

Synthesis of *N*-Oxyureas and Their Applications in Amination Reactions

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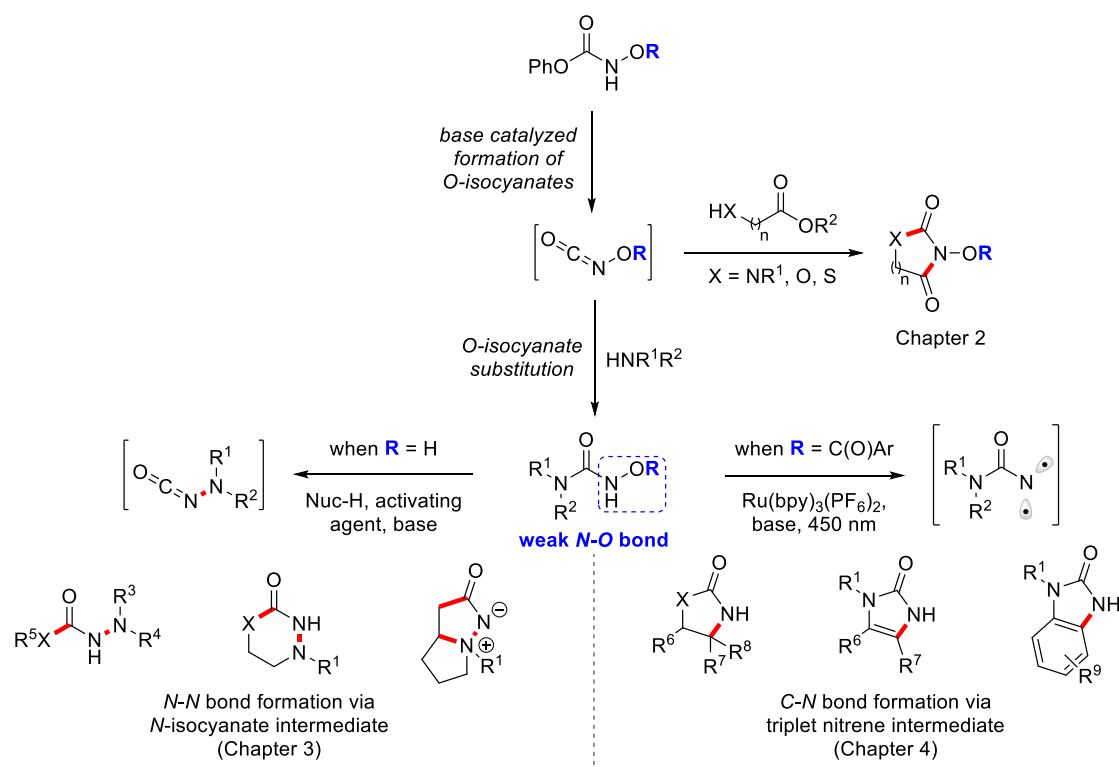
Abstract

Given the occurrence and diversity of nitrogen-containing molecules, the development of new amination methods is of significant importance. Indeed, a recent study shows that 60% of the FDA approved drugs contain a nitrogen heterocycle. Undoubtedly, novel methodologies arising from uncommon intermediates for the incorporation of nitrogen atoms are needed to access more complex molecules. The present document focuses on the development of new methods for the formation of C-N and N-N bonds for the synthesis of acyclic and heterocyclic products.

Isocyanates are useful synthons and reactive intermediates. To overcome their toxicity and instability, blocked (or masked) isocyanates have been developed: an equilibrium generates the isocyanate *in-situ*, allowing for safer precursors and better control over the concentration of the reactive isocyanate. This strategy enables the development of new reactivity, particularly for heteroatom-substituted isocyanates. However, reactions of oxygen-substituted isocyanates (*O*-isocyanates) remained severely underdeveloped. In Chapter 2, bench-stable *N*-oxy-carbamates and *N*-oxyureas are reacted under base-catalysis or thermal conditions to form the corresponding *O*-isocyanate intermediate *in situ*. In the first part of this chapter, a survey was performed and optimum experimental conditions for the controlled formation of *O*-isocyanate intermediates from the block precursors were found. Gratifyingly, the known side-reactions of *O*-isocyanates (trimerization and 1,2-shift) were avoided and different nucleophiles and substituents were studied for the controlled formation of *N*-oxyureas via substitution reaction of blocked *O*-isocyanates. Cascade reactions provided the opportunity to further develop this controlled reactivity of *O*-isocyanates. Herein, the first cascade-reaction of *O*-isocyanates is portrayed using α - and β -aminoester as the partners for the synthesis of hydantoin and dihydrouracil derivatives (>30 examples). Moreover, the conditions were modified to perform the reaction with α -alcohol and α -thioesters. Finally, evidence for the *O*-isocyanate intermediate is provided.

Chapter 3 describes the chemoselective *N*-*N* bond formation via a nitrogen variant of the Lossen rearrangement, the aza-Lossen rearrangement. Despite natural products and pharmaceuticals containing *N*-*N* bonds, the synthesis of complex hydrazine derivatives remains difficult to achieve efficiently. In this chapter, *N*-hydroxyureas were activated *in-situ* in presence of external and internal nucleophiles for the synthesis of complex hydrazine derivatives. The chemoselective activation was performed using carbonate derivatives under thermal conditions. The formation of the *N*-isocyanate intermediate was controlled and the dimerization (side reaction occurring at -40 °C) was not observed. Different conditions were developed for the synthesis of *N*-*N* bonds containing molecules including semicarbazides and different heterocycles, oxadiazin-2-ones, triazine-3-ones and aminimides for example. In addition, exploratory studies toward the formation of protected hydrazines were reported.

Finally, in Chapter 4 the first spin-selective formation of triplet nitrene is presented for the formation of nitrogen heterocycles. Recently, C-H amination reactions have gained a large interest in the formation of nitrogen-containing molecules. The formation of metal metal-nitrenes and catalyst optimization remain the dominant strategies in this field. Alternatively, control over the nitrene formation, compared to the stabilization of the nitrene, can be an efficient strategy to maintain the reactivity of these highly unstable molecules. Herein, the development of photoinduced C-H amination and aziridination reactions arising from the cleavage of a *N*-O bond of *N*-benzoyloxyureas is reported. Indeed, *O*-acylhydroxylamines can undergo a unique proposed mechanism, PCET followed by SET reduction in presence of a photocatalyst, for the spin selective generation of triplet nitrenes via a one-electron variant of the ionic α -elimination pathway commonly used for nitrene formation. Herein, this unique mode of generation suppresses the Lossen rearrangement and allows for highly efficient C-H aminations at non-activated sp^3 and sp^2 hybridized carbon and aziridination reactions. Examples of oxazolidinones and lactams derivatives are also described. Furthermore, an extensive mechanistic study, including control experiments, kinetic and competition experiment studies via ^1H NMR, the formation of the d, cyclic voltammetry and DFT calculations supports the unique proposed mechanism.



Acknowledgments

I always thought that life is about stepping out our comfort zone and having a little bit of chance to accomplish something big. At the end of 2014, I took the risk to contact André Beauchemin for a PhD position and I moved to Canada few months after to join his group. After four years, I know that I could never have done a Ph.D. in another lab: André was always motivated and exciting about my researches and always pushed me to be a better chemist and a better co-worker. I never imagine that I will obtain a Ph.D. degree and André make it possible. I will always be grateful for the chance he gave me and for his supervision.

I was lucky to work with an amazing group of people in the Beauchemin lab and in the chemistry department. To my (self-proclaimed) mentor JF, thank you for always being here and for all the support over the years. To my first Canadian friend Alex, thank you for giving me the escape I needed from the lab and travelling with me over Canada. To Ryan, my lab-partner for 3 years, it was a long journey and doing chemistry without you will definitely be different. To Meredith and Josh, thank you for all the discussions and laughs, I am going to miss our discussion about publications during lunch break, it was always fun to take part of. To Binjie, David, Jasper and William, thank all of you for all the moments in the lab and outside. It was really fun to work by your sides. To all the fellow Beauchemin, we are definitely doing a lab reunion at 3Brewers! To all the people I met in the chemistry department and are now my friends, thank you for the past four years. I am going to miss all these coffee clubs, nights at Father and Son, 3Brewers and the tacos nights! Ottawa is now my second home and will always be happy to visit.

Partir vivre au Canada en laissant ma famille et mes amis a été la décision la plus (stupide ? et) courageuse que j'ai prise dans ma vie. J'ai été chanceuse de rencontrer tant de personnes à Ottawa qui sont maintenant des amis mais je ne peux oublier les personnes qui ont rendu mon choix de partir possible. Les quatre dernières années ont été difficile mais possible grâce au soutien quotidien de mes parents, Florence et Nevzat, et de mon frère, Azad. Je vous remercie d'avoir compris, accepté et soutenu mon choix, j'ai enfin tenu ma promesse faite à 16 ans de partir vivre au Canada. Finalement, à tous les gens que j'ai laissé en France quatre ans plus tôt et qui sont toujours à mes côtés aujourd'hui, merci pour votre amitié. Je sais maintenant sur qui je peux compter et que j'aurais toujours une famille française qui m'attend de l'autre côté de l'Atlantique.

“There is nothing like looking, if you want to find something.
You certainly usually find something, if you look,
but it is not always quite the something you were after. ”

Thorin II Oakenshield - King under the Mountain
J. R. R. Tolkien – The Hobbit (1937)

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Statement of contributions:

For the past four years in the Beauchemin group, I had the occasion to work with graduate students and honor students. By chapter, I outline my contribution to the project along with the contributions of my peers.

Chapter 2: This work was highly collaborative, since this methodology required further development for three different projects that were using its products as starting materials. Ryan Ivanovich discovered the *O*-isocyanate reactivity. Ryan studied the substitution of this reactive intermediate and was joined by Meredith Allen and myself for the complete study and isolation of the *N*-oxyureas. I was in charge of the isolation of the *N*-hydroxyurea products and took part of the leaving groups and nucleophiles studies with Meredith. These products could then be reliably formed and used for the work presented in Chapter 2. Ryan surveyed the impact of oxygen substitution on this reactivity. Ryan optimized the first cascade thermal reaction for the synthesis of hydantoins and dihydrouracils. I joined him for the isolation of the products and was in charge of the optimization of the oxygen and sulfur derivatives, which required different reaction conditions to yield the cascade products.

Chapter 3: The aza-Lossen rearrangement was discovered as a side-reaction in studies presented in Chapter 2. I was interested about this reactivity and performed the first set of optimizations using *N*-benzoyloxyurea as starting materials and obtained the first evidence of formation of semicarbazide via *N-N* bond formation. Then, I studied and optimized the *in-situ* activation using *N*-hydroxyurea in presence of a carbonate or dicarbonate derivative. For the isolation of the semicarbazide products, I was joined by an honor student: David Brzezinski. Together, we isolated twenty examples of semicarbazide and obtained the first evidence of heterocycle formation via chemoselective aza-Lossen rearrangement (some entries were obtained by D. B. after completion of his Honours thesis). We turned our attention to heterocycle synthesis, and we optimized the formation of oxadiazinones and triazinones. David isolated the oxadiazinones where I focused on the obtention of triazinones. The optimization and synthesis of protected hydrazines was performed by me. For the oxa-Lossen rearrangement, preliminary work was performed by Ryan (evidences and synthesis of the first set of starting materials) and the study was then passed onto me (after I discovered the conditions for the aza-Lossen rearrangement). The *in-situ* activation of *N*-oxycarbamates was studied with an honor student, Eric Strotsky, and I isolated all the products. I also wrote the publication.

Chapter 4: The thermal C-H amination was discovered by Ryan during the study of the substitution of *O*-isocyanates. Ryan performed preliminary work and I joined him shortly after the discovery. From then, Ryan and I worked as a team for three years on this project. We optimized the C-H amination under thermal conditions and studied the metal-catalyzed reactions. We then, moved to photoredox

conditions and optimized the C-H amination: we worked together for the substituent study and the optimization of the experimental conditions. Ryan was mostly in charge of the isolation of the tertiary Csp³-H products where I did most of the isolation of the methylene Csp³-H amination products. The synthesis of the benzimidazolidinones, lactams and aziridination reaction were split equally. We both took part of the site-competition experiments and mechanistic study: Ryan performed the DFT calculations and I did the cyclic voltammetry.

Of course, all the text and schemes in this thesis are original content (with the exception of *Figure 1-2* where the copyright permission was obtained).

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Abbreviations

°C – degrees Celsius	<i>i</i> -Pr – isopropyl
¹ H – proton	IR – infrared
¹³ C – carbon-13	J – coupling constant
¹⁹ F – fluorine-19	kcal – kilocalorie
Ac – acetyl	LED – light-emitting diodes
AG – generic activating group	LG – generic leaving group
AIBN – azobisisobutyronitrile	<i>m</i> – meta
Ar – generic aryl	M – molar (moles per litre) or metal
aq. – aqueous	MS – molecular sieves
B3LYP – Becke-3-Lee-Yang-Parr	Me – methyl
BDE – bond dissociation energy	mg – milligram(s)
BDMS – bromodimethylsulfonium bromide	mmol – milimole(s)
Bn – benzyl	NMR yield - conversion to product determined using NMR spectroscopy
Boc – tert-butyloxycarbonyl	mol – mole
Boc-oxyma – (tert-Butoxycarbonyloxyimino)-2-cyanoacetate	MTBD – 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Bz – Benzoyl	nm – nanometer
calcd – calculated	NMR – nuclear magnetic resonance
cat – catalyst	<i>n</i> -Pr – n-propyl
Cbz – benzyloxycarbonyl	Nuc – nucleophile
CDI – carbonyldiimidazole	<i>o</i> – ortho
CFL – compact fluorescent lamp	<i>p</i> – para
cm – centimeter	PCET – Proton Coupled Electron Transfer
Cy – cyclohexyl	ppm – parts per million
DCE – 1,2-dichloroethane	R – generic group
DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene	Rf – retention factor
DFT – density functional theory	r.t. – room temperature
d.r. – diastereomeric ratio	SCE – saturated calomel electrode
E – generic electrophile	SI – supporting information
EDG – electron-donating group	SET – single electron transfer
e.e. – enantiomeric excess	syn – together, same side
EI – electron impact	T3P – propylphosphonic anhydride
EPR – electron paramagnetic resonance	<i>t</i> -Bu – tert-butyl
equiv – stoichiometric equivalent	TCT – Cyanuric chloride
Eq. – equation	Tces – 2,2,2-trichloroethoxysulfuryl
e.r. – enantiomeric ratio	TES – Triethylsilyl ether
ESI – electrospray ionization	temp. – temperature
Et – ethyl	THF – tetrahydrofuran
EWG – electron-withdrawing group	TLC – thin-layer chromatography
Fc – ferrocene	TMG – 1,1,3,3-Tetramethylguanidine
Fmoc – fluorenylmethoxycarbonyl	TMS – trimethylsilyl
FTIR – Fourier transform infrared	Troc – 2,2,2-Trichloroethoxycarbonyl
g – gram	UV – ultraviolet
G – Gibbs free energy	V – volt
ISC – intersystem crossing	X – generic halide, pseudohalide, leaving group, or heteroatom
h – hour	W – watt
HAT – hydrogen atom transfer	Å – angstrom (10 ⁻¹⁰ m)
HRMS – high-resolution mass spectroscopy	β – beta
HPLC – high performance liquid chromatography	γ – gamma
Hz – Hertz	δ – chemical shift in parts per million
hν – light; electromagnetic radiation	μm – micrometer
	μW – microwave

Chapter 1: Introduction

In this first chapter, the synthesis of hydroxylamine and its derivatives is presented. Amination reactions with emphasis on the Cope-type hydroamination and the Lossen rearrangement are discussed. Finally, formation of N-N and C-N bonds through the cleavage of the N-O bond of hydroxylamine derivatives are depicted.

1.1. Hydroxylamines

1.1.1. Discovery, stability and structure

Hydroxylamine (NH_2OH) is an inorganic solid that was first reported in 1865 by Lossen as a hydrochloride salt after the reaction of ethyl nitrate with hydrochloric acid in the presence of tin.¹ Due to its instability and hygroscopicity, it was only 26 years after the first report that two isolations of the pure form were reported by Lobry de Bruyn and Crismer separately.² Lobry de Bruyn isolated the pure hydroxylamine by the distillation of the hydrochloric salt in the presence of a base. Shortly after, Crismer described the displacement of the hydroxylamine in the dichlorobis(hydroxylamine)zinc (II) salt using aniline. The pure hydroxylamine was then collected by distillation which offered a safer isolation than the Lobry de Bruyn system (due to risk of explosion). After these first reports, diverse methodologies have been published for the synthesis of the pure hydroxylamine or its salt form.³

Hydroxylamine possess two electronegative atoms, nitrogen and oxygen, bonded to each other and possess acidic hydrogen(s) as substituents. These two basic atoms have high electronegativities and Lewis basic lone pairs (N-O bond dissociation energy (or BDE: measure the strength of a bond) is approximately 50 kcal/mol⁴), making hydroxylamine unstable, readily detonating in the presence of a flame.⁵

Its geometry has been studied via theoretical and experimental analysis. Hydroxylamine and *N*-alkyl hydroxylamines have two energy minima conformers (*Figure 1-1*), where the structure on the right is more stable by 3.9 kcal/mol, by avoiding repulsion between the proximal lone pairs.⁶

¹ Lossen, W. C. *Zeitschrift für Chemie* **1865**, 8, 551.

² (a) Lobry de Bruyn, C. A. *Recl. Trav. Chim. Pays-Bas* **1891**, 10, 100. (b) Crismer, L. *Bulletin de la Société chimique de Paris* **1891**, 6, 793.

³ (a) Semon, W. L. *Org. Synth.* **1923**, 3, 61. (b) Hurd, C. D. *Inorg. Synth.* **1939**, 1, 87. (c) Benson, R. E.; Cairns, T. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1956**, 78, 4202.

⁴ Luo, Y. R. *Handbook of bond dissociation energies in organic compounds*; CRC Press: Boca Raton; 2003, p 236.

⁵ O'Neil, M. J. *The Merck Index*, Merck, Whitehouse Station, NJ, **2001**; Vol 13.

⁶ Politzer, P.; Murray, J. S.; Concha, M. C. *J. Phys. Org. Chem.* **2008**, 21, 155.

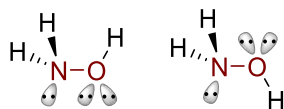


Figure 1-1: The two hydroxylamine conformers

Politzer and co-workers reported the computational characterization of diverse N-OH containing species. Politzer and coworkers used computed electrostatic potential, which is usually used to describe the possibility of noncovalent interactions, for example hydrogen bond (H-bond).⁷ Their study showed that the H-bond donor capacity of N-OH (yellow region) of hydroxylamine is better than ammonia and slightly lower than water (Figure 1-2 (a)).⁶ As expected, the addition of electron withdrawing alkyl groups and aromatic groups on the nitrogen atom increases the donor ability of the H₂N-O and the N-OH. This study also further supported the lower energy conformer with separation of the lone pairs (blue region). The H-accepting character of the nitrogen and oxygen atoms is lower than both water and ammonia because of the lower electronic density on both heteroatoms due to the chemical bond between them (blue region).

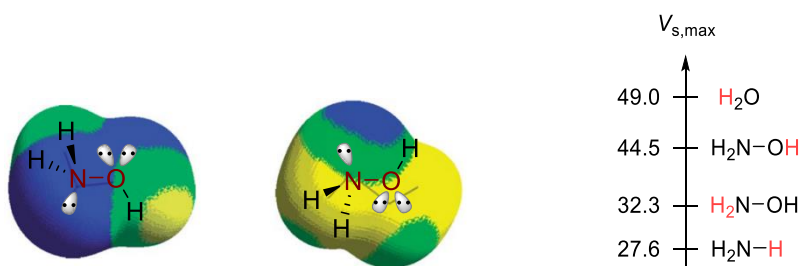


Figure 1-2: (a) Computed electrostatic potential $V(r)$ on the molecular surface of NH₂OH. Colour ranges, in kcal/mole, are: blue, negative; green, between 0 and 35; yellow, greater than 35. (b) Computed local ionization energy $\bar{I}(r)$ on the molecular surface of NH₂OH. Colour ranges, in eV, are: blue, less than 14; green, between 14 and 17; yellow, greater than 17. (copyright obtained).⁶ (c) Comparison of the computed electrostatic potential.

Computed local ionization was also completed by Politzer and coworkers and describes the availability of an electron, at any point in the space of a molecule, to undergo acid/base⁸ or electrophilic⁹ processes. Hydroxylamine possesses two bases sites with the potential loss of acidic amine proton or hydroxyl protons. The reported experimental pK_a of hydroxylammonium ion is 5.94 in water,¹⁰ and can either be the result of the loss of one of these two types of protons, or the expression of the basicity of the nitrogen or the oxygen (pK_b = 14 - pK_a). With computed local ionization, Politzer and co-workers found that the most active site is the amine, and therefore, hydroxylamines are more similar to an amine base (blue region) than a hydroxyl acid (Figure 1-2 (b)). Consequently, the experimental value defines the pK_b (8.06) of the hydroxylamine and not the pK_a. Even after the addition of electron withdrawing groups (e.g. nitro) onto the nitrogen atom, the N-alkyl hydroxylamines remain mildly basic.

⁷ Murray, J. S.; Politzer, P. *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2011**, 1, 153.

⁸ Brinck, T.; Murray, J. S.; Politzer, P. *J. Org. Chem.* **1991**, 56, 5012.

⁹ Sjöberg, P.; Murray, J. S.; Brinck, T.; Politzer, P. *Can. J. Chem.* **1990**, 68, 1440.

¹⁰ Lide, D. R. *Handbook of Chemistry and Physics (87th edn)*, CRC Press, Boca Raton, **2006**.

With these unique features, hydroxylamine is an important key molecule in the different fields of chemistry. With a fine tuning of each of its characteristics, hydroxylamine and its derivatives can be used in many processes, for example in amination reactions, oxidation or radical chemistry.

1.1.1. Hydroxylamine derivatives

The hydroxylamine motif (*N*-O bond) and alkyl hydroxylamines (substituents on nitrogen and/or oxygen)¹¹ can be found in various families of natural products (*Figure 1-3*). The *N*-acylhydroxylamines are named hydroxamic acids and they are a particularly important class of compounds with multiple biological activities.¹² Hydroxamic acids are the *N*-hydroxyl analogue of amides and some of their reactivity is based on their resemblance of amides. Their reactivity will be discussed throughout this thesis. *N*-hydroxyimides are a sub-class of hydroxamic acids, and they are used as masked hydroxylamines, due to facile deprotection. Due to the presence of the acyl group, reactive intermediates arising for the cleavage of the *N*-O bond are «stable» and unique reactivity have been developed. From the reaction of carbonyls and hydroxylamines, oximes and nitrones are synthesized and are two others important hydroxylamine derivatives. Like the other derivatives, they show biological activities and have distinct intrinsic reactivity.

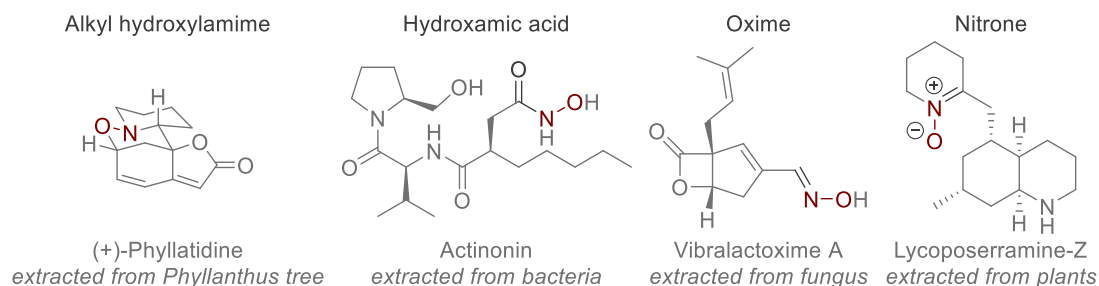


Figure 1-3: Natural compounds containing the N-O motif

In this manuscript, derivatives of hydroxamic acids are used as key starting material for amination reactions. Hydroxamic acids being the only hydroxylamine derivatives studied in this thesis, alkyl hydroxylamines, oximes and nitrones will not be discussed further.

¹¹ Waldman, A. J.; Ng, T. L.; Wang, P.; Balskus, E. P. *Chem. Rev.* **2017**, *117*, 5784.

¹² Bugg, T. *ChemBioChem*, **2014**, *15*, 2467

1.2. Synthesis of hydroxylamines

Hydroxylamine derivatives are key intermediates in many processes including biosynthesis of natural products, important industrial processes for the synthesis of *N*-containing molecules or the synthesis of bioactive products.

1.2.1. Biosynthesis

Hydroxylamine is a key intermediate in diverse biological systems, perhaps the most important system being the microbial nitrogen cycle.¹³ Nitrogen is a crucial element for all living organisms and the microbial nitrogen cycle describes the process that converts nitrogen gas to organic substances needed for the biosynthesis of proteins and nucleic acids. It is a continuous sequence; nitrogen gas being reformed at the end (*Figure 1-4*). Hydroxylamine was hypothesized as a key intermediate for the first time in 1926.¹⁴ The first step of the microbial nitrogen cycle is the fixation of the dinitrogen gas via enzyme nitrogenases found in few groups of bacteria.¹⁵ It is then converted to hydroxylamine by aerobic ammonia-oxidizing bacteria or ammonia-oxidizing archaea. All known bacteria and archaea participate in the *N*-oxidation use the ammonia monooxygenase enzyme (AMO).¹⁶ AMO belongs to the family of copper membrane-associated monooxygenase (CuMO), a superfamily of oxidizing multisubunit prokaryotic enzymes.¹⁷ AMO is a membrane-bound enzyme composed of three subunits (AmoABC)₃ and its full structure is still unknown. Other enzymes from the CuMOs family are capable of oxidizing ammonium to hydroxylamine, yet to lower conversion. Nitrous oxide and hydrazine are also two identified intermediates in the microbial nitrogen cycle.

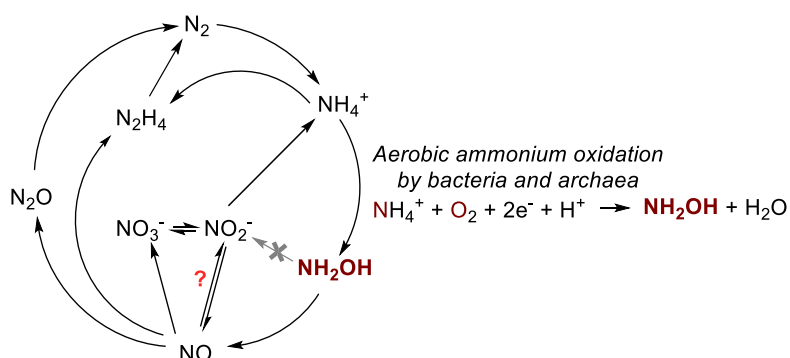


Figure 1-4: Simplified microbial nitrogen cycle up to date (2017)

¹³ Kuypers, M. M. M.; Marchant, H. K.; Kartal, B. *Nat. Rev. Microbiol.* **2018**, *16*, 263.

¹⁴ Kluyver, A. J.; Donker, H. J. K. *Chem. Zelle u. Gewebe* **1926**, *13*, 134.

¹⁵ Eady, R. R. *Chem. Rev.* **1996**, *96*, 3013.

¹⁶ Hooper, A. B.; Vannelli, T.; Bergmann, D. J.; Arciero, D. M. *Antonie van Leeuwenhoek* **1997**, *71*, 59.

¹⁷ Lawton, T. J.; Ham, J.; Sun, T.; Rosenzweig, A. C. *Proteins* **2014**, *82*, 2263.

The full microbial nitrogen cycle is still unknown;¹⁸ indeed, in 2017 the oxidation of hydroxylamine was revised. Previously, it was thought that hydroxylamine was oxidized directly to nitrite (NO₂⁻) using octahaem hydroxylamine oxidoreductase (HAO).¹⁹ However, in 2017, it was proven that the oxidation product is in fact nitric oxide (NO).¹⁸ As of today, the enzyme and process responsible for the oxidation of nitric oxide to nitrite is still unidentified.

Hydroxylamine is also an intermediate in the biosynthesis of hydroxamic acid and oxime derivatives. Hydroxamic acids are one of the most efficient siderophores; they have high affinity for iron(III) and are capable to form very strong chelates.²⁰ For example, deferoxamine, a natural hydroxamic acid, is the medication of choice for iron and aluminum overdose and is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.²¹ The genome identified for the biosynthesis of deferoxamine contains four genes (desA-D),²² the first two desA and desB are responsible for the formation of the *N*-hydroxycadaverine (*Scheme 1-1*). DesA induces the decarboxylation of lysine to produce cadaverine and oxidation mediated with desB form the corresponding hydroxylamine.²³ The formation of the hydroxamic acid is mediated by the gene desC and the consecutive formation of the two amide bonds by the gene desD.²⁴

¹⁸ Caranto, J. D.; Lancaster, K. M. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 8217.

¹⁹ Jetten, M. S. M. *Environ. Microbiol.* **2008**, *10*, 2903.

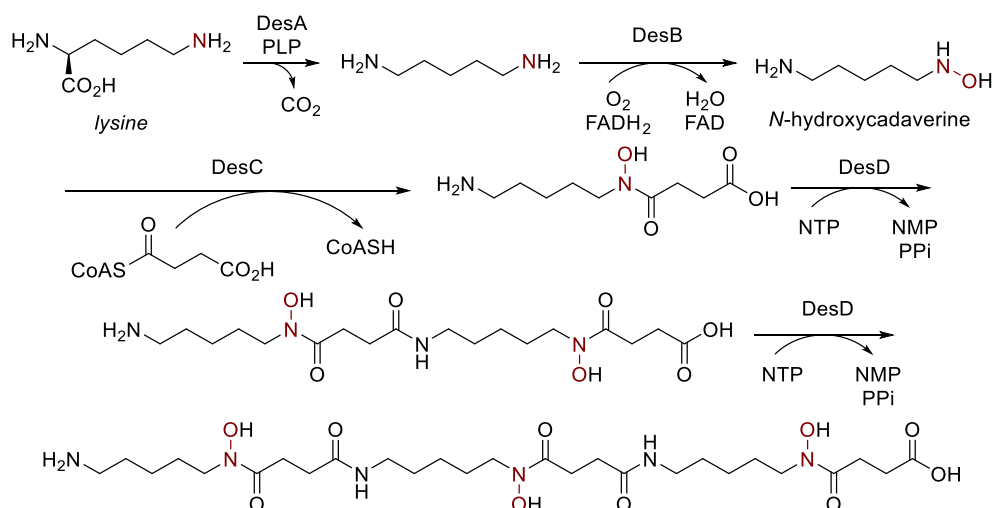
²⁰ Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563.

²¹ Olivieri, N. F.; Brittenham, G. M. *Blood* **1997**, *89*, 739.

²² Bentley, S. D.; Chater, K. F.; Cerdeño-Tarraga, A.-M.; Challis, G. L.; Thomson, N. R.; James, K. D.; Harris, D. E.; Quail, M. A.; Kieser, H.; Harper, D.; Bateman, A.; Brown, S.; Chandra, G.; Chen, C. W.; Collins, M.; Cronin, A.; Fraser, A.; Goble, A.; Hidalgo, J.; Hornsby, T.; Howarth, S.; Huang, C.-H.; Kieser, T.; Larke, L.; Murphy, L.; Oliver, K.; O'Neil, S.; Rabinowitsch, E.; Rajandream, M.-A.; Rutherford, K.; Rutter, S.; Seeger, K.; Saunders, D.; Sharp, S.; Squares, R.; Squares, S.; Taylor, K.; Warren, T.; Wietzorrek, A.; Woodward, J.; Barrell, B. G.; Parkhill, J.; Hopwood, D. A. *Nature* **2002**, *417*, 141.

²³ (a) Schupp, T.; Waldmeier, U.; Divers, M. *FEMS Microbiol. Lett.* **1987**, *42*, 135. (b) Schupp, T.; Toupet, C.; Divers, M. *Gene* **1988**, *64*, 179. (c) Günter, K.; Toupet, C.; Schupp, T. *J. Bacteriol.* **1993**, *175*, 3295.

²⁴ Barona-Gómez, F.; Wong, U.; Giannakopoulos, A. E.; Derrick, P. J.; Challis, G. L. *J. Am. Chem. Soc.* **2004**, *126*, 16282



Scheme 1-1: Deferoxamine biosynthesis

Unlike deferoxamine, the biosynthesis of aerobactin, a natural di-hydroxamic acid siderophore, consists of the direct conversion of lysine to the *N*-hydroxylysine (without decarboxylation) via the gene *lucD* contain in the *lucABCD* enzyme cluster.²⁵ The enzyme responsible is the FAD-dependent-lysine *N*-hydroxylase, that was identified via in-vitro study.²⁶ Over the years, different enzymes and genes were found for the biosynthesis of natural hydroxamic acid siderophores via the intermediacy of hydroxylamine, all being FAD-dependent.²⁷ Owing from the number of natural bioactive hydroxamic acids, their biosynthesis has been studied to access new pharmacophores.²⁸

Another important family of natural bioactive derivates of hydroxylamines are glucosinolates, plant-based thio-glucoses containing a sulfonated oxime moiety.²⁹ Their biological activity, along with the bioactivity of their degradation product (e.g. isothiocyanate) range from pesticides to antitumor agents. Like hydroxamic acids, the biosynthesis of glucosinolates involves the *N*-oxidation of amino acids to form the hydroxylamine that is over-oxidized to the aldoxime, the key intermediate for the biosynthesis of glucosinolate (Scheme 1-2).³⁰ It has been found that the cytochromes P450 from the CYP79s catalyze the *N*-oxidation of amino acids.³¹

²⁵ (a) De Lorenzo, V.; Neilands, J. B. *J. Bacteriol.* **1986**, 167, 350. (b) De Lorenzo, V.; Bindereif, A.; Paw, B. H.; Neilands, J. B. *J. Bacteriol.* **1986**, 165, 570.

²⁶ Thariath, A.; Socha, D.; Valvano, M. A.; Viswanatha, T. *J. Bacteriol.* **1993**, 175, 589.

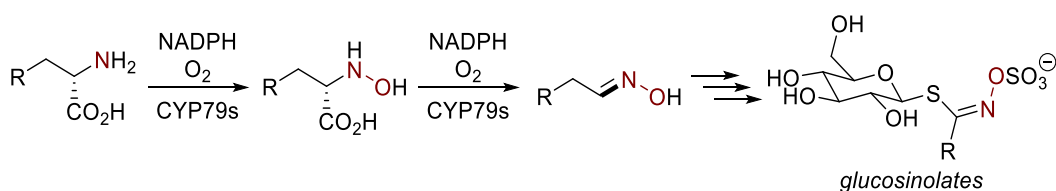
²⁷ Challis, G. L. *ChemBiochem* **2005**, 6, 601.

²⁸ Bertrand, S.; Helesbeux, J.-J.; Larcher, G.; Duval, O. *Mini-Rev. Med. Chem.* **2013**, 13, 1311.

²⁹ Fahey, J. W.; Zalcman, A. T.; Talalay, P. *Phytochemistry* **2001**, 56, 5.

³⁰ Mikkelsen, M. D.; Petersen, B. L.; Olsen, C. E.; Halkier, B. A. *Amino Acids* **2002**, 22, 279.

³¹ (a) Du, L.; Lykkesfeldt, J.; Olsen, C. E. *Proc. Natl. Acad. Sci. U. S. A* **1995**, 92, 12505. (b) Halkier, B. A. Hull, A. K.; Rekha, V.; Celenza, J. L. *Proc. Natl. Acad. Sci. U. S. A* **2000**, 97, 2379. (c) Wittstock, U.; Halkier, B. A. *J. Biol. Chem.* **2000**, 275, 14659. (d) Mikkelsen, M. D.; Hansen, C.H.; Wittstock, U.; Halkier, B. A. *J. Biol. Chem.* **2000**, 275, 33712. (e) Hansen, C. H.; Wittstock, U.; Olsen C. E.; Hick, A.J.; Pickett, J. A.; Halkier, B. A. *J. Biol. Chem.* **2001**, 276, 11078. (f) Reintanz, B.; Lehnen, M.; Reichelt, M.; Gershenzon, J.; Kowalczyk, M.; Sandberg, G.; Godde, M.; Uhl, R.; Palme, K. *Plant Cell* **2001**, 13, 351.

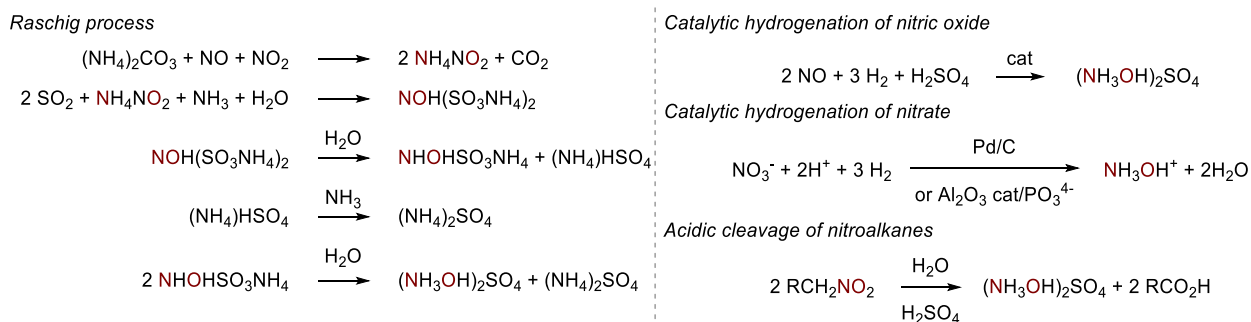


Scheme 1-2: Simplified glucosinolate biosynthesis

Natural primary amines, deriving from the decarboxylation of amino acids or from metabolic activities are similarly oxidized to aldoximes via the formation of hydroxylamines. Different enzymes are known to catalyze this *N*-oxidation, but the flavin-containing monooxygenase (FMO)³² and the cytochrome P450³³ enzymes are involved in most of the enzymatic processes.

1.2.2. Industrial processes

In 2012, the world production capacity of hydroxylamine was estimated to be 800 000 t/a.³⁴ The first industrial patent for the synthesis of hydroxylamine salts dated from 1908, and it is known now as the Raschig process (Scheme 1-3).³⁵ Ammonium carbonate is converted to hydroxylamine sulfonate salt using ammonia, water and carbon dioxide. Diverse catalytic hydrogenations have been developed with the examples of nitric oxide³⁶ and nitrate for the hydroxylamine-phosphate oxime (HPO) process for the manufacturing of caprolactam.³⁷ The cleavage of nitroalkanes has also been used but due to the cost and the limited availability of the corresponding starting materials, only to a limited extent.³⁸



Scheme 1-3: Industrial processes for the synthesis of hydroxylamine salts

³² (a) Poulsen, L. L.; Taylor, K. K.; Williams, D. E.; Masters, B. S. S.; Ziegler, D. M. *Mol. Pharmacol.* **1986**, *30*, 680. (b) Lin, J.; Cashman, J. R. *Chem. Res. Toxicol.* **1997**, *10*, 842.

³³ Hlavica P.; Golly I.; Lehnerer M.; Schulze J. *Hum. Exp. Toxicol.* **1997**, *16*, 441.

³⁴ Ritz, J.; Fuchs, H.; Perryman, H.G. *Hydroxylamine. Ullmann's Encyclop. Ind. Chem.*; Wiley-VCH Verlag GmbH & Co: Weinheim, **2000**.

³⁵ Raschig, F. DE 216 747, **1908**; US 1 010 177, **1911**.

³⁶ Tauszik, G. R.; Crocetta, P. *App. Catal.* **1985**, *17*, 1.

³⁷ De Rooij, A. H.; Dijkhuis, C.; Van Goolen, T. T. J. *Informations Chimie* **1977**, *165*, 121.

³⁸ Jones, L. R. Commercial Solvents, US 2 755 171, **1955**. Agne, R. J. US 3 066 011, **1959**.

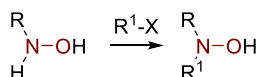
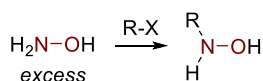
1.2.3. Laboratory synthesis

1.2.3.1. Common syntheses of hydroxylamine derivatives

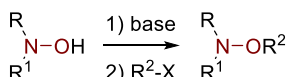
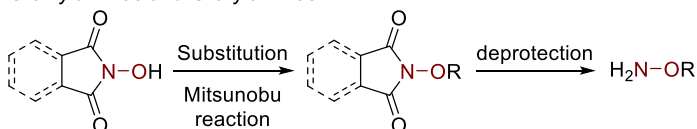
The synthesis of hydroxylamine derivatives has been reviewed recently,³⁹ and a brief summary is presented in this section (Scheme 1-4).

a) Substitution reactions

Mono and di-substituted hydroxylamines

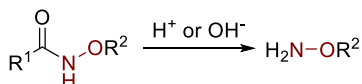


O-alkylamines and O-arylamines

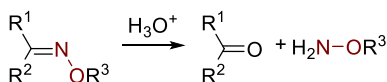


b) Hydrolysis reactions

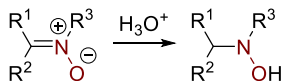
from hydroxamic acids



from oximes

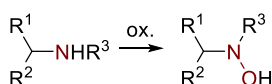


from nitrones

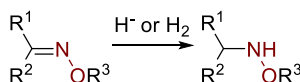


c) Oxidation and reduction reactions

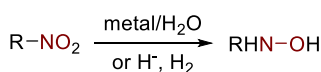
oxidation of amines



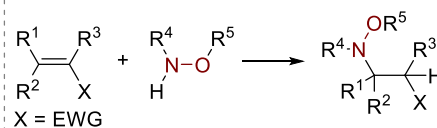
reduction of oximes



reduction of nitro compounds



d) Addition on C=C



Scheme 1-4: Summary of common hydroxylamine syntheses

The main difficulty in the synthesis of hydroxylamine derivatives via substitution reaction is the ambident nucleophilicity of the starting materials under neutral or weakly basic reaction conditions. By using excess of hydroxylamine, the mono *N*-alkylhydroxylamine can be obtained, and the addition of a second alkylating reagent forms the *N,N*-dialkylhydroxylamine. The synthesis of *O*-alkyl- and *O*-arylamines is mostly performed using *N*-hydroxysuccinimide and *N*-hydroxyphthalimide derivatives in the Mitsunobu reaction, or a simple substitution reaction. Facile deprotection gives access to the unprotected *O*-alkyl- or *O*-arylamine. Deprotonation and substitution of the hydroxyl group from a *N,N*-dialkylhydroxylamine leads to the formation of tri-substituted hydroxylamine derivatives.

The most common synthesis of substituted hydroxylamines is the hydrolysis of hydroxamic acids, oximes and nitrones under acidic or base conditions. The formation of more sensitive hydroxylamines is performed under milder conditions using an excess of NH_2OH or N_2H_4 .

³⁹ Melman, A. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; John Wiley & Sons, Ltd.: Southern Gate, **2008**, 117. (b) Geffken, D.; Köllner, M. A. *Sci. Synth.* **2009**, 40b, 937.

Primary and secondary amines are two of the most abundant molecules and their oxidation to hydroxylamine derivatives with peracids has been reported. However, overoxidation of the hydroxylamine limits the generalization of this methods: yields are variable and can not be predicted. Secondary amines can be oxidized using *m*CPBA or 2,2-dimethyldioxirane in good yields, with nitroxyl radicals being the major side-product obtained by overoxidation. Primary amines can be transformed to the corresponding imine first, that will be oxidized to a mixture of oxaziridine and/or nitron. After hydrolysis, the corresponding hydroxylamine is formed in high yield. The reduction of oximes or nitro compounds, proceeds stepwise and both amine and hydroxylamine can be obtained depending on the conditions. The reduction can be performed using metals or other one-electron donors, with complex hydrides and other two-electron donors, and by hydrogenation. Only few examples of nitroso reduction have also been reported, since hydroxylamine and other precursors are more accessible than nitroso compounds.

The addition of hydroxylamines onto activated C-C double bonds is broadly used for the formation of mono- and dialkylhydroxylamines, and the reaction can be intra- and intermolecular, regioselective and stereoselective. The reaction of hydroxylamine with deactivated C-C double bonds is known as the Cope-type hydroamination and it is discussed in the section on amination reactions.

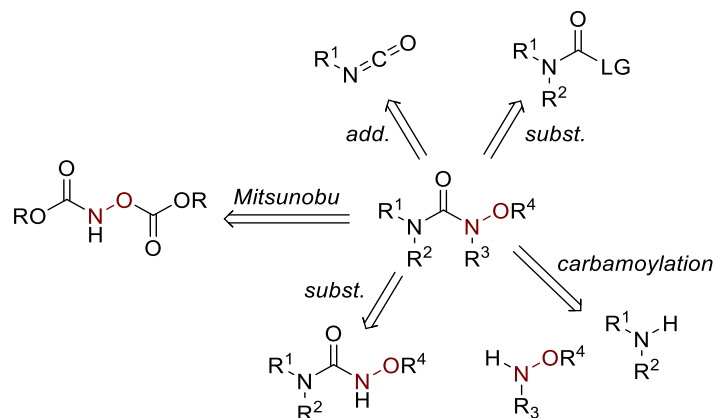
Challenges still exist for the synthesis of sensitive and substituted hydroxylamines: indeed, protection/deprotection steps along with inert conditions (to avoid any oxidation) are the current limitations.

1.2.3.2. Synthesis of *N*-oxyureas

In Chapter 2, the synthesis of N-oxyureas and N-oxyhydantoins via the controlled formation of oxygen substituted isocyanates (O-isocyanates) is discussed. In this part, their current syntheses are organised by reactivity.

1.2.3.2.1. Common syntheses

N-Oxyureas are alkylated derivatives of *N*-hydroxyurea, an anti-cancer agent included in the World Health Organization's List of Essential Medicines.²¹ Non-selective and selective syntheses of alkylated *N*-hydroxyureas have been developed.



Scheme 1-5: Addition of hydroxylamine onto electrophiles

The synthesis of *N*-oxyureas is dominated by the addition and substitution on highly reactive electrophiles (Scheme 1-5). Addition of hydroxylamines on isocyanates is one of the most used synthesis of dialkylated oxyureas.⁴⁰ Due to the toxicity and instability of the isocyanate, multiple methods for its *in-situ* formation from azides, amides or amines have been developed. Carbamoylating reagents derivatives bearing leaving group like *N*-benzotriazolecarbonyl⁴¹ are used for substitution reactions, but some starting materials have low stability. To solve this problem, primary and secondary amines (and amides) can be *in-situ* transformed into carbamoyl chlorides via phosgene derivatives⁴² or coupling reagents like carbonyldiimidazoles.⁴³ The intermediate is then attacked by hydroxylamine and the *N*-oxyurea is obtained. The carbamoylation of hydroxylamine derivatives with cyanic acid leads to the synthesis of hydroxylamines that can be substituted at the oxygen or the nitrogen bearing the hydroxyl group. In 1992, Stewart and Brooks designed the *N,O*-bis(phenoxycarbonyl)hydroxylamine for the selective synthesis of substituted *N*-hydroxyurea at the nitrogen bearing the alcohol.⁴⁴ After Mitsunobu reaction, facile deprotection with ammonia releases the corresponding urea. Selective alkylation of the nitrogen bearing the alcohol can also be performed via the substitution of alcohol under

⁴⁰ For selective examples see: (a) Bock, V.; Klötzer, W.; Singewald, N.; Strieder, G. *Synthesis* **1987**, 1058. (b) Deng, L.; Sundriyal, S.; Rubio, V.; Shi, Z.-Z.; Song, Y. *J. Med. Chem.* **2009**, 52, 6539. (c) Nencetti, S.; La Motta, C.; Rossello, A.; Sartini, S.; Nutia, E.; Ciccone, L.; Orlandini, E. *Bioorg. Med. Chem.* **2017**, 25, 3068.

⁴¹ (a) Opacić, N.; Barbaric, M.; Zorc, B.; Cetina, M.; Nagl, A.; Frković, D.; Kralj, M.; Pavelić, K.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E.; Raić-Maić, S.; Mintas, M. *J. Med. Chem.* **2005**, 48, 475. (b) Perković, I.; Butula, I.; Zorc, B.; Hock, K.; Kraljević Pavelić, S.; Pavelić, K.; De Clercq E.; Balzarini, J.; Mintas, M. *Chem. Bio. Drug Res.* **2008**, 71, 546.

⁴² Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett.* **1996**, 37, 2361.

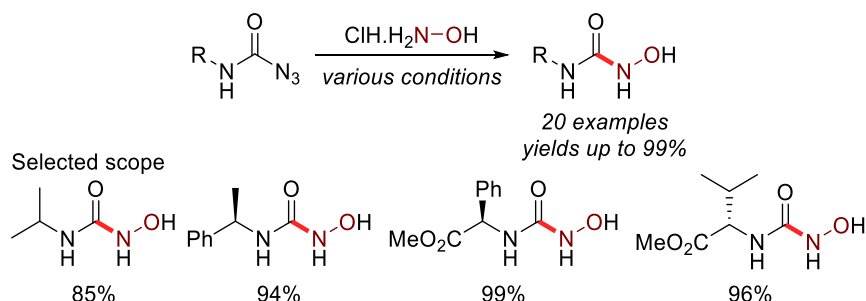
⁴³ (a) Kolasa, T.; Stewart, A. O.; Brooks, Clint D. W. *Tetrahedron: Asymmetry* **1996**, 7, 729. (b) Xu, F.; Shuler, S. A.; Watson, D. A. *Angew. Chem., Int. Ed.* **2018**, 57, 12081.

⁴⁴ Stewart, A. O.; Brooks, D. W. *J. Org. Chem.* **1992**, 57, 5020.

acid catalysis or metal salt conditions. Due to the instability of certain of the starting materials presented, poor derivatization of the substituents on the nitrogen and oxygen limited the generalization of these methods.

1.2.3.2.2. From azides

Many examples of synthesis of *N*-oxyureas used azides as starting materials, regardless of their inherent instability, due to the possibility of derivatization of the substituents. In 2010, the Muñoz group published the efficient formation of *N*-hydroxyureas via the displacement of an azide group from carbamoyl chloride derivatives with hydroxylamine hydrochloric salt (Scheme 1-6).⁴⁵ Several experimental conditions were developed to overcome multiple side-reactions: for example the substitution of the azide by the newly formed *N*-hydroxyurea product, the formation of unknown by-products via unidentified degradation pathways (the authors did not specify, but degradation via Curtius-type rearrangement seems likely), substitution of the oxygen (and not the nitrogen atom) of hydroxylamine. Furthermore, the isolation of small and polar group containing *N*-hydroxyureas was a challenge at the end of the reaction for the first set of condition developed. However, after four different experimental conditions, they were able to synthesize twenty *N*-hydroxyureas bearing a large range of substituents from the small isopropyl group to the complex L-valine methyl ester derivative, in all cases with high yields.

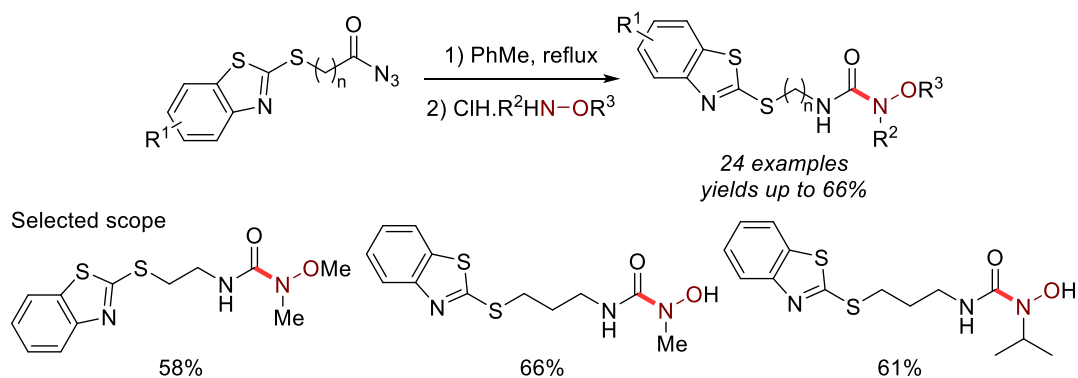


Scheme 1-6: Displacement of azide by hydroxylamine for the synthesis of *N*-hydroxyureas

Acyl azides are mostly known to undergo various type of rearrangements and multiple strategies involving this type of reactivity for the synthesis of *N*-oxyureas have been reported. Acyl azides typically undergo Curtius rearrangement via the *in-situ* formation of an isocyanate intermediate which reacts with a nucleophile. Greco and co-workers reported this rearrangement for the synthesis of benzothiazole hydroxyureas, identified as inhibitors of 5-lipoxygenase (Scheme 1-7).⁴⁶

⁴⁵ Paz, J.; Pérez-Balado, C.; Iglesias, B.; Muñoz, L. *J. Org. Chem.* **2010**, 75, 8039.

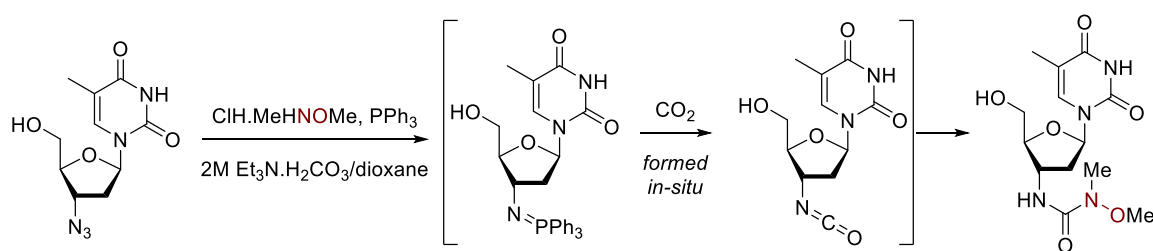
⁴⁶ Greco, M. N.; Hageman, W. E.; Powell, E. T.; Tighe, J. J.; Pérsico, F. J. *J. Med. Chem.* **1992**, 35, 3180.



Scheme 1-7: Synthesis of benzothiazole hydroxyureas via Curtius rearrangement

The azide starting materials were easily obtained from the azidation of the corresponding carboxylic acids and the thermal Curtius rearrangement was performed efficiently and diverse benzothiazole hydroxyureas were obtained and tested in-vitro and in-vivo. Other bioactive *N*-oxyurea derivatives have been synthesized using Curtius rearrangement of azide.⁴⁷ In 2006, Lebel's group published a safer synthesis by forming the reactive (and explosive) azide *in-situ*. Indeed, Lebel and co-workers used a stable carboxylic acid that was first converted to the corresponding acyl chlorides that after substitution led to the in-situ formation of the acyl azide.⁴⁸

The Staudinger reaction is a well-known reaction of azide derivatives, with the formation of an iminophosphorane intermediate with the addition of a phosphine or a phosphite onto azides. When the reaction was performed in aqueous trialkylammonium hydrogen carbonate, the iminophosphorane reacted with CO₂ from the carbonate to form the corresponding isocyanate. Different organic azides along with different nucleophiles were used to trap the isocyanate intermediate, including the *N,O*-dimethylhydroxylamine hydrochloride that lead to the formation of the *N*-oxyurea (Scheme 1-8).⁴⁹



Scheme 1-8: Formation of *N*-oxyurea via Staudinger reaction

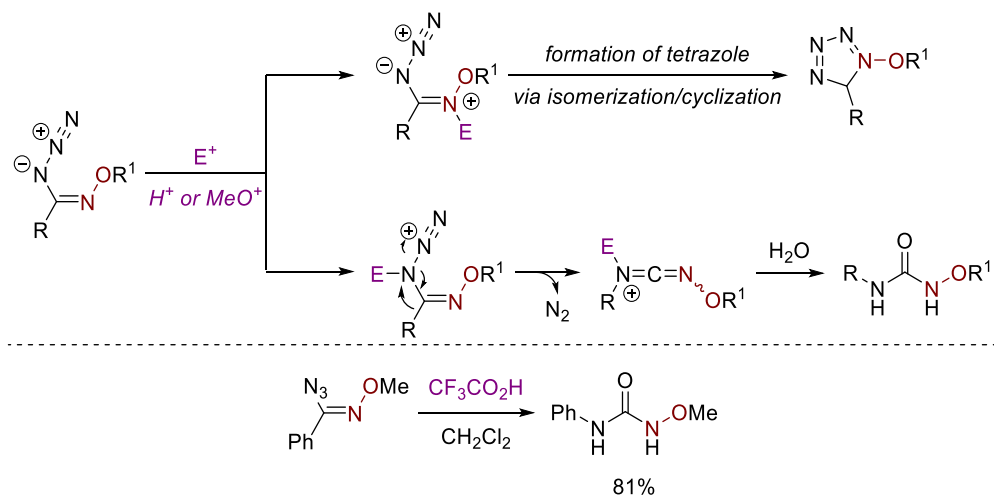
Hydrazonylazides and azidoximes are unique classes of azide derivatives and feature two sole rearrangement mechanisms pending from the α C=N bond. They possess two sites of protonation and depending of the conditions they can either form the tetrazole motif via isomerization/cyclization

⁴⁷ (a) Larsen, S. D.; Stachew, C. F.; Clare, P. M.; Cubbage, J. W.; Leach, K. L. *Bioorg. Med. Chem. Lett.* **2003**, 13, 3491. (b) Gaware, R.; Khunt, R.; Czollner, L.; Stanetty, C.; Da Cunha, T.; Kratschmar, D. V.; Odermatt, A.; Kosma, P.; Jordis, U.; Claßen-Houben, D. *Bioorg. Med. Chem.* **2011**, 19, 1866.

⁴⁸ Lebel, H.; Leogane, O. *Org. Lett.* **2006**, 8, 5717.

⁴⁹ Yagodkina, A.; Löschcke, K.; Weisell, J.; Azhayevab, A. *Tetrahedron* **2010**, 66, 2210.

sequence or linear structure via release of nitrogen gas. Azidoximes has been studied by the group of McKim, which reported in 2010 a general approach for their synthesis along with study of their reactivity in aqueous and acidic media.⁵⁰ Like hydrazonylazides,⁵¹ *N*-alkoxybenzimidoyl azides were transformed to tetrazole rings and the authors were able to selectively form the heterocycle by using acetyl chloride. However, in presence of trifluoroacetic acid, *N*-hydroxyurea was the major product with only trace of the corresponding tetrazole (Scheme 1-9).



Scheme 1-9: Rearrangement of *N*-alkoxybenzimidoyl azides

The proposed mechanism for the *N*-oxyurea formation is identical to the mechanism proposed by Hegarty for the synthesis of semicarbazides from hydrazonylazides.⁵² The aldoxime is protonated at the nitrogen of the azide moiety, and after Schmidt-type rearrangement and release of nitrogen gas, the corresponding protonated carbodiimide is formed. After water addition, the *N*-oxyurea is obtained. Computational calculations show that the urea is more thermodynamically stable than the tetrazole, but the protonation or acetylation is more favorable on the nitrogen of the oxime, leading to the formation of the tetrazole. Despite a thorough mechanistic and computational study, the authors reported the successful synthesis of only one *N*-oxyurea.

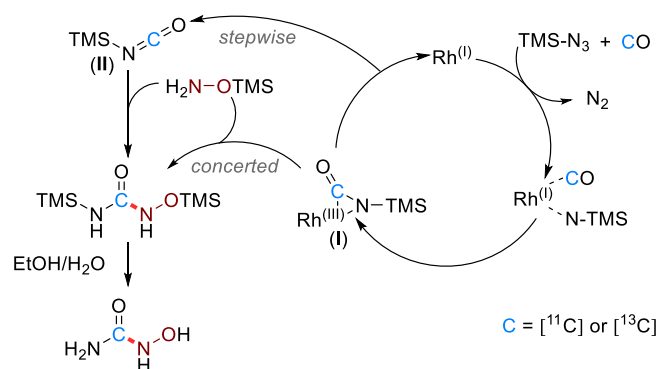
Metal catalyzed reactions for the controlled formation of metal-nitrene species via release of nitrogen gas from azides is an important class of reactivity. Indeed, the use of metal allows for controlled reactivity of azides through stabilization of the nitrene intermediate. Långström and co-workers used this elegant strategy for the synthesis of radiolabeled [¹¹C] and [¹³C] *N*-hydroxyurea using TMS-N₃ and a rhodium (I) catalyst.⁵³

⁵⁰ Dolliver, D. D.; Sommerfeld, T.; Lanier, M. L.; Dinser, J. A.; Rucker, R. P.; Weber, R. J.; McKim, A. S. *J. Phys. Org. Chem.* **2010**, 23, 227.

⁵¹ (a) Pleniewicz, J. *Tetrahedron Lett.* **1975**, 5, 341. (b) Pleniewicz, J. *Tetrahedron* **1978**, 34, 2961.

⁵² Hegarty, A. F.; Aylward, J. B.; Scott, F. L. *Tetrahedron Lett.* **1967**, 14, 1259.

⁵³ Barletta, J.; Karimi, F.; Långström, B. *J. Label. Compd. Radiopharm.* **2006**, 49, 429.



Scheme 1-10: Proposed mechanism for synthesis of radiolabeled *N*-hydroxyurea

The proposed mechanism starts with the formation of an [^{11}C] and [^{13}C] isocyanate from the radiolabeled carbon monoxide and the nitrene (Scheme 1-10). The authors did not probe their mechanism and proposed two pathways. The *N*-hydroxyurea can either be formed via a concerted reaction with the direct addition of *O*-TMS hydroxylamine on the intermediate (I) or via the reductive formation of the isocyanate (II), then subsequent addition of the hydroxylamine. The synthesis of [^{15}N] *N*-hydroxyurea was also published through the addition of [^{15}N] *O*-TMS-hydroxylamine onto the TMS-isocyanate.⁵⁴

1.2.3.3. Synthesis of *N*-oxyhydantoin

The second *N*-heterocycles targeted in this thesis are hydantoin (imidazolidine-2,4-dione) a heterocyclic core of choice in medicinal chemistry due to their different pharmacological and biological activities.⁵⁵ Hydantoin and its derivatives can possess anti-inflammatory, anti-cancer, anti-diabetic properties for example and their syntheses were recently reviewed.⁵⁶ *N*-Oxyhydantoin is a sub-class of hydantoin, where one of the nitrogen possesses a hydroxyl or oxy group. Recently, they have been studied as serine hydrolase inhibitors⁵⁷ and only few examples of these compounds have been reported.

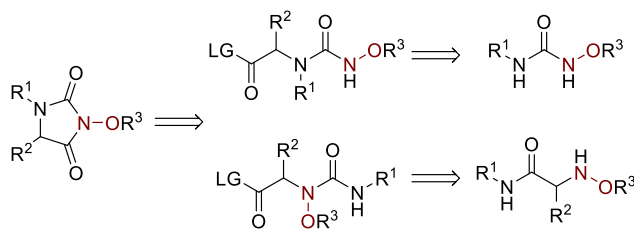
The synthesis of *N*-oxyhydantoin is dominated by the cyclization of β -carbonyl *N*-oxyureas deriving from *N*-oxyurea and β -aminoamide derivatives (Scheme 1-11).

⁵⁴ Yasaki, G.; Xu, Y.; King, S. B. *Synth. Commun.* **2000**, 30, 2041.

⁵⁵ Cho, S.; Kim S.-H.; Shin D. *Eur. J. Med. Chem.* **2019**, 164, 517.

⁵⁶ Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. *Chem. Rev.* **2017**, 117, 13757.

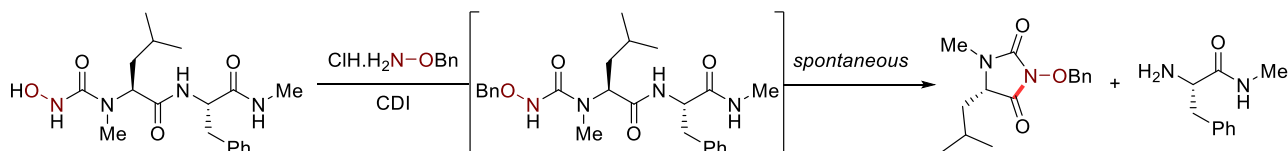
⁵⁷ (a) Cognetta, A. B., 3rd; Niphakis, M. J.; Lee, H.-C.; Martini, M. L.; Hulce, J. J.; Cravatt, B. F. *Chem. Biol.* **2015**, 22, 928. (b) Suciu, R. M.; Cognetta, A. B., 3rd; Potter, Z. E.; Cravatt, B. F. *ACS Med. Chem. Lett.* **2018**, 9, 563.



Scheme 1-11: Retrosynthesis of *N*-oxyhydantoin

Many reports using CDI,⁵⁸ proline derivatives for the synthesis of chiral hydantoin⁵⁹ or oxyurea with dicarbonyl compounds have been published.⁶⁰ Structural complexity can be obtained as reported in the synthesis of chiral spiro *N*-oxyhydantoin derivatives from β -glucopyranose.⁶¹

Peptides possessing an *N*-alkylated amino terminal residue were studied as inhibitors of matrix metalloproteinases (MMPs).⁶² One of their degradation pathways is their spontaneous cyclization with the formation of a hydantoin cycle (Scheme 1-12). This degradation pathway is known as the Edman peptide degradation, named after the chemist who developed this cyclization for the sequencing of proteins.



Scheme 1-12: Spontaneous cyclization via Edman degradation pathway

This cyclization can also be performed under oxidative Nef reaction of nitro derivatives (Scheme 1-13).⁶³ The starting materials were obtained via aza-Henry reaction,⁶⁴ and the cyclization was performed with sodium nitrite and acetic acid. Several *N*-hydantoin were isolated in good yields, which were the first trifluoro *N*-hydantoin to be reported.

⁵⁸ Decicco, C. P.; Senga, J. L.; Kennedy, K. E.; Covington, M. B.; Welch, P. K.; Arner, E. C.; Magolda, R. L.; Nelson, D. J. *Bioorg. Med. Chem. Lett.* **1997**, 7, 2331.

⁵⁹ Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**, 75, 109.

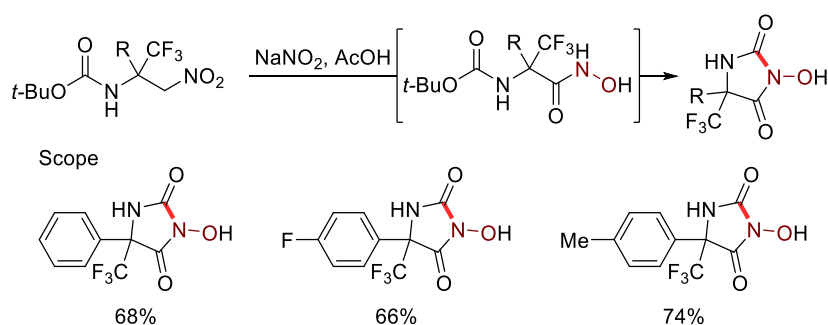
⁶⁰ (a) Shtamburg, V. G.; Anishchenko, A. A.; Shtamburg, V. V.; Shishkin, O. V.; Zubatyuk, R. I.; Mazepa, A. V.; Rakipov, I. M.; Kostyanovsky, R. G. *Mendeleev Commun.* **2008**, 18, 102. (b) Kostyanovsky, R. G.; Shtamburg, V. G.; Shishkin, O. V.; Zubatyuk, R. I.; Shtamburg, V. V.; Anishchenko, A. A.; Mazepa, A. A. *Mendeleev Commun.* **2010**, 20, 167.

⁶¹ Krülle, T. M.; de la Fuente, C.; Watson, K. A.; Gregoriou, M.; Johnson, L. N.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Fleet, G. W. J. *Synlett* **1997**, 211.

⁶² Campeste, C.; Tortorella, P.; Agamennone, M.; Preziuso, A.; Biasone, A.; Nutic, E.; Rossello, A.; Gallina, C. *Eur. J. Med. Chem.* **2008**, 43, 1008.

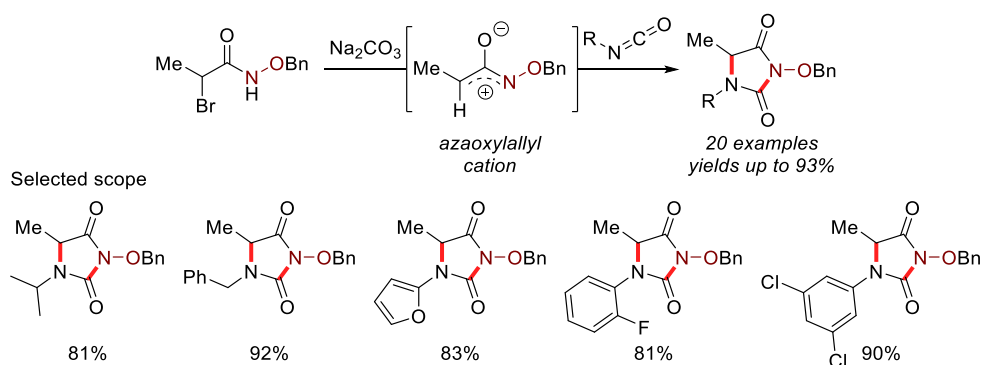
⁶³ Kutovaya, I. V.; Shmatova, O. I.; Tkachuk, V. M.; Sukach, V. A.; Vovk, M. V.; Nenajdenko, V. G. *Mendeleev Commun.* **2016**, 26, 511.

⁶⁴ Kutovaya, I. V.; Shmatova, O. I.; Tkachuk, V. M.; Melnichenko, N. V.; Vovk, M. V.; Nenajdenko, V. G. *Eur. J. Org. Chem.* **2015**, 30, 6749.



Scheme 1-13: Synthesis of trifluoro N-oxyhydantoins via oxidative Nef reaction

An alternative approach to hydantoin synthesis can be accomplished from azaoxylallyl cation cycloadditions with isocyanates. α -Halohydroxamate is a precursor of the azaoxylallyl cation which was proposed for the first time in 1968 by Sheehan.⁶⁵ However, it was only in the 2010's that the azaoxylallyl cation intermediate got attraction, especially due to the work of the Jeffrey group.⁶⁶ Since this renaissance, azaoxylallyl cations, derived from α -halohydroxamates, have been employed in multiple cycloaddition reactions, and, in 2018, the first [3 + 2] cycloaddition of α -halohydroxamates with isocyanates was published (Scheme 1-14).⁶⁷



Scheme 1-14: [3+2] cycloaddition of α -halohydroxamates with isocyanates

The α -bromohydroxamate easily released the azaoxylallyl cation after addition of sodium carbonate, and after reaction with different isocyanates 3-benzyloxy hydantoins were formed. Excellent yields were obtained; however, the reaction was lacking diversity of the α -bromohydroxamate starting material.

The current synthesis of N-oxyureas and N-oxyhydantoins were presented along with their existing limitations. In chapter two, a complimentary methodology for the synthesis of these N-heterocycles is described via O-isocyanates.

⁶⁵ Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed.* **1968**, 7, 25.

⁶⁶ (a) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, 133, 7688. (b) Acharya, A.; Eickhoff, J. A.; Jeffrey, C. S. *Synthesis* **2013**, 45, 1825. (c) Acharya, A.; Anumandla, A.; Jeffrey, C. S. *J. Am. Chem. Soc.* **2015**, 137, 14858.

⁶⁷ Sun, S.; Chen, R.; Wang, G.; Wang, J. *Org. Biomol. Chem.* **2018**, 16, 8011.

1.3. Amination reactions

The work presented in this thesis studies the incorporation of nitrogen atoms into linear and cyclic structures. Hydroxylamine and its derivatives are used as amination reagents in the different chapters. In this section, the common amination reactions using hydroxylamine are reviewed.

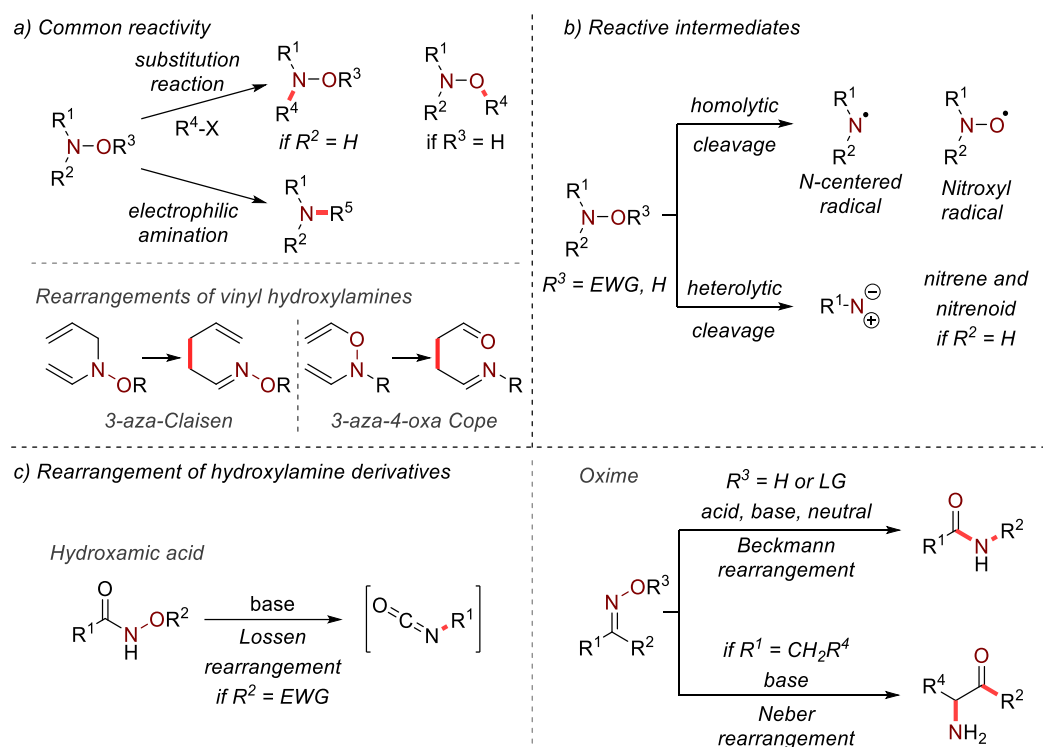
1.3.1. Common reactivity of hydroxylamine

Due to the unique N-O bond of hydroxylamine, several reactions and reactive intermediates were studied and developed by different groups (*Scheme 1-15*). Alkyl hydroxylamines can perform substitution reactions at the nitrogen and at the oxygen for the synthesis of more complex hydroxylamines. The displacement of the OR group by an organometallic reagent follows a S_N2-type mechanism that can be intra- or intermolecular. This C-N bond formation via electrophilic amination has been well developed and reviewed eleven years ago.⁶⁸

Substituted hydroxylamines can undergo thermal [3+3] sigmatropic rearrangements. The rearrangement of vinyl hydroxylamines via the 3-aza-Claisen rearrangement leads to the formation of oximes⁶⁹ and the 3-aza-4-oxa-Cope rearrangement forms the corresponding carbonyl-imine derivatives of vinyl hydroxylamines.

⁶⁸ Erdik, E. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*; John Wiley & Sons, Ltd.: Southern Gate, **2008**, 303.

⁶⁹ Gomes, M. J. S.; Sharma, L.; Prabhakar, S.; Lobo, A. M.; Glória, P. M. C. *Chem. Commun.* **2002**, 746.



Scheme 1-15: Common reactivity of hydroxylamine (a) and possible reactive intermediates (b). Rearrangements of hydroxylamine derivatives (c)

Different reactive intermediates can be obtained from the homolytic or heterolytic cleavage of the weak N-O bonds. In part 1.4.2, several examples of C-N bond formation via generation of N-centered radicals or nitrene/metal-nitrenes are presented. C-H activation and aziridination reactions will also be discussed.

Nitroxyl radical is a particularly important radical in chemistry and also in biochemistry: they are used as inhibitors of free radical processes, promoters of controlled polymerization and oxidation reactions for example.⁷⁰ Nitroxyl radical can be formed via homolytic cleavage of the O-H bond of hydroxylamine derivatives. Several derivatives like TEMPO (a stable radical) or the Frémy's salt, a long-lived free radical used as a standard in EPR⁷¹ are used on a daily basis due to their stability and how easy they are to work with.

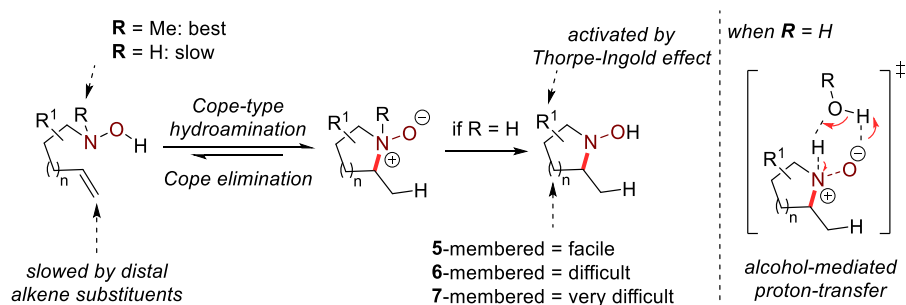
Hydroxamic acids and oximes also have intrinsic rearrangement reactivity due to the particularly weak N-O bond. In part 1.3.2.2., the Lossen rearrangement of hydroxamic acids is presented. The Beckmann rearrangement is the most used reaction of oximes, due to the importance of amides. The Neber rearrangement was found as a side-reaction of the Beckmann rearrangement. The Neber reaction is now

⁷⁰ Galli, C. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids* **2008**, 705.

⁷¹ Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, 71, 229.

used for the synthesis of α -aminocarbonyls.⁷² These general reactions show how hydroxylamines and its derivatives for different aminations reactions and in the next section, Cope-type hydroamination and Lossen rearrangement are presented.

Substituted hydroxylamines can undergo hydroamination for the formation of C-N bonds via the addition of a N-H onto a carbon-carbon bonds of alkenes, alkynes and allenes. Hydroamination can be performed with amines under metal-free or metal catalyzed reactions,⁷³ and has also been reported with hydroxylamines.⁷⁴ This pericyclic reaction can be intra- or intermolecular and allows the incorporation of the N-O motif.



Scheme 1-16: General mechanism and transition state of Cope-type hydroamination

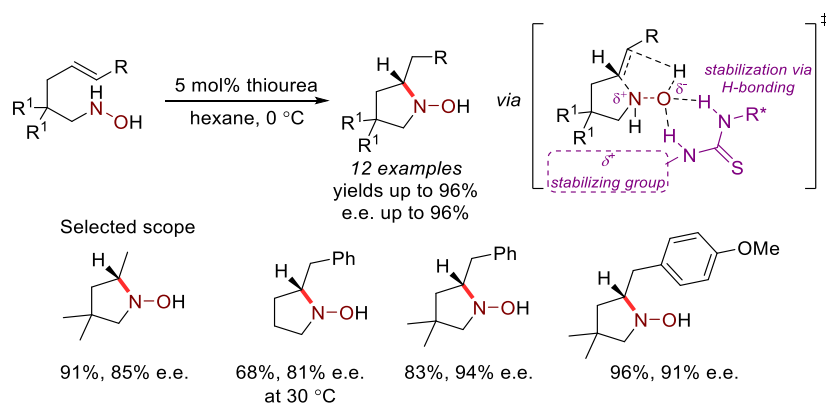
This reaction has been thoroughly studied, and different factors were found to improve the reaction rate (Scheme 1-16). Thorpe-Ingold effect plays an important role due to the structural restriction that accelerates the cyclization. The Cope-type hydroamination was found to be solvent dependent, and *i*-PrOH was initially determined as the optimal solvent due to its strong H-bonding character. This H-bonding was the key parameter to stabilize the N-oxide intermediate and avoid the reverse pathway, the Cope elimination.⁷⁵ It was also suggested that H-bonding helps the proton transfer step through a 5-membered ring transition state. The rate limiting step was proposed to be the proton transfer and the DFT provided more evidence by the facile alcohol-mediated proton transfer step occurring through a five-membered transition state (Scheme 1-16).

⁷² Pereira, M. M. A.; Santos, P. P. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Wiley, **2008**, 343.

⁷³ (a) Hannedouche, J.; Schulz, E. *Chem.-Eur. J.* **2013**, *19*, 4972. (b) Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catal. Sci. Technol.* **2015**, *5*, 2017.

⁷⁴ For reviews on Cope-type hydroamination see: (a) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243. (b) Beauchemin, A. M. *Org. Biomol. Chem.* **2013**, *11*, 7039.

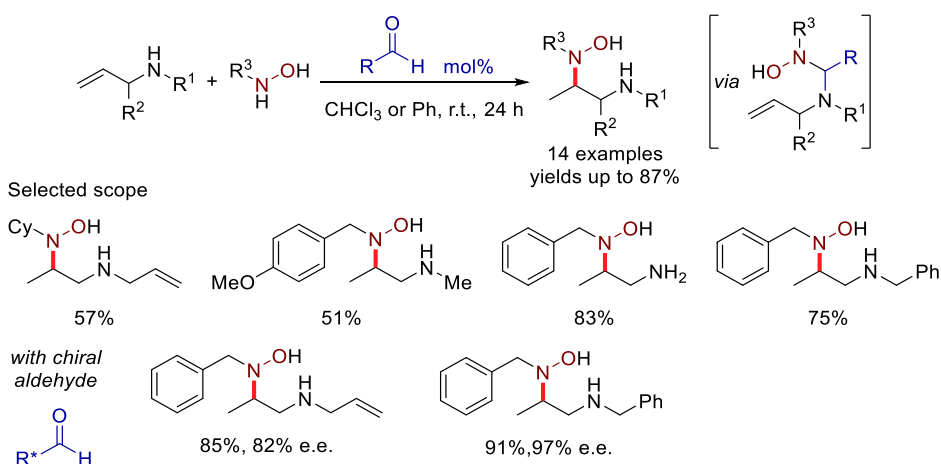
⁷⁵ Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M.-E.; Bédard, A.-C.; Séguin, C. Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.



Scheme 1-17: Synthesis of chiral α -substituted pyrrolidines via Cope-type hydroamination

The H-bonding character of hydroxylamine was used by the Jacobsen group for the enantioselective Cope-type hydroamination using chiral thiourea catalyst (Scheme 1-17).⁷⁶ The authors proposed a 6-membered ring transition state with stabilization via H-bonding and δ^+ stabilization group. The thiourea was suggested to stabilize the polar cyclization transition state, comparable to the role of *i*-PrOH as solvent. This strategy allowed the synthesis of α -substituted pyrrolidines with yields up to 96% and e.e. up to 96%. Without Thorpe-Ingold effect, the yields and enantiomeric excess of pyrrolidines is lower and had to be heated to 30 °C to see reactivity.

Temporary intramolecularity using chiral aldehydes has also been reported for enantioselective Cope-type hydroamination (Scheme 1-18).⁷⁷ Intramolecular reaction of allyl amines and hydroxylamine derivatives was possible through the formation of the aмина intermediate using various aldehydes as catalysts.



Scheme 1-18: Aldehyde-catalyzed Cope-type hydroamination

⁷⁶ Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747.

⁷⁷ (a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100. (b) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571.

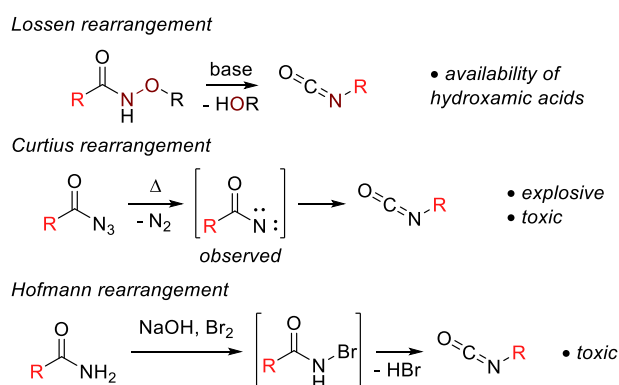
Several vicinal diamines were obtained to moderate to good yields, and when the catalyst was a chiral aldehyde the diamines were obtained with good e.e.⁷⁸

1.3.2. Lossen rearrangement

The Lossen rearrangement is featured as a side-reaction in chapter two and four and a nitrogen analogue version is described in chapter 3. In this part, the discovery and general reactivity is presented.

In this thesis, the Lossen rearrangement is featured as a side-reaction (chapters two and four), and a broadly applicable nitrogen variant, the aza-Lossen rearrangement, is the focus of chapter three for the synthesis of N-N containing molecules.

The Lossen rearrangement⁷⁹ is the most used reaction of hydroxamic acids and was reported by Lossen in 1872.⁸⁰ In presence of the base, hydroxamic acids rearrange to form an isocyanate via the formation of a C-N bond due to the weakness of the N-O bond (Scheme 1-19).



Scheme 1-19: Formation of isocyanate via rearrangement chemistry

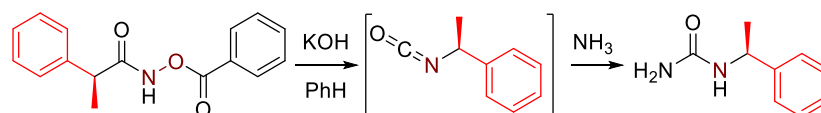
The BDE of N-O bond is diminished by the addition of electron withdrawing group on the oxygen and this mode of activation allows for more stable and less dangerous starting materials and experimental conditions in comparison of the Curtius and Hofmann rearrangements.⁷⁹ Indeed, acyl azides can form isocyanate when heated similar to amides in presence of bromide in basic media. The Curtius rearrangement suffers from the instability (explosive) and toxicity of the acyl azides and the Hofmann rearrangement requires the use of the toxic bromine. Arguably, Lossen rearrangement uses milder conditions, however, it is limited by the availability of the hydroxamic acid starting materials.

⁷⁸ MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem. Eur. J.* **2013**, *19*, 2597

⁷⁹ For a recent review on Lossen, Curtius and Hoffmann rearrangement see: Aubé, J.; Fehl, C.; Liu, R.; McLeod, M. C.; Motiwala, H. F. *Comprehensive Organic Synthesis II* (2nd Ed), Elsevier, **2014**, 598.

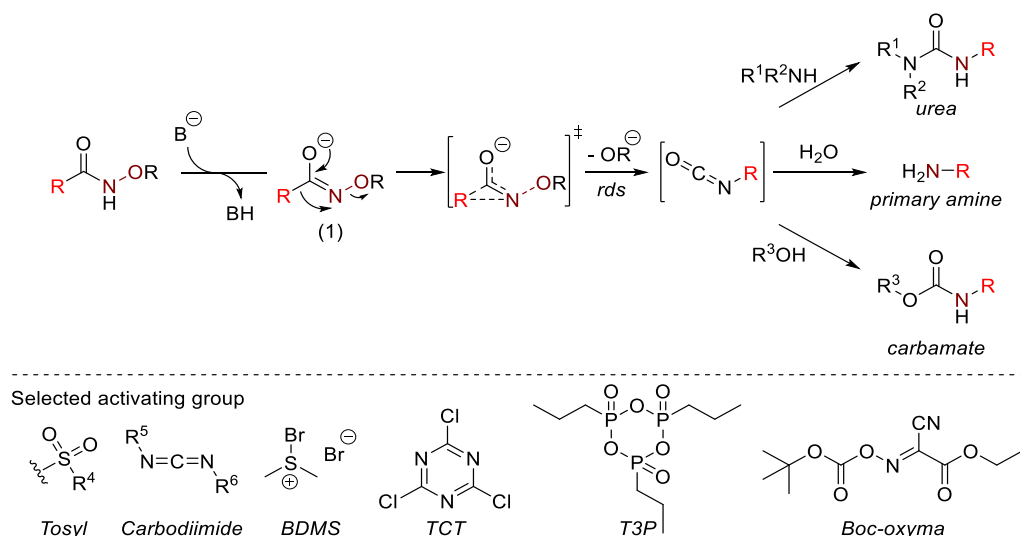
⁸⁰ Lossen, W. *Ann.* **1872**, *161*, 347.

The mechanism of the Lossen rearrangement was believed to go through the formation of a nitrene intermediate via a stepwise pathway. However, at the difference of the Curtius rearrangement,⁸¹ direct observation and/or capture of a nitrene intermediate during Lossen rearrangement was tried unsuccessfully.⁸² In 1933, Wallis and Dripps reported the rearrangement of the enantioenriched *N*-(benzoyloxy)-2-phenylpropanamide and the formation of the corresponding chiral isocyanate and chiral urea after addition of ammonia (Scheme 1-20).⁸³



Scheme 1-20: Formation of chiral urea from chiral hydroxamic acid

After this indirect evidence of a concerted mechanism, the Lossen rearrangement mechanism was suggested to go via a 3-membered ring transition state, which is still the pathway accepted today. Observation of this proposed intermediate is still not reported. In 1937, Renfrow and Hauser performed a kinetic study of the rates of decomposition of potassium dihydroxamates salts.⁸⁴ They concluded that the rate limiting step was the expulsion of the negative OR group from the anion (1, Scheme 1-21), providing evidence contradicting the nitrene pathway. This ionic/concerted pathway has also been found in the study of gas phase Lossen rearrangements using mass spectrometry.⁸⁵



Scheme 1-21: General Lossen rearrangement mechanism and common products

The activation of the hydroxamic acid can be performed using acylating reagents, addition of tosyl or common coupling reagents (like CDI or cyanuric chloride).⁸⁶ The Lossen rearrangement is mainly used

⁸¹ Li, H.; Wan, H.; Wu, Z.; Li, D.; Begue, D.; Wentrup, C.; Zeng, X. *Chem. - Eur. J.* **2016**, 22, 7856.

⁸² Bauer, L.; Exner, O. *Angew. Chem., Int. Ed.* **1974**, 13, 376.

⁸³ Wallis, E.; Dripps, R. D. *J. Am. Chem. Soc.* **1933**, 55, 1701.

⁸⁴ Renfrow, W. B. Jr.; Hauser, C. R. *J. Am. Chem. Soc.* **1937**, 59, 2308.

⁸⁵ Adams, G. W.; Bowie, J. H.; Hayes, R. N. *J. Chem. Soc., Perkin Trans. 2* **1991**, 689.

⁸⁶ (a) Tosyl: Pihuleac, J.; Bauer, I. *Synthesis* **1989**, 61. (b) Carbodiimide: Narendra, N.; Chennakrishnareddy, G.; Sureshbabu, V. V. *Org. Biomol. Chem.* **2009**, 7, 3520. (c) BDMS: Yadav, D. K.; Yadav, A. K.; Srivastava, V. P.; Watal, G.; Yadav, L. D. S. *Tetrahedron Lett.* **2012**, 53, 2890. (d) Hamon, F.; Prié, G.; Lecornué, F.; Papot, S.

for the synthesis of amines, ureas and carbamates and the current focus is on milder *in-situ* activation methods of hydroxamic acids.⁸⁷

1.4. Formation of N-N and C-N bonds

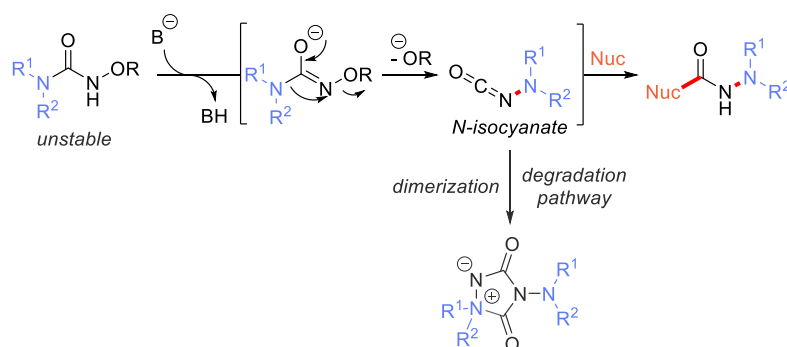
In Chapter three and four, cleavage of the N-O bond of hydroxylamine derivatives is presented for the formation of N-N and C-N bonds. In this section, previous examples of N-N and C-N bond formation with hydroxylamine derivatives as starting materials are discussed.

1.4.1. Formation of N-N bond

1.4.1.1. Aza-Lossen rearrangement

In Chapter three, a broadly applicable nitrogen analogue of the Lossen rearrangement (aza-Lossen rearrangement) is described. In this section, previous examples of aza-Lossen rearrangements are reported, along with discussions of their limitations.

The aza-Lossen rearrangement involves the migration of a nitrogen atom, leading to the formation of *N*-isocyanate intermediate and resulting in the formation of a new N-N bond (Scheme 1-22). The aza-Lossen remains underdeveloped, likely due to the availability (and instability) of the corresponding activated *N*-oxyurea starting materials. Another problem is the controlled formation of the *N*-isocyanate. *N*-Isocyanates are less stable than the corresponding carbon-substituted isocyanates and undergo fast dimerization (occurring at -40 °C⁸⁸), making their productive reactivity more challenging. Over the years, only few examples were published, with limited synthetic applicability.



Scheme 1-22: General mechanism and side products of the aza-Lossen rearrangement

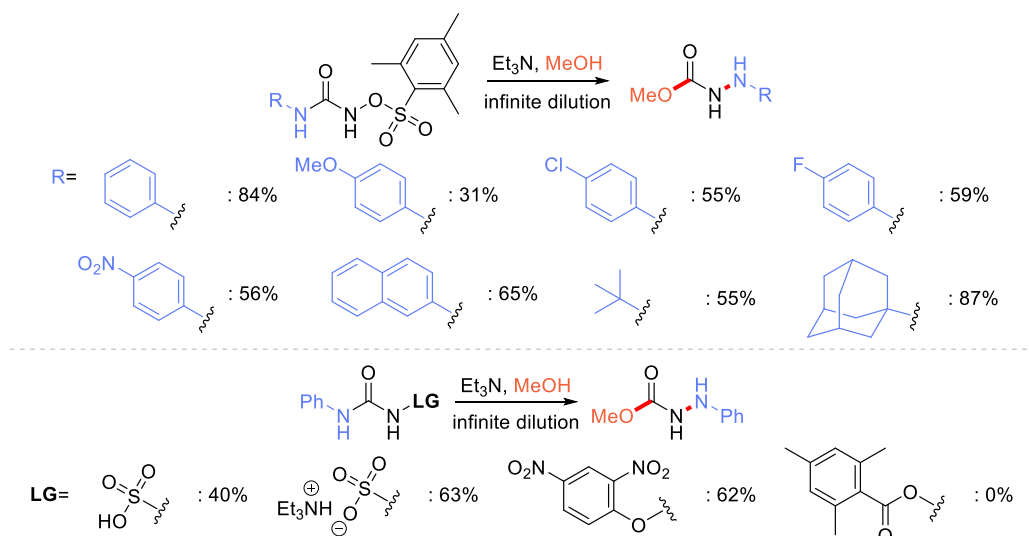
Tetrahedron Lett. **2009**, 50, 6800. (e) Vasantha, B.; Hemantha, H. P.; Sureshbabu, V. V. *Synthesis* **2010**, 17, 2990. (f) Rao Manne, S.; Thalluri, K.; Subhra Giri, R.; Chandra, J.; Mandal, B. *Adv. Synth. Catal.* **2017**, 359, 168.

⁸⁷ (a) Strotman, N. A.; Ortiz, A.; Savage, S. A.; Wilbert, C. R.; Ayers, S.; Kiau, S. *J. Org. Chem.* **2017**, 82, 4044.

(b) Yadav, A. K.; Srivastava, V. P.; Yadav, L. D. S. *RSC Adv.* **2014**, 4, 24498.

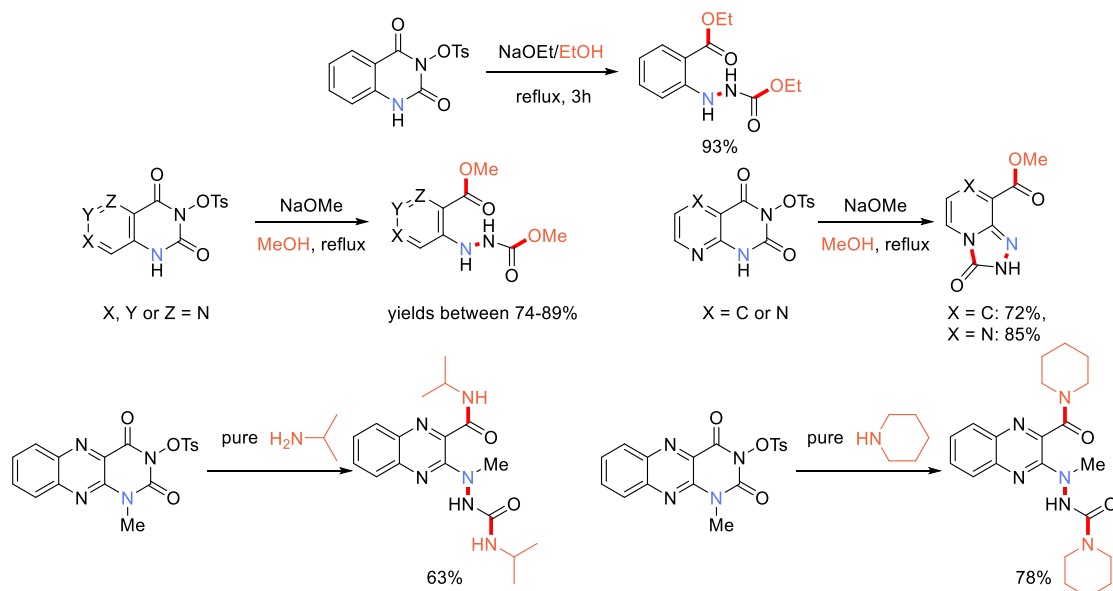
⁸⁸ For a recent review on *N*-isocyanate see: Vincent-Rocan, J.-F.; Beauchemin, A. M. *Synthesis* **2016**, 48, 3625.

of aniline in good yield; however, urea bearing *O*-benzoyl substituents did not undergo aza-Lossen rearrangement.



Scheme 1-25: Study of the aza-Lossen rearrangement via infinite dilution

The Bauer group reported several *N-N* bonds formation via aza-Lossen rearrangement of *N*-containing heterocycles.⁹² In presence of alkoxide in an alcohol media, quinazoline-2,4-dione, pyrimidine-2,4-dione and pteridine-2,4-dione derivatives which bore a *N*-OTs group rearranged to form different *N-N* bond containing molecules with the synthesis of carbamates, triazolopyridin-3-ones and two examples of semicarbazides (Scheme 1-26).



Scheme 1-26: Summary of aza-Lossen rearrangements by the Bauer group

⁹² (a) Tserng, K.-Y.; Bauer, L. *J. Org. Chem.* **1973**, *38*, 3498. (b) Tserng, K.-Y.; Bauer, L. *J. Heterocyclic Chem.* **1974**, *11*, 163. (c) Hamby, J. M.; Bauer, L. *J. Heterocyclic Chem.* **1987**, *24*, 1013.

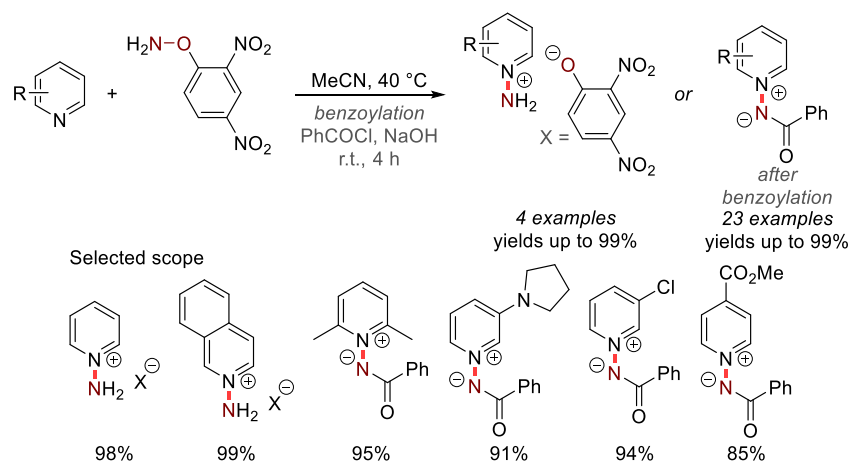
The presence of the strong electron withdrawing group limited this strategy to bicyclic aromatic derivatives due stability by aromaticity. Indeed, the aza-Lossen rearrangement developed by Bauer and co-workers was only limited to the heterocycles shown in *Scheme 1-26*. Based on the clear limitations of the previous aza-Lossen rearrangements reported, this reaction remained underdeveloped. The development of more broadly applicable *N-N* bond forming reactivity served as a goal for the development of the aza-Lossen procedure reported in Chapter 3.

1.4.1.2. Formation of *N-N* bond from hydroxylamine derivatives

Others examples of *N-N* bonds arising from the cleavage of *N-O* bond of hydroxylamine derivatives via substitution reactions have been reported. Several examples are presented in this section.

1.4.1.2.1. From *O*-alkyl and *O*-aryloxyamines

In 2013, Legault and Charette published the synthesis of *N*-benzoyliminopyridinium ylides via *N-N* bond formation using *O*-(2,4-dinitrophenyl)hydroxylamine as an *N*-amination reagent (*Scheme 1-27*).⁹³ The mild conditions allowed the *N*-amination of several heterocycles (pyridine, quinoline and isoquinoline), in excellent yields. Substituents on the pyridine ring were tolerated, and after benzoylation, twenty-three *N*-benzoyliminopyridinium ylides were isolated in good to excellent yields.



*Scheme 1-27: Synthesis of *N*-benzoyliminopyridinium ylides via *N-N* bond formation*

Multiple groups have used this *N*-amination strategy on various *N*-heterocycles, tertiary and secondary amines⁹⁴ and different electron withdrawing groups (mostly tosyl derivatives) on the oxygen were developed.⁹⁵

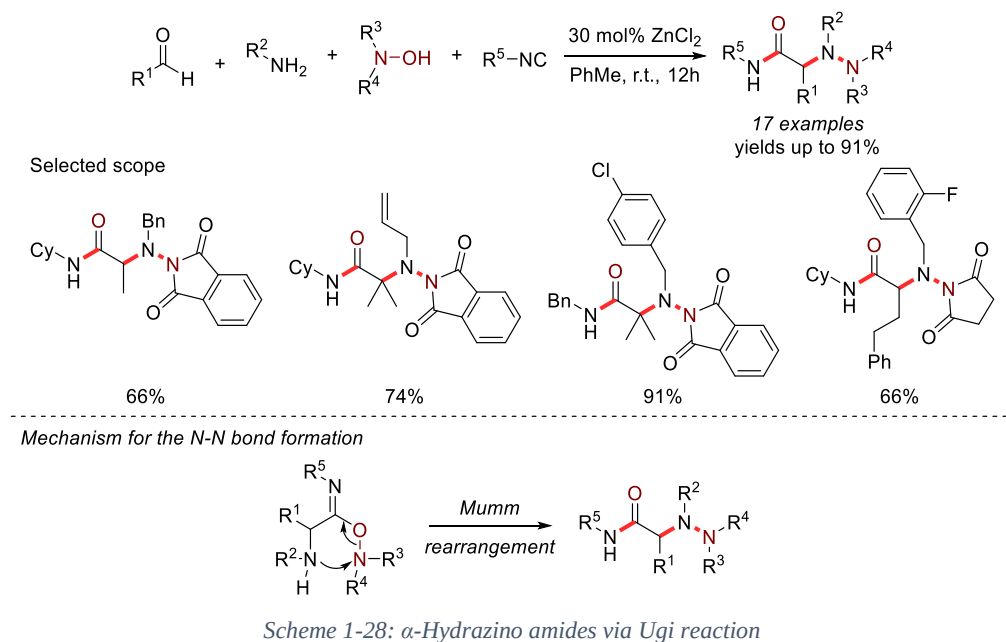
⁹³ Legault, C.; Charette, C. *J. Org. Chem.* **2003**, 68, 7119.

⁹⁴ Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

⁹⁵ Brocklehurst, C. E.; Koch, G.; Rothe-Pöllet, S.; La Vecchia, L. *Synlett* **2017**, 28, 1636.

1.4.1.2.2. From *N*-hydroxyimides

The Ugi - four component reaction is mainly used for the formation of bis-amides starting from a carbonyl, an amine, an isocyanide and a carboxylic acid. Over the years, the different partners have been varied and in 2017, Chandgude and Dömling reported the first Ugi reaction with a *N-N* bond formation, by replacing the classical carboxylic acid by *N*-hydroxyimides (Scheme 1-28).⁹⁶ The proposed mechanism goes through a classical Ugi-type reaction, with the *N-N* bond formation step being hypothesized as an irreversible Mumm-like rearrangement.⁹⁷



With the addition of $ZnCl_2$ as a catalytic Lewis acid, several α -hydrazino amides were synthesized. Electron withdrawing and electron donating groups on the aldehydes and primary amines (with the facie deprotected benzyl group for examples) and three *N*-hydroxyimide derivatives were tolerated (Scheme 1-28). Deprotection using hydrazine hydrate released the free hydrazine and cleavage of the *N-N* bond was accomplished using stoichiometric $AlCl_3$.

In 2018, a second example of *N-N* bond formation via Ugi rearrangement was published for the synthesis of *N*-alkyl-*N*-acylaminophthalimide/*N*-alkyl-*N*-acylaminosuccinimide, using *N*-hydroxyimides as starting materials.⁹⁸

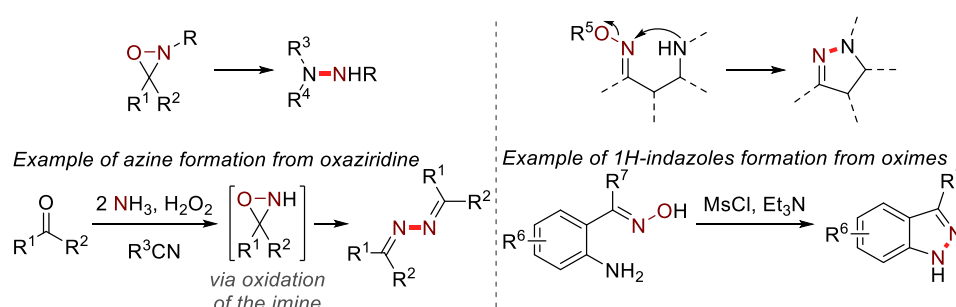
⁹⁶ Chandgude, A. L.; Dömling, A. *Org. Lett.* **2017**, 19, 1228.

⁹⁷ Mumm, O. *Ber. Dtsch. Chem. Ges.* **1910**, 43, 886.

⁹⁸ Wang, J.; Sun, Y.; Jiang, M.-H.; Hu, T.-Y.; Zhao, Y.-J.; Li, X.; Wang, G.; Hao, K.; Zhen, L. *J. Org. Chem.* **2018**, 83, 13121.

1.4.1.2.3. Electrophilic aminations with oxaziridines and oximes

An alternative method for the formation of *N-N* bond via cleavage of a *N-O* bond is the electrophilic aminations with oxaziridines and oximes as starting materials. Oxaziridine is a three membered ring containing a *N-O* bond and it is used for oxygen- and nitrogen-transfer. Multiple examples of *N*-amination using oxaziridines have been published for the synthesis of hydrazine,⁹⁹ *N*-aminopeptide¹⁰⁰ and benzotriazol-1-amine¹⁰¹ derivatives. Example of an *in-situ* formed oxaziridine reacting with an amine was reported for the synthesis of azine¹⁰² and a modified protocol is used for the industrial synthesis of hydrazine.¹⁰³ *N-N* bond formation via electrophilic aminations of oxime derivatives¹⁰⁴ has been developed for the synthesis of many heterocyclic compounds: pyrazolines,¹⁰⁵ cationic triaziniums,¹⁰⁶ indazoles¹⁰⁷ and pyrazolopyrimidines¹⁰⁸ for example (Scheme 1-29).



Scheme 1-29: Examples of *N-N* bond formation via electrophilic amination

1.4.2. Formation of C-N bond from hydroxylamine derivatives

Chapter four is focusing on a new mode of activation of triplet nitrene via the cleavage of the *N-O* bond of *N*-oxyureas. A method allowing for the formation of uridyl and amidyl radicals from *N*-oxyureas using visible-light mediated condition is discussed. In this part, previous formations of *C-N* bonds arising from the cleavage of *N-O* of hydroxylamine derivatives are discussed.

⁹⁹ Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, 7, 713.

¹⁰⁰ Sarnowski, M. P.; Won Kang, C.; Elbatrawi, Y. M.; Wojtas, L.; Del Valle, J. R. *Angew. Chem., Int. Ed.* **2017**, 56, 2083.

¹⁰¹ Knight, D. W.; Qing, X. *Tetrahedron Lett.* **2009**, 50, 3534.

¹⁰² Schirmann, J.-P.; Weiss, F. *Tetrahedron Lett.* **1972**, 13, 635.

¹⁰³ Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, 45, 5703.

¹⁰⁴ Abele, E.; Abele, R. *Curr. Org. Synth.* **2014**, 11, 403.

¹⁰⁵ Hassner, A.; Michelson, M. J. *J. Org. Chem.* **1962**, 27, 298.

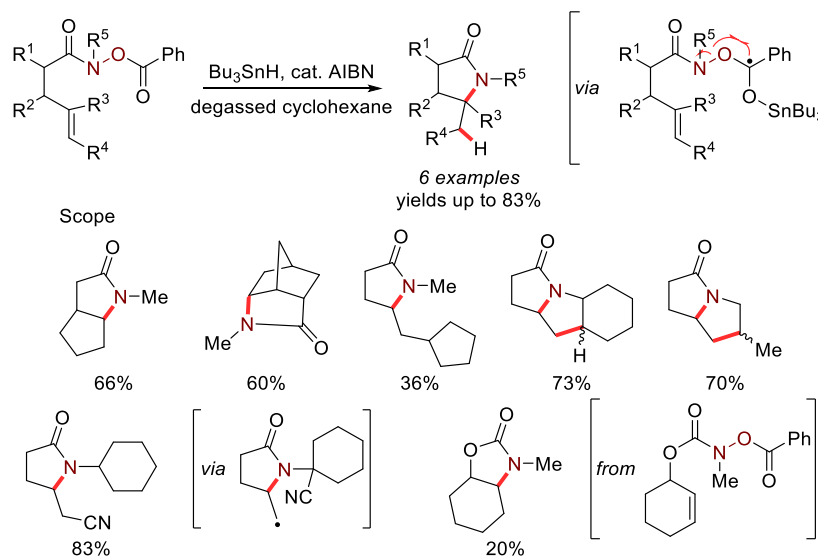
¹⁰⁶ Reeves, J. T.; Han, Z. S.; Goyal, N.; Lee, H.; Busacca, C. A.; Senanayake, C. H. *Tetrahedron Lett.* **2014**, 55, 2492.

¹⁰⁷ Counciller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, 10, 1021.

¹⁰⁸ Evans, L. E.; Cheeseman, M. D.; Jones, K. *Org. Lett.* **2012**, 14, 3546.

1.4.2.1. Via *N*-centered radicals

One of the first examples of the generation of amidyl radicals via *N*-O cleaving of hydroxamic acid was reported by Zard and co-workers in 1994.¹⁰⁹ Inspired by the work of Barton-McCombie, they reacted hydroxamate esters with tributyltin hydride in presence of a catalytic amount of AIBN. After 1) formation of the tributyltin radical, 2) addition onto the carbonyl and 3) fragmentation to access the amidyl radical, a 5-*exo-trig* cyclization occurred to form a *C*-*N* bond. Cascade reactions and/or H-abstractions lead to the formation of lactam derivatives in moderate to good yields (Scheme 1-30).



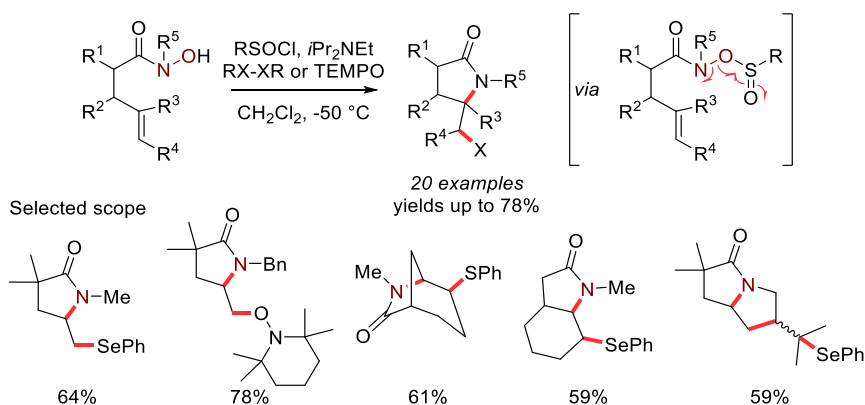
Scheme 1-30: Formation of amidyl radical with Bu_3SnH

The reaction conditions were also compatible with the formation of carbamoyl radical, and one example of carbamate was also reported.

Several years later, the *in-situ* activation of free hydroxamic acids with *tert*-butylsulfinyl chloride was reported.¹¹⁰ After scission and 5-*exo-trig* cyclization the radical was trapped either with diphenyl diselenide, diphenyldisulfane or TEMPO and lactams were obtained in moderate to good yields (Scheme 1-31).

¹⁰⁹ Calliera, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994**, 35, 6109.

¹¹⁰ Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, 41, 2333.

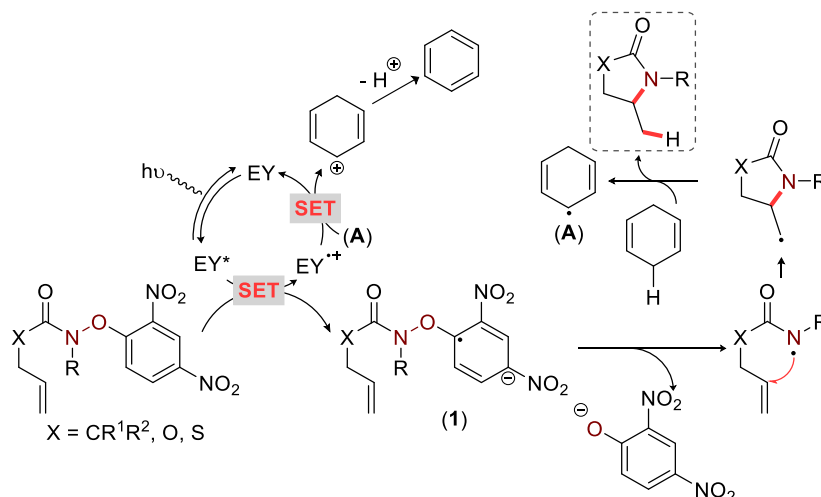


Scheme 1-31: Activation of free hydroxamic acid with *tert*-butylsulfinyl chloride

In 2013, the MacMillan group reported a new mode of activation of hydroxylamine derivatives for the formation of C-N bonds.¹¹¹ This method allows for the enantioselective coupling of an external amine (arising from the cleavage of a N-O bond of an activated hydroxylamine derivative) and an aldehyde via the formation of a chiral enamine, then iminium ion. The N-centered radical was generated through the photo-excitation of the dinitrophenylsulfonyloxyl group. This group (5) can be activated using irradiation with a simple household lightbulb (Scheme 1-32). After reduction, an electrophilic N-centered radical (7) was produced and reacted with a π -rich enamine (2) (resultant from the condensation of an imidazolidinone catalyst (1) with an aldehyde). The carbon radical compound (3) was oxidized to the corresponding iminium ion (4), and after hydrolysis, enantioenriched α -amino aldehydes were formed.

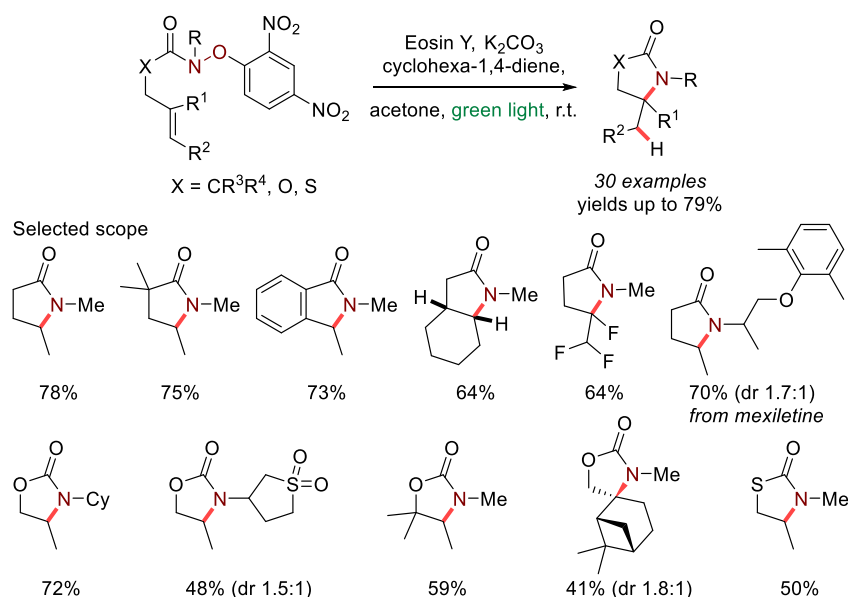
¹¹¹ Cecere, G.; König, C. M.; Allewa, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, 135, 11521.

that the BDE of the N-O was around 40 kcal/mol. The authors proposed a mechanism involving the excitation of Eosin Y by a green light, that underwent SET with the activated hydroxamate ester to form a radical anion (**1**) (Scheme 1-34). Then, thermodynamically driven cleavage of the N-O bond formed the amidyl radical that underwent a 5-*exo-trig* cyclization. Hydrogen atom abstraction from 1,4-cyclohexadiene formed the desired product (lactams and cyclic carbamates) and the corresponding 1,4-cyclohexadiene radical (**A**), regenerated the Eosin Y catalyst.



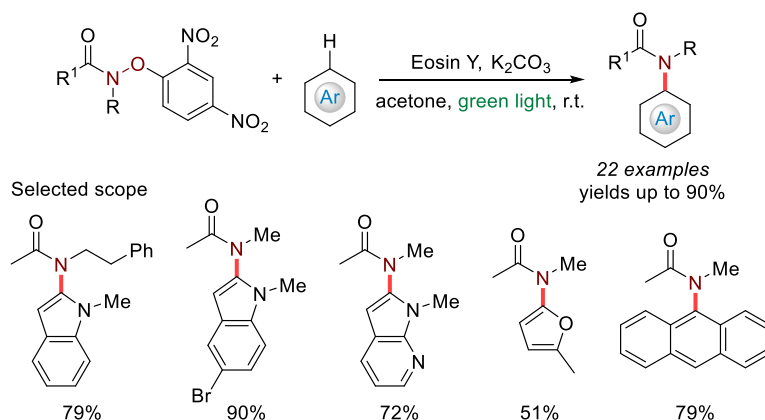
Scheme 1-34: Formation of N-centered radical mediated with Eosin Y

This reaction allowed for the synthesis of lactams in moderate to good yields and was compatible with a large range of functional groups. Protecting groups on the nitrogen were tolerated (Boc, Cbz), as were sugar-like moieties and trifluoro-substituted olefins (Scheme 1-35). Derivation of bioactive molecule (mexiletine for example) and cyclic carbamates and one of sulfur derivative were also reported. For the first time, amidyl radicals were generated via photoredox metal-free from aryloxy-amides. The starting materials were easy to access and the methodology developed allowed for a high functional group tolerance.



Scheme 1-35: Synthesis of lactams and cyclic carbamates via Eosin Y excitation

In the same communication, the authors also reported the *N*-arylation of electron-rich aromatic group using the same mode of amidyl radical formation. Similar *N*-arylations of electron-rich aromatic groups via *N*-O bond cleavage of a hydroxylamine derivatives were previously reported by the group of Sanford (*N*-acyloxyphthalimides),¹¹³ Yu (*N,O*-ditosyl-*N*-methylhydroxylamine)¹¹⁴ and Ooi (3,5-bis(trifluoromethyl)phenylacyloxyphthalimide).¹¹⁵ These others examples suffered from the large excess needed for the Ar-H or from poor functional group tolerance.



Scheme 1-36: N-Arylation of electron-rich aromatic groups

Examples of *N*-arylations of indoles, pyrroles, furans, naphthalenes, and anthracenes among other heteroaromatic molecules were reported with diverse protecting groups on the nitrogen (Ac, Boc, Cbz) (Scheme 1-36). Several years later, the same group reported the *N*-amination of aromatic rings via the

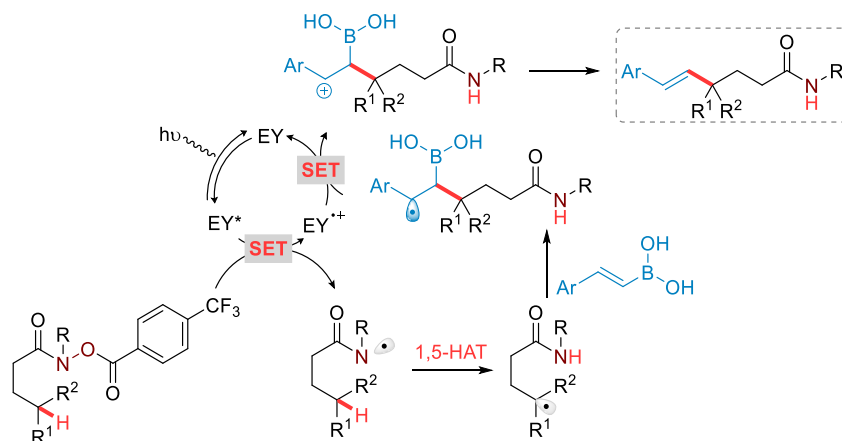
¹¹³ Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, 136, 5607.

¹¹⁴ Qin, Q.; Yu, S. *Org. Lett.* **2014**, 16, 3504.

¹¹⁵ Bhushan Tripathi, C.; Ohtani, T.; Corbetta, M. T.; Ooi, T. *Chem. Sci.* **2017**, 8, 5622.

cleavage of an electron-poor *O*-arylhydroxylamine¹¹⁶ and a modified method for the generation of the amidyl radical based on the SET oxidation of a carboxylate moiety.¹¹⁷

Amidyl radicals can also undergo 1,5-HAT (abstraction of a hydrogen atom five positions away from the *N*-centered radical) for remote functionalization, after the formation of a C-centered radical five positions away from the nitrogen. Different partners have been used to trap this intermediate, including the 2018 report of γ -C(sp³)-H vinylation of amides using alkenylboronic acids as radical trap (Scheme 1-37).¹¹⁸



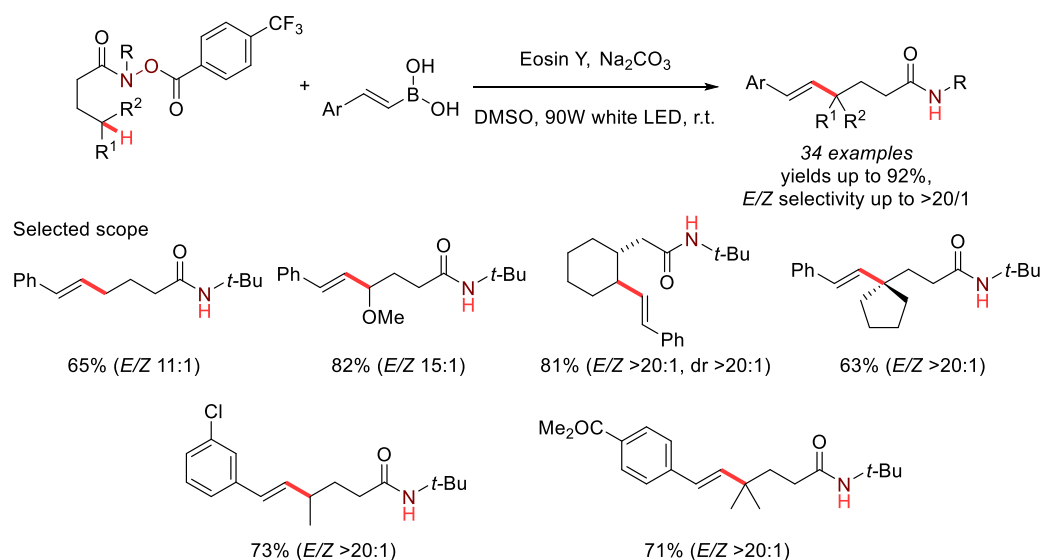
Scheme 1-37: Proposed mechanism of remote functionalization via 1,5-HAT of amidyl radical

Once again, the oxygen was bearing an electron withdrawing group to have a lower reduction potential. After optimization, *p*-CF₃ benzoate was found to be the best substituent for the SET reduction. After formation of the C-centered radical via 1,5-HAT, intermolecular trapping by vinylboronic acid occurred and the newly formed radical is then oxidized by the Eosin Y. Finally, after deboronation γ -vinylamides were obtained.

¹¹⁶ Svejstrup, T. D.; Ruffoni, A.; Juliá, F.; Aubert, V. M.; Leonori, D. *Angew. Chem. Int. Ed.* **2017**, 56, 14948.

¹¹⁷ Morcillo, S. P.; Dauncey, E. D.; Kim, J. H.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. *Angew. Chem. Int. Ed.* **2018**, 57, 12945.

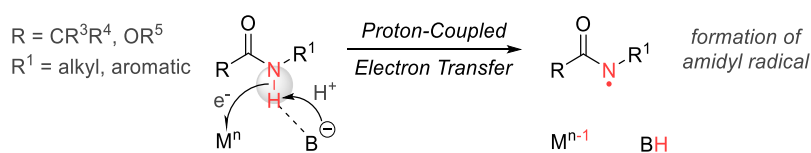
¹¹⁸ Chen, H.; Guo, L.; Yu, S. *Org. Lett.* **2018**, 20, 6255.



Scheme 1-38: γ -C(sp³)-H vinylation of amides

Several γ -vinylamides were obtained in moderate to good yields. To reach good *E/Z* selectivity, the nitrogen was substituted by a *t*-Bu group. The 1,5-HAT step was efficient at primary, secondary and tertiary positions. The reaction remained high yielding when the hydroxamic chain and the boronic acid partner were substituted by electron withdrawing and electron donating groups (Scheme 1-38).

A second approach for the formation of amidyl radicals was developed recently using Proton-Coupled Electron Transfer or PCET (Scheme 1-39). This mode of formation cleaves a *N-H* bond by the concomitant use of the base and the photocatalyst.¹¹⁹ This chemistry will be reviewed in Chapter four.



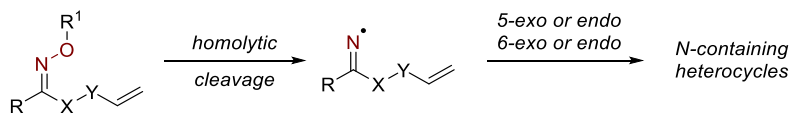
Scheme 1-39: Amidyl radical formation via PCET

With these facile methods for the formation of amidyl radical under photoredox conditions, increase of the derivatizations of amides at the 1,5-positions allows for more complex structures.

Another important *N*-centered radical resulting from the cleavage of the *N-O* bond of hydroxylamine derivatives is the iminyl radical. Under thermolysis, oxidizing, UV radiation or light conditions, oximes can undergo homolytic cleavage and generate iminyl radicals. This radical can then cyclize 5-*exo/endo* or 6-*exo/endo* (Scheme 1-40). Different partners and/or radical traps have been used to form *N*-containing heterocycles. The chemistry of iminyl radicals has been recently reviewed.¹²⁰

¹¹⁹ Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, 49, 1546.

¹²⁰ (a) Walton, J. C. *Molecules* **2016**, 21, 660. (b) Jackman, M. M.; Cai, Y.; Castle, S. L. *Synthesis* **2017**, 49, 1785. (c) Lei, J.; Li, D.; Zhu, Q. *Top. Heterocycl. Chem.* **2018**, 54, 285.



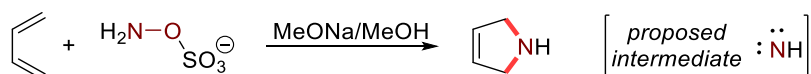
Scheme 1-40: Iminyl radical

This complementary method for the formation of *N*-containing heterocycles was not used during this thesis and will not be discussed in detail.

1.4.2.2. Via Nitrene/Metal-nitrene formation

Nitrenes are important reactive intermediates in amination chemistry. Under specific conditions, nitrogen can form an uncharged and univalent intermediate that is high in energy and highly reactive. This nitrene can undergo non-selective and selective reaction for the formation of *C-N* bond. Due to the reactivity and instability of free nitrenes, development of stabilized nitrene via metal complexes, named metal-nitrenes, has been studied and reported for more selective reactions.

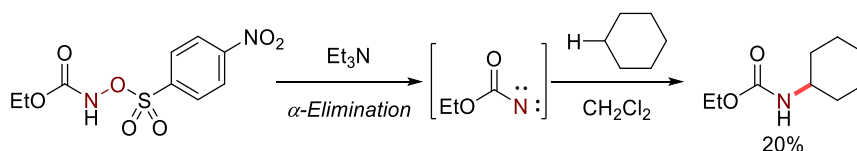
One of the earliest examples of *C-N* formation via a proposed free nitrene intermediate was reported by Appel and Büchner in 1962.¹²¹ The authors described the decomposition of the hydroxylamine-*O*-sulfonic acid in sodium methoxide/methanol in presence of 1,4-butadiene (Scheme 1-41).



Scheme 1-41: Formation of pyrroline from decomposition of hydroxylamine-*O*-sulfonic acid

After distillation a mixture of methanol and pyrroline was obtained. Two mechanisms were envisaged, diradical or electrophilic addition, and as of today, this 1,4-addition mechanism remains unclear. Due to the high instability of nitrene species, the formation of the *NH* nitrene seems unlikely.

In 1965, Lwowski and Maricich conducted a comparison study between the photolysis of the ethyl azidoformate and the α -elimination of the *N-p*-nitrobenzenesulfonyurethane (Scheme 1-42).¹²² In the presence of Et_3N and cyclohexane in CH_2Cl_2 , the *C-H* activation product was found in 20% from the cleavage of the *N-O* bond (versus 6% obtained for the photolysis).

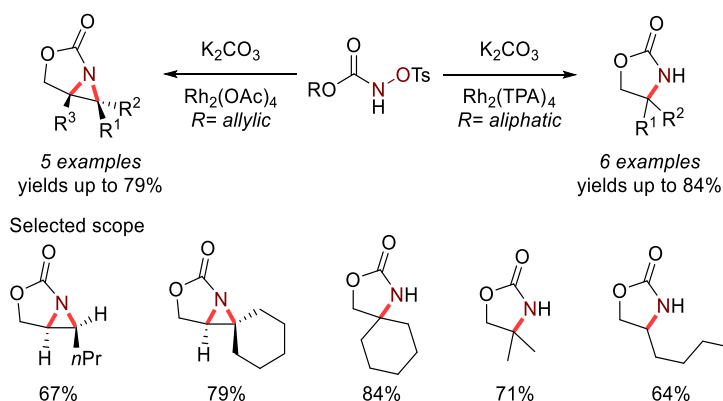


Scheme 1-42: Carbethoxynitrene formation by α -elimination

¹²¹ Appel, R.; Büchner, O. *Angew. Chem.* **1962**, 12, 430.

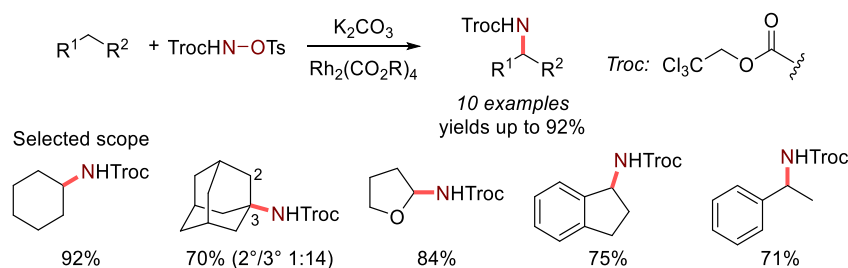
¹²² Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, 87, 3630.

Free nitrenes are highly unstable and reactive resulting to a low yield for the desired products due to a high number of degradation pathways. To overcome these issues development of stable metal derivatives of the free nitrene, metal-nitrenes, have been developed. Various nitrene precursors have been used in such reactions. Notably, in 2005, the Lebel group reported the use of *N*-tosyloxycarbamates as metal-nitrene precursors.¹²³ Indeed, in the presence of di-rhodium catalysts and an inorganic base, the cleavage of the *N*-O bond resulted to the formation of a metal-nitrene intermediate. The stabilization of the nitrene as a metal-nitrene allowed for a longer-lived reactive intermediate that reacted via a C-H activation or aziridination pathways. Examples of 3-oxa-1-azabicyclo[3.1.0]hexan-2-ones and oxazolidinones were reported (Scheme 1-43).



Scheme 1-43: C-H activation and aziridination of metal-nitrene

Several years later, the same group published the first intermolecular rhodium-catalyzed C-H amination of *N*-tosyloxycarbamate (Scheme 1-44).¹²⁴ To achieve high yields for the C-H amination, the nitrogen needed to be protected and stabilized by the 2,2,2-trichloroethoxycarbonyl (Troc).



Scheme 1-44: First intermolecular rhodium-catalyzed C-H amination of *N*-tosyloxycarbamate

Excess of the aliphatic alkanes were necessary to efficiently react with the metal-nitrene. The C-H insertion of non-activated C-H bond ranged from 39 to 92%, with a selectivity for tertiary over secondary positions. With activated substrates (α of heteroatom or benzylic position) five equivalents were also used and the yields were higher. Several mild and easy conditions were developed to the deprotection of the Troc group including indium¹²⁵ or zinc metal catalyzed variants.¹²⁶ This example of

¹²³ Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198.

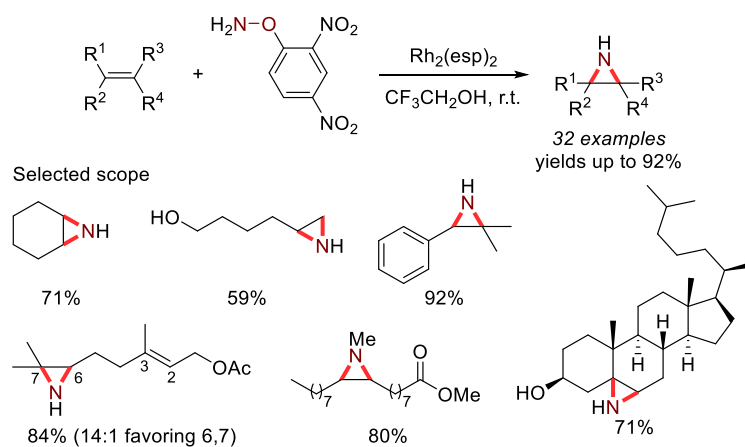
¹²⁴ Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639.

¹²⁵ Mineno, T.; Choi, S. R.; Avery, M. A. *Synlett* **2002**, 883.

¹²⁶ Just, G.; Grozinger, K. *Synthesis* **1976**, 457.

nitrene formation via *N*-O bond cleavage did not require the use of hypervalent iodine which is the most common method for the in-situ formation of nitrene.¹²⁷

The formation of metal-nitrenes was previously limited by the nitrogen requiring a strong electron withdrawing group substituent, however in 2014, the groups of Ess, Kürti and Falck conjointly reported the direct formation of unprotected N-H and N-Me aziridines using *O*-(2,4-dinitrophenyl)hydroxylamine as the starting material.¹²⁸ The authors used Rh₂(esp)₂, a catalyst specifically designed for C-H amination reactions.¹²⁹ DFT calculations confirmed that the formation of the triplet nitrene (arising from the interconversion of the singlet-spin nitrene) was the lowest in energy and multiple N-H and N-Me aziridines were obtained (*Scheme 1-45*).



Scheme 1-45: Direct synthesis of unprotected aziridines

More than thirty aziridines were isolated with a large functional group tolerance (ester, ketone and alcohol for example). Aliphatic mono-, di- and trisubstituted olefins along with di-, tri- and tetra-substituted styrenes were azirinated with only 1.5 equiv. of the hydroxylamine. When several olefins were present on the starting material, the aziridination was regioselective for the most substituted one. The same groups later published the intramolecular C-H arene amination using the same catalyst and *O*-tosylhydroxylamine derivatives.¹³⁰

With the importance of *N*-containing heterocycles in bioactive molecules,¹³¹ the formation of *C*-*N* bond via metal-nitrene formation continues to be a topic of high interest in the synthetic community.

1.4.2.3. Metal catalyzed *N*-O bond cleavage

¹²⁷ Wirth, T. *Angew. Chem., Int. Ed.* **2005**, 44, 3656.

¹²⁸ Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. *Science* **2014**, 343, 61.

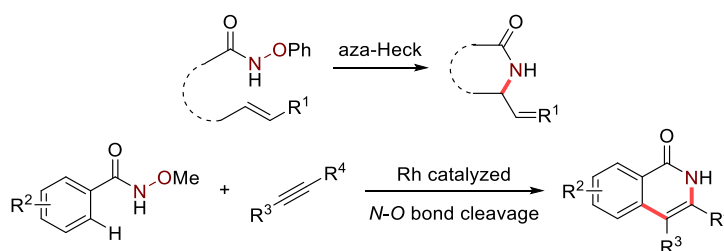
¹²⁹ Espino, C. G.; Williams Fiori, K.; Kim, M.; Du Bois, J. J. *Am. Chem. Soc.* **2004**, 126, 15378.

¹³⁰ Paudyal, M. P.; Adebessin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck J. R. *Science* **2016**, 353, 1144.

¹³¹ Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257.

Two other C-N bond forming reactions from hydroxamic acids must also be discussed due to their importance and breakthrough: indeed, these two methods allowed for the synthesis of N-heterocycles of interests and more than 500 publications derived for these activation manifolds.

In 2016, Watson and co-workers reported the first aza-Heck coupling reaction of hydroxamate esters (that was previously limited to oximes¹³²) for lactam synthesis (*Scheme 1-46*).¹³³ To suppress the possible Lossen degradation pathway, the authors used an electron-deficient phosphine ligand with a Pd(II) catalyst. This ligand is known to facilitate the N-O oxidative addition along with the stabilization of the different palladium intermediates. Multiple lactams including bicyclic and spirocyclic variants were obtained in high yields.



Scheme 1-46: Metal catalyzed N-O bond cleavage

The Fagnou group reported in 2010, the first isoquinolone synthesis via Rh(III) catalyzed N-O bond cleavage (*Scheme 1-46*).¹³⁴ In this manuscript, the authors proposed a Rh(III) catalyzed concomitant N-O bond cleavage and C-C bond formation. This paper unlocked the Rh(III) catalyzed C-H activation of hydroxamic acids¹³⁵ and diverse partners were reported, including alkenes, diazo compounds, and chloro-amines for example along with different metal catalysts. For both reactions, the novelty was using hydroxamic acid derivatives for their incorporation into heterocycles.

In this first chapter, hydroxylamine and hydroxamic acids chemistry was summarized. Then, current syntheses of N-oxyureas and N-oxyhydantoins were described along with previous Cope-type hydroamination and aza-Lossen rearrangement. Finally, formation of C-N bonds via the cleavage of precursors containing N-O bonds was reviewed. In the next chapters new methodologies, based on the chemistry previously presented, will be described.

¹³² Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. *Chem. Sci.* **2017**, 8, 5248.

¹³³ Shuler, S. A.; Yin, G.; Krause, S. B.; Vesper, C. M.; Watson, D. A. *J. Am. Chem. Soc.* **2016**, 138, 13830.

¹³⁴ Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, 132, 6908.

¹³⁵ Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, 44, 1155.

Chapter 2: Oxygen Substituted Isocyanates

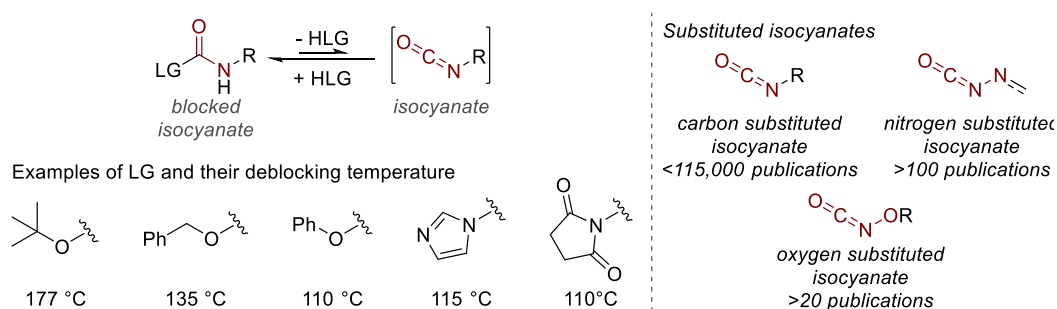
In this chapter, previous work involving blocked (or masked) oxygen-substituted isocyanates (O-isocyanates) is presented, from the early studies to the current formation of the O-isocyanates. Then, the work performed on the controlled formation of these highly reactive intermediates and their

selective reactivity is presented with the synthesis of *N*-oxyureas via addition reaction and heterocycles via cascade reactions.

2.1. Isocyanates and heteroatom isocyanates

2.1.1. Carbon substituted isocyanates

Isocyanates are an important class of heterocumulenes, discovered by Wurtz in 1848.¹³⁶ Since, then they have been extensively studied, with more than 2,500 commercially available isocyanates and over 115,000 publications.¹³⁷ Isocyanates are used as building blocks in pharmaceuticals, paints... and perhaps their most important application are in polymers.¹³⁸ The major disadvantage of using isocyanates is their inherent toxicity; they can cause sensitivity and carcinoma over prolonged exposure. Another intrinsic problem is their kinetic stability: isocyanates dimerize and polymerize overtime to a complex mixture of products. To overcome these issues, blocked or masked isocyanates have been developed (Scheme 2-1) where a thermal or chemical equilibrium releases the isocyanate *in-situ* from carbamates or ureas.¹³⁹



Scheme 2-1: Blocked (or masked) isocyanates and heteroatom substituted isocyanates

Different leaving groups have been developed with specific deblocking temperature or specific catalysis (acid, base or metal) to release the free isocyanate *in-situ*. This strategy allows for 1) the controlled release of the isocyanate resulting in the control of its concentration, which leads to a better reactivity and selectivity; and 2) safer, stable, non-toxic and easily handled starting materials. This approach gives access to more complex isocyanates, including heteroatom substituted isocyanates, an underdeveloped subclass of these reactive intermediates.

2.1.2. Nitrogen-substituted isocyanates (*N*-isocyanates)

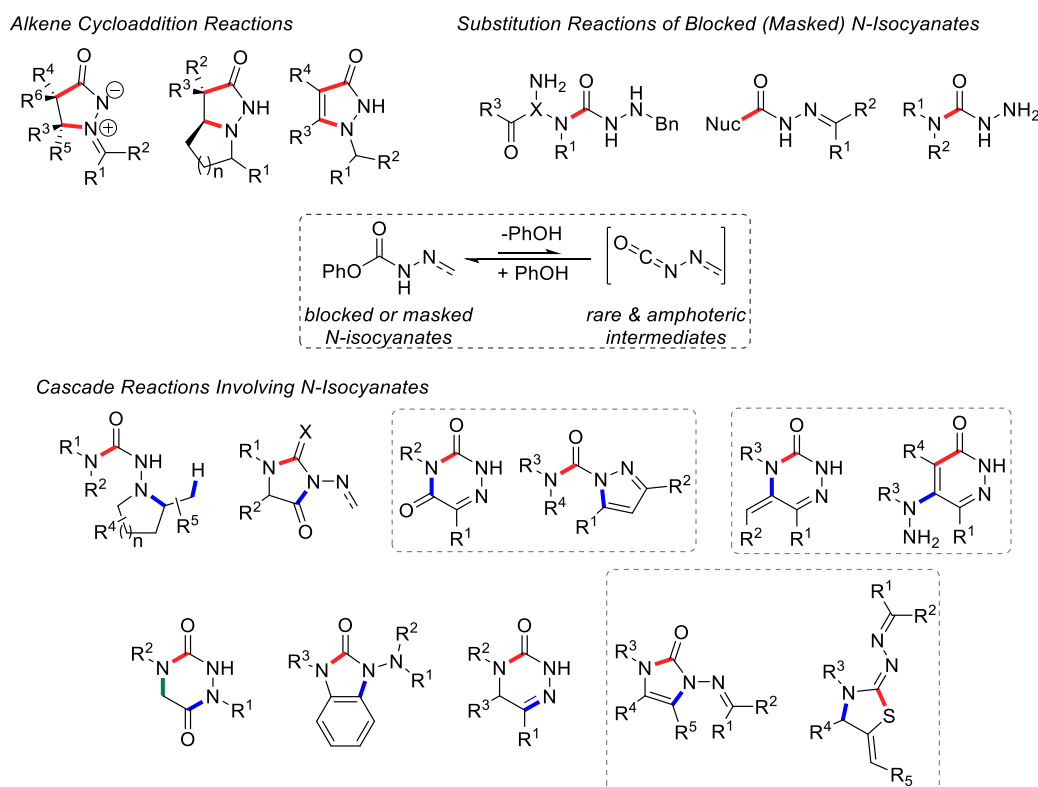
¹³⁶ Wang, Z. *Comprehensive Organic Name Reactions and Reagents*; Wiley: New York, **2009**, 1772-1774.

¹³⁷ Substructures search on Reaxys and «isocyanate» as key word search on Scifinder (June 2019).

¹³⁸ Engels, H.-W.; Pirkel, H.-G.; Albers, R.; Albach, R. W.; Krause, J.; Hoffmann, A.; Casselmann, H.; Dormish, J. *Angew. Chem., Int. Ed.* **2013**, 52, 9422.

¹³⁹ Delebecq, E.; Pascault, J.-P.; Boutevin, B.; Ganachaud, F. *Chem. Rev.* **2013**, 113, 80.

One of the most common heteroatom-substituted isocyanates are *N*-isocyanates, yet there are fewer than hundred publications on this subclass of reagents. Due to the presence of a nucleophilic nitrogen atom and an electrophilic isocyanate moiety, *N*-isocyanates are highly unstable and dimerize at $-40\text{ }^{\circ}\text{C}$.¹⁴⁰ Pioneering work from Stollé and Lwowski used carbamoyl azides as starting materials, allowing formation of the *N*-isocyanate via Curtius rearrangement.¹⁴¹ The formation and chemistry of *N*-isocyanates have been reviewed recently,^{142,140} and including the work by our group. The Beauchemin group has developed mild and selective methods for generation of *N*-isocyanates via thermolysis of suitable blocked (masked) isocyanate precursors, and exploited this approach to enable cycloaddition, substitution and cascade reactions (Scheme 2-2).



Scheme 2-2: Summary of the *N*-isocyanate chemistry developed by the Beauchemin group

With this expertise, the Beauchemin group turned its attention into *O*-isocyanates, a class of rarer heteroatom-substituted isocyanates (less than twenty publications). *O*-Isocyanates are a unique class due to the weak *N*-*O* bond and are underdeveloped. Contributions in this area will be presented in the following section.

¹⁴⁰ Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, *15*, 1745.

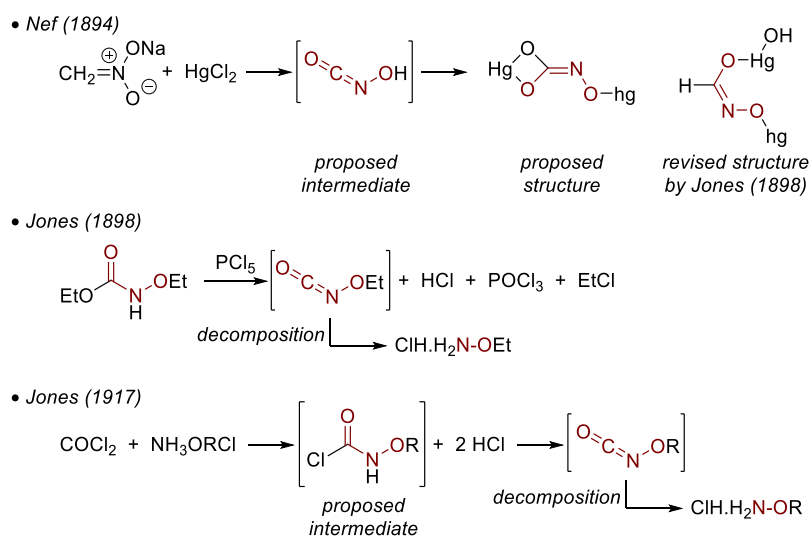
¹⁴¹ (a) Stollé, R. *J. Prakt. Chem.* **1927**, *116*, 192. (b) Stollé, R. *J. Prakt. Chem.* **1928**, *117*, 185. (c) Lwowski, W.; DeMauriac, R.; Mattingly, T. W. Jr.; Scheiffele, E. *Tetrahedron Lett.* **1964**, *5*, 3285. (d) Lwowski, W.; DeMauriac, R. A.; Murray, R. A.; Lunow, L. *Tetrahedron Lett.* **1971**, *12*, 425. For an earlier review on *N*-isocyanates, see: (e) Kurz, M.; Reichen, W. *Tetrahedron Lett.* **1978**, *19*, 1433.

¹⁴² Vincent-Rocan, J.-F.; Beauchemin, A. M. *Synthesis* **2016**, *48*, 3625.

2.1.3. Oxygen-substituted isocyanates (O-isocyanates)

2.1.3.1. Early examples of O-isocyanates

The first reports on O-isocyanates date back to over a century: indeed, in 1894, Nef proposed the formation of the basic mercury salt of carbon dioxide oxime (HO-N=C=O) arising from the reaction of mercuric chloride and sodium isonitromethane (Scheme 2-3).¹⁴³ In 1898, Jones revised the structure obtained by Nef to a basic mercury salt of formhydroximic acid.¹⁴⁴ In the same communication, Jones reported the reaction between the ethyl ethoxycarbamate and the phosphorus pentachloride that resulted supposedly in the formation of the O-Et isocyanate (EtO-N=C=O). This intermediate was not isolated and decomposed in presence of water to form the O-ethylhydroxylamine hydrochloride. Later, in order to directly (or indirectly) isolate RO-N=C=O, Jones and Neuffer enlarged the scope of the reaction between hydroxy urethanes and phosphorus pentachloride.¹⁴⁵ Several derivatives were studied, all resulting in the hydrolysis of the intermediate to the corresponding oxylamine hydrochlorides. They also studied the reaction of phosgene gas with diverse hydroxylamine derivatives, and were only able to isolate the hydroxylamine hydrochloride salts. They suggested the formation of a N-oxycarbamoyl chloride that could expel HCl to form an O-isocyanate.



Scheme 2-3: Early examples of O-isocyanates

2.1.3.2. The structure of O-isocyanates

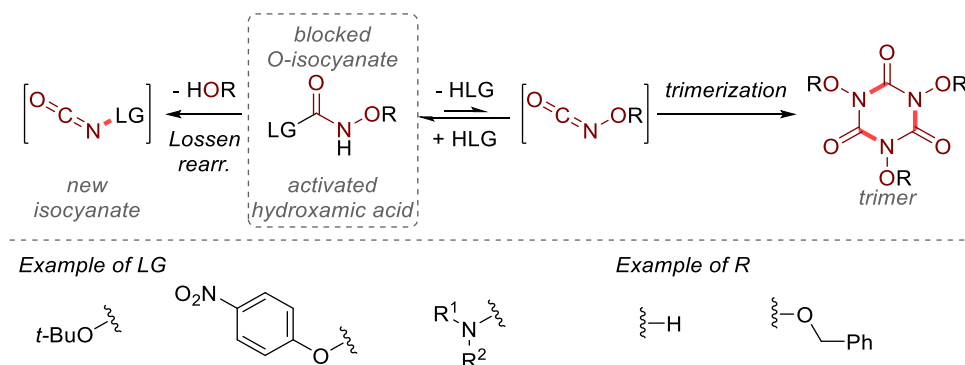
The chemistry of O-isocyanates remains unexplored due to two known side reactions: the Lossen rearrangement of the masked O-isocyanate starting material and the trimerization of the free O-isocyanate. Indeed, various carbonyl derivatives of hydroxylamines can be seen as a blocked /

¹⁴³ Nef, J. U. *Liebigs Ann. Chem.* **1894**, 280, 263.

¹⁴⁴ Jones, L. W. *J. Am. Chem. Soc.* **1898**, 20, 1.

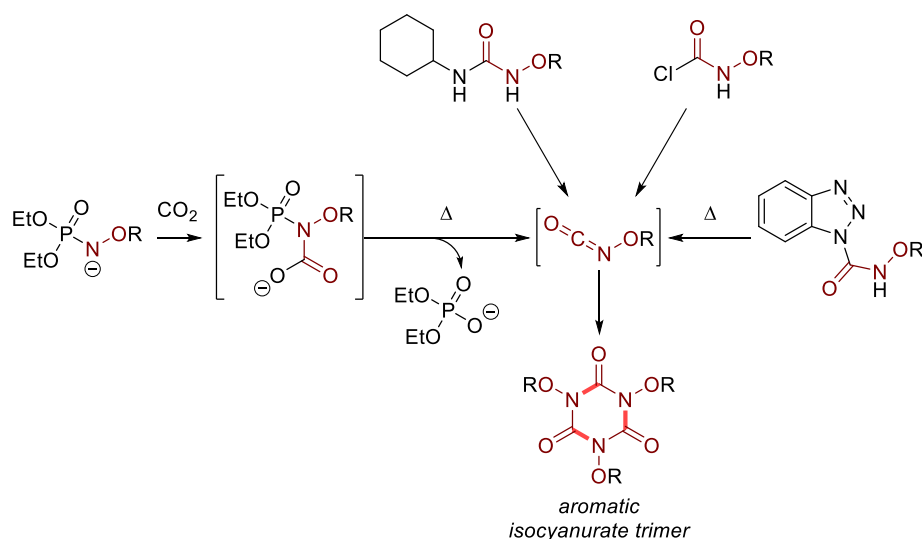
¹⁴⁵ Jones, L. W.; Neuffer, L. *J. Am. Chem. Soc.* **1917**, 39, 652.

masked *O*-isocyanates, are frequently used to perform the Lossen rearrangement due to the weak *N*-*O* bond (Scheme 2-4).¹⁴⁶ The leaving groups/migrating groups in this case are mostly alcohols (few examples are amines, see 1.4.1.1) and this side-reaction results in the formation of a new unwanted isocyanate.



Scheme 2-4: Side reactions of *O*-isocyanates

O-Isocyanates are amphoteric (presence of a somewhat nucleophilic oxygen atom and an electrophilic carbonyl) and trimerize upon heating or under basic conditions to form the aromatic isocyanurate trimer that can be isolated. Different hydroxylamine derivatives have been used to access the free *O*-isocyanate for isolation and characterization, however only the trimerization product was obtained (Scheme 2-5).¹⁴⁷ The trimer formation was, for years, the «proof» of the formation of *O*-isocyanates.



Scheme 2-5: Formation of the isocyanurate trimer via formation of *O*-isocyanate

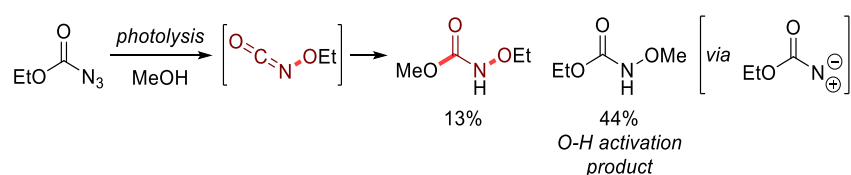
¹⁴⁶ (a) Hoshino, Y.; Okuno, M.; Kawamura, E.; Honda, K.; Inoue, S. *Chem. Commun.* **2009**, 17, 2281. (b) AbdelHafez, E.-S. M. N.; Aly, O. M.; Abuo-Rahma, G. E-D A. A.; King, S. B. *Adv. Synth. Catal.* **2014**, 356, 3456. (c) Ohtsuka, N.; Okuno, M.; Hoshino, Y.; Honda, K. *Org. Biomol. Chem.* **2016**, 14, 9046.

¹⁴⁷ For examples of trimerization of *O*-isocyanate intermediates, see: (a) McKay, A. F.; Garmaise, D. L.; Paris, G. Y.; Gelblum, S. *Can. J. Chem.* **1960**, 38, 343. (b) Staab, H. A.; Benz, W. *Angew. Chem.* **1961**, 73, 657. (c) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, 1, 351. (d) Randolph, M. T.; Hendrick, T. J. *J. Org. Chem.* **1965**, 30, 1268. (e) Butula, I.; Takač, M. J. -M. *Croat. Chem. Acta* **2000**, 73, 569. (f) Kos, I.; Takač, M. J. -M.; Butula, I.; Biruš, M.; Maravić-Vlahoviček, G.; Dabelić, S. *Acta Pharm.* **2013**, 63, 174.

2.1.3.3. Formation of O-isocyanates

2.1.3.3.1. From photolysis of azidoformates

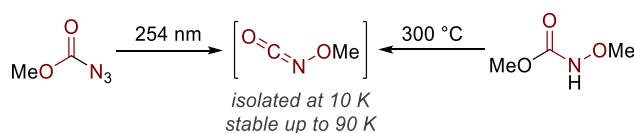
In 1964, Lwowski and co-workers studied the photolysis of ethyl azidoformate, an example of «rigid azides»¹⁴⁸ that allegedly do not undergo rearrangement upon decomposition (other examples included arylsulfonyl azides and certain carbamoyl azides).^{141c} When the photolysis was performed in pure hydrocarbon solvent no products of rearrangement were obtained. However, when the photolysis was performed in MeOH at -10 °C, methyl ethoxycarbamate was obtained in 13% yield, presumably via a proposed O-isocyanate intermediate accessed from a Curtius-type rearrangement (Scheme 2-6). The rearrangement product was obtained in low yield due to the side-reaction of the nitrene intermediate with MeOH via an O-H insertion mechanism.



Scheme 2-6: Photolysis of ethyl azidoformate

At the same time, Kreher and Bockhorn published the same reaction as Lwowski, however, their photolysis was performed in refluxing alcohol and only the O-H insertion was produced.¹⁴⁹ No evidence for the formation of EtO-N=C=O was reported.

Over the years, various studies on the photolysis of azidoformates reported the corresponding O-isocyanates as one of the products of the decomposition of the nitrene intermediate.¹⁵⁰ However, Teles and Maier were the first to successfully form and isolate the methoxyisocyanate (Scheme 2-7). Indeed, after photolysis or thermolysis, the O-isocyanate was kept in an Ar/N₂ matrix at 10 K for several hours and carefully heated to 90 K where decomposition started to happen. To probe the presence of the free O-isocyanate, IR was taken and the stretching peak for the N=C=O was found to be 2204 cm⁻¹, characteristic for the isocyanate moiety.¹⁵¹



Scheme 2-7: Formation and isolation of methoxyisocyanate

¹⁴⁸ Curtius, T. *Angew. Chem.* **1914**, 27, 213.

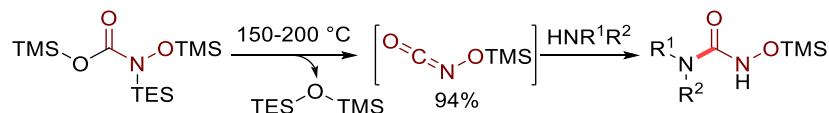
¹⁴⁹ Kreher, R.; Bockhorn, G. H. *Angew. Chem., Int. Ed.* **1964**, 3, 589.

¹⁵⁰ For selected examples see: (a) Wilde, R. E.; Srinivasan, T. K. K.; Lwowski, W. *J. Am. Chem. Soc.* **1971**, 93, 860. (b) Chavez, T. A.; Liu, Y.; Toscano, J. P. *J. Org. Chem.* **2016**, 81, 6320. (c) Wan, H.; Xu, J.; Liu, Q.; Li, H.; Lu, Y.; Abe, M.; Zeng, X. *J. Phys. Chem. A* **2017**, 121, 8604. (d) Li, H.; Wu, Z.; Li, D.; Wan, H.; Xu, J.; Abe, M.; Zeng, X. *Chem. Commun.* **2017**, 53, 4783

¹⁵¹ Teles, J. H.; Maier, G. *Chem. Ber.* **1989**, 122, 745.

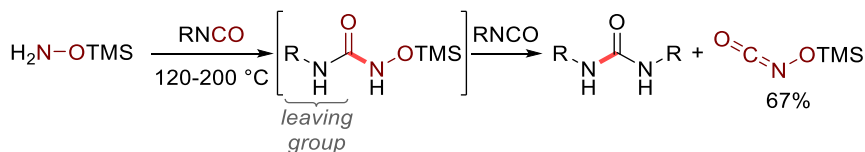
2.1.3.3.2. From thermolysis

The formation of the TMSO-NCO has been reported via thermolysis of carbamate and urea: under high temperature, a silyl protected carbamate released the *O*-isocyanate in a 94% yield. In presence of an external amine, the intermediate was trapped and *N*-oxyureas were obtained (Scheme 2-8).¹⁵²



Scheme 2-8: Thermolysis of trimethylsilyl (triethylsilyl)((trimethylsilyl)oxy)carbamate

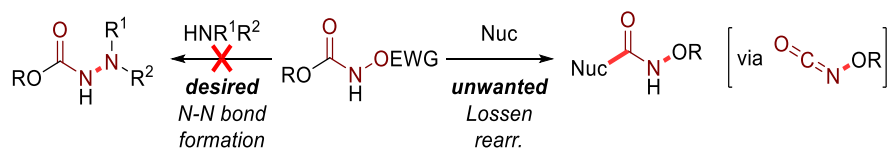
In 1988, Mormann and Leukel reported the isolation of the TMSO-NCO via *in-situ* formation of a *N*-oxyurea (Scheme 2-9).¹⁵³ Under these harsh conditions, the *N*-oxyurea was formed reversibly via addition of *O*-(trimethylsilyl)hydroxylamine onto an isocyanate, and the adduct acted as a blocked *O*-isocyanate. Indeed, the amine group behaved as a leaving group, and released the *O*-isocyanate. The free amine was then trapped with a second equivalent of isocyanate. The authors claimed the isolation of the free *O*-isocyanate and reported its ¹H NMR. Nevertheless, due to the instability and the facile trimerization of *O*-isocyanate, it was more likely that the obtained product was the corresponding trimer.



Scheme 2-9: Formation of TMSO-NCO via thermolysis of *N*-oxyurea

2.1.3.3.3. Via unexpected Lossen rearrangement

Over the years, many groups attempted the formation of *N*-*N* bonds via the cleavage of a weak *N*-*O* bonds of activated carbamates (masked *O*-isocyanates). However, in all cases, the oxygen analogue of the Lossen rearrangement (oxa-Lossen rearrangement) was the more favourable pathway resulting in the formation of *N*-oxyureas via the formation of a new *O*-isocyanate via the migration of an alcohol group (Scheme 2-10). The formation of the *N*-*N* bonds for carbonylhydrazine derivatives synthesis using activated *O*-acyl hydroxylamines remains unpublished.

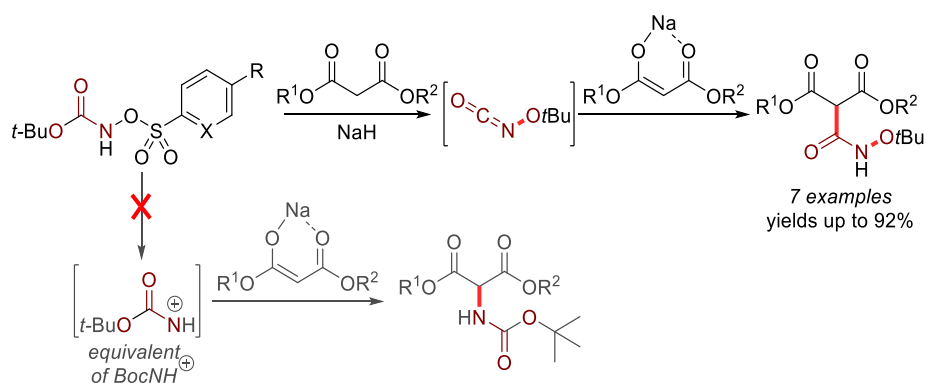


Scheme 2-10: Unwanted Lossen rearrangement of *O*-acyl hydroxylamine

¹⁵² Sheludyakov, V. D.; Dmitrieva, A. B.; Kirilin, A. D.; Chernyshev, E. A. *Zh. Obshch. Khim.* **1983**, 53, 706.

¹⁵³ Mormann, W.; Leukel, G. *Synthesis* **1988**, 990.

For example, Hanessian and Johnstone reported the formation of C-N bonds via unexpected oxa-Lossen rearrangement of *N*-*tert*-butoxycarbonyl-*O*-sulfonyl-substituted hydroxylamines in presence of soft enolates (Scheme 2-11).¹⁵⁴ The authors expected the *N*-*tert*-butoxycarbonyl-*O*-sulfonyl-substituted hydroxylamines to be the starting material for the electrophilic NHBoc via departure of the tosyl derivative group. Electrophilic aminations have previously been reported using *N*-tosyloxycarbamate derivatives,¹⁵⁵ and the reactivity often suffered from lower yields and harsh conditions. Yet, under these milder conditions, the formation of *tert*-butyl *O*-isocyanate via oxa-Lossen was exclusive and only products coming from the nucleophilic carbon addition onto the *O*-isocyanate were reported. Other examples of formation C-N bond have also been reported for the synthesis of cyclic urea derivatives using the same oxa-Lossen rearrangement.¹⁵⁶



Scheme 2-11: Formation of C-N bond via oxa-Lossen rearrangement

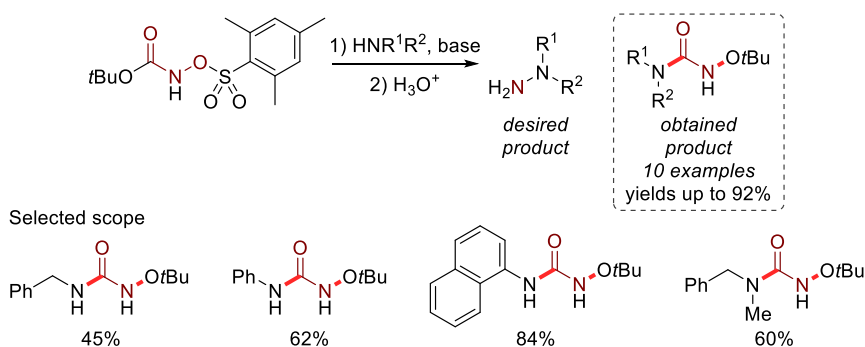
In 2010, Priefer and co-workers studied the substitution/deprotection of the *tert*-butylmesitylenesulfonyloxycarbamate for the synthesis of free hydrazine.¹⁵⁷ During the course of their study, the authors only obtained the corresponding *N*-*tert*-butyloxyureas via an unwanted oxa-Lossen rearrangement pathway (Scheme 2-12). The isolated yields of the *N*-*tert*-butyloxyurea products ranged from moderate to good. Facile deprotection of the *tert*-butyl group using acidic hydrolysis conditions led to the formation of the free *N*-hydroxyureas in moderate to good yields.

¹⁵⁴ Hanessian, S.; Johnstone, S. *J. Org. Chem.* **1999**, *64*, 5896.

¹⁵⁵ (a) Genet, J. P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359. (b) Zheng, N.; Armstrong, J. D.; McWilliams, C.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817.

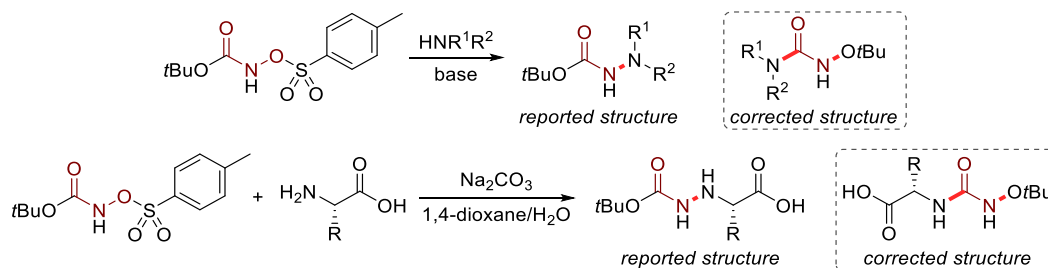
¹⁵⁶ Fioravanti, S.; Marchetti, F.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2003**, *5*, 1019.

¹⁵⁷ Krause, J. G.; Leskiw, B. D.; Emery, M. L.; McGahan, M. E.; McCourt, M. P.; Priefer, R. *Tetrahedron Lett.* **2010**, *51*, 3568.



Scheme 2-12: Synthesis of *N*-hydroxyureas via unwanted oxa-Lossen rearrangement

Baburaja and Thambidurai published two attempts of electrophilic *N*-amination of amino acid derivatives for the synthesis of β -Boc-alkylhydrazines and optically pure terminal Boc-hydrazino acids.¹⁵⁸ The proposed *N-N* bond formation derived from the base-catalyzed cleavage of the *N-O* bond of activated carbamate. However, a few years later, the two publications were corrected: indeed, formation of *N-O* bond via oxa-Lossen rearrangement was the observed pathway and the products obtained were in fact *N*-oxyureas. This misassignment highlights that due to the high heteroatom content of these products, it can be challenging to assign the appropriate structure to the reaction products.



Scheme 2-13: Synthesis of *N*-oxyureas via oxa-Lossen rearrangement

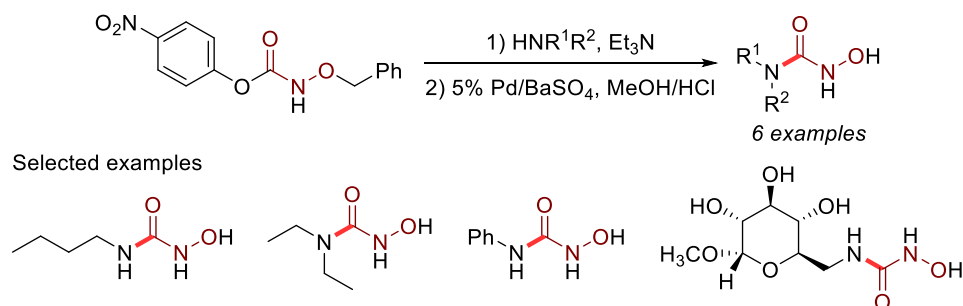
2.1.3.3.4. Examples that likely go through an *O*-isocyanate

Over the years, different publications involved activated carbamates bearing good leaving groups (e.g. *p*-nitrophenol) as starting materials in substitution reactions were reported. Those examples did not specify the reactive intermediate and two different pathways can be envisaged. The formation of an *O*-isocyanate intermediate from the departure of the *p*-nitrophenol leaving group is the first possibility. On the other hand, direct addition/elimination via the formation of a tetrahedral intermediate can also be imagined. Due to the lack of mechanistic study, the operating mechanism is only speculative. However, the intermediacy of *O*-isocyanates seems likely,⁵² and according to the blocked (masked)

¹⁵⁸ (a) Baburaj, T.; Thambidurai, S. *Synlett* **2011**, 1993. For the correction see: Baburaj, T.; Thambidurai, S. *Synlett* **2015**, 1137. (b) Baburaj, T.; Thambidurai, S. *Tetrahedron Lett.* **2012**, 53, 2292. For the correction see: *Tetrahedron Lett.* **2014**, 54, 561.

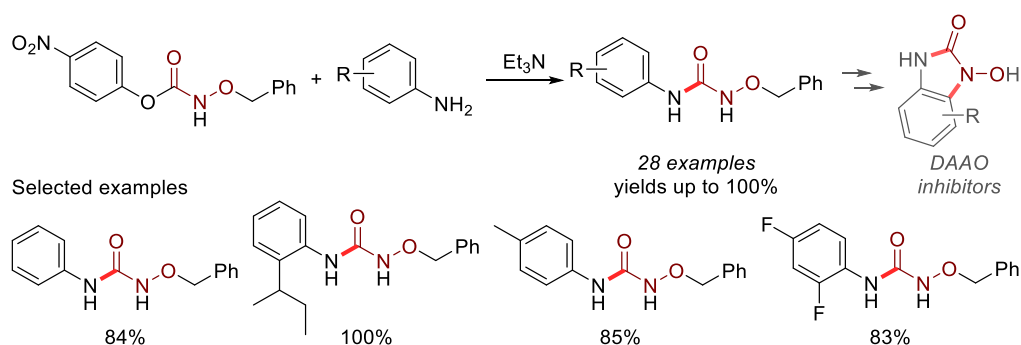
isocyanate literature, such reagents can be described as blocked (masked) isocyanates regardless of the operating mechanism.¹³⁹

King and co-workers published a facile synthesis of *N*-hydroxyureas using *p*-nitrophenyl (benzyloxy)carbamate (*Scheme 2-14*).¹⁵⁹ In presence of an amine and triethylamine, substitution of the *p*-nitrophenol group was effective and the corresponding *O*-benzyl-*N*-oxyureas were isolated with yields between 84-98%. Facile debenzylation using Rosenmund catalyst was achieved, and the *N*-hydroxyureas were obtained in 50-100% isolated yields.



Scheme 2-14: Synthesis of O-benzylhydroxylamines

During a SAR study toward effective inhibitors of D-amino acid oxidase (DAAO), a series of 1-(benzyloxy)-3-phenylureas were obtained as intermediates for the synthesis of 1-hydroxy-1H-benzo[d]imidazol2(3H)-ones (*Scheme 2-15*).¹⁶⁰ Using the same type of conditions as King and co-workers, aniline derivatives underwent substitution reactions to form twenty-eight examples of *O*-benzyl-*N*-oxyureas in good to excellent yields. After cyclization and debenzylation, 1-hydroxy-1H-benzo[d]imidazol2(3H)-ones were obtained and tested as potent DAAO inhibitors.

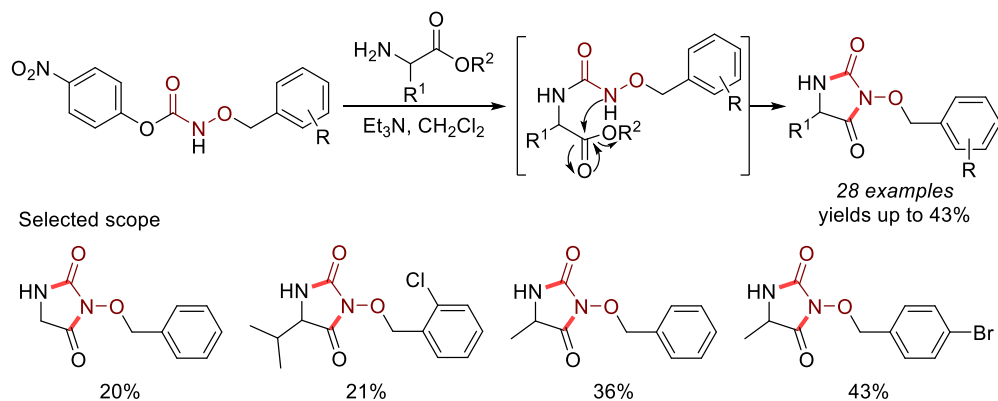


Scheme 2-15: Formation of 1-(benzyloxy)-3-phenylureas

¹⁵⁹ Parrish, D. A.; Zou, Z.; Allen, L.; Day, C. S.; King, B. *Tetrahedron Lett.* **2005**, 46, 8841.

¹⁶⁰ Berry, J. F.; Ferraris, D. V.; Duvall, B.; Hin, N.; Rais, R.; Alt, J.; Thomas, A. G.; Rojas, C.; Hashimoto, K.; Slusher, B. S.; Tsukamoto, T. *ACS Med. Chem. Lett.* **2012**, 3, 839.

Another example was the synthesis of 3-benzyloxyhydantoin derivatives via substitution/cyclization of amino esters onto *p*-nitrophenol carbamate derivatives (Scheme 2-16).¹⁶¹ After substitution, cyclization from the nitrogen atom of the hydroxylamine moiety to the ester, led to the formation of the *N*-oxyhydantoin. Several heterocycles were synthesized, but only in low to moderate yields.



Scheme 2-16: Synthesis of 3-benzyloxyhydantoin

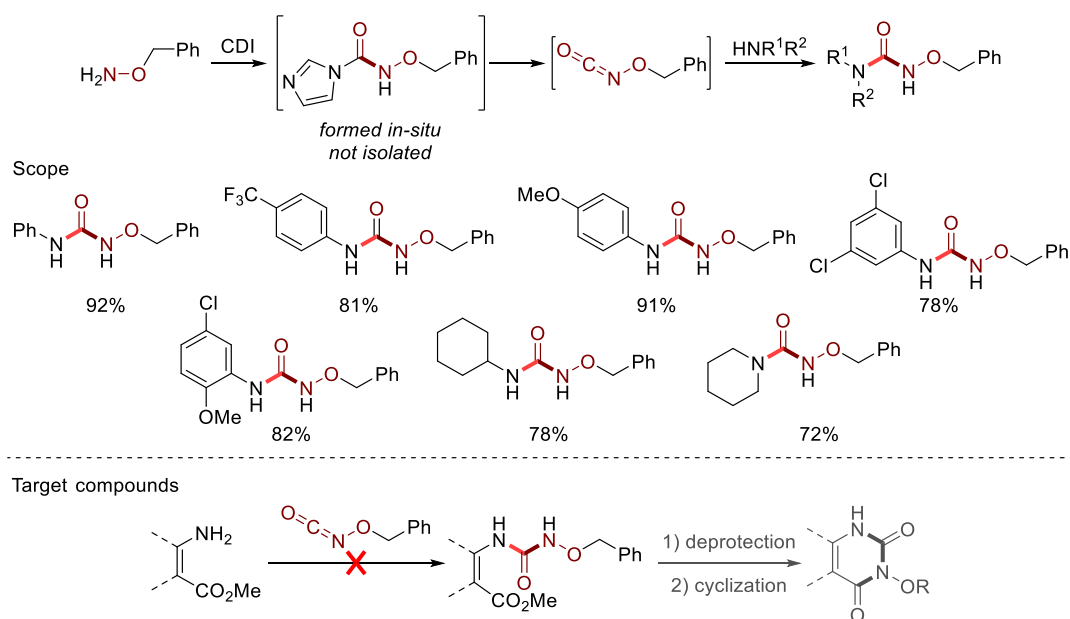
The isolated yields in this study were low and a related study performed in the Beauchemin group for the synthesis of *N*-oxyhydantoin via *O*-isocyanate chemistry can be found in section 2.3.1.

2.1.3.3.5. Cascade reaction of *O*-isocyanates

In 1994, chemists at Bristol-Myers-Squibb reported the only example of work toward a cascade reaction proposing an *O*-isocyanate.¹⁶² By slow addition of *O*-benzylhydroxylamine in a CDI solution, the *N*-(benzyloxy)-1H-imidazole-1-carboxamide was formed *in-situ*. The blocking group choice (e.g. imidazole) resulted in a blocked *O*-isocyanate intermediate too unstable for isolation. After deblocking and formation of the reactive intermediate, addition of amines resulted in the formation of *N*-oxyurea derivatives (Scheme 2-17).

¹⁶¹ Liu, J.; Zhang, K.; Mai, X.; Wei, J.; Liao, Y.; Zhong, Y.; Liu, Y.; Feng, L.; Liu, C. *Med. Chem.* **2016**, *12*, 37.

¹⁶² Romine, J. L.; Martin, S. W.; Meanwell, N. A.; Epperson, J. R. *Synthesis* **1994**, 1994, 846.



Scheme 2-17: First cascade reaction of *O*-isocyanate

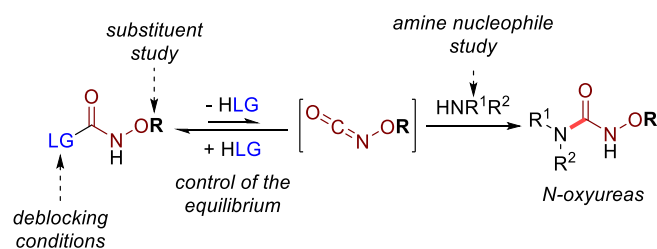
Several examples of *N*-oxyureas were reported with good to excellent isolated yields. The generalization of the method was lacking: indeed, the key nucleophile of this work, anthranilate did not react with the *O*-isocyanate and the authors were forced to use triphosgene to obtain the desired product in two steps.

In summary, *O*-isocyanates remain rarely used due to the instability of the starting materials, and their unisolable nature. In the next two sections, controlled reactivity of *O*-isocyanates is described.

2.2. Controlled reactivity of *O*-isocyanates

The work presented in this part was featured in a communication¹⁶³ and was performed in collaboration of Ryan Ivanovich and Meredith Allen. Ryan discovered the reactivity of *O*-isocyanates and was joined by Meredith and myself for the complete study and isolation of the *N*-oxyureas. I was personally, in charge of the isolation of the *N*-hydroxyureas and took part of the leaving group and nucleophiles studies with Meredith. Ryan investigated the impact of oxygen substitution on the substitution reactivity. In this study, controlled formation and substitution reactivity of *O*-isocyanate intermediates are described (Scheme 2-18).

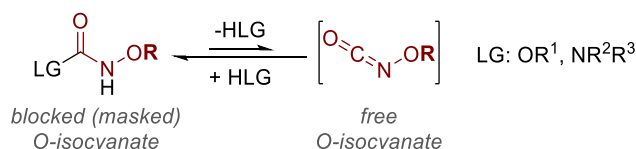
¹⁶³ Allen, M. A.; Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. *Org. Lett.* **2017**, 19, 6574.



Scheme 2-18: Substitution reactions of *O*-isocyanates

2.2.1. Reaction optimization: leaving group study

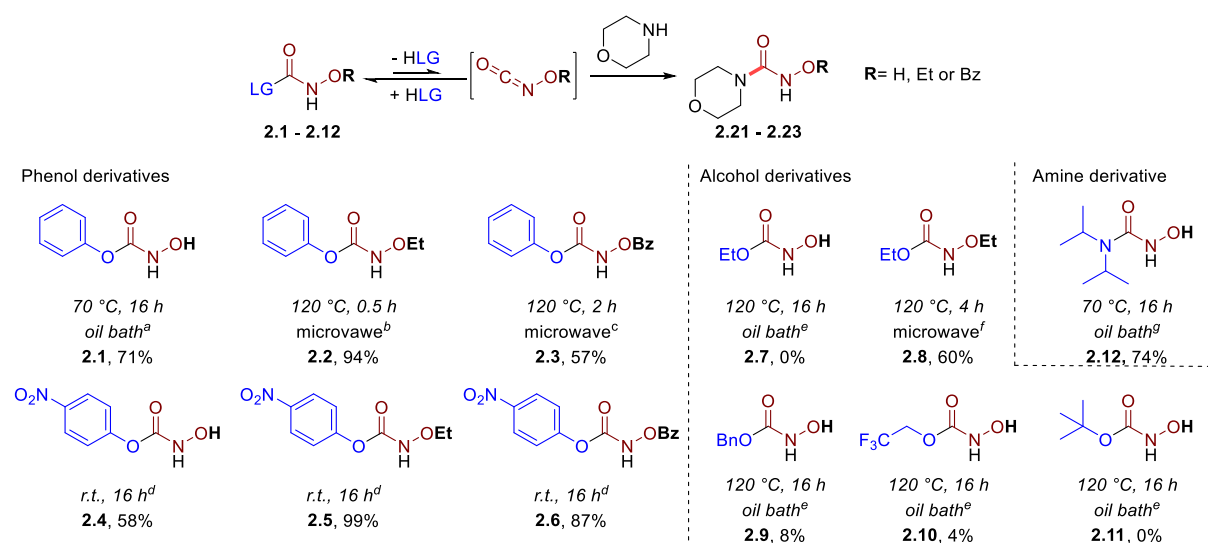
As previously explained, the structure of the leaving group in the masked isocyanate (e.g. hydroxamic acid derivative) is crucial: indeed, each blocked *O*-isocyanate precursor has a specific deblocking temperature and/or the deblocking conditions in order to control the concentration of the isocyanate intermediate at any time. The proposed mechanism is the departure of the leaving group that generates the corresponding *O*-isocyanates *in-situ* and it is an equilibrium between the two forms (with the equilibrium leaning toward the masked *O*-isocyanate) (Scheme 2-19).



Scheme 2-19: Blocking/deblocking of *O*-isocyanates

To obtain the free *O*-isocyanates, different *N*-oxy-carbamates (phenol and alcohol leaving groups) and *N*-oxyureas (amine blocking group) were studied. In order to generalize the method developed, three different R groups were chosen: hydroxyl, ethyl and benzoate. In contrast to the Bristol-Myers-Squibb study, the activated hydroxamic acid starting materials were isolated using classical purification techniques (flash chromatography or recrystallization). These *N*-oxy-carbamates and *N*-oxyureas masked *O*-isocyanates can be stored on the bench and exposed to light and oxygen and are stable for more than 3 years, with the exception of *p*-nitrophenol derivatives (**2.4** - **2.6**) that only proved stable when stored at temperature between 2 to 8 °C. To establish the controlled formation of the *O*-isocyanates, addition reactions with morpholine as the external nucleophile were performed and the reported yields are isolated yields of the corresponding *N*-oxyureas (**2.21** – **2.23**). Optimum deblocking conditions for the different leaving group can be found in Table 2-1.

