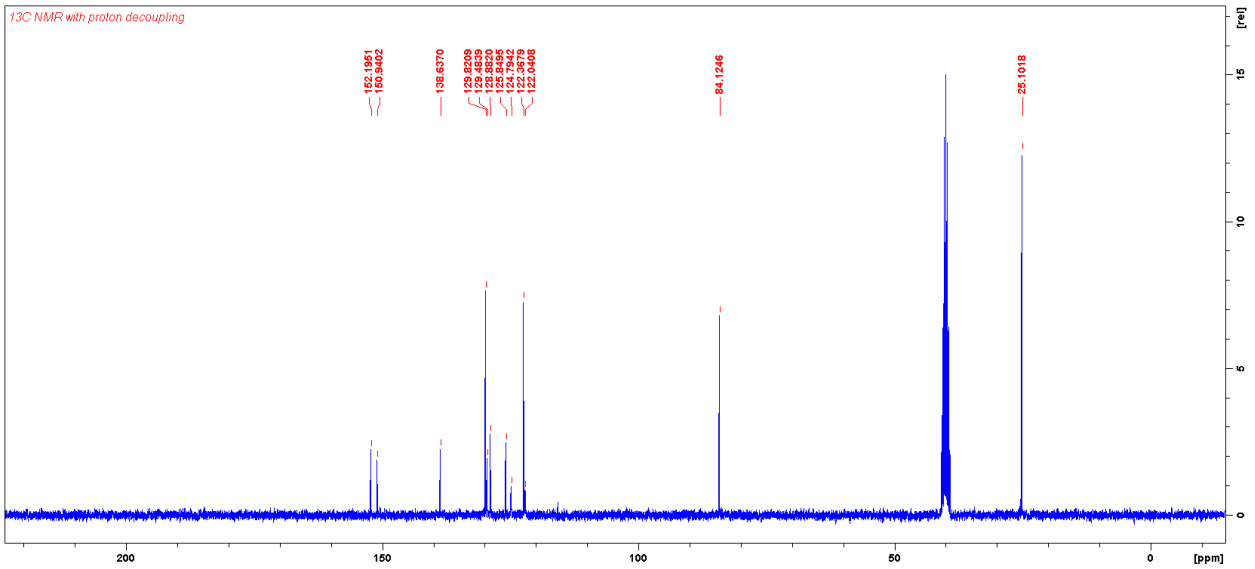

1d_1H_16_scans CDCl3 D:\\ Beau 15
Me
Me
O
N
H
OPh
Me
[ppm]

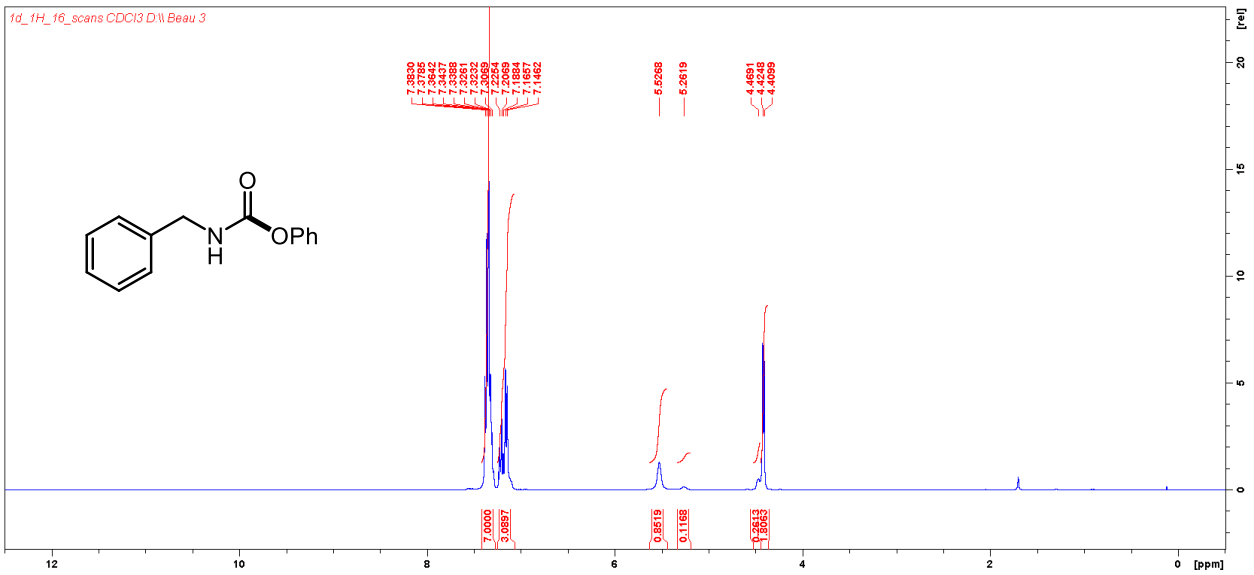

1d_13C_20_minutes CDCl3 D:\\ Beau 15
[ppm]

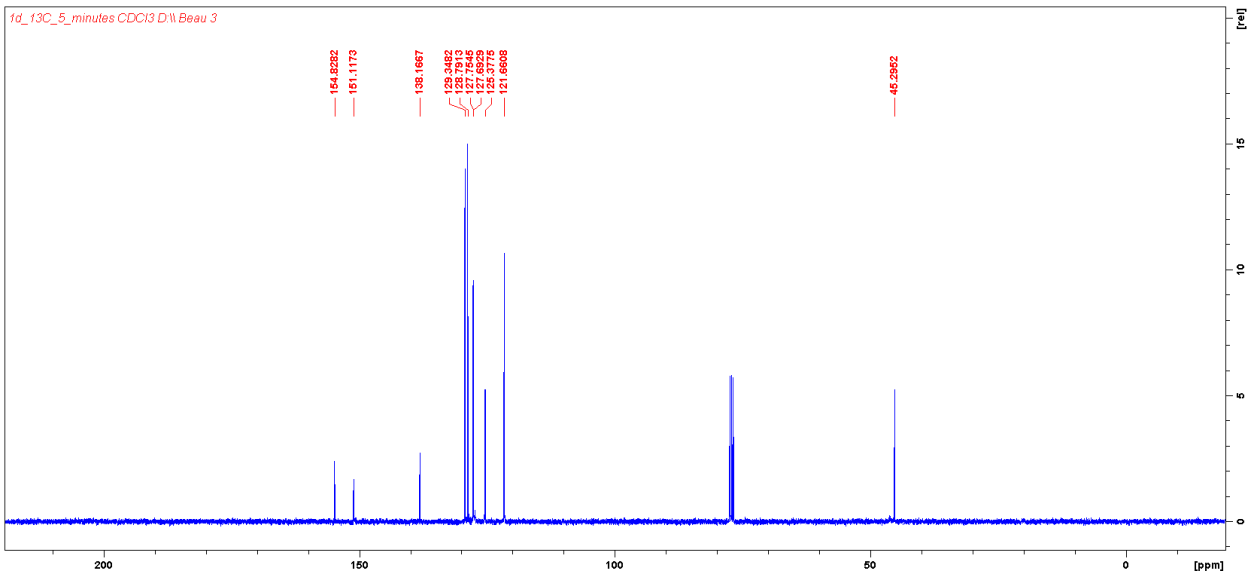

1H NMR
7.3844
7.3661
7.3496
7.3417
7.3230
7.2842
7.2173
7.1988
7.1799
7.0236
6.9976
6.2737
6.0813
3.4257
3.4019
3.3816
3.3666
3.3340
3.3199
3.2980
3.2731
3.2503
3.2270
3.2112
3.2043
1.3117
1.2891
1.2700
1.2557
1.2328
2.8936
3.8849
0.7576
0.5171
0.3559
0.7760
1.1054
12.0000
[ppm]

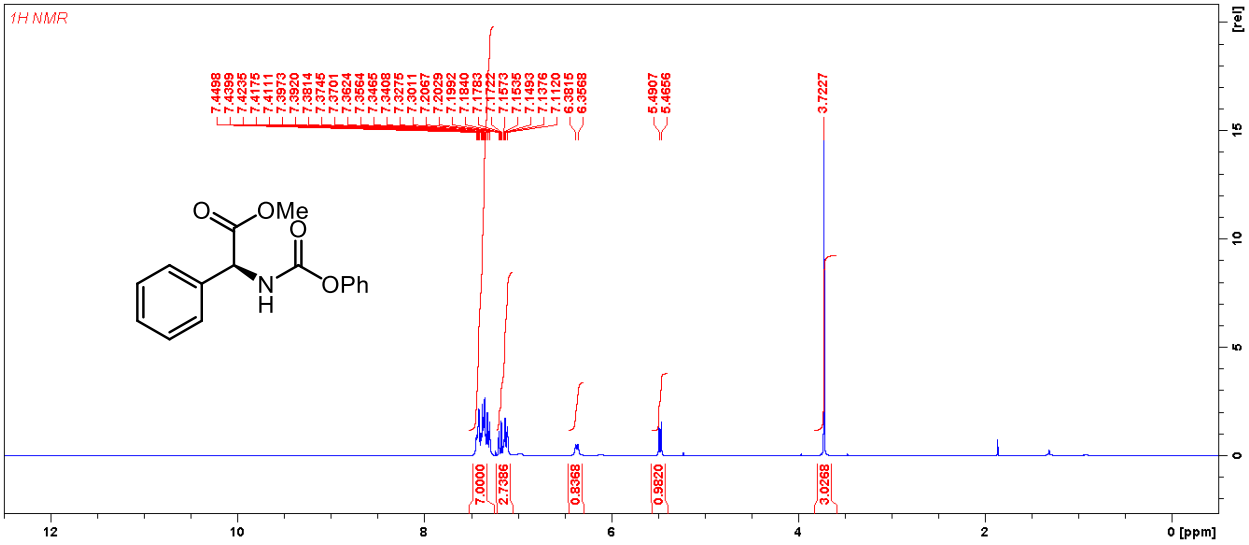

1d_13C_20_minutes CDCl3 D:\\ Beau 16
154.8289
153.3957
151.1446
150.9571
146.7882
130.7649
130.2965
129.3932
128.7519
128.6476
125.6390
125.2241
123.8443
121.6063
121.4036
28.8120
28.6845
23.9804
23.8995
23.3142
[ppm]

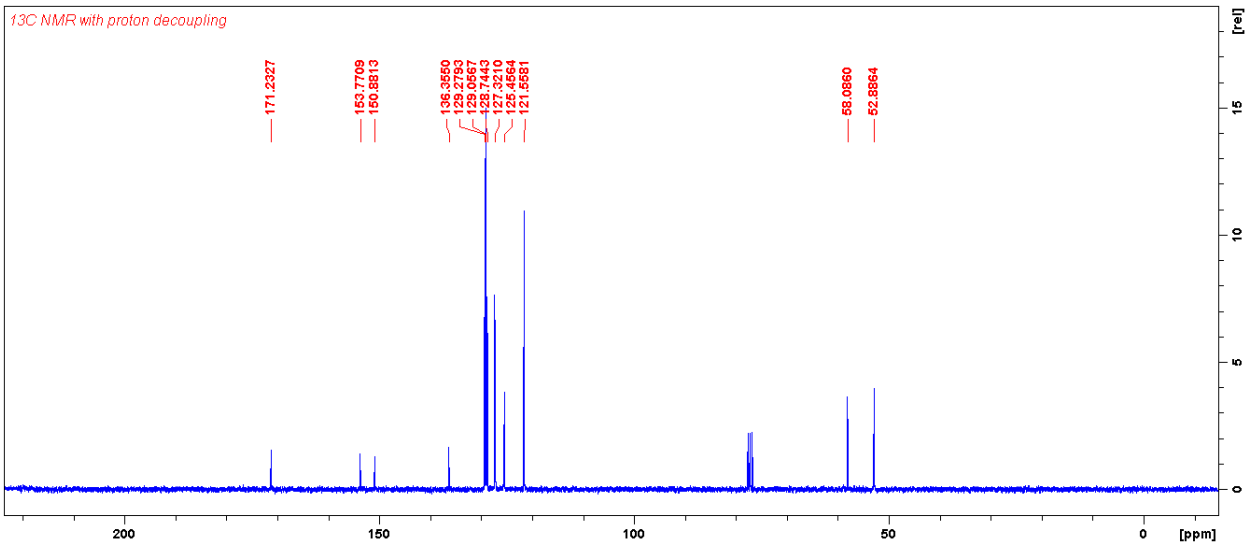

1d_1H_16_scans CDCl3 D:\\ Beau 22
7.7052
7.6854
7.5396
7.5214
7.3890
7.3840
7.3889
7.3749
7.3691
7.3642
7.3482
7.3424
7.3282
7.2283
7.2182
7.2020
7.1995
7.1917
7.1830
7.1800
7.1751
7.1612
7.1530
6.9131
1.3204
1.5062
1.0000
3.0332
3.3464
0.8759
12.2469
O
O
B
O
N
H
OPh
12
10
8
6
4
2
0
[ppm]
[rel]

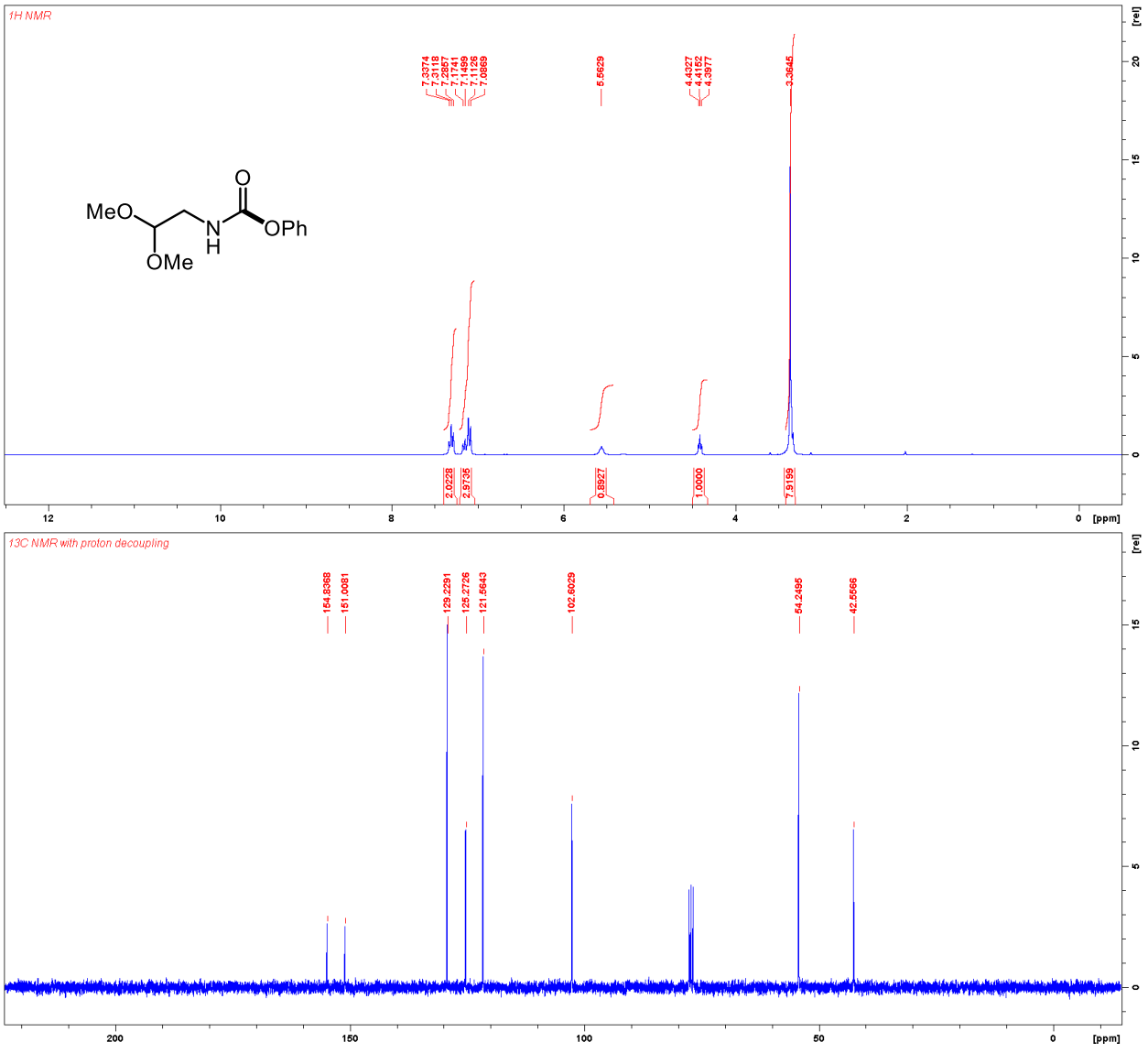

13C NMR with proton decoupling
152.1951
150.9402
138.6370
129.8209
129.4838
128.8820
125.8496
121.7944
122.3575
122.0408
84.1246
25.1018
200
150
100
50
0
[ppm]
[rel]

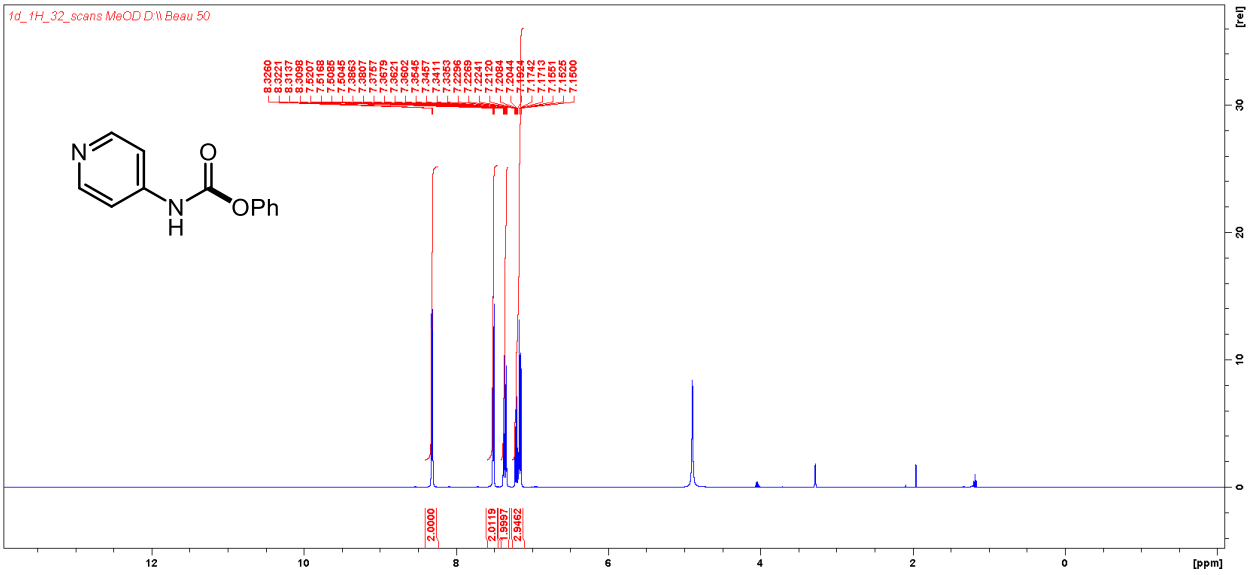

1d_1H_16_scans CDCl3 D:\\ Beau 3
7.3830
7.3785
7.3642
7.3497
7.3387
7.3261
7.3232
7.2059
7.2024
7.2069
7.1884
7.1457
7.1462
5.5268
5.2619
4.4691
4.4248
4.4099
O
N
H
OPh
7.0000
3.0897
0.8519
0.1168
0.2613
1.8063
12
10
8
6
4
2
0
[ppm]
[rel]

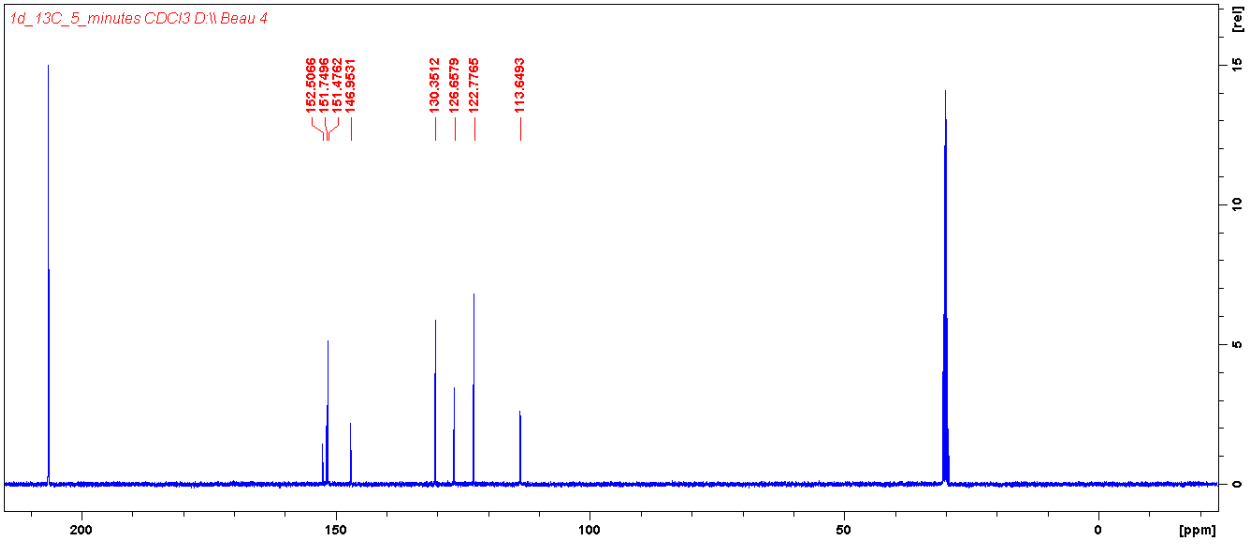

1d_13C_5_minutes CDCl3 D:\\ Beau 3
154.8282
151.1173
138.1667
129.3482
129.7913
127.7644
127.6829
125.3775
121.6608
45.2962
200
150
100
50
0
[ppm]
[rel]

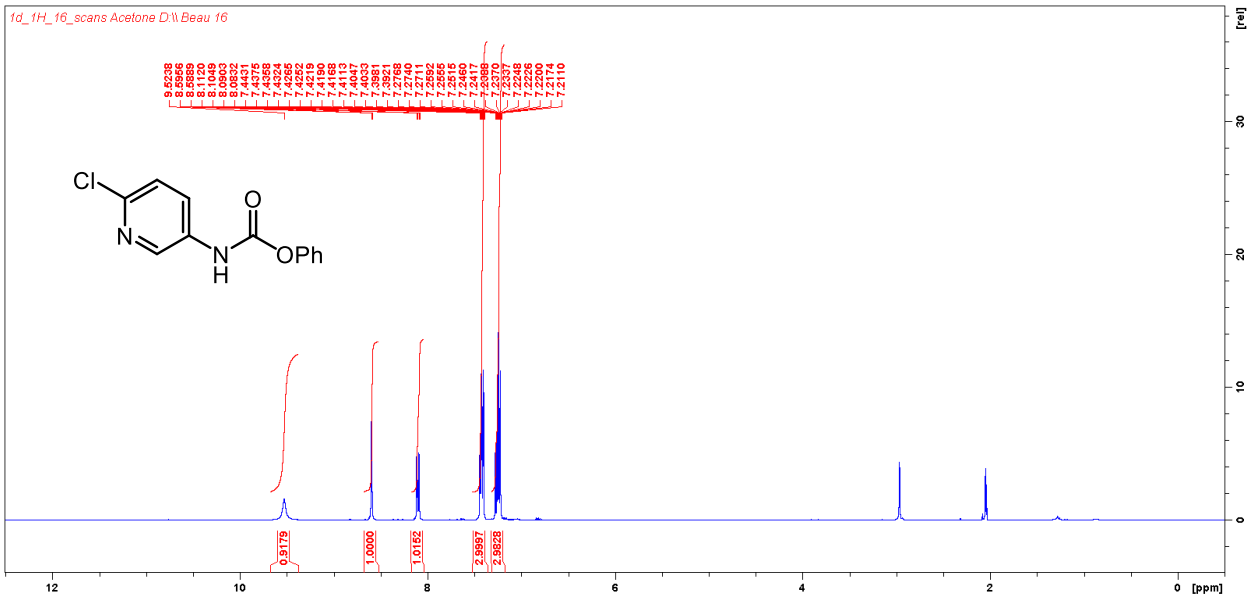

1H NMR
7.4498
7.4398
7.4236
7.4175
7.4111
7.3973
7.3920
7.3814
7.3745
7.3701
7.3624
7.3564
7.3465
7.3408
7.3275
7.3061
7.2967
7.2029
7.1992
7.1840
7.1783
7.1722
7.1573
7.1535
7.1493
7.1376
7.1120
6.3815
6.3568
5.4907
5.4656
3.7227
O
OMe
O
N
H
OPh
7.0000
2.7386
0.8368
0.9820
3.0268
12
10
8
6
4
2
0 [ppm]
[rel]
15
10
5
0


13C NMR with proton decoupling
171.2327
153.7709
150.8813
136.3550
129.2793
129.0867
128.7443
127.3210
125.4564
121.5581
59.0860
52.8864
200
150
100
50
0 [ppm]
[rel]
15
10
5
0


1H NMR
7.3374
7.3118
7.2857
7.1741
7.1499
7.1126
7.0889
5.5629
4.4327
4.4152
4.3977
3.3645
MeO
OMe
N
H
O
OPh
2.0228
2.9736
0.8927
1.0000
7.9199
[rel]
[ppm]
13C NMR with proton decoupling
154.8368
151.0081
129.2291
125.2726
121.5643
102.6029
54.2495
42.5566
[rel]
[ppm]


1d_1H_32_scans MeOD D:\\ Beau 50
8.3260
8.3221
8.3137
8.3098
7.6207
7.5168
7.5085
7.5045
7.3863
7.3807
7.3767
7.3679
7.3621
7.3602
7.3545
7.3447
7.3411
7.3353
7.2296
7.2259
7.2241
7.2120
7.2084
7.2044
7.1934
7.1742
7.1713
7.1551
7.1525
7.1500
N
O
N
H
OPh
2.0000
2.0119
1.9997
2.9462
[rel]
[ppm]


1d_13C_5_minutes CDCl3 D:\\ Beau 4
152.5066
151.7496
151.4762
146.9531
130.3512
126.6579
122.7765
113.6493
[rel]
[ppm]


1d_1H_16_scans Acetone D:\\ Beau 16
9.5238
8.5866
8.4989
8.1130
8.1048
8.0903
8.0832
7.4431
7.4375
7.4358
7.4324
7.4285
7.4262
7.4219
7.4190
7.4168
7.4115
7.4047
7.4033
7.3981
7.3921
7.2788
7.2711
7.2740
7.2592
7.2565
7.2515
7.2460
7.2417
7.2388
7.2370
7.2337
7.2248
7.2226
7.2200
7.2174
7.2110
Cl
N
O
N
H
OPh
0.9179
1.0000
1.0152
2.9997
2.9828
12
10
8
6
4
2
0
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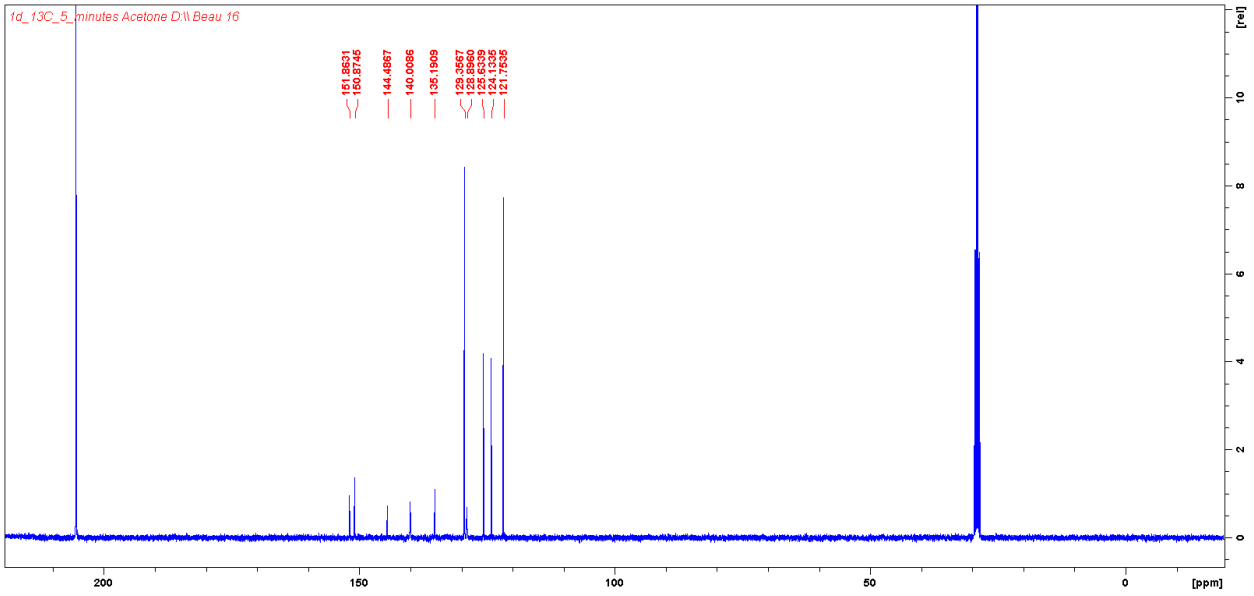
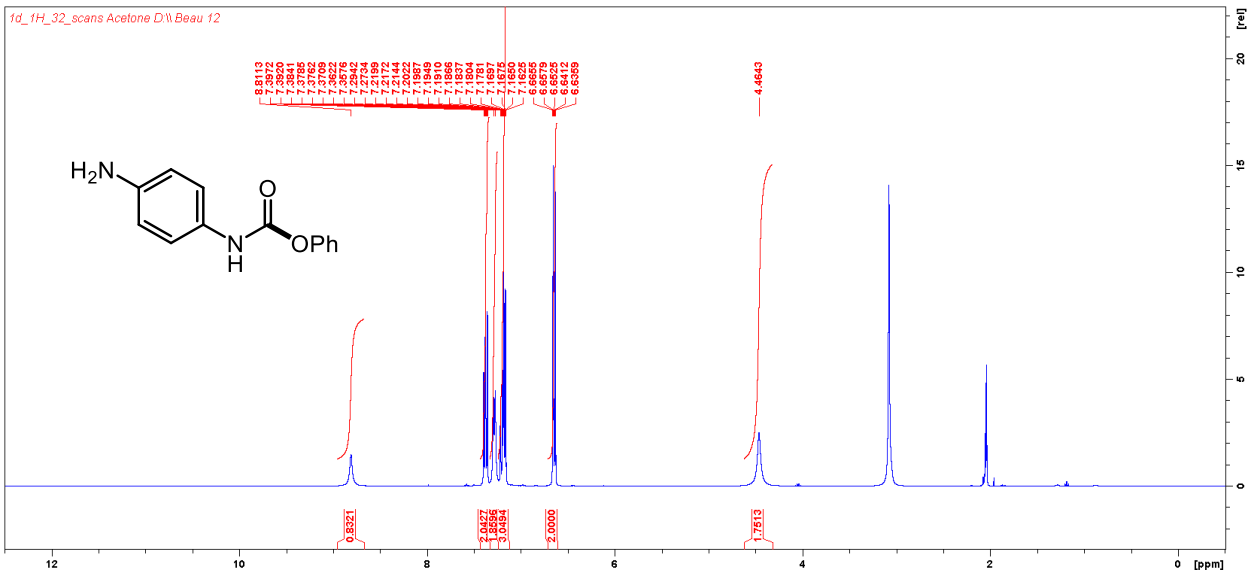
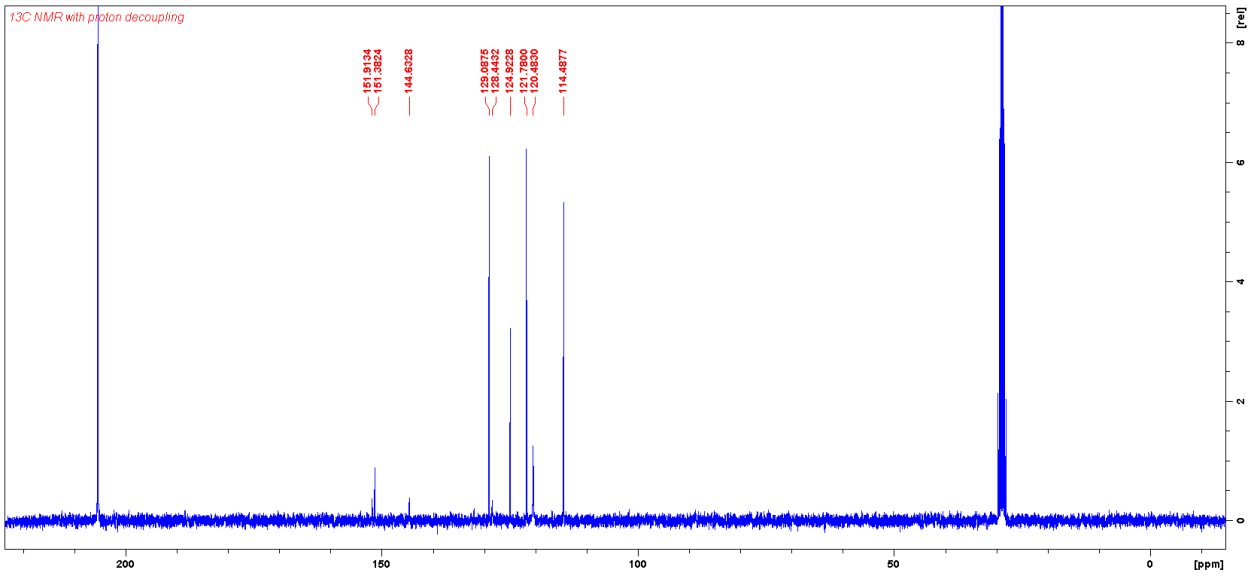
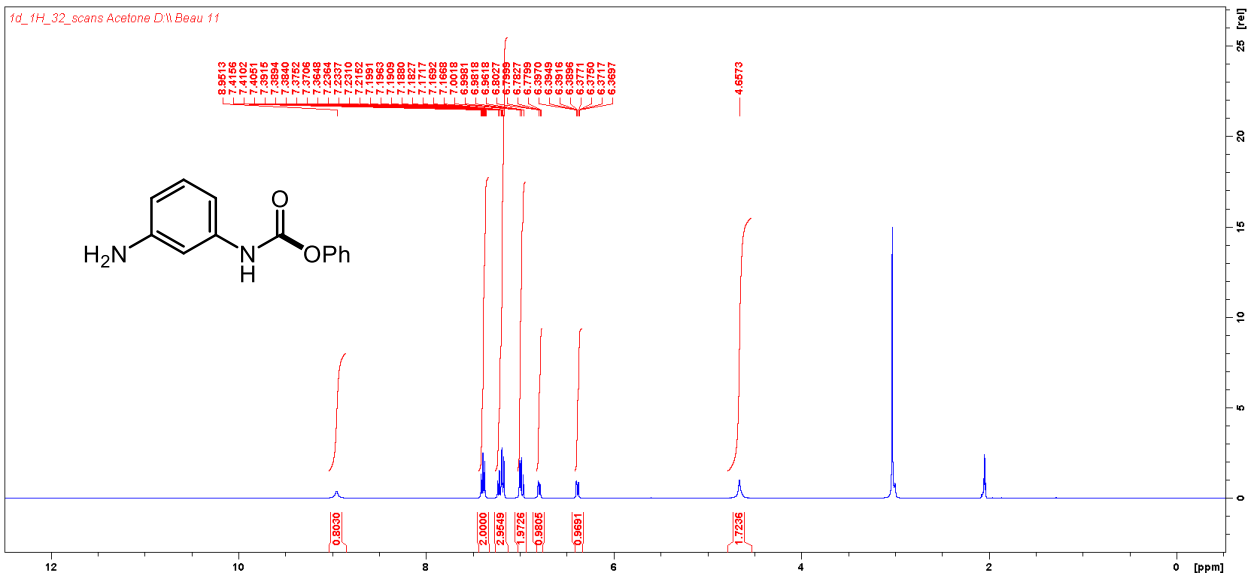
[rel]
0
10
20
30


1d_13C_5_minutes Acetone D:\\ Beau 16
151.8631
150.8745
144.4867
140.0086
135.1909
129.3867
128.8960
126.6538
124.1335
121.7535
200
150
100
50
0
[ppm]
[rel]
0
2
4
6
8
10


1d_1H_32_scans Acetone D:\\ Beau 12
8.8113
7.3972
7.3920
7.3841
7.3785
7.3762
7.3709
7.3622
7.3572
7.2945
7.2734
7.2199
7.2172
7.2144
7.2022
7.1987
7.1948
7.1910
7.1866
7.1837
7.1804
7.1781
7.1697
7.1675
7.1650
7.1625
6.6685
6.6579
6.6415
6.6411
6.6389
4.4643
0.8321
0.0427
1.8556
3.0494
2.0000
1.7513
H2N
O
N
H
OPh
[rel]
[ppm]


13C NMR with proton decoupling
151.9134
151.3824
144.8328
130.0875
129.4452
124.9228
121.7890
120.4830
114.4877
[rel]
[ppm]


1d_1H_32_scans Acetone D:\\ Beau 11
8.8513
7.4166
7.4102
7.4051
7.3915
7.3894
7.3840
7.3752
7.3706
7.3648
7.3584
7.2337
7.2310
7.2152
7.1981
7.1963
7.1909
7.1880
7.1827
7.1717
7.1692
7.1668
7.0018
6.9981
6.9818
6.9618
6.9577
6.7989
6.7827
6.7759
6.7570
6.3949
6.3916
6.3896
6.3777
6.3750
6.3717
6.3697
4.6573
0.8030
2.0000
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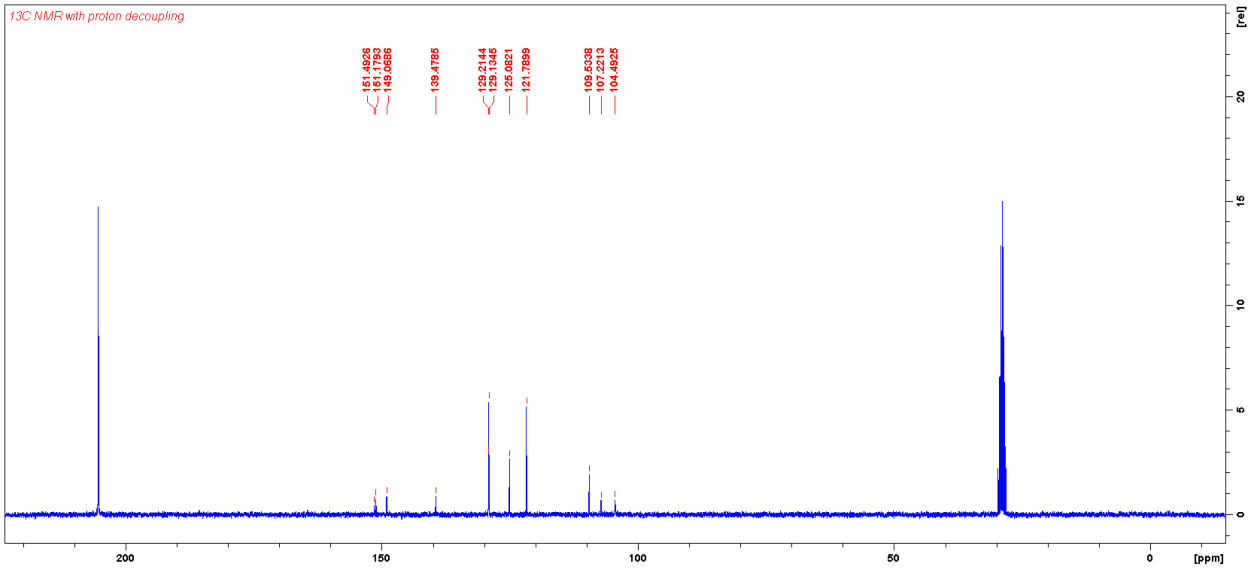
0.9806
0.9691
1.7226
H2N
N
H
O
OPh
[rel]
[ppm]


13C NMR with proton decoupling
151.4926
151.1793
149.0686
139.4785
129.2144
129.1345
125.0821
121.7899
109.5338
107.2213
104.4925
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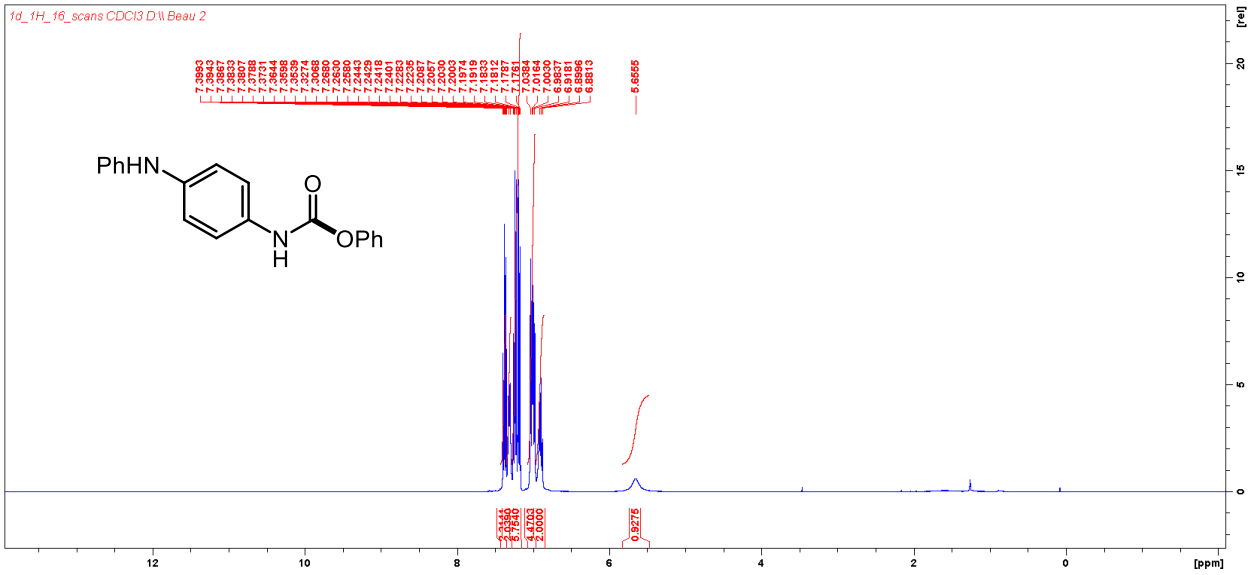
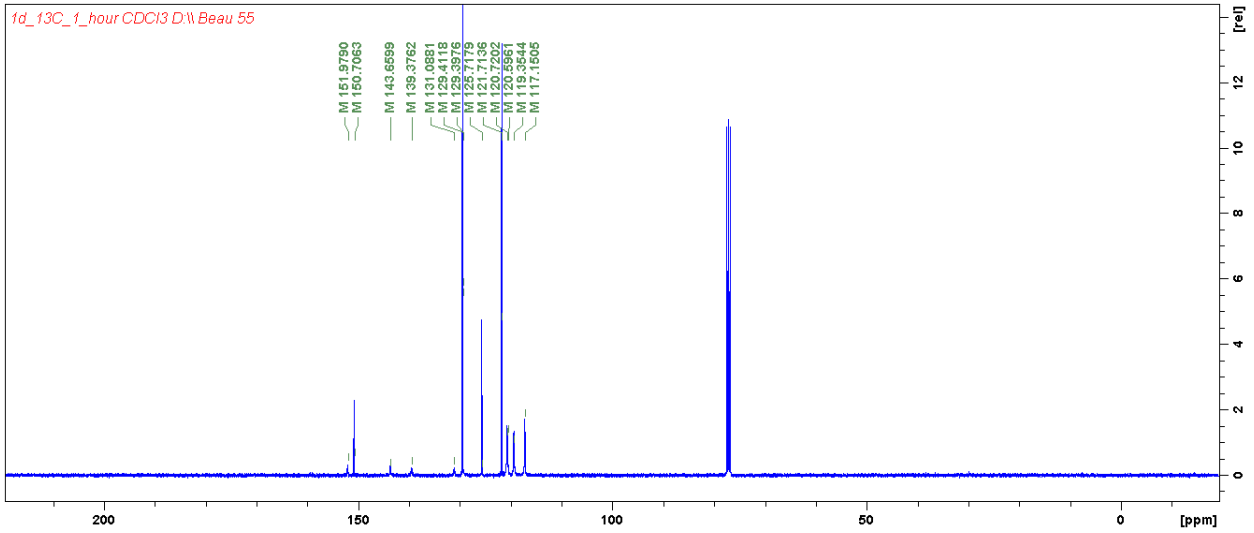
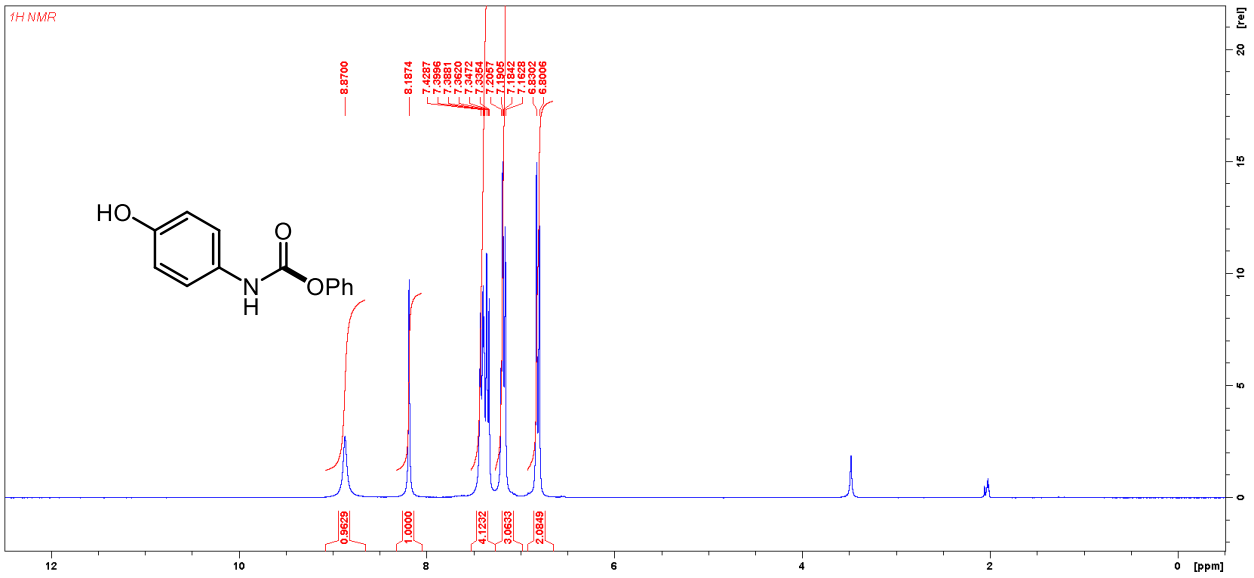
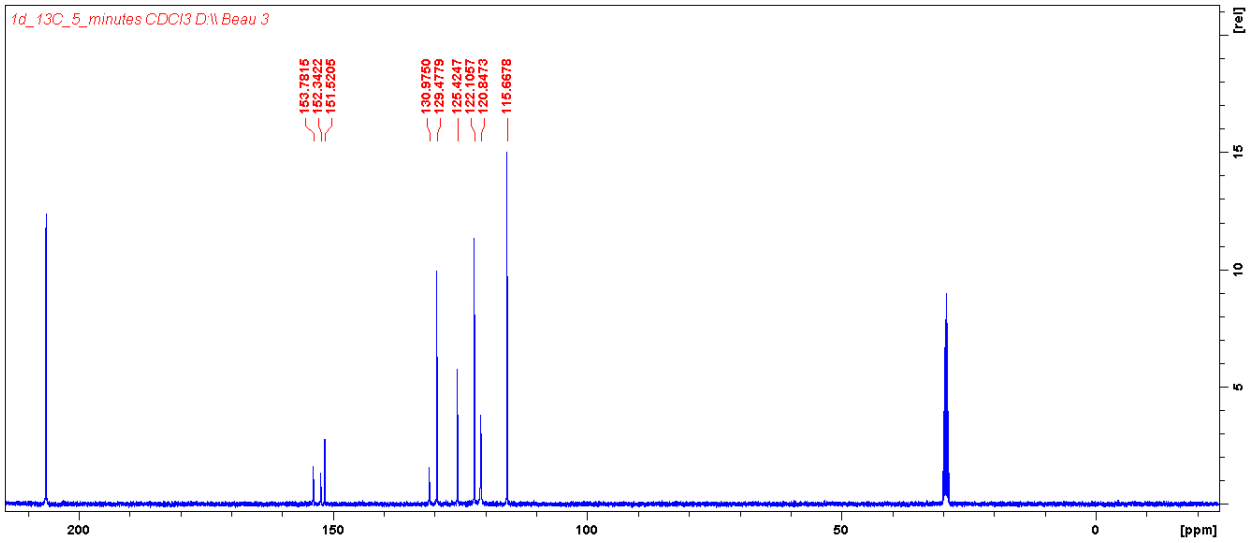
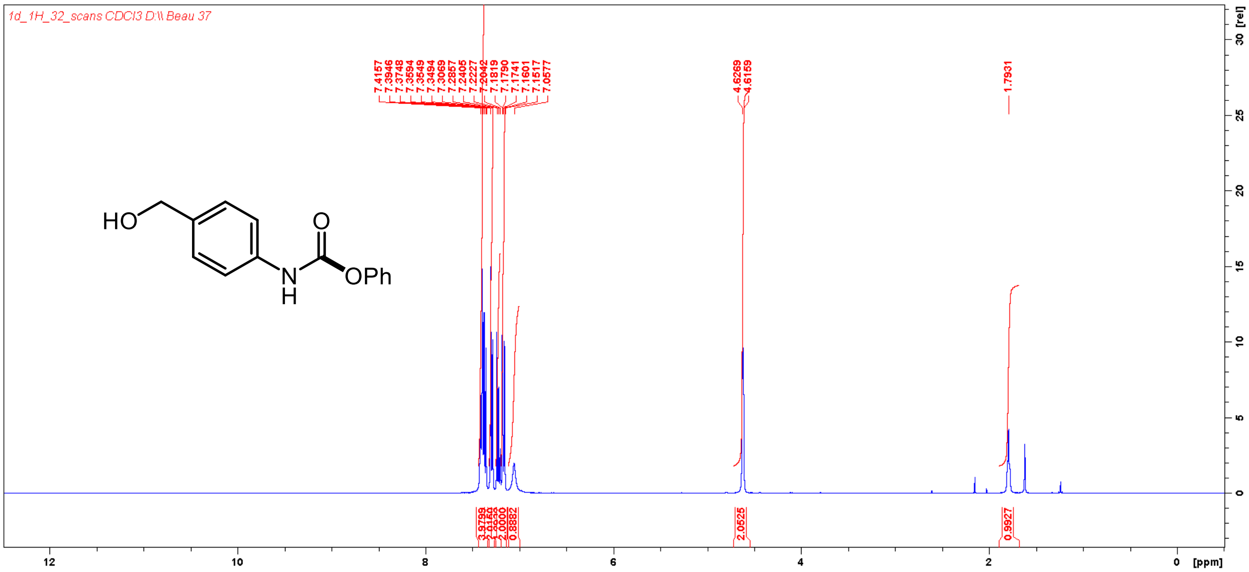
[ppm]