Table 2-1: Leaving group study



Conditions: ^a Carbamate (1.10 equiv), morpholine (1.00 equiv), Et₃N (0.20 equiv) in THF (0.3 M), stir in oil bath at 70 °C overnight. ^b Carbamate (1.05 equiv), morpholine (1.00 equiv) in MeCN (0.2 M), heat in μ W to 120 °C for 0.5 h. ^c Carbamate (1.00 equiv), morpholine (1.05 equiv), imidazole (0.10 equiv) in THF (0.2 M), heat in μ W at 100 °C for 3 h. ^d Carbamate (1.00 equiv), morpholine (1.00 equiv), Et₃N (1.00 equiv) in CH₂Cl₂ (0.08 M), stir at rt overnight. ^e See ^a but 120 °C. ^f See ^b but 4 h. ^g See ^a but *N*-hydroxyurea (1.10 equiv).

The different *N*-oxy-carbamates (**2.1** - **2.10**), with the exception of the *tert*-butyl *N*-hydroxycarbamate (**2.11**), and the *N*-oxyurea (**2.12**) were found to be competent blocked (masked) *O*-isocyanates with the controlled formation of the *N*-oxyurea products (**2.21** - **2.23**). A general trend can be observed: when the *N*-oxycarbamate bore a hydrogen substituent (R= OH, **2.1**, **2.4**, **2.7**, **2.9**, **2.10**, **2.11**, **2.12**), the reaction needed to be run in an oil bath to avoid degradation via trimerization/polymerization of the *O*-isocyanate intermediate. For the two other substituents, ethyl and benzoyl (R= Et or Bz, **2.2**, **2.3**, **2.5**, **2.6**, **2.8**) the reactions were performed under microwave irradiation for a shorter reaction time. Notably, the conditions were mild enough to avoid any Lossen rearrangement with the benzoyl derivatives (**2.3**, **2.6**) even if the *N*-oxycarbamate starting materials possessed a weak *N*-O bond. For most reactions, only a catalytic amount of base (Et₃N or imidazole) was necessary to achieve the reaction in good to excellent yields. However, for the case of *p*-nitrophenol carbamate (**2.4**, **2.5**, **2.6**), one full equivalent of base was needed due, likely to the acidity of the *p*-nitrophenol leaving group.

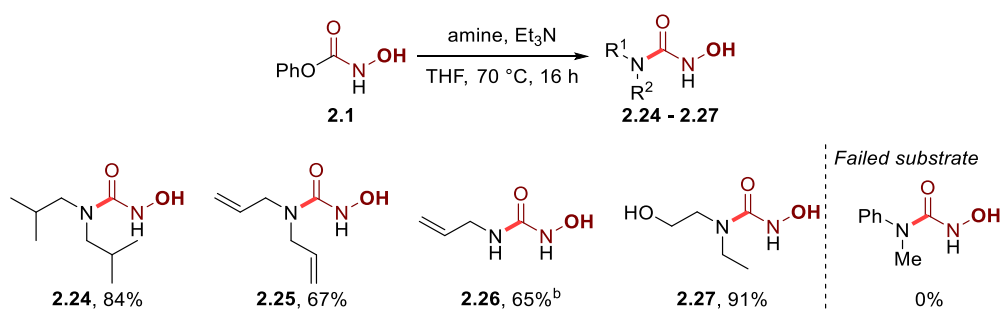
The deblocking aptitude was related to the pK_a and stability of the leaving group. Indeed, where phenol carbamates (**2.1**, **2.2**, **2.3**) (phenol pK_a: 18.0 in DMSO) required heating to form the reactive *O*-isocyanate, the *p*-nitrophenol derivatives (**2.4**, **2.5**, **2.6**) (*p*-nitrophenol pK_a: 10.8 in DMSO) released it at room temperature. Moreover, the deblocking of aliphatic alcohol groups (**2.7** – **2.11**), with pK_a higher than aromatic alcohols, remained inefficient even at higher temperature. Another key parameter of the deblocking/blocking equilibrium was its reversibility, that is required to the good control the

concentration of the *O*-isocyanate intermediate. Indeed, when the leaving group was able to add back onto the *O*-isocyanate (e.g. phenol),¹⁶⁴ the yield of the addition reaction was higher. In the other case, when reversible addition of the blocking/leaving group is difficult, (e.g. **2.11**), a more challenging controlled of the concentration resulted in no formation of the *N*-hydroxyurea. Remarkably, the *N*-hydroxyurea starting material (**2.12**) underwent the reaction in high yield, even if the conditions used for the departure, induced difficult reversible addition of the diisopropylamine. It was suggested that the harder deblocking reaction conditions of the *N*-oxyureas shifted the equilibrium toward the masked formed, resulting in a small concentration of the *O*-isocyanate at any time. Based on this study, phenol was found to be the most competent blocking/masking group for the different *O*-isocyanates and was chosen as the starting material for the rest of the work. It is noteworthy, that phenol was also identified as the most general blocking/masking group in other studies on nitrogen-substituted isocyanates.¹⁴²

2.2.2. Reaction optimization: Nucleophile study

With the optimum deblocking conditions for each carbamate, different amine nucleophiles were surveyed. The study is separated by the substituent on the oxygen of the *O*-isocyanate due to their different reactivity, resulting in different experimental conditions. In Table 2-2, the isolated yields for the different *N*-hydroxyureas can be found.

Table 2-2: Synthesis of *N*-hydroxyureas^a



^a Carbamate (1.10 equiv), amine (1.00 equiv), Et_3N (0.20 equiv) in THF (0.3 M), stir in oil bath at 70°C overnight. ^b See ^a but carbamate (1.00 equiv), amine (5.00 equiv).

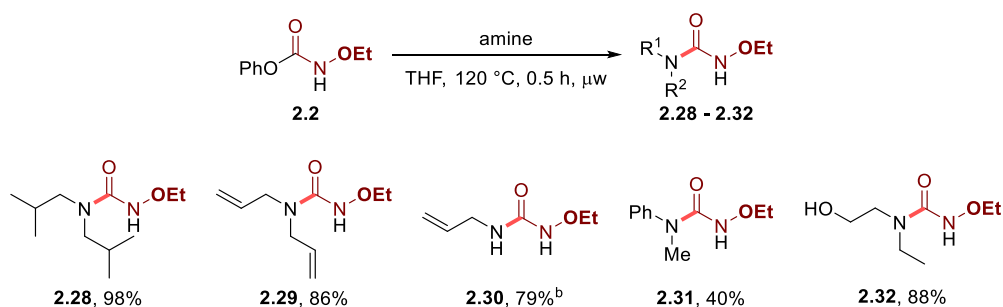
Phenyl hydroxycarbamate (**2.1**) was used as the masked HO-NCO (the simplest *O*-isocyanate) and four *N*-hydroxyureas (**2.24 - 2.27**) were obtained. Secondary aliphatic amines (**2.24**, **2.25**) proved to be competent nucleophiles. The unprotected secondary ethanolamine underwent a chemoselective substitution reaction with the most nucleophilic nitrogen atom in excellent yield (**2.27**). Due to the lower nucleophilicity of primary aliphatic amine, excess of the partner was required to reach a good isolated yield (**2.26**). Unfortunately, the weakly nucleophilic *N*-methylaniline led to no substitution and was

¹⁶⁴ Wicks, D. A.; Wicks, Z. W. Jr. *Prog. Org. Coat.* **1999**, 36, 148.

recovered. No phenyl *N*-hydroxycarbamate (**2.1**) starting material was recovered: it was suggested that the *O*-isocyanate underwent trimerization and/or polymerization with no diagnosable proton for NMR analysis.¹⁶⁵ Higher temperatures and excess of the *N*-methylaniline were tried with no formation of the desired product.

Phenyl *N*-ethoxycarbamate (**2.2**) was chosen as a model substrate for *O*-alkyl isocyanate. The optimum deblocking conditions previously found (microwave irradiation at 120 °C for 30 min) were used: indeed, the *O*-alkyl derivatives were resistant to harsher conditions. The same amines were used and the isolated yields for the corresponding *N*-ethoxyureas were found to be higher than for the *N*-hydroxyureas (**2.28**, **2.29**, **2.32**) (Table 2-3). Excess of the primary amine was still needed (**2.30**) and gratifyingly *N*-methylaniline underwent addition reaction, albeit in low isolated yield (**2.31**).

Table 2-3: Synthesis of *N*-ethoxyureas^a

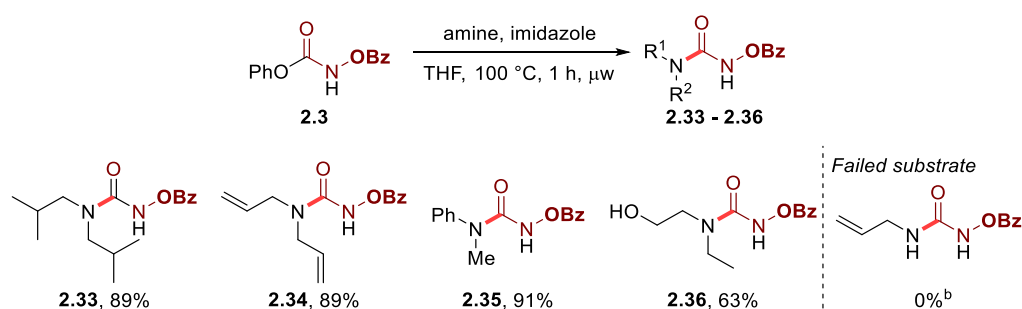


Conditions: ^a Carbamate (1.05 equiv), morpholine (1.00 equiv) in MeCN (0.2 M), heat in μW to 120 °C for 0.5 h. ^b See ^a but carbamate (1.00 equiv), amine (5.00 equiv).

Finally, the last class of *O*-isocyanate, the *O*-acyl was studied using the phenyl *N*-benzoyloxycarbamate (**2.3**) as a model substrate. Microwave irradiation was also used, however at lower temperature for a longer time (100 °C for 1 h) to circumvent any cleavage of the *N*-*O* bond. Multiple *N*-benzoylureas were isolated without trace of Lossen rearrangement. Secondary aliphatic and aromatic amines substituted *N*-benzoyloxyureas were obtained in good isolated yields (**2.33** – **2.36**).

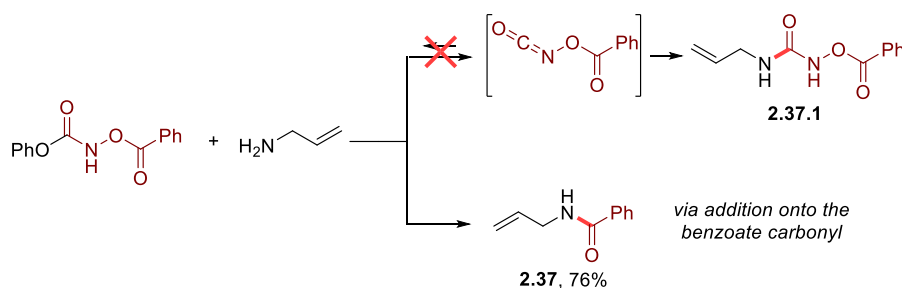
¹⁶⁵ ¹³C NMR was also performed and no carbonyl corresponding for side-product peak was found.

Table 2-4: Synthesis of *N*-benzoyloxyureas^a



Conditions: ^a Carbamate (1.00 equiv), morpholine (1.05 equiv), imidazole (0.10 equiv) in THF (0.2 M), heat in μ w at 100 °C for 1 h. ^b See ^a but carbamate (1.00 equiv), amine (5.00 equiv).

Unfortunately, the use of a model primary aliphatic amine was not productive. Indeed, with only one equivalent of allylamine, no 1-allyl-3-(benzoyloxy)urea was formed and when excess was used only the *N*-allylbenzamide (2.37) was obtained as the only product in a 76% isolated yield. The formation likely proceeds through the addition of the allylamine onto the carbonyl of the benzoate group (Scheme 2-20).



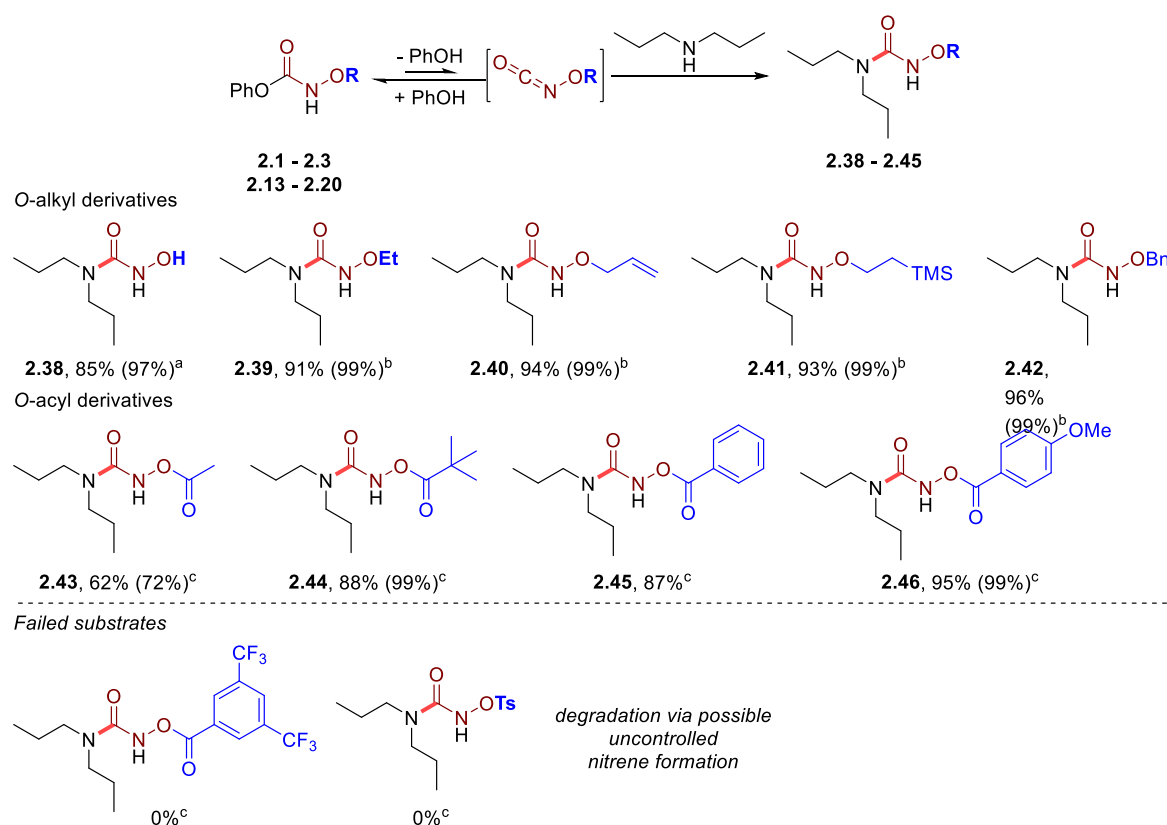
Scheme 2-20: Proposed mechanism for the formation of *N*-allylbenzamide

After study on the nucleophile partner, attention was turned to the substituent to the *N*-oxycarbamates bearing different substituents on the oxygen atom.

2.2.3. Reaction optimization: Oxygen-substituent study

Diverse oxy-carbamates were chosen with a large range of substituents: from H and alkyl substituents to alkoxy derivatives bearing electron rich and poor substituents (Table 2-5). The experimental conditions found for the three classes of *O*-isocyanates (hydrogen, alkyl and alkoxy) were used accordingly and different dipropylamine derived *N*-oxyureas were synthesized.

Table 2-5: Oxy-carbamate scope



Conditions: ^a Carbamate (1.10 equiv), dipropylamine (1.00 equiv), Et₃N (0.20 equiv) in THF (0.3 M), stir in oil bath at 70 °C overnight. ^b Carbamate (1.05 equiv), dipropylamine (1.00 equiv) in MeCN (0.2 M), heat to 120 °C in μ W for 0.5 h. ^c Carbamate (1.00 equiv), dipropylamine (1.05 equiv), imidazole (0.10 equiv) in THF (0.2 M), heat to 100 °C in μ W for 1–3 h.

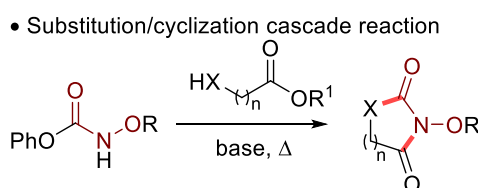
¹H NMR yield based on 1,3,5-trimethoxybenzene shown in parentheses.

The *N*-oxyureas were isolated in good to excellent yields for alkyl and alkoxy derivatives (**2.38 - 2.46**), but substrates with better electron-withdrawing substituents, degradation of the corresponding *N*-oxycarbamate starting materials occurred, possibly via uncontrolled formation of the corresponding uridyl nitrene. Hydrogen (**2.38**) and alkyl substituents, such as ethyl (**2.39**), allyl (**2.40**), alkyl TMS (**2.41**) or benzyl (**2.42**), were tolerated and the corresponding *N*-oxyureas were obtained in excellent yields. Oxy-carbamates bearing electron neutral (**2.43 – 2.45**) or electron rich acyl groups (**2.46**) also formed the corresponding *N*-benzoyloxyureas in good to excellent isolated yields. On the other hand, when the *N*-oxy-carbamate was substituted with an electron withdrawing group, no formation of the corresponding *N*-benzoyloxyurea was observed. The oxy-carbamate starting material underwent uncontrolled Lossen rearrangement. No trace of the desired *N*-benzoyloxyureas were found by ¹H NMR. It should be noted that a possible alternative approach to *N*-benzoyloxyureas with strong electron-withdrawing acyl groups could involve acylation of the product **2.38**, provided that the Lossen rearrangement can be avoided.

In this first section of this chapter thesis, controlled formation of *O*-isocyanates from oxy-carbamates and oxy-ureas was presented. The reaction developed allowed for the synthesis of *N*-oxyureas in moderate to excellent yields with a high degree of versatility. The conditions used were mild enough to avoid the Lossen rearrangement for the oxy-carbamate starting materials, with the exception of substrates with highly activated *N*-O bonds. Based on those results, cascade reactions were studied for the synthesis of more complex structures bearing the *N*-O bond motif.

2.3. Cascade reactions of *O*-isocyanates

In this section, the first cascade reactions involving *O*-isocyanates is described (Scheme 2-21). Indeed, the addition/cyclization cascade reaction for the synthesis of *N*-oxy heterocycles using amino ester as nucleophile is presented. This study was published¹⁶⁶ and was performed with Ryan Ivanovich. Ryan discovered and optimized the cascade thermal reaction and I joined him for the isolation of the different products. I was in charge of the optimization of the oxygen and sulfur derivatives which required different reaction conditions to yield the cascade products.



Scheme 2-21: First cascade reactions of blocked (masked) *O*-isocyanates

2.3.1. Substitution/cyclization cascade reaction

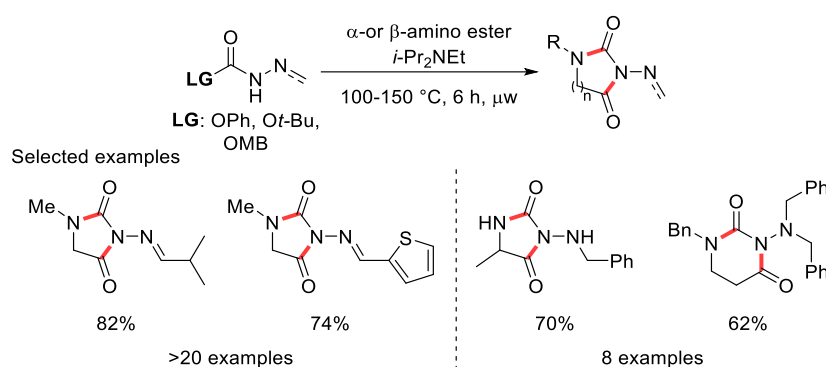
2.3.1.1. Previous examples

Over the years, addition of amino esters onto isocyanates has been reported for the synthesis of hydantoins via addition/cyclization cascade reactions.¹⁶⁷ In 2015, the Beauchemin group reported the first cascade reaction of blocked (masked) *N*-isocyanates with α - or β -amino esters for the synthesis of *N*-aminohydantoin and *N*-aminodihydrouracil derivatives (Scheme 2-22).¹⁶⁸

¹⁶⁶ Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. *Adv. Synth. Catal.* **2017**, 359, 4289.

¹⁶⁷ For selected examples see: (a) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, 38, 4603. (b) Zhang, W.; Lu, Y. *Org. Lett.* **2003**, 5, 2555. (c) Lu, G.-J.; Nie, J.-Q.; Chen, Z.-X.; Yang, G.-C.; Lu, C.-F. *Tetrahedron: Asymmetry* **2013**, 24, 1331.

¹⁶⁸ Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *Chem. Eur. J.* **2015**, 21, 3886.



Scheme 2-22: Aminohydantoins synthesis via *N*-isocyanates

Different hydrazones and hydrazides were tested as blocked *N*-isocyanates (imino and amino isocyanates). Indeed, these two species are bench stable and upon base catalysis and heat can release the free *N*-isocyanate. In this study, more than 20 examples of *N*-iminohydantoins and 8 examples of *N*-aminohydantoins were isolated in good to excellent yields. Moreover, the synthesis of hydantoins with possible carbon-substituted isocyanates (*C*-isocyanates) intermediates were also reported throughout the years.¹⁶⁹

This addition/cyclization procedure was chosen for the first cascade reaction of *O*-isocyanate due to the easy access of amino esters and the well documented previous synthesis of hydantoin derivatives (see 1.2.3.3.). This would also allow a direct comparison of the reactivity between these two different types of heteroatom-substituted isocyanates.

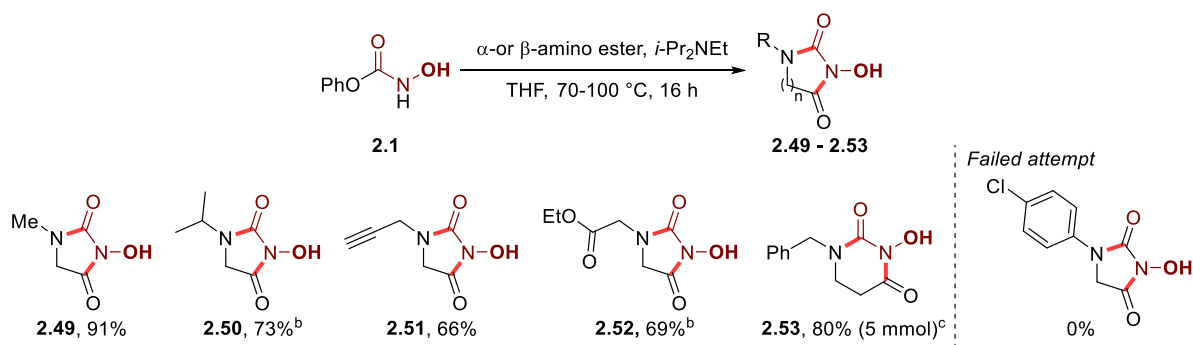
2.3.1.2. Synthesis of oxy-hydantoin derivatives

As in the previous section, the results presented are divided by the substituents of the oxygen due to the different experimental conditions.

To start, the cascade reaction was tested with phenyl *N*-hydroxycarbamate (**2.1**) and sarcosine ethyl ester hydrochloride. The reaction conditions found for the addition onto the HO-NCO were also used with the difference of *i*-Pr₂NEt being found to be the best base for this cascade reaction (see Table 2-2). *N*-Hydroxyhydantoin (**2.49**) was isolated in 91% yield and 4 different α -amino esters were tested (Table 2-6). Higher temperature (90-100 °C) were necessary for some substrates due to a harder cyclization step.

¹⁶⁹ (a) Duan, M.; Kazmierski, W. M.; Tallant, M.; Jun, J. H.; Edelstein, M.; Ferris, R.; Todd, D.; Wheelan, P.; Xiong, Z. *Bioorg. Med. Chem. Lett.* **2001**, 21, 6381. (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.

Table 2-6: Formation of *N*-hydroxy-hydantoins and a *N*-hydroxy-dihydrouracil^a



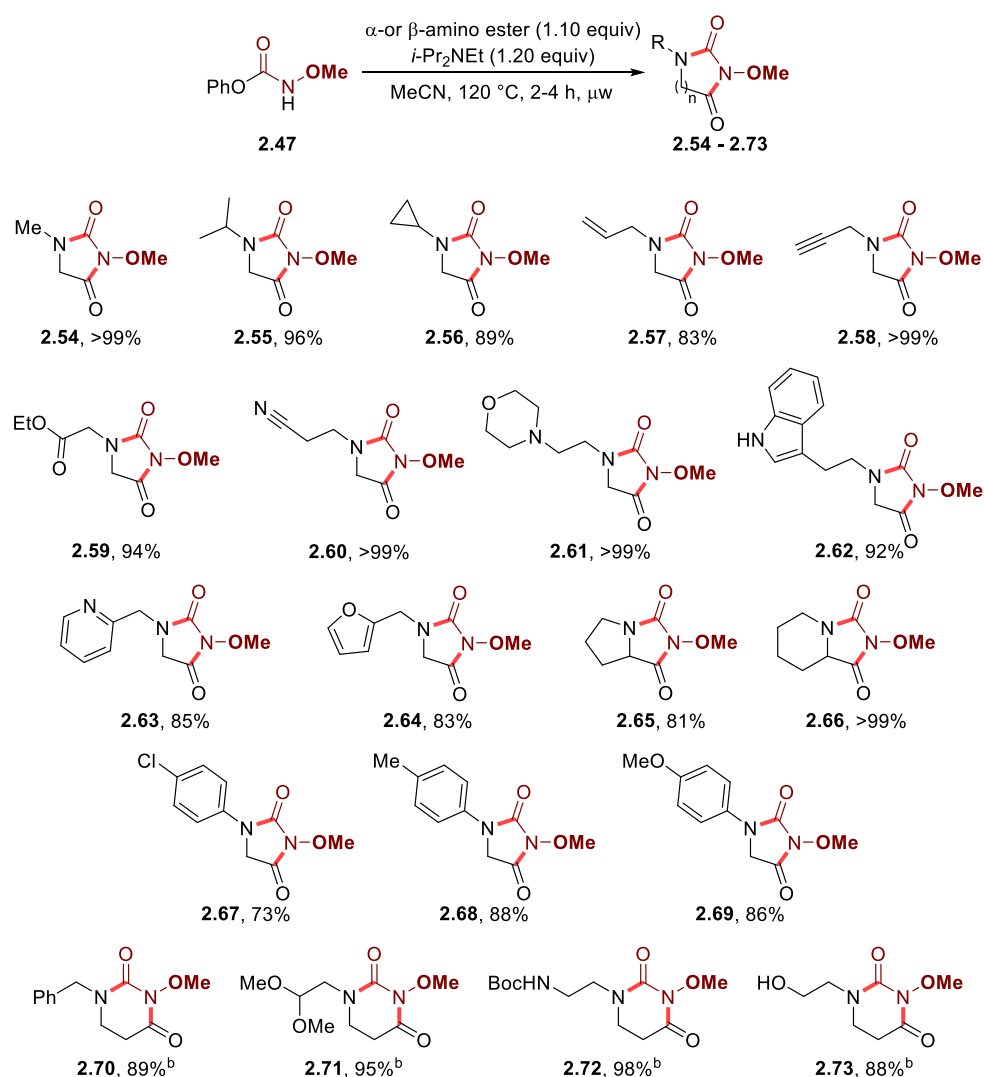
Conditions: ^a Phenyl *N*-hydroxycarbamate (1.10 equiv), α -amino ester¹⁷⁰ (1.00 equiv), *i*-Pr₂NEt (0.10 equiv or 1.10 equiv if the α -amino ester is an HCl salt) in THF (0.3 M), stir in oil bath at 70 °C overnight. ^b See ^a but at 90 °C. ^c See ^a but 100 °C.

Diverse substituents on the nitrogen were tolerated and the desired products (**2.50**), (**2.51**) and (**2.52**) were isolated in good to moderate yields. The reaction was also performed on a 5.00 mmol scale with a β -amino ester, and the *N*-hydroxy-dihydrouracil (**2.53**) was isolated in 80 % yield. Unfortunately, the reaction with a secondary aniline α -amino ester did not occur: indeed, even at higher temperatures, only the aniline was recovered at the end of the reaction as the phenyl *N*-hydroxycarbamate underwent untraceable polymerization.

Phenyl *N*-methoxycarbamate (**2.47**), precursor for the *O*-methoxyisocyanate, was chosen as model *O*-alkyl isocyanate precursor for most of the scope of the addition/cyclization cascade reaction due to its facile synthesis and the easy ¹H NMR identification of the corresponding trimer, the unique side-product of the reaction. The experimental conditions found for the deblocking of *O*-alkyl isocyanates were used (see Table 2-3), with again a change for the *i*-Pr₂NEt as a base and higher temperature and longer reaction time due to the cyclization step. The results are presented in Table 2-7.

¹⁷⁰ The esters used were methyl and ethyl derivatives.

Table 2-7: Synthesis of *N*-methoxy-hydantoin and *N*-methoxy-dihydrouracils^a

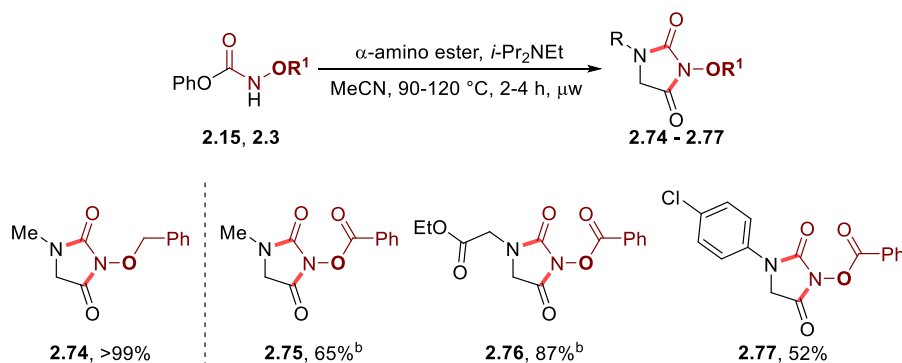


Conditions: ^a Carbamate (1.00 equiv), amino ester¹⁷⁰ (1.00 equiv), *i*-Pr₂NEt (0.10 equiv or 1.10 equiv if the aminoester is an HCl salt), in MeCN (0.3 M), heat in μ W to 120 °C for 2 h. ^b See ^a but 4 h.

Multiple *N*-oxyhydantoin along with several *N*-oxydihydrouracils bearing a large range of substituents were isolated in good to excellent yields. Simple alkyl substituents like methyl (2.54), isopropyl (2.55), cyclopropyl (2.56), allyl (2.57) and propargyl (2.58) were tolerated and the *N*-oxyhydantoin were isolated in excellent yields. Symmetrical diethyl iminodiacetate (2.59) was used, allowing for the presence of a pendant ester group that can be derivatized. Nitrile (2.60) and morpholine (2.61) groups were also tolerated. Alkyl substituents bearing heteroaromatic groups like tryptophan (2.62), pyridine (2.63) or furan (2.64) were tolerated and the cascade also proved efficient for the synthesis of bicyclic products (2.65, 2.66). Gratifyingly, secondary aniline derivatives underwent the cascade reaction using the same conditions and the products (2.67 – 2.69) were obtained in good yields. Dihydrouracils and their derivatives (2.70 – 2.73) were synthesized using β -amino esters in excellent yields. The temperature required was slightly higher than for the *N*-oxyhydantoin (120 °C instead of 90 °C) due to

a more difficult cyclization step. It was found the phenyl *N*-hydroxycarbamate and the corresponding *O*-hydroxy isocyanate were the least selective intermediate due to the facile polymerization. Lastly, benzyl and benzoyl *O*-isocyanate derivatives were also tried for the synthesis of *N*-oxyhydantoins (**2.74** - **2.77**) using microwave irradiation and *i*-Pr₂NEt as a base.

Table 2-8: Formation of benzyl- and alkoxy-hydantoins^a



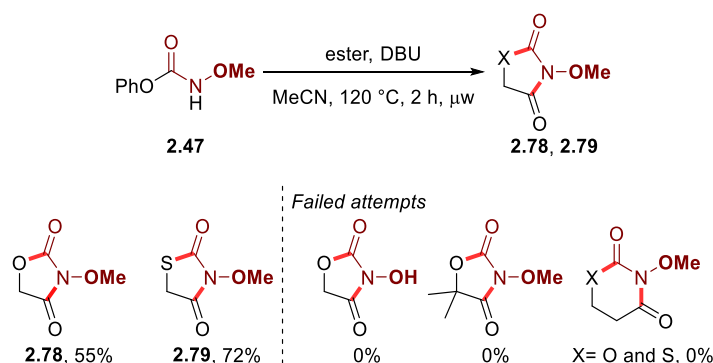
Conditions: ^a Carbamate (1.00 equiv), amino ester¹⁷⁰ (1.00 equiv), *i*-Pr₂NEt (0.10 equiv or 1.10 equiv if the aminoester is an HCl salt), in MeCN (0.3 M), heat in μ W to 120 °C for 2 h. ^b See ^a but at 90 °C.

The excellent yield obtained for the 3-(benzyloxy)-1-methylimidazolidine-2,4-dione (**2.74**) contrasts with the lower isolated yields for the benzoyl derivatives (**2.75** - **2.76**), likely due to minimal Lossen rearrangement degradation. The *O*-benzyl isocyanate was expected to react like the *O*-methylisocyanate and gave a good alternative for *N*-hydroxy hydantoin synthesis. Indeed, its more broadly applicable cascade reaction, followed by facile benzyl deprotection¹⁷¹ could give access to the same products of the phenyl *N*-hydroxycarbamate (**2.1**) when the reaction is not possible with the free N-OH.

Using phenyl *N*-methoxycarbamate (**2.47**) as the blocked *O*-isocyanate, oxygen and sulfur derivatives (using ethyl 2-hydroxyacetate and methyl thioglycolate for nucleophiles) were also tested as partners for the synthesis of the corresponding alkoxyoxazolidine-2,4-dione and alkoxythiazolidine-2,4-dione (Table 2-9).

¹⁷¹ Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**, 75, 109.

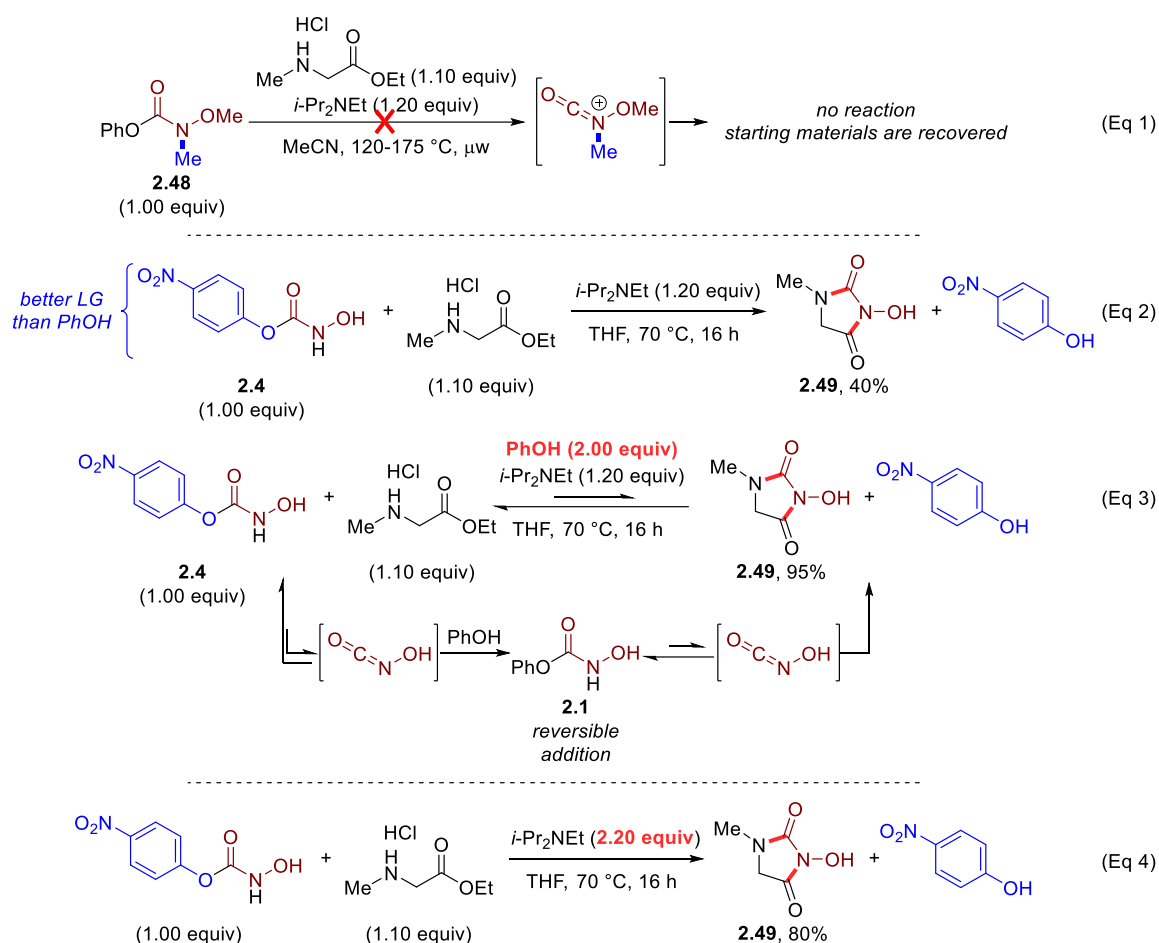
Table 2-9: Synthesis of alkoxyoxazolidine-2,4-dione and alkoxythiazolidine-2,4-dione^a



Conditions: ^a Phenyl methoxycarbamate (1.00 equiv), ethyl 2-hydroxyacetate (2.00 equiv) or methyl thioglycolate (1.00 equiv), DBU (5 mol%), in MeCN (0.3 M), heat in μW to 120 $^\circ\text{C}$ for 2 h.

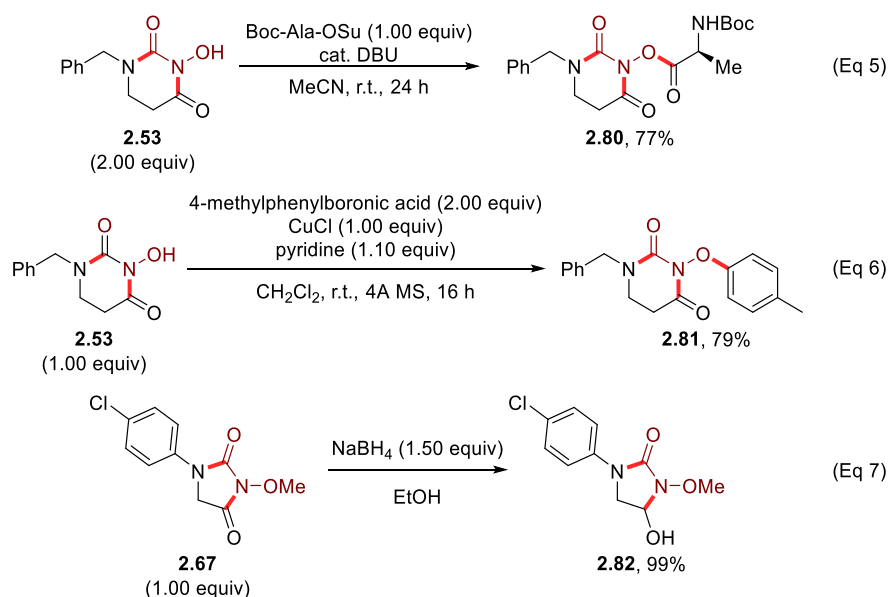
Surprisingly, the cascade reaction also worked and allowed the synthesis of oxygen (**2.78**) and sulfur (**2.79**) heterocyclic analogues (these nucleophiles were not used in previous masked *N*-isocyanate studies).¹⁶⁸ Using the amino ester conditions (catalytic amount of *i*-Pr₂NEt) led to a low yield for the heterocycle, with the corresponding trimer of oxycarbamate (**2.47**) being the major product. Changing the base for a catalytic amount of DBU resulted in the isolation of the oxygen and sulfur heterocycle in 55% and 72% isolated yields respectively (only small traces of the trimer were seen by ¹H NMR). Unfortunately, the analogous cascade reaction using phenyl *N*-hydroxycarbamate (**2.1**) was not possible nor were cascade reactions of the β -alcohol or β -sulfur esters for the formation of 6-membered ring.

A mechanistic study was performed to probe the intermediacy of an *O*-isocyanate. First, an *N*-methyl carbamate (**2.48**) was synthesized and used for the cascade reaction. Indeed, two possible pathways can be envisaged for this reaction: the formation of the *O*-isocyanate or nucleophilic attack on the carbamate and formation of a tetrahedral intermediate. If the reaction proceeded via this tetrahedral intermediate, the presence of the *N*-methyl group should only have a small impact on the formation of the oxyhydantoin. However, when the cascade reaction was performed with sarcosine ethyl ester (Eq 1) using the standard conditions, no formation of hydantoin was observed and the two starting materials were recovered. Using harsher conditions (higher temperatures and stronger bases) led to no hint of hydantoin formation and degradation of the sarcosine ethyl ester started to occur. Based on this first result, the presence of the NH group seemed crucial for the reaction.



The cascade reaction was also achieved with the *p*-nitrophenol carbamate (**2.4**) and the presence of this better leaving group decreased the isolated yield of the hydantoin (**2.49**) to 40 % (Eq 2). Fast generation of *p*-nitrophenol leaving group was observed by TLC and unreacted sarcosine ethyl ester was observed by ¹H NMR at the end of the reaction. These observations fit with an *O*-isocyanate intermediate, and control of the concentration of this hypothetical intermediate was tried. In presence of 2.00 equivalents of phenol, the 3-hydroxy-1-methylimidazolidine-2,4-dione (**2.49**) was isolated in 95% yield (Eq 3). It was suggested that reversible addition of phenol onto the free *O*-isocyanate allowed for the control of the concentration of this intermediate: indeed, during the course of the reaction, a new blocked *O*-isocyanate (**2.1**) could be formed and ensured that the concentration of the free *O*-isocyanate remained low enough for efficient cascade reactions and prevent side-reactions. No phenyl *N*-hydroxycarbamate (**2.1**) was observed at the end of the reaction. It was also thought that the *p*-nitrophenol carbamate (**2.4**) affected the cascade reaction via reversible protonation of the sarcosine ethyl ester by the *p*-nitrophenol leaving group. Gratifyingly, the efficiency of the cascade reaction was restored by using 2.00 equiv of the base (Eq 4). Overall, these results support an *O*-isocyanate pathway: indeed, the NH group was crucial for the reaction and the difference of yields with different leaving groups can only be rationalized with the formation of this reactive intermediate.

Finally, the oxy-hydantoin products were derivatized: first via acylation using the succinate ester to form product **2.80** in 77% isolated yield (Eq 5). Then, the first (to our knowledge) Chan-Evans-Lam coupling reaction between a hydroxyurea and a boronic acid led to the formation of the *O*-aryl substituted dihydouracil (**2.81**) in good yield (Eq 6). Finally, selective reduction using NaBH₄ furnished the hydroxy imidazolidinone (**2.82**) in excellent yield. This product can be used as precursor to an *N*-acyliminium ion (Eq 7).¹⁷²

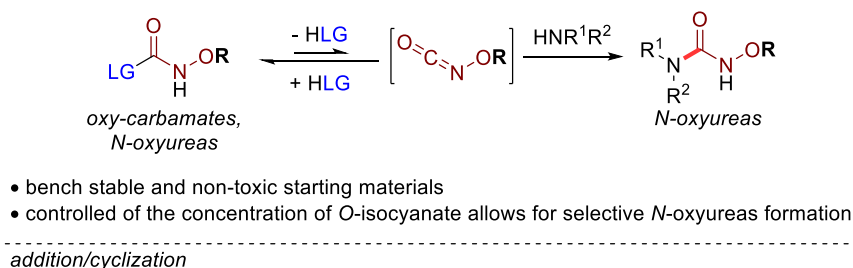


With this first successful cascade reaction using bench stable starting materials as *O*-isocyanate precursors and based on the expertise of the Beauchemin group, the addition/Cope-type hydroamination cascade reaction was tried and optimized by Ryan A. Ivanovich and Meredith A. Allen.¹⁶³

2.3. Conclusion and perspectives

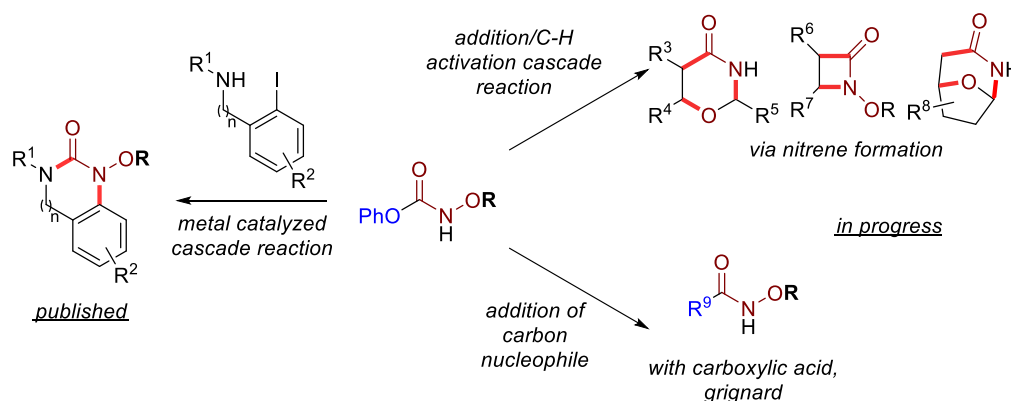
In this chapter, development of the controlled reactivity of *O*-isocyanates with bench stable starting materials was described. Oxy-carbamates and *N*-oxyureas proved to be suitable blocked (masked) *O*-isocyanate precursors. Specific deblocking conditions were found for the different classes of the *O*-substituents: a catalytic amount of base and heat were typically sufficient to release the reactive *O*-isocyanate intermediate and efficient addition and cascade reactions were developed (Scheme 2-23).

¹⁷² Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811.



Scheme 2-23: Summary of chapter 1

With this better understanding of the O-isocyanate intermediate, others cascade reactions were/are studied in the Beauchemin group. In 2017, the Beauchemin group reported the first metal catalyzed cascade reaction of O-isocyanates using a copper catalyst.¹⁷³ This study allowed the synthesis of more than twenty-five examples of benzimidazolones and 3,4-dihydroquinazolin-2(1H)-ones in moderate to good yields. Currently, several projects are being investigated for the synthesis of complex hydroxylamine derivatives via addition/C-H activation cascade reaction and the addition of carbon nucleophiles.



Scheme 2-24: Beauchemin group's study on O-isocyanate

Furthermore, the chemistry developed in this first chapter was critical for the other projects discussed in this thesis. Indeed, a large majority of the starting materials used in Chapter 3 and 4 are N-oxyureas synthesized via O-isocyanate chemistry. In this chapter, it was crucial to keep the N-O bond intact. For the following projects, reaction involving cleavage of this N-O bond of these N-oxyureas are presented with the example of two different amination reactions.

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

***Chapter 3: Formation of N-N bonds via Aza-Lossen
rearrangement***

In this chapter, the importance of the hydrazine motif $\text{NH}_2\text{-NH}_2$ is presented along with selective examples of its incorporation. Then the development of a chemoselective aza-Lossen rearrangement procedure for the formation of *N-N* bond of complex hydrazide derivatives is described.

3.1. The hydrazine motif and its incorporation

3.1.1. Natural occurrence and importance

Hydrazine derivatives have many uses ranging from agrochemicals, polymers to key synthetic intermediates or building blocks for the synthesis of fine chemicals (e.g., heterocycles). Macrozamin was the first natural product containing *N-N* bond found¹⁷⁴ and since then, more than 200 natural products were reported containing the hydrazine motif (Figure 3-1).¹⁷⁵ Furthermore, several hydrazine derivatives are bioactive.

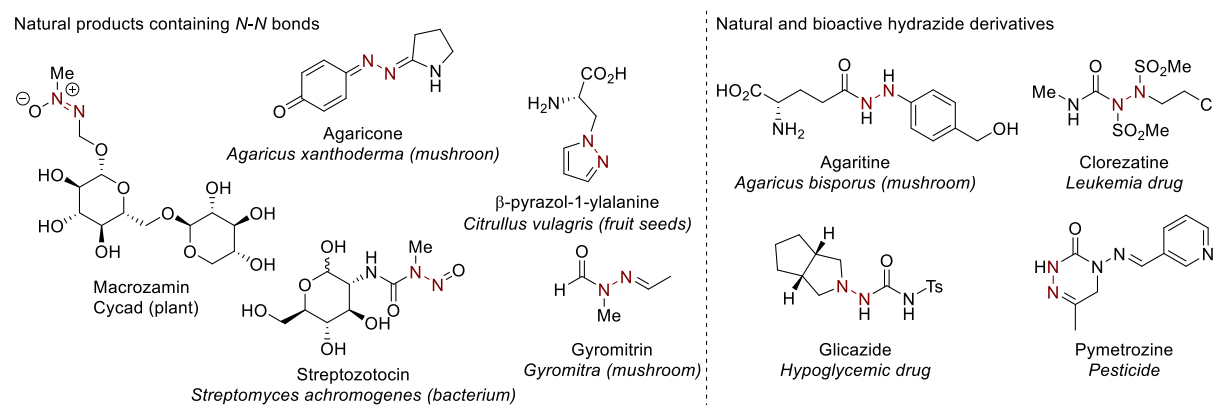


Figure 3-1: Examples of natural products containing *N-N* bonds - Natural and bioactive hydrazides

The present chapter focuses on the synthesis of hydrazide derivatives, which are acylated hydrazines. Hydrazides are naturally occurring and also show bioactivity with the examples Glyclazide and Pymetrozine, a hypoglycemic drug and a pesticide respectively. Semicarbazides, a subclass of hydrazides, containing a N-C(O)-N-N moiety are present on the backbone of azapeptides¹⁷⁶ and their current synthesis usually involves the use of hydrazine and suffers from the poor modulation of the substituents.¹⁷⁷ The chemistry developed in this chapter is aiming toward the synthesis of semicarbazide derivatives via *in-situ* formation of their *N-N* bonds using mild and safe conditions.

¹⁷⁴ (a) Langley, B. W.; Lythgoe, B.; Riggs, N. V. *J. Chem. Soc.* **1951**, 2309. (b) Riggs, N. V. *Aust. J. Chem.* **1954**, 7, 123.

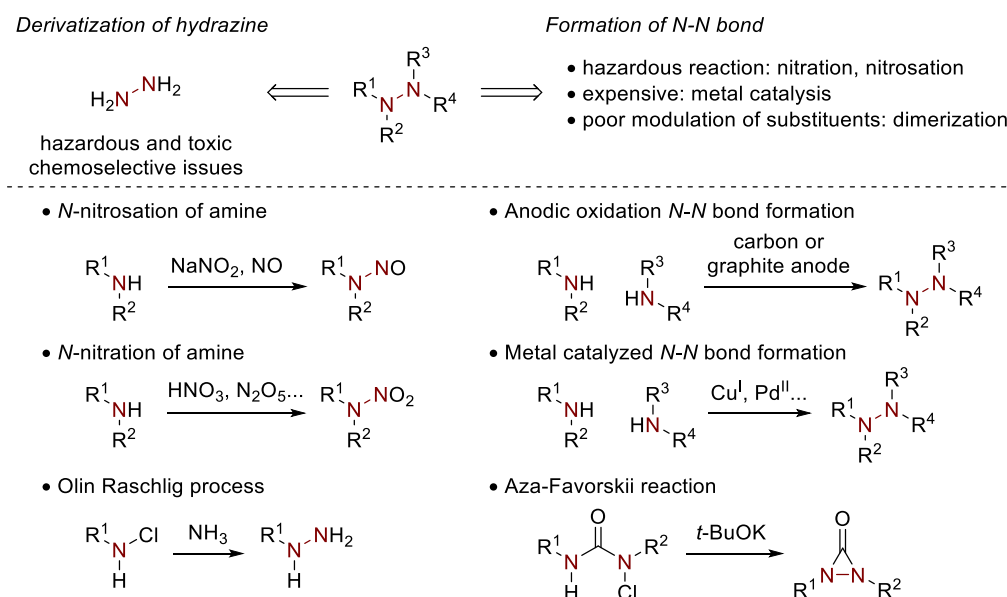
¹⁷⁵ Blair, L. M.; Sperry, J. J. *Nat. Prod.* **2013**, 76, 794.

¹⁷⁶ For a recent review see: Chingle, R.; Proulx, C.; Lubell, W. D. *Acc. Chem. Res.* **2017**, 50, 1541.

¹⁷⁷ Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1995**, 60, 5992.

3.1.2. Formation of N-N bonds

There are two different approaches for the incorporation of the N-N motif: (1) functionalization of hydrazine and (2) formation of the N-N bond (*Scheme 3-1*). The functionalization of hydrazines is often challenging due to inherent chemoselectivity issues arising from the two reactive nucleophilic nitrogen atoms.¹⁷⁸ Moreover, hydrazines are toxic, hazardous and air sensitive making them difficult to work with.



Scheme 3-1: Incorporation of the N-N motif

On the other hand, the formation of N-N bonds¹⁷⁹ often includes the hazardous nitrosation¹⁸⁰ or nitration¹⁸¹ of amines. Cleavage of weak N-X bonds (where X = O, N, or Cl in the Raschig–Olin process) is also used but typically this requires prefunctionalization of the starting material. Many N-N bonds have been formed under metal catalyzed conditions (Pd, Cu, etc.), but rely on expensive catalyst. Additionally, dimerization of amines has also been reported,¹⁸² but typically the formation of heterodimers is difficult. Recently, electrochemistry has gained importance and examples of N-N bond formation via anodic oxidation have been published.¹⁸³ Finally, aza-Favorskii reactions of N-substituted ureas following ring opening of the diaziridone intermediate was also reported to form hydrazine

¹⁷⁸ For reviews of hydrazines and hydrazides, see: (a) Rothgery, E. F. *Kirk-Othmer Encyclopedia Chemical Technology*, 5th ed.; Wiley: New York, **2004**; 13, 562. (b) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, 30, 205.

¹⁷⁹ For a recent review on N-N bonds formation see: Guo, Q.; Lu, Z. *Synthesis* **2017**, 49, 3835.

¹⁸⁰ For a review of nitrosation at nitrogen centres, see: Williams, D. L. H. *Nitrosation Reactions and the Chemistry of Nitric Oxide*, Elsevier: Amsterdam, **2004**; p 35.

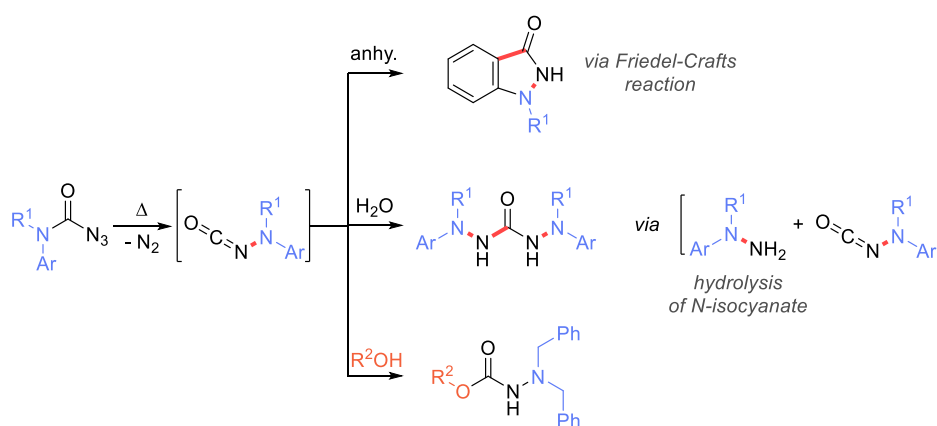
¹⁸¹ For selective examples of N-nitration, see: (a) Park, Y.-D.; Kim, H.-K.; Kim, J.-J.; Cho, S.-D.; Kim, S.-K.; Shiro, M.; Yoon, Y.-J. *J. Org. Chem.* **2003**, 68, 9113. (b) Anikin, O. V.; Pokhvisneva, G. V.; Lipilin, D. L.; Mezhenin, A. V.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2009**, 58, 2043.

¹⁸² (a) Wang, C.; Sperry, J. *Chem. Commun.* **2013**, 49, 4349. (b) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, 136, 5571.

¹⁸³ (a) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, 136, 5571. (b) Gieshoff, T.; Kehl, A.; Schollmeyer, D.; Moeller, K. D.; Waldvogel, S. R. *J. Am. Chem. Soc.* **2017**, 139, 12317.

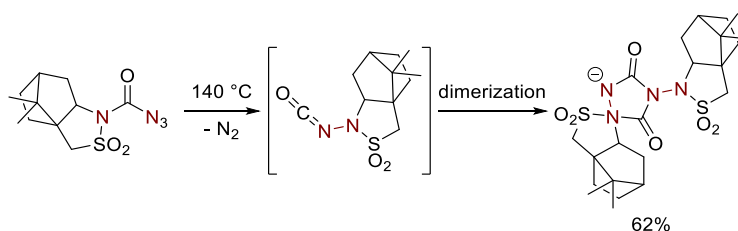
derivatives.¹⁸⁴ Another method to form *N-N* bonds is the use of rearrangement chemistry (see 1.3.2.2. for the aza-Lossen rearrangement) but all the previous examples have limitations.

In the 1920's, Stollé reported the first examples of aza-Curtius (the nitrogen analogue of the Curtius rearrangement).¹⁴¹ Under thermolysis, carbamoyl azides underwent rearrangement and formation of *N-N* bonds via extrusion of N₂ (Scheme 3-2). The proposed intermediate was a *N*-isocyanate, that reacted intra- or inter-molecularly depending on the reaction conditions: indeed, when the aza-Curtius was performed in anhydrous solvent, an indazolone moiety was observed. On the other hand, when the reaction was performed in water, a carbazide was obtained via hydrolysis of the *N*-isocyanate intermediate. Finally, when the thermolysis was run in alcohol solvent, the corresponding carbazate was formed.



Scheme 3-2: Pioneer work on aza-Curtius rearrangement by Stollé

More recently, example of dimerization of carbamoyl azide via thermolysis has been reported as an unwanted reaction.¹⁸⁵



Scheme 3-3: Dimerization of Oppolzer's sultam carbamoyl azide

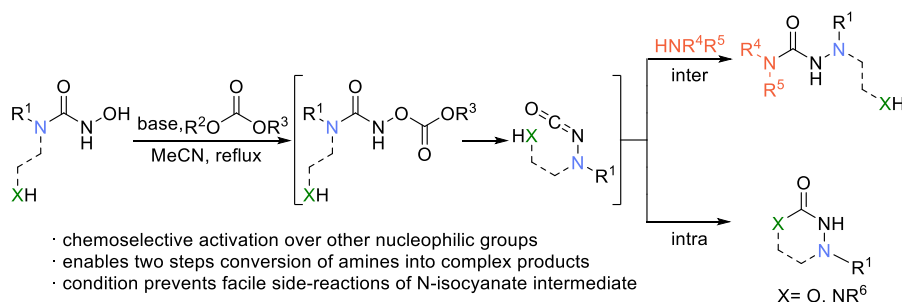
Due to the instability and the non-selectivity reactivity of carbamoyl azides (e.g. nitrene degradation pathway) the aza-Curtius remains unexploited (similar to the aza-Lossen rearrangement). More broadly, given the importance of the hydrazine motif, a versatile *N-N* bond-forming reaction using stable starting materials and mild conditions is needed.

¹⁸⁴ (a) Greene, F. D.; Pazos, J. F. *J. Org. Chem.* **1969**, *34*, 2269. (b) Baumgarten, H. E.; Chen, P. Y.-N.; Taylor, H. W.; Hwang, D.-R. *J. Org. Chem.* **1976**, *41*, 3805.

¹⁸⁵ Del Signore, G.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2001**, *57*, 4623.

3.2. Development of a broadly applicable aza-Lossen rearrangement

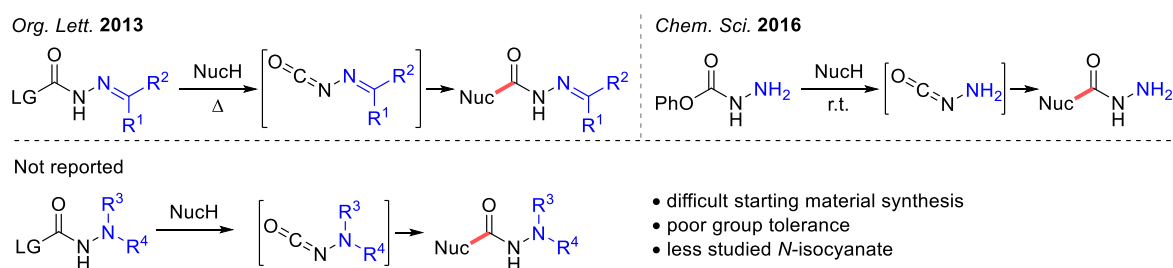
In this study, chemoselective activation of the N-OH of N-hydroxyureas inducing a broadly applicable aza-Lossen rearrangement is described for the formation of N-N bonds leading to acyclic and heterocyclic products. Discovery, optimization and scope are presented and were recently published¹⁸⁶ (Scheme 3-4). The work presented in this chapter was performed with the help of two honor students, David Brzezinski and Eric Strotski. I optimized the aza-Lossen rearrangement and was joined by David for the isolation of the semicarbazides. David obtained the first evidence of the formation of oxadiazin-2-one and isolated the entries for this heterocycle moiety where I focused on the isolation of the triazine-3-one scope. Preliminary work for the oxa-Lossen rearrangement was studied by Ryan Ivanovich and the study was passed on me after I discovered the optimum conditions for the aza-Lossen rearrangement. The oxa-Lossen rearrangement was then studied with Eric and I isolated all the products.



Scheme 3-4: Summary of the aza-Lossen rearrangement

3.2.1. Previous work and context

Over the years, the Beauchemin group has reported the synthesis of hydrazones¹⁸⁷ and unprotected semicarbazides¹⁸⁸ via N-isocyanate intermediates using carbazate derivatives as starting materials (Scheme 3-5).



Scheme 3-5: Hydrazides derivatives synthesis performed by the Beauchemin group

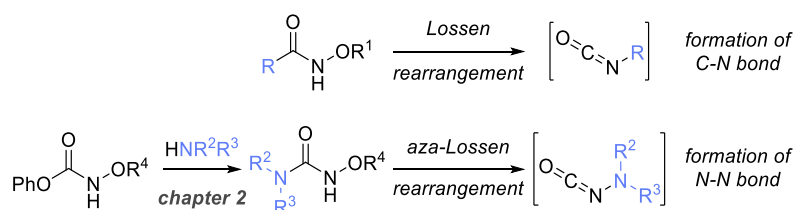
¹⁸⁶ Polat, D. E.; Brzezinski, D. D.; Beauchemin, A. M. *Org. Lett.* **2019**, 51, 4849.

¹⁸⁷ Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, 15, 4074.

¹⁸⁸ Vincent-Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, 7, 315.

The formation of di-substituted carbazates bearing substituents R^3 and R^4 (Scheme 3-5) suffers from several drawbacks arising from the difficult synthesis of the starting materials. Indeed, the use of harsh conditions (e.g. $n\text{BuLi}$) induced a difficult synthesis and a low group tolerance. Moreover, problem of selectivity during the synthesis due to the two nucleophilic nitrogen atoms limited the study and use of the amino-isocyanate intermediate. Surely, a more general approach using milder conditions for the synthesis of this derivative is needed.

An alternative approach to access hydrazine derivatives would be to form the $N\text{-N}$ bond during the course of the reaction. $N\text{-Oxyureas}$ (products obtained from chapter 2) can be seen as the nitrogen analogue of hydroxamic acid and can be expected to undergo the previously reported aza-Lossen rearrangement (Scheme 3-6).

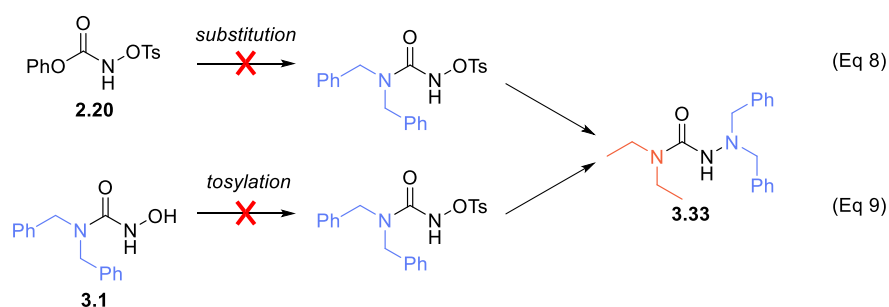


Scheme 3-6: Lossen and aza-Lossen rearrangement

Based on the results of presented in Chapter 2 on the substitution reaction of blocked $O\text{-isocyanates}$, $N\text{-oxyureas}$ can be facile to access with a large range of substituents and are stable under light and oxygen. Previous published examples of aza-Lossen rearrangement had clear limitations (see 1.4.1.1.) and the objectives for this study of $N\text{-N}$ bond formation were: (1) to use stable and easy to handle starting materials, (2) to use mild and safe experimental conditions and (3) to develop a broadly applicable strategy for the incorporation of $N\text{-N}$ bonds into complex hydrazide moieties.

3.2.2. Activated $N\text{-oxyureas}$

The aza-Lossen rearrangement was first tried using diethylamine as the external nucleophile for the formation of semicarbazides. Initial efforts were primary concentrated on the synthesis of starting material bearing an OTs substituent. With the study from Table 2-5, the substitution of the $N\text{-oxy-carbamate}$ (**2.20**) was not selected due to known uncontrolled oxa-Lossen rearrangement degradation (Eq 8). The tosylation of the $N\text{-hydroxyurea}$ (**3.1**) was found to be unproductive due to the instability of the corresponding product: indeed, the desired activated $N\text{-tosyloxyurea}$ degraded promptly to a complex mixture of products (Eq 9).



At that time, it was clear that the desired weak *N*-O bond for the aza-Lossen rearrangement induced instability and led to an unreliable synthesis and reactivity of the *N*-oxyurea starting material. The *N*-oxybenzoate urea derivative (**3.2**) was synthesized and isolated, since this weaker activating group displays improved stability. The *N*-oxyurea (**3.2**) was first heated using microwave irradiation in presence of diethylamine and gratifyingly, the semicarbazide (**3.33**) was observed and isolated. This was the first proof of formation of *N*-N bond via aza-Lossen rearrangement from a stable *N*-oxyurea as starting material and the optimization was undertaken (Table 3.1).

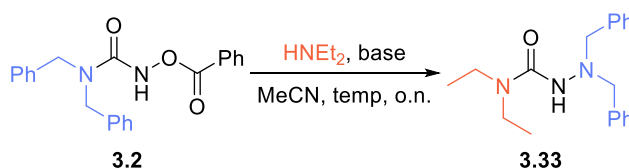
Table 3.1: Study of the aza-Lossen rearrangement under microwave irradiation^a

Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	% 3.2	% 3.33
1	-	MeCN	120	1	16	25
2	-	MeCN	100	1	13	37
3	-	MeCN	70	1	32	21
4	-	(CH ₂ Cl) ₂	120	1	25	25
5	-	(CH ₂ Cl) ₂	100	1	27	19
6	-	(CH ₂ Cl) ₂	70	1	18	15
7	Et ₃ N (1.00)	MeCN	100	1	3	1
8	Et ₃ N (1.00)	MeCN	70	1	74	8
9	Et ₃ N (1.00)	(CH ₂ Cl) ₂	100	1	27	19
10	Et ₃ N (1.00)	MeCN	70	4	57	15

Conditions: ^a 1,1-dibenzyl-3-hydroxyurea **3.2** (1.00 equiv), diethylamine (5.00 equiv), base in solvent (0.3M) stir under microwave irradiation. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Under microwave irradiation, the semicarbazide (**3.33**) was observed in low yields by ¹H NMR, along with unreacted starting material and degradation. The reaction was first tested at different temperatures (entries 1 - 3) and the desired product was observed in low yield due to degradation of the starting material. The solvent was changed to (CH₂Cl)₂ (entries 4 - 6) and yields were similar to those in MeCN. Using 1 equiv of Et₃N (acting as a base) at 100 °C resulted in almost complete degradation of the starting material with only traces of **3.33** being observed (entry 7). Lowering of the temperature to 70 °C (entry

8) led to a lower conversion of the **3.2** (74% remaining) and only 8% of the semicarbazide was found. Changing the solvent for (CH₂Cl)₂ did not improve the aza-Lossen rearrangement (entry 9). Finally, increasing the time of the reaction to 4 h also resulted to a low yield (entry 10). The microwave irradiation led to the degradation of the starting material, and simultaneously to this study, the aza-Lossen rearrangement was also studied using conventional heating (e.g. oil bath) and at room temperature. The results of this study can be seen in *Table 3.2*.

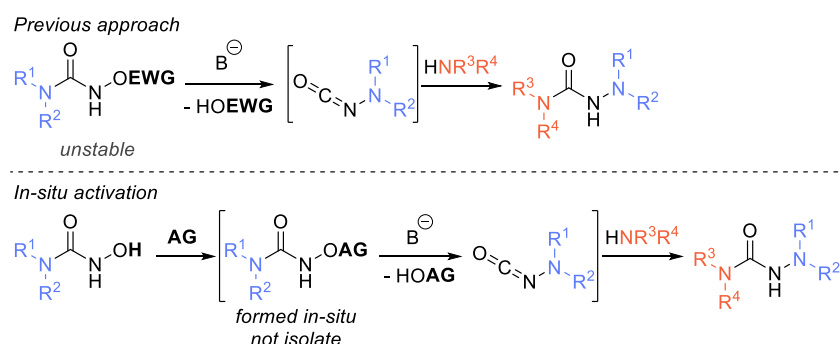


Conditions: ^a 1,1-dibenzyl-3-hydroxyurea **3.2** (1.00 equiv), diethylamine, carbonate, base in solvent (0.3M) stir in an oil bath for 16 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

of 1 equiv of Et₃N (entries 9 and 10), the *N*-benzoyloxyurea starting material degraded, inducing a lower yield for the desired semicarbazide. The use of a more activated benzoate (e.g. bearing electron withdrawing group) only resulted in the degradation of the starting material or to an uncontrolled aza-Lossen rearrangement.

3.2.3. *In-situ* activation

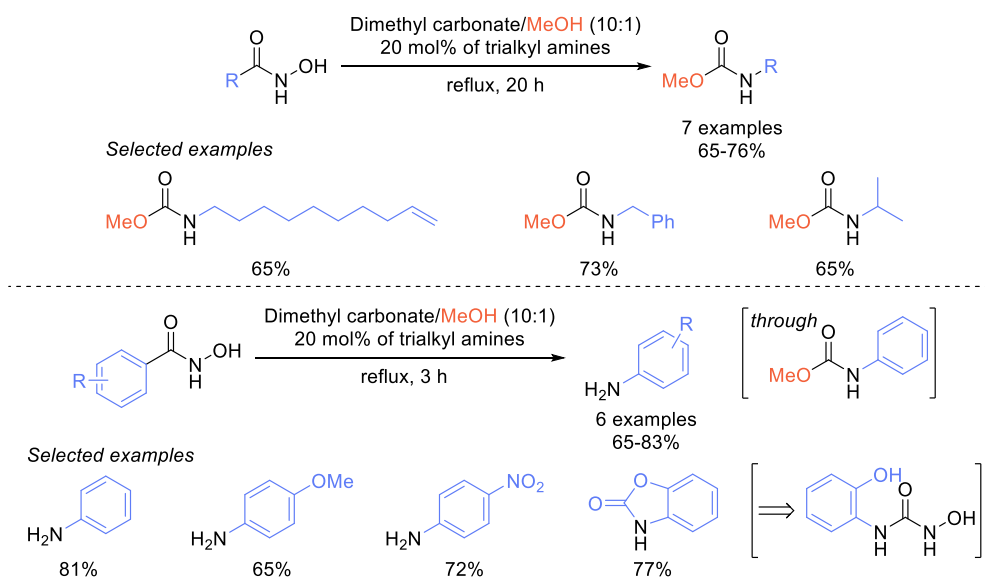
With the incompatibility of having an activated *N*-oxyurea, a controlled aza-Lossen rearrangement and a stable starting material, the attention was turned to an *in-situ* activation of the *N*-O bond. Indeed, a new approach hypothesized the use of an *N*-hydroxyurea as the stable starting material which, in presence of an activating group could lead to the formation of a reactive intermediate capable of undergoing the aza-Lossen rearrangement *in-situ* (Scheme 3-7). The proposed *N*-isocyanate intermediate could be obtained via *N*-N bond formation and react intermolecularly with an amine as the external nucleophile, provided that the external nucleophile is compatible with the activating reagent.



Scheme 3-7: *In-situ* activation of *N*-hydroxyurea

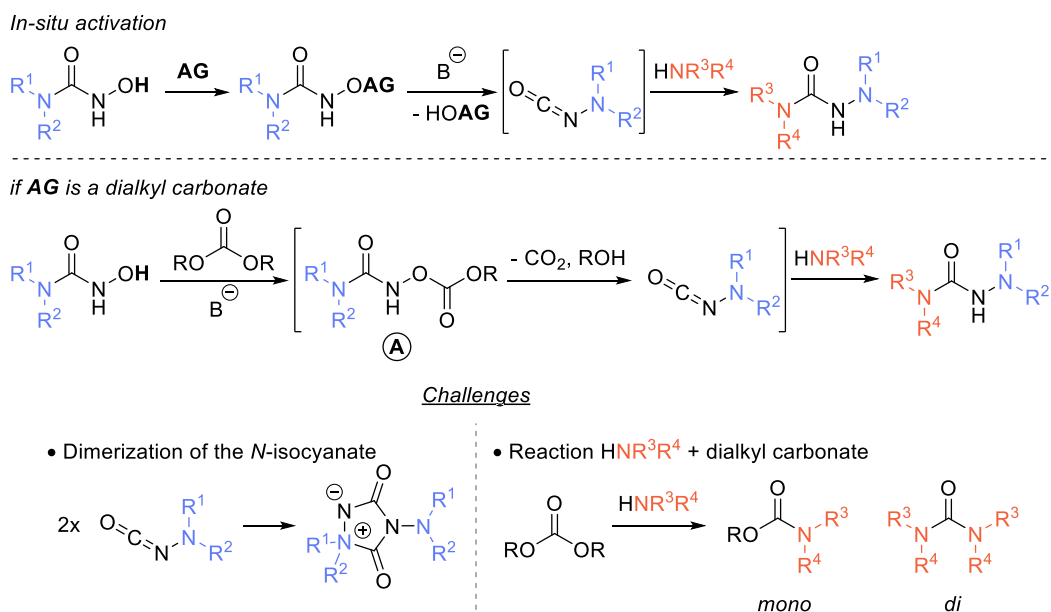
In-situ activation of hydroxamic acids has been reported for the synthesis of carbamates and ureas. In 2013 Meier and co-workers reported an elegant base-catalyzed Lossen rearrangement using a recyclable mixture of dimethylcarbonate/MeOH (Scheme 3-8).¹⁸⁹ In presence of a catalytic amount of base (trialkylamine), hydroxamic acids were activated by dimethyl carbonate and underwent Lossen rearrangement to form the corresponding isocyanate. MeOH was used as the solvent and as the nucleophile and several carbamates were isolated in moderate to good yields. With aromatic derivatives, the carbamates were not stable and the corresponding aniline derivatives were obtained instead. The mixture of dimethyl carbonate/MeOH was recycled and used several times without decreasing the formation of carbamates and anilines.

¹⁸⁹ Kreye, O.; Wald, S.; Meier, M. A. R. *Adv. Synth. Catal.* **2013**, 355, 81.



Scheme 3-8: In-situ activation of hydroxamic acid with dimethyl carbonate

In the case of the aza-Lossen rearrangement proposed here, the activation of the *N*-hydroxyurea with dialkyl carbonate formed the intermediate A, that has been reported previously and generally isolated in low yields (Scheme 3-9).¹⁹⁰ This intermediate was then proposed to undergo aza-Lossen rearrangement via extrusion of CO₂ and the corresponding alcohol as the only two side-products.



Scheme 3-9: Dialkyl carbonate in-situ activation of *N*-hydroxyureas

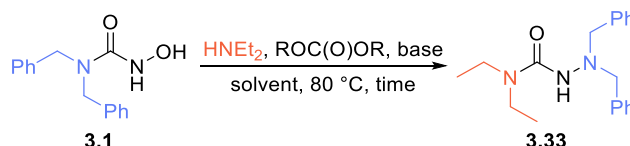
Similar to the previous examples of aza-Lossen rearrangement, the possible dimerization of the *N*-isocyanate intermediate is one of the possible degradation pathways. In addition, this *in-situ* approach

¹⁹⁰ For selective example: (a) Goldstein, S. W.; McDermott, R. E.; Gibbs, E. M.; Stevenson, R. W. *J. Med. Chem.* **1993**, 36, 2238. (b) Tilvawala, R.; Pratt, R. F. *Biochemistry* **2013**, 52, 3712. (c) Nourian, S.; Zilber, Z. A.; Toscano, J. P. *J. Org. Chem.* **2016**, 81, 9138.

led to a new challenge: indeed, possible reaction of the amine and the dialkyl carbonate can form carbamate or urea via mono- or di-substitution.

Inspired by the work of Meier and co-workers, investigation of this *in-situ* mode of activation was started using in 1,1-dibenzyl-3-hydroxyurea (**3.1**) as starting material and can be seen in *Table 3-1*.

Table 3-1: Optimization of the aza-Lossen rearrangement for the semicarbazide synthesis^a

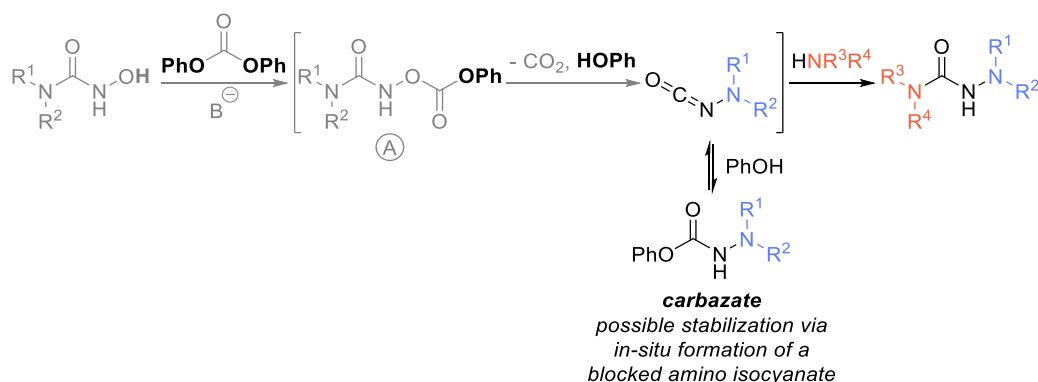


Entry	HNEt ₂ (equiv)	ROC(O)OR (equiv)	Base (equiv)	Additives (equiv)	Temp (°C)	Solvent	% 3.1	% 3.33
1	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (1.00)	DMAP (0.20)	80	MeCN	21	68
2	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (1.00)	DMAP (0.20)	100	MeCN	5	72
3	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (1.00)	DMAP (1.00)	80	MeCN	36	12
4	5.00	(MeO) ₂ CO (1.00)	Et ₃ N (1.00)	-	80	MeCN	28	15
5	5.00	Boc ₂ O (1.00)	Et ₃ N (1.00)	-	80	MeCN	18	16
6	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (1.00)	-	80	MeCN	88	9
7	5.00	(PhO) ₂ CO (1.20)	Et ₃ N (1.00)	-	80	MeCN	28	35
8	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (0.20)	-	80	MeCN	18	57
9	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (1.20)	-	80	MeCN	6	83
10	5.00	(PhO) ₂ CO (1.00)	Et ₃ N (2.00)	-	80	MeCN	17	60
11	5.00	(PhO) ₂ CO (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	-	80	MeCN	9	70
12	5.00	(PhO) ₂ CO (1.00)	Imidazole (1.20)	-	80	MeCN	22	56
13	5.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	-	80	MeCN	2	91
14	5.00	(PhO) ₂ CO (1.00)	Cs ₂ CO ₃ (1.20)	-	80	MeCN	0	88
15	5.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	-	80	THF	3	91
16	5.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	-	80	TFT	38	0
17	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	-	80	MeOH	100	0
18	1.00	(PhO)₂CO (1.00)	K₂CO₃ (1.20)	-	80	MeCN	2	92
19	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	-	50	MeCN	49	51
20	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	-	0	MeCN	66	34
21	1.00	-	K ₂ CO ₃ (1.20)	-	80	MeCN	0	29
22	1.00	(PhO) ₂ CO (1.00)	-	-	80	MeCN	61	23

Conditions: ^a 1,1-dibenzyl-3-hydroxyurea **3.1** (1.00 equiv), diethylamine, carbonate, base in solvent (0.3M) stir in an oil bath for 16 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Gratifyingly, in presence of diphenyl carbonate, triethylamine (acting as a base), a catalytic amount of DMAP and 5 equiv of the diethylamine (acting as the external nucleophile) (entry 1) the semi-carbazide (**3.33**) was obtained in 68% ¹H NMR yield, with 21% of the *N*-hydroxyurea (**3.1**) starting material remaining. Surprisingly, no methyl diethylcarbamate or 1,1,3,3-tetraethylurea, products of the mono or di-substitution of the diethylamine onto the carbonate, were observable and the rest of the mass balance was a complex mixture of side-products. Based on this result, the temperature was increased to 100 °C to induce a higher conversion of the *N*-hydroxyurea (**3.2**) and pleasantly, the product was observed in 72% ¹H NMR yield (entry 2). When 1 equiv of DMAP was used, only 12% of the desired product was

obtained with the majority of the mass balance being degradation (entry 3). Using DMAP as an additive induced degradation of the *N*-hydroxyurea supposedly via an uncontrolled reaction. Indeed, DMAP can react with diphenylcarbonate in a pre-equilibrium reaction, resulting in uncontrolled catalysis of the aza-Lossen rearrangement. The reaction was tried without DMAP and three dialkyl carbonates were chosen: when the di-*tert*-butyl dicarbonate was used (entry 5) the desired semicarbazide was observable in a similar NMR yield than with dimethyl carbonate. Diphenylcarbonate (entry 6) resulted in a poor conversion, however no degradation of the starting material was found and this carbonate was chosen to pursue further optimization. During the course of the reaction, diphenylcarbonate released two equivalents of phenol that can act as a blocking group for the newly formed *N*-isocyanate intermediate. Indeed, based on the previous literature on isocyanates and heteroatom-isocyanates,⁸⁸ it is known that phenol can reversibly add on the isocyanate leading to a better control of the concentration of this isocyanate intermediate. In the case of this study, reversible formation of a carbazate is likely, resulting in the «protection» of the *N*-isocyanate intermediate from dimerization or other degradation pathway (Scheme 3-10). However, it should be mentioned that no trace of the proposed carbazate was observed during the course or at the end of the reaction.



Scheme 3-10: Reversible in-situ formation of an amino isocyanate

By adding an excess of diphenyl carbonate (entry 7), the *N*-hydroxyurea started to degrade, possibly due to a fast formation of the *N*-isocyanate intermediate. Then, the equivalence of the Et₃N was tested (entries 8, 9 and 10) and 1.2 equiv led to the formation of the product in 85% yield. Several bases were surveyed: two organic bases with pKa higher and lower than Et₃N (entries 11 and 12) and two carbonate bases (entries 13 and 14): the yield of the desired semicarbazide increased using these inorganic bases, allegedly due to the similar structure with the dialkyl carbonate. The aza-Lossen rearrangement was then performed in different solvents (entries 15, 16 and 17): THF and MeCN were found to be the two optimum solvents and MeCN was chosen due to a better solubility of the potassium carbonate. On the other hand, PhCF₃ and MeOH were found to be incompatible with the reaction. Then, a stoichiometric amount of the diethylamine was used (entry 18) and the desired product (**3.33**) was obtained in a 92% ¹H NMR yield and these conditions were found to be optimal for the aza-Lossen rearrangement/addition cascade sequence. Indeed, when the aza-Lossen rearrangement was performed at lower temperature, only 66% at 50 °C (entry 19) and 51% at room temperature (entry 20) of semicarbazide formation was

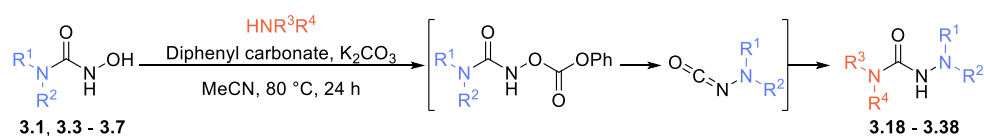
observed after 24 h. Gratifyingly, the rest of the mass balance was unreacted starting material. To conclude the optimization study, control experiments (entries 21 and 22) indicated that both diphenylcarbonate and potassium carbonate were needed for efficient semicarbazide synthesis. The full conversion of *N*-hydroxyurea (**3.1**) and the low formation of the semicarbazide (**3.33**) without the diphenylcarbonate (entry 21) was assumed by a potassium carbonate induced aza-Lossen rearrangement.¹⁹¹ Lastly, diethylamine was proposed to act as organic base when the semicarbazide formation was performed without potassium carbonate (entry 22).

The chemoselectivity of the activation (e.g. no side-reaction between the amine and the dialkyl carbonate) was hypothesised as the result of the α -effect: indeed, the presence of the lone pair of the *N* can stabilize the partial negative charge of the *O* at the transition state, resulting of its higher nucleophilicity.¹⁹² With the optimal conditions found, the scope of semicarbazide was studied, and can be seen in *Table 3-2*.

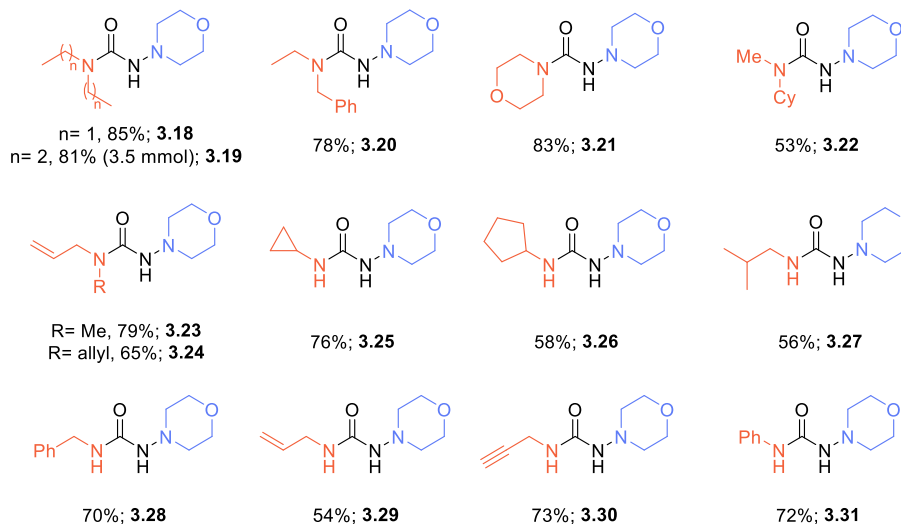
¹⁹¹ Ohtsuka, N.; Okuno, M.; Hoshino, Y.; Honda, K. *Org. Biomol. Chem.*, **2016**, 14, 9046

¹⁹² (a) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, 82, 1778. (b) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, 84, 16.

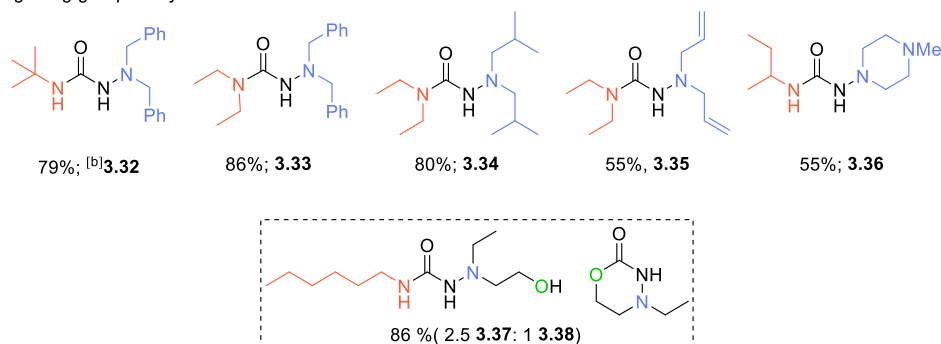
Table 3-2: Scope of semicarbazides formed via this aza-Lossen rearrangement procedure^a



Amine nucleophile study



Migrating group study

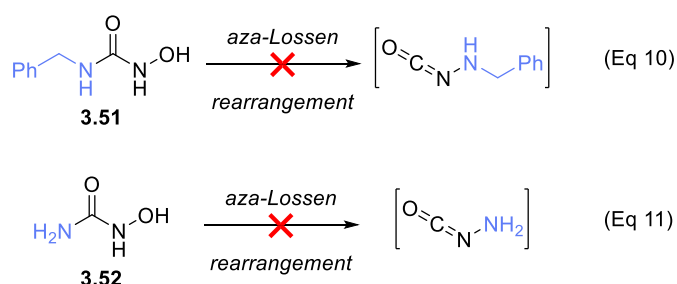


Conditions: ^a *N*-hydroxyurea (1.00 equiv), amine (1.00 equiv), diphenylcarbonate (1.00 equiv), K₂CO₃ (1.20 equiv) in MeCN (0.3 M), stir in an oil bath at 80 °C for 24 h. ^b See ^a but 5.00 equiv of *t*-BuNH₂. Isolated yields are shown.

The amine nucleophile study was performed using 1-morpholin-3-hydroxy-urea (**3.3**) due to its facile synthesis and twenty semicarbazides were isolated in moderate to good yields. First, 1,1-diethyl-3-morpholinourea (**3.18**) was isolated on a 0.6 mmol scale in good yield. To prove the utility of the aza-Lossen rearrangement, the reaction was performed on a 3.5 mmol scale using dipropylamine as the external nucleophile and the desired product (**3.19**) was obtained in 81% isolated yield. *N,N*-Benzylethylamine and morpholine furnished the semicarbazides (**3.20**, **3.21**) in good yields. The more hindered amine, *N,N*-cyclohexylmethylamine led to a lower yield due to steric hindrance (**3.22**). Finally, two allyl derivatives were also used and the products (**3.23**, **3.24**) were isolated in 79% and 65% yields respectively. It was noteworthy that no side-reaction between the amine and the diphenylcarbonate was observable when using secondary amine nucleophiles along with no observation of the dimer from the *N*-isocyanate.

Gratifyingly, the aza-Lossen rearrangement was also compatible with primary amine nucleophiles, with minimal formation of by-products. Fortunately, the carbamate and urea by-products (formed via mono- and di-addition of the primary amine onto the diphenylcarbonate) were found in less than 10% for all the examples. Moderate to good yields were obtained with cyclopropyl- and cyclopentylamine (**3.25**, **3.26**), along with isobutyl and benzyl amine (**3.27**, **3.28**). Allyl and propargyl amine led to the formation of the semicarbazides (**3.29**, **3.30**) in good isolated yields. Agreeably, the weak aniline nucleophile also reacted with the *N*-isocyanate to form the aromatic derivative (**3.31**) in 72% isolated yield.

Different amine migrating groups were also tested; the migration of the dibenzylamine was efficient and the two semicarbazides **3.32** and **3.33** were isolated in good yields. Due to the steric hindrance of the *tert*-butylamine, an excess was used to reach a 79% isolated yield of **3.32** (when 1 equiv of the *tert*-butylamine, the desired semicarbazide was obtained in 57% isolated yield). Diisobutylamine and diallylamine-derived reagents were also compatible with the aza-Lossen rearrangement, and the desired products (**3.34**, **3.35**) were obtained in good yields. Unfortunately, different nucleophiles were tried for the primary *N*-hydroxyurea (**3.51**, Eq. 10) and the free *N*-hydroxyurea (**3.52**, Eq. 11) and no formation of the corresponding semicarbazide was observed: indeed, a complex mixture of products was obtained and no starting material was recovered.



On the other hand, when the *N*-hydroxyurea bore an internal nucleophile (**3.7**), a mixture of semicarbazide (**3.37**) and the heterocycle (**3.38**) were obtained in a 2.5:1 ratio. With this first result, the synthesis of heterocycles was investigated.

3.2.4. Formation of heterocycles

The first heterocycle targeted was the oxadiazin-2-one moiety which has been studied as chiral auxiliary¹⁹³ and are active on the central nervous system.¹⁹⁴ The *N-N* bond formation step is mostly

¹⁹³ Casper, D. M.; Burgeson, J. R.; Esken, J. M.; Ferrence, G. M.; Hitchcock, S. R. *Org. Lett.* **2002**, 4, 3739.

¹⁹⁴ Trepanier, D. L.; Eble, J. N.; Harris, G. H. *J. Med. Chem.* **1968**, 11, 357.

performed by nitrosation of ephedrine derivatives,¹⁹⁴ and few examples go through ring opening of diaziridinones¹⁹⁵ or by functionalization of hydrazines.¹⁹⁶

To start, several *N*-hydroxyureas bearing a pendant alcohol were synthesized and were found to be stable without cyclization (to form the corresponding oxazolidin-2-one) via extrusion of the hydroxylamine. Those *N*-hydroxyureas (**3.7** – **3.11**) are stable even when exposed to ambient light and air for months. These substrates were subjected to the aza-Lossen rearrangement and the optimization can be seen in Table 3-3.

Table 3-3: Optimization of the aza-Lossen rearrangement for the oxadiazin-2-one synthesis^a

Reaction scheme: **3.7** $\xrightarrow[\text{MeCN, 80 } ^\circ\text{C, 24h}]{\text{ROC(O)OR, base}}$ **3.39** + **A**

Entry	ROC(O)OR (equiv)	Base (equiv)	% 3.39	%A
1	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	64	0
2	(MeO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	15	35
3	Boc ₂ O (1.00)	K ₂ CO ₃ (1.20)	72	4
4	Boc ₂ O (1.00)	Et ₃ N (1.20)	77	3
5	Boc₂O (1.00)	<i>i</i>-Pr₂NEt (1.20)	89	4
6	-	<i>i</i> -Pr ₂ NEt (1.20)	0	15
7	Boc ₂ O (1.00)	-	0	25

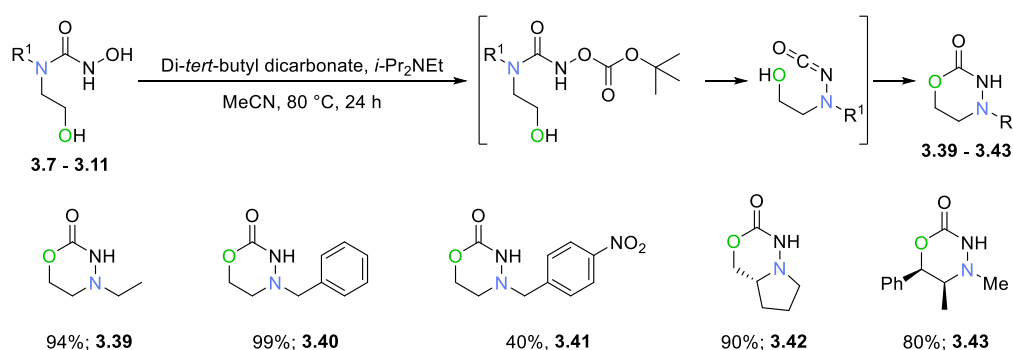
Conditions: ^a 1-(2-(ethylamino)ethyl)-3-hydroxyurea (1.00 equiv), carbonate, base in MeCN (0.3M) stir in an oil bath at 80 °C for 24 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Using the semicarbazide conditions (entry 1), the first oxadiazin-2-one product was obtained in a 64% ¹H NMR yield. By varying the dialkyl carbonate (entry 2 and 3), a side-product was observed and found to be 3-ethyl-2-oxo-1,2,3,4-tetrahydropyridazin-6(1H)-one **A** via direct cyclization onto the carbonyl of the *N*-hydroxyurea. The yield of the oxadiazin-2-one was improved with low conversion to the side-product **A** by using di-*tert*-butyl carbonate (entry 3), which was kept for the remaining of the optimization. It was proposed that the use of diphenylcarbonate (that led to the presence of phenol during the course of the reaction) was not essential in the case of heterocycle formation due to the fast-intramolecular cyclization. Organic bases were then tried (entries 4 and 5) and increased the yield of the desired heterocycles, with *i*-Pr₂NEt being the best. Finally, control experiments (entries 6 and 7) proved the importance of the base and the dicarbonate. Using the optimized conditions indicated in entry 5, different oxadiazin-2-ones were isolated (Table 3-4).

¹⁹⁵ Komatsu, M.; Sakai, N.; Hakotani, A.; Minakata, S.; Ohshiro, Y. *Heterocycles* **2000**, 52, 541.

¹⁹⁶ (a) Mackay, D.; Pilger, C. W. *Can. J. Chem.* **1974**, 52, 1114. (b) Wilson, R. M.; Chow, T. J. *Tetrahedron Lett.* **1983**, 24, 4635.

Table 3-4: Scope of oxadiazin-2-ones via aza-Lossen rearrangement^a



Conditions: ^a *N*-hydroxyurea (1.00 equiv), di-*tert*-butyl carbonate (1.00 equiv), *i*-Pr₂NEt (1.20 equiv) in MeCN (0.3 M), stir in an oil bath at 80 °C for 24 h. Isolated yields are shown.

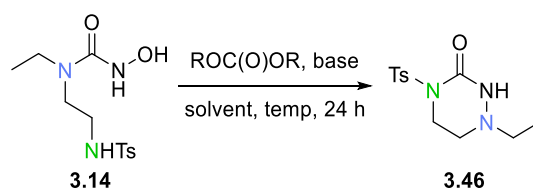
The aza-Lossen rearrangement/cyclization sequence was found to be efficient and five different oxadiazin-2-ones were isolated in moderate to excellent yields. *N*-Ethyl and *N*-benzyl substituents (**3.39**, **3.40**) were first tested and the corresponding heterocycles were obtained in excellent yields. The *p*-nitrobenzyl substituent (**3.41**) led to a moderate yield due to solubility issues during the course of the reaction but also during the purification. However, this example is significant as NO₂ groups are incompatible with other conditions reported for the synthesis of oxadiazin-2-ones (e.g. used of LiAlH₄).¹⁹⁴ Proline derivative furnished the bicycle product (**3.42**) in excellent yield. Finally, the ephedrine derivative (**3.43**) was synthesized for direct comparison of the method: the aza-Lossen rearrangement/cyclization sequence was one step shorter and avoided the use of sodium nitrite and LiAlH₄.¹⁹⁴

Lastly, triazin-3-ones were investigated, pending from the addition of a diamine onto the *O*-isocyanate. Triazin-3-ones are often used as rigid aza-tripeptides¹⁹⁷ and are selective 5-lipoxygenase inhibitors.¹⁹⁸ Their current *N-N* bonds formation involved the incorporation of this motif via the use of hydrazines¹⁹⁹ or the use of strong oxidant (e.g. NaNO₂) for the nitration of amines.¹⁹⁸ The formation of triazinone was optimized using *N*-hydroxyurea (**3.14**) as starting material which was obtained via substitution of the HO-N=C=O using the corresponding diamine under the conditions found in *Chapter 1*. The results can be seen in *Table 3-5*.

¹⁹⁷ Gante, J.; Neunhoeffler, H.; Schmidt, A. *J. Org. Chem.* **1994**, 59, 6487.

¹⁹⁸ Bhatia, P. A.; Brooks, C. D. W.; Basha, A.; Ratajczyk, J. D.; Gunn, B. P.; Bouska, J. B.; Lanni, C.; Young, P. R.; Bell, R. L.; Carter, G. W. *J. Med. Chem.* **1996**, 39, 3938.

¹⁹⁹ Nogrady, T.; Vagi, K. M. *J. Org. Chem.* **1962**, 27, 2270.

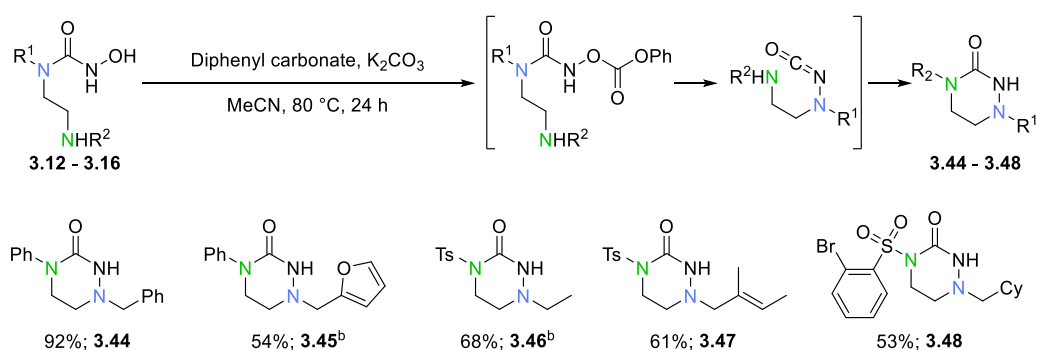
Table 3-5: Triazinone formation optimization^a

Entry	ROC(O)OR (equiv)	Base (equiv)	Solvent	Temp (°C)	% 3.46
1	(PhO)₂CO (1.00)	K₂CO₃ (1.20)	MeCN	80	65
2	Boc ₂ O (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	MeCN	80	40
3	(PhO)₂CO (1.00)	K₂CO₃ (1.20)	MeCN	50	63
4	(PhO) ₂ CO (1.20)	K ₂ CO ₃ (1.20)	MeCN	r.t.	58
5	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	DMF	50	29
6	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	Dioxane	50	24
7	(PhO) ₂ CO (2.00)	K ₂ CO ₃ (2.40)	MeCN	50	50

Conditions: ^a 1-(1-(1-ethylamino)ethyl-4-methylbenzenesulfonamide)-3-hydroxyurea **3.14** (1.00 equiv), carbonate, base in solvent (0.3M) stir in an oil bath for 24 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Gratifyingly, the desired triazinone was observed without any side-reaction involving the secondary amine and the dialkyl carbonate. First, the semicarbazide conditions (diphenyl carbonate with K₂CO₃) (entry 1) and the oxadiazin-2-one conditions (di-*tert*-butyl dicarbonate and *i*-Pr₂NEt) (entry 2) were tested and the heterocycle was obtained in 65% and 40% ¹H NMR yields, respectively. Diphenylcarbonate and K₂CO₃ were kept for the rest of the optimization and the reaction was performed at lower temperatures (entries 3 and 4), and the desired product was obtained in similar yield at room temperature, 50 and 80 °C. DMF and Dioxane were also tried (entries 5 and 6) and the desired triazinone was obtained in lower yields than MeCN. Finally, 2 equiv of diphenyl carbonate and 2.4 equiv of K₂CO₃ were tested at 50 °C and the triazinone was observed in 50% ¹H NMR yield. Degradation of the starting material was observed at the end of the observation supposedly due to the weak nucleophilicity of the nitrogen inducing a difficult addition onto the *N*-isocyanate intermediate. With the optimum conditions found for the synthesis of the triazinones, the scope of the aza-Lossen rearrangement was studied. To avoid any cyclization during the synthesis of the starting materials, the second amine needed to be a weak nucleophile such as *N*-phenyl or a *N*-tosyl amine derivatives. The scope of the reaction can be seen in Table 3.6.

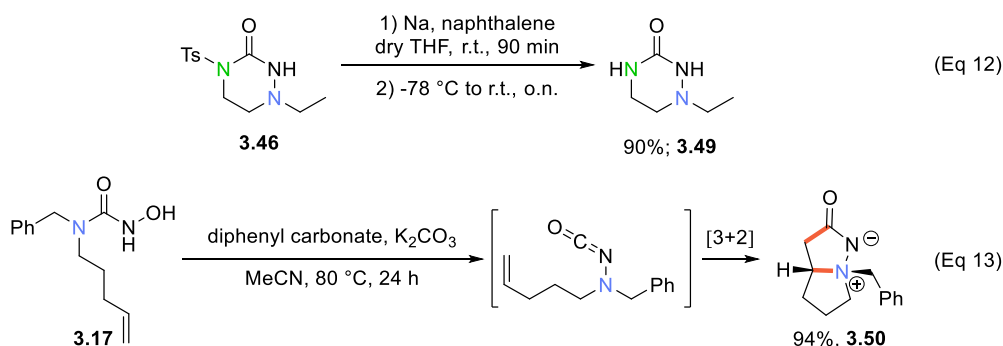
Table 3-6: Scope of triazin-3-ones via aza-Lossen rearrangement^a



Conditions: ^a *N*-hydroxyurea (1.00 equiv), diphenylcarbonate (1.00 equiv), K₂CO₃ (1.20 equiv) in MeCN (0.3 M), stir in an oil bath at 80 °C for 24 h. Isolated yields are shown. ^b See ^a but at 50 °C.

Aniline derivatives were isolated in excellent (**3.44**) and moderate (**3.45**) yields. The isolated yields for the three tosyl derivatives were lower supposedly due to a harder cyclization step, and triazin-3-ones bearing an ethyl (**3.46**), an allyl (**3.47**) and bromo tosyl (**3.48**) were isolated in good yields.

The tosyl group was easily removed using Na, naphthalene conditions via a Birch-type reduction (Eq 12). This result is synthetically useful, supporting that sequential derivatization of the two nitrogen atoms is possible.

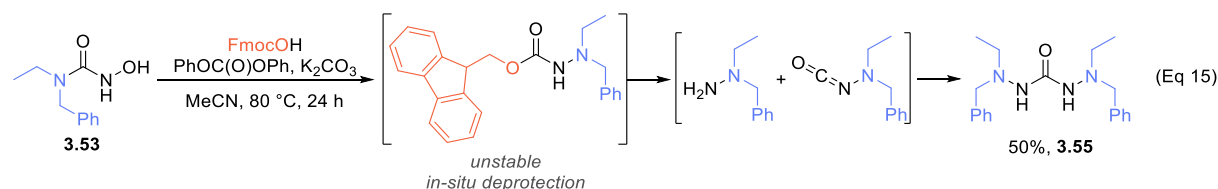
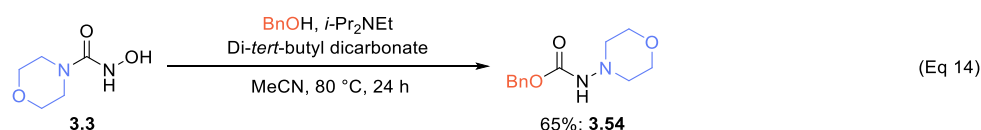


To expand the generality of *N-N* bonds formation via aza-Lossen rearrangement, aminimide (**3.50**) was isolated in excellent yield via the first aza-Lossen rearrangement/aminocarbonylation sequence (Eq 13). This cascade reaction implied a simpler starting material synthesis and milder conditions than the reported synthesis of aminimides.²⁰⁰ Finally, these results also inherently provide strong support for the formation of a nitrogen-substituted isocyanate being formed under the reaction conditions.

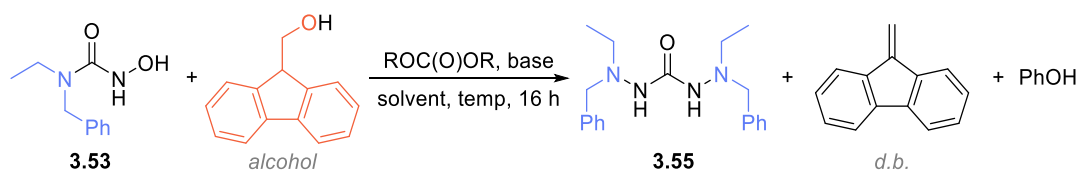
²⁰⁰ (a) Moon, B.; Han, S.; Kim, D. *Org. Lett.* **2005**, 7, 3359. (b) Ivanovich, R. A.; Clavette, C.; Vincent-Rocan, J.-V.; Roveda, J.-G.; Gorelsky, S. I.; Beauchemin, A. M. *Chem.-Eur. J.* **2016**, 22, 7906.

3.2.5. Hydrazine synthesis

The formation of free hydrazine was also investigated using the aza-Lossen rearrangement strategy. The first approach tried was to use alcohol as external nucleophile for the synthesis of protected hydrazine derivatives. For example, the Cbz-protected hydrazine (**3.54**) was isolated in 65% yield when benzyl alcohol was used (Eq 14). Then, (9H-fluoren-9-yl)methanol was also tried for the synthesis of Fmoc-hydrazine. The Fmoc-hydrazine was observed via ^1H NMR, however due to the basic conditions, deprotection happened releasing an equivalent of the free hydrazine (Eq 15).



Due to the better nucleophilicity of the hydrazine than the alcohol, the carbazide (**3.55**) was the only product formed in good yield from the addition onto the *N*-isocyanate (Eq 15). Optimization was undertaken for the synthesis of symmetrical carbazide via aza-Lossen rearrangement/deprotection sequence using *N*-hydroxyurea as starting material (Table 3-7).

Table 3-7: Carbazide formation optimization^a

Entry	Alcohol (equiv)	ROC(O)OR (equiv)	Base (equiv)	Temp (°C)	Solvent	% 3.53	%ROH	% 3.55	%d.b.	%PhOH
1	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	MeCN	0	0	50	54	100
2	1.00	Boc ₂ O (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	80	MeCN	9	0	0	25	-
3	1.00	(PhO) ₂ CO (1.00)	Et ₃ N (1.20)	80	MeCN	0	22	14	49	100
4	1.00	(PhO) ₂ CO (1.20)	Imidazole (1.20)	80	MeCN	8	8	28	36	100
5	1.00	(PhO) ₂ CO (1.00)	<i>N</i> -MeM* (1.20)	80	MeCN	0	0	0	30	100
6	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	CHCl ₃	4	0	30	20	33
7	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	Dioxane	0	0	15	8	44
8	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	PhMe	0	0	27	38	4
9	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	MeCN/H ₂ O	0	0	0	49	100
10	1.50	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	MeCN	0	0	45	67	100
11	2.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	MeCN	0	0	47	98	100
12	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	50	MeCN	0	0	30	34	61
13^b	1.00	(PhO)₂CO (1.00)	K₂CO₃ (1.20)	80	MeCN	0	0	85	59	100
14 ^b	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	50	MeCN	0	0	49	38	90
15 ^b	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	r.t.	MeCN	0	0	0	25	72
16 ^b	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (0.50)	80	MeCN	0	0	60	51	100
17 ^b	1.00	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.00)	80	MeCN	0	0	50	50	81

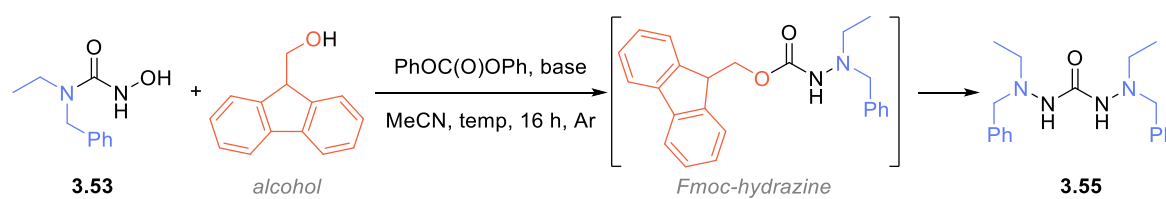
N-MeM = *N*-methylmorpholine

Conditions: ^a 1-benzyl-1-ethyl-3-hydroxyurea (1.00 equiv), (9H-fluoren-9-yl)methanol, dialkyl carbonate and base in solvent (0.3M) stir in an oil bath for 16 h. ^b See ^a but under inert atmosphere. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

The formation of the carbazide was observed along with 9-methylene-9H-fluorene, product of the deprotection, with no traces of the free hydrazine. The two different conditions found during the semicarbazide and oxadiazinone synthesis were tested (entries 1 and 2) and the carbazide was only observed using diphenyl carbonate as the activating reagent. Using different bases (entries 3 - 5) and solvents (entries 6 - 9) resulted in a lower ¹H NMR yield for (**3.55**) than the semicarbazide conditions

(entry 1). Increasing the amount of the (9H-fluoren-9-yl)methanol (entries 10-11) led to the formation of the carbazide in similar yield than using only 1 equivalent. Performing the reaction at 50 °C induced a lowering in the yield with full conversion of the starting material (entry 12). The proposed hydrazine intermediate being sensitive to oxidation, the reaction was then tested under inert atmosphere (after Ar purged) and gratifyingly, the desired carbazide was observed in 85% ¹H NMR yield (entry 13). The aza-Lossen rearrangement was then performed strictly under inert atmosphere, and at lower temperatures (entries 14 and 15) full conversion of the *N*-hydroxyurea was observed with only 0 to 50% formation of the desired product. Finally, the equivalence of the base was diminished (entries 16 and 17) and once again full conversion of the starting material was observed with a lower yield for **3.55** than the reaction performed at 80 °C. Along with the synthesis of the carbazide **3.55**, study for the formation and isolation of the intermediate Fmoc-hydrazine was also performed and the result can be found in *Table 3-8*.

Table 3-8: Study of the formation of the protected Fmoc-hydrazine^a

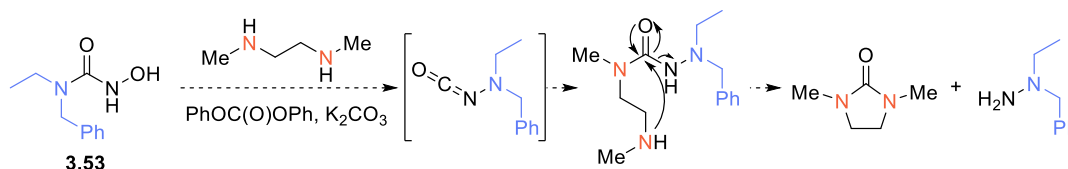


Entry	Base (equiv)	Temp (°C)	%Fmoc-hydrazine	% 3.55
1	K ₂ CO ₃ (1.20)	80	0	85
2	K ₂ CO ₃ (0.20)	80	0	64
3	Imidazole (0.20)	80	34	28
4	-	80	46	17
5	-	50	32	0

Conditions: ^a 1-benzyl-1-ethyl-3-hydroxyurea (1.00 equiv), (9H-fluoren-9-yl)methanol (1.00), diphenyl carbonate (1.00) and base in MeCN (0.3M) stir in an oil bath for 16 h under Ar. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Unfortunately, the protected Fmoc-hydrazine could not be isolated, despite extensive efforts, and was only observable by ¹H NMR. Indeed, with the optimum basic conditions found for the synthesis of the carbazate (**3.55**), the protected Fmoc-hydrazine was not observed and fully deprotected to form the carbazide (entry 1). A catalytic amount of K₂CO₃ was then tried inducing a lower yield for the carbazide with no protected Fmoc-hydrazine found (entry 2). A weaker base was then chosen and when the aza-Lossen rearrangement was performed with a catalytic amount of imidazole (entry 3), the protected Fmoc-hydrazine intermediate was found in 34% isolated yield with 28% of the carbazide. Finally, the reaction was tested without base and the desired intermediate was observed in 46% ¹H NMR yield when heated at 80 °C and 32% at 50 °C. All attempts to isolate the protected hydrazine resulted in its deprotection followed by the degradation of the free hydrazine.

Owing from the reaction of the formed hydrazine and the *N*-isocyanate, a better nucleophile than hydrazine needed to be present during the course of the reaction. Diamine was selected for the formation of the free hydrazine via its extrusion from the adduct of the addition onto the *N*-isocyanate (Scheme 3-11).



Scheme 3-11: Proposed formation of free hydrazine

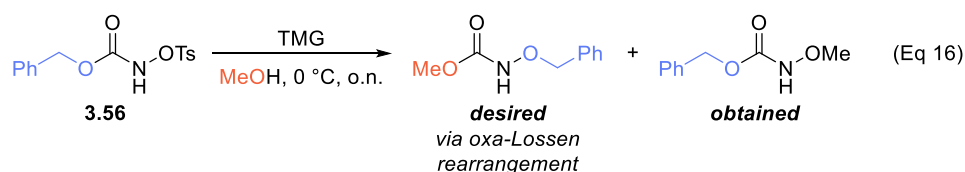
Unfortunately, this strategy was found to be inefficient due to the side-reaction between the diamine and the diphenylcarbonate that formed the cyclic urea (*investigation can be found on the SI*).

For the first part of the study, formation of *N-N* bonds via controlled aza-Lossen rearrangement was presented. The starting materials used were stable and easy to handle and the conditions were mild enough for the synthesis of different hydrazide derivatives. The strategy converted simple amines into complex *N-N* bonds containing molecules in two steps.

3.2.6. Oxa-Lossen rearrangement

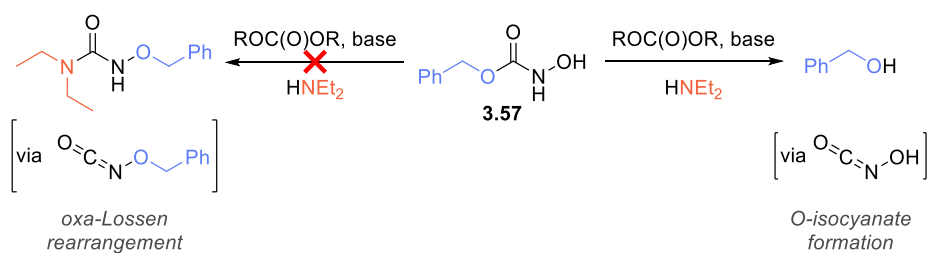
The oxa-Lossen rearrangement has been reported (see 2.1.3.3.3.) often as an unwanted reaction, and similar to the aza-Lossen rearrangement, could potentially be developed to be broadly applicable for the formation of *N-O* bonds of complex hydroxamic acid derivatives. In this section, exploratory trials toward this goal are presented.

At the difference of the *N*-oxyureas, *N*-oxycarbamates bearing strong electron withdrawing group can be synthesized and isolated and are stable when stored in a refrigerator. The OTs derivative (**3.56**) was first used as starting material and in presence of a base in MeOH only the OH insertion product was observed (Eq 16): indeed, no product arising from an oxa-Lossen rearrangement was found. The formation of the benzyl methoxycarbamate can either be explained by an electrophilic amination²⁰¹ or an OH-insertion of a nitrene intermediate.¹²²



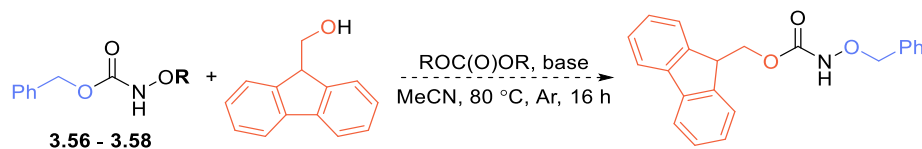
²⁰¹ Zhou, Z.; Kurti, L. *Synlett* **2019**, 30, 1525.

At the same time than the *in-situ* activation of *N*-hydroxyurea was investigated, benzyl hydroxycarbamate (**3.57**) was subjected to dialkyl carbonate and base in presence of diethylamine (*Scheme 3-12*). No trace of oxa-Lossen rearrangement was detected, instead benzyl alcohol was isolated supposedly via its extrusion with the concomitant formation of the HO-N=C=O. Despite investigation (*see SI*), benzyl alcohol was the only product obtained for this strategy. No trace of the addition of the diethylamine onto the supposedly formed *O*-isocyanate was found.



Scheme 3-12: Formation of benzylic alcohol under in-situ activation

The same Fmoc-strategy was also tested and once again the formation of the benzyl alcohol via a proposed formation of an *O*-isocyanate was the only product observable (*see SI*) (*Scheme 3-13*).



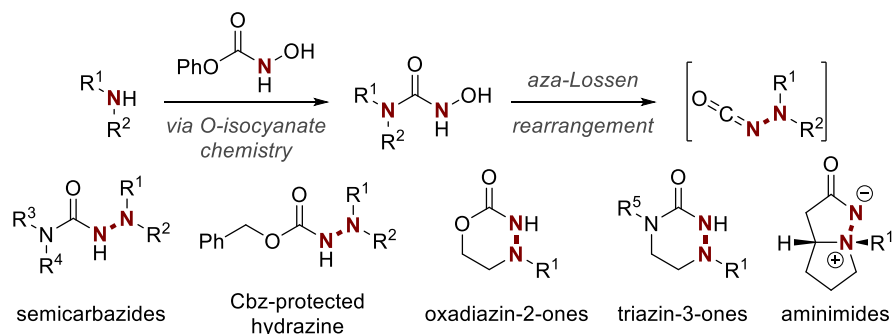
Scheme 3-13: Proposed synthesis of (9H-fluoren-9-yl)methyl (benzyloxy)carbamate

All the attempted oxa-Lossen rearrangement with *N*-oxycarbamates resulted in the formation of the corresponding *O*-isocyanate: indeed, the migrating group for the oxa-Lossen rearrangement can also be a blocking group for *O*-isocyanate. The conditions tested being closed to the deblocking conditions of *O*-isocyanate from *N*-oxycarbamates, this pathway was the most favorable for all the experiments.

3.3. Conclusion and perspectives

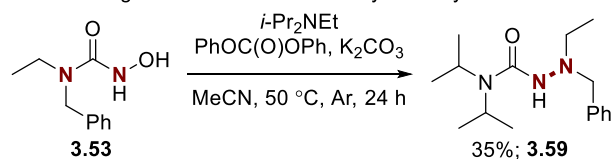
In this chapter, a broadly applicable procedure for *N-N* bond formation via aza-Lossen rearrangement was described (*Scheme 3-14*). The *N*-hydroxyureas used are stable and easy to work with and the experimental conditions are mild and use non-toxic chemicals. This strategy allowed for the synthesis of complex hydrazide derivatives in only two steps for commercially available amines. Moreover, the good control of the *N*-isocyanate reactivity allowed for both inter- and intra-molecular reactivity for the synthesis of acyclic and heterocyclic structures, respectively.

Two steps hydrazide derivatives synthesis from simple amines

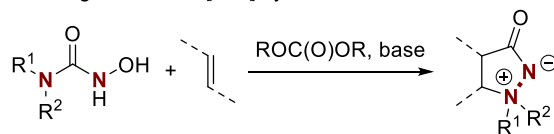


On-going study:

- aza-Lossen rearrangement for blocked *N*-isocyanate synthesis



- aza-Lossen rearrangement/inter [3+2] cycloaddition cascade reaction



Scheme 3-14: Formation of N-N bonds

The chemistry developed here is currently used for the synthesis of blocked *N*-isocyanate: indeed, previous methods for the semicarbazides formation did not permit the synthesis of diisopropylamine derivatives in good yield. Using the semicarbazide conditions, the semicarbazide (**3.59**) was isolated in 35% yield. The aza-Lossen rearrangement inter [3+2] cycloaddition cascade reaction is also under investigation, to increase the scope of aminimides.

Chapter 4: Light induced C-H amination

In this chapter, an overview of prior work involving the formation of *N*-centered radical and nitrene intermediates under light irradiation/photoredox conditions are presented. Then, the development of a photoredox C-H amination procedure using *N*-benzoyloxyurea as starting materials for the synthesis of various heterocycles is described.

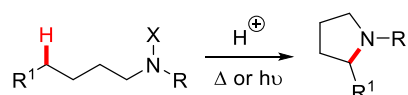
4.1. Formation of *N*-centered radical and nitrenes

Several reactive intermediates can be derived from a nitrogen atom. These intermediates display rich reactivity and reactive intermediates that are relevant to this chapter are: 1) a *N*-centered radical can be formed via one electron chemistry and 2) a nitrene intermediate, in a singlet or triplet state, can also be obtained from azide starting materials. Formation of *N*-centered radical via cleavage of a N-O bond of hydroxylamine derivatives as be reviewed in Chapter 1. In this part, selected examples of formation of *N*-centered radical via PCET and photoinduced formation of nitrene intermediates and/or photoredox conditions are presented.

4.1.1. *N*-centered radical

4.1.1.1. Via Hofmann-Löffler-Freytag reaction

Perhaps, one of the most used cyclization reactions involving a *N*-centered radical intermediate is the Hofmann-Löffler-Freytag reaction that allows for the synthesis of heterocycles from linear *N*-halogenated amines (Scheme 4-1).²⁰²

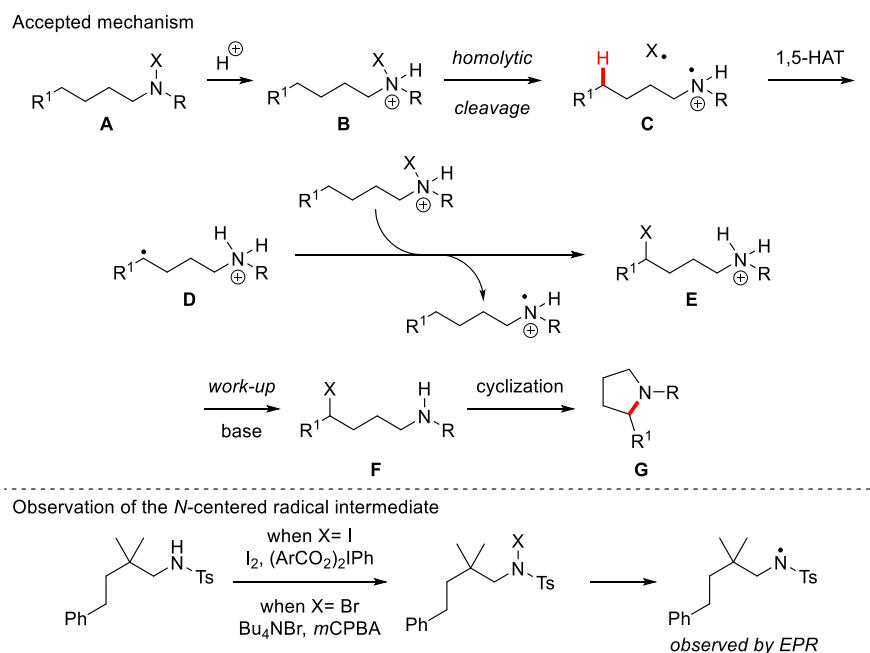


Scheme 4-1: General Hofmann- Löffler-Freytag reaction

The mechanism is now well accepted and involves the homolytic cleavage of a *N*-X intermediate **B** (where X is a halogen) from a protonated *N*-halogenated amine **A** (Scheme 4-2). The cleavage can be induced by heat, irradiation or radical initiators and leads to the formation of a protonated aminium radical **C**. This intermediate undergoes 1,5-HAT, resulting in a new carbon radical **D**. This radical reacts intermolecularly with the protonated *N*-halogenated amine **B** leading to the formation of a γ -halogenated amine **E**. This propagation step generates one full equivalent of the aminium radical **C**. After a basic work-up and deprotonation of the amine (intermediate **F**), intramolecular S_N2 reaction forms the 5-

²⁰² (a) Wolff, M. E. *Chem. Rev.* **1963**, 63, 55. (b) Stella, L. *Angew. Chem., Int. Ed.* **1983**, 22, 337.

membered ring product **G**. Evidences for this mechanism have been published over the years²⁰³ and in 2019, observation by EPR of the *N*-centered radical intermediate **C** was reported.²⁰⁴



Scheme 4-2: Accepted mechanism for the Hofmann-Löffler-Freytag reaction and observation of the reactive intermediate

In the seminal works by Hofmann²⁰⁵ and Löffler and Freytag,²⁰⁶ *N*-bromo amines were heated at high temperature in presence of strong acids. Nowadays, the Hofmann-Löffler-Freytag reaction is performed under milder conditions and different halogens can be used (Scheme 4-3).²⁰⁷ Moreover, the reaction can now be photoinduced.²⁰⁸

²⁰³ (a) Wawzonek, S.; Thelen P. *J. Am. Chem. Soc.* **1950**, 72, 2118. (b) Wawzonek, S.; Nelson, M. F. Jr.; Thelen, P. *J. Am. Chem. Soc.* **1951**, 73, 2806. (c) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, 82, 1657.

²⁰⁴ Bosnidou, A. E.; Duhamel, T.; Muñiz, K. *Eur. J. Org. Chem.* **2019**, 10.1002/ejoc.201900497.

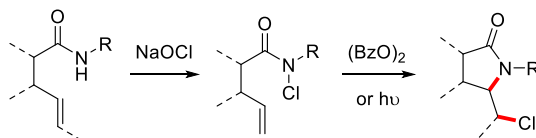
²⁰⁵ Hofmann, A. *W. Ber. Dtsch. Chem. Ges.* **1883**, 16, 558.

²⁰⁶ Löffler, K.; Freytag, C. *Ber. Dtsch. Chem. Ges.* **1909**, 42, 3427.

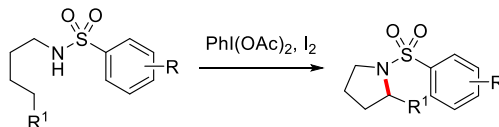
²⁰⁷ For selective examples see: (a) Mackiewicz, P.; Furstoss, R.; Waegell, B.; Cote, R.; Lessard, J. *J. Org. Chem.* **1978**, 43, 3746. (b) Fan, R.; Pu, D.; Wen, F.; Wu, J. *J. Org. Chem.* **2007**, 72, 8994. (c) Chen, R.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, 130, 7247. (d) Martinez, C.; Muñiz, K. *Angew. Chem., Int. Ed.* **2015**, 54, 8287.

²⁰⁸ Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. *Chem. Soc. Rev.* **2016**, 45, 2044.

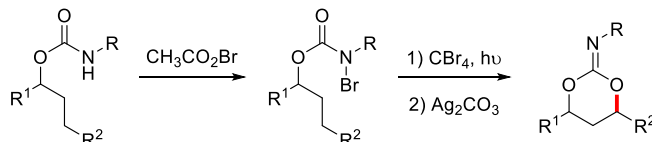
- Lessard (1978)



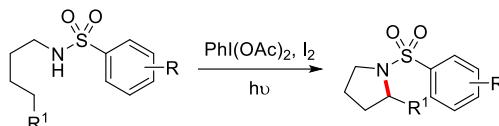
- Wu (2007)



- Baran (2008)



- Muniz (2015)

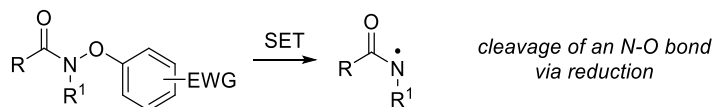


Scheme 4-3: Examples of Hofmann-Löffler-Freytag reaction

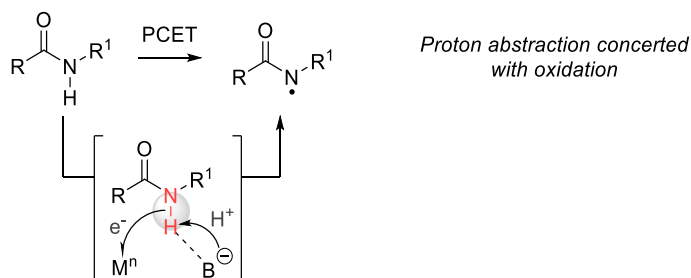
4.1.1.2. Via photoredox conditions

In chapter one, the formation of amidyl radical via SET reduction and cleavage of weak *N*-O bonds of hydroxamic acids was reviewed (see 1.4.2.1.). In the present section, a second approach to access this reactive intermediate is presented: indeed, in the last past years, a new methodology was developed pending from the cleavage of a weak *N*-H bond, usually arising from the presence of an electron withdrawing group on the nitrogen atom (Scheme 4-4).

Formation of amidyl radical via SET



Formation of amidyl radical via PCET

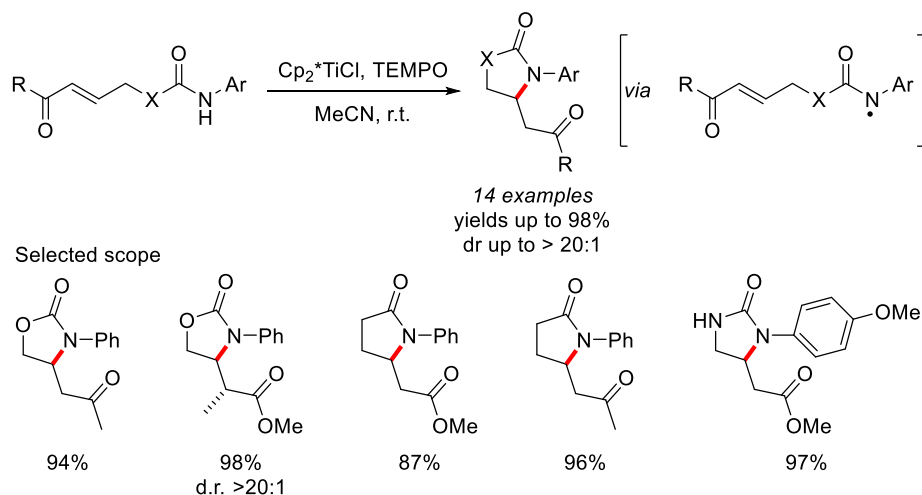


Scheme 4-4: Two approaches for the formation of amidyl radical

This process, called Proton Coupled Electron Transfer (or PCET), uses a base and an oxidant. The formation of the desired amidyl radical is the result concomitant weakening of the *N*-H bond and the

oxidation of the N-H by the oxidant. This method is commonly used with carbamate derivatives, amides and only a handful of examples with ureas. The *N*-centered radical intermediate formed can undergo 1,5-HAT on an alkyl chain or cyclization onto an olefin.¹¹⁹

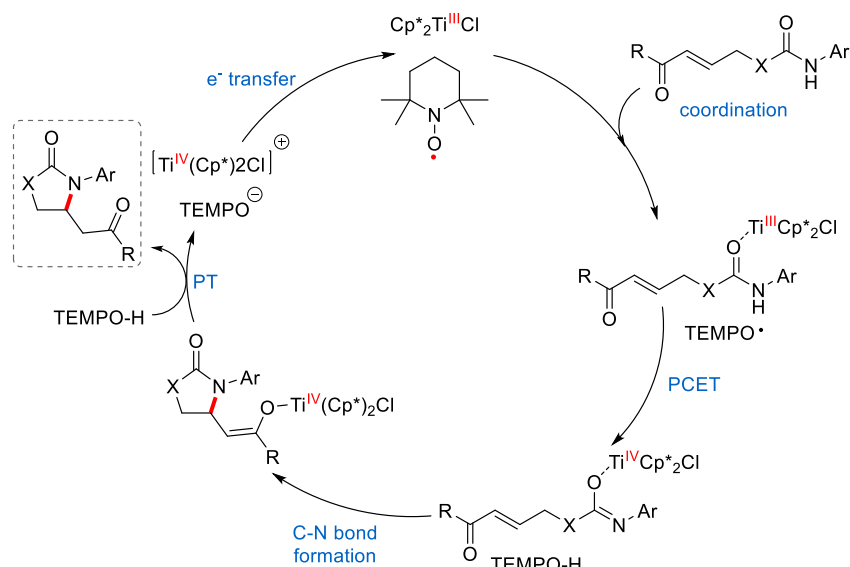
One of the first examples of formation of amidyl radical via a PCET mechanism was reported by the group of Knowles in 2015 for the synthesis of *N*-heterocycles (Scheme 4-5).²⁰⁹



Scheme 4-5: Synthesis of heterocycles via amidyl radical formation via PCET

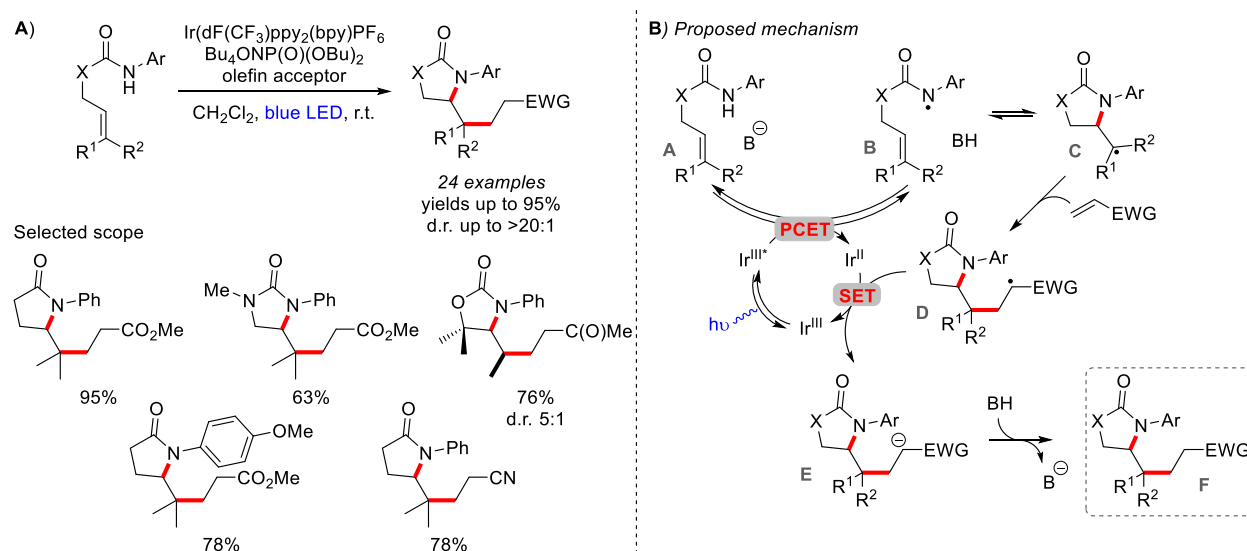
In this first study, fifteen heterocycles bearing a *C-N* bond were isolated with yields ranging from 69 to 98%. However, the reaction was limited to aromatic aniline derivatives and only two examples of uridyl *N*-centered radical were reported. In this remarkable study, the authors destabilized the *N-H* bond of *N*-aryl amides via coordination with a catalytic amount of $\text{Cp}^*_2\text{Ti}^{\text{III}}\text{Cl}$. After this coordination and the lowering of the BDE of the *N-H* bond, TEMPO was used and the corresponding amidyl radical was obtained via PCET (Scheme 4-6). After the formation of the *N*-amidyl radical, 5-*exo-trig* cyclization occurred, leading to the formation of the *C-N* bond. Proton transfer with the newly formed protonated TEMPO-H, released the desired heterocycle. Finally, electron transfer between the reduced form of TEMPO and the oxidized titanocene closed the catalytic cycle.

²⁰⁹ Tarantino, K. T.; Miller, D. C.; Callon, T. A.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, 137, 6440.



Scheme 4-6: Proposed catalytic bond-weakening/PCET sequence for C-N bond formation

After this first publication, Knowles and co-workers reported the first amidyl radical formation via PCET under photoredox conditions (Scheme 4-7).²¹⁰. In presence of a photocatalyst, a Brønsted base and under irradiation, the same *N*-amidyl radical intermediates were obtained.



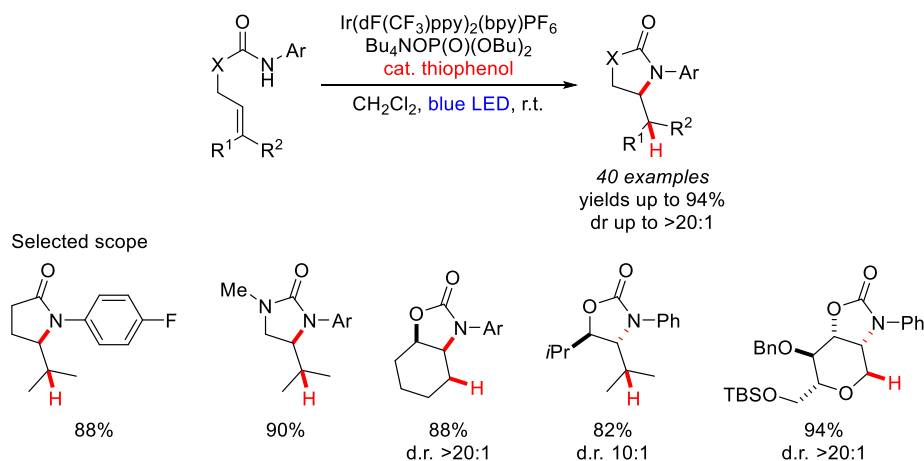
Scheme 4-7: A) Scope of alkene Carboaminations via Oxidative PCET and B) proposed mechanism

This proposed *N*-centered radical underwent 5-*exo-trig* cyclization to form a C-N bond (Scheme 4-7 part B). An iridium photocatalyst was used, and after its photo-excitation, the amide derivative **A** was oxidized in presence of a phosphate base leading to the formation of the *N*-centered radical **B**. 5-*Exo-trig* cyclization resulted in the formation of a carbon radical **C** that reacted intermolecularly with an olefin acceptor bearing electron withdrawing group substituent. Due to the presence of this electron

²¹⁰ Choi, G. J.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226.

withdrawing group, the newly formed carbon radical **D** was easily reduced by Ir^{II} (closing the catalytic cycle of the photocatalyst). Finally, proton abstraction of the protonated base led to the formation of the desired product **F** and regeneration of the base (which was used catalytically). Similarly, to the first report, the reaction was limited to aniline derivatives (due to the weak *N-H* bond) and different electron-poor alkenes were tested bearing for example ester, aldehyde or nitrile moiety. Only one example of imidazolidinone was reported in this study. This first publication unlocked the use of amidyl radical formation via photoredox conditions due to the facile synthesis of the starting materials and the mild conditions used.

The reaction was not only limited to carboamination of alkenes and shortly after those two reports, the catalytic hydroamination of alkenes was published using a catalytic amount of thiophenol acting as a hydrogen donor under the same PCET conditions (Scheme 4-8).²¹¹



Scheme 4-8: Catalytic hydroamination of alkenes via PCET

The hydroamination of alkenes was efficient and forty examples of heterocycles were isolated (lactams, carbamates and imidazolidinones for example) in good to excellent yields. Only one example of urea was reported in this new study. Many reports have been published since then and the reaction is now compatible with aliphatic amides,²¹² sulfonamides²¹³ or even alkyl amines.²¹⁴

In 2016, the group of Knowles²¹⁵ and Rovis²¹⁶ published simultaneously, the 1,5-derivatization of amides using PCET (Scheme 4-9). After formation of the amidyl radical via PCET, the key step was a 1,5-HAT and the formation of a carbon radical. Then, similarly to the oxyamidation strategy,

²¹¹ Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 13492.

²¹² Nguyen, S. T.; Zhu, Q.; Knowles, R. R. *ACS Catal.* **2019**, *9*, 4502.

²¹³ Zhu, Q.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 741.

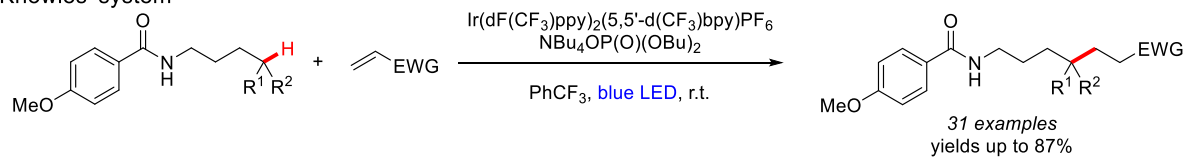
²¹⁴ Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727.

²¹⁵ Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268.

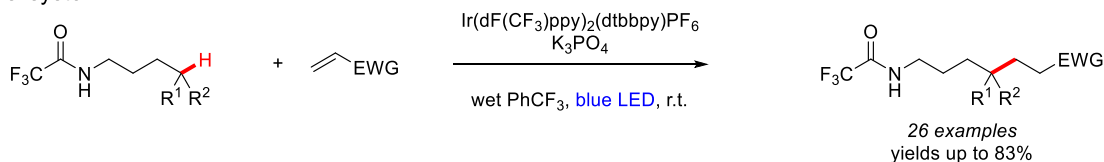
²¹⁶ Chu, J. K. C.; Rovis, T. *Nature*, **2016**, *539*, 272.

intermolecular reaction with an electron-poor olefin, reduction and hydrogen abstraction led to the amide derivatives functionalized at the 1,5-position.

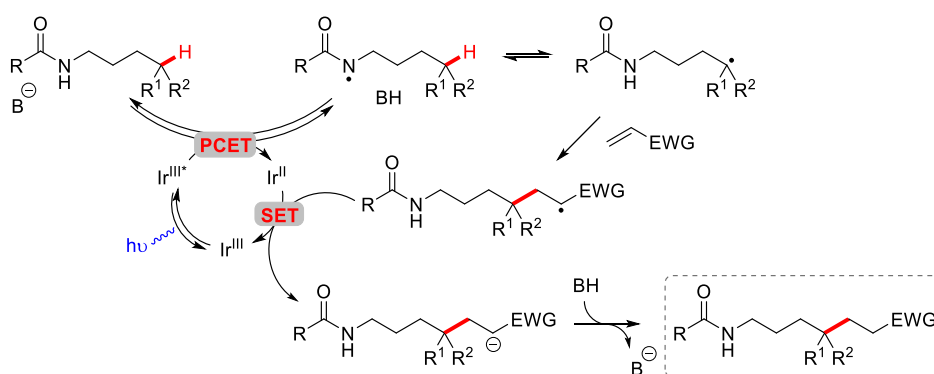
Knowles' system



Rovis' system



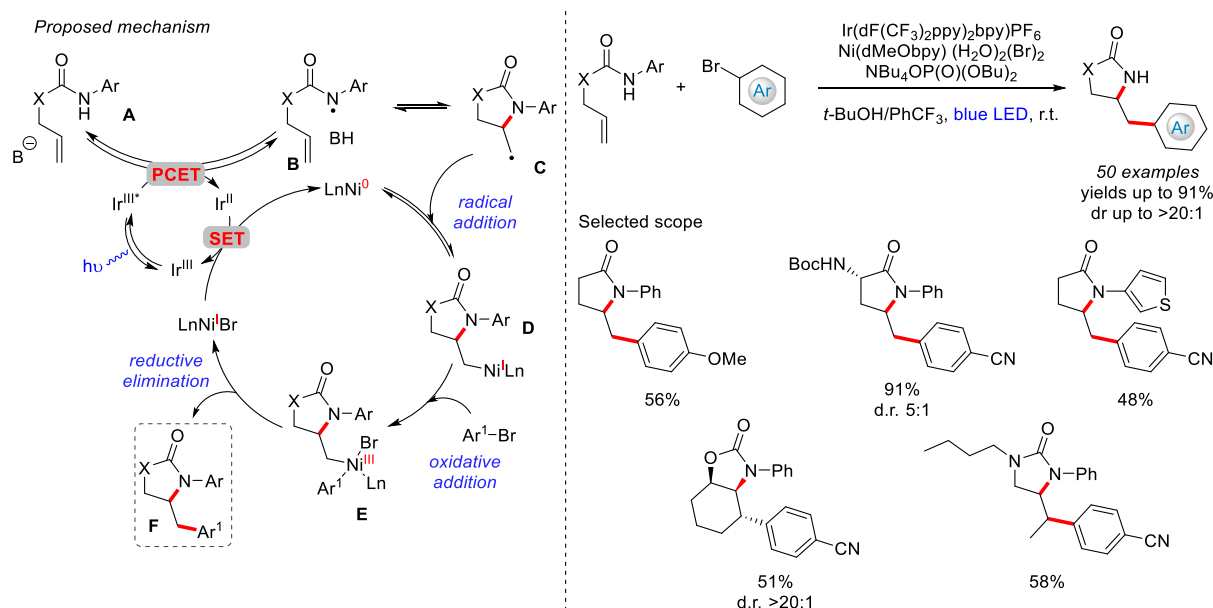
Proposed mechanism



Scheme 4-9: 1,5-Derivatization of amides via PCET

Variants of this PCET method have recently been reported: Molander and co-workers published one of the first PCET/Ni-catalyzed cross-coupling cascade reaction for the amidoarylation of unactivated alkenes (Scheme 4-10).²¹⁷ Using a dual catalysis, the authors synthesized various heterocycles bearing aromatic groups on their alkyl chain.

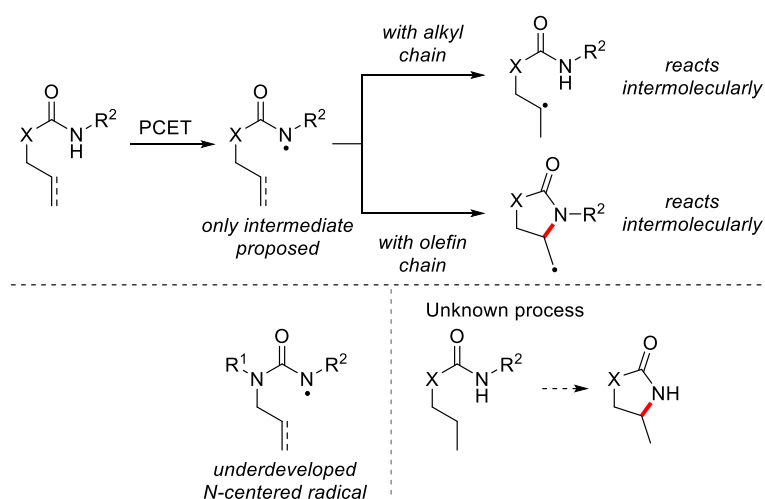
²¹⁷ Zheng, S.; Gutiérrez-Bonet, Á.; Molander, G. A. *Chem* **2019**, 5, 339.



Scheme 4-10: Cascade PCET/Ni-catalyzed cross coupling cascade reaction amidoarylation of alkenes

Under photoredox conditions, the carbon radical (**C**) was formed (via a similar mechanism than the previous reports of carboamination and hydroamination of alkenes) and was then trapped by Ni^0 (to form the intermediate **D**) (Scheme 4-10). The Ni^{I} species (**D**) underwent oxidative addition with an aryl bromide derivative. After reductive elimination of (**E**), the amidoarylation product (**F**) was obtained. SET between the $\text{Ni}^{\text{I}}\text{Br}$ and the reduced form of the Ir^{II} closed the two catalytic systems. This sequence led to fifty examples of the formation of heterocycles in good to excellent yields. The reaction was limited to aniline derivatives for the amidyl radical starting materials where the aryl bromide partner was compatible with electron-withdrawing and donating substituents. Only two examples of imidazolidinones were reported with moderate isolated yields.

Applications of PCET to activate amides increases rapidly each year, however one of the limitations is the use of urea as starting materials. Indeed, uridyl *N*-centered radicals are still rare and only few examples are reported. Moreover, the only intermediate suggested so far is a *N*-centered radical: certainly, being able to access different intermediates will increase the potential of the PCET reactivity and will allow the synthesis of new heterocycles (Scheme 4-11).



Scheme 4-11: Summary of N-centered radical formation under PCET and limitations

4.1.2. Nitrene formation

Another reactive intermediate derived from nitrogen atoms is the nitrene. As explained in *part 1.4.2.2*, nitrenes are high energy species and can exist in two states: singlet (where the two electrons are in the same orbital and triplet where the electrons are in two different orbitals). Nitrenes are usually obtained from α -elimination of activated amide starting materials¹²² and can be stabilized by the use of metal catalysts (*see 1.4.2.2*). Until recently, it was believed that only singlet nitrenes can undergo C-H amination whereas the triplet state was only limited to aziridination.²¹⁸ In 2019, this was supported by DFT calculations showing that the singlet and triplet rhodium nitrenes are close in energy, and that the transition states of C-H amination reactions are lower in energy for reactions of singlet nitrenes.²¹⁹

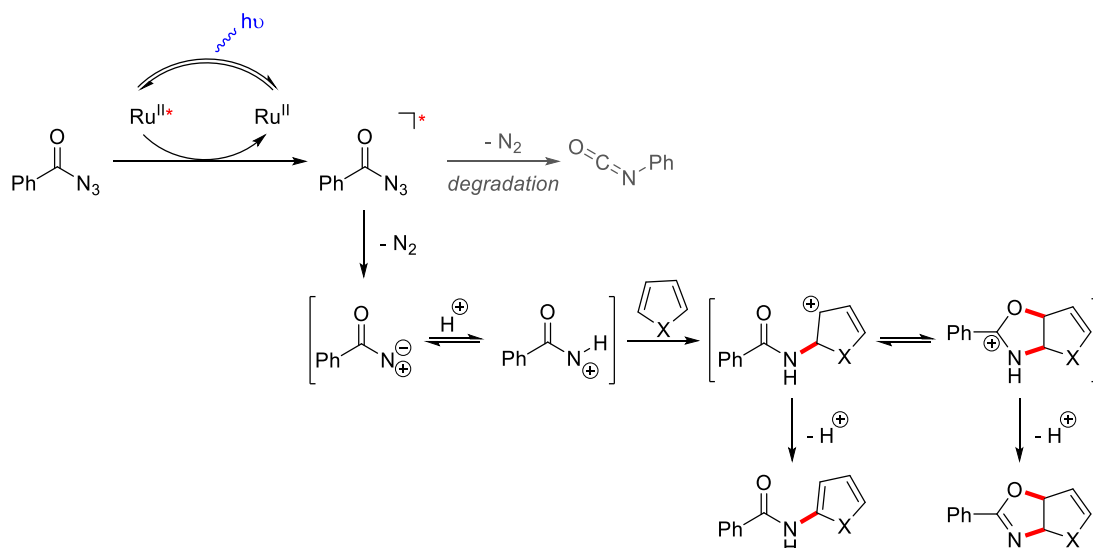
Recently, new formation of nitrene intermediates under irradiation have been reported for C-H amination and aziridination reactions and selective examples are shown in this section. In 2010, König and co-workers published the C-H amination of heteroarenes via energy transfer between an excited photocatalyst and benzoyl azides (*Scheme 4-12*).²²⁰ In this publication, formation of a singlet nitrene was proposed (after loss of nitrogen gas) and allowed for the functionalization of pyrroles, indoles or furans and other electron-rich heteroarenes, along with the synthesis of oxazolines. Remarkably, the Curtius rearrangement that led to the *in-situ* formation of isocyanate derivatives was avoided (known side-reaction of singlet nitrenes).²²¹

²¹⁸ Lwowski, W. *Angew. Chem., Int. Ed.* **1967**, 6, 897.

²¹⁹ Azek, E.; Khalifa, M.; Bartholoméüs, J.; Ernzerhof, M.; Lebel, H. *Chem. Sci.* **2019**, 10, 718.

²²⁰ Brachet, E.; Ghosh, T.; Ghosh, I.; König, B. *Chem. Sci.* **2015**, 6, 987.

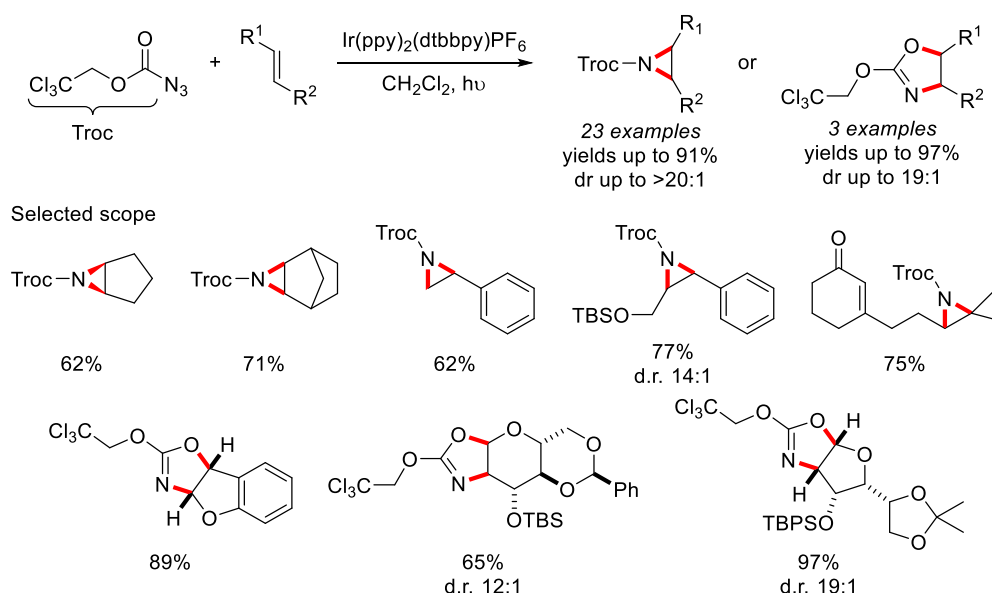
²²¹ Wentrup, C. *Angew. Chem., Int. Ed.* **2018**, 57, 11508.



Scheme 4-12: C-H amidation of heteroarenes with benzoyl azides

This report was the first C-H amination reaction using benzoyl azides under visible light and the mild conditions permitted the formation of more than twenty complex benzamide derivatives in moderate to good yields. Furthermore, isolation of three oxazolines was reported in good yields.

Following this publication, the Yoon group reported the aziridination of alkenes using azidoformates as nitrene precursor (Scheme 4-13).²²² The reaction developed was strictly limited to azides bearing Troc as a protecting group and more than twenty alkenes were used as partners for the synthesis of aziridines. Comparable to the König's publication, oxazolines were also obtained in good to excellent yields.



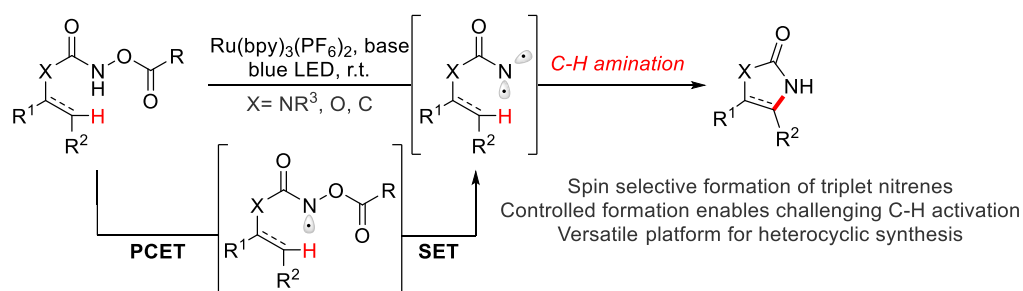
Scheme 4-13: Aziridination of alkenes using azidoformates

²²² Scholz, S. O.; Farney, E. P.; Kim, S.; Bates, D. M.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 2239.

To the best of our knowledge, there are currently no examples of direct C-H amination using non-azide starting materials under photoredox conditions. Undoubtedly, using stable starting materials to perform direct C-H amination processes will lead to more selective reactivity and will allow the synthesis of new heterocycles. This will also be a complimentary chemistry to the examples presented previously.

4.2. C-H amination using *N*-benzoyloxyureas

In this section, C-H amination using *N*-benzoyloxyureas is presented, from the discovery under thermolysis conditions through the study using metals to finally using photoredox conditions. Synthesis of different heterocycles including imidazolidinones and lactams is reported. Additionally, extensive mechanistic study is presented and represents, to our knowledge, the first spin-selective formation of triplet nitrene from non-azide starting materials. The chemistry presenting here is the subject of an ongoing manuscript and was performed with Ryan Ivanovich (Scheme 4-14).²²³ Ryan discovered the thermal C-H amination during the substitution study of *O*-isocyanates. Ryan performed preliminary work and I joined him shortly after the discovery. From then, Ryan and I worked as a team and we studied, optimized and isolated the products of C-H amination. I did most of the isolation of the methylene Csp³-H amination products where Ryan focused on the isolation of the tertiary Csp³-H products. We both took part of the isolation of the synthesis of the benzimidazolidinones, lactams and aziridination reaction, the site-competition experiments and the mechanistic study. I did the kinetic formation study by ¹H NMR and the cyclic voltammetry where Ryan performed the DFT calculations.



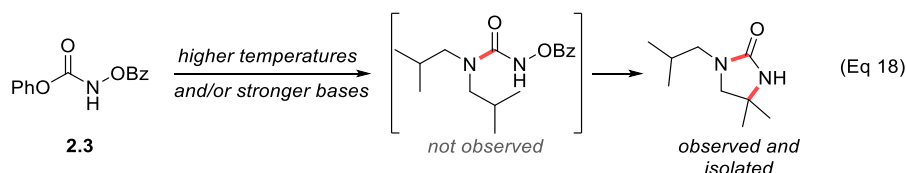
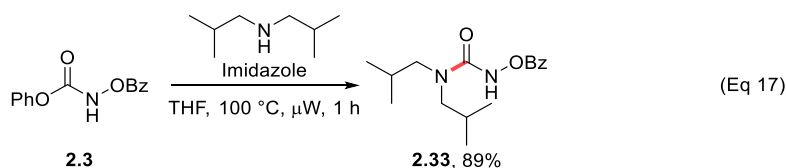
Scheme 4-14: Spin-selective formation of triplet nitrene

4.2.1. C-H amination via thermolysis

The reactivity was discovered during the study of the substitution of the phenyl (benzoyloxy)carbamate (2.3) from Chapter 1. In Eq 17, optimum conditions for the synthesis of *N*-benzoyloxyurea (2.33) via substitution on the *O*-isocyanate intermediate is presented. Under harsher conditions (higher

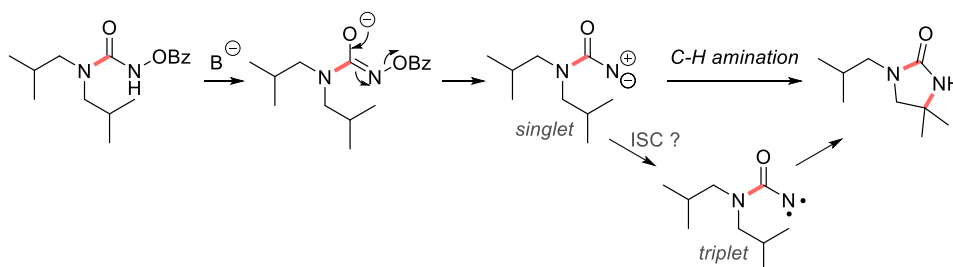
²²³ Ivanovich, R. A.†; Polat, D. E.†; Beauchemin, A. M. Manuscript in preparation.

temperatures and/or stronger bases), **2.33** was not observed: indeed, imidazolidinone was found and isolated.



Concretely, the imidazolidinone formation can be seen as the result of the cleavage of the weak *N-O* bond followed by the cyclization via C-H activation. Indeed, benzoic acid was isolated as the end of the reaction and the cyclization happened on an unactivated *C-H* bond. Similar reactivity discovered here had been reported for the formation of oxazolidinones, and involving a nitrene intermediate was postulated resulting from an α -elimination mechanism (see *Scheme 1-42*).¹²² All previous examples reported low yields for the C-H amination due to competitive side-reactions and degradation of the proposed nitrene intermediate (see 1.4.2.2).

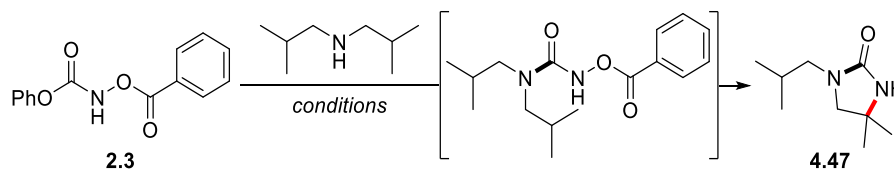
In the case of the *N*-benzoyloxyurea intermediate, obtained after the substitution onto the *O*-isocyanate intermediate, a mechanism was proposed and can be seen in *Scheme 4-15*: first, deprotonation of the acidic proton followed by α -elimination (e.g. departure of the benzoate via cleavage of the *N-O* bond) led to singlet nitrene. This uridyl singlet nitrene can either undergoes concerted C-H amination to form the imidazolidinone or relaxation to the triplet state via intersystem crossing. The triplet nitrene, in a stepwise fashion, can also performs C-H amination leading to the same product than the singlet nitrene. No mechanistic study was performed during the C-H amination under thermolysis conditions, consequently the nitrene state (singlet or triplet) was not determined (in most cases, the triplet nitrene is the ground state²²¹).



Scheme 4-15: Proposed mechanism via α -elimination

Different experimental conditions to control the formation of the proposed nitrene intermediate were tried and the optimization can be found in the *Table 4.1*. The C-H amination was first tried in a cascade reaction: *in-situ* formation of the *O*-isocyanate and addition of the amine to form the *N*-benzoyloxyurea, followed by the C-H amination reaction.

Table 4-1: Cascade reaction of **2.3** via thermolysis using conventional heating^a



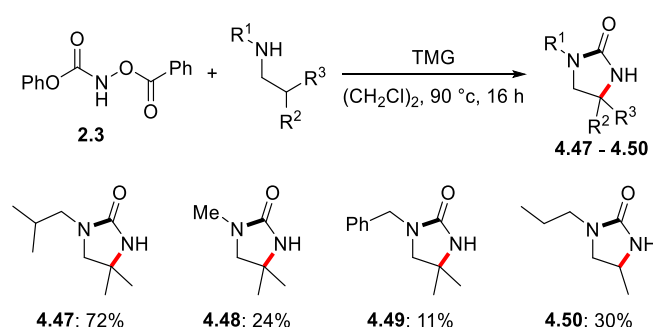
Entry	Base	Solvent	Temp °C	Time h	% 4.47
1	Et ₃ N	THF	70	15	0
2	<i>i</i> -Pr ₂ NEt	THF	90	15	0
3	<i>i</i> -Pr ₂ NEt	EtOH	90	15	<10
4	<i>i</i> -Pr ₂ NEt	MeCN	90	15	16
5	Et ₃ N	MeCN	90	20	23
6	K ₂ CO ₃	MeCN	90	20	11
7	<i>i</i> -Pr ₂ NEt	(CH ₂ Cl) ₂	90	15	20
8	Et ₃ N	(CH ₂ Cl) ₂	90	15	35
9	Et₃N	(CH₂Cl)₂	90	65	73
10	DMAP	(CH ₂ Cl) ₂	90	15	7
11	DABCO	(CH ₂ Cl) ₂	90	15	12
12	TMG	(CH ₂ Cl) ₂	90	15	62
13	Imidazole	(CH ₂ Cl) ₂	90	15	6
14	DBU	(CH ₂ Cl) ₂	90	15	6
15	Pyridine	(CH ₂ Cl) ₂	90	15	5
17	Et ₃ N	(CH ₂ Cl) ₂	120	15	45
18	Et ₃ N	(CH ₂ Cl) ₂	150	15	46
19	Imidazole	(CH₂Cl)₂	120	15	70
20	Imidazole	CHCl ₃	120	15	8
21	Imidazole	DMSO	120	15	53
22	Imidazole	DMF	120	15	50

Conditions: ^a Phenyl *N*-benzoyloxycarbamate **2.3** (1.00 equiv), diisobutylamine (1.00 equiv), base (0.20 equiv) in solvent (0.30 M) stir in oil bath. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

The formation of the desired imidazolidinone was observed along with the *N*-benzoyloxyurea (intermediate obtained from the substitution reaction with the *O*-isocyanate), however, the reaction was suffering from reproducibility issues. Indeed, the yields obtained for the entries varied when the same reaction was tested multiple times, suggesting the high instability of the proposed reactive intermediate. Only the highest yield for each entry is shown (all the entries were performed three times). Using milder conditions known to form the *O*-isocyanate in an oil bath (entries 1 and 2 and see *Scheme 2-19*), the C-H amination product was not observed and only the substitution product (e.g. the *N*-benzoyloxyurea) and starting material were found at the end of the reaction. Changing the solvent for EtOH and MeCN (entries 3 and 4) resulted in the formation of the imidazolidinone along with unreacted starting materials. Two different bases were tested in MeCN (entries 5 and 6) and similar results were found

than the *i*-Pr₂NEt base in entry 2. Several bases were tested using 1,2-dichloroethane as the solvent at 90 °C (entries 7 – 15) and the desired product was observed in low to good yields. Gratifyingly, when the reaction was heated in presence of Et₃N for 65 h (entry 9), the imidazolidinone was found in 73% ¹H NMR yield (in comparison, when the reaction was heated for 15 h, the yield was 35%, entry 8). The reaction was then performed at 120 and 150 °C (entries 17 and 18) and the product was obtained in 45% due to the degradation of the starting material. Finally, imidazole was tested as a weak base in different solvents (entries 19 – 22) and the desired C-H amination product (**4.47**) was obtained in 70% ¹H NMR yield in 1,2-dichloroethane (entry 19). All the other solvents resulted in lower yields. With this first study, 1,2-dichloroethane seemed the solvent of choice to perform the C-H amination. Indeed, it has been reported that solvents containing a chlorine atom can stabilize nitrene intermediate by interaction between the electron pair of the halogen and the empty orbital of the nitrene.²²⁴ The system TMG in 1,2-dichloroethane (entry 12) was chosen for the rest of the study: indeed, those conditions led to the less reproducibility issues supposedly due the possible stabilization of the proposed nitrene intermediate by the solvent. The optimum conditions were tested on different *N*-benzoyloxyureas and the results obtained for the cascade reaction can be seen in Table 4-2.

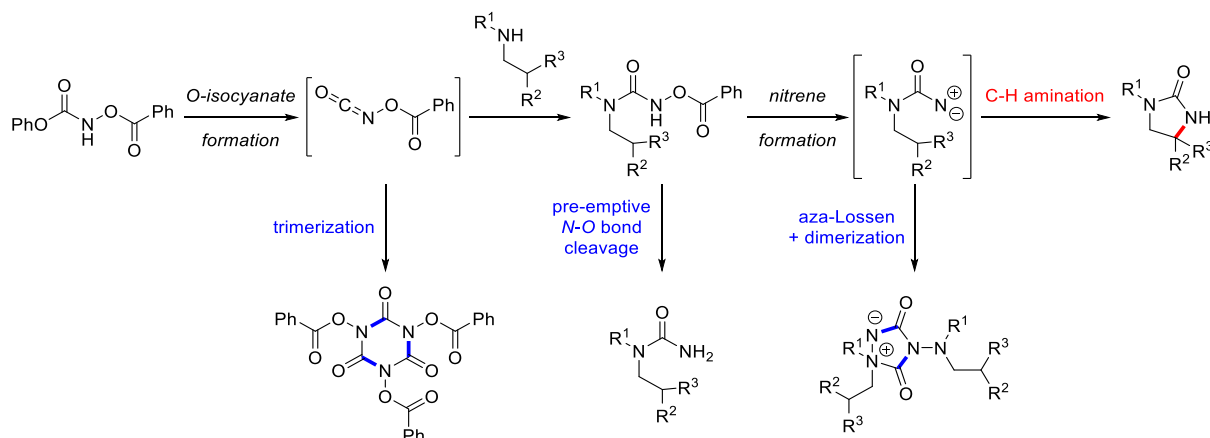
Table 4-2: Summary of the thermal C-H activation via cascade reaction^a



Conditions: ^a Phenyl (benzoyloxy)carbamate **2.3** (1.00 equiv), amine (1.00), TMG (0.10 equiv) in (CH₂Cl)₂ (0.3M), stir in oil bath at 90 °C for 16 h. Isolated yields are shown.

Imidazolidinone products were observed in low yields with the exception of the diisobutylamine-derived substrate (**4.47**) that can be seen as an ideal substrate for the studied reactivity due to its symmetrical nature and the tertiary position C-H amination. *N*-Methyl and *N*-benzyl substituents led to the isolation of the corresponding heterocycles (**4.48**, **4.49** in only 24 and 11% respectively). Surprisingly, the C-H amination at a secondary position (less activated than a tertiary) was also possible and the imidazolidinone (**4.50**) was obtained in a 30% isolated yield. The cascade reaction led to low yields due to different degradation pathways: indeed, traces of the *O*-isocyanate trimer, non-productive *N*-O bond cleavage and aza-Lossen rearrangement side-products were observed by ¹H NMR (Scheme 4-16).

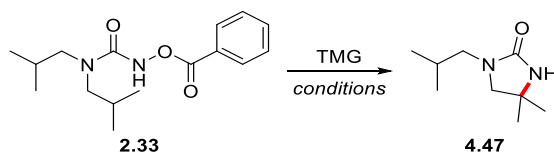
²²⁴ Scriven, E. F. V. *Azides and Nitrenes*; Academic Press, Elsevier, Ltd., Cambridge **1984**, pp. 205-246.



Scheme 4-16: Degradation pathway of the thermal C-H amination cascade sequence

To overcome these side-reactions, the C-H amination process was attempted in a stepwise fashion: the *N*-benzoyloxyureas were first isolated and then subjected to a C-H amination reaction. In this case, using microwave irradiation resulted in a shorter reaction time for substrates undergoing C-H amination at a tertiary position (Table 4-3).

Table 4-3: C-H activation via thermolysis of **2.33** using microwave irradiation^a

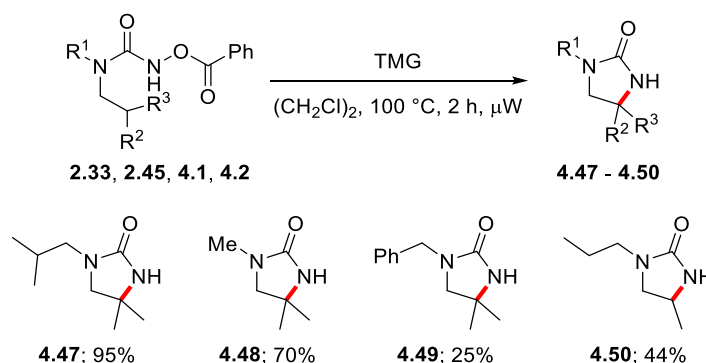


Entry	Solvent	Temp °C	Time h	%Product
1	(CH ₂ Cl) ₂	100	1	66
2	(CH ₂ Cl) ₂	100	2	86
3	(CH ₂ Cl) ₂	150	1	67

Conditions: ^a 3-(Benzoyloxy)-1,1-diisobutylurea **2.33** (1.00 equiv), TMG (0.10 equiv) in solvent (0.30 M) stir under microwave irradiation. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

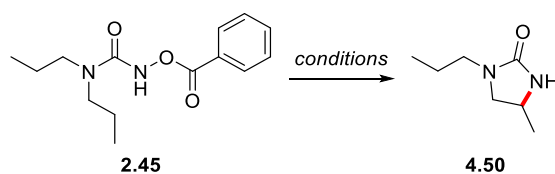
Gratifyingly, the C-H amination product was obtained in higher yields than the cascade reaction due to the minimization of the different degradation pathways. Under microwave irradiation and in presence of a catalytic amount of 1,1,3,3-tetramethylguanidine (TMG) at 100 °C, the imidazolidinone was observed in 66% ¹H NMR yield (entry 1). A longer reaction time led to a higher yield (entry 2) and these conditions were found to be the optimum conditions for the sequential C-H amination. Indeed, when the reaction was performed at higher temperature (150 °C), the observed yield for the cyclized product decreased (entry 3). The optimum conditions (catalytic amount of TMG in (CH₂Cl)₂ at 100 °C under microwave irradiation for 2 h) were tested with the selected substrates and the results can be found in Table 4-3.

Table 4-3: Summary of the thermal C-H activation with *N*-benzoyloxyureas^a



Condition: ^a *N*-benzoyloxyurea (1.00 equiv), TMG (0.10 equiv) in $(\text{CH}_2\text{Cl})_2$, heat in μW at 100 °C for 2 h. Isolated yields are shown.

Increase in the yields were found for the different *N*-benzoyloxyureas attempts with this approach. For example, 70% of product formation instead of 24% for the 1,4,4-trimethylimidazolidin-2-one (**4.48**). Nevertheless, this stepwise process was still suffering from reproducibility issues and was not broadly applicable as low yields were still obtained for the other C-H amination products (**4.49**, **4.50**). Due to the low yield obtained for the symmetrical dipropylamine substrate (44% ¹H NMR yield), optimization was undertaken to increase the yield of the C-H amination at secondary position. It was suggested that due to the more difficult C-H amination step, the formation of the nitrene required to occur under milder conditions to induce a slower formation of the proposed nitrene intermediate (Table 4-4).

Table 4-4: C-H activation via thermolysis of **2.45** using conventional heating^a

Entry	Additive	Solvent	Temp °C	% 4.50
1	TMG	(CH ₂ Cl) ₂	90	20
2	TMG	CHCl ₃	90	13
3	TMG	PhCF ₃	90	<10
4	TMG	DMSO	90	0
5	TMG	EtOH - sieves	90	25
6	TMG	MeCN	90	18
7	TMG	Monoglyme	90	0
8	TMG	Diglyme	90	0
9	TMG	PhCF ₃	150	26
10	TMG	DMSO	150	0
11	TMG	DMF	150	0
12	TMG	Diglyme	150	69
13	TMG	Dichlorobenzene	150	0
14	Phosphazene	CHCl ₃	90	27
15	AIBN	MeCN	90	0
16	-	MeCN	90	0
17	-	DMSO	90	0
18	-	PhCF ₃	90	0
19	-	EtOH - sieves	90	30
20	-	EtOH	90	30
21	-	MeOH	90	0
22	-	<i>i</i> -PrOH	90	15
23	-	<i>t</i> -BuOH	90	0
24	-	CF ₃ CH ₂ OH	90	0
25	-	(CF ₃ CH ₂) ₂ CHOH	90	0
26	-	<i>i</i> PrOAc	90	0

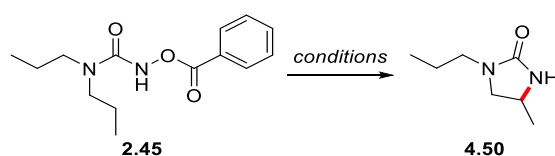
Conditions: ^a 3-(benzoyloxy)-1,1-dipropylurea **2.45** (1.00 equiv), additive (0.10 equiv) in solvent (0.30 M) stir in oil bath overnight. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

Using conventional heat (e.g. oil bath), the formation of 4-methyl-1-propylimidazolidin-2-one was observed but the results obtained suffered similar reproducibility issues than C-H amination at the tertiary position. The reaction was first tested using TMG and 1,2-dichloroethane at 90 °C (entry 1) and the desired product was only obtained in 20% ¹H NMR yield. Different solvents were used at the temperature (entries 2 - 8) all resulted in low yields for the C-H amination. The temperature was then increased to 150 °C (entries 9 - 13) and pleasantly, using diglyme the imidazolidinone was found in 69% ¹H NMR yield. Different additives were then tested: phosphazene are known to stabilize nitrene intermediate²²⁵ and when the C-H amination was performed in presence of a catalytic amount of phosphazene (entry 14), 27% of the desired product was observed. No formation of the heterocycle

²²⁵ (a) McIntosh, M. B.; Hartle, T. J.; Allcock, H. R. *J. Am. Chem. Soc.* **1999**, *121*, 884. (b) Allcock, H. R.; McIntosh, M. B.; Hartle, T. J. *Inorg. Chem.* **1999**, *38*, 5535.

product was observed when AIBN (a radical initiator) was used (entry 15). The C-H amination reaction was then performed thermally without the presence of additives (entries 16 -26). With the exception of EtOH (entries 19 and 20) and *i*-PrOH where the product was obtained in 30 and 15% ^1H NMR yield respectively, the C-H amination product was not observed and the starting material was recovered. Noteworthy, when alcohol solvents were used, no trace of the OH-insertion product were observed. This study was still not broadly applicable as inconsistencies in the ^1H NMR yields obtained were still observed. Simultaneously to the oil bath study, the C-H amination was also tested using microwave irradiation and the results can be seen in Table 4-5.

Table 4-5: C-H activation via thermolysis of **2.45** using microwave irradiation^a



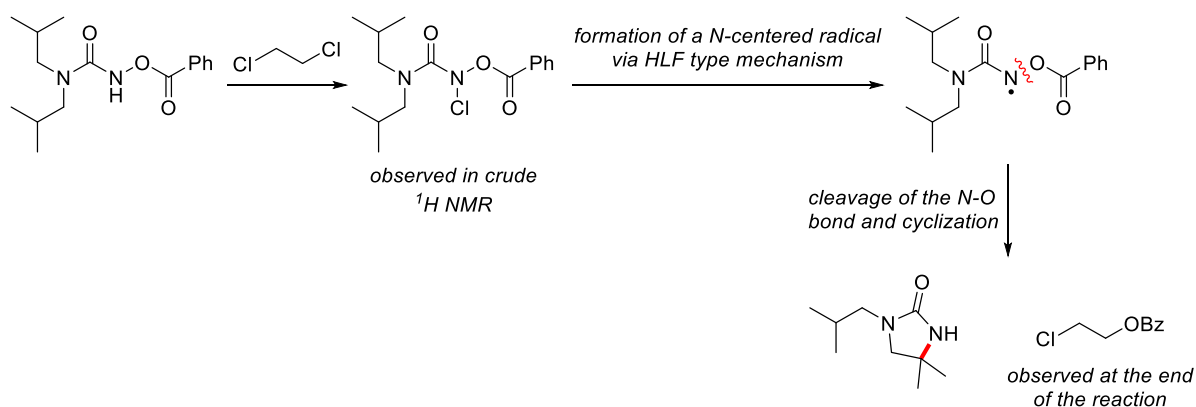
Entry	Additive (equiv)	Solvent	Temp °C	% 4.50
1	TMG (0.10)	(CH ₂ Cl) ₂	100	44
2	TMG (0.10)	(CH₂Cl)₂	120	60
3	DBU (0.10)	(CH ₂ Cl) ₂	120	52
4	Et₃N (0.10)	(CH₂Cl)₂	120	60
5	<i>i</i> -Pr ₂ NEt (0.10)	(CH ₂ Cl) ₂	120	57
6	DMAP (0.10)	(CH ₂ Cl) ₂	120	14
7	PhI(OAc) ₂ (1.20)	MeCN	120	0

Conditions: 3-(benzoyloxy)-1,1-dipropylurea **2.45** (1.00 equiv), additive in solvent (0.30 M) stir under microwave irradiation. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

Using microwave irradiation, the yields observed were lower than those obtained using conventional heating in an oil bath, supposedly due to a faster formation of the proposed nitrene intermediate resulting in its degradation. Using the optimum conditions found for the tertiary position (TMG in 1,2-dichloroethane at 100 °C, entry 1), the C-H amination product was observed only in a 44% ^1H NMR yield. When the reaction was heated at 120 °C (entry 2), the desired imidazolidinone was found in 60%. Different organic bases were tested in a catalytic amount (entries 3 - 6) and Et₃N induced the same yield for the C-H amination product than TMG. Finally, the reaction was performed using PhI(OAc)₂, as hypervalent iodine is known to catalyzed the formation of nitrene,¹²⁶ and full degradation of the starting material was observed (entry 7).

During the course of the thermal activation study (using conventional heating or microwave irradiation), traces of chlorination of the starting material was observed by ^1H NMR when 1,2-dichloroethane was used as the solvent. Indeed, traces of the *N*-chlorobenzoyloxyurea was observed during the course of

the reaction via ^1H NMR. A mechanism was envisaged from this observation: indeed, the *N*-chloro intermediate found in the crude ^1H NMR can undergo a Hofmann-Löffler-Freytag type mechanism and homolytic cleavage a N-Cl bond to form the corresponding *N*-centered radical (Scheme 4-17).



Scheme 4-17: Proposed mechanism via chlorination of the *N*-benzoyloxyurea

After the formation of the uridyl radical intermediate, cleavage of the *N*-O bond and cyclization via C-H amination have to occur to form the desired imidazolidinone. The good yield obtained using 1,2-dichloroethane as a solvent could be an indication of a radical mechanism.

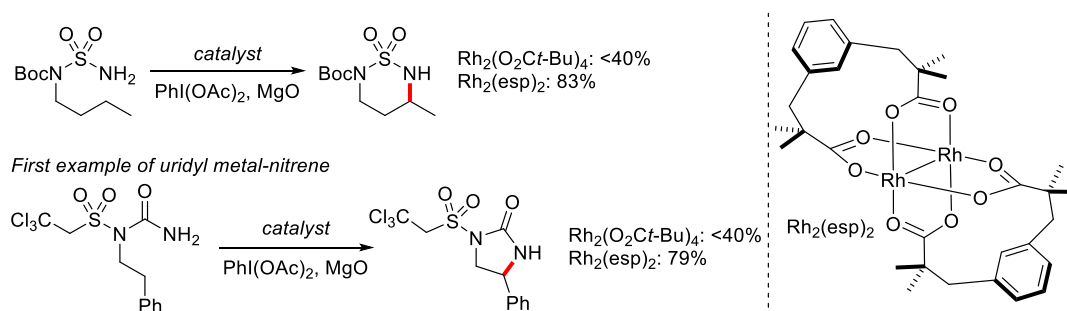
The thermal C-H amination study suffered from poor reproducibility and low yields for the majority of the *N*-benzoyloxyurea starting materials. More study was performed to understand the reaction: indeed, compelled by the complexity of the reaction and the structure of the reactive intermediate, experiments using metal-catalyzed conditions to stabilize the proposed nitrene intermediate and conditions using light irradiation to explore the pathway involving a *N*-centered radical were investigated.

4.2.2. C-H amination via metal-nitrene stabilization

Reports of C-H amination via *N*-O bond cleavage have been reviewed in *part 1.4.2.2* and most of the examples in the literature are carbamate derivatives.²²⁶ To the best of our knowledge, only one example of uridyl metal-nitrenes was reported. Indeed, during the design of the $\text{Rh}_2(\text{esp})_2$ catalyst for the intra- and intermolecular C-H amination reactions, Du Bois and co-workers were able to increase the C-H amination yields of sulfamate derivatives and reported the first example of uridyl metal-nitrenes (Scheme 4-18).²²⁷

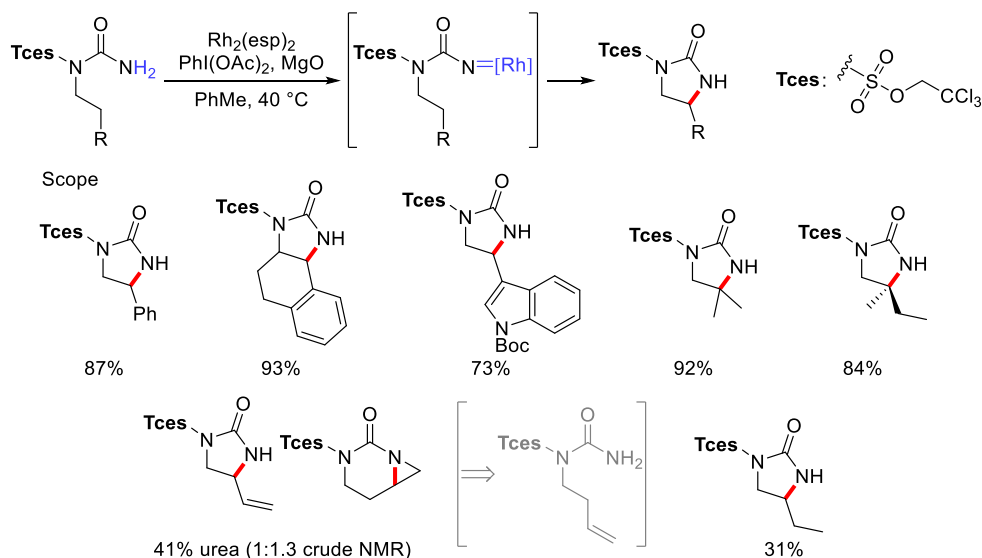
²²⁶ (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (d) Dequierez, G.; Pons, V.; Dauban, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 7384. (d) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247.

²²⁷ Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.



Scheme 4-18: Catalyst design for C-H amination

Two years later, the same group increased the scope of uridyl metal-nitrenes and reported seven more examples of imidazolidinones (Scheme 4-19).²²⁸



Scheme 4-19: Example of uridyl metal-nitrene

Using protected ureas as starting materials and the $\text{Rh}_2(\text{esp})_2$ catalyst that they designed, the C-H amination products were obtained in good yields for activated positions (benzylic and tertiary) and only in low yield for the secondary positions. A mixture of C-H amination at the allylic position and the aziridination was observed with a substrate possessing a homoallyl sidechain (and only the imidazolidinone was isolated). For all the substrates, the nitrogen needed to be protected from oxidation with the Tces group (2,2,2-trichloroethoxysulfonyl) that can be easily cleaved using Zn dust and acetic acid. In the same communication, the authors also reported the C-H amination of *N*-Tces alkylguanidine derivatives for the synthesis of (imino)imidazolidine heterocycles. These reports were published more than fifteen years ago, and to the best of our knowledge, no other examples of uridyl metal-nitrenes were reported since then.²²⁹

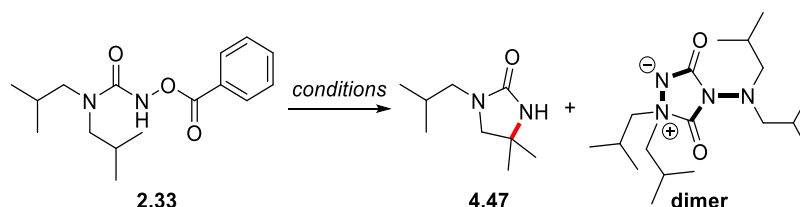
Based on this only example, *N*-benzoyloxyureas were reacted in presence of metal catalysts in order to access the uridyl metal-nitrene intermediate, with the use of an unprotected nitrogen in the *N*-

²²⁸ Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, 8, 1073.

²²⁹ Hazelard, D.; Nocquet, P.-A.; Compain, P. *Org. Chem. Front.* **2017**, 4, 2500.

benzoyloxyurea starting materials. Several metal catalysts and bases were chosen, based on the metal-nitrene literature²²⁶ and were tried (Table 4.6).

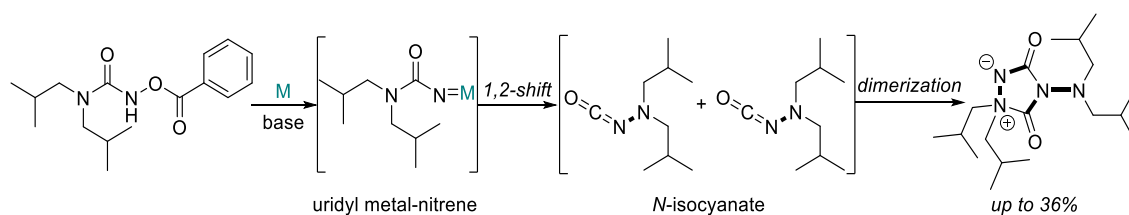
Table 4-6: C-H activation via metal catalyzed reactions of **2.33**^a



Entry	Metal (mol%)	Base (equiv)	Solvent	Temp °C	Time	% 2.33	% 4.47	%dimer
1	[IrCp*Cl ₂] ₂ (2.5)	K ₂ CO ₃ (1.5)	CH ₂ Cl ₂	rt	3	0	16	20
2	[IrCp*Cl ₂] ₂ (2.5)	CsOAc (1.5)	CH ₂ Cl ₂	rt	3	0	20	33
3	[IrCp*Cl ₂] ₂ (2.5)	Imidazole (1.5)	CH ₂ Cl ₂	rt	16	100	0	0
4	[IrCp*Cl ₂] ₂ (2.5)	CsOAc (0.2)	CH ₂ Cl ₂	rt	3	0	17	20
5	[IrCp*Cl₂]₂ (0.5)	CsOAc (0.2)	CH₂Cl₂	rt	3	0	21	15
6	[IrCp*Cl ₂] ₂ (0.5)	CsOAc (5.0)	CH ₂ Cl ₂	rt	3	0	18	14
7	[IrCp*Cl ₂] ₂ (0.5)	CsOAc (0.2)	THF	rt	16	72	11	3
8	[IrCp*Cl ₂] ₂ (0.5)	CsOAc (0.2)	PhCF ₃	rt	16	0	27	18
9	[IrCp*Cl ₂] ₂ (0.5)	CsOAc (0.2)	MeCN	rt	16	37	11	6
10	[IrCp*Cl ₂] ₂ (0.5)	CsOAc (0.2)	DMSO	rt	16	60	0	0
11	[IrCp*Cl ₂] ₂ (0.5)	KOAc (0.2)	CH ₂ Cl ₂	rt	3	24	21	11
12	[IrCp*Cl ₂] ₂ (0.5)	NaOAc (0.2)	CH ₂ Cl ₂	rt	3	25	19	10
13	[IrCp*Cl ₂] ₂ (0.5)	MgO (0.2)	CH ₂ Cl ₂	rt	3	15	7	7
14	[IrcodCl ₂] ₂ (2.5)	CsOAc (1.5)	CH ₂ Cl ₂	rt	16	100	0	0
15	[IrcodCl ₂] ₂ (2.5)	CsOAc (1.5)	MeOH	rt	16	40	24	0
16	[IrcodCl ₂] ₂ (2.5)	CsOAc (0.2)	CH ₂ Cl ₂	rt	16	0	17	20
17	[RhCp*Cl ₂] ₂ (2.5)	K ₂ CO ₃ (1.5)	MeOH	rt	16	0	5	0
18	[RhCp*Cl ₂] ₂ (2.5)	CsOAc (1.5)	MeOH	rt	16	0	0	0
19	[RhCp*Cl ₂] ₂ (2.5)	Cs ₂ OAc ₃ (1.5)	MeOH	rt	16	0	7	0
20	[RhCp*Cl ₂] ₂ (2.5)	<i>t</i> -BuOK (1.5)	MeOH	rt	16	0	13	0
21	[RhCp*Cl ₂] ₂ (2.5)	<i>t</i> -BuOK (1.5)	MeOH	rt	16	0	0	0
22	[RhCp*Cl ₂] ₂ (2.5)	<i>t</i> -BuOK (1.5)	<i>i</i> -PrOH	rt	16	0	0	0
23	[RhOAc] ₂ (5.0)	K ₂ CO ₃ (1.5)	CH ₂ Cl ₂	rt	16	0	10	
24 ^b	[RhOAc] ₂ (5.0)	Imidazole (1.5)	(CH ₂ Cl) ₂	90	16		37	
25	[Rhesp] ₂ (5.0)	K ₂ CO ₃ (1.5)	(CH ₂ Cl) ₂	rt	16	100	0	0

Conditions: ^a 3-(benzoyloxy)-1,1-diisobutylurea **2.33** (1.00 equiv), metal, base in solvent (0.3M) stir at r.t. ^b Cascade reaction with 80% of SM converted. NMR yield are shown using 1,3,5-trimethoxybenzene as an internal standard.

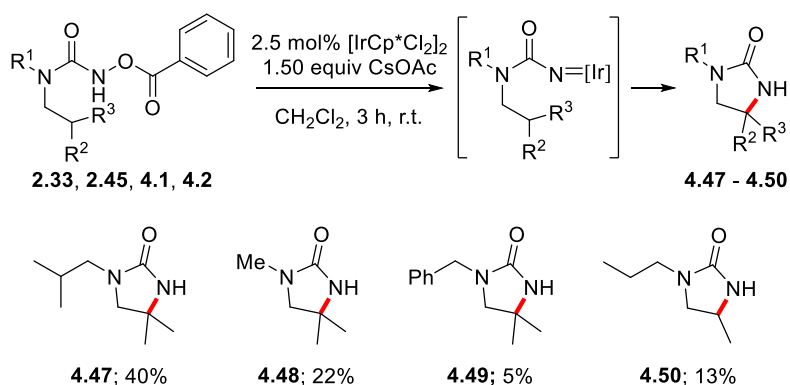
The imidazolidinone product was observed, however in low yields due to the competitive formation of the dimer. Indeed, a side-product was observed during the optimization study: formation of the dimer via aza-Lossen rearrangement was found with up to 36% yield (based on starting material consumption) in crude ¹H NMR. It was proposed that the presence of the metal catalyst, the 1,2-shift (or aza-Lossen rearrangement) is favored via stabilization of the nitrene intermediate (proposed mechanism can be found in (Scheme 4-20). Efforts to isolate the dimer remained vain.



Scheme 4-20: Proposed mechanism for dimer formation

Different metal catalysts and base systems were tested and the best results were obtained using a catalytic amount of $[\text{IrCp}^*\text{Cl}_2]_2$ and CsOAc as a base (entry 5). Indeed, the desired C-H amination product was isolated in 41% yield with 30% of the dimer side-product observed by ^1H NMR. These conditions were tested on three different *N*-benzoyloxyureas and the result can be seen in Table 4-7.

Table 4-7: Summary of the C-H amination via metal-nitrene intermediacy^a



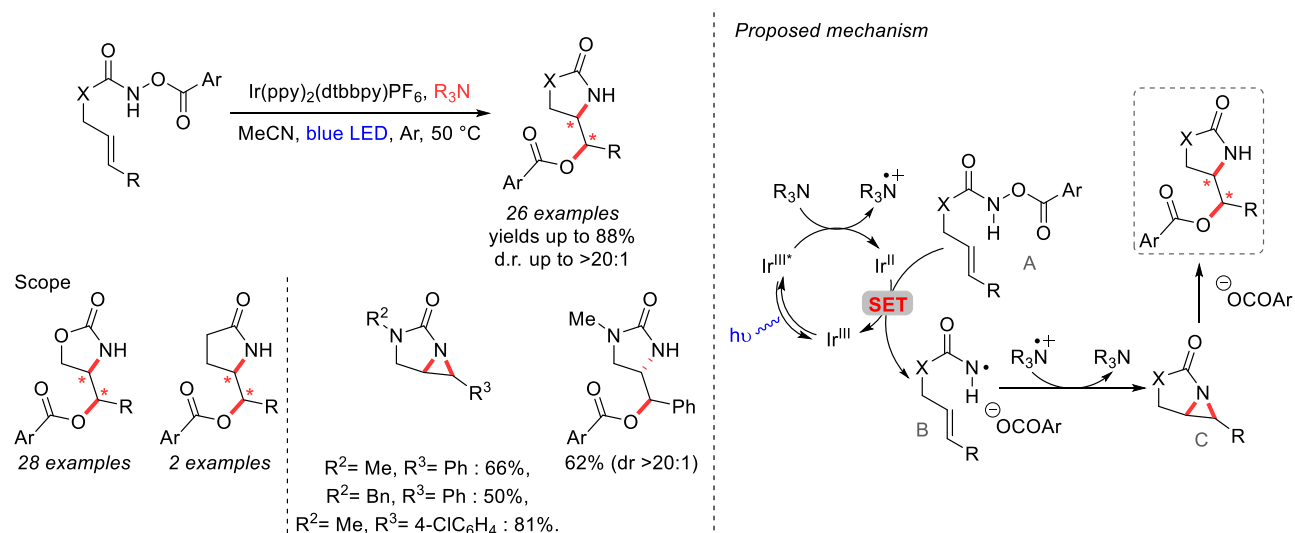
Conditions: ^a *N*-benzoyloxyurea (1.00 equiv), $[\text{IrCp}^*\text{Cl}_2]_2$ (2.5 mol%), CsOAc (1.50 equiv) in CH_2Cl_2 (0.3M), stir at room temperature for 3 h. NMR yields are shown using 1,3,5-trimethoxybenzene as an internal standard.

Formation of the imidazolidinones were observed for all substrates, however in low yields. Indeed, even with the diisobutyl derivative (**4.47**), the C-H amination product was only found in 40% yield (^1H NMR), where for less activated starting materials the yields dropped to less than 25%. Unfortunately, the metal catalyzed C-H amination resulted in no improvement of the C-H amination. Indeed, the yields obtained for this study were lower than the thermal conditions and unwanted aza-Lossen rearrangement for the formation of *N-N* bond was found as an important pathway. The attention was then turned to photoredox conditions to explore the possible radical pathway suggested during the thermal study with 1,2-dichloroethane as a solvent.

4.2.3. C-H amination via photoredox conditions

4.2.3.1. Earlier study

During the course of the metal-nitrene optimization, a report on the oxyamidation of alkenes using photoredox conditions and *N*-benzyloxyureas as starting materials was reported (Scheme 4-21).²³⁰ By using an Ir photocatalyst under light irradiation and heating, intramolecular aziridination followed by ring opening led to the formation of complex heterocycles.

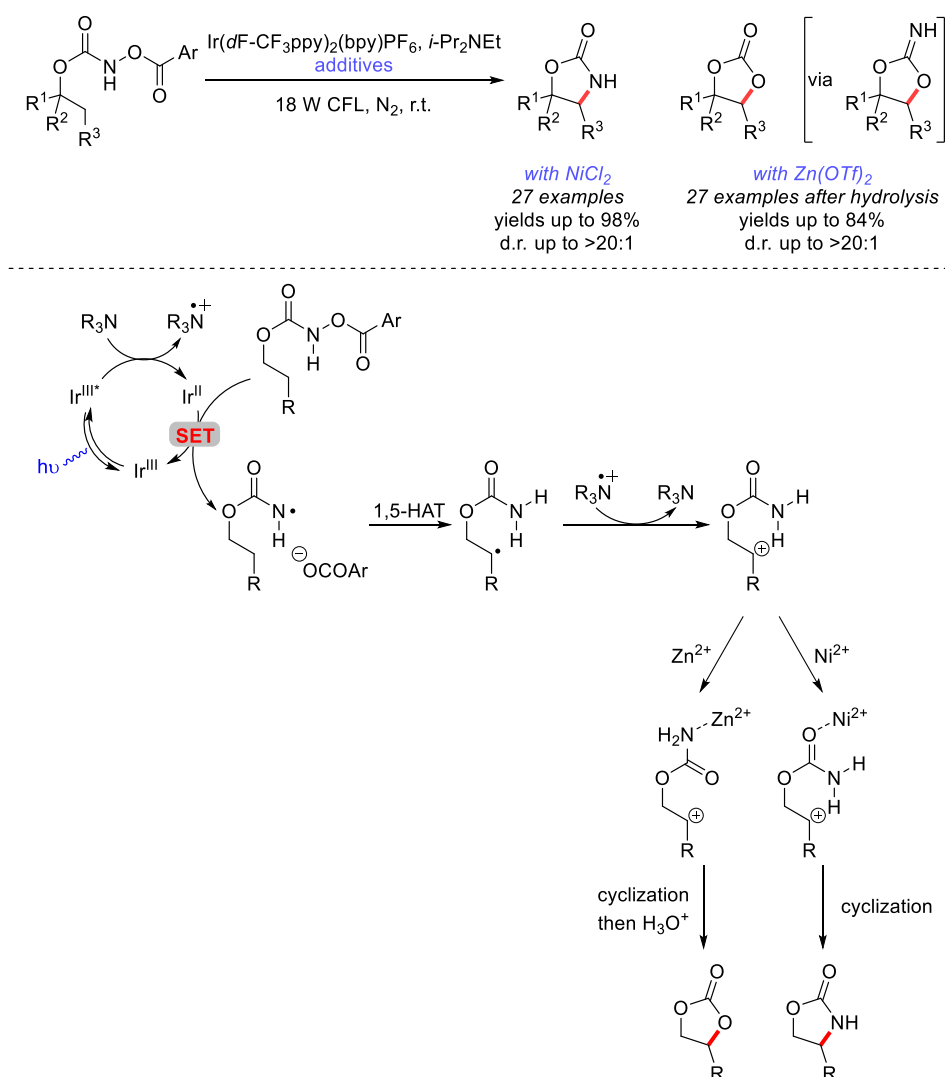


Scheme 4-21: Diastereodivergent intramolecular oxyamidation of alkenes under photoredox conditions and proposed mechanism

The scope of the reaction was mostly using carbamate as starting materials, however two examples of lactams and four examples of imidazolidinones were also reported. In this study, formation of a *N*-centered radical **B** was proposed to be the result of the reduction of the amide carbonyl followed by the departure of the benzoate derivative through cleavage of the *N*-O bond (Scheme 4-21). Intramolecular 5-exo-trig cyclization and oxidation lead to the formation of the bicycle **C**. During the course of the reaction, one equivalent of benzoate was formed and opened the aziridine by nucleophilic attack to form the desired product. Only aziridination reactions were reported in this first publication and in 2019, the same research group published the C-H amination using the same starting materials in a dual catalysis strategy using a catalytic amount of Lewis acid.²³¹ In this new report, the reaction was strictly limited to carbamate derivatives.

²³⁰ Ren, X.; Guo, Q.; Chen, J.; Xie, H.; Xu, Q.; Lu, Z. *Chem.–Eur. J.* **2016**, *22*, 18695.

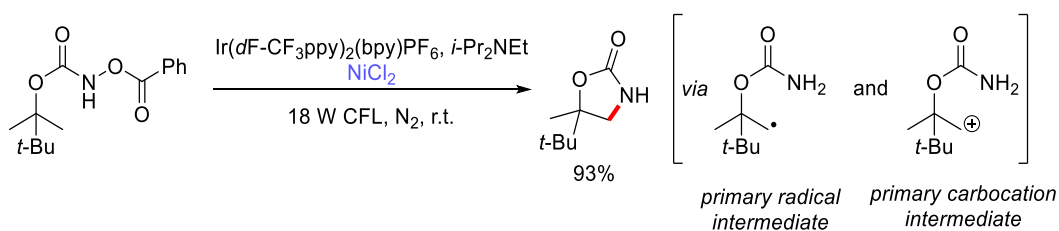
²³¹ Guo, Q.; Ren, X.; Lu, Z. *Org. Lett.* **2019**, *21*, 880.



Scheme 4-22: $\text{C}(\text{sp}^3)\text{-H}$ amination and oxygenation of carbamates via dual catalysis and proposed mechanism

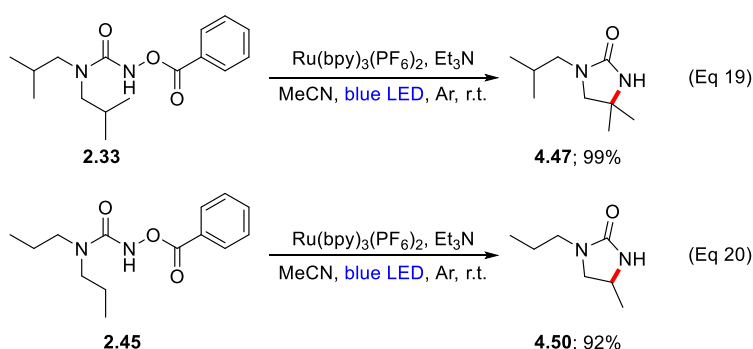
By changing the Lewis acid, the authors were able to isolate two class of heterocycles: indeed, examples of 1,3-dioxolan-2-one and oxazolidinone moieties were obtained using NiCl_2 or ZnCl_2 respectively. However, the proposed mechanism in this new study can be questioned: indeed, the excellent yield obtained with a primary position seems doubtful (Scheme 4-23). To access the heterocycle product, formation of a primary radical and a primary carbocation needs to occur. These two intermediates are really high in energy and difficult to access and to stabilize²³² and the yield reported for this example surpass the secondary position and is comparable to a tertiary position.

²³² Robbins, A.M.; Jin P.; Brinck, T.; Murray, J. S.; Politzer, P. *Int. J. Quantum Chem.* **2006**, 106, 2904.



Scheme 4-23: Primary C-H amination via PCET/Lewis acid dual catalysis

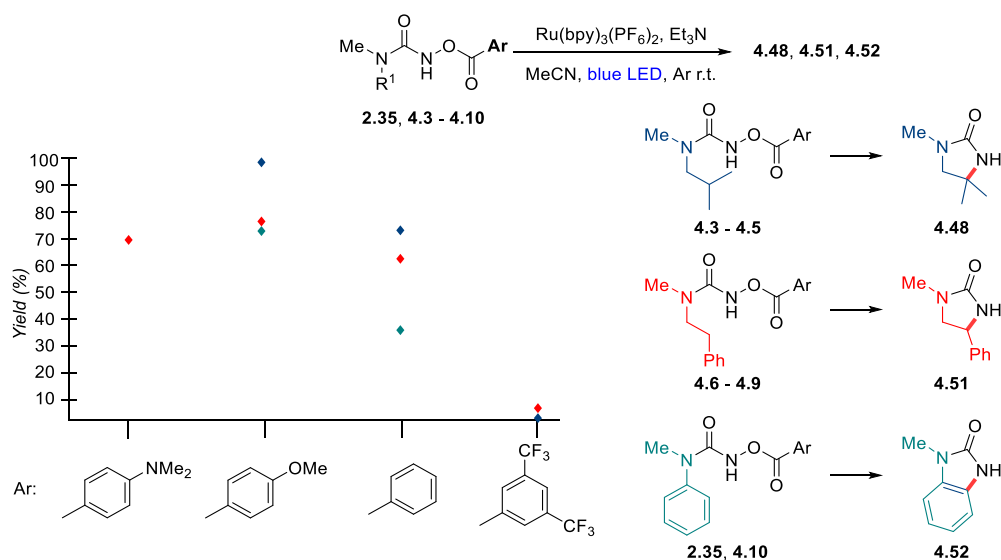
Based on the first publication, photoredox conditions were tried using two different *N*-benzoyloxyureas (**2.33** and **2.45**) to survey C-H amination at a tertiary and at a secondary position. Gratifyingly, using $\text{Ru(bpy)}_3(\text{PF}_6)_2$ and Et_3N under inert atmosphere and blue LED irradiation, imidazolidinones (**4.47**, **4.50**) were obtained in excellent yields with good reproducibility (Eqs 19 - 20).



With these first results using photoredox conditions, optimization was undertaken as at that time there was no report of C-H amination under these types of conditions reported. Indeed, all the chemistry involving nitrogen reactive intermediates (with the exception of azides) and photoinduced reaction is limited to cyclization through addition on alkenes or derivatization via 1,5-HAT derived from *N*-centered radicals (see 4.1.2).

4.2.3.2. Optimization

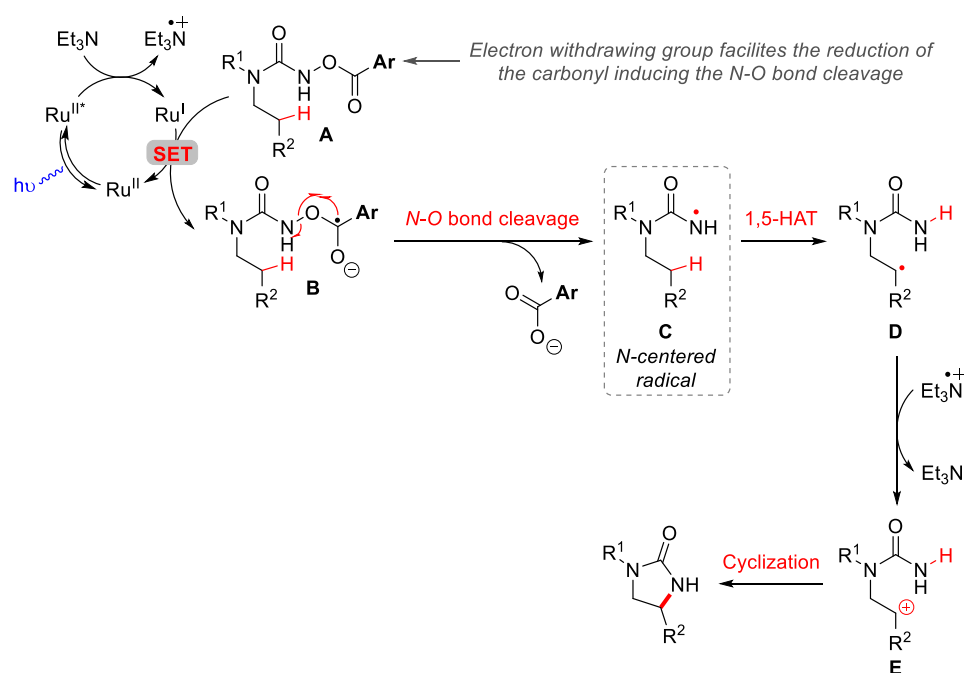
Using photoredox conditions, the first parameter studied was the benzoate substituent and three different *N*-benzoyloxyureas were chosen to perform the amination reaction at a tertiary (**4.3** – **4.5**), benzylic (**4.6** – **4.9**) and aromatic (**2.35**, **4.10**) C-H bonds. Different aromatic groups were then selected ranging from electron poor to electron rich. Using the same system, $\text{Ru(bpy)}_3(\text{PF}_6)_2$ and Et_3N , the C-H amination was studied and the results can be found in Scheme 4-24.



Scheme 4-24: Study of the aromatic group

Surprisingly, when the aromatic group was bearing electron poor substituents (**4.5**, **4.9**, **4.10**), less than 5% of the corresponding C-H amination products were observed: indeed, in contrast to what would be expected from a SET-induced reduction, the highest yields were obtained when the aromatic group was bearing electron-rich substituent (**4.3** – **4.9**). From the data presented in Scheme 4-23, *p*-methoxybenzoate substrates proved the most versatile, allowing C-H amination to occur efficiently at different position (**4.3**, **4.7**).

The results found in the study of the benzoate substituent drastically differed from the previous reports of C-H amination: indeed, in order to cleave the *N*-O bond, electron-withdrawing groups are typically added to lower the BDE of this bond and / or facilitate reduction.^{112,116,123,128} In the Lu group's publication, the reactivity was limited to *N*-benzoyloxyureas bearing electron-withdrawing group on the benzoate substituent (e.g. *p*-NO₂, *p*-CF₃, *o,p*-diCl and few examples with Ph).²³⁰ Due to the complete opposite electronic trend found in our system, a similar mechanism which involved the formation of an *N*-centered radical intermediate (arising from the homolytic *N*-O bond cleavage) seemed unlikely. Based on the proposed mechanism by Lu and co-workers (see Scheme 4-21), a proposed mechanism for the C-H amination involving a *N*-centered radical can be seen in Scheme 4-25. First, a SET reduction of the carbonyl in **A**, followed by homolytic cleavage of the *N*-O bond in **B** results in the formation of the *N*-centered radical **C**. This radical **C**, undergoes then 1,5-HAT and formation of the carbon radical **D**. Oxidation by the radical cation triethylamine and cyclization via the nitrogen leads to the formation of the imidazolidinone.

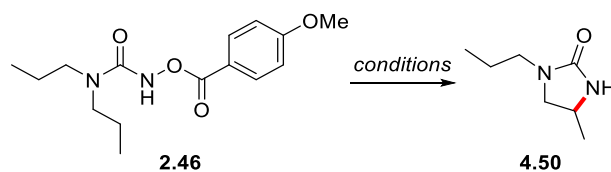


Scheme 4-25: Proposed mechanism via formation of a N-centered radical

The proposed reduction of the carbonyl should be facilitated by the presence of electron-withdrawing group on the aromatic group in this proposed mechanism. However, due to the C-H amination reaction being more productive with an electron-donating substitution, the carbonyl reduction pathway seems unlikely. In addition, the excellent yield obtained with secondary C-H amination position (92% with **4.11** as starting material) also indicated that this mechanism appears questionable: indeed, owing from the lower stability of the secondary carbon radical and following secondary carbocation, the yields for this position are usually low.^{123,228,233} The proposed mechanism (Scheme 4-25), which is based on previous reports, was not set aside. These results suggested that a different mechanism with a different intermediate than a N-centered radical could be operating.

After finding the optimal substituent on the benzoate group, photocatalysts and bases along with solvents were tested. Optimization was performed on the dipropyl starting material (**2.46**), requiring the C-H amination reaction to proceed at a more difficult secondary position (Table 4-8).

²³³ Huh, S.; Hong, S. Y.; Chang, S. *Org. Lett.* **2019**, *21*, 2808.

Table 4-8: Optimization of the photoredox conditions^a

Entry	Photocatalyst	Base	Solvent	% 4.50
1	[Ru(bpy)₃](PF₆)₂	Et₃N	MeCN	92
2	[Ir(ppy) ₂ (dtbpy)](PF ₆)	Et ₃ N	MeCN	40
3	[Ir(dF-CF ₃ -ppy) ₂ (dtbpy)](PF ₆)	Et ₃ N	MeCN	33
4	[Ru(bpm) ₃]Cl ₂	Et ₃ N	MeCN	11
5	TPP	Et ₃ N	MeCN	0
6	Ir(dFppy) ₃	Et ₃ N	MeCN	0
7	[Ru(bpy) ₃](PF ₆) ₂	Ph ₃ P	MeCN	17
8	[Ru(bpy) ₃](PF ₆) ₂	Et ₃ N	PhCF ₃	0
9	[Ru(bpy) ₃](PF ₆) ₂	Et ₃ N	DMSO	57
10	[Ru(bpy) ₃](PF ₆) ₂	Et ₃ N	Dioxane	0
11	[Ru(bpy) ₃](PF ₆) ₂	Et ₃ N	THF	9
12	[Ru(bpy) ₃](PF ₆) ₂	Et ₃ N	(CH ₂ Cl) ₂	78
13	[Ru(bpy) ₃](PF ₆) ₂	Et ₃ N	CH ₂ Cl ₂	77
14	-	Et ₃ N	MeCN	0
15	[Ru(bpy) ₃](PF ₆) ₂	-	MeCN	0

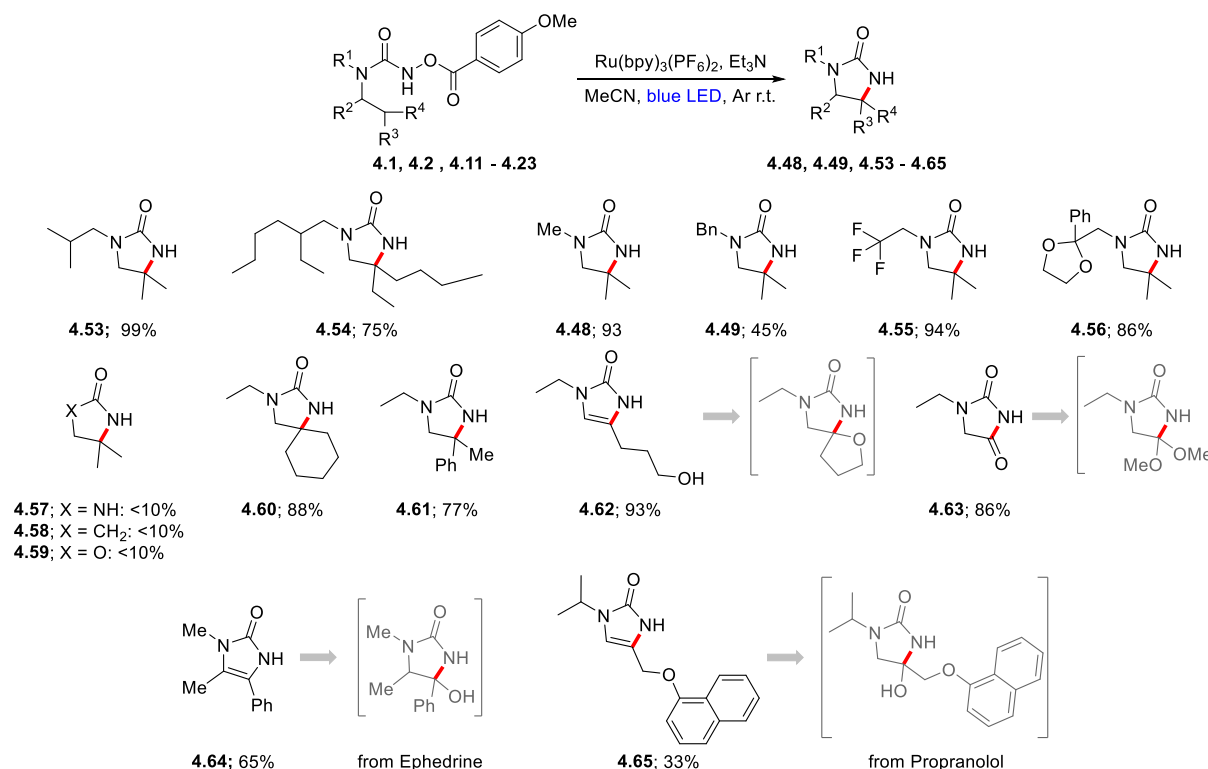
Conditions: ^a 3-(Benzoyloxy)-1,1-dipropylurea **2.46** (1.00 equiv), photocatalyst (2 mol%), additive (1.10 equiv) in solvent (0.3M) irradiated under inert atmosphere with 450 nm blue LED at room temperature overnight.

The reaction was first tested using [Ru(bpy)₃](PF₆)₂ and Et₃N in MeCN (entry 1) and the imidazolidinone (**2.50**) was obtained in 92% yield. Other photocatalysts, [Ir(ppy)₂(dtbpy)](PF₆), [Ir(dF-CF₃-ppy)₂(dtbpy)](PF₆), [Ru(bpm)₃]Cl₂ (entries 2 - 4) were tried and the C-H amination product was obtained in lower yield than [Ru(bpy)₃](PF₆)₂. Triphenylpyrylium, one of the best photo-oxidant and organic photocatalyst, was also tried (entry 5) resulting in complete recovery of the *N*-benzoyloxyurea (**2.46**). On the other end of the spectrum, Ir(dFppy)₃, one of the best photo-reductant, was also tried (entry 6) and clean starting material was observed by ¹H NMR (this result also leaned toward to a mechanism not involving an *N*-centered radical intermediate via reduction of the carbonyl due to unreacted starting material obtained at the end of the reaction). Triphenylphosphine was tried as an external reductant and only 17% of the desired product was obtained (entry 6). Different solvents were tested (entries 8 - 13) and DMSO, (CH₂Cl)₂ and CH₂Cl₂ were found to also be compatible with the reactivity but the desired imidazolidinone was observed by ¹H NMR in lower yields compared to MeCN. Finally, control experiments (entry 14 and 15) showed the importance of the photocatalyst and the base for the formation of the C-H amination product: indeed, in both case unreacted starting material was observed by ¹H NMR at the end of the reaction.

4.2.3.3. Scope of the reaction

After optimization of photoredox set-up and experimental conditions, different *p*-methoxybenzoyl ureas were tested and the results are separated by the hybridization state of the carbon and the number its substituents. The first derivatives tested could react at tertiary Csp³-H bonds and the results are presented in Table 4-9.

Table 4-9: Sp³ Tertiary aliphatic C-H amination scope^a



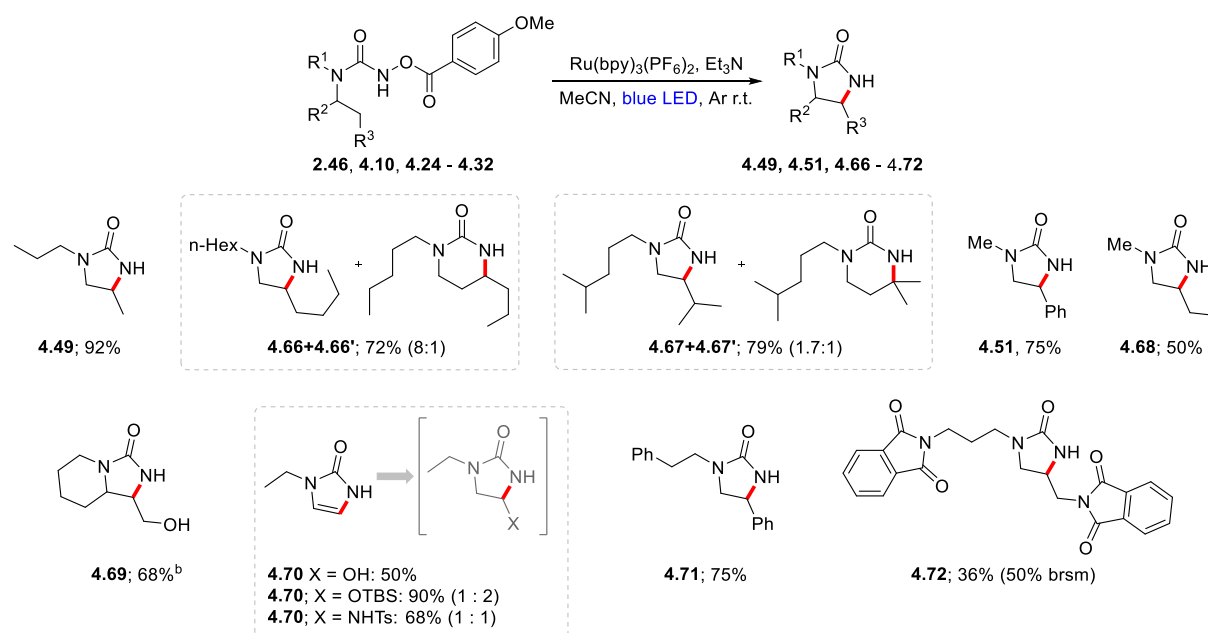
Conditions: ^a *N*-Benzoyloxyurea (1.00 equiv), $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ (2 mol%), Et_3N (1.10 equiv) in MeCN (0.3M) irradiated under inert atmosphere with 450 nm blue LED at room temperature overnight. Isolated yields are shown.

Imidazolidinone products were isolated in moderate to excellent yields using $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ as the catalyst and Et_3N as a base after being irradiated at 450 nm under inert atmosphere overnight. First, symmetrical amines were investigated with the diisobutyl amine (**4.11**) and 2-ethylheptan-1-amine (**4.12**) leading to the formation of the desired products in 99% and 75% isolated yields respectively. A small *N*-methyl group was also tolerated (**4.48**; 93%), and proved significantly better than the parent *N*-benzyl substrate that only led to the imidazolidinone (**4.49**) in 45% isolated yield. In this case, 10% of benzaldehyde was observed by ¹H NMR, supposedly via oxidation of the C-H benzylic position. The reaction was compatible with trifluoro (**4.55**) and acetal (**4.56**) functional groups. Unfortunately, less than 10% of the free NH (**4.57**), lactam (**4.58**) and carbamate (**4.60**) products were observed using these conditions. The reaction was also compatible with the formation of a spirocycle (**4.60**). C-H Amination

at a benzylic position (**4.61**) was effective and the desired product was obtained in 77% isolated yield. C-H amination at α -position to an oxygen resulted in high yields for the cyclization, providing the corresponding aromatic heterocycle (**4.62**) as final product, via extrusion of the oxygen atom and aromatisation. The same C-H amination/extrusion of the oxygen atom was also observed when the C-H amination was performed at an acetal position (**4.63**). Finally, the reaction was also tested with drug-like molecules, with ephedrine (**4.64**) and propranolol (**4.65**) derivatives, and the C-H amination products were isolated in low to good yields. One of the limitations of the method was the substituent on the nitrogen atom: indeed, symmetrical amines or substituents where the C-H amination can not happen (e.g. methyl, ethyl or a quaternary center) were used as the second alkyl chain.

Gratifyingly, the C-H amination was also found to be efficient with methylene C-H bonds under the same experimental conditions. The scope of the reaction with such substrates can be seen in *Table 4-10*.

Table 4-10: Secondary aliphatic C-H amination scope^a



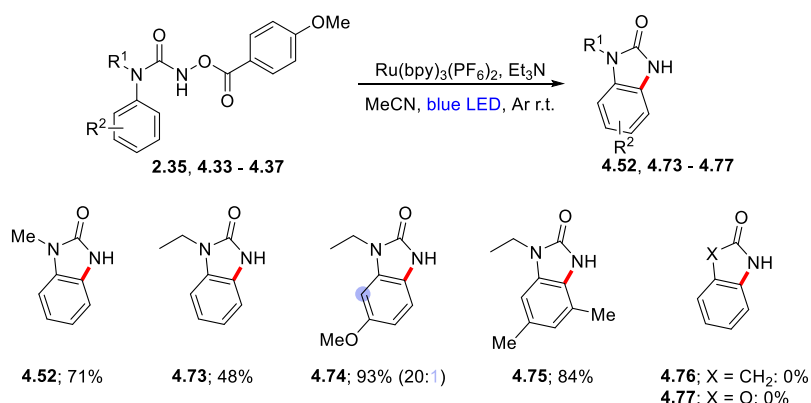
Conditions: ^a *N*-Benzoyloxyurea (1.00 equiv), Ru(bpy)₃(PF₆)₂ (2 mol%), Et₃N (1.10 equiv) in MeCN (0.3M) irradiated under inert atmosphere with 450 nm blue LED at room temperature overnight. ^b NMR yield is shown. Isolated yields are shown.

Multiple imidazolidinones derived from insertion into methylene C-H bonds were isolated in moderate to good yields. The symmetrical dipropylamine derivative (**4.49**) led to the formation of the cyclic product in 92% isolated yield. With longer alkyl chains, formation of the 5- and 6-membered rings was observed in a ratio 8:1 favoring the 5-membered ring (**4.66+4.66'**). In contrast, the parent ratio decreased to 1.7:1 with a substrate offering the possibility of 6-membered ring formation via C-H amination at a tertiary position (**4.67+4.67'**). Insertion could also occur at a benzylic position and the corresponding imidazolidinone (**4.51**) was isolated in 75% isolated yield. The small *N*-methyl

substituent afforded a lower yield of the product (**4.68**; 50%), reflecting that the reaction is disfavored by the conformational preferences of this substrate. Bicyclic product (**4.69**) was obtained in 68% isolated yield and when the C-H amination position was α to a leaving group (OH, OTBS and NHTS), subsequent aromatization via extrusion of this leaving group led to the formation of 1-ethyl-1,3-dihydro-2H-imidazol-2-one (**4.70**) in good to excellent yields. Finally, symmetrical homobenzyl amine and phthalimide derivative formed the desired product (**4.71**) in 75% and (**4.72**) 36% (and 50% brsm) isolated yields respectively. The tolerance of the phthalimide substituent was surprising as this group is used to access alkyl radical under photoredox conditions.²³⁴ Except for the dipropylamine starting material, the corresponding primary urea was observed as a side-product in less than 10% and induced difficult isolation due to the co-elution with the desired imidazolidinone product.

The reaction was not only limited to sp^3 C-H amination and investigation of the sp^2 C-H amination position was undertaken using aniline derivatives as starting materials (Table 4-11). Gratifyingly, the same conditions found for aliphatic substrates were also the optimum conditions for the aromatic *N*-benzoyloxyureas.

Table 4-11: Sp^2 C-H amination scope^a

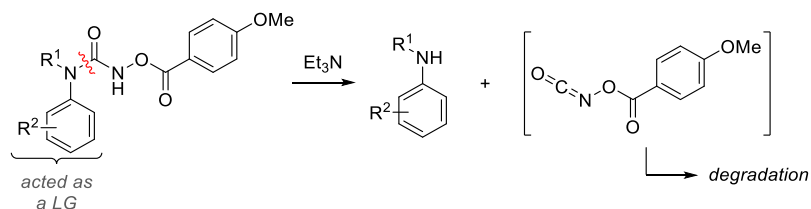


Conditions: ^a *N*-Benzoyloxyurea (1.00 equiv), Ru(bpy)₃(PF₆)₂ (2 mol%), Et₃N (1.10 equiv) in MeCN (0.3M) irradiated under inert atmosphere with 450 nm blue LED at room temperature overnight. Isolated yields are shown.

Several benzimidazolidinones were isolated in moderate to good yields. The *N*-methyl substituent (**4.52**) was isolated in 71% yield, where the *N*-ethyl (**4.73**) was only obtained in 48%. Indeed, with the aromatic derivative a side-reaction was found to occur during the C-H amination: aniline groups acted as leaving group and in presence of Et₃N, the *O*-isocyanate and the corresponding aniline were released (the free aniline was observed and isolated) (Scheme 4-26). However, in presence of electron donating groups (resulting of the aniline being a worst leaving group for the *O*-isocyanate formation), the

²³⁴ For selective examples see: (a) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science* **2018**, 360, 419. (b) Jin, C.; Yan, Z.; Sun, B.; Yang, J. *Org. Lett.* **2019**, 21, 2064. (c) Candish, L.; Teders, M.; Glorius, F. *J. Am. Chem. Soc.* **2017**, 139, 7440.

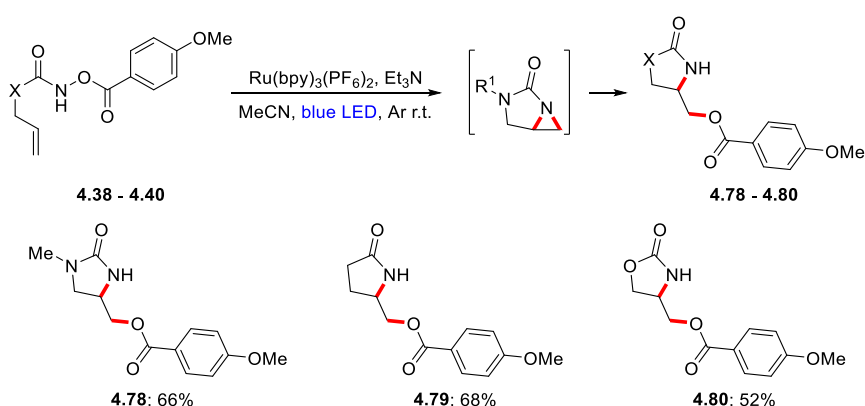
efficiency of the C-H amination increased and the corresponding heterocycles were obtained in good yields (**4.74**, **4.75**). Unfortunately, the reaction was not compatible with carbon and oxygen derivatives (**4.76**, **4.77**) due to conformer issue (traces of the 2-phenylacetamide and phenyl carbamate were observed by ^1H NMR).



Scheme 4-26: Degradation of the aromatic N-benzoyloxyureas

In presence of olefin, reactive nitrogen intermediates can undergo aziridination reaction and different allylic starting materials (urea, amide and carbamate) were synthesized. Similar to the C-H amination the optimum conditions, Ru(bpy)₃(PF₆)₂ in presence of Et₃N were used (Table 4-12).

Table 4-12: Aziridination scope^a



Conditions: ^a N-Benzoyloxyurea (1.00 equiv), Ru(bpy)₃(PF₆)₂ (2 mol%), Et₃N (1.10 equiv) in MeCN (0.3M) irradiated under inert atmosphere with 450 nm blue LED at room temperature overnight. Isolated yields are shown.

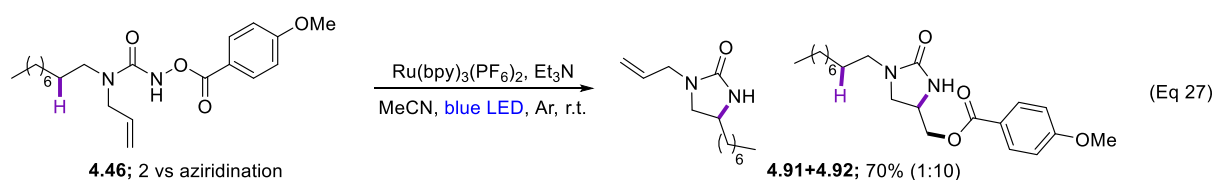
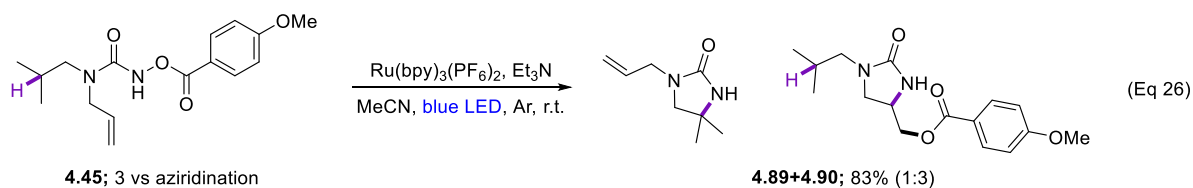
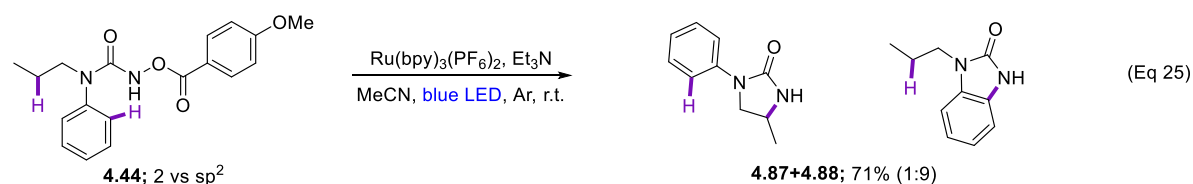
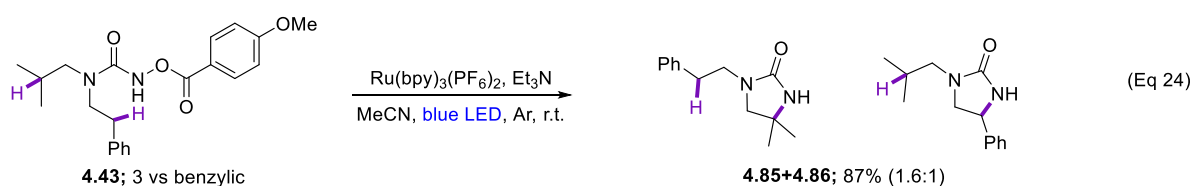
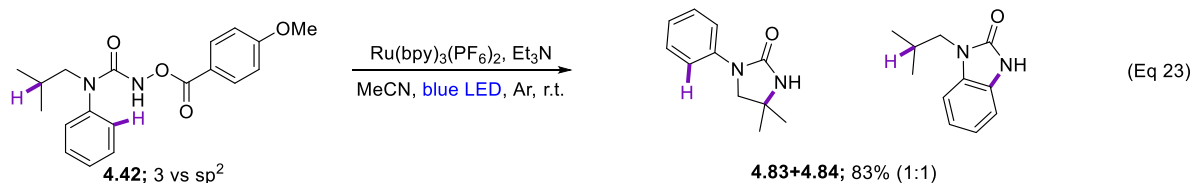
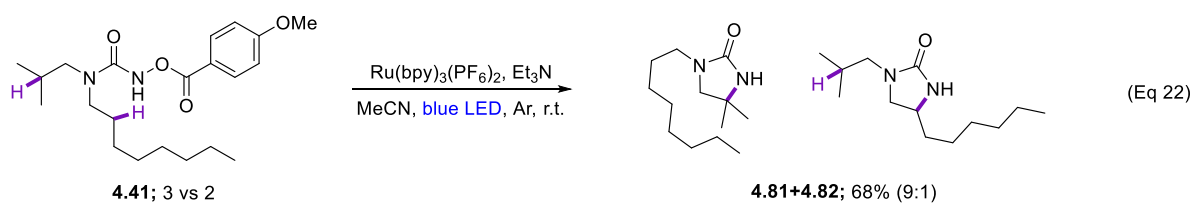
During the course of the reaction, the desired aziridines were observed by ^1H NMR, however at the end of the reaction the corresponding ring opening products were obtained (with minimal traces of the aziridines) for the three different starting materials. Indeed, one full equivalent of *p*-methoxybenzoate is released during the course of the C-H amination, inducing the ring-opening of the strained bicyclic intermediate via nucleophilic addition. In contrast with the C-H amination reactivity, the oxy-amination of alkenes was compatible with carbon (**4.79**) and oxygen (**4.80**) derivatives. It was hypothesized that the compatibility of the amide and carbamate derivatives was the result of a facile aziridination reaction (previous groups reported that aziridination reactions are easier than C-H amination reactions).^{228,235} In

²³⁵ For selective examples see: (a) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, 43, 4349. (b) Hayes, C. J.; Beavis, P. W.; Humphries, L. A. *Chem. Commun.* **2006**, 4501. (c) Olson, D. E.; Du Bois, J. J.

direct comparison with the study of Lu and co-workers,²³⁰ the yields obtained were higher under milder conditions (they needed to irradiate the reaction at 50 °C). Moreover, their reaction was limited to styrene derivatives.

After the scope study, the inherent selectivity of the C-H amination was also explored using competition experiments: different *N*-benzoyloxyureas bearing simultaneously tertiary, secondary, aromatic and aziridination positions were synthesized. First, in presence of sp^3 tertiary and secondary C-H bonds, the tertiary position was favoured in a 9:1 ratio (Eq 21). In contrast no selectivity was observed between sp^3 tertiary and sp^2 positions and the two heterocycles were obtained in a 1:1 ratio (Eq 22). Low selectivity was found when the C-H amination was performed on an *N*-benzoyloxyurea bearing a sp^3 tertiary position and a benzylic position (Eq 23). Sp^2 C-H amination was favoured over a sp^3 secondary position and the corresponding benzimidazolidinone and imidazolidinone were obtained in a 9:1 ratio (Eq 24).

Am. Chem. Soc. **2008**, *130*, 11248. (d) Lu, H.; Jiang, H.; Yang, H.; Wojtas, L.; Zhang, X. P. *Chem. Sci.* **2011**, *2*, 2361.

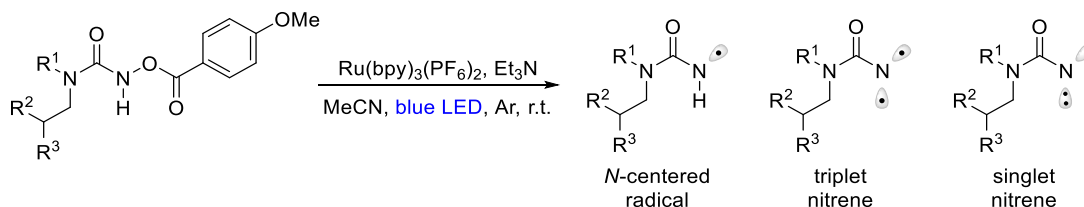


Finally, as expected, aziridination was favoured over sp³ tertiary and secondary positions (Eq 25 and Eq 26). In conclusion, the selectivity observed during the competition experiments was aziridination > arene / 3° C-H ≈ benzylic C-H > 2° C-H > 1° C-H which was in agreement with the inherent selectivity of *N*-centered radical and nitrene intermediates.²³⁶

²³⁶ Williams Fiori, K. ; Espino, C. G. ; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, 65, 3042.

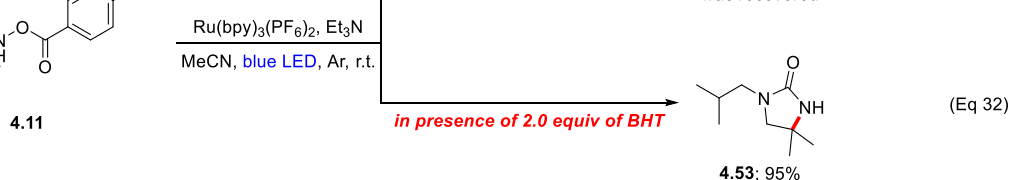
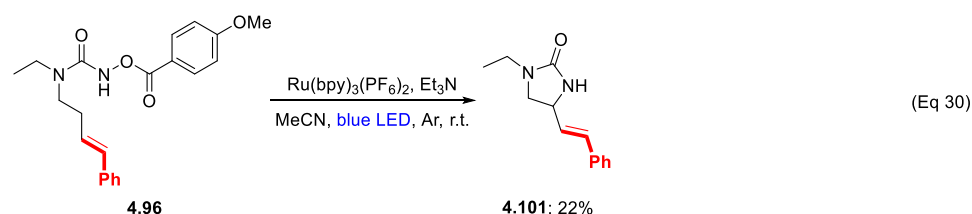
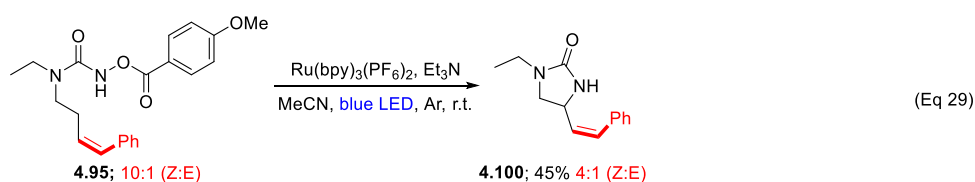
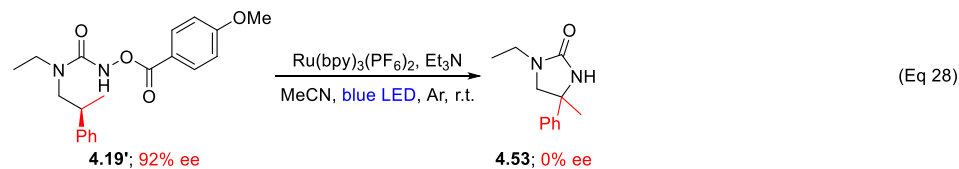
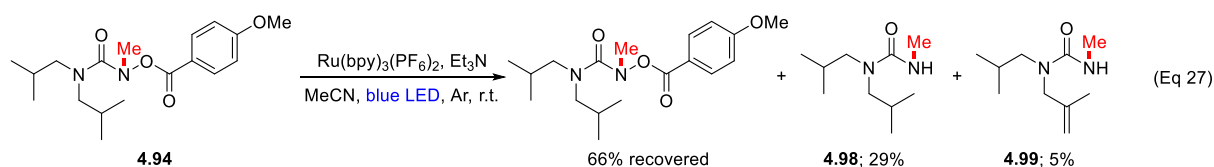
4.2.3.5. Mechanistic study and proposed mechanism

Due to the novelty of the reaction and the trend obtained during the optimization, a mechanistic study was performed to identify the possible intermediate: indeed, three possible reactive nitrogen intermediates can be envisaged from the *N*-benzoyloxyurea: a *N*-centered radical, a triplet nitrene or a singlet nitrene (Scheme 4-27).



Scheme 4-27: The three possible reactive intermediates

The formation of a *N*-centered radical intermediate via carbonyl reduction was already disfavored as a potential pathway during the benzoate substituent study and to gain more evidence, a *N*-methyl derivative (**2.94**) was synthesized. Under the optimum condition, no C-H amination product was found and two different ureas were observed and isolated as a mixture (**4.98**, **4.99**) along with unreacted starting material (Eq 27). The presence of the methyl substituent inhibited the formation of the nitrenes (singlet and triplet) with the formation of the *N*-centered radical still being possible. This experiment accentuated that the *N*-centered radical pathway was unlikely and at that time, singlet and triplet nitrenes were the two intermediates envisaged. An enantioenriched *N*-benzoyloxyurea was synthesized in order to probe the state of the nitrene intermediate. Indeed, as specified earlier,²²¹ nitrenes can exist either in singlet or triplet states. In the case of a C-H amination by a singlet nitrene, the enantiomeric excess would be retained due to the concerted mechanism of this reactive intermediate. On the other hand, triplet nitrenes react in a stepwise mechanism resulting in the erosion of the enantiomeric excess.²¹⁸ Starting with a *N*-benzoyloxyurea with a 92% enantiomeric excess, the C-H amination was performed and complete erosion was observed in the product (Eq 28). This experiment suggested that the reactive intermediate for the C-H amination is a triplet nitrene and more experiments were tried to gain more evidence for this intermediate.



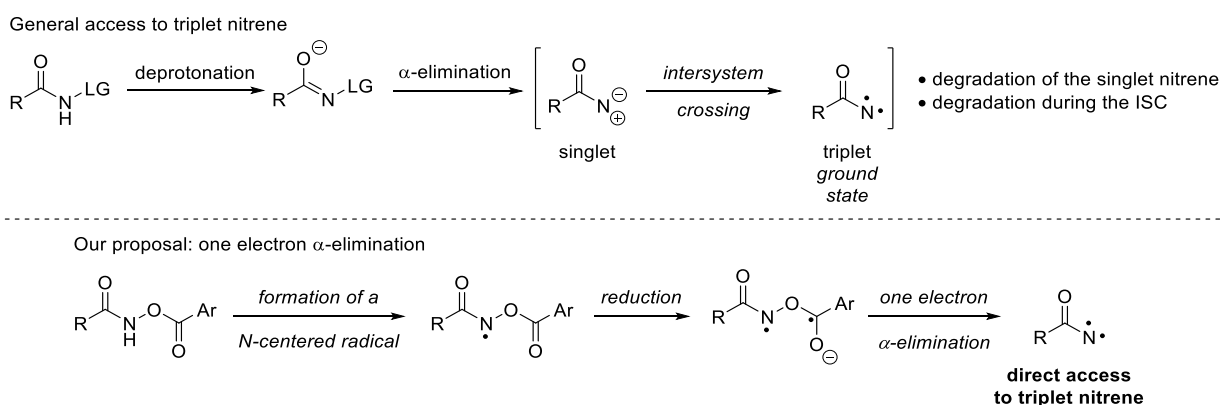
Two derivatives bearing Z- and E-alkenes were synthesized in order to perform the C-H amination at an allylic position: indeed, olefin isomerization can occur in presence of a radical at the allylic position. Starting from a mixture of alkenes (Z:E = 10:1), the products obtained after C-H amination were a mixture of imidazolidinone bearing a double bond with a ratio 4:1 to Z:E (Eq 29) (e.g. 10% of isomerization occurred). Similar erosion of the olefin stereoisomers was also reported for allylic C-H amination with metal triplet metal-nitrene.²³⁷ The fact that the Z-alkene geometry was mostly retained can be explained by the fast recombination of the triplet nitrene mechanism (after C-H abstraction and formation of a carbon-radical rapid radical recombination occurred to form the C-N bond).²²¹ A control experiment with the E-alkene led to the formation of the desired heterocycle with the E-olefin as the sole product (Eq 30).²³⁸ Remarkably, no traces of the aziridination products were observed for these two reactions. Finally, two radical trapping reagents were used: using TEMPO (Eq 31) the reaction was

²³⁷ Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036.

²³⁸ Singh, K.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 5275.

inhibited and the starting material was recovered. It was hypothesized that TEMPO poisoned the catalyst. However, in presence of two equivalents of BHT, 95% of the C-H amination was observed without side-products and clean BHT was recovered at the end of the reaction. In contrast of the proposed triplet nitrene intermediate, *N*-centered radical are usually quenched and no-reactivity is observed in presence of BHT.²³⁹ Other experimental studies were performed to disfavoured an oxidative pathway arising from the deprotonation of the *N*-benzoyloxyurea: indeed, by using ¹H NMR, no evidence of the deprotonation by Et₃N was observed. The conclusion of the experiments presented above was that triplet nitrene is likely the reactive intermediate involved in the C-H amination reaction and a novel mechanism could be suggested for its formation.

Nitrenes are usually formed from amide derivatives which bear a good leaving group on the nitrogen atom: indeed, a two-step mechanism involving the deprotonation of the nitrogen followed by α -elimination leads to the formation of the singlet nitrene intermediate (Scheme 4-28).¹²² This reactive intermediate is high in energy and unstable and can undergo intersystem crossing to corresponding triplet nitrene which is, in most case,, the ground state.²²¹

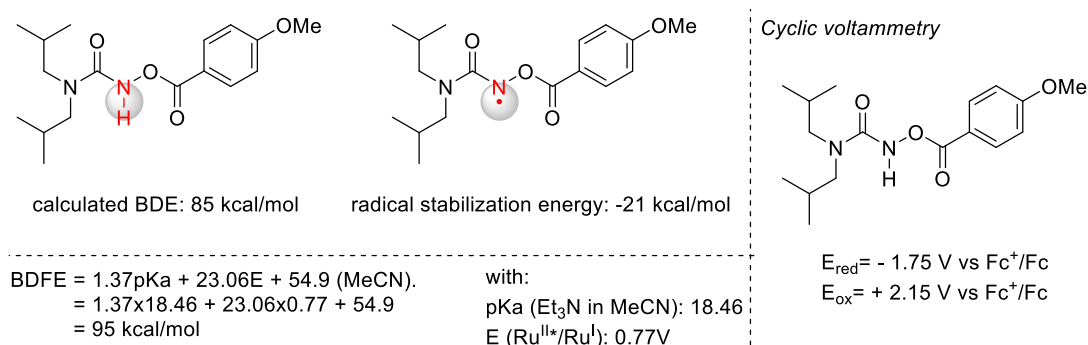


Scheme 4-28: Access to triplet nitrene

Under photoredox conditions, a similar mechanism involving a one-electron α -elimination step was envisaged: indeed, similar steps were proposed to occur in a one-electron fashion. It was hypothesized that a PCET mechanism could form a stabilized *N*-centered radical that can undergo carbonyl reduction followed by one electron α -elimination to directly access the triplet nitrene. A DFT calculation was performed using B3LYP/6-31G(d) and the radical energy stabilization for the *N*-centered radical intermediate was found to be -21 kcal/mol. The BDE of the N-H bond was calculated at 85 kcal/mol and was compared to the BDFE (bond dissociation free energy) of the Ru^{II}/Et₃N system (calculated at 95 kcal/mol) (Scheme 4-29). The BDFE is directly linked to the free energy of the reaction (e.g. the driving force of the reaction) and a direct comparison of the BDE and BDFE of the system can be

²³⁹ For selective examples see: (a) Yuan, W.; Zhou, Z.; Gong, L.; Meggers, E. *Chem. Commun.* **2017**, 53, 8964. (b) Ma, Z.Y.; Guo, L.-N.; You, Y.; Yang, F.; Hu, M.; Duan, X.-H. *Org. Lett.* **2019**, 21, 5500. (c) Bao, X.; Wang, Q.; Zhu, J. *Nat. Commun.* **2019**, 10, 769.

performed. Indeed, the BDE being close to the BDFE of the system supports the likelihood of a PCET process. It was also hypothesized that the kinetics of the PCET pathway would be the most favorable.



Scheme 4-29: DFT calculation and cyclic voltammetry of **4.11**

A precedent DFT study of related *N*-centered radicals supported and quantified that a captodative effect increased the stability of these intermediates.²⁴⁰ In addition, during the course of the study, one example of one-electron α -elimination was reported during the photogeneration Rh₂ metal-nitrene from chloramine-T (the synthetic application was not evaluated).²⁴¹ The proposed mechanism is thus a combination of a PCET-induced amidyl radical formation²⁴² and a subsequent SET-induced *N*-O bond cleavage.²⁴³ It is, to our knowledge, the first proposed spin-selective formation of triplet nitrene under photoredox conditions. The direct access to triplet nitrene allows for a higher selective reaction due to circumvention of the different degradation pathways. Indeed, singlet nitrenes are known to undergo 1,2-shift rearrangement and *in-situ* formation of an isocyanate. Furthermore, degradation can also be happening during the ISC resulting in low yields for the desired reaction.²²¹

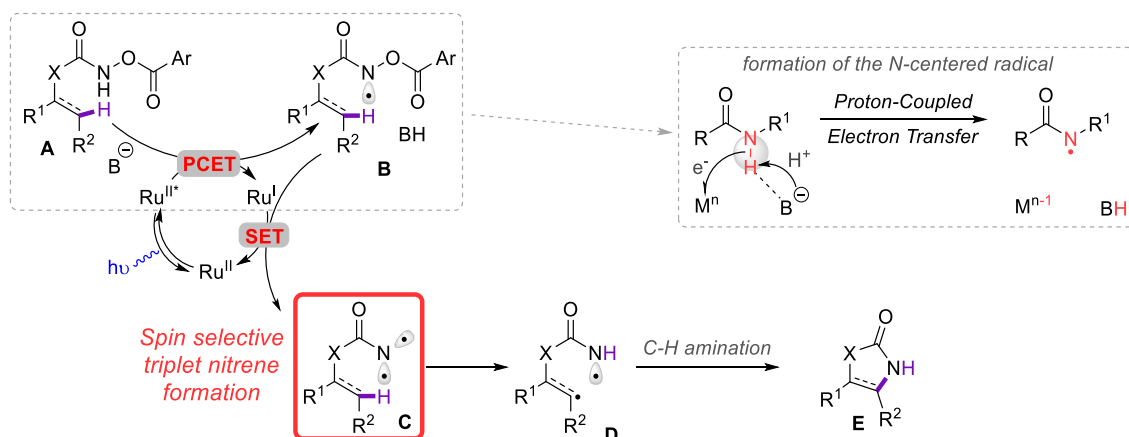
The proposed mechanism to directly access the triplet nitrene is shown in Scheme 4-30. First, the Ru^{II} is excited to Ru^{II}* by the blue LED. This excited state can either be quenched by Et₃N in a reversible non-productive pathway or be quenched by the *N*-benzoyloxyurea starting material **A** via PCET for the formation of a proposed *N*-centered radical **B** (also yielding the reduced Ru^I).

²⁴⁰ Hioe, J.; Šakić, D.; Vrček, V.; Zipse, H. *Org. Biomol. Chem.* **2015**, *13*, 157.

²⁴¹ Das, A.; Maher, A. G.; Telser, J.; Powers, D. C. *J. Am. Chem. Soc.* **2018**, *140*, 10412.

²⁴² Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, *49*, 1546.

²⁴³ Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. *Chem. Eur. J.* **2018**, *24*, 12154.



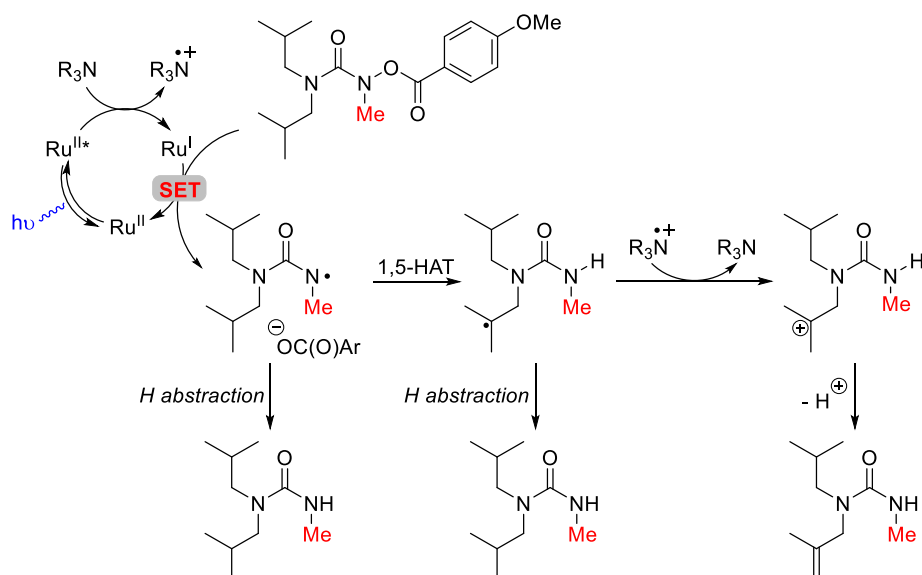
Scheme 4-30: Proposed mechanism for the photoinduced C-H amination

The BDE of the *N*-H bond was calculated at 85 kcal/mol and was compared to the BDFE (bond dissociation free energy) of the Ru^{II}/Et₃N system (calculated at 95 kcal/mol) (Scheme 4-29: DFT calculation and cyclic voltammetry of **4.11**). The BDFE is directly linking to the free energy of the reaction (e.g. the driving force of the reaction)²⁴⁴ and a direct comparison of the BDE and BDFE of the system can be done. Indeed, the BDE being close to the BDFE of the system supports the likelihood of a PCET process.

Cyclic voltammetry was also performed on **4.1** and it was found that *N*-benzoyloxyurea undergoes irreversible reduction at – 1.75 V (vs Fc⁺/Fc) and an irreversible oxidation at + 2.15 V (vs Fc⁺/Fc) (see SI for the spectra). The high reduction potential of the starting material highlighted the difficult reduction of the carbonyl before the formation of the *N*-centered radical (and brought more evidence against the *N*-centered radical mechanism proposed in Scheme 4-25). The radical **B** is then reduced by the Ru^I that undergo one electron α -elimination to release the corresponding benzoate and form directly the nitrene in its triplet state **C**. Alternatively, it is also possible that reduction of **B** could directly afford **C**. Finally, the triplet nitrene intermediate can undergoes first H-abstraction (intermediate **D**) followed by rapid recombination to form the corresponding C-H amination product **E**.

This proposed mechanism corroborated the electronic trend of the aromatic group: indeed, pre-emptive reduction of the *N*-O bond (induced by the presence of electron-withdrawing group) would lead to non-productive pathway involving a *N*-centered radical intermediate. Indeed, it was hypothesized that the formation of the urea side-products was arising from the formation of the *N*-centered radical via reductive cleavage of the *N*-O bond. The proposed mechanism involving the *N*-Me starting material (**4.94**) can be seen in Scheme 4-31.

²⁴⁴ Warren, J. J.; Tronic, T. A; Mayer, J. M. *Chem. Rev.* **2010**, *110*, 6961.



Scheme 4-31: Proposed mechanism for the formation of urea side-products

After formation of the reduced form of the Ru via SET reaction with Et₃N, SET reduction with the carbonyl will lead to the formation of the *N*-centered radical and the corresponding *p*-methoxybenzoate anion via homolytic cleavage of the *N*-O bond. The *N*-centered radical can undergo Hydrogen abstraction to form the *N*-methylurea or form the carbon radical intermediate via 1,5-HAT. This carbon radical can also undergo Hydrogen abstraction (and form the same *N*-methylurea) or can be oxidized by the protonated triethylamine radical and form the corresponding carbocation. Finally, after losing a proton, the allylamine *N*-methyl urea can be formed. It was suggested that the presence of the electron-donating methoxy group on the aromatic benzoate will limit this degradation pathway due to the strong reduction potential of the starting material resulting in a difficult SET reaction between the reduced form of the catalyst and the starting material. It was also hypothesized that the *N*-methyl starting material reacted slowly via the proposed mechanism and more experiments were undertaken. First, the kinetic formation of the Me-urea was studied: the *N*-methylbenzoyloxyurea (**4.94**) was subjected to the optimum conditions in CD₃CN and the conversion was monitored using ¹H NMR (Figure 4-1).

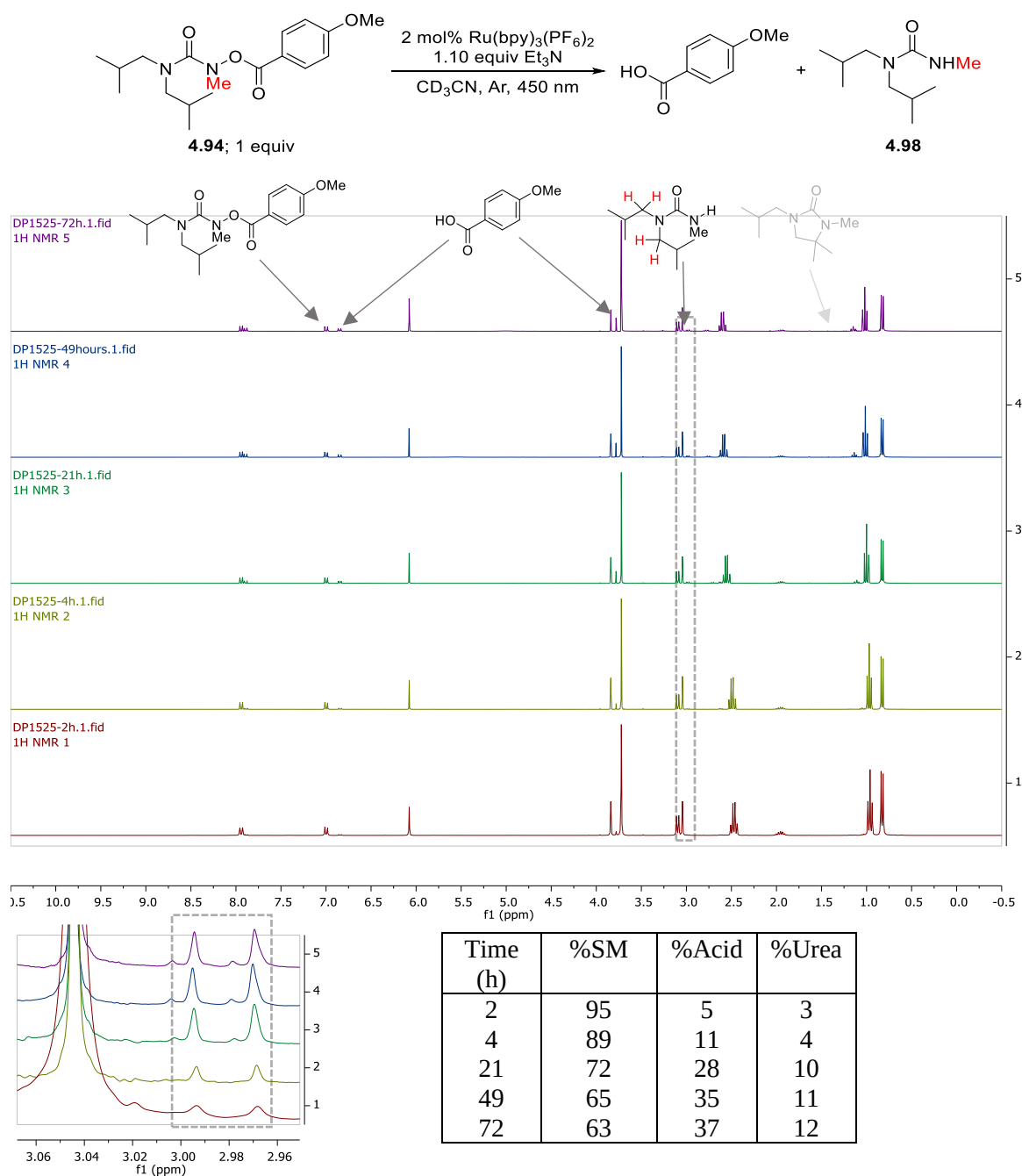
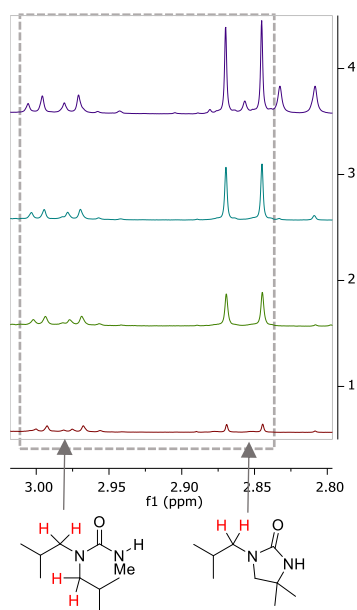
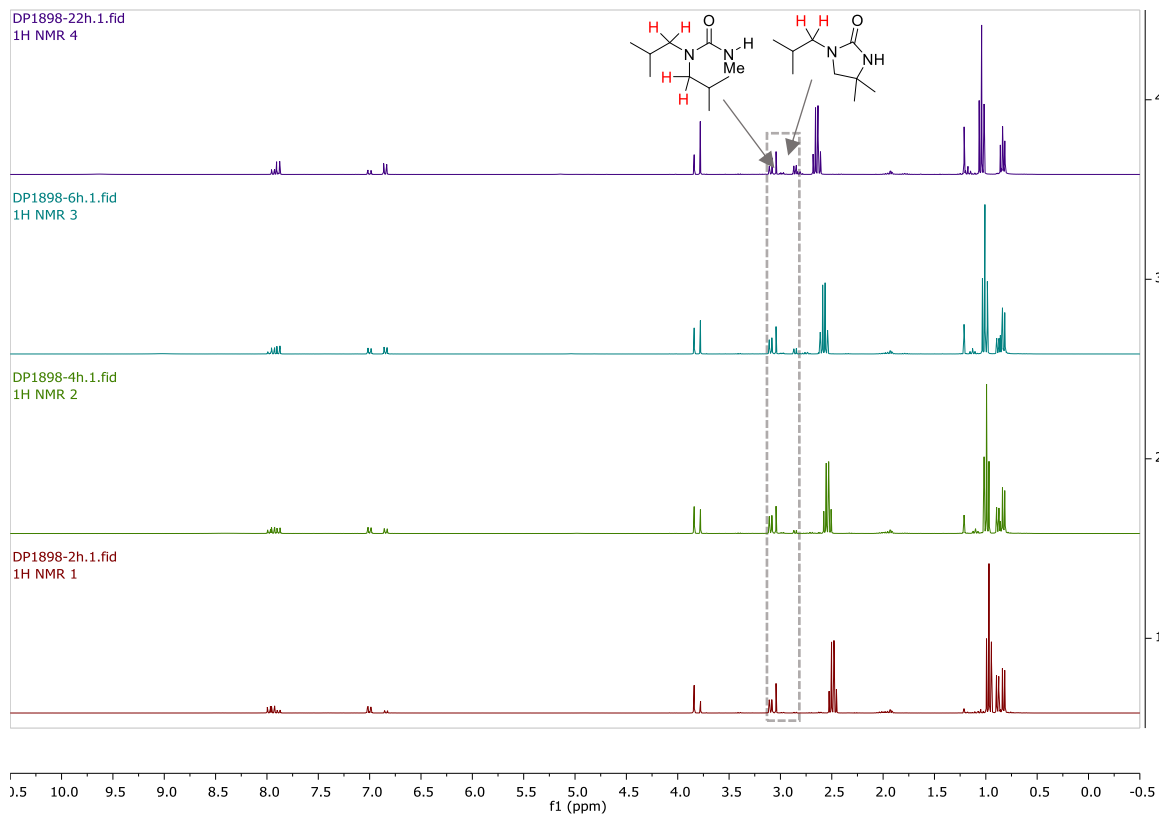
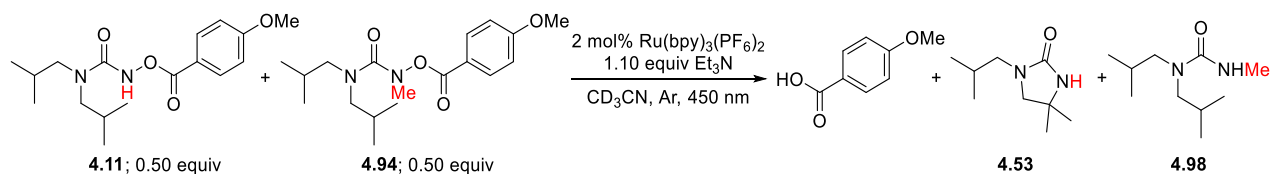


Figure 4-1: Kinetic formation of the *N*-methylurea

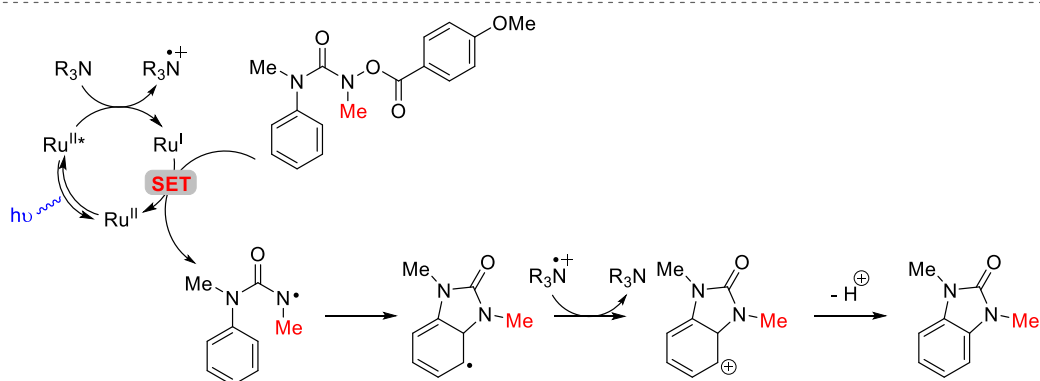
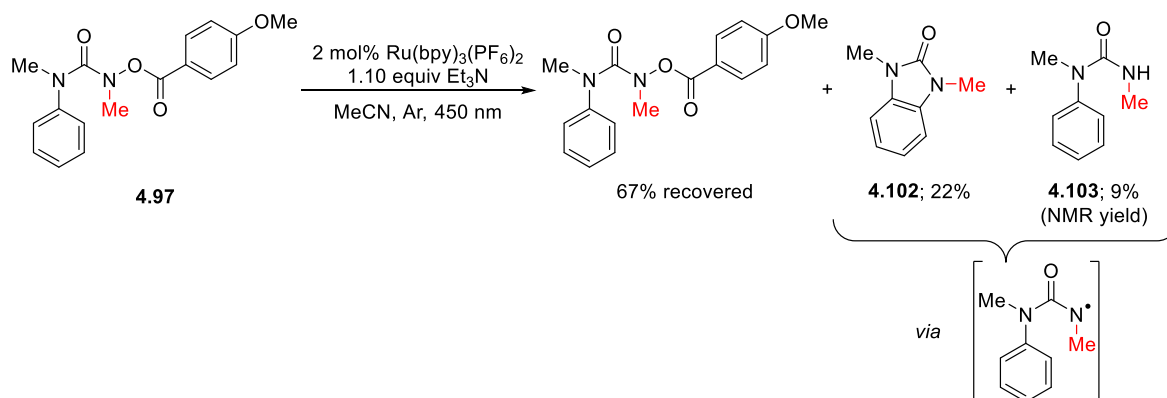
After 72 h of reaction time, only 37% of the starting material reacted, with only 12% of the *N*-methylurea product formed (based on the formation of the benzoic acid). To validate the slow formation of this product, a competition experiment was performed where the *N*-benzoyloxyurea (**4.1**) and *N*-methylbenzoyloxyurea (**4.94**) were reacted together. In the same reaction vial, 0.5 equiv of (**4.1**) and 0.5 (**4.94**) were subjected to the light irradiation and the reaction was monitored.



Time (h)	%SM	%Acid	%C-H Activation	%Urea
2	84	16	8	4
4	63	37	30	6
6	52	48	45	9
22	29	71	63	12

Figure 4-2: Competition experiment for the C-H amination

The formation of the products was calculated from the formation of the benzoic acid and the %SM represents the percentage of conversion of the two starting materials, as all their peaks overlapped. After 2 h, 16% of the conversion was observed for the starting materials and 8% of the C-H amination and 4% of the side-product were found. After 22 h of reaction, 63% of the imidazolidinone and only 12% of the *N*-methylurea were observed. With these two kinetic studies, the formation for the *N*-methylurea side-product was found to be slower than the formation of the imidazolidinone via C-H amination. The same *N*-methyl studied was also tested for the sp^2 C-H amination using the aniline starting material (**4.97**).



Scheme 4-32: Formation of the *N*-methylbenzimidazolidinone

Surprisingly, the 1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one product (**4.102**) was found and isolated in a 22% yield with 67% of the starting material recovered. Moreover, 9% of the *N*-methyl urea was observed by 1H NMR (but not isolated). The formation of the cyclic product indicated that for the sp^2 C-H amination, the *N*-methylcentered radical was capable of undergoing the C-H amination reaction. However, the 22% yield was compared to the result obtained of the corresponding *N*-H starting material (**4.102**) where the formation of the benzimidazolidinone was isolated in 71% yield. The low conversion of the starting material after the same reaction time, indicated that the reductive cleavage of the *N*-O bond is indeed slower than the desired C-H amination reaction.

In conclusion, the intricacies of the proposed mechanism can explain the need of the *p*-methoxybenzoate starting material: indeed, pre-emptive cleavage of the *N*-O bond would result in the formation of the

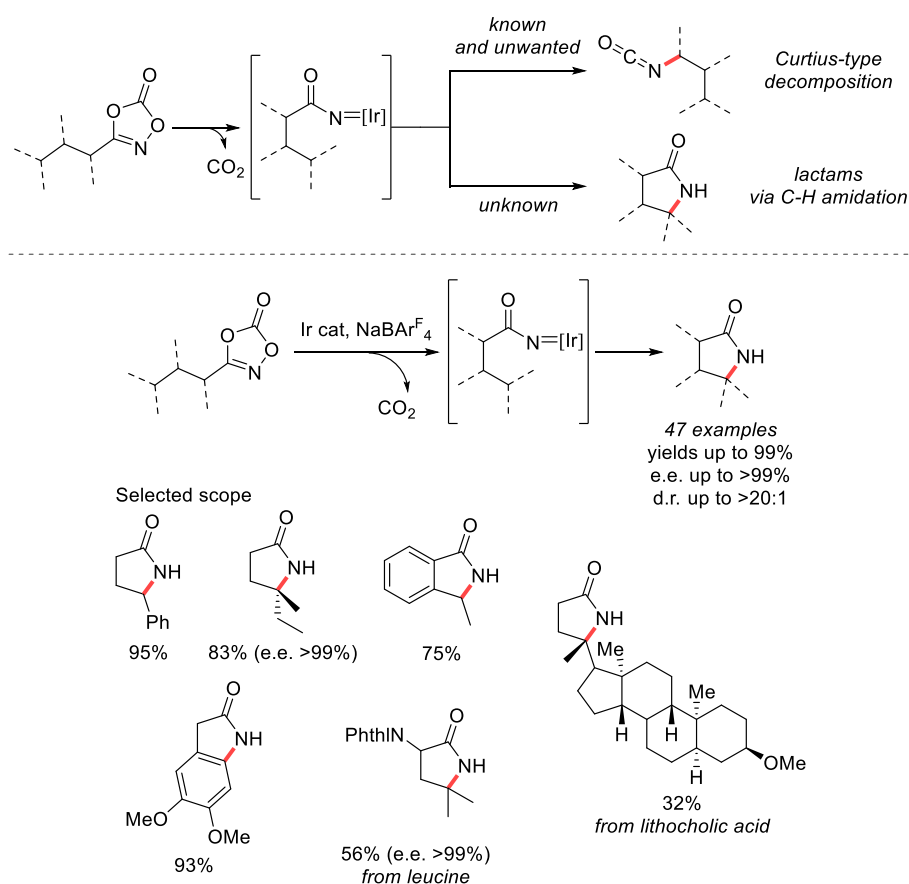
corresponding urea (via the intermediacy of *N*-centered radical). Moreover, a mechanism involving PCET oxidation followed by SET reduction of the N-O bond is proposed to account for the results, requiring perfect orchestration of the different event needs to occur to access the triplet nitrene. To our knowledge, this is the first time that direct formation of triplet nitrene is proposed via cleavage of a *N*-O bond, and experiments to obtain further support for this mechanism are ongoing. The experimental results highlighting broad applicability suggest that the formation of a triplet nitrene under photoredox conditions can be an alternative to the stabilization of nitrene (via metal-catalyzed reaction) to perform selective C-H amination reactions.

4.2.3.4. Lactam synthesis

With this proposed mechanism and the mechanistic study performed, efforts for the synthesis of lactam via C-H amination was investigated due to the scarcity of the reaction. Indeed, beginning of 2018, Chang's group reported the first lactam synthesis via C-H amidation using mechanism-guided catalyst engineering (*Scheme 4-33*).²⁴⁵ Previously, 1,4,2-dioxazol-5-ones were known to undergo Curtius-type rearrangement after ring-opening and extrusion of carbon dioxide.²⁴⁶ The isocyanate intermediate was formed *in-situ* and reacted via metal catalysed C-H amidation for the formation of the *C-N* bond. In the new study, by engineering novel iridium catalysts, the authors were able to limit the Curtius-type rearrangement by trapping (and stabilizing) the nitrene intermediate. Based on DFT calculations, different iridium catalysts bearing different substituents were identified: to inhibit the 1,2-shift, the ligands needed to be electron donor due to the sensitivity of the Curtius-type rearrangement to change of partial charges. Several iridium catalysts bearing oxygen and nitrogen atom donor ligands were synthesized and used in the C-H amidation.

²⁴⁵ Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. *Science* **2018**, 359, 1016.

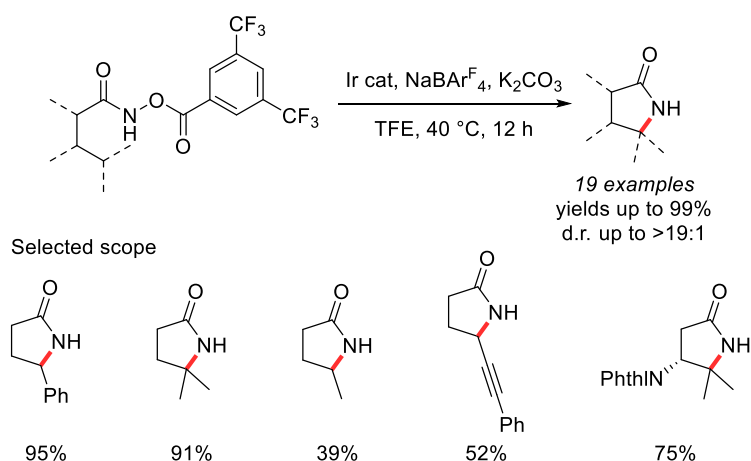
²⁴⁶ (a) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, 137, 4534. (b) Park, J.; Chang, S. *Angew. Chem., Int. Ed.* **2015**, 54, 14103.



More than forty lactams were isolated in high yields, high enantiomeric and diastereomeric excess (when applied) even for non-activated positions. However, the generalisation of the method was lacking: indeed, eight different catalysts were used to the scope of the reaction and no generalisation was deducted. Shortly after this first report, the same C-H amidation was reported by different research groups using commercially available metal-nitrene catalysts.²⁴⁷ The Chang group reported, earlier this year, the same C-H amidation using *N*-benzoyloxyamides as starting materials.²⁴⁸ In this new study, cleavage of the *N*-O bond of *N*-benzoyloxyamides was catalyzed using the previous synthesized iridium catalysts. The presence of electron-withdrawing groups on the aromatic group of the benzoyl substituent was the key parameter for the efficient formation of lactams (*Scheme 4-34*). It can be noted that the electronic substituent is again different than the imidazolidinone study. Lactams were isolated in good to excellent yields with high diastereomeric excess

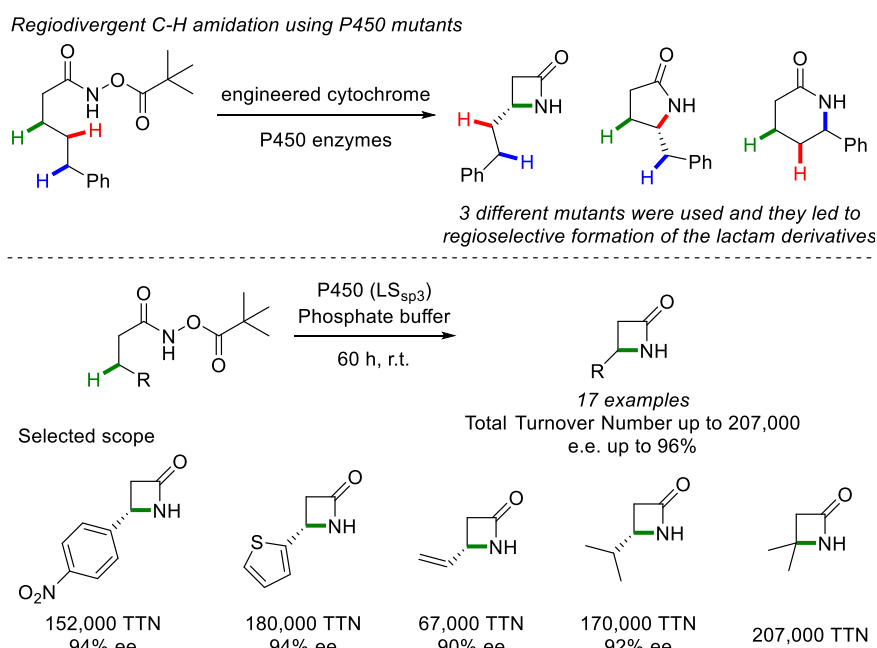
²⁴⁷ (a) Lei, H.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 2268. (b) Xing, Q.; Chan, C.-M.; Yeung, Y.-W.; Yu, W.-Y. *J. Am. Chem. Soc.* **2019**, *141*, 3849.

²⁴⁸ Huh, S.; Hong, S. Y.; Chang, S. *Org. Lett.* **2019**, 21, 2808.



Scheme 4-34: Lactam synthesis from *N*-benzoyloxyamides

After these first examples of lactam synthesis by C-H activation, enabled through mechanism-guided catalyst engineering, the first examples of C-H amidation via engineered cytochrome P450 enzymes was published by the group of Frances Arnold in 2019 (Scheme 4-35).²⁴⁹ By engineering the enzyme, the Curtius rearrangement can again be avoided and different ring can be selectively obtained: indeed three different mutants were evolved, with each leading to a specific heterocycle.



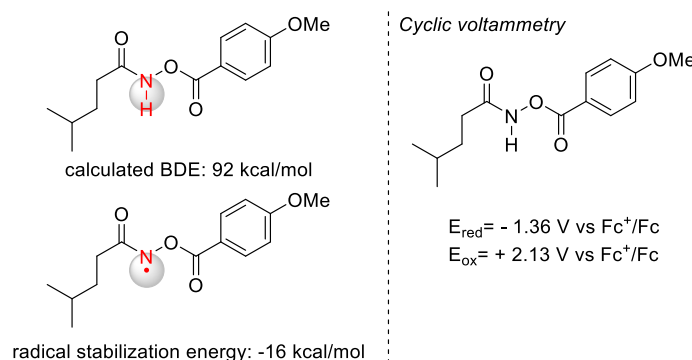
Scheme 4-35: C-H amidation via engineered enzymes

Several β -lactams were obtained with high enantiomeric excess and high turn-over number. The two strategies presented previously, focused on the synthesis and design of specific catalysts for the C-H amidation and formation of lactams. In the case of the photoredox study, emphasis was made on the design of the starting material and not the catalyst. The proposed formation of lactam via photoredox

²⁴⁹ Cho, I.; Jia, Z.-J.; Arnold, F. H. *Science* **2019**, 364, 575.

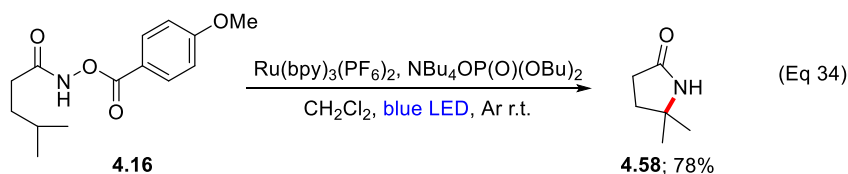
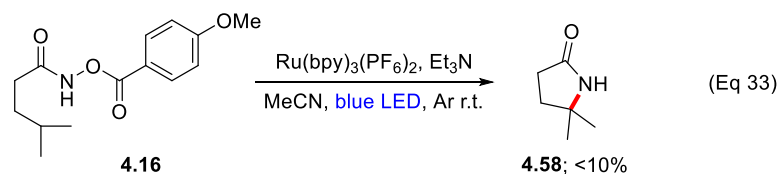
conditions can be seen a complementary method for the synthesis of this important heterocycle, and a probe for the proposed mechanism of one-electron alpha-elimination.

First, DFT calculations were performed with the *N*-benzoyloxyamide starting material (**4.16**) and it was found that the BDE of the *N*-H bond is significantly higher than the *N*-benzoyloxyurea (92 vs 85 kcal/mol) (Scheme 4-36). The radical stabilization energy was calculated to be -16 kcal/mol (vs -21 kcal/mol for the *N*-benzoyloxyurea). It was hypothesized that the stronger *N*-H bond and the lower radical stabilization energy thus lead to a harder PCET step a less stable *N*-centered radical intermediate. In addition, the lower reduction potential of the *N*-benzoyloxyamide (- 1.36V vs Fc⁺/Fc) found by cyclic voltammetry augmented the risk for unproductive SET-induced reduction of the substrate, and increased the risk for the formation of the primary amide as side-product via a *N*-centered radical intermediate.



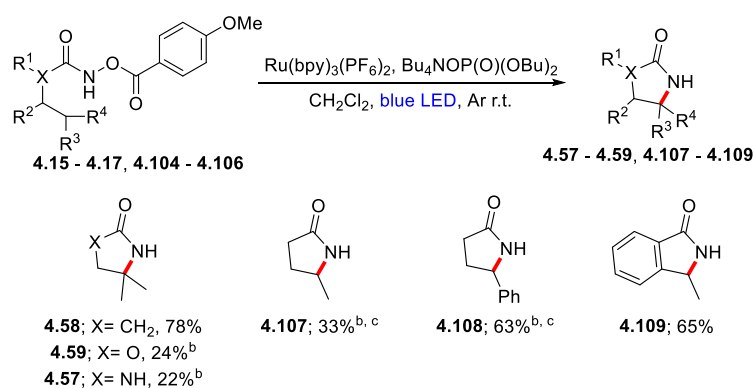
Scheme 4-36: DFT calculations and cyclic voltammetry of **4.16**

Aligned with these expectations, the optimum conditions of the imidazolidinone study (Ru(bpy)₃(PF₆)₂, Et₃N and MeCN) as the solvent), the 5,5-dimethylpyrrolidin-2-one was found in less than 10% by ¹H NMR with traces of the corresponding 4-methylpentanamide observed (Eq 33). Nevertheless, with this optimistic first result, optimization was undertaken.



Different photocatalysts with lower reduction potential (to overcome the pre-emptive *N*-O bond cleavage via reduction) and bases were tested (see *SI*). Unfortunately, the optimization was performed on a 0.1 mmol scale and scalable issues were found during the lactam synthesis study. Indeed, when the reaction was performed at 0.5 mmol, the yields observed were lower than the one observed during the optimization at 0.1 mmol scale. However, it was found that a phosphate base in CH₂Cl₂ (similar conditions than Knowles²¹¹⁻²¹⁵) led to the isolation of the desired lactam in a 78% yield (Eq 34). Indeed, Bu₄NOP(O)(OBu)₂ is the base of choice for the formation of amidyl radical via PCET due to its weak quenching character with photocatalysts and its weak basicity, resulting in a slow deprotonation which is not kinetically in competition with the decay of the excited state of the photocatalyst.¹¹⁹ After the base and solvent modifications, different *N*-benzoyloxyamides were tested for the synthesis of lactams and the results can be seen in *Table 4-13*.

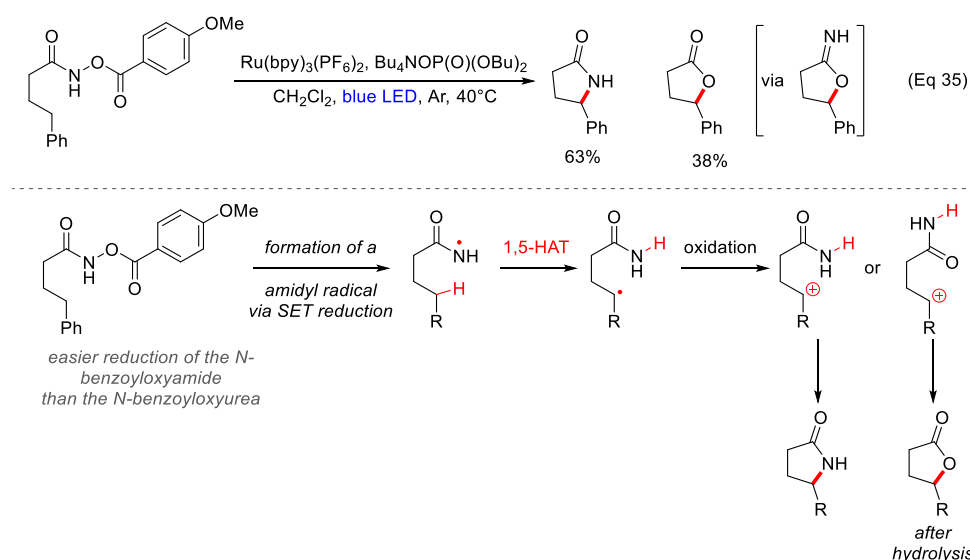
Table 4-13: Lactam synthesis scope^a



Conditions: ^a *N*-Benzoyloxyamide or *N*-benzoyloxycarbamate or *N*-benzoylurea (1.00 equiv), Ru(bpy)₃(PF₆)₂ (2 mol%), Bu₄NOP(O)(OBu)₂ (5 mol%) in CH₂Cl₂ (0.3M) irradiated under inert atmosphere with 450 nm blue LED at room temperature overnight. ^b See ^a but heated in a water bath at 40 °C overnight. Isolated yields are shown. ^c NMR yields using 1,3,5-trimethoxybenzene as an internal standard.

Gratifyingly, the lactams were observed in moderate to good yields and the reaction was now compatible with the carbamate and the primary urea derivatives. Presumably due to conformational issues, the reaction needed to be heated at 40 °C under irradiation to achieve C-H amination for the carbamate and the primary urea at the secondary and benzylic position. Control experiments showed the importance of the heat and the irradiation. Due to isolation issues, the secondary (**4.107**) and benzylic (**4.108**) positions products were only reported as a ¹H NMR yields: indeed, co-elution of the corresponding urea side-product and unreacted starting material led to the impossibility of isolation of clean lactams (the crude NMR spectra matched previous synthesis of the products²⁴⁵). Using only irradiation, the 3-methylisoindolin-1-one was obtained in a 68% isolated yield.

In the case of the benzylic substrate, a side-product was observed and isolated: indeed, 38% of the corresponding lactone was found at the end of the reaction (Eq 35). It was suggested that the lactone was obtained via a different mechanism: indeed, due to the lower reduction potential of the amide, the reductive cleavage of the *N*-O bond was easier and an amidyl radical can be obtained as the first intermediate (Scheme 4-37). This *N*-centered radical can undergo 1,5-HAT for the formation of the carbon radical that can after be oxidized. At that time, the cyclization can occur via the nitrogen atom (leading to the desired lactam) or via the oxygen resulting to the formation of an imino-1,3-dioxane heterocycle. This compound is unstable and after hydrolysis, the corresponding lactone is obtained.



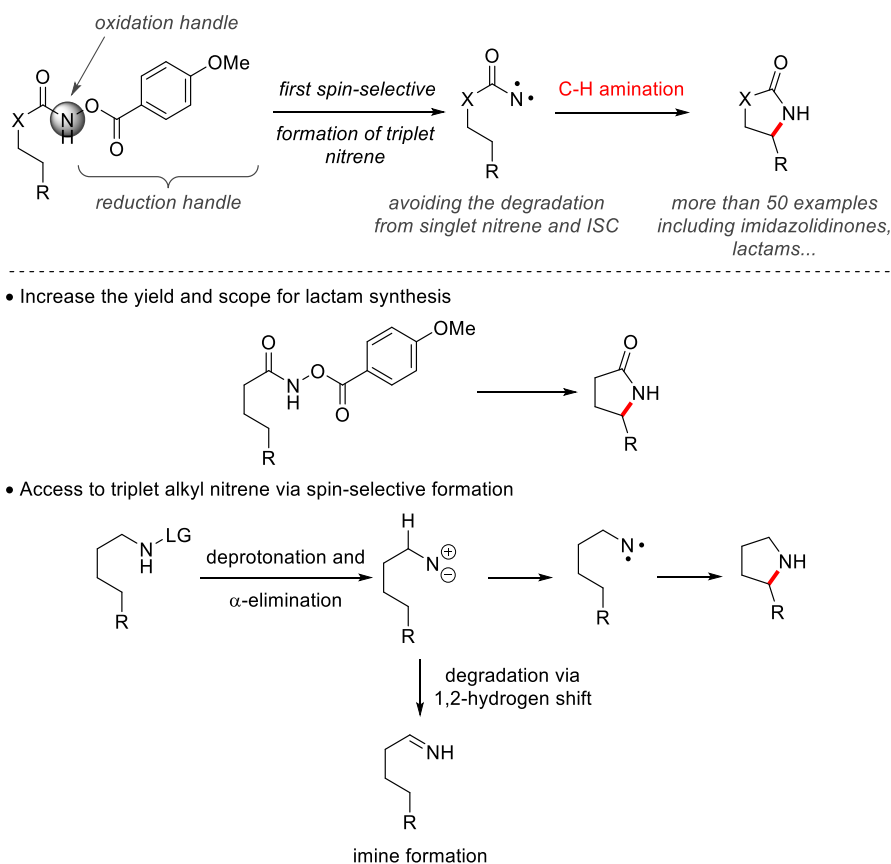
Scheme 4-37: Proposed mechanism for the obtention of the lactone

The preliminary results obtained for the lactam synthesis are promising: indeed, this proposed reactivity focuses on designing specific starting materials and using commercial photocatalyst. It can be used as a complementary method from the previous reports of lactam synthesis via catalyst design. The results also highlight the generalization of the chemistry developed.

4.3 Conclusion and perspective

In this chapter, C-H amination and aziridination reactions using *N*-benzyloxyureas were described. The stability of the conditions and the mild conditions used allow for the synthesis of a variety of heterocycles including imidazolidinones, lactams and oxazolidinones (Scheme 4-38). The proposed mechanism involves the first spin-selective formation of triplet nitrene via a PCET-induced amidyl radical formation followed by a SET reduction in a carefully orchestrated sequence. This novel

mechanism and reactive intermediate using photoredox conditions expand the scope of C-H amination and allow the synthesis of new heterocycles.



Scheme 4-38: C-H amination via triplet nitrene and perspectives

Undoubtedly, more work needs to be done in order to increase the yield of the lactam formation yield and scope. Furthermore, the chemistry developed can also be tested for the synthesis of alkyl nitrenes: indeed, this subclass of nitrene is underdeveloped due to the degradation of the singlet nitrene intermediate.²⁵⁰ During the formation of this reactive intermediate (via deprotonation and α -elimination mechanism), formation of the corresponding imine via 1,2-hydrogen²⁵¹ shift drastically decreased the formation of the triplet nitrene via ISC. Arguably, difficult PCET-induced *N*-centered radical formation due to the strong *N-H* bond of alkyl amine and a less stable aminyl radical intermediate are the challenges of this hypothetical access to spin-selective formation of triplet alkyl nitrene.

²⁵⁰ For selective examples see: (a) Banks, R. E.; Berry, D.; McGlinchey, M. J.; Moore, G. J. *J. Chem. Soc. C* **1970**, 1017. (b) Pancrazi, A.; Khuong-Huu, Q. *Tetrahedron* **1975**, 31, 2041. (c) Singh, P. N. D.; Mandel, S. M.; Robinson, R. M.; Zhu, Z.; Franz, R.; Ault, B. S.; Gudmundsdóttir, A. D. *J. Org. Chem.* **2003**, 68, 7951.

²⁵¹ For selective examples see: (a) Moriarty, R. M.; Reardon, R. C. *Tetrahedron* **1970**, 26, 1379. (b) Abramovitch, R.; Kyba, E. P. *J. Am. Chem. Soc.* **1971**, 93, 1534. (c) Moriarty, R. M.; Serridge, P. *J. Am. Chem. Soc.* **1971**, 93, 1537.

Chapter 5: Conclusion and outlook

In conclusion, new amination reactions have been developed by overcoming known side-reactions and degradation pathway of untapped reactive intermediates. Indeed, the work presented here, demonstrated that control of the *in-situ* formation of highly reactive intermediates, e.g. *O*-isocyanates, *N*-isocyanates and triplet nitrenes, allows for selective reactions for the formation of *C-N* and *N-N* bonds.

First, *N*-oxy-carbamates and *N*-oxyureas were found to be efficient precursors to access *O*-isocyanates under base-catalyzed thermal conditions. Indeed, during this work, the trimerization and the Lossen rearrangement were avoided by controlling the *in-situ* release of the *O*-isocyanate intermediates. A library of blocked *O*-isocyanate precursors was synthesized, allowing the formation of *N*-oxyureas. Moreover, cascade reactions were also developed, allowing for the synthesis of *N*-oxyhydantoin and *N*-oxyimidazolidinone derivatives. Overall, due to the presence of the ONCO motif of *O*-isocyanates being included in a many bioactive molecules, the controlled formation of *O*-isocyanate from stable precursors can be used to quickly assemble molecular complexity.

Then the *N*-oxyureas obtained from the addition reactions onto the *O*-isocyanates were used in two different amination reactions. First, *N*-hydroxyureas were chemoselectively activated using diphenyl carbonate in presence of external and internal nucleophiles. The *in-situ* activation and the controlled formation of *N*-isocyanate intermediates suppressed the known dimerization degradation pathway. The aza-Lossen rearrangement developed, this approach was used to synthesize seven classes of *N-N* bonds containing molecules including semicarbazides, aminimides and protected hydrazines. Certainly, the limitations of the method need to be addressed: substrates derived from primary amines and aniline derivatives can currently not be used as migrating group. Despite this limitation, this *N-N* bond formation strategy can be used to form a variety of hydrazide derivatives.

Finally, *N*-benzoyloxyureas were used to directly access uridyl triplet nitrene intermediates and form cyclic ureas under photoredox conditions. A new mechanism, formation of a *N*-centered radical via PCET followed by SET-induced α -elimination was proposed to account for the experimental and DFT results obtained. In this study, more than fifty examples of heterocycles were synthesized. Arguably, the preliminary results obtained for the lactam formation have to be improved, but could be obtained based on the proposed mechanism. Collectively, these results suggest that nitrene formation under photoredox conditions hold excellent potential to perform selective C-H amination reactions and constitute an alternative to other methods relying on stabilization of nitrene intermediates (via metal-nitrene for example).

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.

^1H 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, DMSO-d_6 at 2.50 ppm or CD_3CN at 1.94 ppm for ^1H NMR and CDCl_3 at 77.0 ppm or DMSO-d_6 at 39.43 for ^{13}C NMR). ^1H 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.

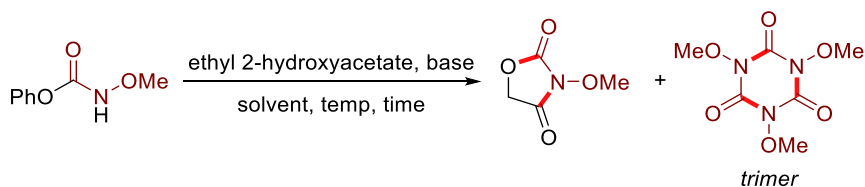
Unless otherwise noted, all commercially available materials were purchased from commercial sources and used without further purification. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and trifluorotoluene (PhCF_3) was passed through an activated alumina column embedded in a solvent purification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

6.2. Supporting information for Chapter 2

6.2.1. Optimization tables

Substitution/cyclization cascade reaction

Table S2.1: Optimization for oxygen^a

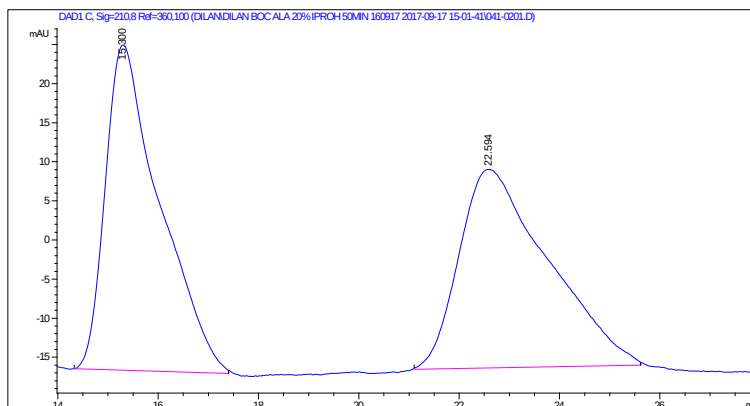
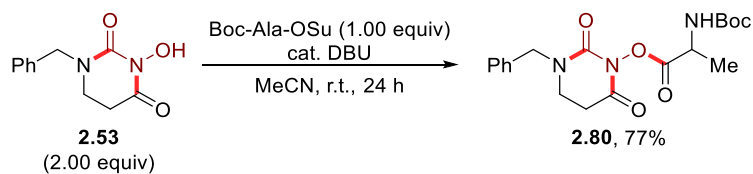


Entry	Ester (equiv)	Base (equiv)	Solvent	Temp (°C)	Time (h)	% Product	%Trimer
1	1.00	<i>i</i> -Pr ₂ NEt (0.05)	MeCN	120	2	0	
2	1.00	<i>i</i> -Pr ₂ NEt (0.05)	MeCN	150	2	37	19
3	1.00	<i>i</i> -Pr ₂ NEt (0.05)	MeCN	130	2	35	21
4	2.00	<i>i</i> -Pr ₂ NEt (0.05)	MeCN	130	2	38	23
5	5.00	<i>i</i> -Pr ₂ NEt (0.05)	MeCN	130	2	7	0
6	2.00	DBU (0.05)	MeCN	120	2	64	14
7	2.00	DBU (0.05)	MeCN	100	2	48	27
8	2.00	DBU (0.05)	MeCN	120	3	69	12
9	2.00	DBU (0.01)	MeCN	120	2	68	14
10	2.00	DBU (0.10)	MeCN	120	2	53	2
11	2.00	DBU (0.05)	THF	120	2	56	<2

Conditions: ^a phenyl methoxycarbamate (1.00 equiv), ethyl 2-hydroxyacetate, base in solvent (0.3M) stir under microwave irradiation. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

6.2.2. Chiral HPLC for compound **2.80**

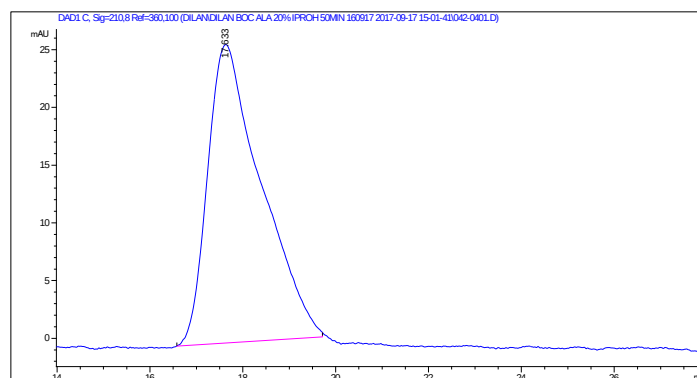
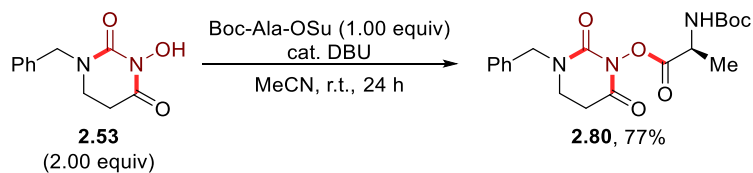
Conditions: Chiral HPLC: ChiralPak OD-H. Solvent: 20% *i*-PrOH/ Hexanes. Flow: 1 mL/min. Pressure: < 55 bar. Time: 50 mins. Program: Prime (50 min), Racemic (50 min), Prime (50 min), Enantiopure (50 min).



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.300	BB	1.0097	3144.21631	41.60325	50.1633
2	22.594	BB	1.4442	3123.74097	25.40977	49.8367

Totals : 6267.95728 67.01301

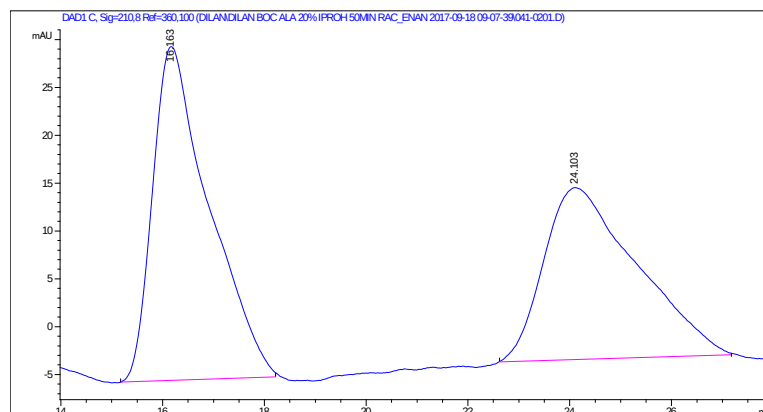


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.633	BB	0.9930	2077.56641	25.86862	100.0000

Totals : 2077.56641 25.86862

Due to the discrepancy of the elution times between racemic and enantiopure samples (see above) we felt it important to run a third of experiment wherein the racemic sample was doped with the enantiopure sample. Herein we clearly see only two peaks, as well as enrichment of the peak which is designated for the enantiopure product.



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.163	BB	1.0145	2692.87524	34.88782	54.1802
2	24.103	BB	1.4884	2277.34546	17.99553	45.8198
Totals :				4970.22070	52.88335	

6.2.3. Characterizations

General procedures

General Procedure 2A: Synthesis of *N*-Acyloxycarbamates

To a roundbottom flask charged with a stir bar was added *N*-hydroxycarbamate (1.00 equiv.) then CH₂Cl₂ (0.3 M) and allowed to stir at 0 °C. *Hydroxycarbamates are insoluble and will not always dissolve completely before the next step of the reaction* Upon observing most of the hydroxycarbamate dissolve, Et₃N was added (1.00 equiv.) and finally the acyl chloride was added dropwise (1.00 equiv.). The reaction was allowed to warm gradually to room temperature. Upon completion, H₂O was added and the reaction mixture was extracted with CH₂Cl₂. The organic layer was recollected and washed with a saturated NaHCO₃ solution, and then the organic phase was recollected and washed with brine. The organic phase was dried over Na₂SO₄ (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to give the corresponding pure acyloxycarbamates.

General Procedure 2B: Substitution of *N*-Hydroxycarbamates

To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-hydroxycarbamate **1a** (1.10 equiv.), then THF (0.3 M), to which was added triethylamine (0.20 equiv.) and the corresponding amine (1.00 equiv.). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via conventional (oil bath) heating. Solvent was removed under reduced pressure and the products were then purified by silica gel chromatography to give the corresponding pure hydroxyureas.

General Procedure 2C: Substitution of *N*-Alkoxy carbamates

To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-alkoxy carbamate (1.05 equiv.), then MeCN (0.3 M), to which was added the corresponding amine (1.00 equiv.). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH and once with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the corresponding pure *N*-ethoxyureas.

General Procedure 2D: Substitution of *N*-Acyloxy carbamates

To a 5 mL microwave vial charged with a stir bar was added the phenyl *N*-acyloxy carbamate (1.00 equiv.), then THF (0.2 M), to which was added the corresponding amine (1.05 equiv.) and then imidazole (0.10 equiv.). The vial was sealed with a microwave cap and heated for 1-3 hours at 100 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH and once with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the corresponding pure acyloxyureas. In some cases, a higher degree of purity was needed after the extraction and the products could easily be recrystallized or purified by silica gel chromatography.

General Procedure 2E: Cascade Addition/Cyclization of *N*-hydroxycarbamates

To a 5 mL microwave vial charged with a stir bar was added the corresponding α - or β -aminoester (1.10 equiv) then THF (0.3 M), to which was added *i*-Pr₂NEt (1.20 equiv), and finally the *N*-hydroxycarbamate (1.00 equiv). The vial was sealed with a microwave cap and heated for 16 h at the temperature specified (70-100 °C) via conventional (oil bath) heating. The crude products were then purified by silica gel chromatography to give the corresponding pure hydroxy-hydantoins and dihydroureacils.

General Procedure 2F: Cascade Addition/Cyclization of *N*-alkoxy carbamates with amino esters

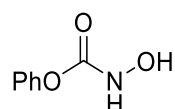
To a 5 mL microwave vial charged with a stir bar was added the corresponding α - or β -aminoester (1.00 equiv) then acetonitrile (0.3 M), to which was added *i*-Pr₂NEt (0.05 equiv, 1.10 equiv for aminoester hydrochlorides), and finally the *N*-alkoxy carbamate (1.00 equiv). The vial was sealed with

a microwave cap and heated for 2 h or 4 h at the temperature specified (90-120 °C) via microwave irradiation. The crude products were then purified by silica gel chromatography to give the corresponding pure alkoxy-hydantoins and dihydrouracils.

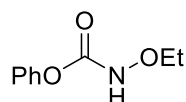
General Procedure 2G: Cascade Addition/Cyclization of *N*-oxycarbamates with alcohol and sulfur esters

To a 5 mL microwave vial charged with a stir bar was added the corresponding ester (1.00 equiv) then acetonitrile (0.3 M), to which was added DBU (0.05 equiv), and finally the *N*-alkoxycarbamate (1.00 equiv). The vial was sealed with a microwave cap and heated for 2 h at the temperature specified (120 °C) via microwave irradiation. The crude products were then purified by silica gel chromatography to give the corresponding pure alkoxy-oxazolidine/ thiazolidines.

Synthesis and characterizations

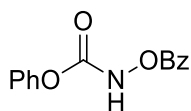


Phenyl *N*-hydroxycarbamate: The title compound was synthesized according to a literature procedure.²⁵² ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.43-10.15 (br s, 1 H), 9.11-9.03 (br s, 1H), 7.45-7.33 (m, 2H), 7.26-7.17 (m, 1H), 7.14-7.06 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 155.5 (C), 150.7 (C), 129.4 (CH), 125.1 (CH), 121.6 (CH).

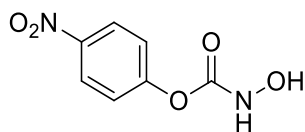


Phenyl *N*-ethoxycarbamate: The title compound was synthesized according to a literature procedure¹ using phenyl chloroformate (12.6 mL, 0.100 mol), *O*-ethoxylamine hydrochloride (11.7 g, 0.120 mol), and sodium bicarbonate (18.5 g, 0.220 mol) in H₂O/CH₂Cl₂ (1:1) (0.4 M). The title compound was obtained as a crystalline white solid (14.9 g, 82%). TLC *R*_f = 0.73 in 2% MeOH/CH₂Cl₂. M. p. 60.5-61.6 °C. ¹H (300 MHz, CDCl₃) δ 7.64-7.57 (br s, 1H), 7.43-7.34 (m, 2H), 7.27-7.20 (m, 1H), 7.19-7.13 (m, 2H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H). ¹³C (75 MHz, CDCl₃) δ 155.3 (C), 150.4 (C), 129.4 (C), 125.8 (CH), 121.3 (CH), 72.7 (CH₂), 13.4 (CH₃). IR (FTIR): 3204, 2983, 1719, 1588, 1475, 1376, 1251 cm⁻¹. HRMS (ESI): Exact mass calcd for C₉H₁₁NO₃Na [M+Na]⁺: 204.0637. Found: 204.0647.

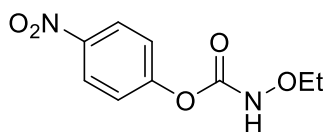
²⁵² Stewart, A. O.; Brooks, D. W. *J. Org. Chem.* **1992**, 57, 5020-5023.



Phenyl *N*-benzoyloxycarbamate: The title compound was synthesized according to general procedure **2A** using phenyl *N*-hydroxycarbamate **2.1** (38.3 g, 0.250 mol), Et₃N (34.9 g, 0.250 mol) and benzoyl chloride (29.0 mL, 0.250 mol) in CH₂Cl₂ (0.83 L, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, H₂O was added and the reaction mixture was extracted with CH₂Cl₂. The organic layer was recollected and washed with NaHCO₃, and then the organic phase was recollected again and washed with brine. The organic phase was dried over Na₂SO₄ (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to yield an amorphous white solid (61.2 g, 95%). TLC R_f = 0.35 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.66 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 2H), 7.66-7.61 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.39-7.34 (m, 2H), 7.25-7.16 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 165.7 (C), 154.7 (C), 150.1 (C), 134.3 (CH), 129.9 (CH), 129.4 (CH), 128.7 (CH), 126.4 (C), 126.1 (CH), 121.2 (CH). IR (FTIR): 3271, 1770, 1739, 1450, 1229, 1030 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₄H₁₁NO₄Na [M+Na]⁺: 280.0587. Found 280.0586.



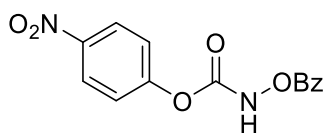
4-Nitrophenyl hydroxycarbamate: The title compound was synthesized according to a literature procedure.²⁵³ ¹H-NMR (300 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 9.31 (s, 1H), 8.30-8.25 (m, 2H), 7.44-7.38 (m, 2H).



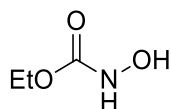
1-(4-Nitrophenyl)-*N*-(*O*-ethylhydroxy) carbamate: The title compound was synthesized according to a modified literature procedure¹ using *O*-ethyl hydroxylamine hydrochloride (0.610 g, 6.20 mmol), sodium bicarbonate (0.949 g, 11.3 mmol) and 4-nitrophenyl chloroformate (0.629 g, 3.10 mmol) in CH₂Cl₂ (10 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with CH₂Cl₂ and transferred to a separatory funnel, then washed with brine, dried over MgSO₄ and filtered. The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether. The title compound was obtained as a crystalline white solid (0.356 g, 51%). TLC R_f = 0.73 in 2% MeOH/CH₂Cl₂. M.p. 128.9-129.9 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.31-8.25 (m, 2H), 7.75-7.67

²⁵³ Higgin, J. J.; Yakovlev, G. I.; Mitkevich, V. A.; Makarov, A. A.; Raines, R. T. *Bioorg. Med. Chem. Lett.*, **2003**, 13, 409.

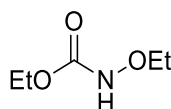
(br s, 1H), 7.40-7.34 (m, 4H), 4.07 (q, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) 155.1 (C), 153.9 (C), 145.1 (C), 125.2 (CH), 121.9 (CH), 72.9 (CH_2), 13.3 (CH_3). IR (FTIR): 3164, 2930, 1755, 1737, 1615, 1519, 1487, 1344 cm^{-1} . HRMS (EI): Exact mass could not be obtained for the molecular ion. Exact mass calcd for fragment $[\text{C}_6\text{H}_5\text{NO}_3]^+$ (*p*-nitrophenol): 139.0264. Found: 139.0276. Exact mass calcd for fragment $[\text{C}_3\text{H}_5\text{NO}_2]^+$ (ethoxy-isocyanate): 87.0315. Found: 87.0321.



1-(4-Nitrophenol)-N-(O-benzoylhydroxy) carbamate: The title compound was synthesized according to general procedure **2A** using 1-(4-nitrophenol)-*N*-hydroxycarbamate **2.4** (0.198 g, 1.00 mmol), triethylamine (0.14 mL, 1.0 mmol) and benzoyl chloride (0.12 mL, 1.0 mmol) in CH_2Cl_2 (3.3 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and transferred to a separatory funnel, then washed with brine, dried over MgSO_4 and filtered. The reaction mixture was concentrated under reduced pressure and recrystallized in diethyl ether. The title compound was obtained as a crystalline white solid (0.109 g, 36%). TLC $R_f = 0.77$ in 2% MeOH/ CH_2Cl_2 . M. p. 152.3-153.0 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 8.69-8.63 (br s, 1H), 8.33-8.27 (m, 2H), 8.17-8.12 (m, 2H), 7.72-7.66 (m, 1H), 7.57-7.50 (m, 2H), 7.45-7.39 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 165.5 (C), 154.7 (C), 153.2 (C), 145.5 (C), 134.7 (CH), 130.1 (CH), 128.9 (CH), 126.0 (C), 125.3 (CH), 122.0 (CH). IR (FTIR): 3167, 1773, 1755, 1520, 1487, 1344 cm^{-1} . HRMS (EI/ESI): Accurate mass could not be obtained due to the instability of this compound. Exact mass calcd for $\text{C}_{24}\text{H}_{15}\text{N}_3\text{O}_9\text{Na}$ $[\text{M}+\text{Na}]^+$ (O-benzoyl isocyanurate trimer): 512.0706. Found: 512.0724.

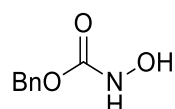


Ethyl hydroxycarbamate: The title compound was synthesized according to a literature procedure²⁵⁴ using ethyl chloroformate (2.9 mL, 0.030 mol), hydroxylamine hydrochloride (10.4 g, 0.150 mol), and sodium hydroxide (7.20 g, 0.180 mol). The title compound was obtained as a clear and colourless liquid (2.40 g, 76 %) and was used without further purification. ^1H NMR (300 MHz, CDCl_3) δ 7.63 (br s, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 1.26 (t, $J = 7.1$ Hz, 3H).

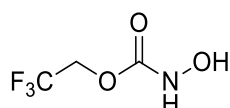


²⁵⁴ Ng, K.-H.; Chan, A. S. C.; Yu, W. -Y. *J. Am. Chem. Soc.* **2010**, 132, 12862.

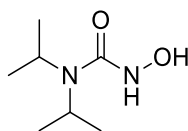
Ethyl ethoxycarbamate: The title compound was synthesized according to a literature procedure¹ using ethyl chloroformate (1.44 mL, 15.0 mmol), *O*-ethoxylamine hydrochloride (1.83 g, 18.9 mmol), and sodium bicarbonate (2.77 g, 33.0 mmol) in CH₂Cl₂/ H₂O (1:1) (0.5 M). The crude reaction mixture was isolated using flash chromatography (25% EtOAc/Hexane). The title compound was obtained as a clear and colourless liquid (1.83 g, 91%). ¹H NMR (300 MHz, CDCl₃) δ 4.21 (q, *J* = 7.2 Hz, 2H), 3.93 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H).



Benzyl hydroxycarbamate: The title compound was synthesized according to a literature procedure¹ using benzyl chloroformate (1.43 mL, 10.0 mmol), hydroxylamine hydrochloride (0.777 g, 11.3 mmol), and sodium bicarbonate (1.85 g, 22.0 mmol) in 1.4 : 1 CH₂Cl₂/H₂O (0.5 M). The crude reaction mixture was isolated using flash chromatography (2% MeOH/CH₂Cl₂, then 5% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.998 g, 60%). ¹H NMR (300 MHz, CDCl₃) δ 7.36 (s, 5H), 7.28 (s, 1H), 6.81 (br s), 5.18 (s, 2H).



2,2,2-Trifluoroethyl hydroxycarbamate: The title compound was synthesized according to a literature procedure.²⁵⁵ ¹H NMR (400 MHz, CDCl₃) δ 7.44 (br s, 1H), 6.18 (br s, 1H), 4.56 (q, *J* = 8.3 Hz, 2H).



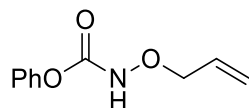
3-Hydroxy-1,1-diisopropylurea: The title compound was synthesized according to a literature procedure²⁵⁶ of *N,N*-diethyl hydroxyurea using diisopropylcarbamic chloride (1.64 g, 10 mmol), hydroxylamine hydrochloride (0.879 g, 11.5 mmol), and potassium carbonate (1.45 g, 10.5 mmol) in EtOAc/H₂O (60:1) (1.45 M). The crude reaction mixture was isolated using flash chromatography (30% EtOAc/Hexane then 40% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.544 g, 34%). TLC *R*_f = 0.34 in 40% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 6.77 (br s, 1H), 6.48 (br s, 1H), 3.77 (sept, *J* = 6.8 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃)

²⁵⁵ Lu, D.-F.; Zhu, C.-L.; Jia, Z.-X.; Xu, H. *J. Am. Chem. Soc.* **2014**, 136 (38), 13186.

²⁵⁶ Huang, J.; Zou, Z.; Kim-Shapiro, D. B.; Ballas, S. K.; King, S. B. *J. Med. Chem.* **2003**, 46 (17), 3748.

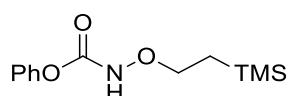
δ 160.6 (C), 45.9 (CH), 20.8 (CH₃). IR (FTIR): 3292, 2964, 2927, 1632, 1493, 1446, 1376, 1367, 1047 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₆N₂O₂ [M]⁺: 160.1212. Found: 160.1208.

calcd for C₇H₁₆N₂O₂ [M]⁺: 160.1212. Found: 160.1208.

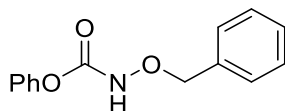


Phenyl allyloxycarbamate: The title compound was synthesized according to a literature procedure.²⁵⁷

¹H NMR (300 MHz, CDCl₃) δ 7.60 (br s, 1H), 7.42-7.35 (m, 2H), 7.26-7.20 (m, 1H), 7.18-7.13 (m, 2H), 6.02 (ddt, J = 17.3, 10.3, 6.4 Hz, 1H), 5.44-5.34 (m, 2H), 4.46 (dt, J = 6.4, 1.2 Hz, 2H).



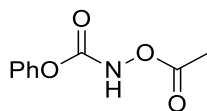
Phenyl 2-(trimethylsilyl)ethoxycarbamate: The title compound was synthesized according to a literature procedure¹ using *O*-(2-(trimethylsilyl)ethyl)hydroxylamine (5.00 g, 37.5 mmol), and phenyl chloroformate (3.93 mL, 31.3 mmol) in 1 : 1 CH₂Cl₂/H₂O (78 mL, 0.40 M). The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction mixture was diluted with CH₂Cl₂ (78 mL) and extracted from the H₂O. The organic phase was recollected and washed three times using saturated NaHCO₃ (25 mL), followed by a single brine wash (25 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (50 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a clear oil (7.51 g, 95%). TLC R_f = 0.75 in 20% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (br s, 1H), 7.40-7.35 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.15 (m, 2H), 4.06-4.01 (m, 2H), 1.09-1.03 (m, 2H), 0.05 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 155.6 (C), 150.6 (C), 129.5 (CH), 125.9 (CH), 121.5 (CH), 75.0 (CH₂), 16.8 (CH₂), -1.3 (CH₃). IR (FTIR): 3273, 2952, 1733, 1593, 1474, 1370, 1248, 1201 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₂H₁₉NO₃Si [M+Na]⁺: 276.1032. Found: 276.1034.



Phenyl benzyloxycarbamate: The title compound was synthesized according to a literature procedure.²⁵⁸ ¹H NMR (300 MHz, CDCl₃) δ 7.68 (br s, 1H), 7.48-7.37 (m, 7H), 7.28-7.23 (m, 1H), 7.18-7.15 (m, 2H), 4.99 (s, 2H).

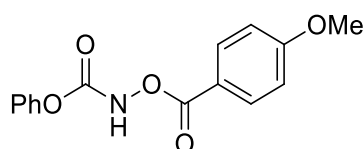
²⁵⁷ Wang, Q.; An, J.; Alper, H.; Xiao, W.-J.; Beauchemin, A. M. *Chem. Comm.* **2017**, 53, 13055.

²⁵⁸ Hirai, N.; Kagayama, T.; Tatsukawa, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2004**, 45, 8277.

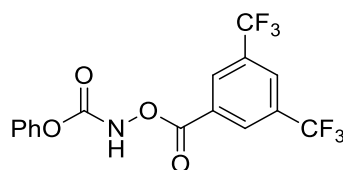


Phenyl acyloxycarbamate: The title compound was synthesized according to a literature procedure.²⁵⁹

¹H NMR (300 MHz, CDCl₃) δ 8.44-8.39 (br s, 1H), 7.41-7.33 (m, 2H), 7.27-7.21 (m, 1H), 7.18-7.10 (m, 2H), 2.23 (s, 3H).



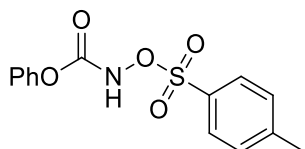
Phenyl (4-methoxybenzoyl)oxycarbamate: The title compound was synthesized according to general procedure **2A** using phenyl *N*-hydroxycarbamate **2.1** (17.8 g, 0.117 mol), triethylamine (16.4 mL, 0.117 mol) and 4-methoxybenzoyl chloride (20.0 g, 0.117 mol) in CH₂Cl₂ (390 mL, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion the organic phase was washed three times using saturated NaHCO₃ (100 mL), followed by a single brine wash (100 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (100 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a white solid (30.92 g, 92%). TLC R_f = 0.35 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.82 (br s, 1H), 8.10 (d, *J* = 8.9 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.28-7.20 (m, 3H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 165.5 (C), 164.6 (C), 154.9 (C), 150.3 (C), 132.3 (CH), 129.6 (CH), 126.2 (CH), 121.3 (CH), 118.6 (C), 114.2 (CH), 55.6 (CH₃). IR (FTIR): 3207, 3020, 2938, 1725, 1605, 1471, 1234 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₅H₁₃NO₅Na [M+Na]⁺: 310.0692. Found: 310.0698.



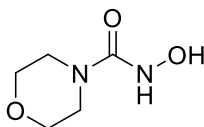
Phenyl (3,5-trifluoromethylbenzoyl)oxycarbamate: The title compound was synthesized according to general procedure **2A** using phenyl *N*-hydroxycarbamate **2.1** (1.02 g, 6.70 mmol), triethylamine (0.93 mL, 6.7 mmol) and 3,5-trifluoromethylbenzoyl chloride (1.21 mL, 6.70 mmol) in CH₂Cl₂ (22 mL, 0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction mixture was diluted with H₂O (5.0 mL) and extracted three times using CH₂Cl₂ (5.0 mL), followed by a single brine wash (5.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15

²⁵⁹ Dias, L. C.; Farina, L. S.; Ferreira, M. A. B. *J. Braz. Chem. Soc.* **2013**, 24, 184.

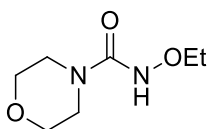
min). The solids were filtered and rinsed with CH₂Cl₂ (10.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a white solid (2.63 g, 99%). TLC R_f = 0.75 in 20% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.57 (s, 2H), 8.17 (s, 1H), 7.43-7.38 (m, 2H), 7.29-7.18 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 163.4 (C), 154.7 (C), 150.1 (C), 132.8 (q, *J* = 34.5 Hz) (C), 130.2 (m) (CH), 129.7 (CH), 128.9 (C), 127.8 (m) (CH), 126.5 (CH), 122.7 (q, *J* = 273.1 Hz) (CH), 121.2 (CH). IR (FTIR): 3214, 3092, 1780, 1734, 1614, 1591, 1475, 1378, 1279 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₆H₉F₆NO₄ [M]⁺: 393.0436. Found: 393.0450.



Phenyl tosyloxycarbamate: The title compound was synthesized according to a literature procedure.²⁶⁰ ¹H-NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 8.00-7.91 (m, 2H), 7.46-7.11 (m, 5H), 6.95-6.84 (m, 2H), 2.48 (s, 3H).



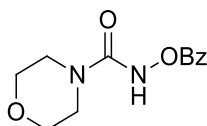
1-Morpholin-3-hydroxy-urea: The title compound was synthesized using a modified general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.754 g, 4.93 mmol), DIPEA (0.013 mL, 0.20 mmol) and morpholine (0.43 mL, 5.0 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath. The reaction mixture was concentrated under reduced pressure and recrystallized in Et₂O/Hexane. The title compound was obtained as a crystalline white solid (0.511 g, 72%). TLC R_f = 0.73 in 2% MeOH/CH₂Cl₂. M. p. 172.0-172.7 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.09-9.06 (br s, 1H), 8.07-8.04 (br s, 1H), 3.54-3.49 (m, 4H), 3.24-3.19 (m, 4H). ¹³C (75 MHz, DMSO-*d*₆) δ 159.7(C), 65.8 (CH₂), 43.6 (CH₂). IR (FTIR): 3303, 3163, 1773, 1519, 1487 cm⁻¹. HRMS (EI): Exact mass calcd for C₅H₁₀N₂O₅ [M]⁺: 146.0691. Found: 146.0688.



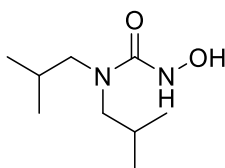
1-Morpholin-3-ethoxy-urea: The title compound was synthesized according to general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.901 g, 1.05 mmol) and morpholine (0.087 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C

²⁶⁰ Steinberg, G. M.; Bolger, J. *J. Org. Chem.* **1956**, 21, 660.

via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over MgSO₄, filtered. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/CH₂Cl₂ then 10% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous yellowish solid (0.174 g, 94%). TLC R_f = 0.35 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 7.15-6.82 (br s, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.73-3.64 (m, 4H), 3.45-3.37 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H). ¹³C (75 MHz, CDCl₃) δ 159.2 (C), 71.8 (CH₂), 66.4 (CH₂), 44.0 (CH₂), 13.5 (CH₃). IR (FTIR): 3165, 1773, 1518, 1487, 1451, 1253 cm⁻¹. HRMS (ESI): Exact mass calcd for C₇H₁₄N₂O₃Na [M+Na]⁺: 197.0902. Found: 197.0902.

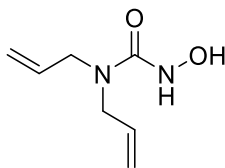


N-(Benzoyloxy)morpholine-4-carboxamide: The title compound was synthesized according to general procedure **2D** using phenyl *N*-benzoyloxycarbamate **2.3** (0.257 g, 1.00 mmol), and diisobutylamine (0.18 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, a small amount of Hexane was added to the crude reaction resulting in a precipitate that was filtered and subsequently washed with a small amount of ether. The title compound was obtained as an off-white amorphous solid (0.156 g, 57 %). TLC R_f = 0.18 in 50% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.67-8.29 (br s, 1H), 8.16-8.08 (m, 2H), 7.69-7.60 (m, 1H), 7.55-7.46 (m, 2H), 3.80-3.69 (m, 4H), 3.59-3.50 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 166.7 (C), 157.2 (C), 134.2 (CH), 129.9 (CH), 128.7 (CH), 126.9 (C), 66.3 (CH₂), 44.2 (CH₂). IR (FTIR): 3162, 3075, 2980, 2960, 2916, 2841, 1752, 1663, 1507, 1424, 1239 cm⁻¹. HRMS (ESI): Exact mass calcd for C₇H₁₄N₂O₃Na [M+Na]⁺: 273.0851. Found: 273.0866.

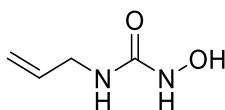


1,1-Diisobutyl-3-hydroxy-urea: The title compound was synthesized according to general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.842 g, 5.50 mmol), triethylamine (0.14 mL, 1.0 mmol) and diisobutylamine (0.87 mL, 5.0 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.785 g, 84%). TLC R_f = 0.54 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.65-6.61 (br s, 1H), 6.60-6.52 (br s, 1H), 3.07 (d, *J* = 7.6 Hz, 4H), 1.99 (sept, *J* = 7.5 Hz, 2H), 0.92 (d, *J* = 6.7 Hz, 12H). ¹³C (75 MHz, CDCl₃) δ 162.0 (C),

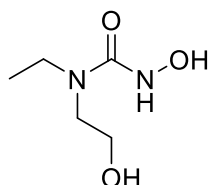
54.4 (CH₂), 27.1 (CH), 20.1 (CH₃). IR (FTIR): 3365, 3295, 1699, 1496, 1276 cm⁻¹. HRMS (EI): Exact mass calcd for C₉H₂₀N₂O₂: 188.1525. Found: 188.1515.



1,1-Diallyl-3-hydroxy-urea: The title compound was synthesized according to general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.168 g, 1.00 mmol), triethylamine (0.03 mL, 0.2 mmol) and diallylamine (0.097 mg, 1.0 mmol) in THF (3.3 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.098 g, 63%). TLC R_f = 0.53 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.86-6.80 (br s, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 5.86-5.72 (m, 2H), 5.27-5.18 (m, 4H), 3.89 (dt, *J* = 5.5, 1.5 Hz, 4H). ¹³C (75 MHz, CDCl₃) δ 161.5 (C), 132.8 (CH), 117.5 (CH₂), 49.0 (CH₂). IR (FTIR): 3246, 2915, 1640, 1471, 1414, 1281 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₄N₂O₂ [M]⁺: 156.0899. Found: 156.0914.

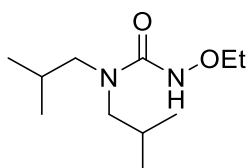


1-Allyl-3-hydroxy-urea: The title compound was synthesized according to a modified general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.306 g, 2.00 mmol), triethylamine (0.006 g, 0.2 mmol) and allylamine (0.75 mL, 10 mmol) in THF (6.7 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/CH₂Cl₂ then 10% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.156 g, 67%). TLC R_f = 0.10 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.57 (d, *J* = 1.2 Hz, 1H), 8.33-8.31 (br s, 1H), 6.82-6.74 (br s, 1H), 5.88-5.74 (m, 1H), 5.13-4.98 (m, 2H), 3.70-3.63 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ 161.3 (C), 136.5 (CH), 114.4 (CH₂), 41.0 (CH₂). IR (FTIR): 3310, 3161, 2853, 1592, 1519, 1488, 1345 cm⁻¹. HRMS (EI): Exact mass calcd for C₄H₈N₂O₂ [M]⁺: 116.0586. Found 116.0607.

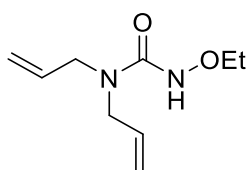


1-Ethyl-3-hydroxy-1-(2-hydroxyethyl)urea: The title compound was synthesized according to general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.842 g, 5.50 mmol), triethylamine (0.14

mL, 1.0 mmol) and 2-(ethylamino)ethanol (0.446 g, 5.00 mmol) in THF (17 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂ then 5% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous yellowish solid (0.671 g, 91%). TLC R_f = 0.10 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (d, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 4.87 (t, *J* = 5.1 Hz, 1H), 3.47 (q, *J* = 5.7 Hz, 2H), 3.24-3.16 (m, 4H), 1.00 (t, *J* = 7.1 Hz, 3H). ¹³C (75 MHz, DMSO-*d*₆) δ 160.1 (C), 59.9 (CH₂), 48.0 (CH₂), 41.4 (CH₂), 13.3 (CH₃). IR (FTIR): 3164, 2931, 1773, 1615, 1519, 1344 cm⁻¹. HRMS (EI): Exact mass calcd for C₅H₁₂N₂O₃ [M]⁺: 148.0848. Found: 148.0845.

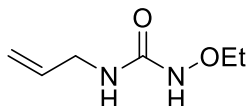


1,1-Diisobutyl-3-ethoxy-urea: The title compound was synthesized according to general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.901 g, 1.05 mmol) and diisobutylamine (0.129 g, 1.00 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The title compound was obtained as an amorphous white solid (0.211 g, 98%). TLC R_f = 0.65 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 7.08-7.05 (br s, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.03 (d, *J* = 7.6 Hz, 4H), 2.04-1.92 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 12H). ¹³C (75 MHz, CDCl₃) δ 159.7 (C), 71.8 (CH₂), 55.1 (CH₂), 27.3 (CH), 20.2 (CH), 13.6 (CH). IR (FTIR): 3197, 2957, 1636, 1520, 1410, 1383 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₁H₂₄N₂O₂Na [M+Na]⁺: 239.1736. Found: 239.1729.

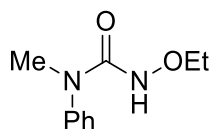


1,1-Diallyl-3-ethoxy-urea: The title compound was synthesized according to general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.901 g, 1.05 mmol) and diallylamine (0.097 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The title compound was obtained as a yellow oil (0.158 g, 86%). TLC R_f = 0.26 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 7.14-7.11 (br s, 1H), 5.85-5.74 (m, 2H), 5.52-

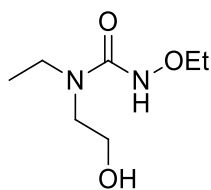
5.18 (m, 4H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.86 (dt, $J = 5.6, 1.4$ Hz, 4H), 1.24 (t, $J = 7.0$ Hz, 3H). ^{13}C (75 MHz, CDCl_3) δ 159.3 (C), 133.4 (CH), 117.3 (CH_2), 71.8 (CH_2), 49.1 (CH_2), 13.5 (CH_3). IR (FTIR): 3228, 2979, 1643, 1471, 1283 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 184.1212. Found 184.1240.



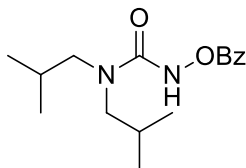
1-Allyl-3-ethoxy-urea: The title compound was synthesized according to a modified general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.901 g, 1.05 mmol) and allylamine (0.37 mL, 5.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The title compound was obtained as a white solid (0.113 g, 79%). TLC R_f = 0.47 in 5% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3) δ 7.07-6.96 (br s, 1H), 5.98-5.74 (m, 2H), 5.33-5.12 (m, 2H), 3.98-3.85 (m, 4H), 1.20 (t, $J = 7.1$ Hz, 3H). ^{13}C (75 MHz, CDCl_3) δ 160.0 (C), 134.5 (CH), 115.9 (CH_2), 71.9 (CH_2), 41.9 (CH_2), 13.7 (CH_3). IR (FTIR): 3164, 2971, 1669, 1650, 1529, 1441, 1364 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 144.0899. Found: 144.0900.



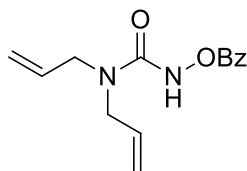
3-Ethoxy-1-methyl-1-phenylurea: The title compound was synthesized according to a modified general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.901 g, 1.05 mmol), *N*-methylaniline (0.107 g, 1.00 mmol) and imidazole (0.006 g, 0.2 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/ CH_2Cl_2 then 10% MeOH/ CH_2Cl_2). The title compound was obtained as an amorphous yellowish solid (0.055 g, 24%). TLC R_f = 0.84 in CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.37 (m, 2H), 7.33-7.27 (m, 1H), 7.24-7.19 (m, 2H), 7.00-6.97 (br s, 1H), 3.83 (q, $J = 6.9$ Hz, 2H), 3.24 (s, 3H), 1.14 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.2 (C), 141.9 (C), 129.9 (CH), 127.7 (CH), 126.9 (CH), 71.8 (CH_2), 37.4 (CH_3), 13.3 (CH_3). IR (FTIR): 3409, 2980, 1747, 1669, 1603, 1507, 1202 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 217.0953. Found: 217.0943.



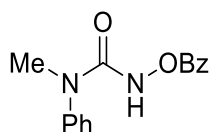
3-Ethoxy-1-ethyl-1-(2-hydroxyethyl)urea: The title compound was synthesized according to general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.901 g, 1.05 mmol) and 2-(ethylamino)ethanol (0.089 g, 1.0 mmol) in MeCN (5.0 mL, 0.20 M). The vial was sealed with a microwave cap and heated for 30 min at 120 °C via microwave irradiation. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel, then washed twice with 1 M NaOH, with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The title compound was obtained as a yellowish solid (0.155 g, 88%). TLC *R*_f = 0.26 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 8.36-8.28 (br s, 1H), 3.87 (q, *J* = 7.0 Hz, 2H), 3.80-3.74 (m, 2H), 3.37-3.26 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ¹³C (75 MHz, CDCl₃) δ 161.4 (C), 71.4 (CH₂), 61.4 (CH₂), 48.5 (CH₂), 41.8 (CH₂), 13.5 (CH₃), 13.0 (CH₃). IR (FTIR): 3383, 3275, 2976, 1625, 1518, 1487, 1382 cm⁻¹. HRMS (ESI): Exact mass calcd for C₇H₁₆N₂O₃Na [M+Na]⁺: 199.1059. Found: 199.1064.



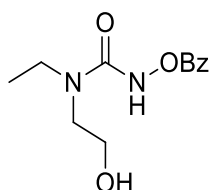
3-(Benzoyloxy)-1,1-diisobutylurea: The title compound was synthesized according to general procedure **2D** using phenyl *N*-benzoyloxycarbamate **2.3** (0.257 g, 1.00 mmol), and diisobutylamine (0.18 mL, 1.05 mmol) and imidazole (0.007 g, 0.10 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.260 g, 89%). TLC *R*_f = 0.35 in 40% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 8.56 (br s, 1H), 8.11 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.62-7.58 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 3.14 (d, *J* = 7.6 Hz, 4H), 2.16-1.97 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃) δ 167.3 (C), 158.1 (C), 134.1 (C), 130.0 (CH), 128.7 (CH), 127.3 (CH), 55.1 (CH₂), 27.3 (CH), 20.3 (CH₃). IR (FTIR): 3125, 2958, 2872, 1760, 1655, 1482, 1417, 1236 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₂₄N₂O₃Na [M+Na]⁺: 315.1685. Found: 315.1700.



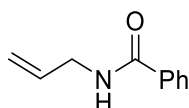
1,1-Diallyl-3-(benzoyloxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl *N*-benzoyloxycarbamate **2.3** (0.257 g, 1.00 mmol), and diallylamine (0.13 mL, 1.05 mmol) and imidazole (0.007 g, 0.10 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 3 h. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.232 g, 89%). TLC *R_f* = 0.35 in 30% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 8.54 (br s, 1H), 8.11 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.61 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.46 (tt, *J* = 7.6, 1.4 Hz, 2H), 5.86 (ddt, *J* = 17.2, 10.4, 5.3 Hz, 2H), 5.35-5.27 (m, 4H), 3.97 (dt, *J* = 5.4, 1.4 Hz, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 166.9 (C), 157.8 (C), 134.1 (C), 132.7 (CH), 130.0 (CH), 128.6 (CH), 127.2 (CH), 117.8 (CH₂), 49.3 (CH₂). IR (FTIR): 3226, 3078, 2959, 1759, 1662, 1600, 1484, 1235 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₄H₁₆N₂O₃H [M+H]⁺: 261.1239. Found: 261.1214.



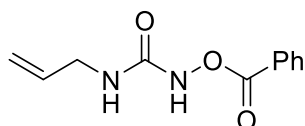
3-(Benzoyloxy)-1-methyl-1-phenylurea: The title compound was synthesized according to general procedure **2D** using phenyl *N*-benzoyloxycarbamate **2.3** (0.257 g, 1.00 mmol), and *N*-methylaniline (0.13 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 6 h at 120 °C. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (10% EtOAc/Hexane then 40% EtOAc/Hexane). The title compound was obtained as an amorphous white solid (0.232 g, 91%). TLC *R_f* = 0.40 in 50% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 8.11 (br s, 1H), 8.07-8.04 (m, 2H), 7.62-7.57 (m, 1H), 7.51-7.35 (m, 7H), 3.33 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.8 (C), 157.1 (C), 141.4 (C), 134.0 (C), 130.4 (CH), 130.0 (CH), 128.7 (CH), 128.6 (CH), 127.2 (CH), 127.1 (CH), 38.0 (CH₃). IR (FTIR): 3125, 2958, 2873, 1760, 1655, 1483, 1452, 1237 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₅H₁₄N₂O₃Na [M+Na]⁺: 293.0902. Found: 293.0900.



3-(Benzoyloxy)-1-ethyl-1-(2-hydroxyethyl)urea: The title compound was synthesized according to general procedure **2D** using phenyl *N*-benzoyloxycarbamate **2.3** (0.257 g, 1.00 mmol), and *N*-ethylethanolamine (0.10 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 6 h at 120 °C. The reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.159 g, 63%). TLC R_f = 0.28 in 50% EtOAc/Hexane. ¹H NMR (400 MHz, CDCl₃) δ 9.66-9.65 (br s, 1H), 8.12-8.08 (m, 2H), 7.62-7.56 (m, 1H), 7.48-7.43 (m, 2H), 3.84 (t, *J* = 4.8 Hz, 2H), 3.47 (t, *J* = 4.8 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 3.20 (br s, 1H), 1.18 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 167.0 (C), 159.1 (C), 134.0 (C), 130.0 (CH), 128.7 (CH), 127.6 (CH), 62.2 (CH₂) 48.7 (CH₂) 42.7 (CH₂) 13.2 (CH₃). IR (FTIR): 3355, 3156, 2987, 2916, 1726, 1655, 1464, 1448, 1268, 1236 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₂H₁₆N₂O₄H [M+H]⁺: 253.1188. Found: 253.1161.

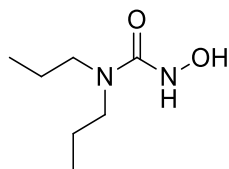


***N*-Allylbenzamide:** The title compound was synthesized according to a modified general procedure **2D** using phenyl *N*-benzoylcarbamate **2.3** (0.257 g, 1.00 mmol), imidazole (0.007 g, 0.1 mmol) and allylamine (0.37 mL, 5.0 mmol) in THF (3.3 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 1 h at 100 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20% EtOAc/Hexane). The title compound was obtained as a colourless oil (0.129 g, 58%). ¹H NMR (300 MHz, CDCl₃) δ 7.82-7.77 (m, 2H), 7.55-7.41 (m, 3H), 6.28-6.13 (br s, 1H), 6.03-5.88 (m, 1H), 5.32-5.17 (m, 2H), 4.11 (tt, *J* = 5.8, 1.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 167.4 (C), 134.4 (C), 134.1 (CH), 131.4 (CH), 128.5 (CH), 126.9 (CH), 116.5 (CH₂), 42.4 (CH₂). The ¹H NMR and ¹³C NMR is in agreement with previous reports.⁶

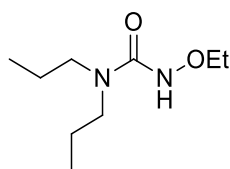


1-Allyl-3-benzoyloxy-urea **3i:** The title compound was synthesized according to a modified general procedure **2A** using 1-allyl-3-hydroxy-urea **3g** (0.192 g, 1.66 mmol), triethylamine (0.23 mL, 1.7 mmol) and benzoyl chloride (0.19 mL, 1.7 mmol) in CH₂Cl₂ (5.5 mL, 0.30 M) were stirred at room temperature overnight. The reaction mixture was diluted with CH₂Cl₂ and transferred to a separatory funnel, then washed with brine, dried over MgSO₄ and filtered. The reaction mixture was concentrated under reduced pressure and isolated using flash

chromatography (50% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.276 g, 76%). TLC R_f = 0.50 in 50% EtOAc/Hexanes. ^1H NMR (300 MHz, DMSO- d_6) δ 9.90-9.85 (br s, 1H), 8.06-8.00 (m, 2H), 7.76-7.68 (m, 1H), 7.61-7.54 (m, 2H), 7.31 (t, J = 5.8 Hz, 1H), 5.80 (ddt, J = 17.1, 10.2, 5.1 Hz, 1H), 5.16-5.00 (m, 2H), 3.68 (tt, J = 5.4, 1.7 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.0 (C), 158.2 (C), 134.6 (CH), 134.0 (CH), 129.9 (CH), 129.1 (CH), 126.8 (C), 116.8 (CH_2), 42.5 (CH_2). IR (FTIR): 3321, 1757, 1658, 1565, 1239 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 243.0746. Found: 243.070.

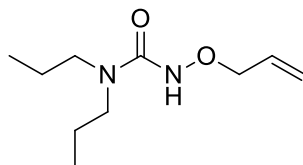


3-Hydroxy-1,1-dipropylurea: The title compound was synthesized according to general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.101 g, 0.660 mmol), triethylamine (0.0121 g, 0.120 mmol) and dipropylamine (0.0607 g, 0.660 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 $^{\circ}\text{C}$ via oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (3% MeOH/ CH_2Cl_2 then 12% MeOH/ CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.081 g, 85%). TLC R_f = 0.18 in 50% EtOAc/Hexane. ^1H NMR (400 MHz, CDCl_3) δ 6.64 (br s, 1H), 6.58 (br s, 1H), 3.19-3.15 (m, 4H), 1.63-1.54 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H). ^{13}C (100 MHz, CDCl_3) δ 161.4 (C), 48.4 (CH_2), 21.3 (CH_2), 11.2 (CH_3). IR (FTIR): 3274, 2959, 2931, 2875, 1613, 1498, 1376, 1250, 1094 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_7\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 160.1212. Found: 160.1209.

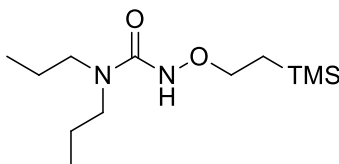


3-Ethoxy-1,1-dipropylurea: The title compound was synthesized according to general procedure **2C** using phenyl *N*-ethoxycarbamate **2.2** (0.181 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 20 min at 120 $^{\circ}\text{C}$. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as a clear oil (0.171 g, 91%). TLC R_f = 0.44 in 20% EtOAc/Hexane. ^1H NMR (400 MHz, CDCl_3) δ 7.03 (br s, 1H), 3.91 (q, J = 7.0 Hz, 2H), 3.13 (t, J = 7.7 Hz, 4H), 1.57 (ap sext, J = 7.6 Hz, 4H), 1.24 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.4 (C), 71.9 (CH_2), 49.1 (CH_2), 21.7 (CH_2), 13.7 (CH_3), 11.4 (CH_3). IR (FTIR): 3216, 2964, 2933, 2875, 1725, 1644, 1478, 1243 cm^{-1} .

HRMS (EI): Exact mass could not be obtained for the molecular ion. Exact mass calcd for fragment $[C_2H_6NO]^+$ (O-ethylhydroxylamine): 60.0449. Found: 60.0440, Exact mass calcd for fragment $[C_7H_{14}NO]^+$ (N,N-dipropyl carbamoyl): 128.1075. Found: 128.1056.

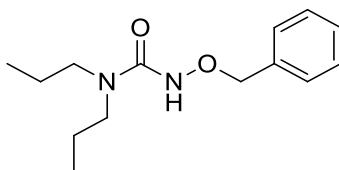


3-(Allyloxy)-1,1-dipropylurea: The title compound was synthesized according to general procedure **2C** using phenyl allyloxycarbamate **2.13** (0.193 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated via microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.188 g, 94%). TLC R_f = 0.43 in 20% EtOAc/Hexane. 1H NMR (400 MHz, $CDCl_3$) δ 7.13 (br s, 1H), 5.97 (ddt, J = 17.1, 10.5, 6.4 Hz, 1H), 5.33-5.24 (m, 2H), 4.34 (dt, J = 6.3, 1.1 Hz, 2H), 3.11 (t, J = 7.7 Hz, 4H), 1.55 (ap sext, J = 7.6 Hz, 4H), 0.87 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C), 133.1 (CH), 119.7 (CH_2), 77.2 (CH_2), 48.9 (CH_2), 21.6 (CH_2), 11.4 (CH_3). IR (FTIR): 3219, 2962, 2927, 2873, 1644, 1481, 1405, 1379, 1244 cm^{-1} . HRMS (ESI): Exact mass calcd for $C_{10}H_{20}N_2O_2Na$ $[M+Na]^+$: 223.1423. Found: 223.1394.

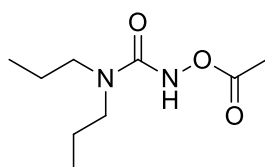


1,1-Dipropyl-3-(2-(trimethylsilyl)ethoxy)urea: The title compound was synthesized according to general procedure **2C** using phenyl 2-(trimethylsilyl)ethoxycarbamate **2.14** (0.253 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered and rinsed with CH_2Cl_2 (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.242 g, 93%). TLC R_f = 0.38 in 20% EtOAc/Hexane. 1H NMR (400 MHz, $CDCl_3$) δ 6.98 (br s, 1H), 3.91-3.87 (m, 2H), 3.11 (dd, J = 8.4, 7.0 Hz, 4H), 1.55 (ap sext, J = 7.6 Hz, 4H), 1.01-0.97 (m, 2H), 0.87 (t, J = 7.4 Hz, 6H), -0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C), 74.1 (CH_2), 49.1 (CH_2), 21.7 (CH_2), 16.9 (CH_2), 11.5 (CH_3), 1.28

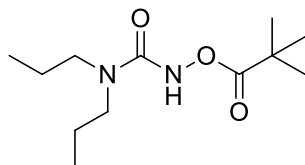
(CH₃). IR (FTIR): 3192, 2959, 2929, 2875, 1636, 1518, 1490, 1405, 1426 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₂H₂₈N₂O₂SiNa [M+Na]⁺: 283.1818. Found: 283.1821.



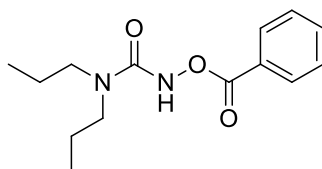
3-(Benzyloxy)-1,1-dipropylurea: The title compound was synthesized according to general procedure **2C** using phenyl benzyloxycarbamate **2.15** (0.243 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) in MeCN (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 20 min. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.240 g, 96%). TLC R_f = 0.39 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.30 (m, 5H), 6.96 (br s, 1H), 4.87 (s, 2H), 3.08 (t, *J* = 7.7 Hz, 4H), 1.51 (ap sext, *J* = 7.6 Hz, 4H), 0.84 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 159.0 (C), 136.3 (C), 129.3 (CH), 128.6 (CH), 128.5 (C), 78.1 (CH₂), 49.0 (CH₂), 21.6 (CH₂), 11.4 (CH₃). IR (FTIR): 3203, 3064, 3033, 2958, 2928, 2872, 1648, 1505, 1473, 1455, 1413, 1239 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₄H₂₂N₂O₂ [M]⁺: 250.1681. Found: 250.1664.



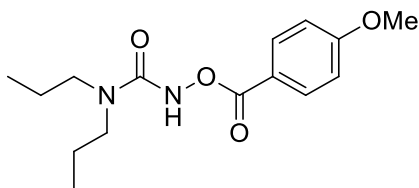
3-Acetoxy-1,1-dipropylurea: The title compound was synthesized according to general procedure **2D** using phenyl acetoxycarbamate **2.16** (0.195 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.05 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.125 g, 62%). TLC R_f = 0.42 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.32 (br s, 1H), 3.17 (t, *J* = 7.6 Hz, 4H), 2.19 (s, 3H), 1.57 (ap sext, *J* = 7.5, 4H), 0.89 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 171.1 (C), 157.5 (C), 48.9 (CH₂), 21.4 (CH₂), 18.6 (CH₃), 11.3 (CH₃). IR (FTIR): 3162, 2964, 2936, 2877, 1782, 1655, 1478, 1376 cm⁻¹. HRMS (EI): Exact mass calcd for C₉H₁₈N₂O₃ [M]⁺: 202.1317. Found: 202.1324.



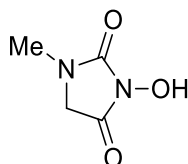
3-(Pivaloyloxy)-1,1-dipropylurea 4g: The title compound was synthesized according to general procedure **2D** with slight modification, phenyl pivaloyloxycarbamate **2.17** (0.237 g, 1.00 mmol) was formed *in situ* following general procedure **1** and used without purification, to which was added dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.215 g, 88%) over two steps. TLC R_f = 0.66 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.17 (s, 1H), 3.19 (t, *J* = 7.7 Hz, 4H), 1.61 (ap sext, *J* = 7.5 Hz, 4H), 1.31 (s, 9H), 0.91 (t, *J* = 7.4, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 179.0 (C), 157.6 (C), 48.9 (CH₂), 38.4 (C), 27.1 (CH₃), 21.4 (CH₂), 11.3 (CH₃). IR (FTIR): 3231, 2964, 2936, 2874, 1773, 1659, 1478, 1241 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₂₄N₂O₃ [M]⁺: 244.1787. Found: 244.1791.



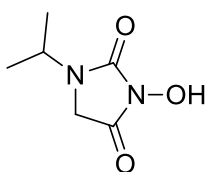
3-(Benzoyloxy)-1,1-dipropylurea: The title compound was synthesized according to general procedure **2D** using phenyl *N*-benzoyloxycarbamate **2.3** (0.257 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 3 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.230 g, 87%). TLC R_f = 0.40 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.57 (br s, 1H), 8.12-8.08 (m, 2H), 7.62-7.56 (m, 1H), 7.44 (tt, *J* = 7.5, 1.3 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 4H), 1.64 (ap sext, *J* = 7.5 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 167.2 (C), 157.6 (C), 134.0 (C), 129.9 (CH), 128.6 (CH), 127.3 (C), 49.0 (CH₂), 21.4 (CH₂), 11.3 (CH₃). IR (FTIR): 3213, 2963, 2931, 2874, 1781, 1762, 1647, 1510, 1483, 1378 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₄H₂₀N₂O₃ [M]⁺: 264.1474. Found: 264.1453.



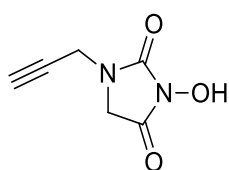
3-((4-Methoxybenzoyl)oxy)-1,1-dipropylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.287 g, 1.00 mmol), and dipropylamine (0.14 mL, 1.1 mmol) and imidazole (0.007 g, 0.1 mmol) in THF (5.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 1 h at 120 °C. Upon completion, the reaction mixture was diluted with EtOAc (5.0 mL) and washed three times using 1 M NaOH (2.0 mL), followed by a single brine wash (2.0 mL). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected and concentrated under reduced pressure to yield the title compound as an amorphous white solid (0.280 g, 95%). TLC R_f = 0.33 in 20% EtOAc/Hexane. ¹H NMR (300 MHz, CDCl₃) δ 8.49 (s, 1H), 8.07-8.04 (m, 2H), 6.93-6.91 (m, 2H), 3.23 (t, *J* = 7.6 Hz, 4H), 1.64 (ap sext, 7.5 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 167.0 (C), 164.3 (C), 157.8 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.6 (CH₃), 49.1 (CH₂), 21.6 (CH₂), 11.4 (CH₃). IR (FTIR): 3218, 2963, 2933, 2874, 1748, 1666, 1604, 1509, 1463, 1238, 1165 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₅H₂₂N₂O₄ [M]⁺: 294.1580. Found: 294.1595.



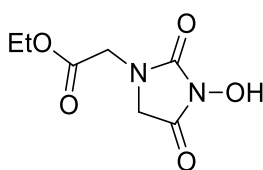
3-Hydroxy-1-methylimidazolidine-2,4-dione: Synthesized according to general procedure **2E** using sarcosine ethyl ester hydrochloride (0.153 g, 1.00 mmol), phenyl hydroxycarbamate (0.168 g, 1.10 mmol) and *i*-Pr₂NEt (0.155 g, 1.20 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1% MeOH/CH₂Cl₂ then 10% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.118 g, 91%). TLC R_f = 0.07 in 50% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 3.91 (s, 2H), 3.02 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): 165.1 (C), 154.5 (C), 49.8 (CH₂), 30.3 (CH₃). IR (film): 2881, 1725, 1717, 1272 cm⁻¹. HRMS (EI): Exact mass calcd for C₄H₆N₂O₃ [M]⁺: 130.0378. Found: 130.0377.



3-Hydroxy-1-isopropylimidazolidine-2,4-dione: Synthesized according to general procedure **2E** using *N*-(ethoxycarbonylmethyl)-*N*-isopropylammonium chloride (0.145 g, 0.800 mmol), phenyl hydroxycarbamate (0.135 g, 0.880 mmol) and *i*-Pr₂NEt (0.124 g, 0.960 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 90 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as a brown oil (0.092 g, 73%). TLC R_f = 0.30 in 50% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃): δ 4.33 (spt, *J* = 6 Hz, 1H), 3.83 (s, 2H), 1.21 (d, *J* = 6Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 165.8 (C), 154.1 (C), 44.2 (CH₂), 43.1 (CH₃), 19.9 (CH₃). IR (film): 2891, 2158, 1735, 1717, 1513, 1236 cm⁻¹. HRMS (EI): Exact mass calcd for C₆H₁₀N₂O₃ [M]⁺: 158.0691. Found: 158.0689.

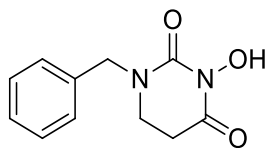


3-Hydroxy-1-(prop-2-yn-1-yl)imidazolidine-2,4-dione: Synthesized according to general procedure **2E** using ethyl 2-(prop-2-yn-1-ylamino)acetate (0.113 g, 0.800 mmol), phenyl hydroxycarbamate (0.135 g, 0.880 mmol) and *i*-Pr₂NEt (0.124 g, 0.960 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1% MeOH/CH₂Cl₂ then 5% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.081g, 66%). TLC R_f = 0.10 in 50% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆): δ 4.13 (d, *J* = 3 Hz, 2H), 3.97 (s, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 165.2 (C), 154.0 (C), 77.8 (CH₂), 75.7 (C), 47.0 (CH₂), 34.2 (CH). IR (film): 2997, 2142, 1734, 1647, 1562 cm⁻¹. HRMS (EI): Exact mass calcd for C₆H₆N₂O₃ [M]⁺: 154.0378. Found: 154.0378.

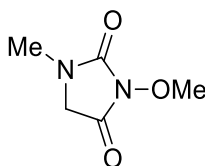


Ethyl 2-(3-hydroxy-2,4-dioxoimidazolidin-1-yl)acetate: Synthesized according to general procedure **2E** using diethyl 2,2'-azanediylldiacetate (0.151 g, 0.800 mmol), phenyl hydroxycarbamate (0.135 g, 0.880 mmol) and *i*-Pr₂NEt (0.124 g, 0.960 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 90 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1% MeOH/CH₂Cl₂ then 5% MeOH/CH₂Cl₂). The title compound was obtained as a brown oil (0.141g, 69%). TLC R_f = 0.23 in 50% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃): δ 4.33 (q, *J* = 6 Hz, 2H), 4.14 (s, 2H), 4.06 (s, 2H), 1.21 (d, *J* = 6Hz, 3H). ¹³C NMR (300 MHz, CDCl₃): δ 168.3 (C), 165.9 (C), 155.0 (C), 61.9 (CH₂), 48.4

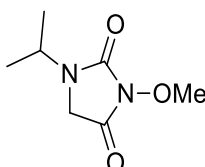
(CH₂), 44.1 (CH₂), 13.9 (CH₃). IR (film): 2842, 1740, 1701, 1684, 1562 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₀N₂O₅ [M]⁺: 202.0590. Found: 202.0592.



1-Benzyl-3-hydroxydihydropyrimidine-2,4(1H,3H)-dione: Synthesized according to general procedure **2E** using ethyl 3-(benzylamino)propanoate (0.842 g, 5.50 mmol), phenyl hydroxycarbamate (1.03 g, 5.00 mmol) and *i*-Pr₂NEt (1.05 mL, 6.00 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 100 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (10% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.868 g, 80%). TLC R_f = 0.16 in 50% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃): δ 7.40-7.21 (m, 5H), 4.62 (s, 2H), 3.29 (t, *J* = 6Hz, 2H), 2.72 (t, *J* = 6 Hz, 2H). ¹³C NMR (300 MHz, CDCl₃): δ 152.7 (C), 135.6 (CH), 128.9 (CH), 128.1 (CH), 51.5 (CH₂), 39.9 (CH₂), 30.9 (CH₂). IR (film): 3090, 2889, 2075, 174, 1719, 1563, 1506, 1471, 1272 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₂N₂O₃ [M]⁺: 220.0848. Found: 220.0858.

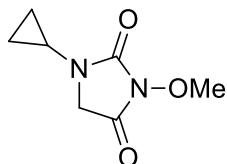


3-Methoxy-1-methylimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using sarcosine ethyl ester hydrochloride (0.123 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.114 g, 0.880 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (10% EtOAc/CH₂Cl₂). The title compound was obtained as a clear oil (0.114 g, >99%). TLC R_f = 0.25 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 3.98 (s, 3H), 3.85 (s, 2H), 3.00 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 163.9 (C), 152.8 (C), 65.3 (CH₃), 49.7 (CH₂), 30.7 (CH₃). IR (film): 3674, 3103, 2923, 1787, 1735, 1558, 1440, 1363, 1276, 1246, 1176 cm⁻¹. HRMS (EI): Exact mass calcd for C₅H₈N₂O₃ [M]⁺: 144.0535. Found: 144.0533.

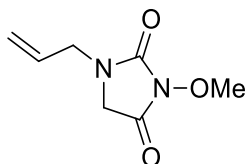


1-Isopropyl-3-methoxyimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-(isopropylamino)acetate hydrochloride (0.145 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.114 g, 0.880 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture

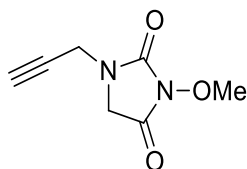
was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 7.5% EtOAc/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.132 g, 96%). TLC R_f = 0.25 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.32 (spt, *J* = 6.8 Hz, 1H), 3.95 (s, 3H), 3.74 (s, 2H), 1.18 (d, *J* = 6.8 Hz, 6H). ¹³C NMR (75 MHz; CDCl₃): δ 164.4 (C), 151.9 (C), 65.3 (CH₃), 43.9 (CH), 42.9 (CH₂), 19.9 (CH₃). IR (film): 2921, 1784, 1730, 1683, 1448, 1417, 1266, 1238, 1078 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₂N₂O₃ [M]⁺: 172.0848. Found: 172.0849.



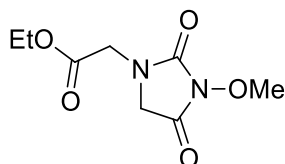
1-Cyclopropyl-3-methoxyimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-(cyclopropylamino)acetate (0.115 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (5% EtOAc/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.121 g, 89%). TLC R_f = 0.60 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 3.97 (s, 3H), 3.82 (s, 2H), 2.69-2.57 (m, 1H), 0.92-0.72 (m, 4H). ¹³C NMR (75 MHz; CDCl₃): δ 164.0 (C), 152.9 (C), 65.3 (CH₃), 48.5 (CH₂), 25.3 (CH), 5.7 (CH₂). IR (film): 2864, 1843, 1778, 1733, 1683, 1647, 1558, 1506, 1448, 1264, 1112 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₀N₂O₃ [M]⁺: 170.0691. Found: 170.0699.



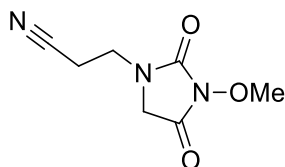
1-Allyl-3-methoxyimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-(allylamino)acetate (0.115 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (5% EtOAc/CH₂Cl₂). The title compound was obtained as clear oil (0.113 g, 83%). TLC R_f = 0.55 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 5.73 (dd, *J* = 10.2, 17.0 Hz, 1H), 5.31-5.20 (m, 2H), 4.00-3.93 (m, 5H), 3.78 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 164.2 (C), 152.5 (C), 131.0 (CH), 120.0 (CH₂), 65.4 (CH₃), 47.2 (CH₂), 45.7 (CH₂). IR (film): 3105, 1787, 1733, 1558, 1454, 1417, 1266, 1232, 1188 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₀N₂O₃ [M]⁺: 170.0691. Found: 170.0729.



3-Methoxy-1-(prop-2-yn-1-yl)imidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-(prop-2-yn-1-ylamino)acetate (0.113 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl₂). The title compound was obtained as clear oil (0.122 g, >99%). TLC R_f = 0.39 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; DMSO-*d*₆): δ 4.14 (d, *J* = 2.5 Hz, 2H), 3.98 (s, 2H), 3.83 (s, 3H), 3.38 (t, *J* = 2.5 Hz, 1H). ¹³C NMR (75 MHz; CDCl₃): δ 164.3 (C), 152.1 (C), 77.6 (CH), 75.8 (C), 64.8 (CH₃), 47.3 (CH₂), 32.3 (CH₂). IR (film): 1816, 1749, 1733, 1662, 1558, 1505, 1446, 1263 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₈N₂O₃ [M]⁺: 168.0535. Found: 168.0539.