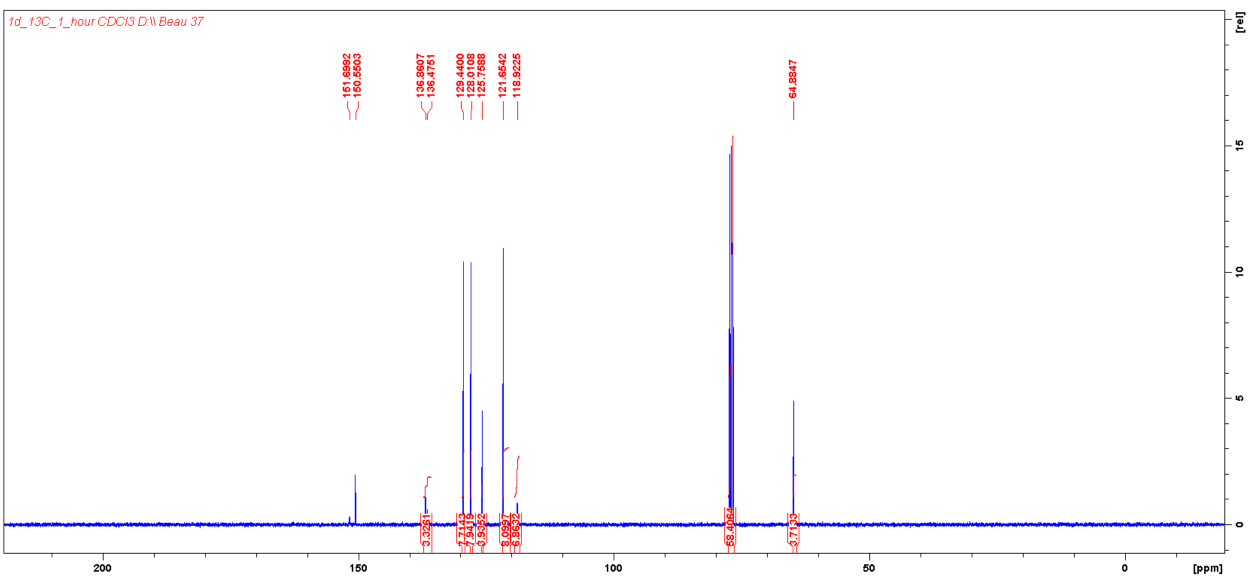

1d_1H_16_scans CDCl3 D:\\ Beau 2
PhHN
O
N
H
OPh
[rel]
[ppm]

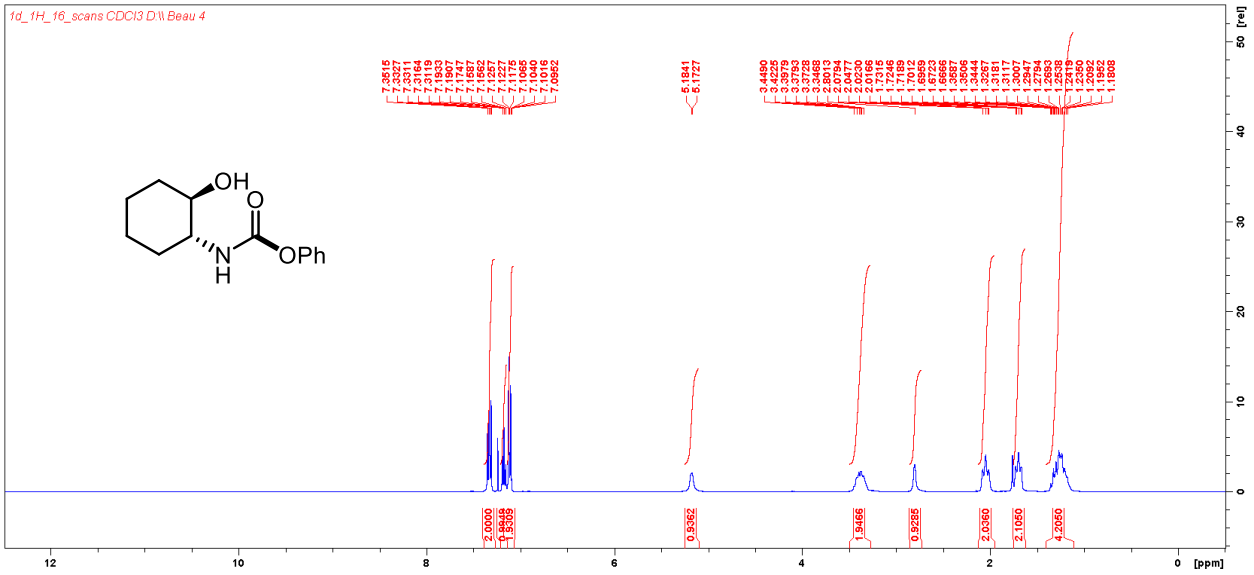

1d_13C_1_hour CDCl3 D:\\ Beau 55
M 151.9790
M 150.7063
M 143.6559
M 139.3762
M 131.0881
M 129.4118
M 129.3976
M 129.3779
M 121.7138
M 120.7202
M 120.5961
M 119.3544
M 117.1505
[rel]
[ppm]

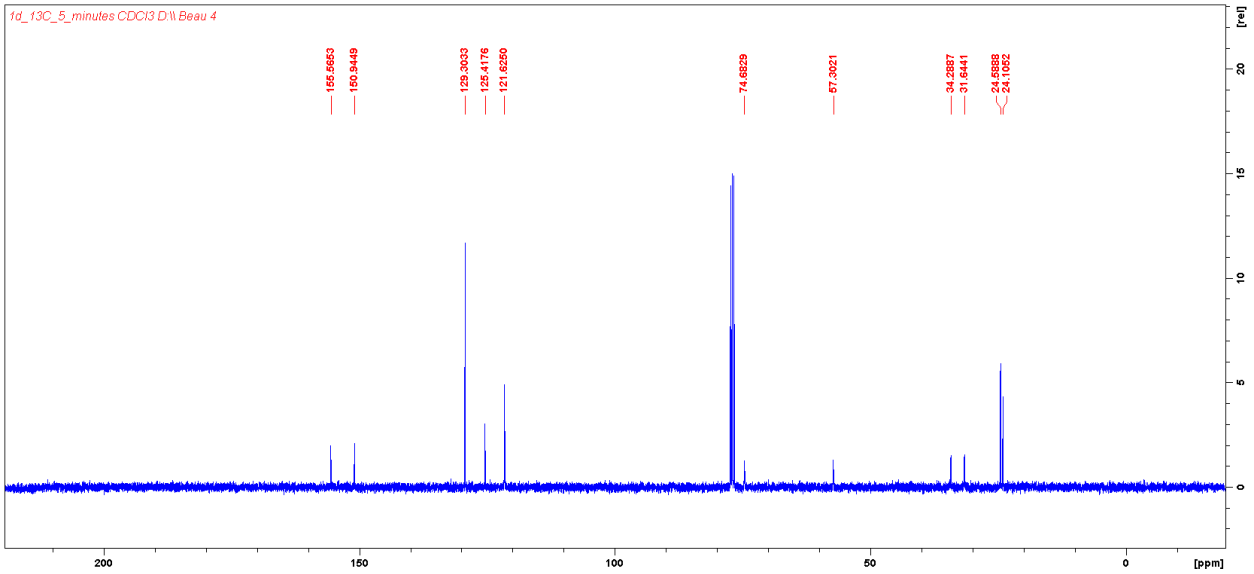

1H NMR
8.8700
8.1874
7.4087
7.3996
7.3881
7.3620
7.3472
7.3354
7.2067
7.1945
7.1840
7.1628
6.8302
6.8006
HO
O
N
H
OPh
0.9629
1.0000
4.1232
3.0633
2.0849
[rel]
[ppm]

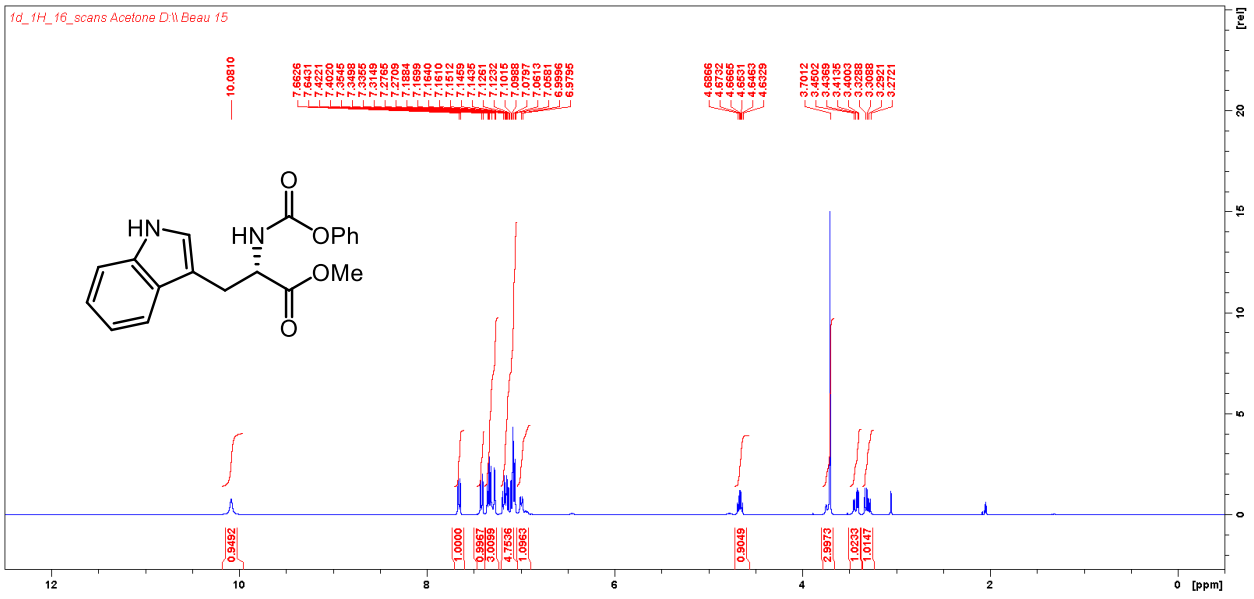

1d_13C_5_minutes CDCl3 D:\\ Beau 3
153.7815
152.3422
151.5205
130.9750
129.4779
125.4247
122.1057
120.8473
115.6678
[rel]
[ppm]

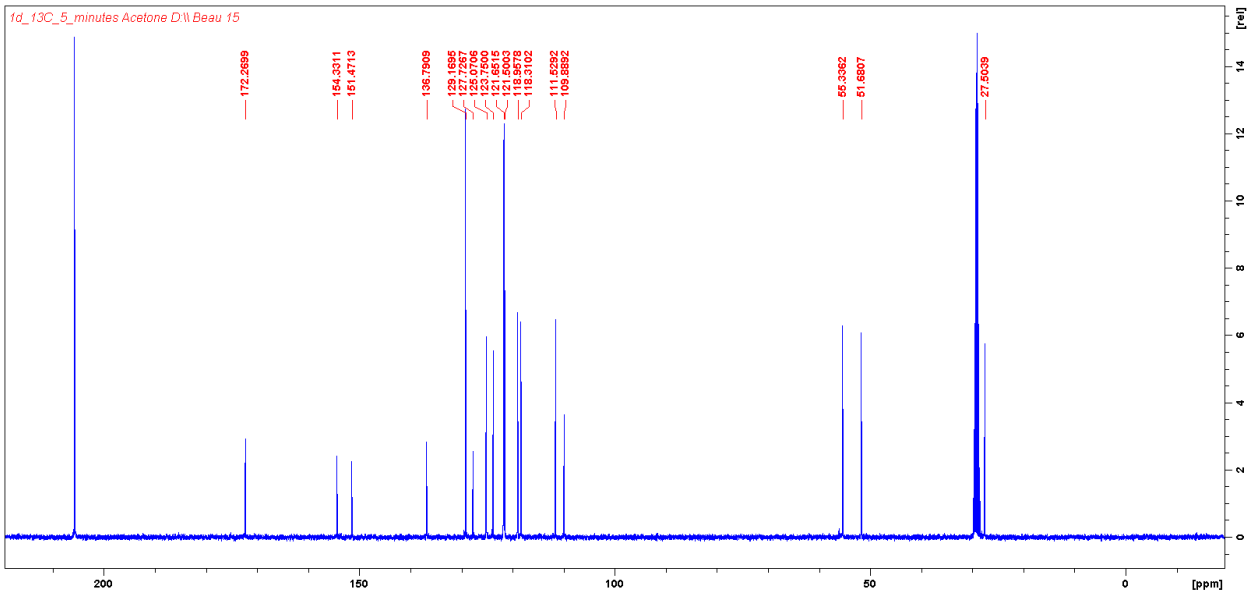

1d_1H_32_scans CDCl3 D:\\ Beau 37
HO
O
N
H
OPh
7.4157
7.3946
7.3748
7.3594
7.3549
7.3494
7.3069
7.2857
7.2405
7.2227
7.2042
7.1819
7.1790
7.1741
7.1601
7.1517
7.0577
4.6269
4.6159
1.7931
0.9927
2.0525
[ppm]
[rel]

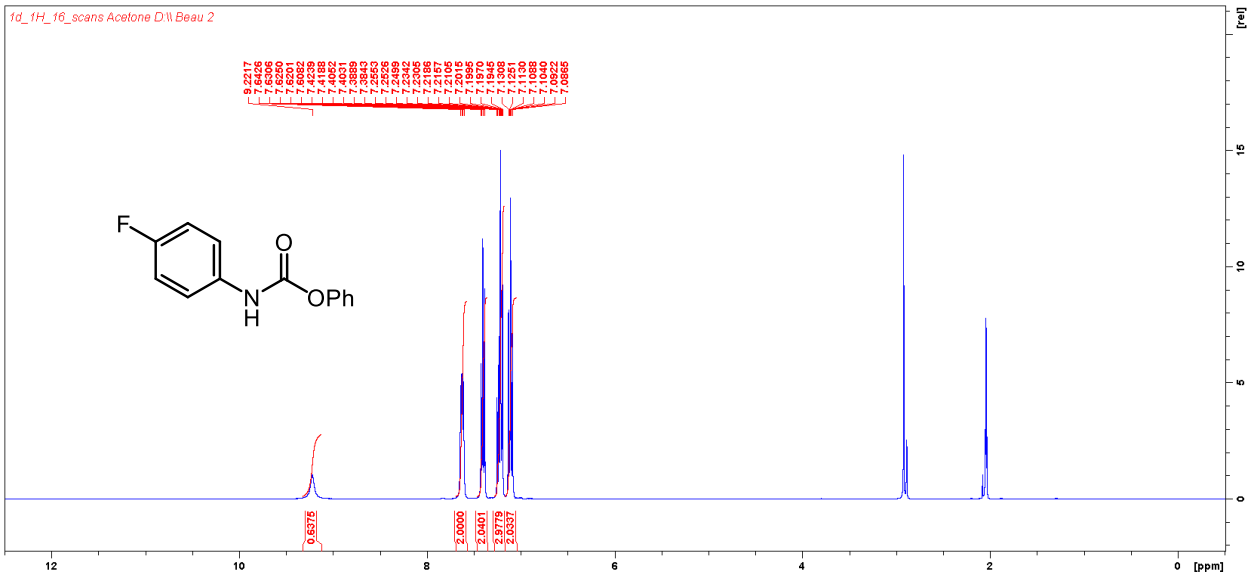

1d_13C_1_hour CDCl3 D:\\ Beau 37
151.6992
150.5503
136.8607
136.4751
129.4400
128.0108
125.7588
121.6542
118.9225
64.8847
[ppm]
[rel]

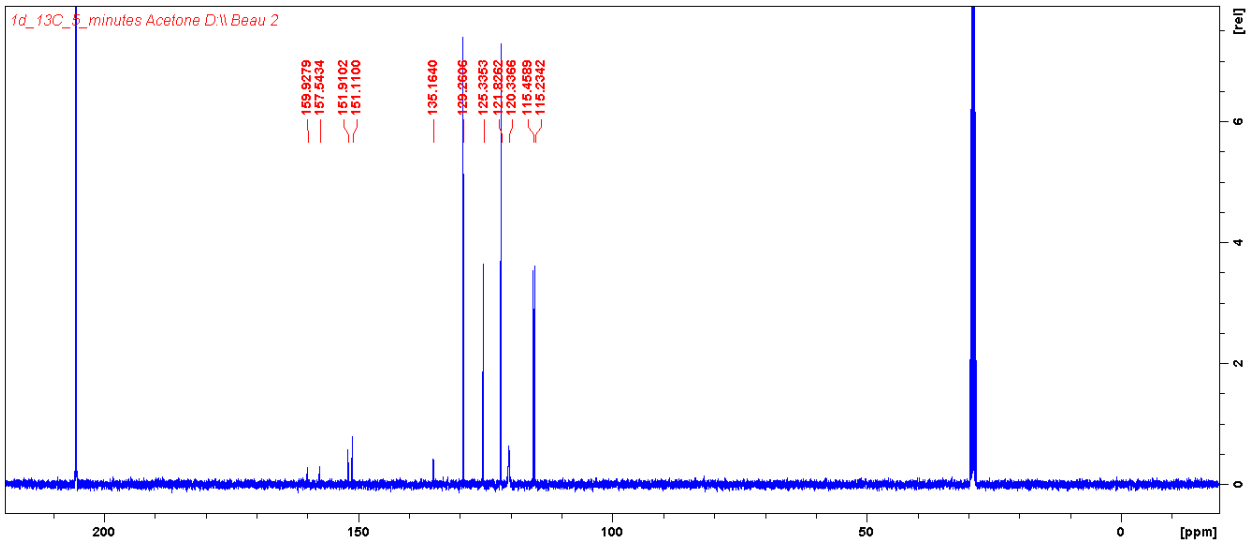

1d_1H_16_scans CDCl3 D:\\ Beau 4
OH
O
N
H
OPh
[rel]
[ppm]

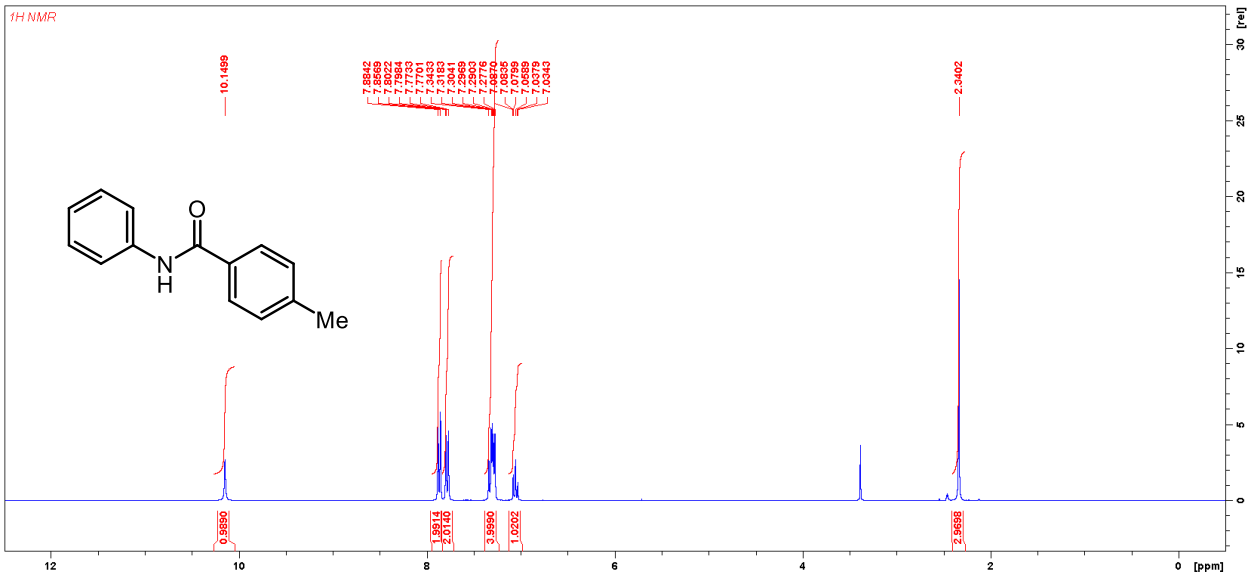

1d_13C_5_minutes CDCl3 D:\\ Beau 4
155.5653
150.9449
129.3033
125.4176
121.6250
74.6829
57.3021
34.2887
31.6441
24.5888
24.1062
[rel]
[ppm]


1d_1H_16_scans Acetone D:\\ Beau 15
10.0810
7.6626
7.6431
7.4221
7.4049
7.3546
7.3498
7.3365
7.3149
7.2785
7.2709
7.1884
7.1699
7.1640
7.1610
7.1512
7.1469
7.1426
7.1361
7.1232
7.1015
7.0888
7.0797
7.0731
7.0581
6.9996
6.9795
4.6966
4.6732
4.6665
4.6631
4.6463
4.6229
3.7012
3.4502
3.4369
3.4135
3.4003
3.3288
3.3088
3.2921
3.2721
HN
HN
O
OPh
OMe
O
0.9492
1.0000
0.9967
3.0089
4.7536
1.0963
0.9049
2.9973
1.0233
1.0147
12
10
8
6
4
2
0
[ppm]
[rel]
0
5
10
15
20


1d_13C_5_minutes Acetone D:\\ Beau 15
172.2699
154.3311
151.4713
136.7909
129.1695
127.7267
125.0706
123.7540
122.6515
121.6003
118.9578
118.3102
111.6292
109.8892
55.3362
51.6807
27.5039
200
150
100
50
0
[ppm]
[rel]
0
2
4
6
8
10
12
14


1d_1H_16_scans Acetone D:\\ Beau 2
F
O
N
H
OPh
0.6375
2.0000
2.0401
2.9779
2.0937
[rel]
[ppm]


1d_13C_5_minutes Acetone D:\\ Beau 2
159.9279
157.5434
151.9102
151.1100
135.1640
129.2606
125.3353
121.8262
120.3366
115.4589
115.2342
[rel]
[ppm]


1H NMR
10.1499
7.8842
7.8569
7.8022
7.7764
7.7701
7.7733
7.3433
7.3151
7.3041
7.2369
7.2903
7.2770
7.0835
7.0799
7.0569
7.0379
7.0343
2.3402
Me
0.9990
1.9814
2.0140
3.9990
1.0202
2.9698
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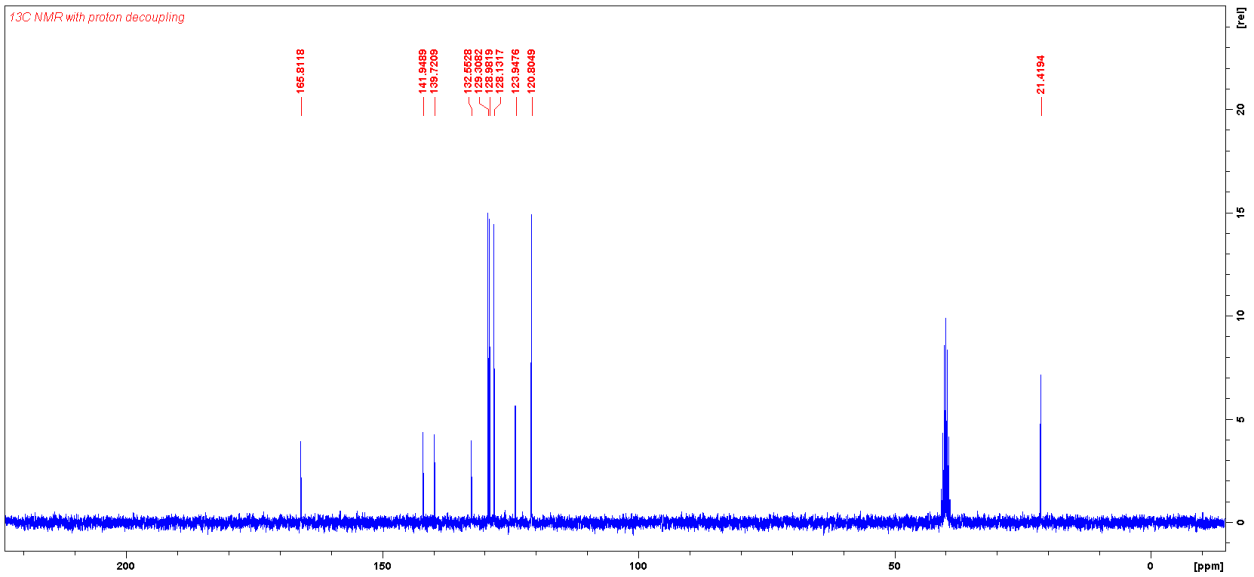
[ppm]


13C NMR with proton decoupling
165.8118
141.9489
139.7209
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129.3082
128.9819
128.1317
123.9476
120.8049
21.4194
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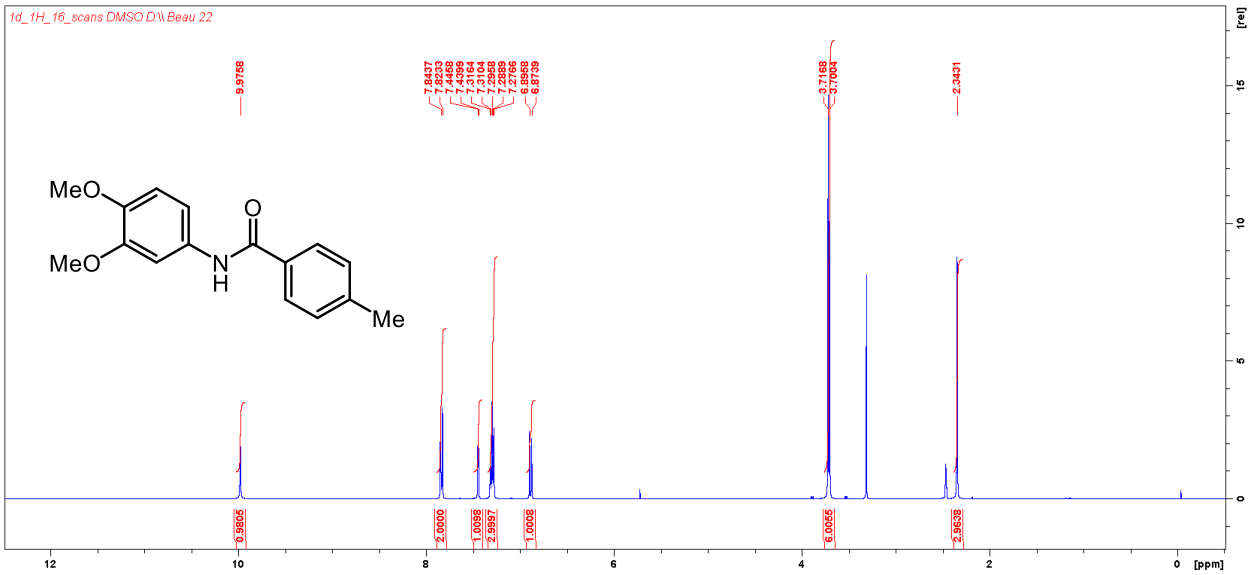
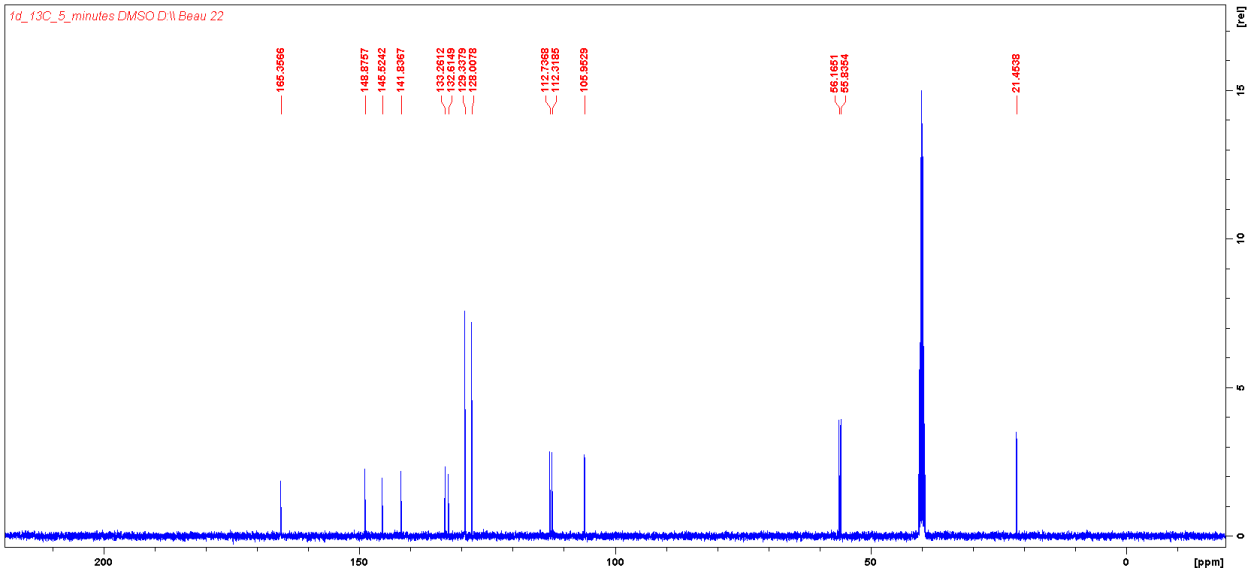
[ppm]


1d_1H_16_scans DMSO D:\\ Beau 22
9.9768
7.8437
7.8233
7.4458
7.4389
7.3164
7.3104
7.2958
7.2889
7.2766
6.8958
6.8739
3.7168
3.7004
2.3431
MeO
MeO
O
N
H
Me
0.9805
2.0000
1.0096
2.9997
1.0008
6.0055
2.9638
[rel]
[ppm]


1d_13C_5_minutes DMSO D:\\ Beau 22
165.3566
148.8757
145.5242
141.8367
133.2612
132.6149
129.3379
128.0078
112.7368
112.3185
105.9529
56.1651
55.8354
21.4538
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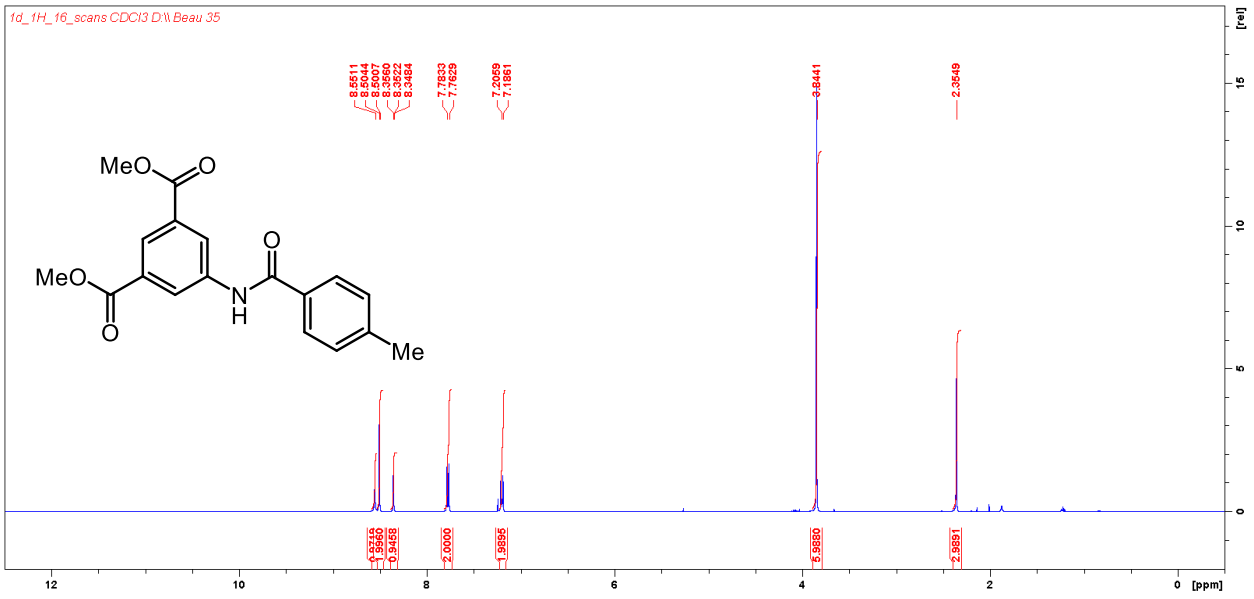
[ppm]


1d_1H_16_scans CDCl3 D:\\ Beau 35
8.5511
8.5044
8.5007
8.3980
8.3922
8.3484
7.7833
7.7629
7.2059
7.1861
3.8441
2.3549
MeO
O
MeO
O
N
H
O
Me
0.5556
1.9960
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1.9896
5.9680
2.9891
12
10
8
6
4
2
0
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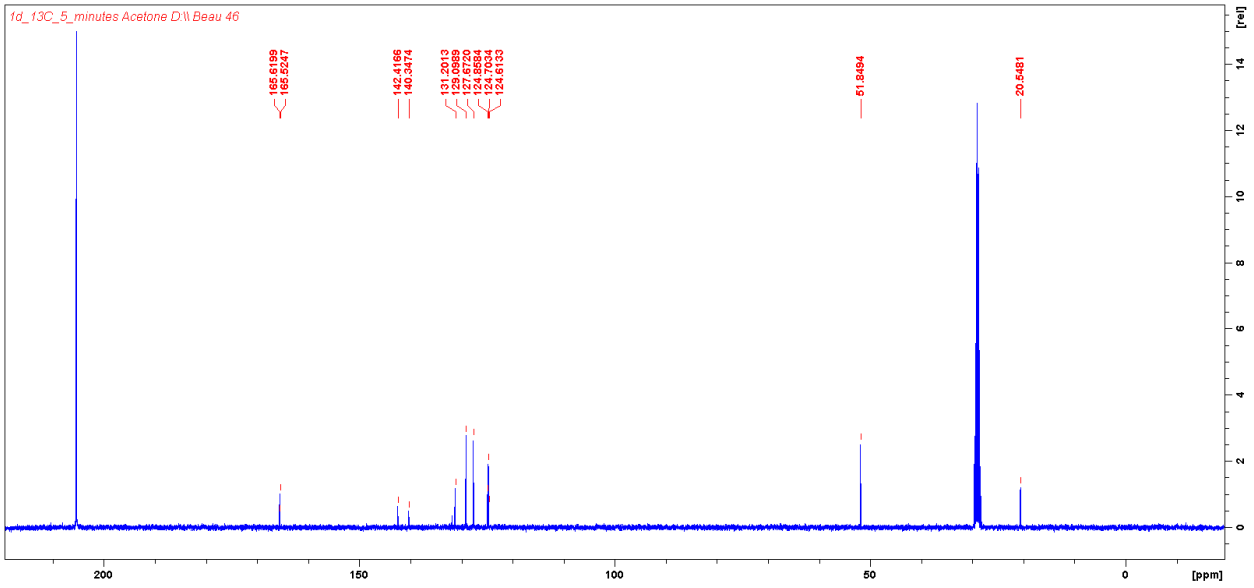
1d_13C_5_minutes Acetone D:\\ Beau 46
165.6199
165.5247
142.4166
140.3474
131.2013
129.6959
127.4720
124.8584
124.7034
124.6133
51.8494
20.5481
200
150
100
50
0
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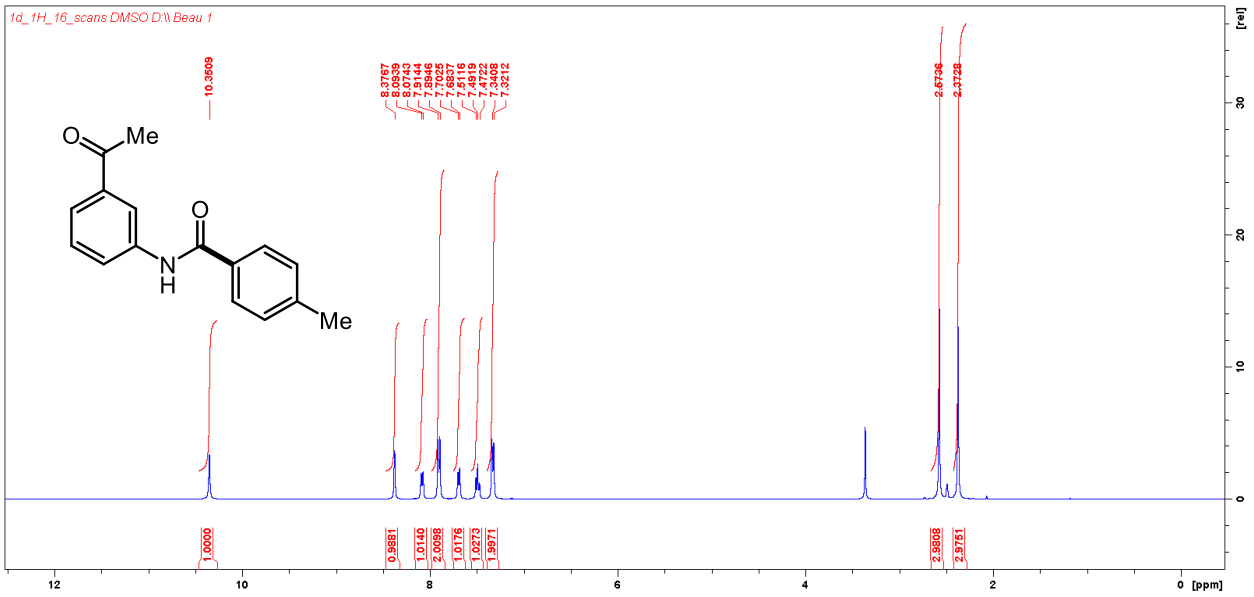
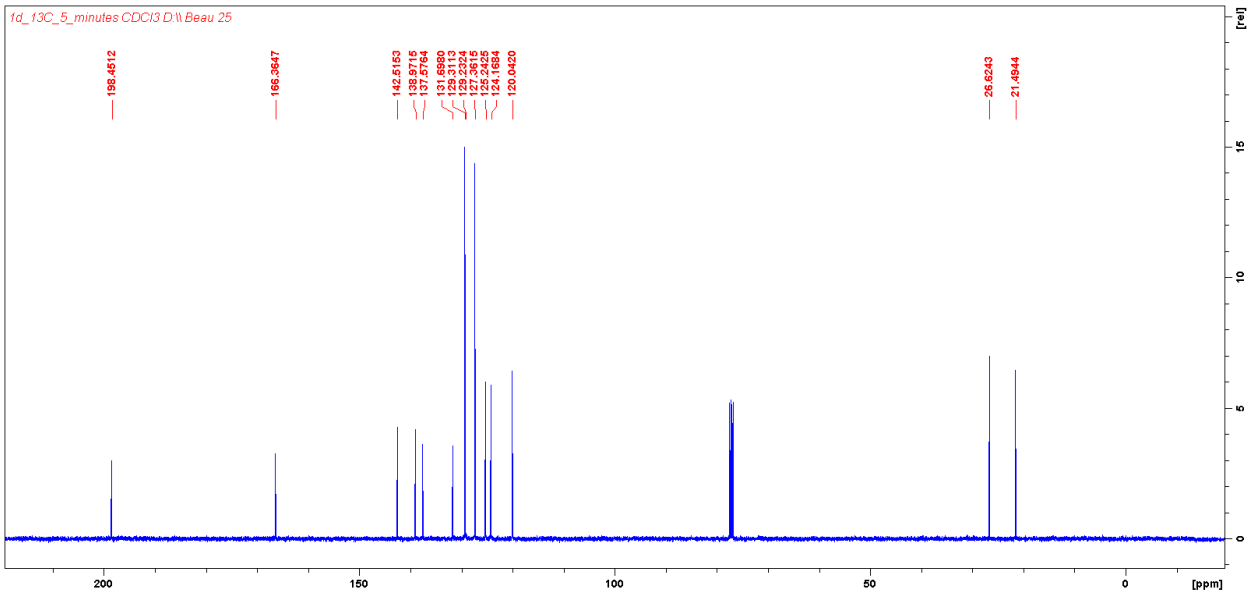
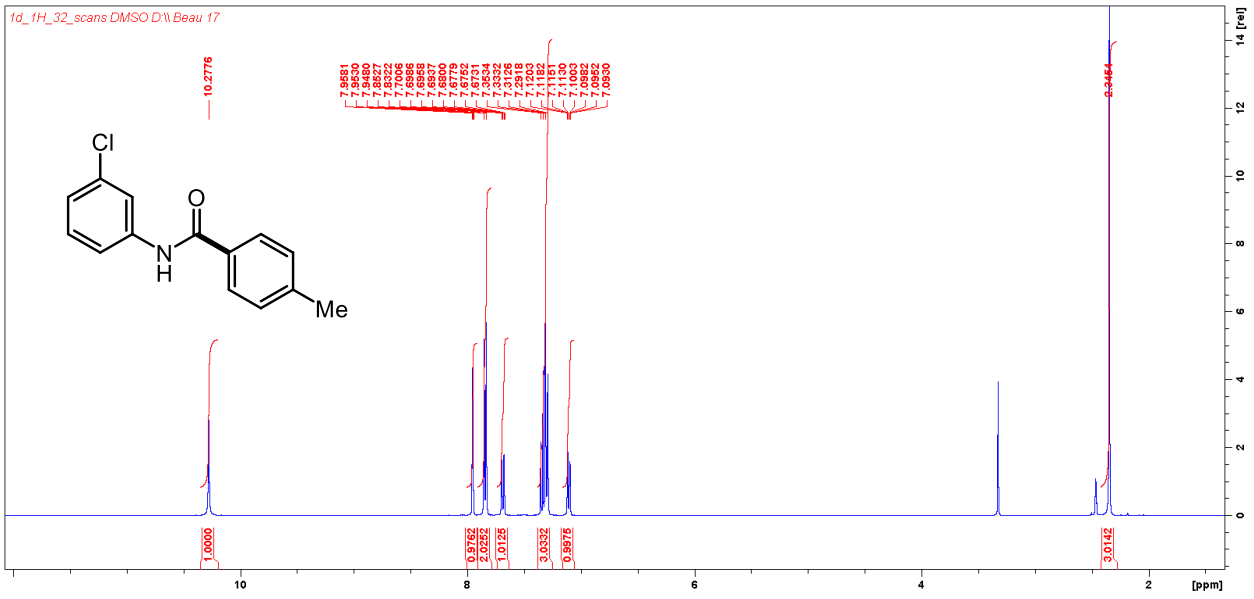
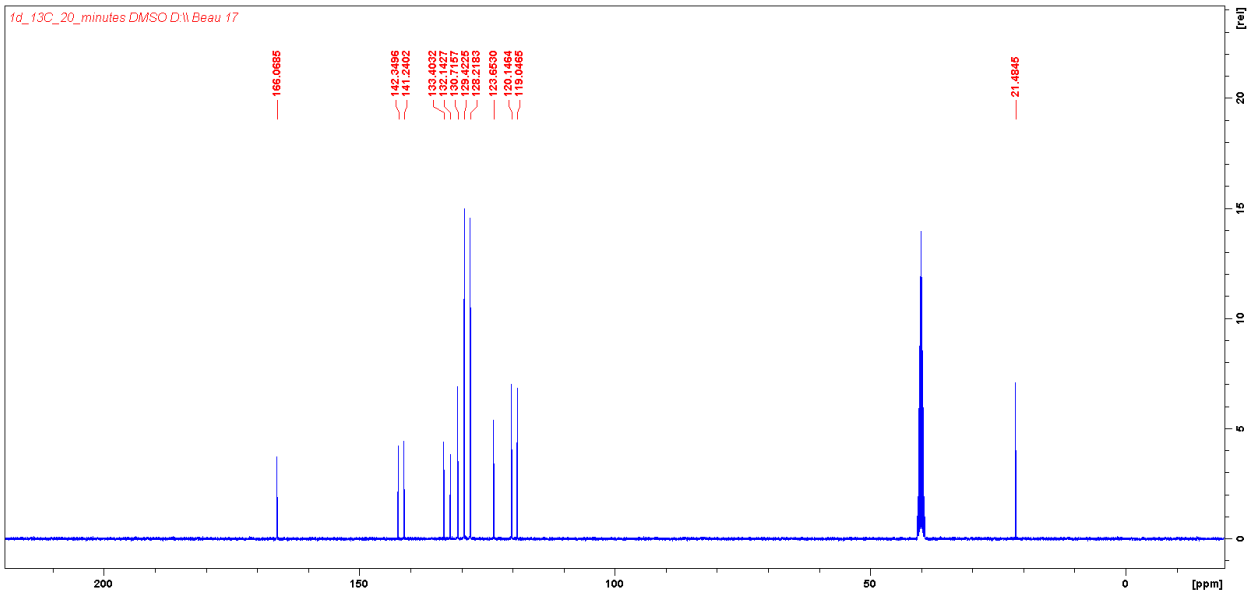
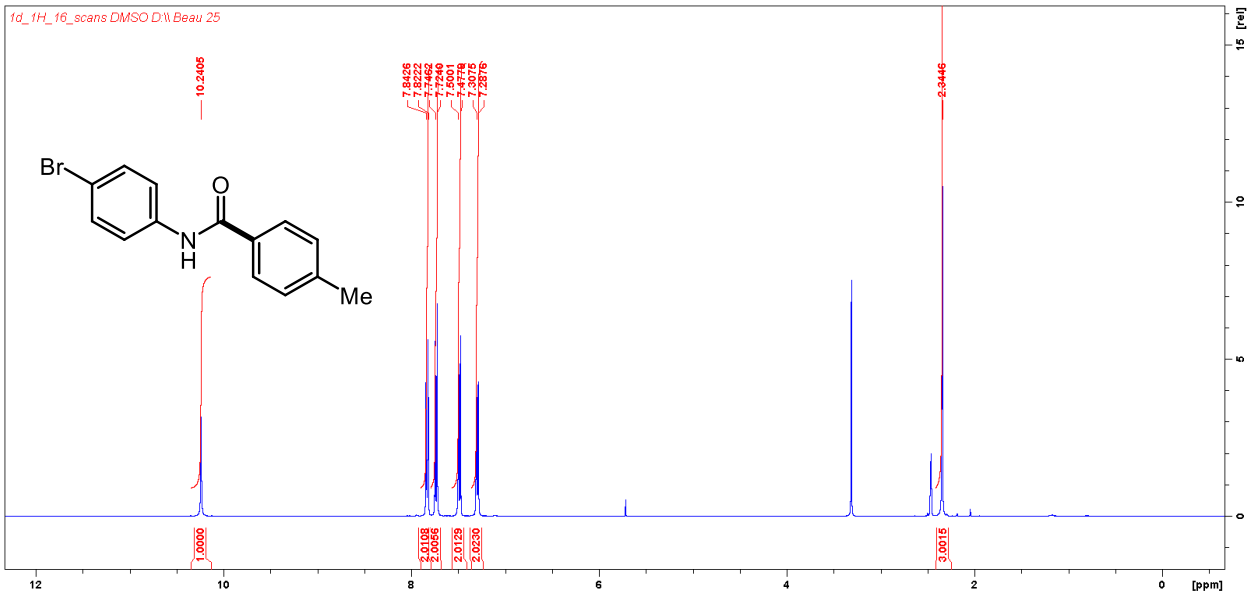
[rel]