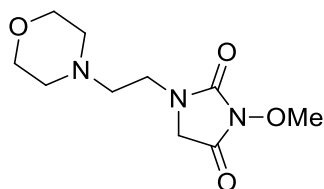


Ethyl 2-(3-methoxy-2,4-dioximidazolidin-1-yl)acetate: Synthesized according to general procedure **2F** using diethyl 2,2'-azanediyldiacetate (0.151 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (10% EtOAc/CH₂Cl₂). The title compound was obtained as clear oil (0.163 g, 94%). TLC R_f = 0.28 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.21 (q, *J* = 7.3 Hz, 2H), 4.11 (s, 2 H), 4.01-3.95 (m, 5H), 1.27 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 168.0 (C), 164.0 (C), 153.2 (C), 65.4 (CH₃), 62.0 (CH₂), 48.4 (CH₂), 44.0 (CH₂), 14.1 (CH₃). IR (film): 3647, 1733, 1683, 1662, 1558, 1506, 1466, 1262 cm⁻¹. HRMS (EI): Exact mass calcd for C₈H₁₂N₂O₃ [M]⁺: 216.0746. Found: 216.0743.

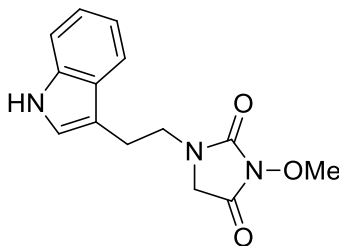


3-(3-Methoxy-2,4-dioximidazolidin-1-yl)propanenitrile: Synthesized according to general procedure **2F** using ethyl 2-((2-cyanoethyl)amino)acetate (0.125 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation.

The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.147 g, >99%). TLC R_f = 0.18 in 30% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.04 (s, 2H), 3.97 (s, 3H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 163.5 (C), 152.8 (C), 117.4 (C), 65.6 (CH₃), 48.8 (CH₂), 39.8 (CH₂), 17.4 (CH₂). IR (film): 2804, 1868, 1791, 1735, 1700, 1653, 1558, 1606, 1264 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₉N₃O₃ [M]⁺: 183.0644. Found: 183.0651.

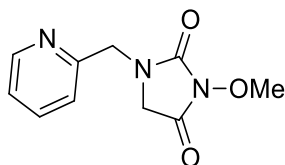


3-Methoxy-1-(2-morpholinoethyl)imidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-((2-morpholinoethyl)amino)acetate (0.0865 g, 0.400 mmol), phenyl methoxycarbamate (0.0669 g, 0.400 mmol) and *i*-Pr₂NEt (0.0026 g, 0.020 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (10% EtOAc/CH₂Cl₂ then 5% CH₃OH/CH₂Cl₂). The title compound was obtained as a clear oil (0.0972 g, >99%). TLC R_f = 0.33 in 5% CH₃OH/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.05-3.86 (m, 5H), 3.68 (br s, 4H), 3.51 (t, *J* = 5.9 Hz, 2H), 2.50 (br s, 3H), 2.57 (br s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 164.5 (C), 152.9 (C), 67.0 (CH₂), 65.4 (CH₃), 56.3 (CH₂), 53.5 (CH₂), 48.3 (CH₂), 39.3 (CH₂). IR (film): 3514, 2864, 1789, 1792, 1733, 1652, 1455, 1263 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₀H₁₇N₃O₄ [M]⁺: 243.1219. Found: 243.1226.

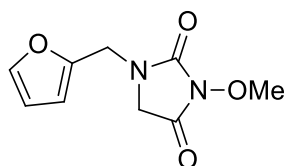


1-(2-(1H-Indol-3-yl)ethyl)-3-methoxyimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-((2-(1H-indol-3-yl)ethyl)amino)acetate (0.0986 g, 0.400 mmol), phenyl methoxycarbamate (0.0669 g, 0.400 mmol) and *i*-Pr₂NEt (0.0026 g, 0.020 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/CH₂Cl₂ then 2.5% CH₃OH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.101 g, 92%). TLC R_f = 0.44 in 2.5% CH₃OH/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 8.09 (br s, 1H), 7.63-7.56 (m, 1H), 7.39 (td, *J* = 0.9, 8.1 Hz, 1H), 7.26-7.20 (m, 1H), 7.18-7.12 (m, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 3.74 (t, *J* = 7.0 Hz, 2H), 3.63 (s, 2H), 3.09 (dt, *J* = 0.8, 7.0 Hz, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 164.3 (C), 152.7 (C), 136.3 (C), 127.0 (C), 122.5 (CH), 121.9

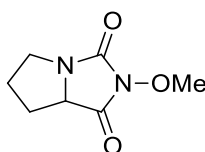
(CH), 119.8 (CH), 118.3 (CH), 112.0 (C), 111.5 (CH), 65.3 (CH₃), 48.3 (CH₂), 43.7 (CH₂), 23.9 (CH₂). IR (film): 3569, 2931, 1818, 1733, 1706, 1679, 1647, 1263, 1220, 1010 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₃H₁₂N₃O₃ [M]⁺: 273.1113. Found: 273.1069.



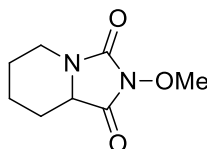
3-Methoxy-1-(pyridin-2-ylmethyl)imidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-((pyridin-2-ylmethyl)amino)acetate (0.155 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/CH₂Cl₂ then 5% CH₃OH/CH₂Cl₂). The title compound was obtained as a dark yellow oil (0.150 g, 85%). TLC R_f = 0.22 in 5% CH₃OH/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 8.56-8.47 (m, 1H), 7.67 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.29-7.14 (m, 2H), 4.62 (s, 2H), 3.99-3.92 (m, 5H). ¹³C NMR (75 MHz; CDCl₃): δ 164.5 (C), 154.8 (C), 153.2 (C), 149.7 (CH), 137.2 (CH), 123.0 (CH), 122.4 (CH), 65.4 (CH₃), 48.3 (CH₂), 48.2 (CH₂). IR (film): 3524, 2935, 2402, 1733, 1706, 1555, 1539, 1489, 1254, 1191 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₀H₁₁N₃O₃ [M]⁺: 221.0800. Found: 221.0804.



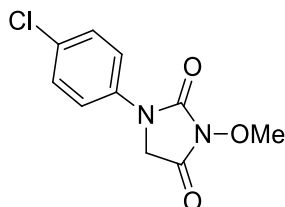
1-(Furan-2-ylmethyl)-3-methoxyimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-((furan-2-ylmethyl)amino)acetate (0.147 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (5% EtOAc/CH₂Cl₂). The title compound was obtained as a dark yellow oil (0.139 g, 83%). TLC R_f = 0.58 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 7.38 (dd, *J* = 0.8, 1.7 Hz, 1H), 6.37-6.27 (m, 2H), 4.52 (s, 2H), 3.97 (s, 3H), 3.80 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 164.1 (C), 152.5 (C), 148.3 (C), 143.2 (CH), 110.7 (CH₂), 109.6 (CH₂), 65.4 (CH₃), 47.5 (CH₂), 39.6 (CH₂). IR (film): 3550, 2955, 2415, 1788, 1772, 1735, 1716, 1647, 1542, 1240, 1085 cm⁻¹. HRMS (EI): Exact mass calcd for C₉H₁₀N₂O₄ [M]⁺: 210.0641. Found: 210.0633.



2-Methoxytetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione: Synthesized according to general procedure **2F** using methyl pyrrolidine-2-carboxylate hydrochloride (0.133 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.114 g, 0.880 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl₂). The title compound was obtained as a clear oil (0.110 g, 81%). TLC R_f = 0.31 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.05 (dd, *J* = 7.3, 9.5 Hz, 1H), 3.97 (s, 3H), 3.66 (td, *J* = 7.9, 11.2 Hz, 1H), 3.30 (ddd, *J* = 4.2, 8.3, 11.2 Hz, 1H), 2.38-2.27 (m, 1H), 2.21-2.10 (m, 1H), 2.10-1.98 (m, 1H), 1.80-1.66 (m, 1H). ¹³C NMR (75 MHz; CDCl₃): δ 168.3 (C), 156.3 (C), 65.2 (CH₃), 61.0 (CH), 45.6 (CH₂), 27.6 (CH₂), 26.5 (CH₂). IR (film): 2935, 1865, 1791, 1731, 1718, 1668, 1558, 1392, 1257, 1224 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₀N₂O₃ [M]⁺: 170.0691. Found: 170.0693.

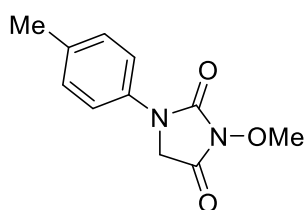


2-Methoxytetrahydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dione: Synthesized according to general procedure **2F** using methyl piperidine-2-carboxylate (0.126 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl). The title compound was obtained as a clear oil (0.147 g, >99%). TLC R_f = 0.30 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.17-4.03 (m, 1H), 3.94 (s, 3H), 3.73 (dd, *J* = 4.2, 11.9 Hz, 1H), 2.79 (dt, *J* = 3.5, 12.8 Hz, 1H), 2.20 (dd, *J* = 3.1, 12.7 Hz, 1H), 2.05-1.91 (m, 1H), 1.80-1.66 (m, 1H), 1.51-1.27 (m, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 167.2 (C), 150.7 (C), 65.3 (CH₃), 55.7 (CH), 39.4 (CH₂), 27.5 (CH₂), 24.9 (CH₂), 22.5 (CH₂). IR (film): 3647, 2360, 1890, 1855, 1780, 1737, 1683, 1558, 1521, 1446, 1276 cm⁻¹. HRMS (EI): Exact mass calcd for C₈H₁₂N₂O₃ [M]⁺: 184.0848. Found: 184.0861.

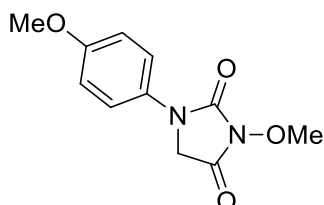


1-(4-Chlorophenyl)-3-methoxyimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-((4-chlorophenyl)amino)acetate (0.167 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction

mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH₂Cl₂ and then recrystallized in CH₂Cl₂/hexanes. The solid was then filtered and washed with Et₂O to give pure product. The title compound was obtained as a crystalline tan solid (0.141 g, 73%). TLC R_f = 0.13 in 100% CH₂Cl₂. M.p 192.2-193.1 °C. ¹H NMR (300 MHz; CDCl₃): δ 7.56-7.46 (m, 2H), 7.43-7.34 (m, 2H), 4.27 (s, 2H), 4.06 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 162.3 (C), 150.2 (C), 135.7 (C), 130.3 (C), 129.5 (CH), 119.3 (CH), 65.6 (CH₃), 47.7 (CH₂). IR (film): 2921, 1789, 1743, 1729, 1683, 1496, 1436, 1406, 1298, 1184, 1093 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₀H₉ClN₂O₃ [M]⁺: 240.0302. Found: 240.0302.

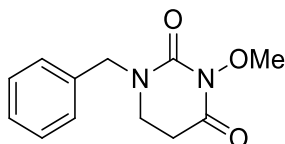


3-Methoxy-1-(p-tolyl)imidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-(p-tolylamino)acetate (0.118 g, 0.610 mmol), phenyl methoxycarbamate (0.102 g, 0.610 mmol) and *i*-Pr₂NEt (0.0039 g, 0.030 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH₂Cl₂ and then recrystallized in CH₂Cl₂/hexanes. The solid was then filtered and washed with Et₂O to give pure product. The title compound was obtained as an amorphous white solid (0.118 g, 88%). TLC R_f = 0.15 in 100% CH₂Cl₂. M.p 172.6-173.8 °C. ¹H NMR (300 MHz; CDCl₃): δ 7.44-7.37 (m, 2H), 7.24-7.17 (m, 2H), 4.26 (s, 2H), 4.06 (s, 3H), 2.35 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 162.9 (C), 150.3 (C), 134.8 (C), 134.5 (C), 129.9 (CH), 118.4 (CH), 65.5 (CH₃), 47.9 (CH₂), 20.8 (CH₃). IR (film): 3197, 2956, 1791, 1735, 1683, 1647, 1616, 1558, 1515, 1436, 1404, 1363, 1184, 1107 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₂N₂O₃ [M]⁺: 220.0848. Found: 220.0854.

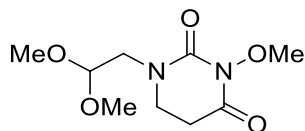


3-methoxy-1-(4-methoxyphenyl)imidazolidine-2,4-dione: Synthesized according to general procedure **2F** using ethyl 2-((4-methoxyphenyl)amino)acetate (0.167 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH₂Cl₂ and then recrystallized in CH₂Cl₂/hexanes. The solid was then filtered and washed with Et₂O

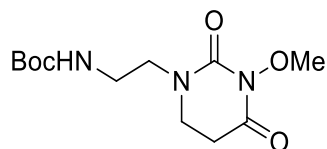
to give pure product. The title compound was obtained as a crystalline tan solid (0.163 g, 86%). TLC Rf = 0.10 in 100% CH₂Cl₂. M.p 183.7-184.3 °C. ¹H NMR (300 MHz; CDCl₃): δ 7.49-7.36 (m, 2H), 7.00-6.88 (m, 2H), 4.26 (s, 2H), 4.06 (s, 3H), 3.82 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 162.9 (C), 157.1 (C), 150.4 (C), 130.4 (C), 120.6 (CH), 114.7 (CH), 65.5 (CH₃), 55.5 (CH₃), 48.3 (CH₂). IR (film): 3601, 1772, 1733, 1652, 1516, 1261, 1199, 1056 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₂N₂O₄ [M]⁺: 236.0797. Found: 236.0805.



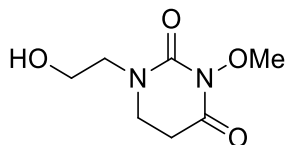
1-Benzyl-3-methoxydihydropyrimidine-2,4(1H,3H)-dione: Synthesized according to general procedure **2F** using ethyl 3-(benzylamino)propanoate (0.166 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl₂). The title compound was obtained as a clear oil (0.209 g, 89%). TLC Rf = 0.23 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 7.43-7.28 (m, 5H), 4.64 (s, 2H), 3.95 (s, 3H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.71 (t, *J* = 6.7 Hz, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 165.1 (C), 151.6 (C), 135.8, (C), 128.9 (CH), 128.2 (CH), 64.3 (CH₃), 51.4 (CH₂), 39.9 (CH₂), 31.5 (CH₂). IR (film): 3396, 2935, 2460, 1773, 1706, 1630, 1558, 1539, 1488, 1191 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₄N₂O₃ [M]⁺: 234.1004. Found: 234.1001.



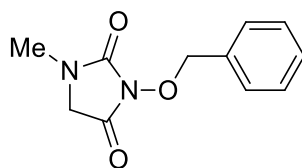
1-(2,2-Dimethoxyethyl)-3-methoxydihydropyrimidine-2,4(1H,3H)-dione: Synthesized according to general procedure **2F** using methyl 3-((2,2-dimethoxyethyl)amino)propanoate (0.153 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 30% EtOAc/CH₂Cl₂). The title compound was obtained as a clear oil (0.176 g, 95%). TLC Rf = 0.33 in 30% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.50 (t, *J* = 5.2 Hz, 1H), 3.90 (s, 3H), 3.53-3.45 (m, 4H), 3.45-3.41 (m, 6H), 2.73 (t, *J* = 6.8 Hz, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 165.5 (C), 151.5 (C), 103.1 (CH), 64.2 (CH₃), 55.1 (CH₃), 50.0 (CH₂), 42.6 (CH₂), 31.8 (CH₂). IR (film): 3186, 2942, 2680, 1773, 1709, 1631, 1488, 1436, 1286, 1109 cm⁻¹. HRMS (EI): Exact mass calcd for C₉H₁₆N₂O₅ [M]⁺: 232.1059. Found: 232.1021.



tert-Butyl (2-(3-methoxy-2,4-dioxotetrahydropyrimidin-1(2H)-yl)ethyl)carbamate: Synthesized according to general procedure **2F** using methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)amino)propanoate (0.197 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 30% EtOAc/CH₂Cl₂). The title compound was obtained as a clear oil (0.225 g, 98%). TLC R_f = 0.18 in 30% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.97 (br s, 1H), 3.87 (s, 3 H), 3.57-3.49 (m, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 3.34 (q, *J* = 5.7 Hz, 2H), 2.78 (t, *J* = 6.7 Hz, 2H), 1.37 (s, 9H). ¹³C NMR (75 MHz; CDCl₃): δ 165.3 (C), 156.2 (C), 151.7 (C), 79.6 (C), 64.1 (CH₃), 47.7 (CH₂), 41.1 (CH₂), 38.3 (CH₂), 31.5 (CH₂), 28.3 (CH₃). IR (film): 3333, 2385, 1730, 1697, 1683, 1515, 1367, 1272, 1247, 1191, 1161 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₂₁N₃O₅ [M]⁺: 287.1481. Exact mass calcd for C₈H₁₂N₃O₅ [M - C₄H₉]⁺: 230.0777. Found: 231.0859.

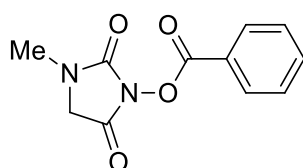


1-(2-Hydroxyethyl)-3-methoxydihydropyrimidine-2,4(1H,3H)-dione: Synthesized according to general procedure **2F** using methyl 3-((2-hydroxyethyl)amino)propanoate (0.118 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 4 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 30% EtOAc/CH₂Cl₂). The title compound was obtained as a clear oil (0.132 g, 88%). TLC R_f = 0.18 in 30% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 3.87 (s, 3H), 3.81 (t, *J* = 5.1 Hz, 2H), 3.62-3.54 (m, 2H), 3.53-3.46 (m, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 2.70 (br s, 1H). ¹³C NMR (75 MHz; CDCl₃): δ 165.6 (C), 151.9 (C), 64.2 (CH₃), 60.7 (CH₂), 50.9 (CH₂), 42.2 (CH₂), 31.5 (CH₂). IR (film): 3301, 2671, 2027, 1735, 1699, 1652, 1558, 1276, 1197, 1053 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₂N₂O₄ [M]⁺: 188.0797. Found: 188.0801.

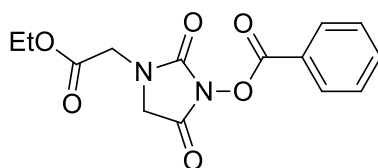


3-(Benzyloxy)-1-methylimidazolidine-2,4-dione: Synthesized according to general procedure **2F** using sarcosine ethyl ester hydrochloride (0.0614 g, 0.400 mmol), phenyl benzyloxycarbamate (0.0972

g, 0.400 mmol) and *i*-Pr₂NEt (0.0568 g, 0.44 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.0873 g, >99%). TLC R_f = 0.52 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 7.58- 7.47 (m, 2H), 7.45-7.33 (m, 3H), 5.14 (s, 2H), 3.80 (s, 2H), 2.98 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 164.1 (C), 153.1 (C), 133.5 (C), 129.8 (CH), 129.3 (CH), 128.5 (CH), 79.4 (CH₂), 49.6 (CH₂), 30.1 (CH₃). IR (film): 3450, 2470, 1791, 1736, 1558, 1506, 1446, 1244, 1085 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₂N₂O₃ [M]⁺: 220.0848. Found: 220.0845.

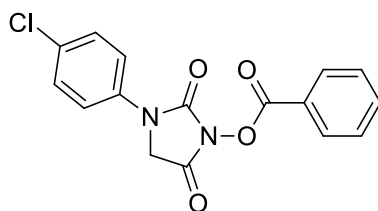


3-Methyl-2,5-dioximidazolidin-1-yl benzoate: Synthesized according to general procedure **2F** using sarcosine ethyl ester hydrochloride (0.0614 g, 0.400 mmol), phenyl benzoyloxycarbamate (0.103 g, 0.400 mmol) and *i*-Pr₂NEt (0.0568 g, 0.440 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 90 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.061g, 65%). TLC R_f = 0.50 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 8.18-8.06 (m, 2H), 7.66 (tt, *J* = 1.2, 7.5 Hz, 1H), 7.55-7.44 (m, 2H), 4.04 (s, 2H), 3.05 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 163.4 (C), 162.6 (C), 151.7 (C), 134.9 (CH), 130.7 (CH), 128.9 (CH), 125.2 (C), 50.0 (CH₂), 30.4 (CH₃). IR (film): 3444, 2988, 1755, 1735, 1718, 1690, 1597, 1422, 1406, 1398, 1284, 1083 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₀N₂O₄ [M]⁺: 234.0641. Found: 234.0627.

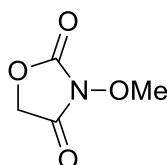


3-(2-Ethoxy-2-oxoethyl)-2,5-dioximidazolidin-1-yl benzoate: Synthesized according to general procedure **2F** using diethyl 2,2'-azanediylldiacetate (0.151 g, 0.400 mmol), phenyl benzoyloxycarbamate (0.103 g, 0.400 mmol) and *i*-Pr₂NEt (0.0026 g, 0.020 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 90 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (100% CH₂Cl₂ then 10% EtOAc/CH₂Cl₂). The title compound was obtained as clear oil (0.107 g, 87%). TLC R_f = 0.60 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 8.26-8.10 (m, 2H), 7.69 (tt, *J* = 1.2, 7.5 Hz, 1H), 7.58-7.46 (m, 2H), 4.36-4.07 (m, 6H), 1.32 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 167.8 (C), 163.2 (C), 162.3 (C), 134.9 (CH), 130.6 (CH), 128.8 (CH), 125.0 (C), 62.0 (CH₃),

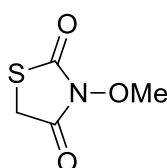
48.7 (CH₂), 44.2 (CH₂), 14.1 (CH₃). IR (film): 3180, 2999, 1760, 1733, 1725, 1680, 1497, 1433, 1306, 1098 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₄H₁₄N₂O₆ [M]⁺: 306.0852. Found: 306.0849.



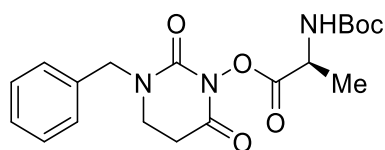
3-(4-Chlorophenyl)-2,5-dioxoimidazolidin-1-yl benzoate: Synthesized according to general procedure **2F** using ethyl 2-((4-chlorophenyl)amino)acetate (0.0855 g, 0.400 mmol), phenyl benzyloxycarbamate (0.103 g, 0.800 mmol) and *i*-Pr₂NEt (0.0052 g, 0.040 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH₂Cl₂ and then recrystallized in CH₂Cl₂/hexanes. The solid was then filtered and washed with Et₂O to give pure product. The title compound was obtained as an amorphous white solid (0.138 g, 52%). TLC R_f = 0.13 in 100% CH₂Cl₂. M.p 213.3-214.8 °C. ¹H NMR (300 MHz; CDCl₃): δ 8.24-8.13 (m, 2H), 7.76-7.67 (m, 1H), 7.61-7.47 (m, 4H), 7.46-7.33 (m, 2H), 4.49 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 162.4 (C), 161.7 (C), 149.1 (C), 135.6 (C), 135.1 (C), 130.7 (CH), 129.6 (CH), 128.9 (CH), 124.8 (C), 119.5 (CH), 48.1 (CH₂). IR (film): 3335, 2884, 1758, 1733, 1718, 1622, 1597, 1335, 1306 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₆H₁₁ClN₂O₄ [M]⁺: 330.0407. Found: 330.0406.



3-Methoxyoxazolidine-2,4-dione: Synthesized according to general procedure **2G** using ethyl 2-hydroxyacetate (0.0833 g, 0.800 mmol), phenyl methoxycarbamate (0.066 g, 0.40 mmol) and DBU (0.006 g, 0.05 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/hexanes then 40% EtOAc/hexanes). The title compound was obtained as an amorphous white solid (0.030 g, 55%). TLC R_f = 0.38 in 100% CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 4.74 (s, 2H), 4.04 (s, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 164.0 (C), 151.0 (C), 66.2 (CH₂), 65.5 (CH₃). IR (film): 2956, 1772, 1757, 1259, 1122 cm⁻¹. HRMS (ESI): Exact mass calcd for C₄H₅NO₄Na [M+Na]⁺: 154.0111. Found: 154.0116.



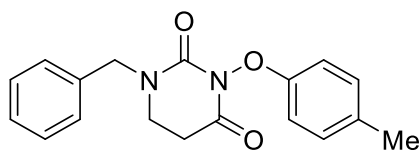
3-Methoxythiazolidine-2,4-dione: Synthesized according to general procedure **2G** using methyl thioglycolate (0.0849 g, 0.800 mmol), phenyl methoxycarbamate (0.134 g, 0.800 mmol) and DBU (0.006 g, 0.05 mmol) in acetonitrile (0.30 M). The vial was sealed with a microwave cap and heated for 2 h at 120 °C via microwave irradiation. The reaction mixture was concentrated under reduced pressure and purified using flash chromatography (30% EtOAc/hexanes then 40% EtOAc/hexanes). The title compound was obtained as a yellow oil (0.090 g, 72%). TLC R_f = 0.50 in 100% CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 3.99 (s, 3H), 3.90 (s, 2H). ¹³C NMR (75 MHz; CDCl₃): δ 165.8 (C), 164.9 (C), 64.8 (CH₂), 29.8 (CH₃). IR (film): 2896, 2827, 1713, 1697, 1192 cm⁻¹. HRMS (EI): Exact mass calcd for C₄H₅NO₃S [M]⁺: 146.9990. Found: 147.0013.



(S)-3-Benzyl-2,6-dioxotetrahydropyrimidin-1(2H)-yl

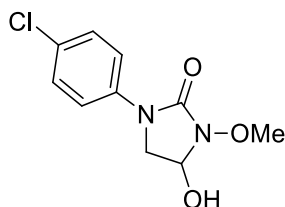
2-((tert-butoxycarbonyl)amino)propanoate:

The title compound was synthesised using hexahydro-3-hydroxy-1-benzyl-1,3-diazine-2,4-dione **2.53** (0.215 g, 0.980 mmol) and Boc-Ala-OSu (0.143 g, 0.500 mmol) and a catalytic amount of DBU in acetonitrile (0.30 M). The reaction was stirred 24 h at r.t. Water was added and the reaction was extracted with DCM, washed with brine, dried over MgSO₄ filtered and concentrated under reduced pressure and purified using flash chromatography (5% MeOH/DCM). The title compound was obtained as an amorphous white solid (0.150 g, 77%). TLC R_f = 0.08 in 100% CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 7.37-7.22 (m, 5H), 5.10-5.00 (br s, 1H), 4.76-4.64 (m, 1H), 4.63-4.52 (m, 2H), 3.37-3.25 (m, 2H), 2.85-2.65 (m, 2H), 1.56 (t, *J* = 3Hz, 3H), 1.43 (s, 9H). ¹³C NMR (75 MHz; CDCl₃): δ 170.0 (C), 163.8 (C), 150.3 (C), 150.2 (C), 135.5 (CH), 135.4 (CH), 129.0 (CH), 128.2 (CH), 128.0 (CH), 77.2 (CH₂), 51.5 (CH₂), 51.4 (CH₂), 39.8 (CH), 31.2 (CH₃), 28.3 (CH₃). IR (film): 2827, 1792, 1772, 1684, 1653, 1558, 1506, 1272 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₉H₂₅N₃O₆Na [M+Na]⁺: 414.1641. Found: 414.1657.



1-Benzyl-3-(p-tolyloxy)dihydropyrimidine-2,4(1H,3H)-dione: The title compound was synthesized using hexahydro-3-hydroxy-1-benzyl-1,3-diazine-2,4-dione **2.53** (0.111 g, 0.500 mmol), CuCl (0.0908 g, 0.500 mmol), freshly activated 4 Å molecular sieves (~25 mg), and 4-methylphenylboronic acid (0.136 g, 1.00 mmol). DCM was added (0.30 M) was added followed by pyridine (0.044 g, 0.55 mmol). The reaction was open to the atmosphere during 16 h. The reaction was filtered over silica gel and the solvent was removed under reduced pressure and purified using flash chromatography (1% MeOH/DCM). The title compound was obtained as a brown oil (0.123 g, 79%). TLC R_f = 0.19 in 100% CH₂Cl₂. ¹H NMR (300 MHz; CDCl₃): δ 7.41-7.29 (m, 5H), 7.15-7.09 (m, 2H), 7.00-6.95 (m,

2H), 4.65 (s, 2H) 3.36 (t, $J = 6$ Hz, 2H), 2.80 (t, $J = 6$ Hz, 2H), 2.31 (3H, s). ^{13}C NMR (75 MHz; CDCl_3): δ 165.1 (C), 156.8 (C) 151.4 (CH), 135.7 (CH), 133.4 (CH), 129.9 (CH), 129.0 (CH), 128.2 (CH), 113.9 (CH), 51.6 (CH), 39.9 (CH), 31.6 (CH), 20.6 (CH_3). IR (film): 2987, 1743, 1700, 1558, 1506, 1472, 1277, 1205 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M}]^+$: 310.1317. Found: 310.1318.



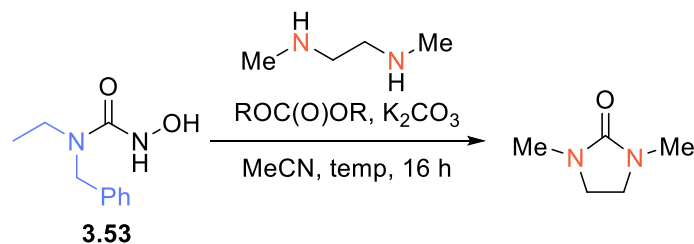
1-(4-Chlorophenyl)-4-hydroxy-3-methoxyimidazolidin-2-one: The title compound was synthesized using 1-(4-chlorophenyl)-3-methoxyimidazolidine-2,4-dione **2.67** (0.120 g, 0.500 mmol), ethanol (0.30 M), and then NaBH_4 (0.029 g, 0.75 mmol). The reaction was refluxed for 16 h. Upon completion, the reaction was concentrated under reduced pressure to remove the ethanol, and then the crude concentrate was dissolved in CH_2Cl_2 . The compound was extracted using 1 M HCl. The organic phase was dried over Na_2SO_4 and then concentrated under reduced pressure to give the pure product as a white solid (0.121 g, 99%). TLC $R_f = 0.15$ in 100% CH_2Cl_2 . ^1H NMR (300 MHz; CDCl_3): δ 7.50-7.46 (m, 2H), 7.33-7.29 (m, 2H), 5.40 (dd, $J = 5.9, 3.0$ Hz, 1H), 3.91 (s, 3H), 3.84 (dd, $J = 9.9, 5.9$ Hz, 1H), 3.62 (dd, $J = 9.9, 3.0$ Hz, 1H), 3.47 (s, 1H). ^{13}C NMR (75 MHz; CDCl_3): δ 156.8 (C) 137.6 (CH), 129.2 (CH), 129.1 (C), 119.2 (CH), 78.8 (CH), 64.7 (CH_3), 48.8 (CH_2). IR (film): 3350, 2987, 1743, 1556, 1526, 1373, 1250, 1205 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M}]^+$: 242.0458. Found: 242.0463.

6.3. Supporting information for Chapter 3

6.3.1. Optimization tables

- Aza-Lossen rearrangement for synthesis of protected hydrazines

Table S3.1: Diamine study^a

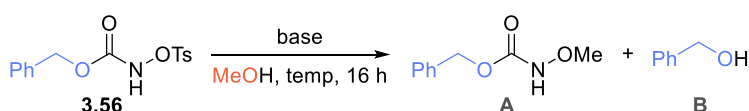


Entry	ROC(O)OR (equiv)	Base (equiv)	Temp (°C)	%SM	%Urea	%PhOH
1	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	80	0	65	89
2	Boc ₂ O (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	80	25	7	-
3	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	r.t.	0	82	100
4	Boc ₂ CO (1.20)	<i>i</i> -Pr ₂ NEt (1.20)	r.t.	72	0	-
5	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	50	0	82	100

Conditions: ^a 1-benzyl-1-ethyl-3-hydroxyurea (1.00 equiv), N¹,N²-dimethylethane-1,2-diamine (1.00 equiv), dialkyl carbonate and base in MeCN (0.3M) stir in an oil bath for 16 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

- Oxa-Lossen rearrangement using O-Ts starting material

Table S3.2: Oxa-Lossen optimization^a

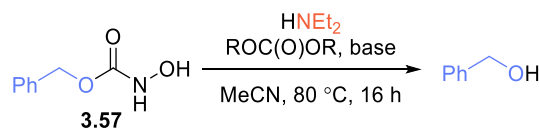


Entry	Base (equiv)	Temp (°C)	%A	%B
1	TMG (1.10)	0	62	0
2	TMG (1.10)	50	64	0
3	TMG (1.10)	80	33	34
4	DBU (1.10)	80	40	32
5	TMG (1.10)	80	50	20

Conditions: ^a benzyl (tosyloxy)carbamate (1.00 equiv), base in MeOH (0.3M) stir in an oil bath for 16 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

- Oxa-Lossen rearrangement via in-situ activation

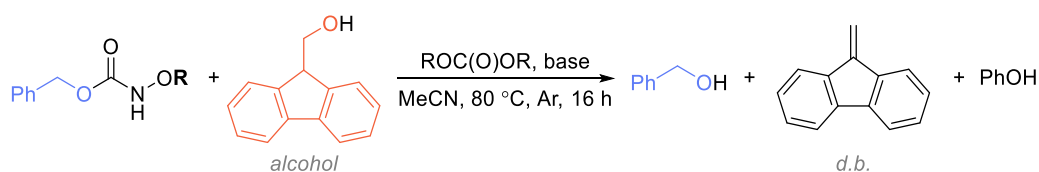
Table S3.3: Oxa-Lossen study^a



Entry	ROC(O)OR (equiv)	Base (equiv)	%BnOH
1	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	76
2	Boc ₂ O (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	57
3	Me ₂ CO (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	44

Conditions: ^a benzyl hydroxycarbamate (1.00 equiv), diethylamine (1.00 equiv), dialkyl carbonate and base in MeCN (0.3M) stir in an oil bath for 16 h. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Table S3.4: Synthesis of Fmoc-protected O-alkylamine^a



Entry	R	ROC(O)OR (equiv)	Base (equiv)	%SM	%BnOH	%d.b.	%PhOH
1	H	(PhO) ₂ CO (1.00)	K ₂ CO ₃ (1.20)	31	15	20	66
2	H	Boc ₂ O (1.00)	<i>i</i> -Pr ₂ NEt (1.20)	30	20	5	-
3	H	(PhO) ₂ CO (1.00)	Et ₃ N (1.20)	22	44	27	100
4	C(O)OPh	-	Et ₃ N 1.20)	0	30	19	71
5	Ts	-	Et ₃ N (1.20)	0	0	0	0

Conditions: ^a benzyl oxycarbamate (1.00 equiv), (9H-fluoren-9-yl)methanol (1.00 equiv), dialkyl carbonate and base in MeCN (0.3M) stir in an oil bath for 16 h under Ar. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

6.3.2. Characterizations

General procedures

General procedure 3A: N-hydroxyureas substrate synthesis²⁶¹

To a 20 mL microwave vial charged with a stir bar was added *N*-hydroxycarbamate (1.10 equiv) then THF (0.3 M), to which was added the corresponding amine (1.00 equiv), and finally Et₃N (0.20 equiv).

²⁶¹ M. A. Allen, R. A. Ivanovich, D. E. Polat, A. M. Beauchemin, *Org. Lett.* **2017**, 19, 6574–6577.

The vial was sealed with a microwave cap and heated for 16 h at 70 °C via conventional (oil bath) heating. After cooling to room temperature, solvent was removed under reduced pressure and the crude products were then purified by silica gel chromatography or recrystallization to give the corresponding *N*-hydroxyureas.

General procedure 3B: Synthesis of semicarbazides via chemoselective aza-Lossen rearrangement

To a 2 mL microwave vial charged with a stir bar was added the corresponding *N*-hydroxyurea (1.00 equiv) then MeCN (0.3 M), to which was added the corresponding amine (1.00 equiv), potassium carbonate (1.20 equiv), and finally diphenyl carbonate (1.00 equiv). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via conventional (oil bath) heating. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL), washed with an aqueous solution sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude products were then purified by silica gel chromatography to give the corresponding pure semicarbazides.

Note: The order of addition is crucial to avoid any decomposition of the *N*-hydroxyureas.

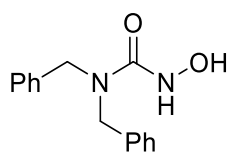
General procedure 3C: Synthesis of oxadiazin-2-ones via chemoselective aza-Lossen rearrangement

To a 2 mL microwave vial charged with a stir bar was added the corresponding *N*-hydroxyurea (1.00 equiv) then MeCN (0.3 M), to which was added di-*tert*-butyl dicarbonate (1.00 equiv.) and *N,N*-diisopropylethylamine (1.20 equiv.). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via conventional (oil bath) heating. After cooling to room temperature, the reaction was concentrated under reduced pressure and the crude products were then purified by silica gel chromatography to give the corresponding pure oxadiazin-2-ones.

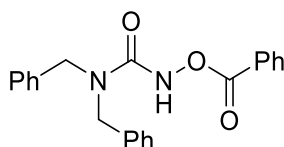
General procedure 3D: Synthesis of triazin-3-ones via chemoselective aza-Lossen rearrangement

To a 2 mL microwave vial charged with a stir bar was added the corresponding *N*-hydroxyurea (1.00 equiv) then MeCN (0.3 M), to which was added diphenyl dicarbonate (1.00 equiv.) and potassium carbonate (1.20 equiv.). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via conventional (oil bath) heating. After cooling to room temperature, the reaction was concentrated under reduced pressure and the crude products were then purified by silica gel chromatography to give the corresponding pure triazin-3-ones.

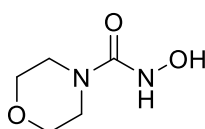
Synthesis and characterizations



1,1-Dibenzyl-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), Et₃N (0.14 mL, 1.0 mmol) and dibenzylamine (0.87 mL, 5.0 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.710 g, 55%). TLC R_f = 0.32 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.28 (m, 6H), 7.26-7.20 (m, 4H), 6.66-6.62 (br s, 1H), 6.54-6.36 (br s, 1H), 4.51 (s, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 162.0 (C), 136.1 (C), 129.0 (CH), 128.0 (CH), 127.3 (CH), 50.0 (CH₂). IR (FTIR): 3257, 3029, 1627, 1518, 1428 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₅H₁₆N₂O₂ [M]⁺: 256.1212. Found 256.1204.

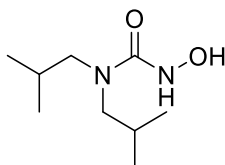


3-(Benzoyloxy)-1,1-dibenzylurea: The title compound was synthesized according to general procedure **2D** using phenyl benzoyloxycarbamate (1.29 g, 5.00 mmol), and dibenzylamine (0.96 mL, 3.00 mmol) and imidazole (0.034 g, 0.5 mmol) in THF (0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (10% EtOAc/Hexanes) to yield the title compound as a colorless oil (1.56 g, 87%). TLC R_f: 0.78 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 8.41-8.33 (br s, 1H), 8.14-8.05 (m, 2H), 7.61 (ddt, *J* = 8.8, 7.0, 1.3 Hz, 1H), 7.49-7.43 (m, 4H), 7.42-7.36 (m, 4H), 7.35-7.29 (m, 6H), 4.57 (s, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 166.9 (C), 158.4 (C), 136.3 (C), 134.1 (CH), 130.1 (CH), 129.2 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 50.2 (CH₂). FTIR: 3139, 2917, 175, 1649, 1517, 1452, 1232 cm⁻¹. HRMS (ESI) C₂₂H₂₀N₂O₃Na [M+Na]⁺: 383.1372. Found: 383.1349.

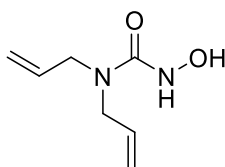


1-Morpholin-3-hydroxy-urea: The title compound was synthesized according to a modified general procedure **3A** using phenyl *N*-hydroxycarbamate (0.754 g, 4.93 mmol), *N,N*-diisopropylethylamine (0.03 mL, 0.2 mmol) and morpholine (0.43 mL, 5.0 mmol) in THF (0.30 M). The vial was sealed with

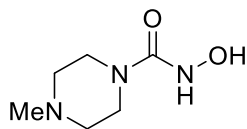
a microwave cap and heated for 16 h at 70 °C via an oil bath. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and recrystallized in Et₂O/Hexanes. The title compound was obtained as a crystalline white solid (0.511 g, 72%). TLC R_f = 0.73 in 2% MeOH/CH₂Cl₂. M. p. 172.0-172.7 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.09-9.06 (br s, 1H), 8.07-8.04 (br s, 1H), 3.54-3.49 (m, 4H), 3.24-3.19 (m, 4H). ¹³C (100 MHz, DMSO-*d*₆) δ 159.7(C), 65.8 (CH₂), 43.6 (CH₂). IR (FTIR): 3303, 3163, 1773, 1519, 1487 cm⁻¹. HRMS (EI): Exact mass calcd for C₅H₁₀N₂O₃ [M]⁺: 146.0691. Found 146.0688.



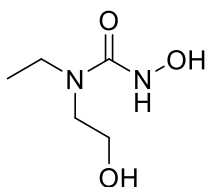
1,1-Diisobutyl-3-hydroxy-urea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), Et₃N (0.14 mL, 1.0 mmol) and diisobutylamine (0.87 mL, 5.0 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.785 g, 84%). TLC R_f = 0.54 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.65-6.61 (br s, 1H), 6.60-6.52 (br s, 1H), 3.07 (d, *J* = 7.6 Hz, 4H), 1.99 (ap sept, *J* = 7.5 Hz, 2H), 0.92 (d, *J* = 6.7 Hz, 12H). ¹³C (100 MHz, CDCl₃) δ 162.0 (C), 54.4 (CH₂), 27.1 (CH), 20.1 (CH₃). IR (FTIR): 3365, 3295, 1699, 1496, 1276 cm⁻¹. HRMS (EI): Exact mass calcd for C₉H₂₀N₂O₂: 188.1525. Found: 188.1515.



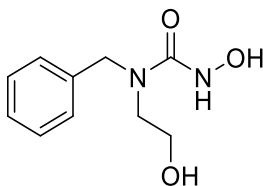
1,1-Diallyl-3-hydroxy-urea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.168 g, 1.00 mmol), Et₃N (0.03 mL, 0.2 mmol) and diallylamine (0.097 g, 1.0 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.098 g, 63%). TLC R_f = 0.53 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.86-6.80 (br s, 1H), 6.69 (d, *J* = 3.1 Hz, 1H), 5.86-5.72 (m, 2H), 5.27-5.18 (m, 1H), 3.89 (dt, *J* = 5.5, 1.5 Hz). ¹³C (100 MHz, CDCl₃) δ 161.5 (C), 132.8 (CH), 117.5 (CH₂), 49.0 (CH₂). IR (FTIR): 3246, 2915, 1640, 1471, 1414, 1281 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₄N₂O₂ [M]⁺: 156.0899. Found: 156.0914.



1-(4-Methylpiperazine)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), Et₃N (0.14 mL, 1.0 mmol) and *N*-methylpiperazine (0.501 g, 5.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and recrystallized in Et₂O/Hexanes. The title compound was obtained as a crystalline white solid (0.203 g, 64%). TLC *R*_f = 0.22 in 10:89:1 MeOH/CH₂Cl₂/NH₄OH. M.p. 161.7-161.9 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.03-8.99 (br s, 1H), 8.01-7.93 (br s, 1H), 3.26-3.19 (m, 4H), 2.22-2.19 (m, 4H), 2.15 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.7 (C), 54.3 (CH₂), 45.8 (CH₂), 43.0 (CH₃). IR (FTIR): 3297, 2785, 2359, 1608, 1463, 1005 cm⁻¹. HRMS (EI): Exact mass calcd for C₆H₁₃N₃O₂ [M]⁺: 159.1008. Found 159.0993.

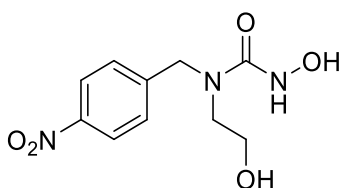


1-(2-(Ethylamino)ethanol)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), Et₃N (0.14 mL, 1.0 mmol) and 2-(ethylamino)ethanol (0.446 g, 5.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂ then 5% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous yellowish solid (0.671 g, 91%). TLC *R*_f = 0.10 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 (d, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 4.87 (t, *J* = 5.1 Hz, 1H), 3.47 (q, *J* = 5.7 Hz, 2H), 3.24-3.16 (m, 4H), 1.00 (t, *J* = 7.1 Hz, 3H). ¹³C (100 MHz, DMSO-*d*₆) δ 160.1 (C), 59.9 (CH₂), 48.0 (CH₂), 41.4 (CH₂), 13.3 (CH₃). IR (FTIR): 3164, 2931, 1773, 1615, 1519, 1344 cm⁻¹. HRMS (EI): Exact mass calcd for C₅H₁₂N₂O₃ [M]⁺: 148.0848. Found: 148.0848.

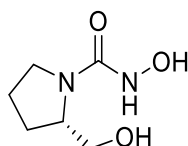


1-(2-(benzyl)ethanol)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), Et₃N (0.14 mL, 1.0 mmol) and

N-benzylethanolamine (0.71 mL, 5.0 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and precipitated out of solution. The title compound was obtained as an amorphous white solid (1.09 g, 96%). TLC *R*_f = 0.1 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (d, *J* = 2.2 Hz, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 7.35-7.29 (m, 2H), 7.27-7.19 (m, 3H), 4.95 (t, *J* = 4.9 Hz, 1H), 4.46 (s, 2H), 3.46 (q, *J* = 5.7 Hz, 2H), 3.16 (t, *J* = 5.8 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.0 (C), 138.8 (C), 128.3 (CH), 127.2 (CH), 126.8 (CH), 59.5 (CH₂), 49.6 (CH₂), 48.0 (CH₂). IR (FTIR): 3266, 2815, 1615, 1494, 1273, 1060 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₀H₁₄N₂O₃Na [M+Na]⁺: 233.0902. Found: 233.0917.

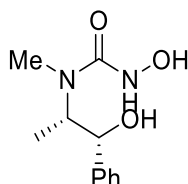


1-(2-(4-Nitrobenzyl)ethanol)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.505 g, 3.30 mmol), Et₃N (0.08 mL, 0.6 mmol) and 2-((4-nitrobenzyl)amino)ethan-1-ol (0.588 g, 3.00 mmol) in THF (0.30 M). After cooling to room temperature, the vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and recrystallized in THF/Hexanes. The title compound was obtained as a crystalline orange solid (0.604 g, 79%). TLC *R*_f = 0.1 in 5% MeOH/CH₂Cl₂. M.p. 182.7-183.1 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97 (d, *J* = 2.0 Hz, 1H), 8.23-8.17 (m, 2H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.50-7.44 (m, 2H), 4.98 (t, *J* = 4.9 Hz, 1H), 4.60 (s, 2H), 3.49 (q, *J* = 5.4 Hz, 2H), 3.22 (t, *J* = 5.6 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.5 (C), 147.4 (C), 146.5 (C), 128.1 (CH), 123.5 (CH), 59.6 (CH₂), 49.6 (CH₂), 48.7 (CH₂). IR (FTIR): 3415, 3222, 2882, 2359, 1653, 1341 cm⁻¹. Exact mass calcd for C₁₀H₁₃N₃O₅Na [M+Na]⁺: 278.0753. Found: 278.0733.

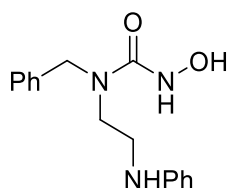


1-(S-Prolinol)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.505 g, 3.30 mmol), Et₃N (0.08 mL, 0.6 mmol) and (*S*)-pyrrolidin-2-ylmethanol (0.30 mL, 3.0 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (1:9:90 NH₄OH/MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.398 g, 83%).

TLC R_f = 0.83 in 5% MeOH/CH₂Cl₂. $[\alpha]_D^{24^\circ}$: -76° (C 0.1M, MeOH).²⁶² ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.70 (d, J = 1.9 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 4.97 (t, J = 5.3 Hz, 1H), 3.83-3.72 (m, 1H), 3.42 (dt, J = 10.3, 5.1 Hz, 1H), 3.28-3.10 (m, 3H), 1.86-1.67 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.5 (C), 63.1 (CH₂), 58.6 (CH₂), 45.6 (CH₂), 27.1 (CH₂), 23.2 (CH₂). IR (FTIR): 3208, 2889, 1641, 1531, 1394, 1031 cm⁻¹. HRMS [ESI]: Exact mass calcd for C₆H₁₂N₂O₃Na [M+Na]⁺: 183.0745. Found: 183.0742.



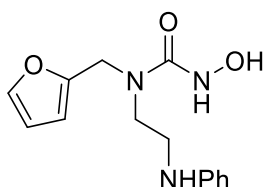
3-hydroxy-1-((1R,2S)-1-hydroxy-1-phenylpropan-2-yl)-1-methylurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.758 g, 4.95 mmol), Et₃N (0.13 mL, 0.9 mmol) and (1*R*,2*S*)-(-)-ephedrine (0.745 g, 4.50 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as a clear oil (0.727 g, 72%). TLC R_f = 0.18 in 5% MeOH/CH₂Cl₂. $[\alpha]_D^{24^\circ}$: -12 (C 0.1M, MeOH). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.67 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.33-7.26 (m, 4H), 7.18 (m, 1H), 5.42 (d, J = 4.7 Hz, 1H), 4.27-4.19 (m, 1H), 2.59 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.3 (C), 143.9 (C), 127.8 (CH), 126.8 (CH), 126.3 (CH), 75.0 (CH), 55.2 (CH), 29.0 (CH), 12.6 (CH). IR (FTIR): 3254, 2930, 1628, 1486, 1450. 1061 cm⁻¹. HRMS [ESI]: Exact mass calcd for C₁₁H₁₆N₂O₃Na [M+Na]⁺: 247.1059. Found: 247.1047.



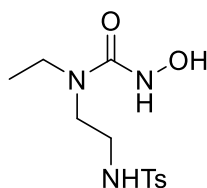
1-(1-Benzyl-2-phenyl-ethylene-1,2-diamine)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.482 g, 3.15 mmol), Et₃N (0.08 mL, 0.6 mmol) and *N*-benzyl-*N'*-phenyl-1,2-diaminoethane (0.678 g, 3.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.421 g, 49%). TLC R_f = 0.17 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.28

²⁶² A. Defoin, A. Brouillard-Poichet, J. Streith, *Helv. Chim. Acta.* **1992**, 75, 109-123.

(m, 3H), 7.27-7.16 (m, 4H), 7.15-7.11 (br s, 1H), 6.81-6.73 (m, 1H), 6.64-6.57 (m, 2H), 6.38-6.25 (br s, 1H), 4.53 (s, 2H), 4.07-3.90 (br s, 1H), 3.60-3.56 (m, 2H), 3.35-3.31 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 162.5 (C), 147.4 (C), 136.3 (C), 129.5 (CH), 129.1 (CH), 128.1 (CH), 127.1 (CH), 118.4 (CH), 113.1 (CH), 50.6 (CH_2), 47.0 (CH_2), 43.1 (CH_2). IR (FTIR): 3351, 3270, 2919, 1645, 1600, 1491, 1470 cm^{-1} . HRMS [ESI]: Exact mass calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 308.1375. Found: 308.1384.

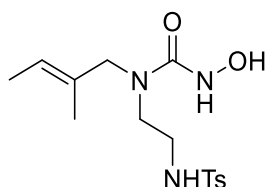


1-(1-(Furan-2-ylmethyl)-2-phenylethane-1,2-diamine)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.505 g, 3.30 mmol), Et_3N (0.08 mL, 0.6 mmol) and *N*-(furan-2-ylmethyl)-*N'*-phenylethane-1,2-diamine (0.648 g, 3.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 $^\circ\text{C}$ via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/ CH_2Cl_2 then 5% MeOH/ CH_2Cl_2) followed by a recrystallization in Et_2O . The title compound was obtained as a crystalline pale brown solid (0.474 g, 57%). TLC R_f = 0.17 in 2% MeOH/ CH_2Cl_2 . M.p. 119.4-120.1 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ 7.49-7.43 (br s, 1H), 7.40 (dd, J = 1.9, 0.8 Hz, 2H), 7.24-7.15 (m, 2H), 6.79-6.72 (m, 1H), 6.66-6.58 (m, 2H), 6.36 (dd, J = 3.1, 1.9 Hz, 1H), 6.29 (ap d, J = 3.1 Hz, 1H), 4.44 (s, 2H), 3.60-3.56 (m, 2H), 3.33-3.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 162.3 (C), 150.0 (C), 147.5 (C), 142.9 (CH), 129.4 (CH), 118.2 (CH), 113.0 (CH), 110.6 (CH), 108.8 (CH), 46.9 (CH_2), 43.8 (CH_2), 42.9 (CH_2). IR (FTIR): 3352, 3273, 2870, 1644, 1301, 1505, 1213 cm^{-1} . HRMS [ESI]: Exact mass calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 298.1168. Found: 298.1166.

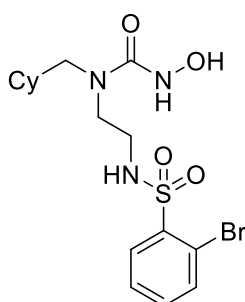


1-(1-(Ethylamino)ethyl-4-methylbenzenesulfonamide)-3-hydroxyurea: The title compound was synthesized according to a modified general procedure **3A** using phenyl *N*-hydroxycarbamate (0.473 g, 3.09 mmol), Et_3N (0.08 mL, 0.6 mmol) and *N*-(2-ethylamino)ethyl-4-methylbenzenesulfonamide (0.679 g, 2.81 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 $^\circ\text{C}$ via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/ CH_2Cl_2 then 5% MeOH/ CH_2Cl_2). The title compound was obtained as an amorphous pale brown solid (0.455 g, 54%). TLC R_f = 0.20 in 2% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3) δ 8.80 (d, J = 1.7 Hz, 1H),

7.97 (d, J = 1.7 Hz, 1H), 7.70-7.63 (m, 2H), 7.61-7.51 (m, 1H), 7.43-7.35 (m, 2H), 3.20-3.04 (m, 4H), 2.84-2.73 (m, 2H), 2.38 (s, 3H), 0.94 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.6 (C), 142.7 (C), 137.3 (C), 126.7 (CH), 126.5 (CH), 45.4 (CH_2), 41.3 (CH_2), 41.1 (CH_2), 21.0 (CH), 13.2 (CH). IR (FTIR): 3339, 3207, 2880, 1623, 1323, 2254, 1079 cm^{-1} . Exact mass calcd for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 324.0994. Found: 324.0974.

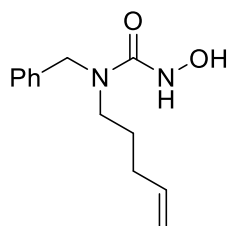


1-(1-(2-Methylbut-3-enamino)ethyl-4-methylbenzenesulfonamide)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.482 g, 3.15 mmol), Et_3N (0.08 mL, 0.6 mmol) and *N*-(2-methylbut-3-enamino)ethyl-4-methylbenzenesulfonamide (0.846 g, 3.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 $^\circ\text{C}$ via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.370 g, 36%). TLC R_f = 0.17 in 2% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3) δ 7.80-7.71 (m, 2H), 7.43-7.28 (m, 3H), 5.94-5.76 (br s, 1H), 5.40-5.26 (m, 1H), 3.60 (s, 2H), 3.45-3.35 (m, 2H), 3.15-3.02 (m, 2H), 2.43 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 162.4 (C), 143.3 (C), 136.7 (C), 130.4 (C), 129.7 (CH), 127.1 (CH), 121.7 (CH), 54.0 (CH_2), 46.7 (CH_2), 41.4 (CH_2), 21.5 (CH), 13.7 (CH), 13.1 (CH). IR (FTIR): 3270, 2919, 1645, 1436, 1323, 1154 cm^{-1} . HRMS [ESI]: Exact mass calcd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 364.1307. Found: 364.1314.

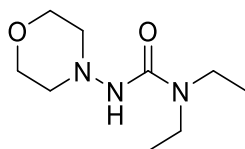


1-(1-(1-Methylcyclohexylamino)ethyl-2-bromobenzenesulfonamide)-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.482 g, 3.15 mmol), Et_3N (0.08 mL, 0.6 mmol) and *N*-(1-methylcyclohexylamino)ethyl-4-methylbenzenesulfonamide (1.12 g, 3.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 $^\circ\text{C}$ via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography

(2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.618 g, 48%). TLC *R_f* = 0.17 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 8.19-8.11 (m, 1H), 7.77-7.69 (m, 1H), 7.51-7.36 (m, 2H), 2.99-2.91 (m, 2H), 2.72-2.62 (m, 2H), 2.33 (d, *J* = 6.6 Hz, 2H), 1.77-1.60 (m, 5H), 1.42-1.09 (m, 3H), 0.97-0.78 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 138.7 (C), 135.0 (CH), 133.6 (CH), 131.7 (CH), 127.7 (CH), 119.8 (C), 55.9 (CH₂), 47.9 (CH₂), 42.5 (CH₂), 38.0 (CH), 31.3 (CH₂), 26.6 (CH₂), 26.0 (CH₂). IR (FTIR): 3271, 2922, 2850, 1634, 1447, 1327, 1157 cm⁻¹. HRMS [ESI]: Exact mass calcd for C₁₆H₂₄BrN₃O₄SNa [M+Na]⁺: 456.0569. Found: 456.0559.

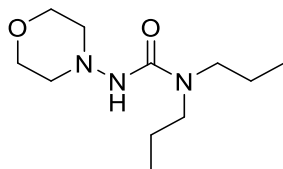


1-Benzyl-1-pent-4-en-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.482 g, 3.15 mmol), Et₃N (0.08 mL, 0.6 mmol) and *N*-benzylpent-4-en-1-amine (0.525 g, 3.00 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (50% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.538 g, 46%). TLC *R_f* = 0.14 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.29 (m, 3H), 7.26-7.20 (m, 2H), 6.70-6.60 (br s, 1H), 6.59-6.41 (br s, 1H), 5.79 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.10-4.99 (m, 2H), 4.48 (s, 2H), 3.37-3.27 (m, 2H), 2.14-2.03 (m, 2H), 1.70 (quin, *J* = 7.4 Hz, 2H). ¹³C (100 MHz, CDCl₃) δ 161.7 (C), 137.4 (CH), 136.4 (C), 129.0 (CH), 127.9 (CH),

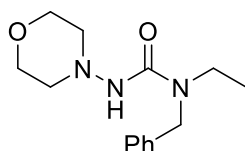


1,1-Diethyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), diethylamine (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.160 g, 86%). TLC *R_f* = 0.25 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz,

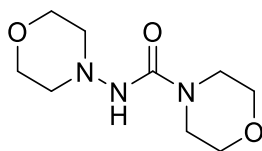
CDCl₃) δ 5.01-4.98 (br s, 1H), 3.82-3.78 (m, 4H), 3.26 (q, J = 7.1 Hz, 4H), 2.84-2.79 (m, 4H), 1.16 (t, J = 7.2 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 156.9 (C), 66.7 (CH₂), 56.8 (CH₂), 41.4 (CH₂), 13.7 (CH₃). IR (FTIR): 3226, 2958, 1612, 1266, 1107 cm⁻¹. HRMS (ESI): Exact mass calcd for C₉H₂₀N₃O₂ [M+H]⁺: 202.1556. Found: 202.1559.



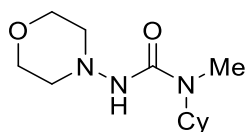
1,1-Dipropyl-3-morpholinourea (3b): The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.511 g, 3.50 mmol), dipropylamine (0.48 mL, 3.5 mmol), potassium carbonate (0.581 g, 4.20 mmol) and diphenyl carbonate (0.784 g, 3.50 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.653 g, 81%). ¹H NMR (500 MHz, CDCl₃) δ 5.03 (br s, 1H), 3.81-3.70 (m, 4H), 3.18-3.06 (m, 4H), 2.85-2.73 (m, 4H), 1.64-1.46 (m, 4H), 0.87 (t, J = 7.4 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 157.3 (C), 66.8 (CH₂), 56.8 (CH₂), 49.2 (CH₂), 21.7 (CH₂), 11.5 (CH₃).



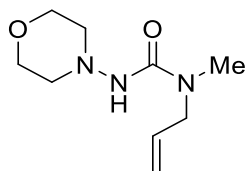
1-Benzyl-1-ethyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), *N*-ethylbenzylamine (0.09 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield a yellow oil (0.123 g, 78%). TLC R_f = 0.53 in 10% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.25 (m, 5H), 5.15-5.03 (br s, 1H), 4.47 (s, 2H), 3.74-3.69 (m, 4H), 3.36 (q, J = 7.1 Hz, 2H), 2.76-2.70 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 157.5 (C), 138 (C), 128.9 (CH), 127.6 (CH), 127 (CH), 66.6 (CH₂), 56.8 (CH₂), 50.2 (CH₂), 42.5 (CH₂), 13.4 (CH₃). IR (FTIR): 3230, 2962, 1610, 1270, 1107 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₁₄H₂₂N₃O₂ [M+H]⁺: 264.1713. Found: 264.1698.



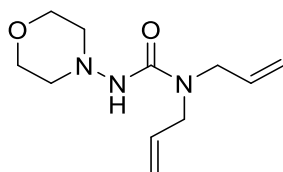
1-Morpholino-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), morpholine (0.05 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.107 g, 83%). TLC R_f = 0.08 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 5.40-5.24 (br s, 1H), 3.83-3.75 (m, 4H), 3.72-3.64 (m, 4H), 3.49-3.41 (m, 4H), 2.89-2.78 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.7 (C), 66.6 (CH₂), 66.5 (CH₂), 56.7 (CH₂), 44.8 (CH₂). IR (FTIR): 3221, 2860, 1629, 1551, 1256, 1108 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₁₉H₂₆N₃O [M+H]⁺: 238.1168. Found: 238.1156.



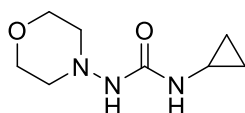
1-Cyclohexyl-1-methyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), *N*-methylcyclohexylamine (0.08 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.077g, 53%). TLC R_f = 0.34 in 10% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.22-7.20 (br s, 1H), 3.86-3.76 (m, 1H), 3.60-3.55 (m, 4H), 2.79-2.74 (m, 4H), 2.60 (s, 3H), 1.76-1.68 (m, 2H), 1.61-1.44 (m, 3H), 1.41-1.19 (m, 4H), 1.11-0.97 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 156.9 (C), 66.3 (CH₂), 54.8 (CH₂), 53.0 (CH₂), 29.8 (CH₂), 27.9 (CH), 25.4 (CH₂), 25.1 (CH₂). IR (FTIR): 3244, 2923, 1627, 1312, 1109 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₂H₂₄N₃O₂ [M+H]⁺: 242.1869. Found: 242.1877.



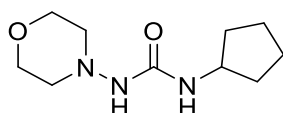
1-Allyl-1-methyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), *N*-allylmethylamine (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.095 g, 79%). TLC R_f = 0.06 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 5.88-5.74 (m, 1H), 5.24-5.13 (m, 2H), 5.11-5.06 (br s, 1H), 3.87 (t, *J*=1.5 Hz, 1H), 3.85 (t, *J*= 1.5Hz, 1H), 3.78 (dd, *J*= 9.3, 4.5 Hz, 4H), 2.89 (s, 3H), 2.79 (dd, *J*= 9.2, 4.6 Hz, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.6 (C), 133.5 (CH), 116.7 (CH₂), 66.6 (CH₂), 56.7 (CH₂), 51.6 (CH₂), 34.5 (CH₃). IR (FTIR): 3252, 2818, 1632, 1545, 1265, 1229, 1107 cm⁻¹. HRMS (ESI): Exact mass calcd for C₉H₁₈N₃O₂ [M+H]⁺: 200.1400. Found: 200.1384.



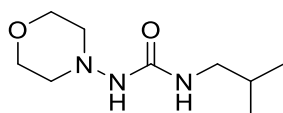
1,1-Diallyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), diallylamine (0.07 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield a yellow oil (0.088 g, 65%). TLC R_f = 0.34 in 10% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 5.90-5.76 (m, 2H), 5.24-5.14 (m, 5H), 3.86 (dt, *J*= 5.5, 1.5 Hz, 4H), 3.81-3.76 (m, 4H), 2.82-2.76 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.4 (C), 135.4 (CH), 115.4 (CH₂), 66.7 (CH₂), 56.7 (CH₂), 41.9 (CH₂). IR (FTIR): 3355, 2854, 1667, 1530, 1265, 1109 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₁H₁₉N₃O₂Na [M+Na]⁺: 248.1375. Found: 244.1369.



1-Cyclopropyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), cyclopropylamine (0.04 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.084 g, 76%). TLC R_f = 0.19 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.13-6.05 (br s, H), 5.19-5.14 (br s, 1H), 3.90-3.60 (br s, 4H), 3.03-2.45 (br s, 5H), 0.81-8.72 (m, 2H), 0.57-0.49 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 158.5 (C), 66.7 (CH₂), 56.7 (CH₂), 22.1 (CH₂), 6.7 (CH). IR (FTIR): 3321, 3219, 2951, 1677, 1514, 1104 cm⁻¹. HRMS (ESI): Exact mass calcd for C₈H₁₆N₃O₂ [M+H]⁺: 186.1243. Found: 186.1248.

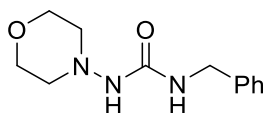


1-Cyclopentyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), cyclopentylamine (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.074 g, 58%). TLC R_f = 0.30 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 5.95-5.82 (br s, 1H), 5.22-5.12 (br s, 1H), 4.10 (sxt, J = 7.2 Hz, 1H), 3.95-3.48 (br s, 4H), 3.07-2.34 (br s, 4H), 2.04-1.94 (m, 2H), 1.72-1.53 (m, 4H), 1.43-1.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 157.3 (C), 66.7 (CH₂), 56.7 (CH₂), 51.3 (CH), 33.5 (CH₂), 23.6 (CH₂). IR (FTIR): 3365, 2949, 1667, 1525, 1108 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₀H₂₀N₃O₂ [M+H]⁺: 214.1556 Found: 214.1562.

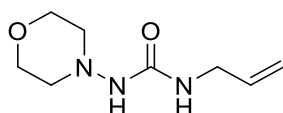


1-Isobutyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), isobutylamine (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution

of sodium bicarbonate (1 x 0.5 mL). The organic phase dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.067 g, 56%). TLC R_f = 0.16 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.15-6.05 (br s, 1H), 5.14-5.06 (br s, 1H), 3.99-3.56 (br s, 4H), 3.05 (t, *J* = 6.5 Hz, 2H), 3.01-2.40 (m, 4H), 1.77 (sept, *J* = 6.5 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 157.7 (C), 66.8 (CH₂), 56.7 (CH₂), 46.8 (CH₂), 28.9 (CH), 20.0 (CH). IR (FTIR): 3431, 2954, 1662, 1529, 1275, 1115 cm⁻¹. HRMS (ESI): Exact mass calcd for C₉H₂₀N₃O₂ [M+H]⁺: 202.1556. Found: 202.1564.

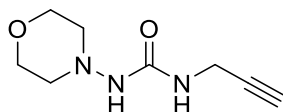


1-Benzyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), benzylamine (0.07 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.098 g, 70%). TLC R_f = 0.28 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.27 (m, 5H), 6.41-6.32 (br s, 1H), 5.39-5.27 (br s, 1H), 4.47 (d, *J* = 6.1 Hz, 2H), 3.96-3.53 (m, 4H), 3.08-2.48 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.6 (C), 139.4 (C), 128.6 (CH), 127.4 (CH), 127.3 (CH), 66.7 (CH₂), 56.8 (CH₂), 43.5 (CH₂). IR (FTIR): 3344, 3221, 1668, 1532, 1271, 1108 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₁₂H₁₇N₃O₂ [M+H]⁺: 236.1399. Found: 236.1399.

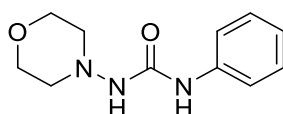


1-Allyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), allylamine (0.05 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.060 g, 54%). TLC R_f = 0.19 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 6.17-6.07 (br s, 1H), 5.96-5.84 (m, 1H), 5.28-5.10 (m, 3H), 4.00-3.57 (m, 6H), 3.09-2.48 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.4 (C), 135.4 (CH), 115.3 (CH₂), 66.7 (CH₂), 56.7 (CH₂), 41.9

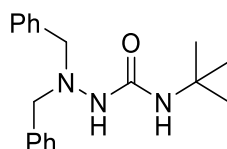
(CH₂). IR (FTIR): 3355, 2854, 1667, 1530, 1265, 1109 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₈H₁₅N₃O₂Na [M+Na]⁺: 208.1062. Found: 208.1060.



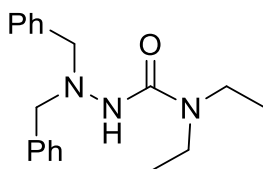
1-(Prop-2-yn-1-yl)-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), propargylamine (0.038 mL, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield as an amorphous white solid (0.080 g, 73%). TLC R_f = 0.44 in 10% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 6.23-6.14 (br s, 1H), 5.51-5.39 (br s, 1H), 4.06 (dd, J = 5.8, 2.4 Hz, 2H), 3.97-3.55 (m, 4H), 3.10-2.45 (m, 4H), 2.24 (t, J = 2.5 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 157.1 (C), 80.5 (CH), 71.0 (CH), 66.6 (CH₂), 56.6 (CH₂), 29.3 (CH₂). IR (FTIR): 3362, 2950, 2113, 1670, 1514, 1106 cm⁻¹. HRMS (ESI): Exact mass calcd for C₈H₁₄N₃O₂ [M+H]⁺: 184.1087. Found: 184.1079.



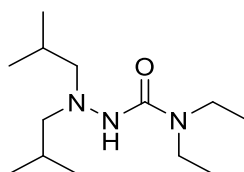
1-Phenyl-3-morpholinourea: The title compound was synthesized according to general procedure **3B** using 1-morpholin-3-hydroxyurea (0.088 g, 0.60 mmol), aniline (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.096 g, 72%). TLC R_f = 0.20 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.57-8.52 (br s, 1H), 7.77-7.73 (br s, 1H), 7.57-7.52 (m, 2H), 7.27-7.21 (m, 2H), 6.97-6.92 (m, 1H), 3.73-3.66 (m, 4H), 2.75-2.69 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 154.7 (C), 139.4 (C), 128.4 (CH), 121.9 (CH), 118.9 (CH), 65.9 (CH₂), 55.7 (CH₂). IR (FTIR): 3344, 3221, 2949, 1668, 1532, 1108 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₁H₁₅N₃O₂Na [M+Na]⁺: 244.1062. Found: 244.1074.



1-*tert*Butyl-3,3-dibenzylaminourea: The title compound was synthesized according to a modified general procedure **3B** using 1,1-dibenzyl-3-hydroxyurea (0.094 g, 0.60 mmol), *tert*butylamine (0.13 mL, 1.20 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield a yellow oil (0.147 g, 79%). TLC R_f = 0.34 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.29 (m, 10H), 5.60-5.56 (br s, 1H), 4.92-4.89 (br s, 1H), 3.97-3.61 (br s, 4H), 1.05 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 157.0 (C), 136.1 (CH), 129.7 (CH), 128.5 (CH), 127.8 (CH), 62.3 (CH₂), 49.3 (CH₂), 28.9 (CH₃). IR (FTIR): 3396, 2963, 1668, 1531, 1361, 697 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₁₉H₂₆N₃O [M+H]⁺: 312.2077. Found: 312.2060.

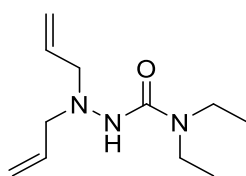


1,1-Diethyl-3,3-dibenzylaminourea: The title compound was synthesized according to general procedure **3B** using 1,1-dibenzyl-3-hydroxyurea (0.094 g, 0.60 mmol), diethylamine (0.06 mL, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (20% EtOAc/Hexanes) to yield an amorphous white solid (0.160 g, 86%). TLC R_f = 0.44 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.22 (m, 10H), 5.54-5.50 (br s, 1H), 4.21 (s, 4H), 3.05 (q, *J* = 7.1 Hz, 4H), 0.9 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 157.0 (C), 138.2 (C), 129.4 (CH), 128.2 (CH), 127.2 (CH), 59.5 (CH₂), 41.1 (CH₂), 29.7 (CH), 13.5 (CH). IR (FTIR): 3199, 3036, 2693, 2848, 1624, 1493, 1287 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₁₉H₂₅N₃O [M+H]⁺: 312.1998. Found: 312.2076.

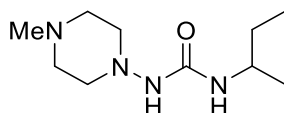


1,1-Diethyl-3,3-diisobutylaminourea: The title compound was synthesized according to general procedure **3B** using 3-hydroxy-1,1-diisobutylurea (0.146 g, 0.60 mmol), diethylamine (0.06 mL, 0.60

mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.117g, 80%). TLC R_f = 0.59 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 5.38-5.35 (br s, 1H), 3.26 (q, *J* = 7.2 Hz, 4H), 2.60 (d, *J* = 7.3 Hz, 4H), 1.72 (sept, *J* = 6.7 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃) δ 157.0 (C), 66.1 (CH₂), 41.1 (CH₂), 26.7 (CH), 20.8 (CH), 13.8 (CH). IR (FTIR): 3284, 2951, 2868, 1633, 1541, 1270 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₃H₂₉N₃O [M]⁺: 243.2311. Found 243.2309.

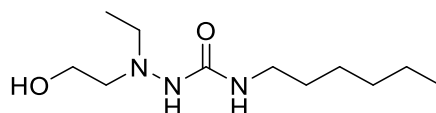


1,1-Diethyl-3,3-diallylaminourea: The title compound was synthesized according to general procedure **3B** using 1,1-diallyl-3-hydroxyurea (0.094 g, 0.60 mmol), diethylamine (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield a yellow oil (0.065 g, 52%). TLC R_f = 0.22 in 5% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃) δ 5.99-5.88 (m, 2H), 5.40-5.36 (br s, 1H), 5.25-5.15 (m, 4H), 3.50 (d, *J* = 6.7 Hz, 4H), 3.21 (q, *J* = 7.3 Hz, 4H), 1.11 (t, *J* = 7.2 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 156.9 (C), 134.1 (CH), 118.7 (CH₂), 59.7 (CH₂), 41.2 (CH₂), 13.7 (CH₃). IR (FTIR): 3241, 2971, 1630, 1547, 1270, 916 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₁H₂₂N₃O [M+H]⁺: 212.1764. Found: 212.1765.

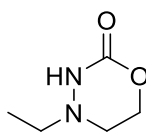


1-secButyl-3-(4-methylpiperazine)urea: The title compound was synthesized according to general procedure **3B** using 1-(4-methylpiperazine)-3-hydroxyurea (0.095 g), sec-butylamine (0.06 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to

yield an amorphous white solid (0.091g, 71%). TLC R_f = 0.30 in 10% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆, 80°C) δ 6.67-6.58 (br s, 1H), 5.88 (d, J = 6.9 Hz, 1H), 3.57 (dq, J = 8.3, 6.6 Hz, 1H), 2.71-2.64 (m, 4H), 2.44-2.36 (m, 4H), 2.19 (s, 3H), 1.43 (q, J = 7.2 Hz, 2H), 1.06 (d, J = 6.6 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 157.0 (C), 54.8 (CH₂), 54.5 (CH₂), 45.7 (CH), 45.4 (CH₃), 29.4 (CH₂), 21.0 (CH₃), 10.4 (CH₃). IR (FTIR): 3199, 2960, 2794, 1676, 1517, 1450, 1167 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₀H₂₂N₄ONa [M+Na]⁺: 237.1677. Found: 237.1691

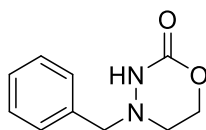


1-Hexyl-3-(2-(ethylamino)ethanol)urea: The title compound was synthesized according to general procedure **3B** using 1-(2-(ethylamino)ethanol)-3-hydroxyurea (0.088 g, 0.60 mmol), hexylamine (0.08 mL, 0.6 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.124 g, 0.600 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield a yellow oil (0.085g, 61%). TLC R_f = 0.24 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆) δ 6.69-6.65 (br s, 1H), 6.42-6.35 (m, 1H), 4.45 (t, J = 5.5 Hz, 1H), 3.46-3.36 (br s, 2H), 3.04-2.93 (m, 2H), 2.72-2.53 (br s, 4H), 1.41-1.30 (m, 2H), 1.29-1.19 (m, 6H), 0.96 (t, J = 7.1 Hz, 3H), 0.89-0.82 (m, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 159.1 (C), 60.5 (CH₂), 58.1 (CH₂), 52.1 (CH₂), 38.7 (CH₂), 31.0 (CH₂), 30.0 (CH₂), 25.9 (CH₂), 22.1 (CH₂), 13.9 (CH₃), 11.8 (CH₃). IR (FTIR): 3336, 2927, 1652, 1538, 1057 cm⁻¹. HRMS [ESI]: Exact Mass calcd for C₁₁H₂₅N₃O₂ [M+H]⁺: 232.1947. Found: 232.2031.

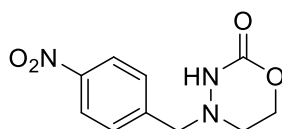


4-Ethyl-1,3,4-oxadiazin-2-one: The title compound was synthesized according to general procedure **3C** using 1-(2-(ethylamino)ethanol)-3-hydroxyurea (0.089 g, 0.60 mmol), di-*tert*-butyl dicarbonate (0.131 g, 0.60 mmol) and *N,N*-diisopropylethylamine (0.12 mL, 0.72 mmol) in MeCN (0.30 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.072 g, 94%). TLC R_f = 0.32 in 10% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 6.60-6.67 (br s, 1H), 4.50-4.46 (m, 2H), 3.21-3.18 (m, 2H), 2.86 (q, J = 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ

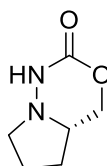
152.1 (C), 62.8 (CH₂), 51.8 (CH₂), 47.3 (CH₂), 12.2 (CH₃). IR (FTIR): 3208, 3092, 2920, 1671, 1482, 1104 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₅H₁₀N₂O₂ [M]⁺: 130.0742. Found: 130.0754.



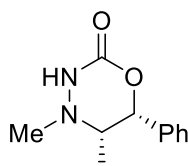
4-Benzyl-1,3,4-oxadiazin-2-one: The title compound was synthesized according to general procedure **3C** using 1-(2-(benzyl)ethanol)-3-hydroxyurea (0.126 g, 0.60 mmol), di-*tert*-butyl dicarbonate (0.131 g, 0.60 mmol) and *N,N*-diisopropylethylamine (0.12 mL, 0.72 mmol) in MeCN (0.30 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the title compound was obtained as an amorphous white solid (0.115 g, 99%). TLC R_f = 0.32 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.29 (m, 5H), 6.46-6.38 (br s, 1H), 4.57-4.50 (m, 2H), 3.97 (s, 2H), 3.25-3.18 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 152.0 (C), 135.2 (C), 129.1 (CH), 128.7 (CH), 128.1 (CH), 62.8 (CH₂), 61.7 (CH₂), 46.4 (CH₂). (FTIR): 3233, 2929, 1683, 1425, 1359, 1094 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₀H₁₂N₂O₂ [M]⁺: 192.0899. Found: 192.0897.



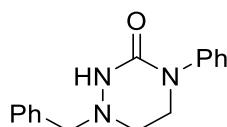
4-(4-Nitrobenzyl)-1,3,4-oxadiazin-2-one: The title compound was synthesized according to general procedure **3C** using 1-(2-(4-nitrobenzyl)ethanol)-3-hydroxyurea (0.153 g, 0.60 mmol), di-*tert*-butyl dicarbonate (0.131 g, 0.60 mmol) and *N,N*-diisopropylethylamine (0.12 mL, 0.72 mmol) in MeCN (0.30 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.056 g, 40%). TLC R_f = 0.30 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97-8.89 (br s, 1H) 8.26-8.18 (m, 2H), 7.67-7.59 (m, 2H), 4.46 (t, *J* = 5.0 Hz, 2H), 4.08 (s, 2H), 3.08 (t, *J* = 5.1 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 150.9 (C), 146.8 (C), 144.8 (C), 130.2 (CH), 123.4 (CH), 62.6 (CH₂), 59.8 (CH₂), 46.7 (CH₂). IR (FTIR): 3352, 3007, 2359, 1682, 1507, 1343 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₀H₁₁N₃O₄ [M]⁺: 237.0750. Found: 237.0723.



(5S)-Tetrahydropyrrolo[1,2-d]-1,3,4-oxadiazin-2-one: The title compound was synthesized according to general procedure **3C** using 1-(S-prolinol)-3-hydroxyurea (0.096 g, 0.60 mmol), di-*tert*-butyl dicarbonate (0.131 g, 0.6 mmol) and *N,N*-diisopropylethylamine (0.12 mL, 0.72 mmol) in MeCN (0.30 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.077 g, 90%). TLC R_f = 0.21 in 5% MeOH/CH₂Cl₂. [α]_D^{24°C}: -17 (C 0.1M, MeOH). ¹H NMR (300 MHz, CDCl₃) δ 7.03-6.61 (br s, 1H), 4.24-4.09 (m, 2H), 3.54-3.47 (m, 1H), 3.36-3.30 (m, 1H), 2.82 (q, *J* = 9.3 Hz, 1H), 2.17-2.05 (m, 1H), 1.92-1.82 (m, 2H), 1.56-1.45 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 152.4 (C), 65.7 (CH₂), 54.4 (CH₂), 52.6 (CH), 23.4 (CH₂), 20.5 (CH₂). IR (FTIR): 3196, 2952, 1674, 1418, 1364, 1053 cm⁻¹. HRMS (EI): Exact mass calcd for C₆H₁₀N₂O₂ [M]⁺: 142.0742. Found: 142.0749.



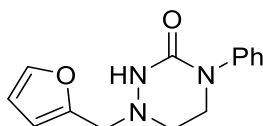
(5S,6R)-4,5-dimethyl-6-phenyl-1,3,4-oxadiazinan-2-one: The title compound was synthesized according to general procedure **3C** using 3-hydroxy-1-((1R,2S)-1-hydroxy-1-phenylpropan-2-yl)-1-methylurea (0.128 g, 0.60 mmol), di-*tert*-butyl dicarbonate (0.131 g, 0.60 mmol) and *N,N*-diisopropylethylamine (0.12 mL, 0.72 mmol) in MeCN (0.30 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.099 g, 80%). TLC R_f = 0.29 in 5% MeOH/CH₂Cl₂. [α]_D^{24°C}: -9.6 (C 0.1M, CHCl₃).²⁶³ ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.29 (m, 5H), 6.99-6.75 (br s, 1H), 5.80 (d, *J* = 2.7 Hz, 1H), 3.10 (qd, *J* = 6.9, 3.1 Hz, 1H), 2.88 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 152.0 (C), 136.2 (C), 128.6 (CH), 128.0 (CH), 125.2 (CH), 74.2 (CH), 57.0 (CH), 46.6 (CH), 11.6 (CH). IR (FTIR): 3219, 2920, 1680, 1452, 1327, 1118, 1009 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₄N₂O₂ [M]⁺: 206.1055. Found: 206.1051.



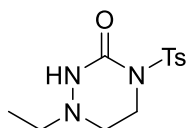
1-Benzyl-4-phenyl-1,2,4-triazin-3-one: The title compound was synthesized according to general procedure **3D** using 1-(1-benzyl-2-phenyl-ethylene-1,2-diamine)-3-hydroxyurea (0.171 g, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.129 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling

²⁶³ D. L. Trepanier, J. N. Eble, G. H. Harris, *J. Med. Chem.* **1968**, *11*, 357–360

to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (1% MeOH/CH₂Cl₂ then 2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.148 g, 92%). TLC R_f = 0.23 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.30 (m, 9H), 7.26-7.20 (m, 1H), 6.19-6.10 (br s, 1H), 4.04 (s, 2H), 3.88-3.83 (m, 2H), 3.38-3.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 154.1 (C), 142.4 (C), 136.0 (C), 129.2 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 126.1 (CH), 125.5 (CH), 61.5 (CH₂), 48.2 (CH₂), 44.4 (CH₂). IR (FTIR): 3248, 3078, 2914, 2390, 1670, 1487, 1337, 1162 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₆H₁₇N₃O [M]⁺: 267.1372. Found: 267.1366.

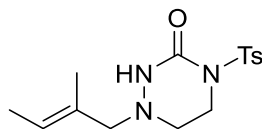


1-(Furan-2-ylmethyl)-4-phenyl-1,2,4-triazin-3-one: The title compound was synthesized according to a modified general procedure **3D** using 1-(1-(furan-2-ylmethyl)-2-phenylethane-1,2-diamine)-3-hydroxyurea (0.165 g, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.129 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 50 °C in an oil bath. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.083 g, 54%). TLC R_f = 0.14 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃) δ 7.43 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.42-7.34 (m, 4H), 7.26-7.21 (m, 1H), 6.40-6.35 (m, 2H), 6.25-6.20 (br s, 1H), 4.06 (s, 2H), 3.85-3.79 (m, 2H), 3.39-3.32 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 153.9 (C), 149.7 (C), 142.9 (CH), 142.3 (C), 129.1 (CH), 126.2 (CH), 125.5 (CH), 110.6 (CH), 109.8 (CH), 53.9 (CH₂), 48.1 (CH₂), 44.3 (CH₂). IR (FTIR): 3175, 3048, 2923, 1646, 1490, 1442, 1321 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₄H₁₅N₃O₂ [M]⁺: 257.1164. Found: 257.1151.

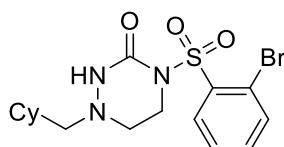


1-Ethyl-4-tosyl-1,2,4-triazin-3-one: The title compound was synthesized according to a modified general procedure **3D** using 1-(1-ethylamino)ethyl-4-methylbenzenesulfonamide)-3-hydroxyurea (0.181 g, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.129 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 50 °C in an oil bath. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.116 g, 68%). TLC R_f = 0.09 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃) δ 7.97-7.90 (m, 2H), 7.36-7.29 (m, 2H), 6.35-6.29 (br s, 1H), 4.05-3.98 (m, 2H), 3.26-3.19 (m, 2H), 2.80 (q, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 150.7 (C), 144.7 (C), 136.

(C), 129.4 (CH), 128.5 (CH), 50.8 (CH₂), 48.5 (CH₂), 41.3 (CH₂), 21.6 (CH), 12.3 (CH). IR (FTIR): 3248, 3078, 2914, 2840, 1671, 1337, 1162 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₇N₃O₃S [M]⁺: 283.0991. Found: 283.1006.

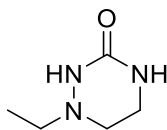


(E)-1-(2-Methylbut-2-en-1-yl)-4-tosyl-1,2,4-triazin-3-one: The title compound was synthesized according to general procedure **3D** using 1-(1-(2-methylbut-3-enamino)ethyl-4-methylbenzenesulfonamide)-3-hydroxyurea (0.205 g, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.129 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20% EtOAc/Hexanes then 30% EtOAc/Hexanes then 50% EtOAc/Hexanes) to yield an amorphous white solid (0.118 g, 61%). TLC R_f = 0.26 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃) δ 7.96-7.90 (m, 2H), 7.36-7.29 (m, 2H), 6.20-6.14 (br s, 1H), 5.49-5.37 (m, 1H), 4.03-3.96 (m, 2H), 3.24 (s, 2H), 3.20-3.12 (m, 2H), 2.44 (s, 3H), 1.66-1.58 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 150.6 (C), 144.6 (C), 136.5 (C), 130.5 (C), 129.3 (CH), 128.4 (CH), 125.4 (CH), 65.4 (CH₂), 47.7 (CH₂), 14.6 (CH₂), 21.6 (CH), 14.3 (CH), 13.4 (CH). IR (FTIR): 3200, 3077, 2918, 1667, 1340, 1162 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₅H₂₁N₃O₃S [M]⁺: 323.1304. Found: 323.1301.

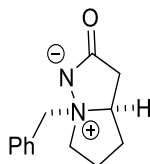


4-((2-Bromophenyl)sulfonyl)-1-(cyclohexylmethyl)-1,2,4-triazin-3-one: The title compound was synthesized according to general procedure **3D** using 1-(1-methylcyclohexylamino)ethyl-2-bromobenzenesulfonamide)-3-hydroxyurea (0.260 g, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.129 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc/Hexanes) to yield an amorphous yellow solid (0.132 g, 53%). TLC R_f = 0.40 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.04-8.96 (br s, 1H), 8.17-8.08 (m, 1H), 7.89-7.81 (m, 1H), 7.67-7.51 (m, 2H), 4.08-3.96 (m, 2H), 3.24-3.14 (m, 2H), 2.54 (d, *J* = 7.2 Hz, 2H), 1.82-1.55 (m, 5H), 1.54-1.37 (m, 1H), 1.29-1.02 (m, 3H), 0.93-0.73 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 149.5 (C), 139.7 (C), 134.9 (CH), 134.5 (CH), 132.8 (CH), 128.0 (CH), 118.6 (C), 63.0 (CH₂), 48.3 (CH₂), 40.6 (CH₂), 34.4 (CH), 30.8 (CH₂), 26.2 (CH₂), 25.4 (CH₂). IR (FTIR): 3188, 3072, 2926, 2841,

1668, 1349, 1170 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{BrN}_3\text{O}_3\text{SNa}$ $[\text{M}]^+$: 438.0463. Found: 438.0453.

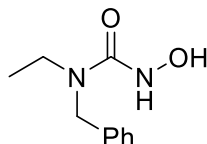


1-Ethyl-1,2,4-triazin-3-one: To a 25mL flame dried round bottom flask charged with a stir bar was added sodium (0.118 g, 5.15 mmol) then dry THF (0.3 M). The flask was purged with argon for 10 min, and naphthalene was added (0.660 g, 5.15 mmol). The reaction was stirred at room temperature for 90 minutes (or when the solution turned dark green) and then cooled to -78°C . 1-ethyl-4-tosyl-1,2,4-triazin-3-one (**7c**) (0.142 g, 0.50 mmol) was diluted in dry THF (0.25 M) and added dropwise at -78°C to the dark green solution of sodium naphthalide. The reaction was allowed to warm to room temperature and stir overnight. The reaction mixture (pale orange solution) was diluted with EtOAc (15 mL) and transferred to a separatory funnel then washed with sodium bicarbonate (1x 20 mL) and brine (1x 20 mL). The water phase was collected and concentrated under reduced pressure. The resulting mixture was diluted in CH_2Cl_2 (15 mL) and filtered. The organic phase was reduced under pressure to yield the pure compound as an amorphous white solid (0.055 g, 85 %). TLC R_f = 0.16 in 5% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.74-7.66 (br s, 1H), 6.50-6.39 (br s, 1H), 3.21 (app td, J = 5.5, 2.0 Hz, 2H), 2.90 (t, J = 5.6 Hz, 2H), 2.64 (q, J = 7.2 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 154.5 (C), 49.9 (CH_2), 47.1 (CH_2), 35.4 (CH_2), 12.4 (CH_3). IR (FTIR): 3215, 3065, 2918, 1673, 1518, 1432 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_5\text{H}_{12}\text{N}_3\text{O}$ $[\text{M}]^+$: 129.0902. Found: 129.0879.

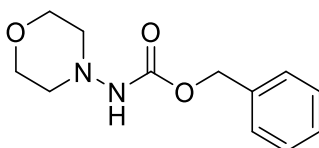


7-Benzyl-2-oxohexahydro-2H-pyrrolo[1,2-b]pyrazol-7-ium-1-ide: The title compound was synthesized according to general procedure **3D** using 1-benzyl-1-pent-4-en-3-hydroxyurea (0.140 g, 0.60 mmol), potassium carbonate (0.099 g, 0.72 mmol) and diphenyl carbonate (0.129 g, 0.60 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80°C in an oil bath. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10 % MeOH/ CH_2Cl_2 + 1 % Et_3N) to yield the title compound as a white solid (0.122 g, 94%). TLC R_f = 0.09 in 10% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3) δ 7.60-7.53 (m, 2H), 7.49-7.39 (3H), 4.59 (d, J = 12.2 Hz, 1H), 4.34-4.18 (m, 2H), 3.85-3.75 (m, 1H), 3.53-3.42 (m, 1H), 2.42-2.26 (m, 2H), 2.25-2.11 (m, 2H), 2.03-1.82 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 178.7 (C), 132.4 (CH), 130.1 (CH), 129.0 (C), 128.9 (CH), 70.8 (CH), 69.8 (CH_2), 66.8 (CH_2),

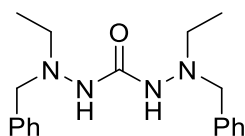
40.9 (CH₂), 32.8 (CH₂), 23.2 (CH₂). IR (FTIR): 2960, 2945, 1610, 1592, 1576, 1396, 1386, 1310 cm⁻¹. HRMS (ESI): exact mass calcd for C₁₃H₁₆N₂O₂Na⁺ [M + Na]⁺: 239.1160; found 239.1161.



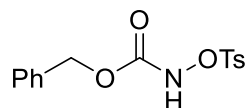
1-Benzyl-1-ethyl-3-hydroxyurea: The title compound was synthesized according to general procedure **3A** using phenyl *N*-hydroxycarbamate (0.842 g, 5.50 mmol), Et₃N (0.14 mL, 1.0 mmol) and *N*-ethylbenzylamine (0.74 mL, 5.0 mmol) in THF (0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂ then 5% MeOH/CH₂Cl₂). The title compound was obtained as orange oil (0.809 g, 83%). TLC R_f: 0.13 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.27 (m, 3H), 7.26-7.20 (m, 2H), 7.08-6.99 (br s, 1H), 6.84-6.78 (br s, 1H), 4.46 (s, 2H), 3.35 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 161.7 (C), 137.0 (C), 129.1 (CH), 127.9 (CH), 127.2 (CH), 49.6 (CH₂), 42.0 (CH₂), 13.1 (CH₃). IR (FTIR): 3233, 2927, 1634, 1490, 1529, 1261 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₀H₁₄N₂O₂ [M]⁺: 194.1055. Found: 194.1050.



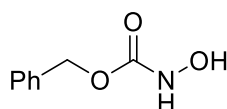
Benzyl morpholinocarbamate: The title compound was synthesized according to a modified general procedure **3B** using 1-morpholin-3-hydroxyurea (0.073 g, 0.50 mmol), benzyl alcohol (1.00 mL, 10.0 mmol), *N,N*-diisopropylethylamine (0.10 mL, 0.60 mmol) and), di-*tert*-butyl dicarbonate (0.109 g, 0.50 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and heated for 24 h at 80 °C in an oil bath. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40% EtOAc/Hexanes) to yield a yellow oil (0.080 g, 68%). TLC R_f = 0.31 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃) δ 7.47-7.28 (m, 5H), 5.79-5.65 (br s, 1H), 5.15 (s, 2H), 3.85-3.74 (m, 4H), 2.90-2.78 (m, 4H). ¹³C NMR (100 MHz/CDCl₃) δ 155.1 (C), 137.0 (C), 128.7 (CH), 128.4 (CH), 128.4 (CH), 67.1 (CH₂), 66.6 (CH₂), 56.5 (CH₂). IR (FTIR): 3227, 3056, 2864, 1698, 1540, 1256 cm⁻¹. HMRS C₁₂H₁₆N₂O₃Na [M+Na]⁺: 259.1059. Found: 259.1049.



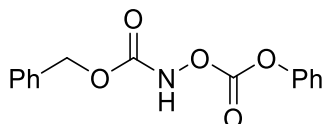
N'-2-Dibenzyl-N'-diethylhydrazine-1-carbohydrazide: The title compound was synthesized according to general procedure **3C** using 1-benzyl-1-ethyl-3-hydroxyurea (0.097 g, 0.50 mmol), 9-fluorenmethanol (0.098 g, 0.50 mmol), potassium carbonate (0.083 g, 0.60 mmol) and diphenylcarbonate (0.107 g, 0.500 mmol) in MeCN (0.3 M). The vial was sealed, placed in an ice bath and purged with Argon for 10 min. The reaction was heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂ + 1% Et₃N) to yield an orange oil (0.064 g, 85%). TLC R_f: 0.25 in 5% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆, 70°C) δ 7.30-7.16 (m, 10H), 6.72-6.64 (br s, 2H), 3.70 (s, 4H), 2.60 (q, *J*= 7.1 Hz, 4H), 0.85 (t, *J*= 7.1 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 159.3 (C), 128.4 (CH), 127.5 (C), 127.2 (CH), 126.2 (CH), 60.6 (CH₂), 50.1 (CH₂), 11.2 (CH₃). IR (FTIR): 3200, 2970, 1747, 1672, 1492, 1247 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₉H₂₆N₄ONa [M+Na]⁺: 349.2005. Found: 349.2027.



Benzyl (tosyloxy)carbamate: The title compound was synthesized according to a literature procedure.²⁶⁴ ¹H NMR (300 MHz, CDCl₃) δ 7.87-7.77 (m, 2H), 7.39-7.15 (m, 7H), 5.02 (s, 2H), 2.43 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 155.4 (C), 146.2 (C), 134.7 (C), 130.3 (C), 129.8 (CH), 129.7 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 68.8 (CH₂), 22.0 (CH). The ¹H NMR and ¹³C NMR is in agreement with previous reports.



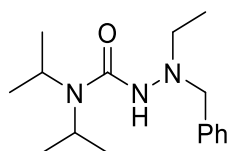
Benzyl hydroxycarbamate: The title compound was synthesized according to a literature procedure.²⁶⁵ ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.31 (m, 5H), 7.26-7.22 (br s, 1H), 6.67-6.33 (br s, 1H), 5.18 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 159.1 (C), 135.5 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 68.1 (CH₂). The ¹H NMR and ¹³C NMR is in agreement with previous reports.



²⁶⁴ Masruri; Willis, A. C.; McLeod, M. D. *J. Org. Chem.* **2012**, 77, 8480-8491.

²⁶⁵ Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, 132, 12862 – 12864.

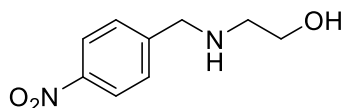
Benzyl ((phenoxycarbonyl)oxy)carbamate: The title compound was synthesized according to a literature procedure²⁶⁶ using benzyl *N*-hydroxycarbamate (0.778 g, 4.80 mmol), phenyl chloroformate (0.60 mL, 4.8 mmol) and Et₃N (0.67 mL, 4.8 mmol) in CH₂Cl₂ (0.3 M). The reaction was allowed to stir at room temperature overnight. Upon completion, H₂O was added and the reaction mixture was extracted with CH₂Cl₂. The organic layer was recollected and washed with NaHCO₃, and then the organic phase was recollected again and washed with brine. The organic phase was dried over Na₂SO₄ (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under and the title compound was isolated using flash chromatography (10% AcOEt/Hexanes) to yield an amorphous white solid (0.523 g, 36%). TLC R_f: 0.72 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 8.04-7.99 (br s, 1H), 7.44-7.33 (m, 7H), 7.32-7.27 (m, 1H), 7.22-7.15 (m, 2H), 5.27 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 156.3 (C), 154.0 (C), 151.0 (C), 134.9 (C), 129.9 (CH), 128.9 (CH), 128.9 (CH), 128.6 (CH), 126.9 (CH), 120.7 (CH), 68.9 (CH₂). IR (FTIR): 3207, 2964, 1803, 1715, 1466, 1195 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₅H₁₃NO₅Na⁺ [M+Na]⁺: 310.0692. Found: 310.0711.



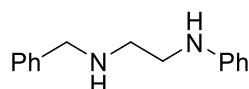
2-Benzyl-2-ethyl-*N,N*-diisopropylhydrazine-1-carboxamide: The title compound was synthesized according to a modified procedure **3B** using 1-benzyl-1-ethyl-3-hydroxyurea (0.582 g, 3.00 mmol), diisopropylamine (0.84 mL, 6.00 mmol), imidazole (0.041 g, 0.06 mmol) and diphenyl carbonate (0.642 g, 3.00 mmol) in MeCN (0.3 M). The vial was sealed with a microwave cap and purged with Ar for 10 min. The reaction mixture was heated for 24 h at 80 °C in an oil bath. After cooling to room temperature, the reaction was diluted with EtOAc (5 mL) and washed with an aqueous solution of sodium bicarbonate (1 x 0.5 mL). The organic phase was dried over MgSO₄, filtered and concentrated. The title compound was purified by column chromatography (2% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.313 g, 35%). TLC R_f: 0.72 in 2% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.20 (m, 5H), 5.15-5.03 (br s, 1H), 4.07 (s, 2H), 3.76 (hept, *J* = 7.2 Hz, 2H), 2.96 (q, *J* = 7.1 Hz, 2H), 1.19-1.05 (m, 15H). ¹³C NMR (75 MHz, CDCl₃) δ 157.5 (C), 137.8 (C), 129.9 (CH), 128.4 (CH), 127.4 (CH), 60.4 (CH₂), 50.8 (CH₂), 45.3 (CH), 21.3 (CH), 13.0 (CH). IR (FTIR): 3289, 3238, 2966, 2931, 1629, 1543, 1451, 1325 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₂₇N₃O₂Na⁺ [M+Na]⁺: 300.2052. Found: 300.2065.

Extra compounds

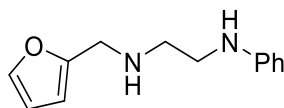
²⁶⁶ Allen, M. A.; Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M. *Org. Lett.* **2017**, *19*, 6574-6577.



2-((4-nitrobenzyl)amino)ethanol: The title compound was synthesized according to a literature procedure.²⁶⁷ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17-8.12 (m, 2H), 7.61-7.55 (m, 2H), 4.45 (t, *J* = 5.4 Hz, 1H), 3.80 (s, 2H), 3.43 (q, *J* = 5.7 Hz, 2H), 2.52 (t, *J* = 5.8 Hz, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 150.1 (C), 146.7 (C), 129.3 (CH), 123.7 (CH), 60.9 (CH₂), 52.6 (CH₂), 51.5 (CH₂). The ¹H NMR and ¹³C NMR is in agreement with previous reports.



N-Benzyl-N'-phenylethane-1,2-diamine: The title compound was synthesized according to a literature procedure.²⁶⁸ ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.30 (m, 4H), 7.31-7.23 (m, 1H), 7.22-7.12 (m, 2H), 6.1 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.67-6.60 (m, 2H), 3.82 (s, 2H), 3.24 (dd, *J* = 6.5, 5.1 Hz, 2H), 3.00-2.84 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 148.6 (C), 140.2 (C), 129.3 (CH), 128.6 (CH), 128.2 (CH), 127.2 (CH), 117.5 (CH), 113.1 (CH), 53.7 (CH₂), 48.1 (CH₂), 43.6 (CH₂). The ¹H NMR and ¹³C NMR is in agreement with previous reports.

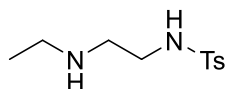


N-(Furan-2-ylmethyl)-N'-phenylethane-1,2-diamine: To a solution of *N*-phenylethylenediamine (1.30 mL, 10.0 mmol) in CH₂Cl₂ (0.3 M) was added 2-furancarboxyl chloride (0.99 mL, 10.0 mmol) and Et₃N (1.39 mL, 10.0 mmol) at 0°C and the solution was allowed to stir at room temperature overnight. Upon completion, the reaction was extracted with NaHCO₃ (20 mL x1), and then brine (20 mL x1). The organic phase was collected and dried with MgSO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-(2-anilinoethyl)furan-2-carboxamide, which could be used in the next step without further purification. To the crude *N*-(2-anilinoethyl)furan-2-carboxamide (2.30 g, 10.0 mmol) was added dry THF (0.3 M) and the solution was cooled to 0°C. To this was added lithium aluminum hydride (0.873 g, 23.0 mmol) portion wise and the reaction was allowed to stir at 0°C for 15 min and then at reflux overnight. The excess of lithium aluminum hydride was quenched by a Fisser work-up (0.90 mL of H₂O, 0.90 mL of NaOH 2M and 2.7 mL of H₂O) at 0°C. The solution was filtered to remove the aluminium-lithium salt.

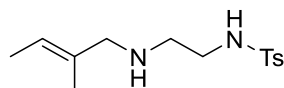
²⁶⁷ R. C. Foitzik, N. Choi, B.J. Morrow, C.F. Hemley, G.E. Lunniss, M. A. Camerino, D. Ganame, P.A. Stupple, R. Lessene, W. J. A. Kersten, A. J. Harvey, I. P. Holmes. Cancer Therapeutics CRC PTY Limited. WO2014/26242 A1, February 20, 2104.

²⁶⁸ Y. Ota, S. Miyamura, M. Araki, Y. Itoh, S. Yasuda, M. Masuda, T. Taniguchi, Y. Sowa, T. Sakai, K. Itami, J. Yamaguchi, T. Suzuki, *Bioorg. Med. Chem.* **2018**, 26, 775-785.

Solvent was removed and the title compound was purified by column chromatography (30 % EtOAc/Hexanes) to yield colourless oil (1.07, 49%). TLC R_f = 0.67 in 10% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.38 (dd, J = 1.7, 0.8 Hz, 1H), 7.23-7.15 (m, 2H), 6.76-6.68 (m, 1H), 6.68-6.62 (m, 2H), 6.33 (dd, J = 3.1, 1.9 Hz, 1H), 6.20 (dd, J = 3.1, 0.6 Hz, 1H), 3.8 (s, 2H), 3.26-3.20 (m, 2H), 2.93-2.86 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 153.7 (C), 148.3 (C), 141.8 (CH), 129.1 (CH), 117.3 (CH), 112.8 (CH), 110.0 (CH), 106.9 (CH), 47.6 (CH₂), 45.7 (CH₂), 43.3 (CH₂). IR (FTIR): 3373, 3050, 2836, 1601, 1504, 1462, 1146 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₃H₁₆N₂O [M]⁺: 216.2363. Found: 216.1268.



***N*-(2-(ethylamino)ethyl)-4-methylbenzenesulfonamide:** The title compound was synthesized according to a literature procedure.²⁶⁹ ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.35 (m, 2H), 7.36-7.27 (m, 2H), 2.98 (dd, J = 6.9, 4.5 Hz, 2H), 2.69 (dd, J = 6.4, 4.7 Hz, 2H), 2.50 (s, 3H), 2.58-2.44 (m, 2H), 1.10-0.93 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 143.5 (C), 137.0 (C), 129.8 (CH), 127.3 (CH), 47.8 (CH₂), 43.5 (CH₂), 42.5 (CH₂), 21.7 (CH), 15.4 (CH). The ¹H NMR and ¹³C NMR is in agreement with previous reports.

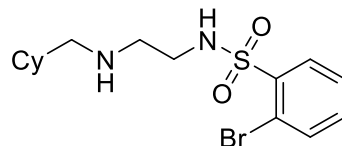


***N*-(2-Methylbut-3-enamino)ethyl-4-methylbenzenesulfonamide:** To a solution of ethylenediamine (3.34 mL, 50.0 mmol) in CH₂Cl₂ (0.3 M) was added tosyl chloride (1.91 g, 10.0 mmol) portion wise at room temperature and the solution was allowed to stir for 3 h. Upon completion, the reaction was extracted with NaHCO₃ (20 mL x1), and then brine (20 mL x1). The organic phase was collected and dried with MgSO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-tosylethylenediamine, which could be used in the next step without further purification.

To the crude *N*-tosylethylenediamine (2.14 g, 10.0 mmol) was added CH₂Cl₂ (0.3 M) and the solution was cooled to 0°C. To this was added (E)-methylbut-2-enal (0.97 mL, 10.0 mmol) and the reaction was allowed to warm to room temperature and stir for 8 h. Sodium cyanoborohydride (1.78 g, 47.0 mmol) and a catalytic amount of acetic acid were added and the reaction was stirred at room temperature overnight. Water was added and the reaction was extracted with NaHCO₃ (20 mL x1), and then brine (20 mL x1). The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure. The title compound was purified by column chromatography (10% MeOH/CH₂Cl₂) to yield an amorphous yellow solid (1.85 g, 65%). TLC R_f = 0.61 in 10% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃) δ 7.80-7.72 (m, 2H), 7.35-7.28 (m, 2H), 5.38-5.23 (m, 1H), 3.04-2.93 (m, 4H), 2.70-2.61 (m,

²⁶⁹ F. Cheng, J. J. Soldevila-Barreda, I. Romero-Canelón, J. P. C. Coverdale, J.-I. Song, G. J. Clarkson, J. Kasparkova, A. Habtemariam, V. Brabec, J. A. Wolny, V. Schünemann, P. J. Sadler, *Dalton Trans.*, **2018**, 47, 7178-7189.

2H), 2.43 (s, 3H), 1.61-1.54 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.3 (C), 136.8 (C), 133.4 (C), 129.6 (CH), 127.1 (CH), 121.2 (CH), 56.7 (CH_2), 46.7 (CH_2), 42.2 (CH_2), 21.5 (CH), 14.3 (CH), 13.2 (CH). IR (FTIR): 3277, 2918, 2859, 1446, 1322, 1155 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 282.1402. Found: 282.1409.



***N*-(1-Methylcyclohexylamino)ethyl-4-methylbenzenesulfonamide:** To a solution of ethylenediamine (3.34 mL, 50.0 mmol) in CH_2Cl_2 (0.3 M) was added *o*-bromobenzenesulfonyl chloride (2.56 g, 10.0 mmol) portion wise at room temperature and the solution was allowed to stir for 3 h. Upon completion, the reaction was extracted with NaHCO_3 (20 mL x1), and then brine (20 mL x1). The organic phase was collected and dried with MgSO_4 . The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-(*o*-bromobenzenesulfonyl)ethylenediamine, which could be used in the next step without further purification.

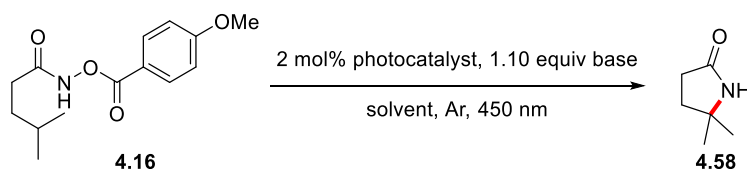
To the crude *N*-(*o*-bromobenzenesulfonyl)ethylenediamine (2.30 g, 8.32 mmol) was added CH_2Cl_2 (0.3 M) and the solution was cooled to 0°C . To this was added cyclohexanecarbaldehyde (1.00 mL, 8.32 mmol) and the reaction was allowed to warm to room temperature and stir for 24 h. Sodium cyanoborohydride (1.48 g, 39.1 mmol) and a catalytic amount of acetic acid were added and the reaction was stirred at room temperature overnight. Water was added and the reaction was extracted with NaHCO_3 (20 mL x1), and then brine (20 mL x1). The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure. The title compound was purified by column chromatography (2% MeOH/ CH_2Cl_2 then 10% MeOH/ CH_2Cl_2) to yield a yellow oil (2.55 g, 82%). TLC R_f = 0.67 in 10% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3) δ 8.16 (dd, J = 7.4, 2.1 Hz), 7.74 (dd, J = 7.6, 1.4 Hz, 1H), 7.50-7.30 (m, 2H), 3.00-2.91 (m, 2H), 2.74-2.63 (m, 2H), 2.34 (d, J = 6.6 Hz, 2H), 1.78-1.60 (m, 5H), 1.49-1.08 (m, 4H), 0.99-0.80 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 138.7 (C), 135.0 (CH), 133.6 (CH), 131.7 (CH), 127.7 (CH), 119.8 (C), 55.9 (CH_2), 47.9 (CH_2), 42.5 (CH_2), 38.0 (CH), 31.3 (CH_2), 26.6 (CH_2), 26.0 (CH_2). IR (FTIR): 3311, 2920, 2848, 1447, 1329, 1160 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{23}\text{BrN}_2\text{O}_2\text{SNa}$ $[\text{M}+\text{Na}]^+$: 397.0561. Found: 397.0545.

4. Supporting information for Chapter 4

6.4.1. Optimization tables

- Substitution/cyclization cascade reaction

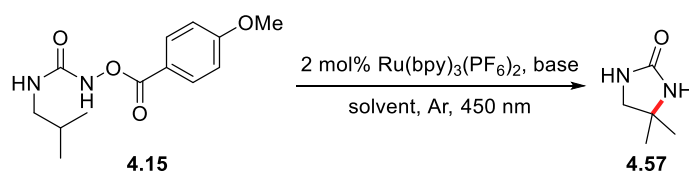
Table S4.1. C-H activation via photoinduced reactions of *N*-((4-methoxybenzoyl)oxy)-4-methylpentanamide **4.16**



Entry	Base	Photocatalyst	Solvent	%Conversion 4.16	% 4.58
1	Et ₃ N	Ru(bpy) ₃ (PF ₆) ₂	MeCN	80	<10
2	<i>i</i> -Pr ₂ NEt	Ru(bpy) ₃ (PF ₆) ₂	MeCN	80	22
3	DABCO	Ru(bpy) ₃ (PF ₆) ₂	MeCN	100	28
4	DMAP	Ru(bpy) ₃ (PF ₆) ₂	MeCN	100	0
5	<i>N</i> -Methylmorpholine	Ru(bpy) ₃ (PF ₆) ₂	MeCN	100	42
6	Trifluoroethylamine	Ru(bpy) ₃ (PF ₆) ₂	MeCN	0	0
7	Hexamine	Ru(bpy) ₃ (PF ₆) ₂	MeCN	7	5
8	Imidazole	Ru(bpy) ₃ (PF ₆) ₂	MeCN	0	0
9	<i>N</i> -Methylmorpholine	Ru(bpy) ₃ (PF ₆) ₂	PhCF ₃	<5	<5
10	<i>N</i> -Methylmorpholine	Ru(bpy) ₃ (PF ₆) ₂	CDCl ₃	<5	<5
11	<i>N</i> -Methylmorpholine	Ru(bmp) ₃	MeCN	<5	<5
12	<i>N</i> -Methylmorpholine	Ir(dtbpy)(ppy) ₂	MeCN	<5	<5
13	<i>N</i> -Methylmorpholine	Ir(dF-CF ₃ -ppy) ₂ (dtbpy)	MeCN	<5	<5
14	<i>N</i> -Methylmorpholine	Ir(dF-CF ₃ -ppy) ₂ (ppy)	MeCN	<5	<5

Conditions: *N*-((4-methoxybenzoyl)oxy)-4-methylpentanamide **4.16** (1.00 equiv), photocatalyst (2 mol%), additive (1.10 equiv) in solvent (0.3M) irradiated under inert atmosphere with 450 nm blue LED. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

Table S4.2. C-H activation via photoinduced reactions of 1-isobutyl-3-((4-methoxybenzoyl)oxy)urea **4.15**



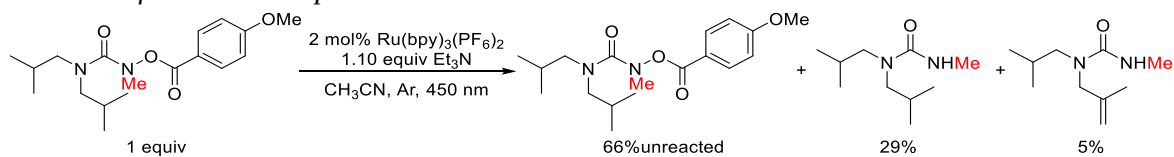
Entry	Base (equiv)	Solvent	Temp °C	%Product
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1	Et ₃ N (1.10 equiv)	MeCN	r.t.	0
2	Phosphate (5 mol%)	CH ₂ Cl ₂	r.t.	18
3	Phosphate (5 mol%)	CH ₂ Cl ₂	40	45
4	Phosphate (5 mol%)	CH ₂ Cl ₂	60	50
5	Phosphate (5 mol%)	CH ₂ Cl ₂	80	17

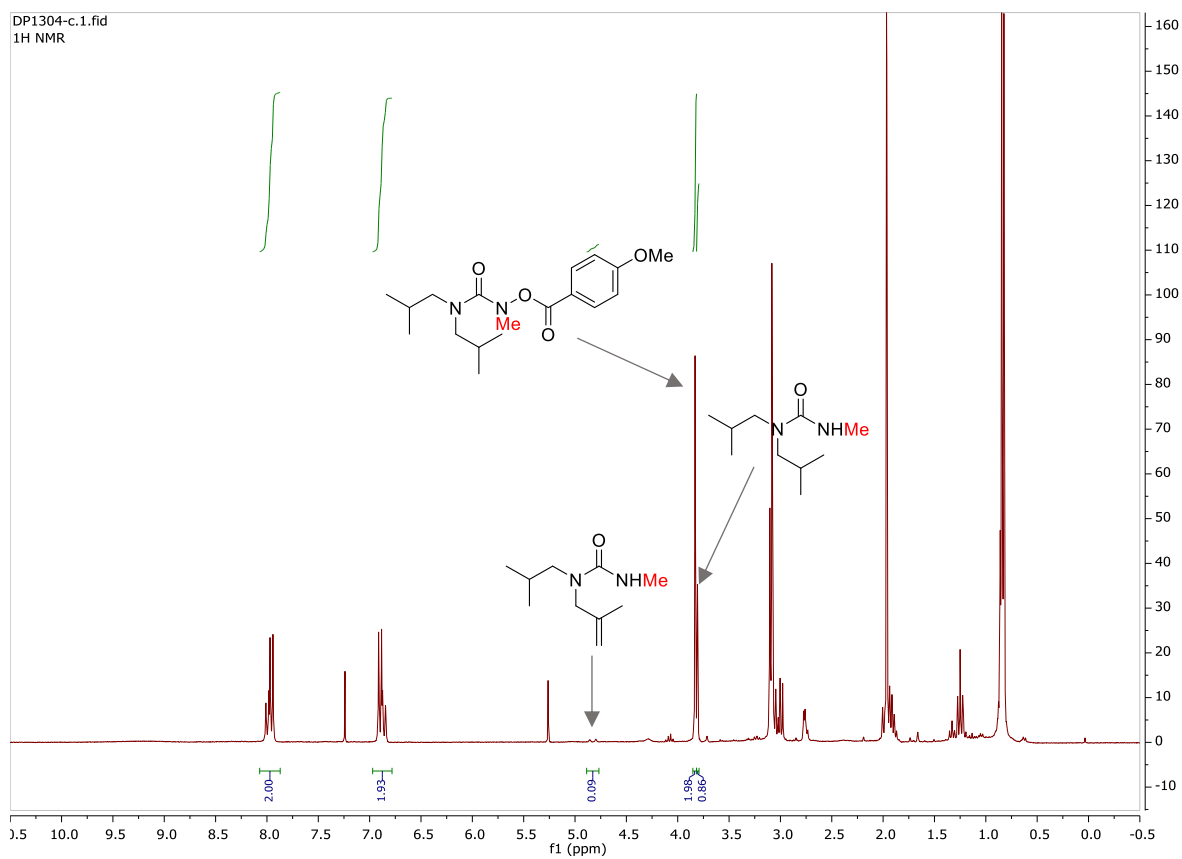
Conditions: 1-isobutyl-3-((4-methoxybenzoyl)oxy)urea **4.15** with 450 nm blue LED. NMR yields are shown using 1,3,5-trimethoxybenzene as internal standard.

6.4.2 Mechanistic study

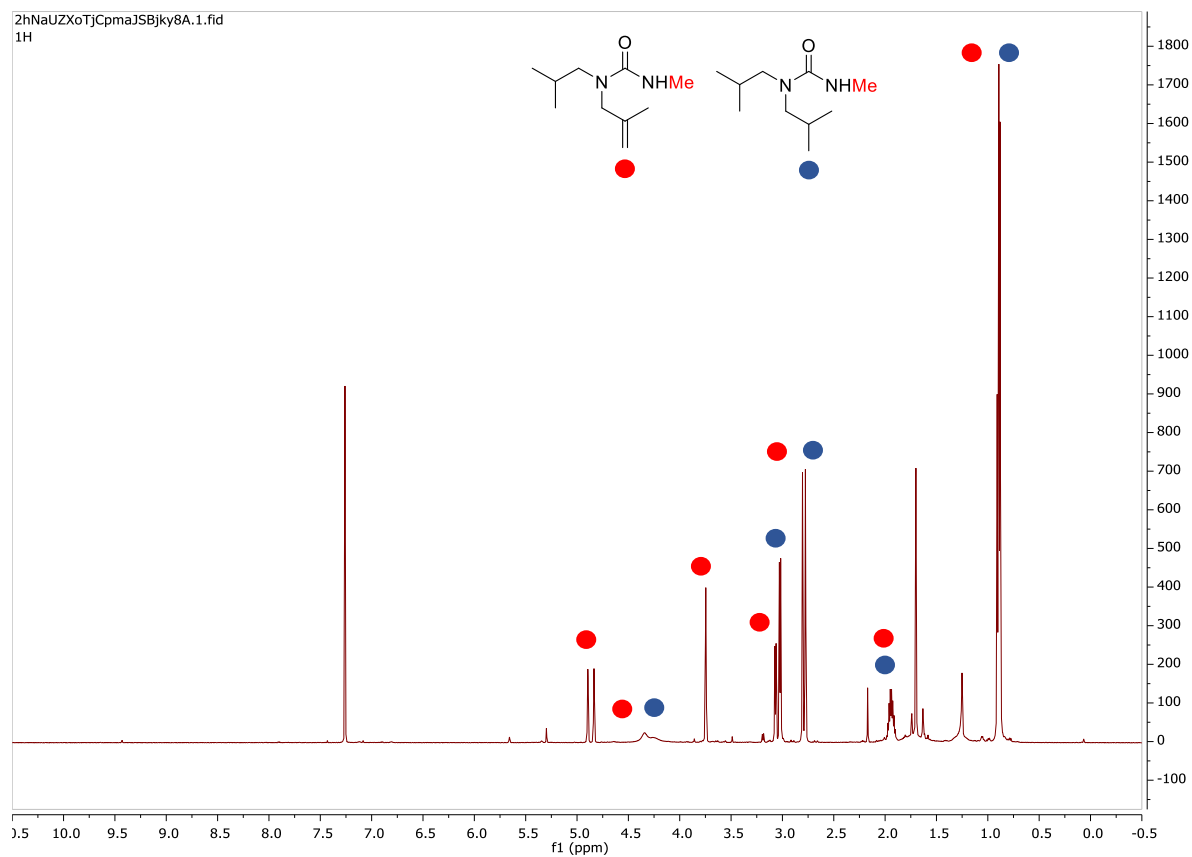
- NMR of the urea side-products

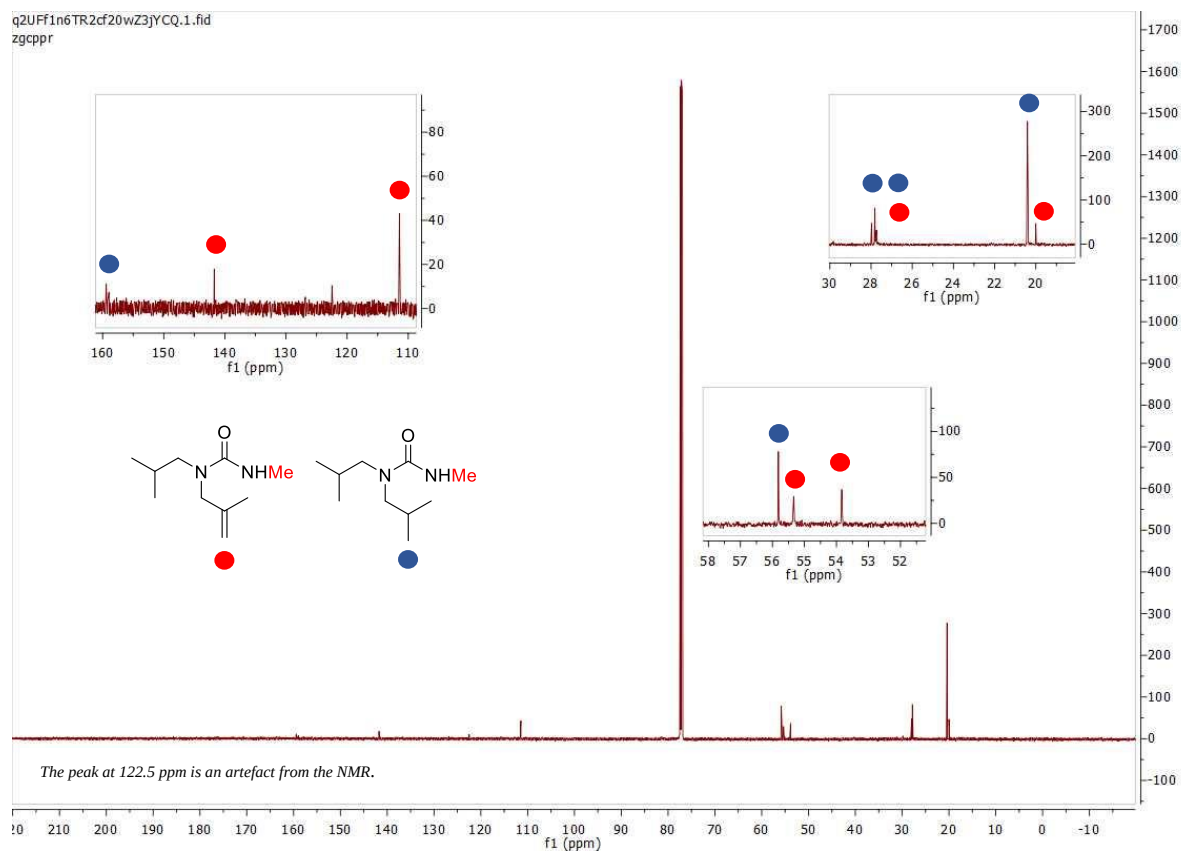


Crude NMR

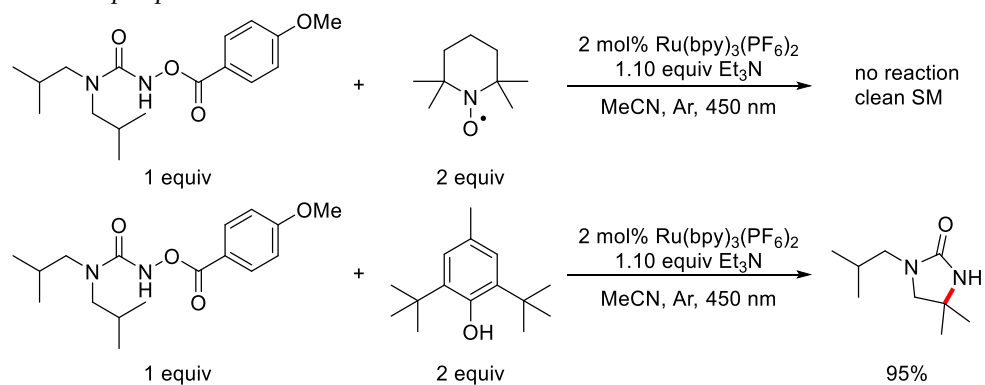


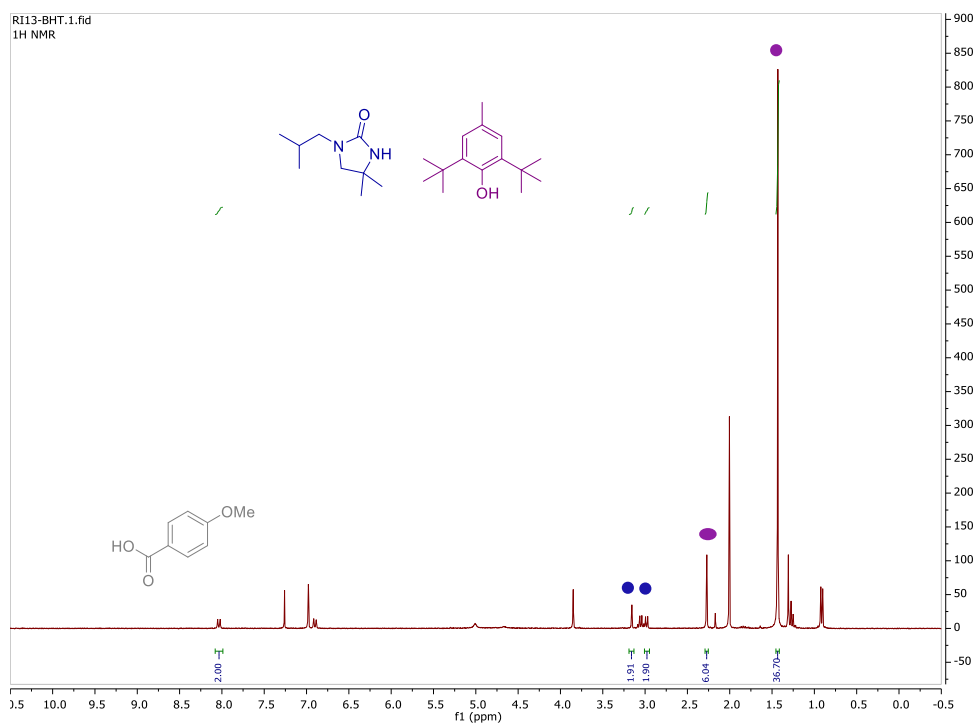
NMR of the two ureas





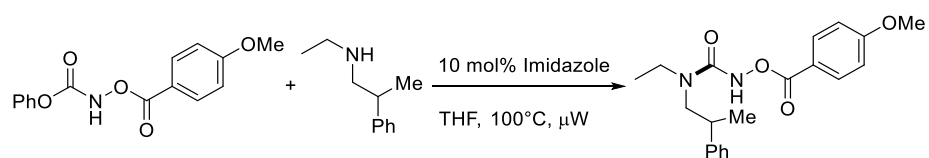
- Radical trap experiments



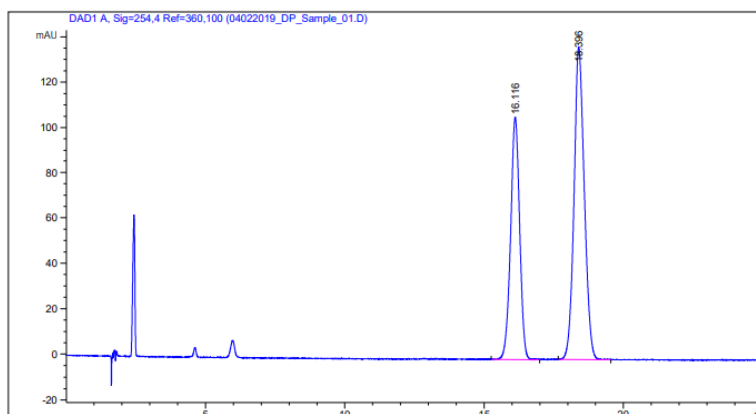


6.4.3. Chiral HPLC for compound **4.19**

*HPLC spectrum of racemic 1-(2-hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.19***

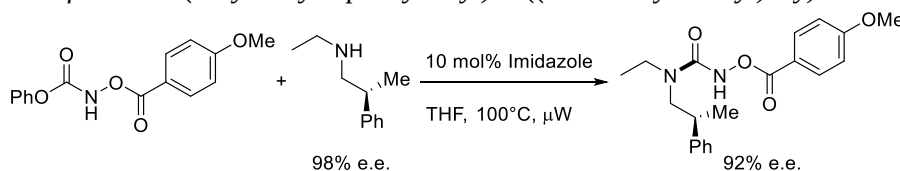


Sample Info : SFC IB, 5% *MeOH 200 bar/60 degC, colTemp 40 degC, 2.0 mL/min

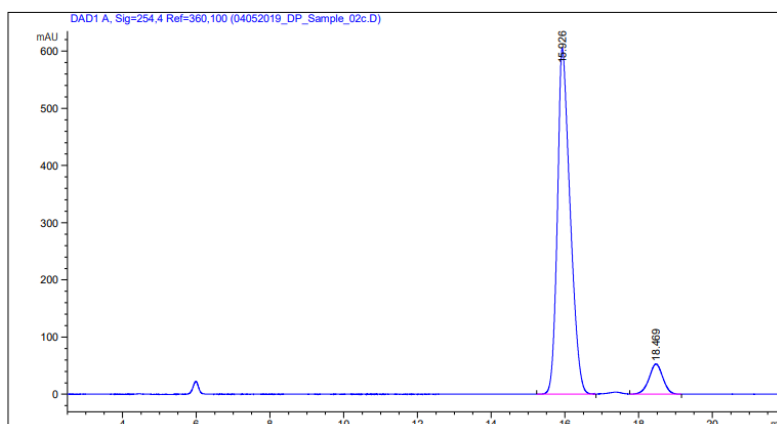


#	Time	Area	Height	Width	%
1	16.116	2402.9	106.9		40.4366
2	18.396	3539.2	137.9		59.5634

HPLC spectrum of chiral 1-(2-hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.19'**



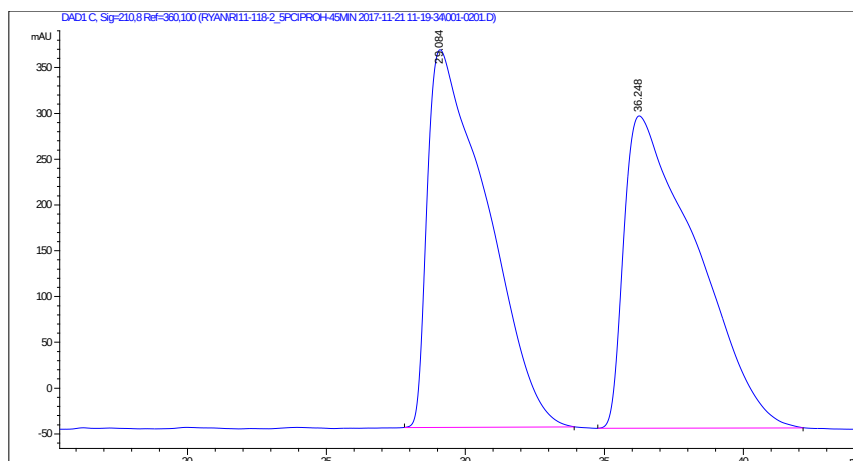
Sample Info : SFC IB, 5% *MeOH 200 bar/60 degC, colTemp 40 degC, 2.0 mL/min



#	Time	Area	Height	Width	%
1	15.926	14526.3	604.9		91.3709
2	18.469	1371.9	52.9		8.6291

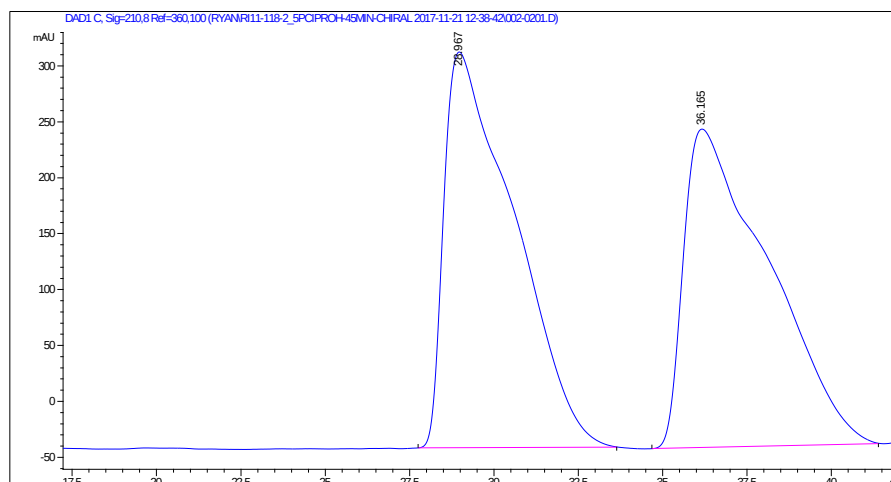
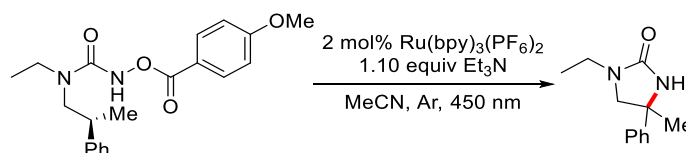
HPLC spectrum of C-H activation of racemic 1-(2-hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.61**





#	Time	Area	Height	Width	%
1	29.084	61505.5	412.4		49.893
2	36.248	61769.7	341		50.107

HPLC spectrum of C-H activation of chiral 1-(2-hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.61'**



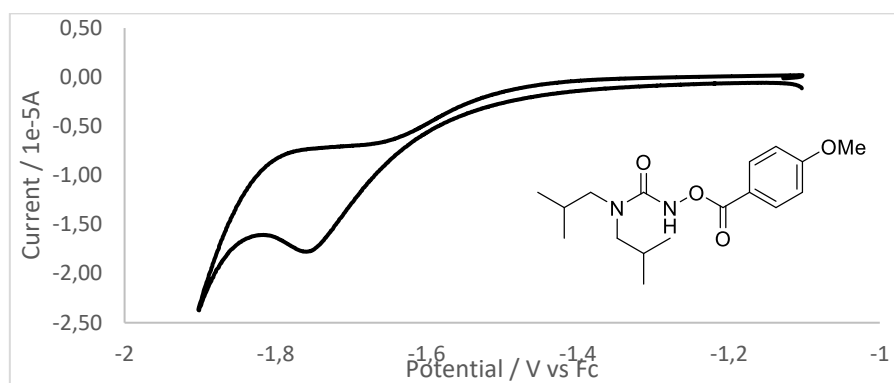
#	Time	Area	Height	Width	%
1	28.967	51326.1	354		50.790
2	36.165	49730.3	284.8		49.210

6.4.4 Cyclic voltammetry

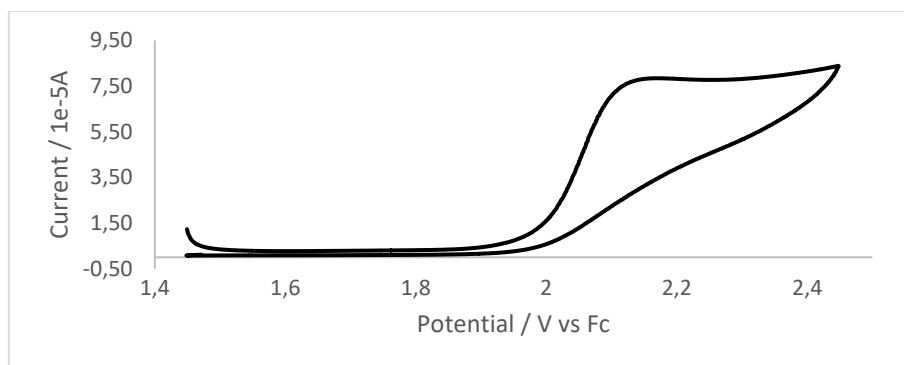
Cyclic voltammetry was performed using a Princeton Applied Research Versastat 3 potentiostat employing a glass cell and platinum auxiliary wires for the counter and pseudo-reference electrodes, where a 1.6 mm platinum disk electrode was used for the working electrode. The measurements were

carried out in CH₃CN solutions (dried by J. C. Meyer solvent system and stored over molecular sieves) containing 0.1 M tetrabutylammonium hexafluorophosphate (Sigma Aldrich) as supporting electrolyte with a scan rate of 100 mV/s. The experiments were referenced to the Fc/Fc⁺ redox couple of ferrocene (Sigma Aldrich).

*Cyclic voltammetry of 3-(benzoyloxy)-1,1-dipropylurea **4.11***

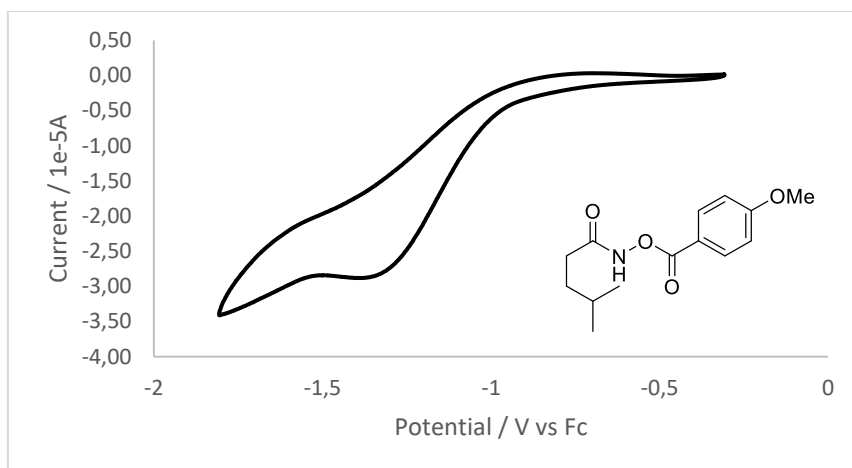


Irreversible reduction at -1.75V vs Fc⁺/Fc.

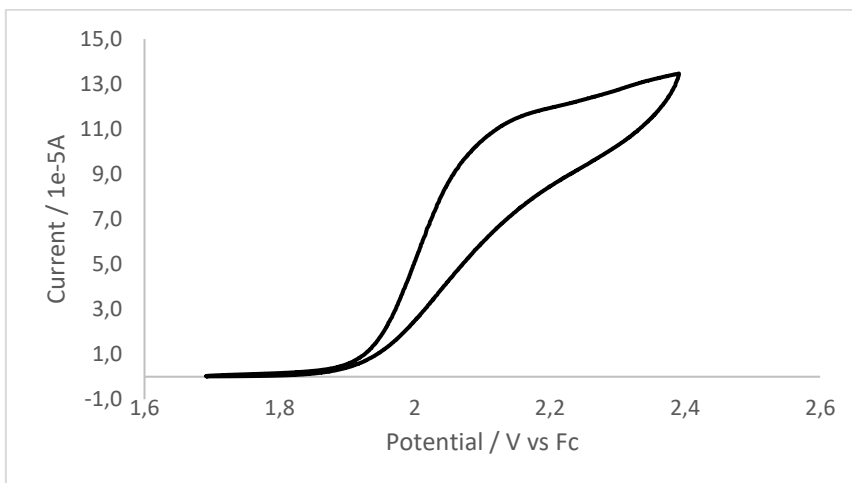


Irreversible oxidation at +2.15V vs Fc⁺/Fc.

*Cyclic voltammetry of N-((4-methoxybenzoyl)oxy)-4-methylpentanamide **4.16***



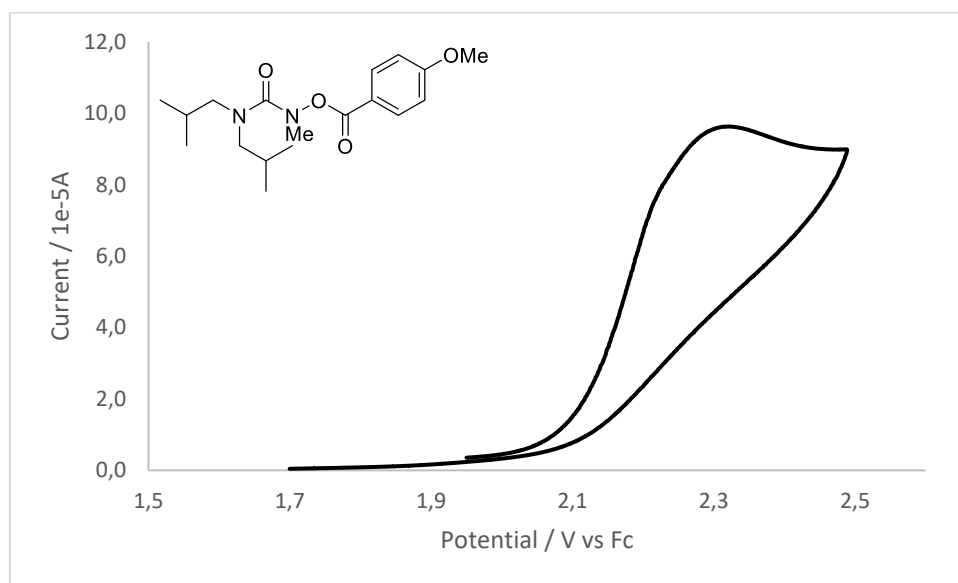
Irreversible reduction at -1.36 vs Fc^+/Fc



Irreversible oxidation at +2.13 vs Fc^+/Fc

Cyclic voltammetry of 1,1-diisobutyl-3-((4-methoxybenzoyl)oxy)-3-methylurea **4.94**

No reduction was observed at potential -2.3 V vs Fc^+/Fc .



Irreversible oxidation at +2.30 vs Fc^+/Fc

6.4.5 Characterizations

General procedures

General Procedure 4A: Synthesis of *N*-oxyureas via carbamoyl chloride formation

To a clean 50 mL round bottom flask charged with a stir bar was added the amine (1.00 equiv.) then PhMe (0.8 M) to which was added KOH pellets (1.00 equiv.) and water (2.9 M). A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes at 0°C. Phosgene (15% in toluene) (2.30 equiv.) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0°C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na_2SO_4 . The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude carbamoyl chloride which was used in the next step without further purification.

To the crude carbamoyl chloride was added CH_2Cl_2 (0.30 M) and cooled to 0°C. To this was added hydroxylamine hydrochloride (1.00 equiv.), and followed immediately by Et_3N (2.00 equiv.). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO_3 (5 mL x1), and then brine (5 mL x1). The organic phase was collected and

dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-hydroxyurea, which could be used in the next step without further purification.

To the crude *N*-hydroxyurea was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (1.00 equiv.) followed immediately by addition of *p*-methoxybenzoylchloride (1.00 equiv.). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-oxyurea which was be recrystallized or purified by silica gel chromatography.

General Procedure 4B: Synthesis of hydroxamic acids²⁷⁰

To a clean 50 mL round bottom flask charged with a stir bar was added the carboxylic acid (1.00 equiv.), then CH₂Cl₂ (0.07 M) and cooled to 0°C. To this was added oxalyl chloride (2.00 equiv.) and DMF (2 drops) and the reaction was allowed to stir for an additional 2.5 to 4 hours at room temperature. Upon completion, the crude reaction was evaporated under reduced pressure to provide the crude hydroxamic acid which was used in the next step without further purification.

To a clean 50 mL round bottom flask charged with a stir bar was added the hydroxylamine hydrochloride (1.20 equiv.), then a 2:1 mixture of EtOAc and H₂O (0.08 M) and cooled to 0°C. To this was added K₂CO₃ (2.00 equiv.) and the crude hydroxamic acid was added dropwise. The reaction was allowed to stir for 12 hours at room temperature. Upon completion, the reaction was separated and extracted twice with EtOAc (20 mL x2). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-oxyurea which was be recrystallized or purified by silica gel chromatography.

General Procedure 4C: Synthesis of *N*-*p*-methoxybenzoylhydroxamic acid

To a clean 50 mL round bottom flask charged with a stir bar was added the pure hydroxamic acid (1.00 equiv.), then CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (1.00 equiv.) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (1.00 equiv.). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x2), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under

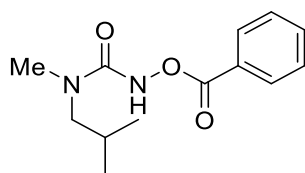
²⁷⁰ Hong, S.Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M.-H.; Chang, S. *Science* **2018**, 359, 1016.

reduced pressure to provide the crude *N*-*p*-methoxybenzoylhydroxamic acid which was be recrystallized or purified by silica gel chromatography.

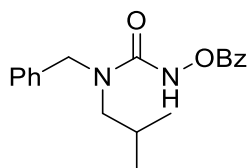
General Procedure 4D: Photoinduced C-H amination of *N*-oxyureas

To a 8 mL Kimax glass vial charged with a stir bar was added the *N*-oxyurea (1.00 equiv.), then MeCN (0.2m), to which was added tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (2 mol%), and then triethylamine (1.10 equiv.). The vial was closed with Teflon screw cap and was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm form the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by silica gel chromatography.

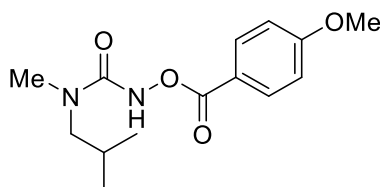
Synthesis and characterizations



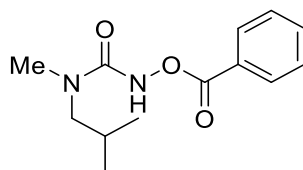
3-(Benzoyloxy)-1-isobutyl-1-methylurea: The title compound was synthesized according to general procedure **2D** using phenyl benzoyloxycarbamate **2.3** (1.29 g, 5.00 mmol), and *N*-methylisobutylamine (0.60 mL, 5.00 mmol) and imidazole (0.034 g, 0.5 mmol) in THF (16.7 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Et₂O) to yield the title compound as a colourless oil (1.05 g, 84%). TLC R_f: 0.30 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.54-8.43 (br s., 1H), 8.17-8.10 (m, 2H), 7.67-7.58 (m, 1H), 7.53-7.44 (m, 2H), 3.17 (d, *J* = 7.7 Hz, 2H), 3.02 (s, 3H), 2.04-1.97 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 157.9 (C), 134.0 (CH), 129.9 (CH), 128.6 (CH), 127.1 (C), 56.6 (CH₂), 34.6 (CH), 27.2 (CH), 20.0 (CH). IR (FTIR): 3269, 2657, 1747, 167, 1489, 1243 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₈N₂O₃Na [M+Na]⁺: 273.1317. Found: 273.1302.



3-(benzoyloxy)-1-benzyl-1-isobutylurea: The title compound was synthesized according to general procedure **2D** using phenyl benzoyloxycarbamate **2.3** (0.630 g, 2.45 mmol), and *N*-benzyl-2-methylpropan-1-amine (0.400 g, 2.45 mmol) and imidazole (0.017 g, 0.3 mol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 4 h at 100 °C. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in hexanes and then recrystallized in Et₂O/hexanes. The solid was then filtered and washed with hexanes to give pure product. The title compound was obtained as a crystalline white solid (0.763 g, 78%). M.p.: 140.1-140.4 °C. TLC R_f: 0.55 in 25% EtOAc/Hexanes. ¹H NMR (300 MHz; CDCl₃): δ 8.50-8.40 (1H, br. s.), 8.18-8.08 (2H, m), 7.67-7.57 (1H, m), 7.53-7.27 (7H, m), 4.61 (2H, s), 3.20 (2H, d, *J* = 6 Hz), 2.09 (1H, sept, *J* = 6 Hz), 0.99 (6H, d, *J* = 6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 158.3 (C), 136.4 (C), 134.0 (CH), 129.9 (CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 127.1 (CH), 127.0 (C), 54.6 (CH₂), 50.6 (CH₂), 27.3 (CH), 20.2 (CH). IR (FTIR): 3106, 2955, 1756, 1645, 1495, 1232 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₉H₂₂N₂O₃Na [M+Na]⁺: 349.1528. Found: 349.1515.

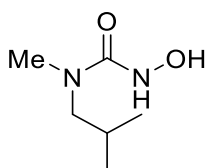


1-Isobutyl-3-((4-methoxybenzoyl)oxy)-1-methylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-methyl-isobutylamine (0.262 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (10% EtOAc/Hexanes, 33% EtOAc/Hexanes) to yield the title compound as an amorphous white solid (0.800 g, 95%). TLC R_f: 0.36 in 40% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 8.50-8.37 (br s, 1H), 8.12-7.99 (m, 2H), 7.04-6.86 (m, 2H), 3.85 (s, 3H), 3.14 (d, *J* = 10.7 Hz, 2H), 2.98 (s, 3H), 1.98 (dq, *J* = 13.8, 6.9 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 166.9 (C), 164.3 (C), 158.1 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 56.7 (CH₃), 55.6 (CH₃), 51.4 (CH₂), 34.9 (CH₂), 27.4 (CH), 20.1 (CH₃). IR (FTIR): 3158, 3005, 2959, 1751, 1663, 1604, 1507, 1315, 1249, 1159 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₄H₂₀N₂NaO₄⁺ [M+Na]⁺: 303.1315. Found: 303.1325.

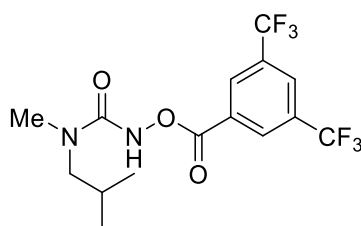


3-(Benzoyloxy)-1-isobutyl-1-methylurea: The title compound was synthesized according to general procedure **2D** using phenyl benzoyloxycarbamate **2.3** (1.29 g, 5.00 mmol), and *N*-methylisobutylamine

(0.60 mL, 5.00 mmol) and imidazole (0.034 g, 0.5 mmol) in THF (16.7 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Et₂O) to yield the title compound as a colourless oil (1.05 g, 84%). TLC R_f: 0.30 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.54-8.43 (br s., 1H), 8.17-8.10 (m, 2H), 7.67-7.58 (m, 1H), 7.53-7.44 (m, 2H), 3.17 (d, *J* = 7.7 Hz, 2H), 3.02 (s, 3H), 2.04-1.97 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 157.9 (C), 134.0 (CH), 129.9 (CH), 128.6 (CH), 127.1 (C), 56.6 (CH₂), 34.6 (CH), 27.2 (CH), 20.0 (CH). IR (FTIR): 3269, 2657, 1747, 167, 1489, 1243 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₈N₂O₃Na [M+Na]⁺: 273.1317. Found: 273.1302.

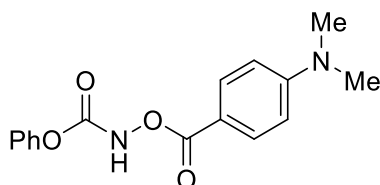


1-Isobutyl-1-methyl-3-hydroxyurea: The title compound was synthesized according to general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.841 g, 5.50 mmol), and *N*-methylisobutylamine (0.436 g, 5.00 mmol) and Et₃N (0.14 mL, 1.0 mmol) in THF (16.6 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (2% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.530 g, 73%). TLC R_f: 0.12 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.07-6.95 (br s, 1H), 6.86-6.77 (br s, 1H), 3.09 (d, *J* = 7.6 Hz, 2H), 2.89 (s, 3H), 2.02-1.86 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 161.8 (C), 56.2 (CH₂), 34.1 (CH₃), 27.2 (CH), 19.9 (CH₃). IR (FTIR): 3220, 2956, 1615, 1521, 1386, 1287, 1108 cm⁻¹. HRMS (EI): Exact mass calcd for C₆H₁₄N₂O₂ [M]⁺: 146.1055. Found: 146.1040.

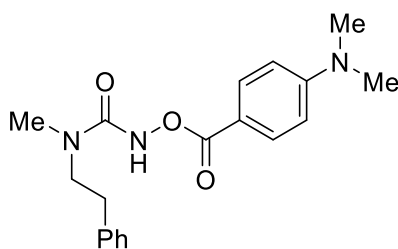


3-((3,5-Bistrifluoromethylbenzoyl)oxy)-1-isobutyl-1-methylurea: The title compound was synthesized according to general procedure **2A** using the pure 1-isobutyl-1-methyl-3-hydroxyurea (0.530 g, 3.60 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (0.50 mL, 3.60 mmol) followed immediately by dropwise addition of 3,5-bis(trifluoromethyl)benzoyl chloride (0.65 mL, 3.60 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude which was purified by flash column chromatography (20% EtOAc/Hexanes). The title compound was obtained as an

amorphous white solid (0.831 g, 60%). TLC R_f : 0.94 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 8.58-8.56 (br s, 2H), 8.43-8.41 (br s, 1H), 8.14-8.11 (br s, 1H), 3.17 (d, J = 7.4 Hz, 2H), 3.03 (s, 3H), 2.07-1.95 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 164.7 (C), 157.3 (C), 132.5 (C, q, J = 23 Hz), 130.0 (CH, m), 129.5 (C), 127.3 (CH, m), 122.6 (C, d, J = 203 Hz), 56.6 (CH₂), 34.6 (CH), 27.1 (CH), 19.9 (CH₃). IR (FTIR): 2697, 1767, 1664, 1221, 1127, 697 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₅H₁₆N₂O₃F₆Na [M+Na]⁺: 409.0963. Found: 409.0983.

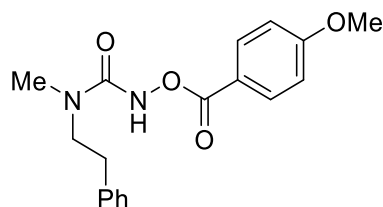


Phenyl (4-(dimethylamino)benzoyl)oxycarbamate: The title compound was synthesized according to a literature procedure²⁵⁷ using phenyl *N*-hydroxycarbamate (1.53 g, 10.0 mmol), *p*-*N,N*-dimethylbenzoylchloride (1.83 g, 10.0 mmol) and Et₃N (1.36 mL, 10.0 mmol) in CH₂Cl₂ (0.30 M). The reaction was allowed to stir at room temperature overnight. Upon completion, H₂O was added and the reaction mixture was extracted with CH₂Cl₂. The organic layer was recollected and washed with NaHCO₃, and then the organic phase was recollected again and washed with brine. The organic phase was dried over Na₂SO₄ (stirring for 15 minutes). Solids were filtered and the filtrate was collected and concentrated under reduced pressure to yield an amorphous white solid (2.79 g, 93%). TLC R_f : 0.75 in 50% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 8.60-8.51 (br s, 1H), 8.03-7.95 (m, 2H), 7.43-7.35 (m, 2H), 7.27-7.17 (m, 3H), 6.71-6.64 (m, 2H), 3.08 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 166.0 (C), 155.0 (C), 154.1 (C), 150.3 (C), 131.9 (CH), 129.5 (CH), 126.0 (CH), 121.3 (CH), 112.2 (C), 110.8 (CH), 40.0 (CH₃). IR (FTIR): 3223, 2916, 1722, 1611, 1478, 1206 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₁₆N₂O₄Na⁺ [M+Na]⁺: 323.1008. Found: 323.1010.

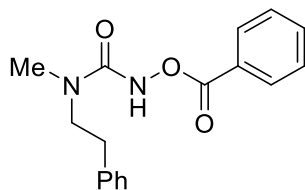


3-((4-(Dimethylamino)benzoyl)oxy)-1-methyl-1-phenethylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-(dimethylamino)benzoyl)oxycarbamate (0.900 g, 3.00 mmol), and *N*-methyl-2-phenylethanamine (0.406 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and upon dilution in Et₂O precipitated from solution providing a pale yellow amorphous solid (0.860 g, 84%). TLC R_f : 0.21 in 33% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 8.35 (s, 1H), 7.95 (d, J = 9.2 Hz, 2H), 7.32-7.20 (m, 5H), 6.63 (d, J =

9.2 Hz, 2H), 3.54 (dd, $J = 8.1, 6.9$ Hz, 2H), 3.04 (s, 6H), 2.92-2.87 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.1 (C), 158.2 (C), 154.1 (C), 138.8 (C), 131.9 (CH), 128.9 (CH), 128.8 (CH), 126.6 (CH), 113.2 (C), 110.9 (CH), 51.4 (CH₂) 40.0 (CH₃), 34.8 (CH₃), 34.2 (CH₂). IR (FTIR): 3287, 2623, 1687, 1598, 1460, 1265, 1171 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{NaO}_3^+$ $[\text{M}+\text{Na}]^+$: 364.1632. Found: 364.1639.

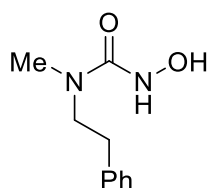


3-((4-Methoxybenzoyl)oxy)-1-methyl-1-phenethylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate (0.862 g, 3.00 mmol), and *N*-methyl-2-phenylethanamine (0.406 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Hexanes $\rightarrow$ 40% EtOAc/Hexanes) to yield the title compound as an amorphous off-white solid (0.896 g, 91%). TLC R_f : 0.22 in 33% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 8.30 (br s, 1H), 8.07 (d, $J = 9.0$ Hz, 2H), 7.34-7.21 (m, 5H), 6.94 (d, $J = 9.0$ Hz, 2H), 3.87 (s, 3H), 3.56 (t, $J = 7.4$ Hz, 2H), 2.93-2.89 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.6 (C), 164.3 (C), 157.9 (C), 138.7 (C), 132.2 (CH), 129.0 (CH), 128.9 (CH), 126.7 (CH), 119.4 (C), 114.0 (CH), 55.6 (CH₃), 51.4 (CH₂), 34.9 (CH₃), 34.3 (CH₂). IR (FTIR): 3302, 3065, 2972, 2934, 1737, 1702, 1602, 1508, 1456 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$: 351.1315. Found: 351.1321.

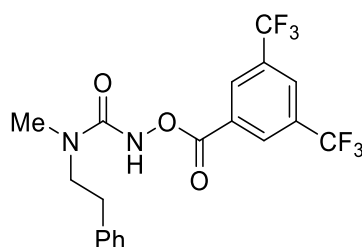


3-(Benzoyloxy)-1-methyl-1-phenethylurea: The title compound was synthesized according to general procedure **2D** using phenyl benzoyloxycarbamate **2.3** (0.772 g, 3.00 mmol), and *N*-methyl-2-phenylethanamine (0.406 mg, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (16.7 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.841 g, 95%). TLC R_f : 0.35 in 33% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 8.25 (s, 1H), 8.11-8.08 (m, 2H), 7.63-7.57 (m, 1H), 7.48-7.43 (m, 2H), 7.33-7.28 (m, 2H), 7.23-7.19 (m, 3H), 3.56 (t, $J = 7.4$ Hz, 2H), 2.92-2.88 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.9 (C), 157.7 (C), 138.7 (C), 134.1 (C), 130.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH),

127.3 (C), 126.8 (CH), 51.5 (CH₂), 34.9 (CH₃), 34.3 (CH₂). IR (FTIR): 3257, 3071, 3027, 2948, 1750, 1672, 1485, 1253, 1079 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₇H₁₈N₂NaO₃⁺ [M+Na]⁺: 321.1210. Found: 321.1215.

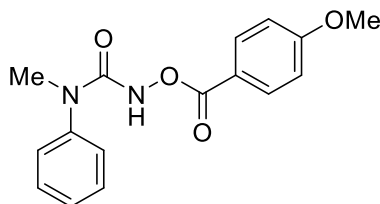


1-methyl-1-phenethyl-3-hydroxyurea: The title compound was synthesized according to general procedure **2B** using phenyl *N*-hydroxycarbamate **2.1** (0.337 g, 2.20 mmol), and *N*-methyl-*N*-phenethylamine (0.270 g, 2.20 mmol) and Et₃N (0.6 mL, 0.4 mmol) in THF (6.0 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (1% MeOH/CH₂Cl₂ → 5% MeOH/CH₂Cl₂). The title compound was obtained as an amorphous white solid (0.321 g, 83%). TLC R_f: 0.15 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.30 (m, 2H), 7.29-7.23 (m, 1H), 7.22-7.18 (m, 2H), 6.43-6.38 (br s, 1H), 6.30-6.23 (br s, 1H), 3.52 (t, *J* = 7.1 Hz, 2H), 2.90-2.83 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ 161.5 (C), 138.5 (C), 128.9 (CH), 128.8 (CH), 126.9 (CH), 50.6 (CH₂), 34.1 (CH₂), 33.9 (CH₃). IR (FTIR): 3326, 3023, 2924, 1645, 1491, 1390, 1296 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₀H₁₄N₂O₂Na [M+Na]⁺: 217.0948. Found: 217.0926.

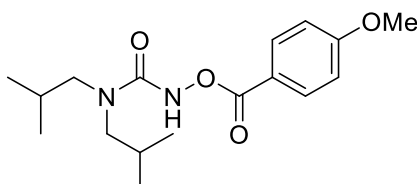


3-((3,5-Bistrifluoromethylbenzoyl)oxy)-1-methyl-1-phenethylurea: The title compound was synthesized according to the general procedure **2A** using the pure 1-methyl-1-phenethyl-3-hydroxyurea (0.321 g, 1.66 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (0.23 mL, 1.66 mmol) followed immediately by dropwise addition of 3,5-bis(trifluoromethyl)benzoyl chloride (0.30 mL, 1.66 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude which was purified by flash column chromatography (20% EtOAc/Hexanes). The title compound was obtained as an amorphous white solid (0.370 g, 46%). TLC R_f: 0.97 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 8.56-8.53 (br s, 2H), 8.14-8.11 (br s, 1H), 8.10-8.06 (br s, 1H), 7.38-7.32 (m, 2H), 7.30-7.23 (m, 3H), 3.60 (t, *J* = 7.2 Hz, 2H), 2.96-2.89 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): δ 164.3 (C), 157.0

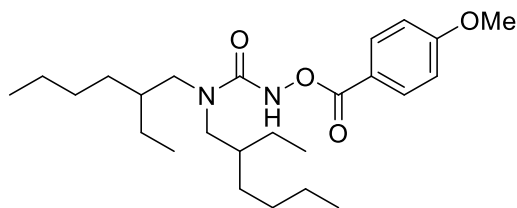
(C), 138.4 (C), 132.5 (C, q, $J = 26$ Hz), 130.0 (CH), 129.5 (C), 128.9 (CH), 128.8 (CH), 127.3 (CH, m), 126.8 (CH), 122.7 (C, d, $J = 203$ Hz), 51.3 (CH₂), 34.7 (CH), 34.1 (CH₂). IR (FTIR): 3208, 1774, 1670, 1497, 1279, 1121 cm⁻¹. HRMS (ESI): Exact mass calcd for C₉H₁₆F₆N₂O₃Na [M+Na]⁺: 457.0963. Found: 457.0954.



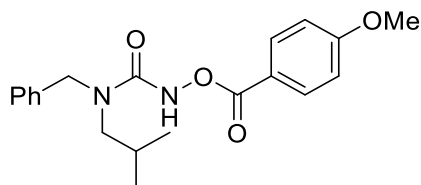
3-((4-Methoxybenzoyl)oxy)-1-methyl-1-phenylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-methyl aniline (0.325 mL, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.896 g, 91%). TLC R_f: 0.22 in 33% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.07 (br s, 1H), 8.03-7.99 (m, 2H), 7.49-7.36 (m, 5H), 6.92 (d, $J = 9.0$ Hz, 2H), 3.85 (s, 3H), 3.32 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.6 (C), 164.3 (C), 157.2 (C), 141.5 (C), 132.2 (CH), 130.4 (CH), 128.5 (CH), 127.2, (CH), 119.4 (C), 114.0 (CH), 55.6 (CH₃), 38.0 (CH₃). IR (FTIR): 3307, 2936, 1693, 1596, 1453, 1249 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₁₆N₂NaO₄⁺ [M+Na]⁺ 323.1011. Found: 323.1108.



1-Diisobutyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N,N*-diisobutylamine (0.388 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.940 g, 97%). TLC R_f: 0.28 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.51 (br s, 1H), 8.07-8.04 (m, 2H), 6.93-6.90 (m, 2H), 3.84 (s, 3H), 3.12 (d, $J = 7.6$ Hz, 4H), 2.04 (dq, $J = 13.7, 6.9$ Hz, 2H), 0.93 (d, $J = 6.7$ Hz, 12H). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 164.3 (C), 158.3 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.5 (CH₃), 55.0 (CH₂), 27.2 (CH), 20.2 (CH₃). IR (FTIR): 3186, 2954, 2870, 1748, 1655, 1605, 1509, 1484, 1316, 1242 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₇H₂₆N₂NaO₄⁺ [M+Na]⁺: 345.1785. Found: 345.1799.

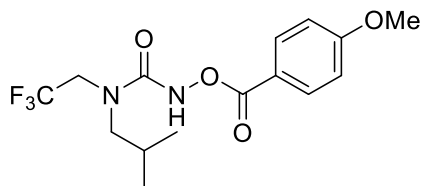


3-((4-Methoxybenzoyl)oxy)-1,1-bis(2-methylhexyl)urea: The title compound was synthesized according to a modified general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.639 g, 3.00 mmol), and bis(2-ethylhexyl)amine (0.640 g, 2.65 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (10% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.917 g, 85%). TLC R_f : 0.40 in 10% EtOAc/Hexanes. ^1H NMR (300 MHz, $\text{DMSO-}d_6$): δ 10.21-10.18 (br s, 1H), 7.99-7.91 (m, 2H), 7.14-7.04 (m, 2H), 3.86 (s, 3H), 3.21-3.01 (m, 4H), 1.76-1.58 (m, 2H), 1.36-1.12 (m, 16H), 0.94-0.76 (m, 12H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 165.5 (C), 163.4 (C), 158.4 (C), 131.9 (CH), 120.4 (C), 114.7 (CH), 56.1 (CH), 49.5 (CH_2), 49.5 (CH_2), 37.1 (CH), 30.2 (CH_2), 28.6 (CH_2), 23.6 (CH_2), 23.0 (CH_2), 14.4 (CH_3), 11.0 (CH_3). IR (FTIR): 3177, 2959, 2925, 1756, 1658, 1509, 1241 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{25}\text{H}_{42}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$: 457.3043. Found: 457.3058.



1-Benzyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and benzyl-2-methylpropan-1-amine (0.490 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/hexanes) to yield the title compound as an amorphous off-white solid (0.930 g, 87%). TLC R_f : 0.28 in 20% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 8.43 (br s, 1H), 8.06 (d, J = 9.0 Hz, 2H), 7.40-7.30 (m, 6H), 6.93 (d, J = 9.0 Hz, 2H), 4.59 (s, 2H), 3.86 (s, 3H), 3.17 (d, J = 7.5 Hz, 2H), 2.07 (dq, J = 13.7, 6.9 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.7 (C), 164.2 (C), 158.5 (C), 136.5 (C), 132.1 (CH), 129.0 (CH), 127.8 (CH), 127.1 (CH), 119.4 (C), 113.9 (CH), 55.5 (CH_3), 54.6 (CH_2), 27.4 (CH), 20.2 (CH_3). IR (FTIR): 3116, 2959, 2840, 1751, 1647, 1603,

1509, 1419, 1315, 1238 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{NaO}_4^+$ $[\text{M}+\text{Na}]^+$: 379.1628. Found: 379.1634.

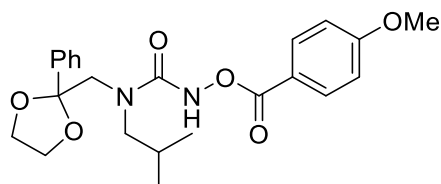


1-Isobutyl-3-((4-methoxybenzoyl)oxy)-1-(2,2,2-trifluoroethyl)urea: The title compound was synthesized according to general procedure **4A** using *N*-propylaniline (1.55 g, 10.00 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.00 mmol), and water (2.9 M) at 0°C . A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0°C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na_2SO_4 . The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude isobutyl(2,2,2-trifluoroethyl)carbamic chloride which was used in the next step without further purification.

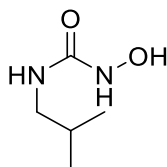
To the crude isobutyl(2,2,2-trifluoroethyl)carbamic chloride was added CH_2Cl_2 (0.30 M) and cooled to 0°C . To this was added hydroxylamine hydrochloride (0.691 g, 10.00 mmol), and followed immediately by Et_3N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO_3 (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na_2SO_4 . The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-propylanilinehydroxyurea, which could be used in the next step without further purification.

To the crude 3-hydroxy-1-isobutyl-1-(2,2,2-trifluoroethyl)urea was added CH_2Cl_2 (0.30 M) and cooled to 0°C . To this was added Et_3N (1.39 mL, 10.0 mmol) followed immediately by addition of *p*-methoxybenzoylchloride (1.70 g, 10.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO_3 (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na_2SO_4 . The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-(2,2,2-trifluoroethyl)urea which was purified by recrystallization with Et_2O to yield a white crystalline solid (2.43 g, 70% over 3 steps). TLC R_f : 0.57 in 33% EtOAc/Hexanes.

M.p.: 105.8-106.2 °C. ^1H NMR (400 MHz, CDCl_3): δ 8.66 (br s, 1H), 8.07 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 4.01 (q, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.26 (d, J = 7.7 Hz, 2H), 2.13 (dsept, J = 13.7, 6.9 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.4 (C), 164.4 (C), 158.1 (C), 132.2 (CH), 124.5 (q, J = 278 Hz, C), 118.9 (C), 114.0 (CH), 55.5 (CH_3), 55.3 (CH_2), 48.1 (q, J = 34 Hz, CH_2), 27.1 (CH), 19.9 (CH_3). IR (FTIR): 3144, 2971, 2889, 2360, 1749, 1660, 1606, 1249, 1160, 1143 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{F}_3\text{N}_2\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 371.1188. Found: 371.1195.

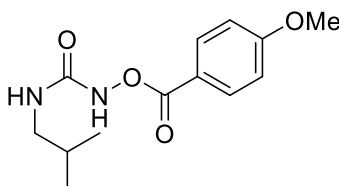


1-Isobutyl-1-(2-phenyl-1,3-dioxolan-2-yl)isobutyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.574 g, 2.00 mmol), and isobutylamine (0.470 g, 2.00 mmol) and imidazole (0.014 g, 0.6 mmol) in THF (6.60 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (10% EtOAc/Hexanes). The title compound was obtained as an amorphous pale orange solid (0.770 g, 90%). TLC R_f : 0.24 in 20% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 10.28-10.21 (br s, 1H), 8.16-8.07 (m, 2H), 7.58-7.51 (m, 2H), 7.45-7.32 (m, 3H), 7.00-6.90 (m, 2H), 4.30-4.23 (m, 2H), 3.96-3.85 (m, 5H), 3.75-3.65 (br s, 2H), 3.33-3.21 (d, J = 6.9 Hz, 2H), 2.18-2.01 (m, 1H), 0.88 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.8 (C), 163.9 (C), 159.5 (C), 139.9 (C), 132.0 (CH), 128.8 (CH), 128.5 (CH), 125.7 (CH), 119.9 (C), 113.8 (CH), 110.6 (C), 65.4 (CH_2), 56.7 (CH_2), 55.4 (CH), 54.0 (CH_2), 26.8 (CH), 20.1 (CH_3). IR (FTIR): 3221, 2941, 1740, 1691, 1468, 1257 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_6\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 451.1845. Found: 451.1825.

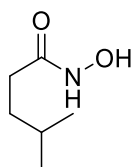


1-Isobutyl-3-hydroxyurea: The title compound was synthesized according to a modified general procedure **2A** using phenyl *N*-hydroxycarbamate **2.1** (0.765 g, 5.00 mmol), and *N*-isobutylamine (2.48 mL, 25.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) in THF (16.6 mL, 0.30 M). The vial was sealed with a microwave cap and heated for 16 h at 70 °C via an oil bath heating. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/ CH_2Cl_2 then 7% MeOH/ CH_2Cl_2). The title compound was obtained as an amorphous white solid (0.380 g, 58%).

TLC R_f : 0.28 in 10% MeOH/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.52 (d, J = 1.2 Hz, 1H), 8.21 (br s, 1H), 6.61 (t, J = 6.2 Hz, 1H), 2.86 (t, J = 6.9 Hz, 2H), 1.78-1.65 (m, 1H), 0.82 (d, J = 6.7 Hz, 6H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 162.0 (C), 46.7 (CH₂), 28.9 (CH), 20.4 (CH₃). IR (FTIR): 3389, 3123, 2955, 2871, 1617, 1549, 1424 cm⁻¹. HRMS (EI): Despite multiple attempts to obtain an accurate mass using both ESI and EI, one could not be obtained for this compound. However, this product was a precursor to **4.16** for which all characterization was obtained, thereby clearly demonstrating this to be the desired product.



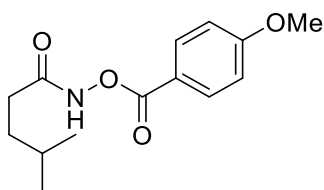
3-((4-Methoxybenzoyl)oxy)-1-isobutylurea: The title compound was synthesized according to general procedure **2A** using the pure 1-isobutyl-3-hydroxyurea (0.330 g, 2.50 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (0.35 mL, 0.4 mmol) mmol) followed immediately by addition of p-methoxybenzoylchloride (0.427 g, 2.50 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated vacuo and purified by recrystallization with Et₂O to yield a white crystalline solid (0.548 g, 82%). TLC R_f : 0.21 in 2% MeOH/CH₂Cl₂. M.p.: 139.7-140.5 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.68-9.60 (br s, 1H), 7.98 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 7.04 (t, J = 6.0 Hz, 1H), 3.84 (s, 3H), 2.86 (t, J = 6.4 Hz, 2H), 1.80-1.63 (m, 1H), 0.81 (d, J = 6.7 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 165.5 (C), 164.1 (C), 159.3 (C), 132.2 (CH), 120.2 (C), 114.7 (CH), 56.1 (CH), 47.0 (CH₂), 28.8 (CH), 20.4 (CH₃). IR (FTIR): 3304, 2959, 1748, 1663, 1571, 1510, 1249 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₈N₂O₄Na [M+Na]⁺: 289.1165. Found: 289.1176.



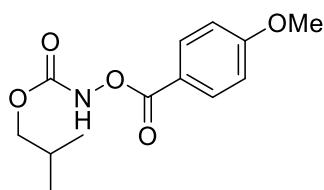
N-Hydroxy-4-methylpentanamide: The title compound was synthesized according to modified literature procedure.²⁵²

¹H NMR (400 MHz, CDCl₃): δ 8.28 (br s, 2H), 2.18-2.13 (m, 2H), 1.62-1.49 (m, 3H), 0.90 (d, J = 6.2 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 172.1 (C), 34.2 (CH₂), 31.0 (CH₂), 27.7 (CH), 22.2 (CH₃).

The ^1H NMR and ^{13}C NMR is in agreement with previous reports.²⁷¹



N-((4-Methoxybenzoyl)oxy)-4-methylpentanamide: The title compound was synthesized according to general procedure **2A** using *N*-hydroxy-4-methylpentanamide (0.656 g, 5.00 mmol) and 4-methoxybenzoyl chloride (0.853 g, 5.00 mmol) and triethylamine (0.70 mL, 5.00 mmol) in CH_2Cl_2 (0.30 M). Upon completion the reaction mixture was extracted with saturated NaHCO_3 three times (10 mL x 3) followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (20.0 mL). The filtrate was collected, and concentrated in vacuo and isolated using flash chromatography (50% EtOAc/Hexanes) to yield the title compound as a white solid (1.12 g, 82% yield). TLC R_f : 0.71 in 50% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 9.11 (br s, 1H), 8.03 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 1.67-1.57 (m, 4H), 0.90 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 171.7 (C), 164.8 (C), 164.4 (C), 132.2 (CH), 118.9 (C), 114.0 (CH), 55.5 (CH_3), 33.9 (CH_2), 31.2 (CH_2), 27.7 (CH), 22.2 (CH_3). IR (FTIR): 3147, 2959, 1759, 1657, 1603, 1509, 1248, 1167, 1024 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 288.1210. Found: 288.1212.

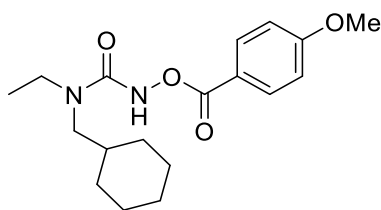


Isobutyl (4-methoxybenzoyl)oxycarbamate (1i): Isobutyl hydroxycarbamate was synthesized according to a modified literature procedure.²⁵²

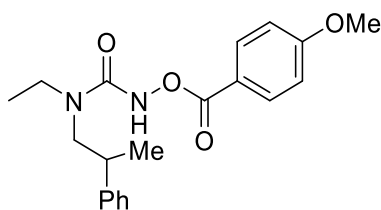
The title compound was synthesized according to general procedure **2A** using the crude isobutyl hydroxycarbamate (0.666 g, 5.00 mmol) to this was added CH_2Cl_2 (0.30 M) and cooled to 0°C . To this was added Et_3N (0.70 mL, 5.00 mmol) followed immediately by addition of *p*-methoxybenzoylchloride (0.853 g, 5.00 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion the reaction mixture was extracted with saturated NaHCO_3 three times (10 mL x 3) followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4

²⁷¹ Dube, P.; Nathel, N. F. F.; Vetelino, M.; Couturier, M.; Aboussafy, C. L.; Pichette, S.; Jorgensen, M. L.; Hardink, M. *Org. Lett.* **2009**, *11*, 5622.

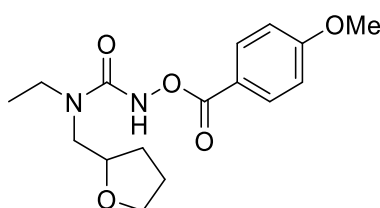
(stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (20.0 mL). The filtrate was collected, and concentrated in vacuo and isolated using flash chromatography (15% EtOAc/Hexanes) to yield the title compound as a clear oil (1.17 g, 88% yield). TLC R_f: 0.70 in 33% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.24 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.98 (d, *J* = 6.6 Hz, 2H), 3.86 (s, 3H), 1.96 (dq, *J* = 13.4, 6.7 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 165.7 (C), 164.4 (C), 157.0 (C), 132.2 (CH), 118.9 (C), 114.1 (CH), 72.7 (CH₂), 55.6 (CH₃), 27.9 (CH), 18.9 (CH₃). IR (FTIR): 3147, 2960, 1759, 1656, 1603, 1509, 1459, 1248, 1167 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₇NO₅Na⁺ [M+Na]⁺: 290.1005. Found: 290.1004.



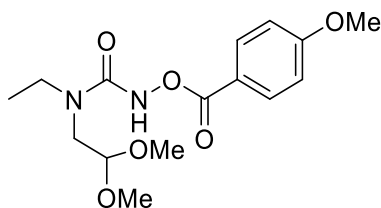
3-((4-Methoxybenzoyl)oxy)-1-cyclohexylmethyl-1-ethylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and *N*-(cyclohexylmethyl)-*N*-ethylamine (0.555 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using silica plug (15% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.653 g, 54%). TLC R_f: 0.30 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 10.21-10.14 (br s, 1H), 8.00-7.91 (m, 2H), 7.14-7.05 (m, 2H), 3.85 (s, 3H), 3.25 (q, *J* = 7.0 Hz, 2H), 3.05 (d, *J* = 6.9 Hz, 2H), 1.74-1.45 (m, 6H), 1.27-1.12 (m, 3H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.98-0.80 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 165.2 (C), 163.6 (C), 157.2 (C), 131.4 (CH), 119.8 (C), 114.3 (CH), 55.6 (CH), 51.4 (CH₂), 41.2 (CH₂), 36.2 (CH), 30.2 (CH₂), 26.1 (CH₂), 25.4 (CH₂), 13.0 (CH₃). IR (FTIR): 3251, 2923, 2850, 1741, 1660, 1604, 1248, 1164 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₃₄N₂O₄Na [M+Na]⁺: 401.2417. Found: 401.2423.



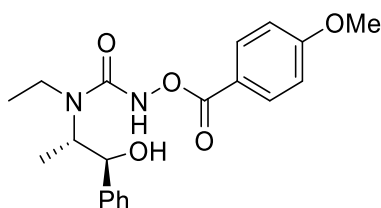
1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-phenylpropyl)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-(cyclohexylmethyl)-*N*-ethylamine (0.490 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using silica plug (20% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.919 g, 86%). TLC R_f: 0.19 in 20% EtOAc/Hexanes. [α]_D^{26°C}: 45.5 (C= 0.1 M in CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ 8.26 (br s, 1H), 8.11-7.99 (m, 2H), 7.35-7.27 (m, 2H), 7.27-7.17 (m, 3H), 6.98-6.86 (m, 2H), 3.85 (s, 3H), 3.58 (dd, *J* = 6.4, 13.6 Hz, 1H), 3.27-3.11 (m, 3H), 2.96 (qd, *J* = 7.2, 14.6 Hz, 1H), 1.35-1.27 (m, 3H), 1.18-1.03 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.4 (C), 164.2 (C), 157.7 (C), 144.0 (C), 132.1 (CH), 128.8 (CH), 127.3 (CH), 126.8 (CH), 119.4 (C), 113.9 (CH), 55.5 (CH₃), 54.6 (CH₂), 42.6 (CH₂), 38.8 (CH), 18.6 (CH₃), 12.9 (CH₃). IR (FTIR): 3216, 2966, 1747, 1668, 1604, 1509, 1454, 1245, 1167 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₀H₂₄N₂NaO₄⁺ [M+Na]⁺: 379.1628. Found: 379.1634.



1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-((tetrahydrofuran-2-yl)methyl)urea (1l): The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-((tetrahydrofuran-2-yl)methyl)ethanamine (0.388 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (20% EtOAc/Hexanes) to yield the title compound as a clear oil (0.580 g, 59%). TLC R_f: 0.34 in 50% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 10.08 (br s, 1H), 8.05 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.10-4.02 (m, 2H), 3.86-3.81 (m, 4H), 3.50-3.26 (m, 4H), 2.02-1.90 (m, 3H), 1.63-1.58 (m, 1H), 1.15 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.2 (C), 164.0 (C), 156.0 (C), 132.1 (CH), 120.1 (C), 113.9 (CH), 79.5 (CH), 68.6 (CH₂), 55.5 (CH₃), 54.6 (CH₂), 43.8 (CH₂), 28.8 (CH₂), 26.1 (CH₂), 13.0 (CH₃). IR (FTIR): 3192, 2962, 1685, 1604, 1566, 1245, 1067 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₂₂N₂NaO₅⁺ [M+Na]⁺: 345.1421. Found: 345.1426.