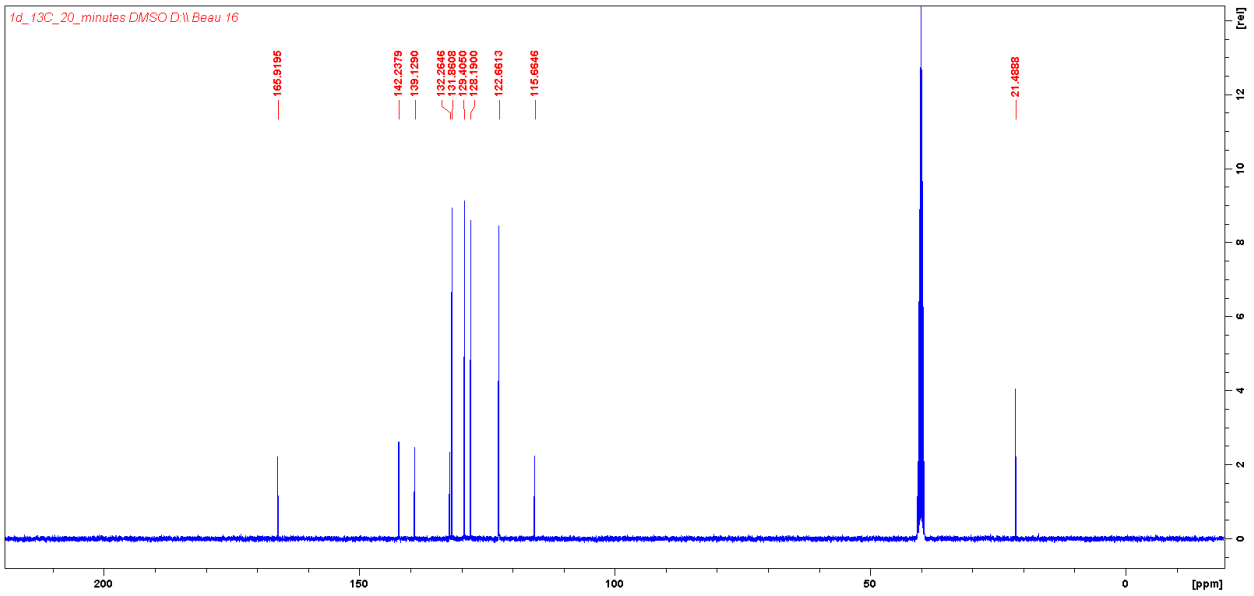

1d_1H_16_scans DMSO D:\\ Beau 1
10.3509
8.3767
8.0939
8.0743
7.9144
7.8946
7.7035
7.6837
7.5116
7.4919
7.4722
7.3402
7.3212
2.6706
2.3728
O
Me
O
N
H
Me
1.0000
0.9881
1.0140
2.0098
1.0176
1.0273
1.9971
2.9808
2.9761
12
10
8
6
4
2
0 [ppm]
[rel]

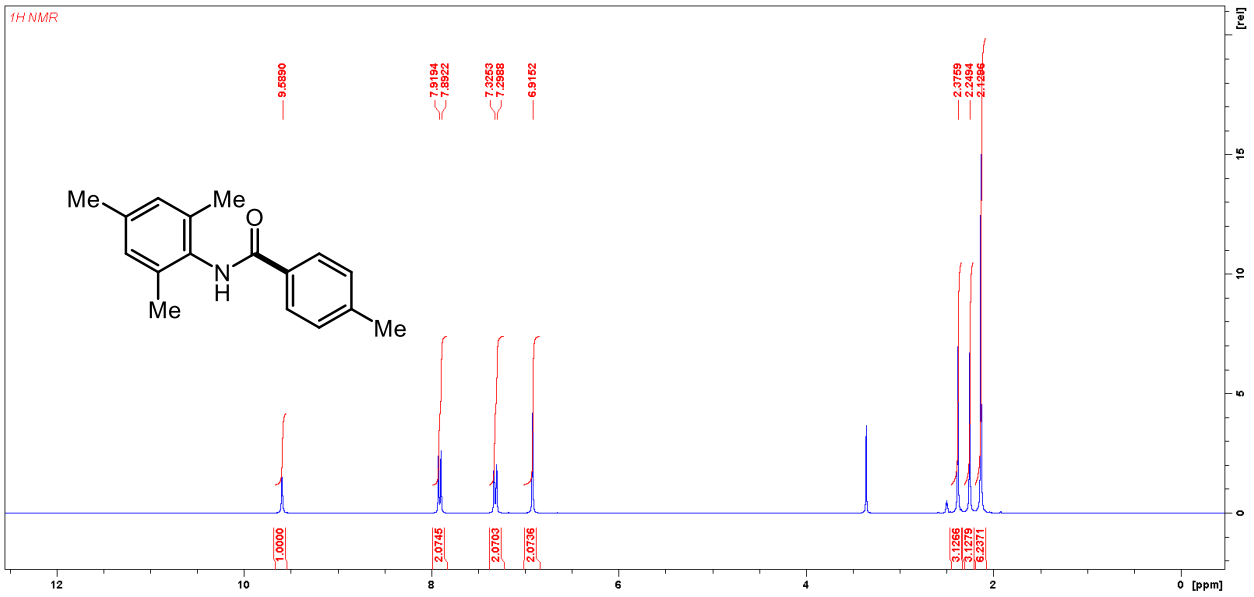

1d_13C_5_minutes CDCl3 D:\\ Beau 25
198.4512
166.3647
142.5153
138.9716
137.5764
131.6880
129.3113
129.2324
127.3615
125.7425
124.1694
120.0420
26.6243
21.4944
200
150
100
50
0 [ppm]
[rel]

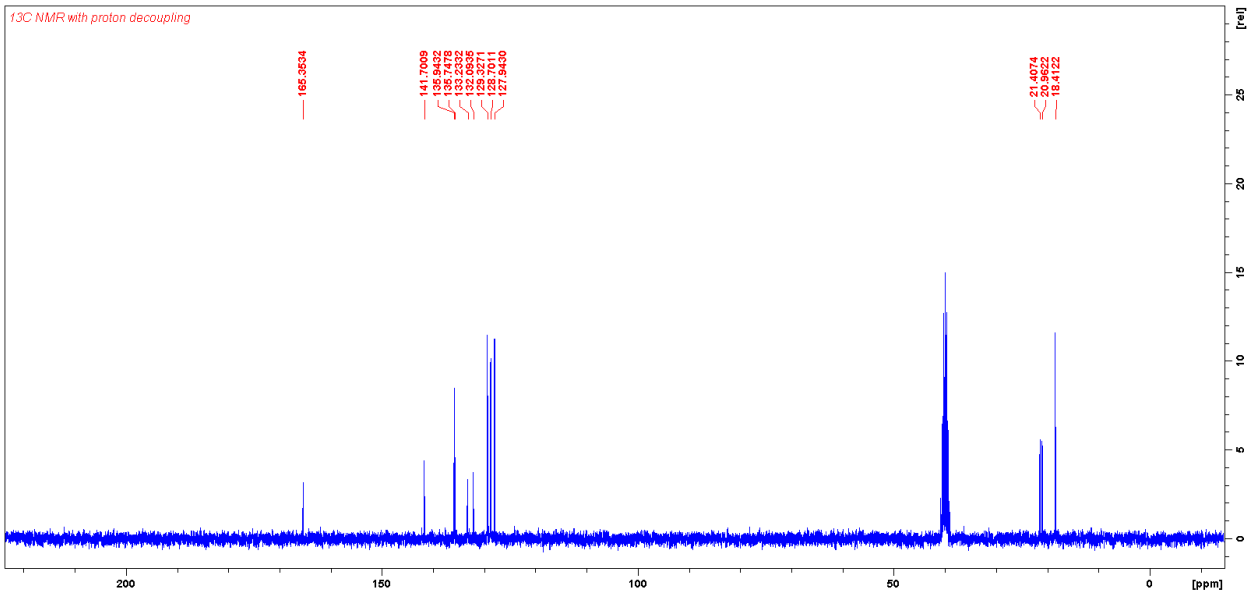

1d_1H_32_scans DMSO D:\\ Beau 17
10.2776
7.9591
7.9480
7.8827
7.8622
7.7066
7.6988
7.6958
7.6837
7.6800
7.6779
7.6762
7.6731
7.3834
7.3632
7.3125
7.2918
7.1203
7.1182
7.1151
7.1130
7.1003
7.0882
7.0662
7.0530
2.3464
Cl
O
N
H
Me
1.0000
0.9762
2.0292
1.0125
3.0332
0.9975
3.0142
[rel]
[ppm]

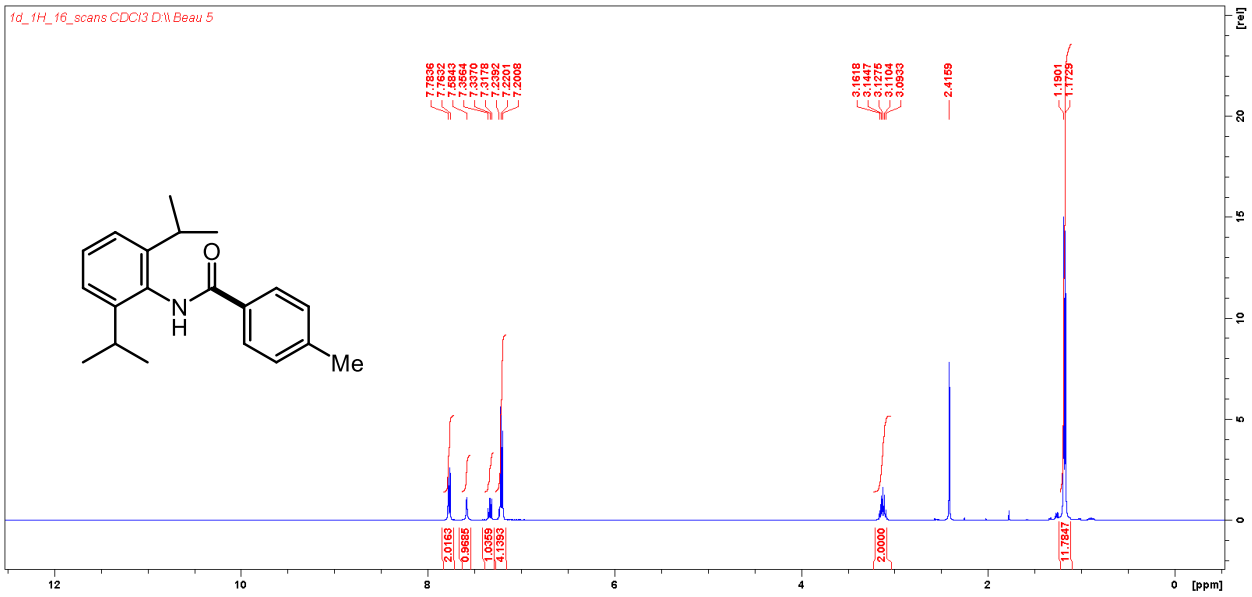

1d_13C_20_minutes DMSO D:\\ Beau 17
166.0685
142.3496
141.2402
133.4032
132.1427
130.3757
129.4225
128.2183
123.6530
120.1464
119.0465
21.4845
[rel]
[ppm]

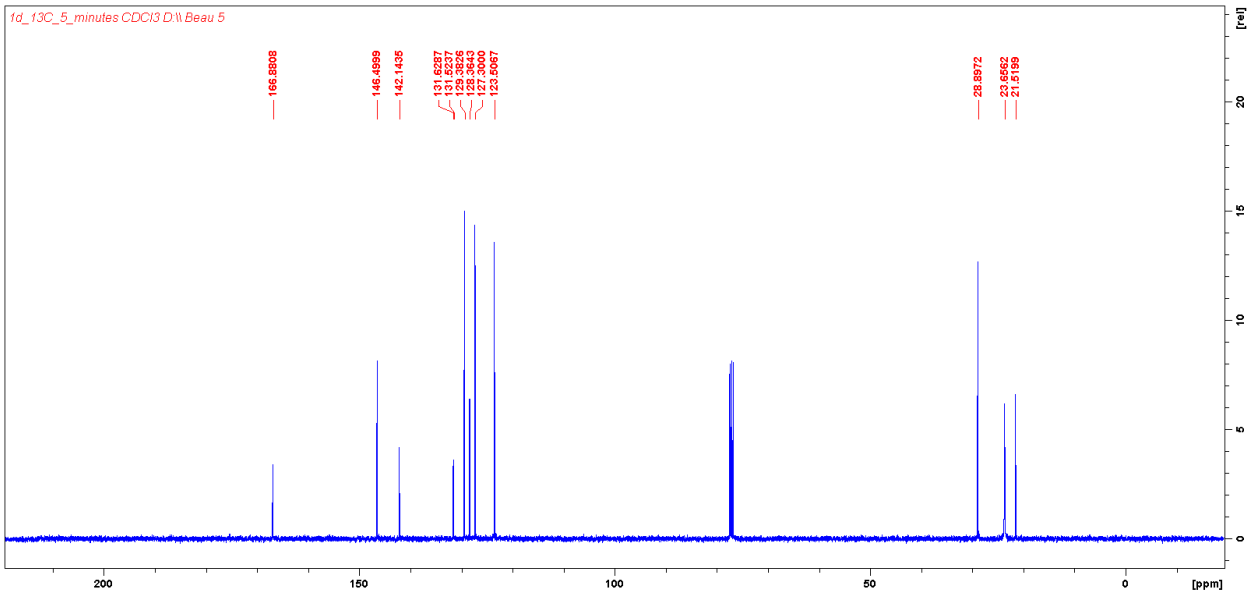

1d_1H_16_scans DMSO D:\\ Beau 25
10.2405
7.8426
7.8222
7.7462
7.7260
7.5001
7.4778
7.3075
7.2876
2.3446
Br
O
N
H
Me
1.0000
2.0108
2.0056
2.0129
2.0230
3.0015
12
10
8
6
4
2
0
[ppm]
[rel]

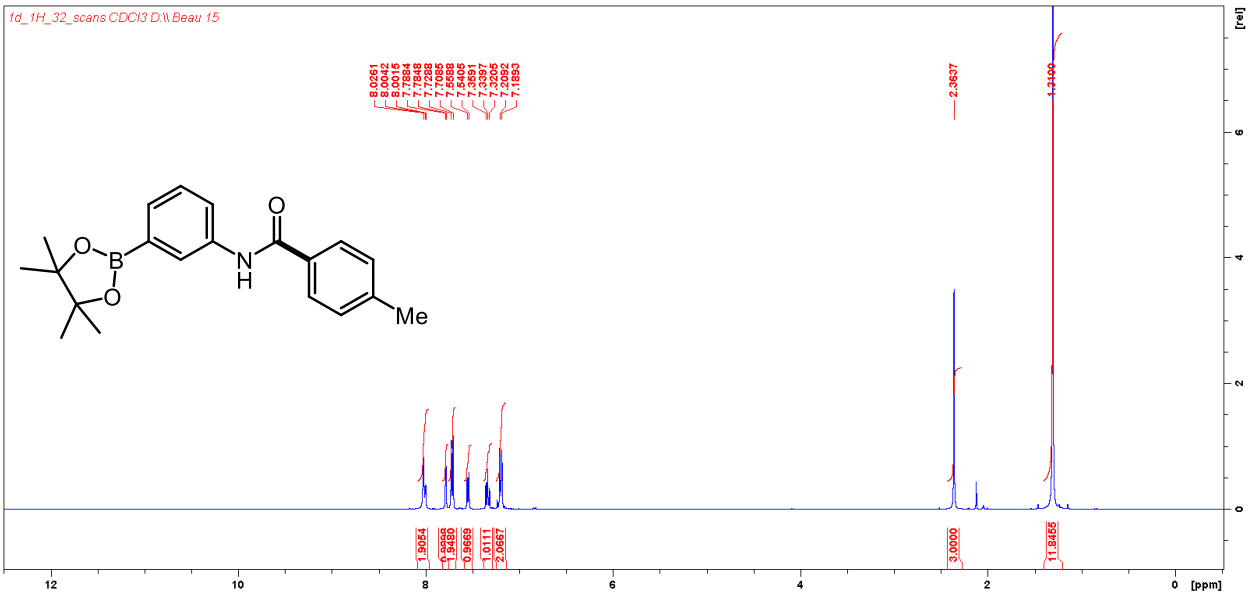

1d_13C_20_minutes DMSO D:\\ Beau 16
165.9195
142.2379
139.1290
132.2646
131.8808
129.4050
128.1900
122.6613
115.6646
21.4888
200
150
100
50
0
[ppm]
[rel]

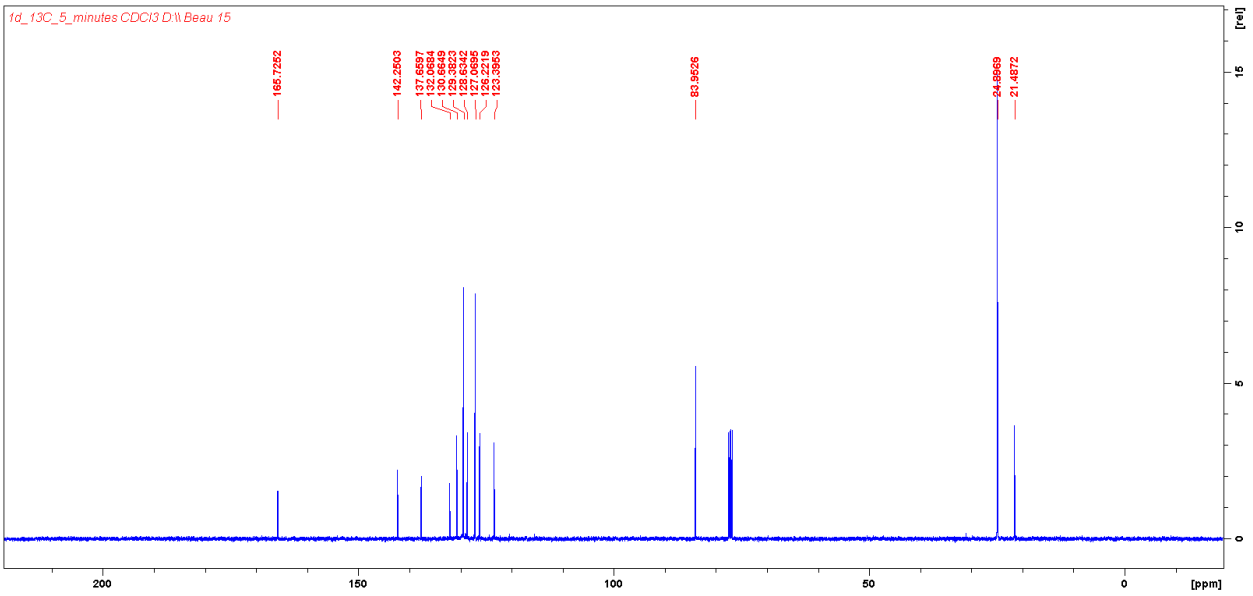

1H NMR
9.5890
7.9194
7.8922
7.3253
7.2988
6.9152
2.3759
2.2494
2.1396
Me
Me
O
N
H
Me
Me
1.0000
2.0745
2.0703
2.0736
3.1266
3.1279
6.2371
[rel]
[ppm]

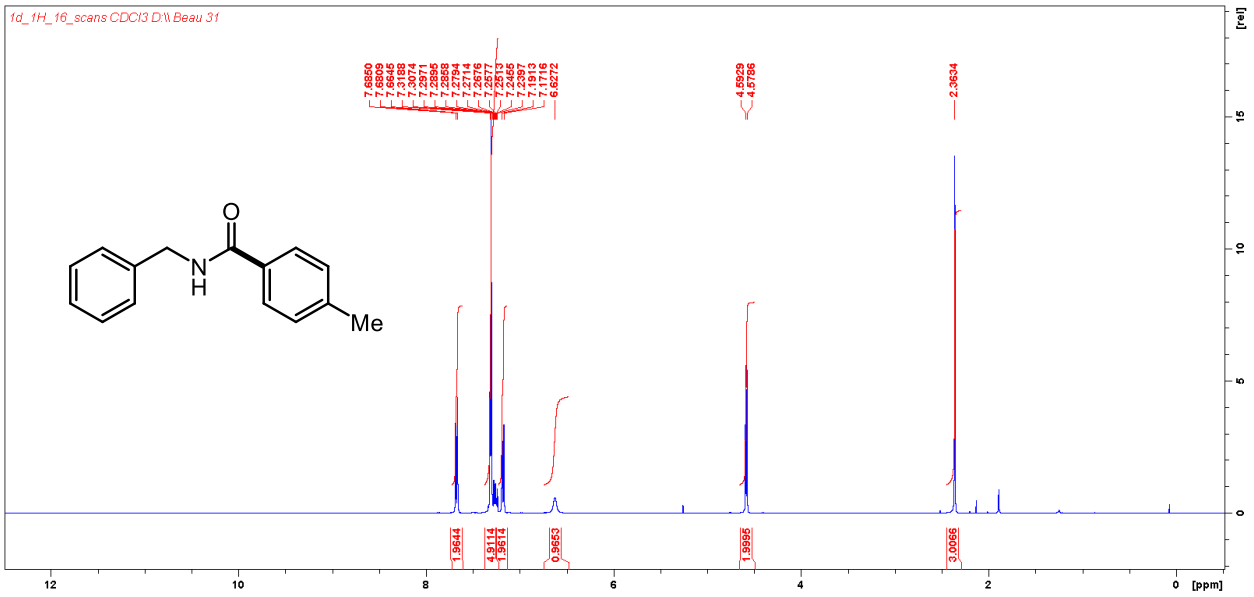

13C NMR with proton decoupling
165.3534
141.7009
135.8432
135.7478
133.2332
129.3925
128.8271
128.7011
127.9430
21.4074
20.9622
18.4722
[rel]
[ppm]

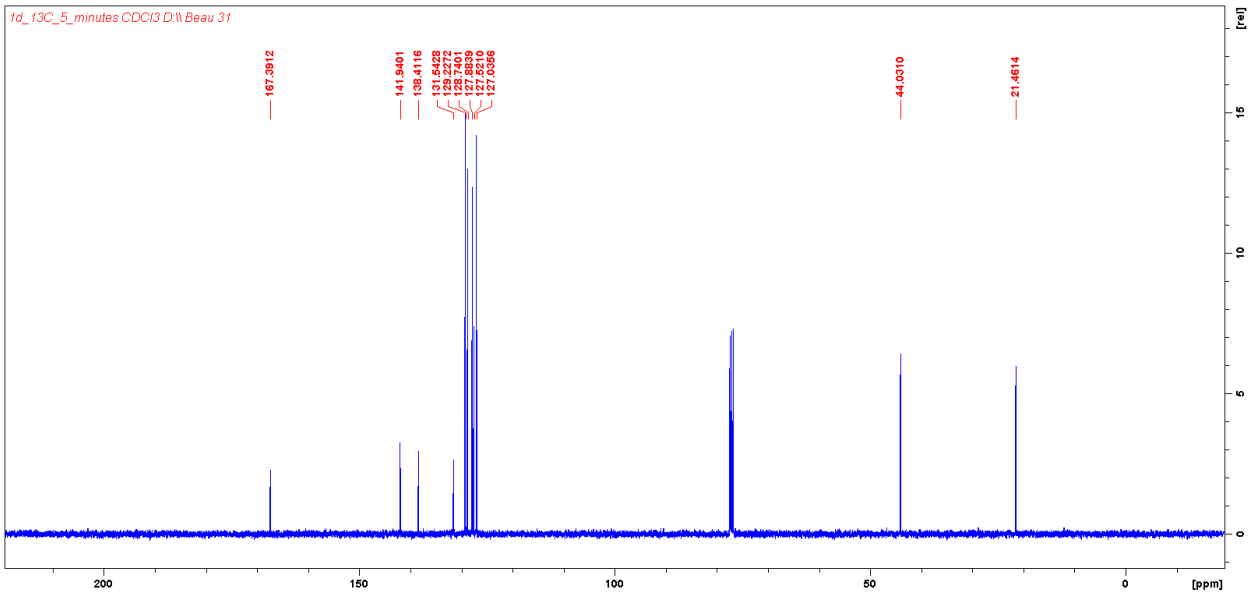

1d_1H_16_scans CDCl3 D:\\ Beau 5
7.7836
7.7632
7.5843
7.3564
7.3370
7.3178
7.2982
7.2201
7.2008
3.1618
3.1447
3.1275
3.1104
3.0933
2.4169
1.1901
1.1729
2.0163
0.9685
1.0359
4.1393
2.0000
11.7847
O
N
H
Me
12
10
8
6
4
2
0
[ppm]
[rel]

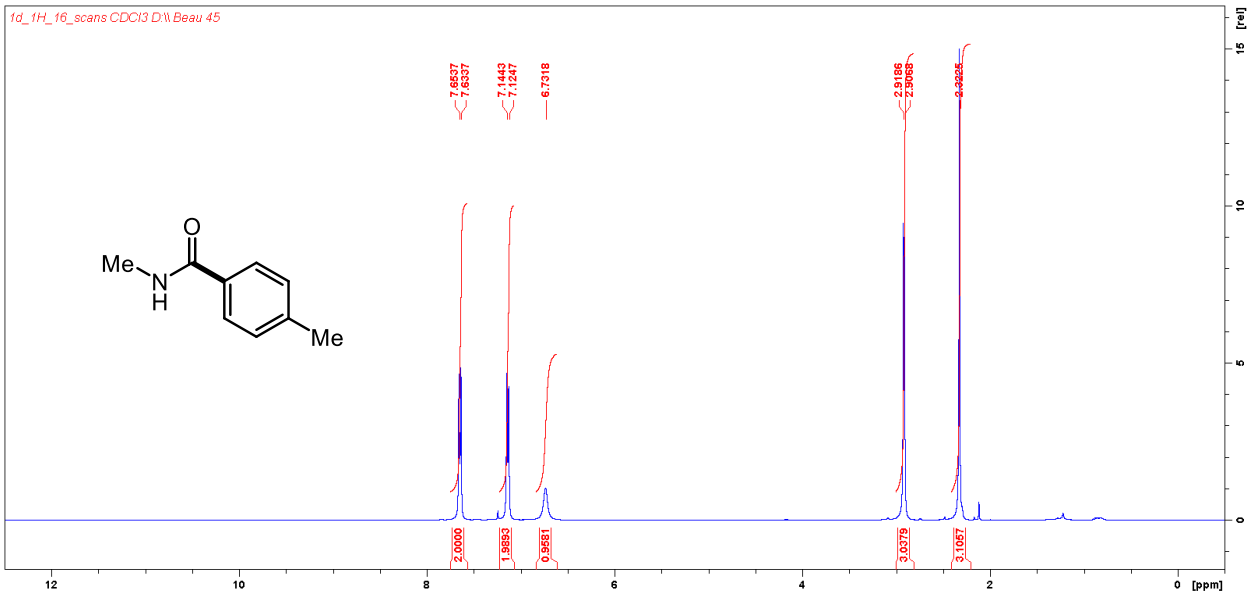

1d_13C_5_minutes CDCl3 D:\\ Beau 5
166.8808
146.4999
142.1435
131.6287
131.5237
129.3826
128.3643
127.2000
123.5067
28.8972
23.6562
21.5199
200
150
100
50
0
[ppm]
[rel]

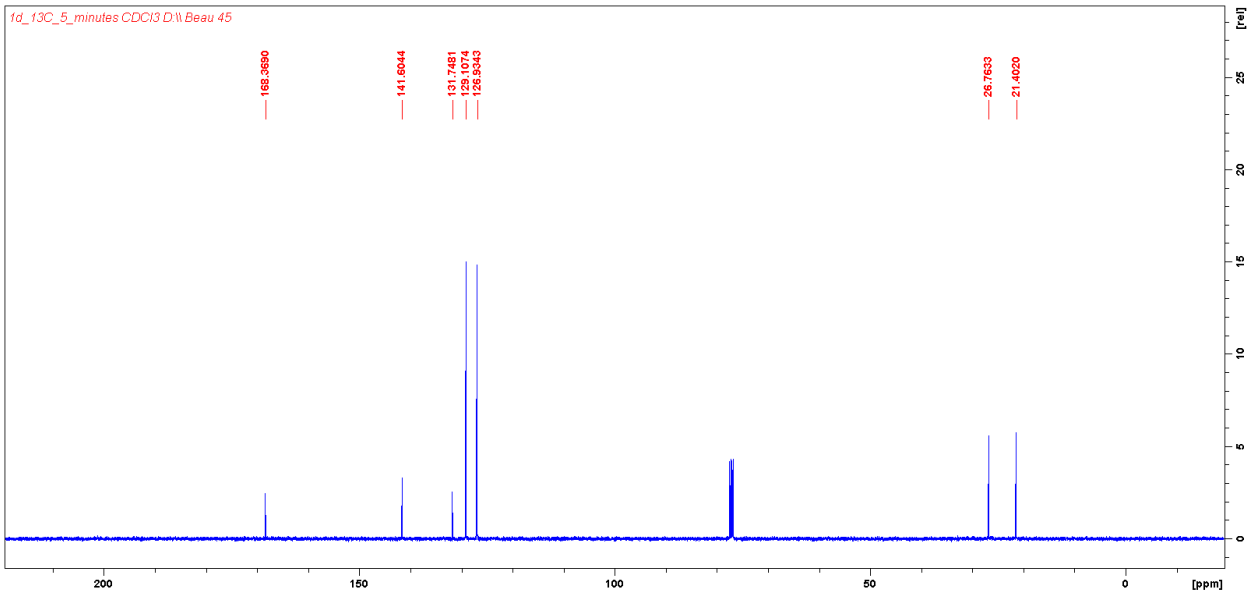

1d_1H_32_scans CDCl3 D:\\ Beau 15
8.0281
8.0042
8.0016
7.7884
7.7848
7.7288
7.7088
7.5588
7.5405
7.3891
7.3397
7.3296
7.2092
7.1893
2.3637
1.3100
O
O
B
O
N
H
Me
1.9054
1.9486
0.9669
1.0111
2.0667
3.0000
11.8455
12
10
8
6
4
2
0
[ppm]
[rel]

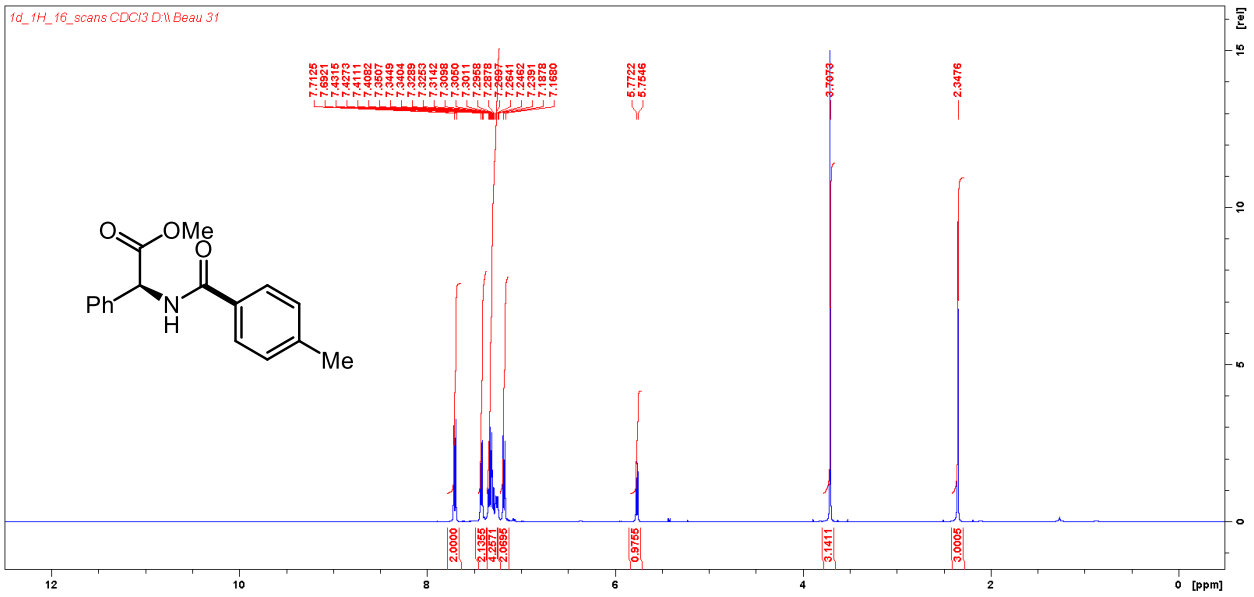

1d_13C_5_minutes CDCl3 D:\\ Beau 15
165.7252
142.2503
137.6597
132.0684
130.8848
129.3823
128.6342
127.0695
126.2219
123.3953
83.9526
24.8969
21.4872
200
150
100
50
0
[ppm]
[rel]


1d_1H_16_scans CDCl3 D:\\ Beau 31
7.6850
7.6809
7.6645
7.3188
7.3074
7.2971
7.2896
7.2868
7.2794
7.2714
7.2676
7.2577
7.2513
7.2467
7.2397
7.1913
7.1716
6.8272
4.5929
4.5786
2.3634
O
N
H
Me
1.9644
4.9114
1.9614
0.9653
1.9985
3.0066
[rel]
[ppm]


1d_13C_5_minutes CDCl3 D:\\ Beau 31
167.3912
141.9401
138.4116
131.5428
129.2272
128.7401
128.5839
127.6210
127.0356
44.0310
21.4614
[rel]
[ppm]


1d_1H_16_scans CDCl3 D:\\ Beau 45
7.6537
7.6337
7.1443
7.1247
6.7318
2.9186
2.9068
2.3825
O
Me
N
H
Me
2.0000
1.9853
0.9581
3.0079
3.1067
12
10
8
6
4
2
0
[ppm]
[rel]


1d_13C_5_minutes CDCl3 D:\\ Beau 45
168.3690
141.6044
131.7481
129.1074
126.9343
26.7633
21.4020
200
150
100
50
0
[ppm]
[rel]


1d_1H_16_scans CDCl3 D:\\ Beau 31
7.7125
7.6921
7.4315
7.4273
7.4111
7.4082
7.3507
7.3449
7.3384
7.3288
7.3253
7.3142
7.3098
7.3060
7.3011
7.2958
7.2878
7.2697
7.2641
7.2462
7.2391
7.1878
7.1680
5.7722
5.7546
3.7973
2.3476
O
OMe
O
Ph
N
H
Me
2.0000
2.1355
4.2571
2.0695
0.9755
3.1411
3.0005
12
10
8
6
4
2
0
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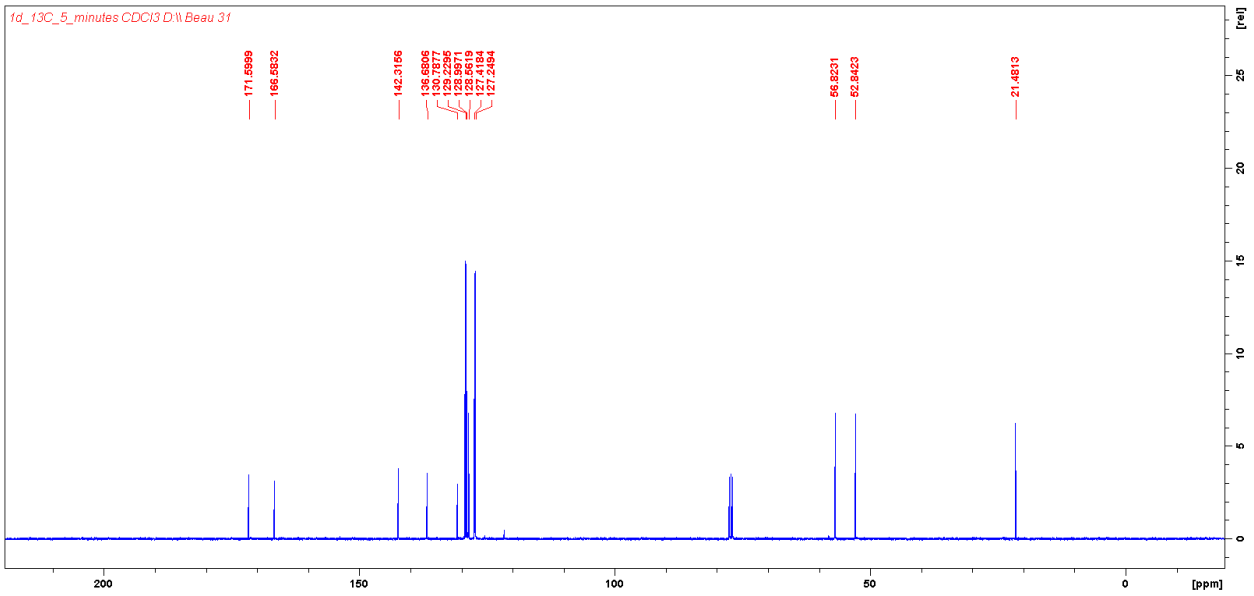
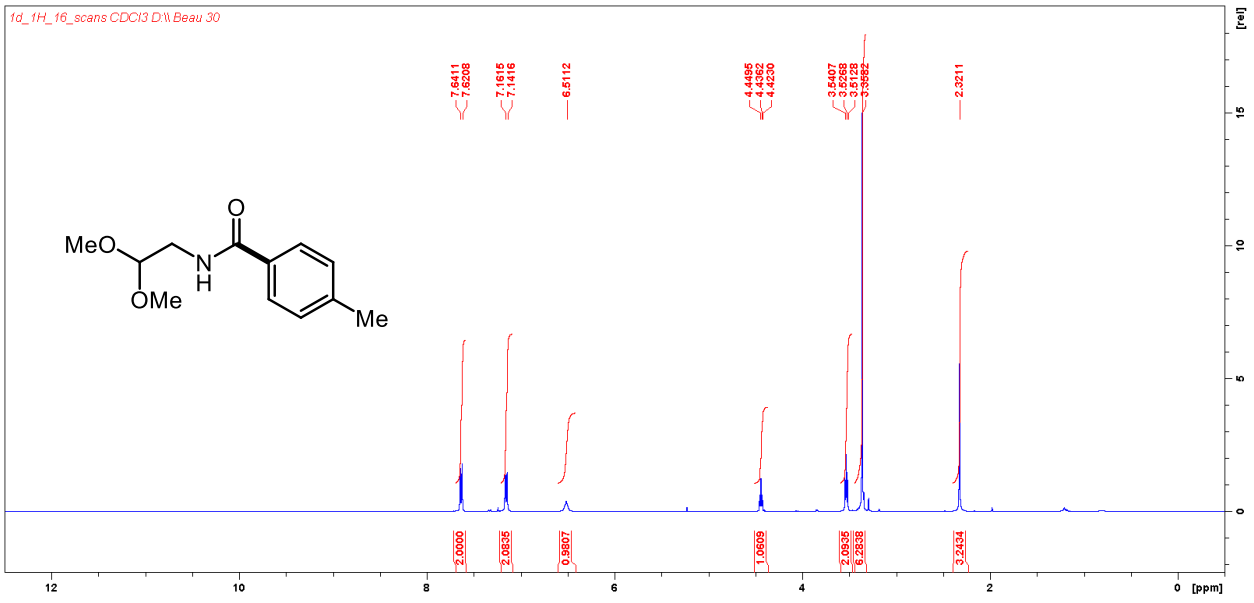
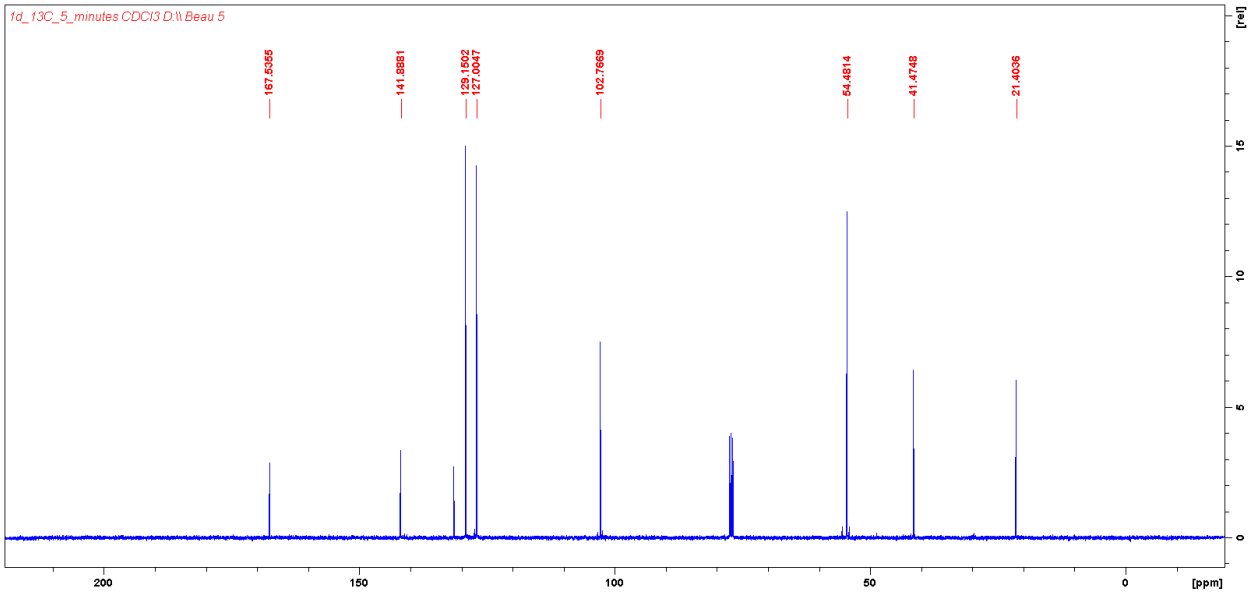
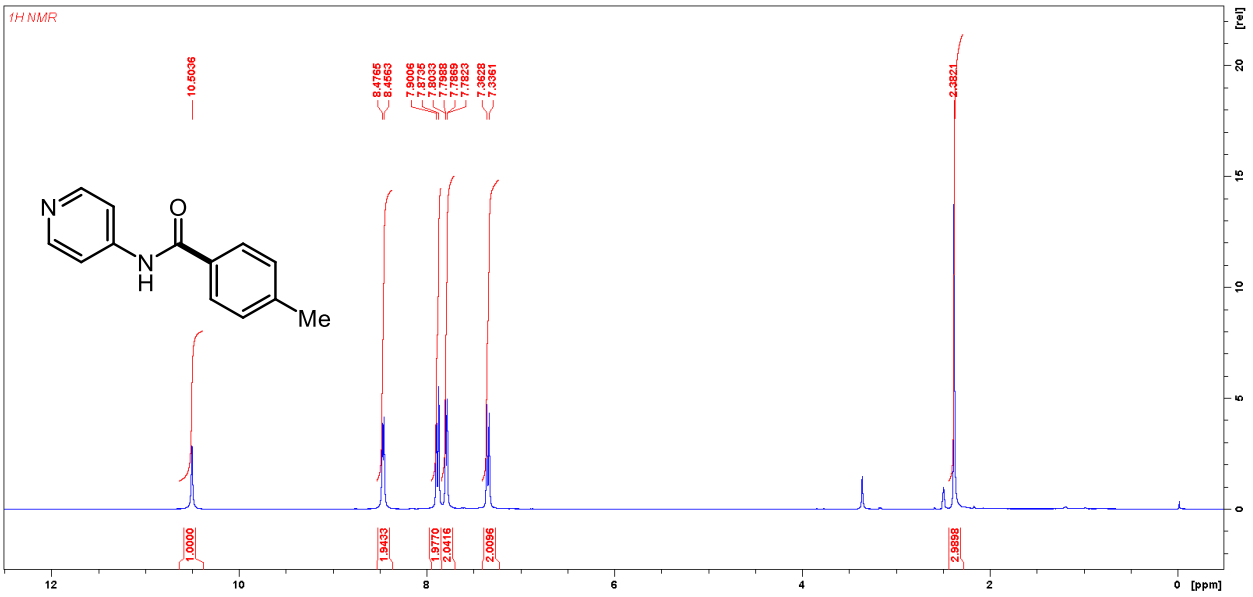
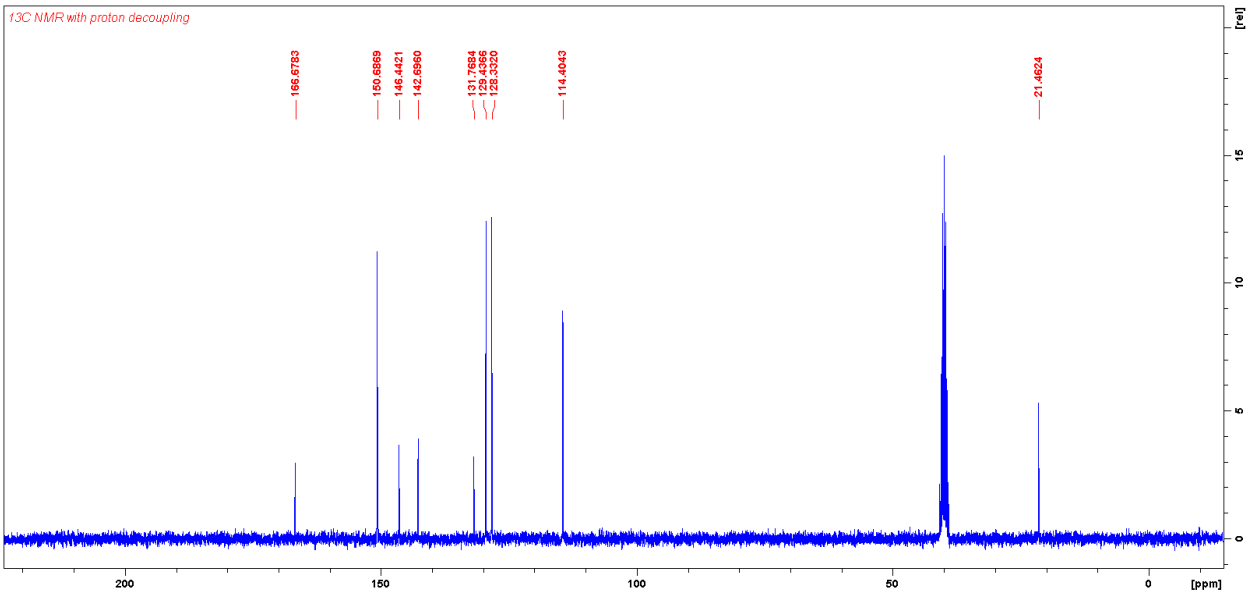
[rel]

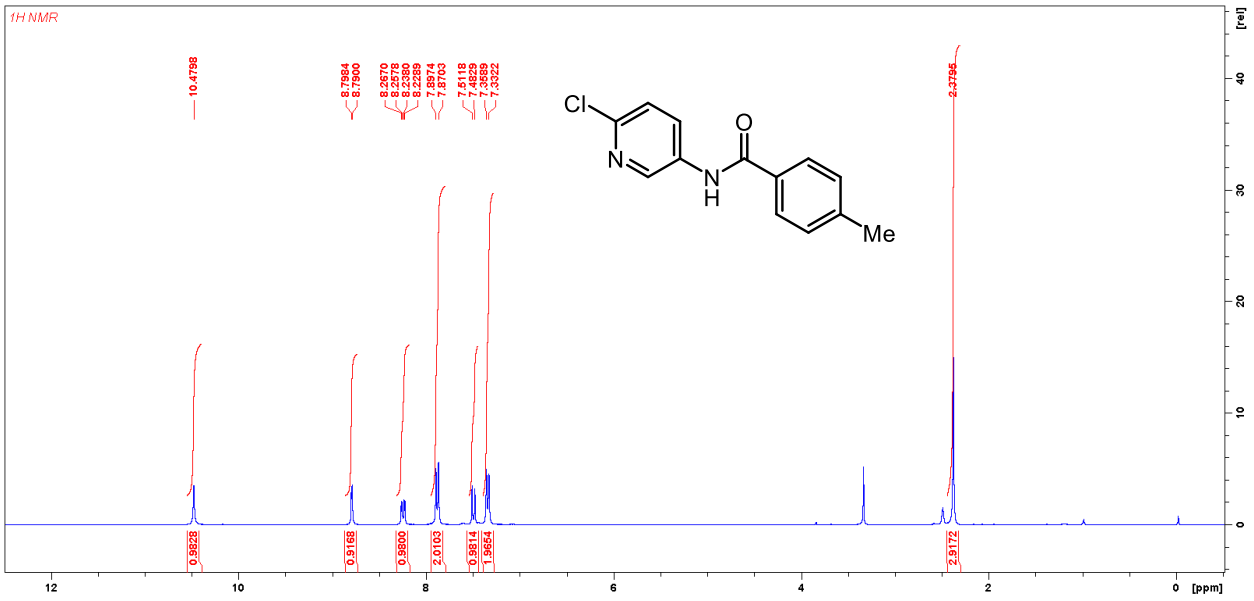

1d_13C_5_minutes CDCl3 D:\\ Beau 31
171.5999
166.6832
142.3156
136.6806
130.7877
129.2295
128.9971
128.5578
127.4184
127.2494
56.8231
52.8423
21.4813
200
150
100
50
0
[ppm]
[rel]

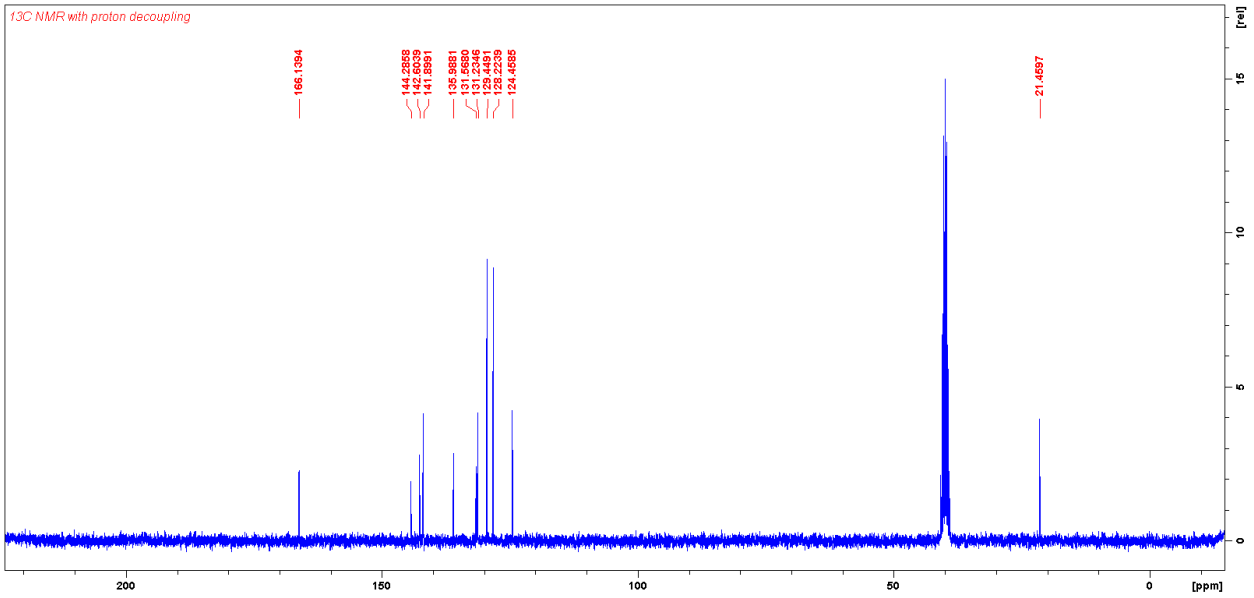

1d_1H_16_scans CDCl3 D:\\ Beau 30
7.6411
7.6208
7.1615
7.1416
6.5112
4.4495
4.4362
4.4230
3.5407
3.5268
3.5128
3.3682
2.3211
MeO
OMe
N
H
O
Me
2.0000
2.0835
0.9807
1.0509
2.0535
6.2838
3.2434
[rel]
[ppm]

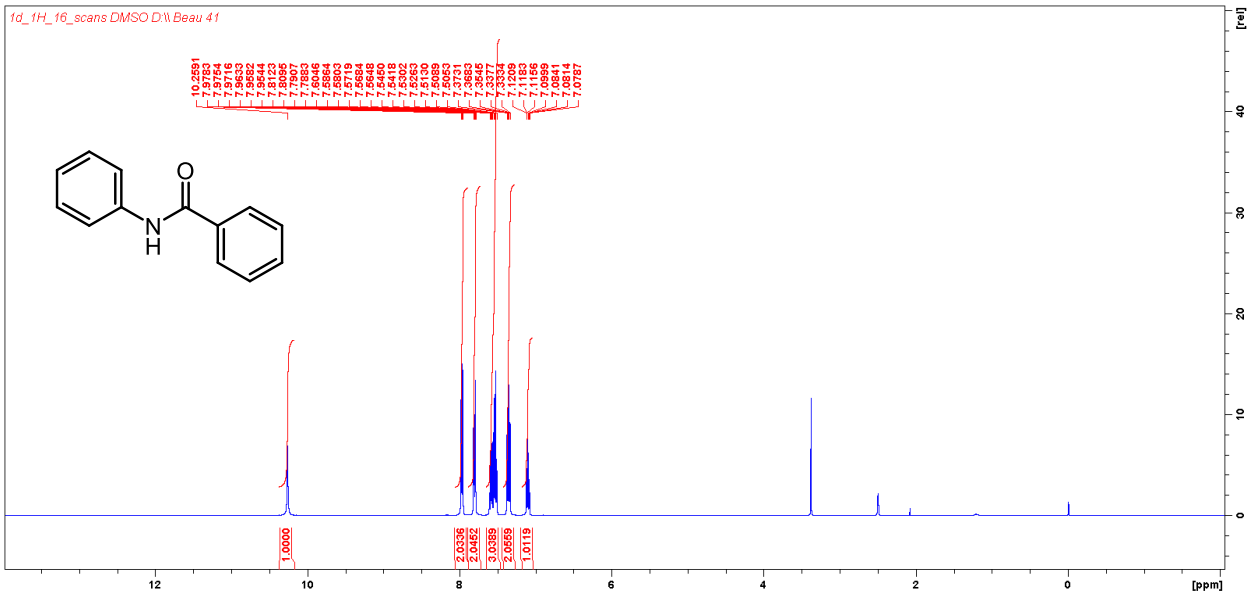

1d_13C_5_minutes CDCl3 D:\\ Beau 5
167.5355
141.8881
129.1502
127.0047
102.7669
54.4814
41.4748
21.4036
[rel]
[ppm]

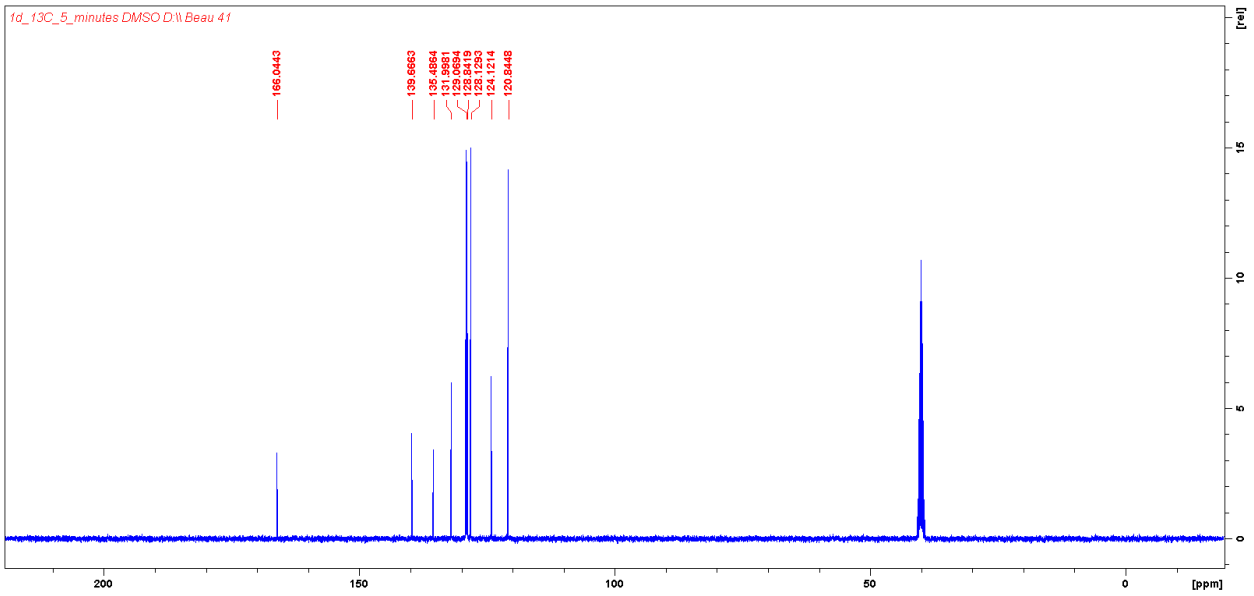

1H NMR
10.5036
8.4765
8.4663
7.9006
7.8736
7.8033
7.7988
7.7889
7.7823
7.3629
7.3361
2.3821
N
O
N
H
Me
1.0000
1.9433
1.9770
2.0416
2.0096
2.9698
[rel]
[ppm]

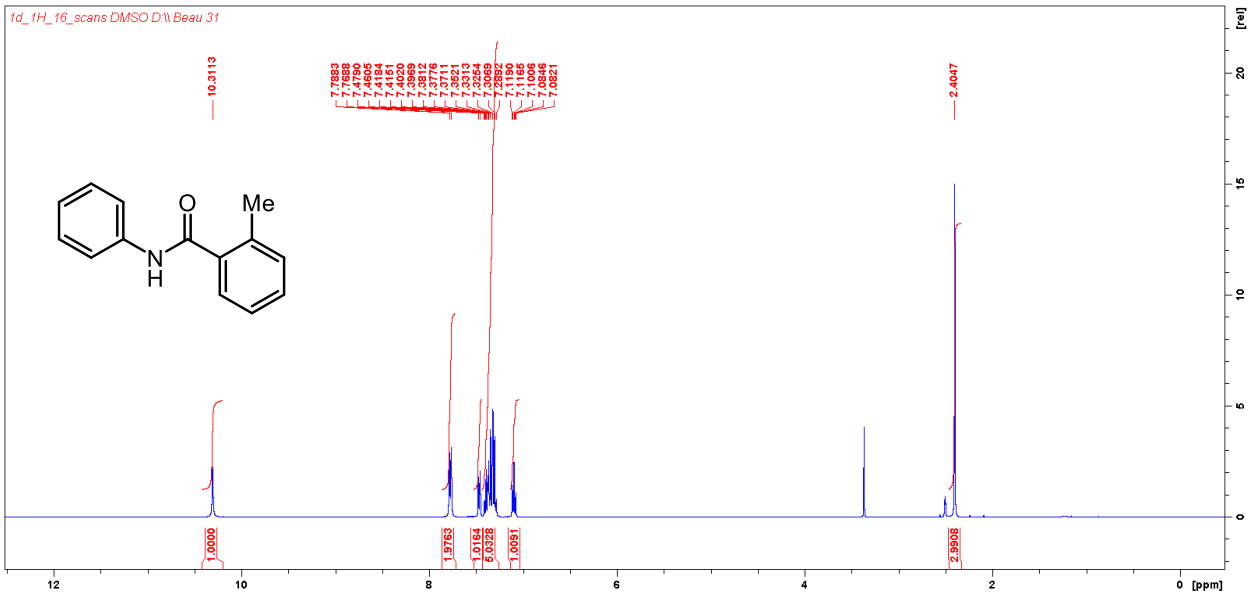

13C NMR with proton decoupling
166.6783
150.6869
146.4421
142.6960
131.7684
129.4356
128.3350
114.4043
21.4624
[rel]
[ppm]

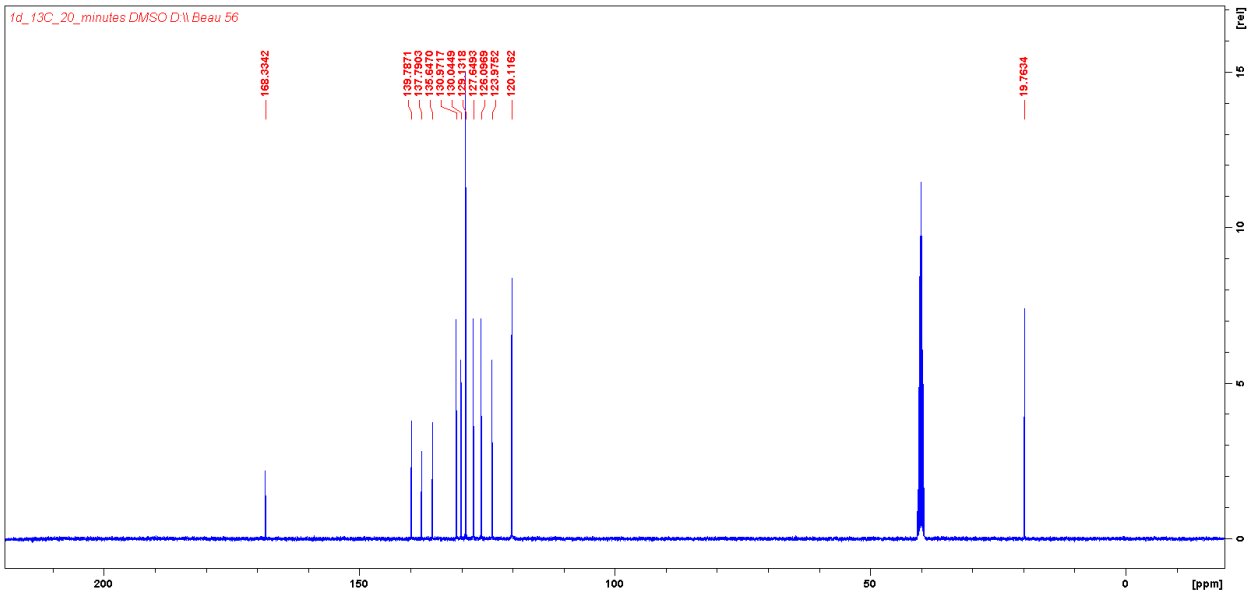

1H NMR
10.4798
8.7984
8.7900
8.2670
8.2578
8.2380
8.2289
7.8974
7.8703
7.5118
7.4829
7.3939
7.3722
2.3796
Cl
N
O
N
H
Me
0.9828
0.9168
0.9800
2.0103
0.9814
1.9654
2.9172
[rel]
[ppm]

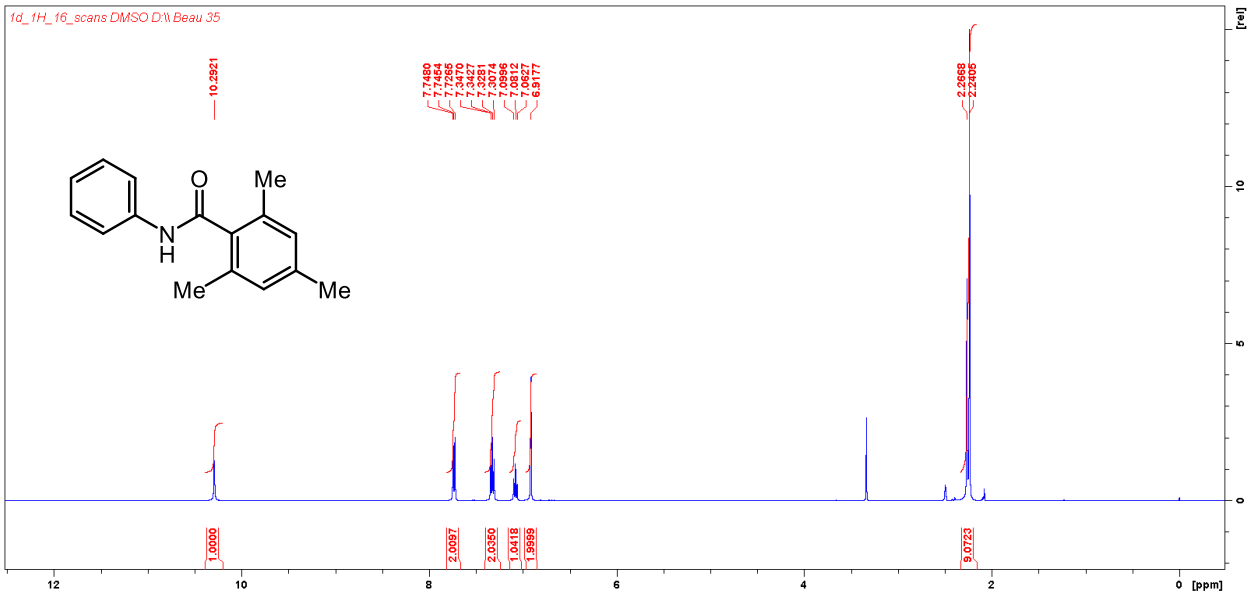

13C NMR with proton decoupling
166.1394
144.2858
142.6039
141.8991
135.9881
131.5680
131.2346
129.4491
128.2239
124.4685
21.4597
[rel]
[ppm]

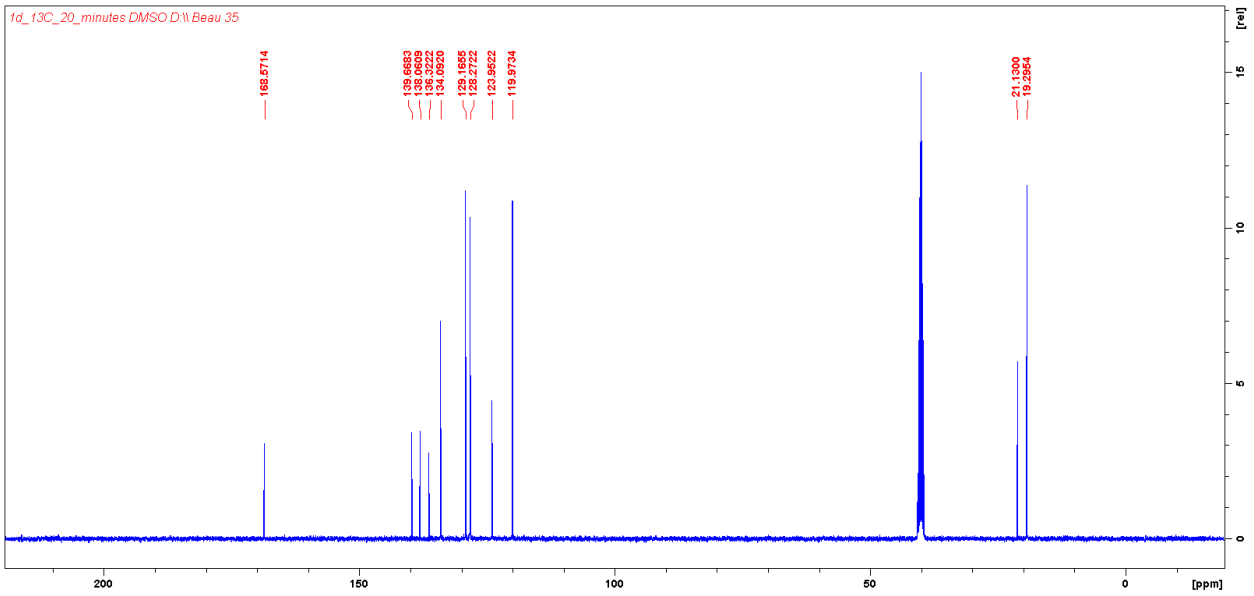

1d_1H_16_scans DMSO D:\\ Beau 41
10.2691
7.9783
7.9754
7.9716
7.9633
7.9582
7.9544
7.8823
7.8096
7.7907
7.7883
7.6946
7.6894
7.5803
7.5719
7.5684
7.5646
7.5450
7.5418
7.5302
7.5263
7.5130
7.5089
7.5053
7.4731
7.4683
7.3546
7.3377
7.3334
7.1183
7.1163
7.1156
7.0999
7.0841
7.0814
7.0787
O
N
H
1.0000
2.0336
2.0452
3.0389
2.0659
1.0119
12
10
8
6
4
2
0
[ppm]
[re]

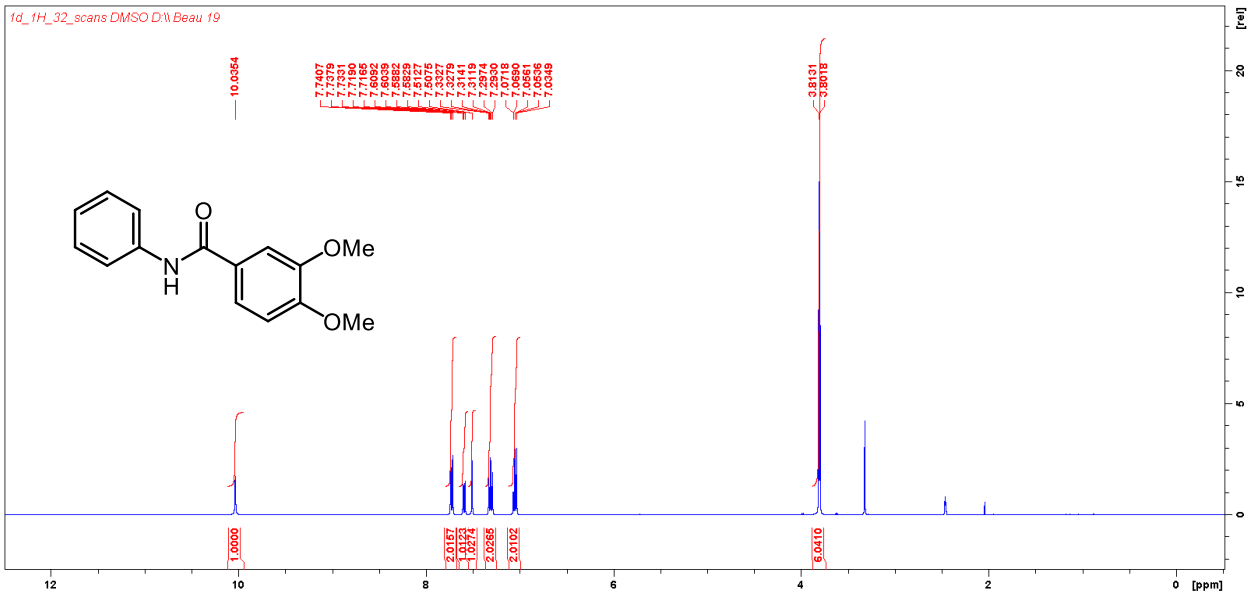

1d_13C_5_minutes DMSO D:\\ Beau 41
166.0443
139.6663
135.4864
131.9981
129.0834
128.4419
128.1293
124.1214
120.8448
200
150
100
50
0
[ppm]
[re]

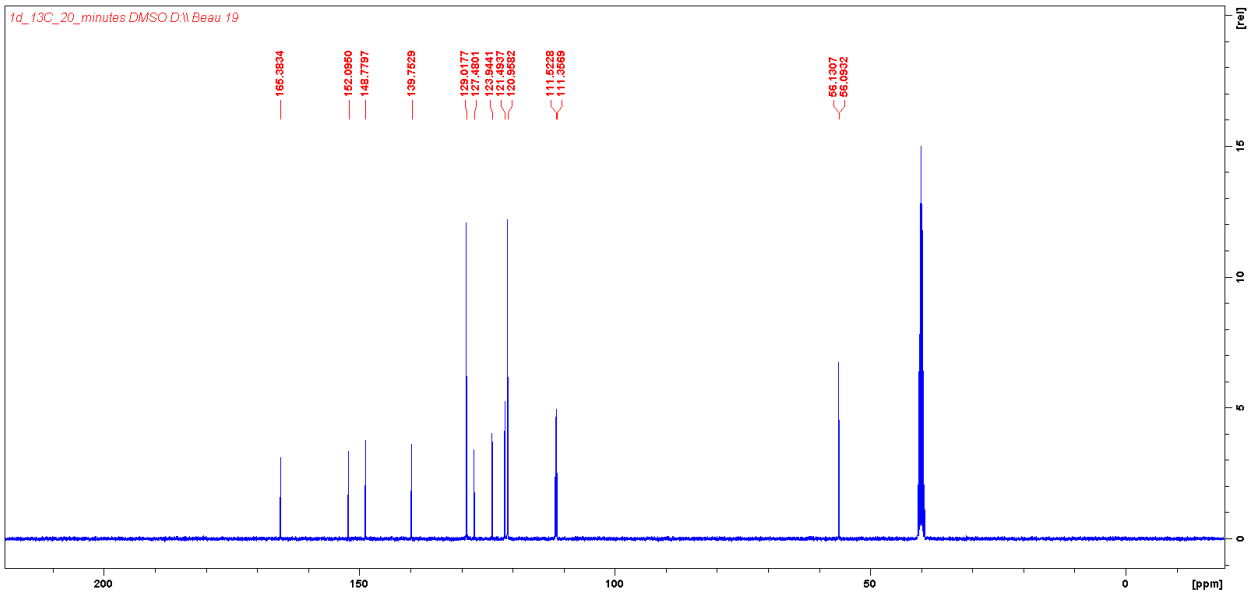

1d_1H_16_scans DMSO D:\\ Beau 31
10.3113
7.7883
7.7688
7.4799
7.4605
7.4184
7.4151
7.4020
7.3969
7.3812
7.3776
7.3711
7.3567
7.3313
7.3254
7.3069
7.2892
7.1189
7.1165
7.1006
7.0846
7.0821
2.4047
O
Me
N
H
1.0000
1.9763
1.0164
5.0328
1.0091
2.9906
12
10
8
6
4
2
0
[ppm]
[rel]

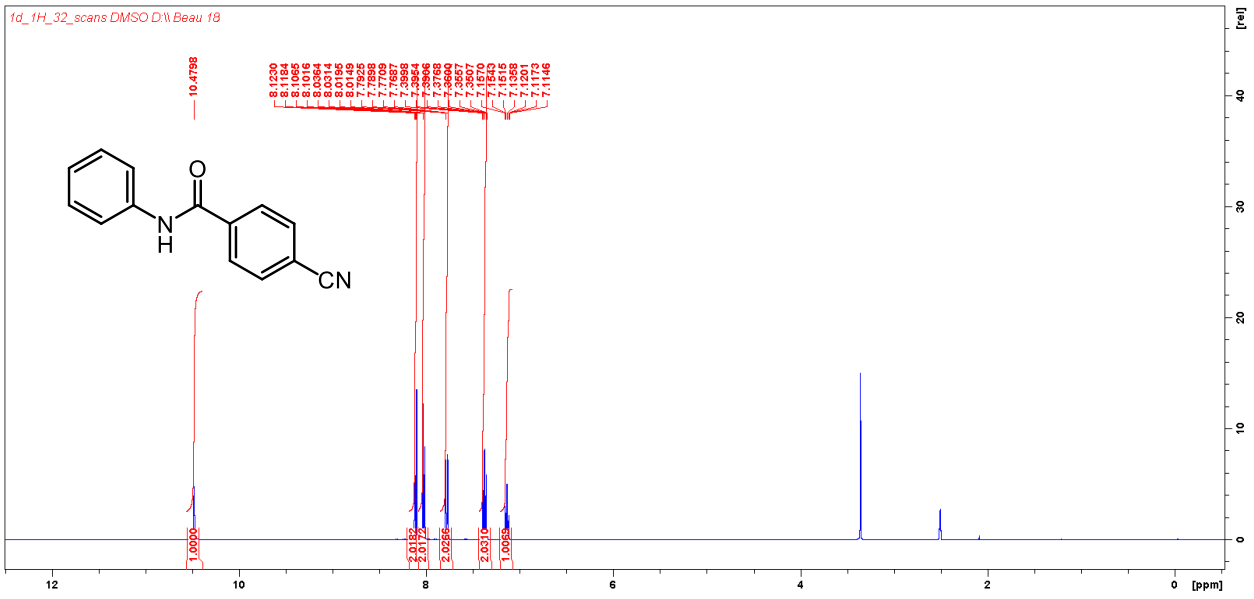

1d_13C_20_minutes DMSO D:\\ Beau 56
168.3342
139.7871
137.7903
135.8470
130.8777
130.0449
129.1318
127.6483
125.9959
123.9782
120.1162
19.7634
200
150
100
50
0
[ppm]
[rel]

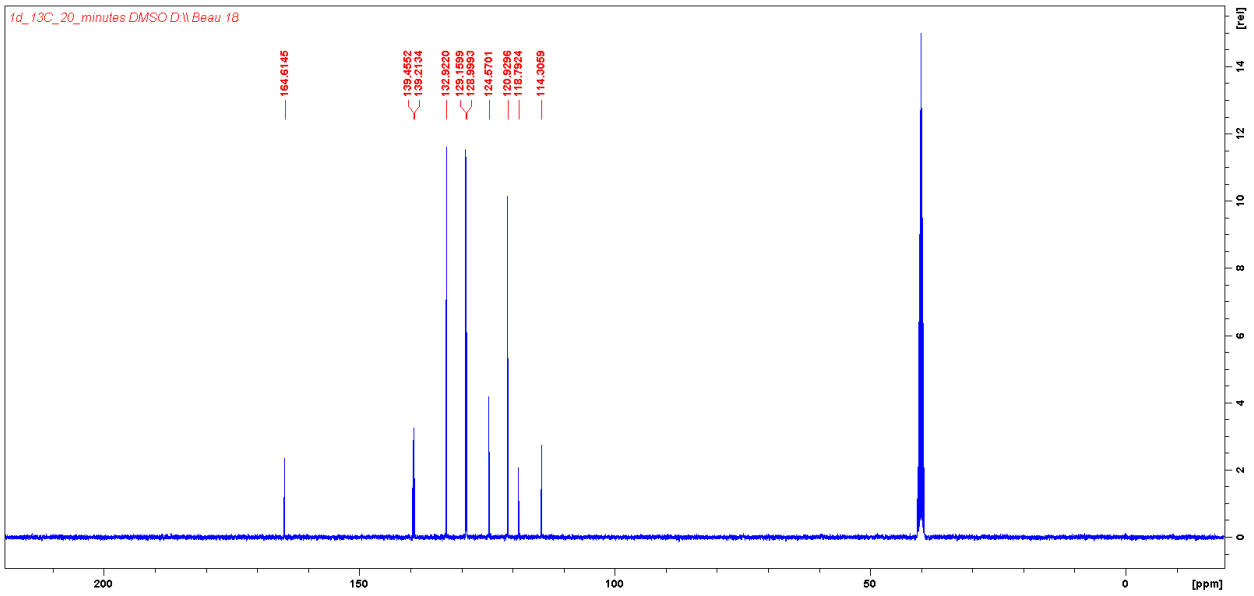

1d_1H_16_scans DMSO D:\\ Beau 35
10.2921
7.7480
7.7454
7.7265
7.3470
7.3427
7.3281
7.3074
7.0996
7.0812
7.0627
6.9177
2.2868
2.2405
O
Me
N
H
Me
Me
1.0000
2.0097
2.0350
1.0418
1.9999
9.0723
12
10
8
6
4
2
0
[ppm]

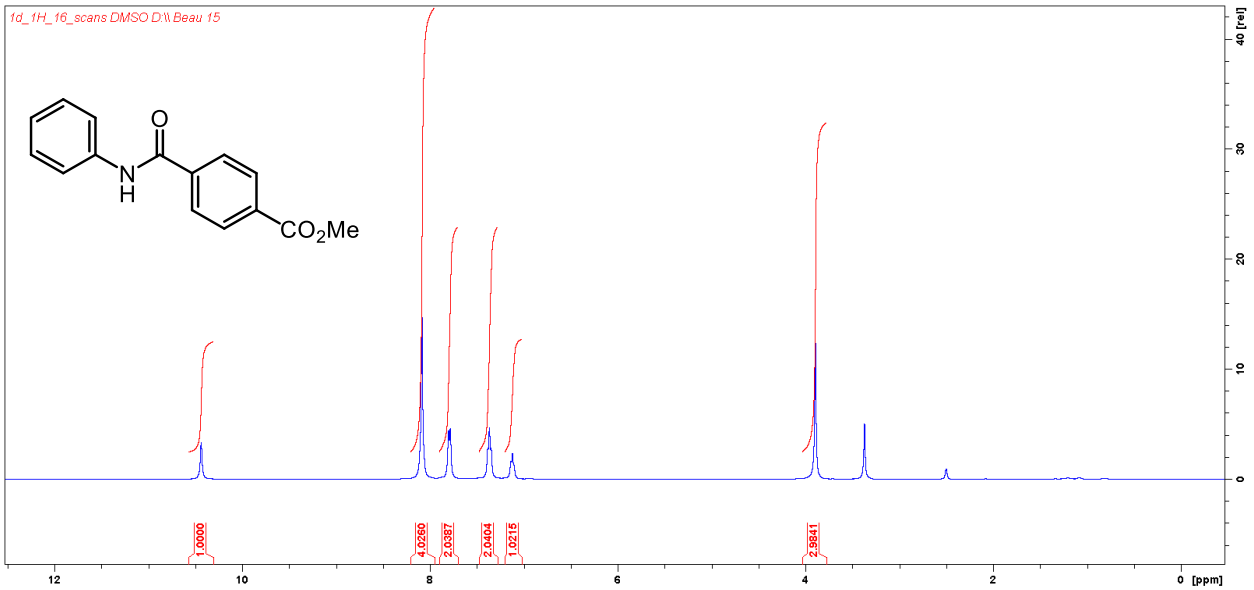

1d_13C_20_minutes DMSO D:\\ Beau 35
168.5714
139.6683
138.0609
135.3222
134.0820
129.1655
128.2722
123.9522
119.9734
21.1300
19.2564
200
150
100
50
0
[ppm]

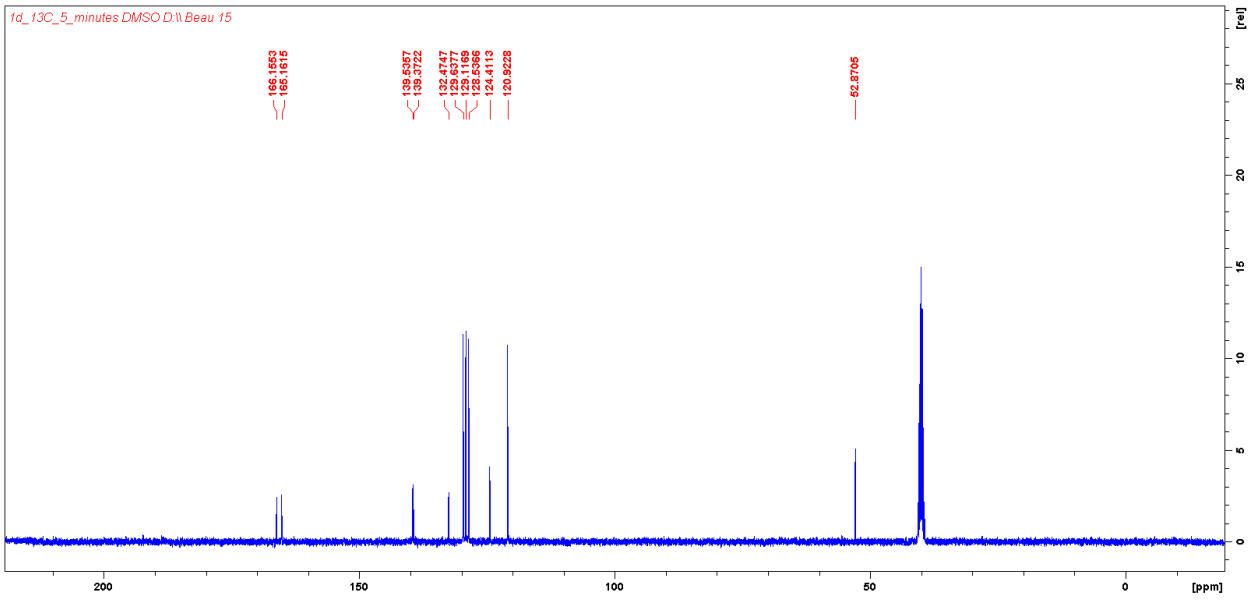

1d_1H_32_scans DMSO D:\\ Beau 19
10.0354
7.7407
7.7379
7.7331
7.7190
7.7165
7.6892
7.6859
7.6829
7.5882
7.5829
7.5127
7.5075
7.4927
7.3279
7.3141
7.3119
7.2974
7.2930
7.0718
7.0690
7.0561
7.0536
7.0349
3.8131
3.8018
O
N
H
OMe
OMe
1.0000
2.0157
1.0123
1.0274
2.0255
2.0102
6.0410
12
10
8
6
4
2
0
[ppm]
[rel]