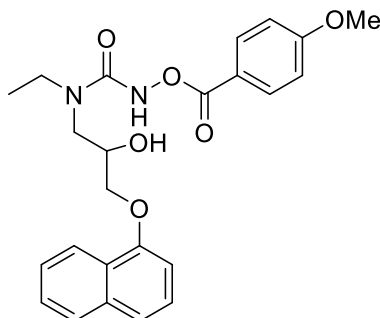


1-(2,2-Dimethoxyethyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-ethyl-2,2-dimethoxyethanamine (0.399 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Solvent was removed under reduced pressure and the crude product isolated using flash chromatography (30% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield the title compound as a clear oil (0.979 g, 99%). TLC *R_f*: 0.40 in 40% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 9.63 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 2H), 6.93-6.90 (m, 2H), 4.46 (t, *J* = 5.3 Hz, 1H), 3.84 (s, 3H), 3.50 (s, 6H), 3.36-3.45 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.3 (C), 163.9 (C), 158.6 (C), 132.0 (CH), 119.8 (C), 113.9 (CH), 104.4 (CH), 55.6 (CH₃), 55.5 (CH₃), 49.4 (CH₂), 43.3 (CH₂), 13.4 (CH₃). IR (FTIR): 3216, 2943, 1740, 1686, 1466, 1247, 1169, 1068 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₅H₂₂N₂NaO₆⁺ [M+Na]⁺: 349.1370. Found: 349.1376.

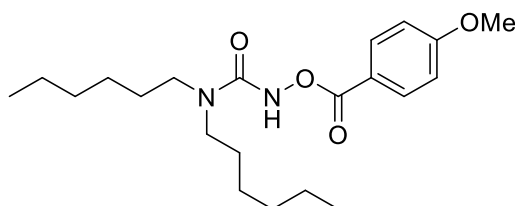


1-(2-Hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and (–)-(1*R*,2*S*)-ephedrine (0.495 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using flash chromatography (20% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield the title compound as a colourless oil (1.16 g, 97%). TLC *R_f*: 0.30 in 20% EtOAc/Hexanes. ¹H NMR (600 MHz, CDCl₃): δ 9.53-8.83 (br s, 1H), 8.10-8.01 (m, 2H), 7.43-7.25 (m, 5H), 6.98-6.89 (m, 2H), 4.84 (d, *J* = 3.2 Hz, 1H), 4.36 (qd, *J* = 6.8, 3.0 Hz, 1H), 3.86 (s, 3H), 3.62-3.01 (br s, 1H), 2.51 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.6 (C), 164.2 (C), 159.5 (C), 132.2 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 119.6 (CH), 119.8 (C), 114.3 (CH), 77.7 (CH), 57.5 (CH), 55.6 (CH), 30.7

(CH), 13.4 (CH₃). IR (FTIR): 3251, 2923, 2850, 1741, 1660, 1604, 1248, 1164 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₃₄N₂O₄Na [M+Na]⁺: 401.2417. Found: 401.2423.

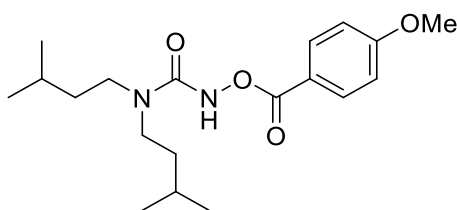


1-(2-Hydroxy-3-(naphthalen-1-yloxy)propyl)-1-isopropyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and propranolol (0.778 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (12.0 mL, 0.25 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using flash chromatography (40% Et₂O/Toluene) to yield the title compound as a white solid (0.855 g, 60%). TLC R_f: 0.22 in 20% Et₂O/Toluene. ¹H NMR (300 MHz, CDCl₃): δ 9.85-9.73 (br s, 1H), 8.26-8.16 (m, 2H), 8.12-8.03 (m, 2H), 7.87-7.78 (m, 1H), 7.56-7.44 (m, 3H), 7.42-7.34 (m, 1H), 6.97-6.90 (m, 2H), 6.86-6.80 (m, 1H), 4.57-4.36 (m, 2H), 4.17 (qd, *J* = 9.5, 6.0 Hz, 2H), 3.86 (s, 3H), 3.68 (dd, *J* = 15.8, 9.0 Hz, 1H), 3.52 (dd, *J* = 15.7, 2.2 Hz, 1H), 1.28 (app dd, *J* = 24.1, 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 166.7 (C), 164.1 (C), 159.7 (C), 153.8 (C), 134.6 (C), 132.2 (CH), 127.8 (CH), 126.7 (CH), 125.9 (CH), 125.6 (CH), 125.5 (C), 121.6 (CH), 121.2 (CH), 119.7 (C), 114.0 (CH), 105.7 (CH), 72.4 (CH), 69.9 (CH₂), 55.6 (CH₃), 47.8 (CH), 45.6 (CH₂), 21.2 (CH), 20.0 (CH₃). IR (FTIR): 3205, 2973, 1742, 1633, 1604, 1509, 1249 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₅H₂₈N₂O₆Na⁺ [M+Na]⁺: 475.1845. Found: 475.1823.

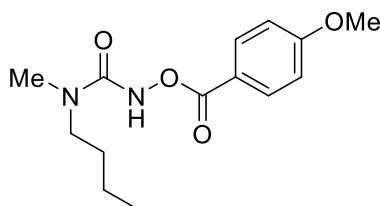


1,1-Dihexyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N,N*-dihexylamine (0.555 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄

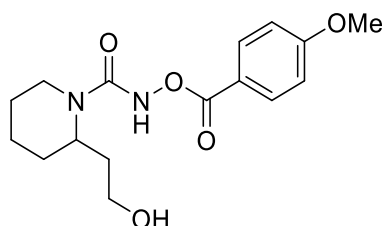
(stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes → 20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.840 g, 74%). TLC R_f: 0.24 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.47 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.24 (t, *J* = 7.7 Hz, 4H), 1.62-1.58 (m, 4H), 1.32-1.27 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 164.3 (C), 157.7 (C), 132.2 (CH), 119.5 (C), 114.0 (CH), 55.6 (CH₃), 47.5 (CH₂), 31.7 (CH₂), 28.3 (CH₂), 26.7 (CH₂), 22.7 (CH₂), 14.2 (CH₃). IR (FTIR): 3156, 2955, 2930, 2856, 1753, 1652, 1509, 1486, 1264 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₃₄N₂NaO₄⁺ [M+Na]⁺: 401.2411. Found: 401.2416.



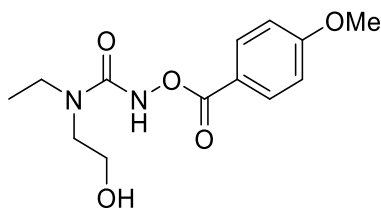
1,1-Diisopentyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N,N*-diisopentylamine (0.472 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica column chromatography (15% EtOAc/Hexanes → 30% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.800 g, 79%). TLC R_f: 0.38 in 33% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.46 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.26 (t, *J* = 7.9 Hz, 4H), 1.63-1.54 (m, 2H), 1.54-1.47 (m, 4H), 0.93 (d, *J* = 6.5 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 164.3 (C), 157.5 (C), 132.2 (CH), 119.5 (C), 114.1 (CH), 55.6 (CH₃), 45.8 (CH₂), 37.1 (CH₂), 26.2 (CH), 22.6 (CH₃). IR (FTIR): 3263, 2953, 2868, 1745, 1655, 1604, 1510, 1249, 1166 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₉H₃₀N₂NaO₄⁺ [M+Na]⁺: 373.2098. Found: 373.2103.



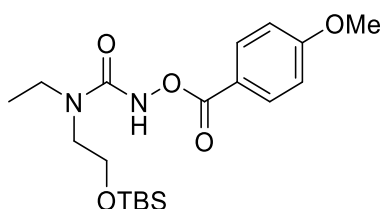
3-((4-Methoxybenzoyl)oxy)-1-butyl-1-methylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and *N*-methylbutylamine (0.262 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using flash chromatography (25% EtOAc/Hexanes) to yield the title compound as a yellow oil (0.466 g, 55%). TLC R_f: 0.16 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.45-8.42 (br s, 1H), 8.12-8.06 (m, 2H), 6.98-6.92 (m, 2H), 3.88 (s, 3H), 3.37-3.30 (m, 2H), 3.00 (s, 3H), 1.66-1.54 (m, 2H), 1.43-1.30 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.6 (C), 164.1 (C), 157.8 (C), 132.0 (CH), 119.3 (C), 113.9 (CH), 55.4 (CH), 48.8 (CH₂), 33.9 (CH₃), 29.7 (CH₂), 19.9 (CH₂), 13.8 (CH₃). IR (FTIR): 3213, 2956, 2870, 1752, 1649, 1503, 1244, 1074 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₄H₂₀N₂O₄Na [M+Na]⁺: 303.1321. Found: 303.1298.



2-(2-Hydroxyethyl)-*N*-((4-methoxybenzoyl)oxy)piperidine-1-carboxamide: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and 2-(piperidin-2-yl)ethanol (0.388 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (50% EtOAc/Hexanes → 40% EtOAc/DCM) to yield the title compound as a white foam (0.919 g, 95%). TLC R_f: 0.40 in 40% EtOAc/DCM. ¹H NMR (400 MHz, CDCl₃): δ 9.36 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.37-4.10 (m, 2H), 3.84 (s, 3H), 3.77-3.67 (m, 2H), 2.77-2.67 (m, 2H), 2.11-2.02 (m, 1H), 1.82-1.78 (m, 1H), 1.67-1.49 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 167.0 (C), 164.3 (C), 158.2 (C), 132.2 (CH), 119.7 (C), 114.0 (CH), 58.4 (CH₂), 55.6 (CH₃), 47.0 (CH), 38.5 (CH₂), 31.3 (CH₂), 29.2 (CH₂), 25.5 (CH₂), 19.3 (CH₂). IR (FTIR): 3372, 3146, 2938, 1742, 1653, 1603, 1508, 1420, 1247, 1166 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₂₂N₂NaO₅⁺ [M+Na]⁺: 345.1421. Found: 345.1426.

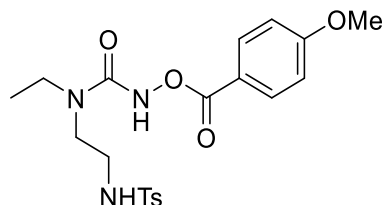


1-Ethyl-1-(2-hydroxyethyl)-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and 2-(ethylamino)ethanol (0.267 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (50% EtOAc/Hexanes → 40% EtOAc/DCM) to yield the title compound as a white solid (0.788 g, 93%). TLC R_f: 0.20 in 40% EtOAc/DCM. ¹H NMR (400 MHz, CDCl₃): δ 9.55 (br s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.81 (t, *J* = 4.8 Hz, 2H), 3.45 (t, *J* = 4.8 Hz, 2H), 3.37 (q, *J* = 7.1 Hz, 2H), 3.14 (br s, 1H), 1.16 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.7 (C), 164.1 (C), 159.1 (C), 132.1 (CH), 119.6 (C), 113.9 (CH), 62.2 (CH₂), 55.6 (CH₃), 48.8 (CH₂), 42.7 (CH₂), 13.2 (CH₃). IR (FTIR): 3404, 3181, 2864, 1720, 1678, 1600, 1514, 1475, 1325, 1262, 1246, 1172 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₈N₂NaO₅⁺ [M+Na]⁺: 305.1108. Found: 305.1113.

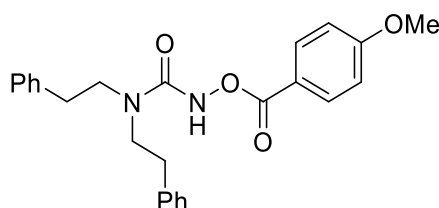


3-((4-Methoxybenzoyl)oxy)-1-ethyl-1-(2-(tert-butyldimethylsilyloxy)ethyl)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.574 g, 2.00 mmol), and 2-((tert-butyldimethylsilyl)oxy)-*N*-ethylethan-1-amine (0.406 g, 2.00 mmol) and imidazole (0.014 g, 0.2 mmol) in THF (10.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using flash chromatography (20% Et₂O/Toluene) to yield the title compound as a colourless oil (0.463 g, 58%). TLC R_f: 0.17 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 9.34-9.29 (br s, 1H), 8.10-8.03 (m, 2H), 6.96-6.90 (m, 2H), 3.87 (s, 3H), 3.83 (t, *J* = 4.8 Hz, 2H), 3.49 (t, *J* = 4.7 Hz, 2H), 3.41 (q, *J* = 7.0 Hz, 2H), 1.2 (t, *J* = 7.1

Hz, 3H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 165.5 (C), 163.8 (C), 158.9 (C), 132.0 (CH), 120.1 (C), 113.7 (CH), 63.1 (CH_2), 55.4 (CH), 48.9 (CH_2), 42.6 (CH_2), 25.9 (CH), 18.4 (C), 13.2 (CH_3), -5.6 (CH). IR (FTIR): 3186, 2933, 1743, 1686, 1253, 1064, 834, 780 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_5\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 419.1978. Found: 419.1959.

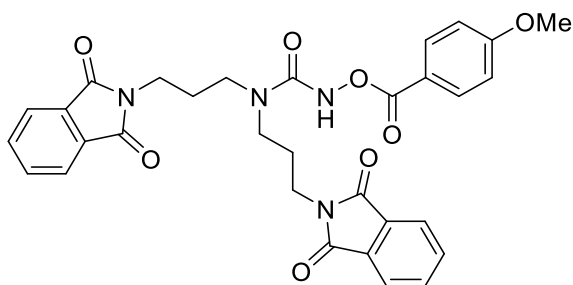


***N*-(2-(1-Ethyl-3-((4-methoxybenzoyl)oxy)ureido)ethyl)-4-methylbenzenesulfonamide (1v3):** The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and *N*-(2-ethylamino)ethyl-4-methylbenzenesulfonamide (0.726 g, 3.00 mmol) and imidazole (0.020 g, 0.2 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na_2SO_4 (stirring for 15 min). The solids were filtered over a frit and rinsed with CH_2Cl_2 (5.0 mL). The title compound was purified by recrystallization using Et_2O to yield a crystalline pale brown solid (0.563 g, 43%). TLC R_f : 0.09 in 20% EtOAc/Hexanes. M.p.: 168.7-169.3°C. ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 10.37-10.23 (br s, 1H), 8.00-7.91 (m, 2H), 7.74-7.57 (m, 3H), 7.48-7.33 (m, 2H), 7.14-7.01 (m, 2H), 3.84 (s, 3H), 3.29-3.17 (m, 4H), 2.90-2.80 (m, 2H), 2.38 (s, 3H), 1.04 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 165.1 (C), 163.6 (C), 157.0 (C), 142.7 (C), 137.3 (C), 131.5 (CH), 129.7 (CH), 126.5 (CH), 119.6 (C), 114.3 (CH), 55.6 (CH), 45.5 (CH_2), 41.4 (CH_2), 41.0 (CH_2), 21.0 (CH_3). IR (FTIR): 3223, 3081, 2983, 1671, 1595, 1337, 1163 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_6\text{SNa}$ $[\text{M}+\text{Na}]^+$: 458.1362. Found: 458.1344.

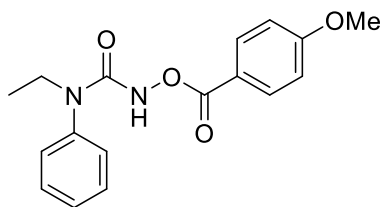


3-((4-Methoxybenzoyl)oxy)-1,1-diphenethylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N,N*-diphenethylamine (0.676 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (20% EtOAc/Hexanes) to yield the title compound as a white solid (0.880 g, 70%). TLC R_f : 0.31 in 20%

EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 8.21 (br s, 1H), 8.09-8.06 (m, 2H), 7.35-7.19 (m, 10H), 6.96-6.93 (m, 2H), 3.87 (s, 3H), 3.43 (t, $J = 7.5$ Hz, 4H), 2.89 (t, $J = 7.4$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.5 (C), 164.3 (C), 157.7 (C), 138.7 (C), 132.2 (CH), 128.93 (CH), 128.90 (CH), 126.8 (CH), 119.4 (C), 114.1 (CH), 55.6 (CH_3), 50.1 (CH_2), 34.7 (CH_2). IR (FTIR): 3209, 2931, 1744, 1673, 1604, 1475, 1247, 1166 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{NaO}_4^+[\text{M}+\text{Na}]^+$: 441.1785. Found: 441.1790.



1,1-Bis(3-(1,3-dioxoisindolin-2-yl)propyl)-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N,N*-diphenethylamine (1.17 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 $^{\circ}\text{C}$. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (gradient: 50% EtOAc/Hexanes $\rightarrow$ 100% EtOAc) to yield the title compound as a white foam (1.45 g, 83%). TLC R_f : 0.75 in 100% EtOAc. ^1H NMR (400 MHz, CDCl_3): δ 8.95 (br s, 1H), 8.04 (d, $J = 9.0$ Hz, 2H), 7.84-7.78 (m, 4H), 7.73-7.67 (m, 4H), 6.92 (d, $J = 9.0$ Hz, 2H), 3.85 (s, 3H), 3.76 (t, $J = 6.8$ Hz, 4H), 3.42 (t, $J = 7.3$ Hz, 4H), 2.02 (quintet, $J = 7.1$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 168.4 (C), 166.5 (C), 164.1 (C), 157.9 (C), 134.0 (CH), 132.0 (CH), 123.3 (CH), 119.3 (C), 113.9 (CH), 55.5 (CH), 44.8 (CH_2), 35.5 (CH_2), 27.4 (CH_2). IR (FTIR): 2939, 1694, 1604, 1389, 1244, 1167, 1025 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{31}\text{H}_{28}\text{N}_4\text{O}_8\text{Na}^+[\text{M}+\text{Na}]^+$: 607.1805. Found: 607.1791.

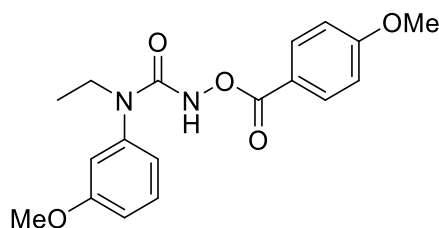


3-((4-Methoxybenzoyl)oxy)-1-ethyl-1-phenylurea: The title compound was synthesized according general procedure **4A** using *N*-ethylaniline (1.26 mL, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0 $^{\circ}\text{C}$. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour

at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-ethylanilinecarbamoyl chloride which was used in the next step without further purification.

To the crude *N*-ethylanilinecarbamoyl chloride was added CH₂Cl₂ (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et₃N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-ethylanilinehydroxyurea, which could be used in the next step without further purification.

To the crude *N*-ethylanilinehydroxyurea (1.53 g, 8.53 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0 °C. To this was added Et₃N (1.19 mL, 8.53 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.45 g, 8.53 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1-ethyl-1-phenylurea which was purified by flash column chromatography (10 % Et₂O/Toluene) to yield a colourless oil (1.93 g, 62% over 3 steps). TLC R_f: 0.23 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.05-8.00 (m, 2H), 7.97-7.95 (br s, 1H), 7.53-7.46 (m, 2H), 7.44-7.37 (m, 3H), 6.96-6.90 (m, 2H), 3.86 (s, 3H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.4 (C), 164.1 (C), 156.6 (C), 138.5 (C), 132.0 (CH), 130.2 (CH), 128.4 (CH), 119.2 (C), 113.9 (CH), 55.5 (CH), 45.0 (CH₂), 13.3 (CH₃). IR (FTIR): 3302, 2972, 1737, 1701, 1602, 1508, 1646, 1168 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₇H₁₈N₂O₄Na [M+Na]⁺: 337.1165. Found: 337.1194.

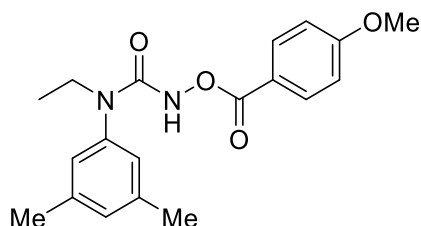


1-Ethyl-3-((4-methoxybenzoyl)oxy)-1-(3-methoxyphenyl)urea: The title compound was synthesized according general procedure **4A** using *N*-ethyl-3-methoxyaniline (1.51 g, 10.0 mmol), toluene (0.8 M),

KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0°C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-ethyl(3-methoxyphenyl)carbamic chloride which was used in the next step without further purification.

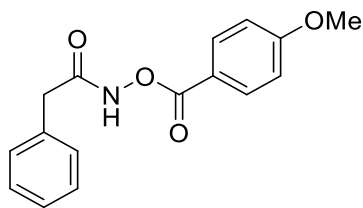
To the crude ethyl(3-methoxyphenyl)carbamic chloride was added CH₂Cl₂ (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et₃N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-ethyl-3-hydroxy-1-(3-methoxyphenyl)urea, which could be used in the next step without further purification.

To the crude 1-ethyl-3-hydroxy-1-(3-methoxyphenyl)urea was added CH₂Cl₂ (0.30 M) and cooled to 0 °C. To this was added Et₃N (1.39 mL, 10.0 mmol) followed immediately by addition of *p*-methoxybenzoylchloride (1.70 g, 10.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(3-methoxyphenyl)urea which was purified by flash column chromatography (20 % EtOAc/Hexanes) to yield a light pink solid (2.60 g, 76% over 3 steps). TLC R_f: 0.15 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.03 (br s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.97-6.89 (m, 5H), 3.84 (s, 3H), 3.82 (s, 3H), 3.73 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.6 (C), 164.3 (C), 161.0 (C), 156.8 (C), 140.8 (C), 132.2 (CH), 131.0 (CH), 120.5 (CH), 119.4 (C), 114.5 (CH), 114.04 (CH), 113.94 (CH), 55.6 (CH₃), 45.2 (CH₂), 13.5 (CH₃). IR (FTIR): 3294, 2940, 2842, 2360, 1748, 1701, 1601, 1446, 1286, 1246, 1209, 1172 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₈H₂₀N₂O₅Na [M+Na]⁺: 367.1291. Found: 367.1270.



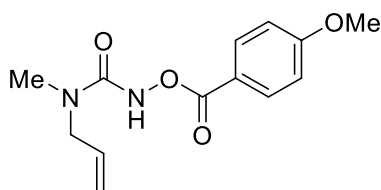
1-(3,5-Dimethylphenyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **4A** using *N*-ethyl-3,5-dimethylaniline (1.49 g, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0°C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude (3,5-dimethylphenyl)(ethyl)carbamic chloride which was used in the next step without further purification. To the crude (3,5-dimethylphenyl)(ethyl)carbamic chloride was added CH₂Cl₂ (0.30 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et₃N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-(3,5-dimethylphenyl)-1-ethyl-3-hydroxyurea, which could be used in the next step without further purification.

To the crude 1-(3,5-dimethylphenyl)-1-ethyl-3-hydroxyurea was added CH₂Cl₂ (0.30 M) and cooled to 0 °C. To this was added Et₃N (1.39 mL, 10.0 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.70 g, 10.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-(3,5-dimethylphenyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea which was purified by flash column chromatography (20% EtOAc/Hexanes → 40% EtOAc/Hexanes) to yield a colourless oil (2.74 g, 80% over 3 steps). TLC R_f: 0.21 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.02-7.98 (m, 2H), 7.97 (br s, 1H), 7.00 (d, *J* = 0.6 Hz, 1H), 6.96 (d, *J* = 0.5 Hz, 2H), 6.91-6.88 (m, 2H), 3.83 (d, *J* = 3.6 Hz, 3H), 3.70 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 6H), 1.13 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.5 (C), 164.1 (C), 156.7 (C), 140.0 (C), 139.3 (C), 132.1 (CH), 130.3 (CH), 125.8 (CH), 119.3 (C), 113.9 (CH), 55.5 (CH₃), 45.0 (CH₂), 21.2 (CH₃), 13.4 (CH₃). IR (FTIR): 2970, 1744, 1695, 1602, 1510, 1454, 1310, 1245, 1167, 1062 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₉H₂₂N₂O₄Na [M+Na]⁺: 365.1458. Found: 365.1477.



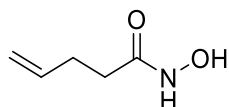
***N*-((4-Methoxybenzoyl)oxy)-2-phenylacetamide (1ae):** *N*-hydroxy-2-phenylacetamide was synthesized according to general procedure **2B** using phenylacetyl chloride (1.55 g, 10.00 mmol) and hydroxylamine hydrochloride (0.695 g, 10.00 mmol) and NaHCO₃ (1.85 g, 44.00 mmol) in 2 : 1 CH₂Cl₂ : H₂O (0.30 M). The reaction allowed to stir at room temperature overnight; the following day a substantial amount of white solid had precipitated out of solution. The white solid was collected over a fritted funnel and used directly in the subsequent step without further purification.

The title compound was synthesized using the general procedure **2A** using the crude hydroxamic acid was dissolved in CH₂Cl₂ (0.30 M, sparingly soluble). To the crude solution of phenylacetyl hydroxamic acid was added 4-methoxybenzoyl chloride (1.71 g, 10.00 mmol) and triethylamine (1.39 mL, 10.00 mmol). Upon completion the reaction mixture was extracted with saturated NaHCO₃ three times (10 mL x 3) followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (20 mL). The filtrate was collected, and concentrated in vacuo and isolated using flash chromatography (50% EtOAc/Hexanes) to yield the title compound as a white solid (2.51 g, 88% yield over two steps). TLC R_f: 0.57 in 50% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.94 (br s, 1H), 8.04-8.01 (m, 2H), 7.41-7.31 (m, 5H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.7 (C), 164.7 (C), 164.6 (C), 133.2 (C), 132.3 (CH), 129.5 (CH), 129.2 (CH), 127.8 (CH), 118.7 (C), 114.2 (CH), 55.7 (CH), 41.9 (CH₂). IR (FTIR): 3162, 2963, 1753, 1669, 1600, 1501, 12050, 1025 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₆H₁₅NO₄Na⁺ [*M*+Na]⁺: 308.0899. Found: 308.0897.



1-Allyl-3-((4-methoxybenzoyl)oxy)-1-methylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.511 g, 1.78 mmol), and *N*-methylallylamine (0.17 mL, 1.78 mmol) and imidazole (0.012 g, 0.2 mmol) in THF (9.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The

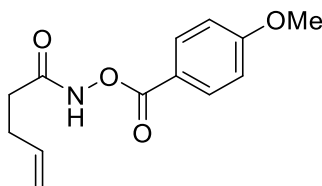
filtrate was collected, concentrated in vacuo and isolated using silica plug (20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.376 g, 80%). TLC R_f: 0.11 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.46-8.43 (br s, 1H), 8.11-8.05 (m, 2H), 6.99-6.93 (m, 2H), 5.93-5.78 (m, 1H), 5.35-5.26 (m, 2H), 3.97 (dt, *J* = 5.3, 1.6 Hz, 2H), 3.88 (s, 3H), 3.01 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.6 (C), 164.2 (C), 157.0 (C), 132.3 (CH), 132.1 (CH), 119.3 (C), 117.5 (CH₂), 114.0 (CH), 55.5 (CH), 51.3 (CH₂), 34.2 (CH). IR (FTIR): 3184, 3010, 1744, 1651, 1506, 1238 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₆N₂O₄Na [M+Na]⁺: 287.1008. Found: 287.1014.



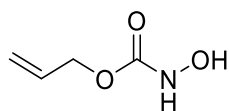
***N*-Hydroxypent-4-enamide:** The title compound was synthesized according to a modified literature procedure.²⁵²

¹H NMR (300 MHz, DMSO-*d*₆): δ 10.46-10.25 (br s, 1H), 8.78-8.57 (br s, 1H), 5.78 (ddt, *J* = 17.0, 10.4, 6.4 Hz, 1H), 5.08-4.91 (m, 2H), 2.29-2.17 (m, 2H), 2.08-1.97 (m, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.4 (C), 137.5 (CH), 115.2 (CH₂), 31.5 (CH₂), 29.0 (CH₂).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.



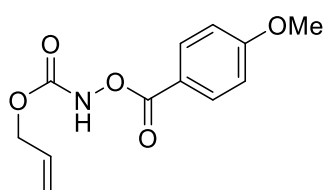
***N*-((4-Methoxybenzoyl)oxy)pent-4-enamide:** The title compound was synthesized according to general procedure **2A** using *N*-hydroxypent-4-enamide (1.15 g, 10.0 mmol), and *p*-methoxybenzoyl chloride (1.71 g, 10.0 mmol), and Et₃N (1.39 mL, 10.0 mmol) in CH₂Cl₂ (0.30 M) at 0 °C to rt. Upon completion the reaction was extracted three times using sat. NaHCO₃ (10.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (50.0 mL). The filtrate was collected, concentrated in vacuo to yield the title compound as a white solid (2.49 g, 99%). TLC R_f: 0.27 in 33% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.85 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.13-5.03 (m, 2H), 3.87 (s, 3H), 2.48-2.41 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 164.7 (C), 164.4 (C), 136.4 (CH), 132.2 (CH), 131.7 (CH), 118.7 (C), 116.1 (CH₂), 114.1 (C), 55.6 (CH₃), 32.4 (CH₂), 28.9 (CH₂). IR (FTIR): 3186, 2971, 2840, 1759, 1663, 1604, 1506, 1419, 1248, 1168 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₅NO₄Na [M+Na]⁺: 272.0897. Found: 272.0899.



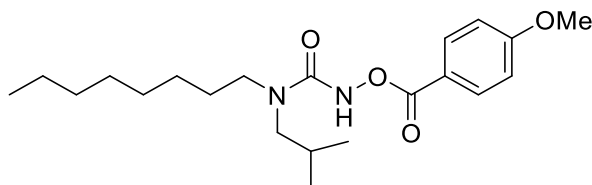
Allylhydroxycarbamate (4ai): The title compound was synthesized according to a literature procedure.²⁷²

¹H NMR (300 MHz, DMSO-*d*₆): δ 9.69-9.57 (br s, 1H), 8.73-8.70 (br s, 1H), 5.95-5.85 (m, 1H), 5.31-5.16 (m, 2H), 4.50 (dt, *J* = 5.3, 1.5 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 157.5 (C), 133.5 (CH), 117.2 (CH₂), 64.4 (CH₂).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.

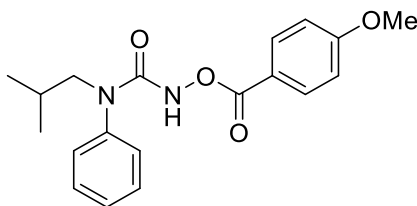


Allyl (4-methoxybenzoyl)oxycarbamate: The title compound was synthesized according to general procedure **2A** using allyl hydroxycarbamate (1.17 g, 10.0 mmol), and *p*-methoxybenzoyl chloride (1.71 g, 10.0 mmol), and Et₃N (1.39 mL, 10.0 mmol) in CH₂Cl₂ (0.30 M) at 0 °C to rt. Upon completion the reaction was extracted three times using sat. NaHCO₃ (10.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (50.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica gel column chromatography (solvent system) to yield the title compound as a white solid (2.20 g, 88%). TLC R_f: 0.54 in 33% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.36 (s, 1H), 8.06-7.98 (m, *J* = 9.0 Hz, 2H), 6.97-6.88 (m, *J* = 9.0 Hz, 2H), 5.97-5.85 (m, 1H), 5.37-5.19 (m, 2H), 4.68 (td, *J* = 1.4, 5.7 Hz, 2H), 3.85 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 165.5 (C), 164.4 (C), 156.4 (C), 132.1 (CH), 131.4 (CH), 118.9 (CH₂), 118.8 (C), 114.0 (CH), 67.1 (CH₂), 55.5 (CH). IR (FTIR): 3199, 2953, 2844, 1754, 1718, 1602, 1492, 1238 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₂H₁₃NO₅Na [M+Na]⁺: 274.0696. Found: 274.0691.



²⁷² Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514.

3-((4-Methoxybenzoyl)oxy)-1-isobutyl-1-octylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and *N*-isobutyloctylamine (0.555 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (15.0 mL, 0.20 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated in vacuo and isolated using silica plug (20% EtOAc/Hexanes) to yield the title compound as a colourless oil (0.957 g, 84%). TLC R_f: 0.54 in 20% EtOAc/Hexanes. ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.21-10.13 (br s, 1H), 8.01-7.91 (m, 2H) 7.15-7.03 (m, 2H), 3.85 (s, 3H), 3.23-3.14 (m, 2H), 3.03 (d, *J* = 7.4 Hz, 2H), 2.01-1.84 (m, 1H), 1.57-1.45 (m, 2H), 1.32-1.18 (m, 10H), 0.89-0.81 (m, 9H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 165.2 (C), 163.5 (C), 157.4 (C), 131.4 (CH), 119.8 (C), 114.3 (CH), 55.6 (CH), 53.0 (CH₂), 46.4 (CH₂), 31.2 (CH₂), 28.8 (CH₂), 28.7 (CH₂), 27.4 (CH₂), 26.7 (CH), 26.2 (CH₂), 22.1 (CH₂), 19.8 (CH), 13.9 (CH₃). IR (FTIR): 3230, 2924, 2854, 1750, 1669, 1605, 1510, 1248 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₃₄N₂O₄Na [M+Na]⁺: 401.2417. Found: 401.2423.

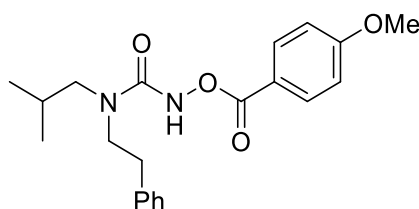


3-((4-Methoxybenzoyl)oxy)-1-isobutyl-1-phenylurea: The title compound was synthesized according to general procedure **4A** using *N*-isobutylaniline (1.07 g, 7.20 mmol), toluene (0.8 M), KOH pellets (0.389 g, 7.20 mmol), and water (2.9 M) at 0°C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (11.8 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0°C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-isobutylanilinecarbamoyl chloride which was used in the next step without further purification.

To the crude *N*-isobutylanilinecarbamoyl chloride was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added hydroxylamine hydrochloride (0.500 g, 7.20 mmol), and followed immediately by Et₃N

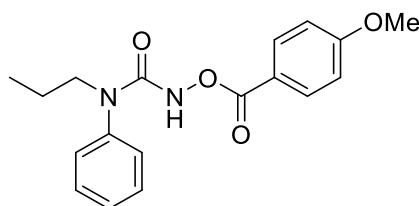
(1.00 mL, 14.4 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-isobutylanilinehydroxyurea, which could be used in the next step without further purification.

To the crude *N*-isobutylanilinehydroxyurea (1.38 g, 6.63 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (0.92 mL, 6.63 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.13 g, 6.63 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1-isobutyl-1-phenylurea which was purified by recrystallization with Et₂O to yield a white crystalline solid (1.23 g, 36% over 3 steps). TLC R_f: 0.34 in 20% EtOAc/Hexanes. M.p.: 137.0-137.7°C. ¹H NMR (400 MHz, CDCl₃): δ 8.06-8.00 (m, 2H), 7.98-7.96 (br s, 1H), 7.53-7.46 (m, 2H), 7.45-7.37 (m, 3H), 6.96-6.90 (m, 2H), 3.87 (s, 3H), 3.57 (d, *J* = 7.4 Hz, 2H), 1.87-1.75 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 166.5 (C), 164.1 (C), 157.3 (C), 140.0 (C), 132.1 (CH), 130.2 (CH), 128.5 (CH), 128.2 (CH), 119.2 (C), 113.9 (CH), 57.2 (CH₂), 55.5 (CH), 26.9 (CH), 19.9 (CH). IR (FTIR): 2960, 1741, 1709, 1604, 1490, 1246, 1173, 1053 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₉H₂₂N₂O₄Na [M+Na]⁺: 365.1478. Found: 365.1501.



1-Isobutyl-3-((4-methoxybenzoyl)oxy)-1-phenethylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and 2-(ethylamino)ethanol (0.532 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes → 30% EtOAc/Hexanes) to yield the title compound as a white solid (1.06 g, 95%). TLC R_f: 0.80 in 40% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.45 (br s, 1H), 8.06 (d, *J* = 9.0 Hz, 2H), 7.38-7.15 (m, 5H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.50 (t, *J* = 7.7 Hz, 2H), 3.00 (d, *J* = 7.6 Hz, 2H), 2.92 (t, *J* = 7.7 Hz, 2H), 1.99 (dsextet, *J* = 13.7, 6.9 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 166.7 (C), 164.2 (C), 157.8 (C), 138.7 (C), 132.1 (CH), 128.8 (CH), 128.7 (CH), 126.6 (CH), 119.3 (C), 113.9 (CH), 55.5 (CH), 55.1 (CH₂), 50.0 (CH₂), 34.2

(CH₂), 27.6 (CH), 20.1 (CH₃). IR (FTIR): 3181, 2957, 1744, 1649, 1603, 1509, 1244, 1168 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₂₆N₂NaO₄⁺ [M+Na]⁺: 393.1784. Found: 393.1790.

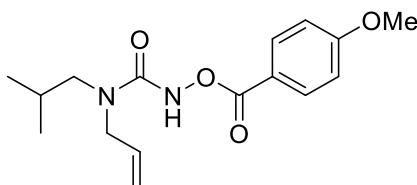


3-((4-Methoxybenzoyl)oxy)-1-phenyl-1-propylurea: The title compound was synthesized according to general procedure **4A** using *N*-propylaniline (0.812 g, 6.00 mmol), toluene (0.8 M), KOH pellets (0.336 g, 6.00 mmol), and water (2.9 M) at 0°C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (9.8 mL, 14 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0°C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-propylanilinecarbamoyl chloride which was used in the next step without further purification.

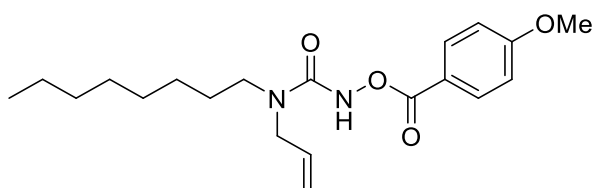
To the crude *N*-propylanilinecarbamoyl chloride was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added hydroxylamine hydrochloride (0.417 g, 6.00 mmol), and followed immediately by Et₃N (1.67 mL, 12.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-propylanilinehydroxyurea, which could be used in the next step without further purification.

To the crude *N*-propylanilinehydroxyurea (0.927 g, 5.45 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (0.76 mL, 5.45 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.06 g, 5.45 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1-phenyl-1-propylurea which was purified by recrystallization with Et₂O to yield a white crystalline solid (0.935 g, 48% over 3 steps). TLC R_f: 0.40 in 20% EtOAc/Hexanes. M.p.: 118.3-119.4°C. ¹H NMR (400 MHz, CDCl₃): δ 8.06-7.99 (m, 2H), 7.98-7.95 (br s, 1H), 7.54-7.46 (m, 2H),

7.45-7.37 (m, 3H), 6.97-6.89 (m, 2H), 3.87 (s, 3H), 3.71-3.66 (m, 2H), 1.59 (dq, $J = 14.9, 7.5$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.5 (C), 164.2 (C), 156.9 (C), 139.7 (C), 132.1 (CH), 130.2 (CH), 128.6 (CH), 128.3 (CH), 119.2 (C), 113.9 (CH), 55.5 (CH), 51.7 (CH₂), 21.2 (CH₂), 11.0 (CH₃). IR (FTIR): 3291, 2913, 1748, 1716, 1605, 1490, 1247, 1175 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 351.1321. Found: 351.1347.

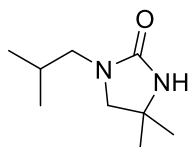


1-Allyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-isobutylprop-2-en-1-amine (0.340 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes $\rightarrow$ 20% EtOAc/Hexanes) to yield the title compound as a white solid (0.919 g, 95%). TLC R_f : 0.22 in 20% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 8.53 (br s, 1H), 8.08-8.05 (m, 2H), 6.95-6.92 (m, 2H), 5.92-5.81 (m, 1H), 5.37-5.30 (m, 2H), 3.95 (td, $J = 3.4, 1.7$ Hz, 2H), 3.86 (d, $J = 5.3$ Hz, 3H), 3.16 (d, $J = 7.5$ Hz, 2H), 1.98 (dsxtet, $J = 13.7, 6.8$ Hz, 1H), 0.95 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.7 (C), 164.2 (C), 158.2 (C), 132.7 (CH), 132.1 (CH), 119.3 (C), 117.5 (CH₂), 113.9 (CH), 55.5 (CH₃), 55.1 (CH₂), 49.9 (CH₂), 27.5 (CH), 20.1 (CH₃). IR (FTIR): 3277, 2953, 1739, 1685, 1463, 1253, 1024 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 329.1491. Found: 329.1477.

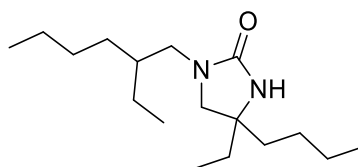


1-Allyl-3-((4-methoxybenzoyl)oxy)-1-octylurea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.862 g, 3.00 mmol), and *N*-allyloctan-1-amine (0.508 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10.0 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was concentrated in vacuo and isolated using silica column chromatography (10% EtOAc/Hexanes $\rightarrow$ 20% EtOAc/Hexanes) to yield the title compound as a white solid (0.870 g, 80%). TLC R_f : 0.28 in 20% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 8.47 (s, 1H), 8.05 (d, $J = 9.0$ Hz, 2H), 6.91 (d, $J = 9.0$ Hz, 2H), 5.85 (ddt, $J = 17.3, 10.3, 5.2$ Hz, 1H), 5.35-5.27 (m, 2H), 3.92 (dt, J

= 5.2, 1.6 Hz, 2H), 3.84 (s, 3H), 3.30 (t, J = 7.6 Hz, 2H), 1.60 (s, 3H), 1.28-1.25 (m, 11H), 0.85 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 166.7 (C), 164.2 (C), 157.8 (C), 132.9 (CH), 132.1 (CH), 119.3 (C), 117.4 (CH_2), 113.9 (CH), 55.5 (CH_3), 49.5 (CH_2), 47.8 (CH_2), 31.8 (CH_2), 29.34 (CH_2), 29.22 (CH_2), 28.2 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3). IR (FTIR): 3270, 2922, 2854, 1737, 1692, 1601, 163, 1251 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_4\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 385.2099. Found: 385.2103.



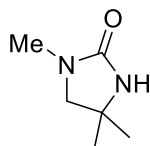
1-Isobutyl-4,4-dimethylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1,1-diisobutyl-3-((4-methoxybenzoyl)oxy)urea **4.11** (0.161 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/ CH_2Cl_2) to yield an amorphous white solid (0.080 g, 95%). TLC R_f : 0.30 in 50% EtOAc/ CH_2Cl_2 . ^1H NMR (400 MHz, CDCl_3): δ 4.34 (br. s, 1H), 3.14 (s, 2H), 2.96 (d, J = 7.5 Hz, 2H), 1.89-1.76 (m, 1H), 1.29 (s, 6H), 0.90 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 161.4 (C), 58.7 (CH_2), 52.1 (C), 50.9 (CH_2), 28.6 (CH_3), 27.1 (CH), 20.1 (CH_3). IR (FTIR): 3208, 3074, 2955, 2871, 1683, 1488, 1448, 1295, 1240 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_9\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}]^+$: 170.1419. Found: 170.1407.



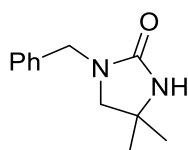
4-Butyl-4-methyl-1-(2-ethylhexyl)imidazolidin-2-one

The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1,1-bis(2-ethylhexyl)urea **4.12** (0.196 g, 0.450 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4

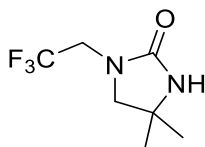
cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (60% EtOAc/ CH_2Cl_2) to yield an amorphous white solid (0.095 g, 75% as a 1:1 diastereoisomers mixt). TLC R_f : 0.21 in 2% MeOH/ CH_2Cl_2 . ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 6.37-6.34 (br s, 1H), 3.02-2.99 (m, 2H), 2.91-2.86 (m, 2H), 1.51-1.33 (m, 5H), 1.32-1.11 (m, 14H), 0.91-0.75 (m, 14H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 160.6 (C), 56.0 (C), 56.0 (C), 54.0 (CH_2), 53.9 (CH_2), 46.2 (CH_2), 38.7 (CH_2), 38.7 (CH_2), 37.0 (CH_2), 36.9 (CH), 31.8 (CH_2), 31.8 (CH_2), 30.1 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.3 (CH_2), 23.5 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.0 (CH), 13.9 (CH), 10.5 (CH_3), 10.5 (CH_3), 7.7 (CH_3), 7.7 (CH_3). IR (FTIR): 3196, 3069, 2967, 2893, 1685, 1441, 1118 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{15}\text{H}_{30}\text{N}_2\text{O}^+$ $[\text{M}]^+$: 282.2671. Found: 282.2655.



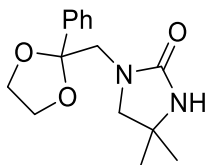
1,4,4-Trimethylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.1** (0.140 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/ CH_2Cl_2) to yield an amorphous white solid (0.060 g, 93%). TLC R_f : 0.16 in 50% EtOAc/ CH_2Cl_2 . ^1H NMR (300 MHz, CDCl_3): δ 4.57 (br. s, 1H), 3.13 (s, 2H), 2.77 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 161.5 (C), 60.7 (CH_2), 51.9 (C), 30.6 (CH_3), 28.6 (CH_3). IR (FTIR): 3540, 3475, 3224, 2955, 2927, 2846, 1673, 1502, 1446, 1405, 1305 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}]^+$: 128.0950. Found: 128.0945.



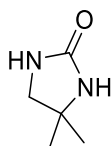
1-Benzyl-4,4-dimethylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1-benzyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea **4.2** (0.190 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂) to yield an amorphous white solid (0.051 g, 50%). TLC R_f: 0.35 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.23 (m, 5H), 4.50 (br s, 1H), 4.35 (s, 2H), 3.00 (s, 2H), 1.24 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 160.9 (C), 137.2 (C), 128.6 (CH), 128.0 (CH), 127.4 (CH), 57.4 (CH₂), 52.0 (C), 47.4 (CH₂), 28.5 (CH₃). IR (FTIR): 3201, 3069, 2962, 2861, 1688, 1492, 1437, 1363, 1299 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₆N₂ [M]⁺: 204.1263. Found: 204.1252.



4,4-Dimethyl-1-(2,2,2-trifluoroethyl)imidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-(2,2,2-trifluoroethyl)urea **4.13** (0.174 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (30% EtOAc/CH₂Cl₂) to yield an amorphous white solid (0.092 g, 94%). TLC R_f: 0.45 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 4.87 (br s, 1H), 3.78 (q, *J* = 9.1 Hz, 2H), 3.30 (s, 2H), 1.32 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 160.3 (C), 124.7 (q, *J* = 278 Hz, C), 59.0 (CH₂), 52.5 (C), 45.4 (q, *J* = 34 Hz, CH₂), 28.4 (CH₃). IR (FTIR): 3223, 3082, 2976, 1697, 1446, 1416, 1313, 1265, 1221, 1149 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₁N₂OF₃ [M]⁺: 196.0823. Found: 196.0807.



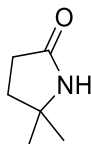
4,4-Dimethyl-1-((2-phenyl-1,3-dioxolan-2-yl)methyl)imidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1-isobutyl-1-(2-phenyl-1,3-dioxolan-2-yl)isobutyl-3-((4-methoxybenzoyl)oxy)urea **4.14** (0.214 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂) to yield an amorphous white solid (0.118 g, 86%). TLC R_f: 0.13 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.56-7.46 (m, 2H), 7.41-7.30 (m, 3H), 4.19-4.10 (br s, 1H), 4.09-4.00 (m, 2H), 3.91-3.79 (m, 2H), 3.58 (s, 2H), 3.23 (s, 2H), 1.20 (s, 6H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 160.8 (C), 140.3 (C), 128.3 (CH), 128. (CH), 109.7 (C), 64.7 (CH₂), 59.6 (CH₂), 51.8 (C), 50.5 (CH₂), 28.3 (CH₃). IR (FTIR): 3197, 3070, 2967, 2893, 1685, 1442, 1243, 1023 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₅H₂₀N₂O₃Na⁺ [M+Na]⁺: 299.1372. Found: 299.1394.



4,4-Dimethylimidazolidin-2-one: The title compound was synthesized according to a modified general procedure **4D** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)urea **4.15** (0.133 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.026 g, 5 mol%) in CH₂Cl₂ (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and heated in a water bath at 60 °C overnight. Upon completion, the reaction was diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (5% MeOH/CH₂Cl₂ + 1% Et₃N) to yield a clear oil (0.013 g, 22%). ¹H NMR

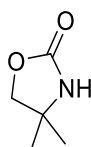
(400 MHz, CDCl₃): δ 4.94-4.62 (br s, 2H), 3.23 (s, 2H), 1.31 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 162.9 (C), 55.3 (C), 54.0 (CH₂), 28.4 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁷³



5,5-Dimethylpyrrolidin-2-one: The title compound was synthesized according to general procedure **4D** using *N*-((4-methoxybenzoyl)oxy)-4-methylpentanamide **4.16** (0.265 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), triethylamine (0.026 g, 5 mol%) in CH₂Cl₂ (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂ $\rightarrow$ 100% EtOAc) to yield a clear oil (0.088 g, 78%). ¹H NMR (400 MHz, CDCl₃): δ 6.09 (s, 1H), 2.41 (dd, *J* = 8.4, 7.6 Hz, 2H), 1.93 (t, *J* = 8.0 Hz, 2H), 1.28 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 177.1 (C), 56.7 (C), 35.5 (CH₂), 30.8 (CH₂), 29.3 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁷⁰

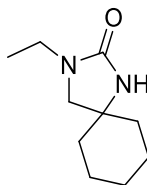


4,4-Dimethyloxazolidin-2-one: The title compound was synthesized according to general procedure **4D** using isobutyl ((4-methoxybenzoyl)oxy)carbamate **4.17** (0.134 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.011 g, 5 mol%) in CH₂Cl₂ (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (20% EtOAc/CH₂Cl₂ $\rightarrow$ 100% EtOAc) to yield a clear oil (0.014 g, 24%).

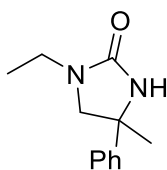
²⁷³ Leung, M.-K.; Lai, J.-L.; Lau, K.-H.; Yu, H.-H.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175.

^1H NMR (300 MHz, CDCl_3): δ 5.21-5.00 (br s, 1H), 4.09 (s, 2H), 1.37 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 159.3 (C), 77.1 (C), 55.4 (CH_2), 27.7 (CH_3).

The ^1H NMR and ^{13}C NMR is in agreement with previous reports.²⁷⁰

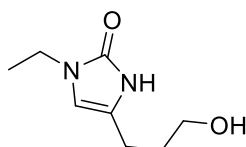


3-Ethyl-1,3-diazaspiro[4.5]decan-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-Methoxybenzoyl)oxy)-1-cyclohexylmethyl-1-ethylurea **4.18** (0.167 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.22 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/Hexanes) to yield an amorphous white solid (0.080 g, 88%). TLC R_f : 0.39 in 2% MeOH/ CH_2Cl_2 . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.65-6.60 (br s, 1H), 3.08-3.01 (m, 4H), 1.62-1.21 (m, 10H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 159.9 (C), 54.5 (CH_2), 53.6 (C), 37.3 (CH_2), 37.1 (CH_2), 24.9 (CH_2), 22.1 (CH_2), 12.6 (CH_3). IR (FTIR): 3202, 2926, 2853, 1677, 1489, 1330, 1258, 1198 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}]^+$: 182.1419. Found: 182.1413.

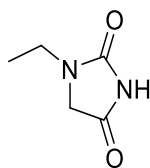


1-Ethyl-4-methyl-4-phenylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(2-phenylpropyl)urea **4.19** (0.163 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced

pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂) to yield an amorphous white solid (0.079 g, 77%). TLC R_f: 0.42 in 30% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.27 (m, 5H), 4.69-4.68 (m, 1H), 3.45 (q, *J* = 10.0 Hz, 2H), 3.39-3.17 (m, 2H), 1.68 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.8 (C), 145.9 (C), 128.8 (CH), 127.4 (CH), 124.9 (CH), 58.9 (CH₂), 57.2 (C), 37.9 (CH₂), 28.6 (CH₃), 12.8 (CH₃). IR (FTIR): 3194, 3069, 2969, 2925, 2854, 1679, 1493, 1444, 1299, 1283, 1089 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₆N₂O [M]⁺: 204.1263. Found: 204.1237.



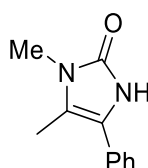
1-Ethyl-4-(3-hydroxypropyl)-1H-imidazol-2(3H)-one (2l): The title compound was synthesized according to general procedure **4D** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-((tetrahydrofuran-2-yl)methyl)urea **4.20** (0.161 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The majority of the product was found to dissolve in the aqueous phase, and so the aqueous phase was collected, and concentrated under reduced pressure. The combined organic and aqueous phases were purified by column chromatography (50% EtOAc/CH₂Cl₂ → 5% MeOH/CH₂Cl₂) to yield an amorphous white solid (0.079 g, 93%). TLC R_f: 0.06 in 50% EtOAc/CH₂Cl₂; 0.53 in 10% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 10.63 (s, 1H), 5.91 (br. s, 1H), 3.74 (s, 1H), 3.68-3.56 (m, 4H), 2.50 (t, *J* = 6.9 Hz, 2H), 1.81-1.72 (m, 2H), 1.27-1.20 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 154.2 (C), 122.6 (C), 106.3 (CH), 60.9 (CH₂), 37.8 (CH₂), 31.8 (CH₂), 21.7 (CH₂), 14.9 (CH₃). IR (FTIR): 3271, 2962, 1683, 1428, 1351, 1242, 1047 cm⁻¹. HRMS (EI): Despite multiple attempts to obtain an accurate mass using both ESI and EI, one could not be obtained for this compound. However, C¹³ peaks at 122.6 and 106.3 ppm align with known structures and provides solid evidence for structural assignment.



1-Ethylimidazolidine-2,4-dione: The title compound was synthesized according to general procedure **4D** using 1-(2,2-dimethoxyethyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea **4.21** (0.148 g, 0.500 mmol),

tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure and then purified by column chromatography (50% EtOAc/CH₂Cl₂ → 5% CH₃OH/ CH₂Cl₂) to yield an amorphous white solid (0.055 g, 86%). ¹H NMR (400 MHz, CDCl₃): δ 8.46 (s, 1H), 3.91 (s, 2H), 3.43 (q, *J* = 7.3 Hz, 2H), 1.19 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 170.4 (C), 156.0 (C), 50.2 (CH₂), 37.2 (CH₂), 12.9 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁷⁴

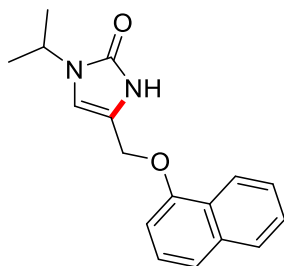


1,5-Dimethyl-4-phenyl-1H-imidazol-2(3H)-one: The title compound was synthesized according to general procedure **4D** using 1-(2-hydroxy-2-phenylethyl)-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.22** (0.167 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the product precipitated from solution and was collected by filtration to yield an amorphous white solid (0.047 g, 50%) the filtrate was evaporated to reveal product in solution which could be purified by silica column chromatography (50% EtOAc/CH₂Cl₂ → 5% CH₃OH/ CH₂Cl₂) (0.020 g, 18%). The combined isolated yield is therefore 0.067 g, 71%. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (s, 1H), 7.32 (d, *J* = 39.5 Hz, 6H), 3.24 (s, 3H), 2.22 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 154.4 (C), 131.0 (C), 129.1 (CH), 127.0 (CH), 126.5 (CH), 117.7 (C), 116.4 (C), 27.2 (CH₃), 9.8 (CH₃).

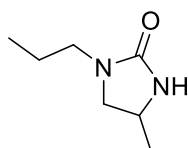
The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁷⁵

²⁷⁴ Sigachev, A. S.; Kravchenko, A. N.; Belyakov, P. A.; Lebedev, O. V.; Makhova N. N. *Russ. Chem. Bull.* **2006**, 55, 865-872.

²⁷⁵ Holzmann, G.; Krieg, B.; Lautenschläger, H.; Konieczny, P. *J. Heterocycl. Chem.* **1979**, 16, 983-985.

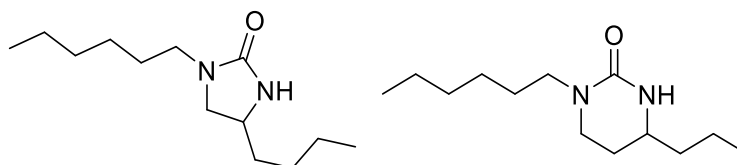


1-Ethyl-4-((naphthalen-1-yloxy)methyl)-1H-imidazol-2(3H)-one: The title compound was synthesized according to general procedure **4D** using 1-(2-hydroxy-3-(naphthalen-1-yloxy)propyl)-1-isopropyl-3-((4-methoxybenzoyl)oxy)urea **4.23** (0.158 g, 0.350 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.006 g, 2 mol%), triethylamine (0.039 g, 0.385 mmol) in MeCN (1.75 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the product precipitated from solution and was collected by filtration to yield an amorphous white solid (0.035 g, 35%) the filtrate was evaporated to reveal an additional product in solution which could coelute with *p*-methoxybenzoic acid upon silica column chromatography (50% EtOAc/CH₂Cl₂ → 5% CH₃OH/ CH₂Cl₂) (0.020 g, 18%). The combined isolated yield is therefore 0.067 g, 71%. TLC R_f: 0.07 in 50% EtOAc/CH₂Cl₂; 0.45 in 5% MeOH/CH₂Cl₂. ¹H NMR (600 MHz, DMSO-*d*₆): δ 10.36-10.35 (m, 1H), 8.17-8.15 (m, 1H), 7.88-7.86 (m, 1H), 7.54-7.43 (m, 5H), 7.09-7.08 (m, 1H), 6.78-6.78 (m, 1H), 4.92 (d, *J* = 5.4 Hz, 2H), 4.19 (dt, *J* = 0.8, 0.4 Hz, 1H), 1.25-1.21 (m, 6H). ¹³C NMR (151 MHz, DMSO-*d*₆): δ 154.0 (C), 153.4 (C), 134.5 (C), 127.9 (CH), 127.0 (CH), 126.6 (CH), 125.7 (CH), 125.5 (C), 122.3 (CH), 120.7 (CH), 116.7 (C), 108.8 (CH), 106.2 (CH), 62.1 (CH₂), 43.7 (CH), 22.3 (CH₃). IR (FTIR): 3292, 3227, 2952, 2878, 1681, 1577, 1491, 1453, 1394 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₇H₁₈N₂O₂ [M]⁺: 282.1368. Found: 282.1378.

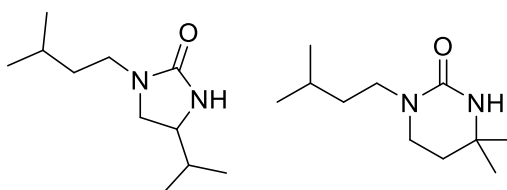


4-Methyl-1-propylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1,1-dipropylurea **2.46** (0.147 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.059 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase

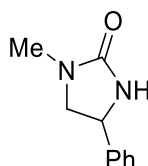
was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂) to yield an amorphous white solid (0.065 g, 92%). TLC R_f: 0.15 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 5.13-4.23 (br s, 1H), 3.84-3.68 (m, 1H), 3.50 (t, *J* = 8.5 Hz, 1H), 3.25 – 3.01 (m, 2H), 2.94 (dd, *J* = 8.5, 6.3 Hz, 1H), 1.50 (h, *J* = 7.4 Hz, 1H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 162.2 (C), 52.3 (CH), 45.6 (CH₂), 45.0 (CH₂), 21.6 (CH₂), 20.9 (CH₃), 11.3 (CH₃). IR (FTIR): 3327, 2973, 2866, 1666, 1381, 1045 cm⁻¹. HRMS (EI): Exact mass calcd for C₇H₁₄N₂ [M]⁺: 142.1106. Found: 142.1124.



1-Hexyl-4-butyl-imidazol-2-one and 1-hexyl-4-propyltetrahydropyrimidin-2(1H)-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1,1-dihexylurea **4.24** (0.189 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.059 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (97:2:1 CH₂Cl₂/iPrOH/AcOH) to yield an inseparable mixture as a colourless oil (0.051 g, 72%). TLC R_f: 0.18 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 6.50-6.40 (br s, 1H), 6.08-5.99 (br s, 1H), 3.53-3.26 (m, 3H), 3.21-2.90 (m, 3H), 2.89-2.83 (m, 1H), 1.47-1.14 (m, 1H), 0.90-0.81 (m, 8H). Compound **4.66**: ¹³C NMR (100 MHz, DMSO-*d*₆): δ 161.3 (C), 49.9 (CH₂), 49.1 (CH), 42.5 (CH₂), 35.3 (CH₂), 30.9 (CH₂), 27.0 (CH₂), 25.9 (CH₂), 22.1 (CH₂), 22.0 (CH₂), 22.0 (CH₂), 13.9 (CH₃), 13.9 (CH₃). Compound **4.66'**: ¹³C NMR (100 MHz, DMSO-*d*₆): δ 155.1 (C), 49.8 (CH), 46.2 (CH₂), 43.3 (CH₂), 37.8 (CH₂), 31.1 (CH₂), 28.1 (CH₂), 27.3 (CH₂), 27.1 (CH₂), 26.0 (CH₂), 18.0 (CH₂), 14.0 (CH₃). (one carbon is missing due to overlap with compound **4.66**). IR (FTIR): 3213, 2956, 2923, 2856, 1687, 1449, 1261 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₃H₂₆N₂O [M]⁺: 226.2045. Found: 226.2030.

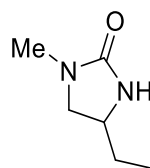


1-Isopentyl-4-isopropylimidazolidin-2-one and 1-isopentyl-4-isopropylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1,1-diisopentyl-3-((4-methoxybenzoyl)oxy)urea **4.25** (0.175 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (96:3:1 CH₂Cl₂/iPrOH/AcOH) to yield an inseparable mixture as a colourless oil (0.078 g, 79%). TLC R_f: 0.51 in 50% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.55-6.50 (br s, 1H), 6.08-6.02 (br s, 1H), 3.29-2.88 (m, 10H), 1.66-1.58 (m, 2H), .56-1.41 (m, 4H), 1.38-1.22 (m, 6H), 1.09 (s, 6H), 0.91-0.77 (m, 27H). ¹³C (100 MHz, DMSO-*d*₆): δ 161.4 (C), 154.7 (C), 54.9 (CH), 49.3 (C), 47.8 (CH₂), 44.4 (CH₂), 41.5 (CH₂), 40.8 (CH₂), 36.0 (CH₂), 35.9 (CH₂), 34.3 (CH₂), 32.7 (CH), 29.0 (CH), 25.4 (CH), 25.2 (CH), 22.5 (CH), 22.4 (CH), 22.3 (CH), 18.2 (CH₃), 17.7 (CH₃). IR (FTIR): 3210, 2956, 2870, 1685, 1644, 1459, 1261 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₂₂N₂O [M]⁺: 198.1732. Found: 198.1716.

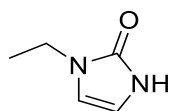


1-Methyl-4-phenylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-methyl-1-phenethylurea **4.10** (0.164 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/Hexanes → 100% EtOAc) to yield a white solid (0.067 g, 75%). TLC R_f: 0.29 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.27 (m, 5H), 4.77 (br. s, 1H), 4.72 (ddd, *J* = 8.8, 7.4, 1.5 Hz, 1H), 3.76 (t, *J* = 8.8 Hz, 1H), 3.20 (dd, *J* = 8.8, 7.4 Hz, 1H), 2.79 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 162.3 (C), 141.7 (C), 129.0 (CH), 128.3 (CH), 126.2 (CH), 56.2 (CH₂), 53.8 (CH), 30.7 (CH₃). IR (FTIR): 3198, 3083, 2919, 2852,

1681, 1500, 1440, 1403, 1252 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}]^+$: 176.0950. Found: 176.0974.

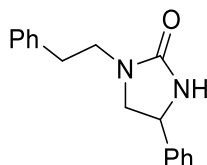


1-Methyl-4-ethyl-imidazol-2-one (2t): The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-butyl-1-methylurea **4.26** (0.140 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (96:3:1 CH_2Cl_2 /iPrOH/AcOH) to yield an amorphous white solid (0.032 g, 50%). TLC R_f : 0.36 in 2% MeOH/ CH_2Cl_2 . ^1H NMR (400 MHz, CDCl_3): δ 4.64-4.28 (br s, 1H), 3.64-3.46 (m, 2H), 3.03 (dd, J = 8, 6.1 Hz, 1H), 2.78 (s, 3H), 1.61-1.56 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 162.2 (C), 52.9 (CH_2), 51.1 (CH), 30.5 (CH), 28.6 (CH_2), 9.6 (CH_3). IR (FTIR): 3203, 2960, 1683, 1507, 1311, 161, 1231 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}]^+$: 128.0950. Found: 128.0946.

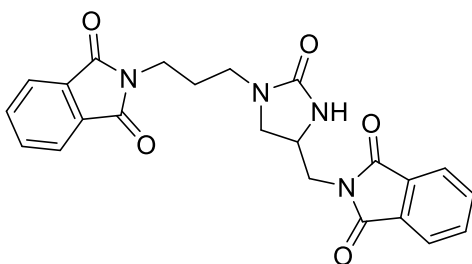


1-Ethyl-1H-imidazol-2(3H)-one: The title compound was synthesized according to general procedure **4D** using 1-ethyl-1-(2-hydroxyethyl)-3-((4-methoxybenzoyl)oxy)urea **4.28** (0.141 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/ CH_2Cl_2 $\rightarrow$ 5% MeOH/ CH_2Cl_2) to yield a white solid (0.028 g, 50%). TLC R_f : 0.07 in 50% EtOAc/ CH_2Cl_2 ; 0.45 in 5% MeOH/ CH_2Cl_2 . ^1H NMR (400 MHz, CDCl_3): δ 9.89 (s, 1H), 6.29 (t, J = 2.6 Hz, 1H), 6.20 (t, J = 2.5 Hz, 1H), 3.67 (q, J

7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 154.3 (C), 110.8 (CH), 108.0 (CH), 37.9 (CH_2), 14.8 (CH_3). IR (FTIR): 3200, 2929, 1663, 1455, 1258, 1088 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_5\text{H}_8\text{N}_2\text{O}$ $[\text{M}]^+$: 112.0637. Found: 112.0618.

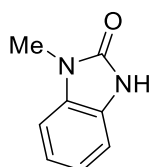


Phenethyl-4-phenylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1,1-diphenethylurea **4.31** (0.209 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/Hexanes) to yield a white solid (0.100 g, 75%). TLC R_f : 0.50 in 50% EtOAc/ CH_2Cl_2 . ^1H NMR (400 MHz, CDCl_3): δ 7.37-7.19 (m, 10H), 4.73 (br. s, 1H), 4.68 (ddd, J = 8.8, 7.1, 1.4 Hz, 1H), 3.68 (t, J = 8.8 Hz, 1H), 3.56-3.43 (m, 2H), 3.14 (dd, J = 8.8, 7.1 Hz, 1H), 2.85 (t, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 161.7 (C), 141.7 (C), 139.0 (C), 129.0 (CH), 128.9 (C), 128.6 (CH), 128.3 (CH), 126.5 (CH), 126.2 (CH), 54.2 (CH_2), 53.9 (CH), 44.9 (CH_2), 34.5 (CH_2). IR (FTIR): 3216, 3083, 3028, 2917, 2854, 1680, 1490, 1452, 1360, 1318, 1255 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}]^+$: 266.1419. Found: 233.1431.



2-(3-(4-((1,3-Dioxisoindolin-2-yl)methyl)-2-oxoimidazolidin-1-yl)propyl)isoindoline-1,3-dione (2z): The title compound was synthesized according to general procedure **G** using 1,1-bis(3-(1,3-dioxisoindolin-2-yl)propyl)-3-((4-methoxybenzoyl)oxy)urea (0.292 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4

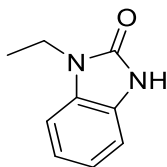
cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂ → 100% EtOAc) to yield a white solid (0.078 g, 36%). TLC R_f: 0.16 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.82 (ddd, *J* = 13.4, 5.5, 3.0 Hz, 4H), 7.70 (ddd, *J* = 14.6, 5.5, 3.0 Hz, 4H), 4.74 (s, 1H), 3.98 (dq, *J* = 9.0, 4.8 Hz, 1H), 3.90 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.78 (dd, *J* = 14.0, 4.7 Hz, 1H), 3.68 (td, *J* = 7.3, 3.2 Hz, 2H), 3.56 (t, *J* = 8.8 Hz, 1H), 3.34 (dd, *J* = 9.0, 5.6 Hz, 1H), 3.25-3.12 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 168.5 (C), 138.2 (C), 161.1 (C), 134.3 (CH), 133.9 (CH), 131.1 (C), 131.7 (C), 123.6 (CH), 123.2 (CH), 49.3 (CH), 48.6 (CH₂), 41.1 (CH₂), 40.9 (CH₂), 35.4 (CH₂), 26.6 (CH₂). IR (FTIR): 3200, 2864, 1693, 1387, 1258, 1027 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₃H₂₀N₄O₅Na [M+Na]⁺: 455.1325. Found: 455.1331.



1-Methyl-1H-benzo[d]imidazol-2(3H)-one: The title compound was synthesized following general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-methyl-1-phenylurea **2.35** (0.240 g, 0.800 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (10% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield a white solid (0.085 g, 72%). ¹H NMR (400 MHz, CDCl₃): δ 9.94 (s, 1H), 7.11-7.05 (m, 3H), 6.98-6.95 (m, 1H), 3.42 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 156.0 (C), 131.1 (C), 128.0 (C), 121.8 (CH), 121.5 (CH), 109.7 (CH), 107.8 (CH), 27.0 (CH₃).

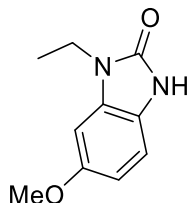
The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁷⁶

²⁷⁶ Ando, K.; Kobayashi, T.; Uchida, N. *Org. Lett.* **2015**, *17*, 2554–2557.



1-Ethyl-1,3-dihydro-benzoimidazol-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-ethyl-1-phenylurea **4.33** (0.157 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂) to yield an amorphous white solid (0.039 g, 48%). ¹H NMR (400 MHz, CDCl₃): δ 10.49-10.20 (br s, 1H), 7.19-6.96 (m, 4H), 3.98 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 155.5 (C), 130.0 (C), 128.1 (C), 121.4 (CH), 121.2 (CH), 109.7 (CH), 107.7 (CH), 35.6 (CH₂), 13.6 (CH₃).

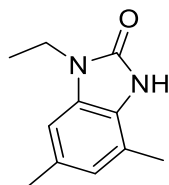
The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁷⁷



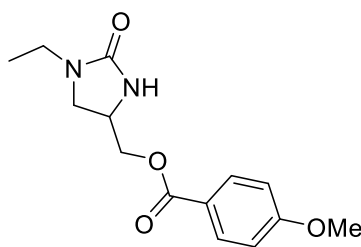
1-Ethyl-5-methoxy-1H-benzo[d]imidazol-2(3H)-one: The title compound was synthesized according to general procedure **4D** using 1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(3-methoxyphenyl)urea **4.34** (0.276 g, 0.800 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (40% EtOAc/CH₂Cl₂) to yield a white solid (0.143 g, 93%). TLC R_f: 0.33 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃):

²⁷⁷ Peng, L.; Zhiming, W.; Xianming, H. *Eur. J. Org. Chem.* **2012**, 10, 1994 – 2000.

δ 9.57 (d, J = 0.3 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.4, 2.4 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.9 (C), 155.5 (C), 131.1 (C), 122.2 (C), 109.9 (CH), 106.7 (CH), 95.3 (CH), 56.1 (CH_3), 35.8 (CH_2), 13.7 (CH_3). IR (FTIR): 2978, 2934, 1681, 1629, 1609, 1493, 1447, 1396, 1223, 1081 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 192.0899. Found: 192.0876.

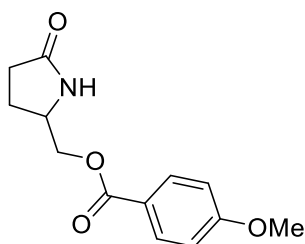


1-Ethyl-4,6-dimethyl-1H-benzo[d]imidazol-2(3H)-one: The title compound was synthesized according to general procedure **4D** using 1-(3,5-dimethylphenyl)-1-ethyl-3-((4-methoxybenzoyl)oxy)urea **4.35** (0.273 g, 0.80 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the product precipitated out of solution and was collected over a fritted funnel (0.128 g, 84%). TLC R_f : 0.42 in 50% EtOAc/ CH_2Cl_2 . ^1H NMR (400 MHz, CDCl_3): δ 10.04 (br s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 3.90 (q, J = 7.2 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.7 (C), 130.8 (C), 129.8 (C), 125.0 (C), 123.3 (CH), 119.1 (C), 105.9 (CH), 35.6 (CH_2), 21.5 (CH_3), 16.2 (CH_3), 13.7 (CH_3). IR (FTIR): 2978, 1687, 1459, 1396, 1280 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}]^+$: 190.1106. Found: 190.1120.

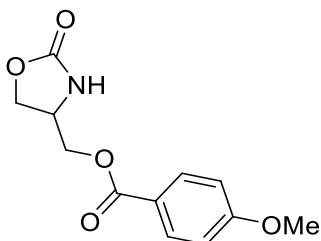


(1-Methyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate: The title compound was synthesized according to general procedure **4D** using 1-allyl-3-((4-methoxybenzoyl)oxy)-1-methylurea **4.38** (0.132 g, 0.50 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in CH_2Cl_2 (5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL). The organic phase was collected,

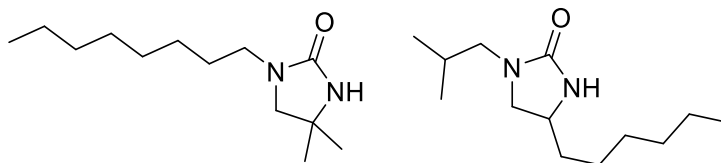
dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂ → 30% EtOAc/CH₂Cl₂) to yield a white solid (0.089 g, 66%). TLC R_f: 0.51 in 2% MeOH/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 8.01-7.94 (m, 2H), 6.97-6.91 (m, 2H), 4.68-4.58 (br s, 1H), 4.41-4.35 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.26-4.20 (dd, *J* = 11.2, 7.1 Hz, 1H), 4.09-4.00 (m, 1H), 3.88 (s, 3H), 3.62 (t, *J* = 9.0 Hz, 3H), 3.26 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.79 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 165.9 (C), 163.7 (C), 161.5 (C), 131.7 (CH), 121.8 (C), 113.8 (CH), 66.2 (CH₂), 55.5 (CH), 49.8 (CH₂), 48.4 (CH), 30.5 (CH₃). IR (FTIR): 3200, 2942, 2866, 1699, 1600, 1444, 1252 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₁H₁₄N₂O₂ [M]⁺: 264.1110. Found: 264.1080.



(5-Oxopyrrolidin-2-yl)methyl 4-methoxybenzoate: The title compound was synthesized according to general procedure **4D** using *N*-((4-methoxybenzoyl)oxy)pent-4-enamide **4.39** (0.249 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.022 g, 5 mol%) in CH₂Cl₂ (5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL). The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂ → 100% EtOAc) to yield a white solid (0.169 g, 68%). TLC R_f: 0.12 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.12 (br s, 1H), 4.40 (dd, *J* = 11.2, 3.7 Hz, 1H), 4.11 (dd, *J* = 11.2, 7.2 Hz, 1H), 4.04-3.98 (m, 1H), 3.84 (s, 3H), 2.45-2.26 (m, 3H), 1.95-1.86 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 177.9 (C), 166.0 (C), 163.7 (C), 131.7 (CH), 121.8 (C), 113.8 (CH), 67.2 (CH₂), 55.5 (CH₃), 53.0 (CH), 29.5 (CH₂), 23.4 (CH₂). IR (FTIR): 3168, 3079, 2965, 2841, 1680, 1605, 1511, 1461, 1383, 1252 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₃H₁₅NO₄Na [M]⁺: 272.0899. Found: 272.0904.



(2-Oxooxazolidin-4-yl)methyl 4-methoxybenzoate: The title compound was synthesized according to general procedure **4D** using allyl (4-methoxybenzoyl)oxycarbamate **4.40** (0.126 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in CH₂Cl₂ (5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL). The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/CH₂Cl₂ → 100% EtOAc) to yield a white solid (0.065 g, 52%). TLC R_f: 0.32 in 50% EtOAc/CH₂Cl₂. ¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.79 (br s, 1H), 4.59-4.55 (m, 1H), 4.44-4.41 (m, 1H), 4.31-4.22 (m, 3H), 3.87 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.1 (C), 164.0 (C), 159.4 (C), 132.0 (CH), 121.5 (C), 114.0 (CH), 67.2 (CH₂), 65.3 (CH₂), 55.6 (CH₃), 51.5 (CH). IR (FTIR): 3277, 2941, 2840, 1750, 1706, 1603, 1580, 1511, 1417, 1281, 1251 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₃NO₅ [M]⁺: 251.0794. Found: 251.0799.

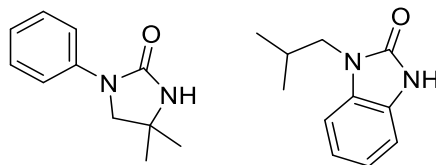


1-Octyl-4,4-dimethylimidazolidin-2-one and 4-hexyl-1-isobutylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-isobutyl-1-octylurea **4.41** (0.189 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (30% EtOAc/Hexanes) to yield a colourless oil (0.077 g, 68%). TLC R_f: 0.48 in 50% EtOAc/CH₂Cl₂.

1-Octyl-4,4-dimethylimidazolidin-2-one: ¹H NMR (400 MHz, DMSO-*d*₆): δ 6.36-6.33 (br s, 1H), 3.03-2.97 (m, 4H), 1.42-1.35 (m, 3H, 2aj and 2aj'), 1.30-1.18 (m, 13H, 2aj and 2aj'), 1.15 (s, 6H), 0.85 (app t, *J* = 6.9 Hz, 4H, 2aj and 2aj'), 0.81 (app dd, *J* = 6.6, 2.4 Hz, 2H, 2aj and 2aj'). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 160.3 (C), 57.1 (CH₂), 51.1 (C), 42.2 (CH₂), 31.2 (CH₂), 28.6 (CH₂), 28.6 (CH), 28.0 (CH), 27.0 (CH₂), 26.1 (CH₂), 22.1 (CH₂), 13.9 (CH₃).

4-Hexyl-1-isobutylimidazolidin-2-one: ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 6.46-6.44 (br s, 1H), 3.52-3.46 (m, 1H), 3.43-3.38 (m, 2H), 2.89-2.85 (m, 1H), 2.83-2.74 (m, 2H), 1.81-1.71 (m, 1H), 1.42-1.35 (m, 3H, , 2aj and 2aj'), 1.30-1.18 (m, 13H, , 2aj and 2aj'), 0.85 (app t, J = 6.9 Hz, 4H, , 2aj and 2aj'), 0.81 (app dd, J = 6.6, 2.4 Hz, 2H, , 2aj and 2aj'). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 161.4, 50.6, 50.3, 49.1, 35.7, 26.4, 24.7, 22.0, 20.0, 19.9, 13.9 (one carbon is missing due to overlap).

IR (FTIR): 3202, 2917, 2852, 1686, 1457, 1303, 1240 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{13}\text{H}_{26}\text{N}_2\text{O}$ $[\text{M}]^+$: 226.2045. Found: 226.2020.



4,4-Dimethyl-1-phenylimidazolidin-2-one and 1-isobutyl-1,3-dihydro-2H-benzo[d]imidazol-2-one: The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-isobutyl-1-phenylurea **4.42** (0.171 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (10% EtOAc/ CH_2Cl_2 $\rightarrow$ 20% EtOAc/ CH_2Cl_2).

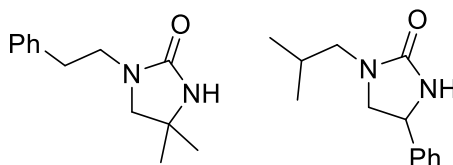
4,4-Dimethyl-1-phenyl-2-imidazolidinone: as a white solid (0.039 g, 41%). ^1H NMR (300 MHz, CDCl_3): δ 7.58-7.51 (m, 2H), 7.39-7.30 (m, 2H), 7.10-7.02 (m, 1H), 4.61-5.43 (br s, 1H), 3.66 (s, 2H), 1.41 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 158.2 (C), 140.2 (C), 128.8 (CH), 122.5 (CH), 117.7 (CH), 58.2 (CH_2), 51.3 (C), 28.6 (CH_3).

The ^1H NMR and ^{13}C NMR is in agreement with previous reports.²⁷⁸

1-Isobutyl-1,3-dihydro-benzoimidazol-2-one: as a pink solid (0.033 g, 35%). ^1H NMR (300 MHz, CDCl_3): δ 8.92-8.83 (br s, 1H), 7.13-7.05 (m, 3H), 7.02-6.97 (m, 1H), 3.70 (d, J = 7.5 Hz, 2H), 2.33-2.17 (m, 1H), 1.00 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 155.8 (C), 130.8 (C), 127.9 (C), 121.3 (CH), 121.1 (CH), 109.5 (CH), 108.1 (CH), 48.3 (CH_2), 27.9 (CH), 20.1 (CH_3).

²⁷⁸ Kim, T. H.; Lee, G.-J. *J. Org. Chem.* **1999**, 64, 2941-2943.

The ^1H NMR and ^{13}C NMR is in agreement with previous reports.²⁷⁹

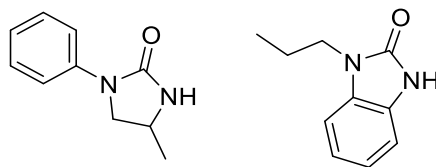


4,4-Dimethyl-1-phenethylimidazolidin-2-one and 1-Isobutyl-4-phenylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using 1-isobutyl-3-((4-methoxybenzoyl)oxy)-1-phenethylurea **4.43** (0.185 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.056 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (gradient 20% EtOAc/Hexanes $\rightarrow$ 40% EtOAc/Hexanes) to yield a white solid (0.037 g, 37%).

4,4-Dimethyl-1-phenethylimidazolidin-2-one: as an amorphous white solid (0.037 g, 37%). TLC R_f : 0.13 in 30% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.19 (m, 5H), 4.31 (s, 1H), 3.44 (dd, J = 7.9, 6.8 Hz, 2H), 3.02 (s, 2H), 2.83 (t, J = 7.4 Hz, 2H), 1.21 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.9 (C), 139.3 (C), 128.9 (CH), 128.6 (CH), 126.5 (CH), 58.6 (CH_2), 52.1 (C), 44.8 (CH_2), 34.6 (CH_2), 28.5 (CH_3). IR (FTIR): 3202, 3069, 2967, 2956, 2857, 1683, 1489, 1452, 1365, 1302 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}]^+$: 218.1419. Found: 218.1396.

1-Isobutyl-4-phenylimidazolidin-2-one: as amorphous white solid (0.059 g, 50%). TLC R_f : 0.28 in 30% EtOAc/Hexanes. ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.29 (m, 5H), 4.77-4.73 (m, 2H), 3.79 (t, J = 9.0 Hz, 1H), 3.22 (dd, J = 8.8, 7.3 Hz, 1H), 3.09-2.95 (m, 2H), 1.82 (dq, J = 13.7, 6.9 Hz, 1H), 0.91 (dd, J = 6.7, 4.4 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ 162.2 (C), 141.9 (C), 129.1 (CH), 128.3 (CH), 126.2 (CH), 54.4 (CH_2), 54.0 (CH), 51.2 (CH_2), 27.1 (CH), 20.16 (CH_3). IR (FTIR): 3200, 3082, 2953, 1682, 1491, 1449, 1255 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}]^+$: 218.1419. Found: 218.1404.

²⁷⁹ Vernin, G.; Domlog, H.; Siv, C.; Metzger, J., El-Shafei, A. K. *J. Heterocycl. Chem.* **1981**, *18*, 85-89.



4-Methyl-1-phenylimidazolidin-2-one and 1-propyl-1,3-dihydro-2H-benzo[d]imidazol-2-one:

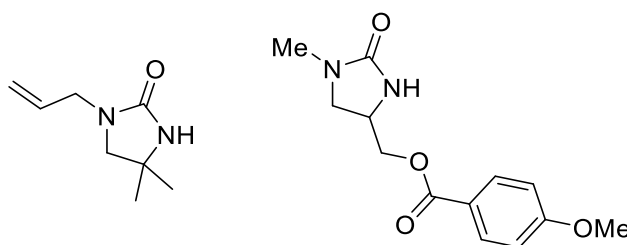
The title compound was synthesized according to general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-phenyl-1-propylurea **4.44** (0.164 g, 0.500 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), triethylamine (0.057 g, 0.55 mmol) in MeCN (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compounds were purified by column chromatography (10% EtOAc/CH₂Cl₂ → 20% EtOAc/CH₂Cl₂).

4-Methyl-1-phenylimidazolidin-2-one: as a yellow solid (0.009 g, 10%). ¹H NMR (300 MHz, CDCl₃): δ 7.58-7.51 (m, 2H), 7.39-7.31 (m, 2H), 7.10-7.02 (m, 1H), 4.87-4.79 (br s, 1H), 4.08-3.90 (m, 2H), 3.50 (dd, *J* = 8.3, 7.7 Hz, 1H), 1.36 (d, *J* = 5.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 158.8 (C), 140.1 (C), 128.8 (CH), 122.7 (CH), 117.8 (CH), 52.5 (CH₂), 44.8 (CH), 21.7 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁸⁰

1-Propyl-1,3-dihydro-2H-benzo[d]imidazol-2-one: as a yellow solid (0.056 g, 63%). ¹H NMR (300 MHz, CDCl₃): δ 10.69-10.36 (br s, 1H), 7.20-6.97 (m, 4H), 3.93-3.84 (m, 2H), 1.83 (apt sxt, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 155.8 (C), 130.4 (C), 128.0 (C), 121.3 (CH), 121.1 (CH), 109.7 (CH), 107.9 (CH), 42.4 (CH₂), 21.7 (CH₂), 11.3 (CH).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁸¹



²⁸⁰ Kim, T. H.; Lee, G.-J. *J. Org. Chem.* **1999**, 64, 2941-2943.

²⁸¹ Tapia, I.; Alonso-Cires, L.; López-Tudanca, P. L.; Mosquera, R.; Labeaga, L.; Inneráritu, A.; Orjales, A. *J. Med. Chem.* **1999**, 42 (15), 2870-2880.

1-Allyl-4,4-dimethylimidazolidin-2-one and (1-isobutyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate: The title compound was synthesized according to general procedure **4D** using 1-allyl-1-isobutyl-3-((4-methoxybenzoyl)oxy)urea **4.45** (0.306 g, 1.00 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), triethylamine (0.111 g, 0.55 mmol) in MeCN (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compounds were isolated as a mixture by column chromatography (20% EtOAc/CH₂Cl₂ → 40% EtOAc/CH₂Cl₂), white solid (59%, 1.8 : 1 (**4.89** : **4.90**)).

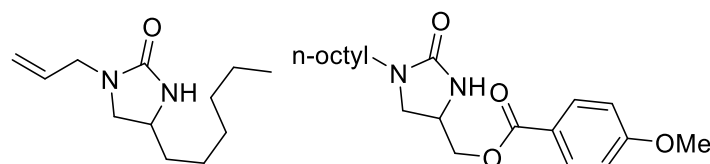
TLC R_f: 0.30 in 50% EtOAc/CH₂Cl₂.

1-Allyl-4,4-dimethylimidazolidin-2-one: ¹H NMR (400 MHz, CDCl₃): δ 5.73 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.19-5.12 (m, 2H), 4.50 (br s, 1H), 3.76 (dt, *J* = 6.0, 1.4 Hz, 2H), 3.09 (s, 2H), 1.27 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 160.7 (C), 133.5 (CH), 117.4 (CH₂), 57.7 (CH₂), 52.0 (C), 46.1 (CH₂), 28.5 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁸²

1-Isobutyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate: ¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.07 (br s, 1H), 4.33 (dd, *J* = 11.1, 4.9 Hz, 1H), 4.19 (dd, *J* = 11.1, 7.0 Hz, 1H), 4.05-3.98 (m, 1H), 3.84 (s, 3H), 3.57 (t, *J* = 9.1 Hz, 1H), 3.22 (dd, *J* = 9.2, 5.3 Hz, 1H), 2.97 (qd, *J* = 12.5, 7.5 Hz, 2H), 1.84 (tt, *J* = 13.8, 6.9 Hz, 1H), 0.88 (dd, *J* = 6.7, 3.2 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 166.0 (C), 163.7 (C), 161.7 (C), 131.8 (CH), 121.9 (C), 113.8 (CH), 66.4 (CH₂), 55.5 (CH₃), 51.0 (CH₂), 48.6 (CH), 48.0 (CH₂), 26.9 (CH), 20.0 (CH₃).

IR (FTIR): 3210, 2950, 1681, 1604, 1450, 1254, 1113 cm⁻¹.



1-Allyl-4-hexylimidazolidin-2-one and (1-octyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate: The title compounds were synthesized according to general procedure **4F** using 1-allyl-3-((4-methoxybenzoyl)oxy)-1-octylurea **4.46** (0.362 g, 1.00 mmol), tris(2,2'-

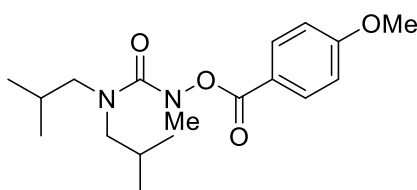
²⁸² Kim, T. H.; Lee, G.-J. *J. Org. Chem.* **1999**, 64, 2941-2943.

bipyridine)ruthenium(II) hexafluorophosphate (0.017 g, 2 mol%), triethylamine (0.111 g, 0.55 mmol) in MeCN (5.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compounds co-eluted upon flash column chromatography (20% EtOAc/CH₂Cl₂ → 40% EtOAc/CH₂Cl₂), (0.175 g, 48% yield) white solid (10 : 1 (**4.91** : **4.92**)). TLC R_f = 0.41 in 100% EtOAc.

1-Allyl-4-hexylimidazolidin-2-one: ¹H NMR (400 MHz, CDCl₃): δ (300 MHz, CDCl₃) δ 5.74 (ddt, *J* = 17.1, 10.1, 6.0 Hz, 1H), 5.20-5.13 (m, 2H), 4.45 (br s, 1H), 3.82-3.69 (m, 2H), 3.63-3.61 (m, 1H), 3.01-2.94 (m, 1H), 1.53-1.44 (m, 10H), 0.90-0.88 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.3 (C), 133.4 (CH), 117.5 (CH₂), 50.5 (CH₂), 50.1 (CH), 46.2 (CH₂), 36.0 (CH₂), 31.6 (CH₂), 29.1 (CH₂), 25.5 (CH₂), 22.5 (CH₂), 14.1 (CH₃).

(1-Octyl-2-oxoimidazolidin-4-yl)methyl 4-methoxybenzoate: ¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.67 (br s, 1H), 4.33 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.20 (dd, *J* = 11.1, 6.9 Hz, 1H), 4.03-3.99 (m, 1H), 3.85 (s, 3H), 3.58 (t, *J* = 9.0 Hz, 1H), 3.45 (s,), 3.24-3.12 (m, 3H), 1.29-1.23 (m, 12H), 0.87-0.84 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.0 (C), 163.7 (C), 161.4 (C), 131.8 (CH), 121.8 (C), 113.8 (CH), 66.3 (CH₂), 55.5 (CH₃), 48.6 (CH), 47.4 (CH₂), 43.4 (CH₂), 31.8 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 27.6 (CH₂), 26.8 (CH₂), 22.6 (CH₂), 14.1 (CH₃).

IR (FTIR): 3205, 2920, 2855, 1681, 1605, 1455, 1255, 1118 cm⁻¹.

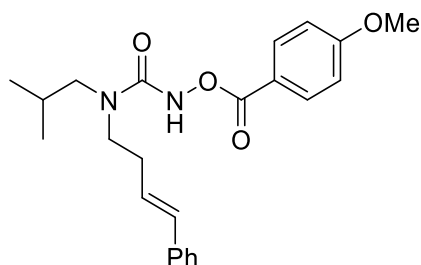


3-((4-Methoxybenzoyl)oxy)-1,1-diisobutyl-3-methylurea: The title compound was synthesized according to general procedure **4A** using *N,N*-diisobutylamine (1.75 mL, 10.0 mmol), toluene (0.8 M), NaOH pellets (0.400 g, 10.0 mmol), and water (2.9 M) at 0°C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0°C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to

release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N,N*-diisobutylaminecarbamoyl chloride which was used in the next step without further purification.

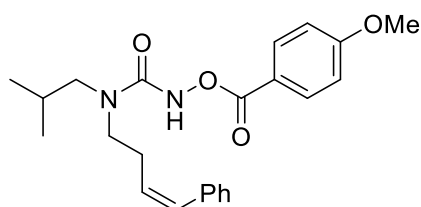
To the crude *N,N*-diisobutylaminecarbamoyl chloride was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added hydroxylamine hydrochloride (0.835 g, 10.0 mmol), and followed immediately by Et₃N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N,N*-diisobutylaminehydroxyurea, which could be used in the next step without further purification.

To the crude *N,N*-diisobutylaminehydroxyurea (1.77 g, 8.80 mmol) was added CH₂Cl₂ (0.30 M) and cooled to 0°C. To this was added Et₃N (1.23 mL, 8.80 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.19 mL, 8.80 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 3-((4-methoxybenzoyl)oxy)-1,1-diisobutyl-3-methylurea which was purified by flash column chromatography (10 % EtOAc/Hexanes) to yield a colourless oil (0.760 g, 23% over 3 steps). TLC R_f: 0.65 in 20% EtOAc/Hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.04-7.97 (m, 2H), 6.98-6.90 (m, 2H), 3.88 (s, 3H), 3.17-3.09 (m, 7H), 1.98 (dt, *J* = 13.8, 7 Hz, 2H), 0.88 (d, *J* = 6.9 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃): δ 164.0 (C), 163.9 (C), 163.3 (C), 131.7 (CH), 120.3 (C), 113.9 (CH), 55.5 (CH), 54.6 (CH₂), 40.1 (CH), 26.4 (CH), 20.0 (CH₃). IR (FTIR): 2655, 1692, 1622, 1534, 1332, 1261 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₈H₂₈N₂O₄Na [M+Na]⁺: 359.1947. Found: 359.1957.

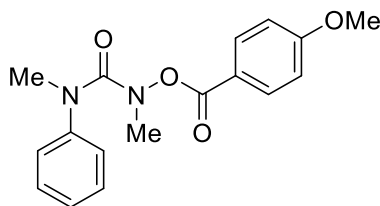


(*E*)-1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.565 g, 1.97 mmol), and (*E*)-*N*-ethyl-4-phenylbut-3-en-1-amine (0.289 g, 1.97 mmol) and imidazole (0.014 g, 0.2 mmol) in THF (6.5 mL, 0.30 M). The reaction was heated under microwave irradiation

for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using flash chromatography (30% EtOAc/Hexanes) to yield the title compound as a yellow oil (0.307 g, 42%). TLC R_f: 0.37 in 40% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 8.53-8.49 (br s, 1H), 8.11-8.04 (m, 2H), 7.38-7.26 (m, 4H), 7.24-7.17 (m, 2H), 6.96-6.90 (m, 2H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.8, 7.1 Hz), 3.87 (s, 3H), 3.48-3.34 (m, 4H), 2.56 (qd, *J* = 7.3, 1.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.8 (C), 164.4 (C), 157.6 (C), 137.4 (C), 132.8 (CH), 132.2 (CH), 128.7 (CH), 127.4 (CH), 126.3 (CH), 126.3 (CH), 119.4 (C), 114.1 (CH), 55.6 (CH), 47.1 (CH₂), 42.4 (CH₂), 32.2 (CH₂), 13.6 (CH₃). IR (FTIR): 3222, 2931, 1745, 1670, 1603, 1478, 1245 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₂₄N₂O₄Na⁺ [M+Na]⁺: 391.1634. Found: 391.1658.



(Z)-1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea: The title compound was synthesized according to general procedure **2D** using phenyl (4-methoxybenzoyl)oxycarbamate **2.18** (0.861 g, 3.00 mmol), and (Z)-N-ethyl-4-phenylbut-3-en-1-amine (0.525 g, 3.00 mmol) and imidazole (0.020 g, 0.3 mmol) in THF (10 mL, 0.30 M). The reaction was heated under microwave irradiation for 2 h at 100 °C. Upon completion, the reaction mixture was diluted with EtOAc (20 mL) and washed three times using 1 M NaOH (2.0 mL x 3), followed by a single brine wash (10 mL x 1). The organic phase was collected and dried over Na₂SO₄ (stirring for 15 min). The solids were filtered over a frit and rinsed with CH₂Cl₂ (5.0 mL). The filtrate was collected, concentrated vacuo and isolated using flash chromatography (20% EtOAc/hexanes) to yield the title compound as a clear oil yield (0.890 g, 80%). TLC R_f: 0.14 in 20% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 8.48 (br s, 1H), 8.06 (d, *J* = 9.1 Hz, 2H), 7.34-7.30 (m, 2H), 7.26-7.19 (m, 3H), 6.92 (d, *J* = 9.1 Hz, 2H), 6.57 (d, *J* = 11.6 Hz, 1H), 5.67 (dt, *J* = 11.6, 7.4 Hz, 1H), 3.85 (s, 3H), 3.39 (dd, *J* = 8.0, 6.8 Hz, 2H), 3.28 (q, *J* = 7.2 Hz, 2H), 2.63 (qd, *J* = 7.4, 1.5 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 166.7 (C), 164.2 (C), 157.5 (C), 137.1 (C), 132.1 (CH), 131.8 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.9 (CH), 119.3 (C), 114.0 (CH), 55.5 (CH₃), 46.6 (CH₂), 41.8 (CH₂), 27.4 (CH₂), 13.3 (CH₃). IR (FTIR): 2931, 1746, 1668, 1602, 1477, 1245, 1165 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₂₄N₂NaO₄⁺ [M+Na]⁺: 391.1658. Found: 391.1620.

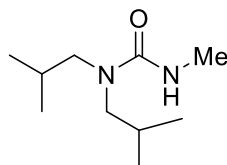


1-((4-Methoxybenzoyl)oxy)-1,3-dimethyl-3-phenylurea : The title compound was synthesized according to general procedure **4A** using *N*-methylaniline (1.08 mL, 10.0 mmol), toluene (0.8 M), KOH pellets (0.561 g, 10.0 mmol), and water (2.9 M) at 0 °C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (16.4 mL, 23.0 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude methyl(phenyl)carbamic chloride which was used in the next step without further purification.

To the crude methyl(phenyl)carbamic chloride was added CH₂Cl₂ (0.3 M) and cooled to 0 °C. To this was added hydroxylamine hydrochloride (0.695 g, 10.0 mmol), and followed immediately by Et₃N (2.79 mL, 20.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-hydroxy-1,3-dimethyl-3-phenylurea, which could be used in the next step without further purification.

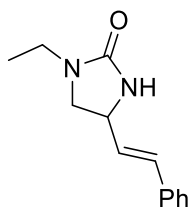
To the crude 1-hydroxy-1,3-dimethyl-3-phenylurea (1.75 g, 9.70 mmol) was added CH₂Cl₂ (0.3 M) and cooled to 0 °C. To this was added Et₃N (1.35 mL, 9.70 mmol) followed immediately by dropwise addition of *p*-methoxybenzoylchloride (1.65 g, 9.70 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (10 mL x1), and then brine (10 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude 1-((4-methoxybenzoyl)oxy)-1,3-dimethyl-3-phenylurea which was purified by flash column chromatography (20% EtOAc/Hexanes) to yield a amorphous white solid (2.10 g, 67% over 3 steps). TLC R_f: 0.15 in 20% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃) δ 7.63-7.54 (m, 2H), 7.18-7.07 (m, 4H), 7.03-6.93 (m, 1H), 6.83-6.75 (m, 2H), 3.85 (s, 3H), 3.30 (s, 3H), 3.18 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 163.9 (C), 163.5 (C), 161.0 (C), 144.6 (C), 131.8 (CH), 129.3 (CH), 126.0 (CH), 125.6 (CH),

119.6 (C), 113.5 (CH), 55.6 (CH₃), 39.9 (CH₃), 39.1 (CH₃). IR (FTIR): 3310, 2965, 1737, 1699, 1601, 1520, 1346, 1168 cm⁻¹. HRMS (ESI): C₁₇H₁₈N₂O₄Na [M+Na]⁺: 337.1165. Found: 337.1143.



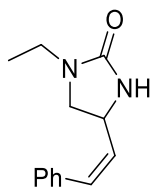
1,1-diisobutyl-3-methylurea: The title compound was synthesized according general procedure **4A** using diisobutylamine (0.87 mL, 5.00 mmol), toluene (0.8 M), KOH pellets (0.280 g, 5.00 mmol), and water (2.9 M) at 0°C. A dripping funnel was affixed on top of the roundbottom flask and this apparatus was purged with argon for 10 minutes. Phosgene (15% in toluene) (8.2 mL, 11.5 mmol) was added to the dripping funnel under inert atmosphere, and was allowed to drip over 1 hour at 0 °C while stirring vigorously. The reaction was allowed to stir for an additional 30 minutes after complete addition of phosgene solution. Upon completion, the crude reaction mixture was bubbled with an argon balloon for 20 minutes in a well ventilated fumehood, to release any excess phosgene gas. The crude reaction mixture was then extracted to remove the aqueous layer, and then the organic phase was washed with brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure to provide the crude *N*-diisobutylcarbamoyl chloride which was used in the next step without further purification.

To the crude *N*-diisobutylcarbamoyl chloride was added CH₂Cl₂ (0.3 M) and cooled to 0 °C. To this was added methylamine hydrochloride (0.338 g, 5.00 mmol), and followed immediately by Et₃N (1.39 mL, 10.0 mmol). The reaction was allowed to warm to room temperature and stir overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x1), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure which was purified by flash column chromatography (30% EtOAc/Hexanes → 70% EtOAc/Hexanes) to yield a colourless oil (0.507 g, 54% over 2 steps). ¹H NMR (400 MHz, CDCl₃): δ 4.33-4.20 (br s, 1H), 3.2 (d, *J* = 7.5 Hz, 2H), 2.79 (d, *J* = 4.7 Hz, 4H), 2.08-1.78 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃): δ 159.0 (C), 55.7 (CH₂), 27.7 (CH), 27.0 (CH), 20.4 (CH₃).

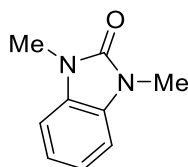


(E)-1-Ethyl-4-styrylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using (*E*)-1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea **4.95** (0.074 g, 0.20 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.004 g, 2 mol%),

triethylamine (0.022 g, 5 mol%) in MeCN (1.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (5% MeOH/CH₂Cl₂ + 1% Et₃N) to yield a clear oil (0.013 g, 22%). TLC R_f: 0.23 in 10% EtOAc/CH₂Cl₂. ¹H NMR (300 MHz, CDCl₃): δ 7.40-7.24 (m, 5H), 6.58 (d, *J* = 15.8 Hz, 1H), 6.19 (dd, *J* = 15.8 Hz, 7.7 Hz, 1H), 4.56-4.46 (br s, 1H), 4.32 (app q, *J* = 7.7 Hz, 1H), 3.65 (t, *J* = 8.7 Hz, 1H), 3.37-3.16 (m, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 161.5 (C), 136.9 (C), 136.1 (CH), 132.4 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.0 (CH), 52.7 (CH), 50.7 (CH₂), 38.1 (CH₂), 12.8 (CH₃). IR (FTIR): 3232, 2925, 2852, 1680, 1485, 1449, 1247 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₃H₁₆N₂O [M]⁺: 216.1263. Found: 216.1250.

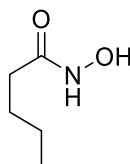


(Z)-1-Ethyl-4-styrylimidazolidin-2-one: The title compound was synthesized according to general procedure **4D** using (*E*)-1-ethyl-3-((4-methoxybenzoyl)oxy)-1-(4-phenylbut-3-en-1-yl)urea **4.96** (0.074 g, 0.20 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.004 g, 2 mol%), triethylamine (0.022 g, 5 mol%) in MeCN (1.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. Analysis of the crude NMR revealed a 4:1 ratio of Z:E olefin totaling 64%. The title compound was purified by column chromatography (5% MeOH/CH₂Cl₂ + 1% Et₃N) to yield a clear oil (0.026 g, 45%). TLC R_f: 0.23 in 10% EtOAc/CH₂Cl₂. ¹H NMR (600 MHz, DMSO-*d*₆): δ 7.40-7.37 (m, 2H), 7.32-7.28 (m, 3H), 6.73 (br s, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 5.67 (dd, *J* = 11.5, 9.3 Hz, 1H), 4.46-4.42 (m, 1H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.13 (dq, *J* = 13.9, 7.0 Hz, 1H), 3.07-3.01 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆): δ 161.6 (C), 136.3 (C), 133.1 (CH), 131.5 (CH), 129.06 (CH), 128.88 (CH), 127.9 (CH), 50.4 (CH), 47.4 (CH₂), 37.9 (CH₂), 13.1 (CH₃). IR (FTIR): 3230, 2922, 2857, 1680, 1486, 1449, 1243 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₁H₂₄N₂O₄Na [M+Na]⁺: 391.1634. Found: 391.1620.



1,3-dimethyl-1,3-dihydrobenzimidazol-2-one: The title compound was synthesized following general procedure **4D** using 3-((4-methoxybenzoyl)oxy)-1-methyl-1-phenylurea **4.97** (0.240 g, 0.800 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.014 g, 2 mol%), triethylamine (0.089 g, 0.88 mmol) in MeCN (4.0 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was concentrated under reduced pressure, diluted in CH₂Cl₂ (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (10% EtOAc/Hexanes → 50% EtOAc/Hexanes) to yield a white solid (0.085 g, 72%). ¹H NMR (300 MHz, CDCl₃): δ 7.14-7.01 (m, 2H), 7.02-6.92 (m, 2H), 3.43 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 154.8 (C), 130.2 (C), 121.3 (CH), 107.5 (CH), 27.3 (CH₃).

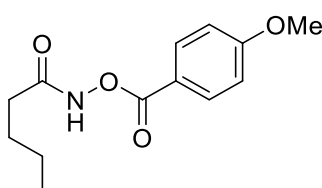
The ¹H NMR and ¹³C NMR is in agreement with previous reports.²⁸³



Pentanehydroxamic acid: The title compound was synthesized according to a literature procedure.²⁷⁰

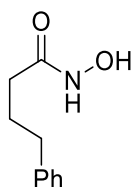
¹H NMR (300 MHz, DMSO-d₆): δ 10.43-10.24 (br s, 1H), 8.74-8.54 (br s, 1H), 1.98-1.88 (m, 2H), 1.53-1.38 (m, 2H), 1.33-1.17 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, DMSO-d₆): δ 169.6 (C), 32.4 (CH₂), 27.7 (CH₂), 22.2 (CH₂), 14.1 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.



²⁸³ Jin, Y.; Ou, L.; Yang, H.; Fu, H. *J. Am. Chem. Soc.* **2017**, 139, 14237-14243.

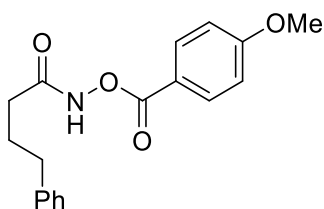
***N*-((4-methoxybenzoyl)oxy)pentanamide:** The title compound was synthesized according to general procedure **4C** using pentanehydroxamic acid (0.369 g, 3.15 mmol), CH₂Cl₂ (0.30 M) at 0°C. To this was added Et₃N (0.42 mL, 3.00 mmol) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (0.516 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x2), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure and the crude product isolated using flash column chromatography (50 % EtOAc/Hexanes) to yield the title compound as an amorphous white solid (0.728 g, 97%). TLC R_f: 0.12 in 20% EtOAc/Hexanes. ¹H NMR (300 MHz, DMSO-d₆): δ 10.46-10.25 (br s, 1H), 8.76-8.56 (br s, 1H), 1.98-1.88 (m, 2H), 1.53-1.39 (m, 2H), 1.32-1.17 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 164.9 (C), 164.6 (C), 132.3 (CH), 118.8 (C), 114.2 (CH), 55.7 (CH), 32.7 (CH₂), 27.3 (CH₂), 22.4 (CH₂), 13.8 (CH₃). IR (FTIR): 3145, 2959, 1759, 1657, 1602, 1510, 1248 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₃H₁₇NO₄Na [M+Na]⁺: 274.1056. Found: 274.1062.



***N*-hydroxy-4-phenylbutanamide:** The title compound was synthesized according to a literature procedure.²⁷⁰

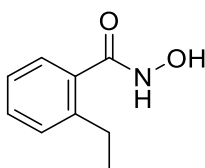
¹H NMR (300 MHz, CDCl₃): δ 10.49-10.17 (br s, 1H), 8.85-8.49 (br s, 1H), 7.33-7.24 (m, 2H), 7.23-7.13 (m, 3H), 2.59-2.52 (m, 2H), 2.01-1.91 (m, 2H), 1.84-1.71 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 169.4 (C), 142.1 (C), 128.8 (CH), 126.3 (CH), 35.1 (CH₂), 32.3 (CH₂), 27.5 (CH₂) (one C_{quat} is missing).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.



***N*-((4-methoxybenzoyl)oxy)-4-phenylbutanamide:** The title compound was synthesized according to general procedure **4C** using *N*-hydroxy-4-phenylbutanamide (0.940 g, 5.25 mmol), CH₂Cl₂ (0.30 M) at 0°C. To this was added Et₃N (0.68 mL, 3.00 mmol) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (0.853 g, 5.00 mmol). The reaction was allowed to warm to room

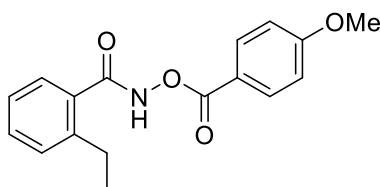
temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x2), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure and the crude product isolated using flash column chromatography (33 % EtOAc/Hexanes) to yield the title compound as an amorphous white solid (1.55 g, 98%). TLC R_f: 0.15 in 20% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 10.63-10.08 (br s, 1H), 8.88-8.49 (m, 2H), 7.39-7.22 (m, 2H), 7.23-7.11 (m, 2H), 2.60-2.52 (m, 2H), 2.01-1.91 (m, 2H), 1.84-1.71 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 164.7 (C), 164.4 (C), 141.2 (C), 132.2 (CH), 128.6 (CH), 128.5 (CH), 126.1 (CH), 118.7 (C), 114.1 (CH), 55.6 (CH), 34.9 (CH₂), 32.2 (CH₂), 26.5 (CH₂). IR (FTIR): 3119, 3018, 2943, 1752, 1648, 1506, 1253 cm⁻¹. HRMS (ESI): Exact mass calcd for C₁₈H₁₉NO₄Na [M+Na]⁺: 336.1212. Found: 336.1219.



2-Ethyl-N-hydroxybenzamide (4au): The title compound was synthesized according to a literature procedure.²⁷⁰

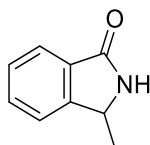
¹H NMR (300 MHz, CDCl₃): δ 8.87-8.09 (br s, 2H), 7.47-7.38 (m, 1H), 7.38-7.29 (m, 2H), 7.26-7.19 (m, 1H), 2.81 (q, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 168.8 (C), 143.3 (C), 131.3 (C), 131.0 (CH), 129.6 (CH), 127.3 (CH), 125.8 (CH), 26.2 (CH₂), 15.7 (CH₃).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.



2-Ethyl-N-((4-methoxybenzoyl)oxy)benzamide: The title compound was synthesized according to the general procedure **4C** using 2-ethyl-N-hydroxybenzamide (0.520 g, 3.15 mmol), CH₂Cl₂ (0.30 M) at 0°C. To this was added Et₃N (0.42 mL, 3.0 mmol) followed immediately by portionwise addition of *p*-methoxybenzoylchloride (0.516 g, 3.00 mmol). The reaction was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction was extracted with NaHCO₃ (5 mL x2), and then brine (5 mL x1). The organic phase was collected and dried with Na₂SO₄. The solids were filtered over a cotton plug, and the filtrate was evaporated under reduced pressure and the crude product isolated using flash column chromatography (20 % EtOAc/Hexanes) to yield the title compound as an amorphous white solid (0.592 g, 67%). TLC R_f: 0.21 in 20% EtOAc/Hexanes. ¹H NMR (300 MHz, CDCl₃): δ 9.36-9.27 (br s, 1H), 8.15-8.07 (m, 2H), 7.55 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.48-7.42 (m, 1H),

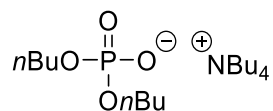
7.36-7.30 (m, 1H), 7.29-7.22 (m, 1H), 7.00-6.94 (m, 2H), 3.90 (s, 3H), 2.87 (q, $J = 7.5$ Hz, 2H), 1.28 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 164.9 (C), 164.5 (C), 143.9 (C), 132.3 (CH), 131.4 (CH), 131.3 (C), 127.7 (CH), 125.8 (CH), 118.6 (CH), 114.1 (CH), 55.6 (CH), 26.3 (CH_2), 16.0 (CH_3). IR (FTIR): 3138, 2957, 1751, 1653, 1505, 1252 cm^{-1} . HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 322.1056. Found: 322.1056.



3-methylisoindolin-1-one: The title compound was synthesized according to general procedure **4D** using 2-ethyl-N-((4-methoxybenzoyl)oxy)benzamide **4.106** (0.150 g, 0.50 mmol), tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate (0.009 g, 2 mol%), tetrabutylammonium dibutyl phosphate (0.011 g, 5 mol%) in CH_2Cl_2 (2.5 mL, 0.2 M) in a 8 mL Kimax glass vial with a Teflon screw cap and a stir bar. The vial was placed in an ice bath and purged with Argon for 10 min. The vial was positioned between 2 and 4 cm from the light source (blue LED strips) and allowed to stir overnight at ambient temperature. Upon completion, the reaction was diluted in CH_2Cl_2 (5 mL) and extracted three times with sodium bicarbonate (3 x 2 mL) to remove the benzoic acid. The organic phase was collected, dried with Na_2SO_4 , filtered, and concentrated under reduced pressure. The title compound was purified by column chromatography (50% EtOAc/ CH_2Cl_2) to yield an amorphous white solid (0.048 g, 65%). ^1H NMR (300 MHz, CDCl_3): δ 7.85 (dt, $J = 7.5, 1.0$ Hz, 1H), 7.58 (td, $J = 7.5, 1.2$ Hz, 1H), 7.52 – 7.40 (m, 2H), 6.73-6.57 (br s, 1H), 4.70 (q, $J = 6.7$ Hz, 1H), 1.51 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 170.7 (C), 149.0 (C), 132.1 (CH), 131.6 (C), 128.3 (CH), 124.0 (CH), 122.3 (CH), 52.6 (CH), 20.5 (CH_3).

The ^1H NMR and ^{13}C NMR is in agreement with previous reports.²⁷⁰

Extra compounds



Tetrabutylammonium dibutyl phosphate: The title compound was synthesized according to a literature procedure.²⁸⁴

^1H NMR (300 MHz, CDCl_3): δ 3.81 (q, $J = 6.6$ Hz, 4H), 3.44-3.31 (m, 8H), 1.75-1.52 (m, 12H), 1.51-1.29 (m, 12H), 0.99 (t, $J = 7.3$ Hz, 12H), 0.89 (t, $J = 7.3$ Hz, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 64.7 (CH_2),

²⁸⁴ Zhu, Q.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 741.

59.0 (CH₂), 33.3 (CH₂), 24.3 (CH₂), 19.0 (CH₂), 19.3 (CH₂), 14.0 (CH₃), 13.8 (CH₃). ³¹P NMR (121 MHz, CDCl₃): δ -2.26 (s).

The ¹H NMR and ¹³C NMR is in agreement with previous reports.

Appendix

Copyright obtained for Figure 1-2.

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Will you be translating?	No
Title of your thesis / dissertation	Synthesis of N-Oxyureas and Their Applications in Amination Reactions
Expected completion date	Jul 2019
Expected size (number of pages)	500
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Claims to Original Research:

- Synthesis of a library of stable blocked Oxygen-substituted isocyanates (*O*-isocyanates).
- Study of controlled reactivity of *O*-isocyanates to access *N*-oxyureas via substitution reaction using base catalysis.
- Development of the first cascade reaction of *O*-isocyanates for the synthesis of hydantoin and dihydrouracil derivatives.
- Development a broadly applicable aza-Lossen rearrangement procedure for the chemoselective formation of *N-N* bonds, affording semicarbazide and heterocyclic products.
- Synthesis of protected hydrazines via chemoselective formation of *N-N* bonds.
- Discovery of a thermal C-H amination using *N*-benzoyloxyureas.
- Exploration of formation of uridyl metal-nitrene from *N*-benzoyloxyureas under metal catalysis.
- Optimization and development of C-H amination under photoredox conditions for the synthesis of heterocycles (imidazolidinones and lactams for example).
- Cyclic voltammetry performed on *N*-benzoyloxyureas.

- Mechanistic studies in support of a proposed pathway for the spin-selective generation of triplet nitrene (one-electron α -elimination).

Publications from this work ($\dagger$ equal contributions):

- Ivanovich, R. A. $\dagger$; Polat, D. E. $\dagger$; Beauchemin A. M. Single Electron α -Elimination: Photoredox Illuminates a Radical Approach to Triplet Nitrenes. *Manuscript in preparation*.
- **Polat, D. E.**; Brzezinski, D. D.; Beauchemin A. M. Formation of Complex Hydrazine Derivatives via aza-Lossen Rearrangement. *Org. Lett.* **2019**, 21, 4849.
- Allen, M. A. $\dagger$; Ivanovich, R. A. $\dagger$; **Polat, D. E.**; Beauchemin, A. M. Synthesis of *N*-Oxyureas by Substitution and Cope-Type Hydroamination Reactions Using O-Isocyanate Precursors. *Org. Lett.* **2017**, 19, 6574-6577.
- Ivanovich, R. A.; **Polat, D. E.**; Beauchemin, A. M. Oxygen-Substituted Isocyanates: Blocked (Masked) Isocyanates Enable Controlled Reactivity. *Adv. Synth. Catal.* **2017**, 359, 4289-4293. (Selected as VIP).

Presentation from this work (O = oral; P = poster; *indicates presenter):

P10. **Polat, D. E.***; Brzezinski, D. D.; Beauchemin, A. M. Formation of *N-N* bonds via controlled aza-Lossen rearrangement. 102th Canadian Chemistry Conference and Exhibition, Quebec, QC: June 3-7, 2019.

P9. Ivanovich, R. A.*; **Polat, D. E.**; Beauchemin A. M. C-H Amination using Triplet Nitrenes: Photoredox Illuminates a Radical Approach to Triplet Nitrenes. 102th Canadian Chemistry Conference and Exhibition, Quebec, QC: June 3-7, 2019.

P8. **Polat, D. E.***; Brzezinski, D. D.; Skrotzki, E. A.; Beauchemin, A. M. Formation of *N-N* bonds via controlled aza-Lossen rearrangement. 29th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Toronto, ON: Nov 16-18, 2018.

P7. Ivanovich, R. A.*; **Polat, D.E.**; Beauchemin, A. M. Singlet Electron α -Elimination: Photoredox Illuminates a New Approach to Triplet Nitrenes. 29th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Toronto, ON: Nov 16-18, 2018.

O6. **Polat, D. E.***; Ivanovich, R. A.; Allen, M. A.; Brzezinski, D. D.; Beauchemin, A. M. Oxygen-Substituted Isocyanates: Key intermediates for heterocyclic synthesis. Ottawa-Carleton Chemistry Institute Day, Ottawa, ON: May 12, 2018.

P5. **Polat, D. E.***; Ivanovich, R. A.; Beauchemin, A. M. *O*-Benzoyl ureas as precursors for photoinduced C-H amination. 28th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Montréal, QC: Nov 17-19, 2017.

P4. Brzezinski, D. D.*; **Polat, D. E.**; Beauchemin, A. M. Formation of the *N-N* bond via controlled azaloss rearrangement. 28th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Montréal, QC: Nov 17-19, 2017.

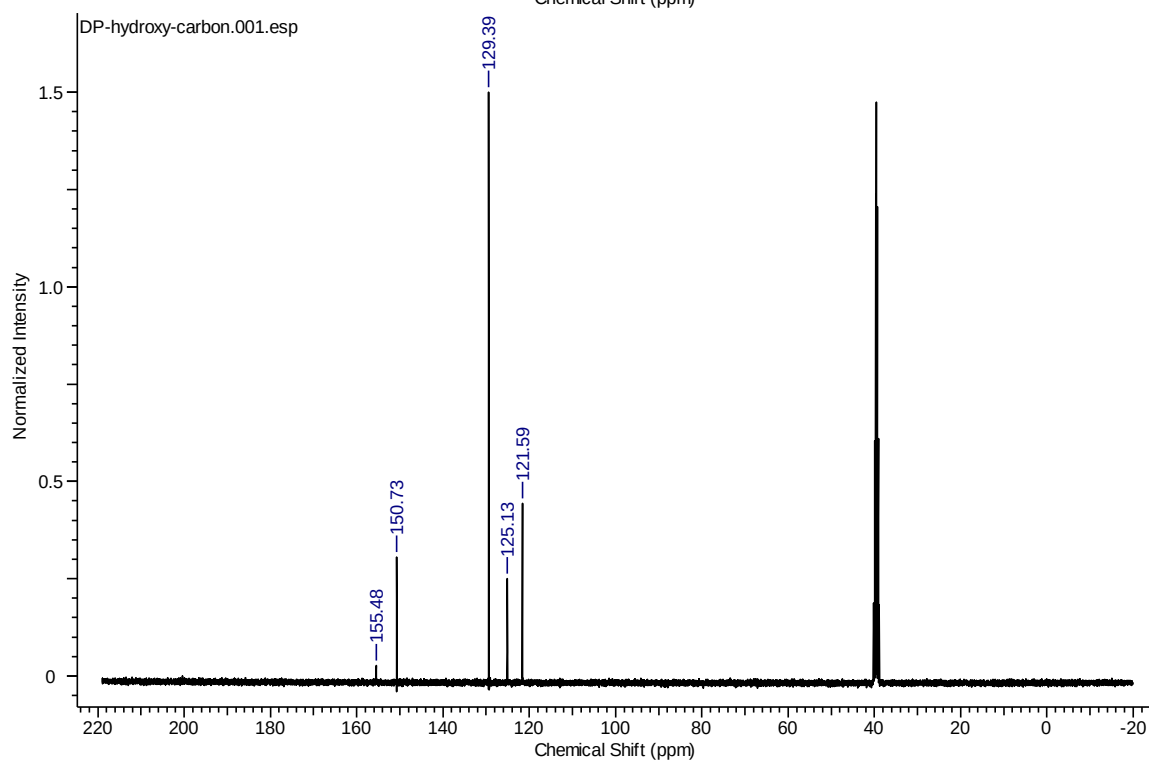
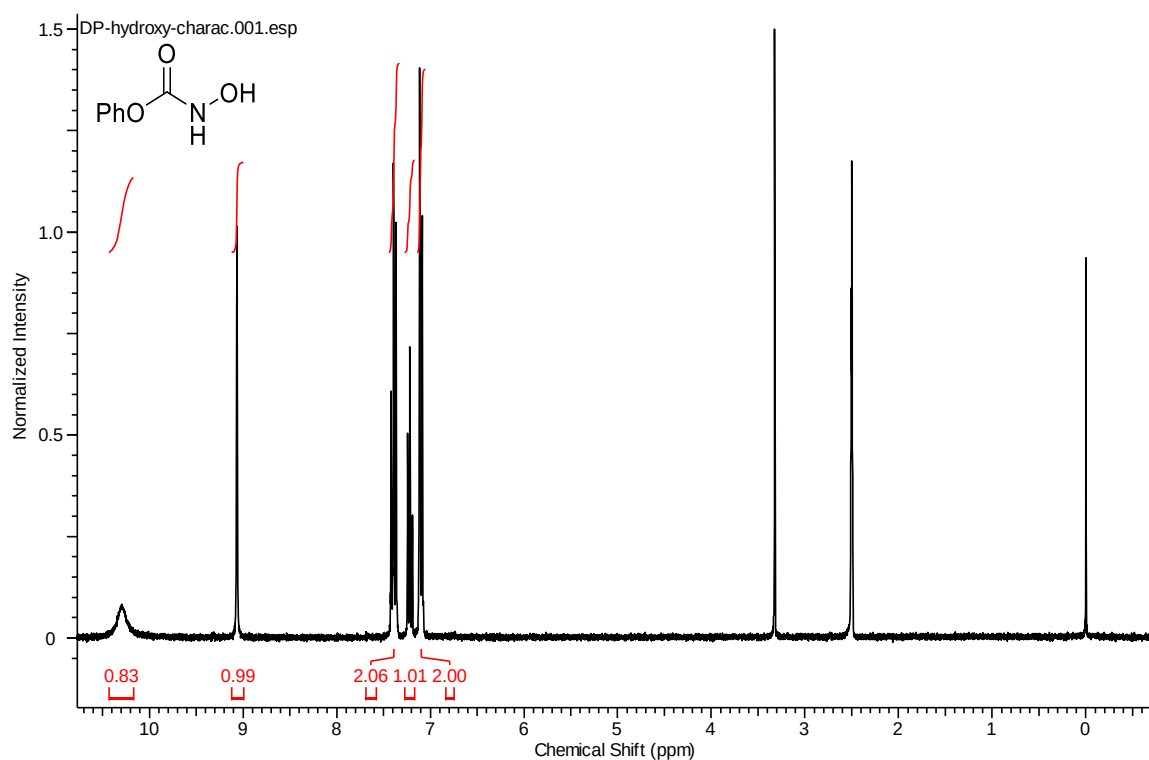
P3. Allen, M. A.*; Ivanovich, R. A.; **Polat, D. E.**; Beauchemin, A. M. Synthesis of *N*-Oxyureas via Substitution and Cope-Type Hydroamination Reactions with *O*-Isocyanate Precursors. 28th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Montréal, QC: Nov 17-19, 2017.

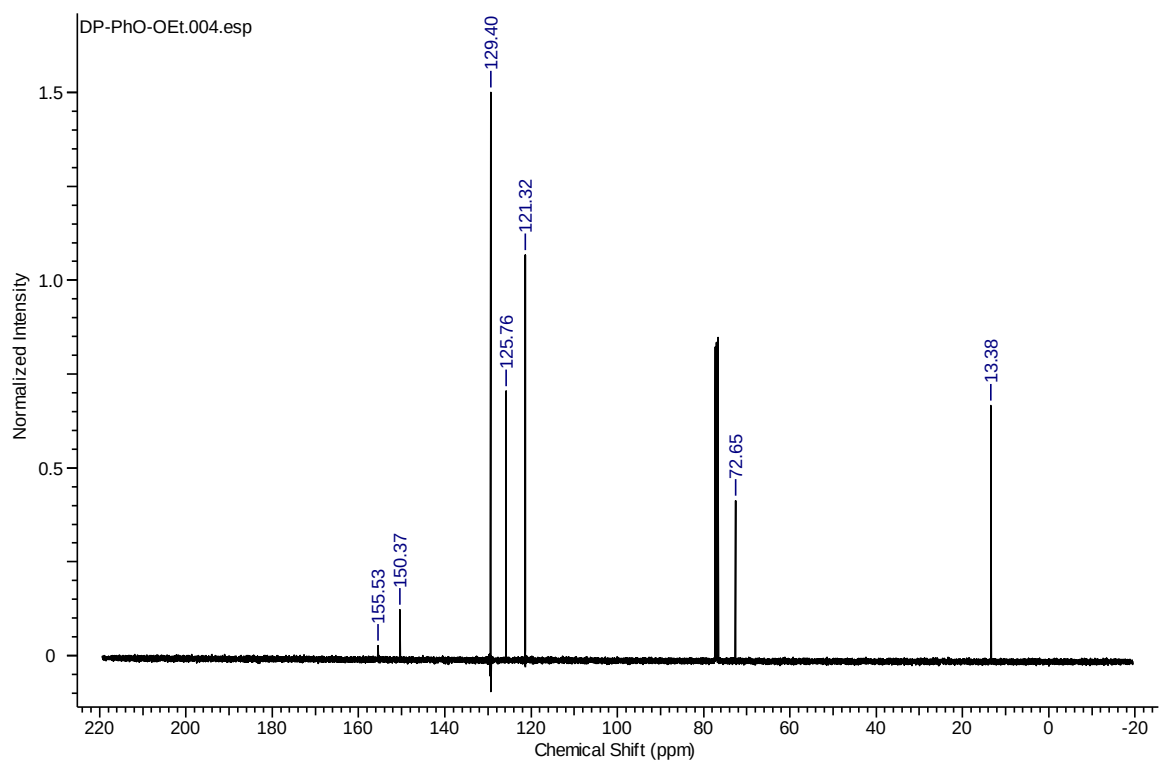
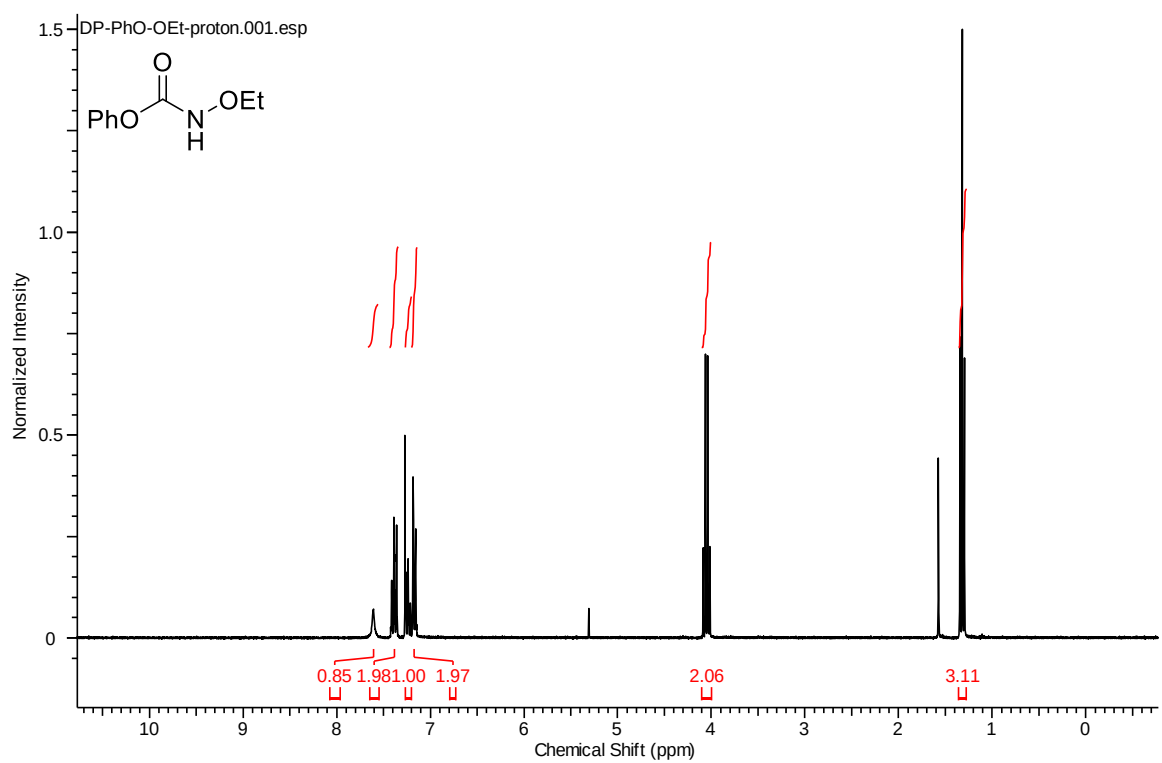
O2. **Polat, D. E.***; Ivanovich, R. A.; Beauchemin, A. M. *O*-Substituted isocyanates: A versatile tool for the synthesis of heterocycles. 100th Canadian Chemistry Conference and Exhibition, Symposium: Advances in Heterocycle Synthesis, Toronto, ON: May 28 - June 1, 2017.

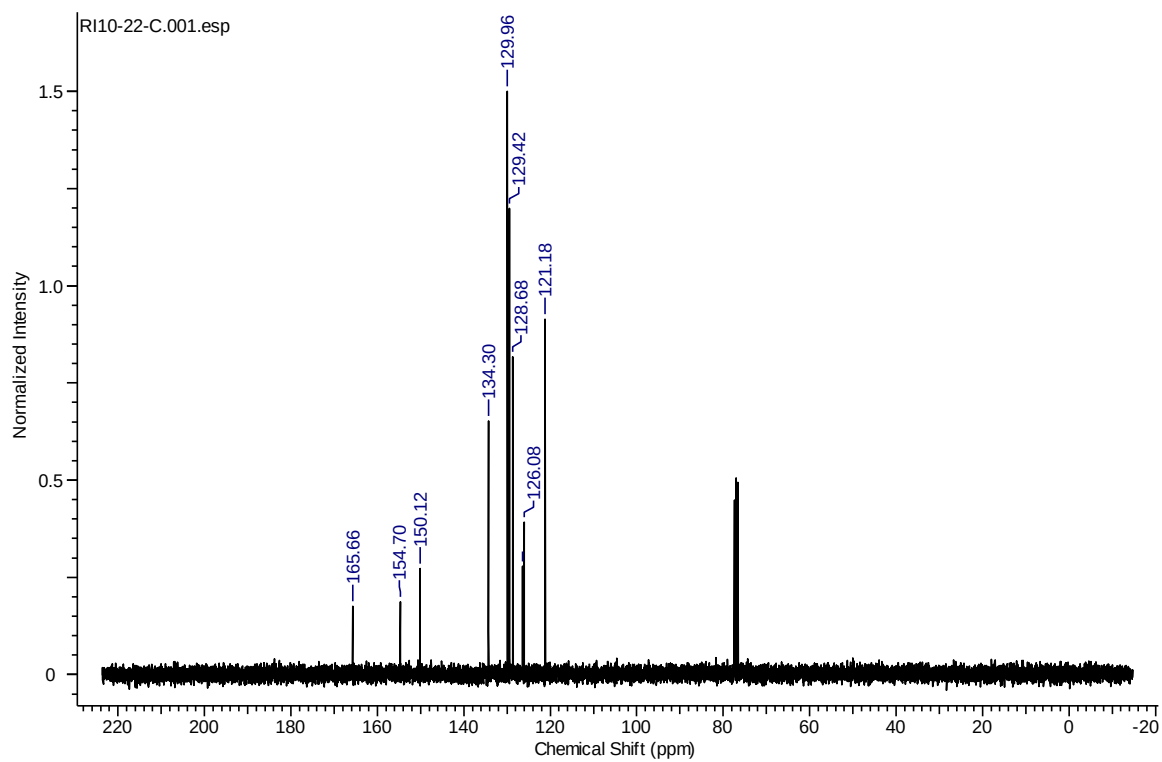
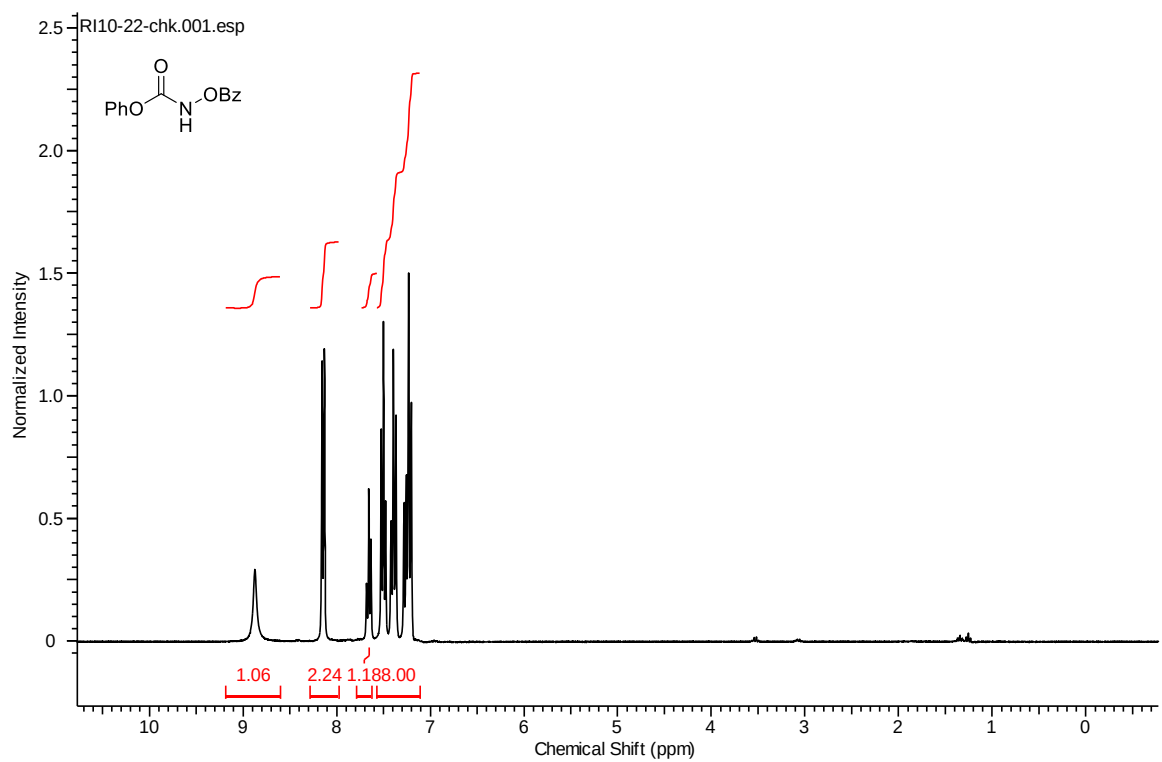
P1. **Polat, D. E.***; Ivanovich, R. A.; Beauchemin, A. M. *O*-substituted isocyanates: A simple approach to oxyamino heterocycles. 27th Québec-Ontario Mini-Symposium for Synthetic and Bioorganic Chemistry, Waterloo, ON: Nov 11 - 13, 2016.

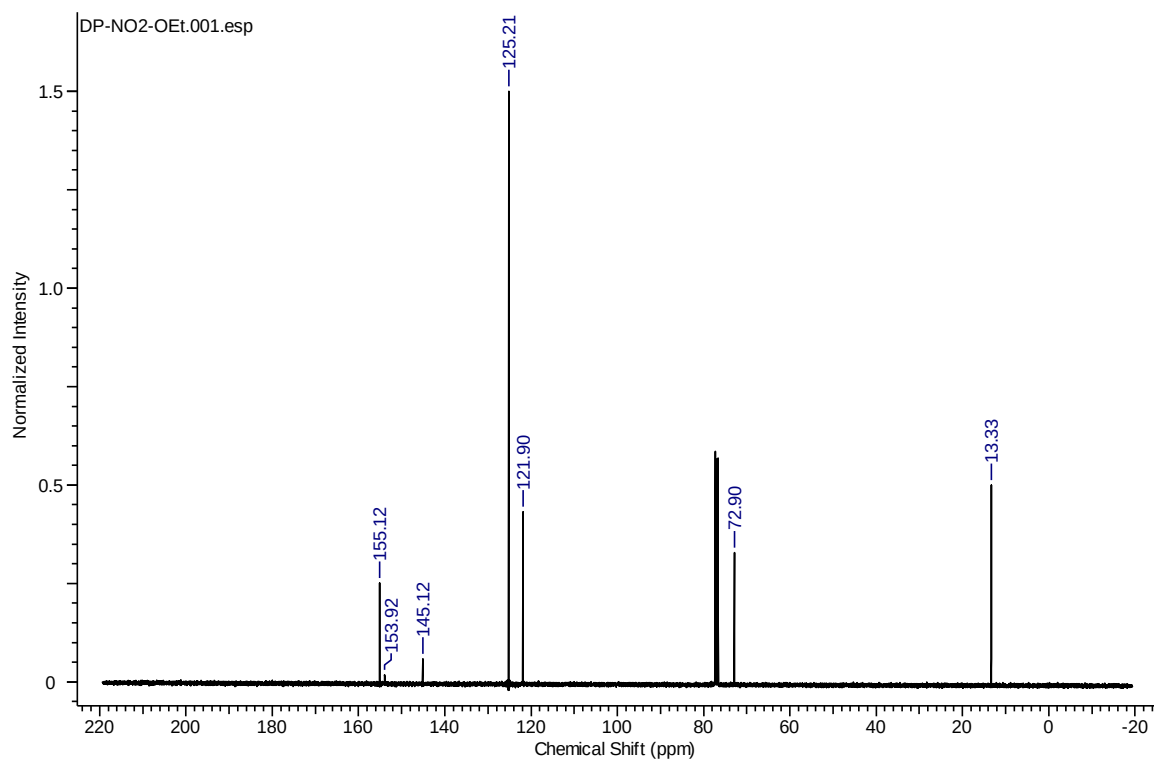
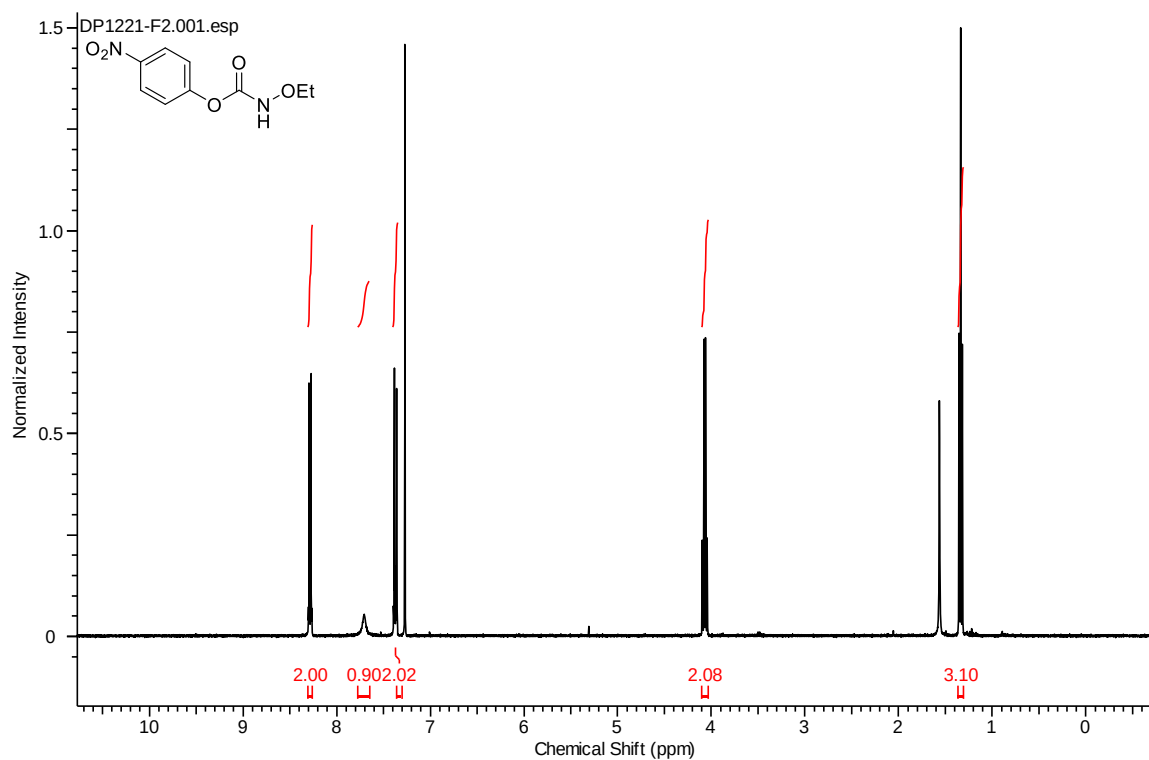
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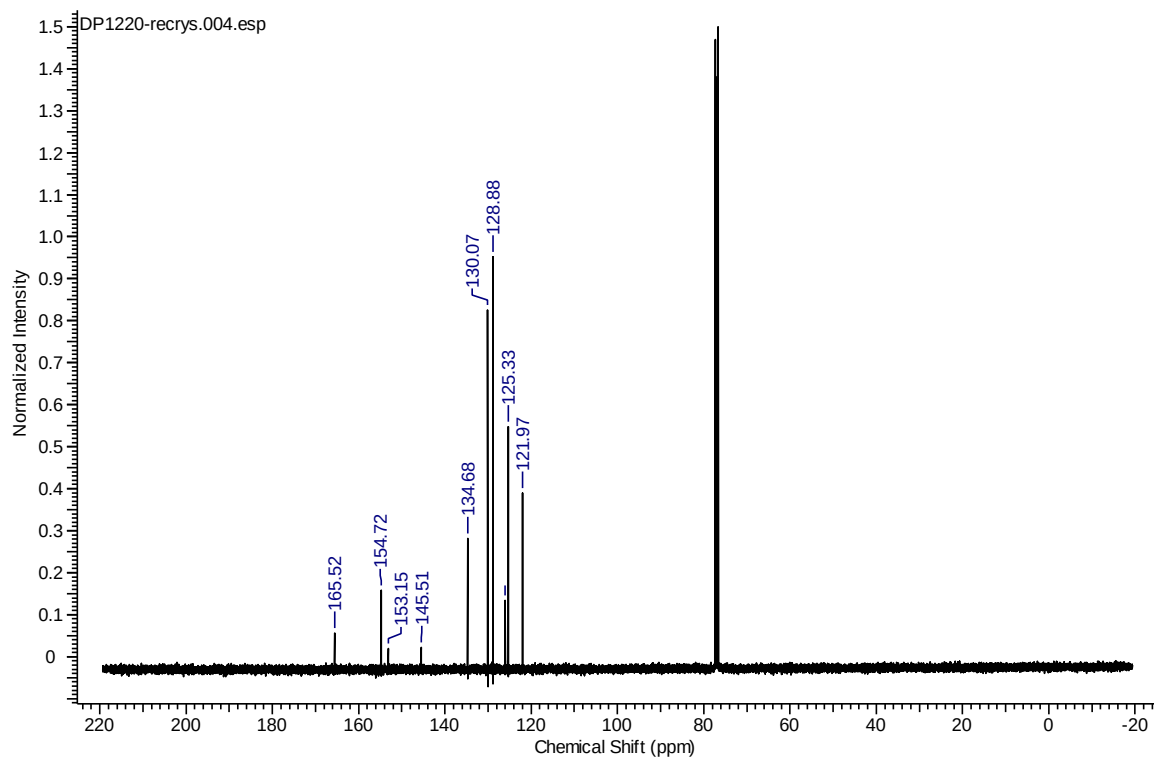
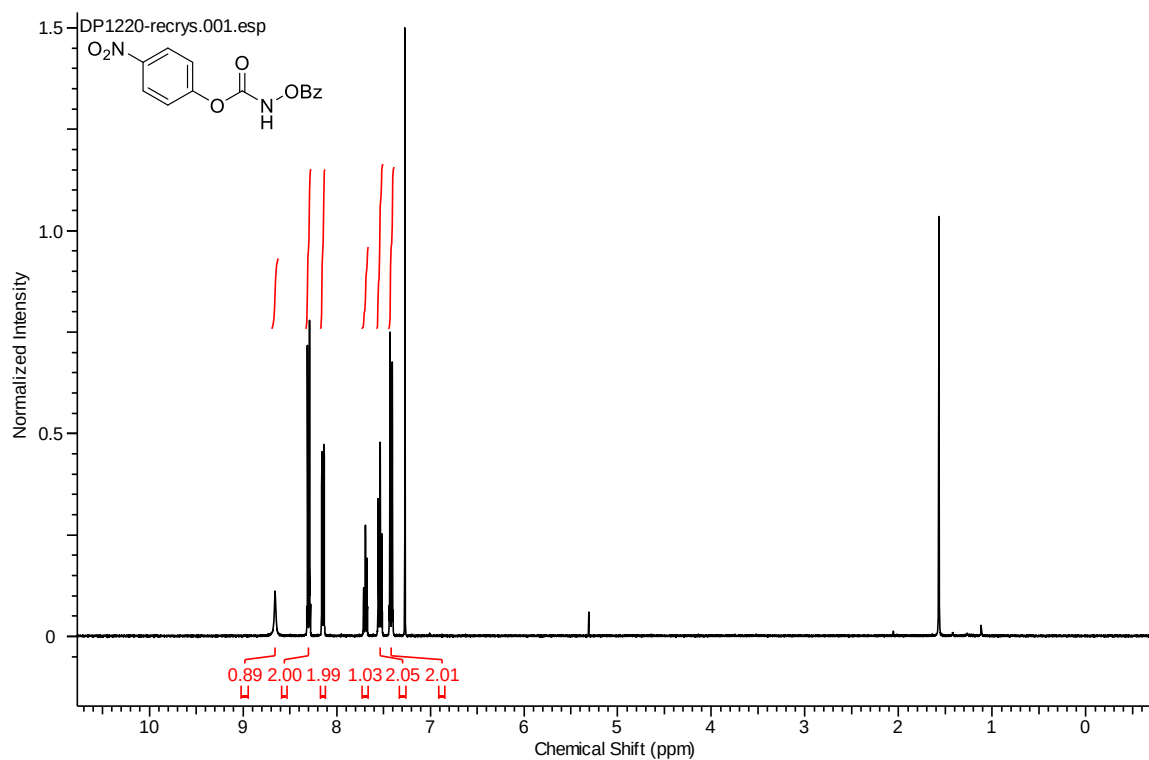
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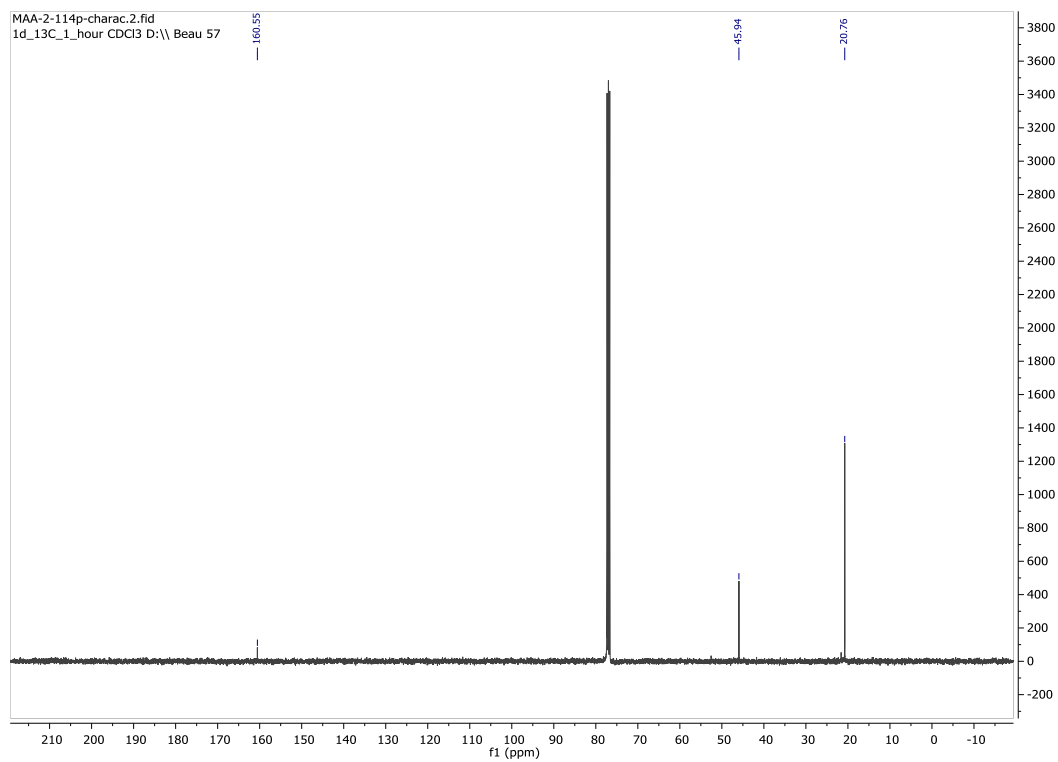
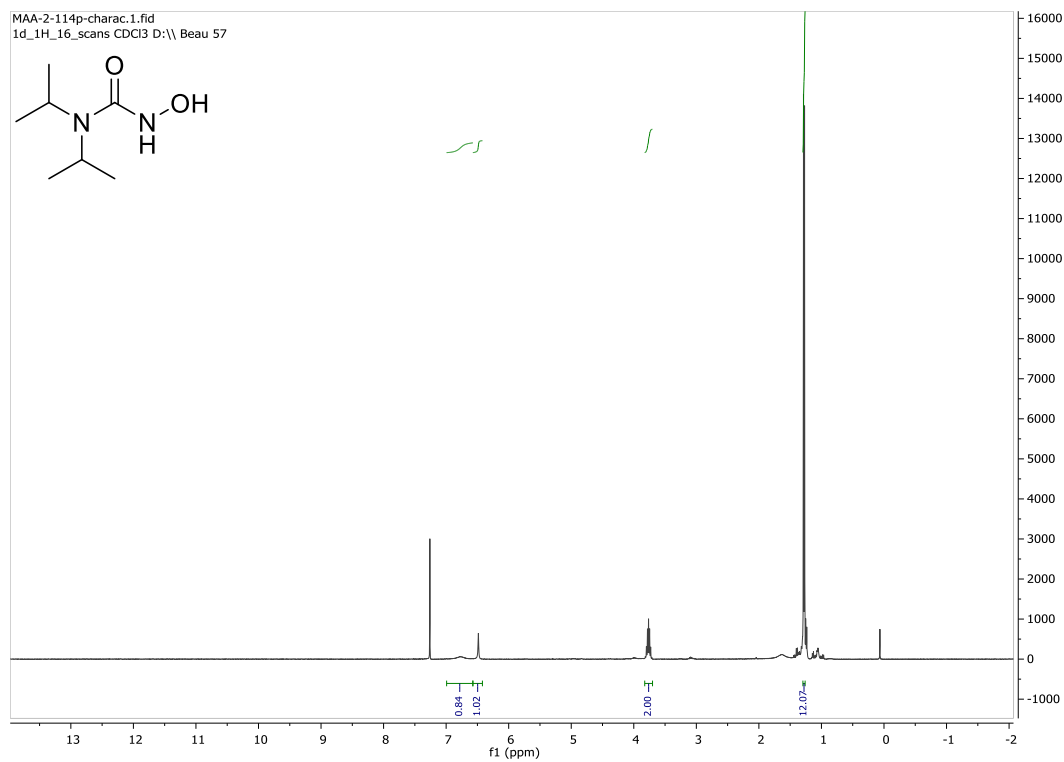


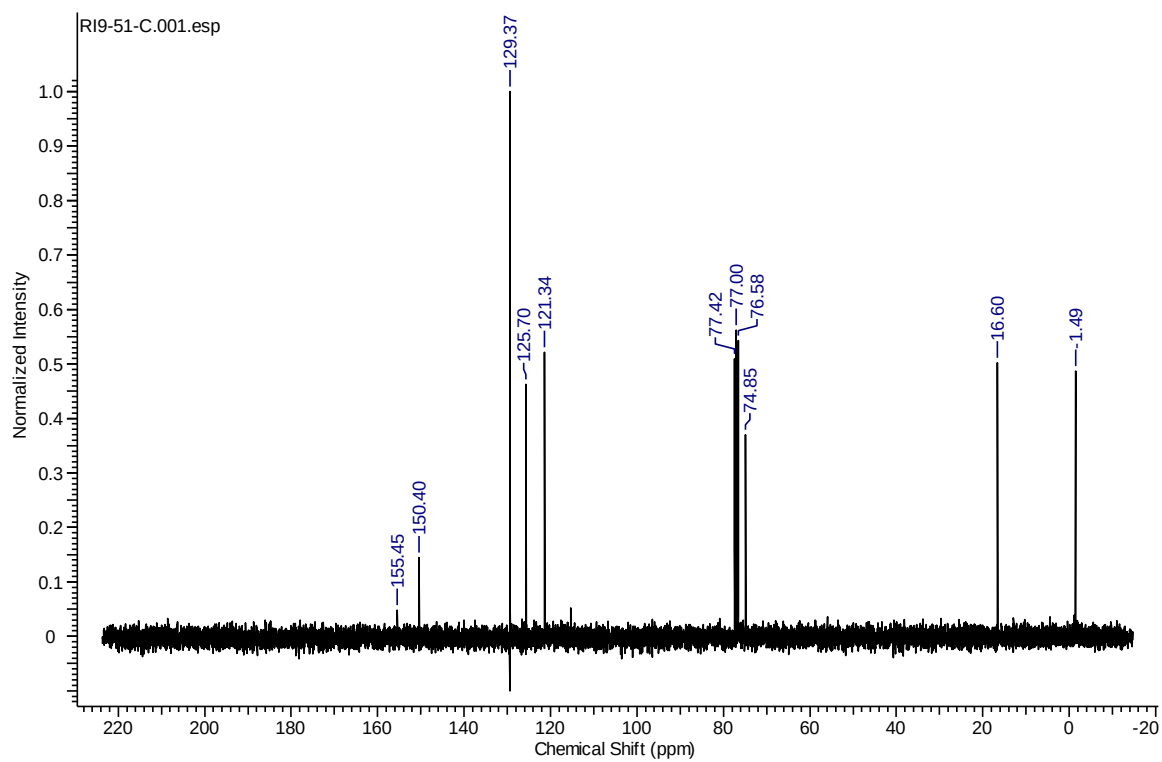
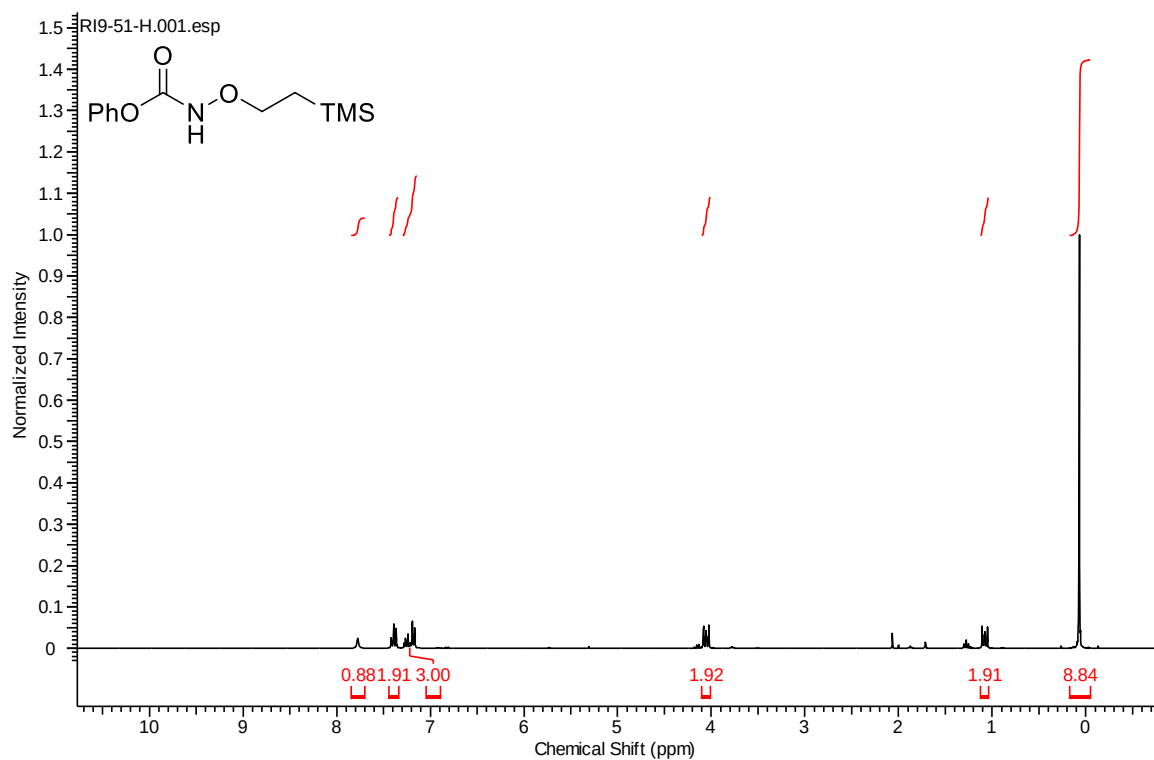


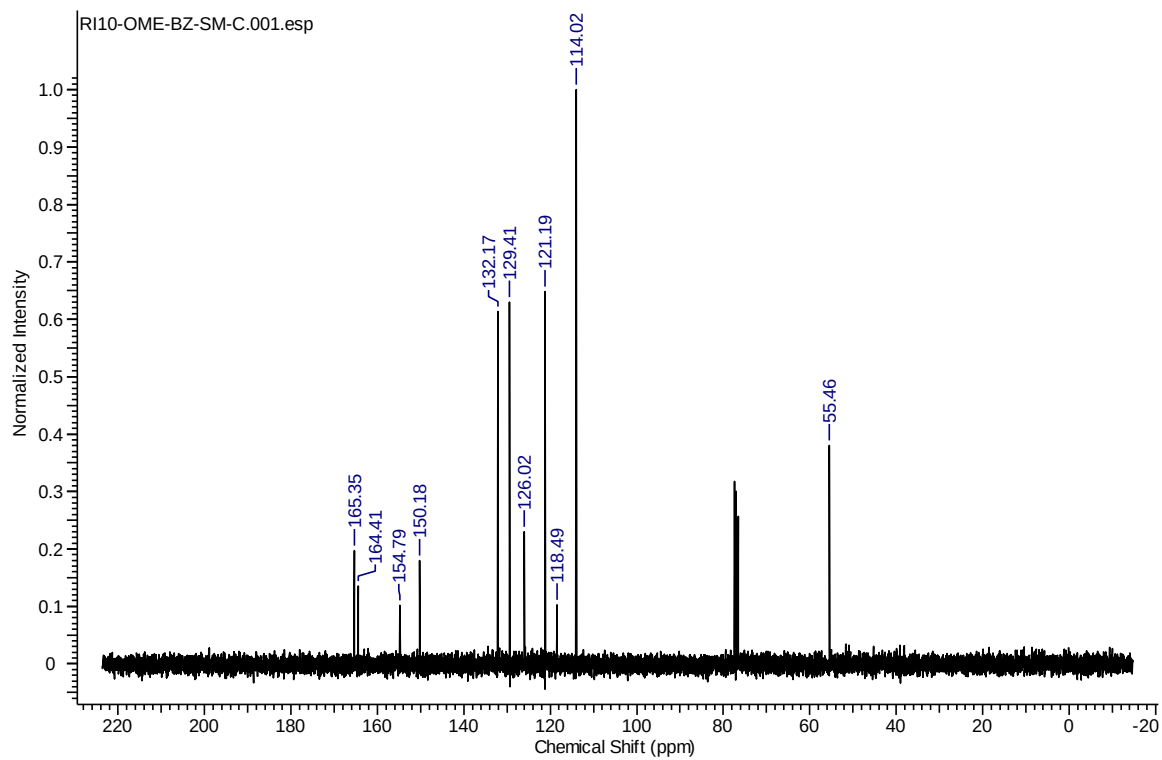
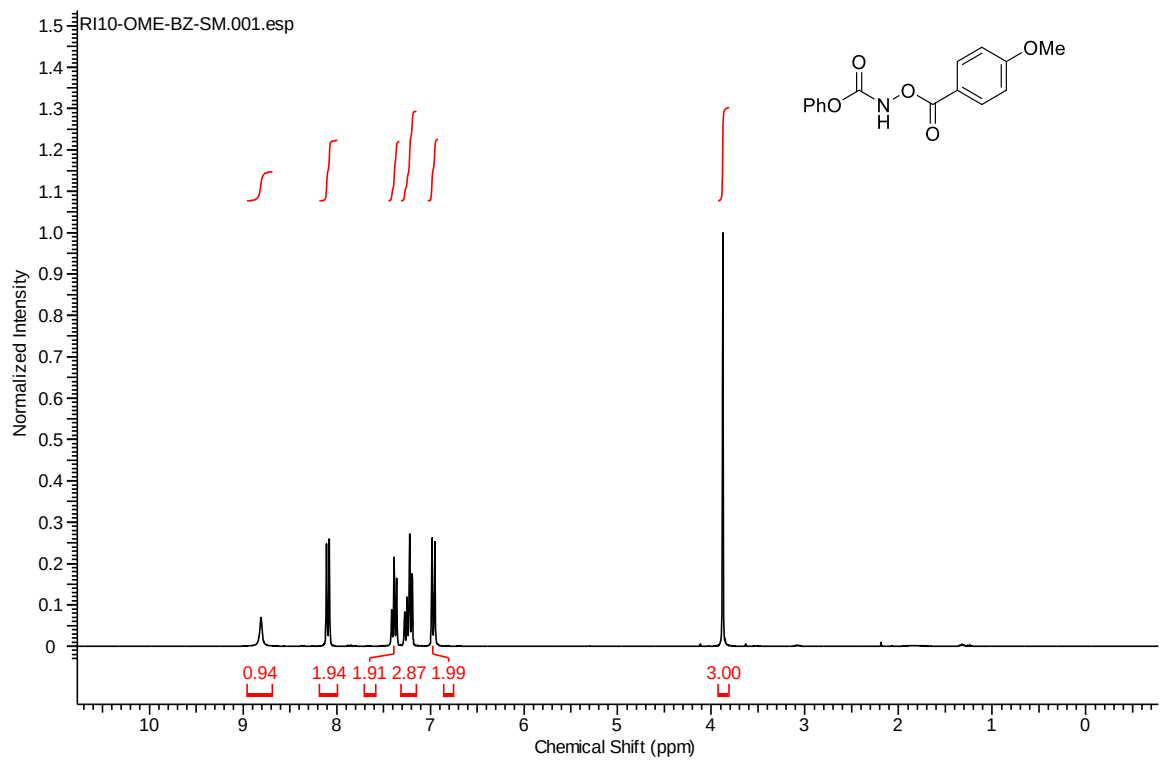


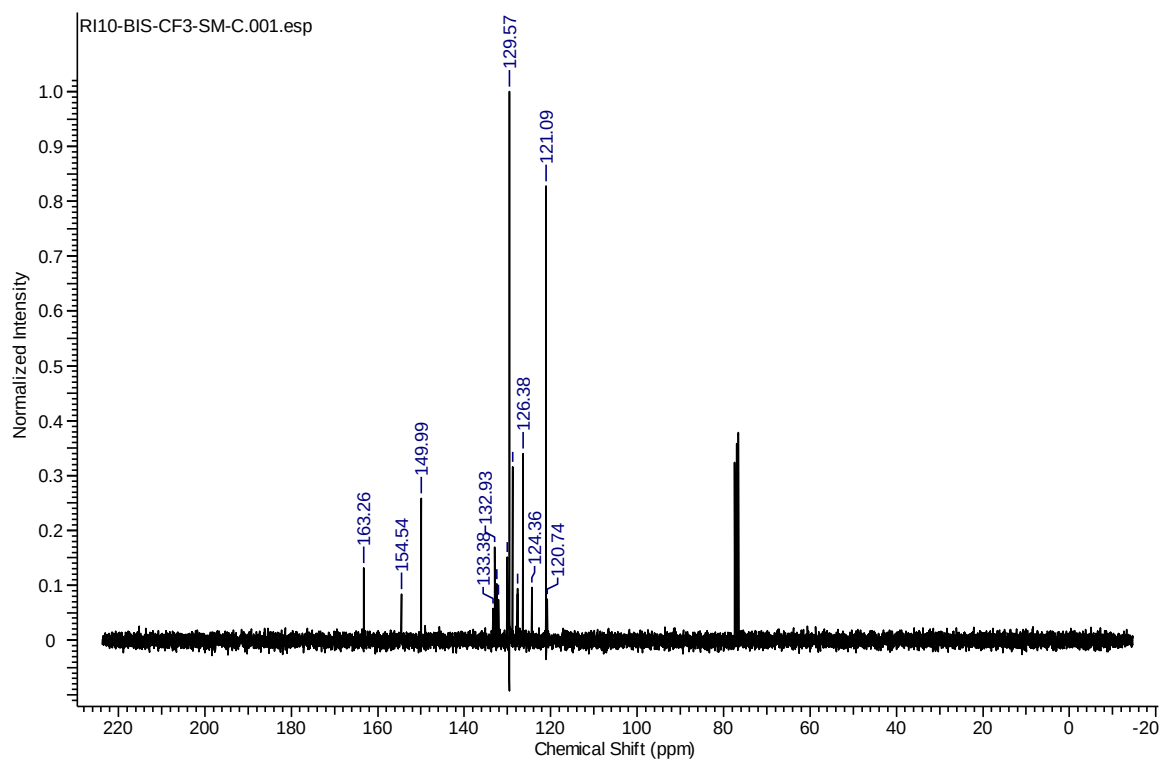
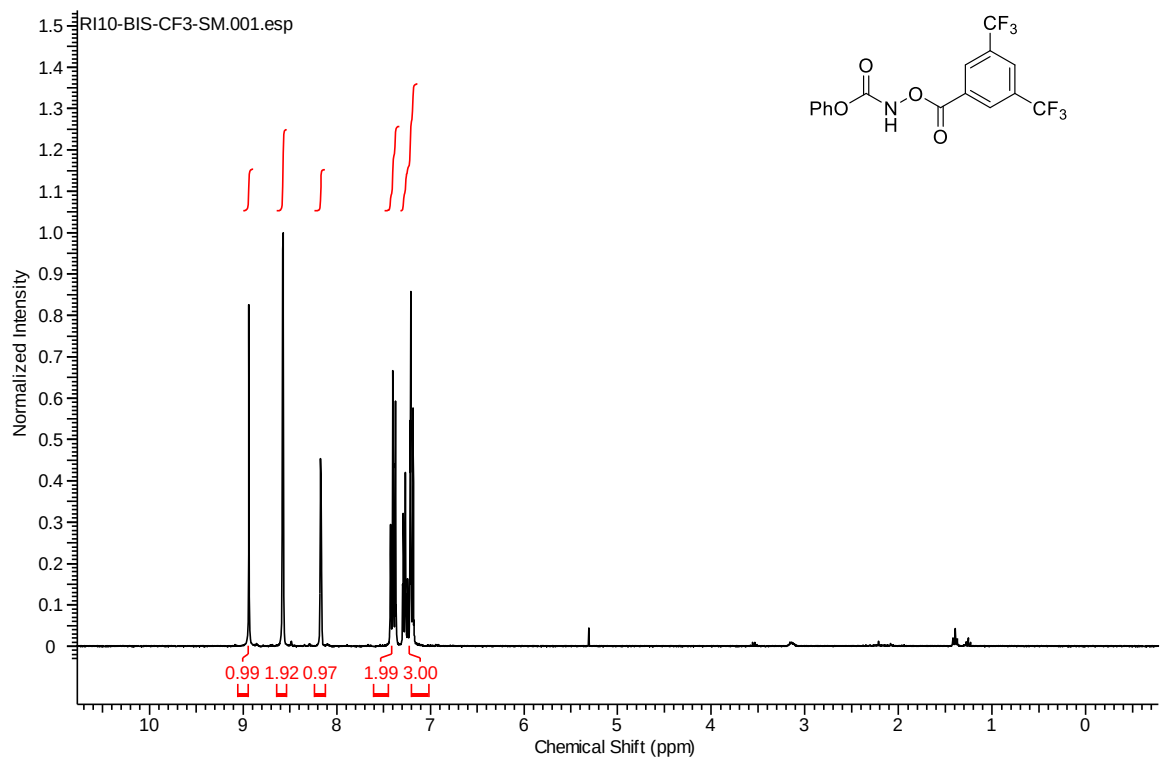


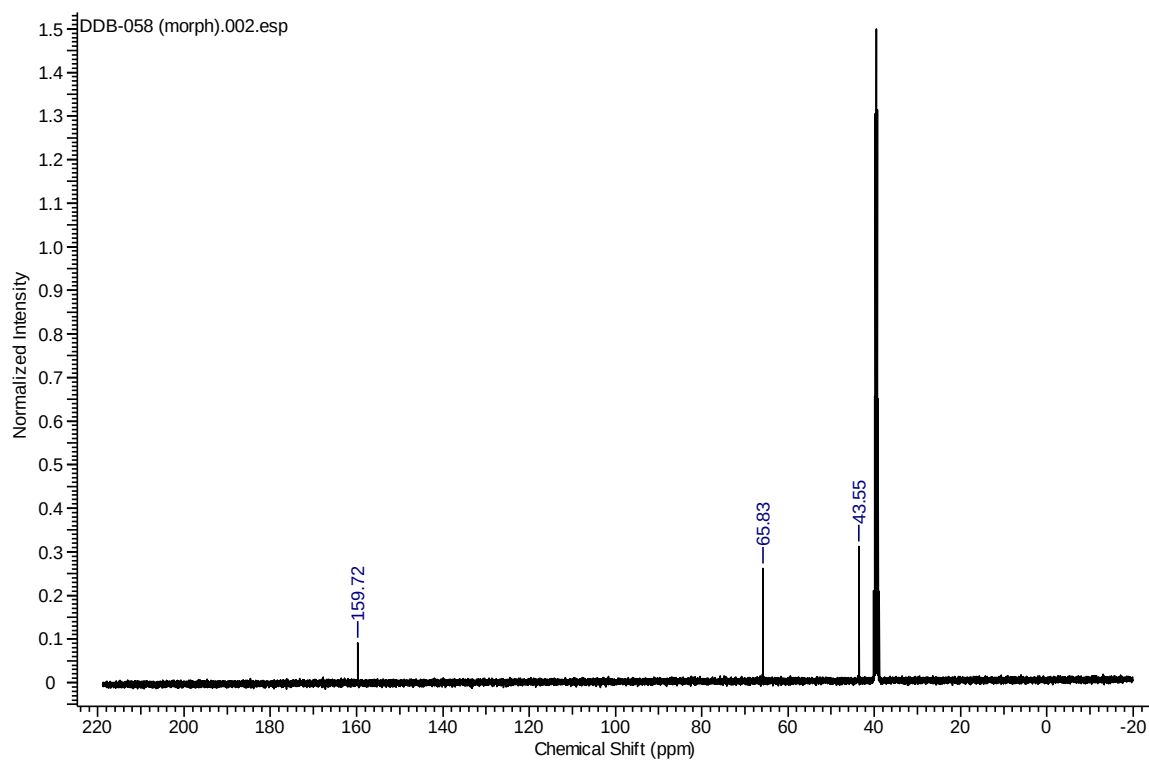
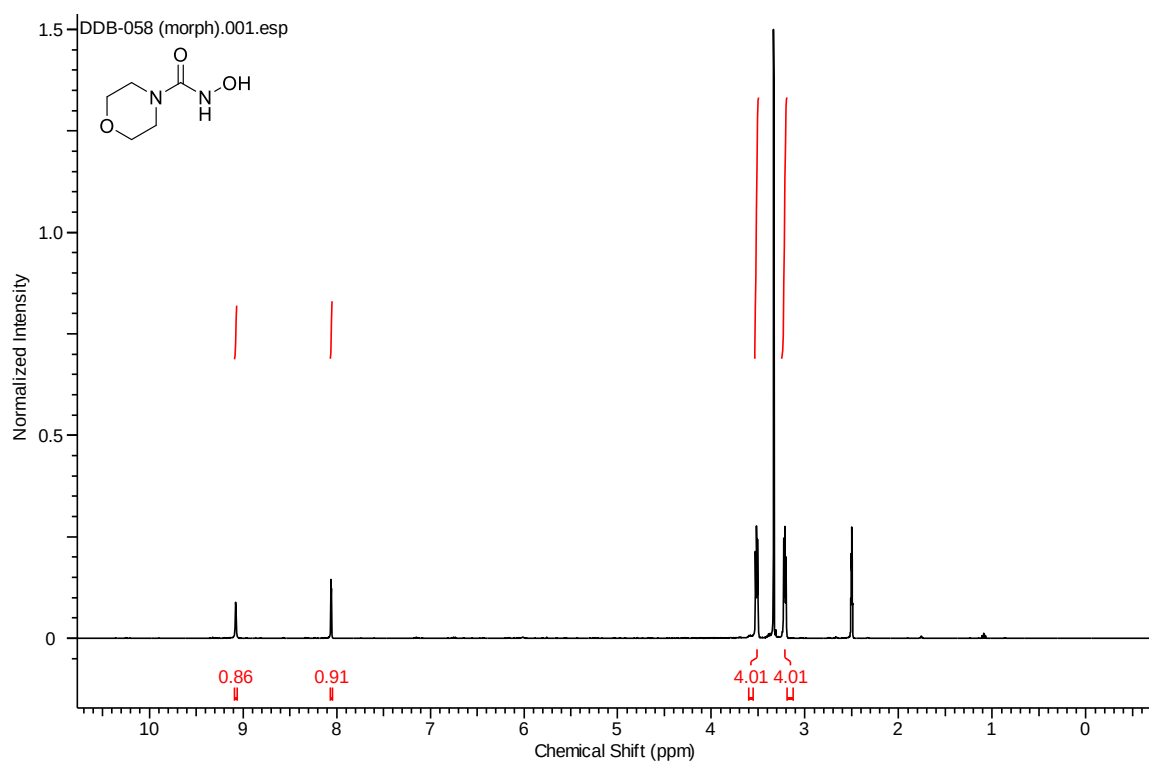


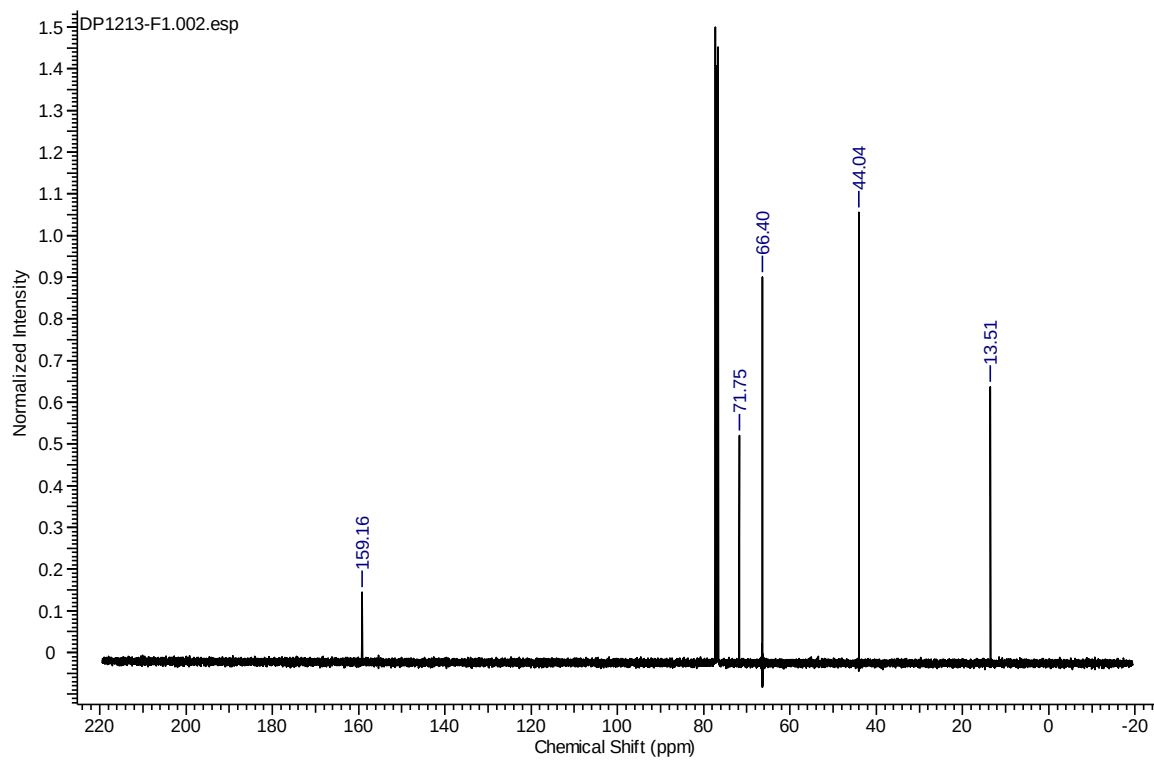
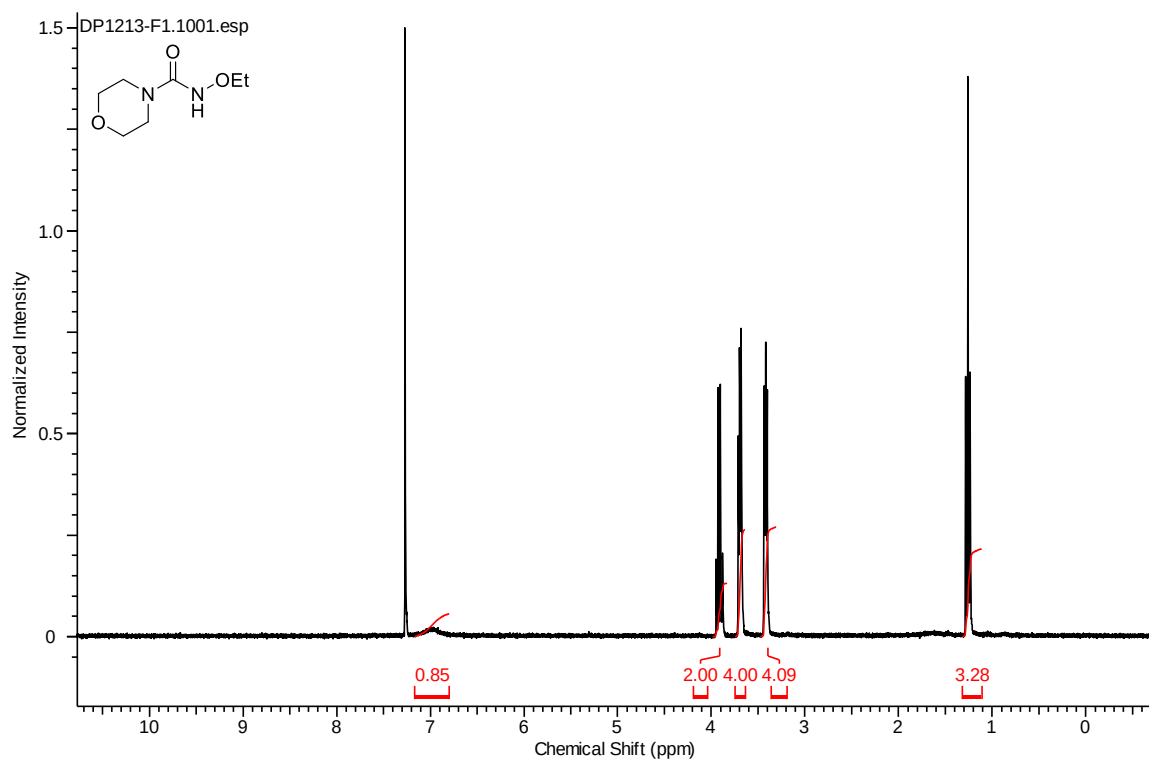