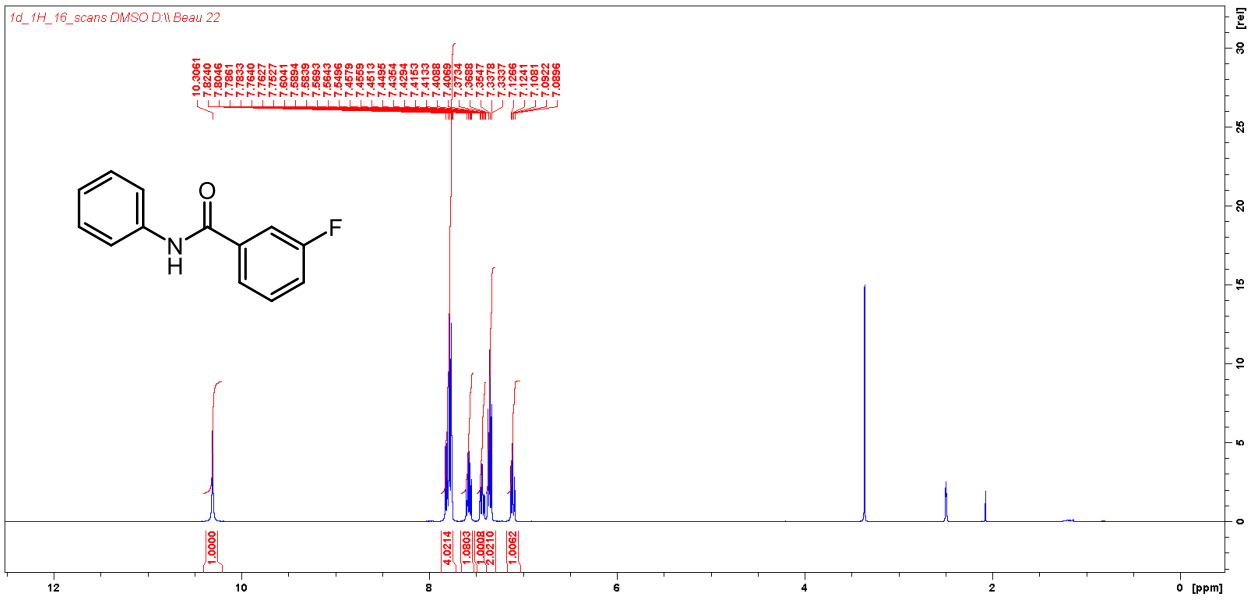

1d_13C_20_minutes DMSO D:\\ Beau 19
165.3834
152.0950
148.7797
139.7529
129.0177
127.4801
123.9441
121.4937
120.3582
111.6228
111.3569
56.1307
56.0932
200
150
100
50
0
[ppm]
[rel]

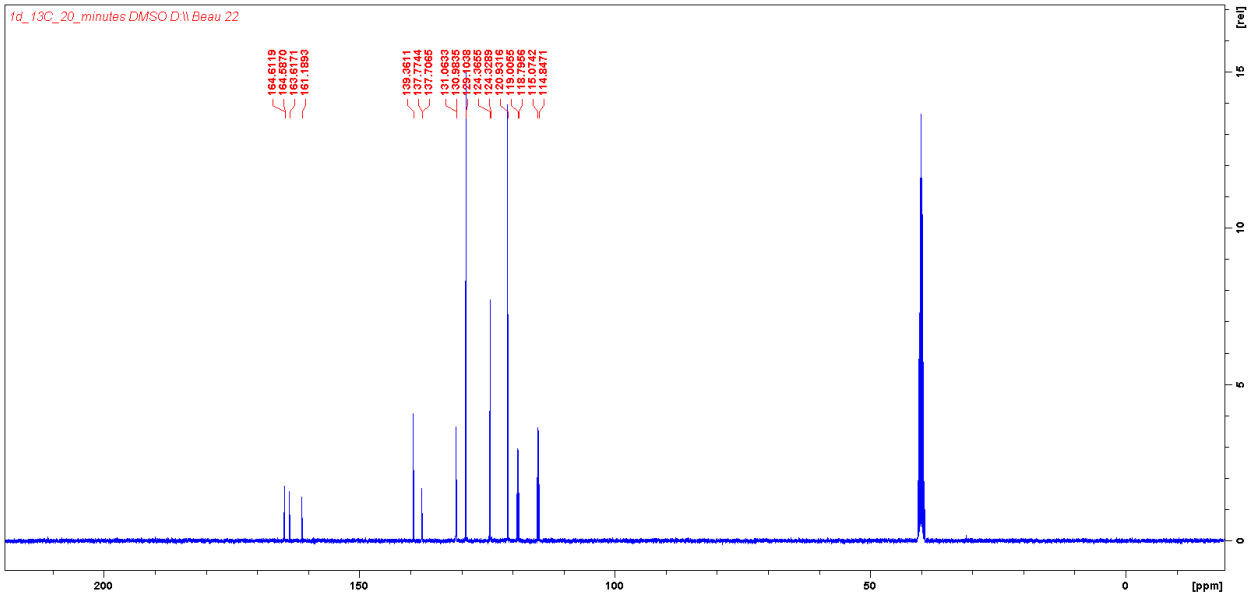

1d_1H_32_scans DMSO D:\\ Beau 18
10.4798
8.1230
8.1184
8.1065
8.1016
8.0364
8.0314
8.0195
8.0149
7.7925
7.7898
7.7687
7.3988
7.3954
7.3866
7.3768
7.3690
7.3557
7.1570
7.1543
7.1515
7.1368
7.1201
7.1173
7.1146
1.0000
2.0162
2.0172
2.0258
2.0310
1.0053
O
N
H
CN
[rel]
[ppm]

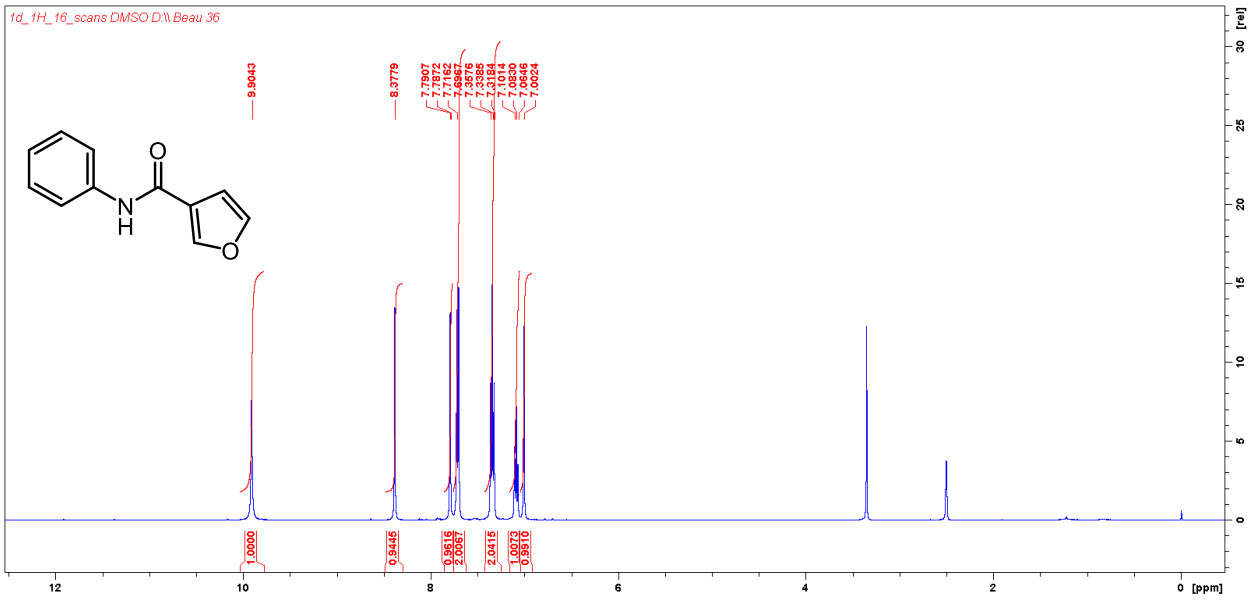

1d_13C_20_minutes DMSO D:\\ Beau 18
164.6145
139.4552
139.2134
132.9220
129.1599
128.9993
124.5701
120.8296
118.7924
114.3059
[rel]
[ppm]

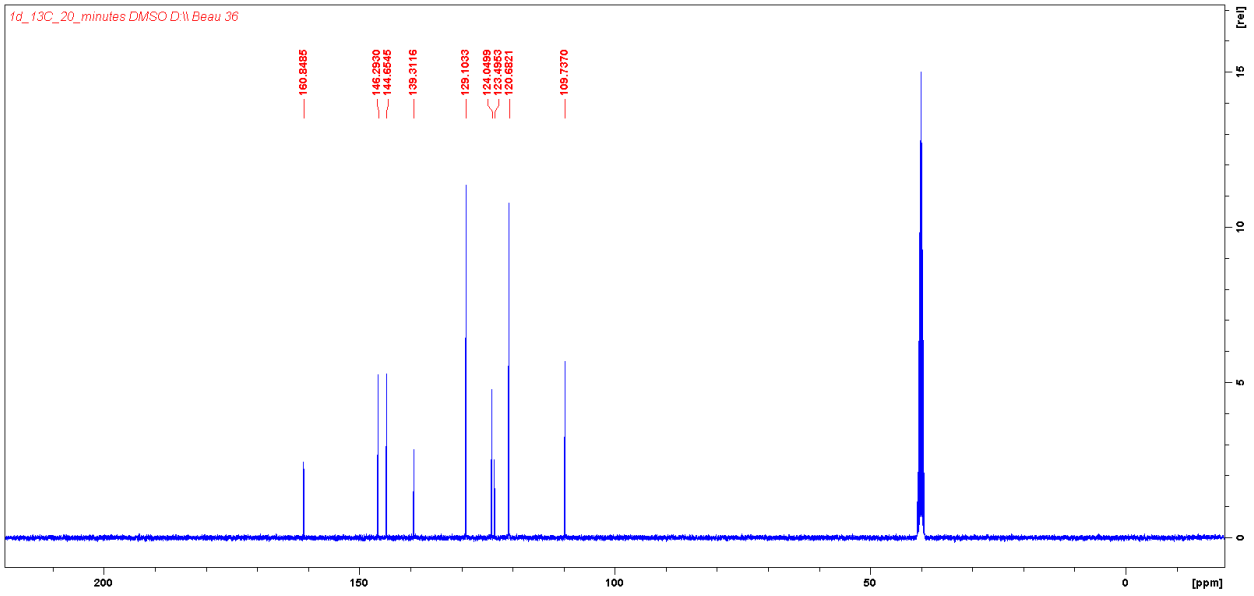

1d_1H_16_scans DMSO D:\\ Beau 15
O
N
H
CO2Me
1.0000
4.0260
2.0387
2.0404
1.0215
2.9841
12
10
8
6
4
2
0 [ppm]
40 [e]
30
20
10
0

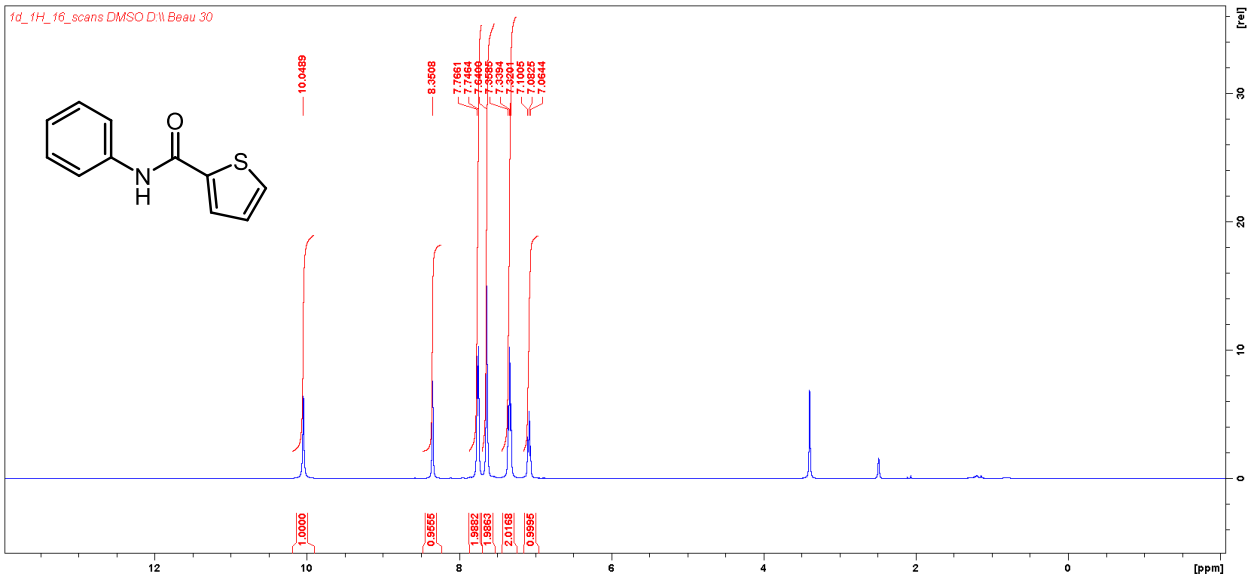

1d_13C_5_minutes DMSO D:\\ Beau 15
166.1563
165.1615
139.5357
139.3722
132.4747
129.6577
129.1169
128.5366
124.4113
120.9228
52.8705
200
150
100
50
0 [ppm]
[e]
25
20
15
10
5
0

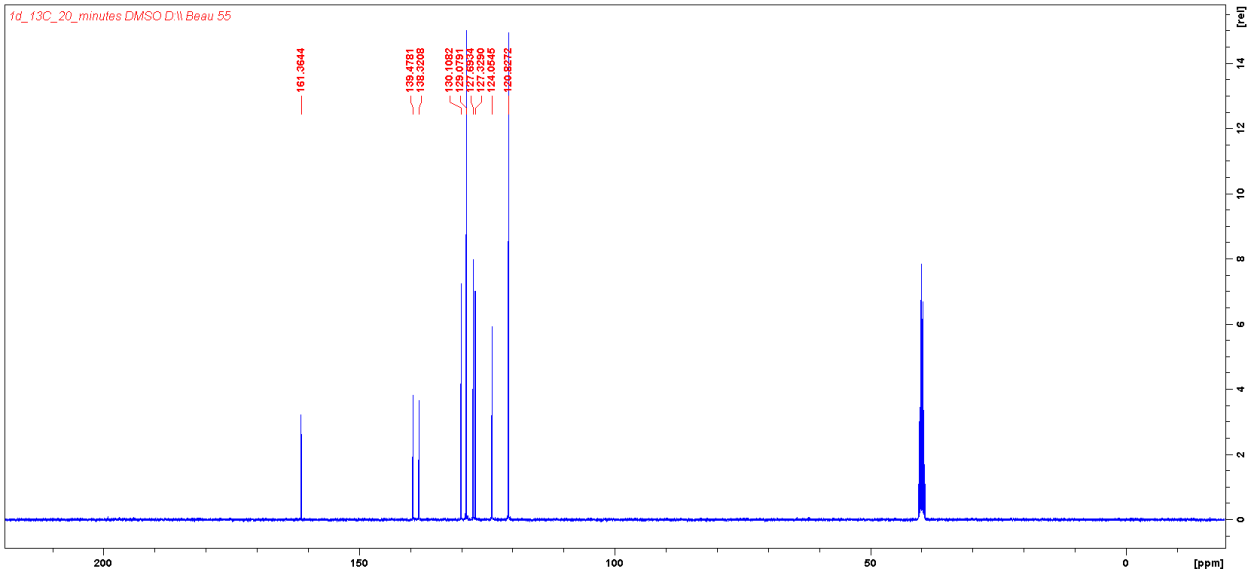

1d_1H_16_scans DMSO D:\\ Beau 22
10.3061
7.8240
7.8046
7.7851
7.7833
7.7640
7.7627
7.7577
7.6041
7.5894
7.5839
7.5693
7.5643
7.5496
7.4579
7.4569
7.4513
7.4495
7.4354
7.4294
7.4153
7.4133
7.4088
7.4069
7.3754
7.3588
7.3547
7.3378
7.3337
7.1286
7.1244
7.1081
7.0922
7.0896
O
N
H
F
1.0000
4.0214
1.0803
1.0008
2.0210
1.0062
[rel]
[ppm]

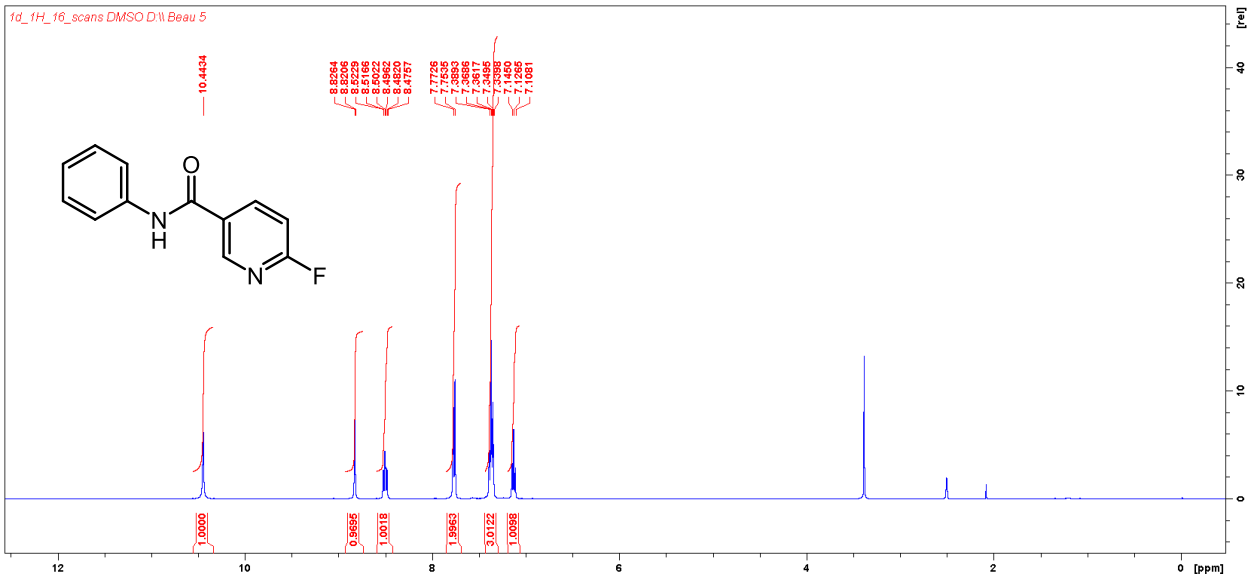

1d_13C_20_minutes DMSO D:\\ Beau 22
164.6119
164.5870
163.6171
161.1893
139.3611
137.7744
137.7065
131.0633
130.9838
130.9039
124.3855
124.3289
120.5316
120.0965
118.7956
115.0742
114.8471
[rel]
[ppm]

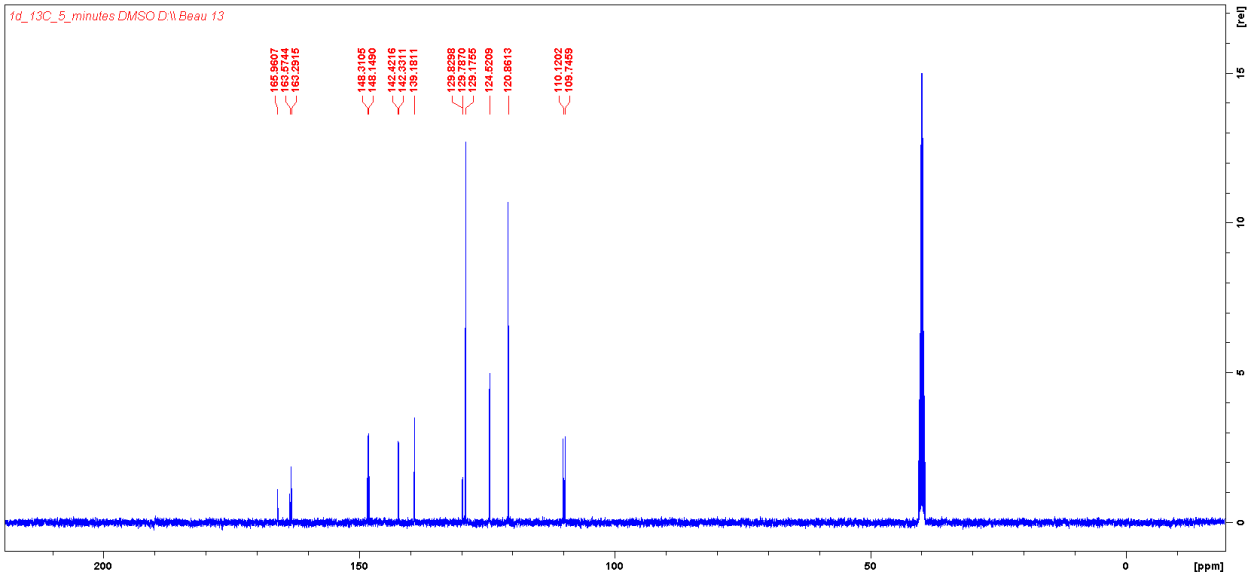

1d_1H_16_scans DMSO D:\\ Beau 36
9.9043
8.3779
7.7907
7.7872
7.7162
7.6967
7.6925
7.3386
7.3184
7.1014
7.0630
7.0585
7.0024
1.0000
0.9445
0.9616
2.0067
2.0415
1.0073
0.9910
[rel]
[ppm]

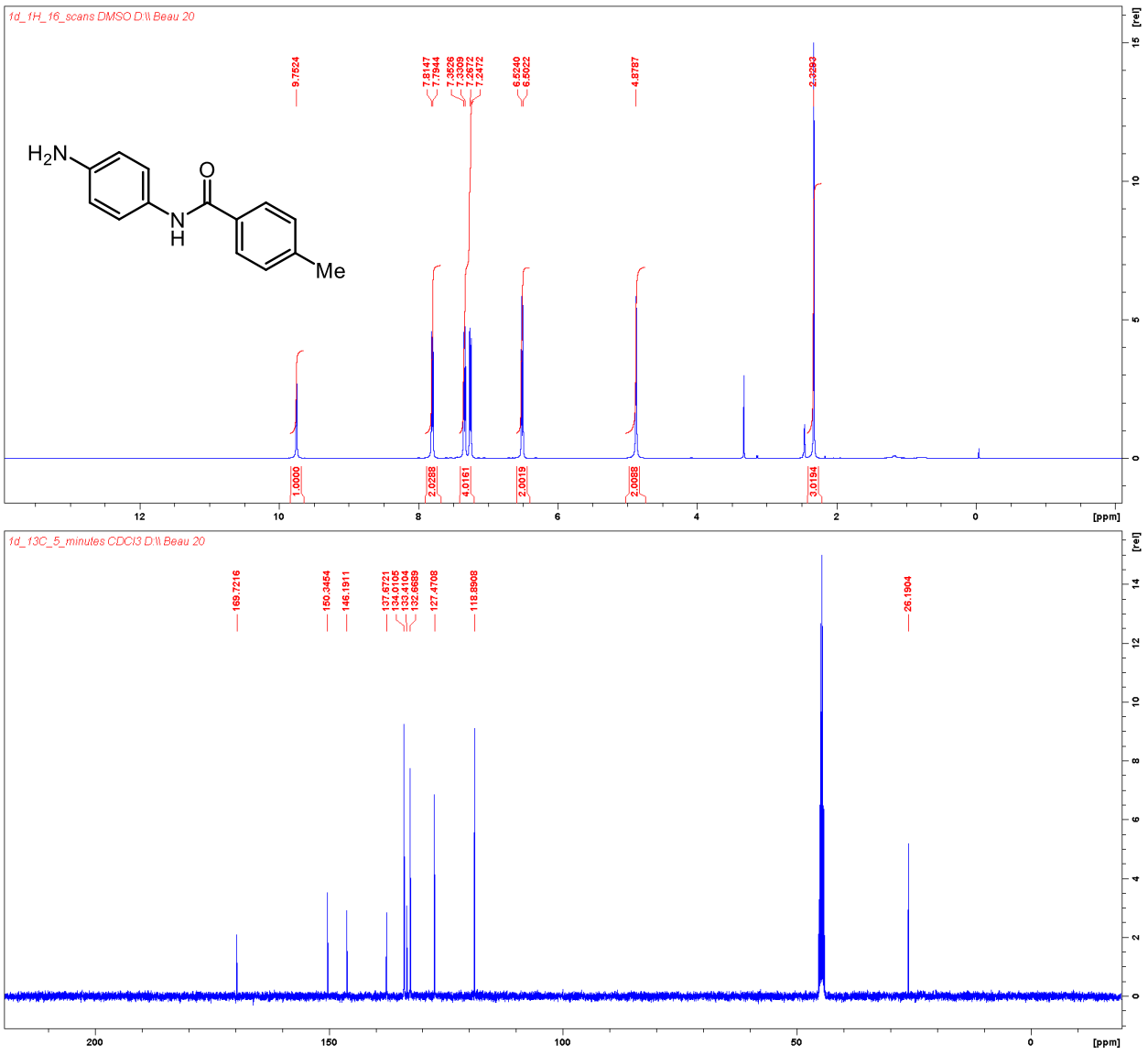

1d_13C_20_minutes DMSO D:\\ Beau 36
160.8485
146.2930
144.6845
139.3116
129.1033
124.0489
123.4853
120.8921
109.7370
[rel]
[ppm]

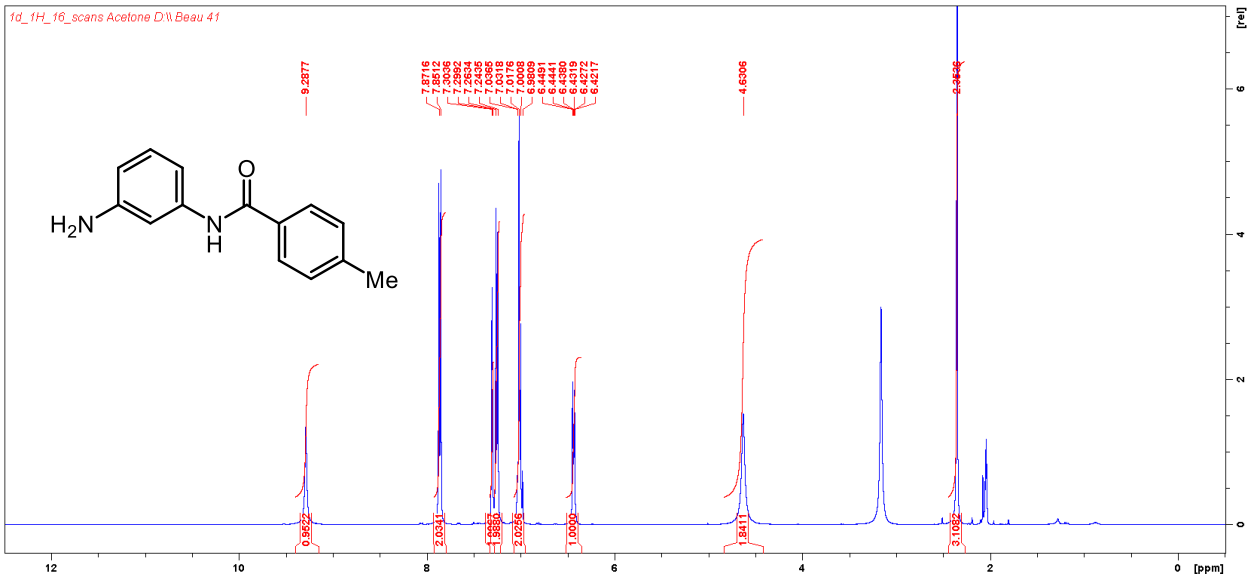

1d_1H_16_scans DMSO D:\\ Beau 30
10.0489
8.3608
7.7661
7.7464
7.6490
7.3585
7.3394
7.3204
7.1005
7.0825
7.0644
1.0000
0.9656
1.9882
1.9863
2.0168
0.9996
12
10
8
6
4
2
0
[ppm]
[rel]

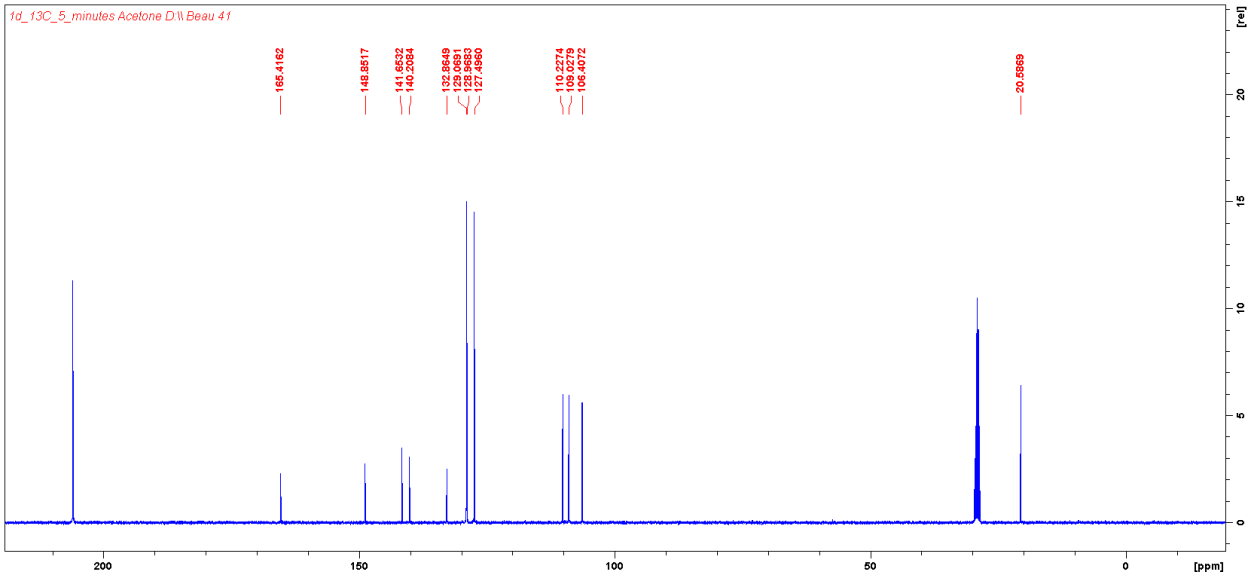

1d_13C_20_minutes DMSO D:\\ Beau 55
161.3644
139.4781
138.3208
130.1082
129.0791
127.8934
127.3253
124.0545
120.8272
200
150
100
50
0
[ppm]
[rel]

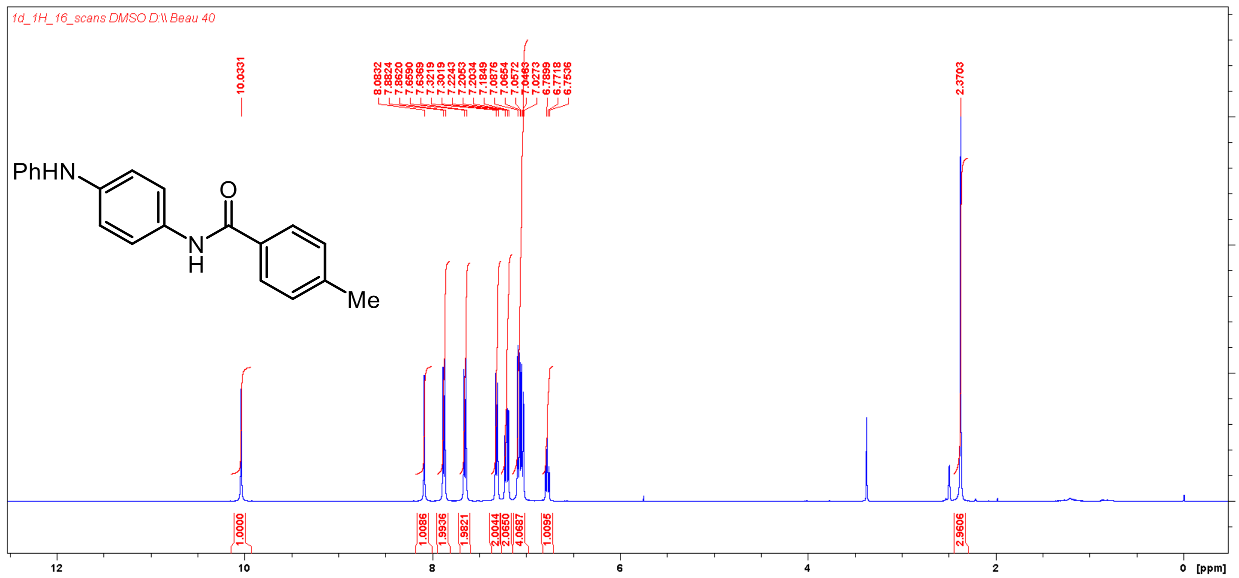

1d_1H_16_scans DMSO D:\\ Beau 5
10.4434
8.8264
8.8206
8.5229
8.5166
8.5022
8.4852
8.4800
8.4757
7.7726
7.7535
7.7393
7.3689
7.3617
7.3495
7.3388
7.1480
7.1265
7.1081
1.0000
0.9695
1.0018
1.9963
3.0122
1.0098
12
10
8
6
4
2
0
[ppm]
[rel]
O
N
H
N
F

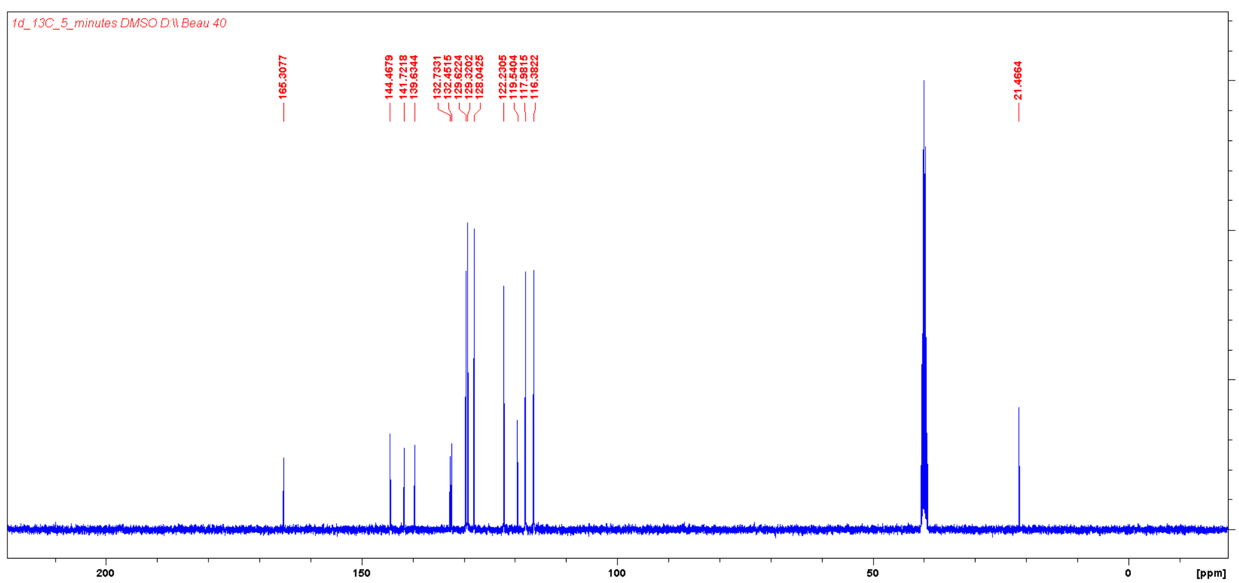

1d_13C_5_minutes DMSO D:\\ Beau 13
165.9647
163.5744
163.2915
148.3105
148.1490
142.4216
142.3311
139.1811
129.8238
129.7870
129.1755
124.5209
120.8613
110.1202
109.7469
200
150
100
50
0
[ppm]
[rel]

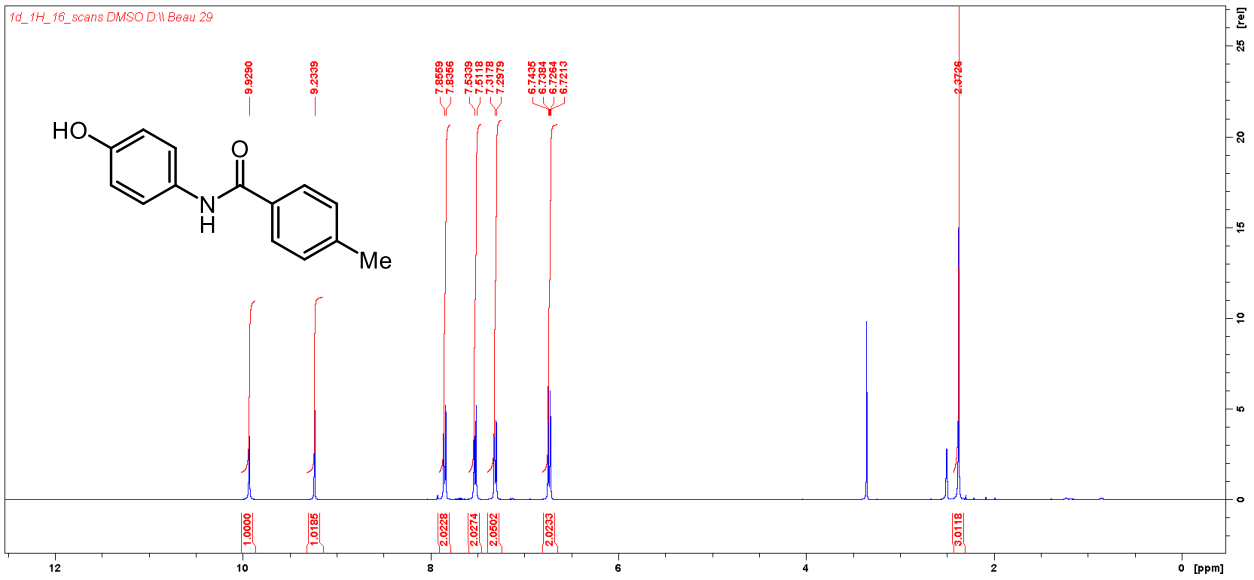

1d_1H_16_scans DMSO D:\\ Beau 20
9.7624
7.8147
7.7944
7.3626
7.3309
7.2872
7.2472
6.5240
6.5022
4.8787
2.3293
1.0000
2.0288
4.0161
2.0019
2.0088
3.0194
[rel]
[ppm]
1d_13C_5_minutes CDCl3 D:\\ Beau 20
169.7216
150.3454
146.1911
137.6721
134.0105
132.4184
132.0899
127.4708
118.8908
26.1904
[rel]
[ppm]

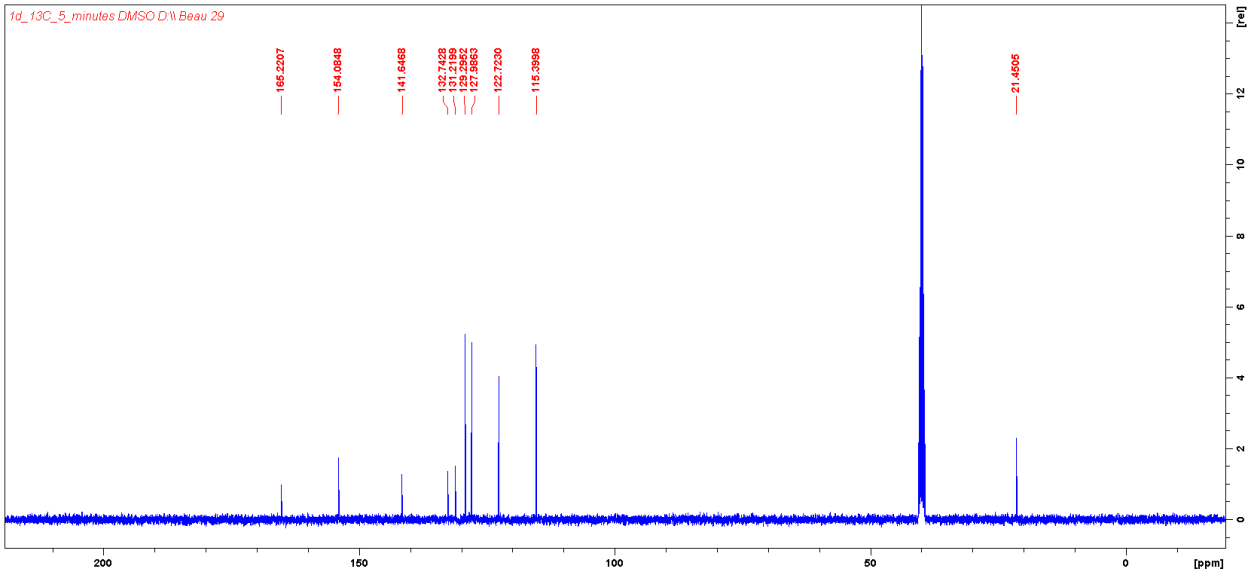

1d_1H_16_scans Acetone D:\\ Beau 41
9.2877
7.8716
7.8512
7.3036
7.2892
7.2694
7.2435
7.0365
7.0318
7.0175
7.0008
6.9809
6.4491
6.4441
6.4380
6.4319
6.4272
6.4217
4.6306
2.3626
0.9622
2.0341
1.9855
1.9650
2.0255
1.0000
1.8411
3.1082
O
N
H
H_2N
Me
[rel]
[ppm]

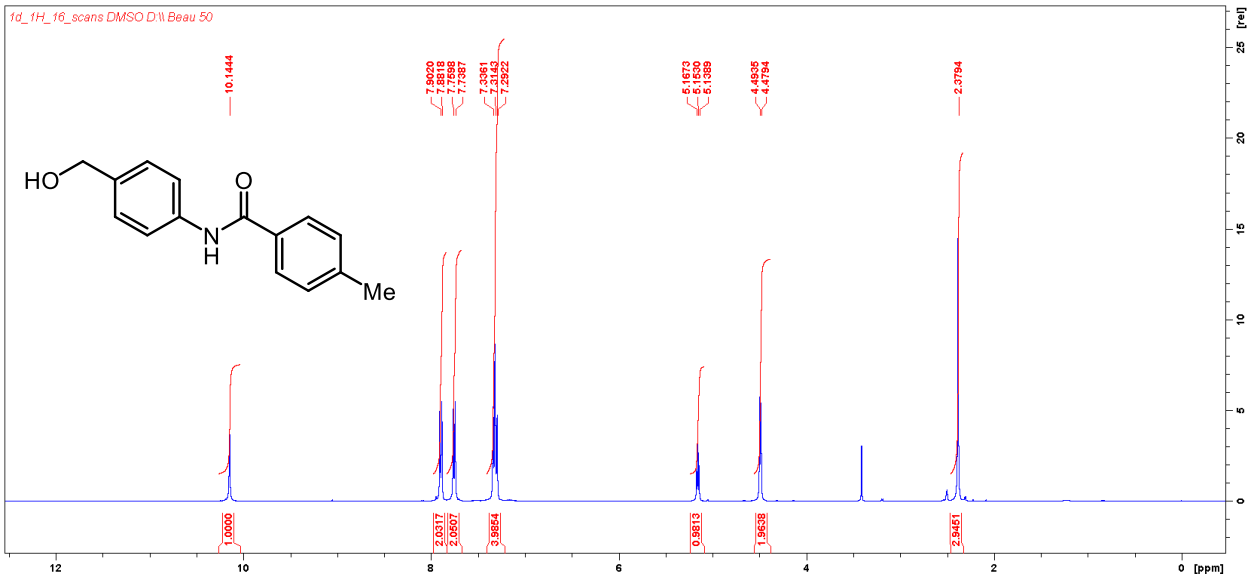

1d_13C_5_minutes Acetone D:\\ Beau 41
165.4162
148.8517
141.6532
140.2084
132.8649
129.0691
128.8953
127.4960
110.2274
109.0279
106.4072
20.5889
[rel]
[ppm]

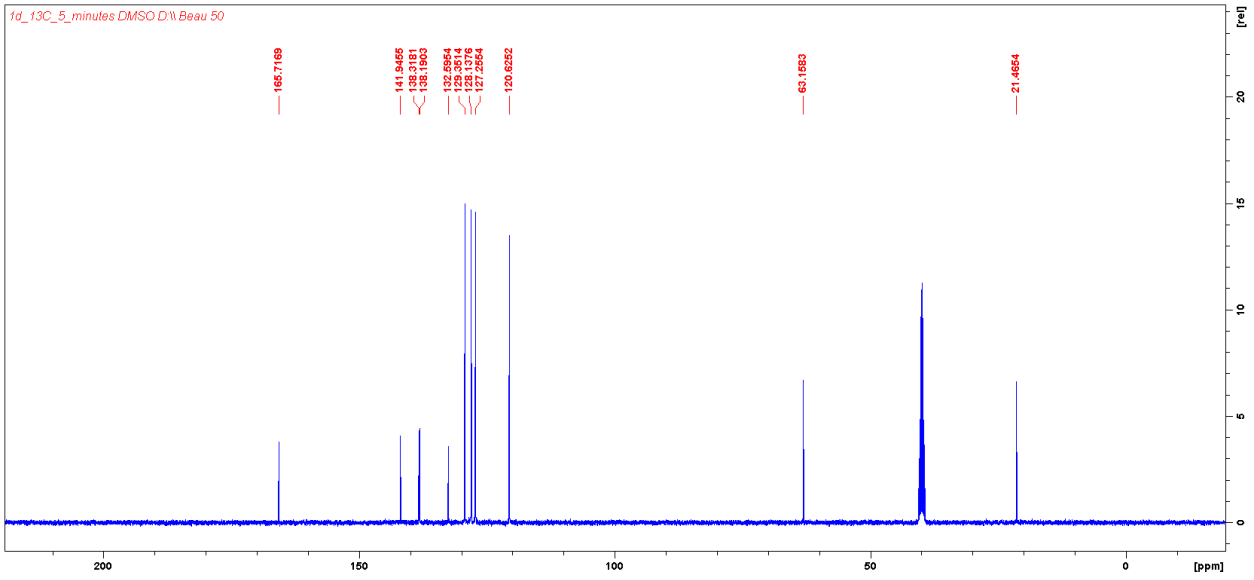

1d_1H_16_scans DMSO D:\\ Beau 40
10.0331
8.0832
7.8824
7.8620
7.6580
7.6369
7.3219
7.3019
7.2243
7.2063
7.2034
7.1849
7.0876
7.0684
7.0572
7.0483
7.0273
6.7899
6.7718
6.7536
2.3703
PhHN
O
N
H
Me
1.0000
1.0086
1.9936
1.9821
2.0044
2.0650
4.0687
1.0095
2.9606
[ppm]
[rel]

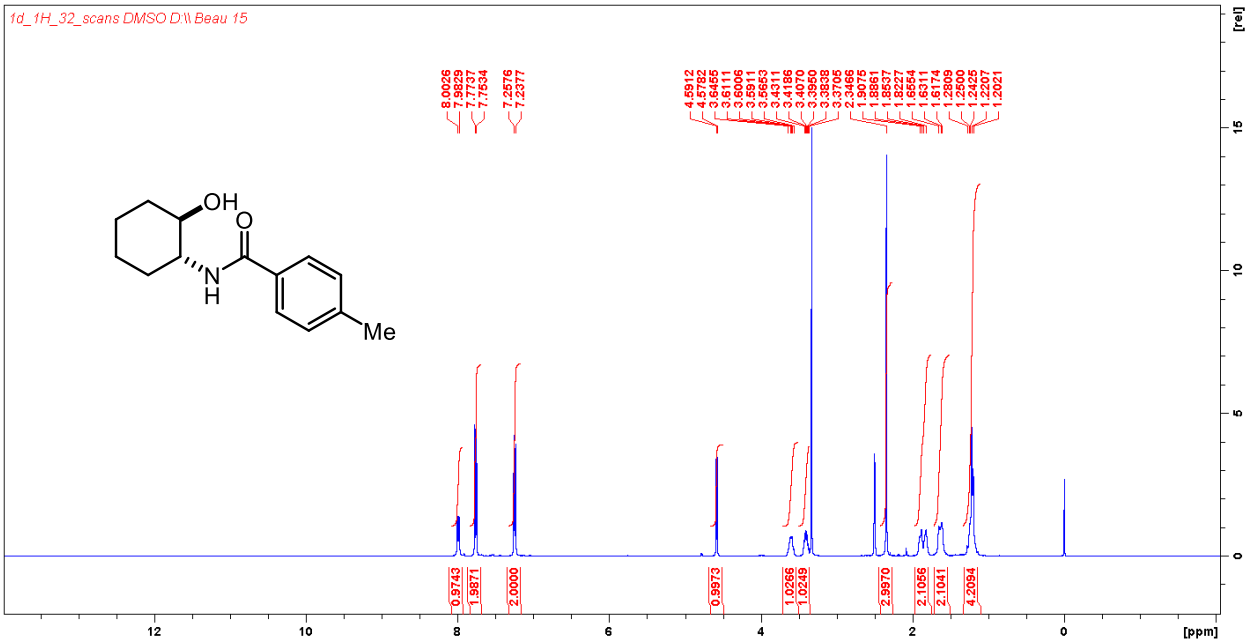

1d_13C_5_minutes DMSO D:\\ Beau 40
165.3077
144.4679
141.7218
139.6344
132.7331
132.4515
129.6224
129.3202
128.0425
122.2305
119.5404
117.9815
116.3822
21.4664
[ppm]
[rel]

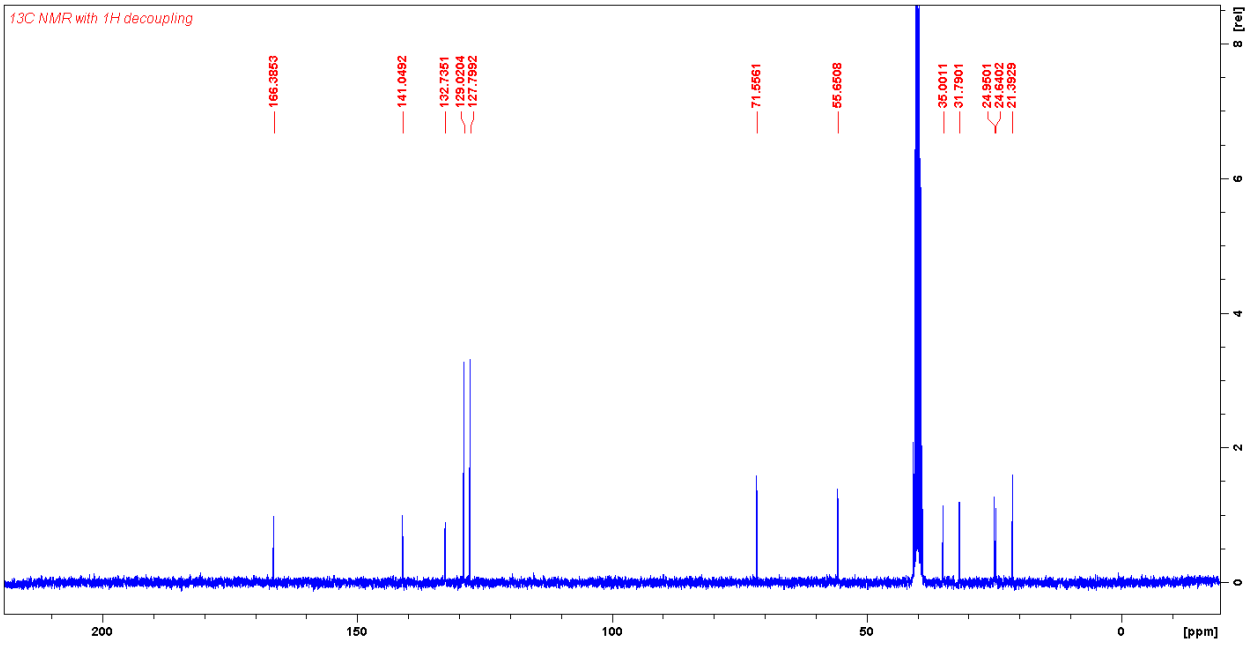

1d_1H_16_scans DMSO D:\\ Beau 29
HO
O
N
H
Me
9.9290
9.2339
7.8559
7.8356
7.5339
7.5118
7.3178
7.2979
6.7435
6.7384
6.7254
6.7213
2.3726
1.0000
1.0185
2.0228
2.0274
2.0502
2.0233
3.0118
[rel]
[ppm]

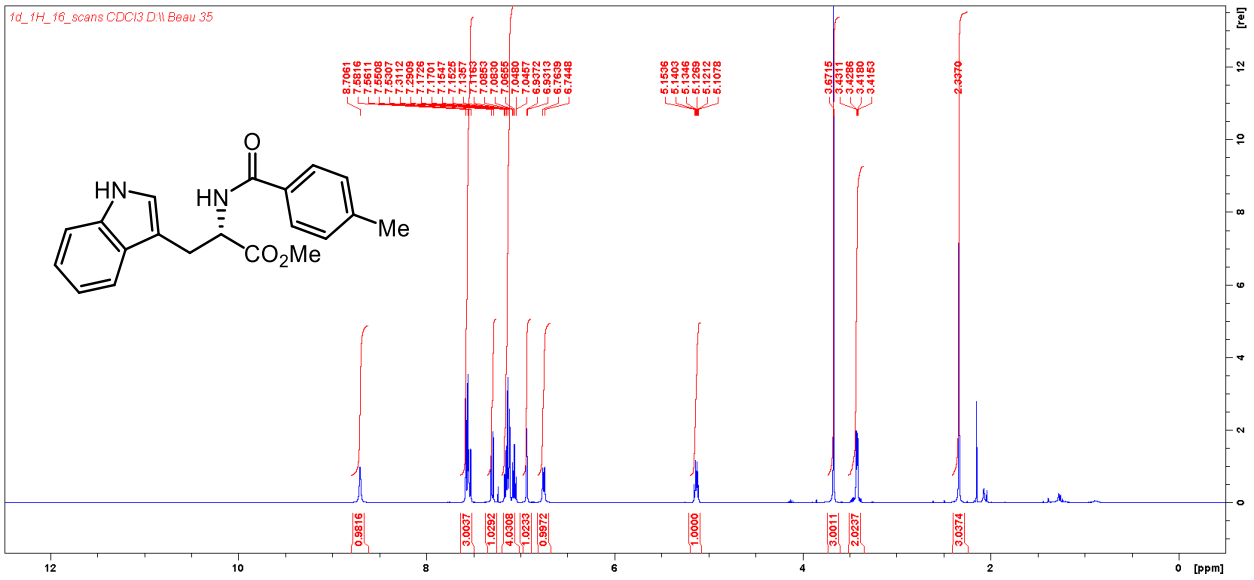

1d_13C_5_minutes DMSO D:\\ Beau 29
165.2207
154.0848
141.6468
132.7428
131.2159
129.2952
127.9863
122.7230
115.3998
21.4505
[rel]
[ppm]

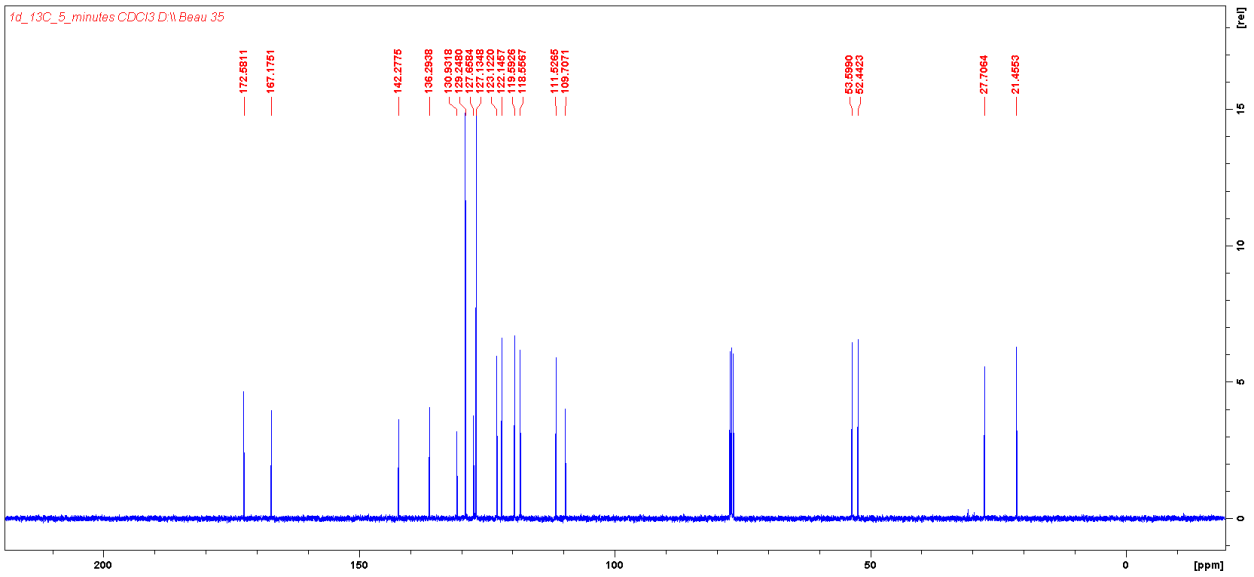

1d_1H_16_scans DMSO D:\\ Beau 50
10.1444
7.8020
7.7813
7.7598
7.7387
7.3361
7.3143
7.2922
6.1673
6.1530
6.1389
4.4935
4.4794
2.3794
HO
O
N
H
Me
1.0000
2.0317
2.0697
3.9654
0.9813
1.9638
2.9451
[rel]
[ppm]

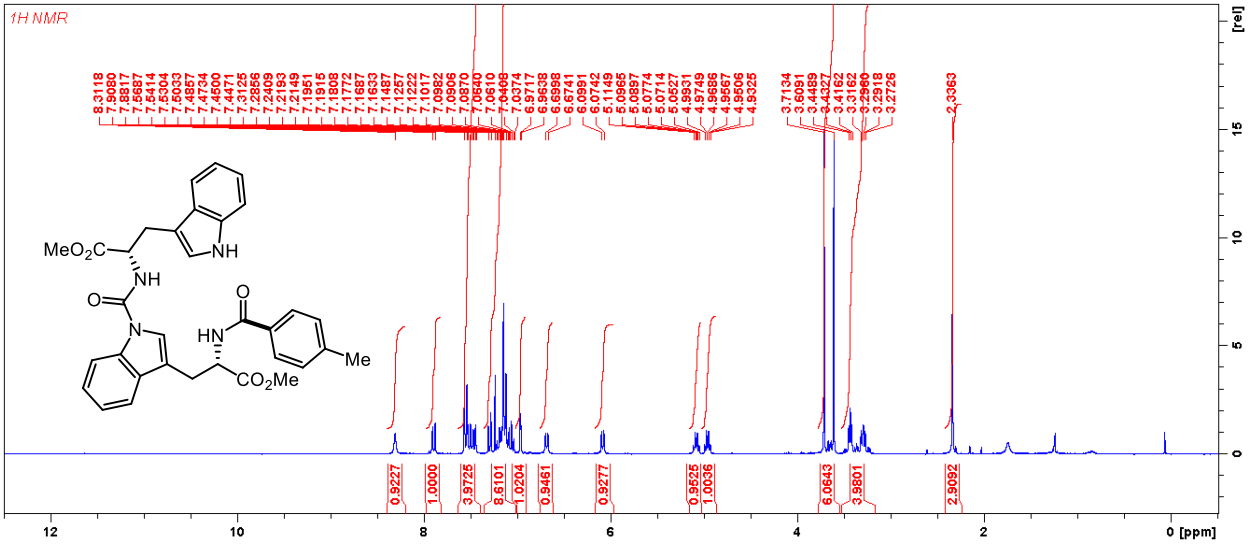

1d_13C_5_minutes DMSO D:\\ Beau 50
165.7169
141.9455
138.3181
138.1943
132.5954
129.3514
128.1376
127.2554
120.6252
63.1553
21.4654
[rel]
[ppm]

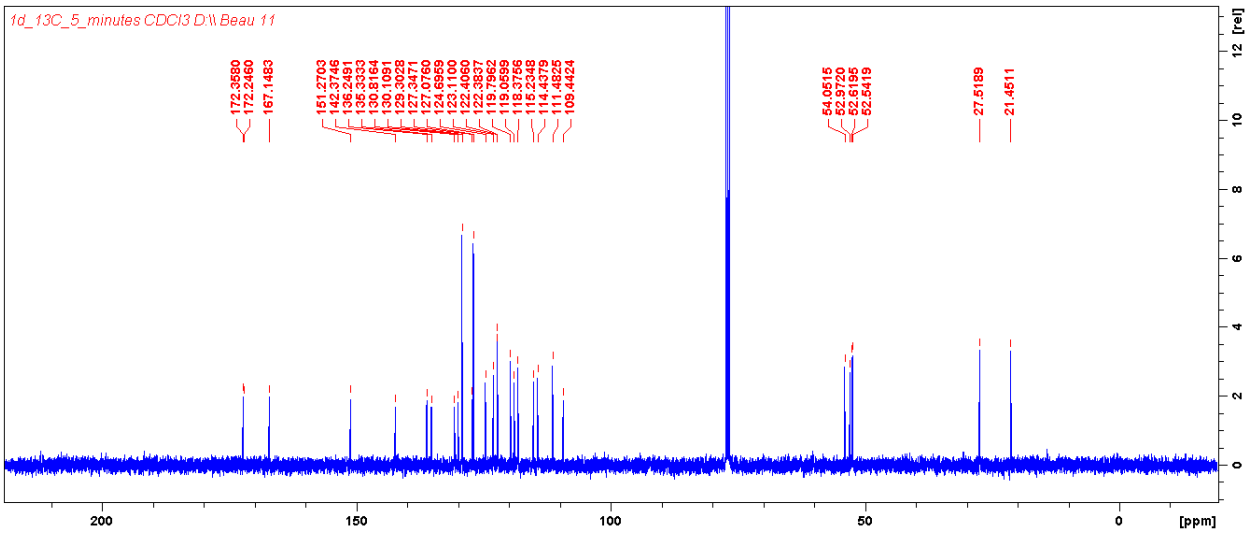

1d_1H_32_scans DMSO D:\\ Beau 15
8.0026
7.9829
7.7737
7.7534
7.2576
7.2377
4.5912
4.5782
3.6455
3.6111
3.6006
3.5911
3.5653
3.4311
3.4186
3.4070
3.3950
3.3838
3.3705
2.3466
1.9075
1.8851
1.8651
1.8227
1.6554
1.6311
1.6174
1.2809
1.2500
1.2425
1.2207
1.2021
OH
O
N
H
Me
0.9743
1.9871
2.0000
0.9973
1.0266
1.0249
2.9970
2.1056
2.1041
4.2094
[rel]
[ppm]

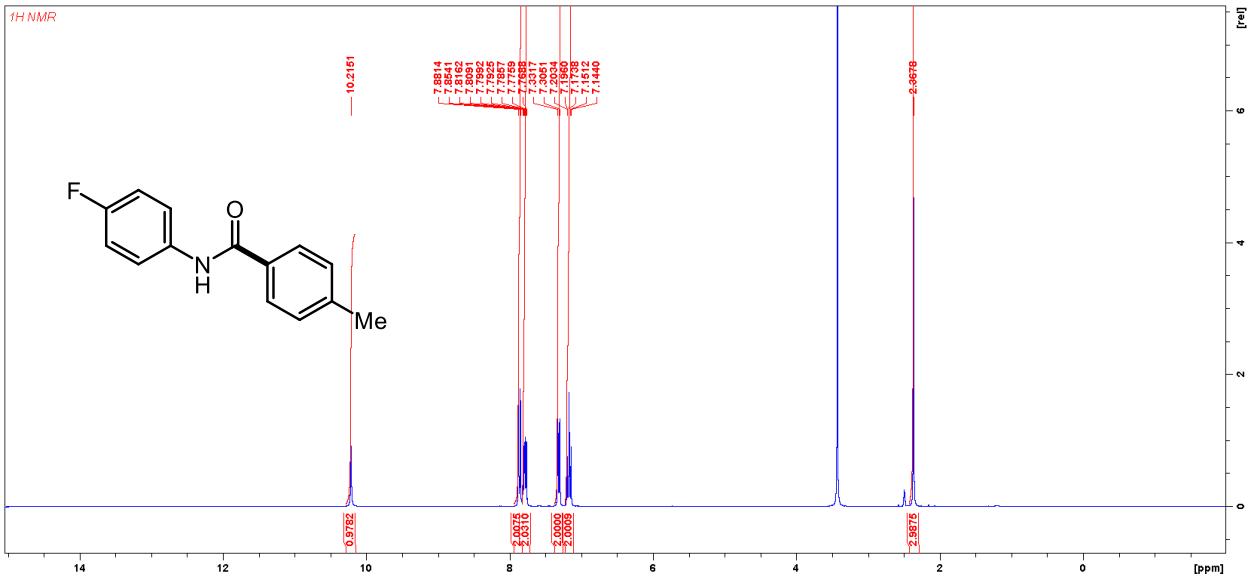

13C NMR with 1H decoupling
166.3853
141.0492
132.7351
129.0204
127.7992
71.5561
55.6508
35.0011
31.7901
24.9501
24.6402
21.3929
[rel]
[ppm]

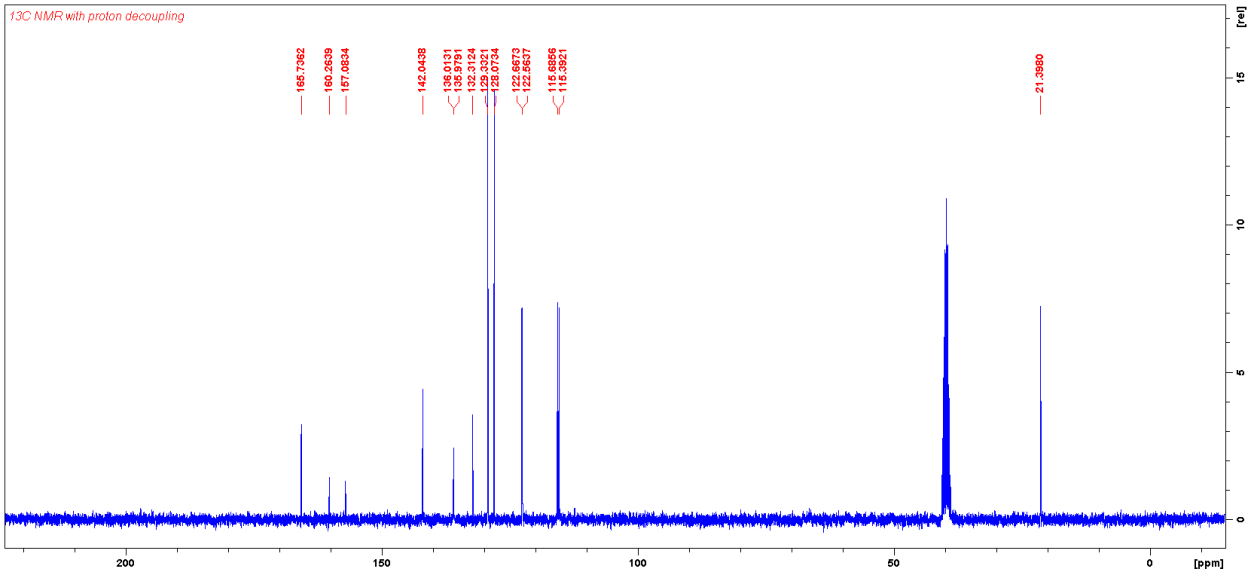

1d_1H_16_scans CDCl3 D:\\ Beau 35
HN
HN
O
Me
CO2Me
[rel]
[ppm]

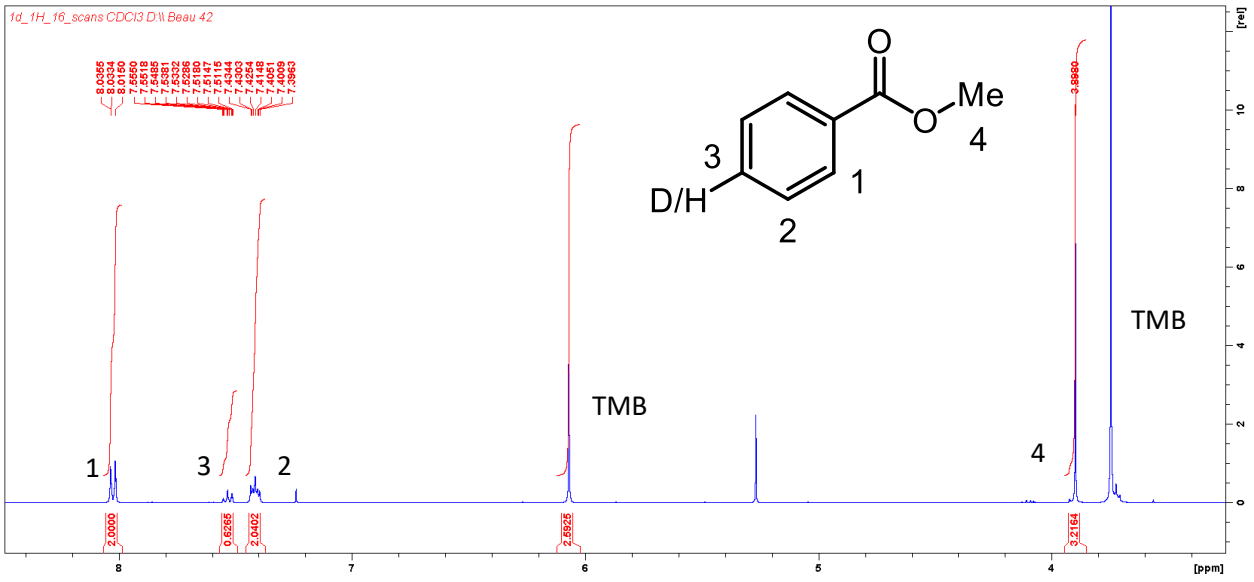

1d_13C_5_minutes CDCl3 D:\\ Beau 35
172.5811
167.1751
142.2775
136.2938
130.9318
129.2480
127.6694
127.1348
123.1220
122.1457
119.6926
118.5567
111.5285
109.7071
53.5990
52.4423
27.7064
21.4553
[rel]
[ppm]

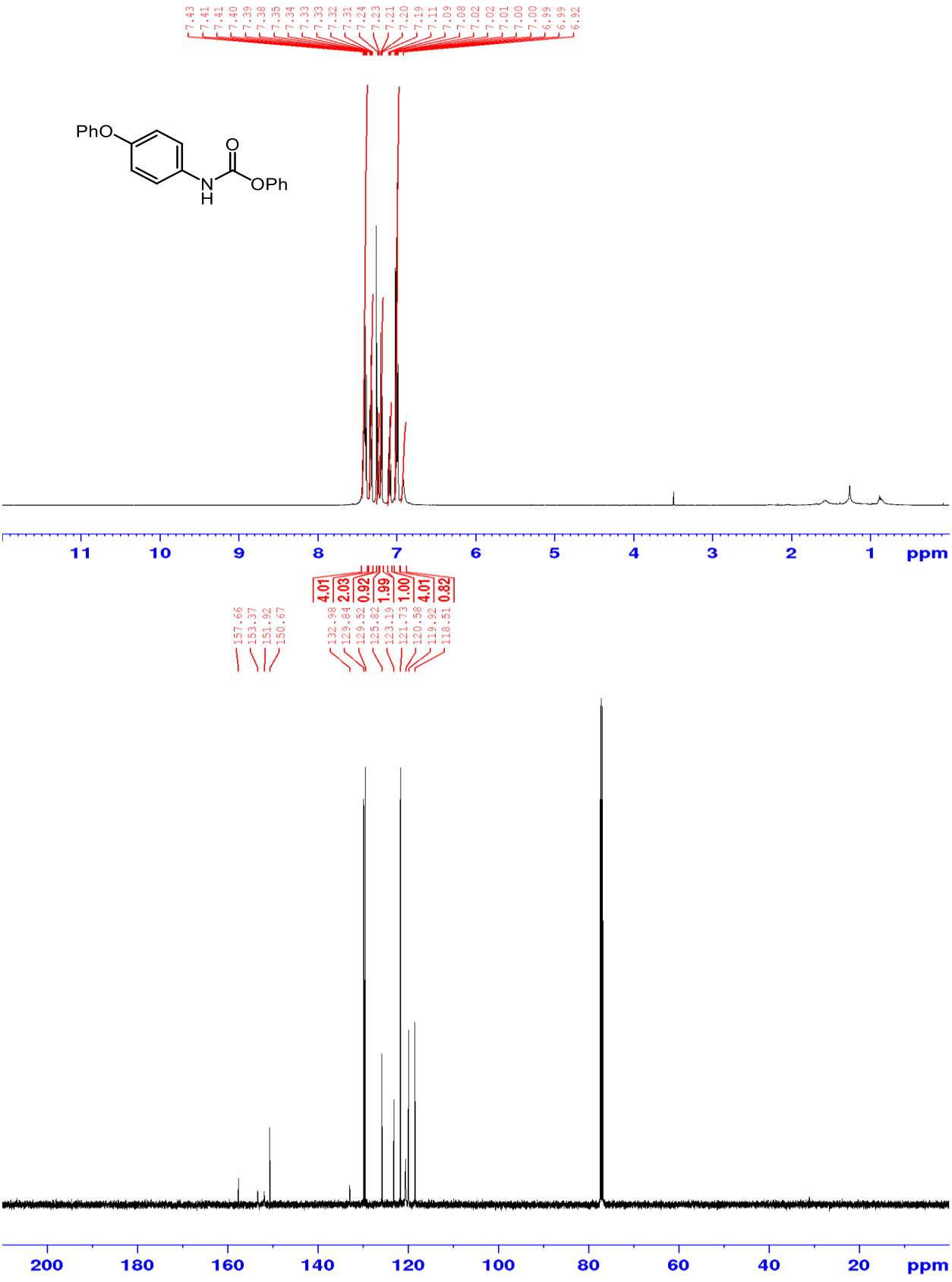

1H NMR
8.3118
7.9080
7.8817
7.5687
7.5414
7.5304
7.5033
7.4857
7.4734
7.4600
7.4471
7.3125
7.2856
7.2409
7.2193
7.2149
7.1951
7.1915
7.1808
7.1772
7.1687
7.1633
7.1487
7.1257
7.1222
7.1017
7.0982
7.0906
7.0870
7.0640
7.0610
7.0468
7.0374
6.9717
6.9638
6.6998
6.6741
6.0991
6.0742
5.1149
5.0965
5.0897
5.0774
5.0714
5.0527
4.9931
4.9749
4.9686
4.9567
4.9506
4.9325
3.7134
3.6091
3.4489
3.4327
3.4162
3.3162
3.2960
3.2918
3.2726
2.3363
MeO2C
NH
NH
O
N
HN
O
Me
CO2Me
0.9227
1.0000
3.9725
8.6101
1.0204
0.9461
0.9277
0.9525
1.0036
6.0643
3.9801
2.9092
12
10
8
6
4
2
0 [ppm]
[rel]

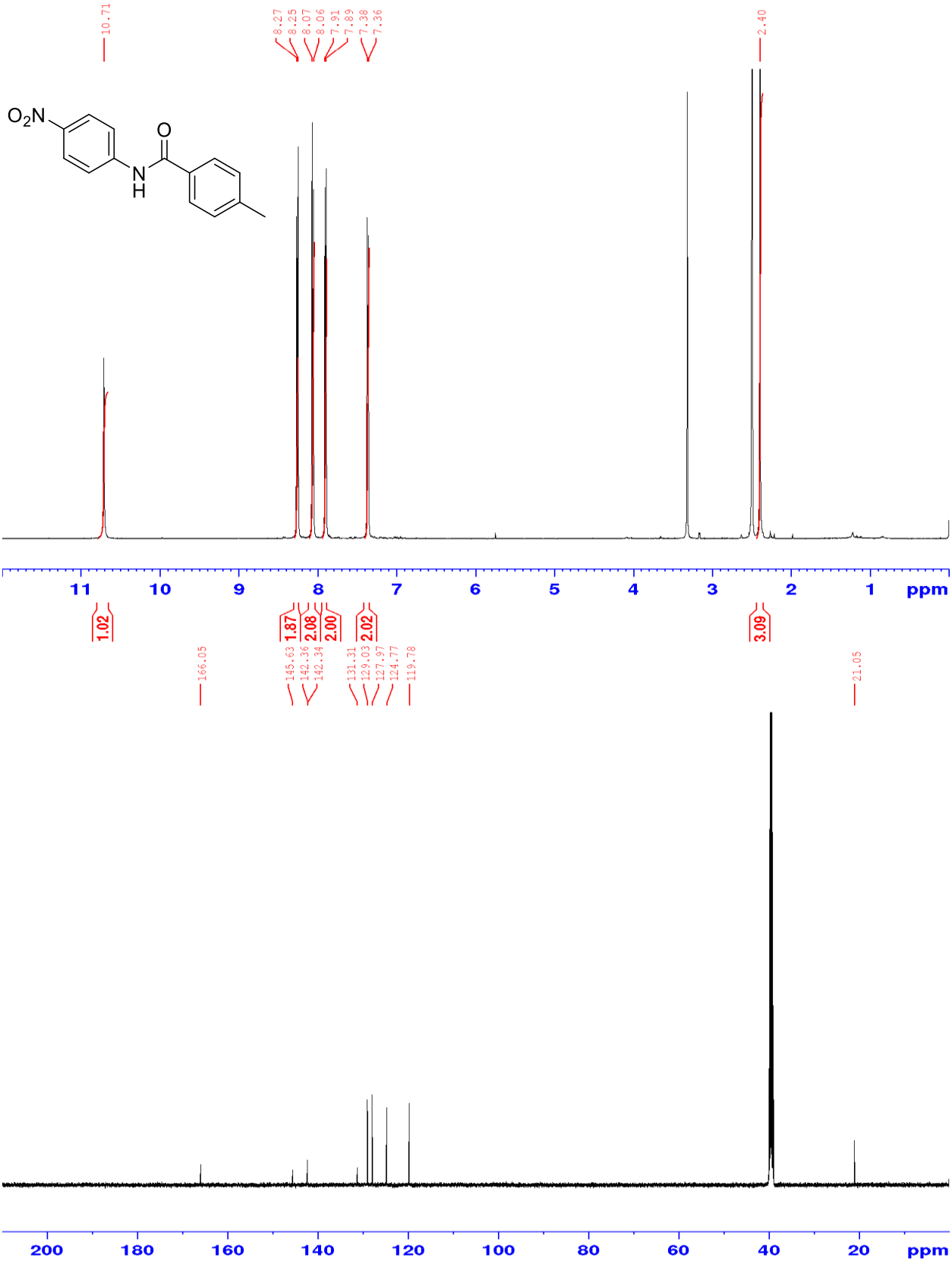

1d_13C_5_minutes CDCl3 D:\\ Beau 11
172.3580
172.2460
167.1483
151.2703
142.3746
136.2491
136.3333
130.8164
130.1091
129.3028
127.3471
127.0780
124.6958
123.1100
122.4060
122.3837
119.7962
119.0599
118.3756
115.2348
114.4379
111.4825
109.4424
54.0515
52.9720
52.6195
52.5419
27.5189
21.4511
200
150
100
50
0
[ppm]
[rel]

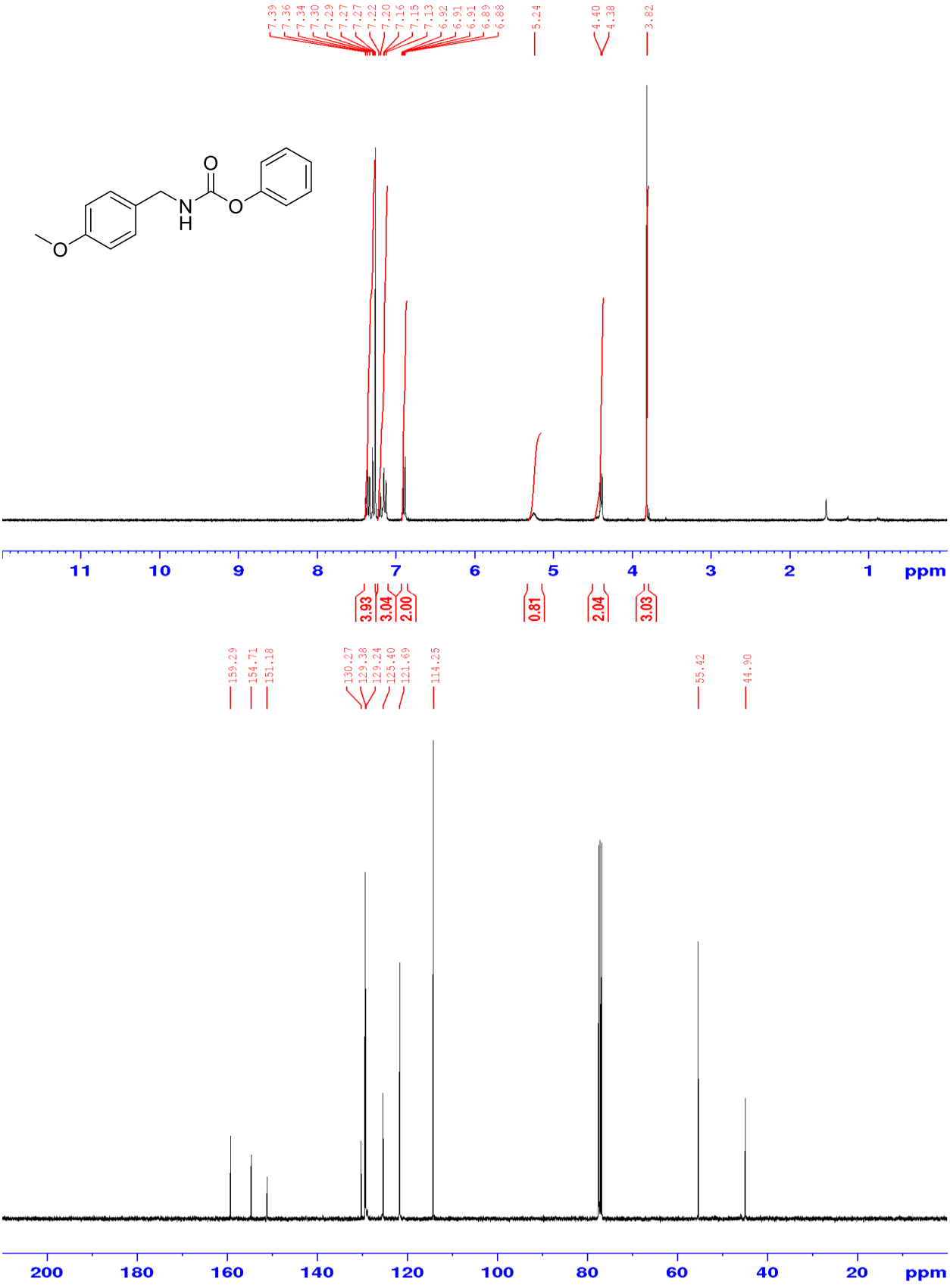

1H NMR
10.2151
7.8814
7.8541
7.8162
7.8091
7.7992
7.7925
7.7887
7.7769
7.7688
7.3317
7.3061
7.2934
7.1980
7.1738
7.1512
7.1440
2.3678
F
O
N
H
Me
0.9762
2.0075
2.0310
2.0000
2.0009
2.3875
14
12
10
8
6
4
2
0
[ppm]

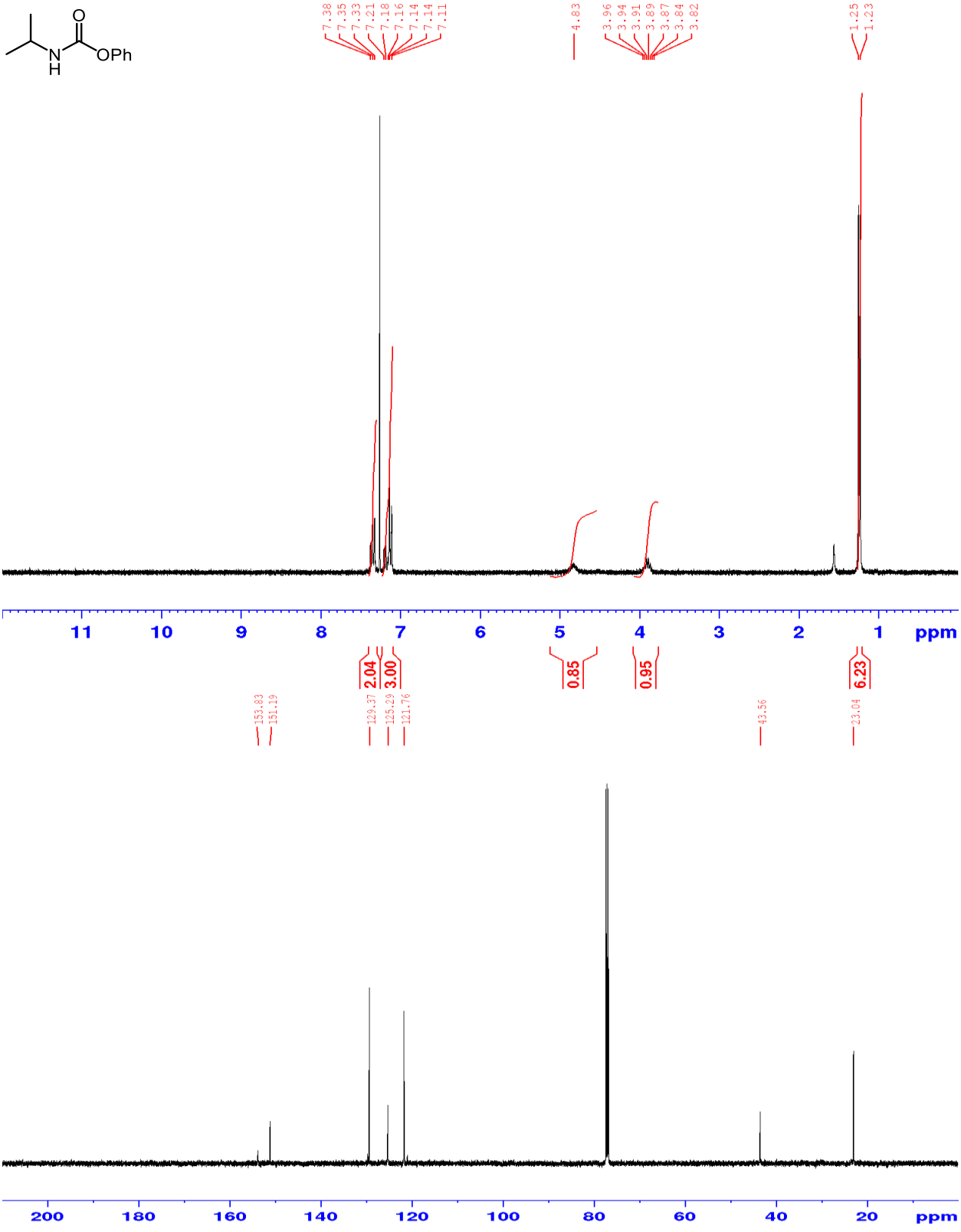

13C NMR with proton decoupling
165.7362
160.2639
157.0834
142.0438
136.0131
135.9791
132.3124
129.3321
129.0744
128.0704
122.6673
122.5637
115.6856
115.3921
21.3980
200
150
100
50
0
[ppm]

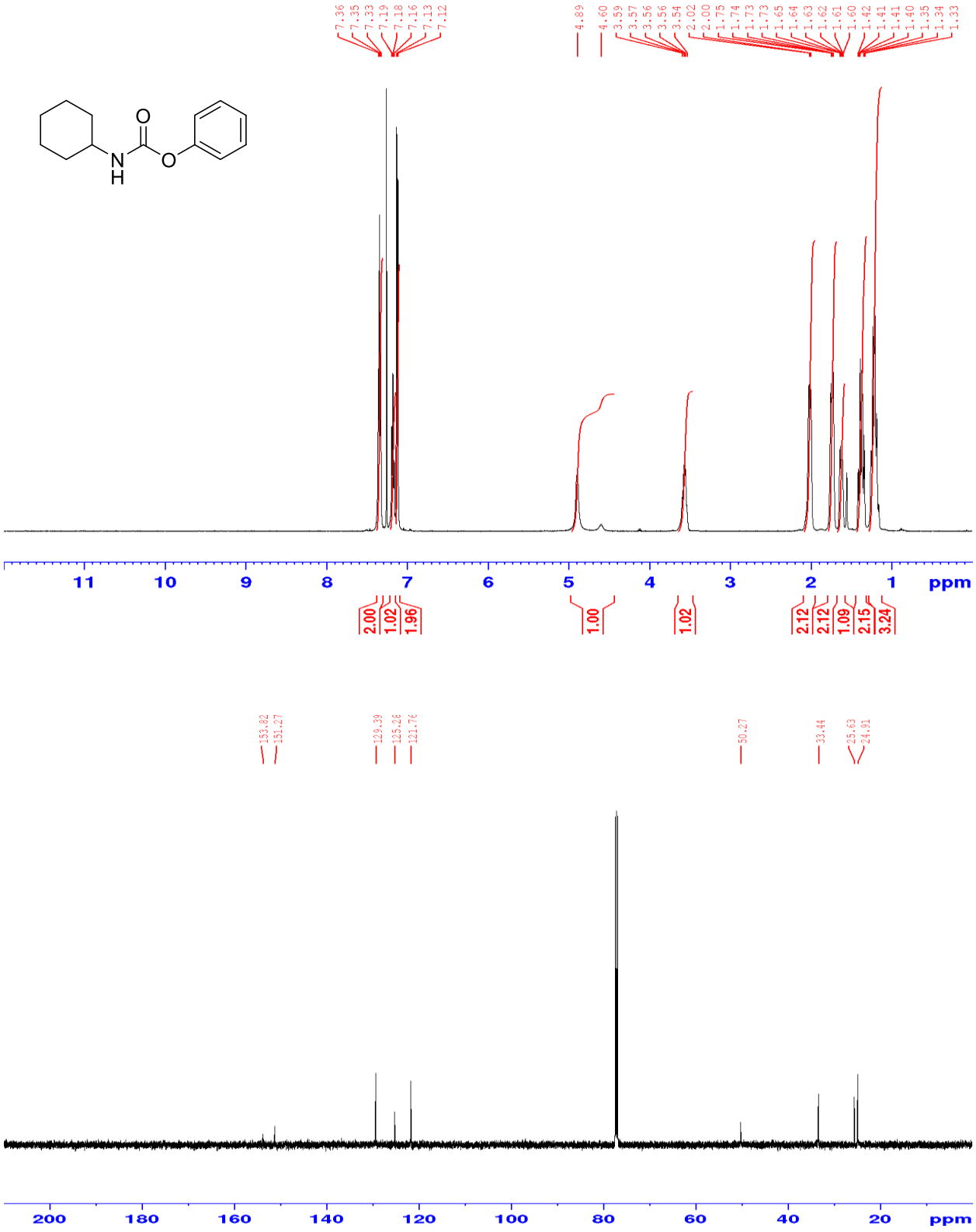

1d_1H_16_scans CDCl3 D:\\ Beau 42
O
Me
O
4
3
D/H
1
2
TMB
TMB
1
3
2
4
2.0000
0.6265
2.0402
2.5925
3.2164
8
7
6
5
4
[ppm]
[rel]