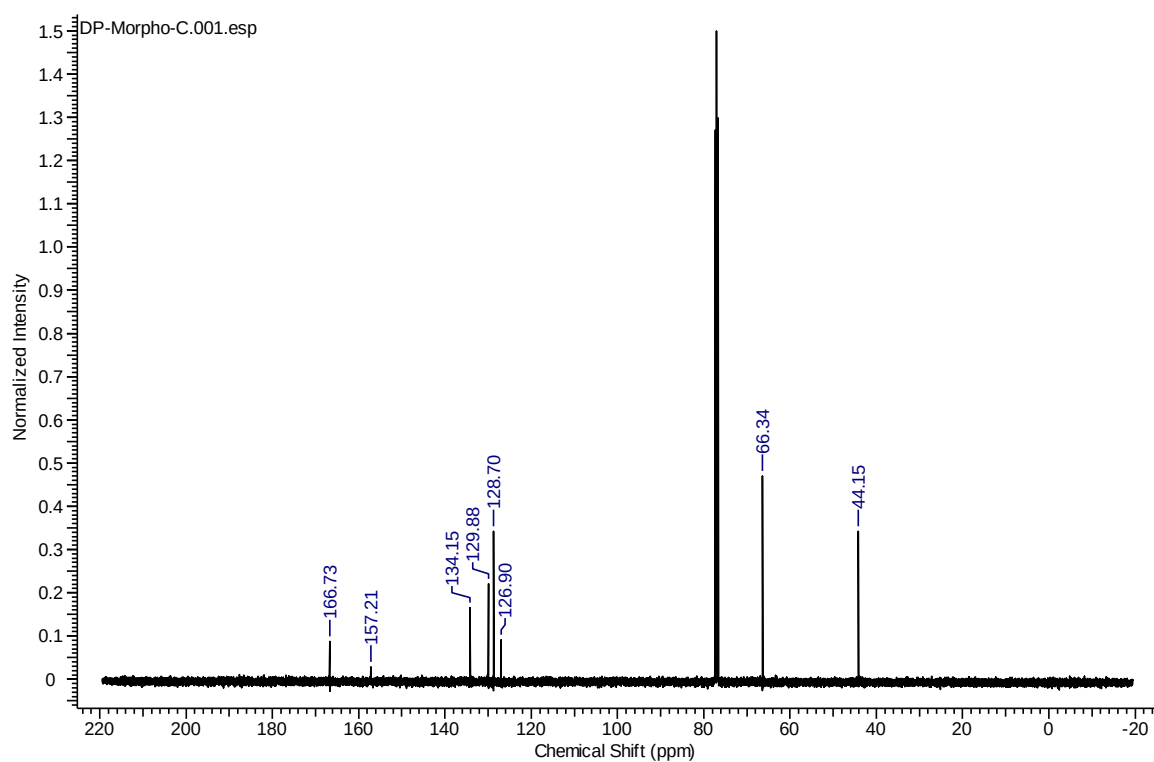
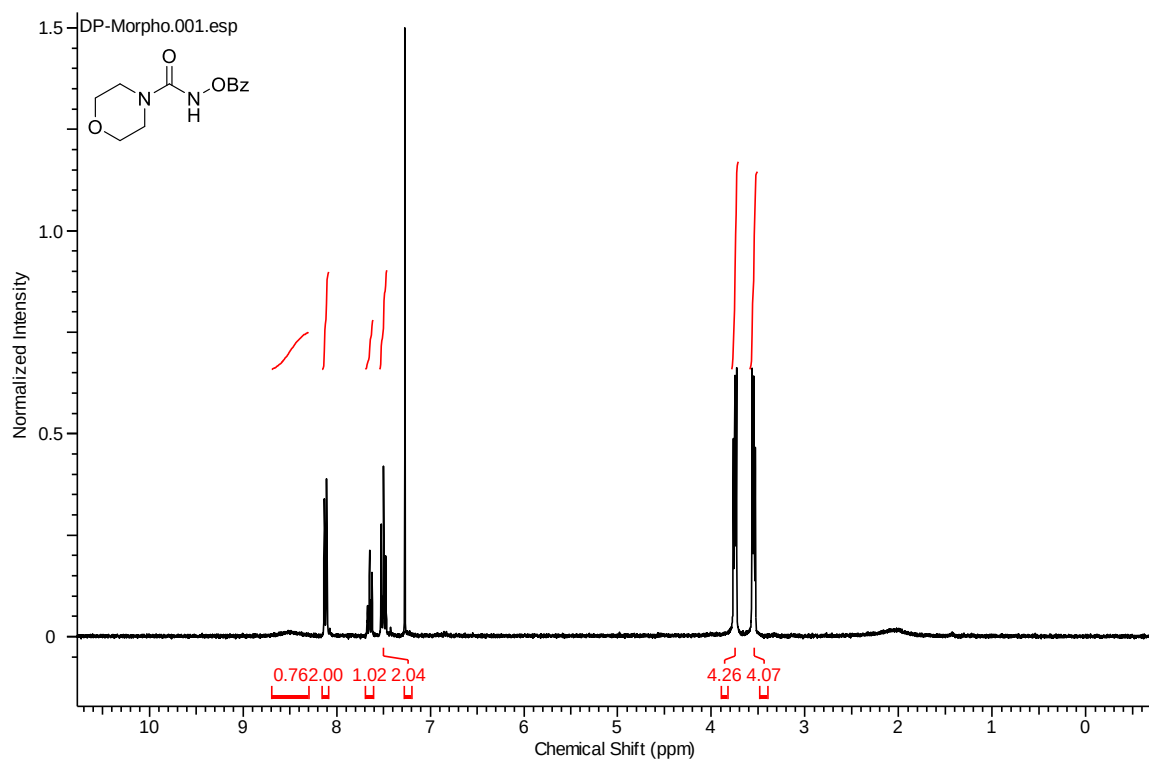


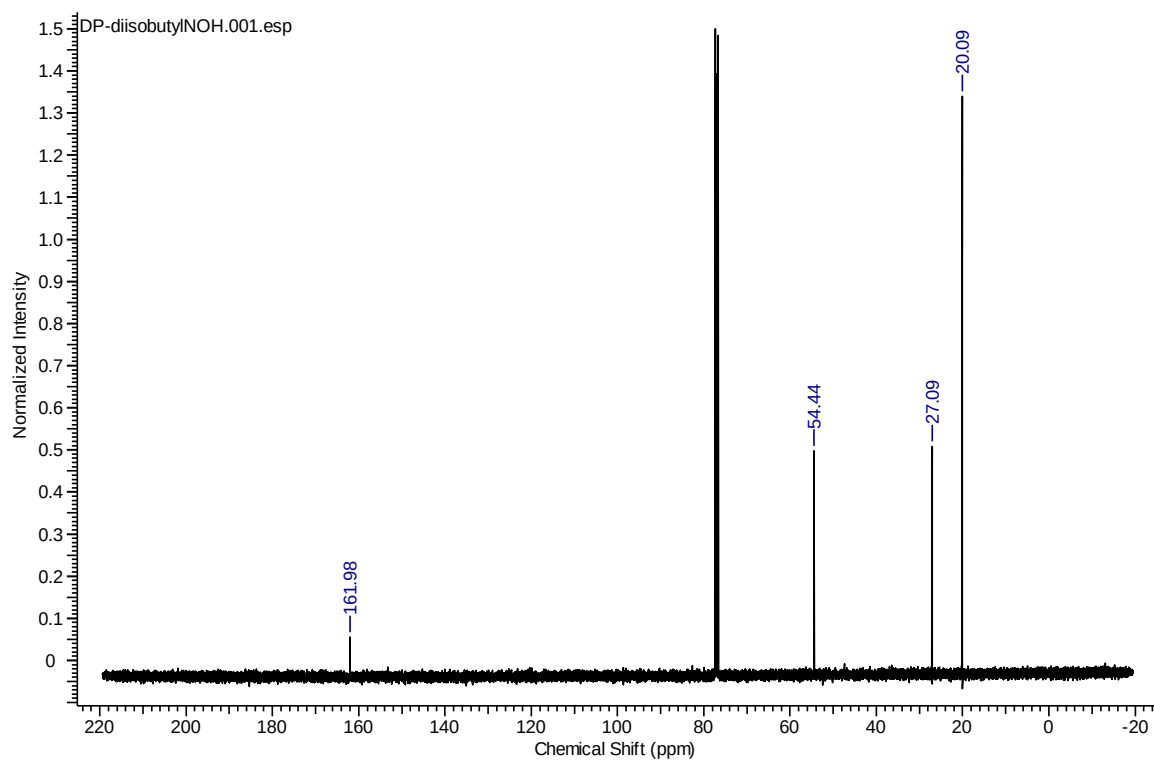
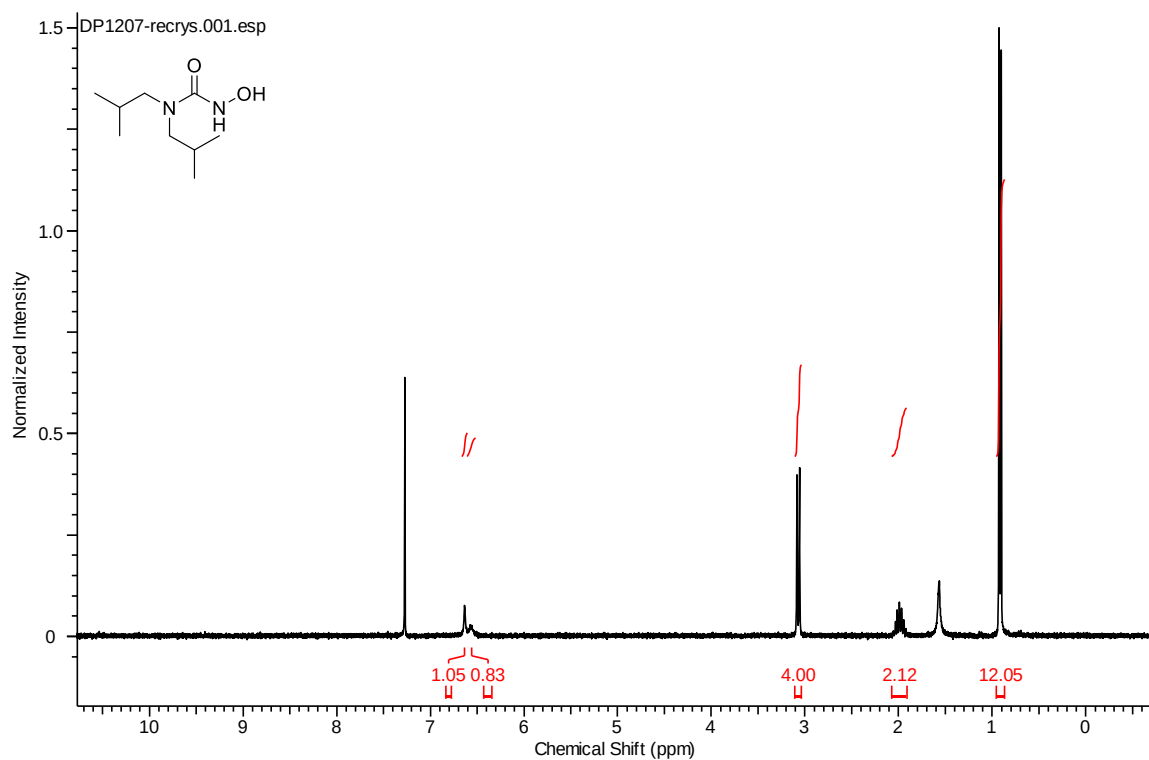


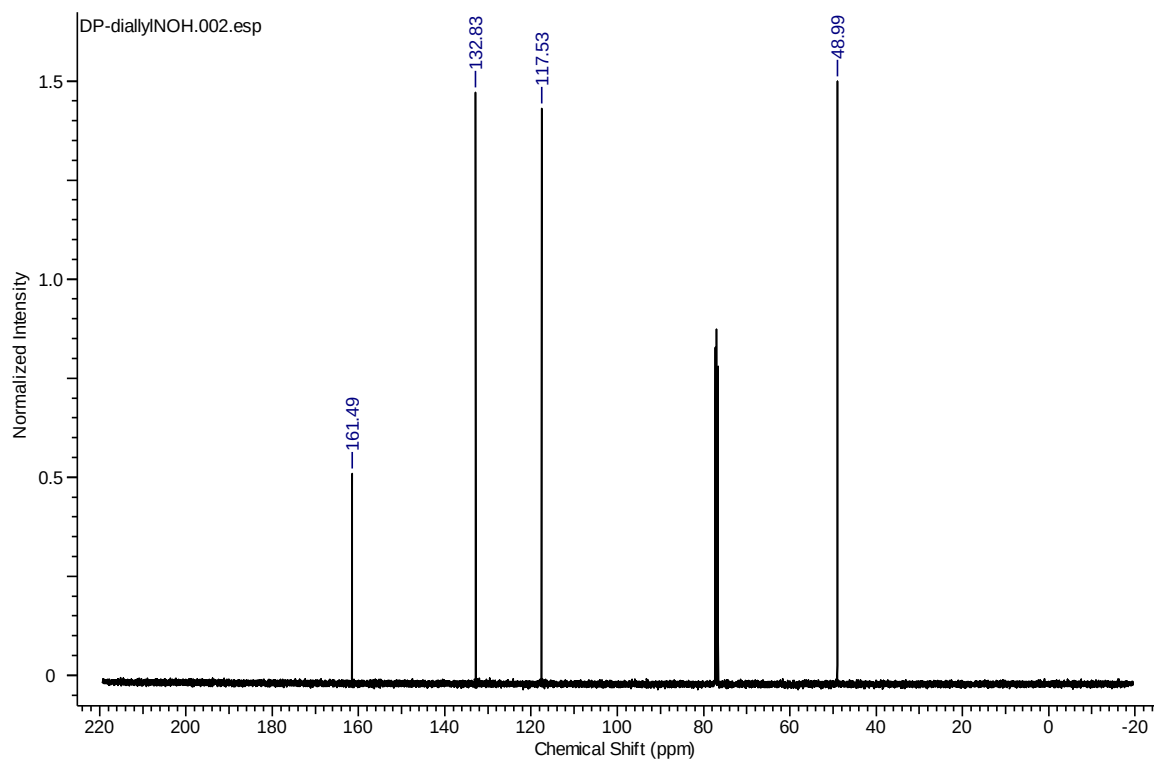
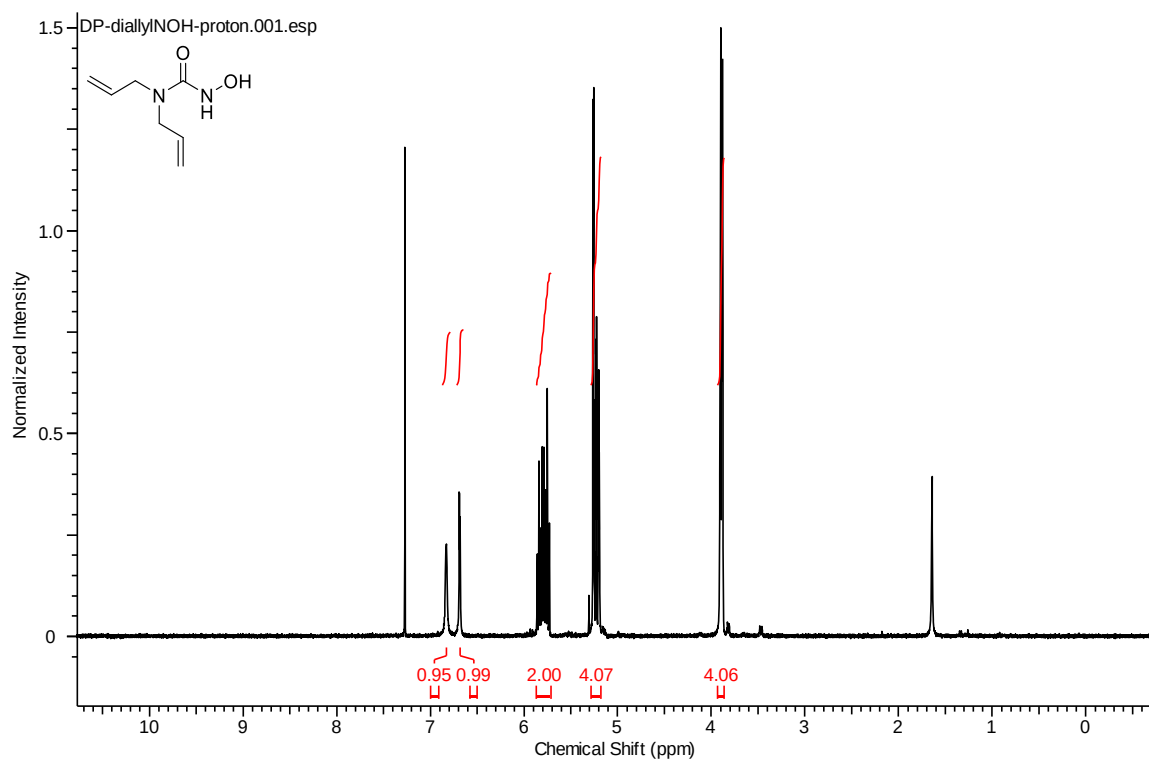


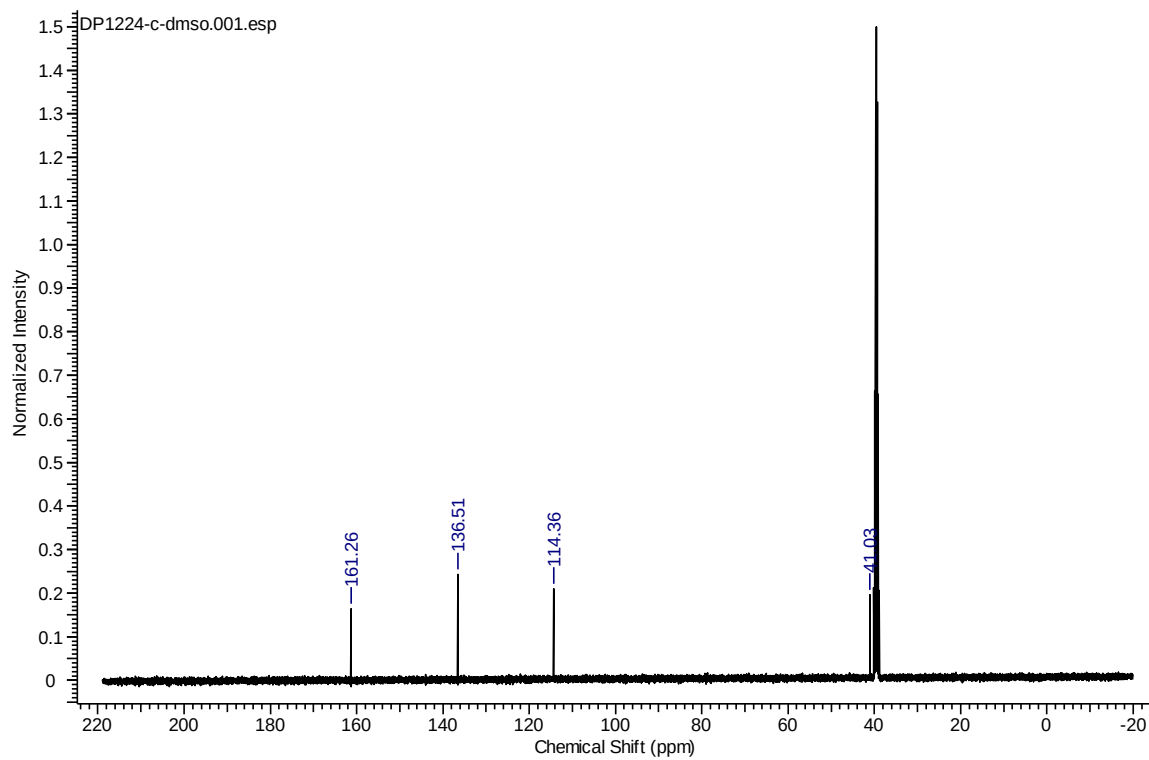
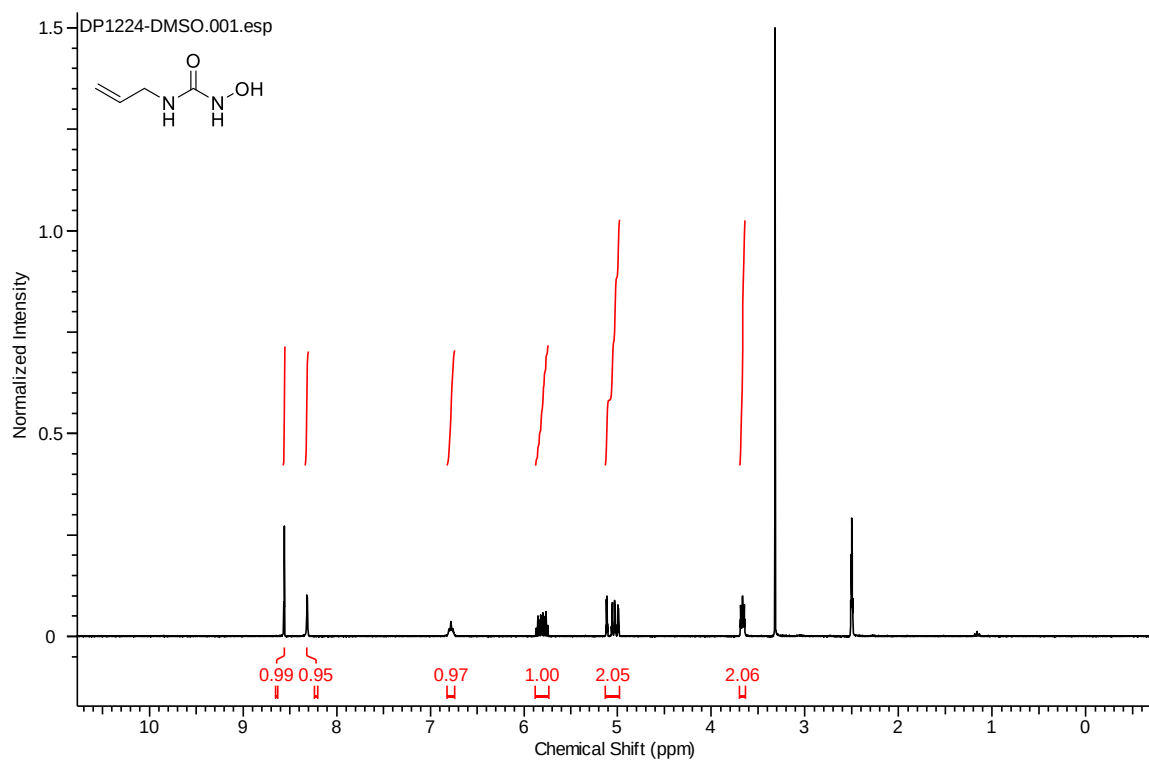


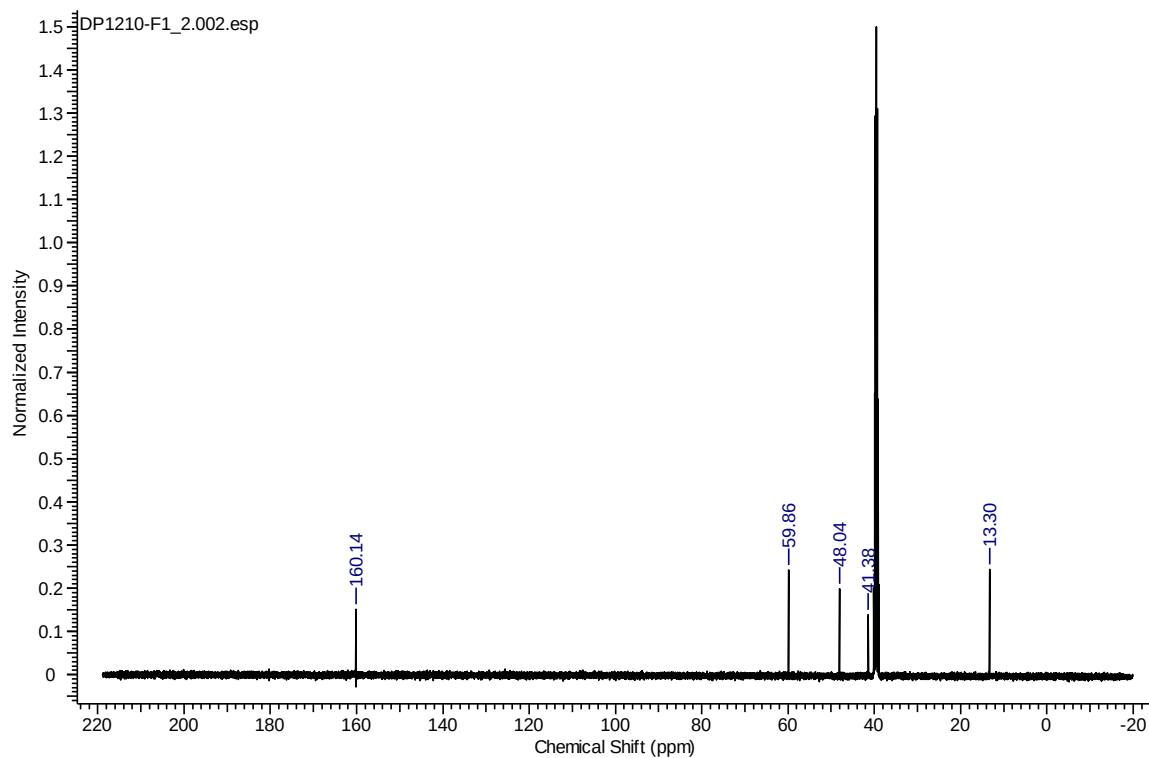
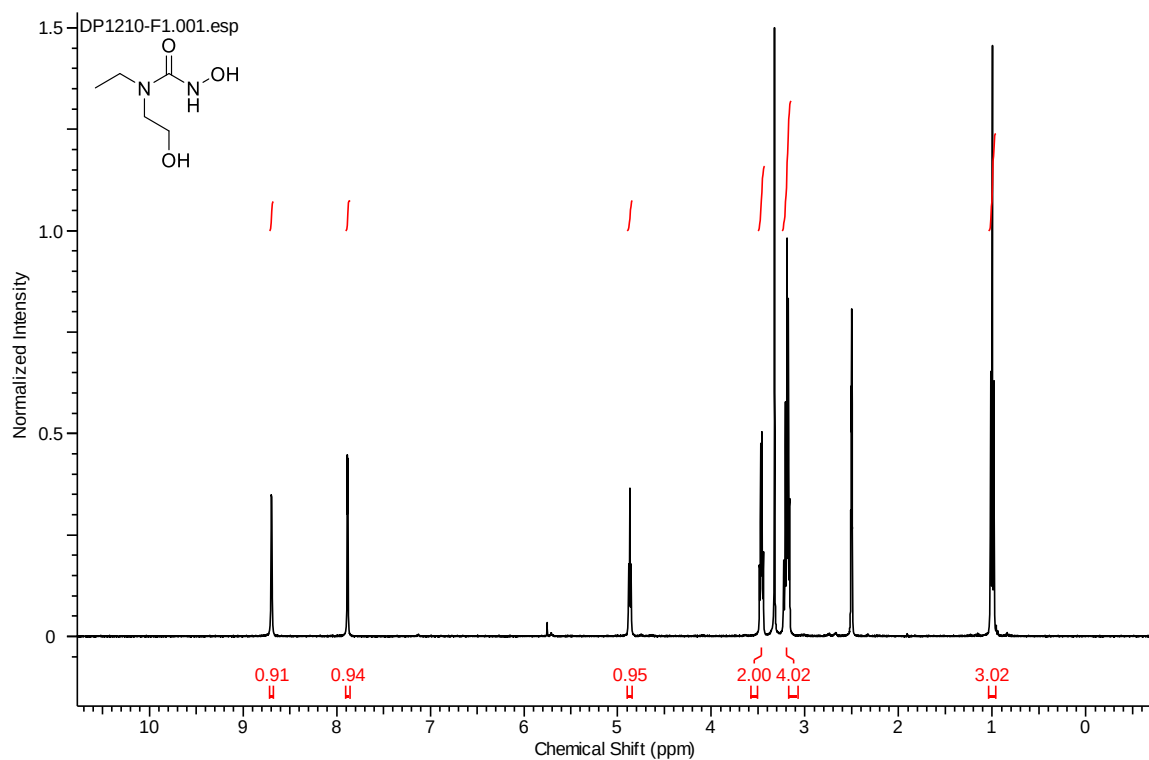


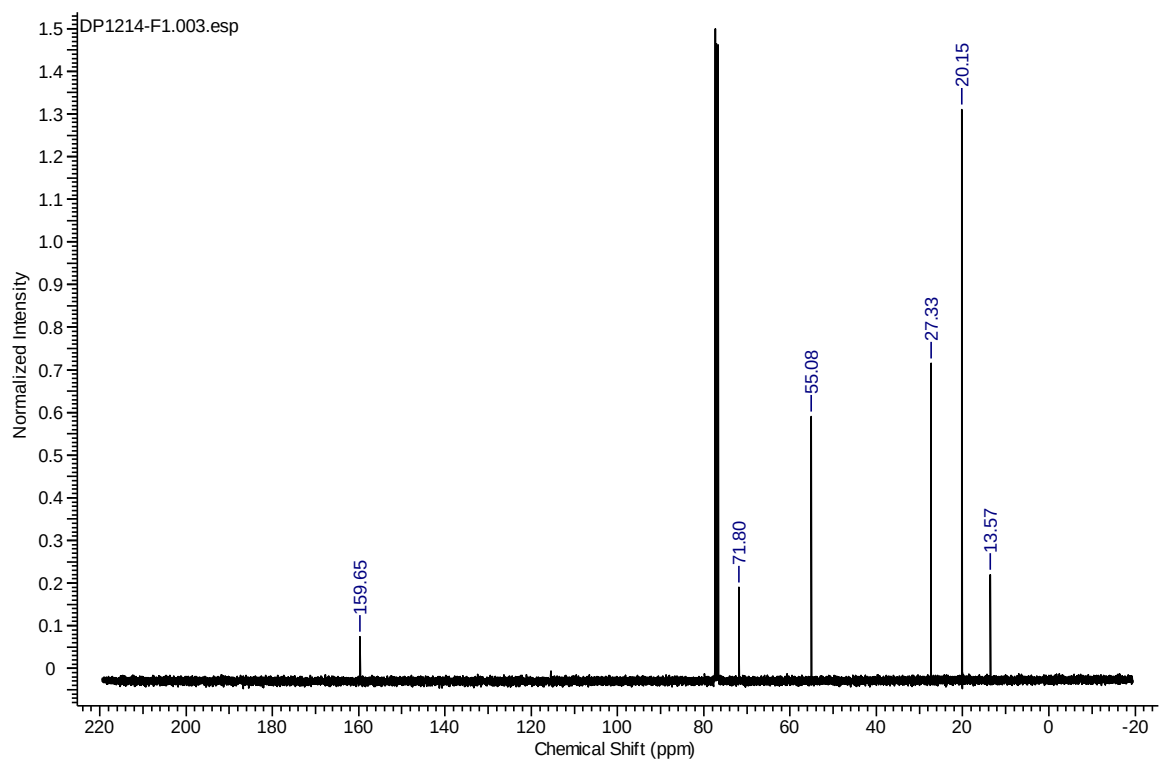
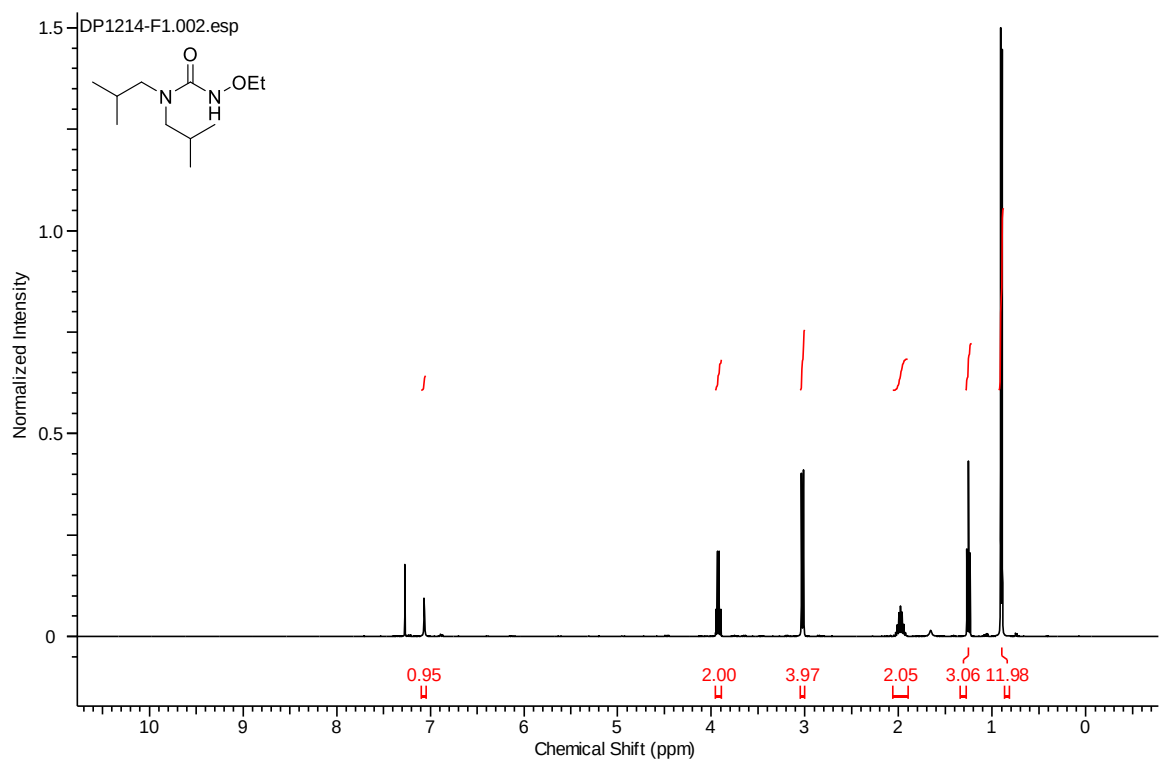


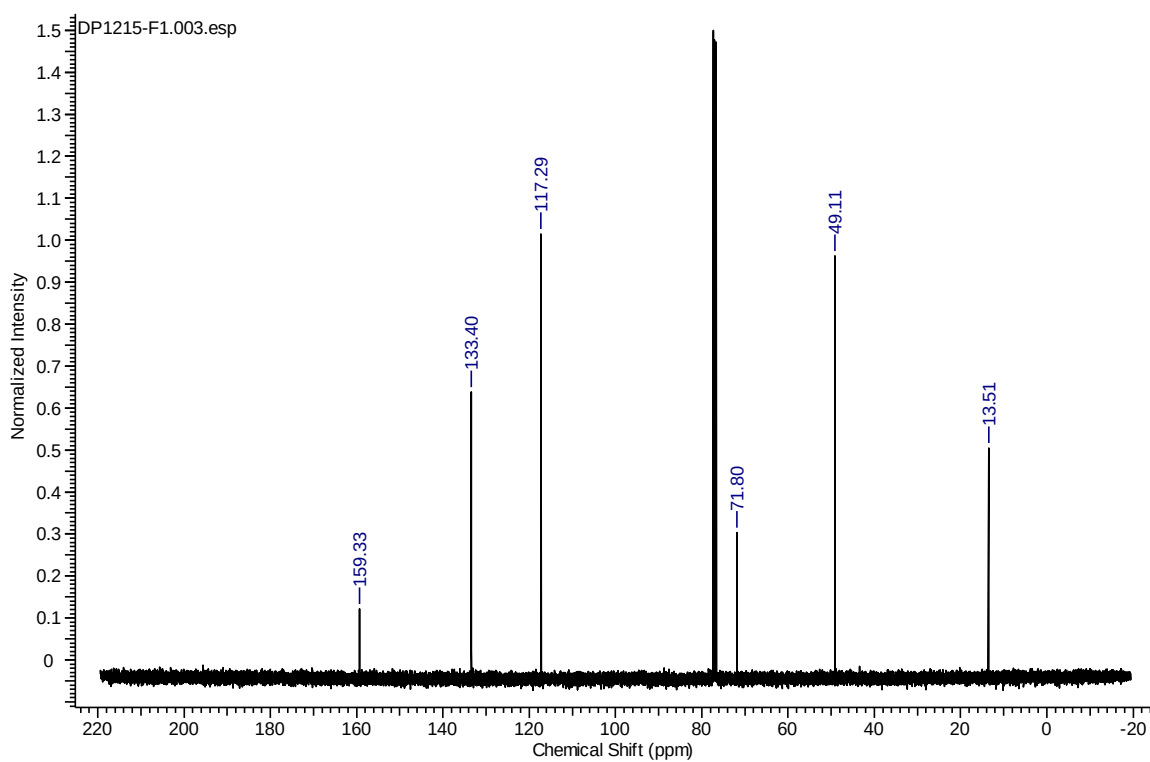
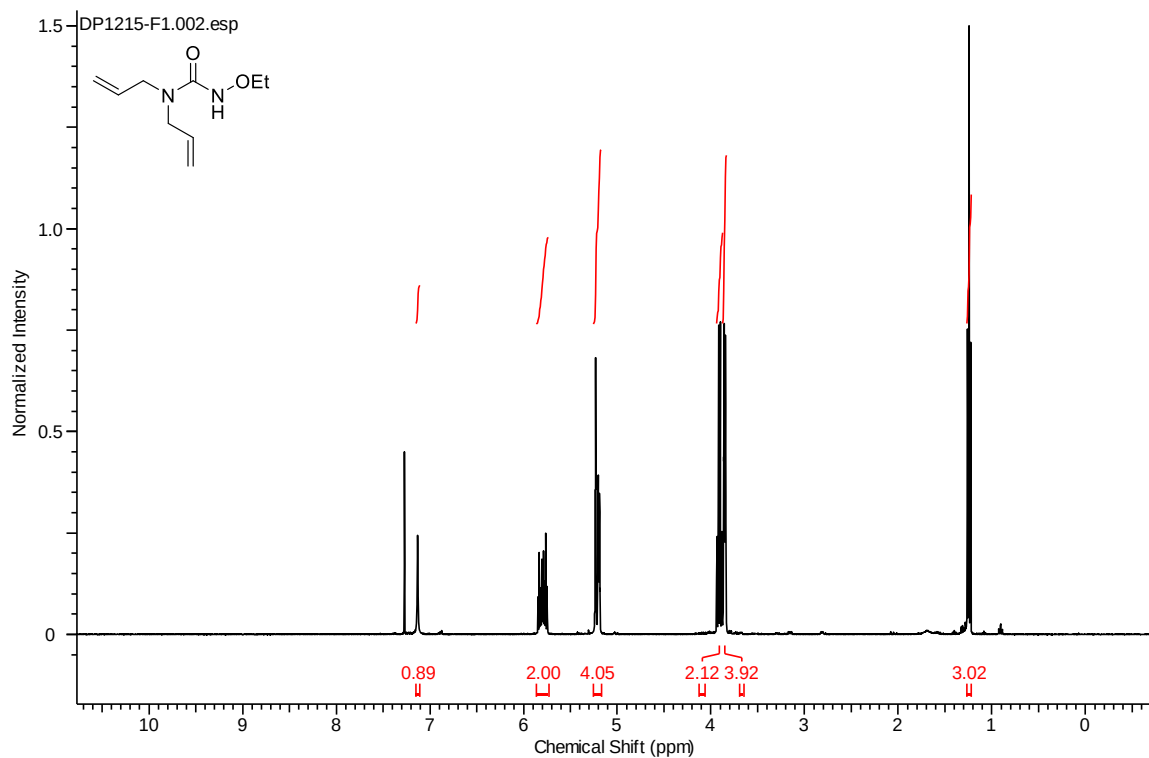


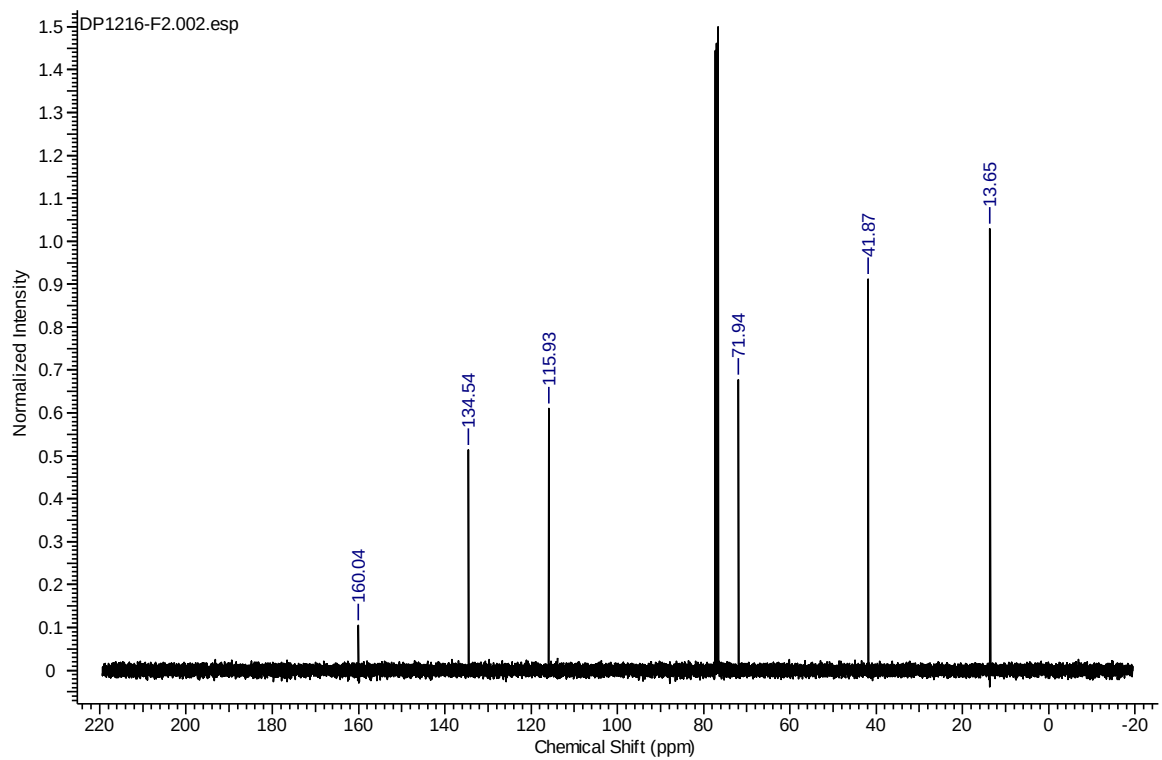
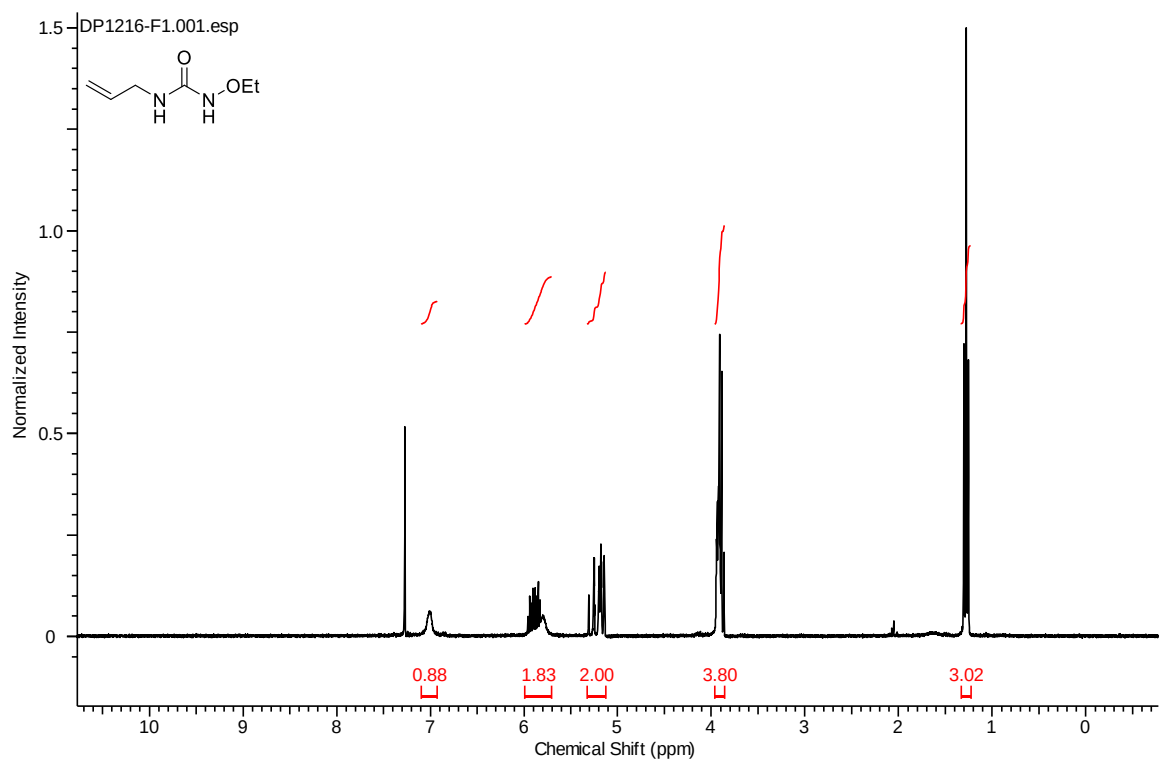


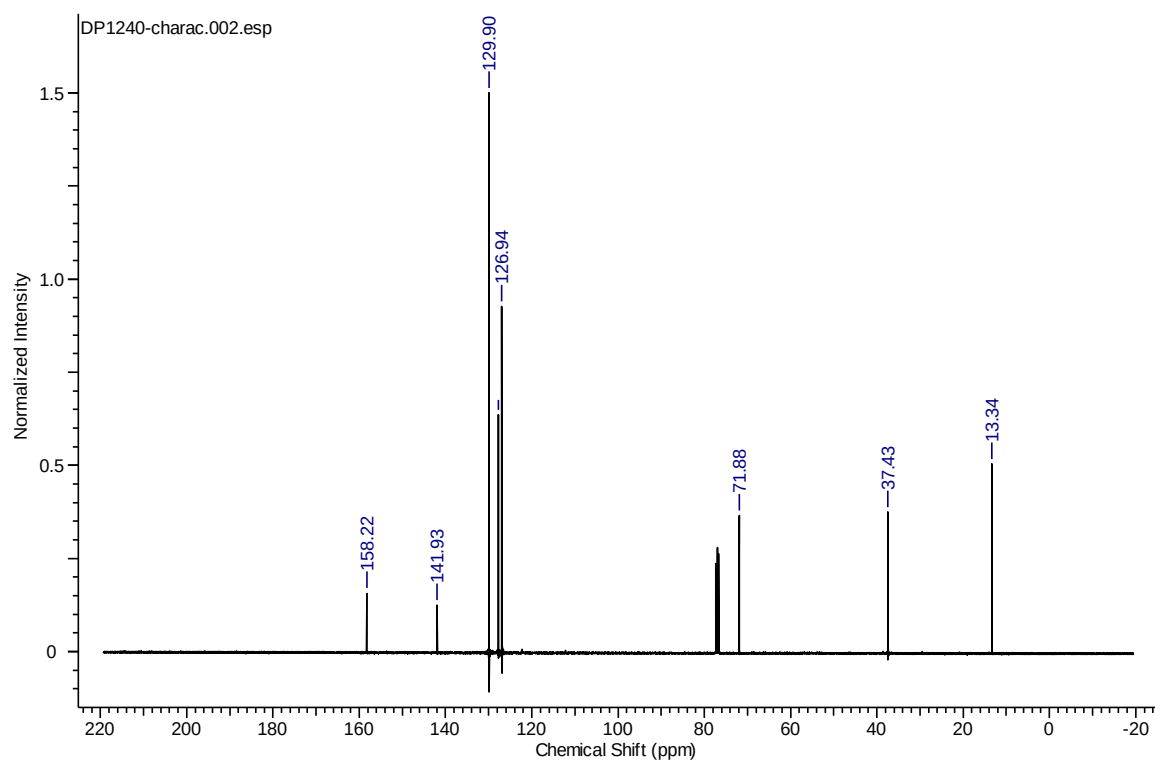
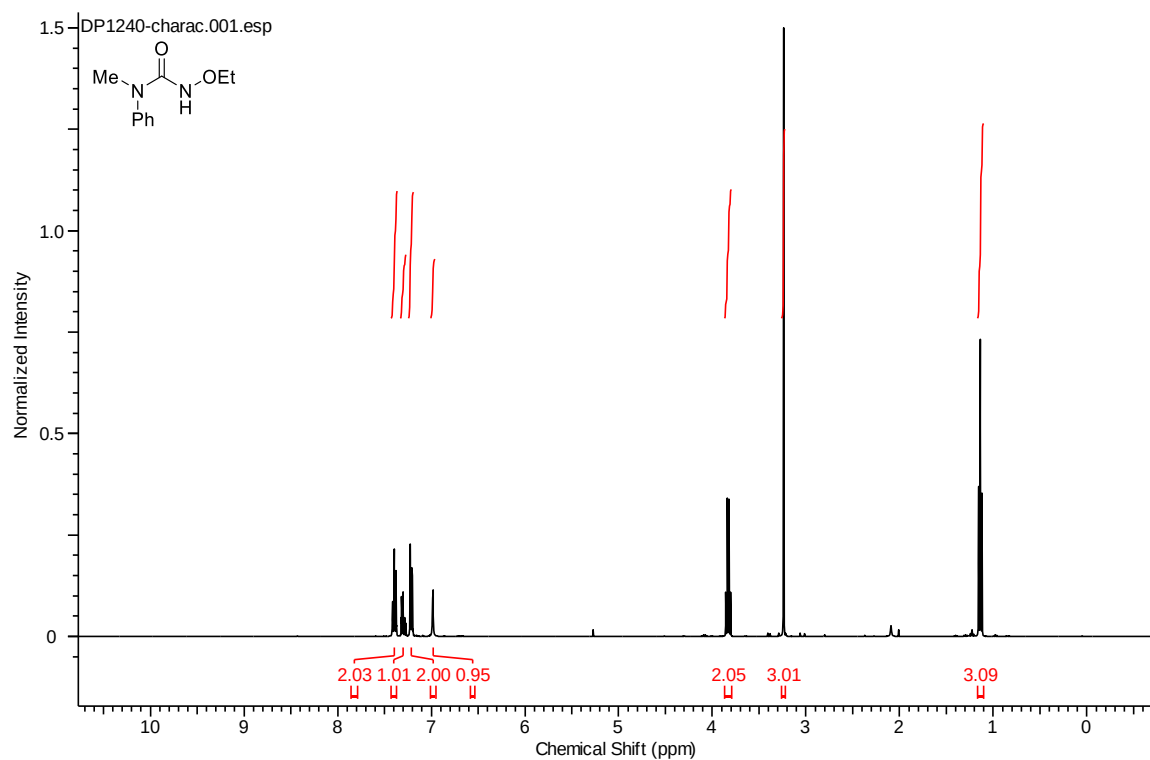


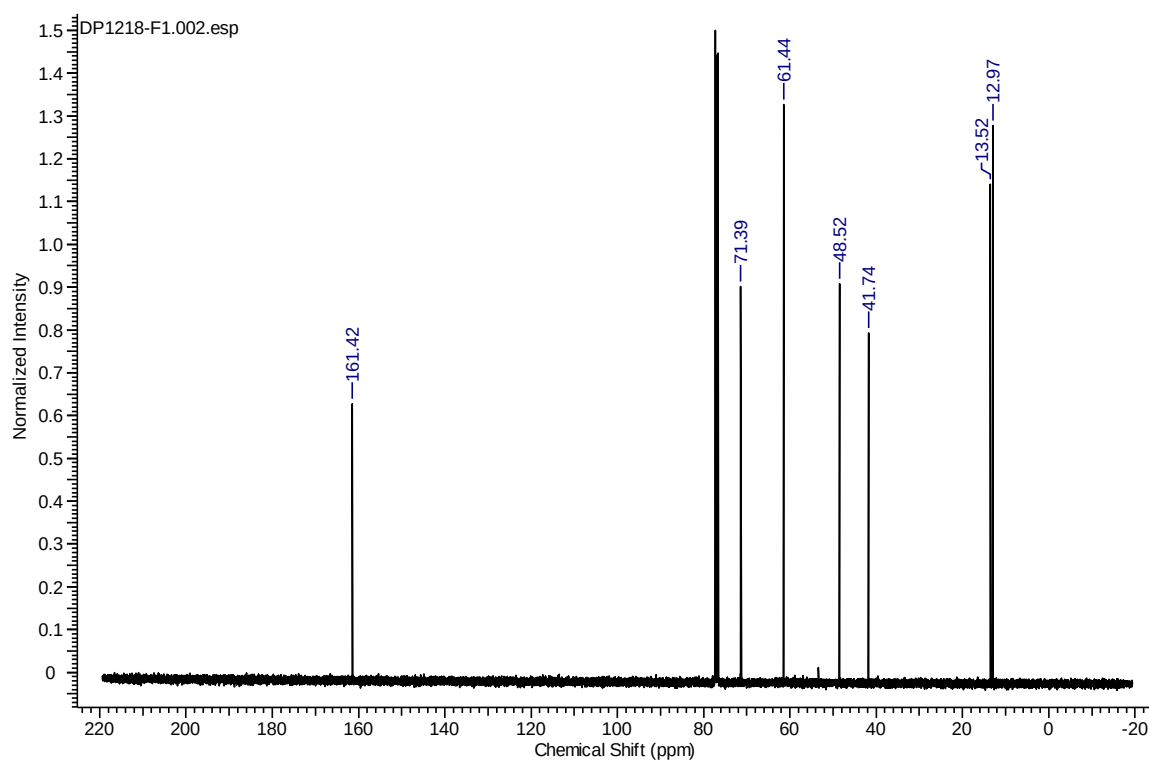
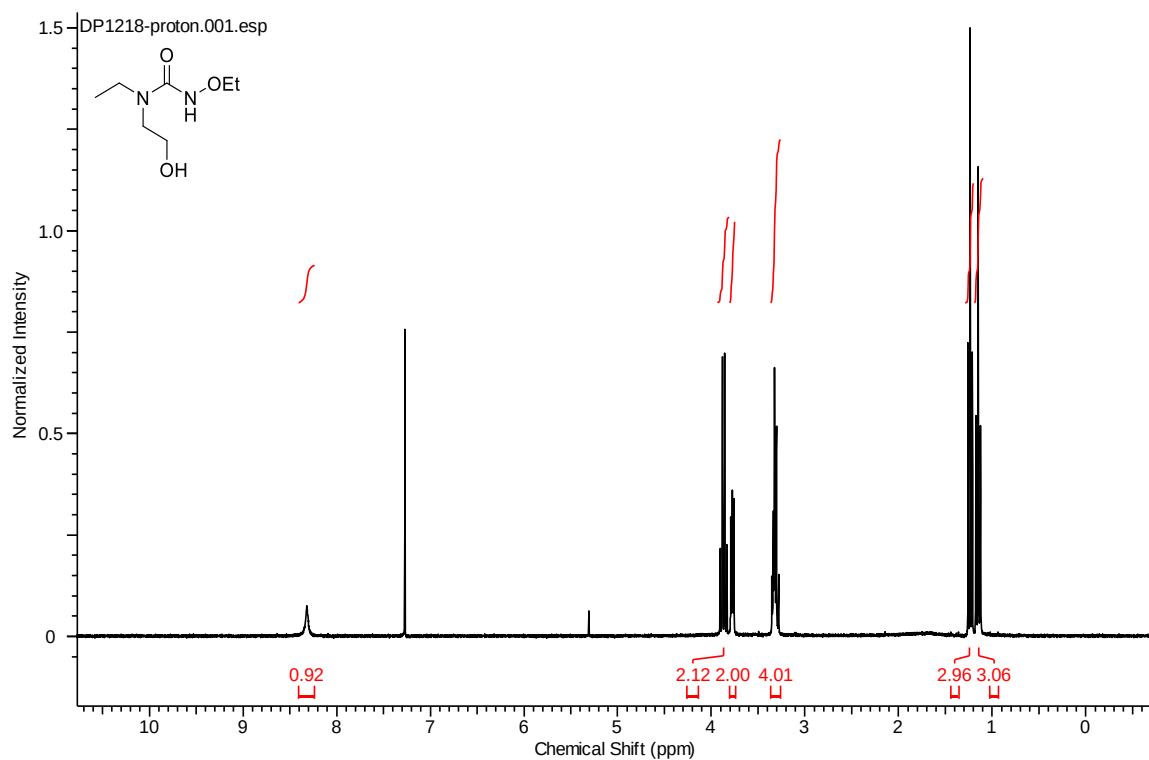


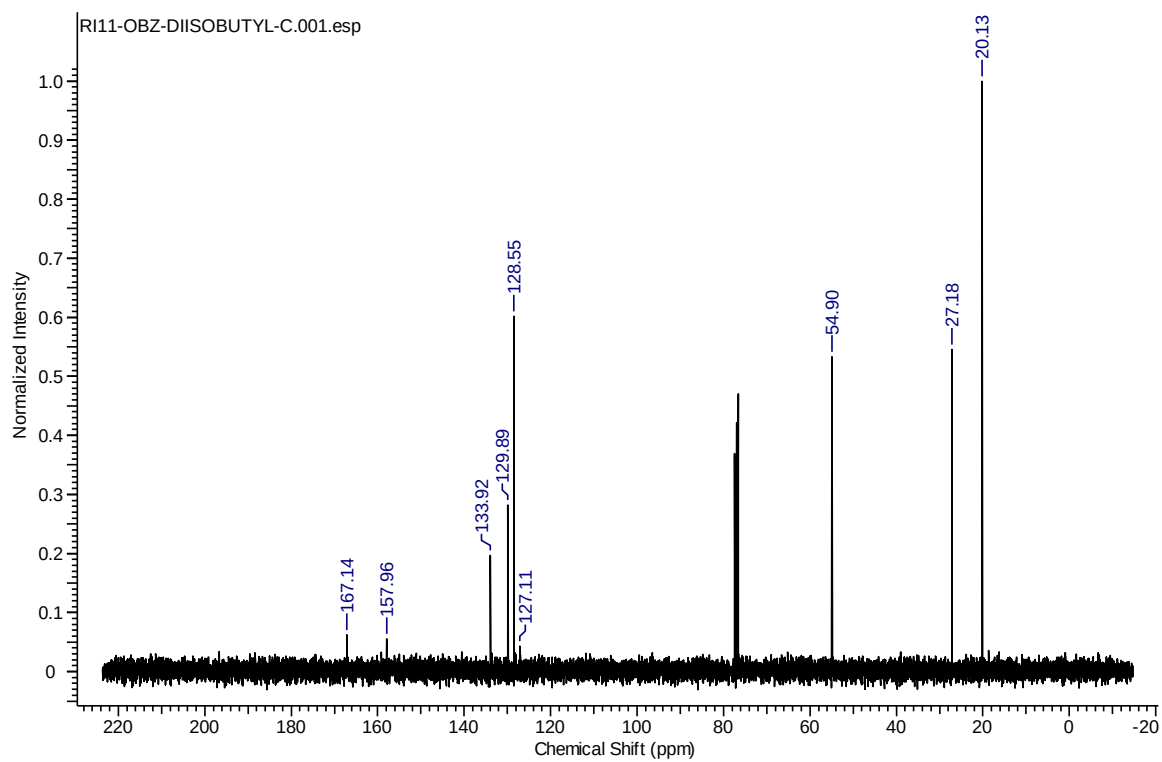
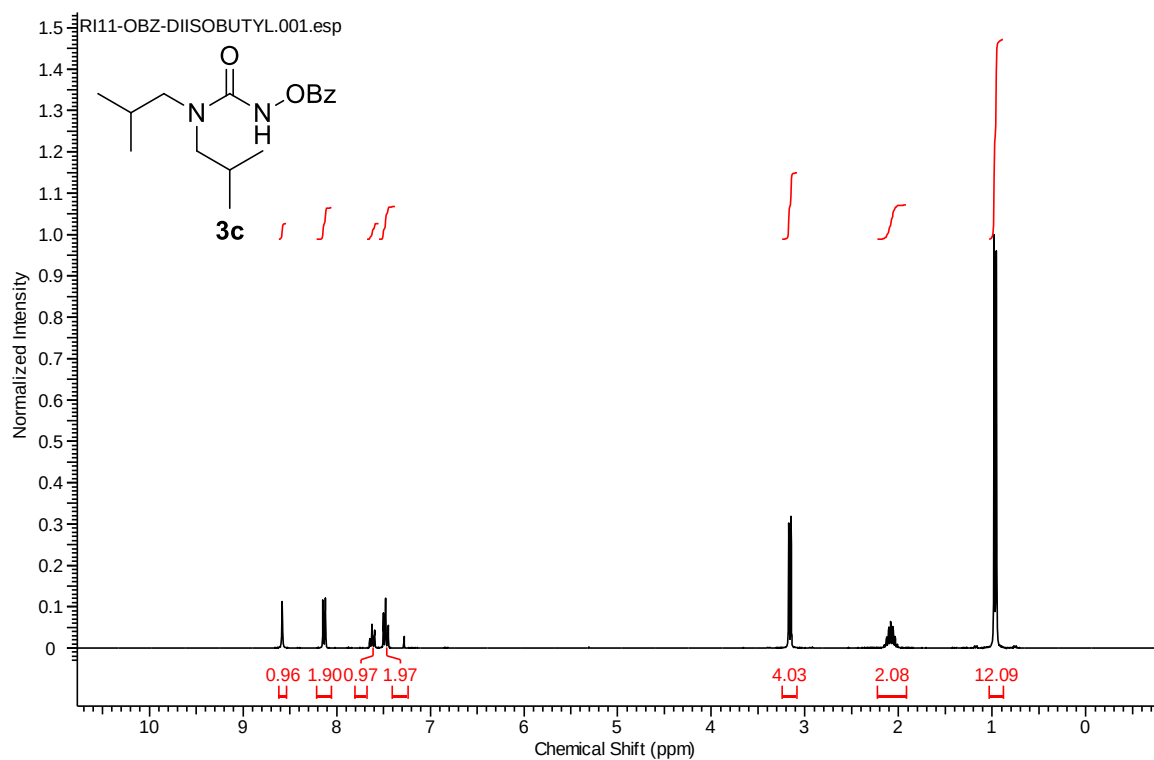


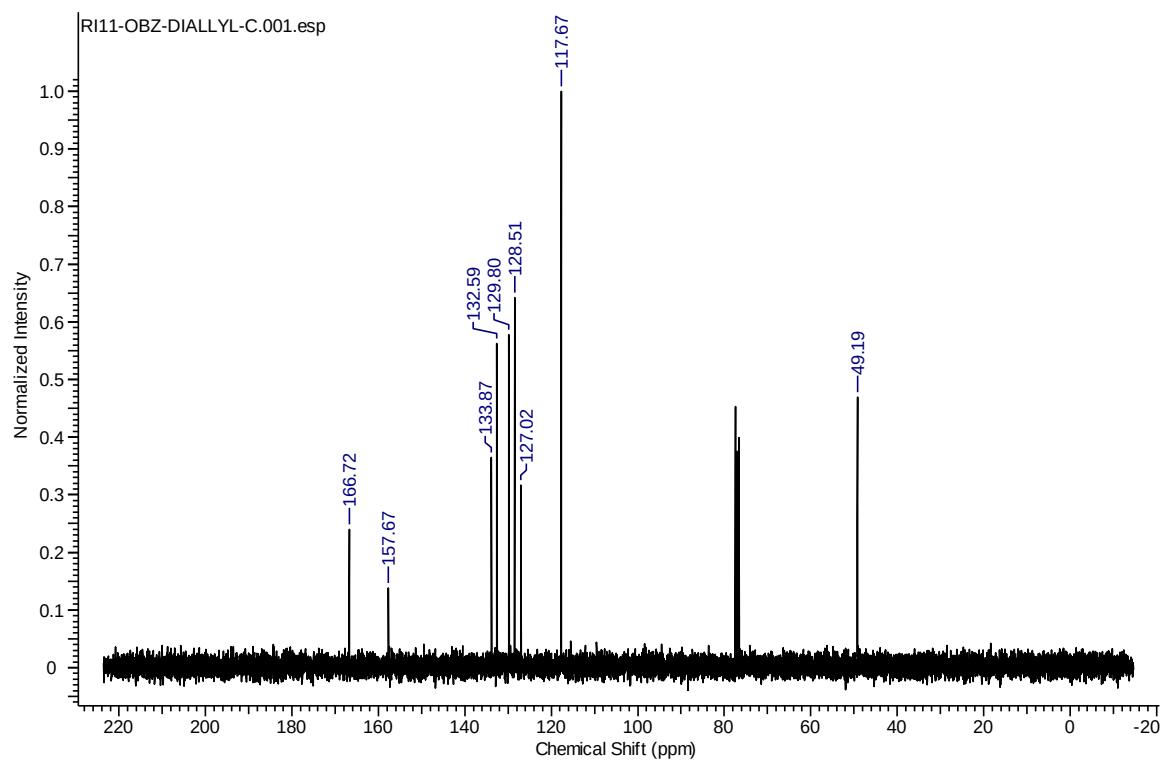
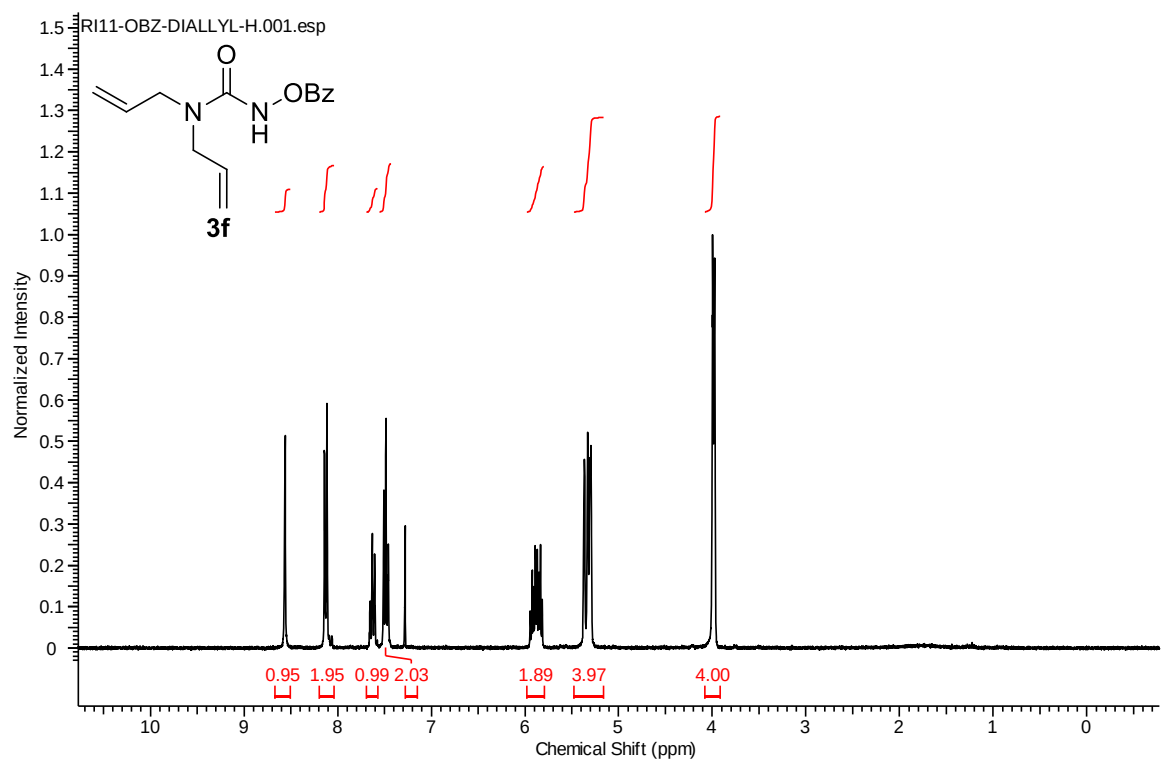


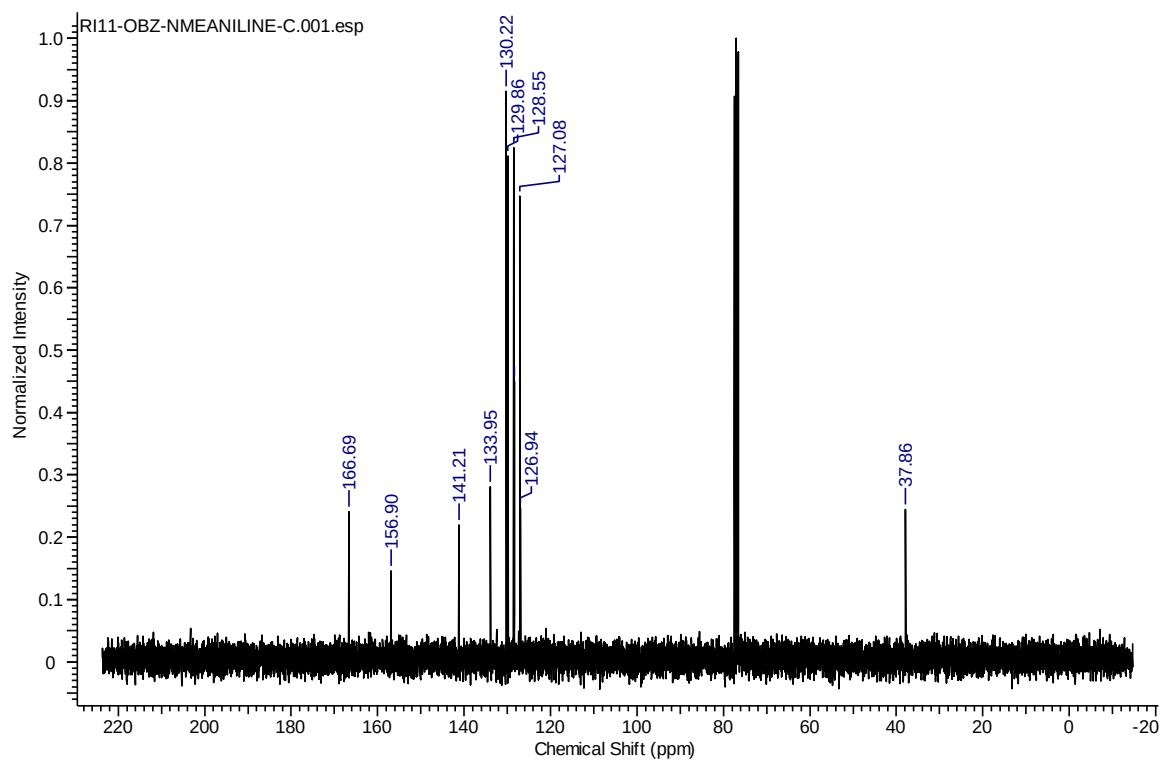
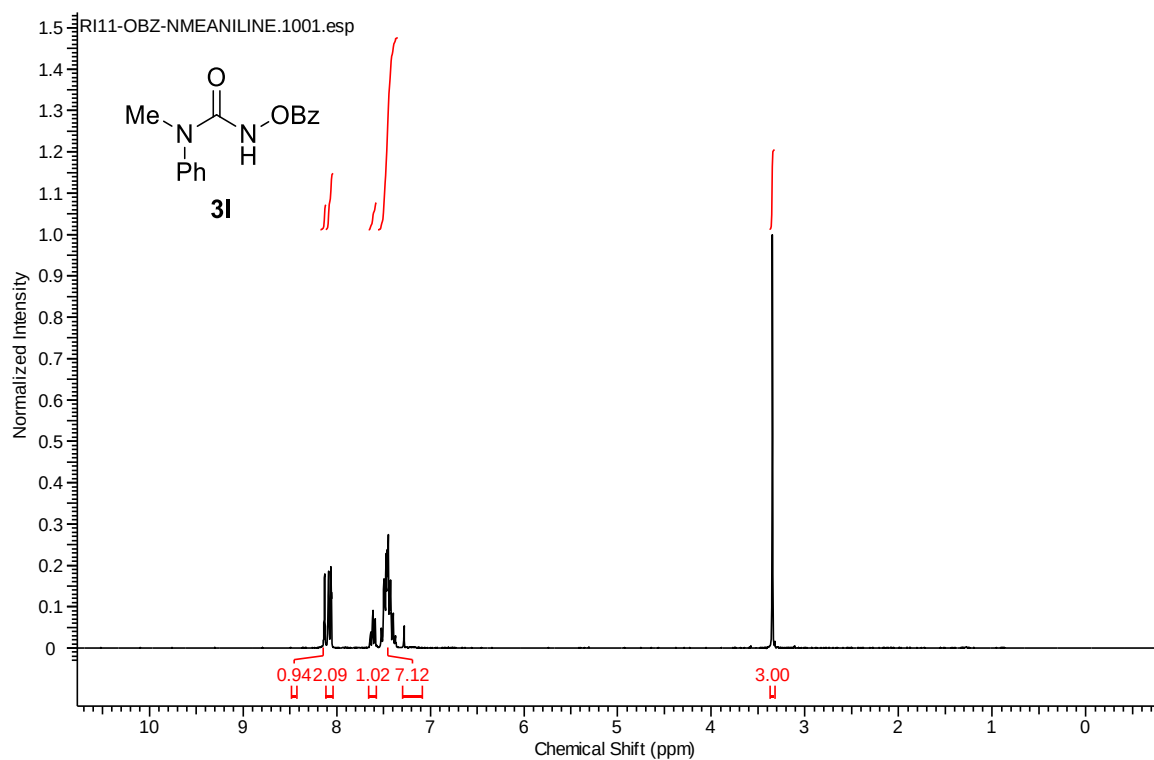


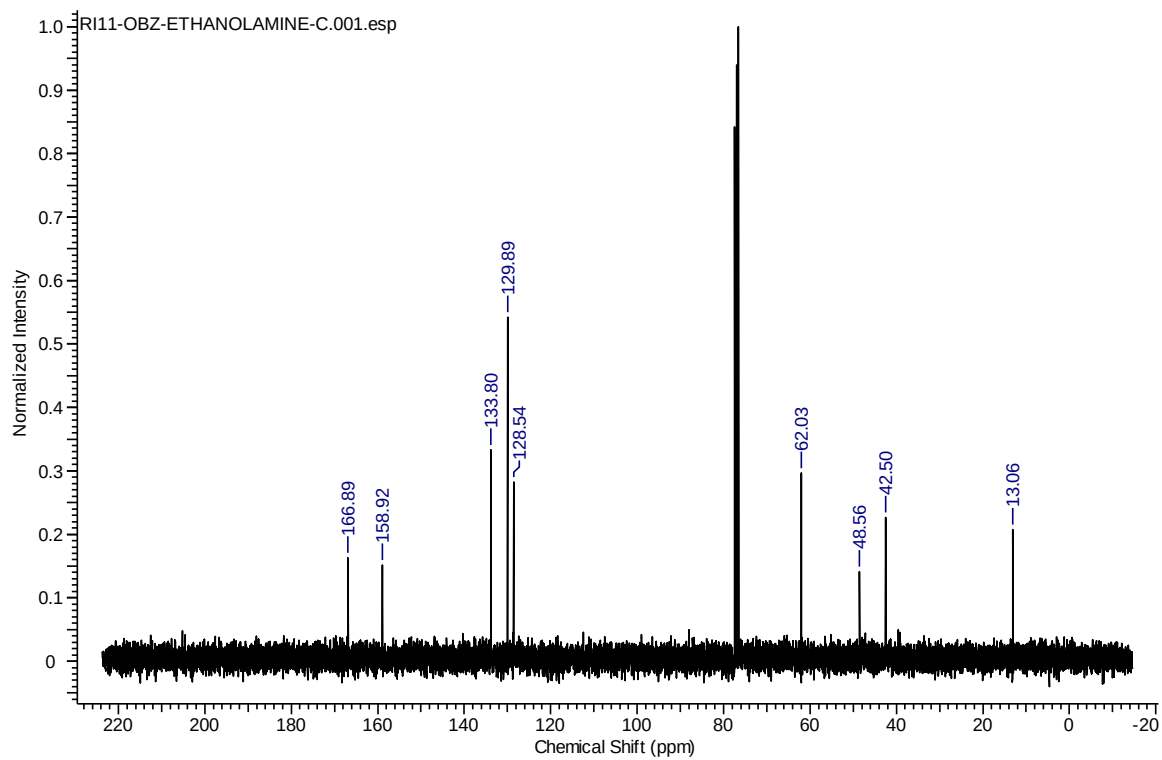
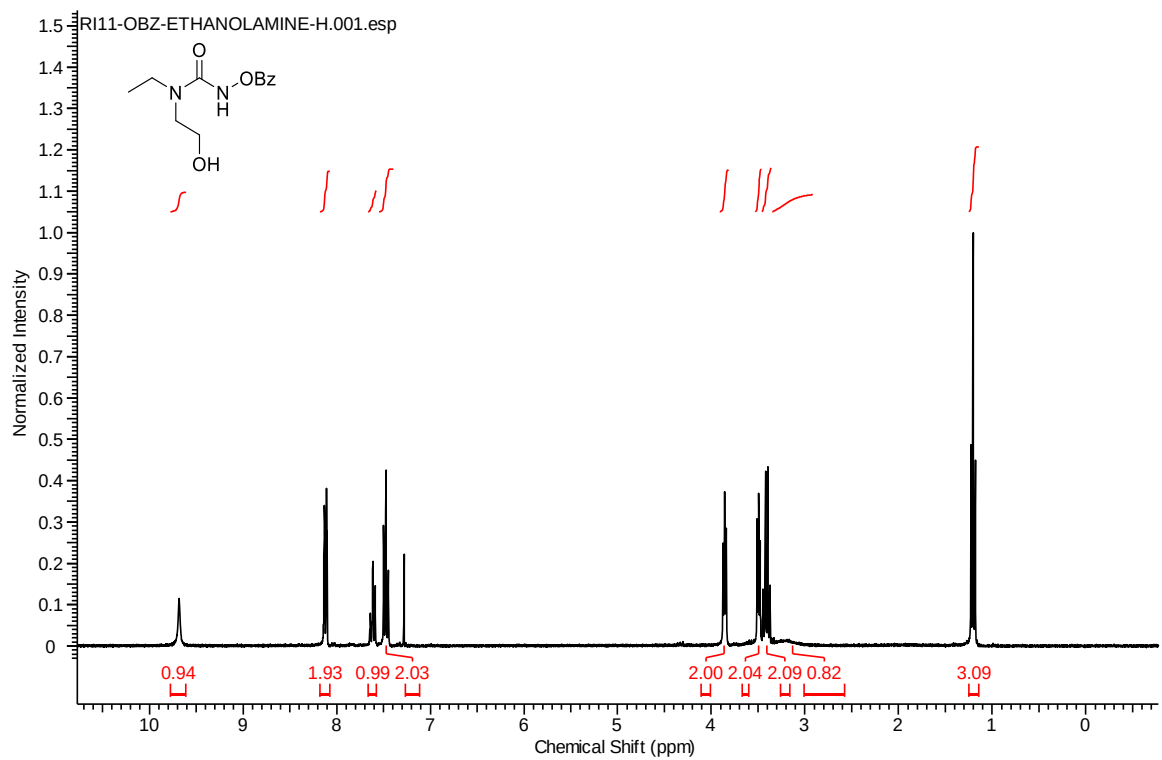


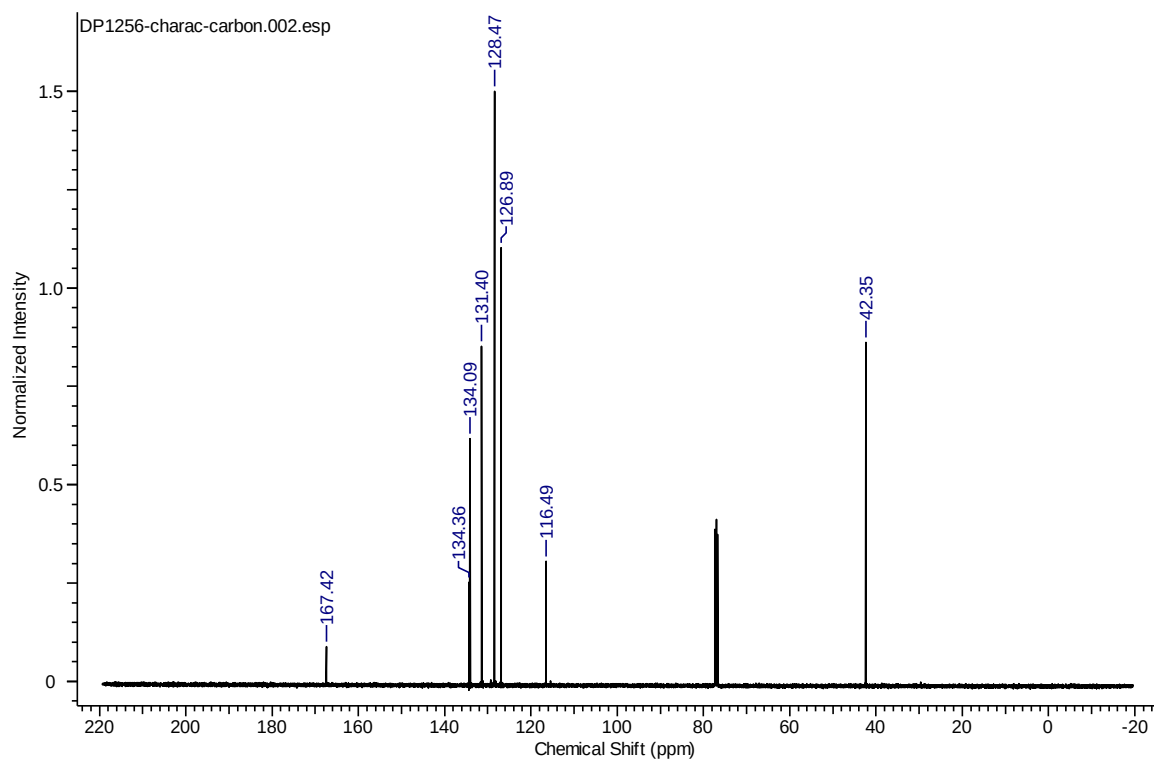
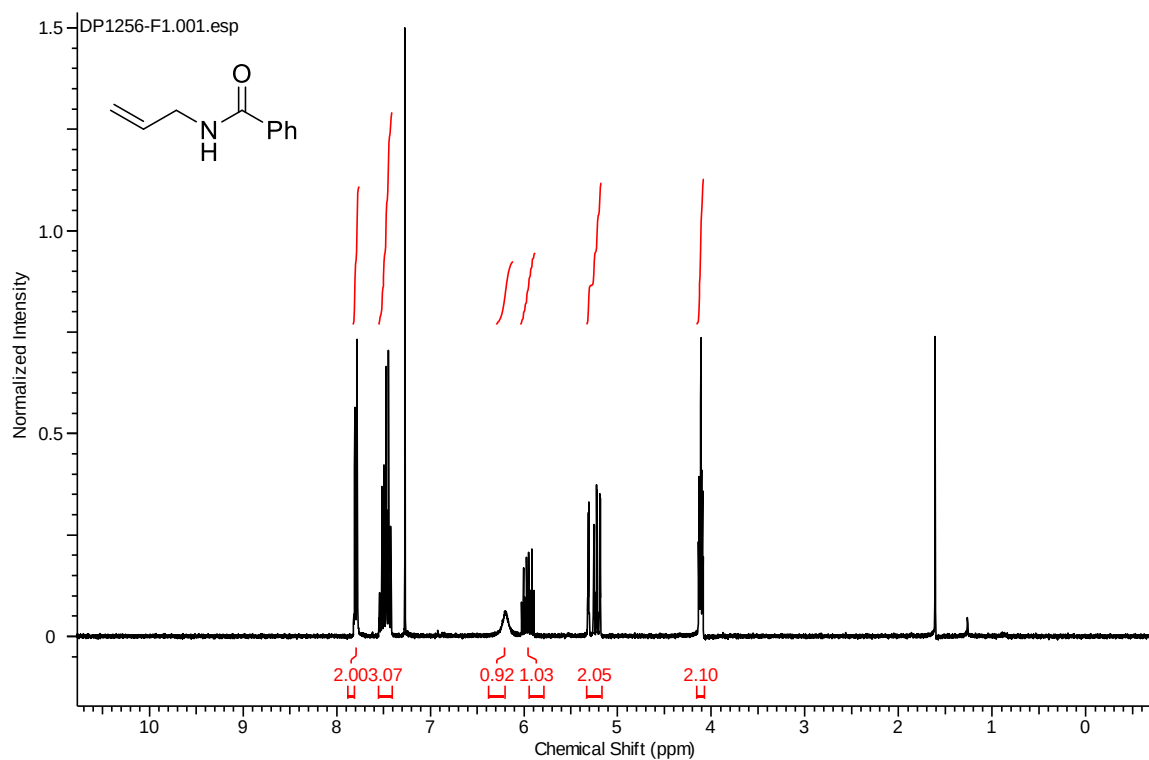


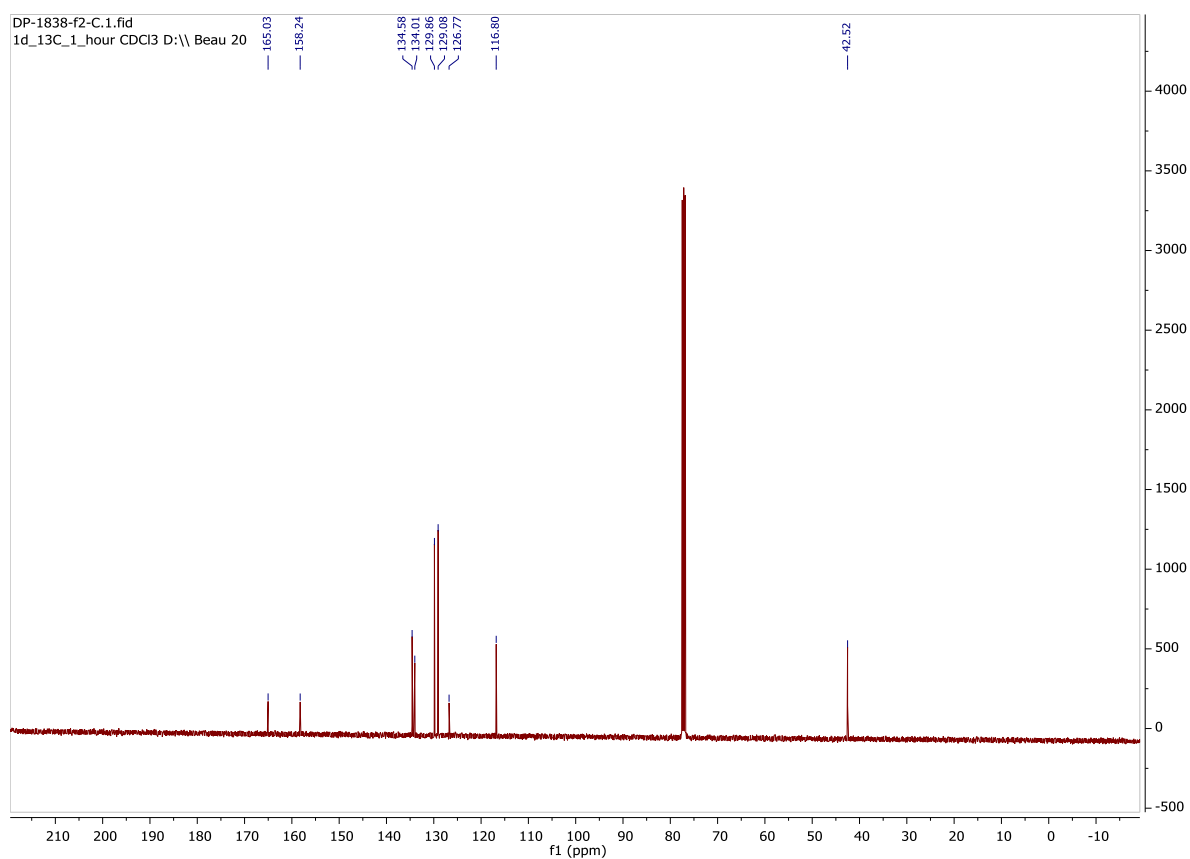
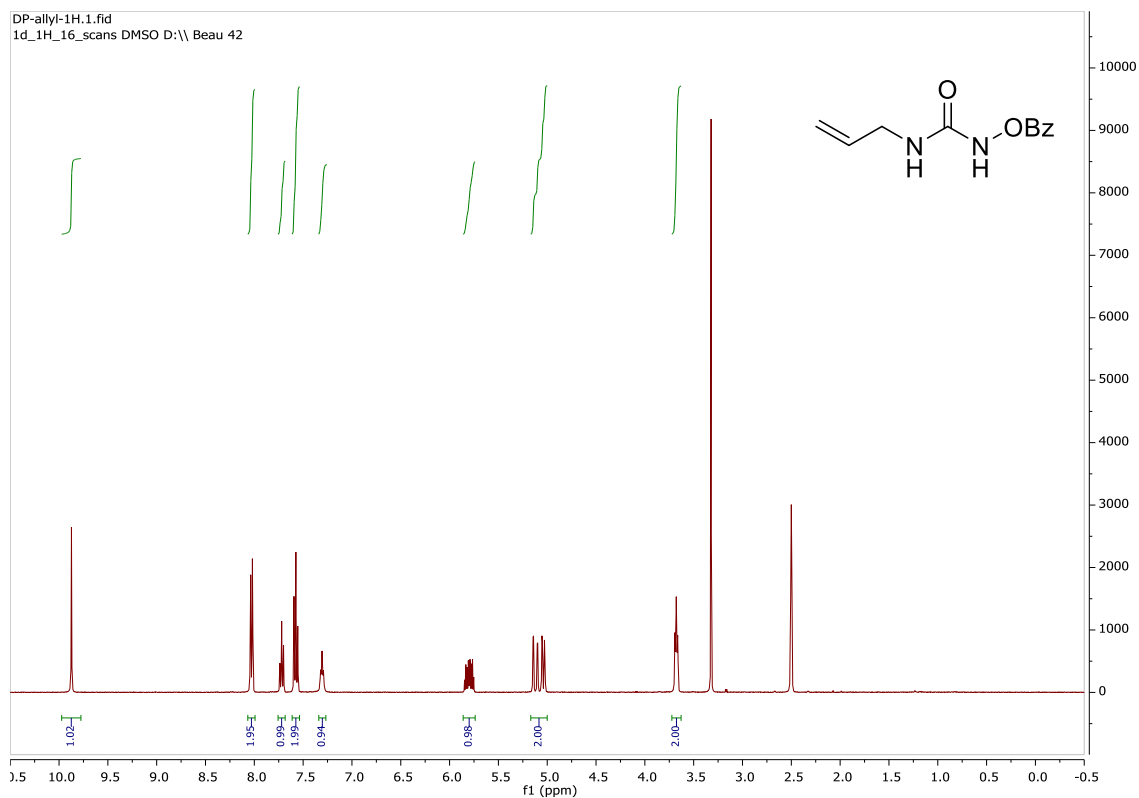


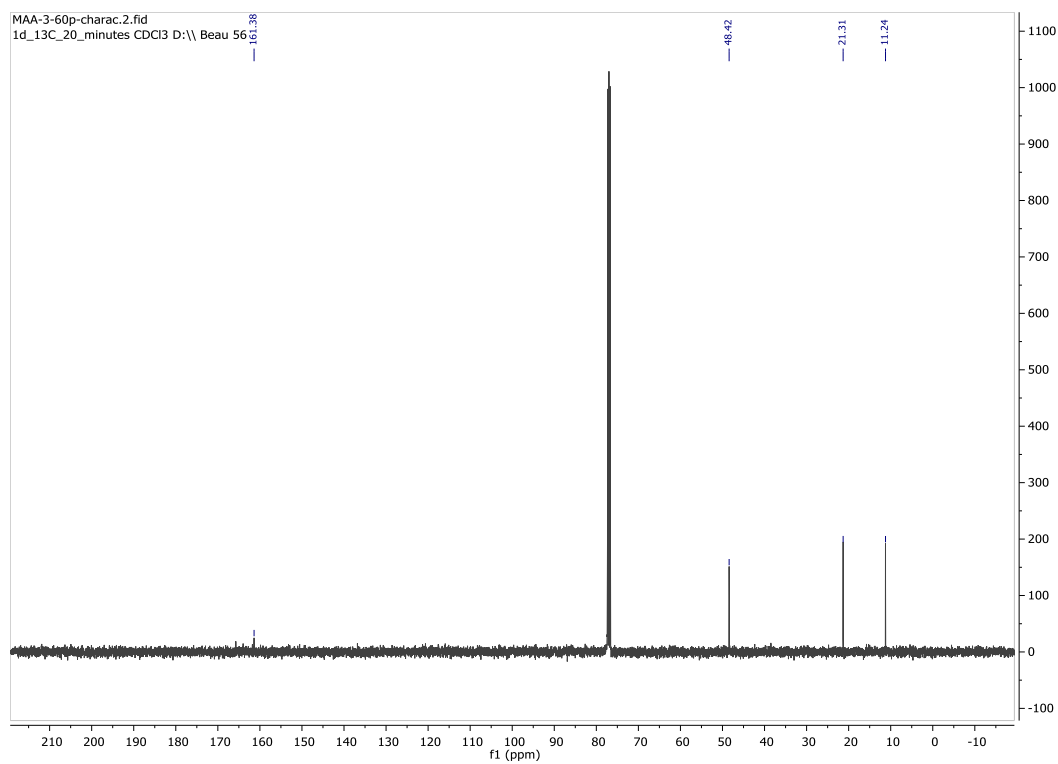
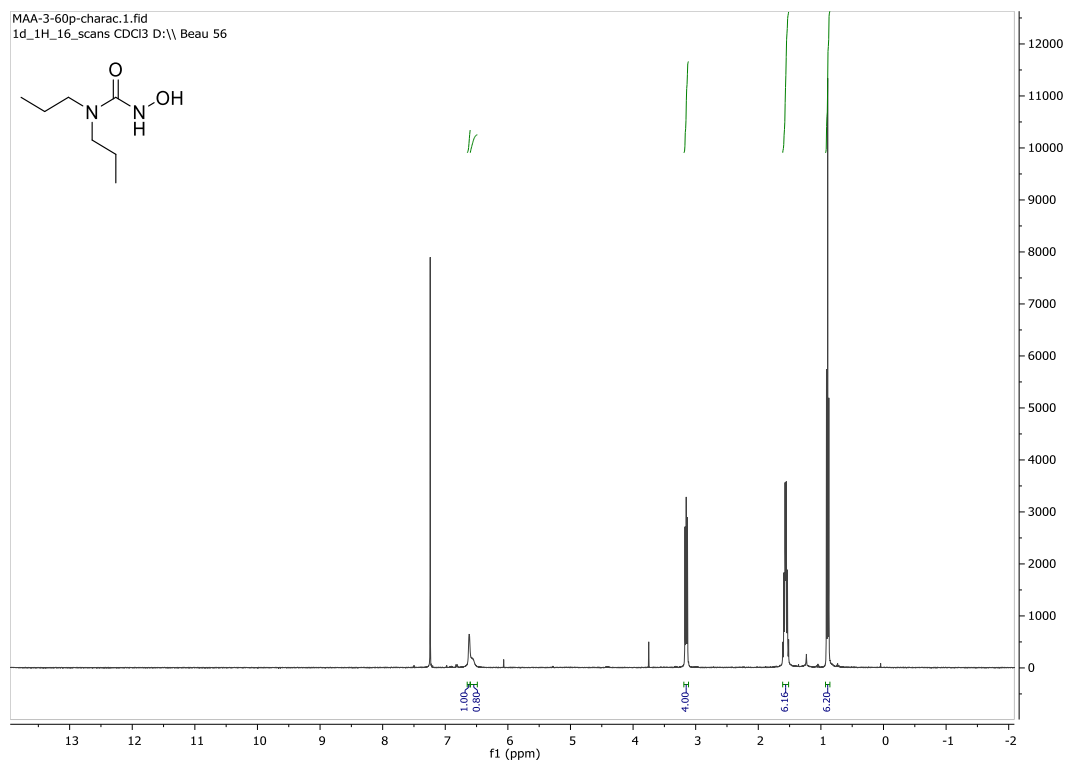


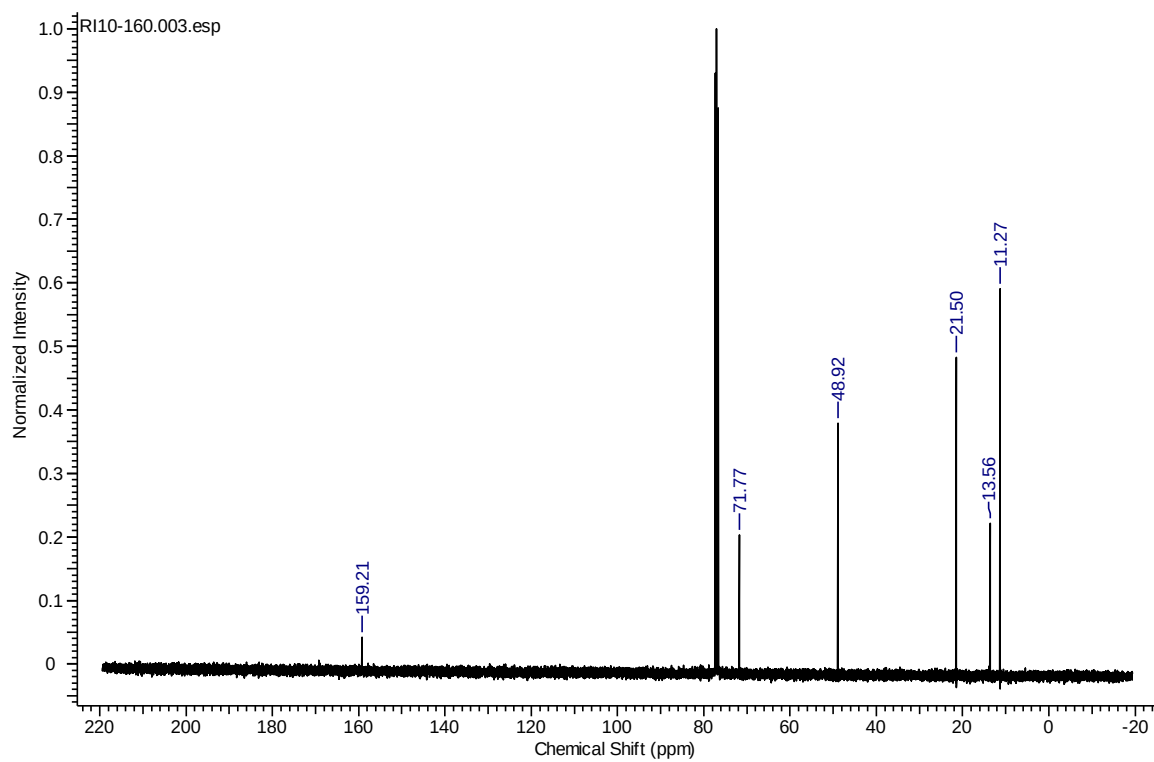
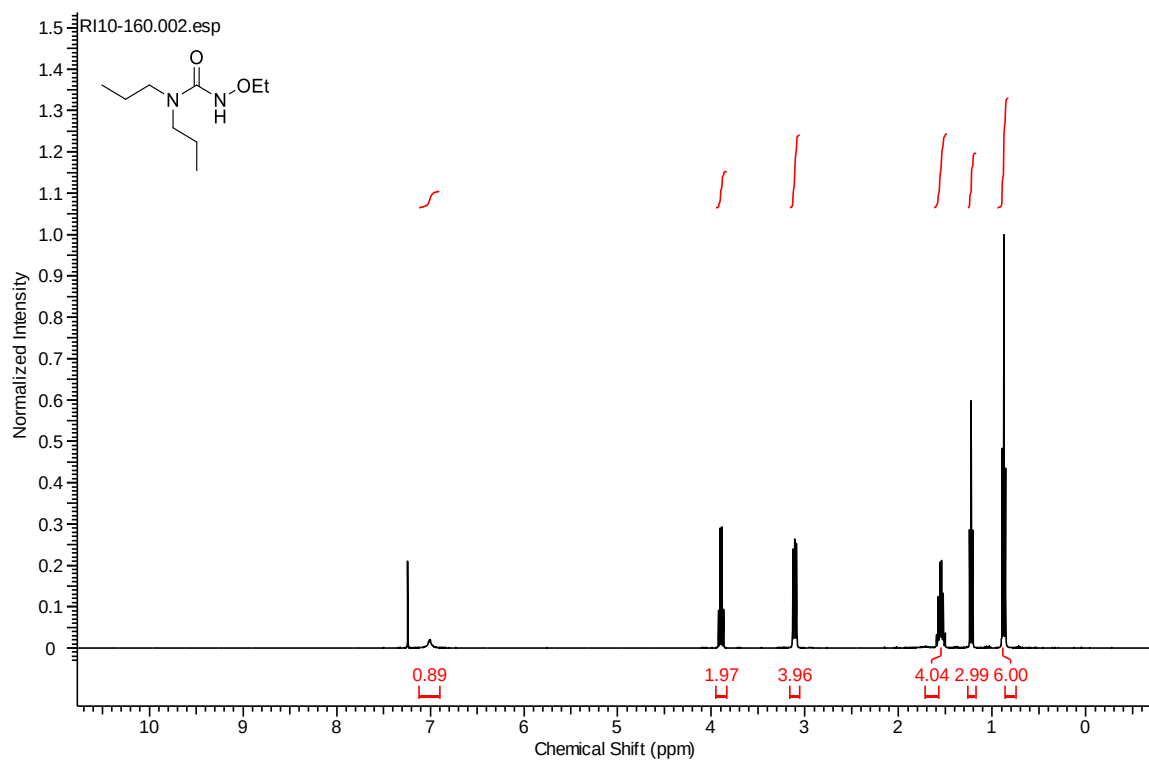


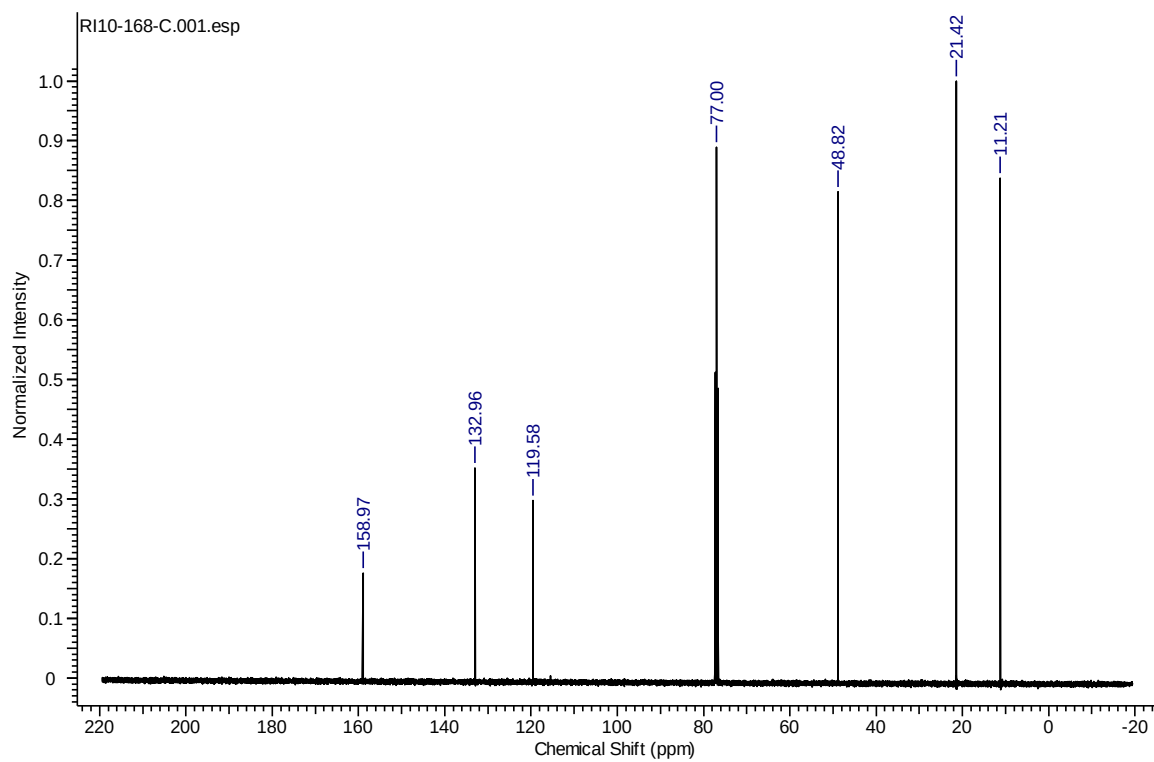
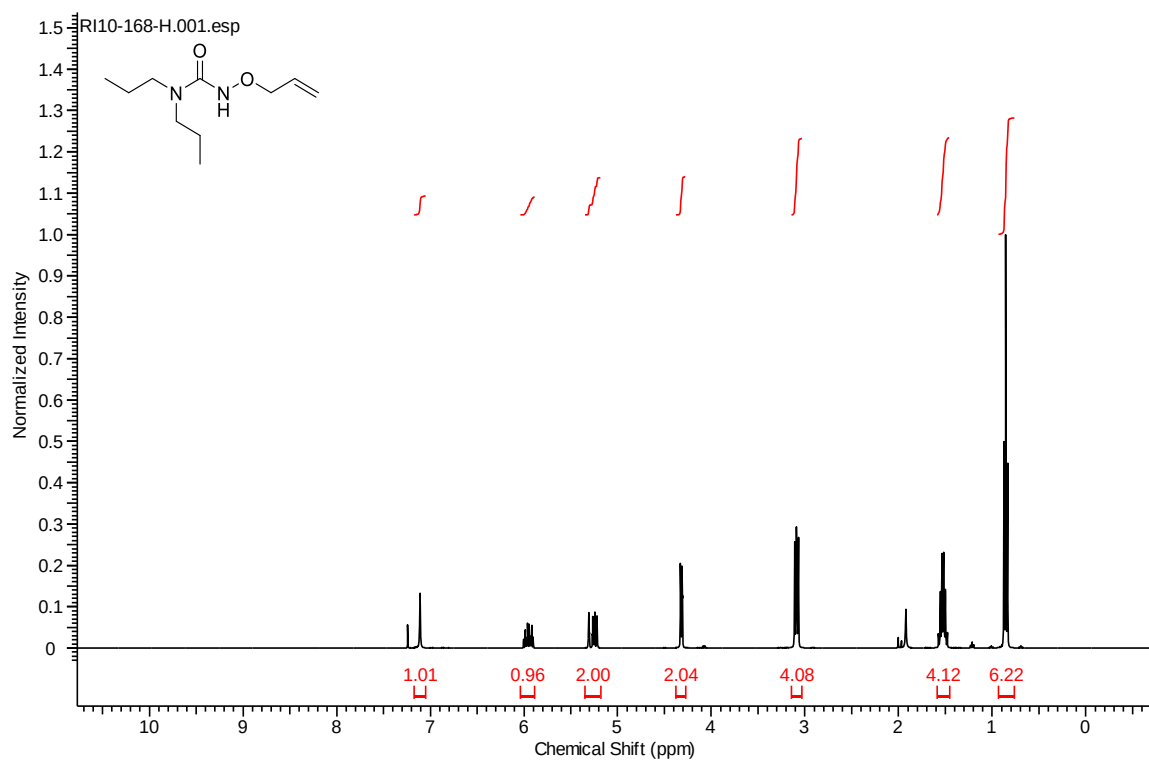


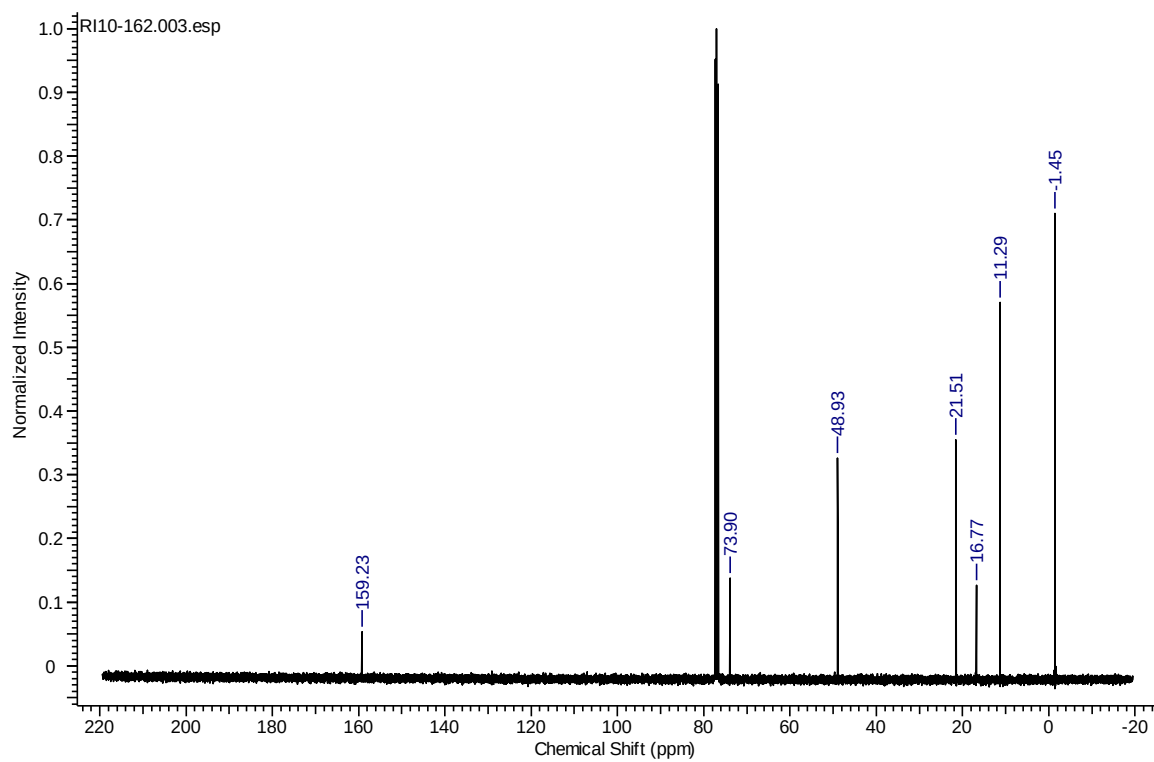
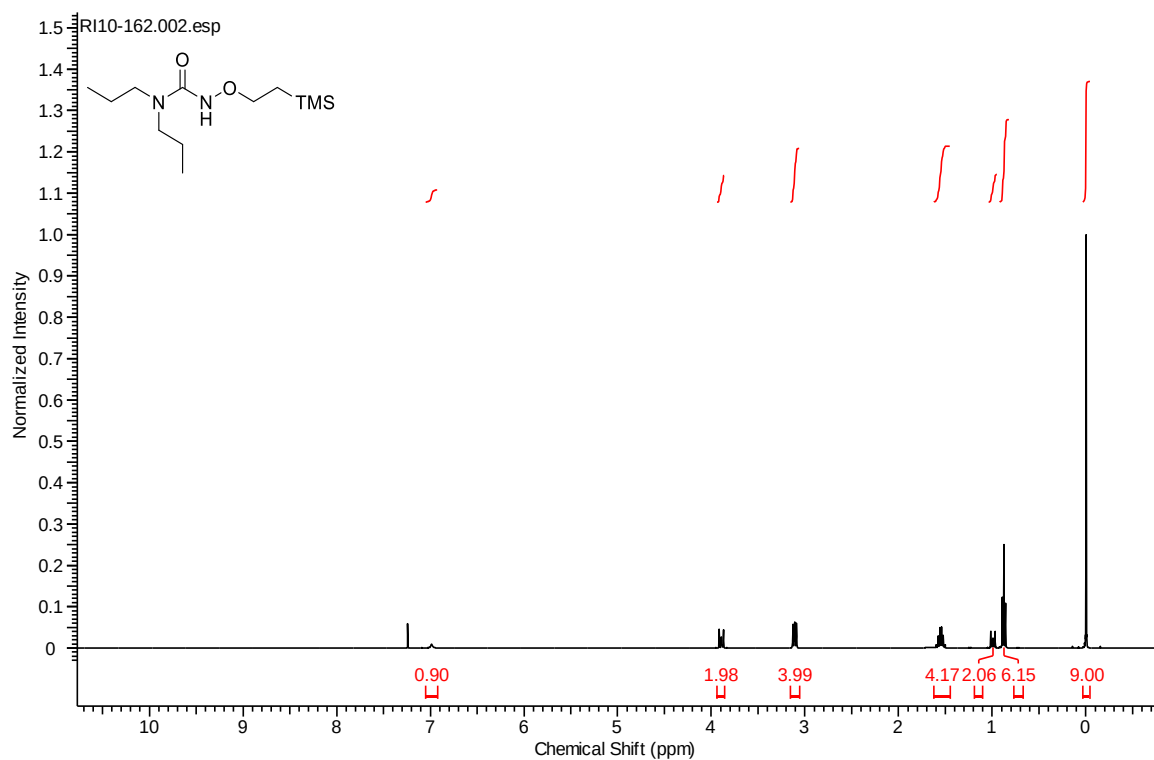


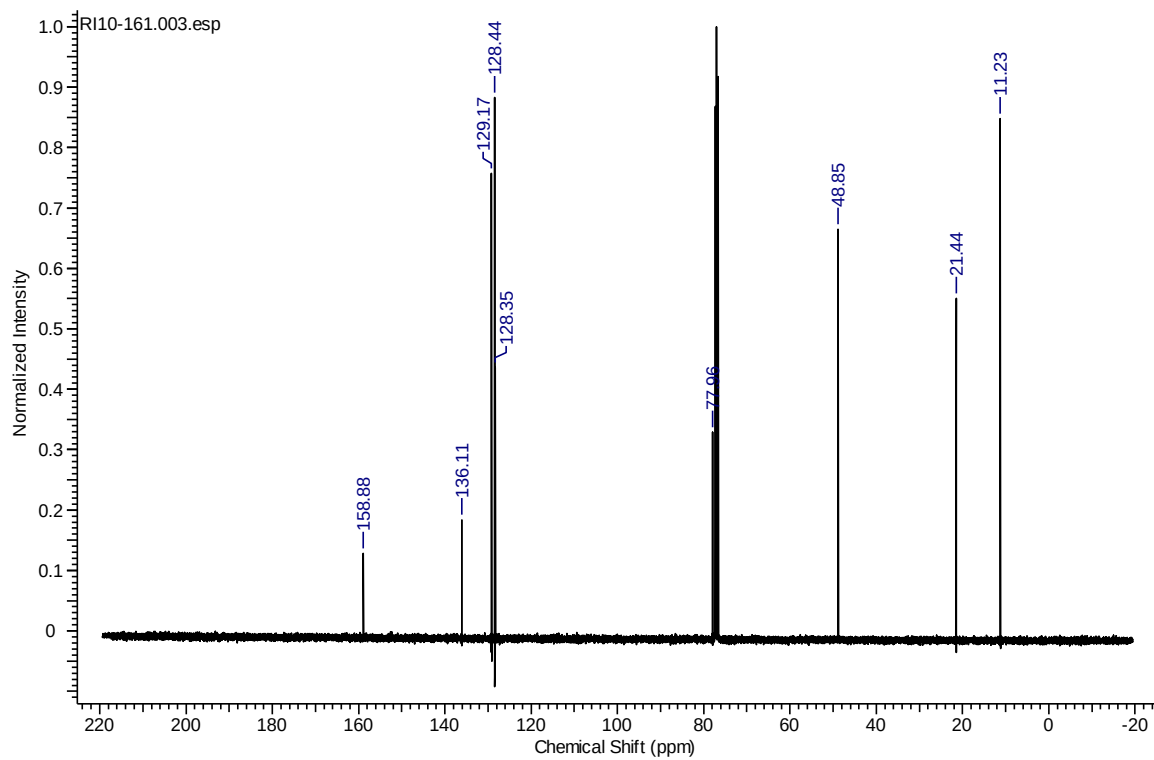
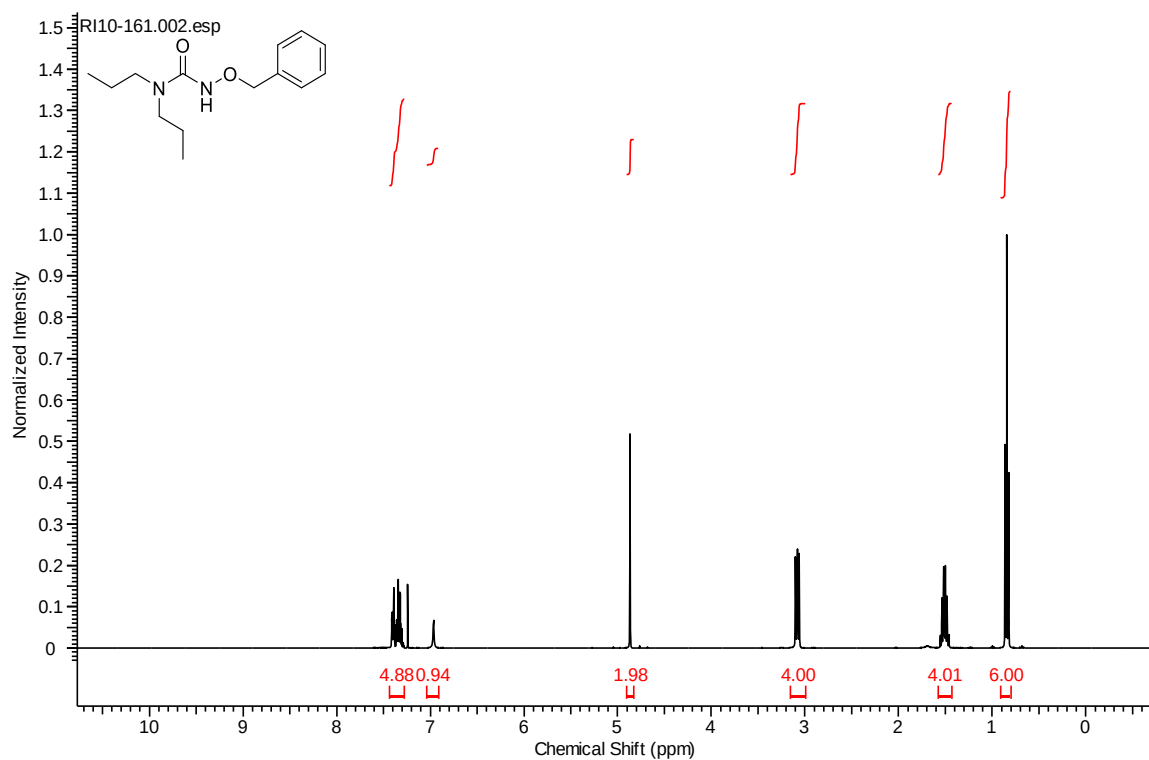


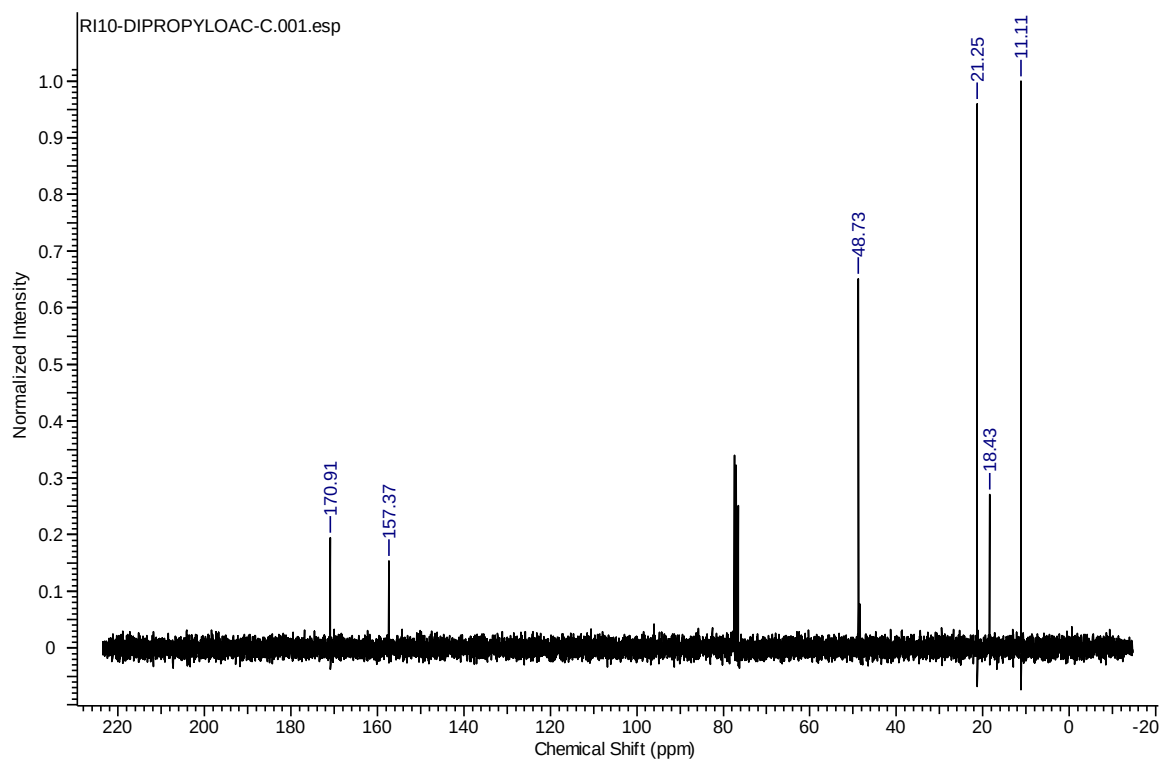
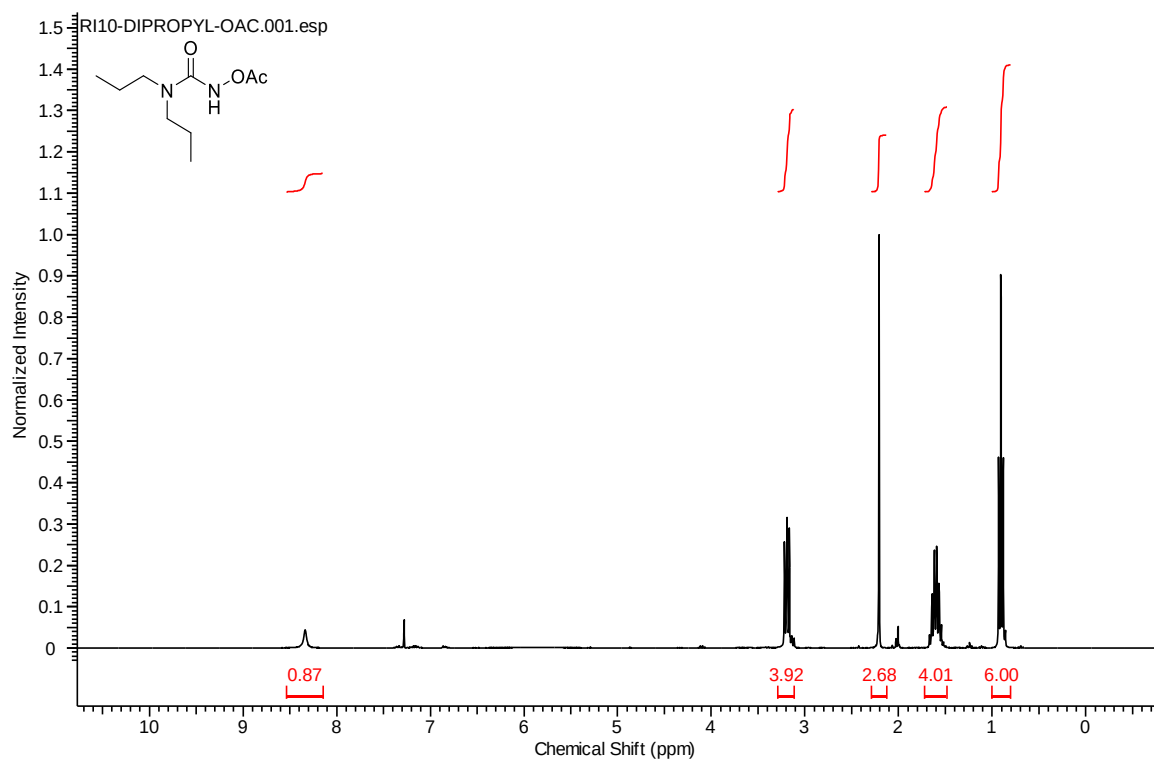


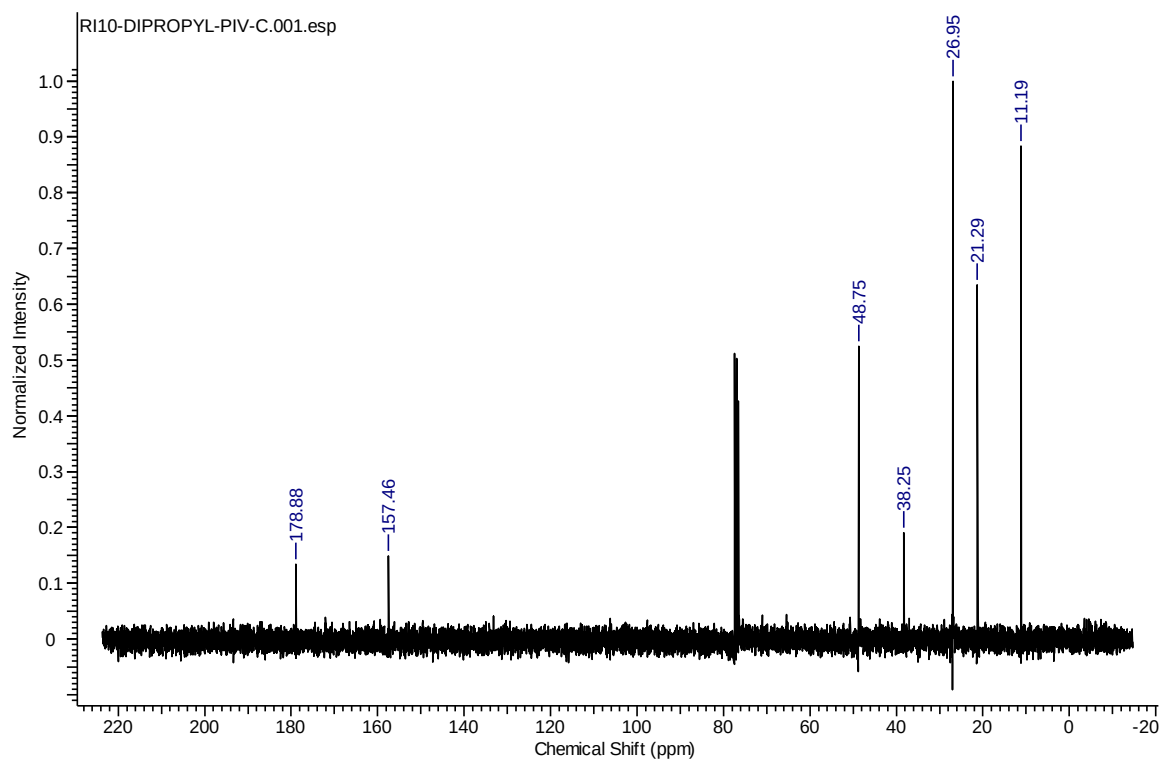
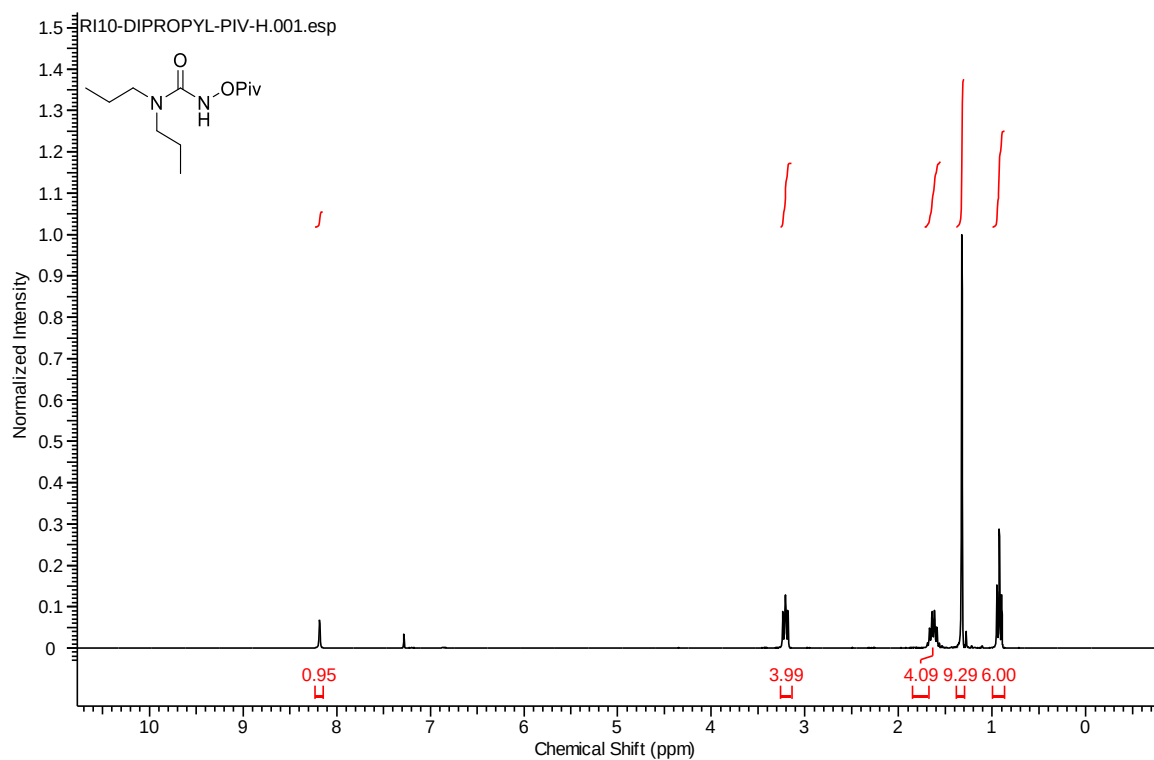


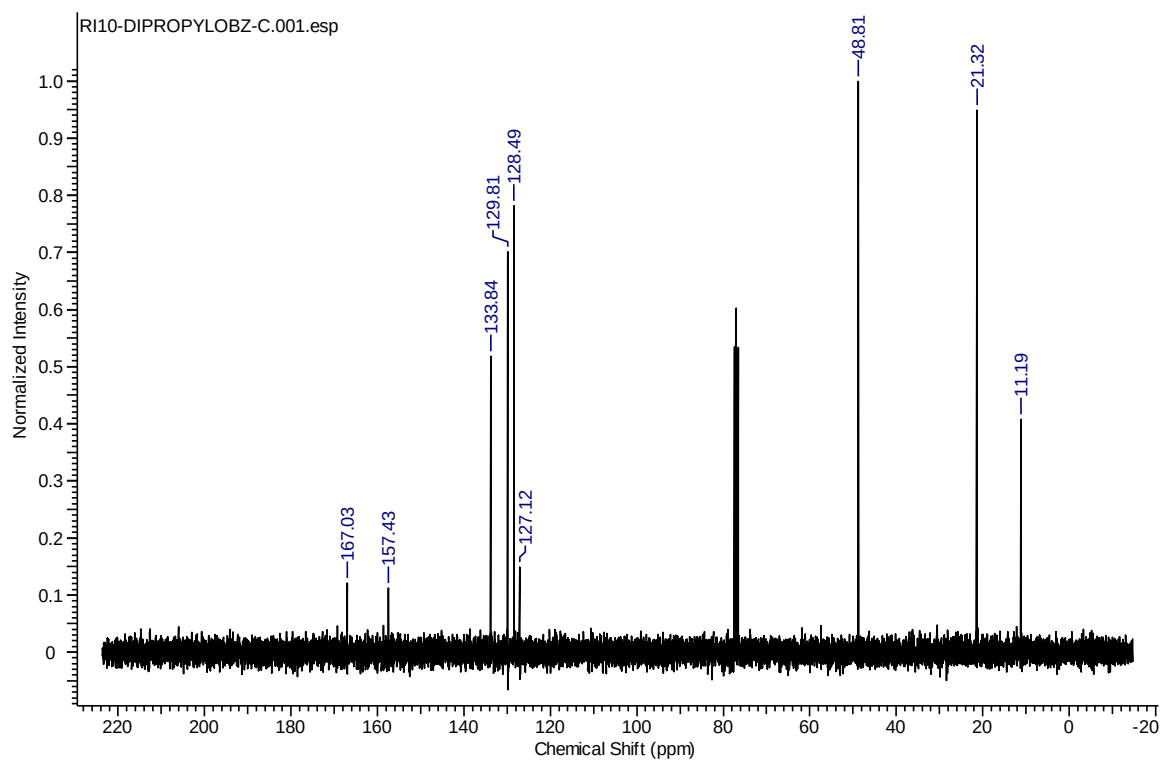
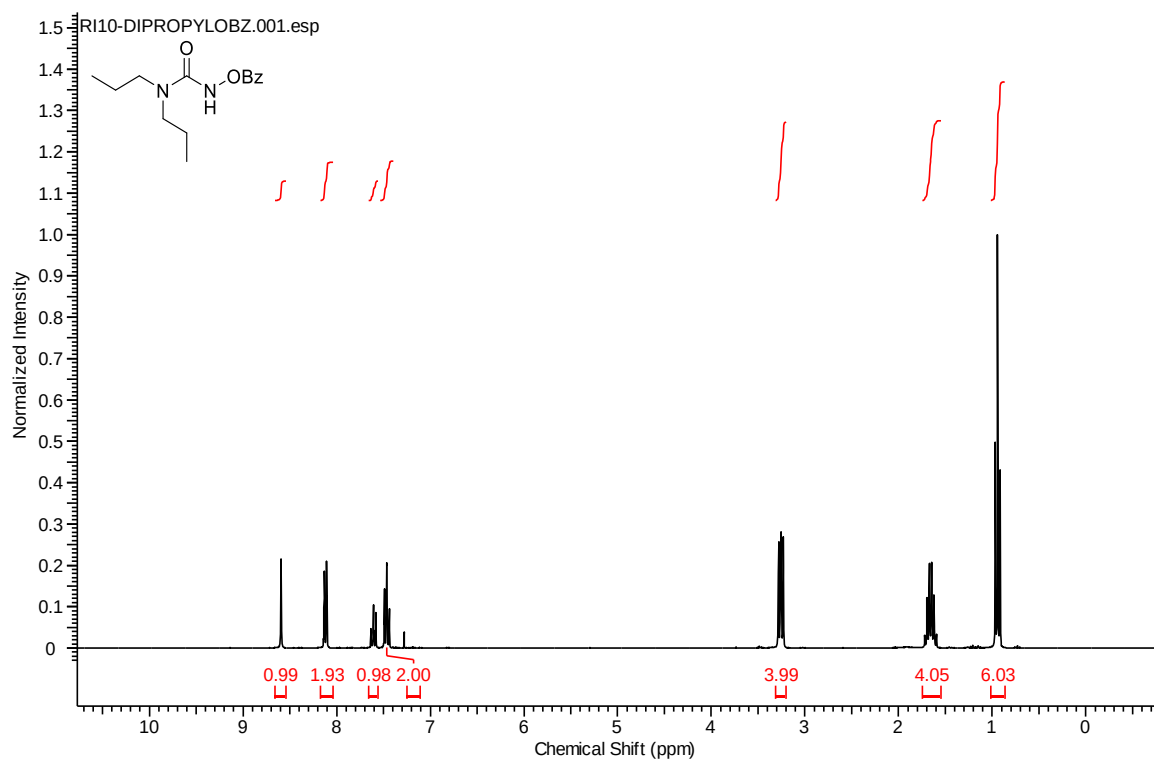


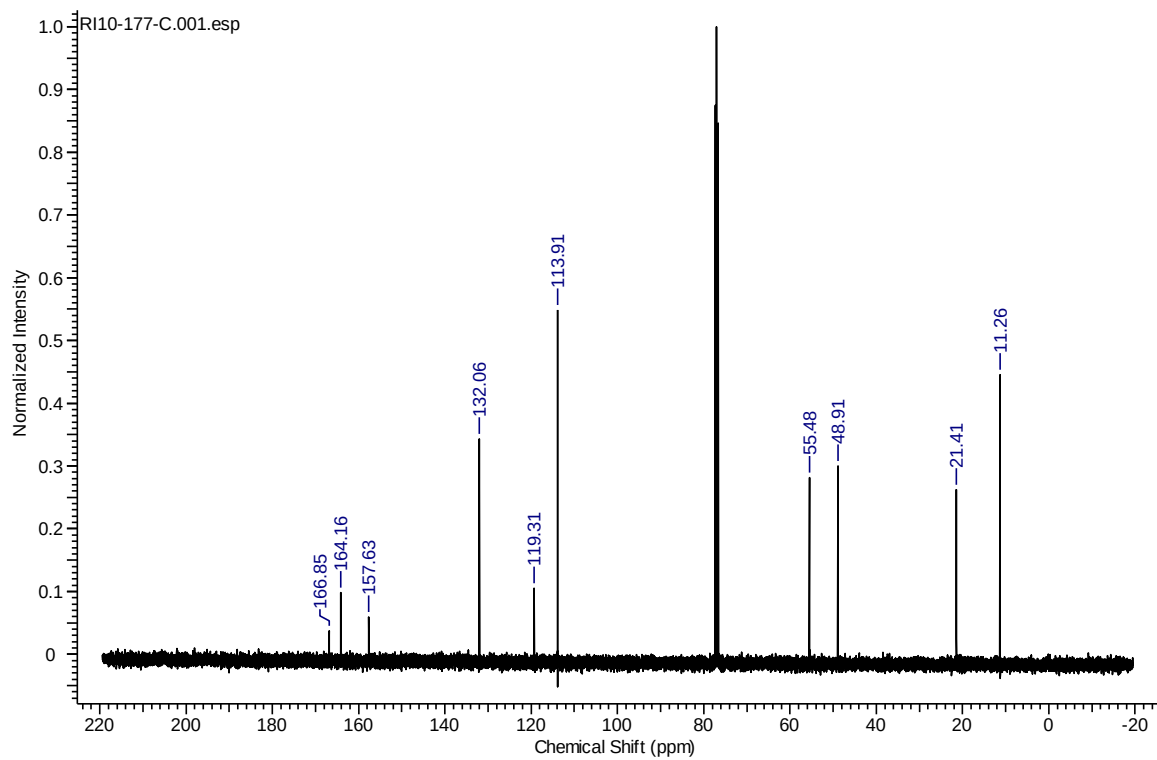
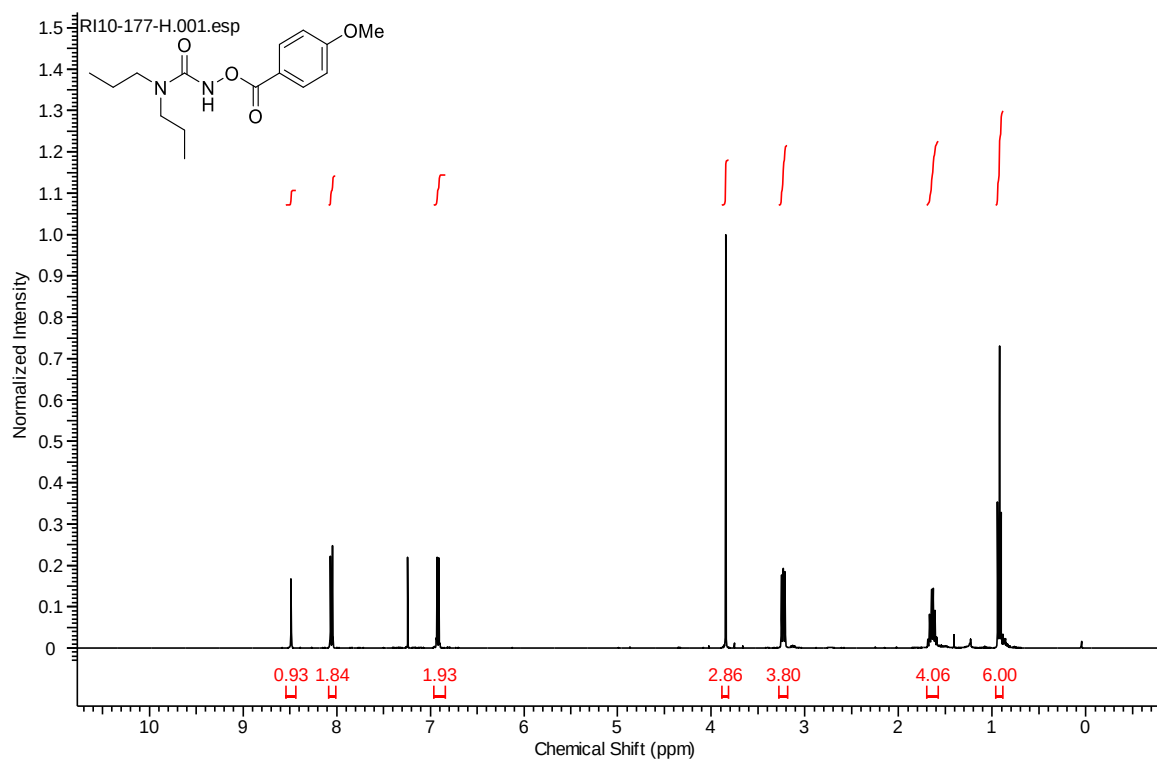


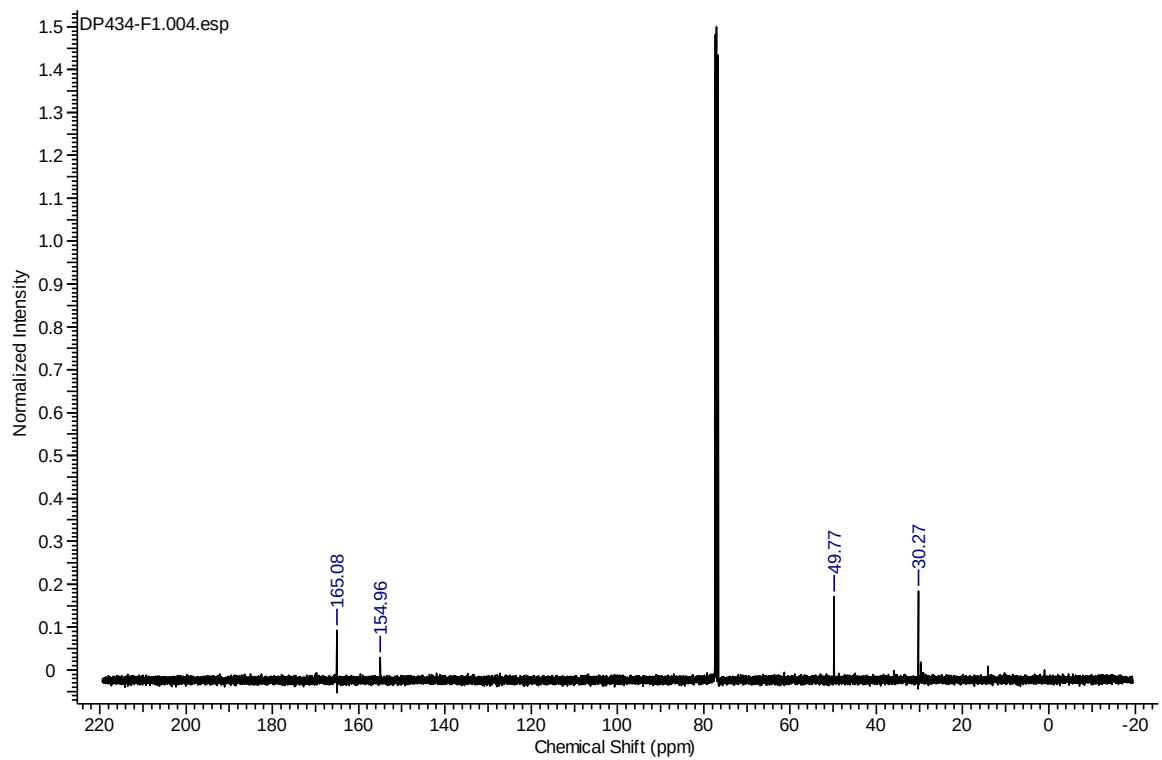
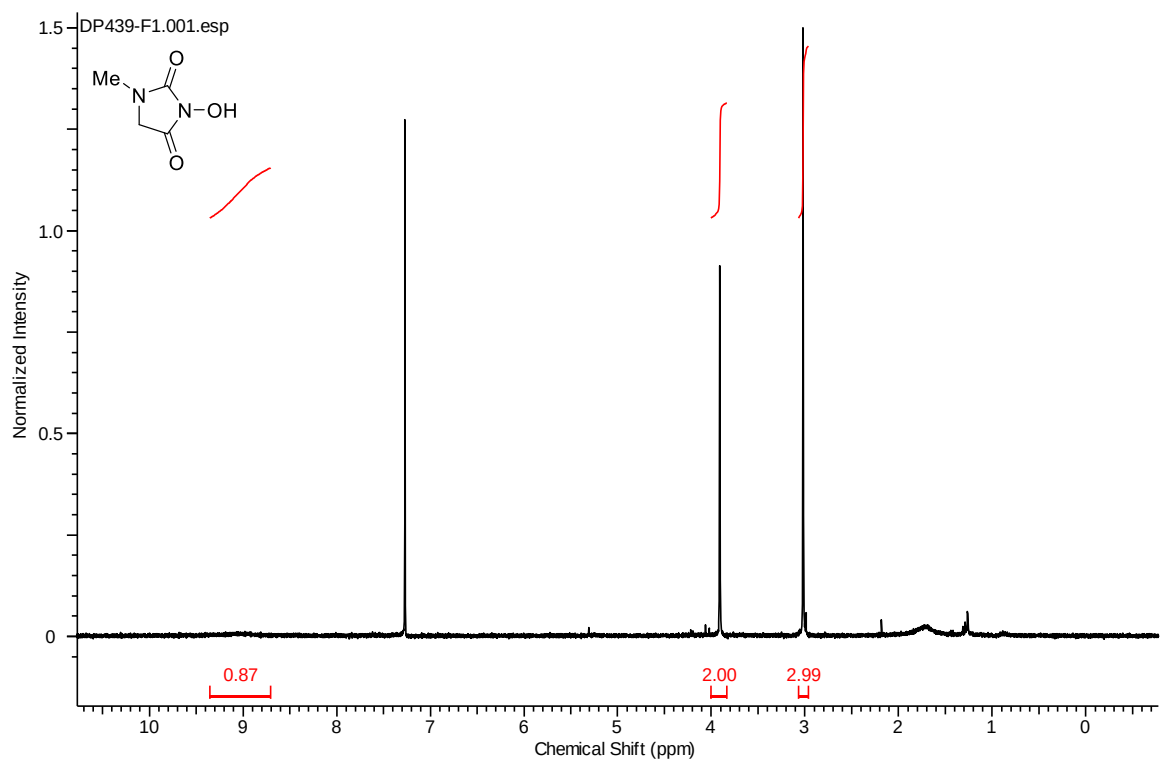


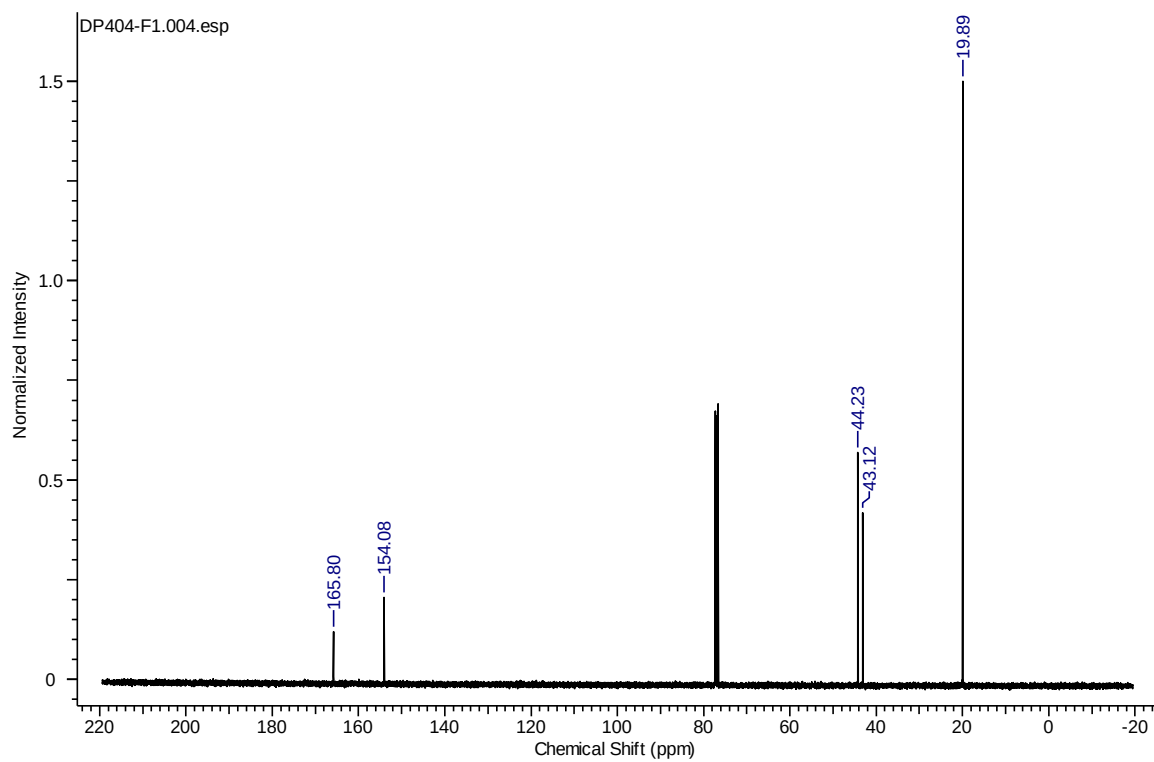
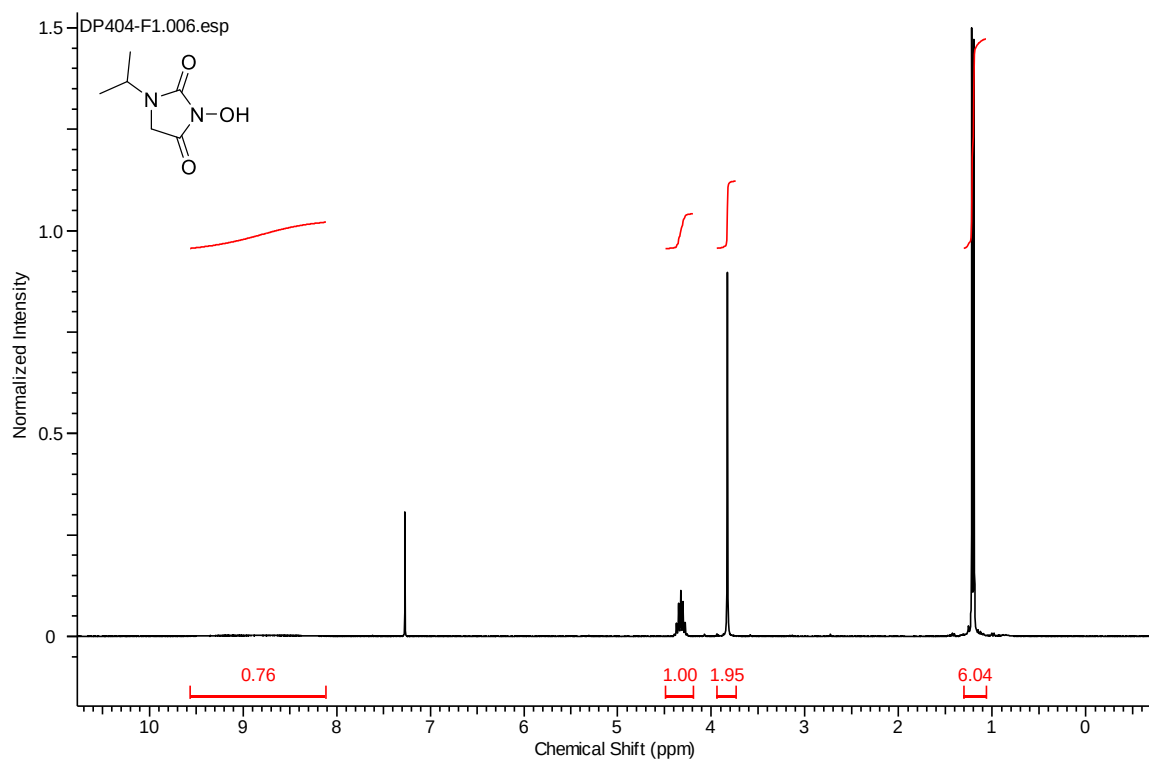


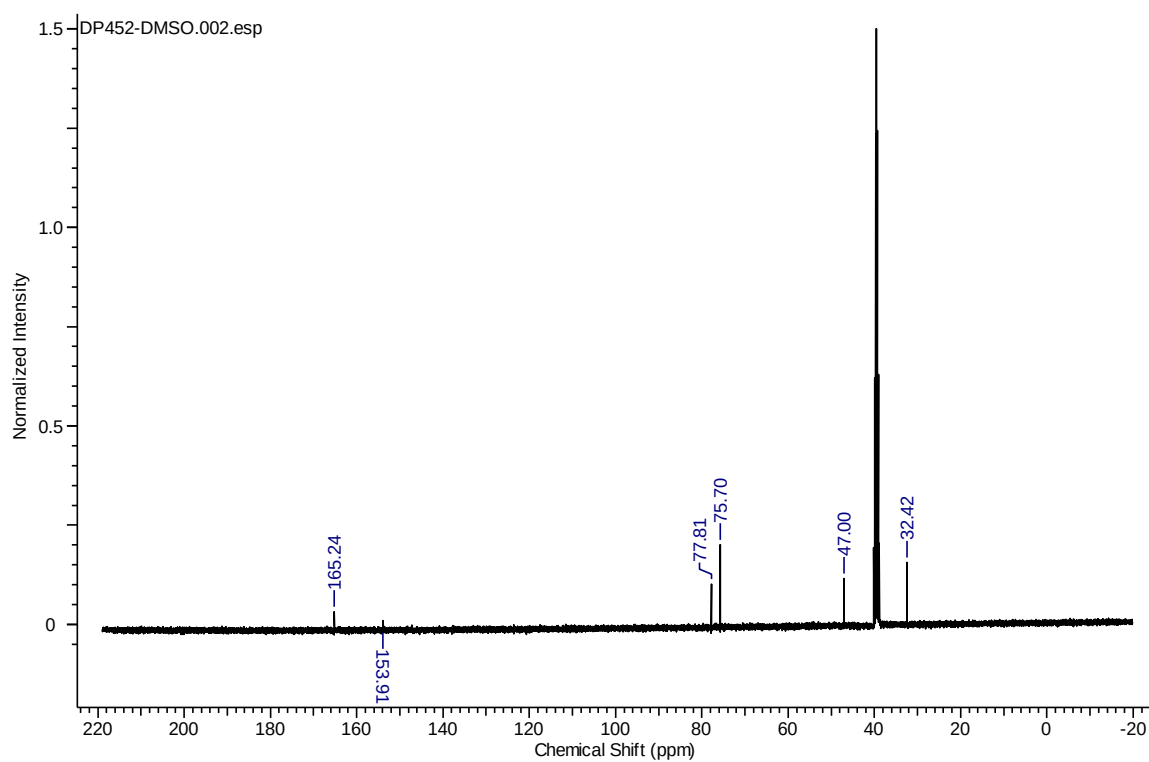
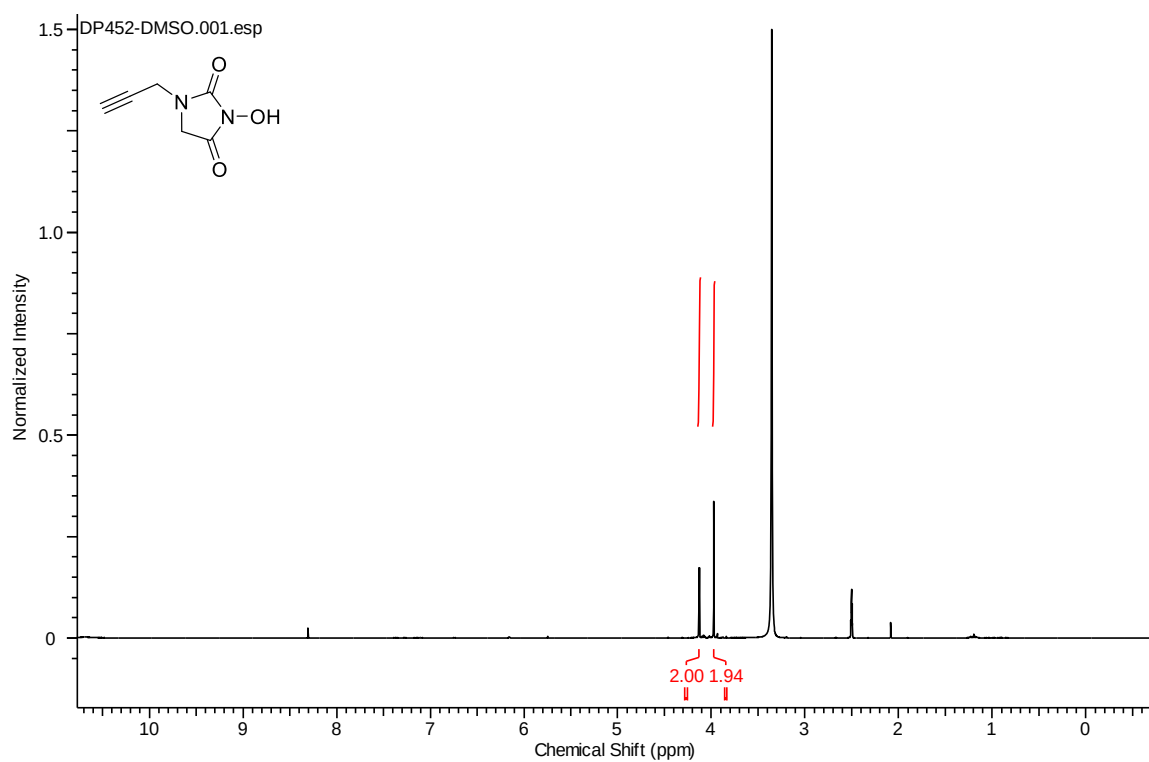


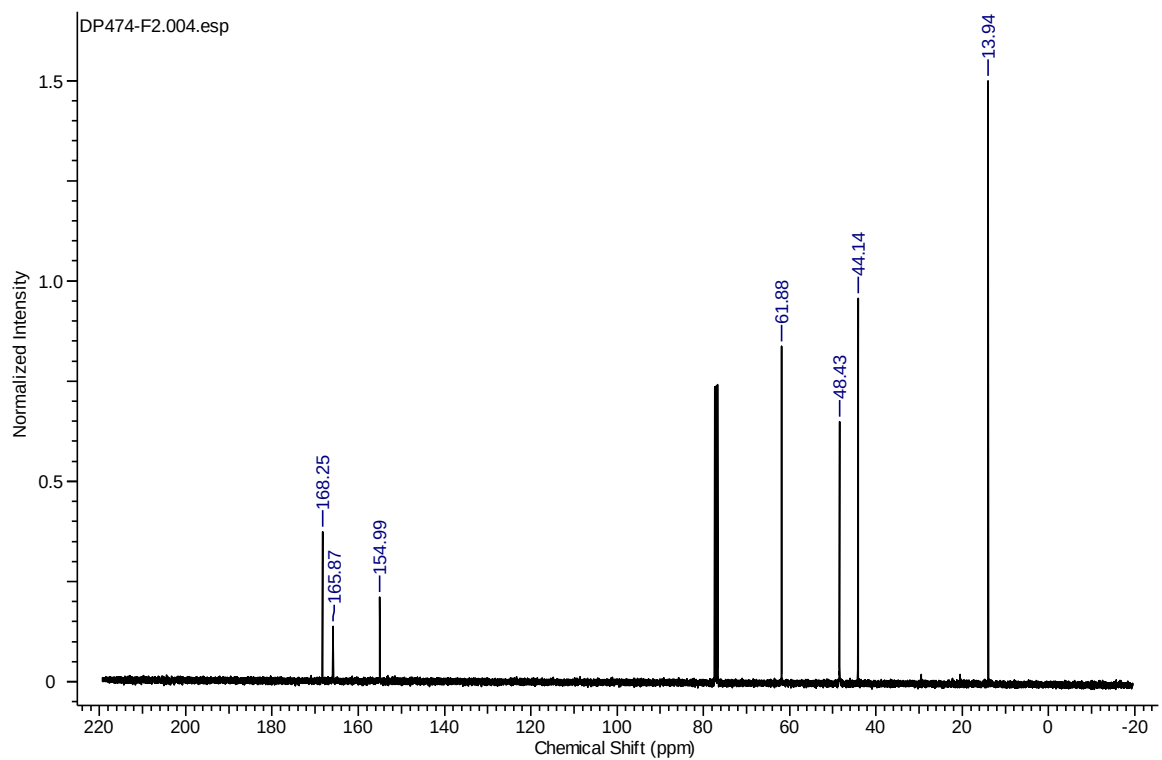
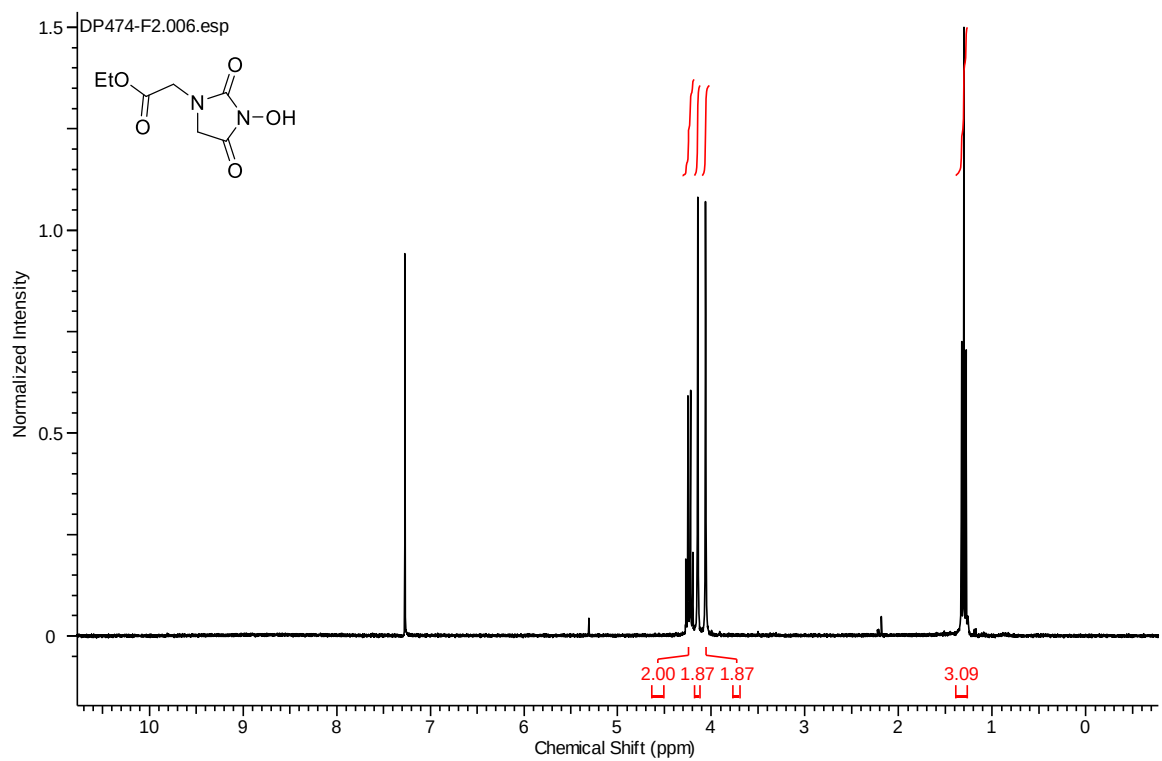


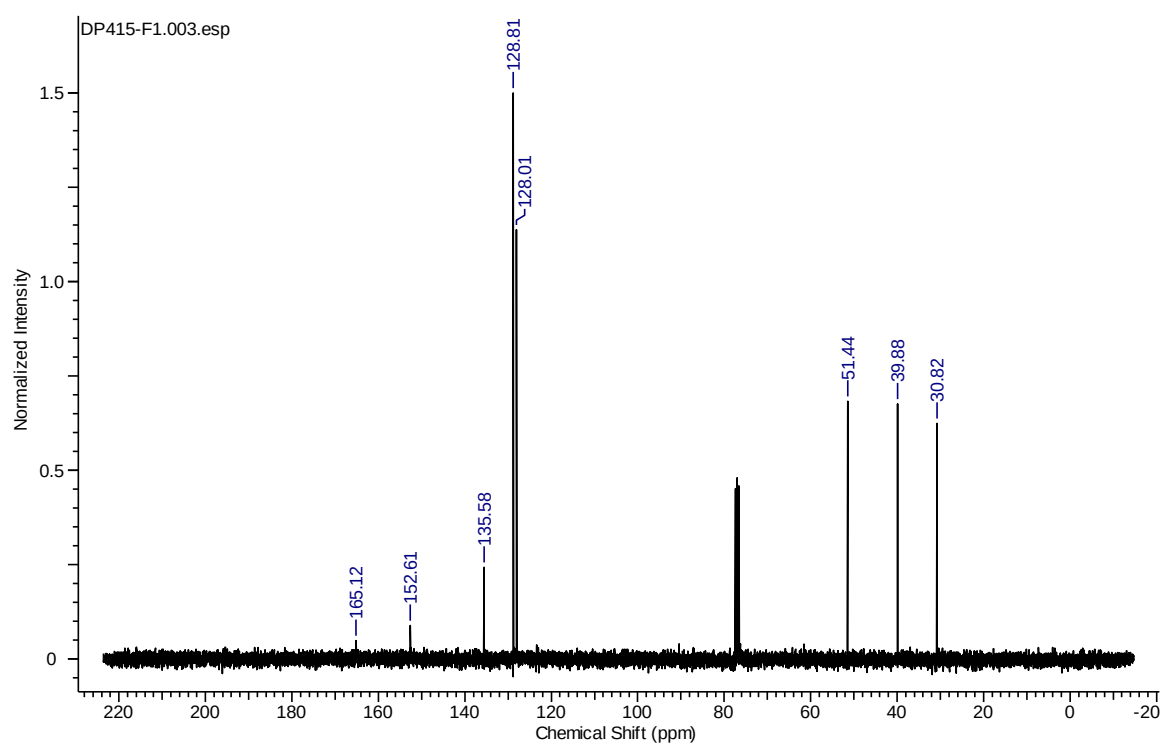
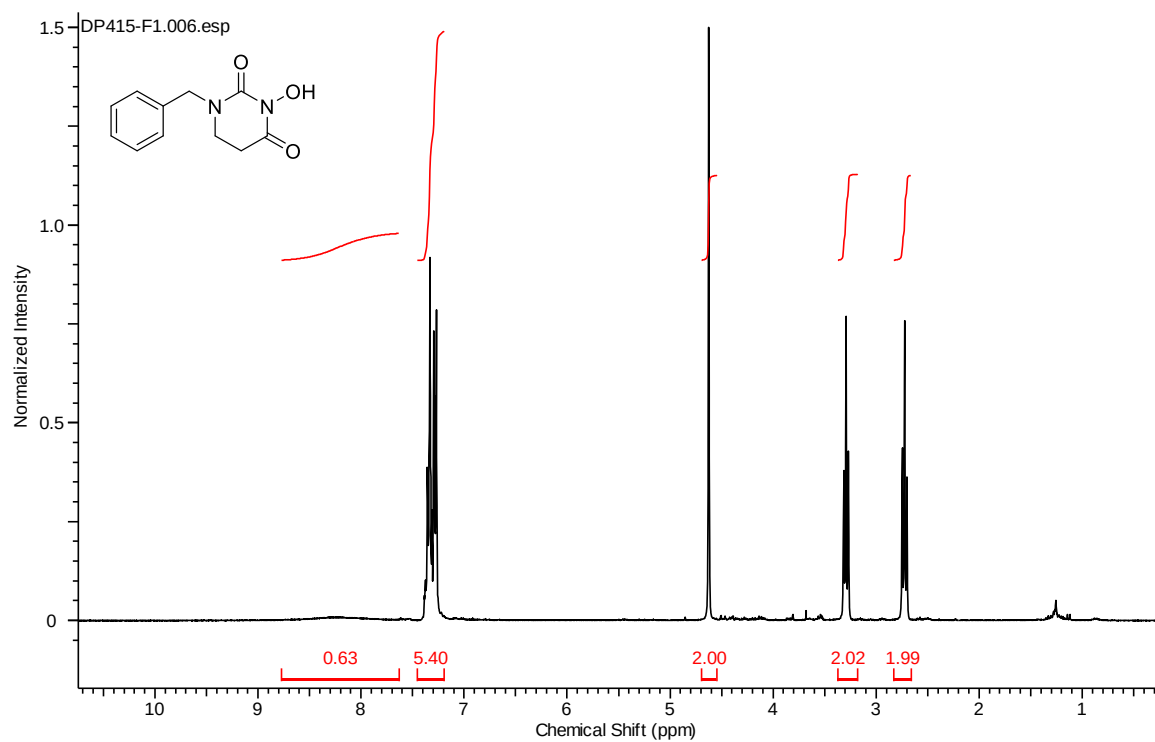


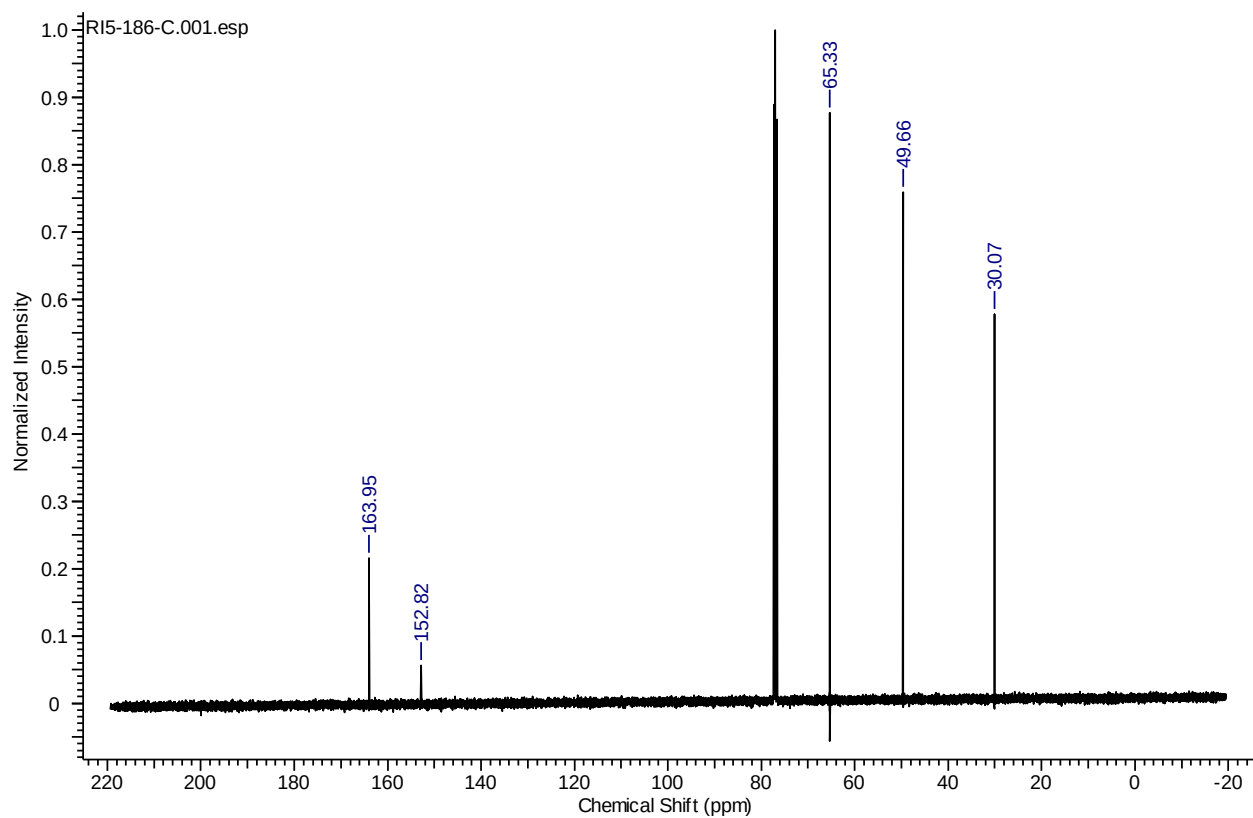
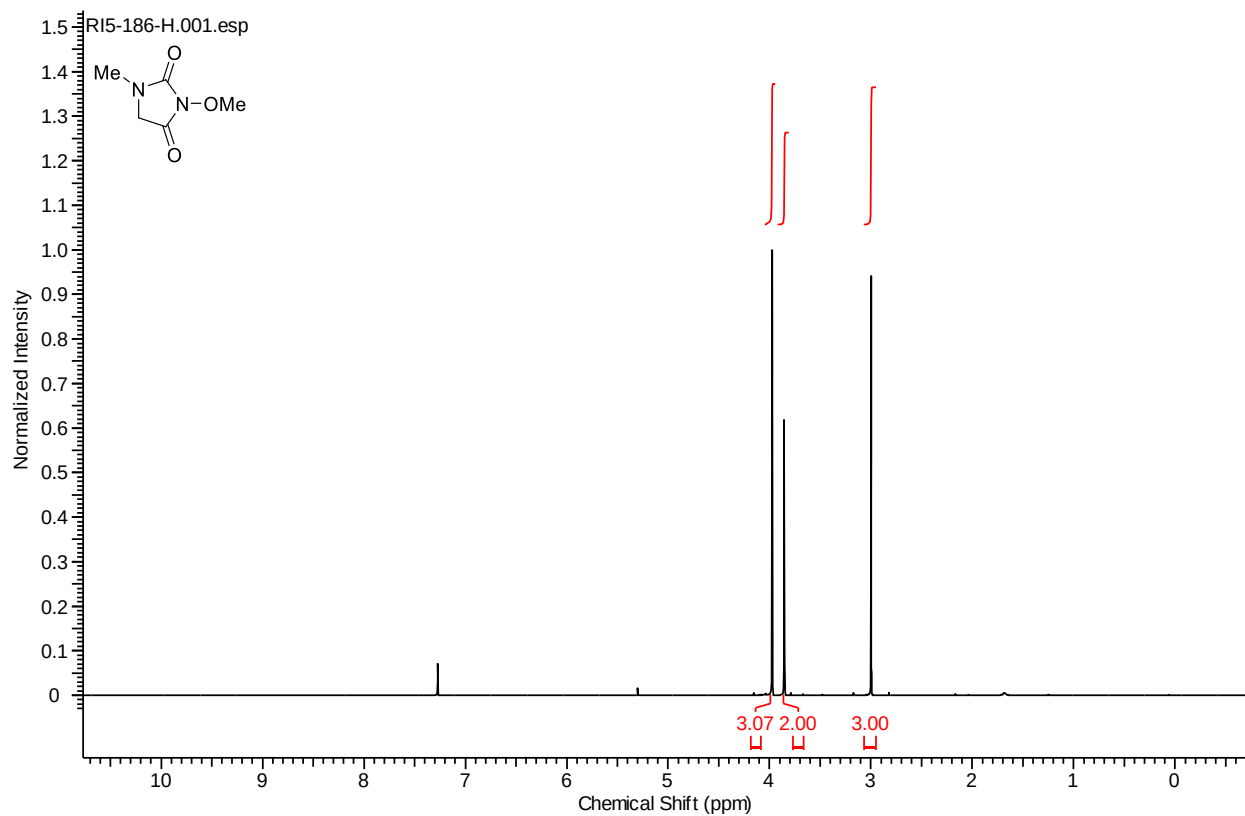


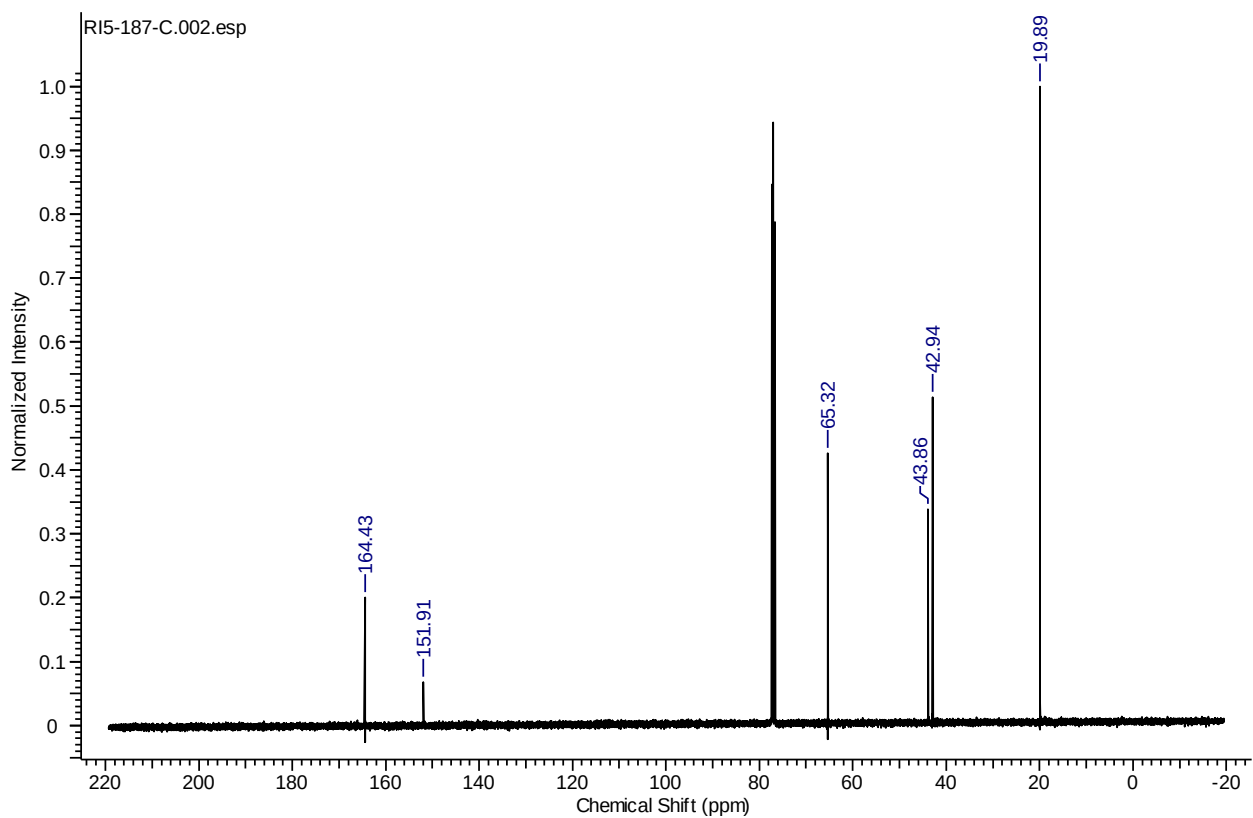
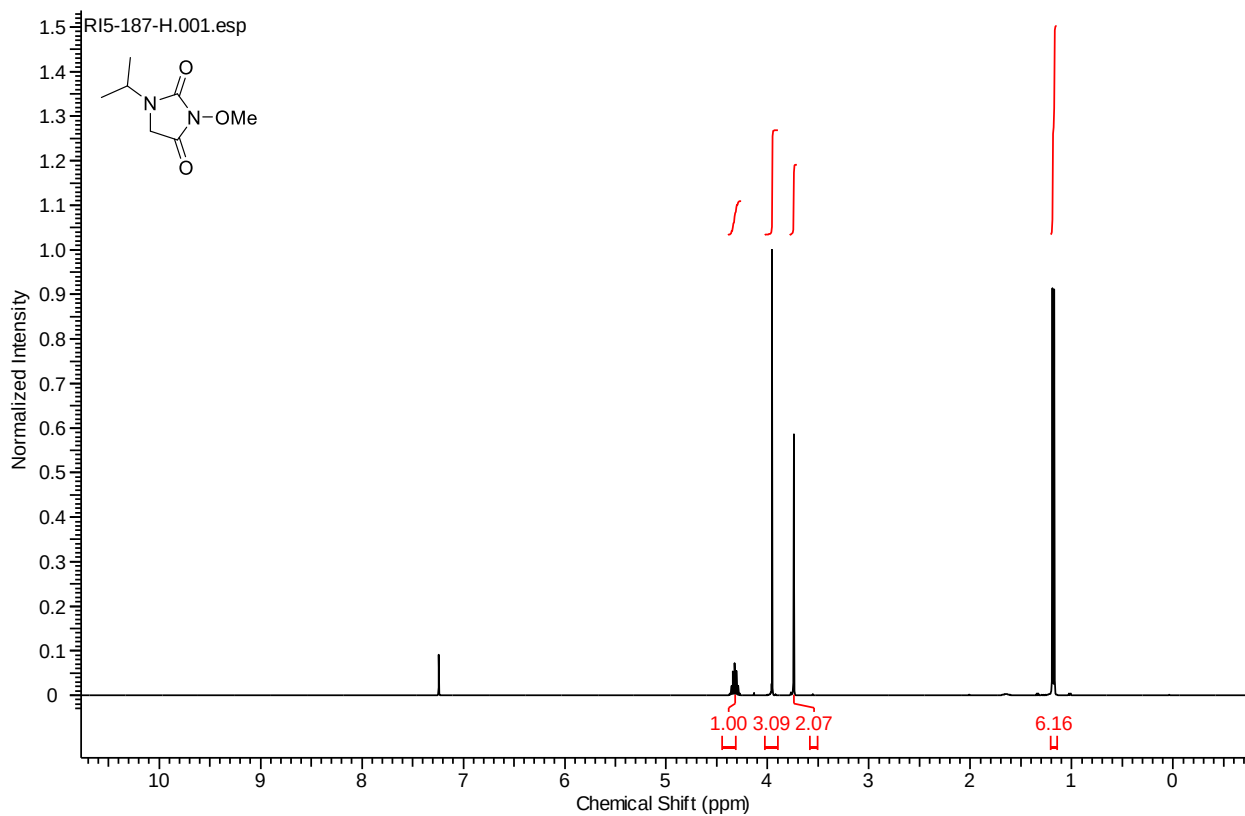