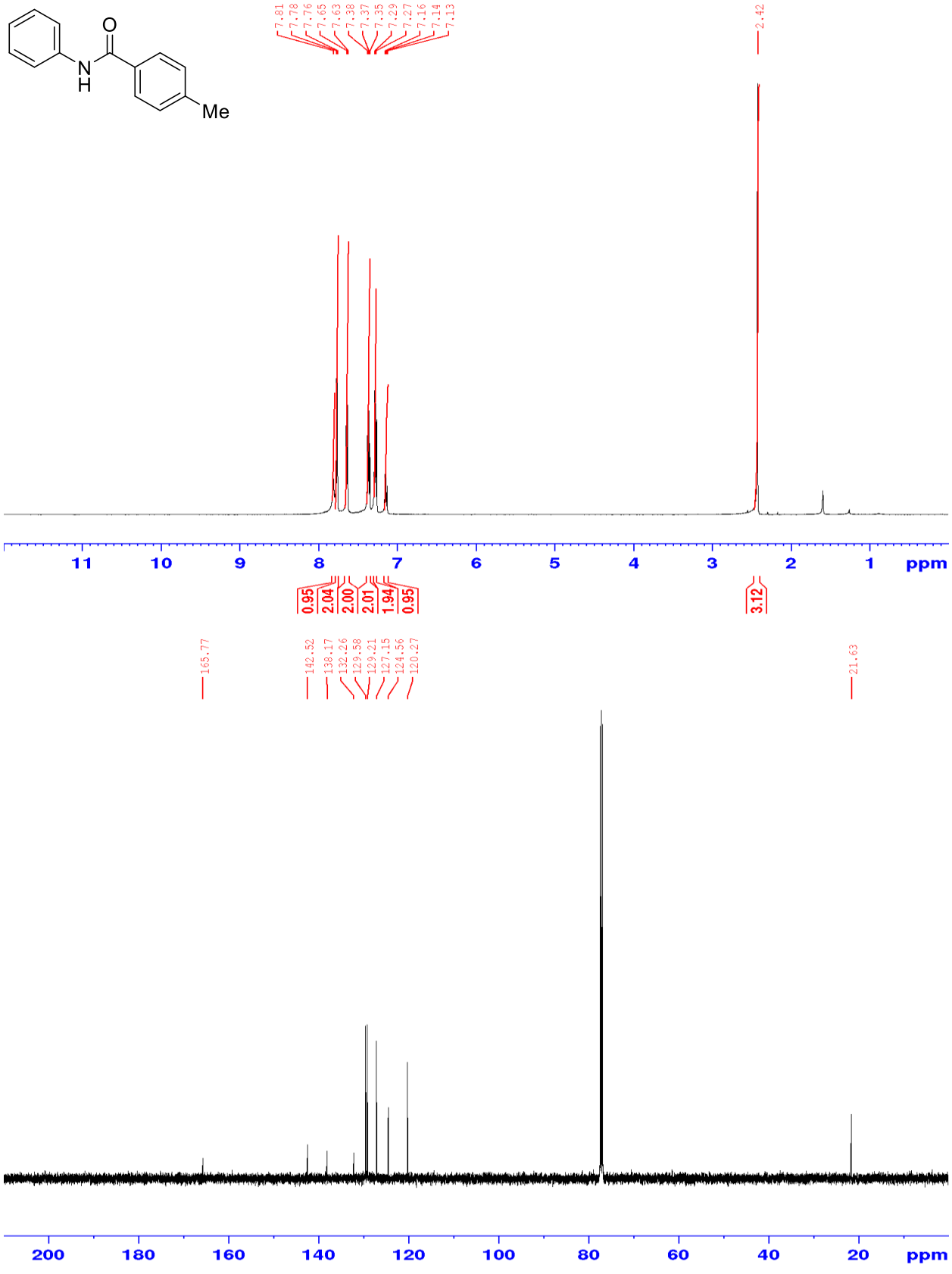

7.43
7.41
7.41
7.40
7.39
7.38
7.35
7.34
7.33
7.33
7.32
7.31
7.24
7.23
7.21
7.20
7.19
7.11
7.09
7.08
7.02
7.02
7.01
7.00
7.00
6.99
6.99
6.92
PhO
O
N
H
OPh
11
10
9
8
7
6
5
4
3
2
1
ppm
4.01
2.03
0.92
1.99
1.00
4.01
0.82
157.66
153.37
151.92
150.67
132.98
129.84
129.52
125.82
123.19
121.73
120.58
119.92
118.51
200
180
160
140
120
100
80
60
40
20
ppm

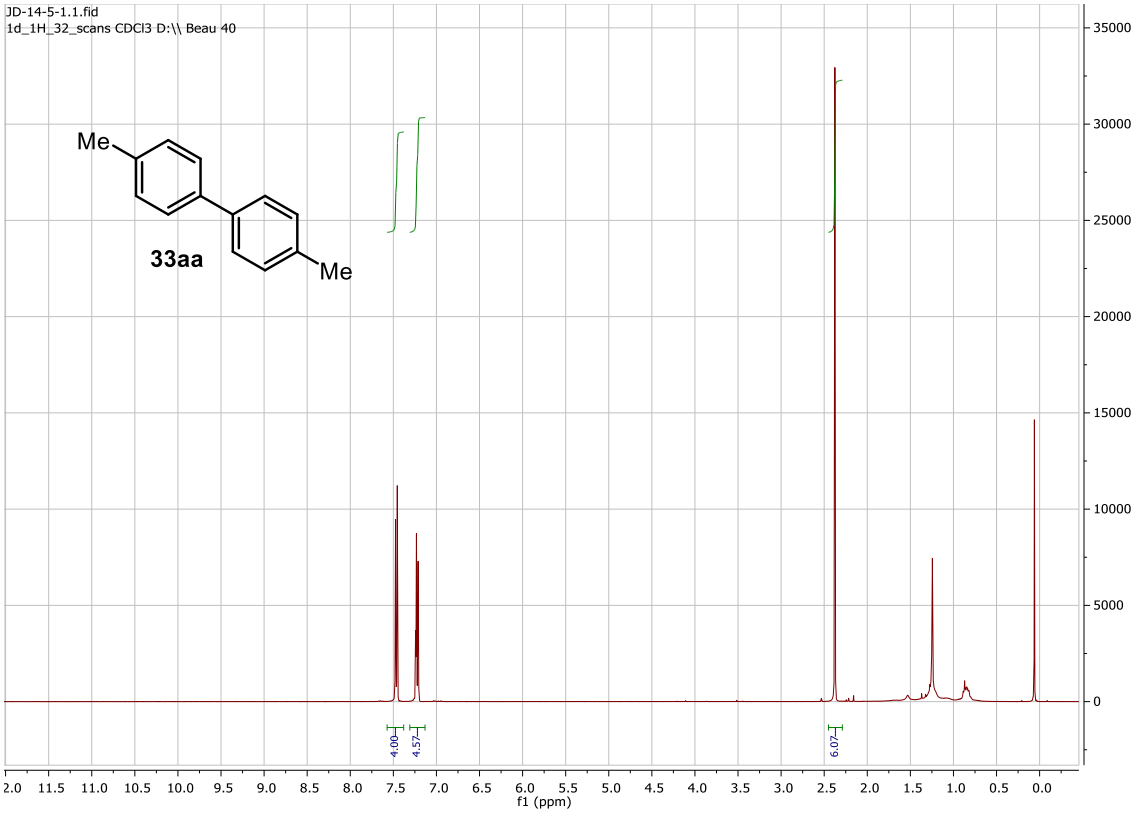

10.71
8.27
8.25
8.07
8.06
7.91
7.89
7.38
7.36
2.40
O2N
O
N
H
11
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.87
2.08
2.00
2.02
3.09
166.05
145.63
142.36
142.34
131.31
129.03
127.97
124.77
119.78
21.05
200
180
160
140
120
100
80
60
40
20
ppm

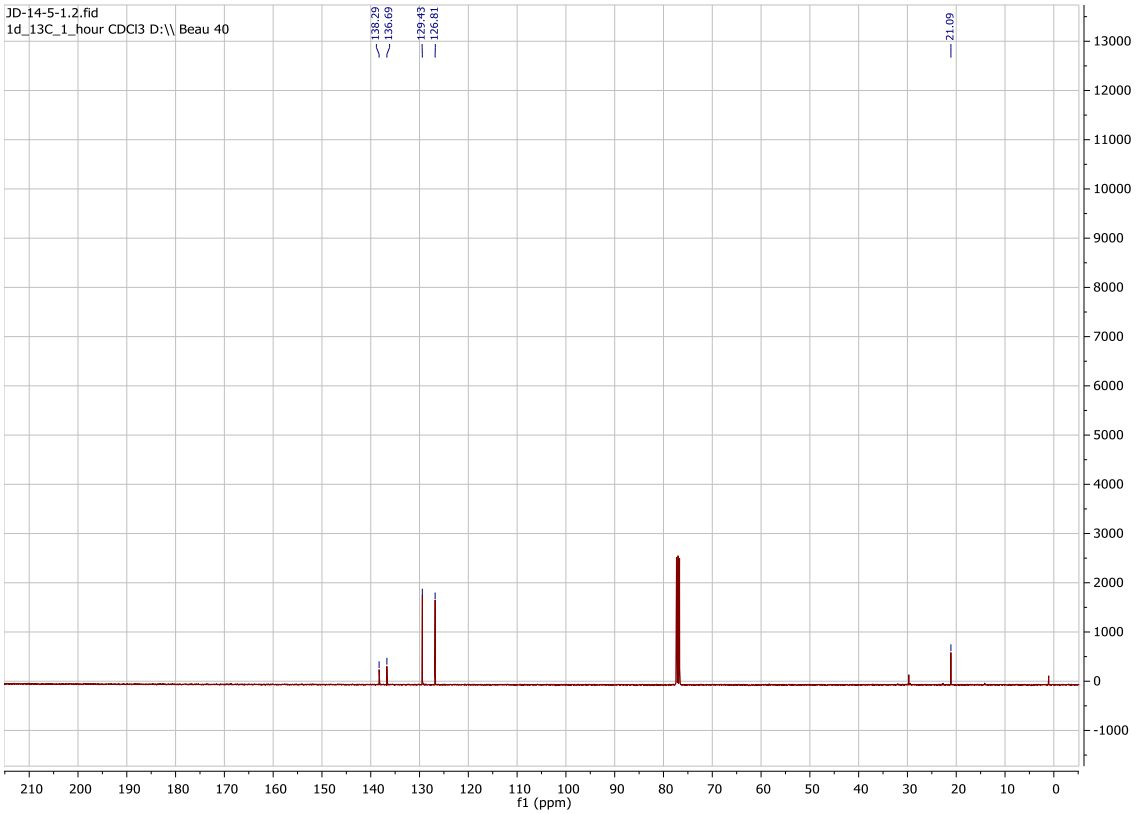

7.39
7.36
7.34
7.30
7.29
7.27
7.27
7.22
7.20
7.16
7.15
7.13
6.92
6.91
6.91
6.89
6.88
5.24
4.40
4.38
3.82
O
N
H
O
O
11
10
9
8
7
6
5
4
3
2
1
ppm
3.93
3.04
2.00
0.81
2.04
3.03
159.29
154.71
151.18
130.27
129.38
129.24
125.40
121.69
114.25
55.42
44.90
200
180
160
140
120
100
80
60
40
20
ppm

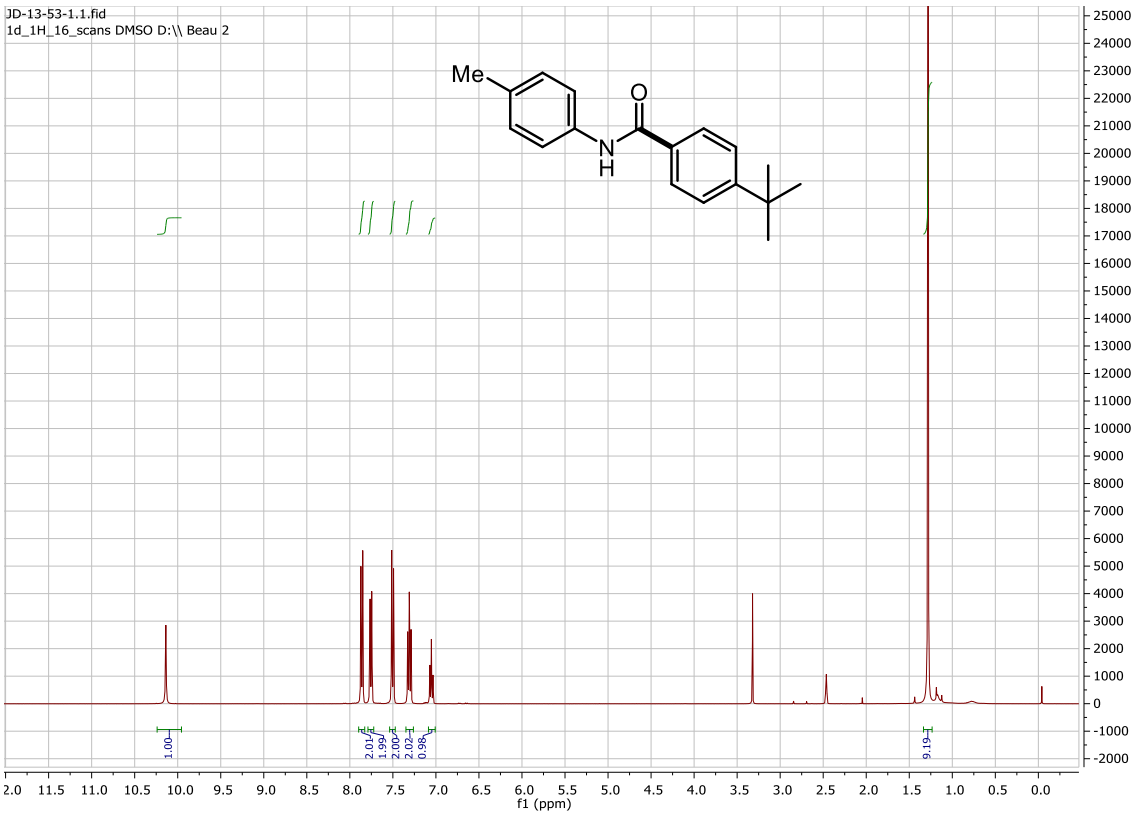

O
N
H
OPh
7.38
7.35
7.33
7.21
7.18
7.16
7.14
7.14
7.11
4.83
3.96
3.94
3.91
3.89
3.87
3.84
3.82
1.25
1.23
11
10
9
8
7
6
5
4
3
2
1
ppm
2.04
3.00
0.85
0.95
6.23
153.83
151.19
129.37
125.29
121.76
43.56
23.04
200
180
160
140
120
100
80
60
40
20
ppm

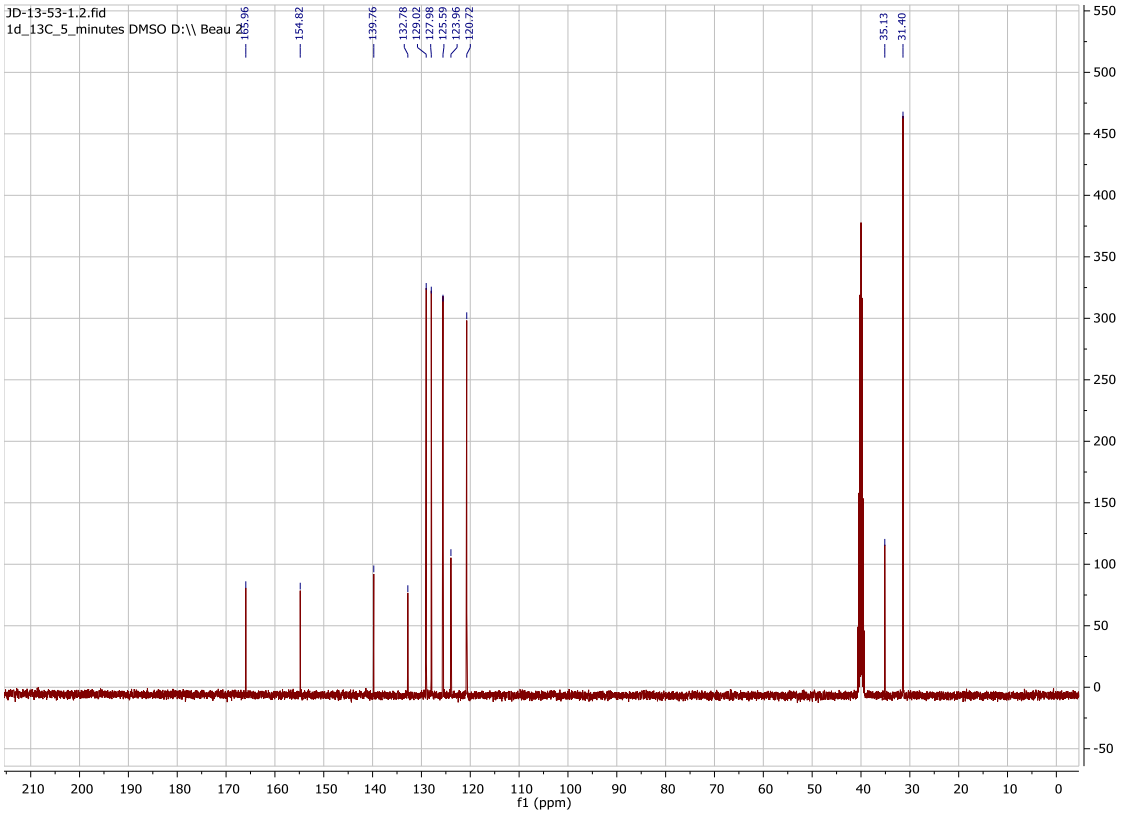

7.36
7.35
7.33
7.19
7.18
7.16
7.13
7.12
4.89
4.60
3.59
3.57
3.56
3.56
3.54
2.02
2.00
1.75
1.74
1.73
1.73
1.65
1.64
1.63
1.62
1.61
1.60
1.42
1.41
1.41
1.40
1.35
1.34
1.33
O
N
H
O
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
1.02
1.96
1.00
1.02
2.12
2.12
1.09
2.15
3.24
153.82
151.27
129.39
125.08
121.76
50.27
33.44
25.63
24.91
200
180
160
140
120
100
80
60
40
20
ppm

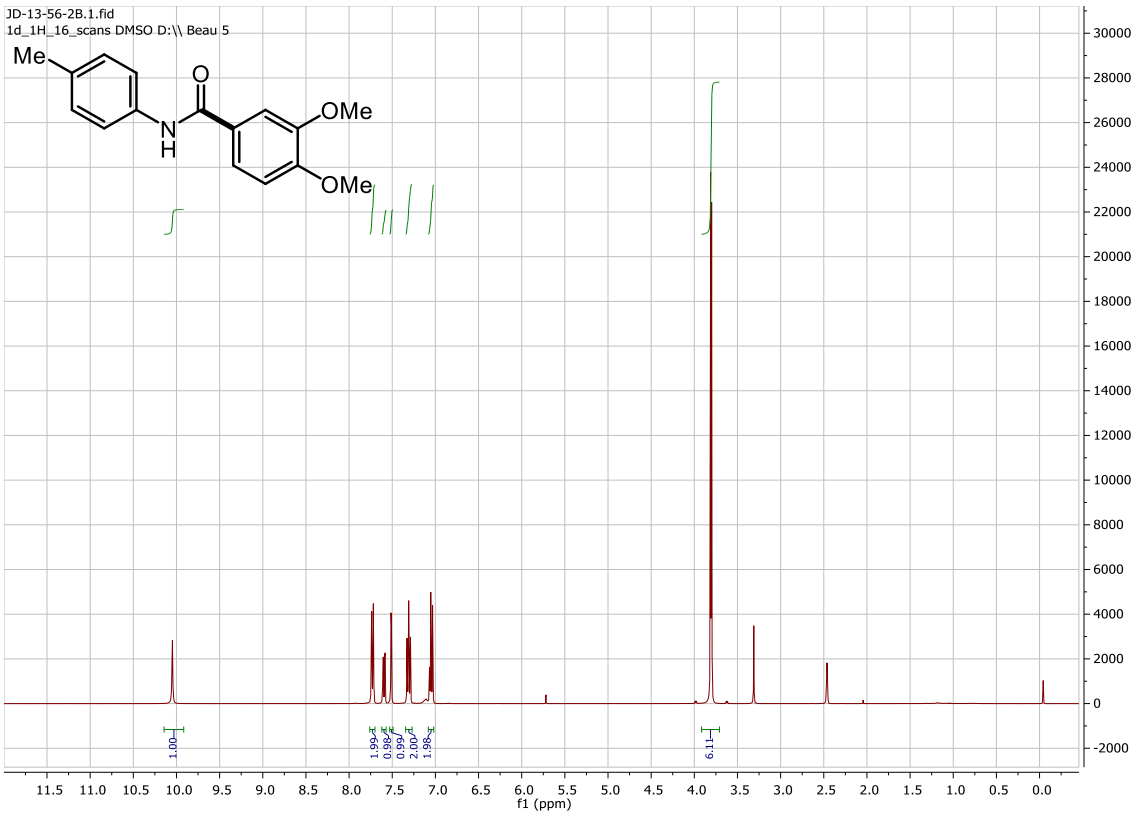

O
N
H
Me
7.81
7.78
7.76
7.65
7.63
7.38
7.37
7.35
7.29
7.27
7.16
7.14
7.13
2.42
11
10
9
8
7
6
5
4
3
2
1
ppm
0.95
2.04
2.00
2.01
1.94
0.95
3.12
165.77
142.52
138.17
132.26
129.58
129.21
127.15
124.56
120.27
21.63
200
180
160
140
120
100
80
60
40
20
ppm

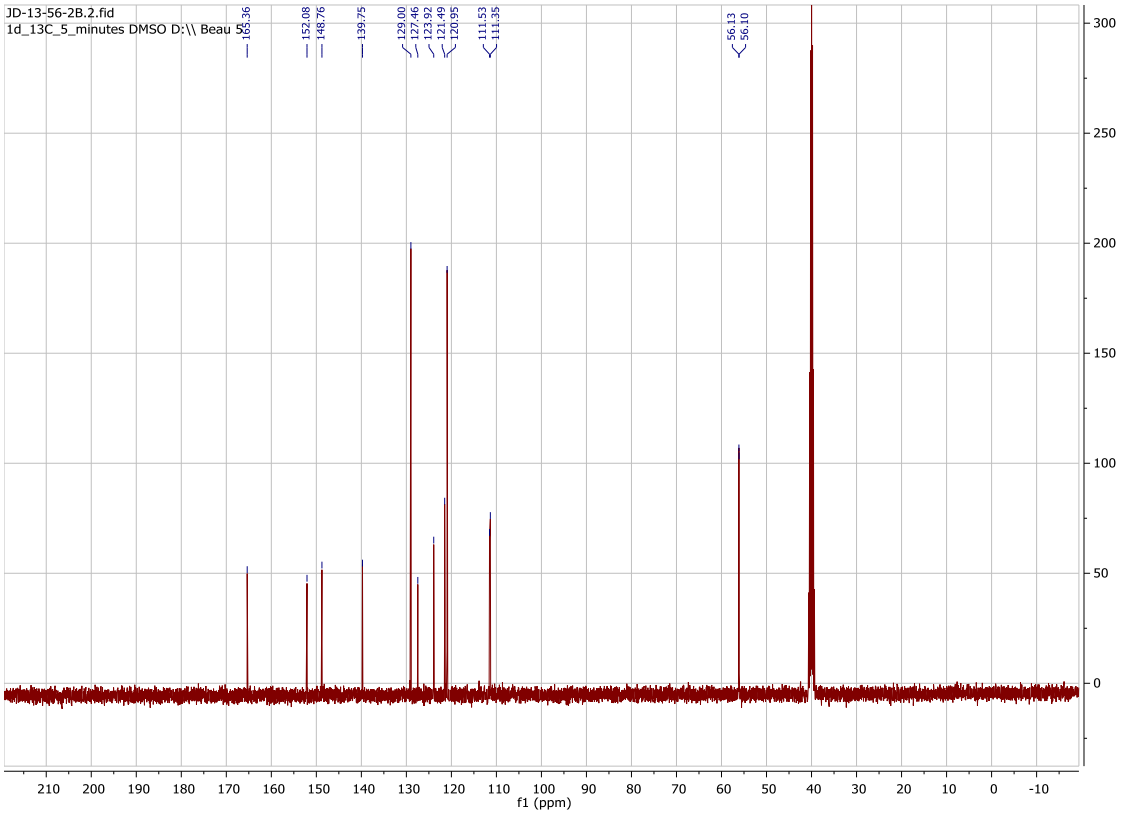

JD-14-5-1.1.fid
1d_1H_32_scans CDCl3 D:\\ Beau 40
Me
33aa
Me
4.00
4.57
6.07
f1 (ppm)

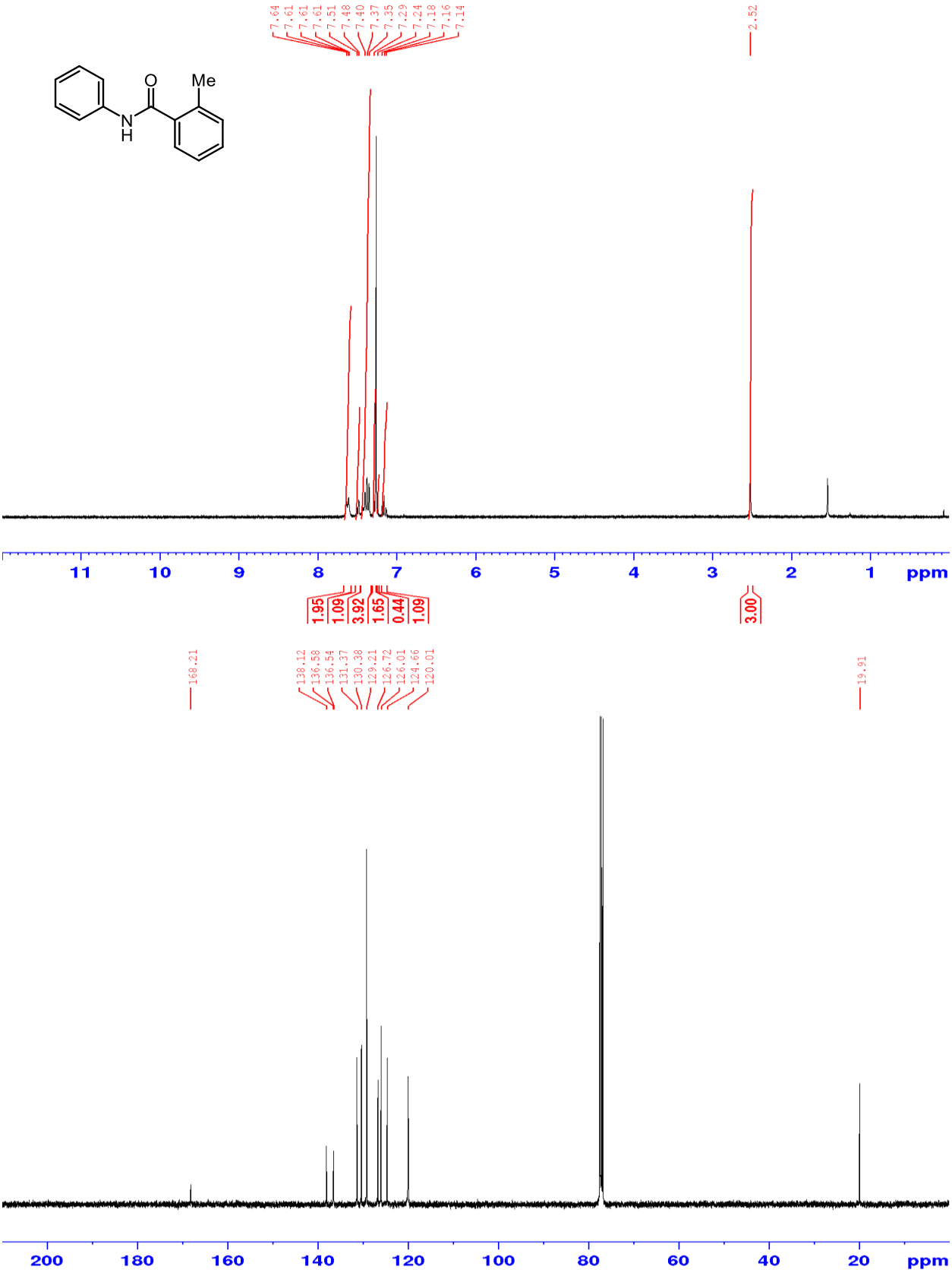

JD-14-5-1.2.fid
1d_13C_1_hour CDCl3 D:\\ Beau 40
138.29
136.69
129.43
126.81
21.09
f1 (ppm)

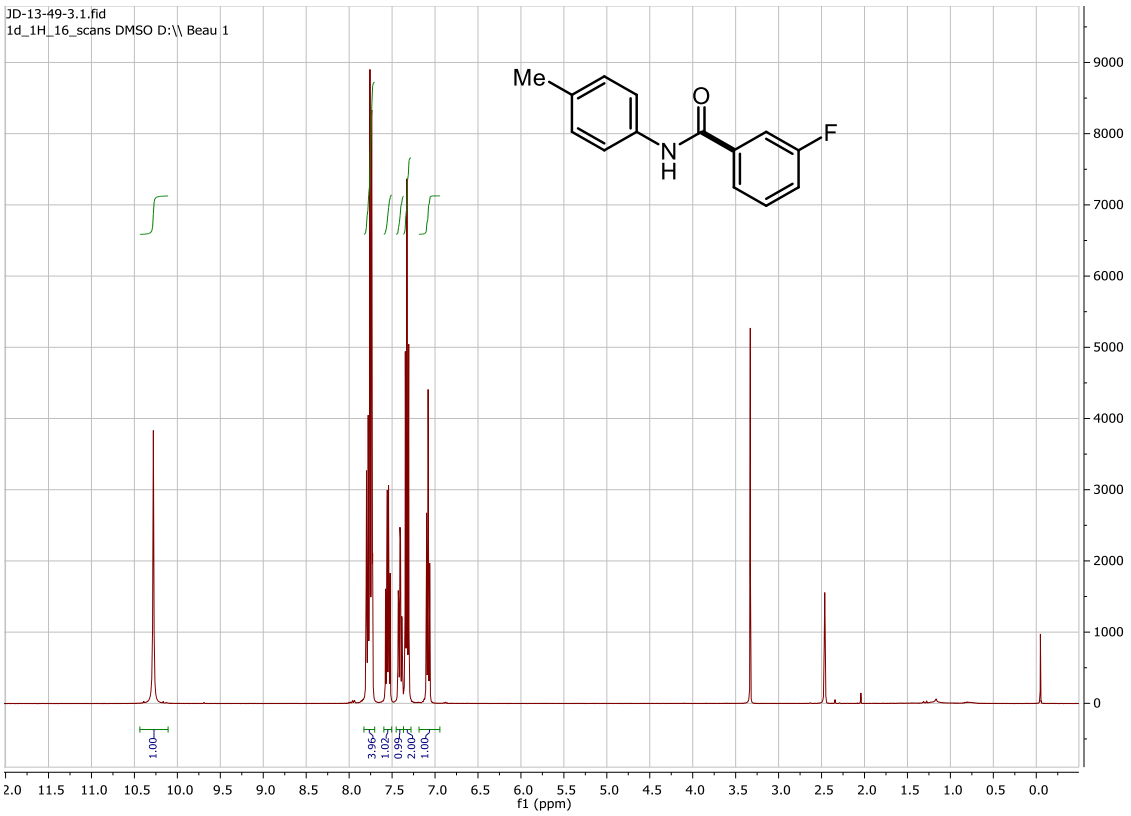

JD-13-53-1.1.fid
1d_1H_16_scans DMSO D:\\ Beau 2
Me
O
N
H
1.00
2.01
1.99
2.00
2.02
0.98
9.19
f1 (ppm)

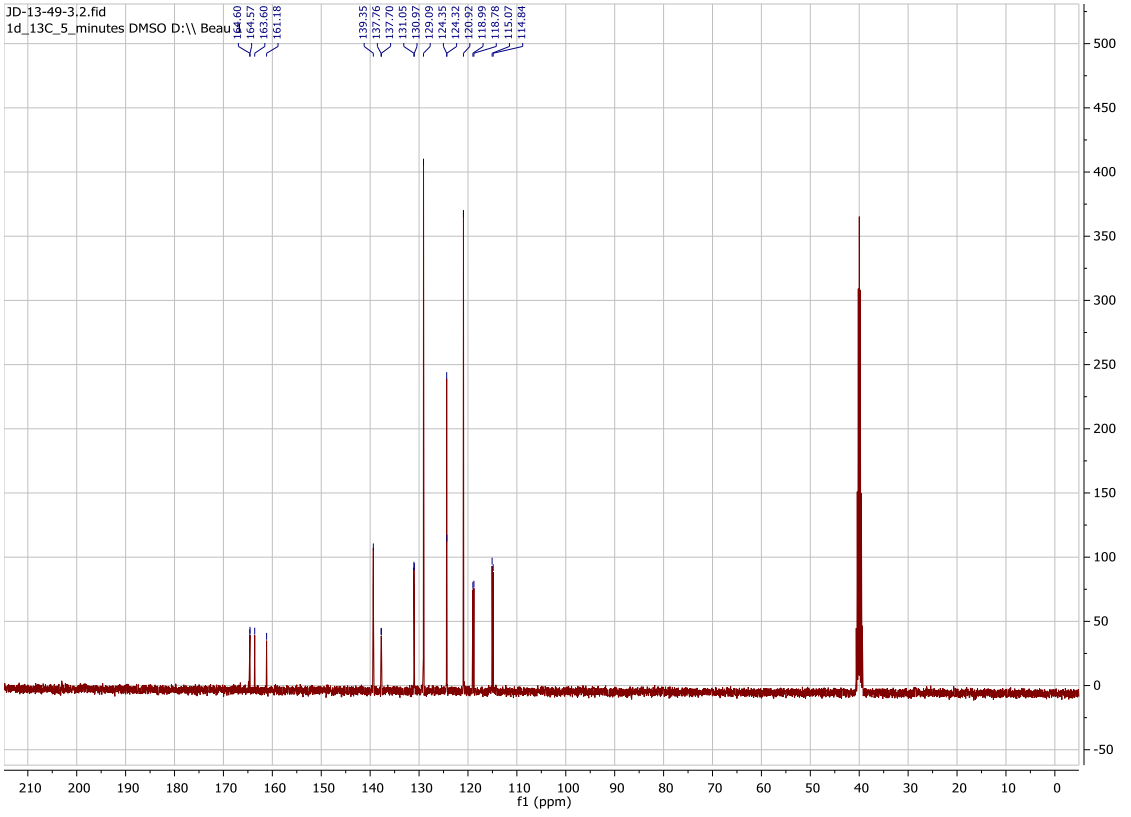

JD-13-53-1.2.fid
1d_13C_5_minutes DMSO D:\\ Beau 2
165.96
154.82
139.76
132.78
129.02
127.98
125.59
123.96
120.72
35.13
31.40
f1 (ppm)

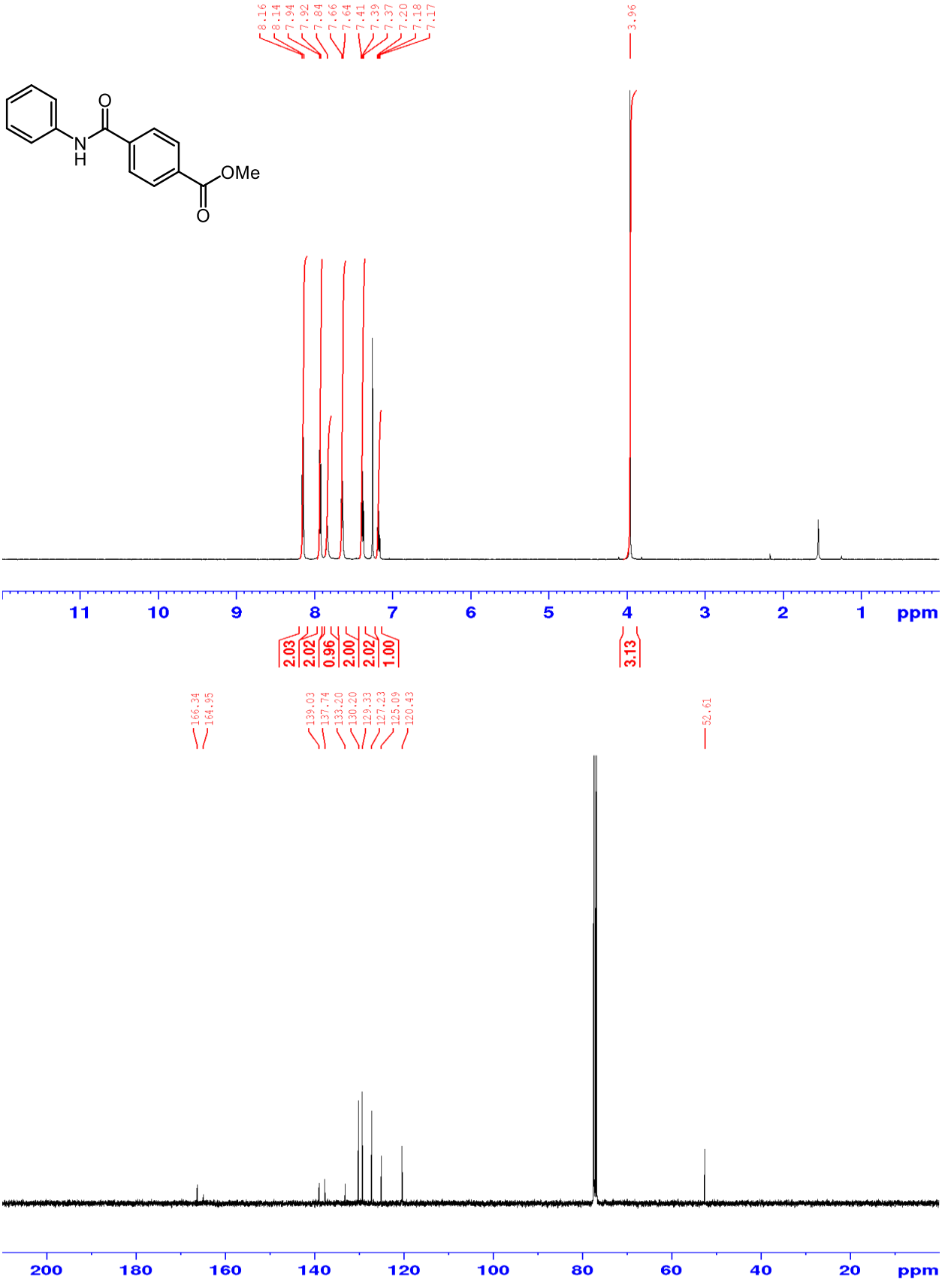

JD-13-56-2B.1.fid
1d_1H_16_scans DMSO D:\\ Beau 5
Me
O
N
H
OMe
OMe
1.00
1.99
0.98
0.99
2.00
1.98
6.11
f1 (ppm)

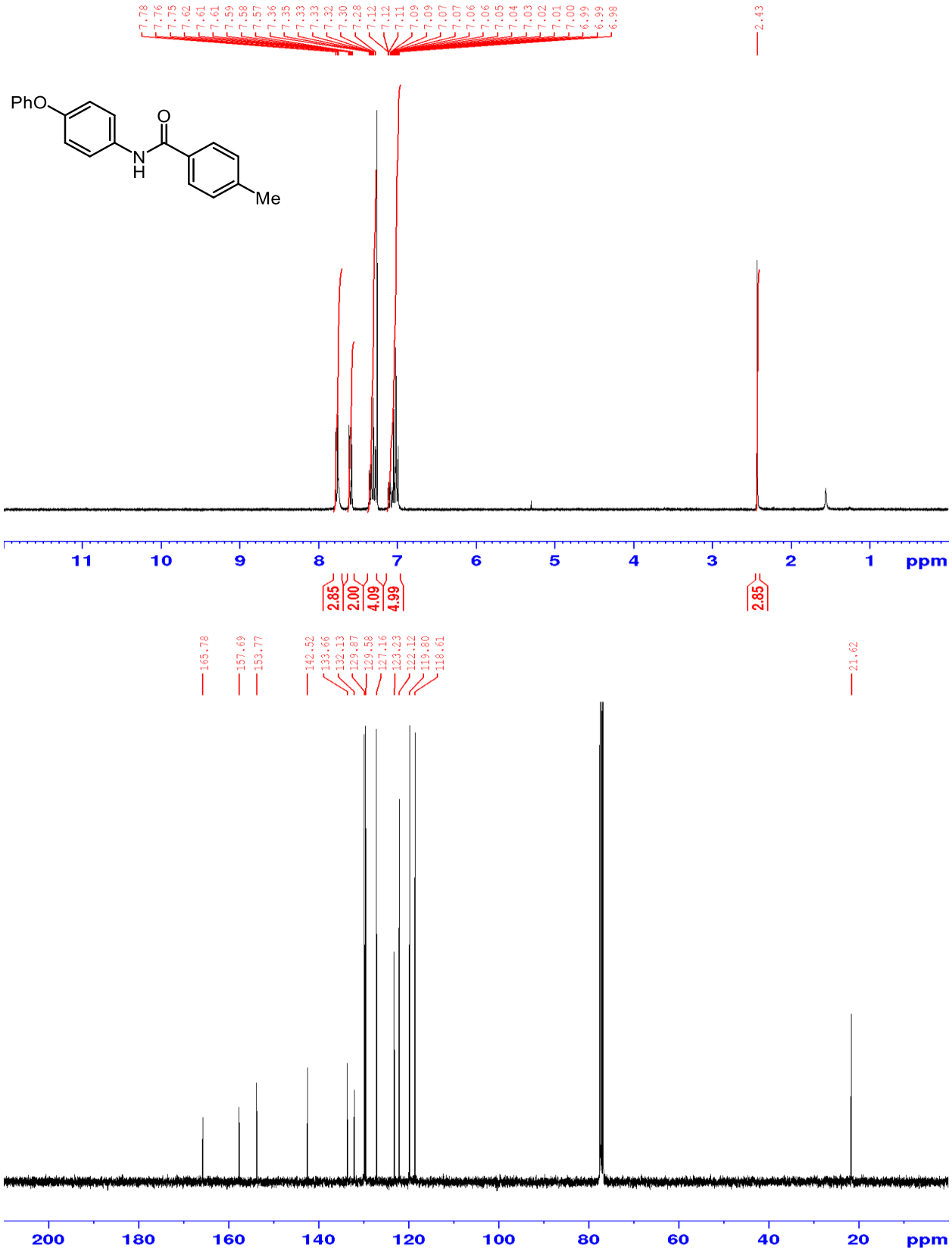

JD-13-56-2B.2.fid
1d_13C_5_minutes DMSO D:\\ Beau 5
165.36
152.08
148.76
139.75
129.00
127.46
123.92
121.49
120.95
111.53
111.35
56.13
56.10
f1 (ppm)

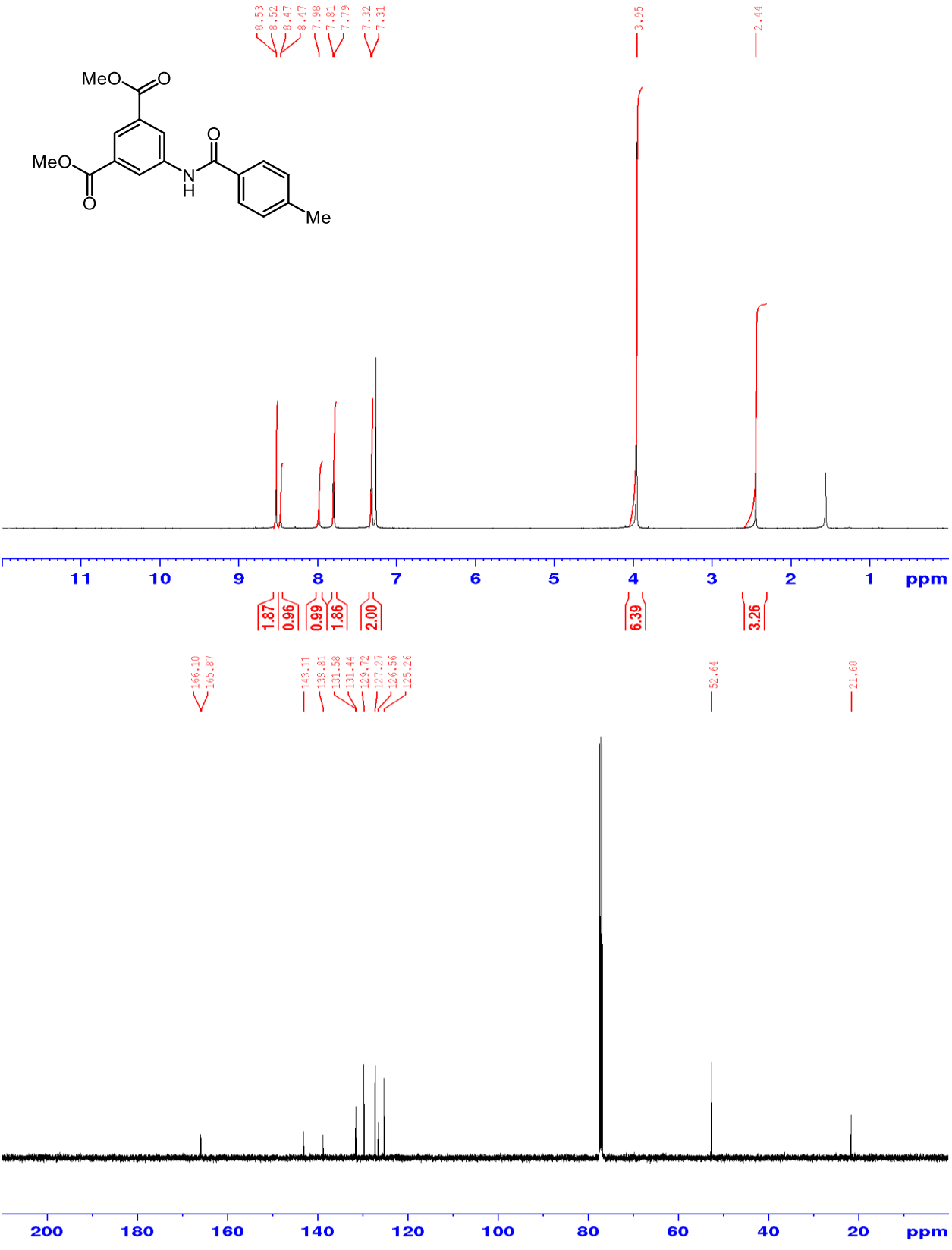

7.64
7.61
7.61
7.61
7.51
7.48
7.40
7.37
7.35
7.29
7.24
7.18
7.16
7.14
2.52
O
Me
N
H
11
10
9
8
7
6
5
4
3
2
1
ppm
1.95
1.09
3.92
1.65
0.44
1.09
3.00
168.21
138.12
136.58
136.54
131.37
130.38
129.21
126.72
126.01
124.66
120.01
19.91
200
180
160
140
120
100
80
60
40
20
ppm