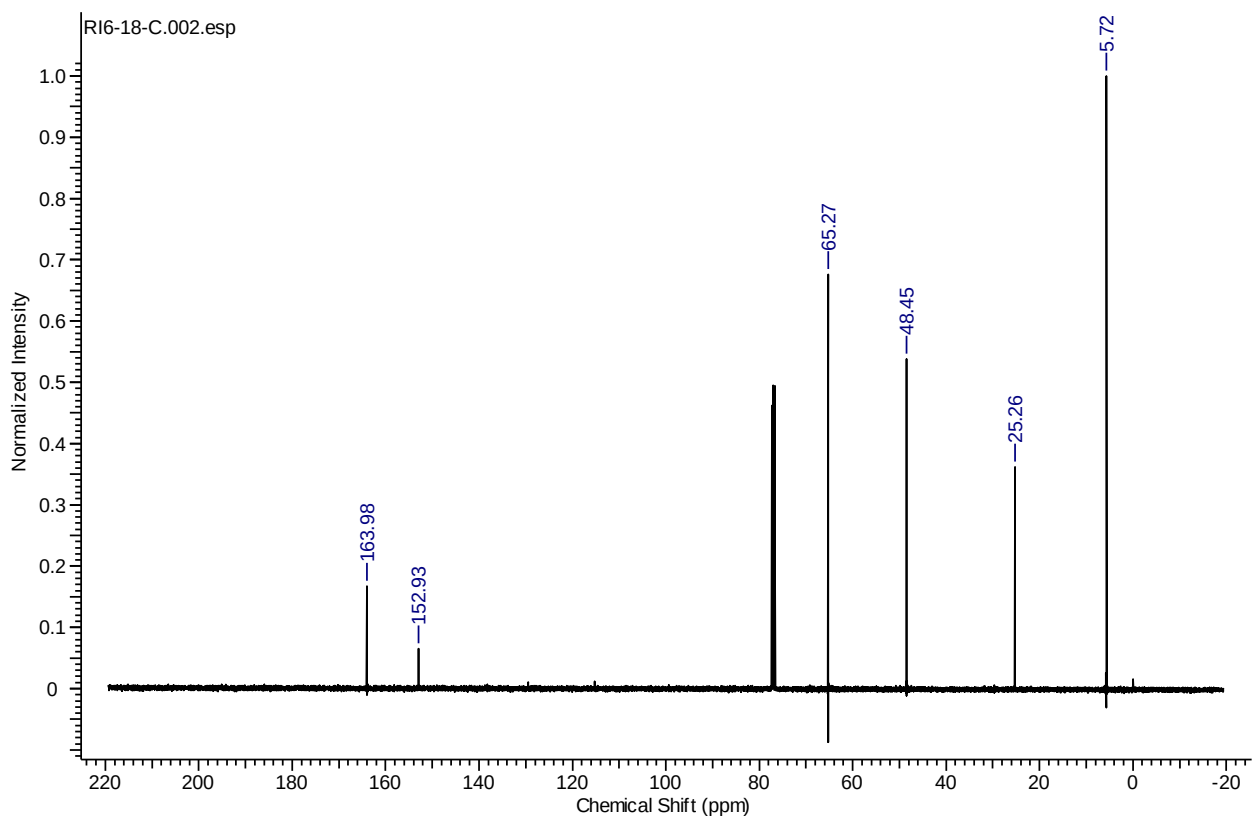
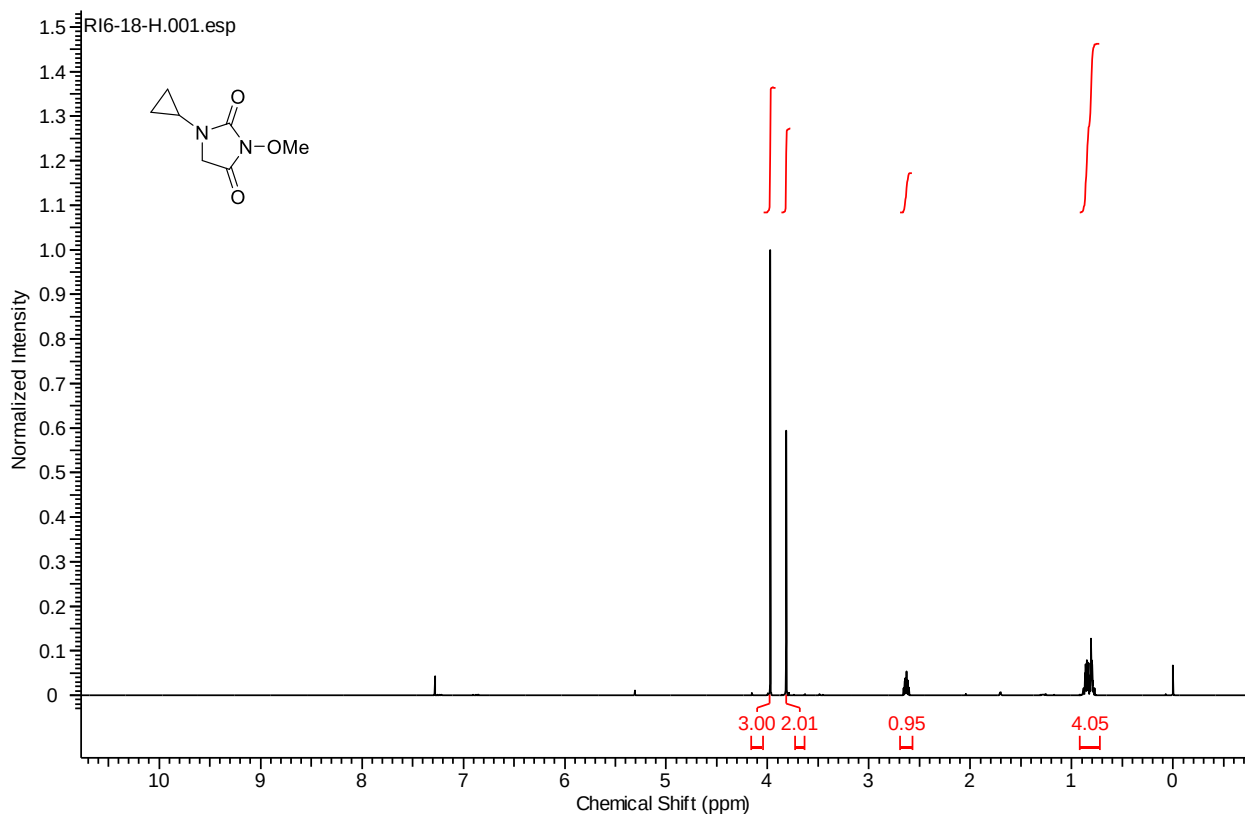


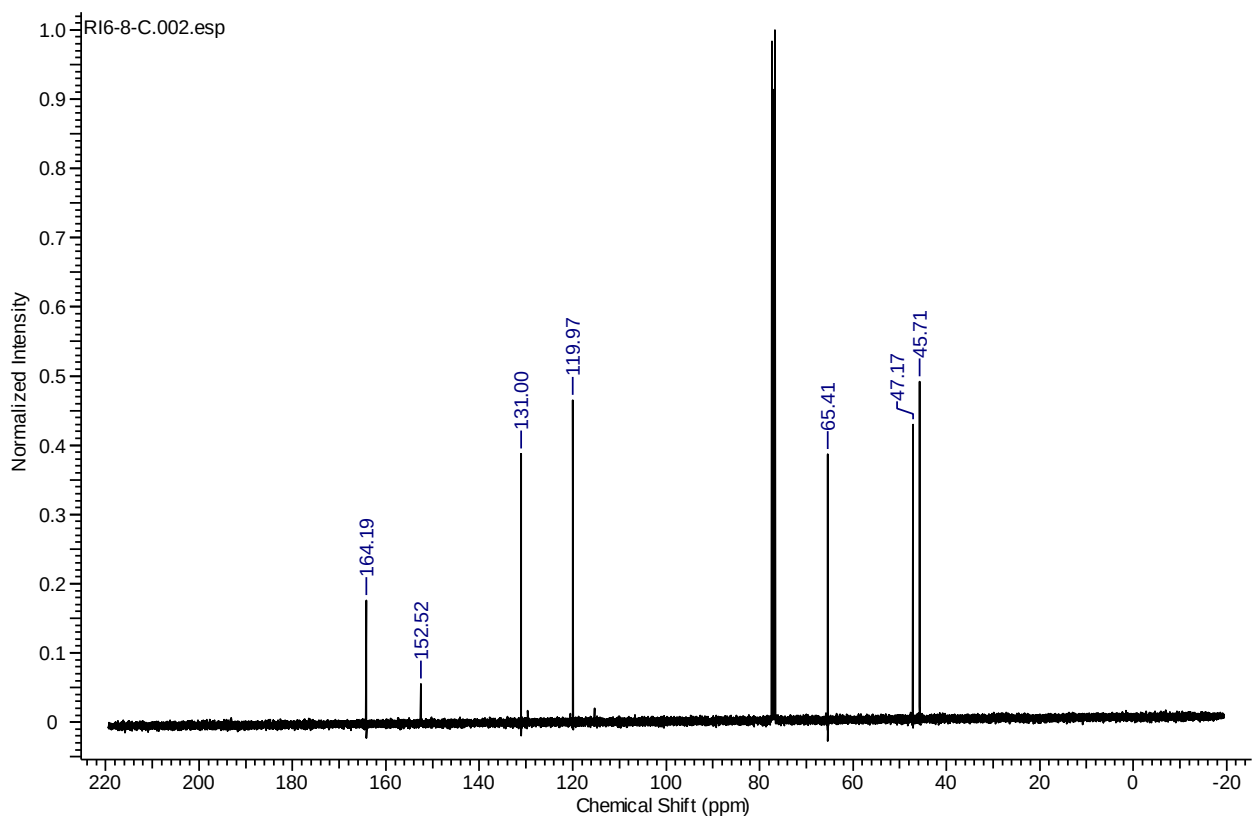
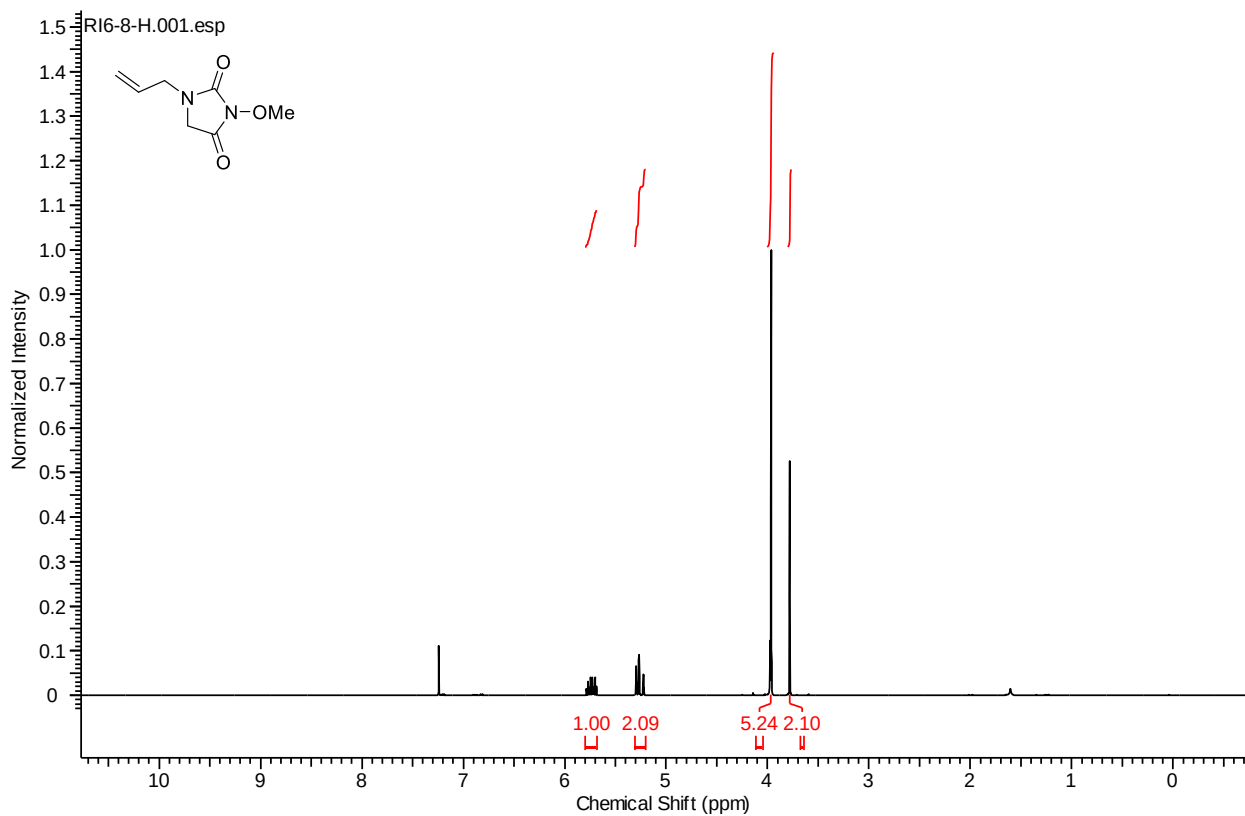


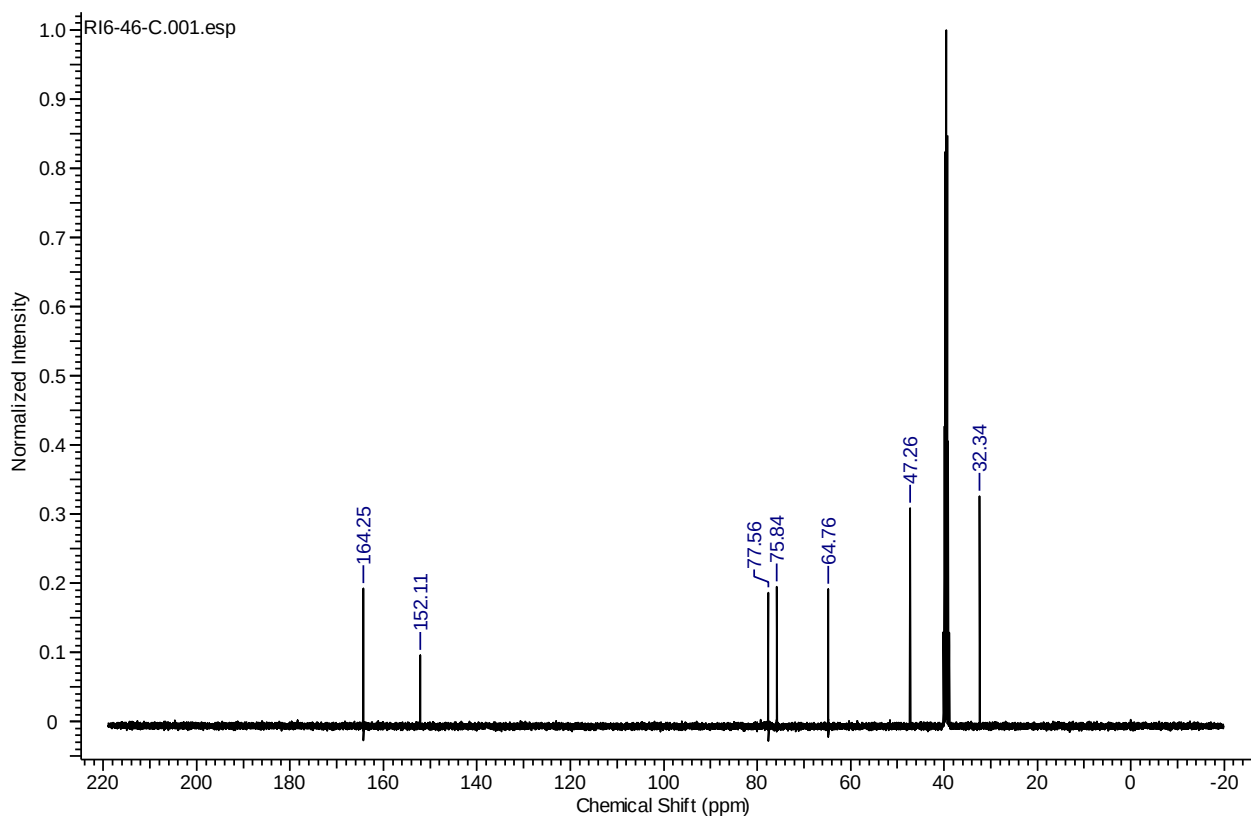
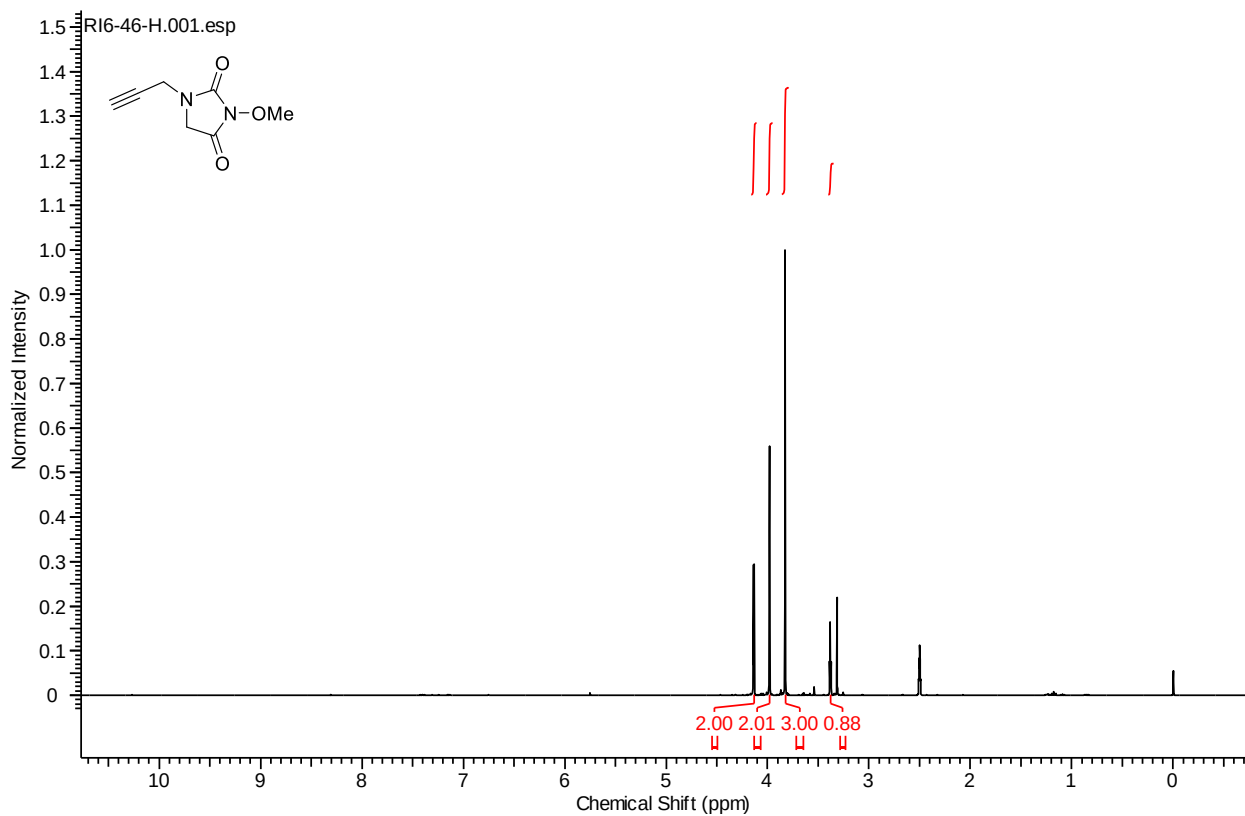


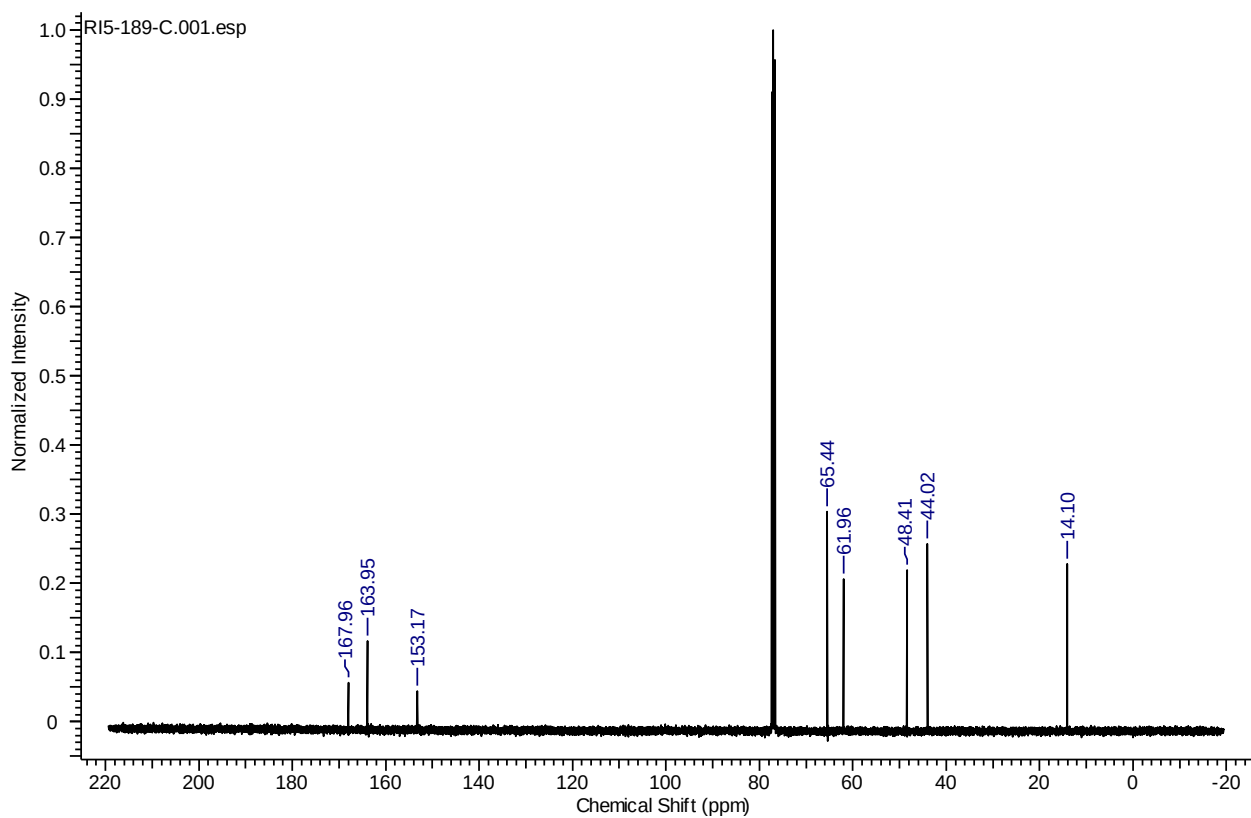
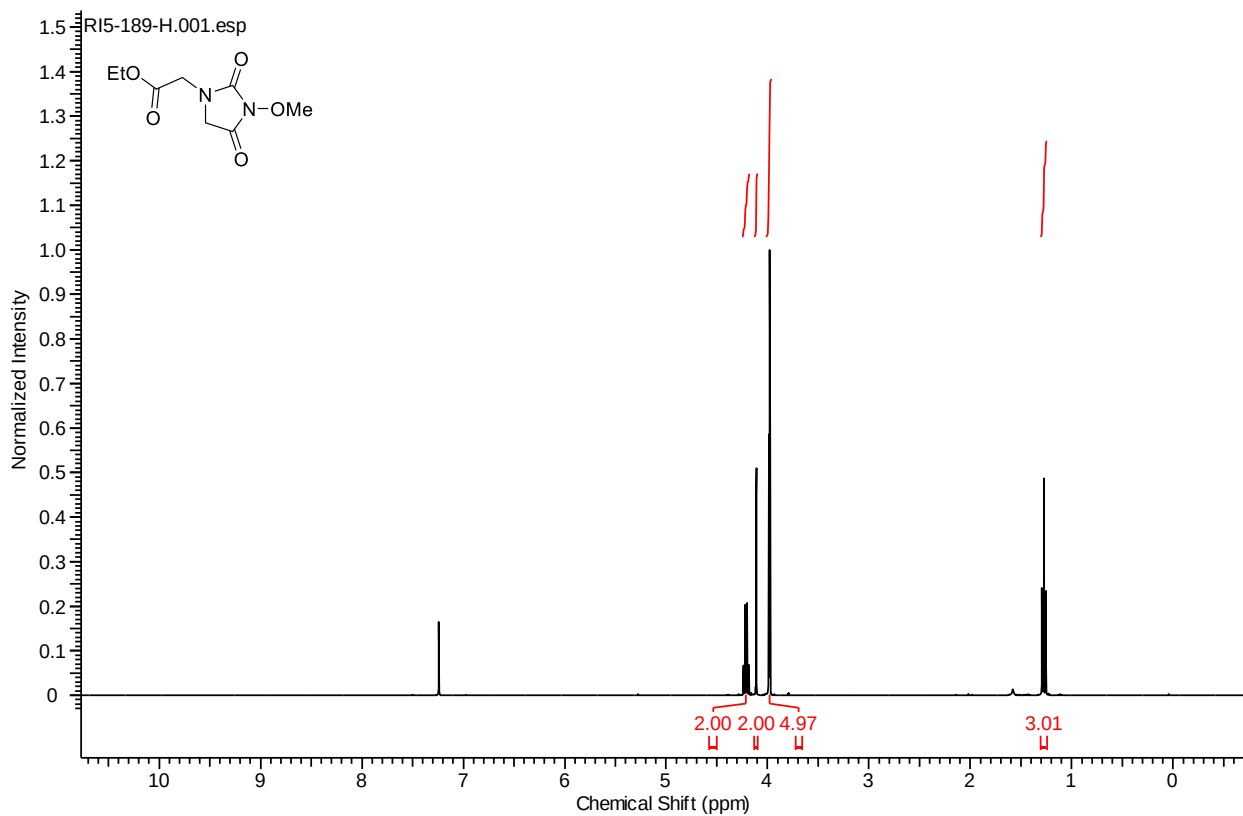


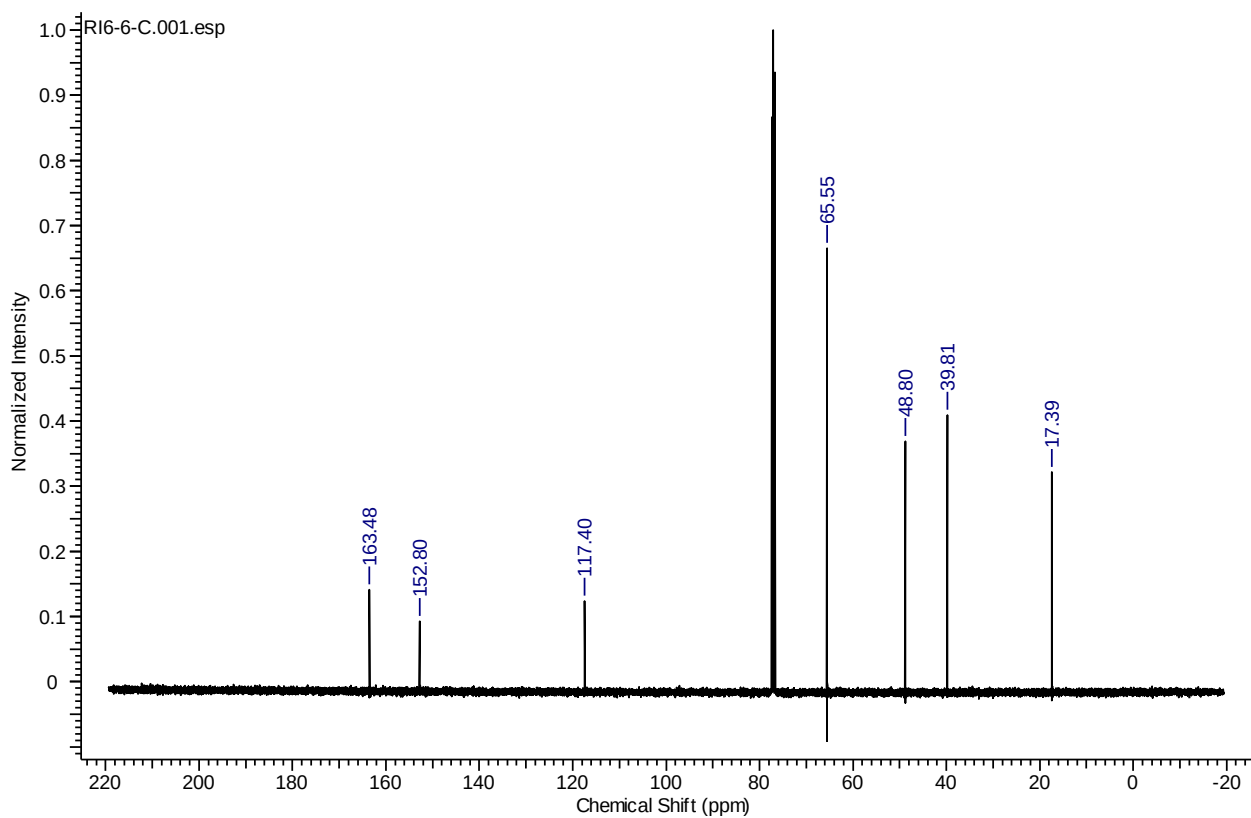
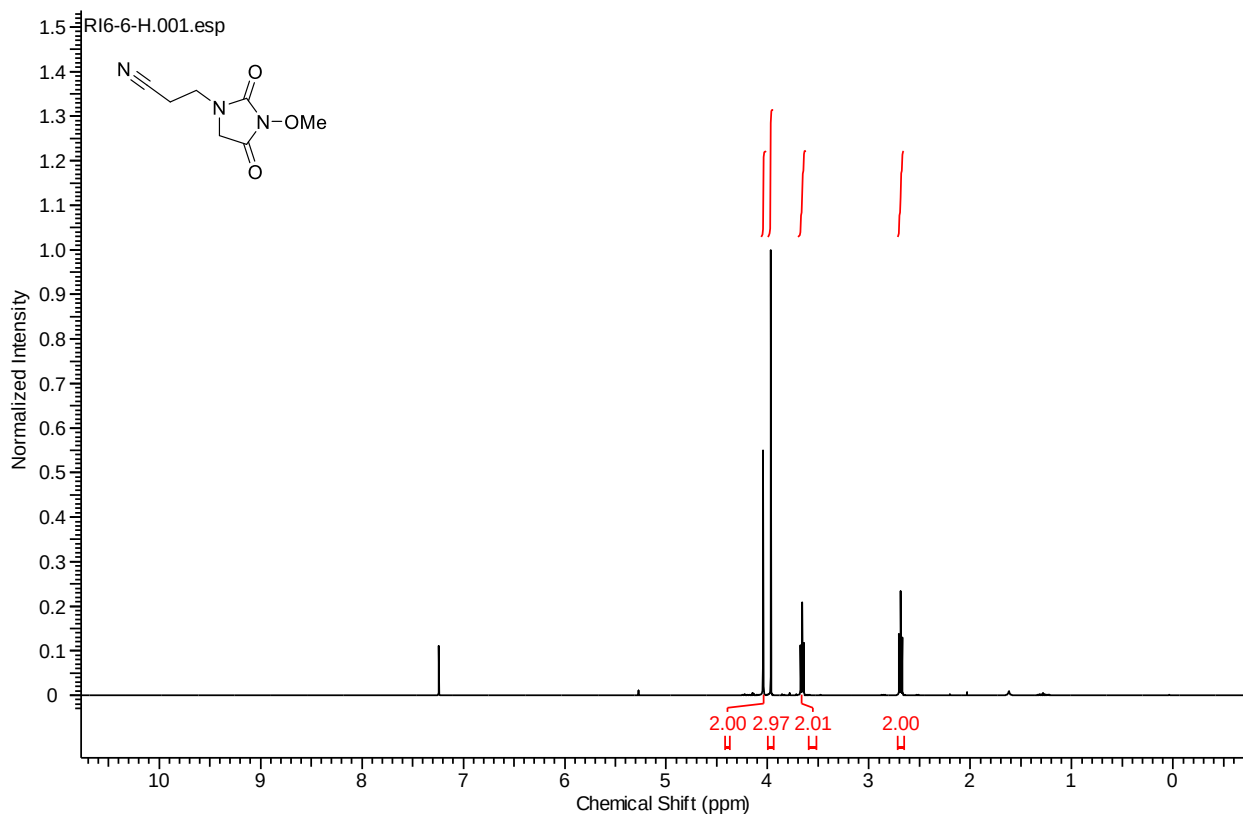


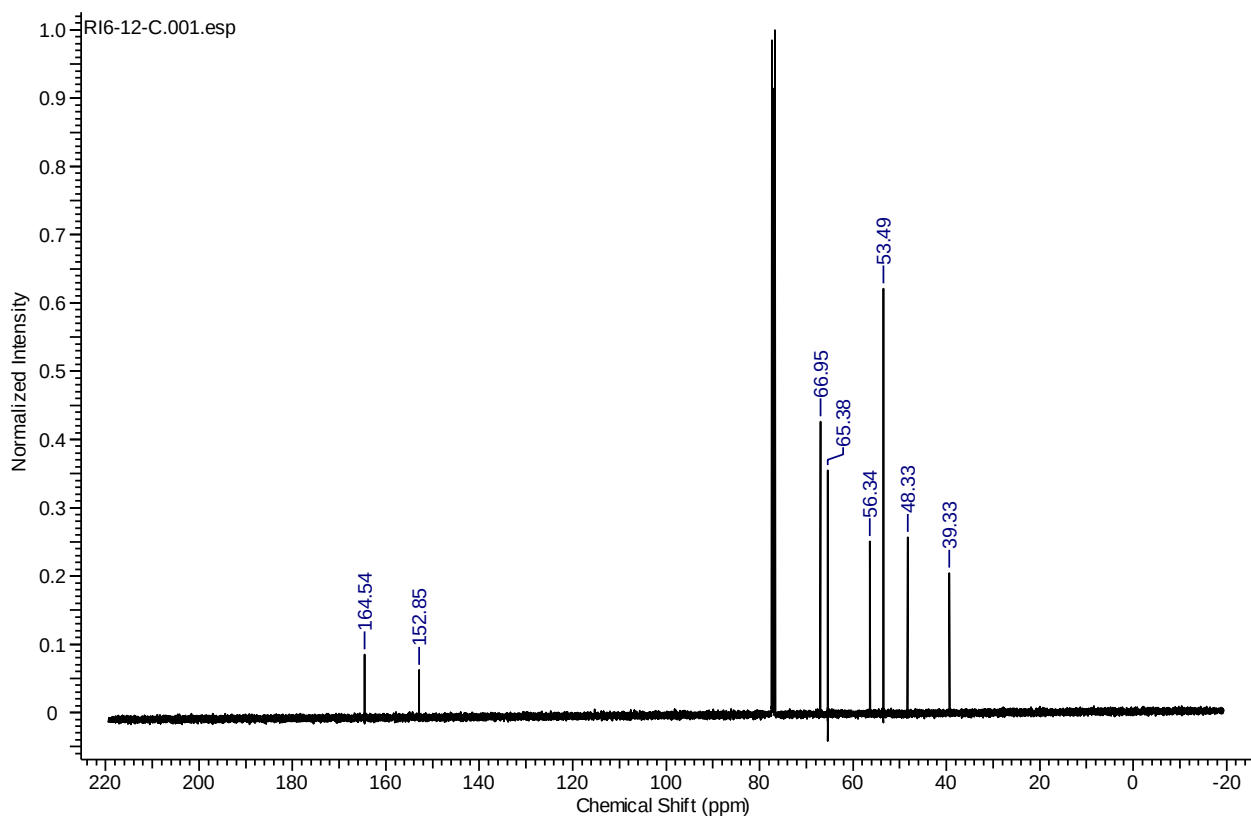
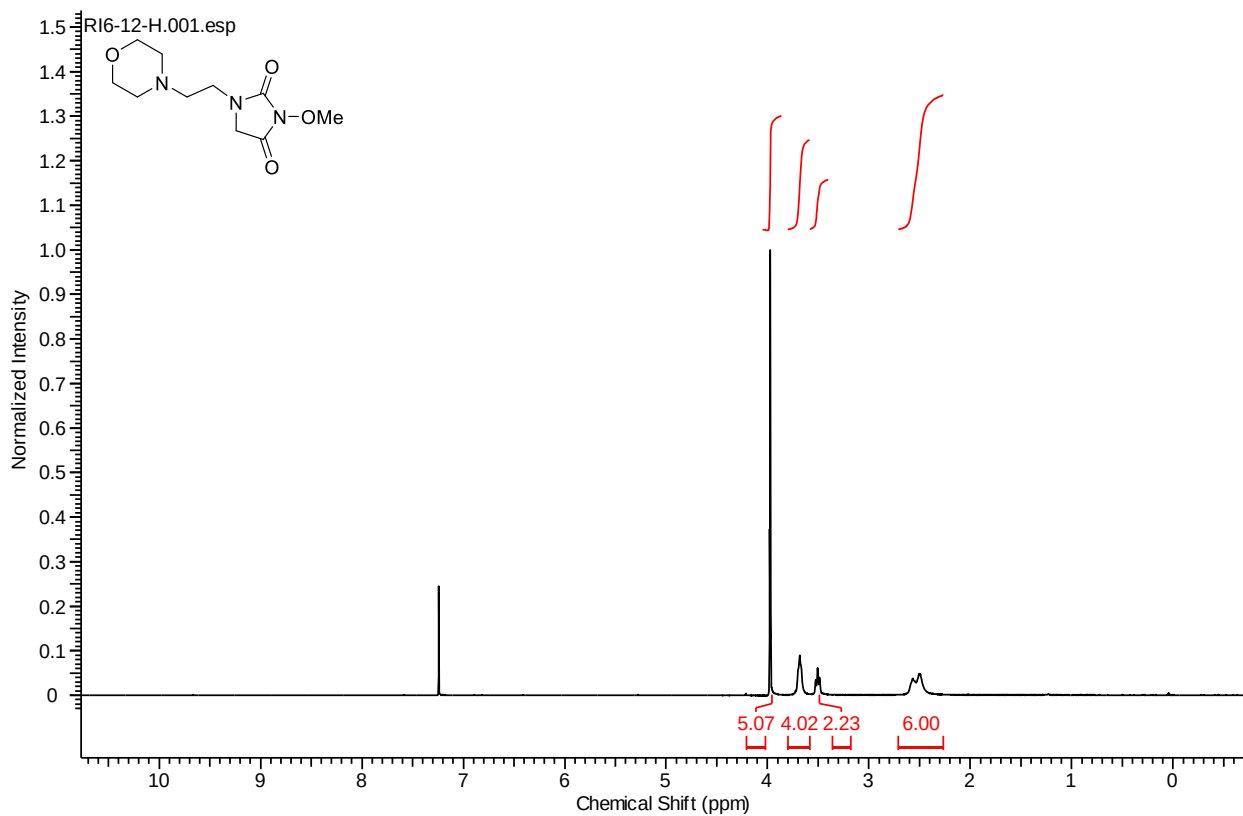


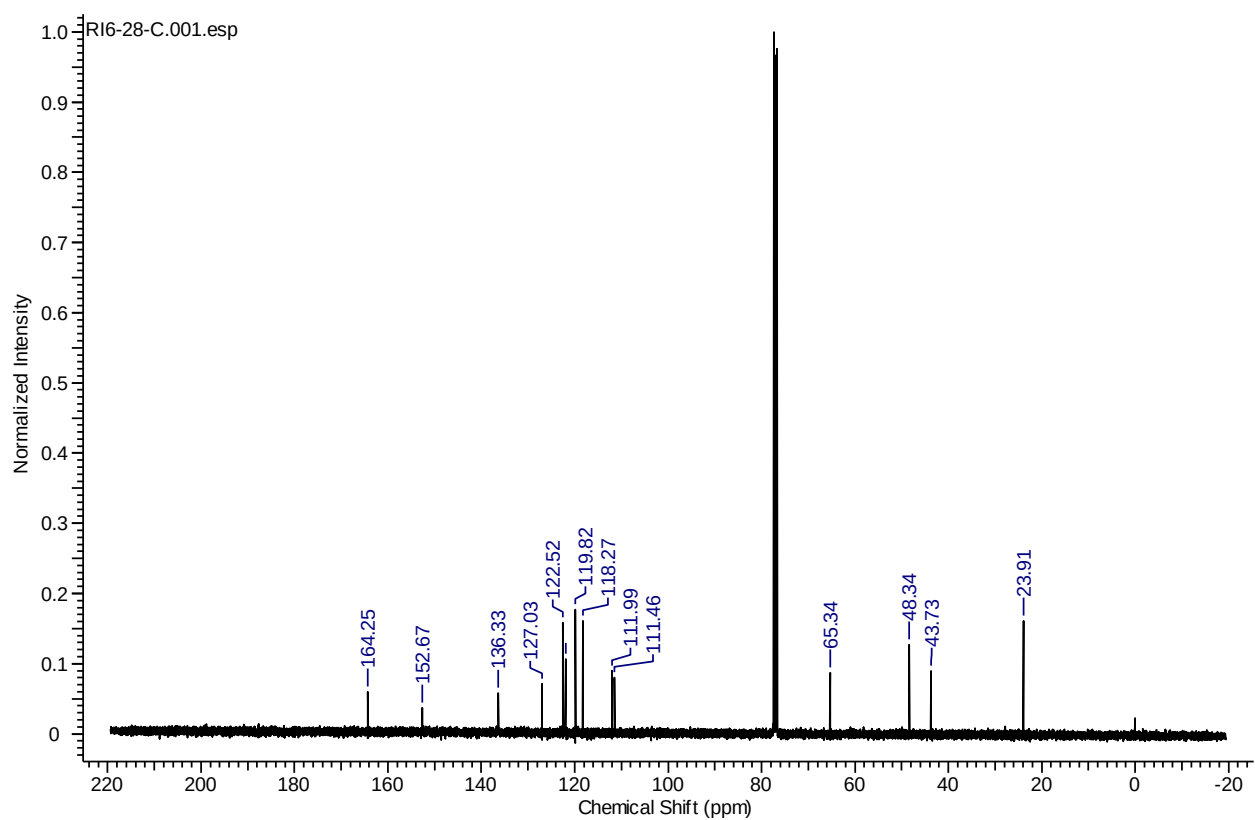
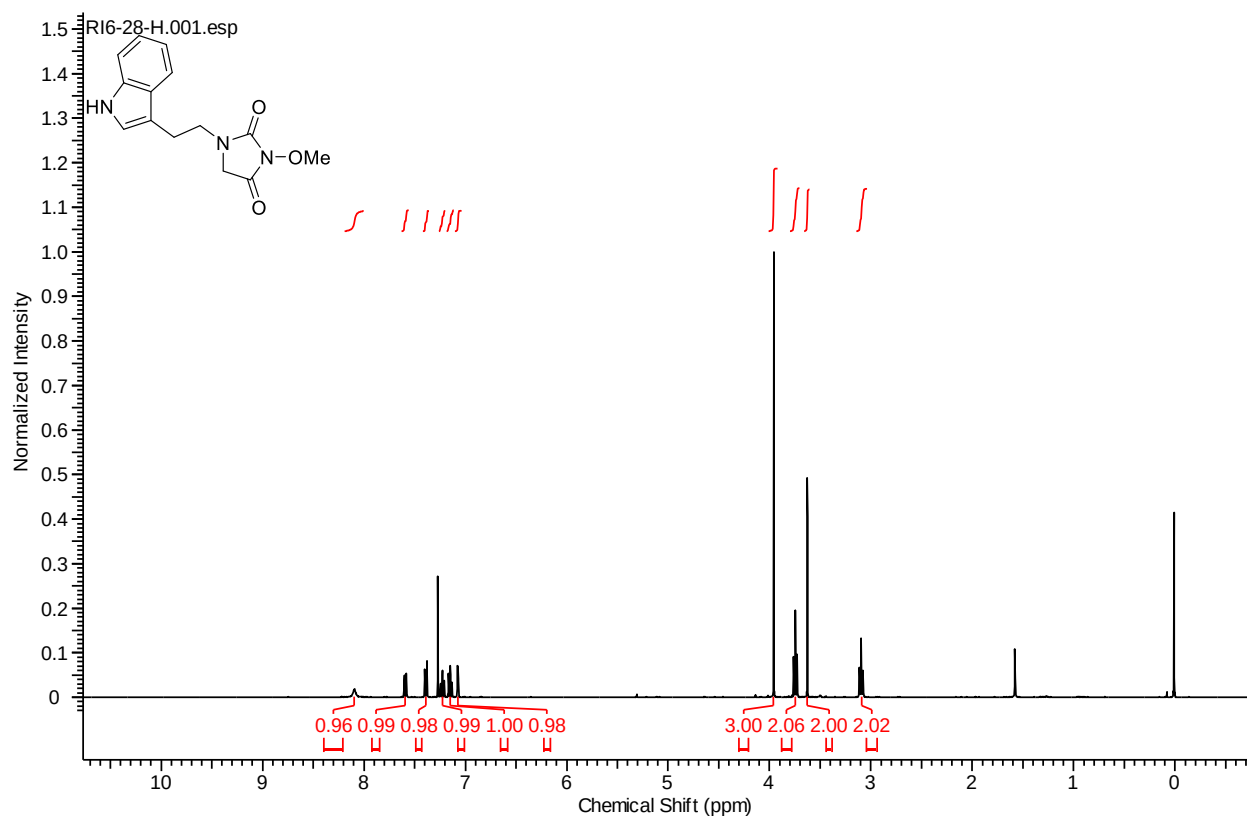


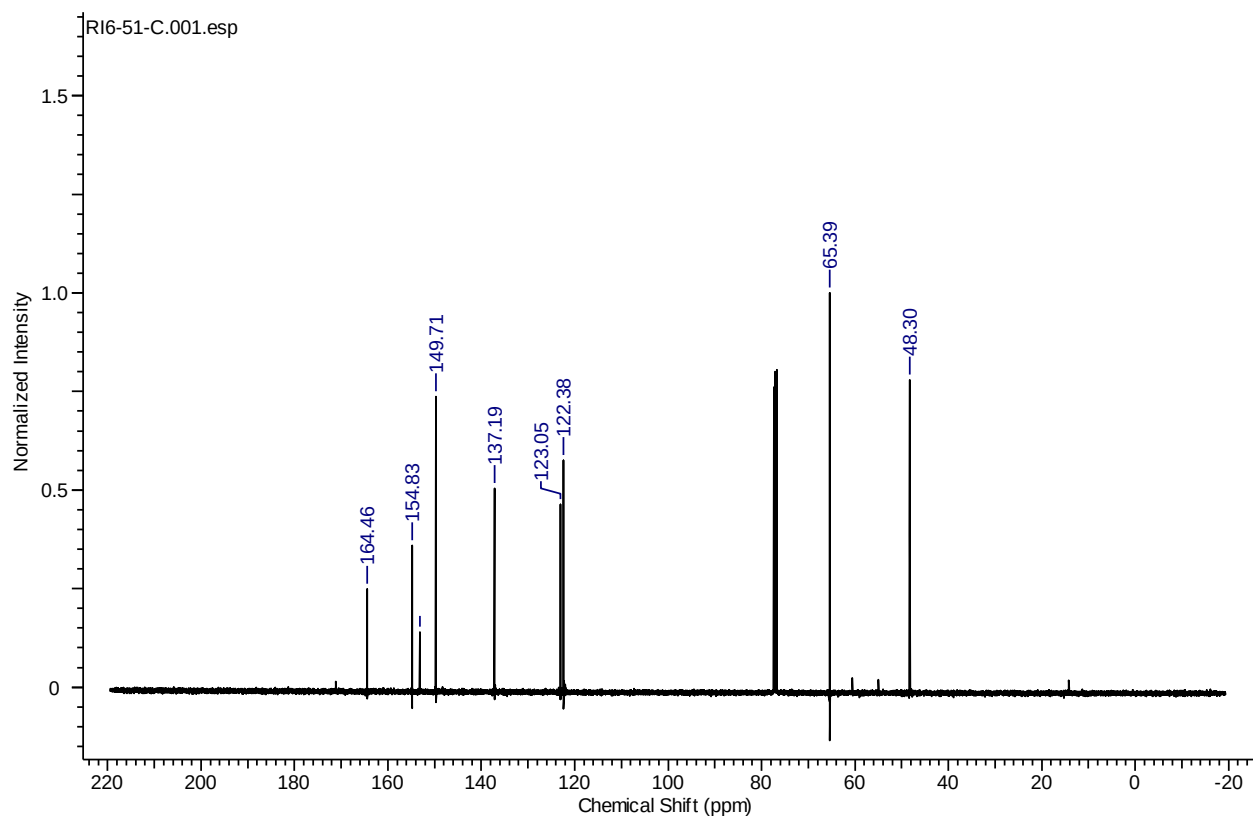
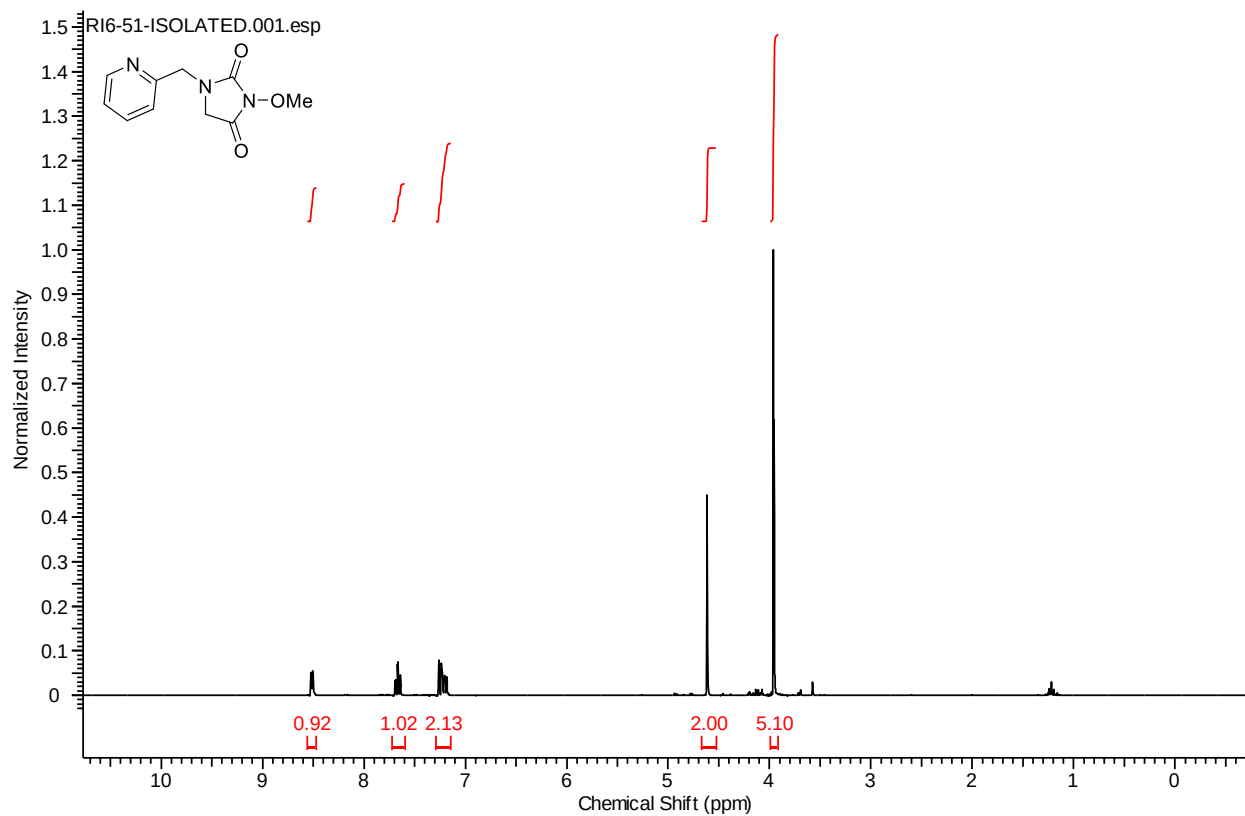


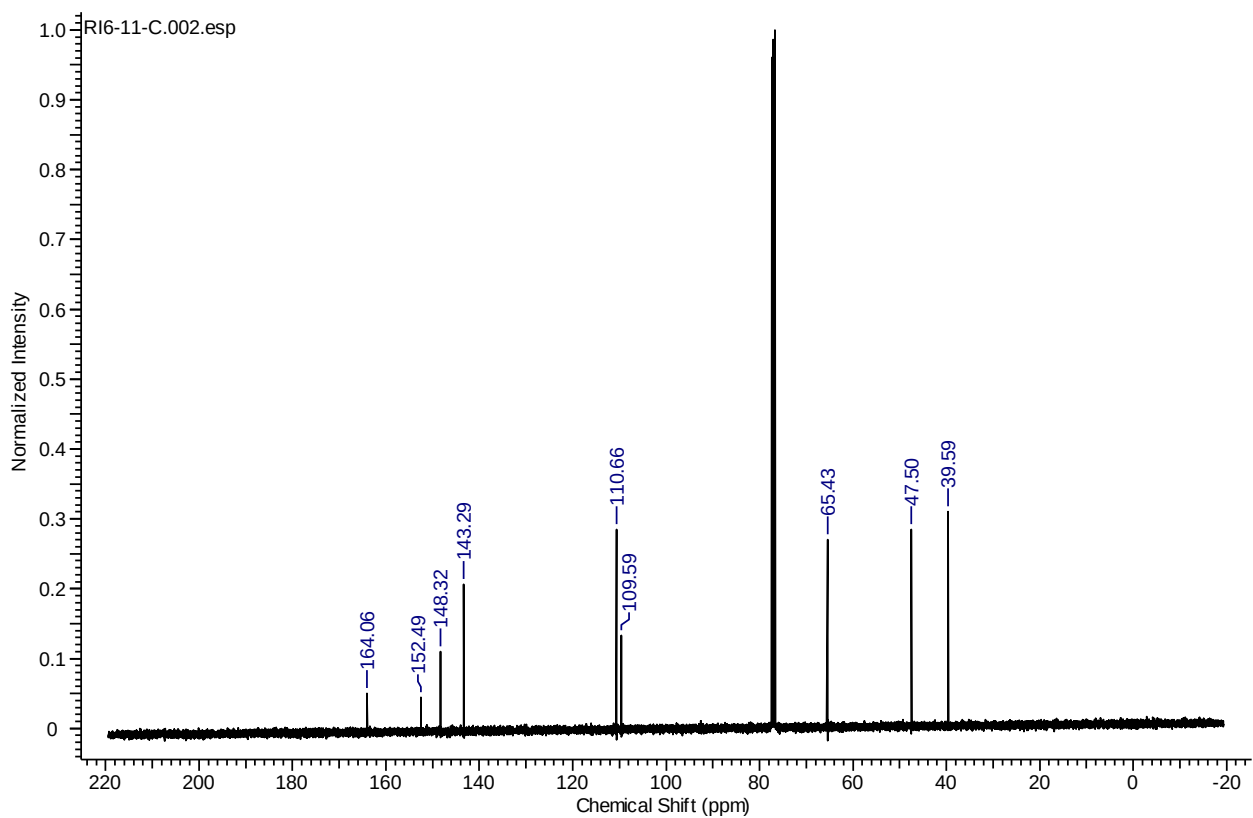
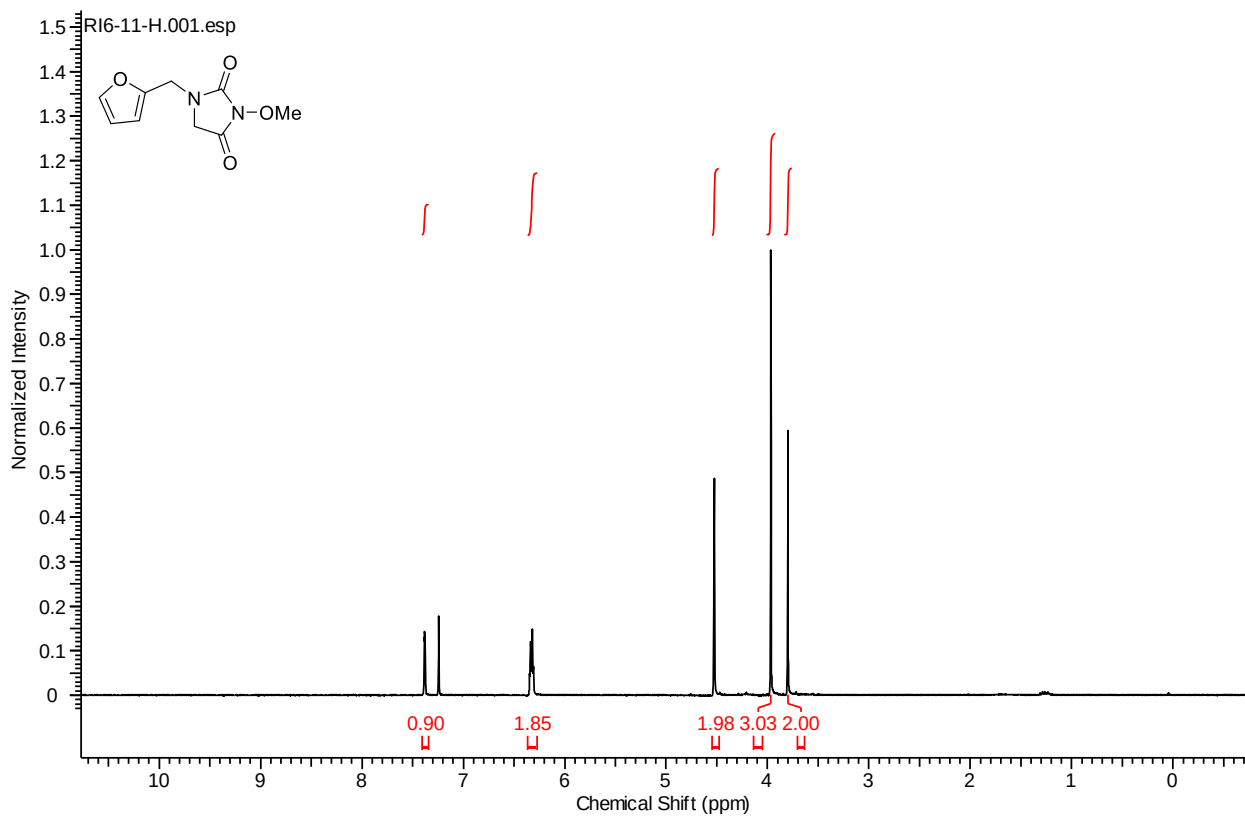


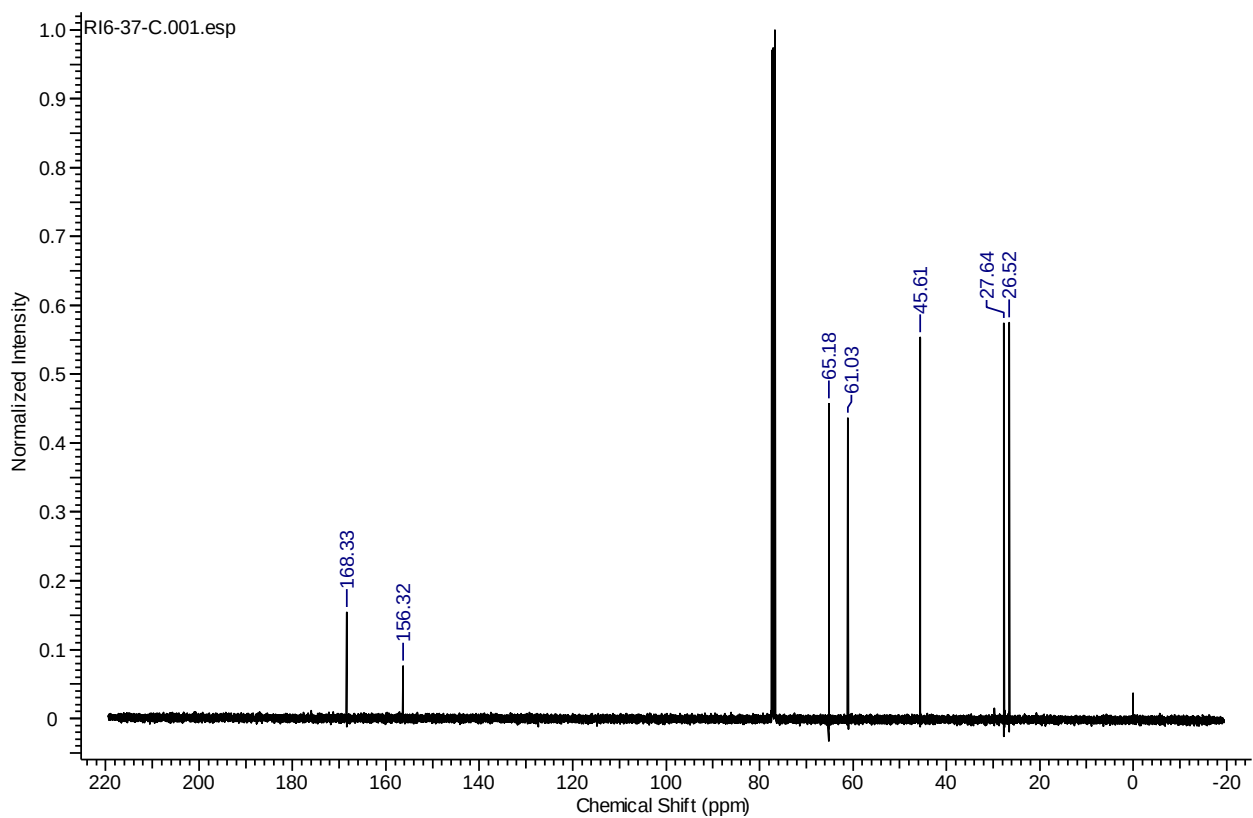
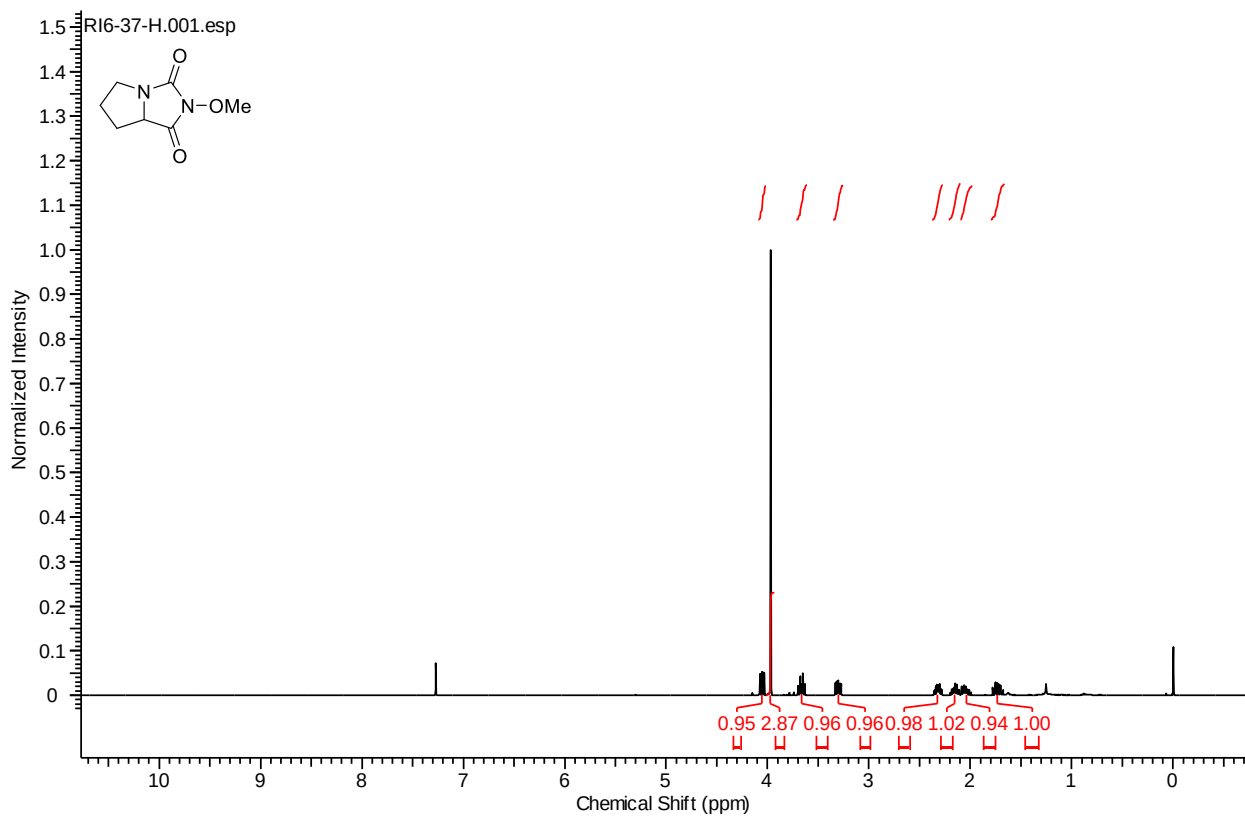


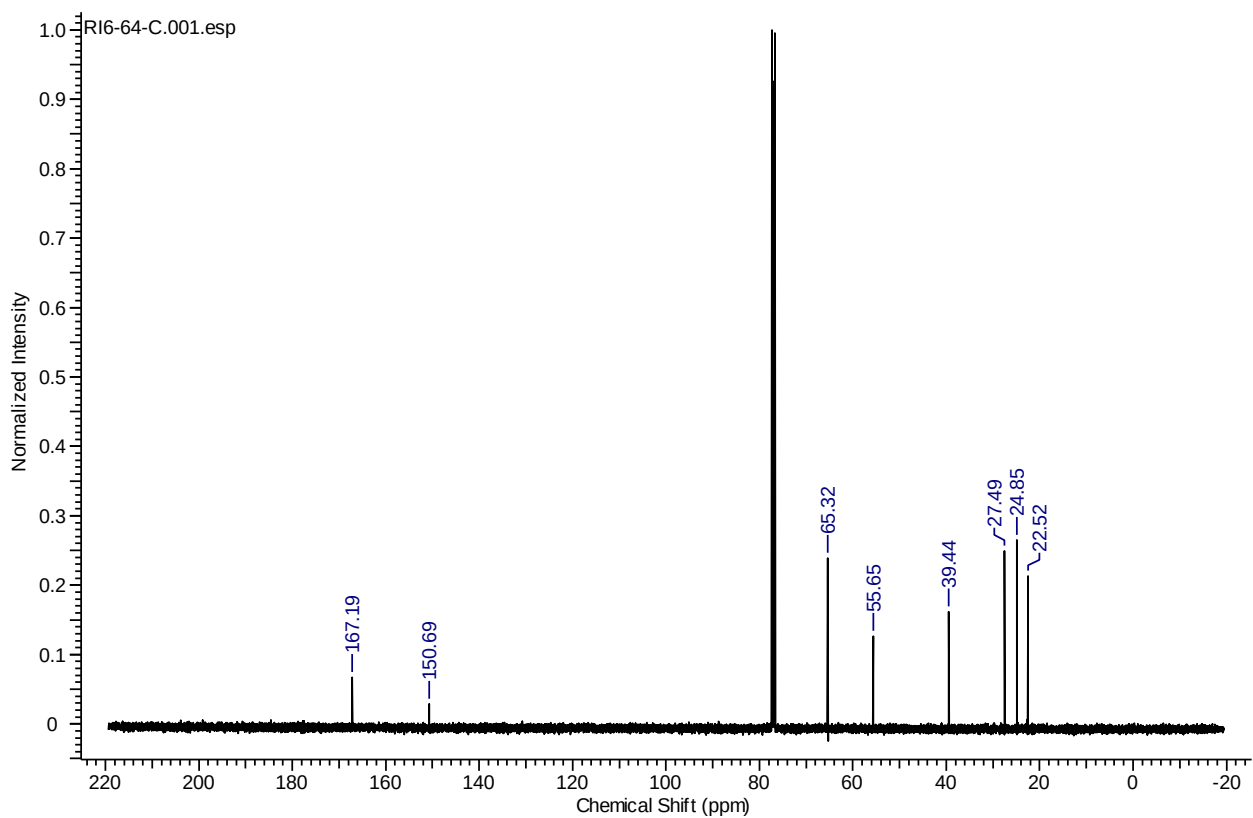
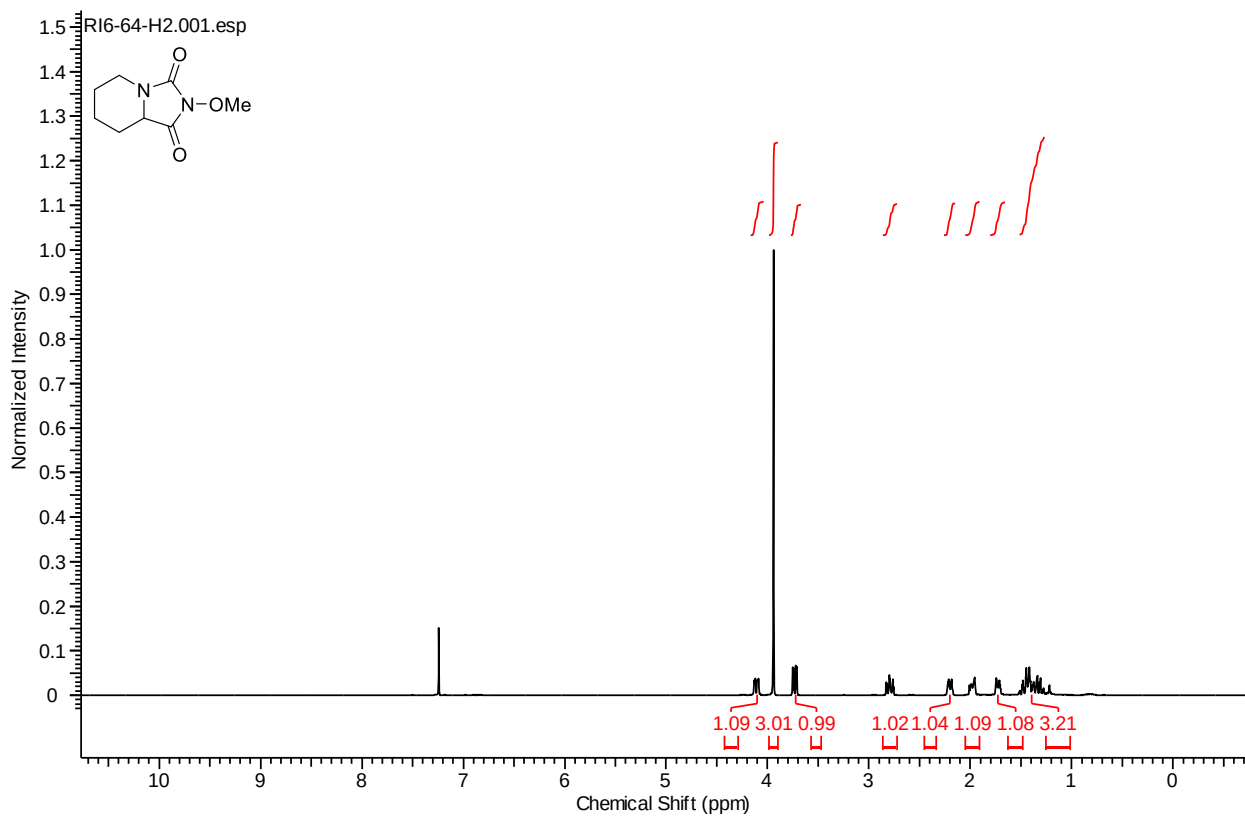


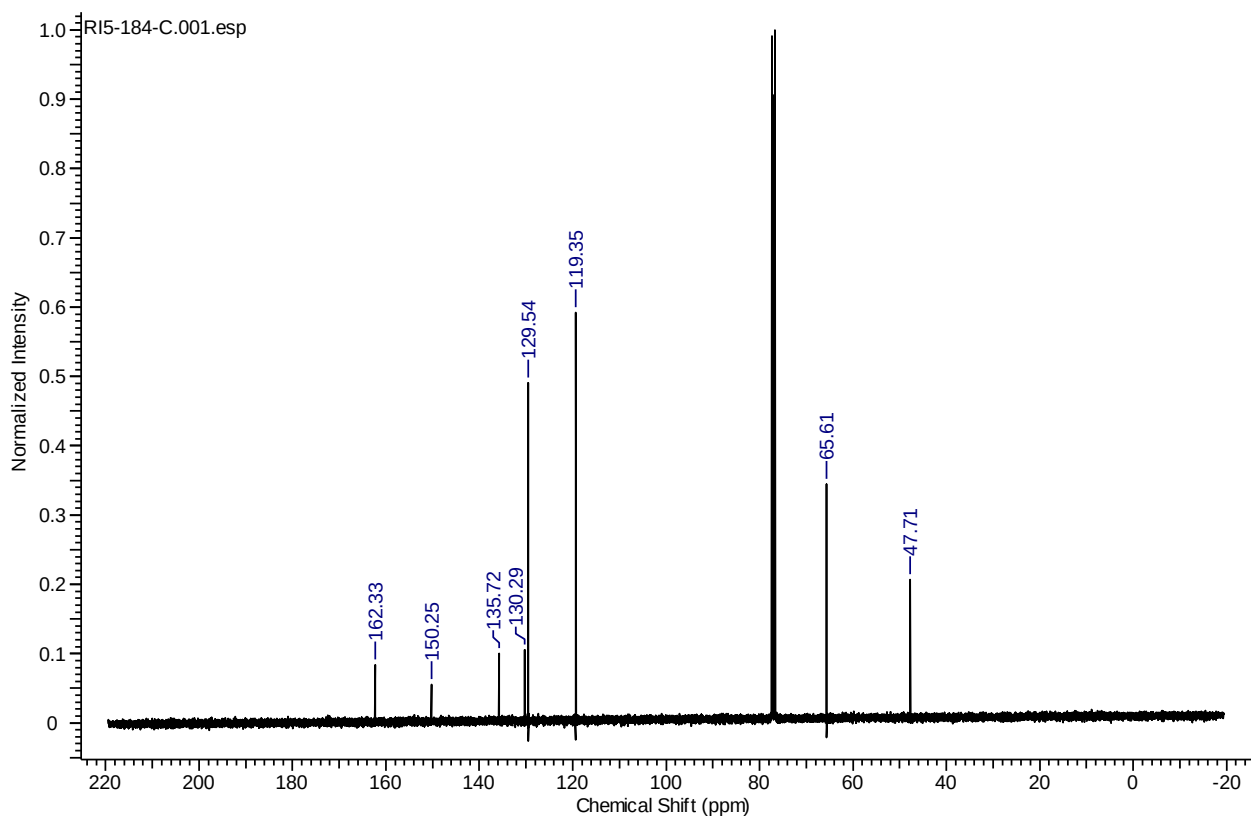
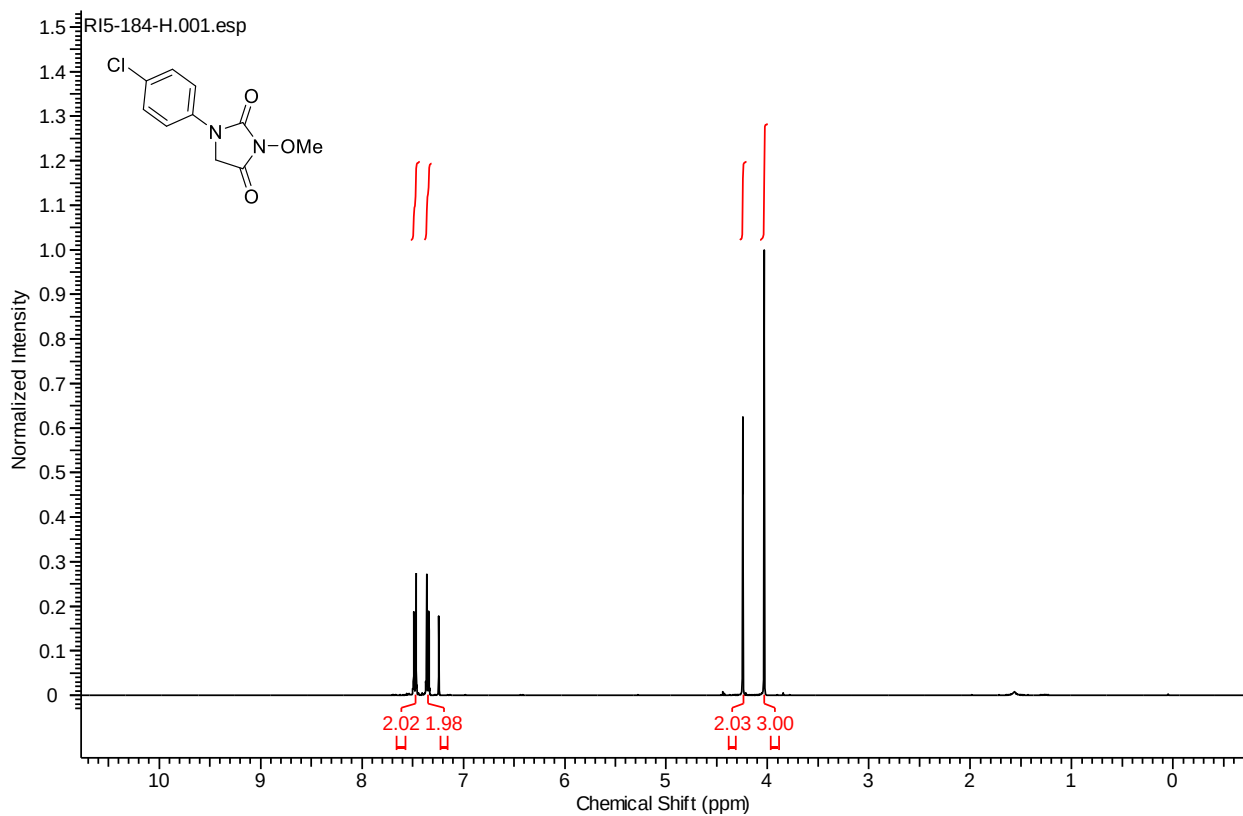


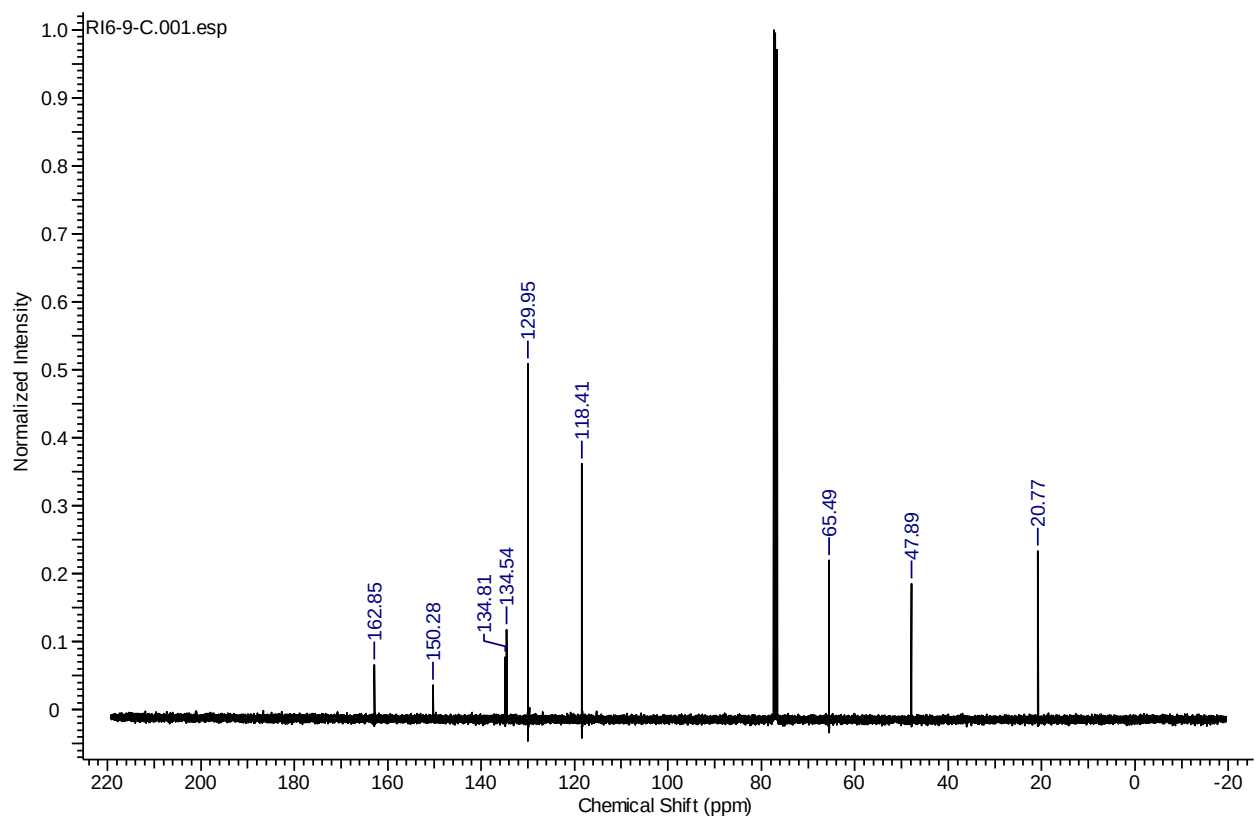
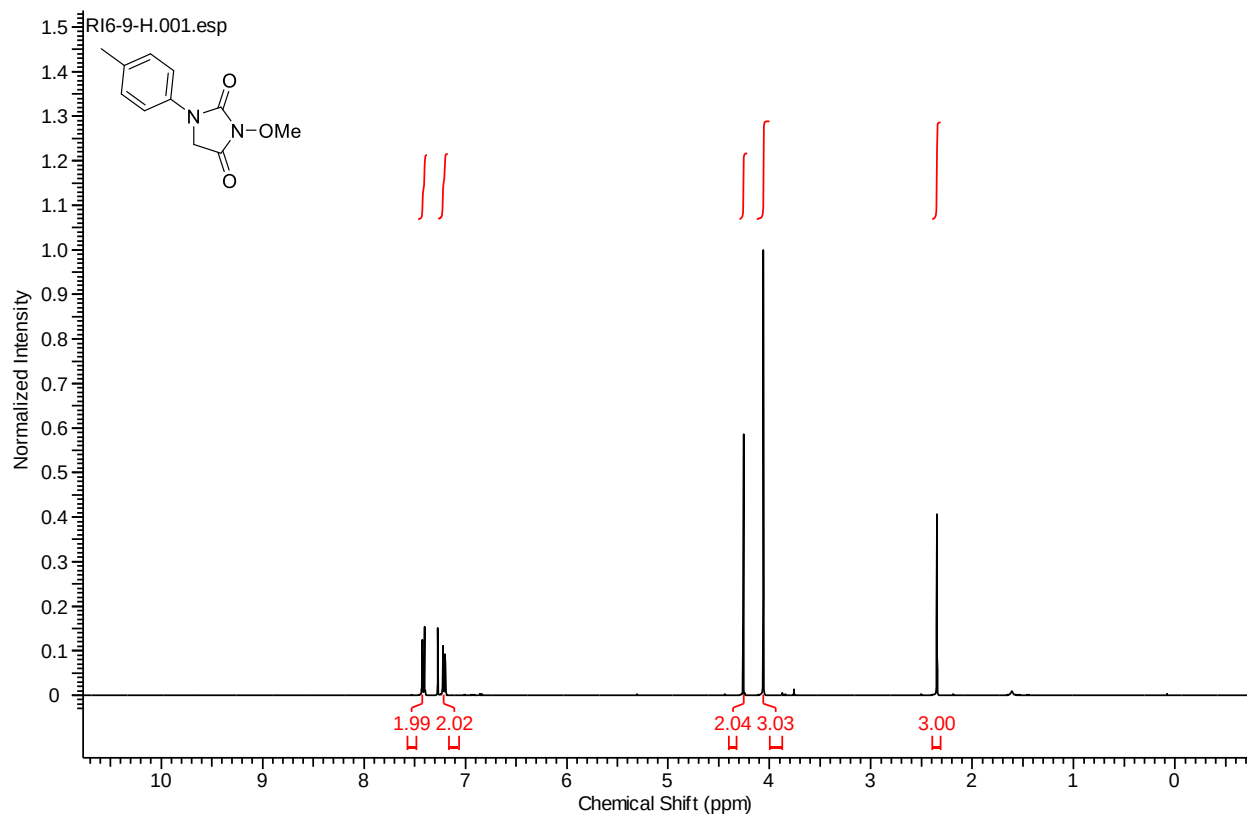


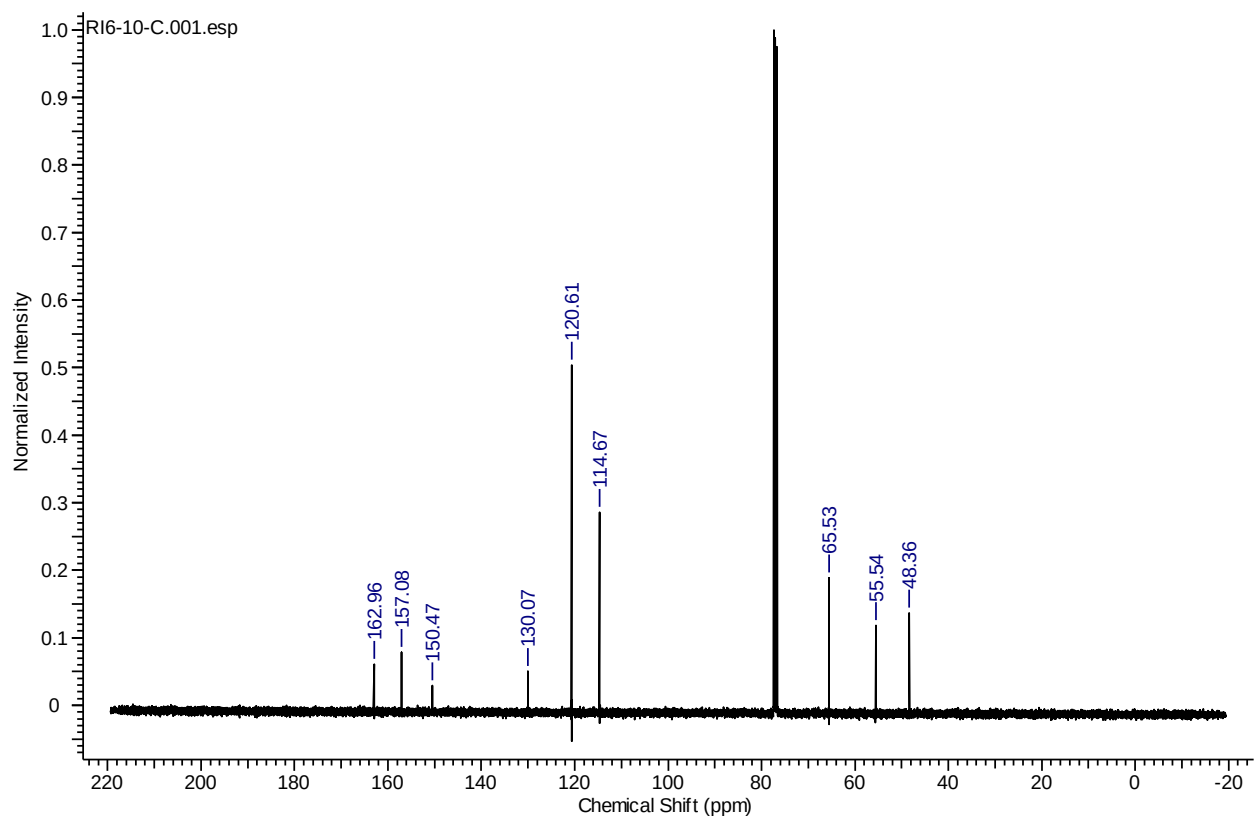
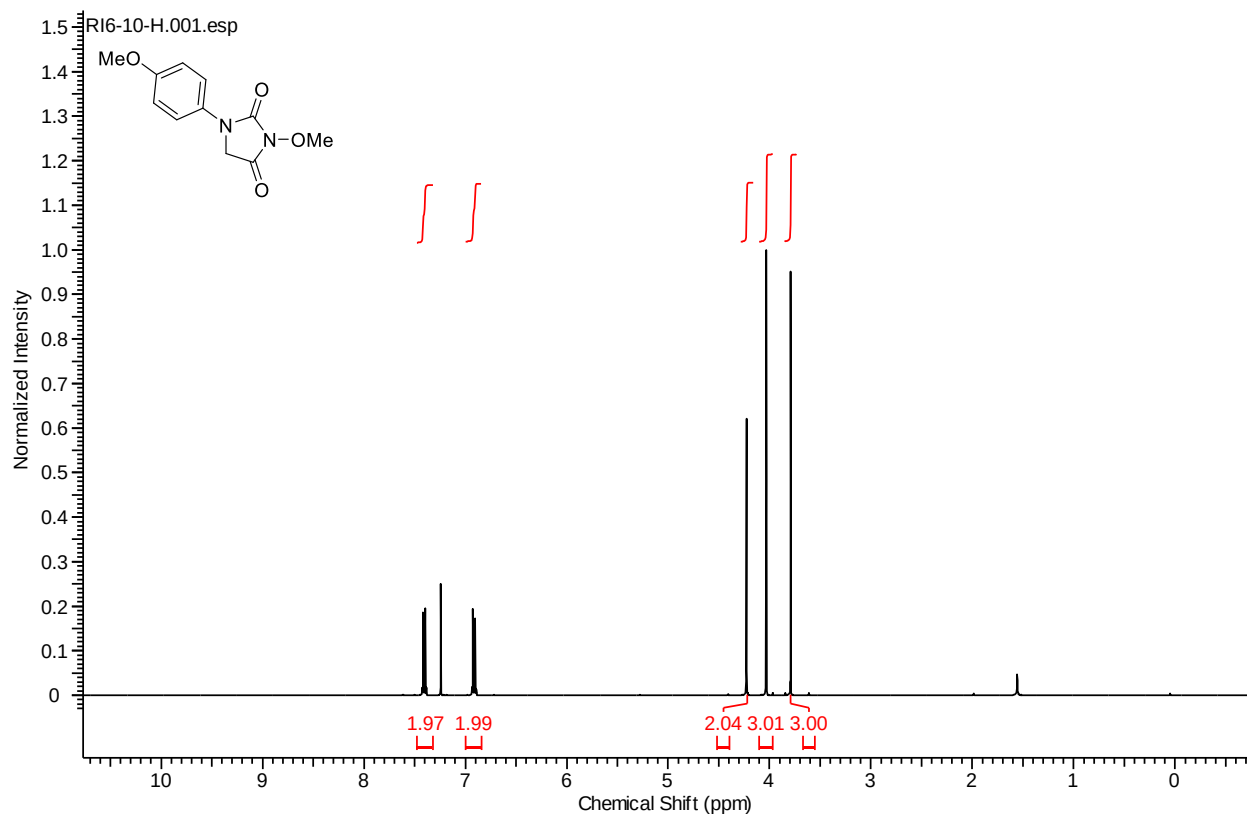


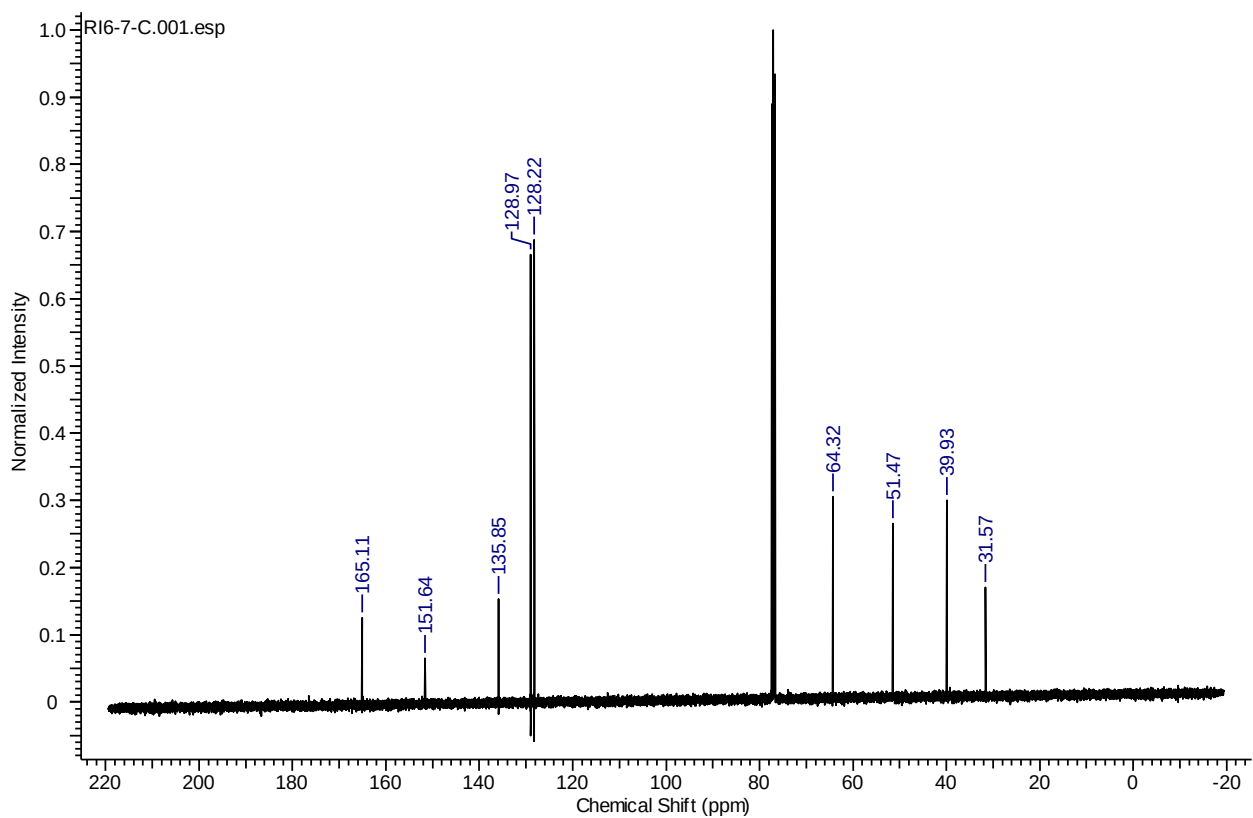
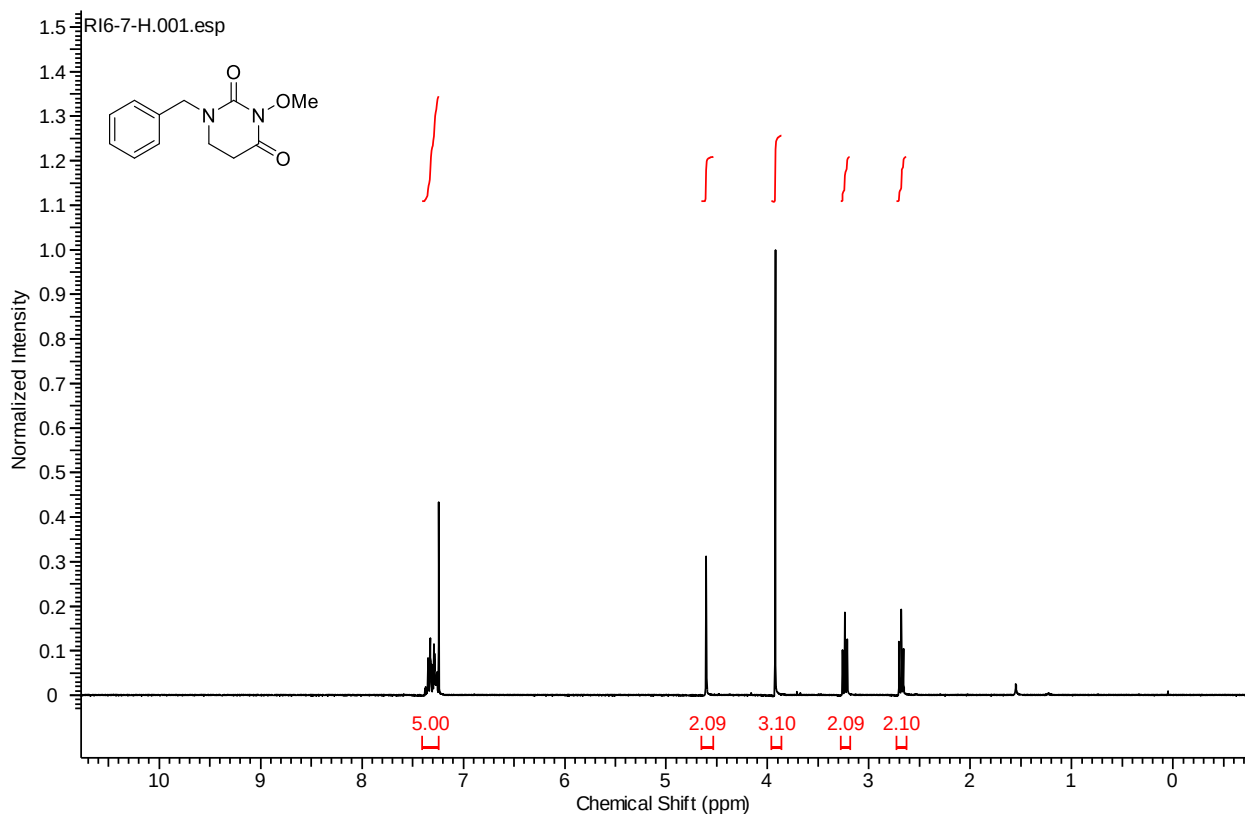


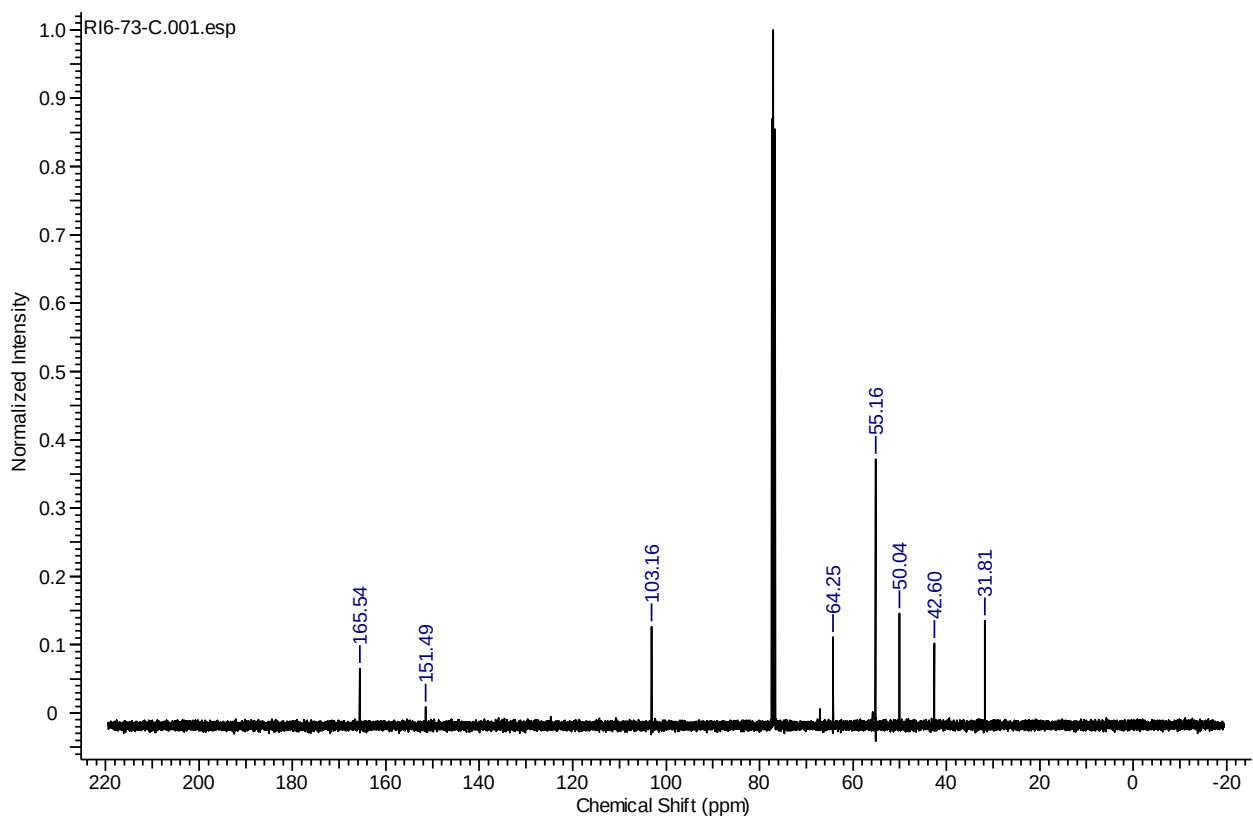
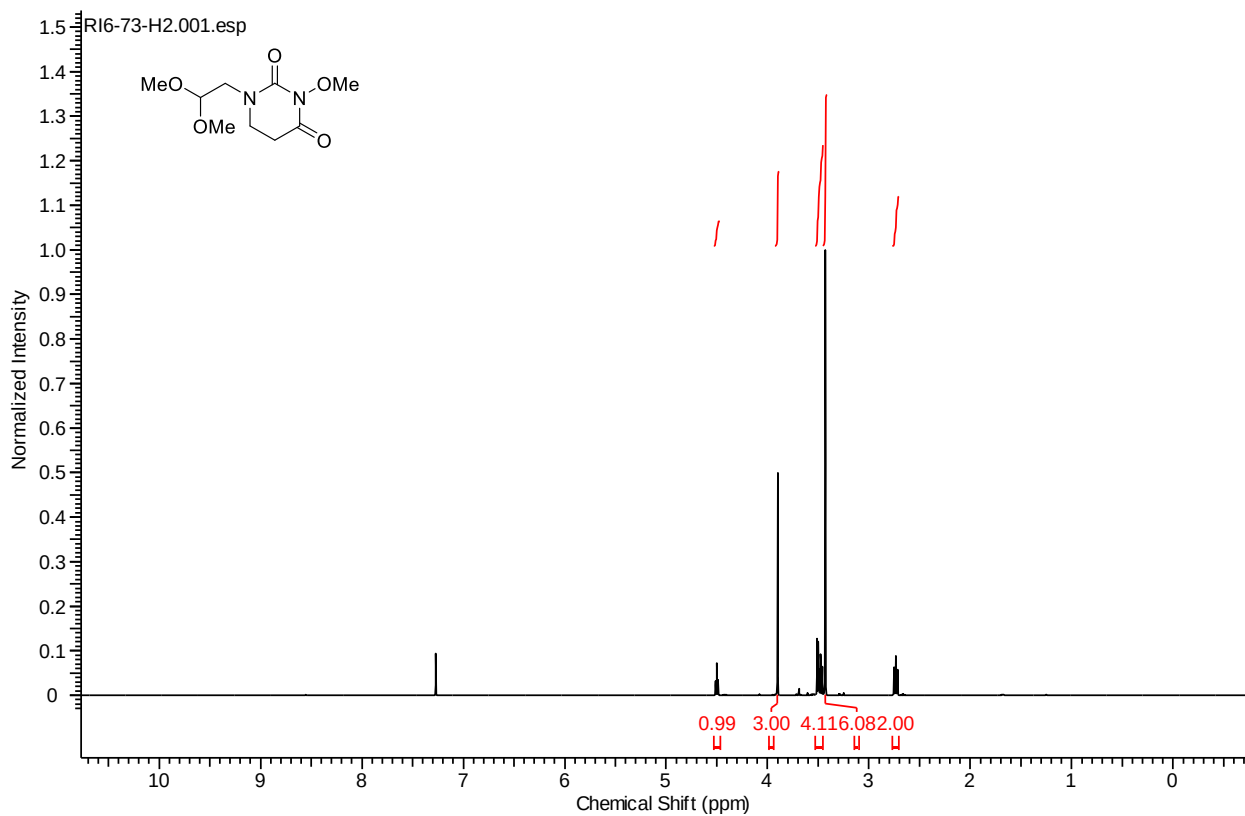


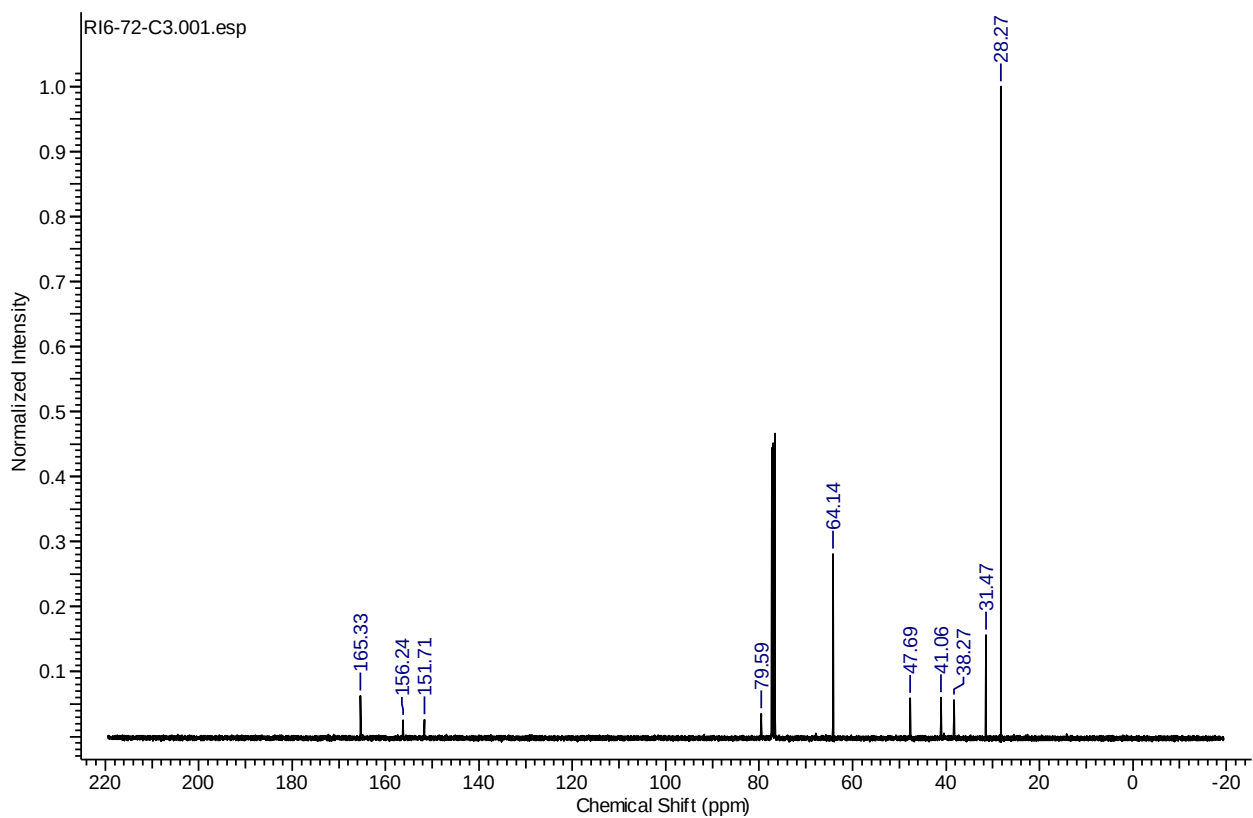
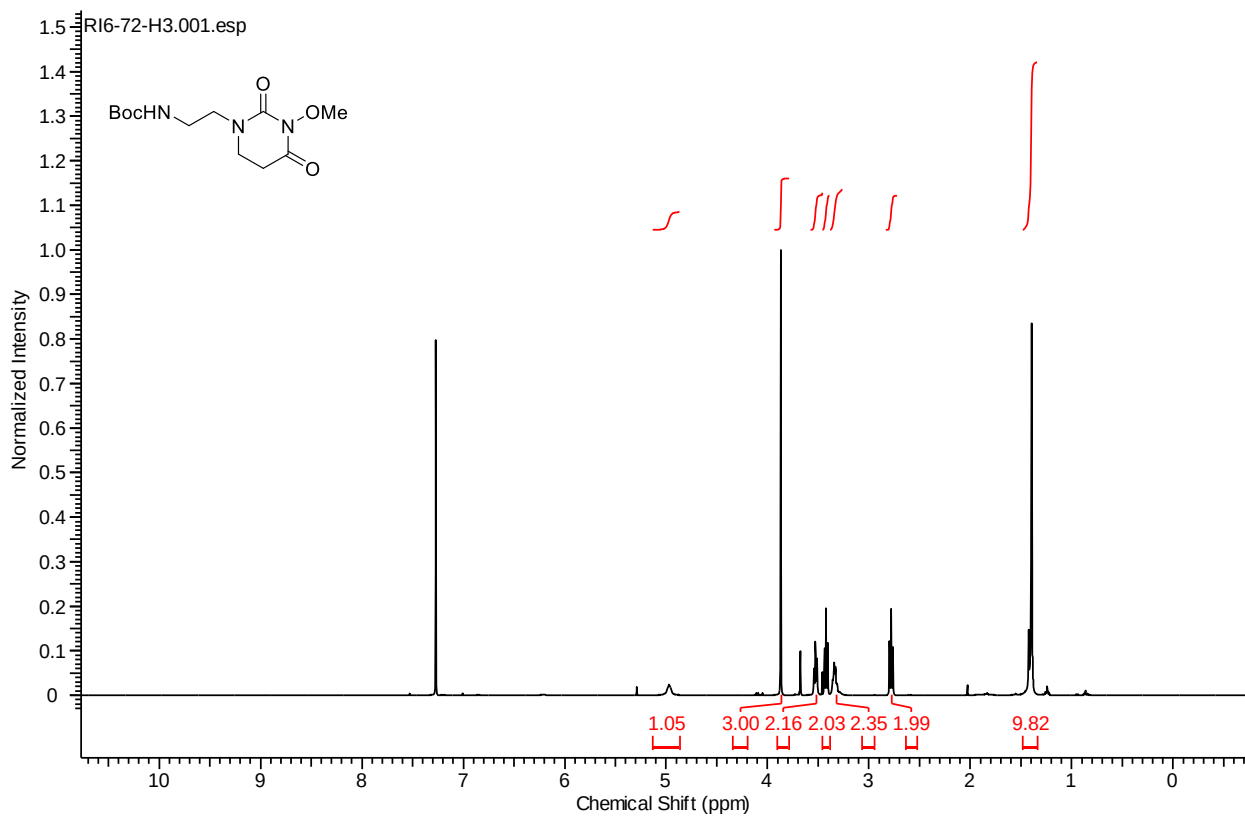


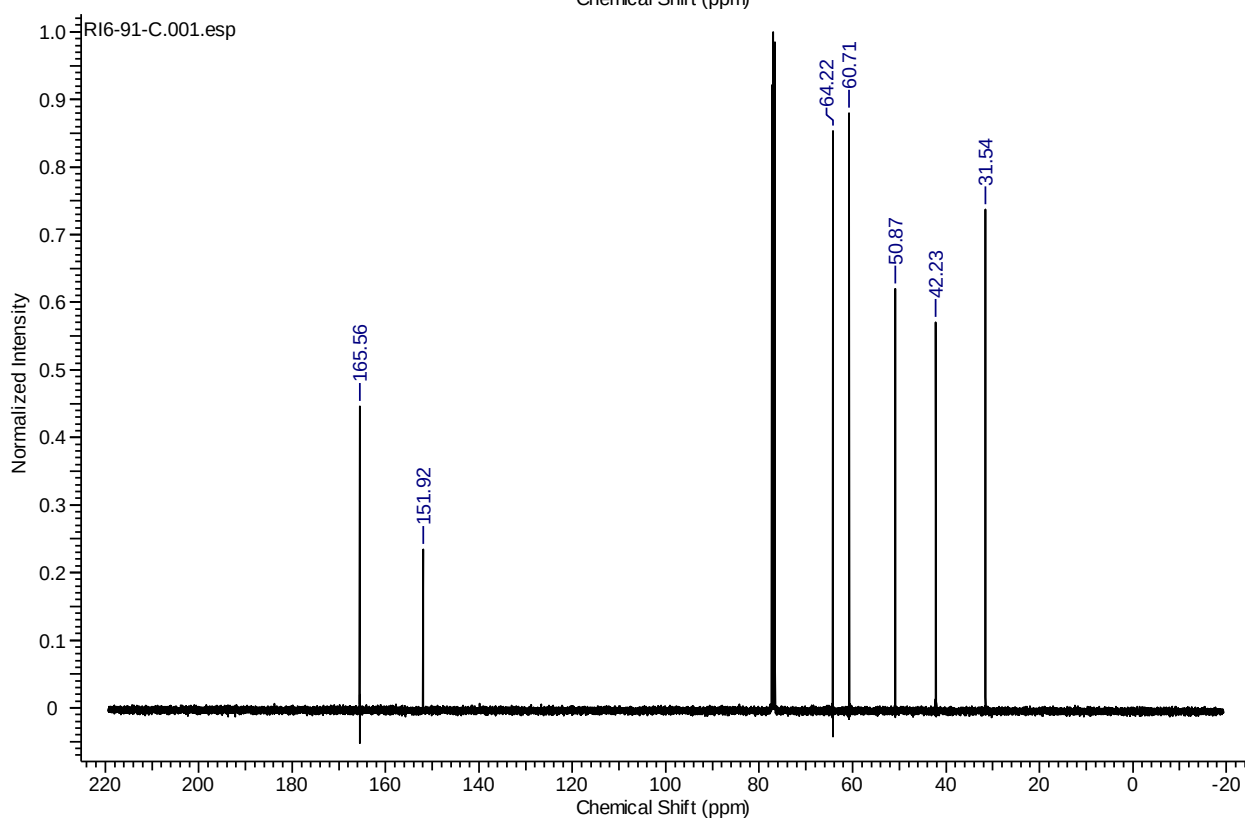
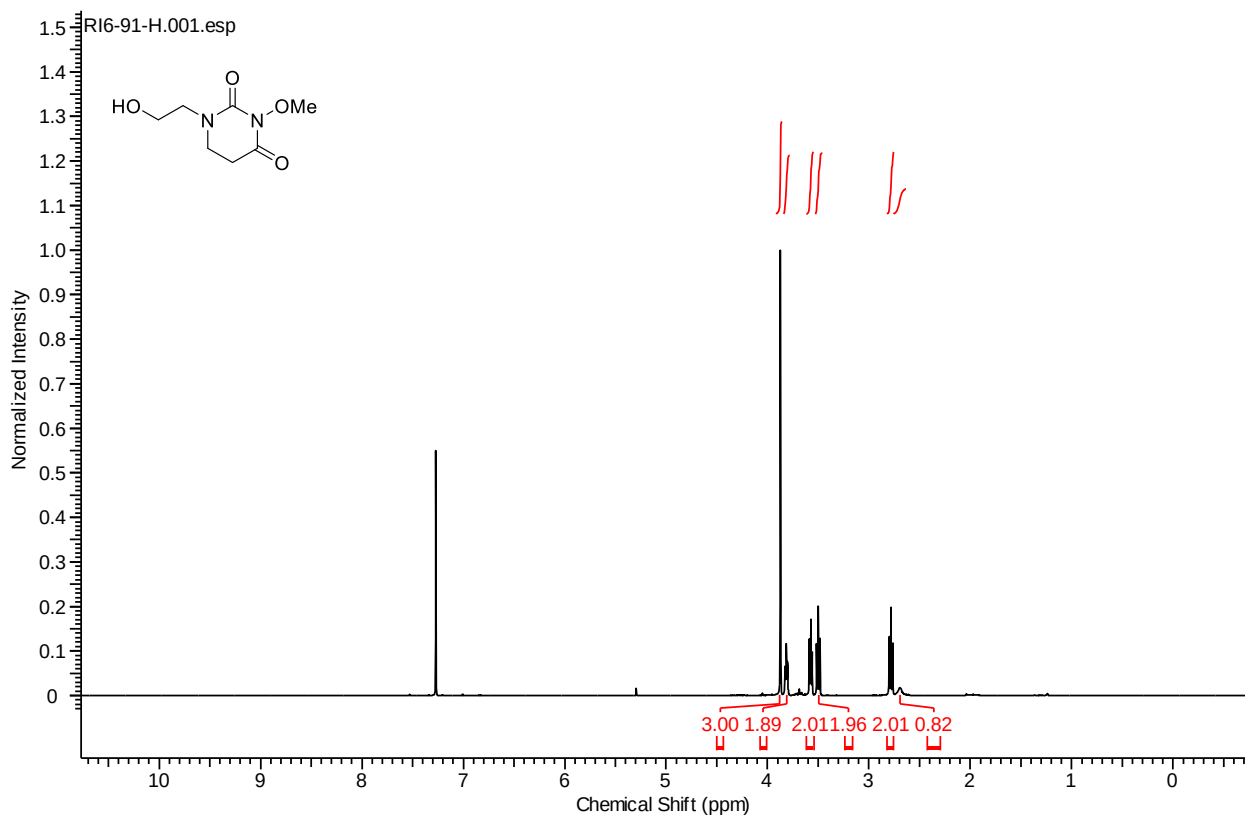


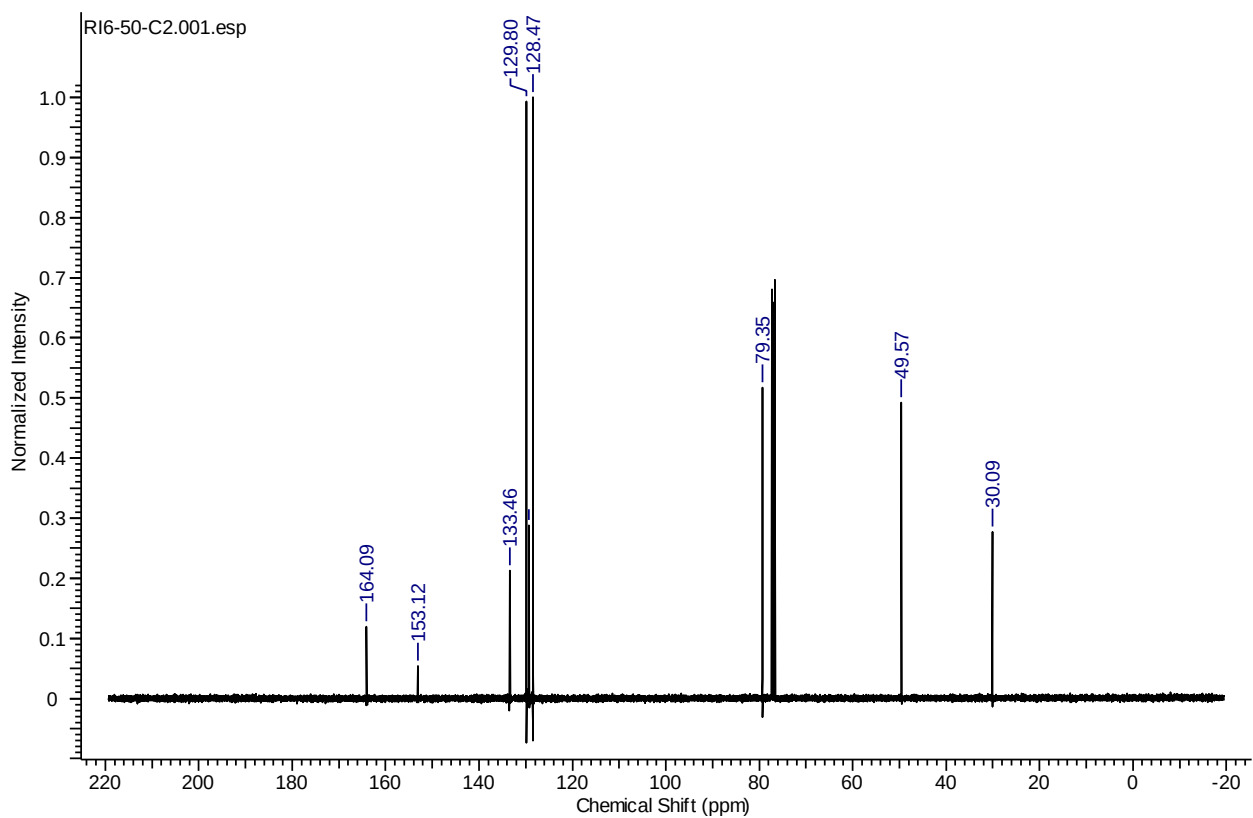
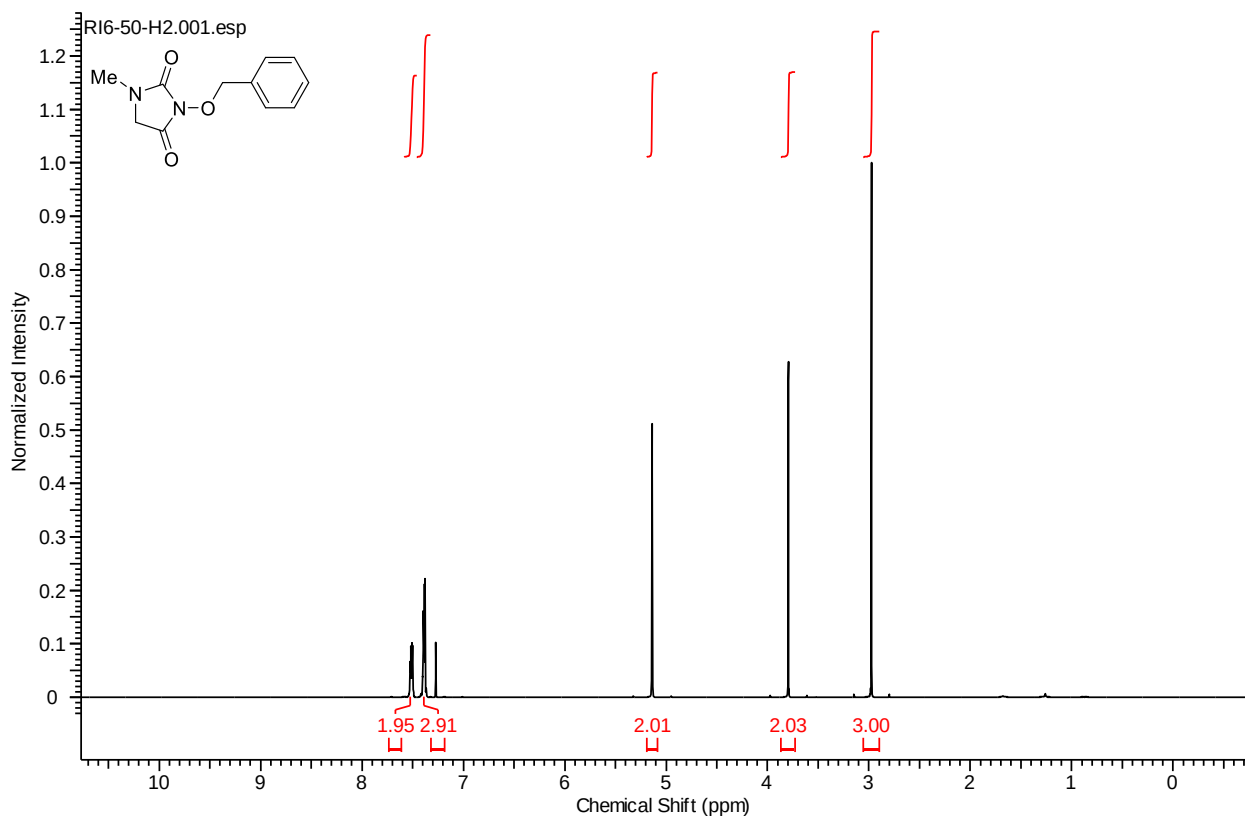


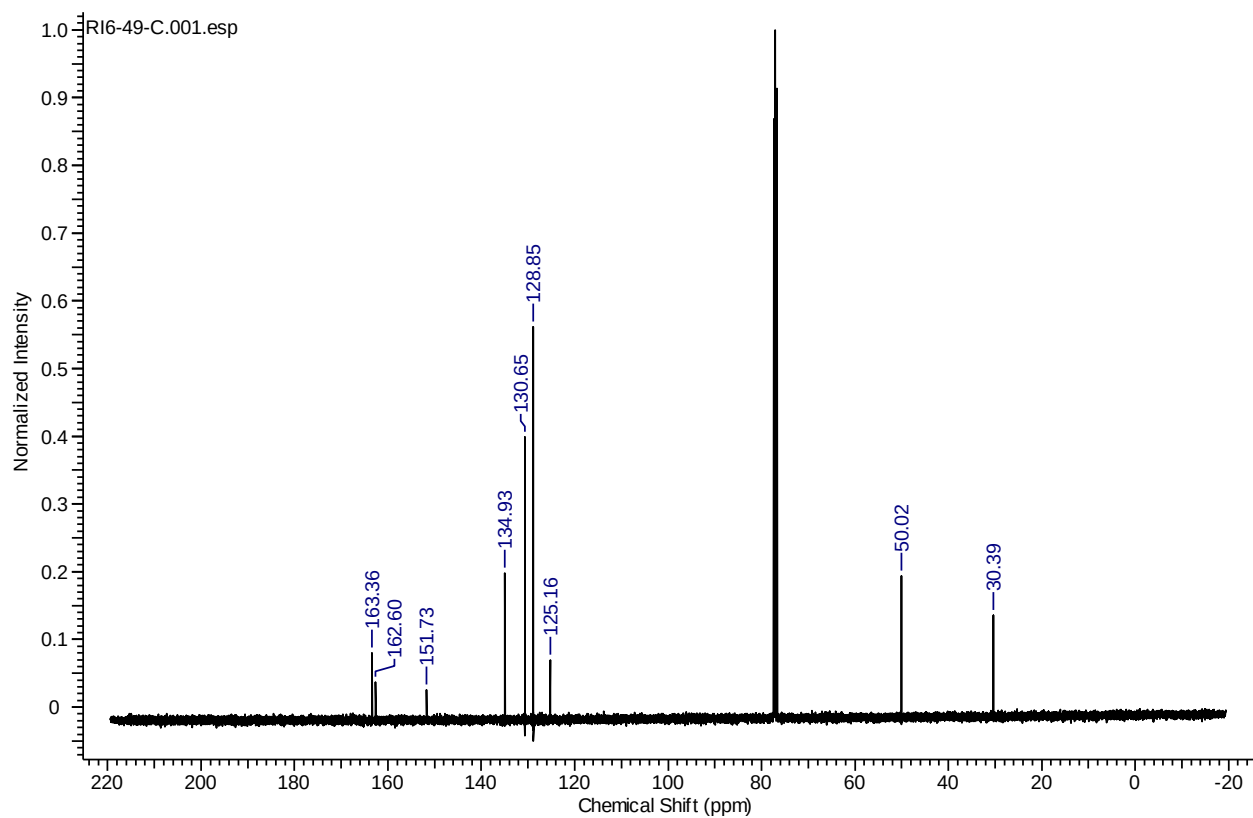
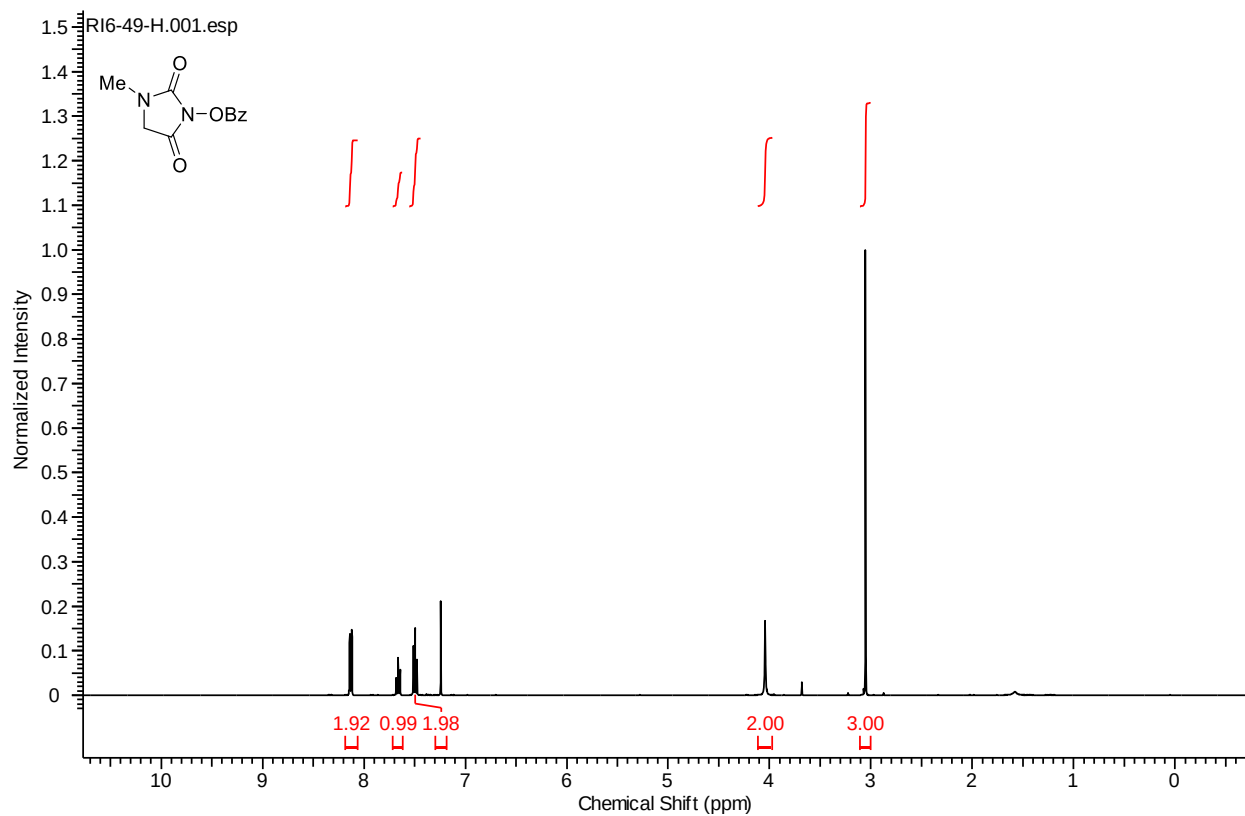


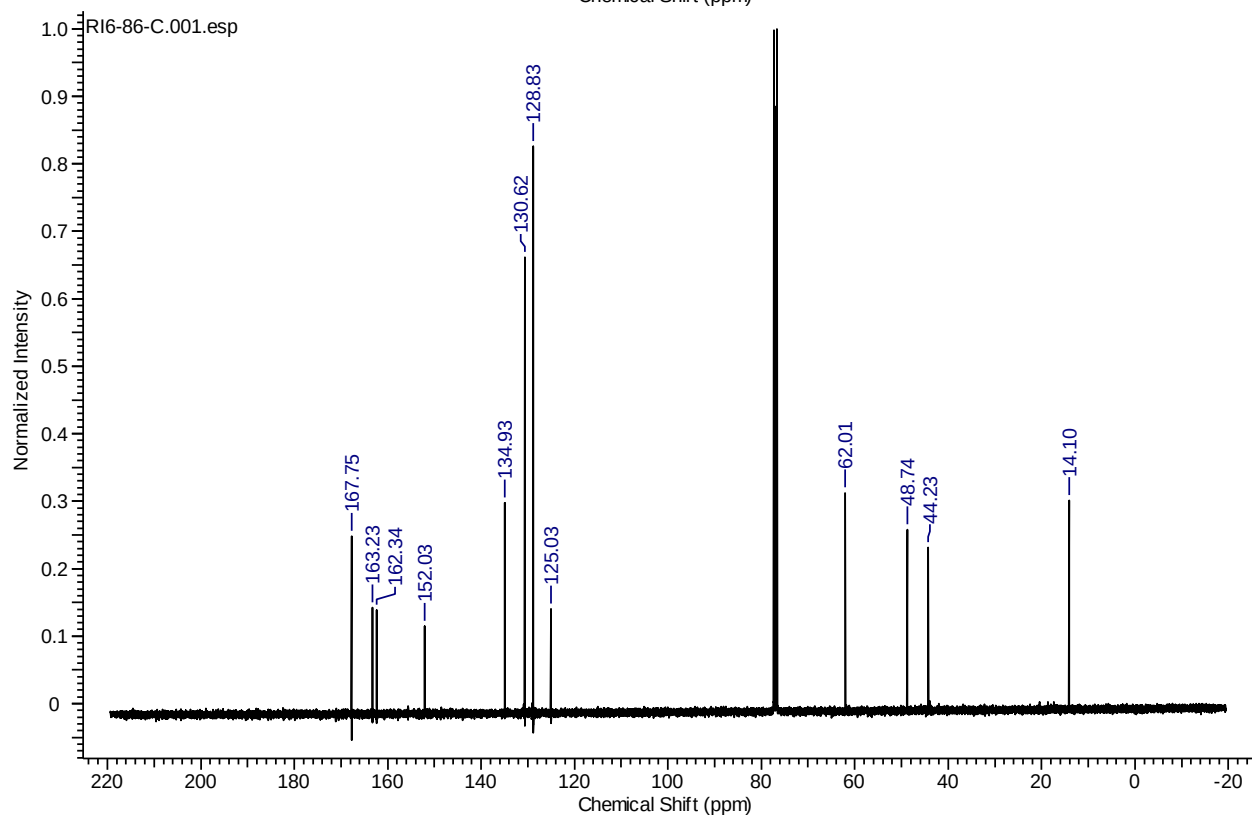
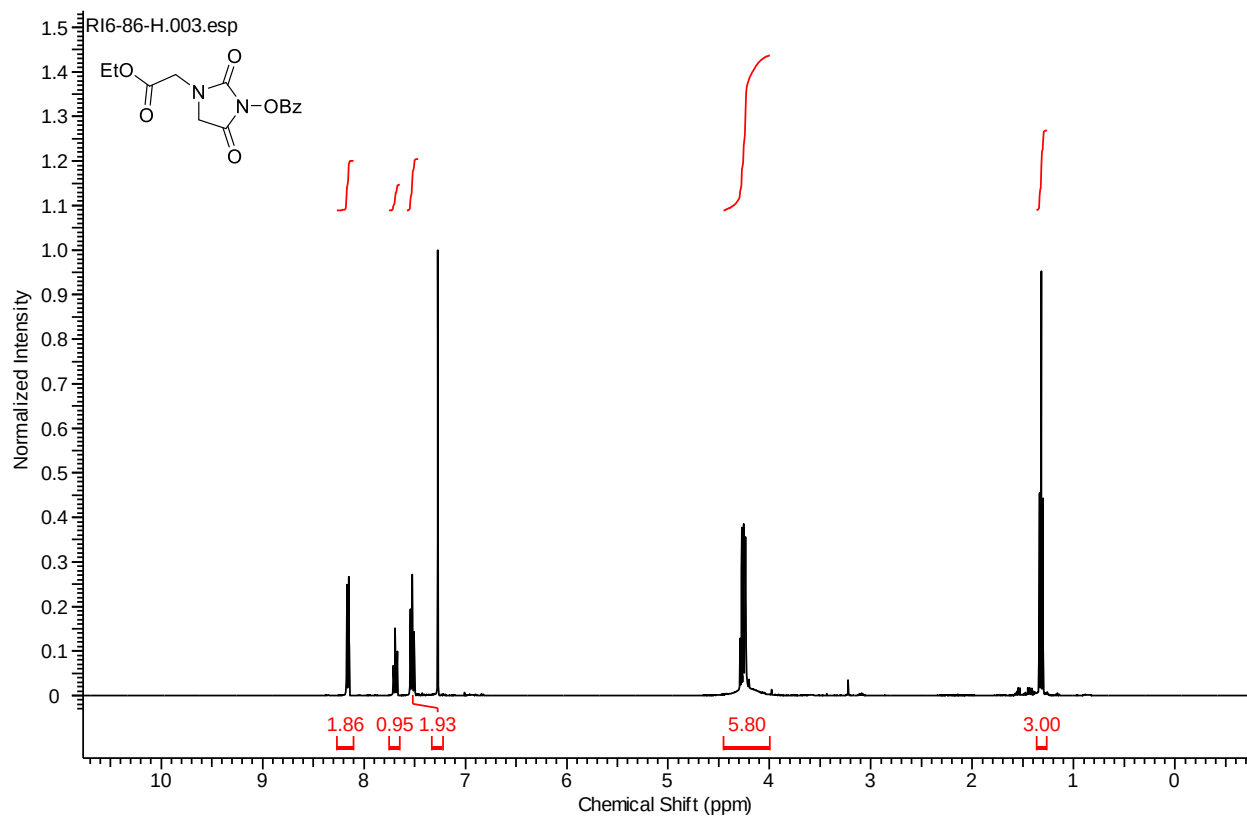


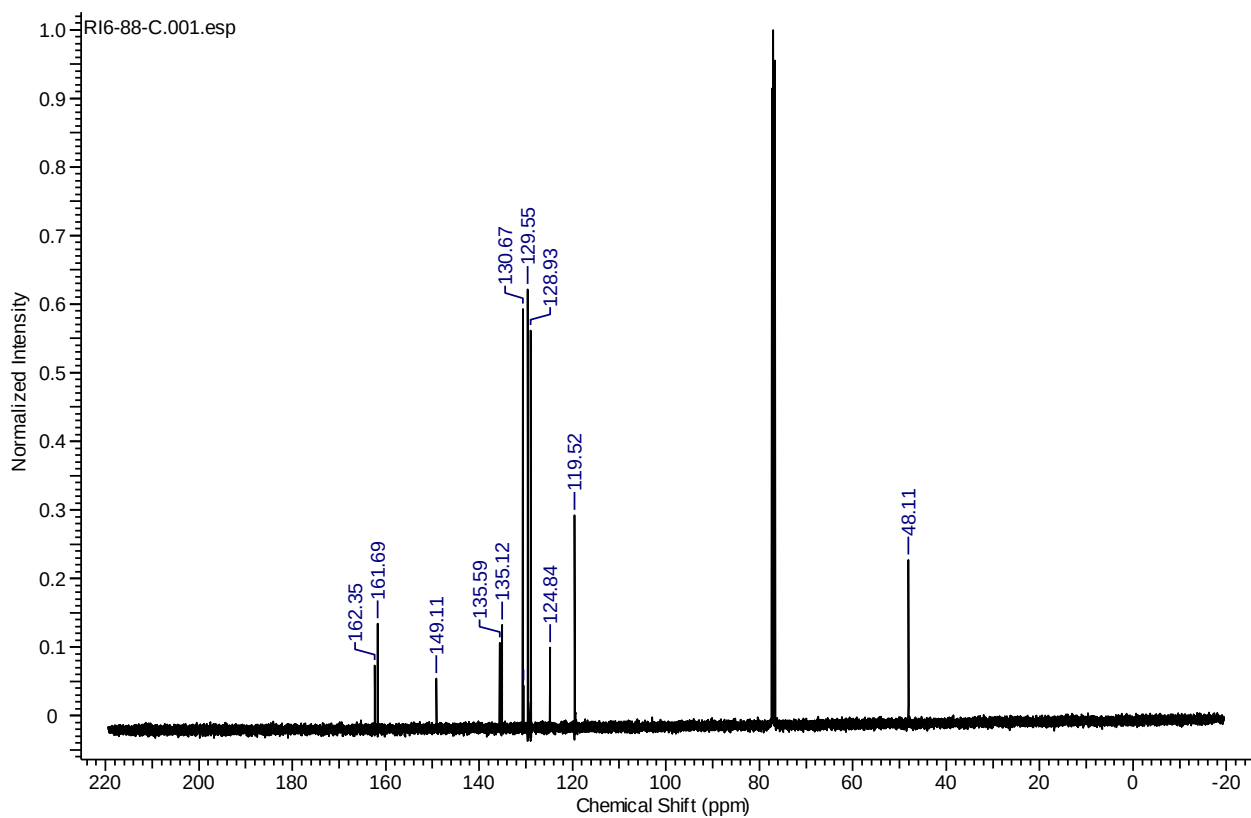
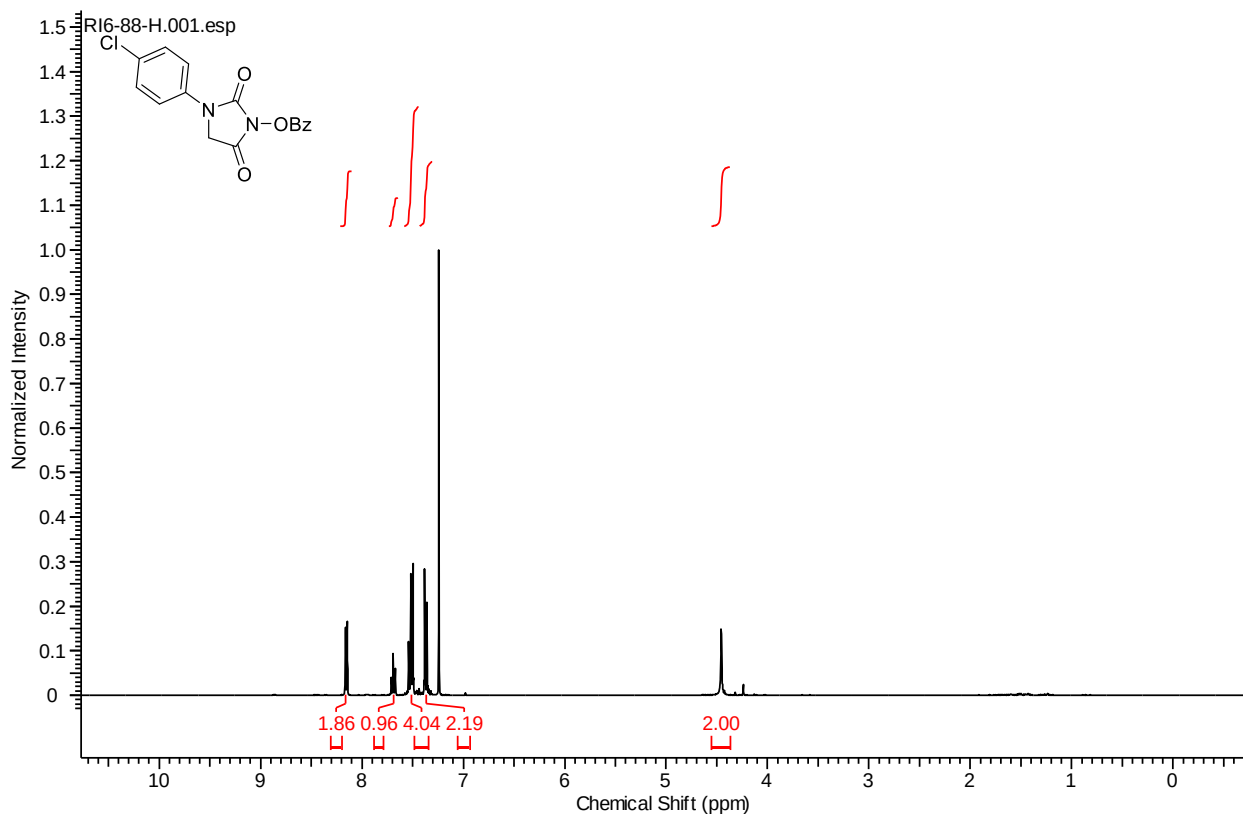


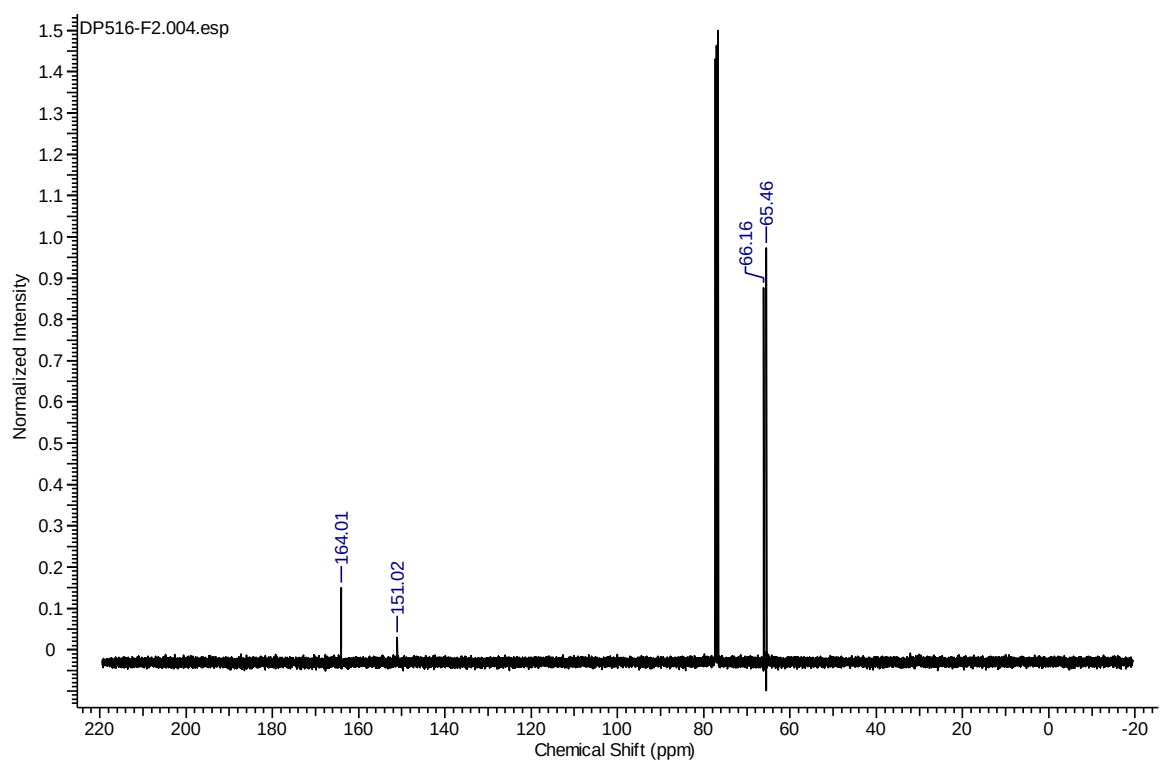
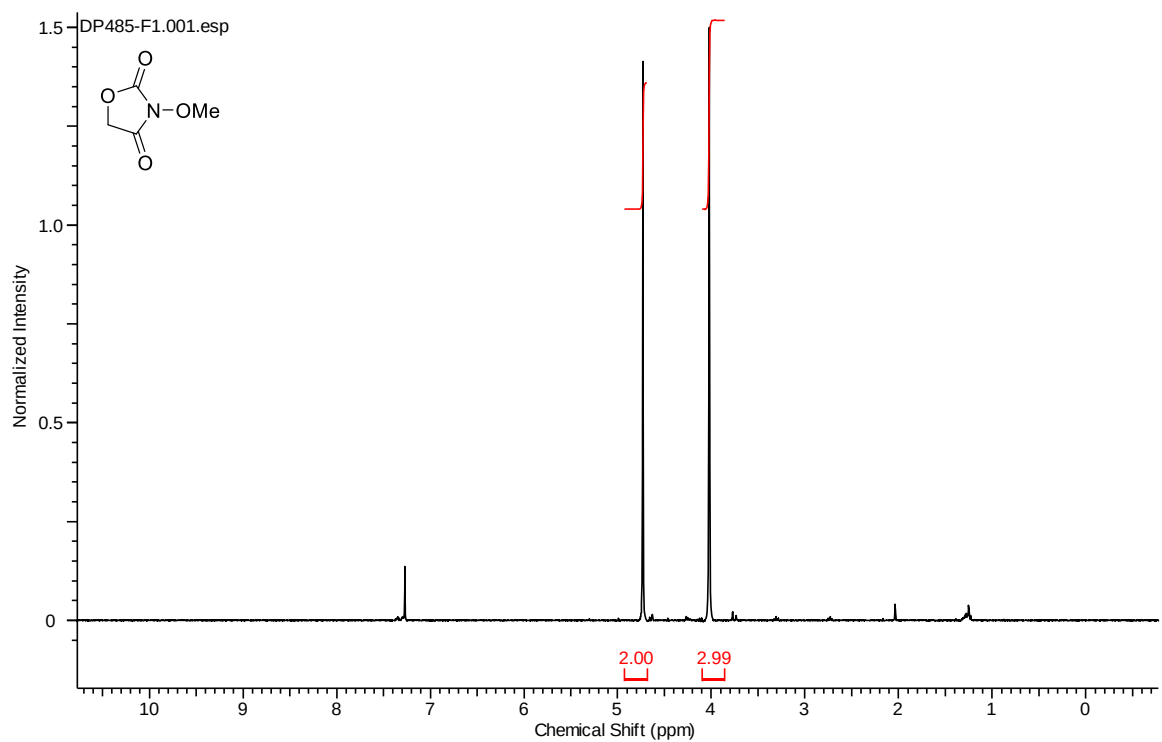


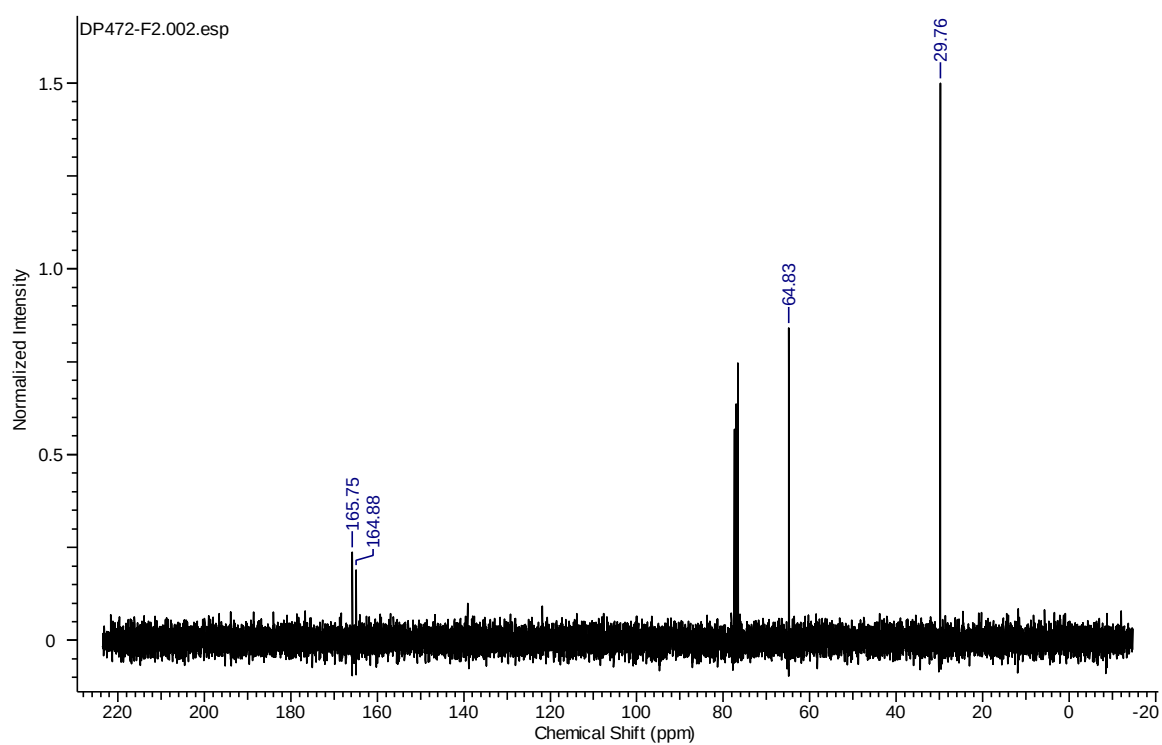
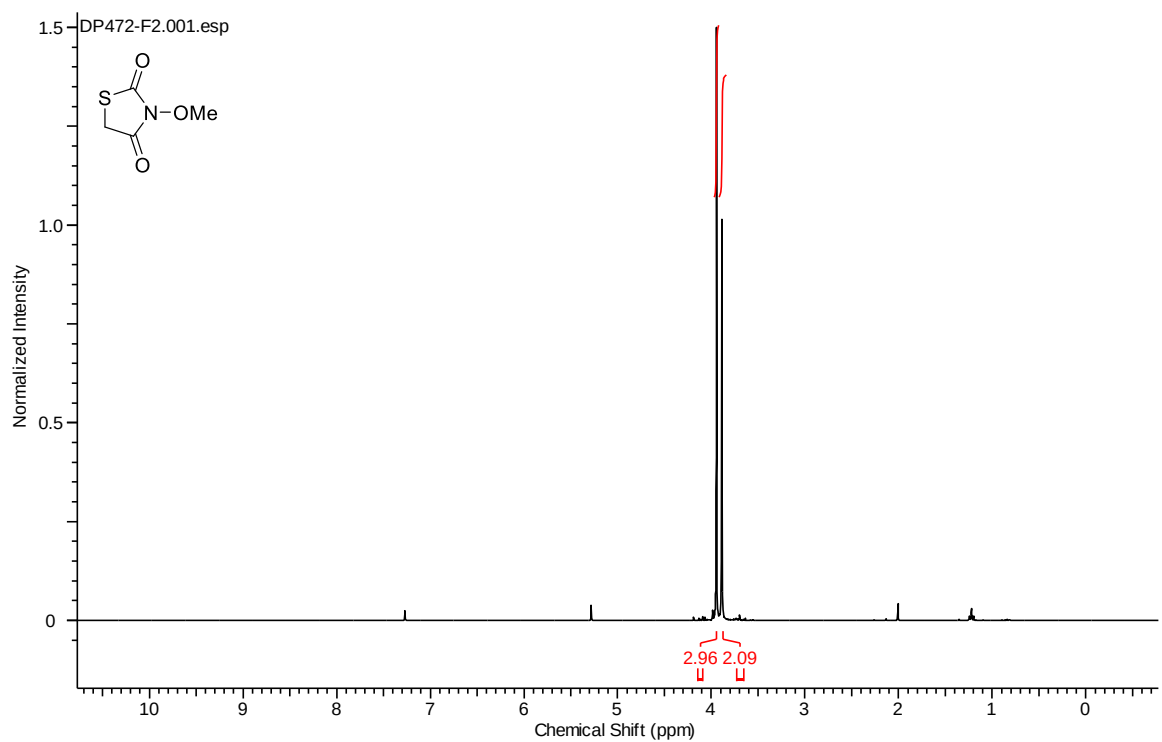


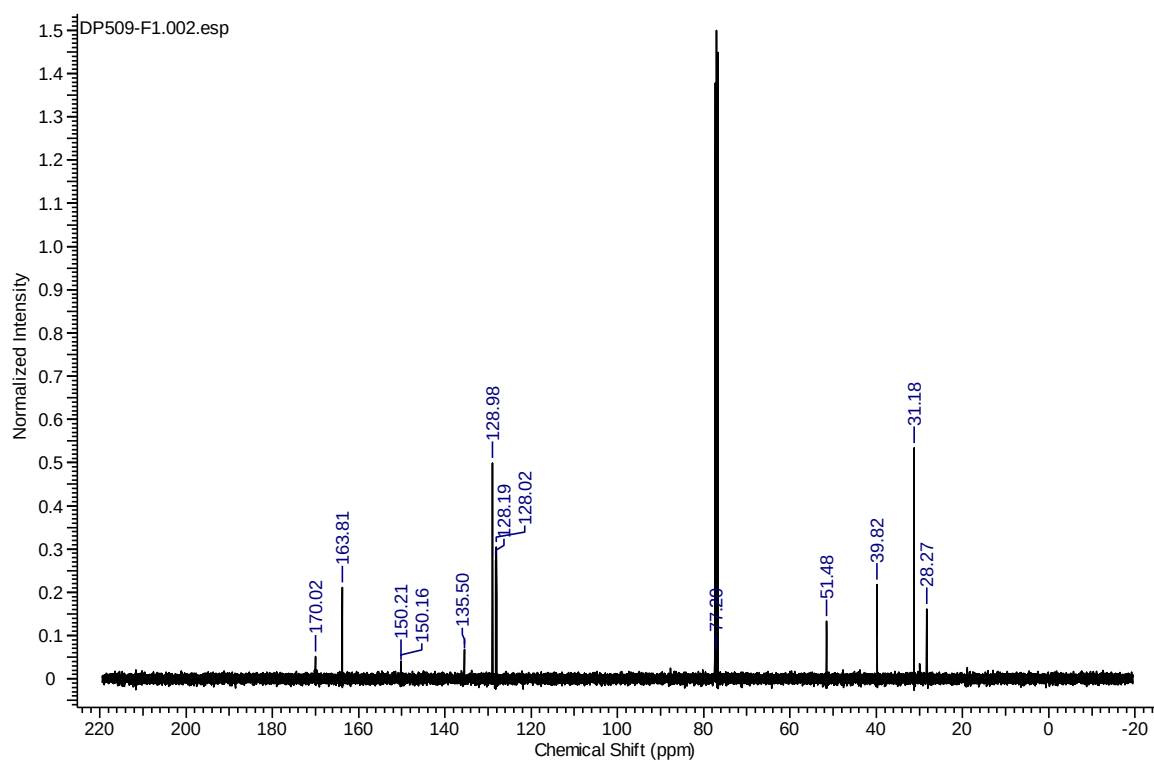
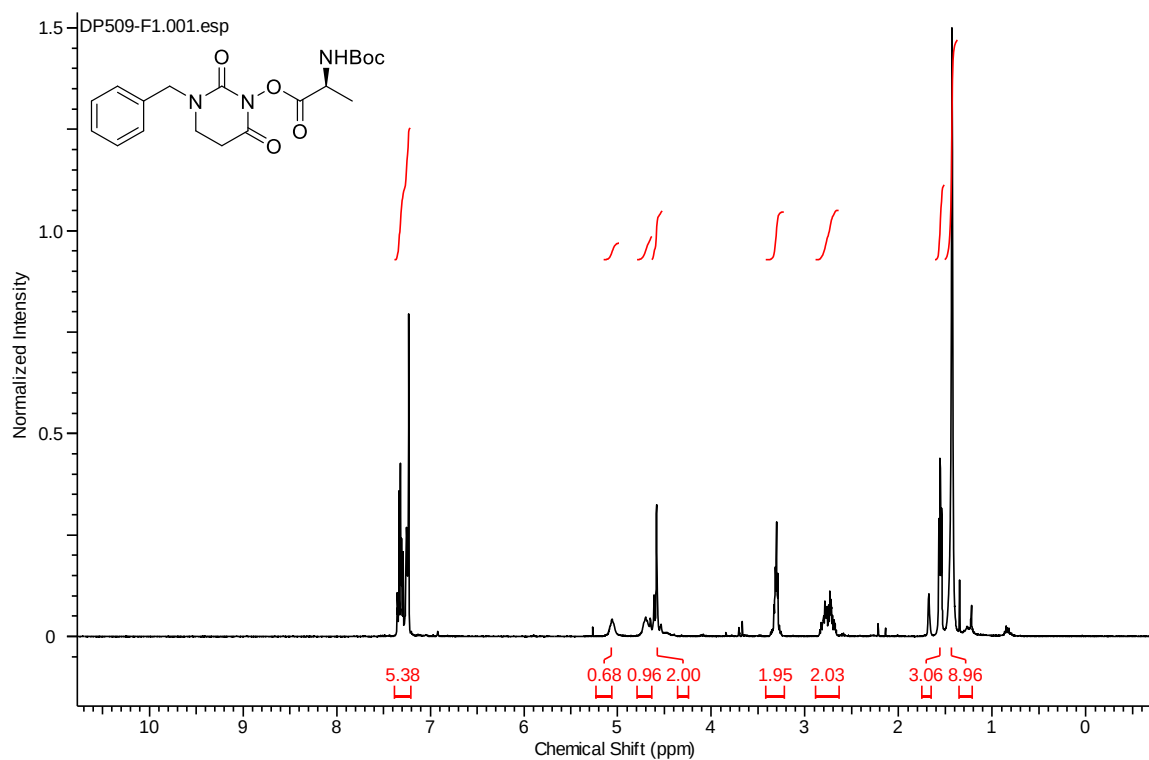


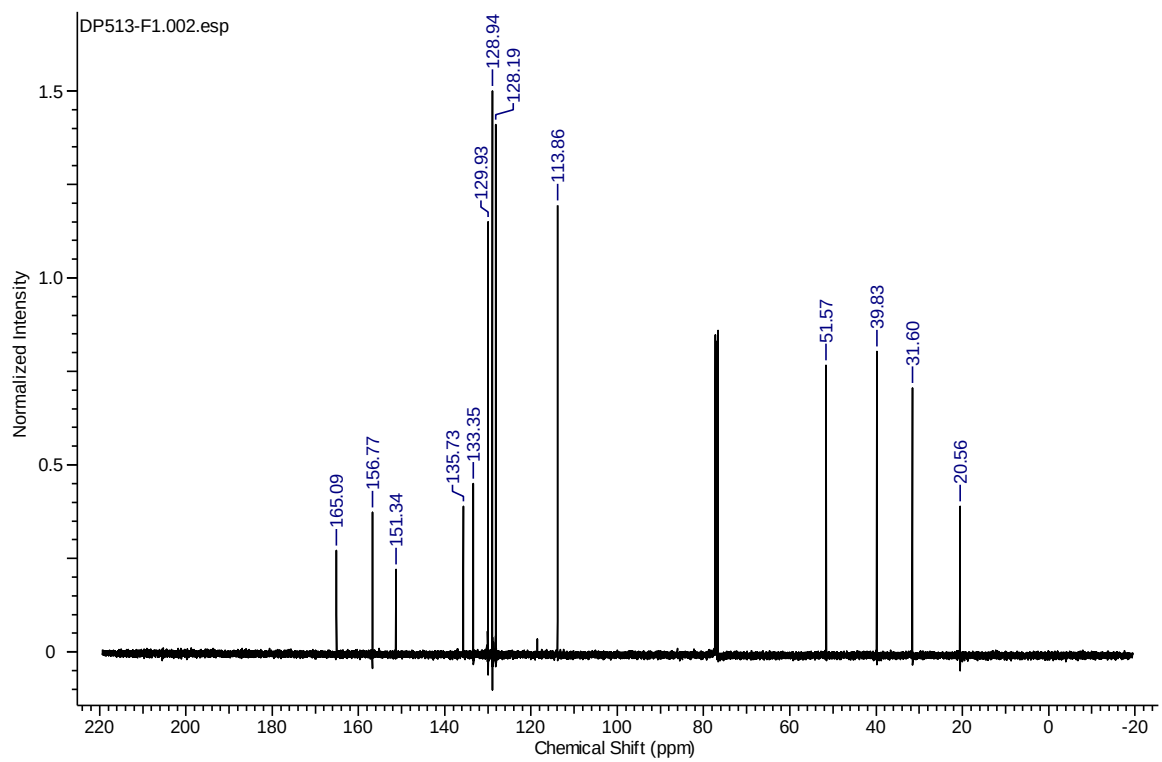
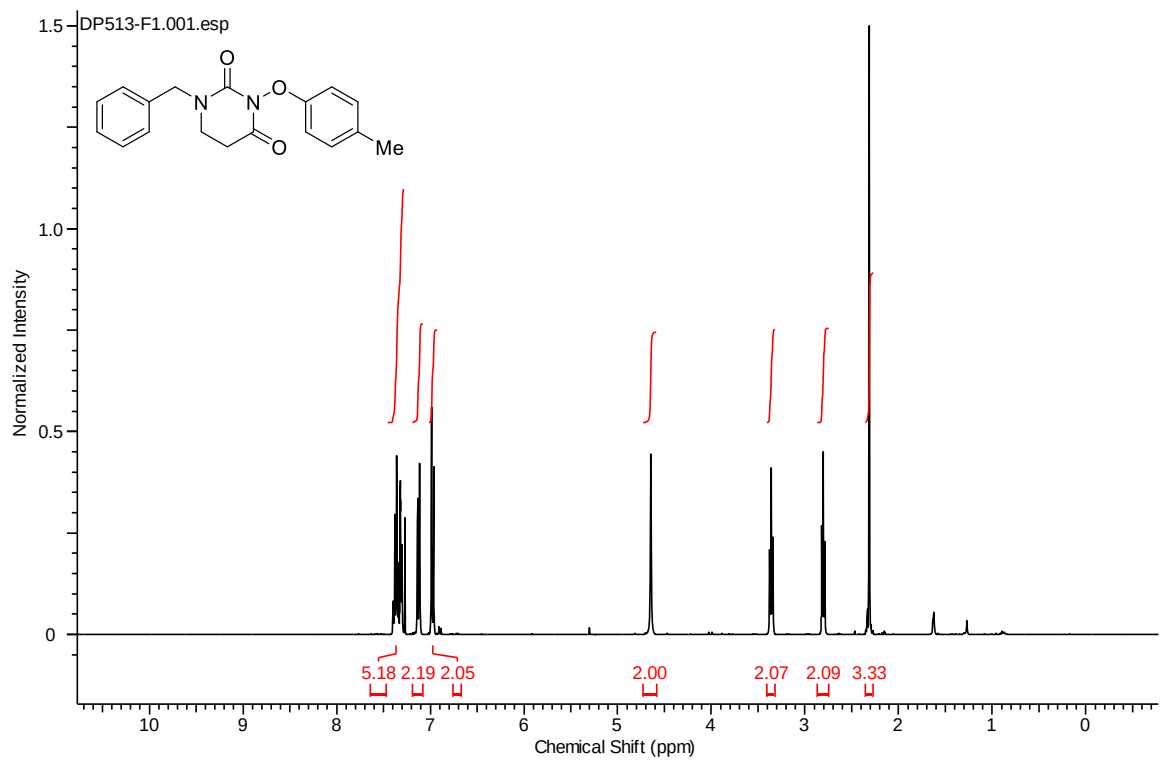


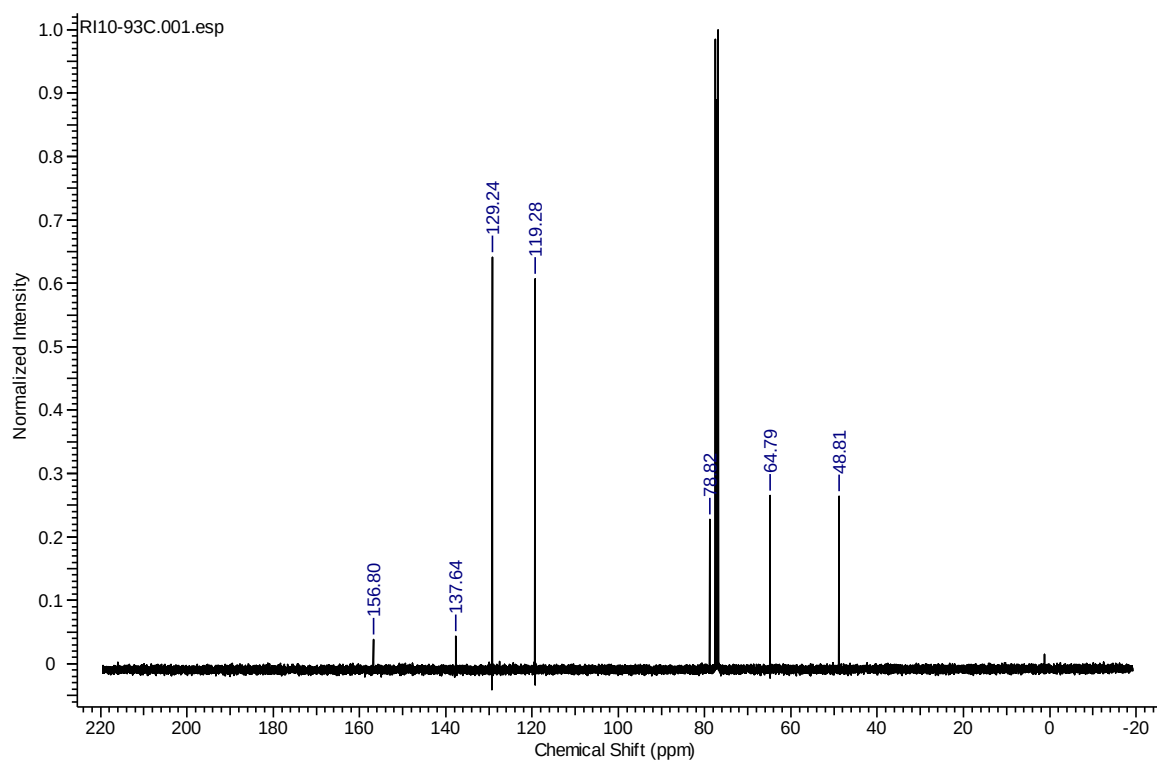
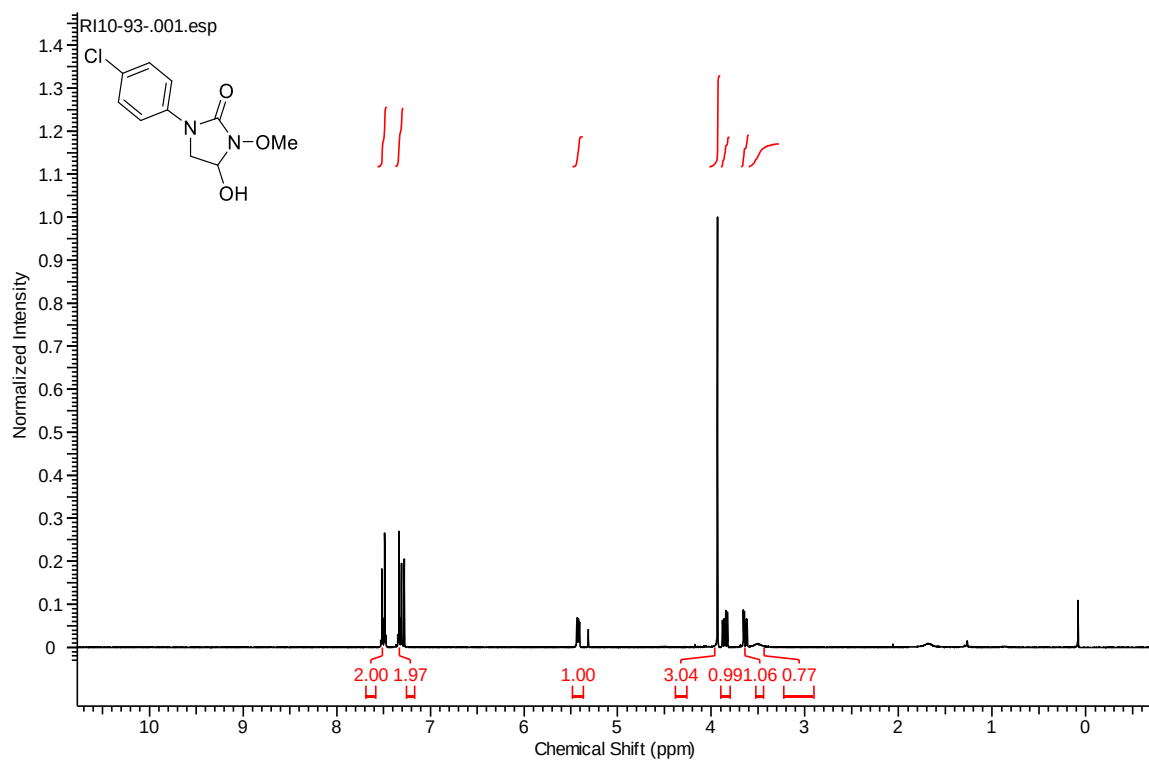




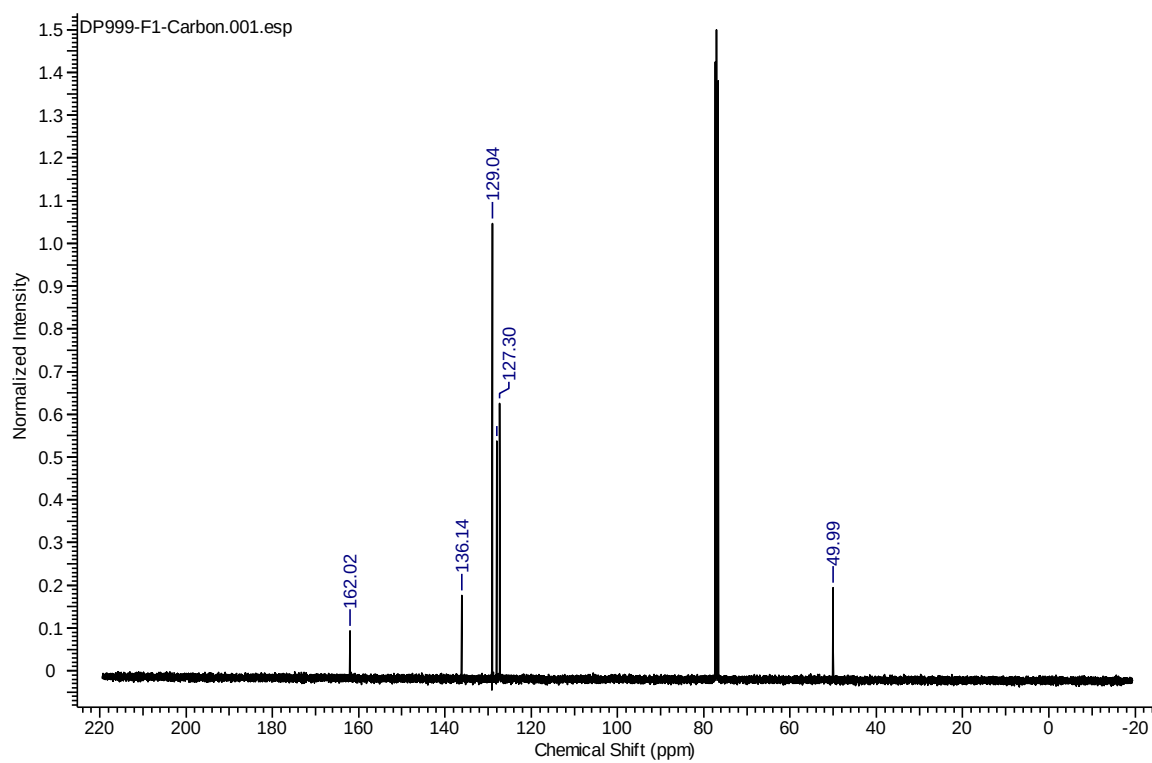
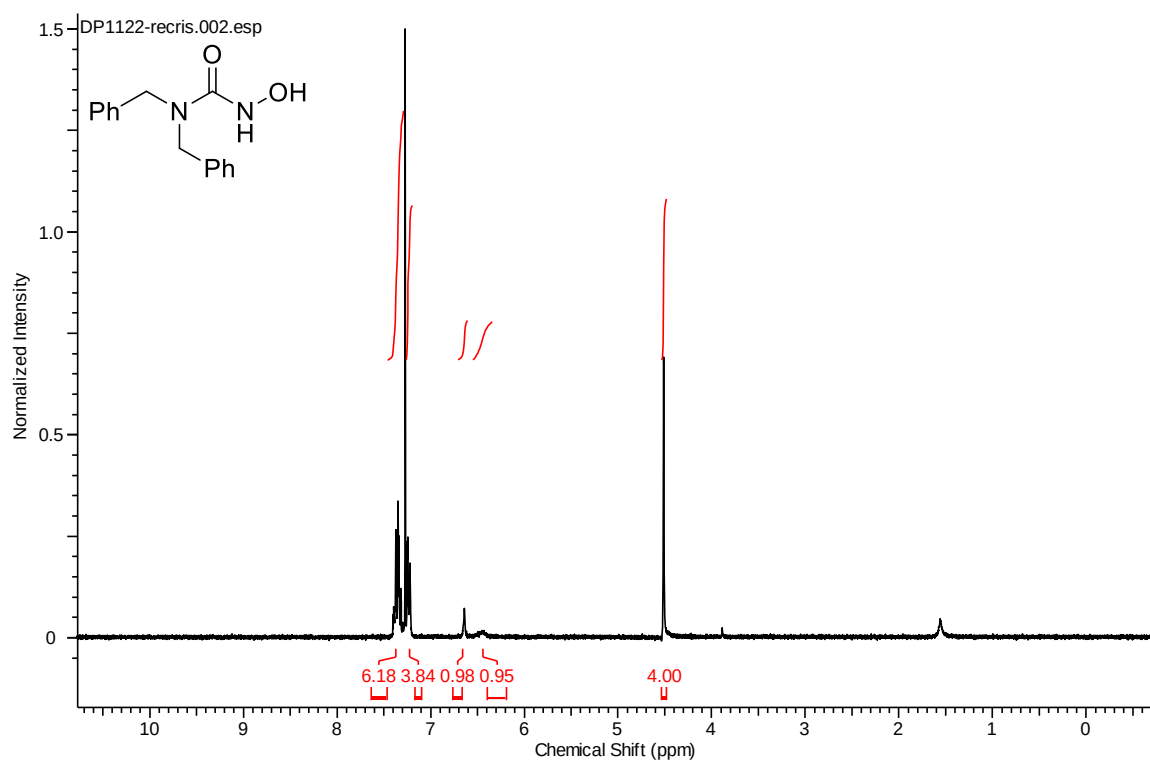


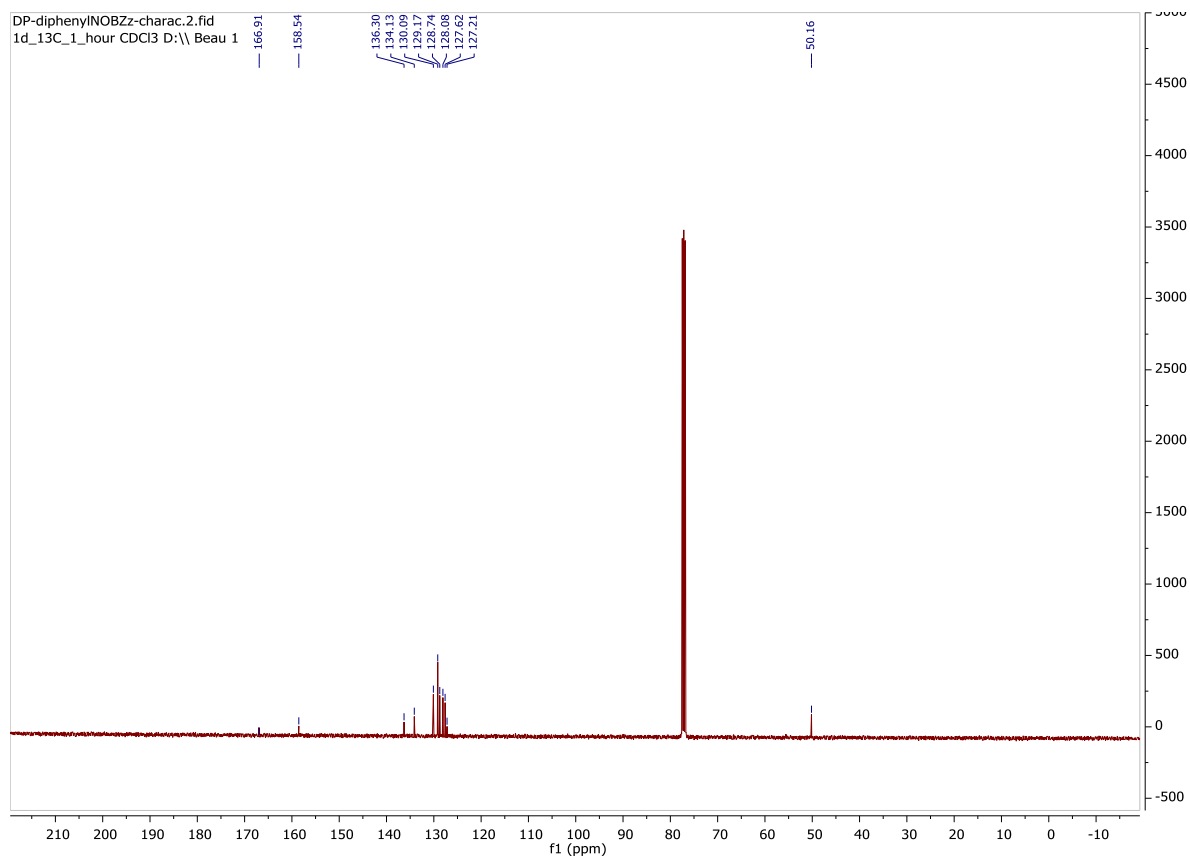
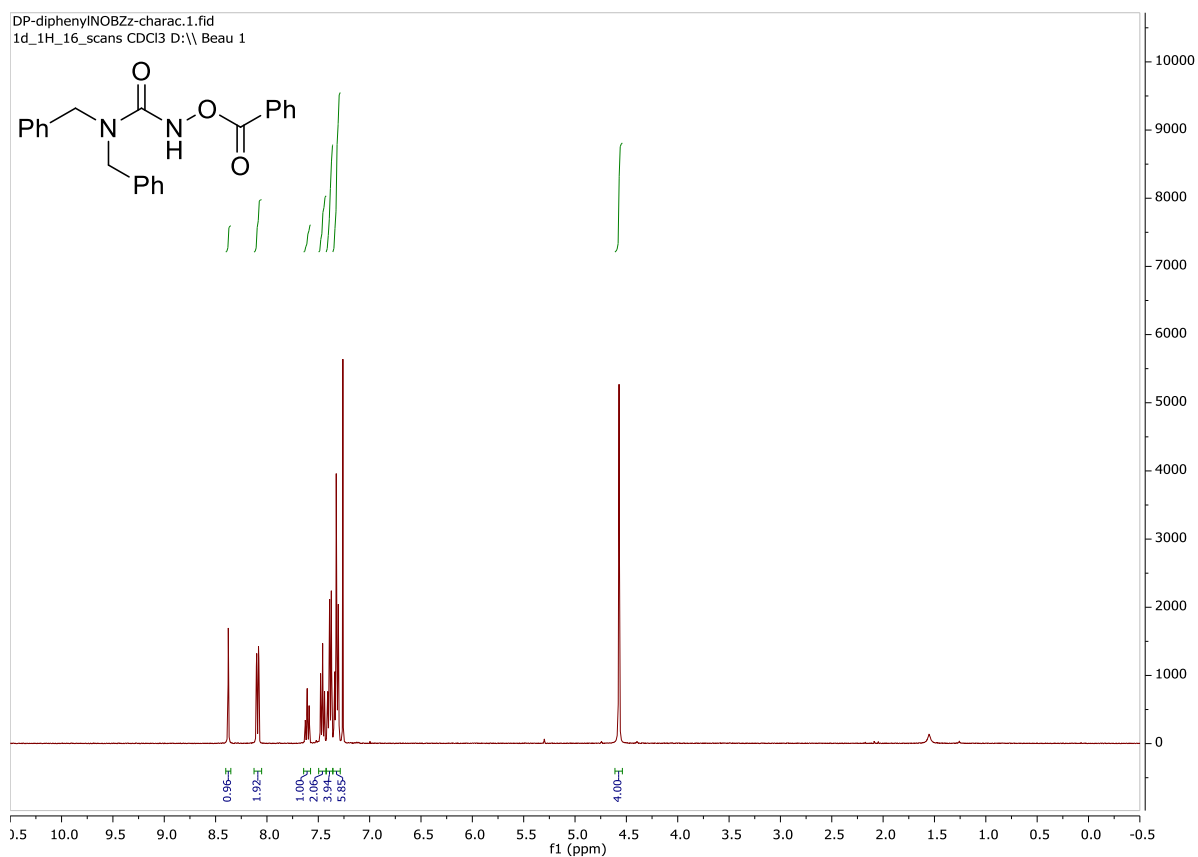


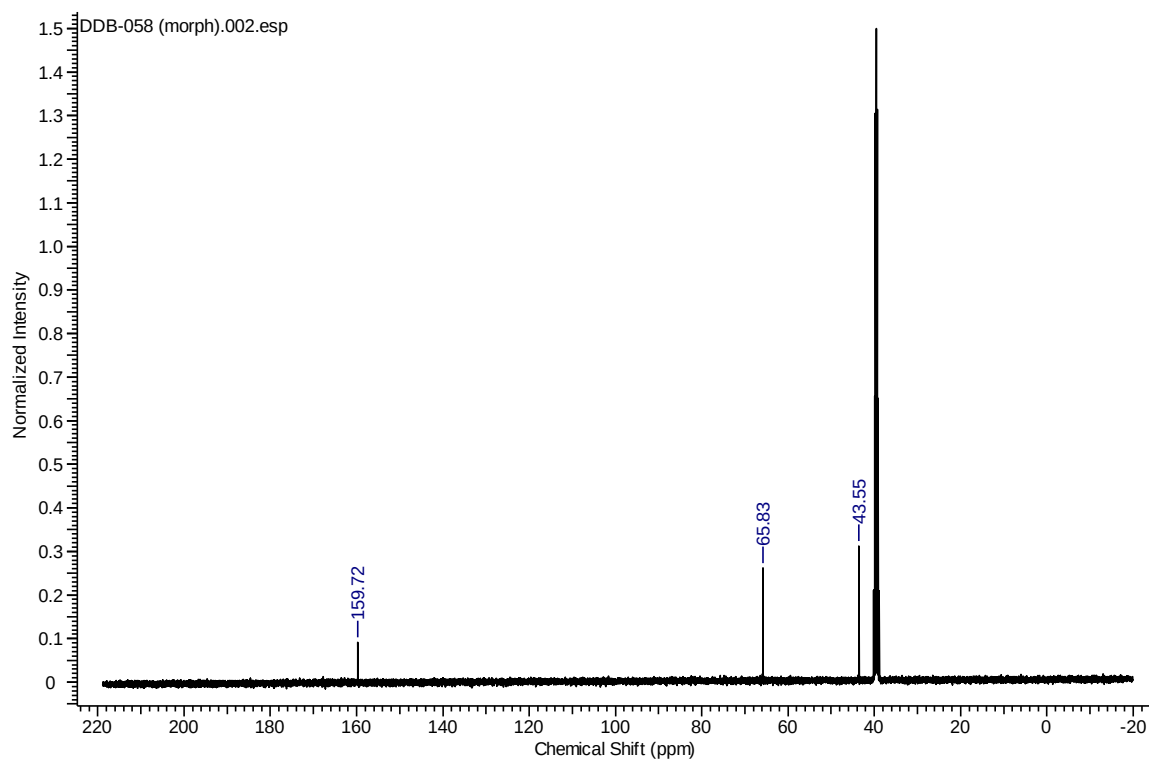
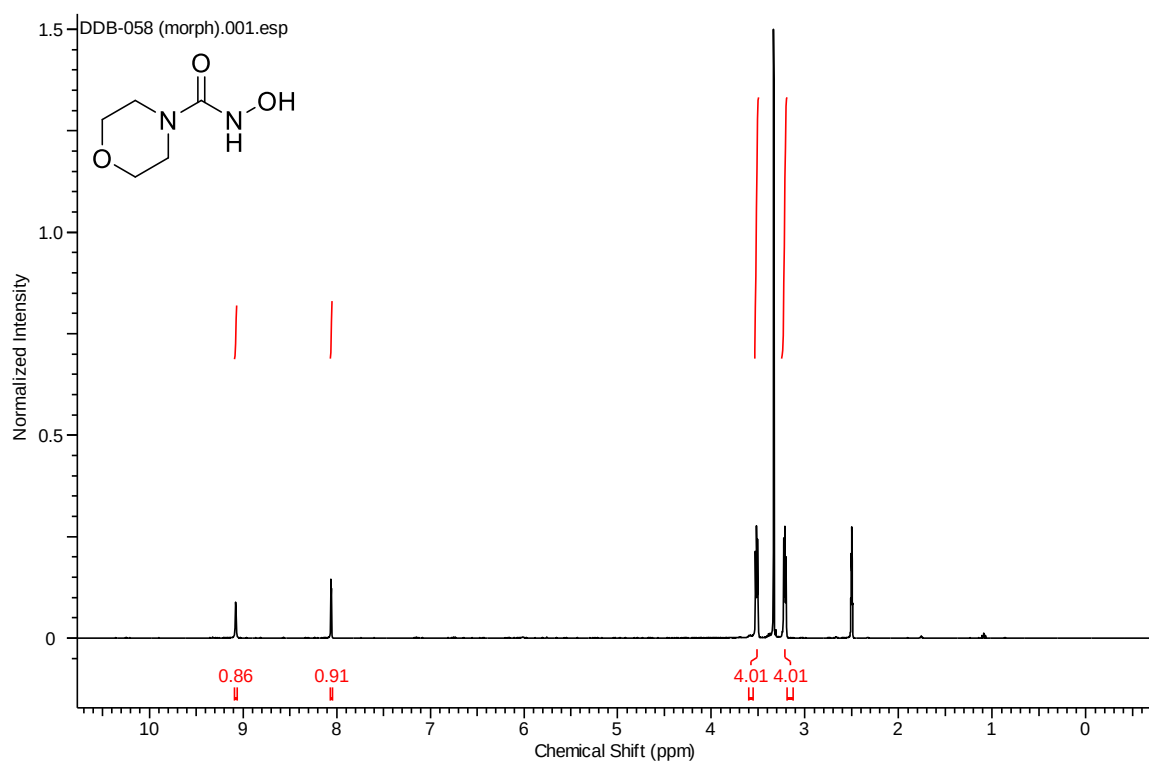