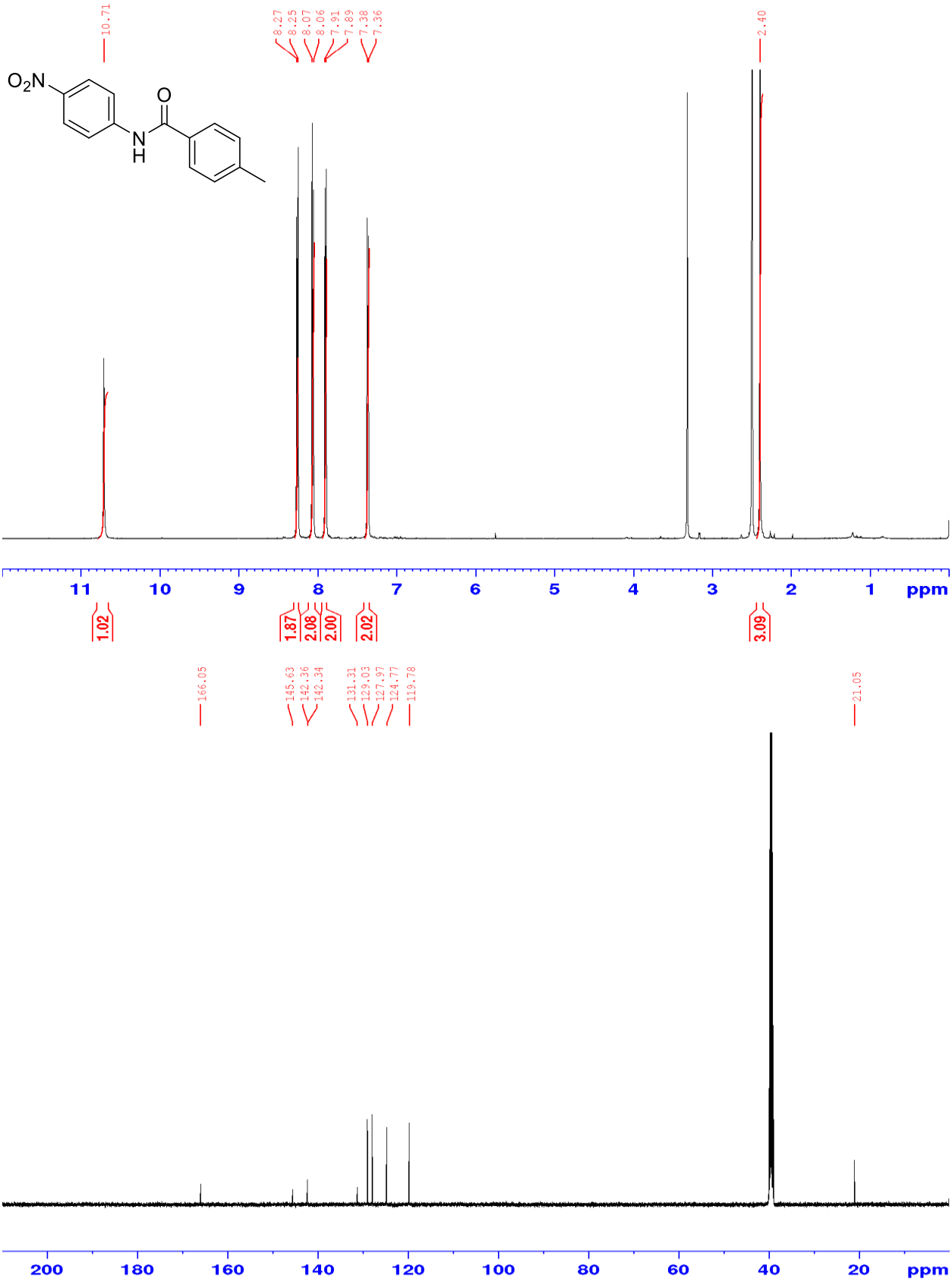

JD-13-49-3.1.fid
1d_1H_16_scans DMSO D:\\ Beau 1
Me
O
N
H
F
1.00
3.96
1.02
0.94
2.00
1.05
f1 (ppm)


JD-13-49-3.2.fid
1d_13C_5_minutes DMSO D:\\ Beau 1
164.60
164.57
163.60
161.18
139.35
137.76
137.70
131.05
130.97
129.09
124.35
124.32
120.92
118.99
118.78
115.07
114.84
f1 (ppm)


8.16
8.14
7.94
7.92
7.84
7.66
7.64
7.41
7.39
7.37
7.20
7.18
7.17
3.96
O
N
H
OMe
O
11
10
9
8
7
6
5
4
3
2
1
ppm
2.03
2.02
0.96
2.00
2.02
1.00
3.13
166.34
164.95
139.03
137.74
133.20
130.20
129.33
127.23
125.09
120.43
52.61
200
180
160
140
120
100
80
60
40
20
ppm


7.78
7.76
7.75
7.62
7.61
7.61
7.59
7.58
7.57
7.36
7.35
7.33
7.33
7.32
7.30
7.28
7.12
7.12
7.11
7.09
7.09
7.07
7.07
7.06
7.06
7.05
7.04
7.03
7.02
7.01
7.00
6.99
6.99
6.98
2.43
PhO
O
N
H
Me
11
10
9
8
7
6
5
4
3
2
1
ppm
2.85
2.00
4.09
4.99
2.85
165.78
157.69
153.77
142.52
133.66
132.13
129.87
129.58
127.16
123.23
122.12
119.80
118.61
21.62
200
180
160
140
120
100
80
60
40
20
ppm


8.53
8.52
8.47
8.47
7.98
7.81
7.79
7.32
7.31
3.95
2.44
MeO
O
MeO
O
N
H
O
Me
11
10
9
8
7
6
5
4
3
2
1
ppm
1.87
0.96
0.99
1.86
2.00
6.39
3.26
166.10
165.87
143.11
138.81
131.58
131.44
129.72
127.27
126.56
125.26
52.64
21.68
200
180
160
140
120
100
80
60
40
20
ppm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8.25
8.07
8.06
7.91
7.89
7.38
7.36
2.40
O2N
O
N
H
11
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.87
2.08
2.00
2.02
3.09
166.05
145.63
142.36
142.34
131.31
129.03
127.97
124.77
119.78
21.05
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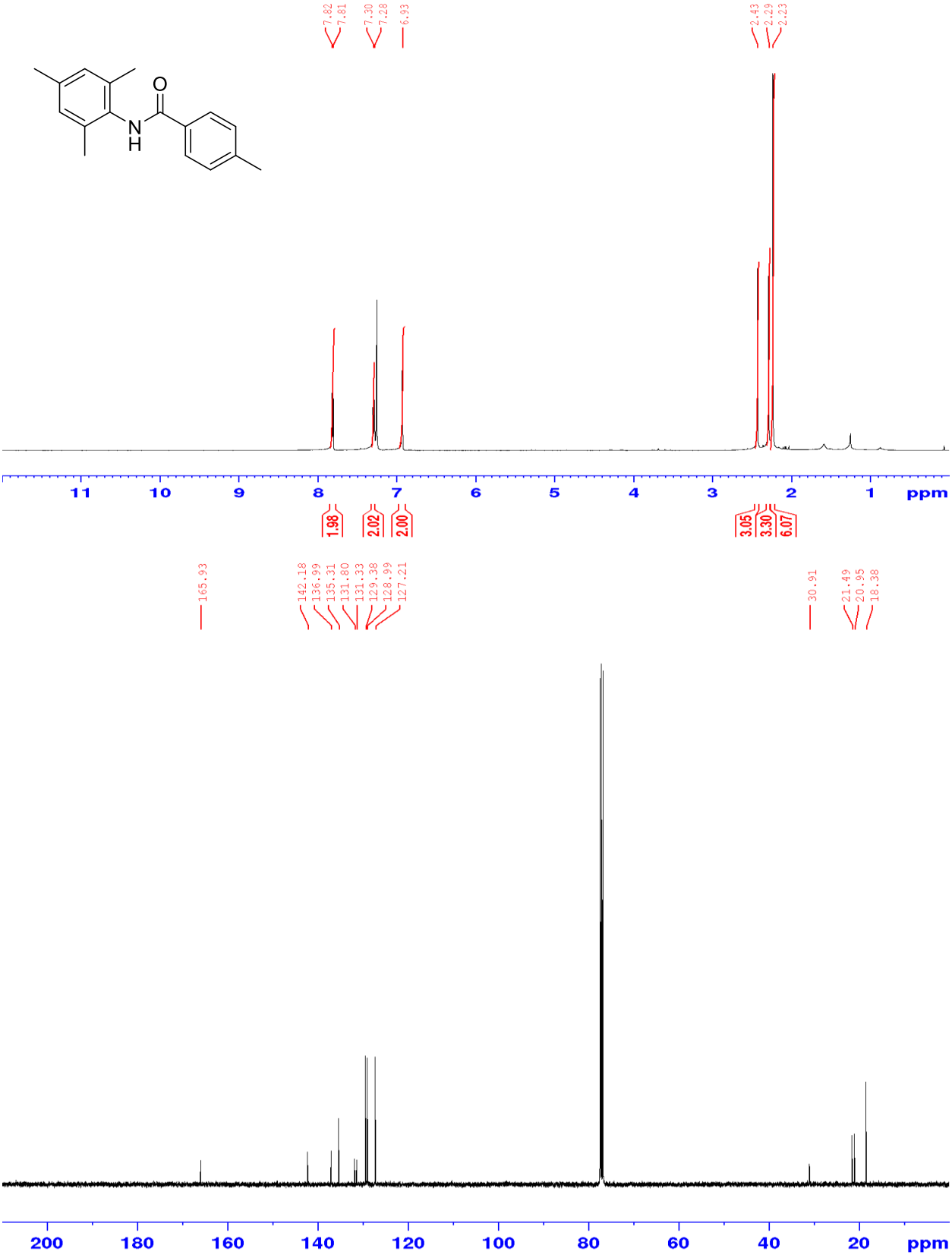
140
120
100
80
60
40
20
ppm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7.30
7.28
6.93
2.43
2.29
2.23
O
N
H
11
10
9
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7
6
5
4
3
2
1
ppm
1.98
2.02
2.00
3.05
3.30
6.07
165.93
142.18
136.99
135.31
131.80
131.33
129.38
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21.49
20.95
18.38
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140
120
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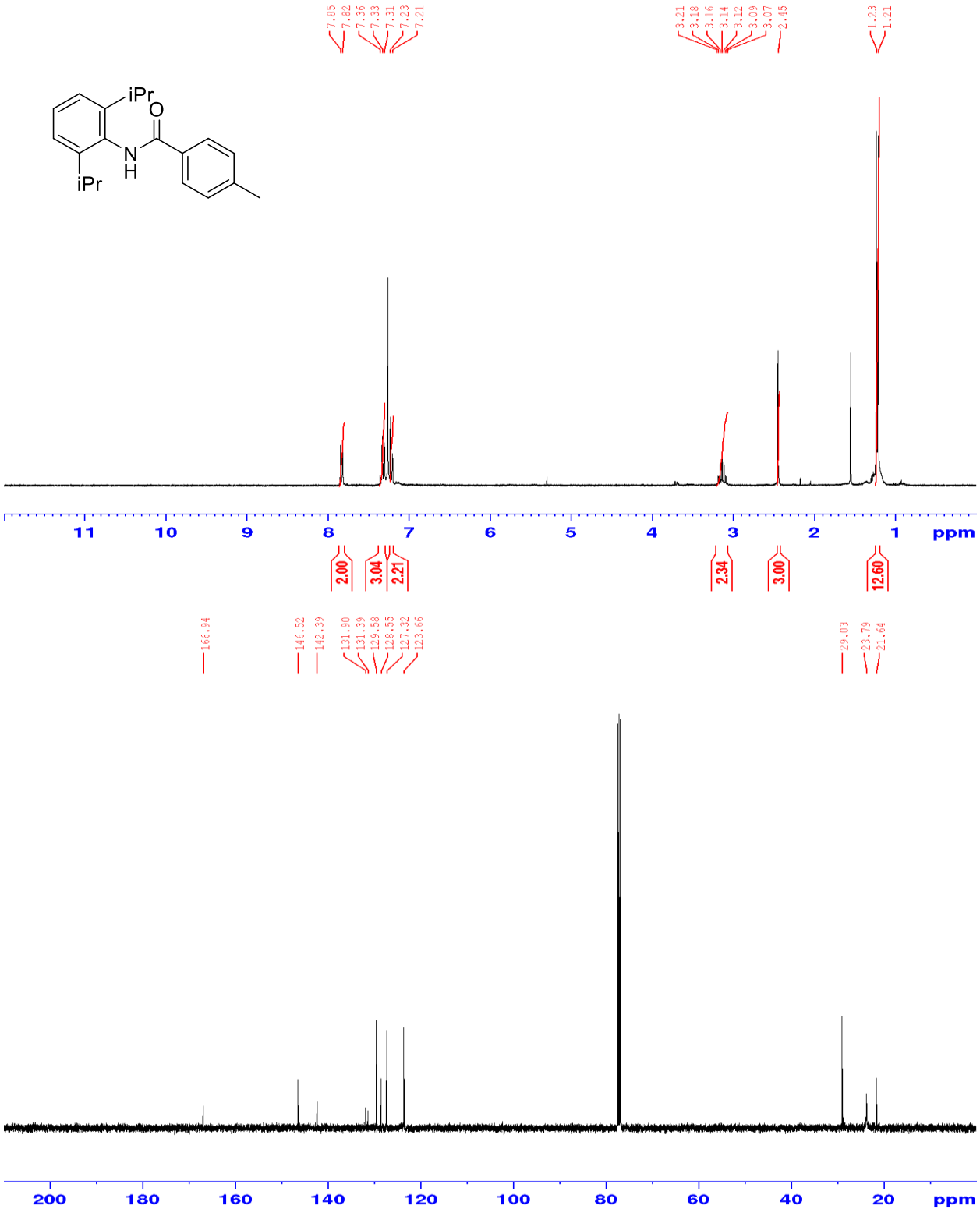
80
60
40
20
ppm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7.36
7.33
7.31
7.23
7.21
3.21
3.18
3.16
3.14
3.12
3.09
3.07
2.45
1.23
1.21
iPr
O
N
H
iPr
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
3.04
2.21
2.34
3.00
12.60
166.94
146.52
142.39
131.90
131.39
129.58
128.55
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29.03
23.79
21.64
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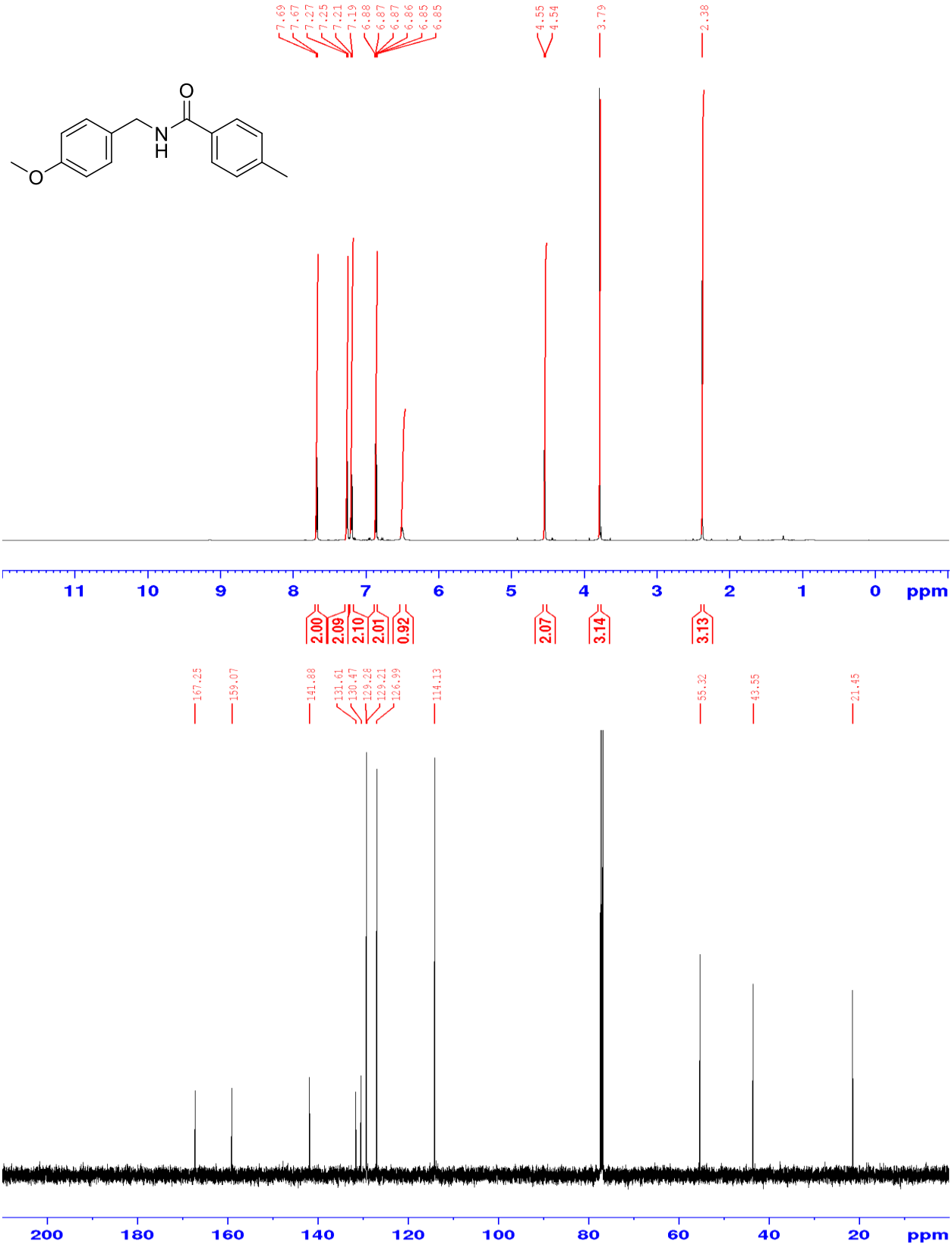
140
120
100
80
60
40
20
ppm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7.27
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7.21
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6.87
6.87
6.86
6.85
6.85
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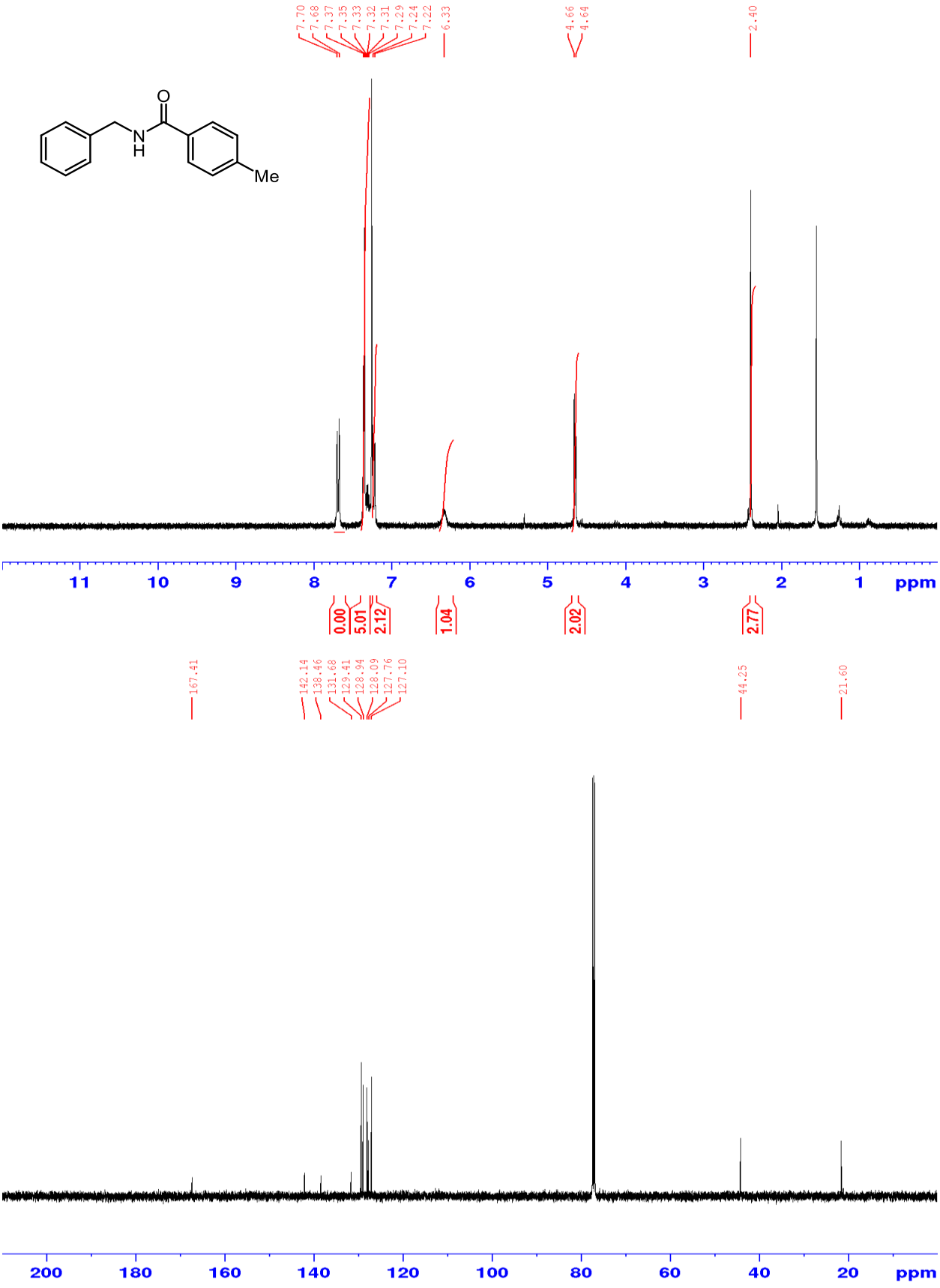
4.54
3.79
2.38
O
N
H
O
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.09
2.10
2.01
0.92
2.07
3.14
3.13
167.25
159.07
141.88
131.61
130.47
129.28
129.21
126.99
114.13
55.32
43.55
21.45
200
180
160
140
120
100
80
60
40
20
ppm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7.37
7.35
7.33
7.32
7.31
7.29
7.24
7.22
6.33
4.66
4.64
2.40
O
N
H
Me
11
10
9
8
7
6
5
4
3
2
1
ppm
0.00
5.01
2.12
1.04
2.02
2.77
167.41
142.14
138.46
131.68
129.41
128.94
128.09
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127.10
44.25
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200
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140
120
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80
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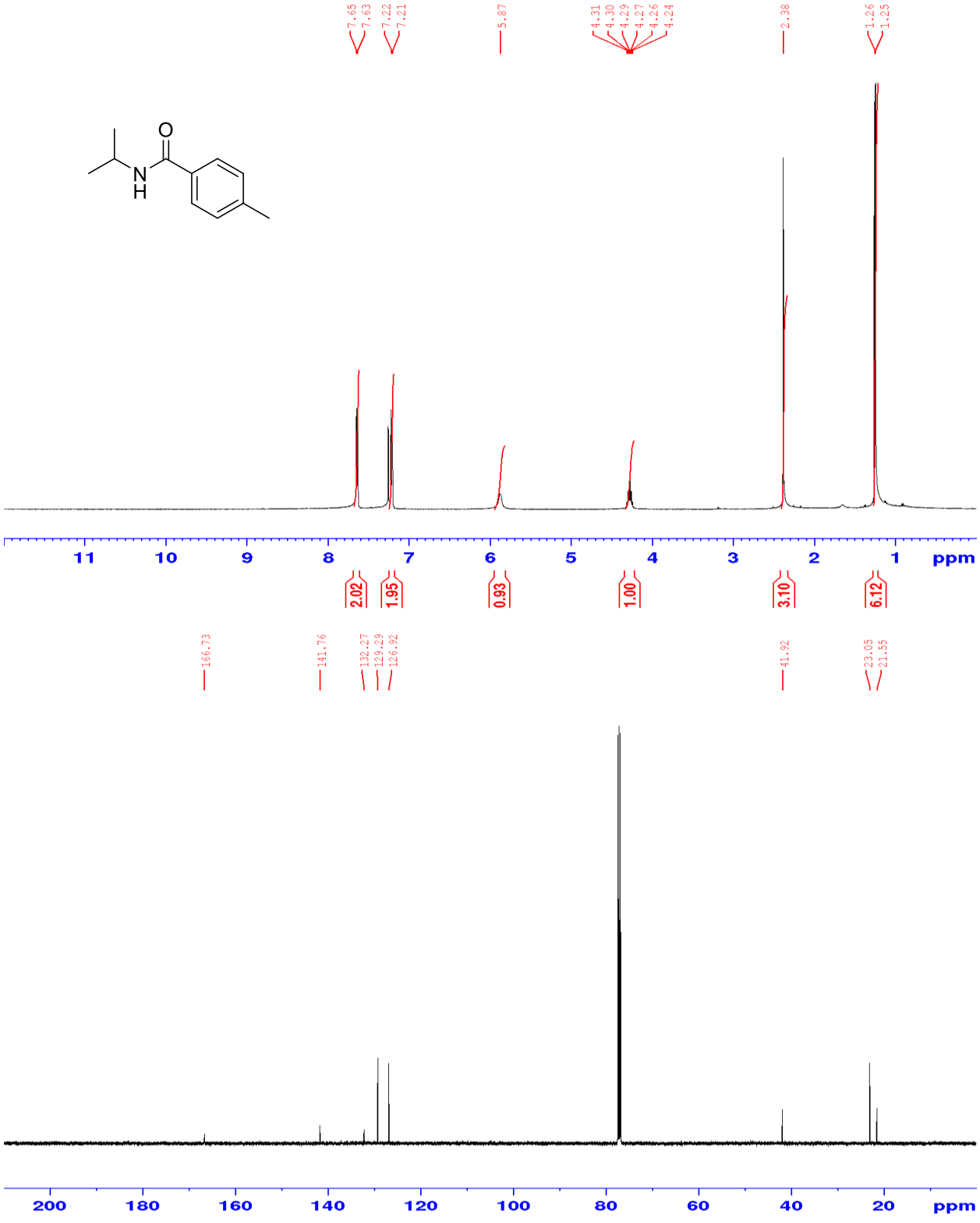
20
ppm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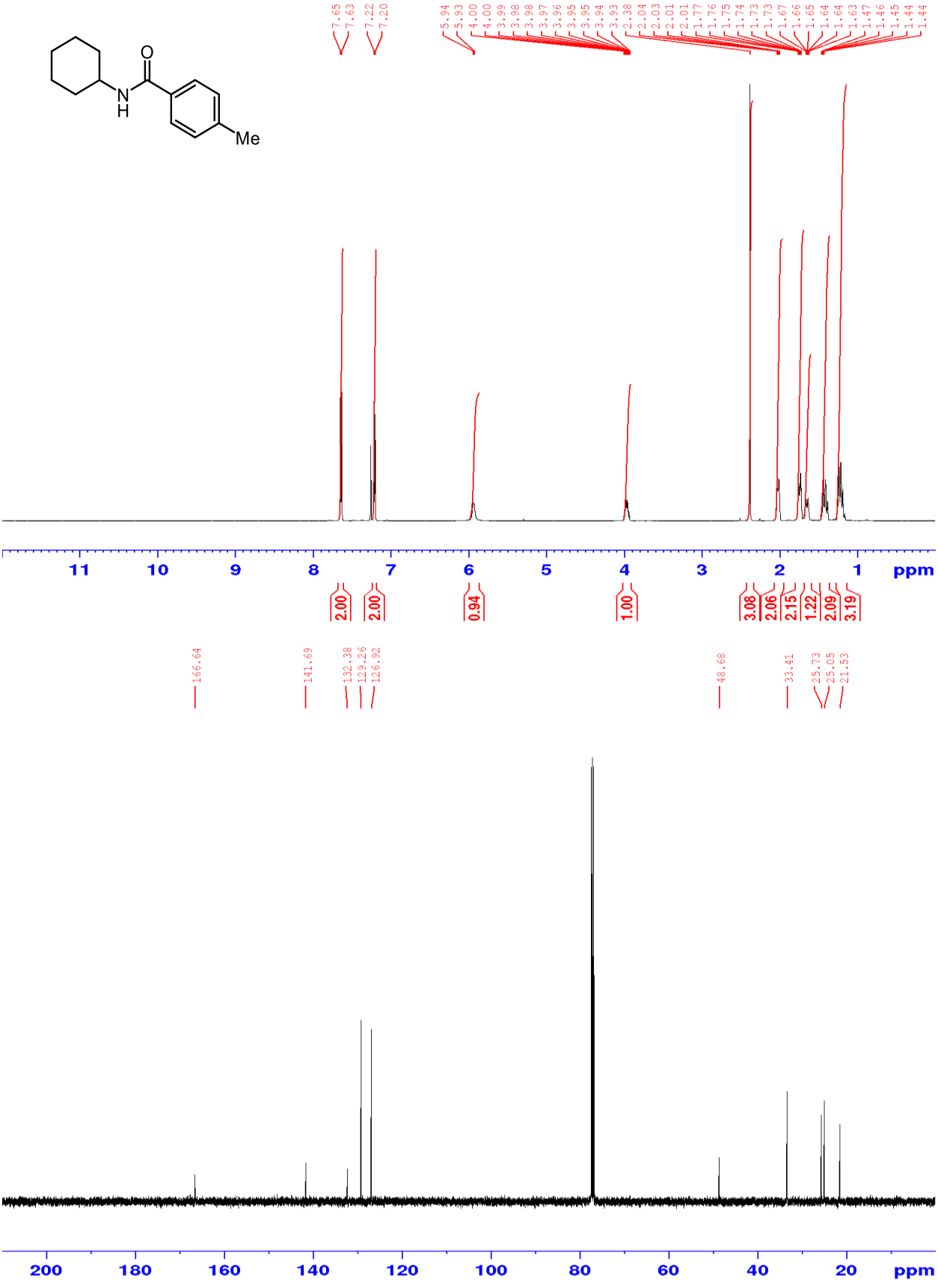
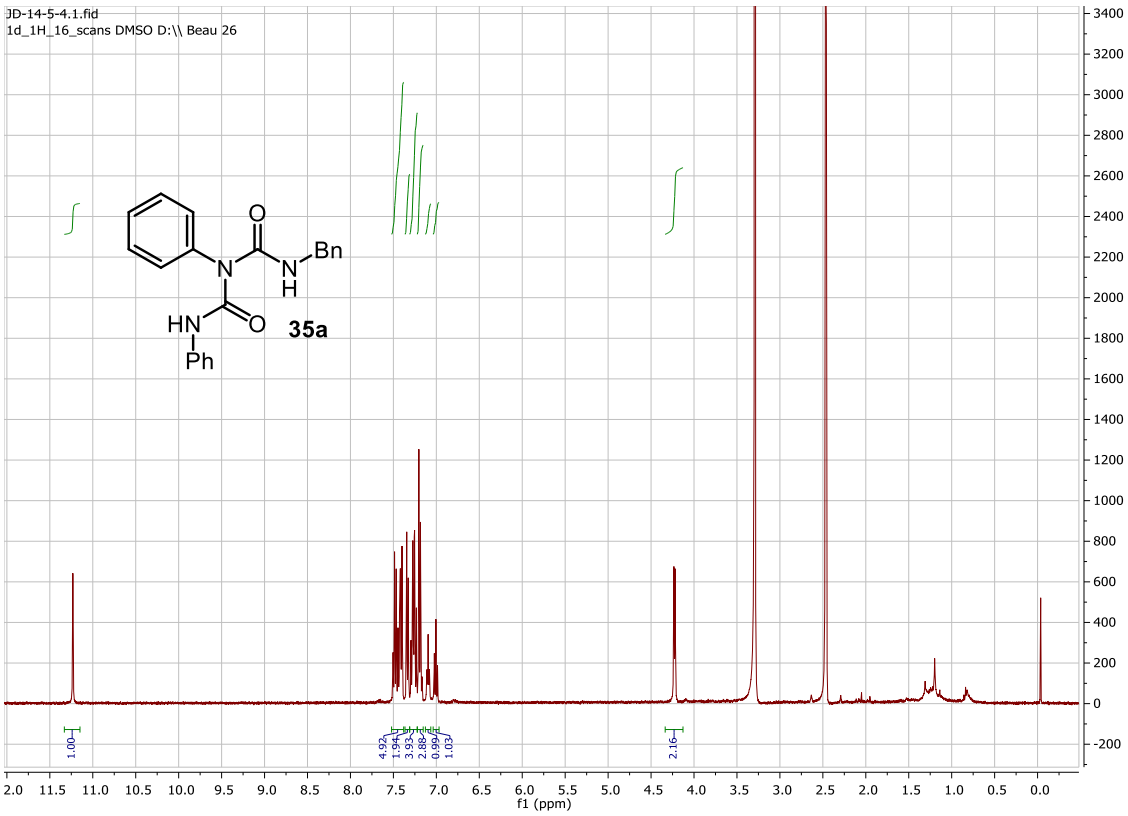
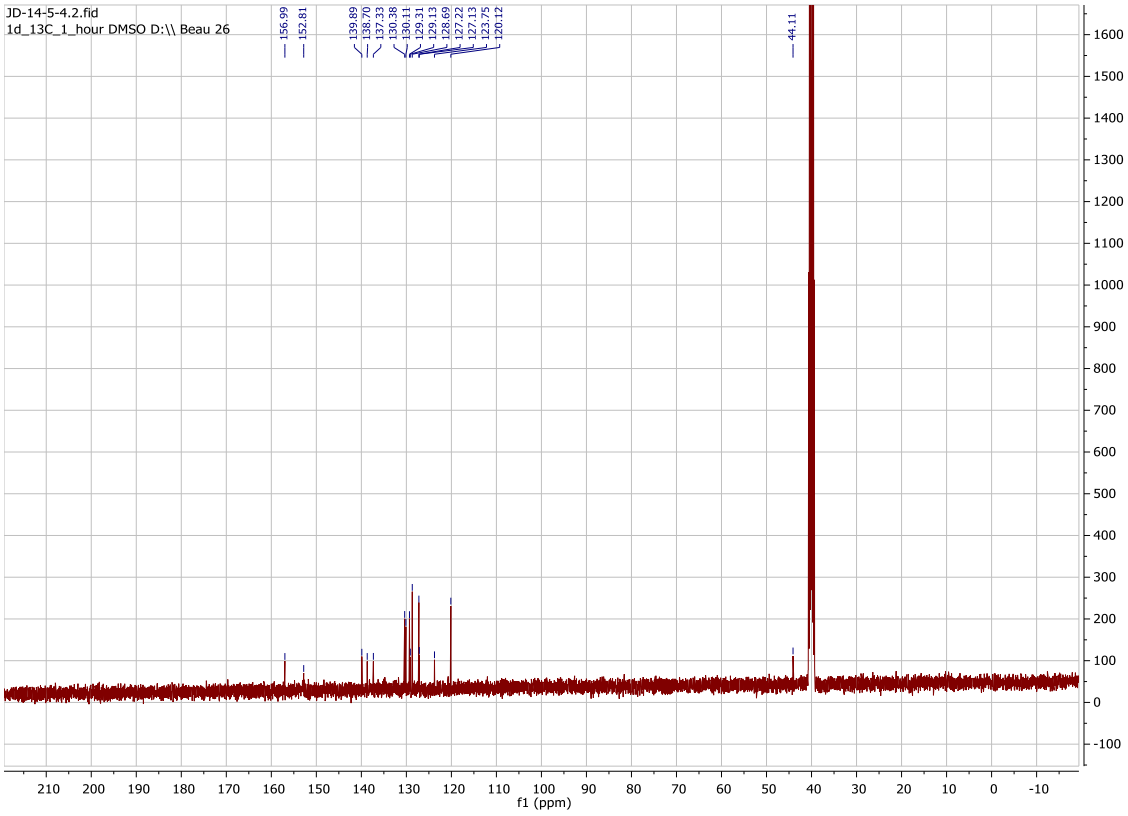
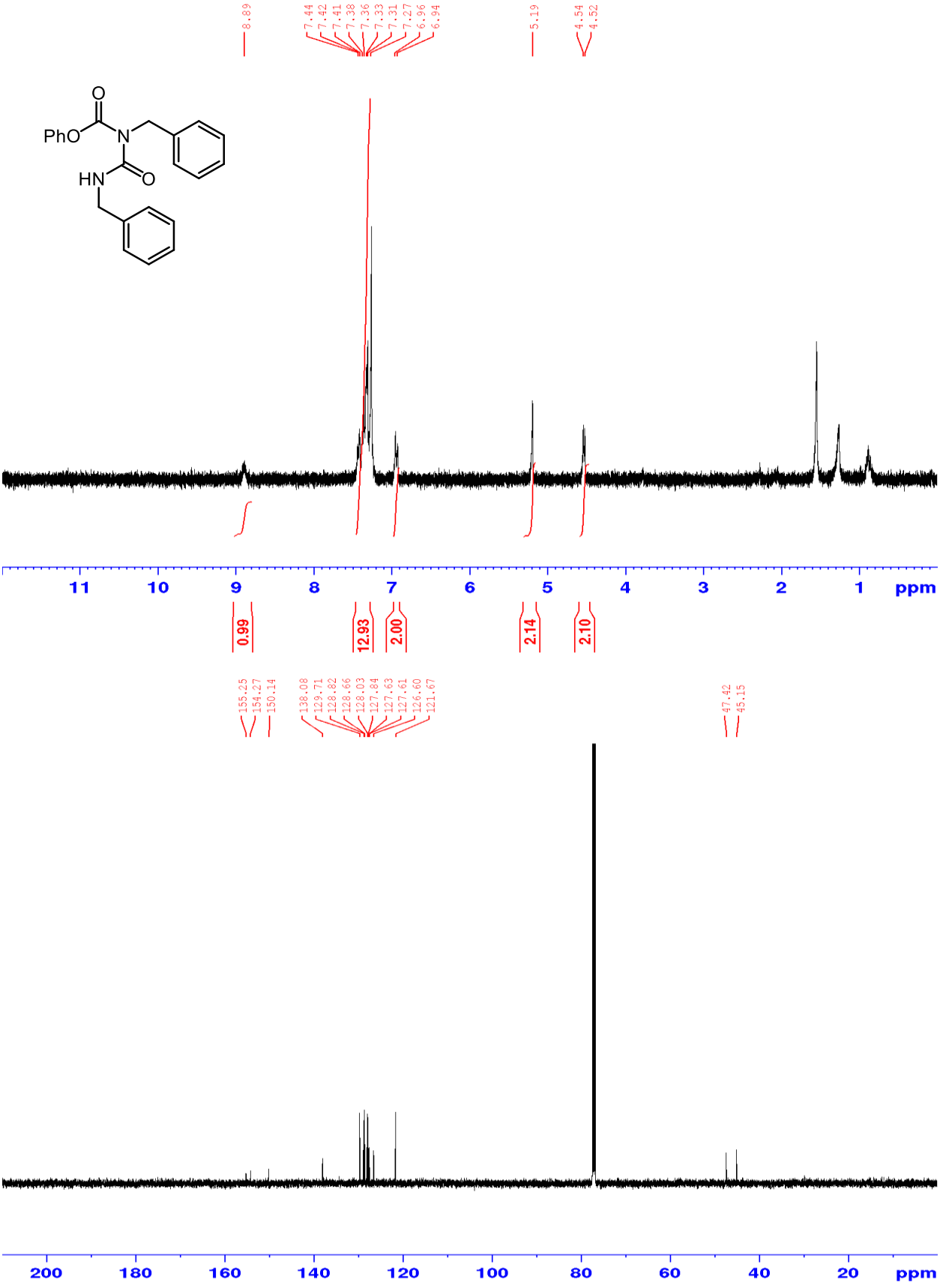
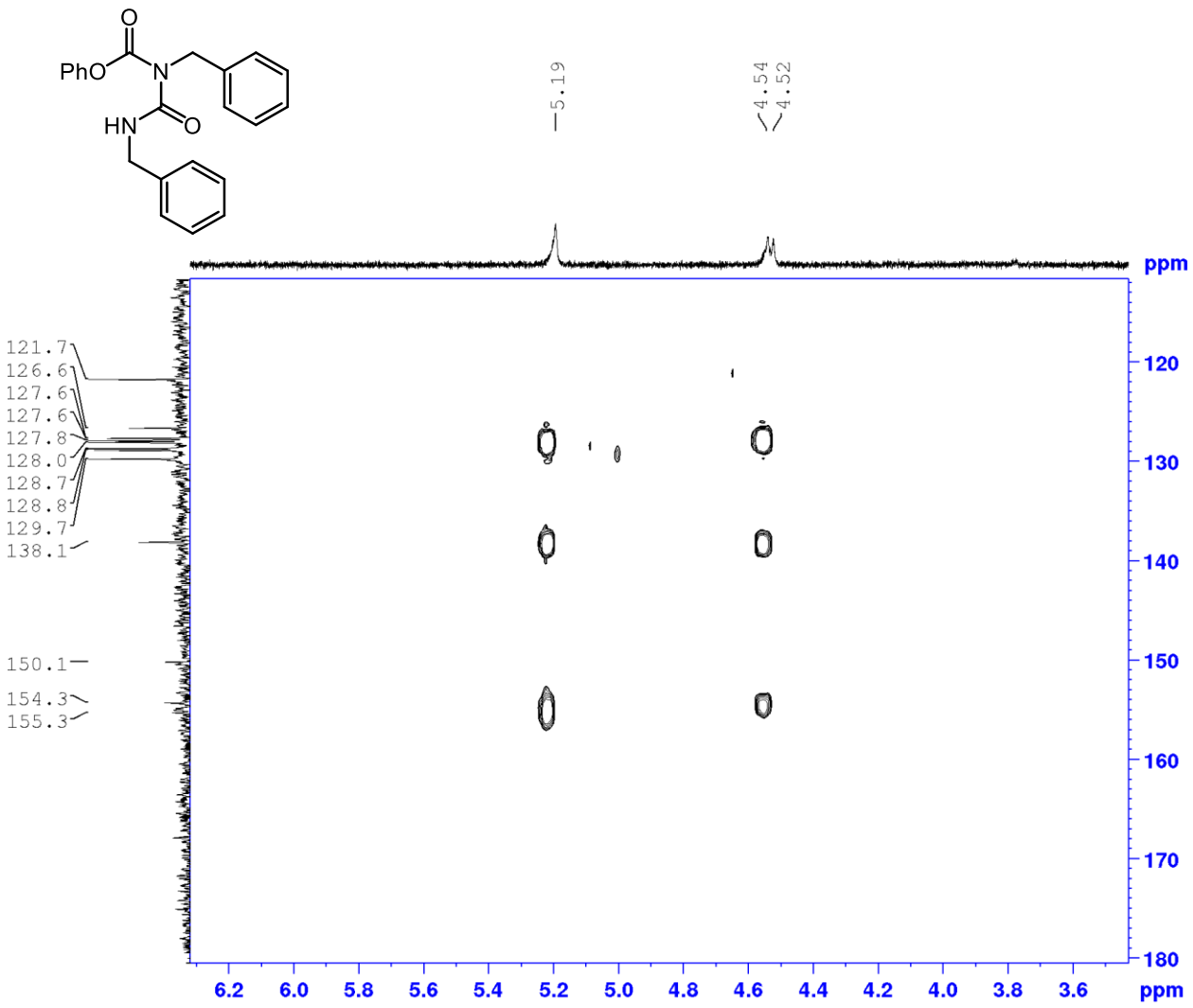
7.63
7.22
7.21
5.87
4.31
4.30
4.29
4.27
4.26
4.24
2.38
1.26
1.25
O
N
H
11
10
9
8
7
6
5
4
3
2
1
ppm
2.02
1.95
0.93
1.00
3.10
6.12
166.73
141.76
132.27
129.29
126.92
41.92
23.05
21.55
200
180
160
140
120
100
80
60
40
20
ppm


7.65
7.63
7.22
7.20
5.94
5.93
4.00
4.00
3.99
3.98
3.98
3.97
3.96
3.95
3.95
3.94
3.93
2.38
2.04
2.03
2.01
2.01
1.77
1.76
1.75
1.74
1.73
1.73
1.67
1.66
1.65
1.64
1.64
1.63
1.47
1.46
1.45
1.44
1.44
N
H
O
Me
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.00
0.94
1.00
3.08
2.06
2.15
1.22
2.09
3.19
166.64
141.69
132.38
129.26
126.92
48.68
33.41
25.73
25.05
21.53
200
180
160
140
120
100
80
60
40
20
ppm


JD-14-5-4.1.fid
1d_1H_16_scans DMSO D:\\ Beau 26
Bn
HN
Ph
35a
f1 (ppm)


JD-14-5-4.2.fid
1d_13C_1_hour DMSO D:\\ Beau 26
156.99
152.81
139.89
138.70
137.33
130.38
130.11
129.31
129.13
128.69
127.22
127.13
123.75
120.12
44.11
f1 (ppm)


8.89
7.44
7.42
7.41
7.38
7.36
7.33
7.31
7.27
6.96
6.94
5.19
4.54
4.52
PhO
O
N
HN
O
11
10
9
8
7
6
5
4
3
2
1
ppm
0.99
12.93
2.00
2.14
2.10
155.25
154.27
150.14
138.08
129.71
128.82
128.66
128.03
127.84
127.63
127.61
126.60
121.67
47.42
45.15
200
180
160
140
120
100
80
60
40
20
ppm


PhO
O
N
HN
O
5.19
4.54
4.52
ppm
121.7
126.6
127.6
127.6
127.8
128.0
128.7
128.8
129.7
138.1
150.1
154.3
155.3
120
130
140
150
160
170
180
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
ppm