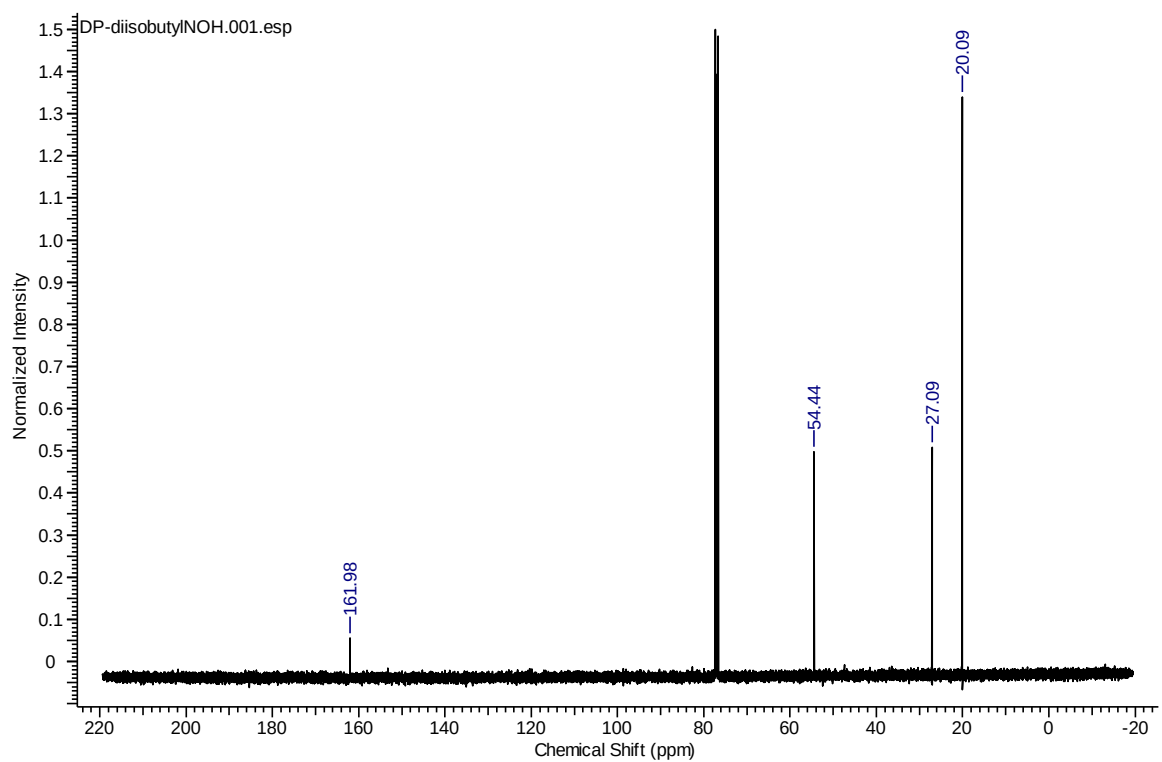
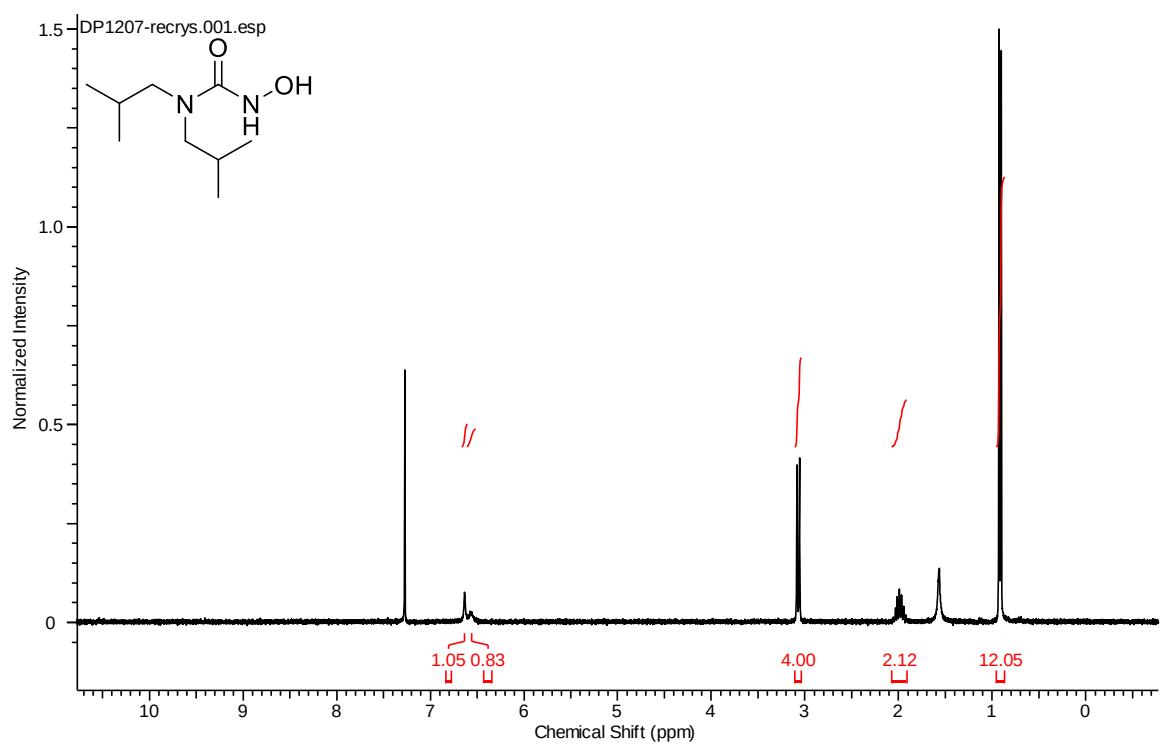


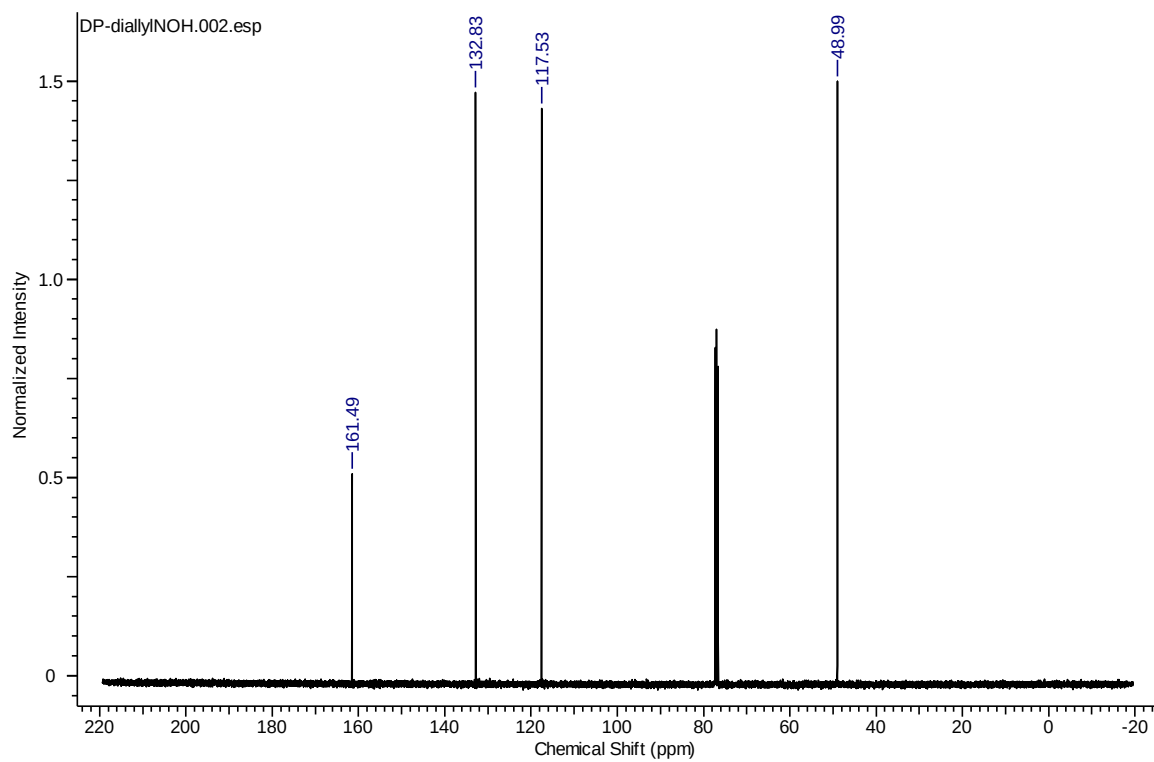
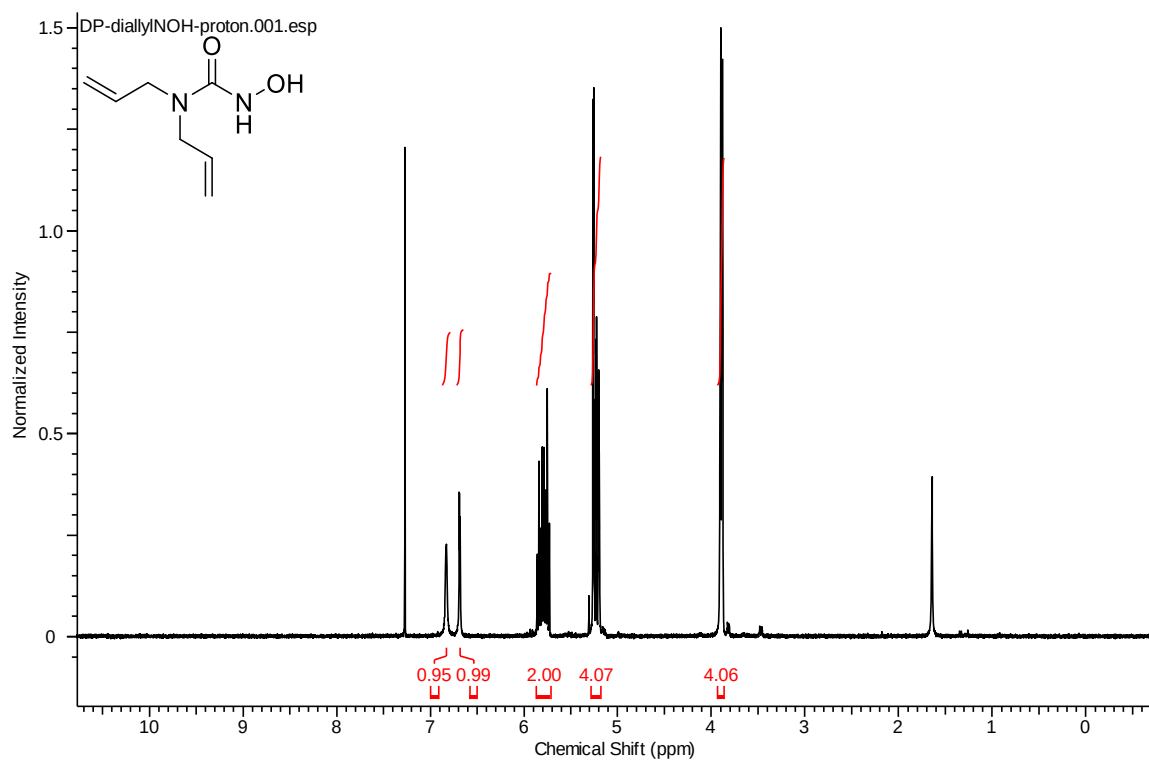
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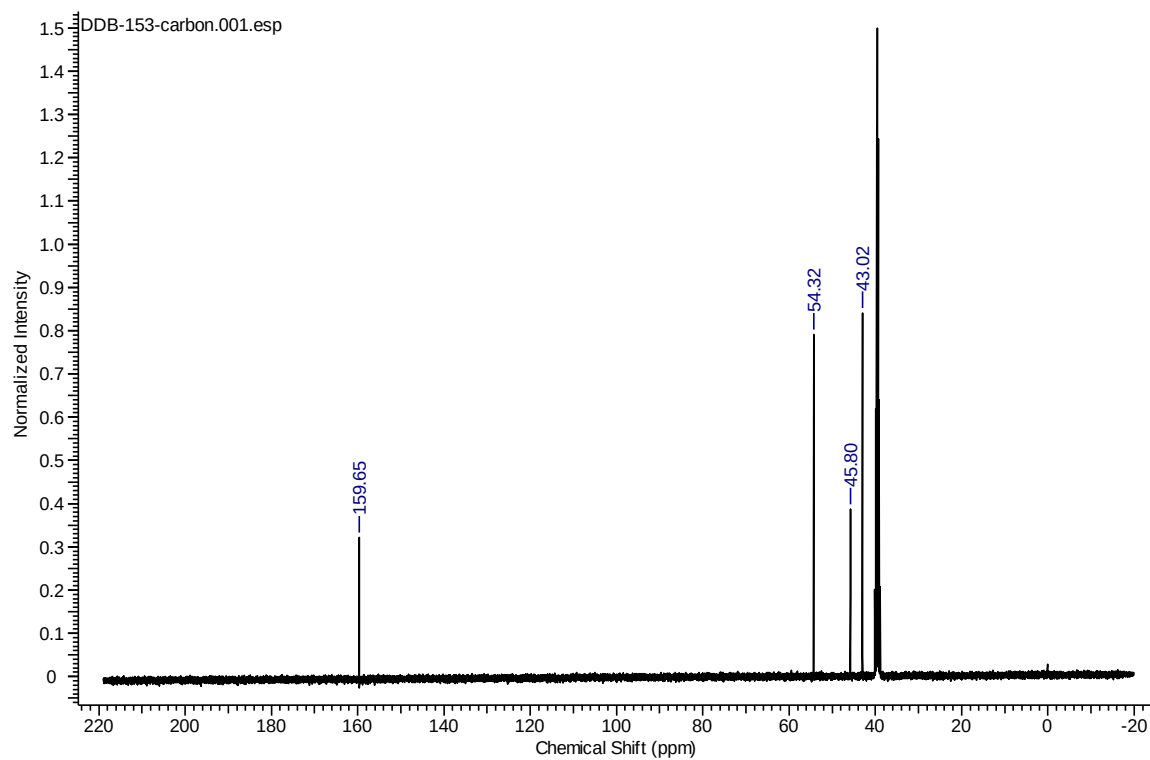
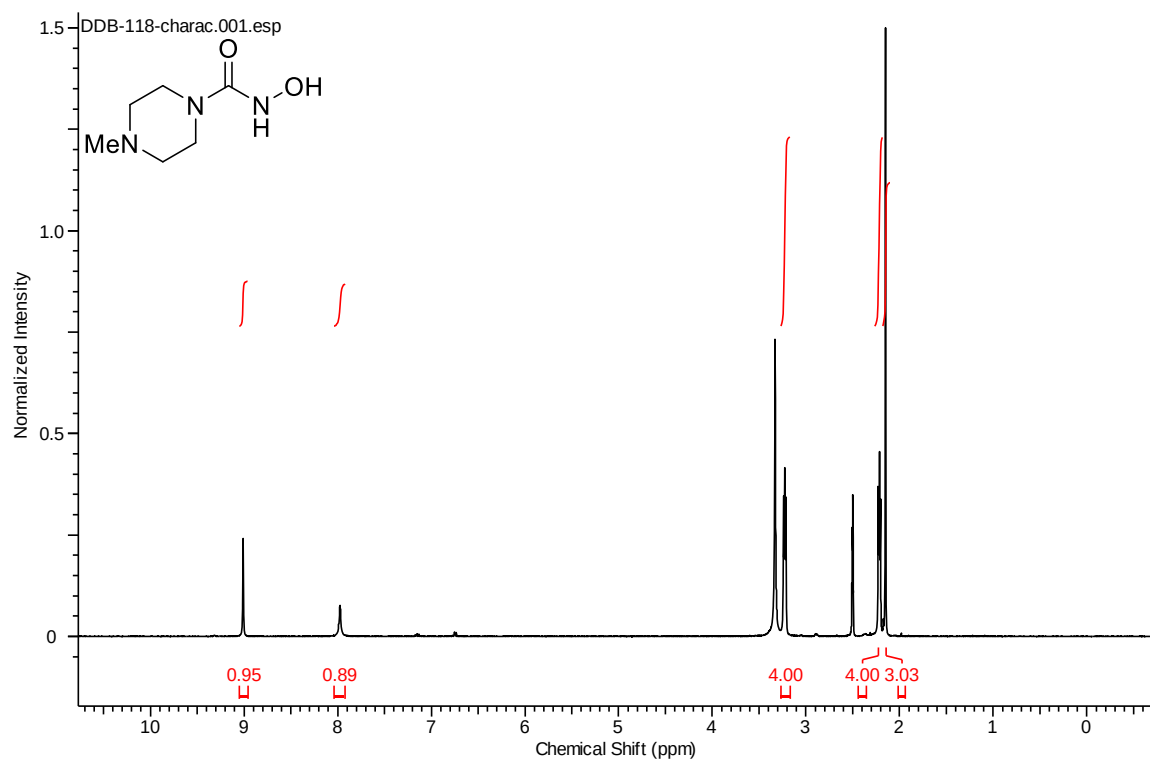


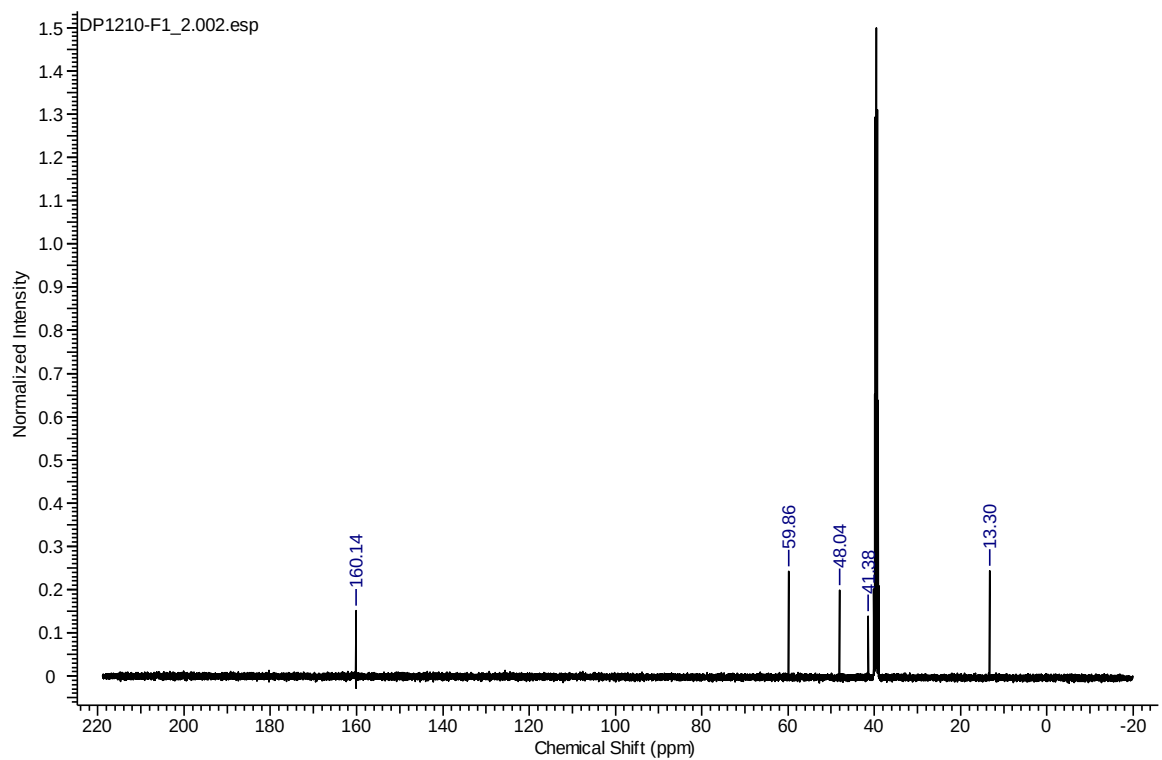
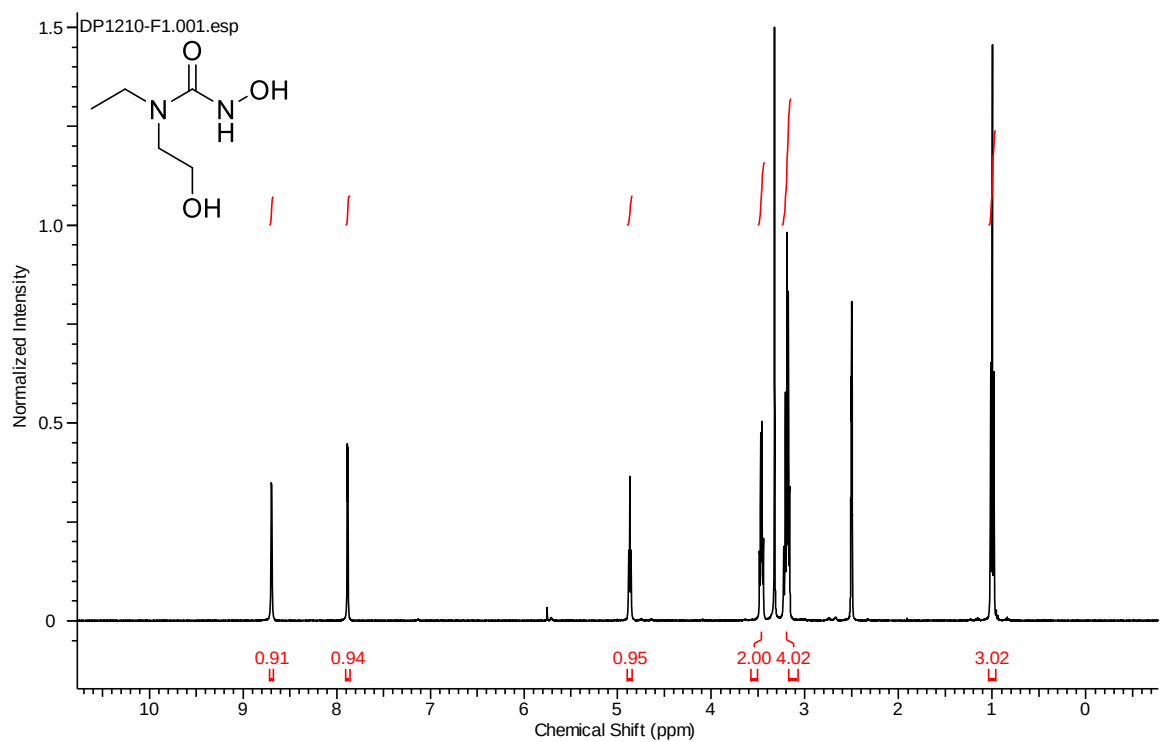


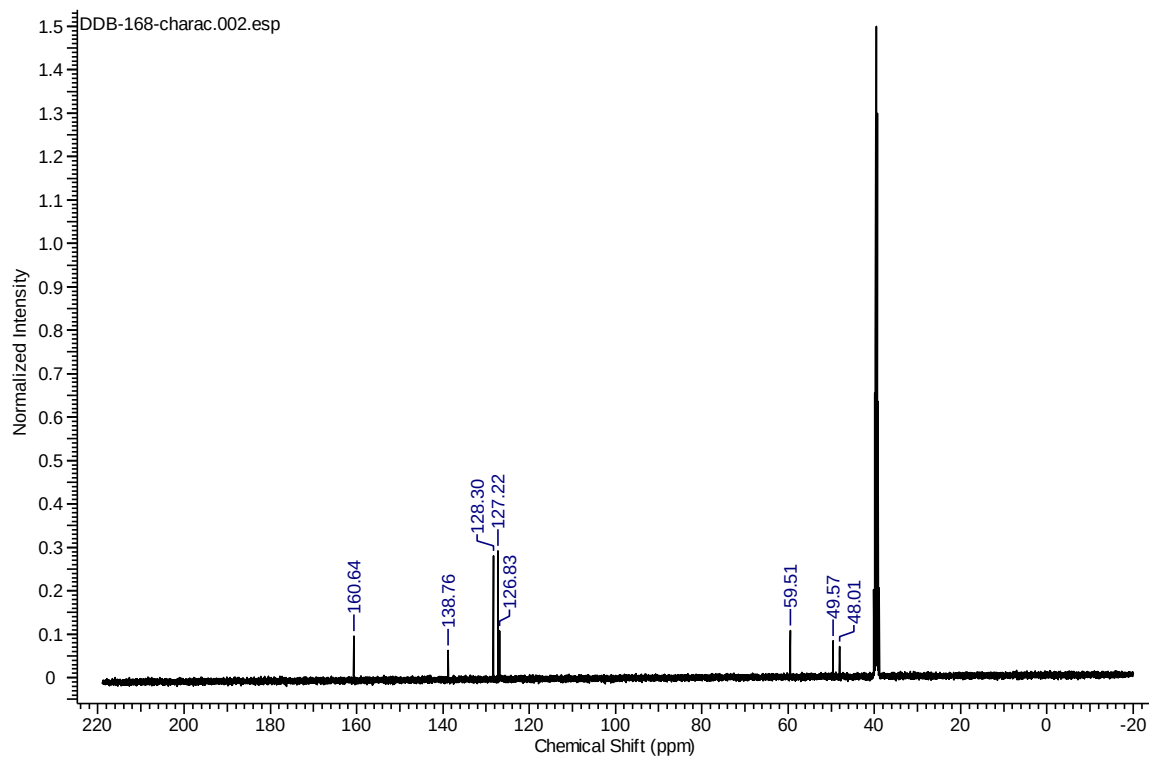
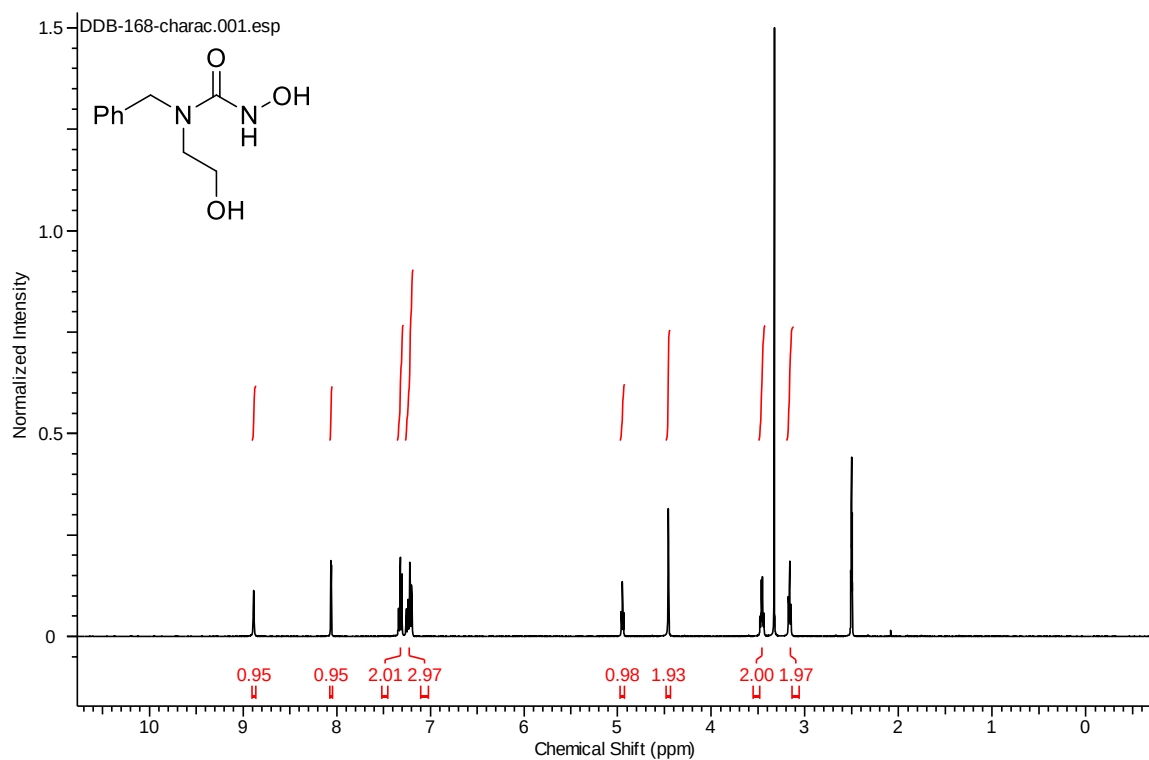


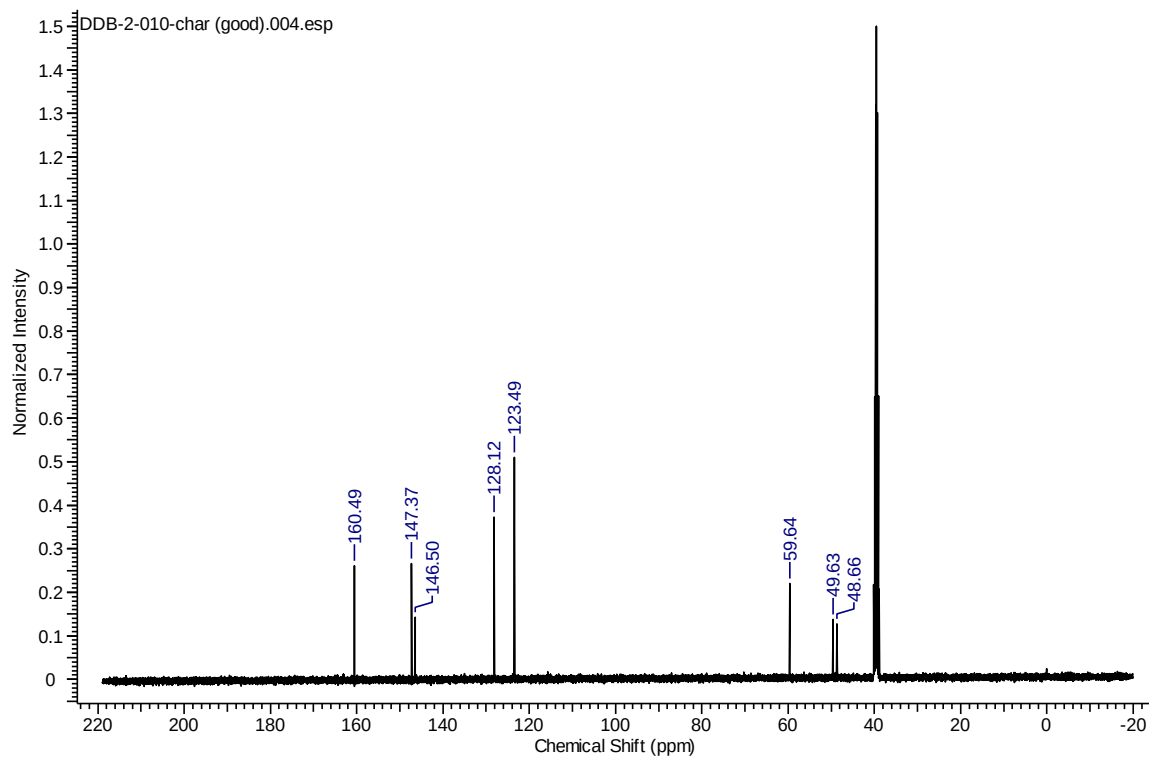
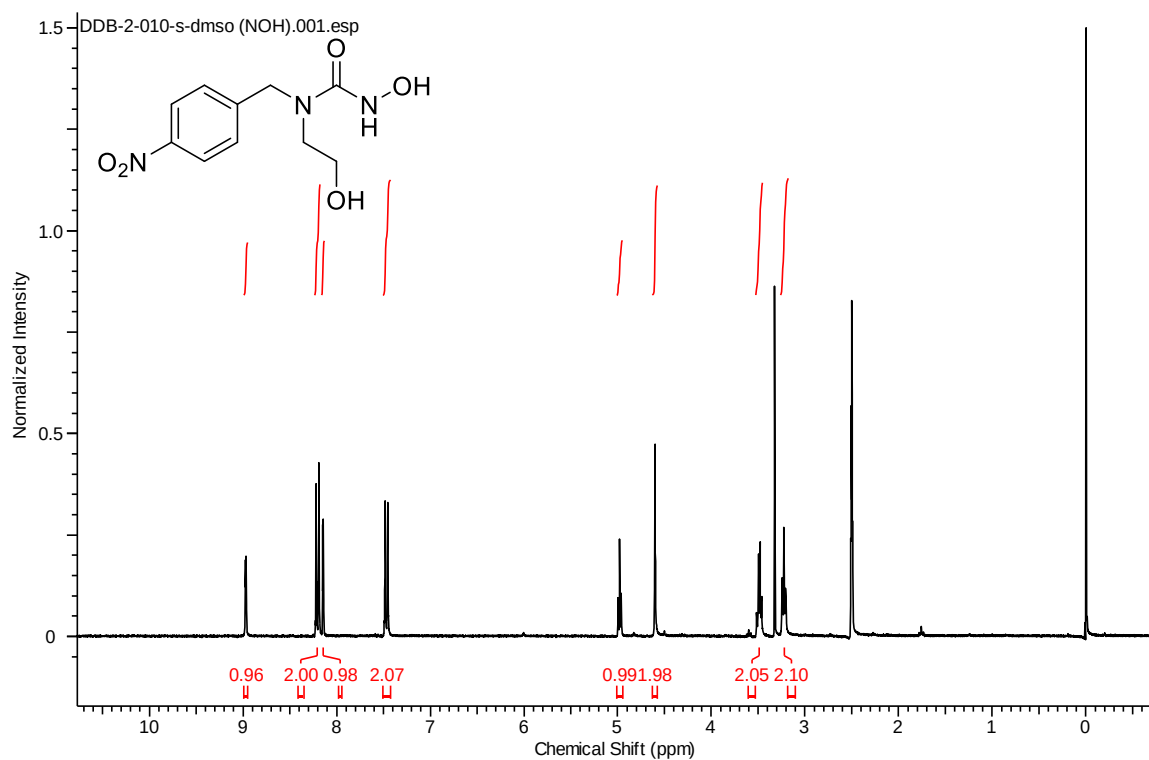


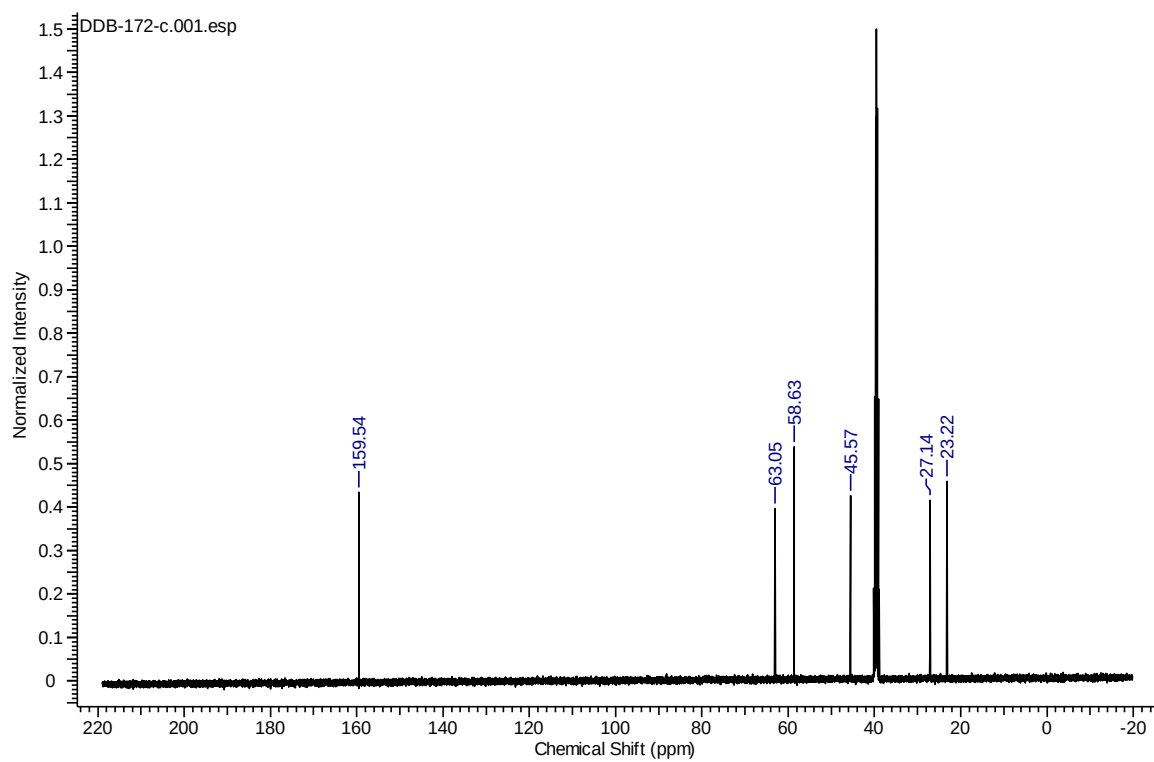
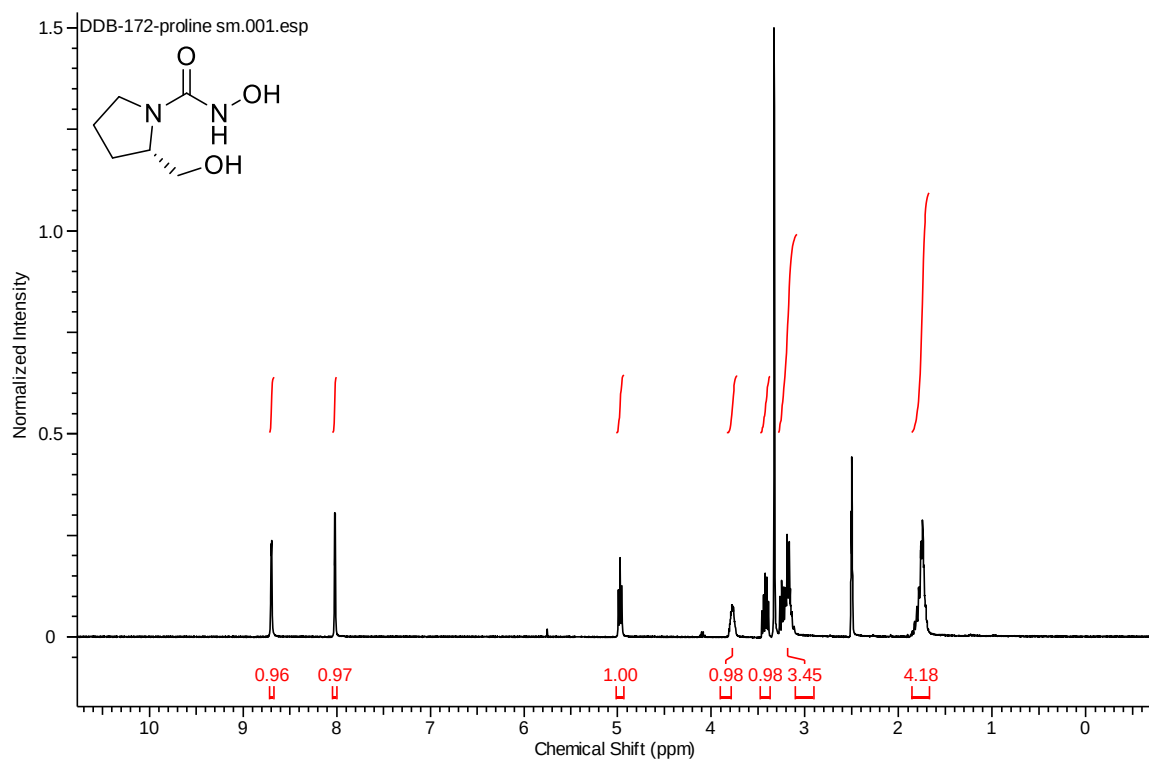


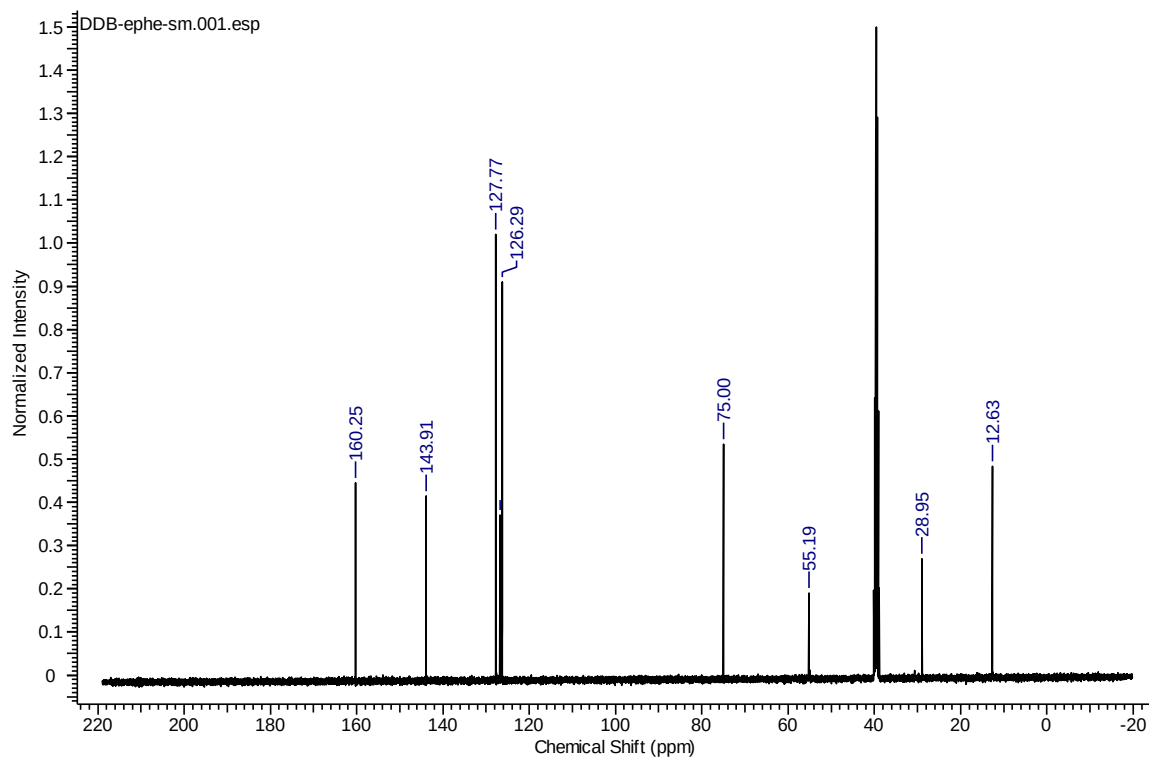
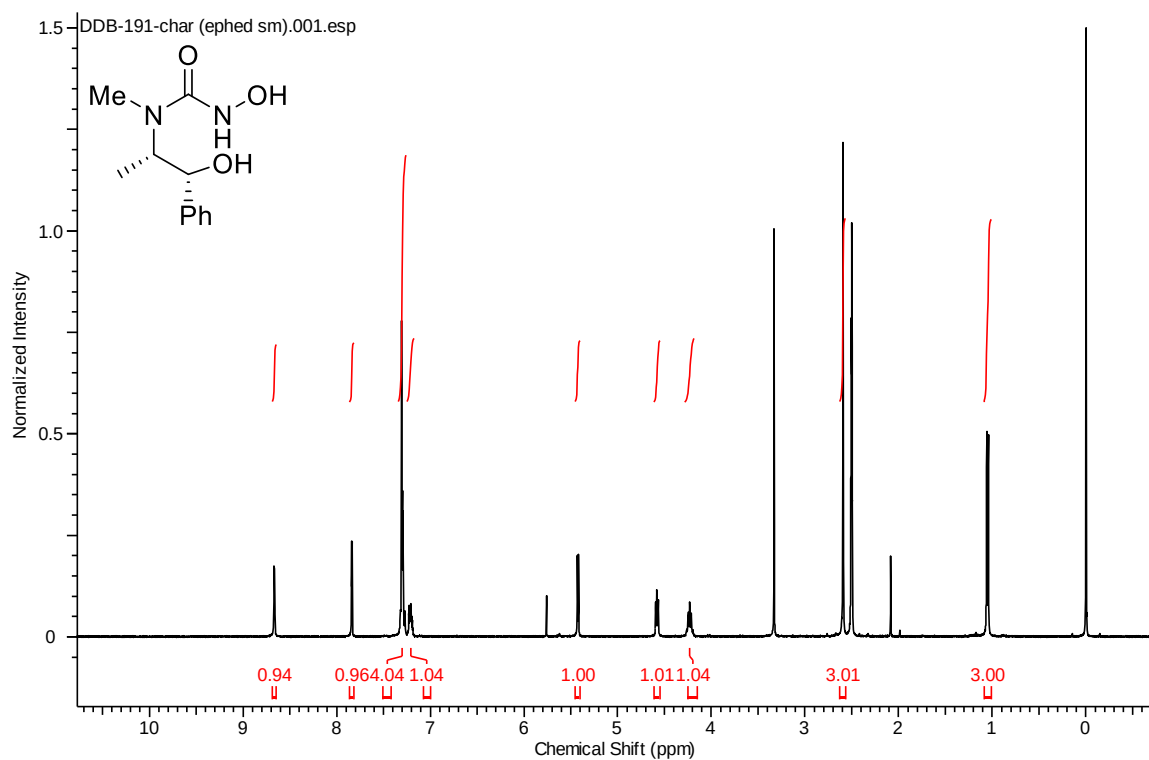


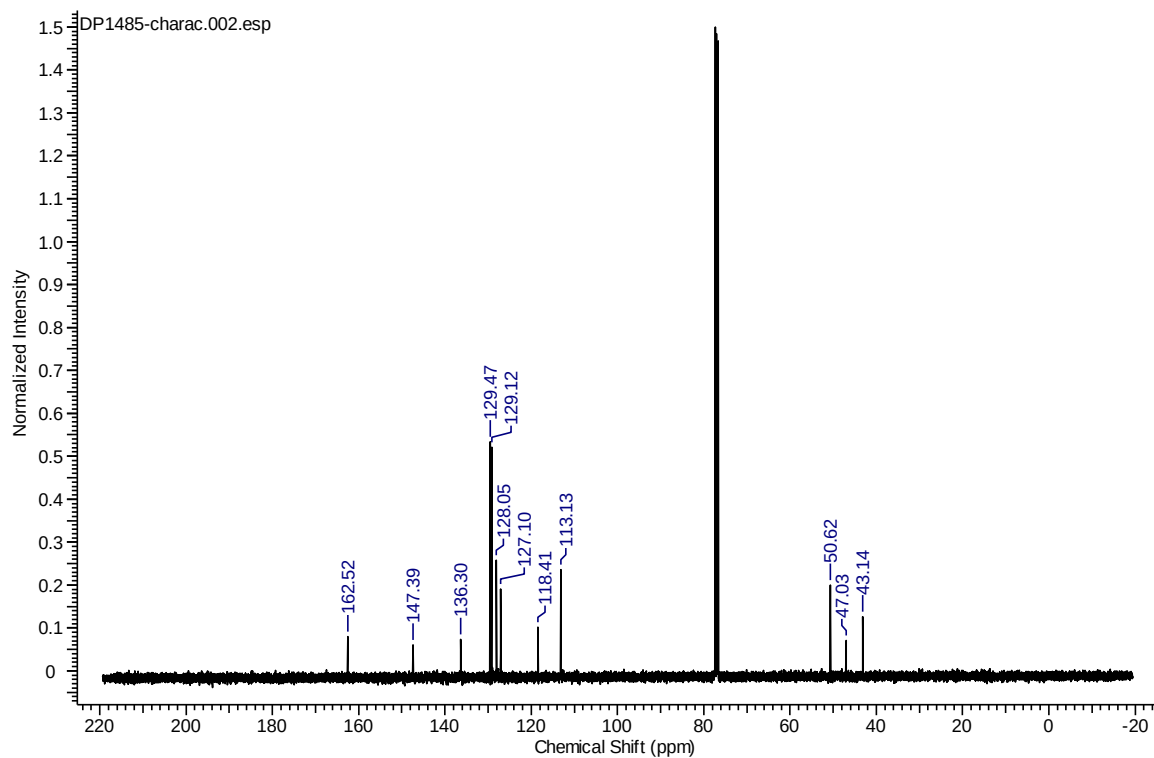
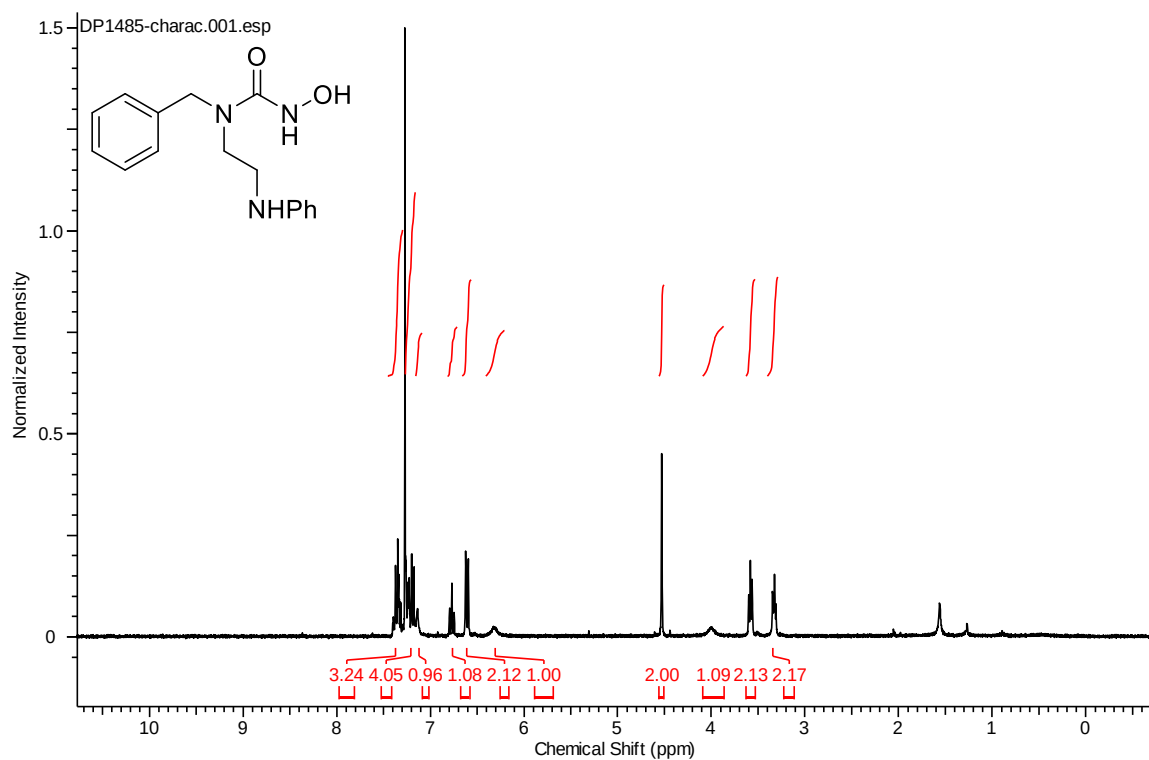


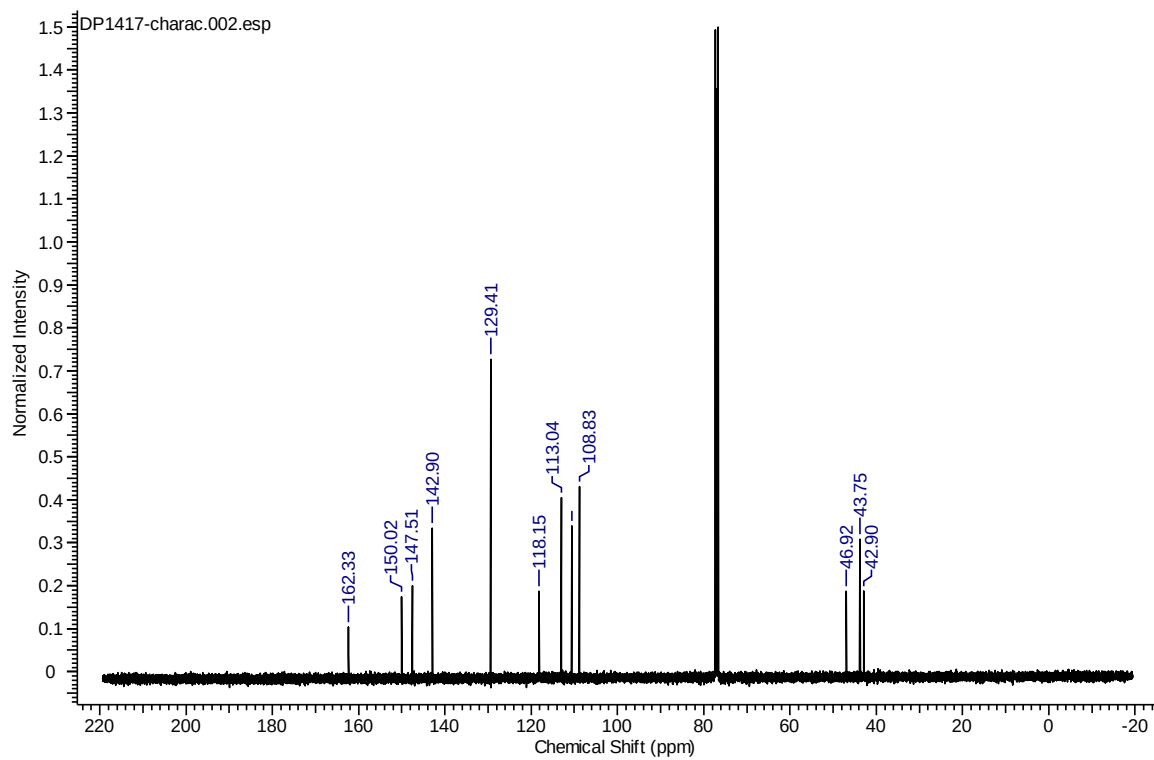
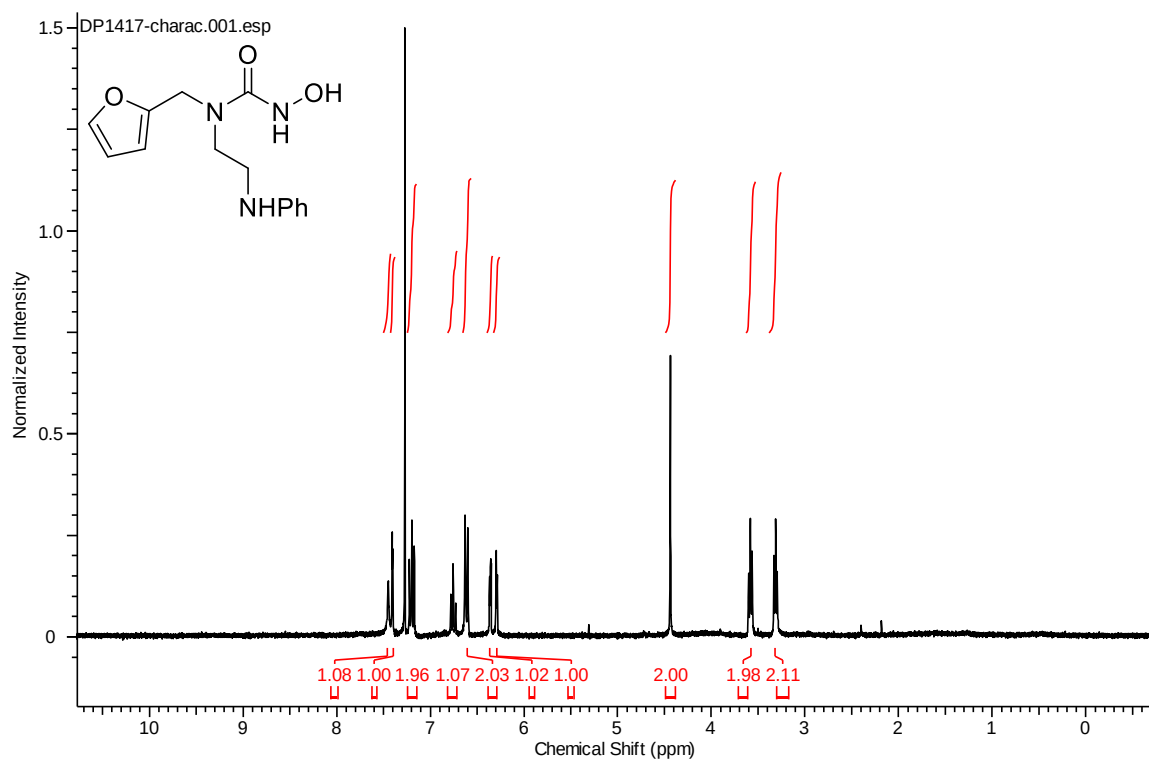


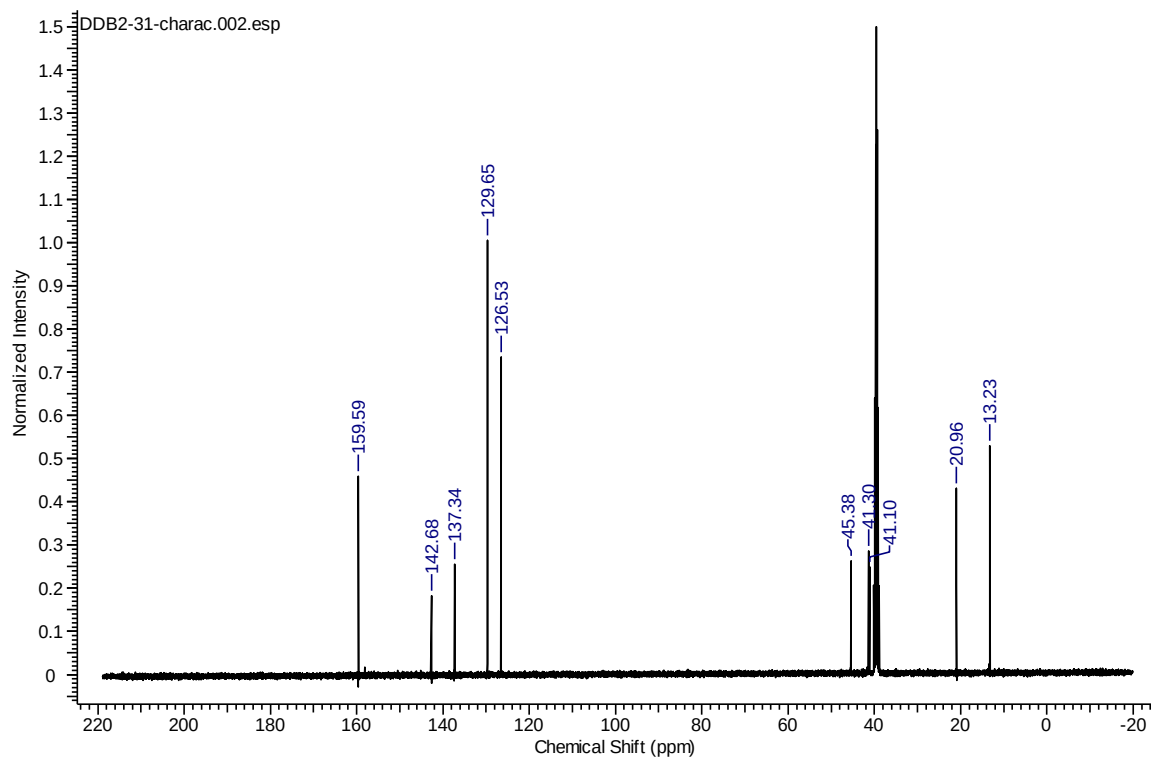
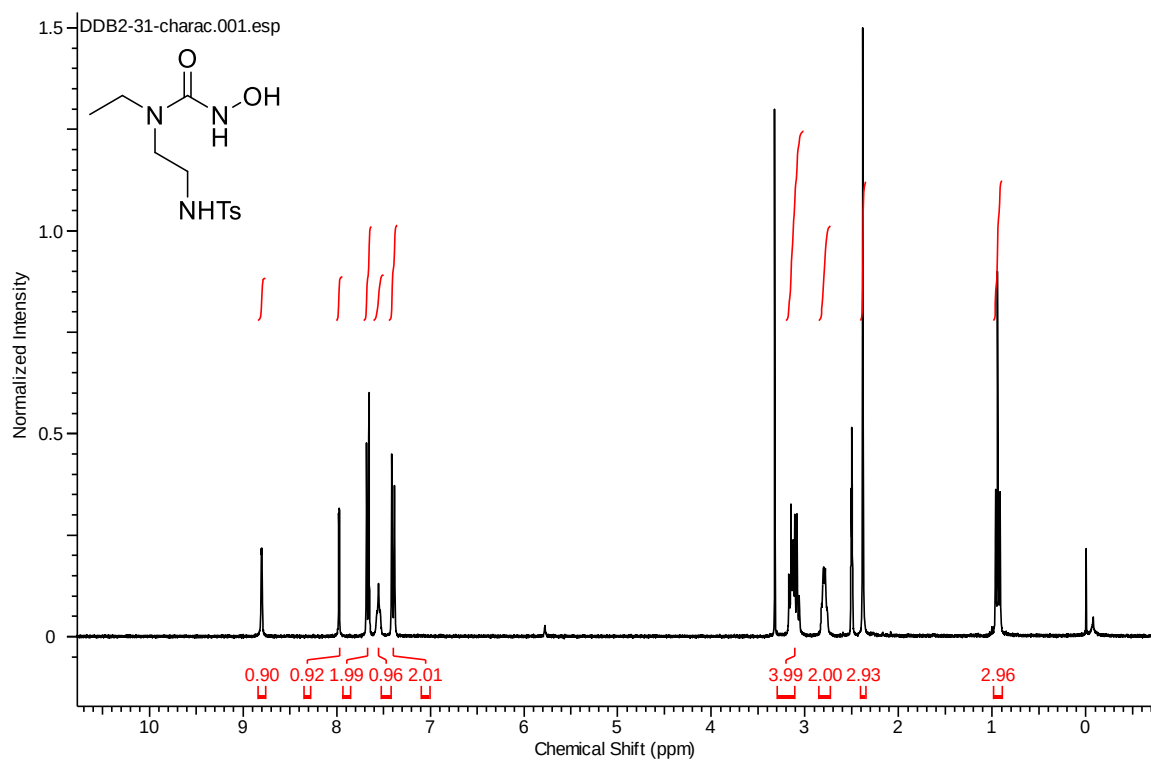


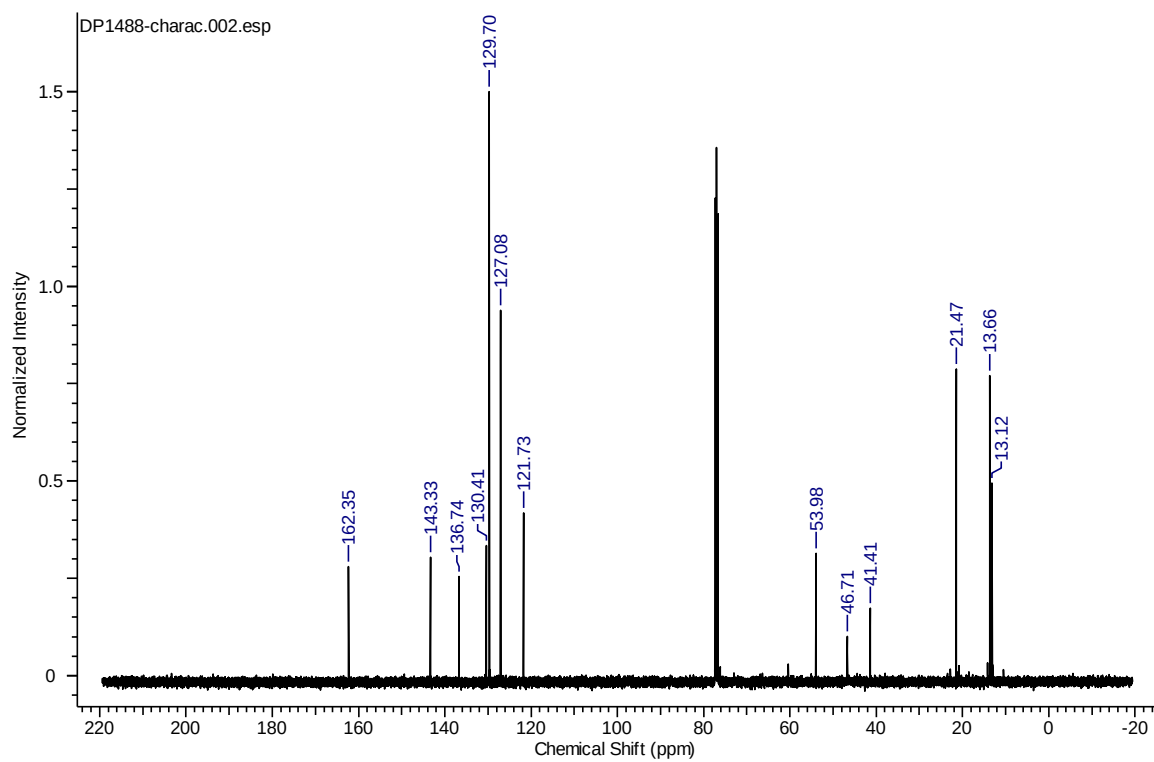
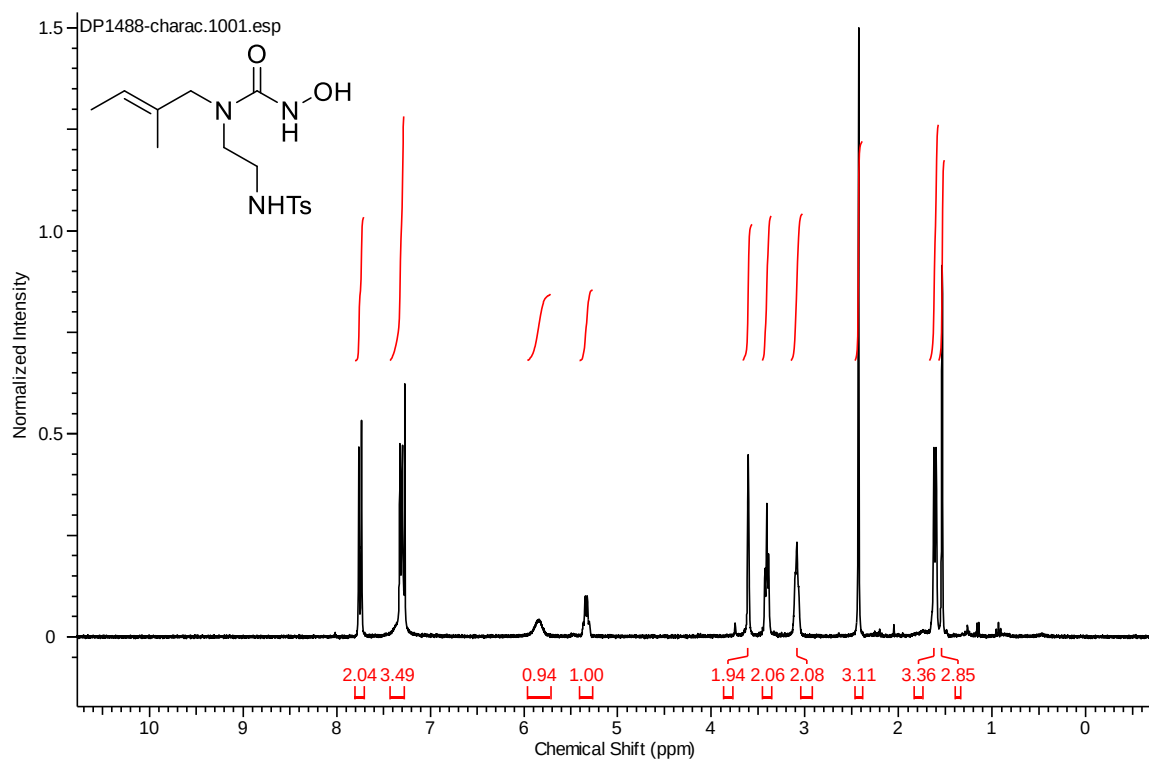


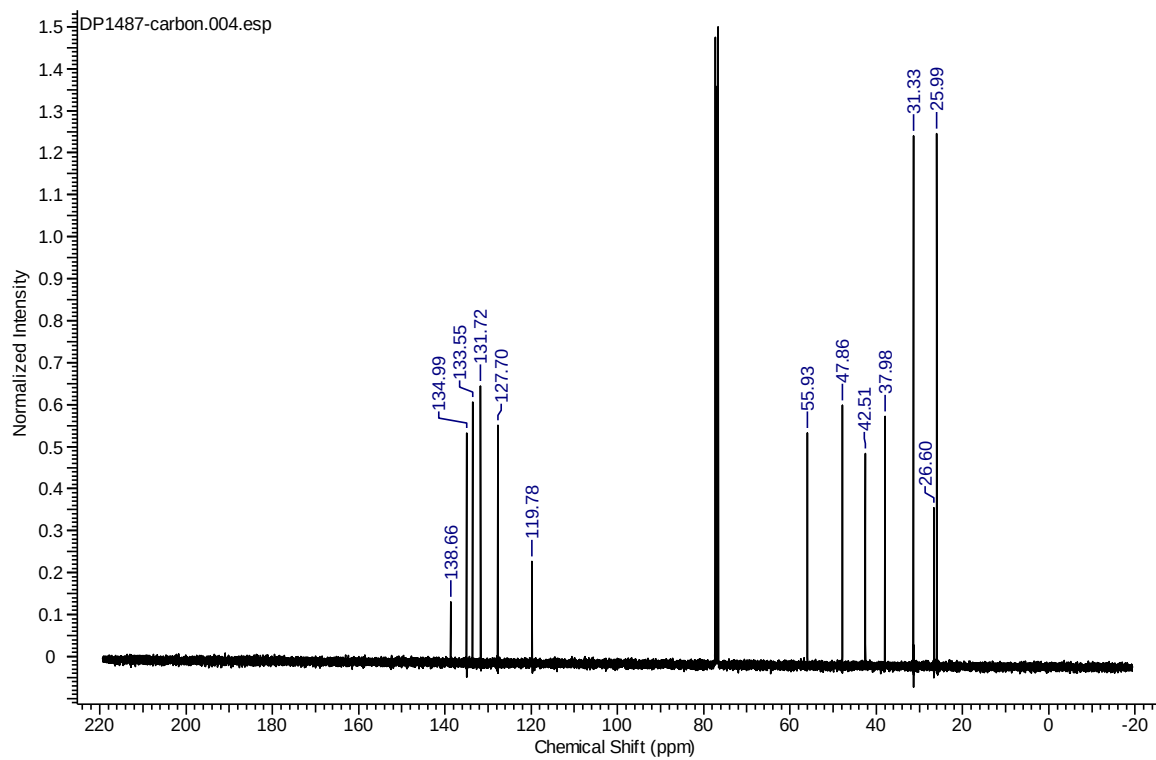
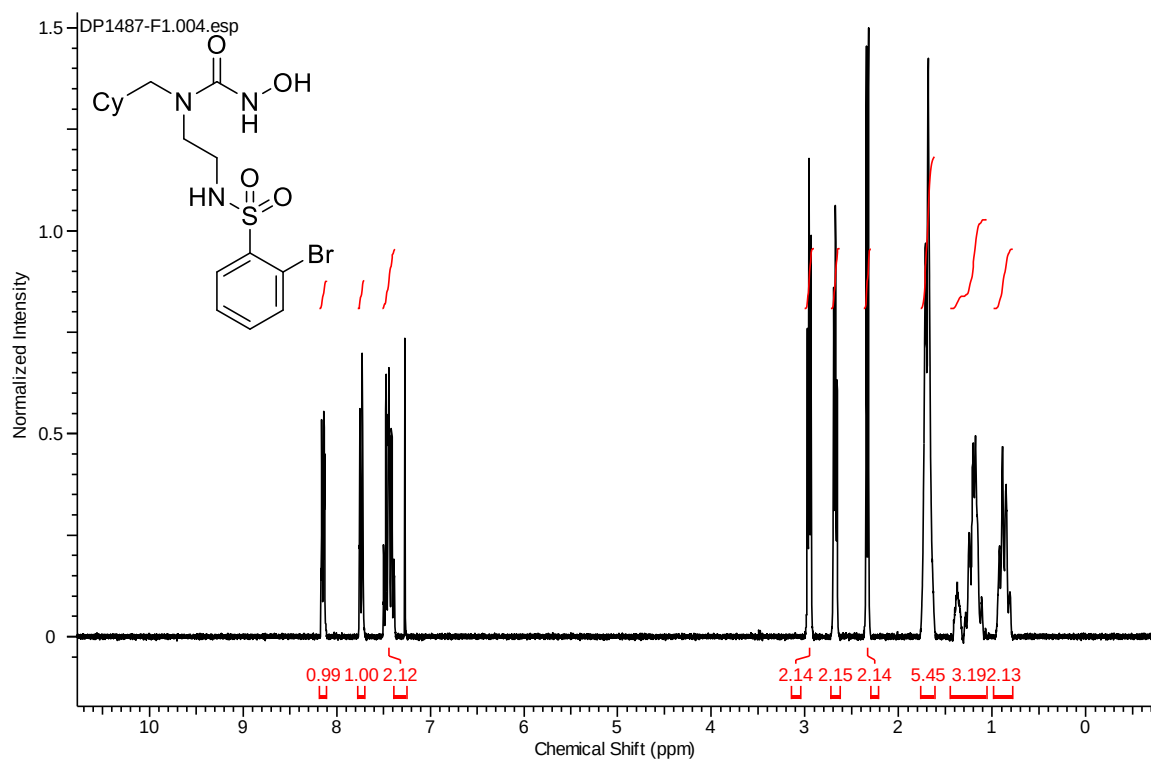


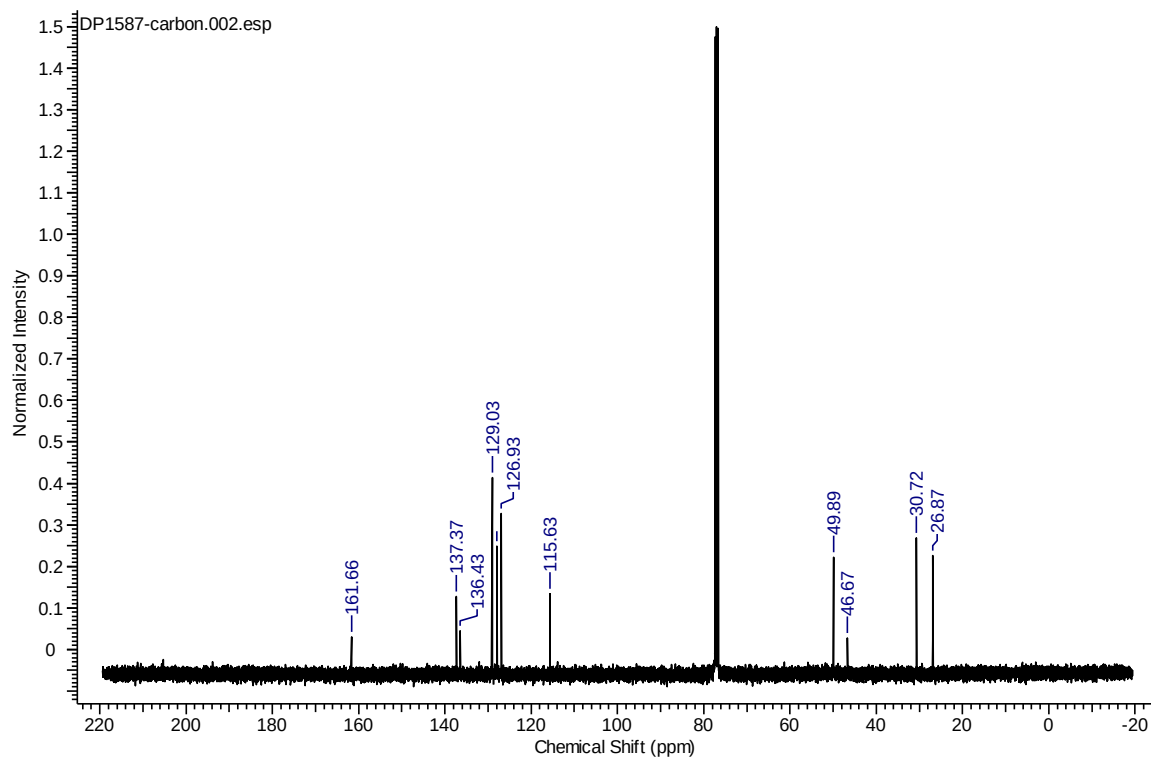
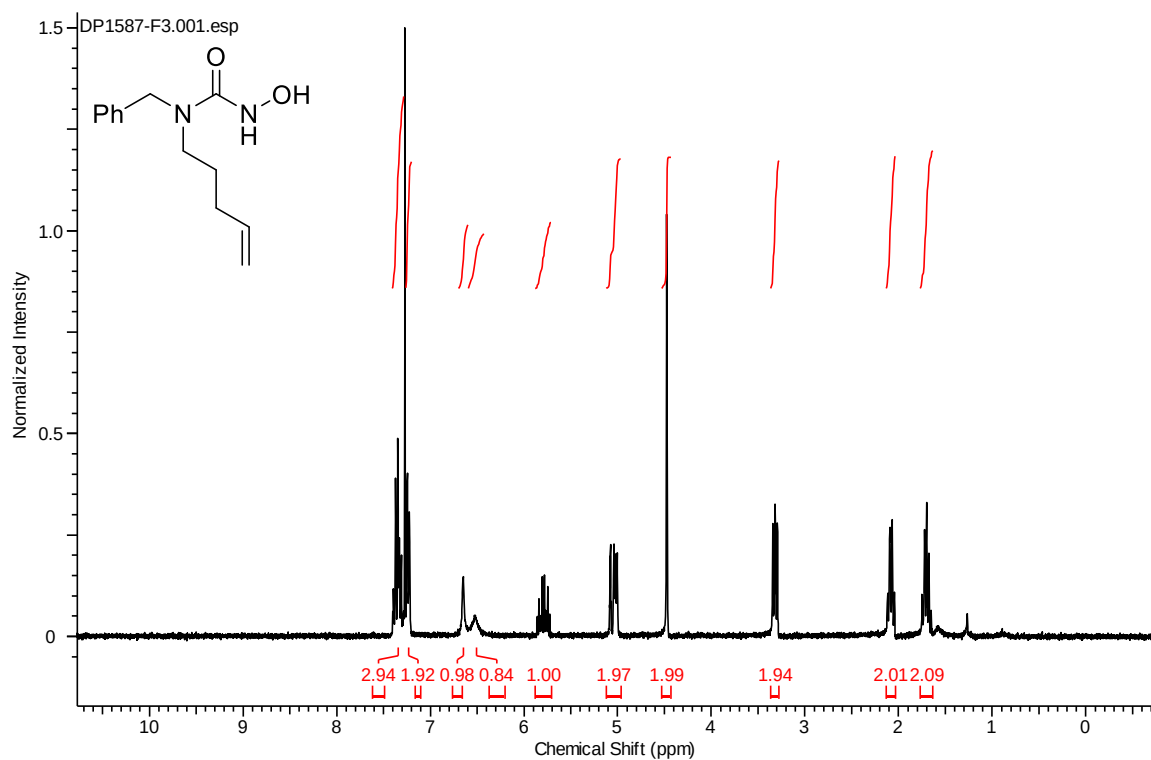


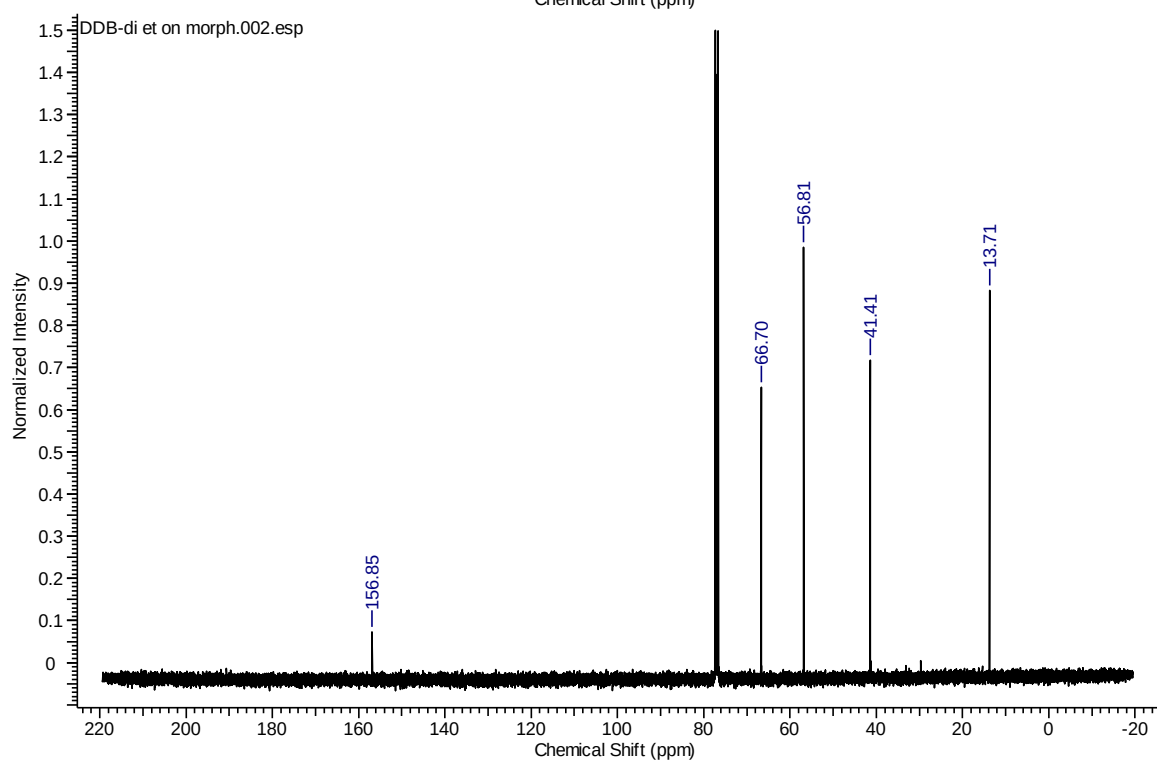
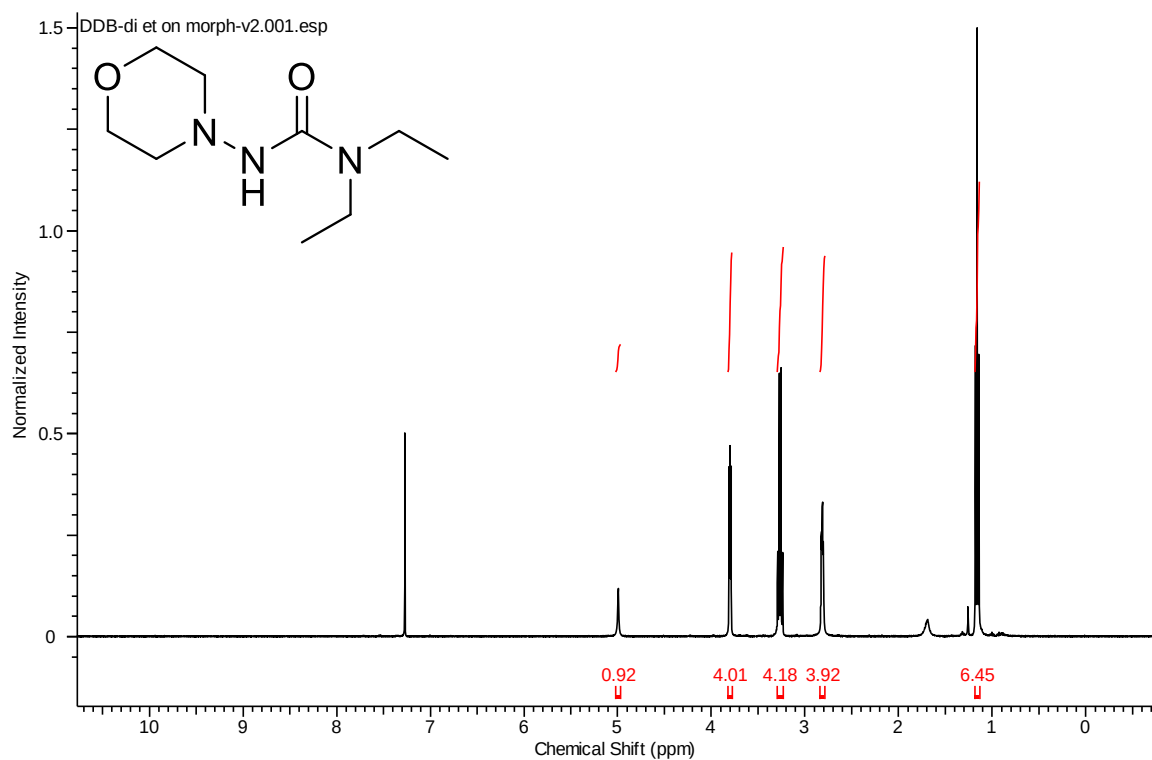


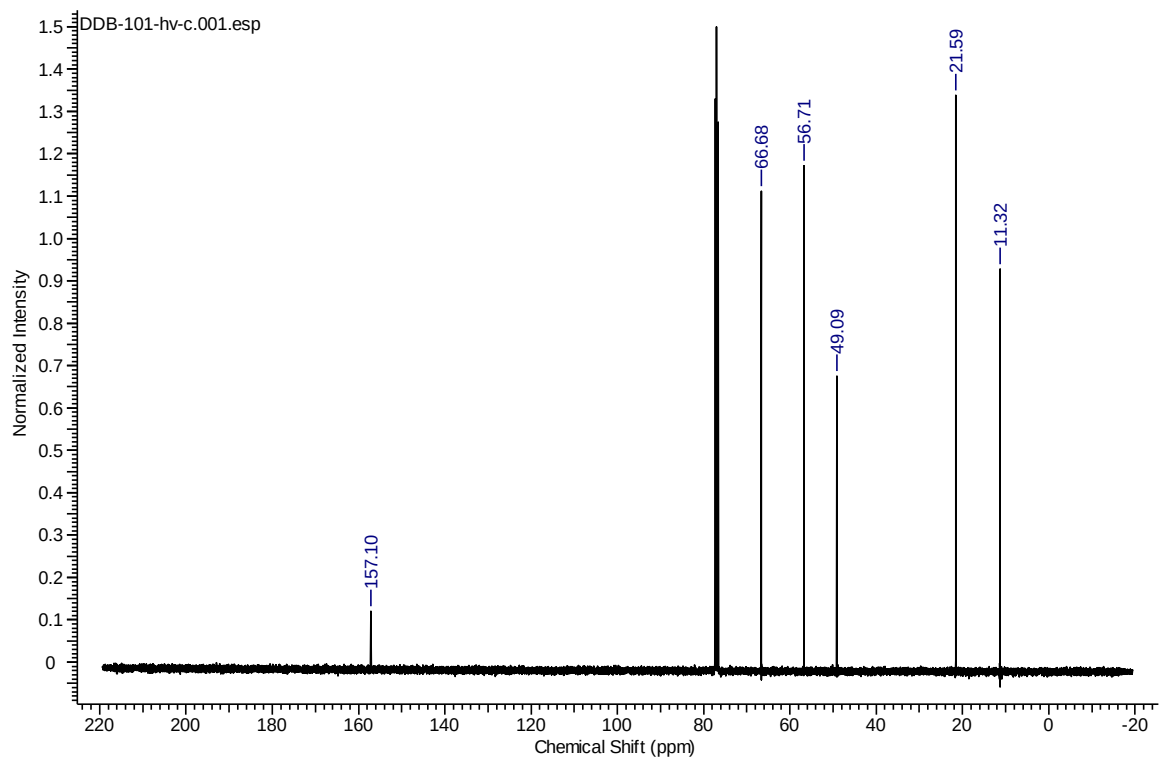
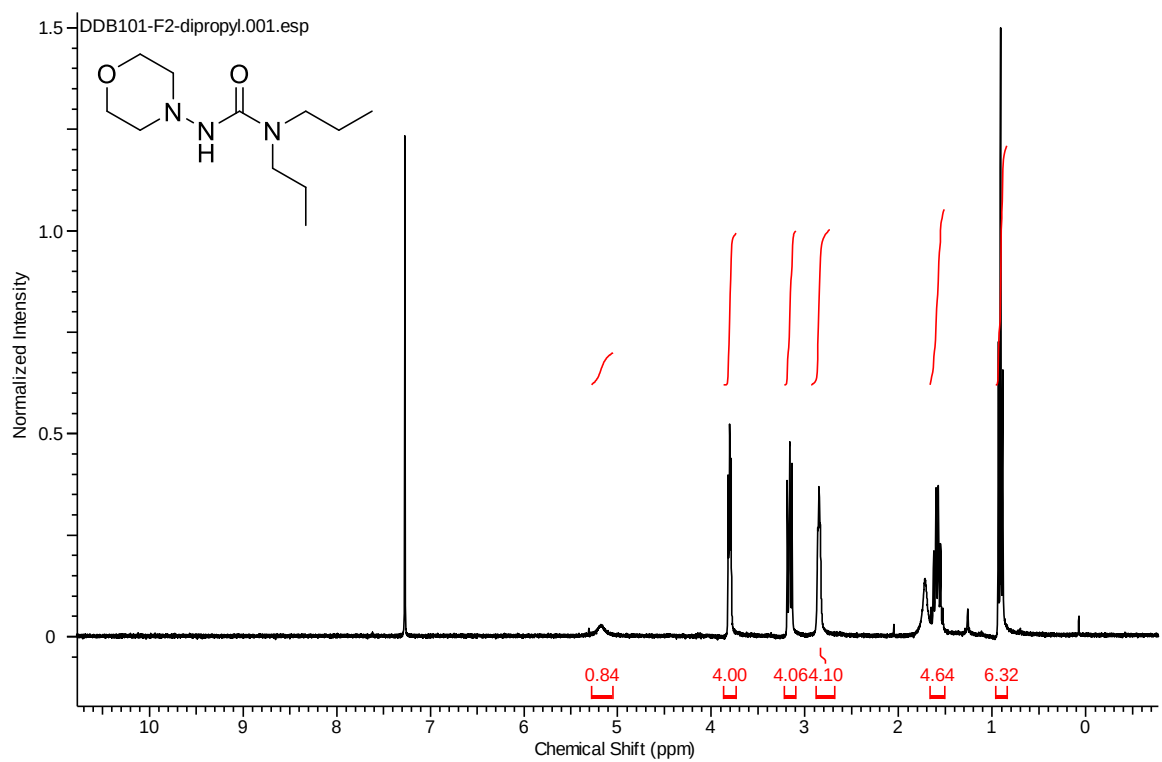


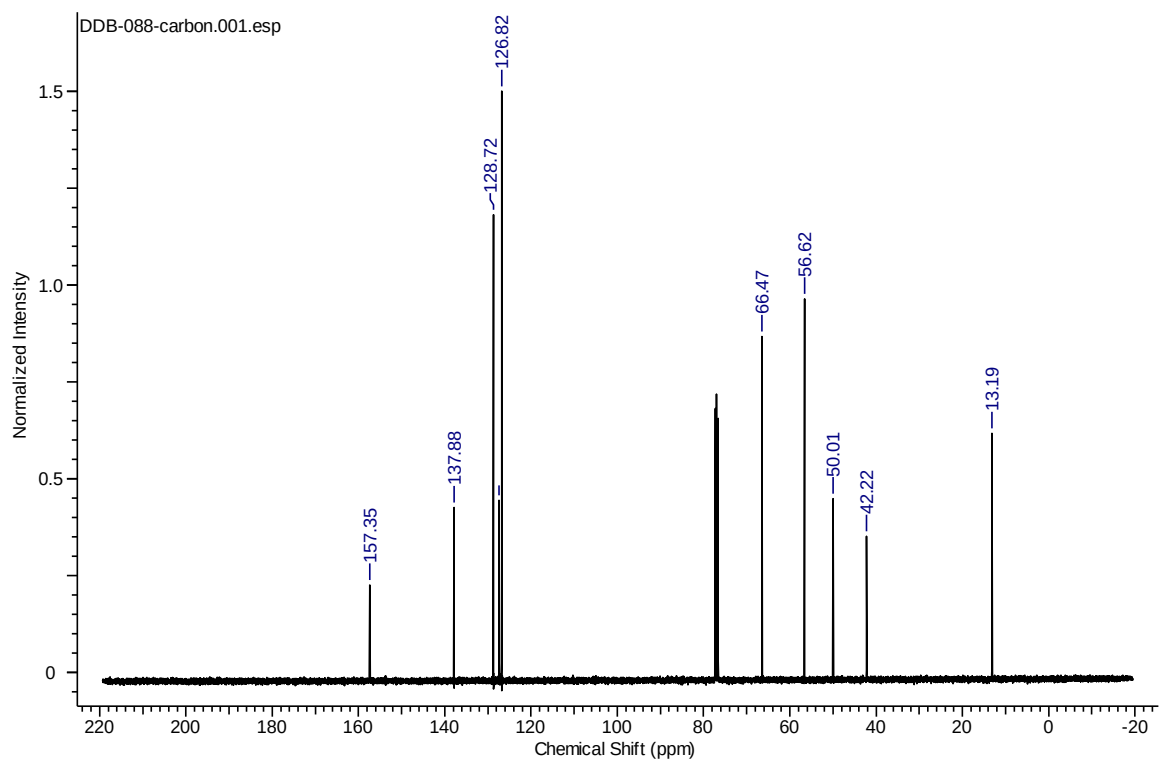
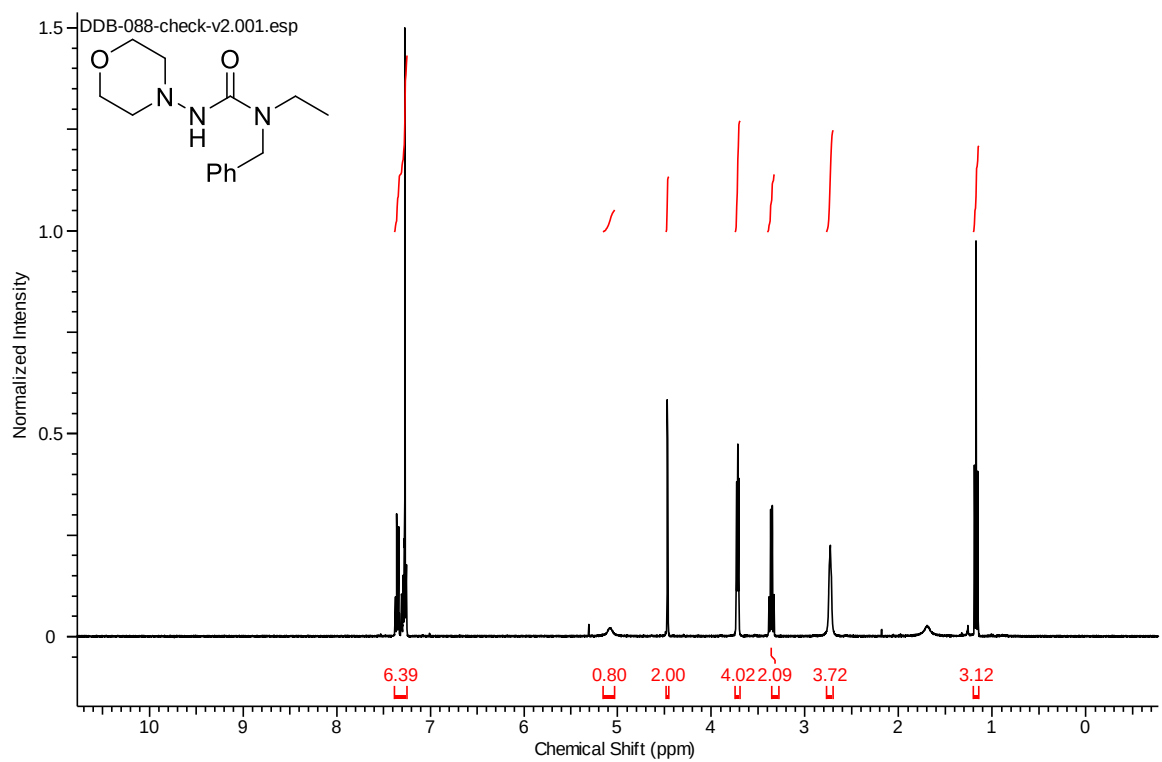


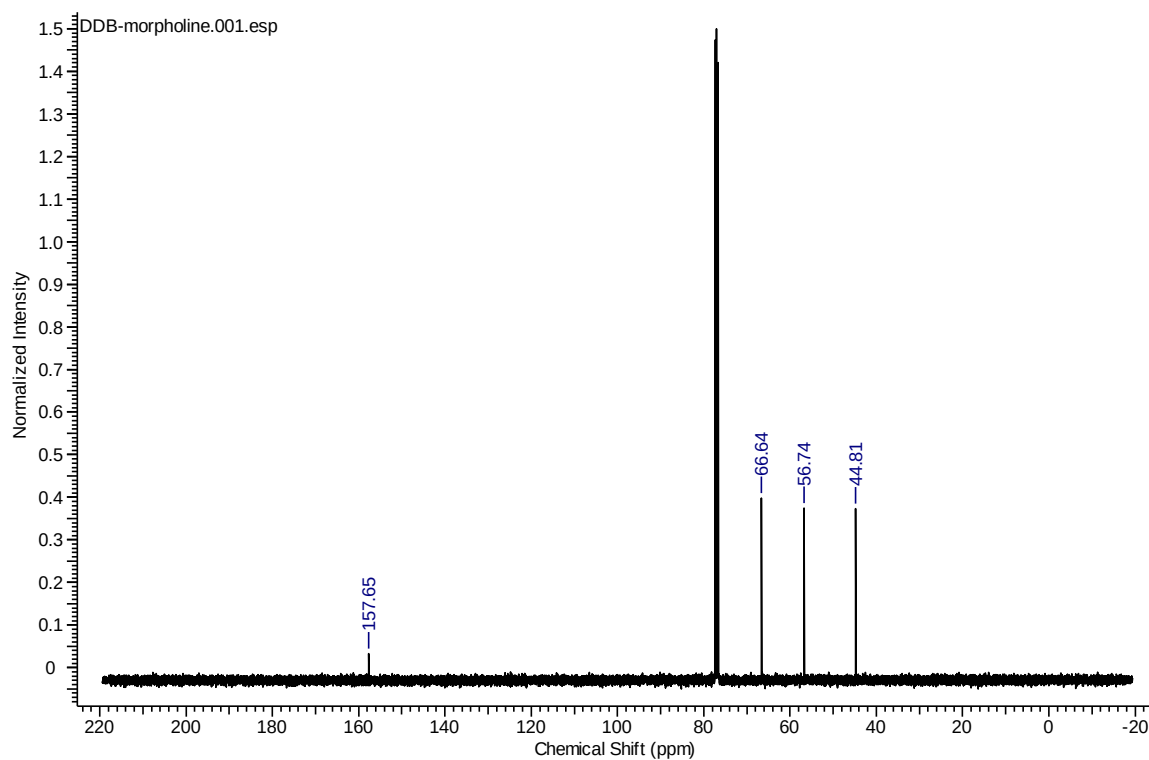
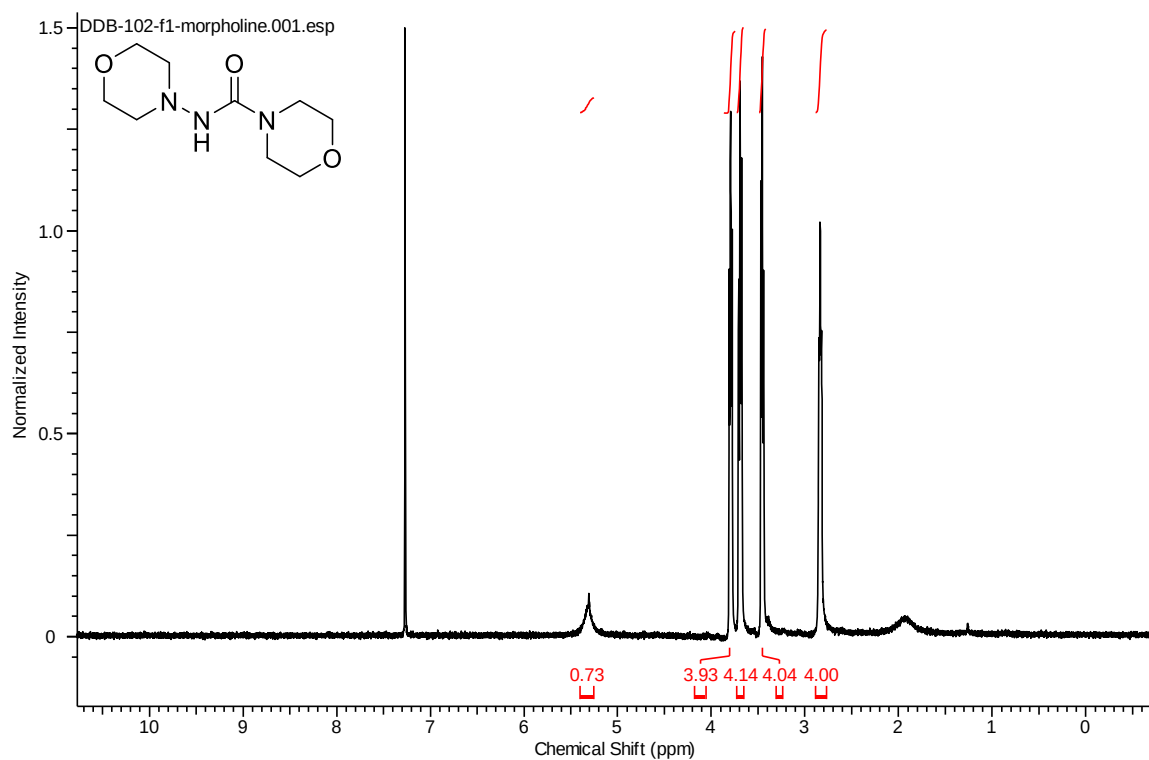


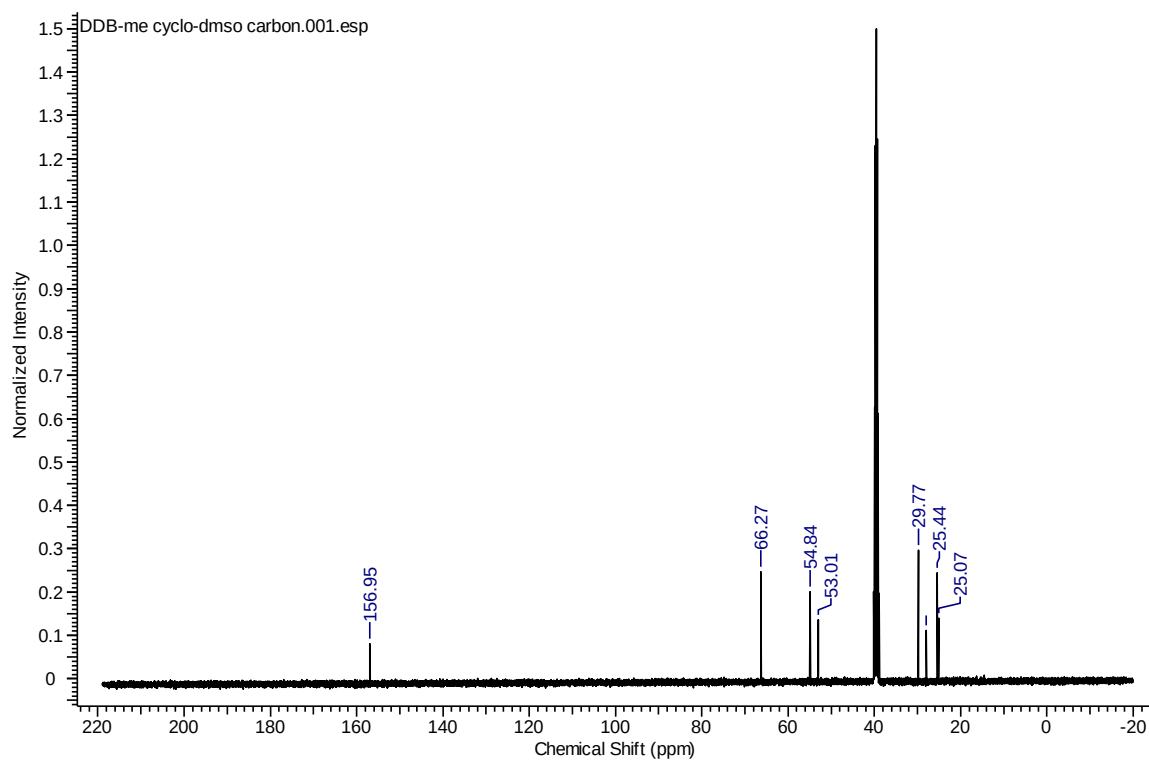
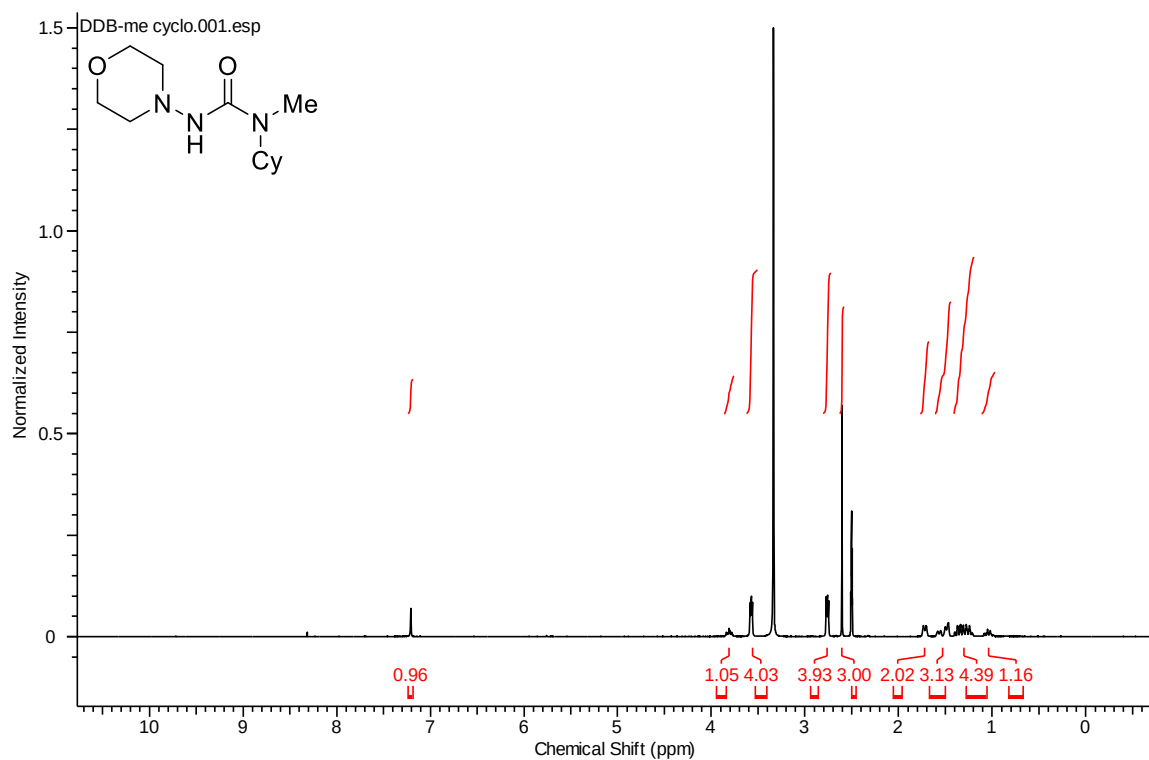


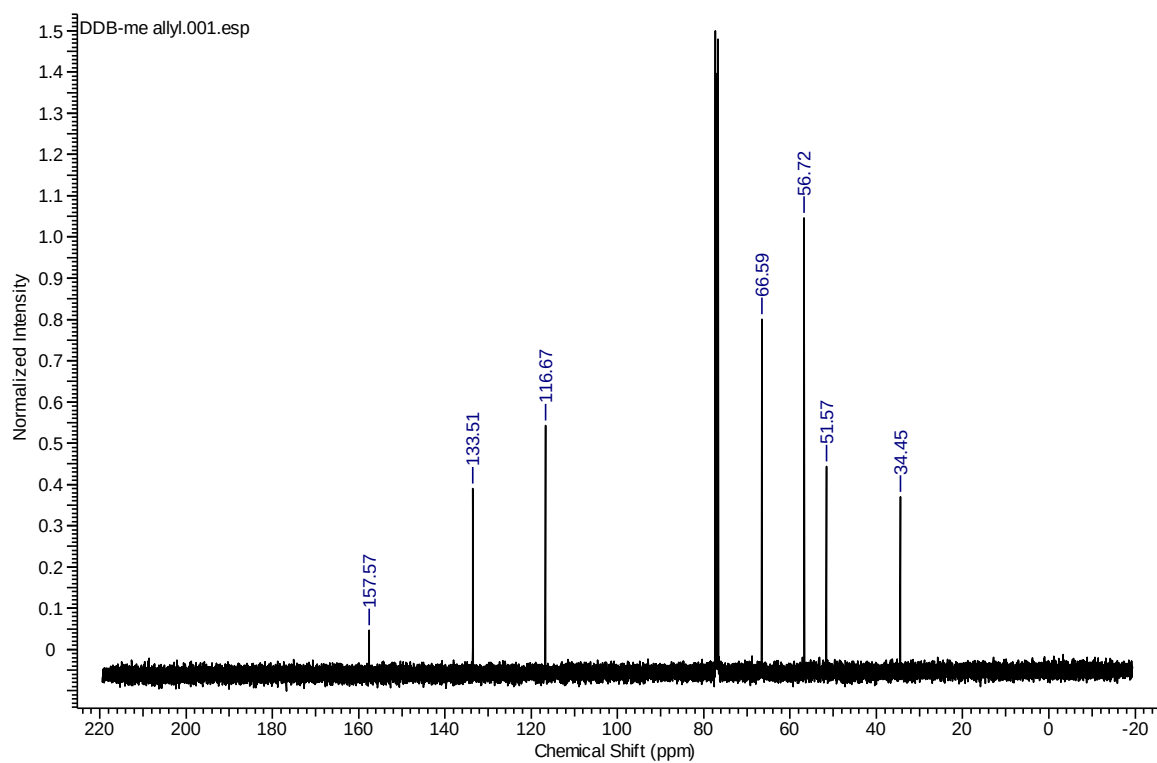
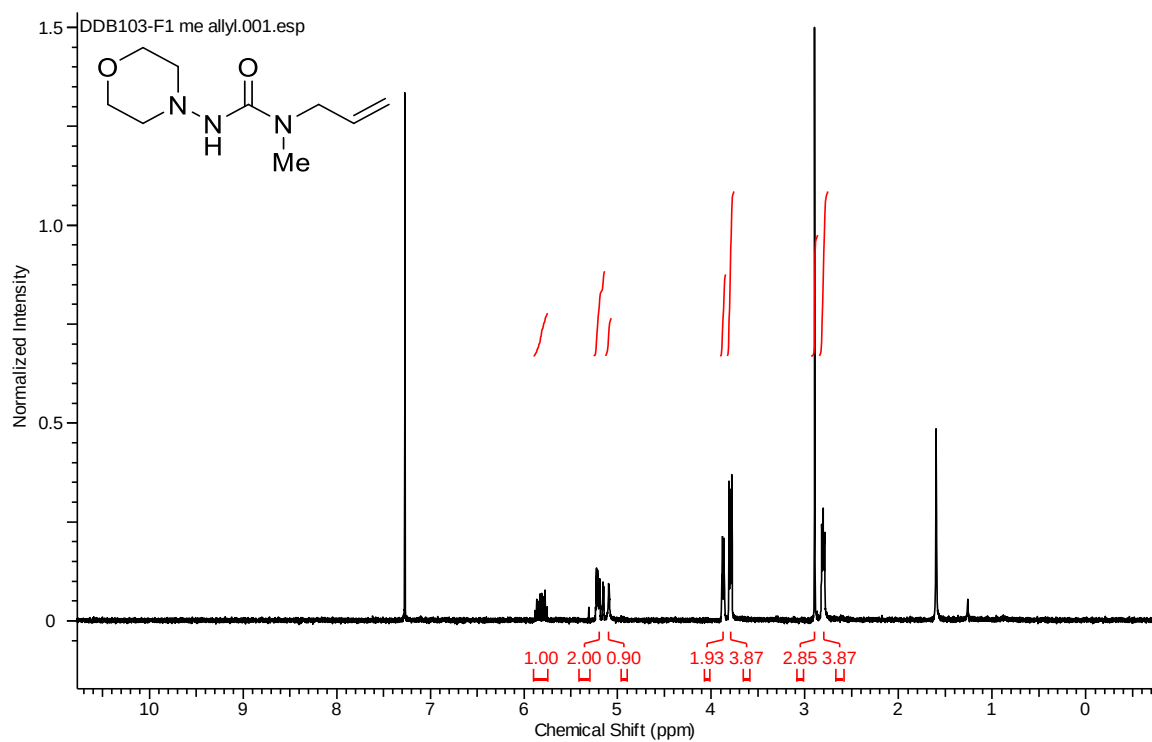


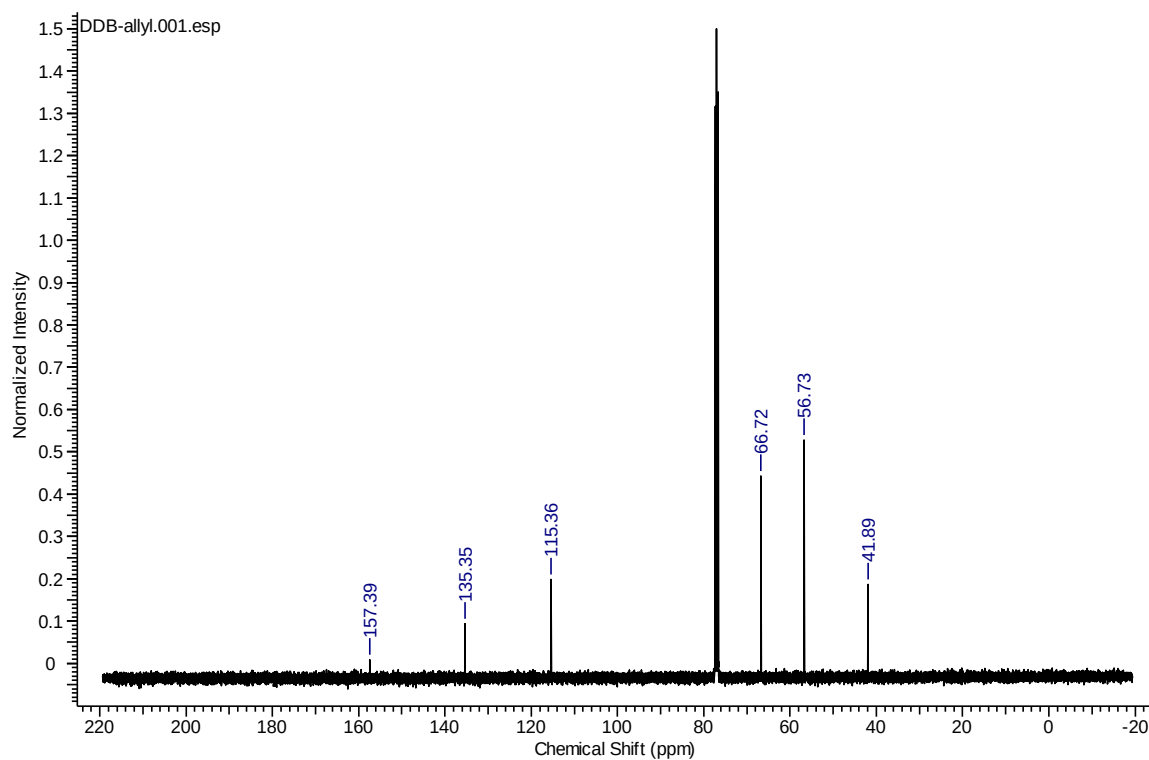
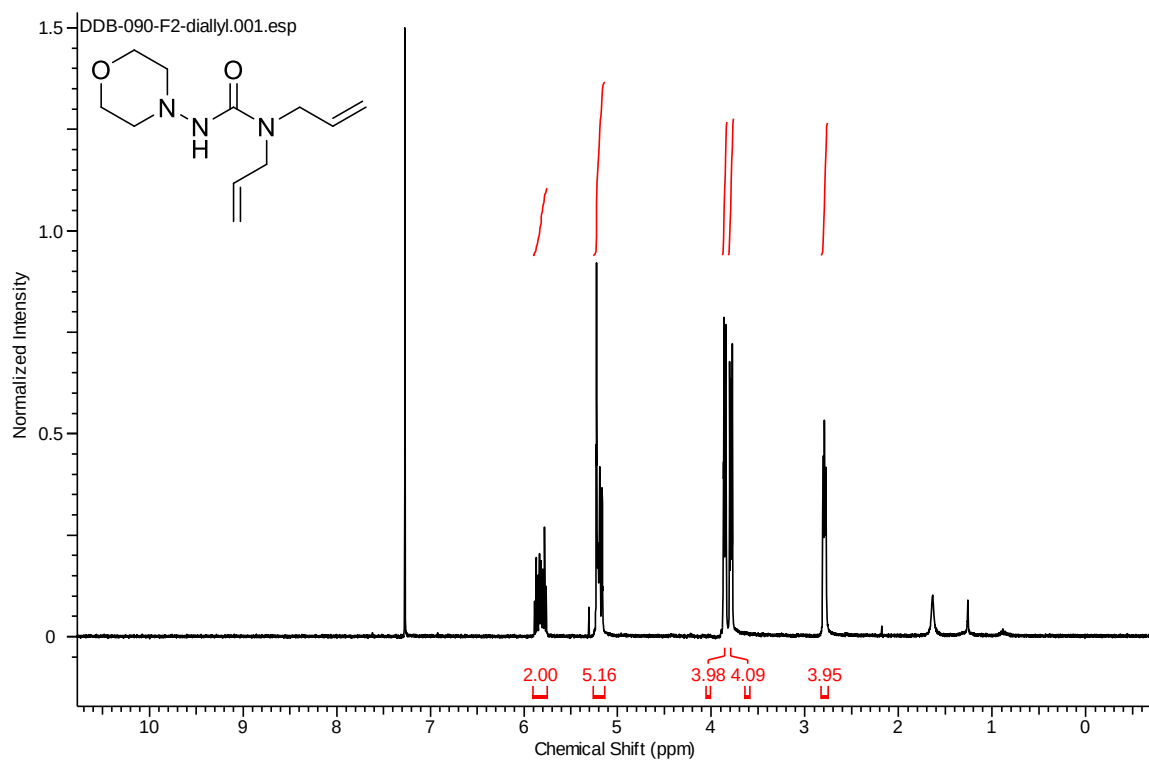


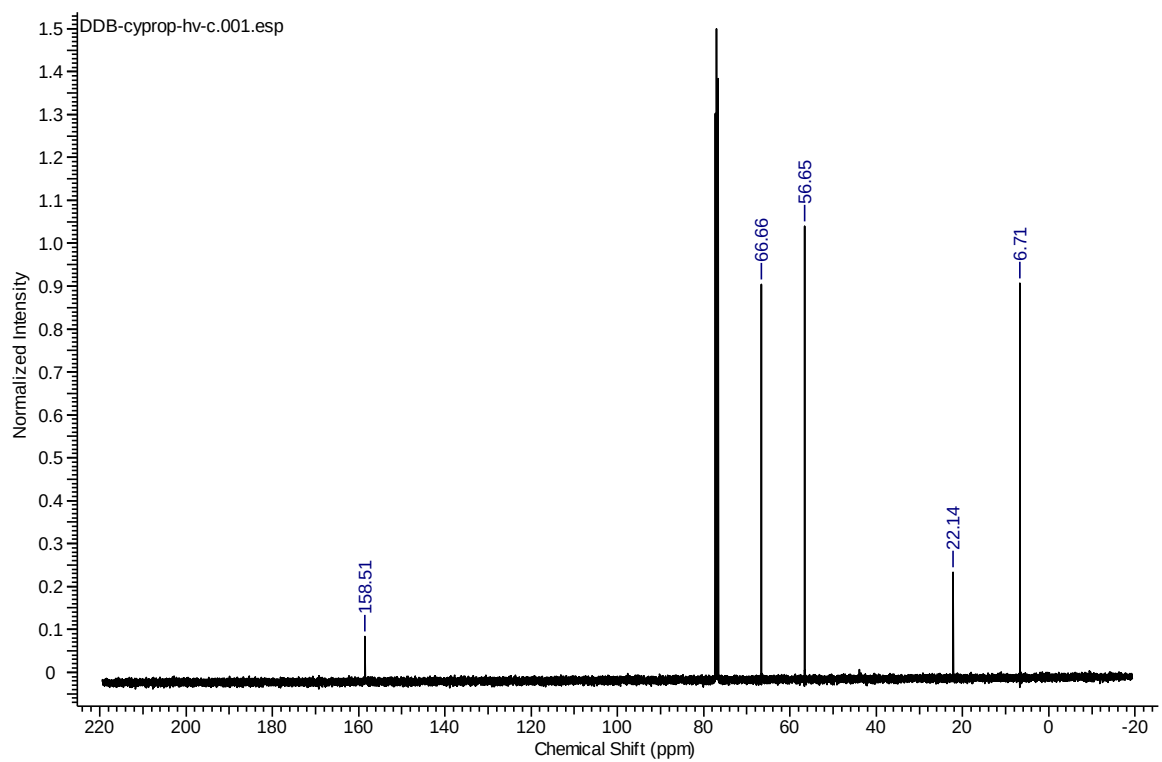
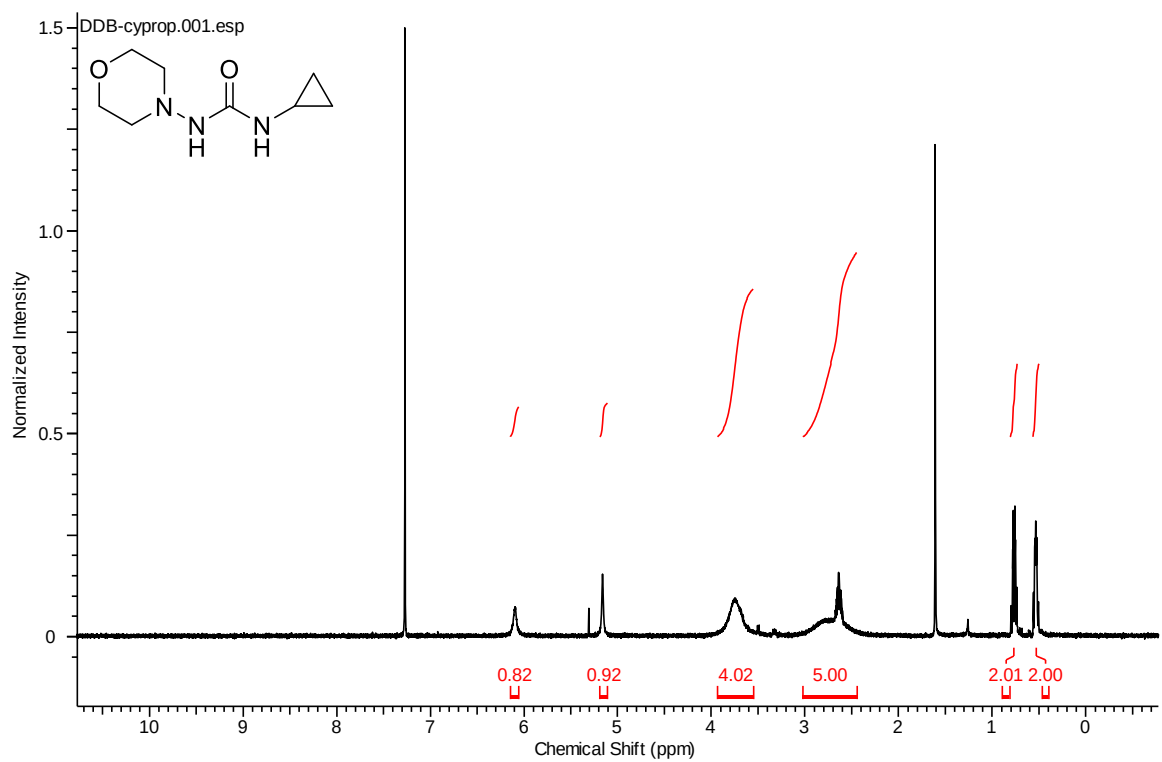


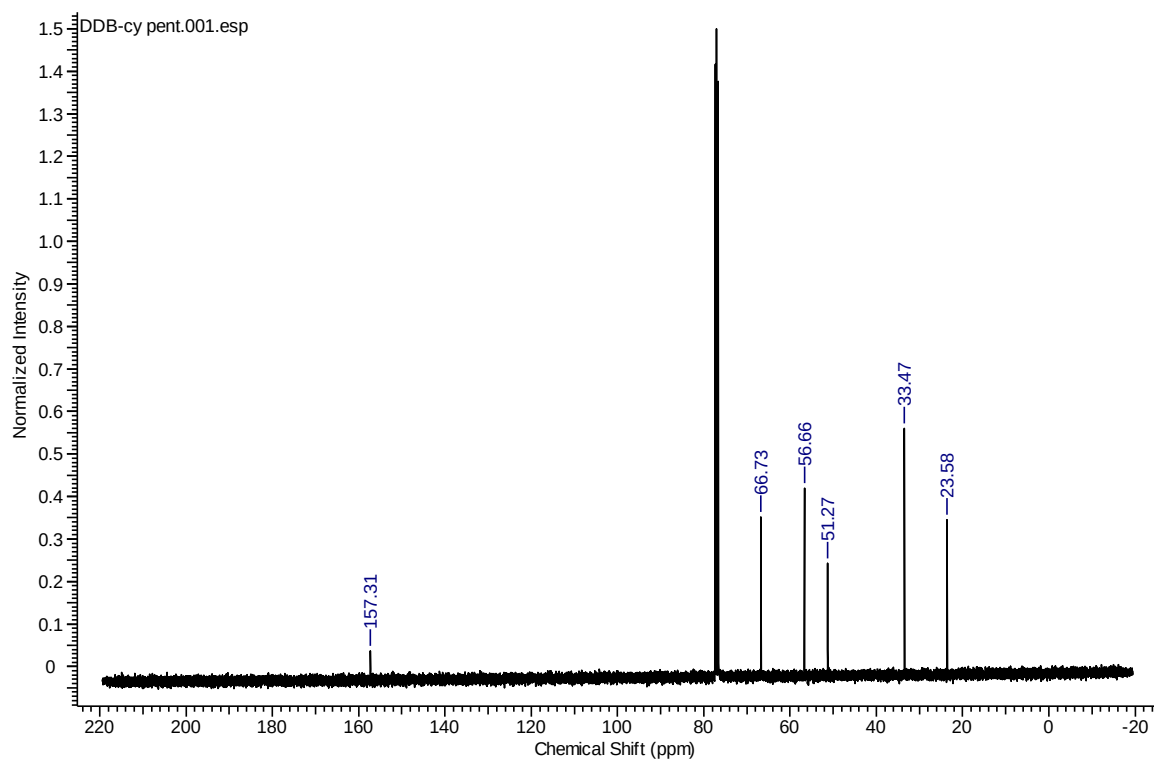
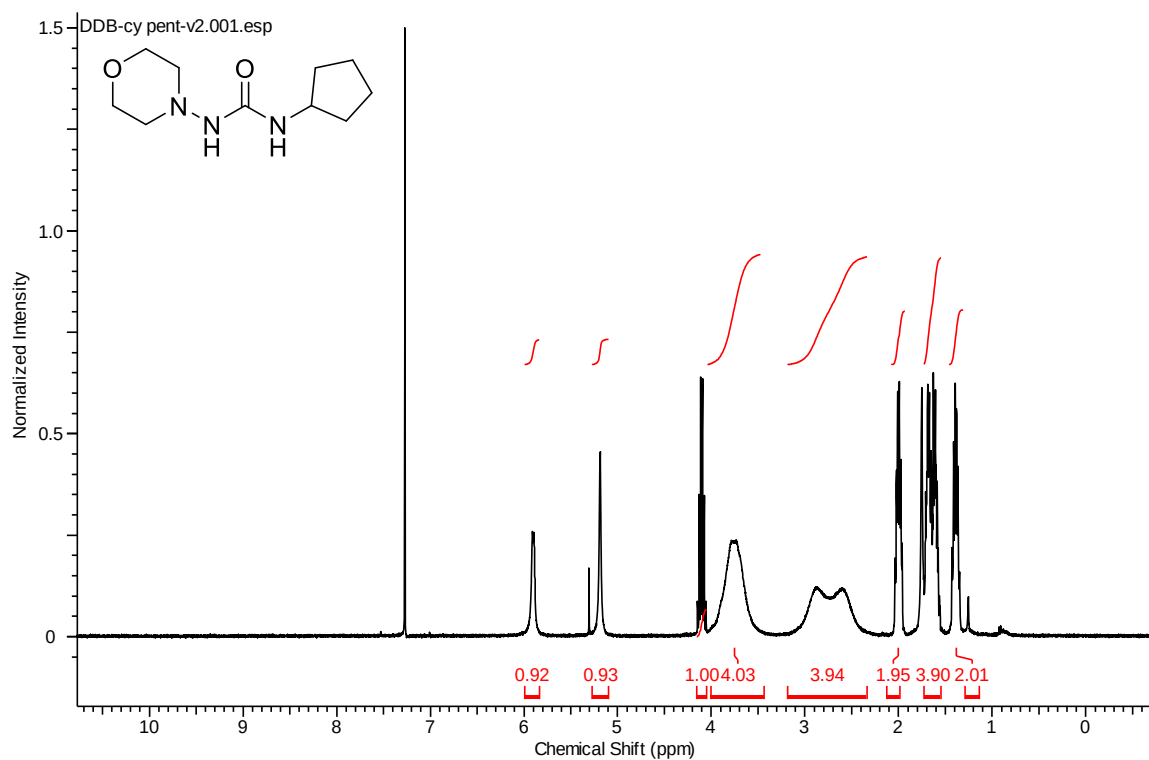


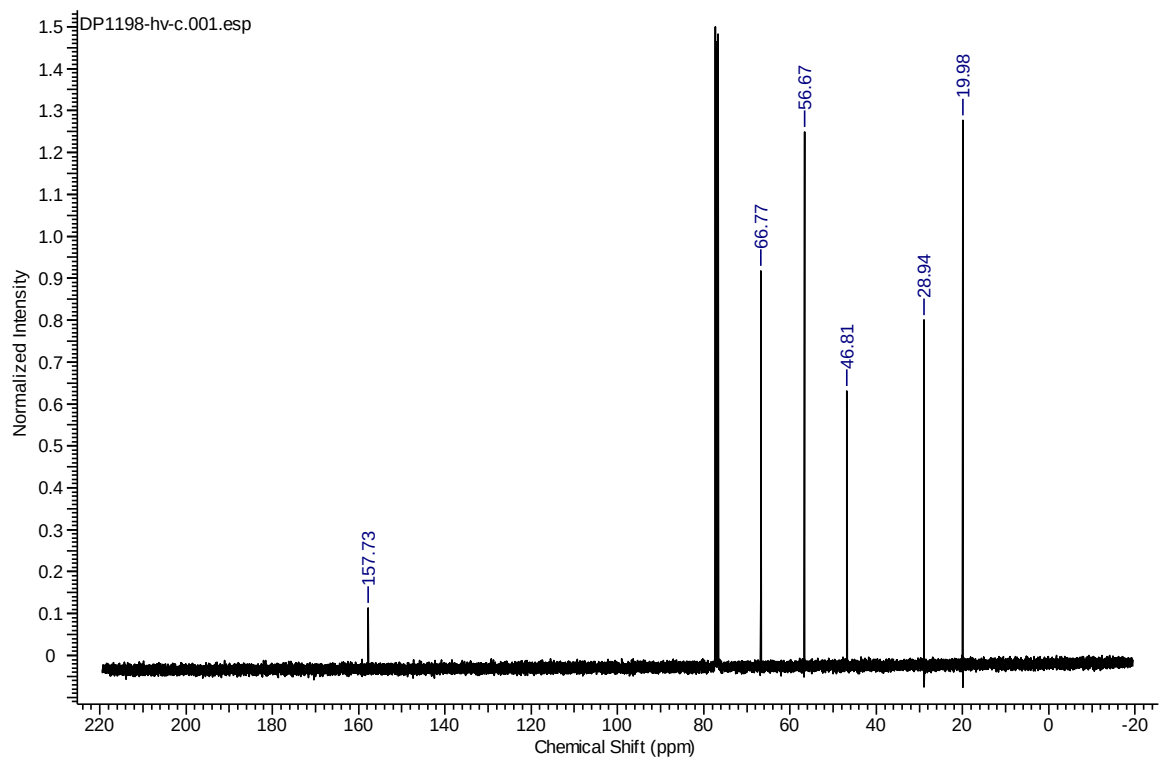
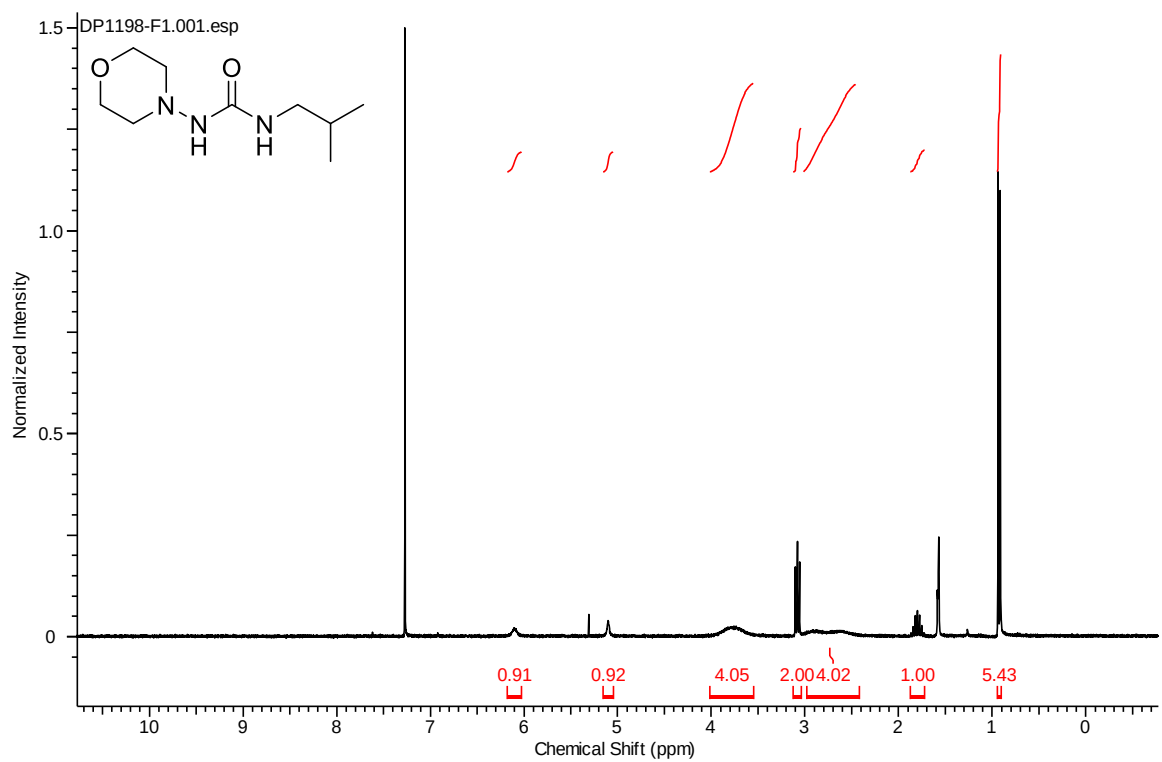


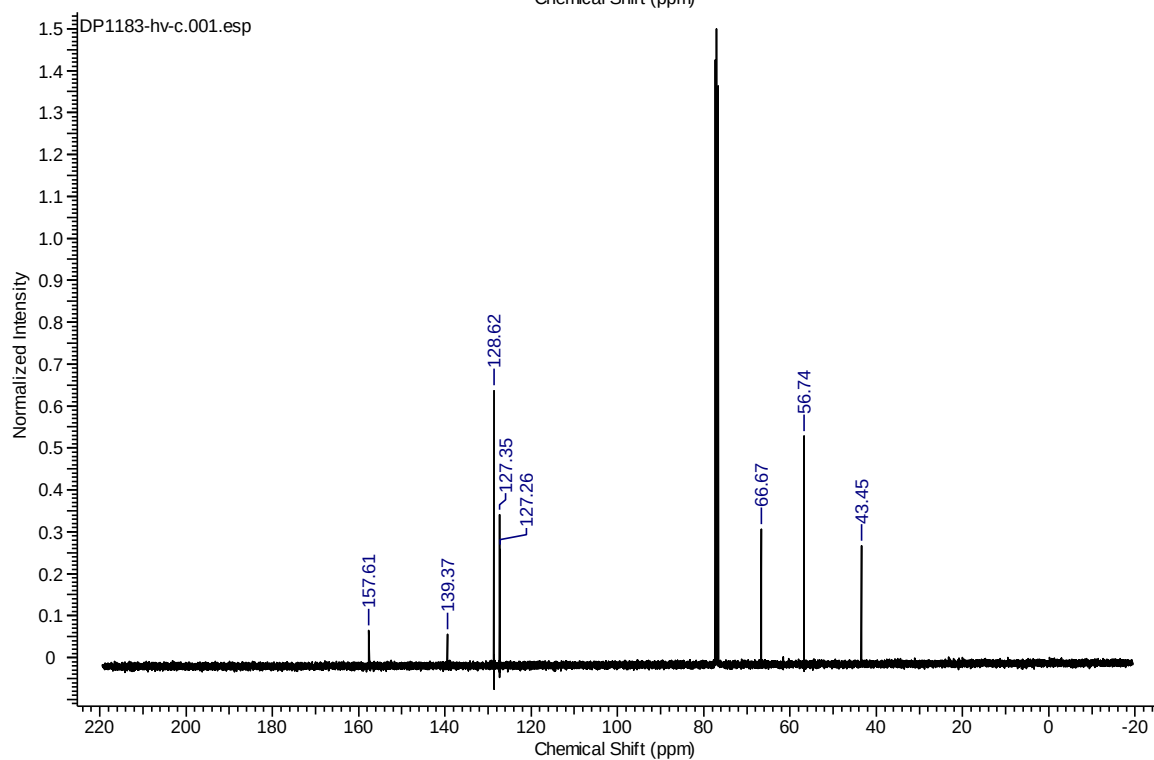
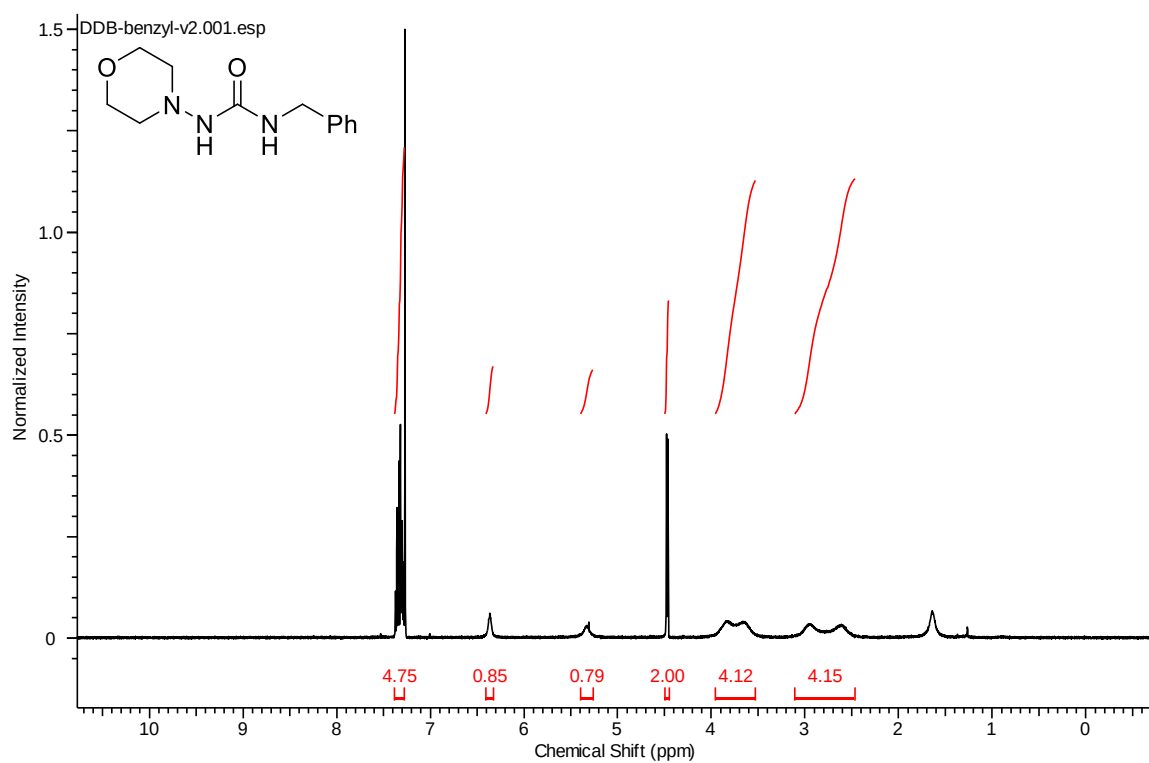


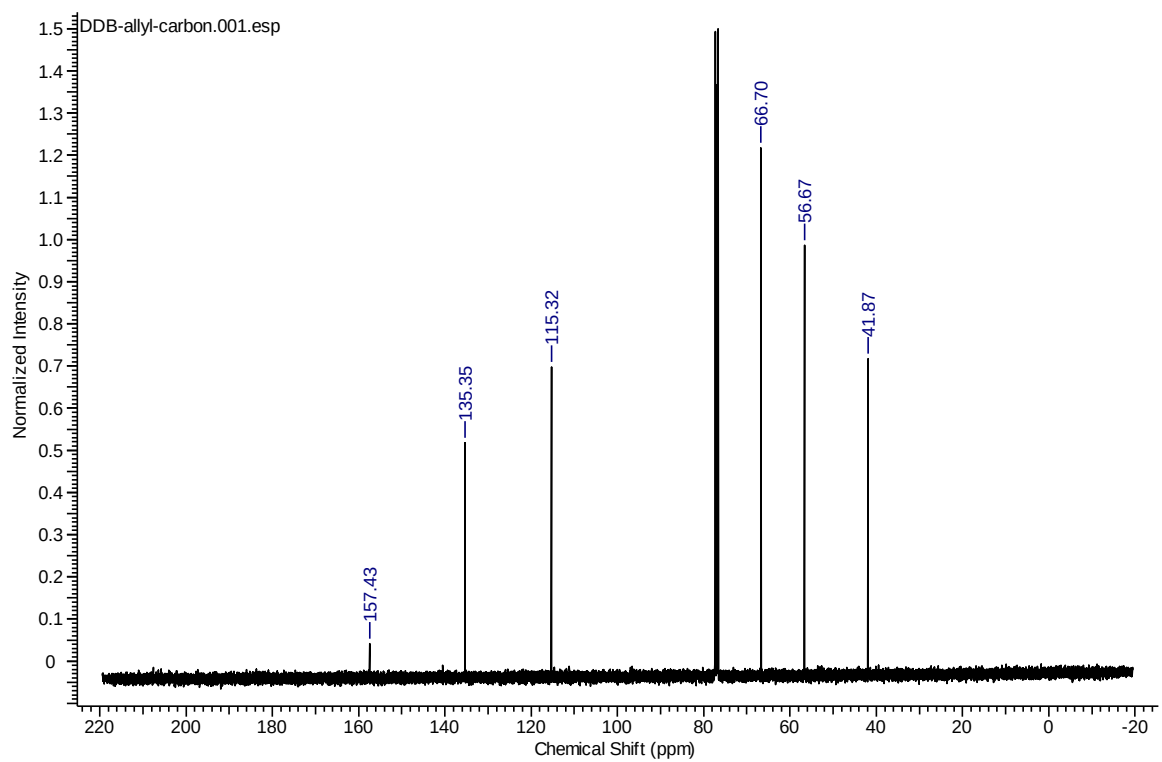
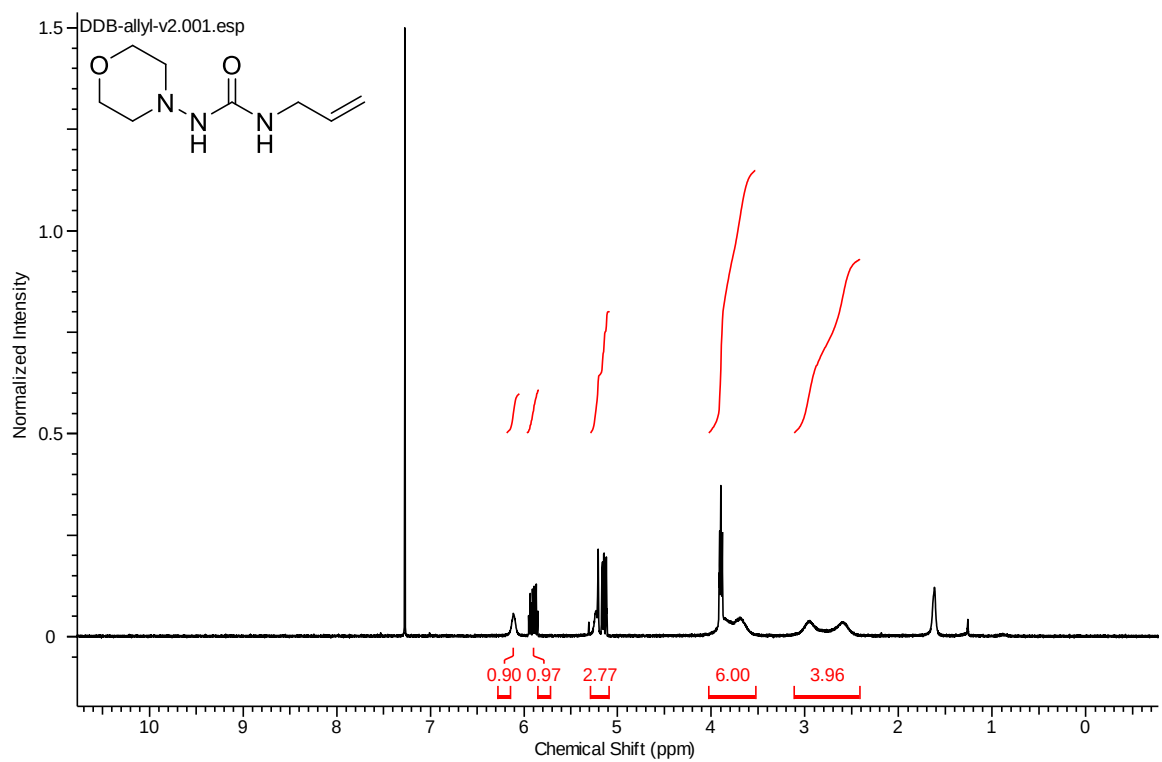


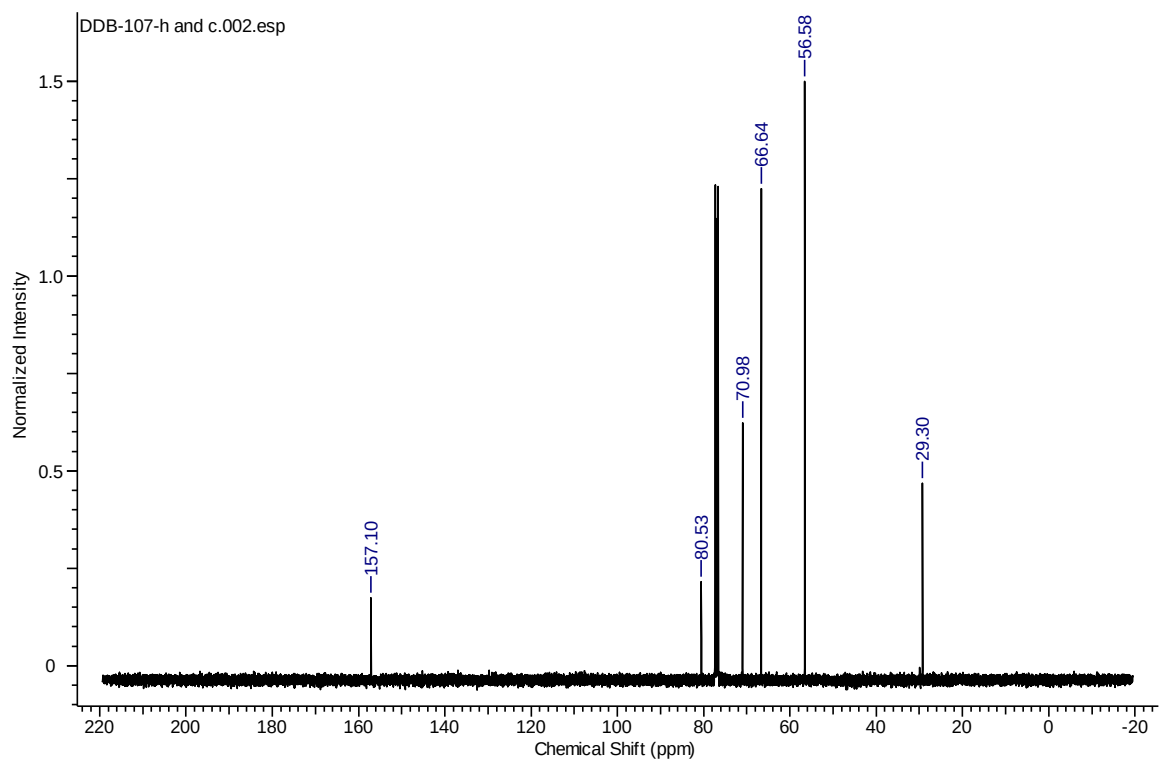
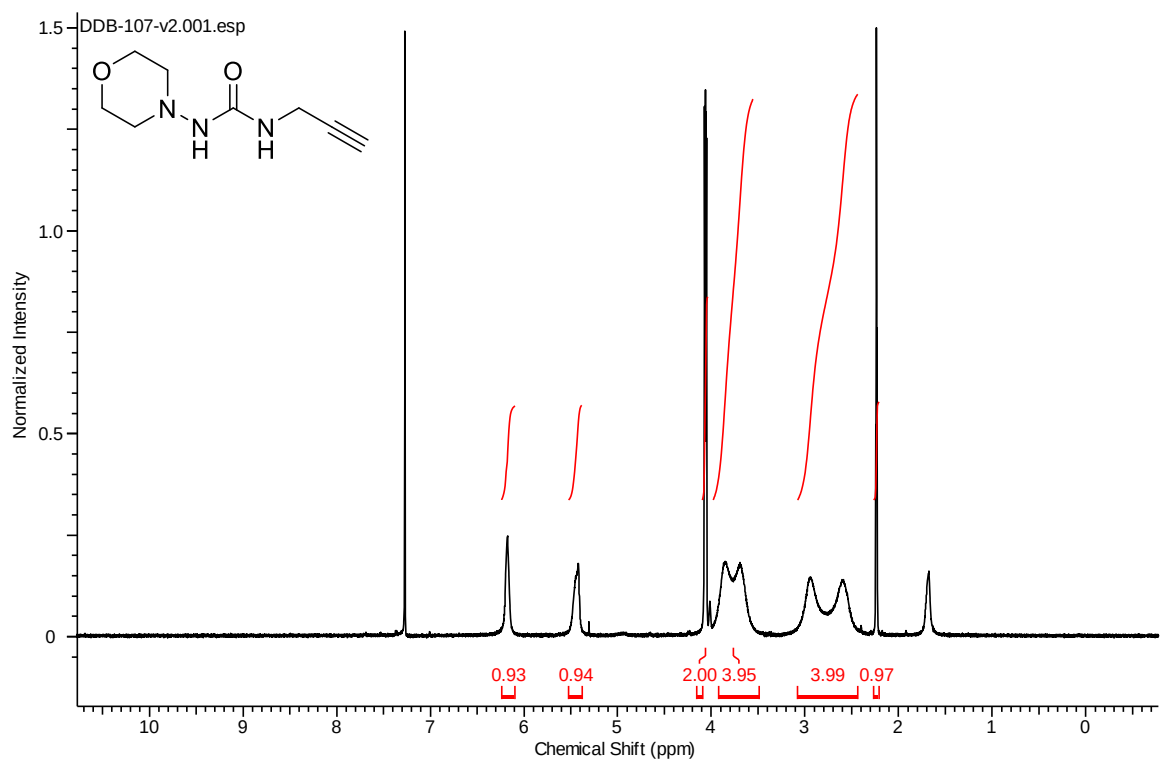


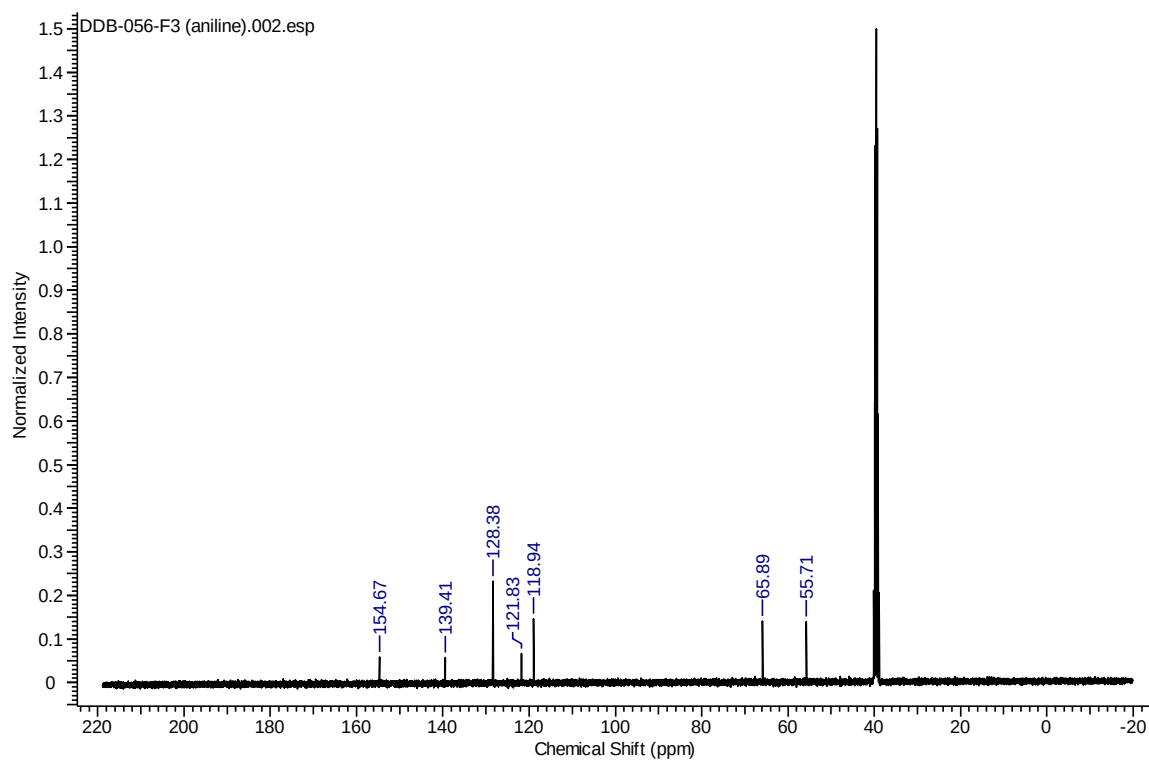
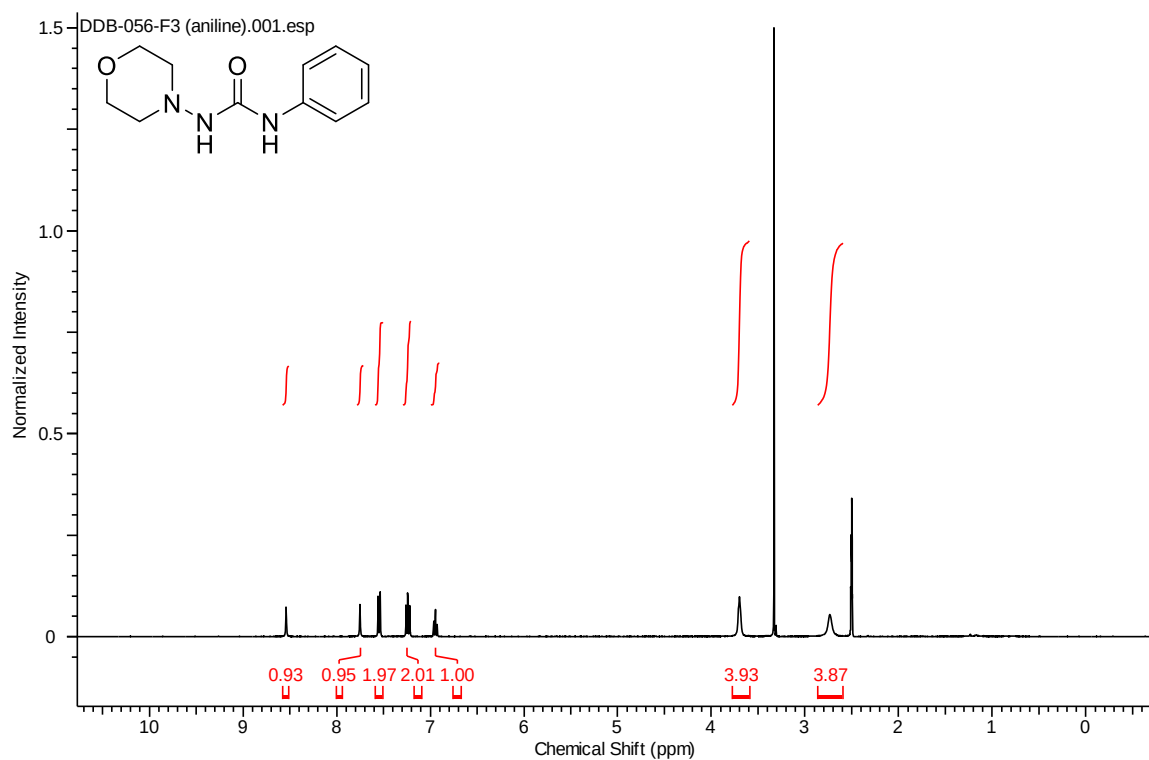


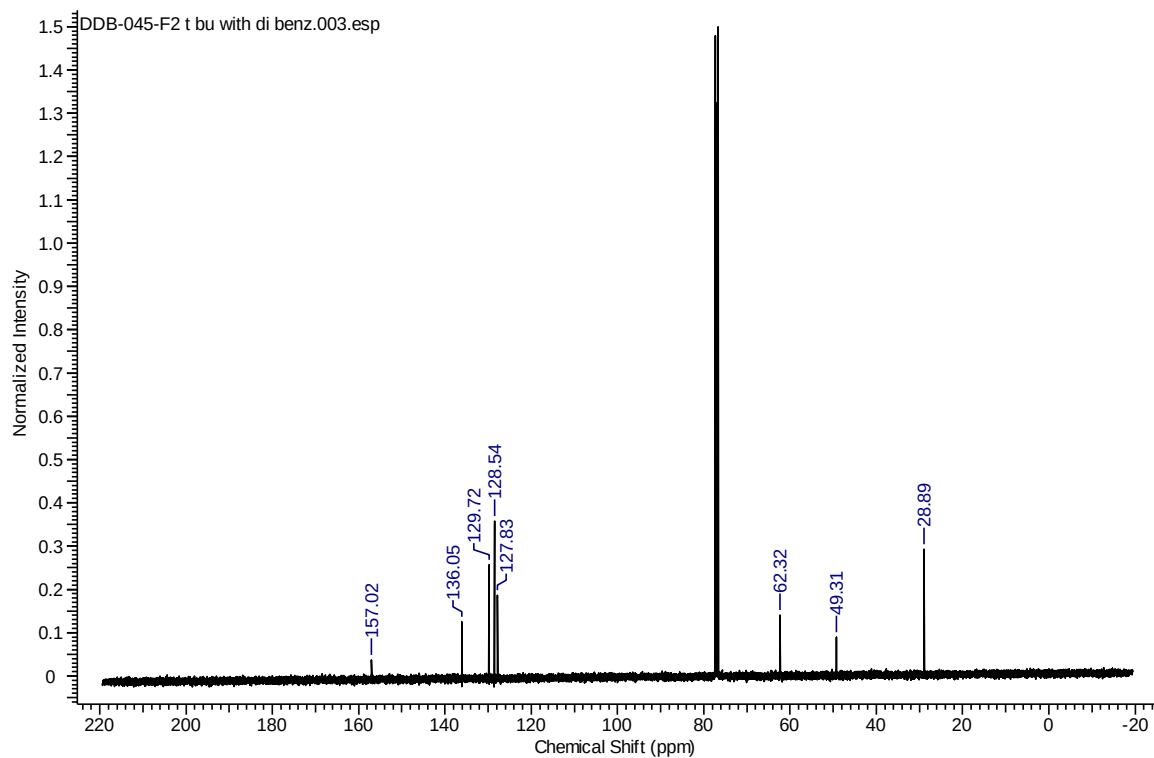
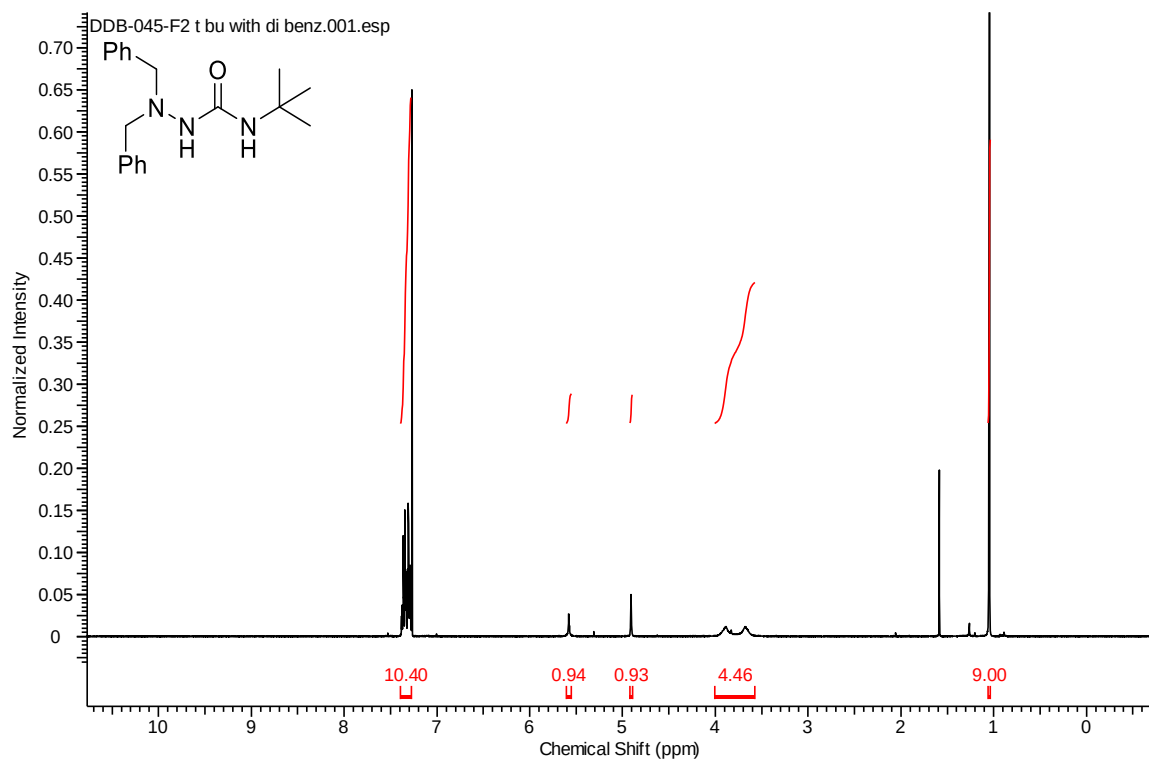


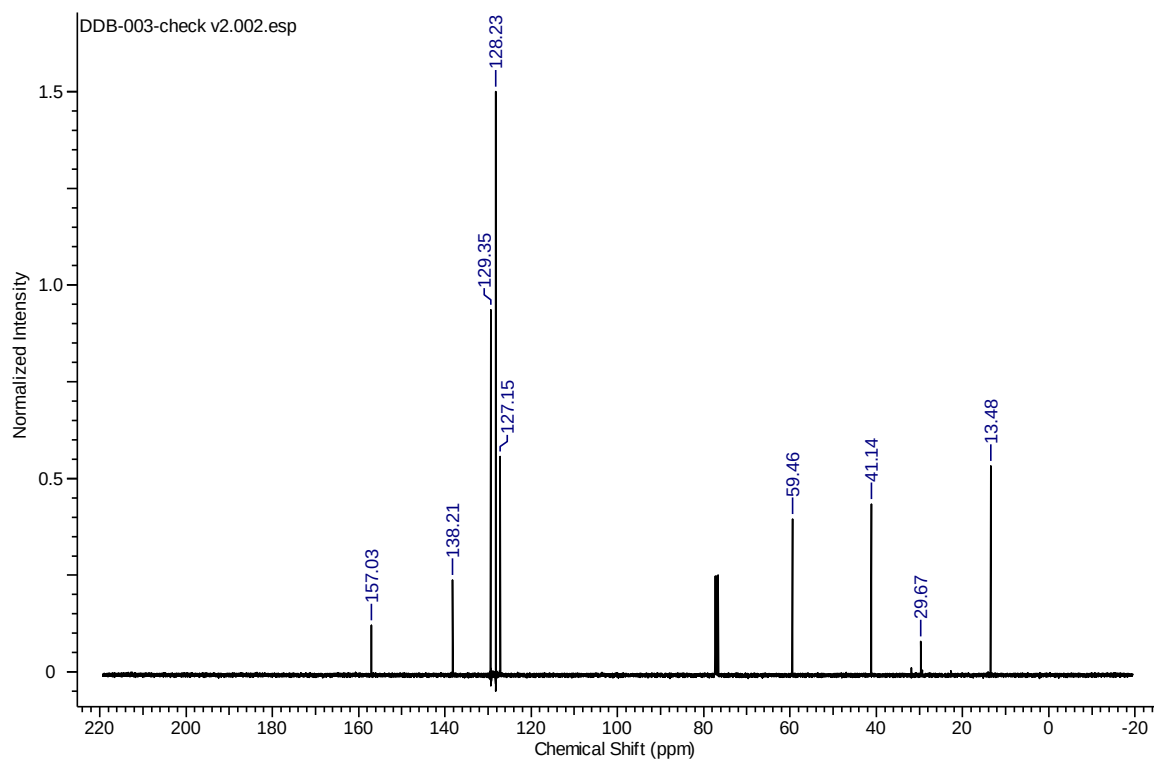
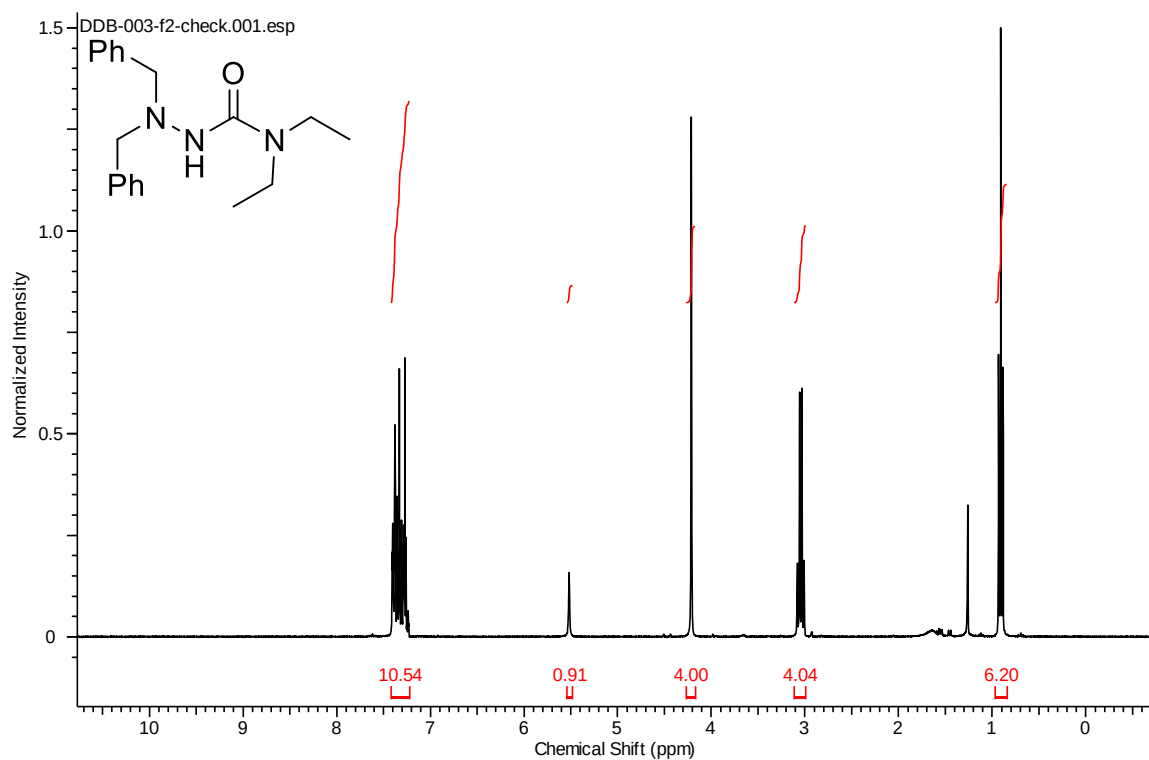


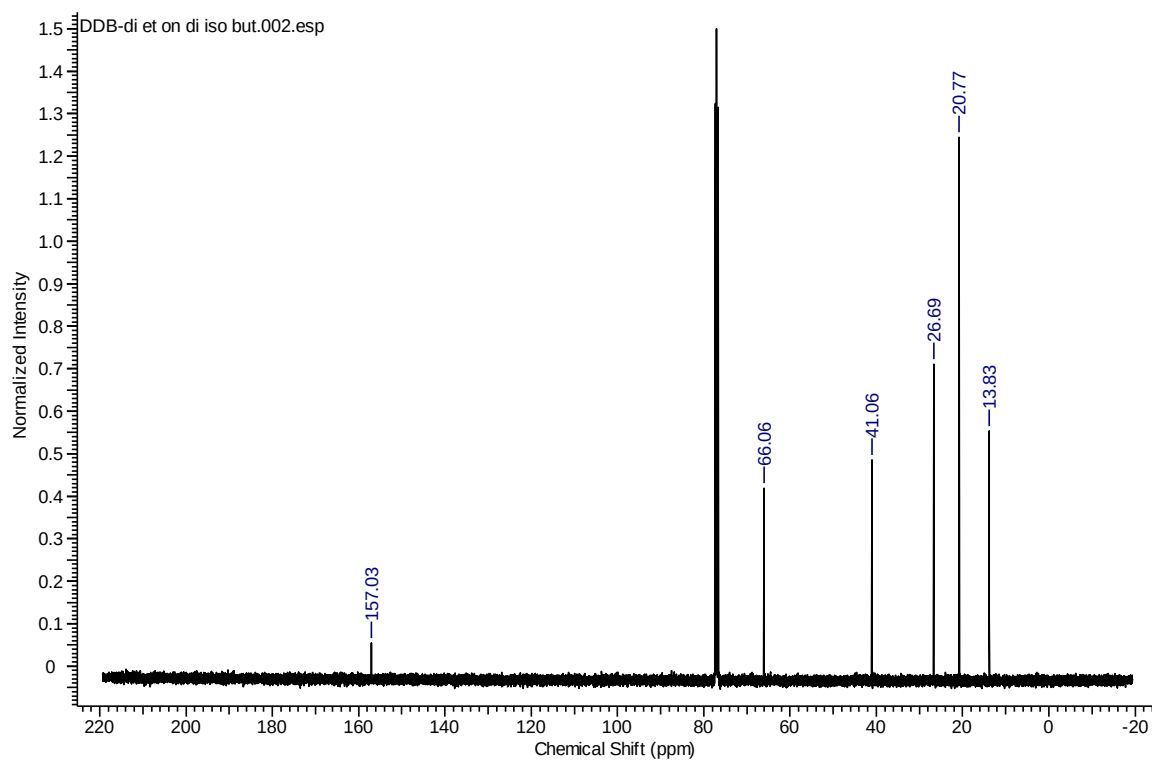
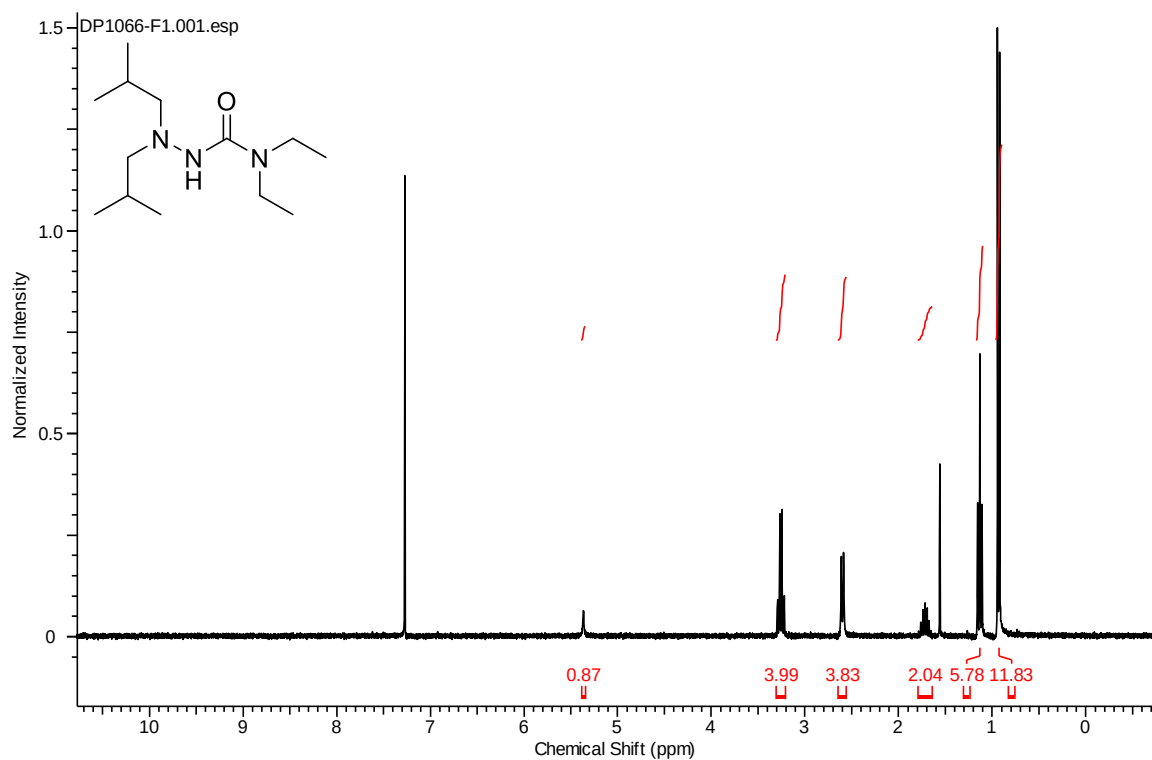


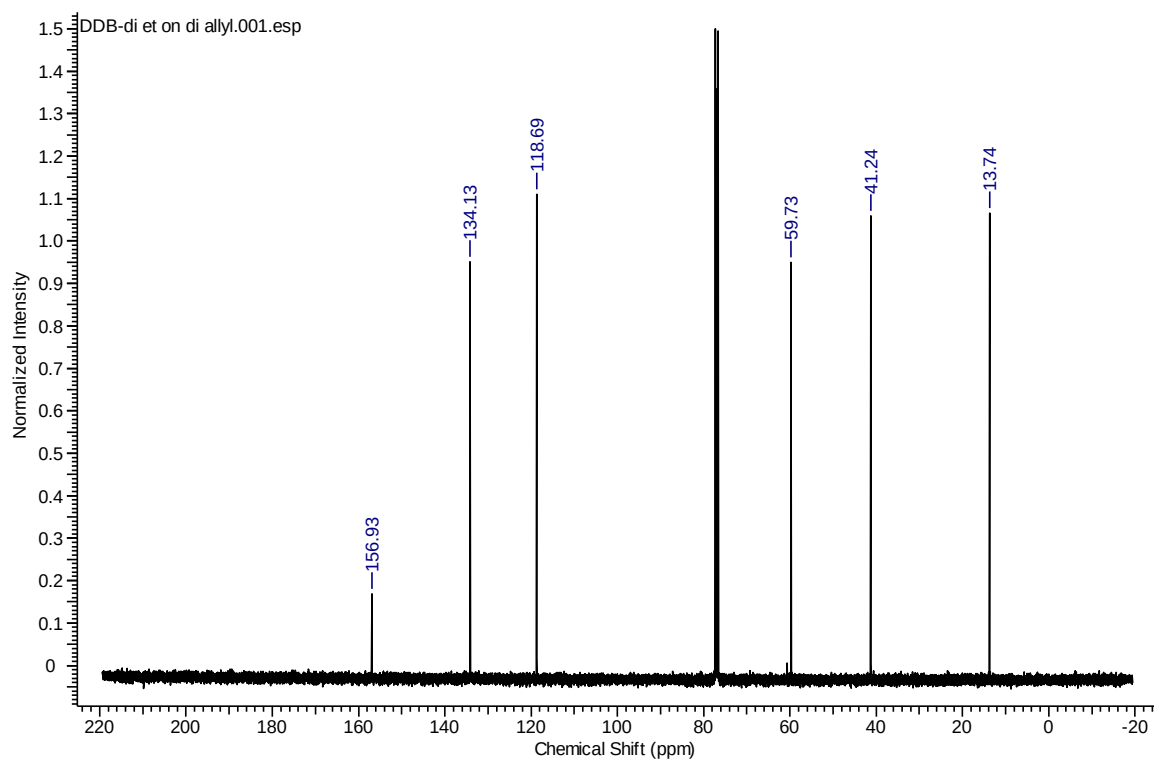
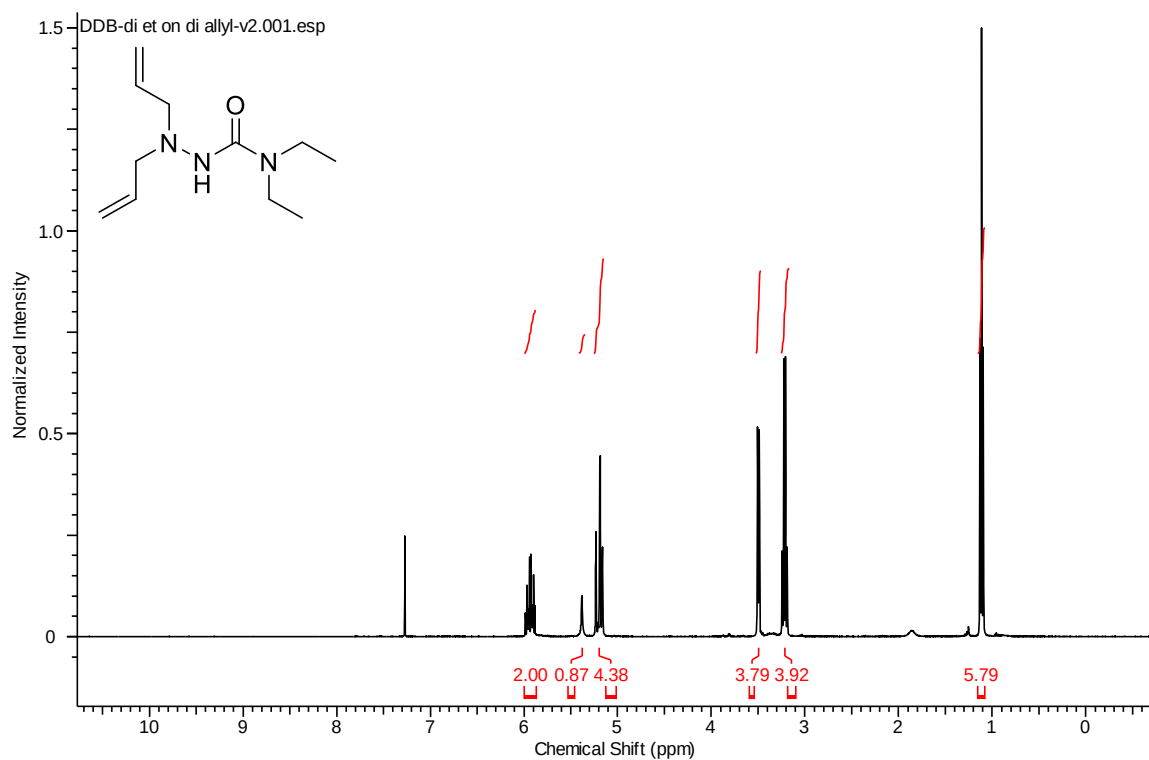


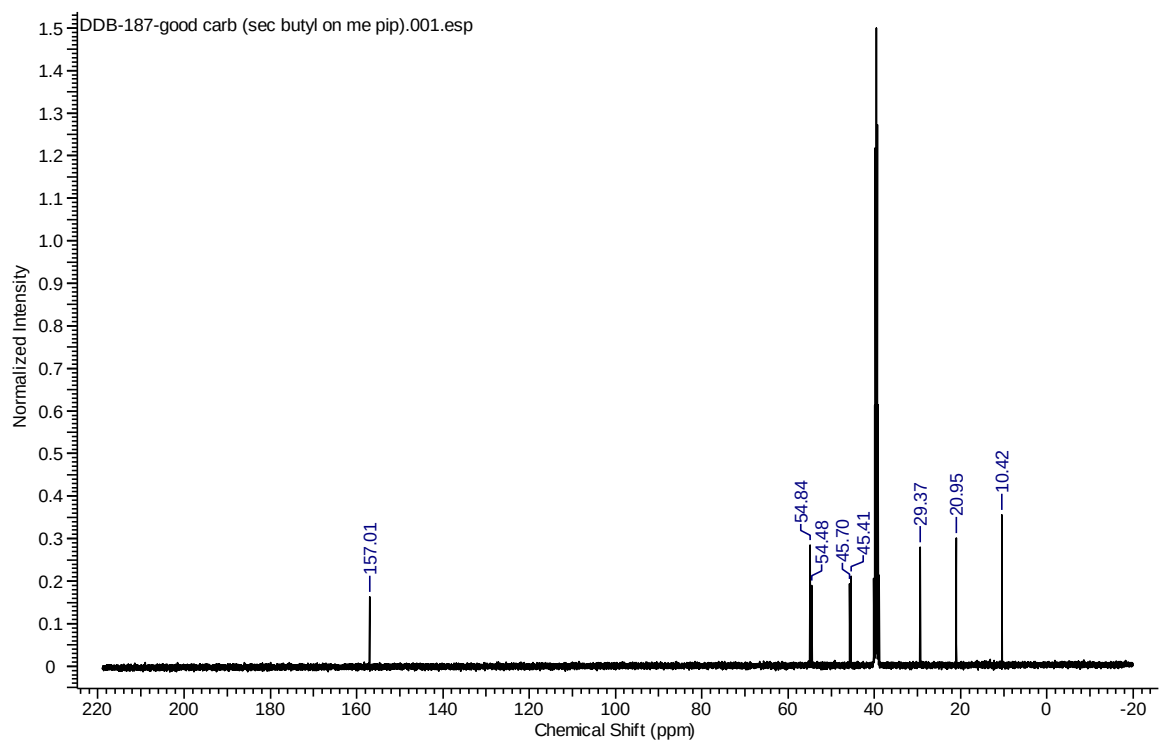
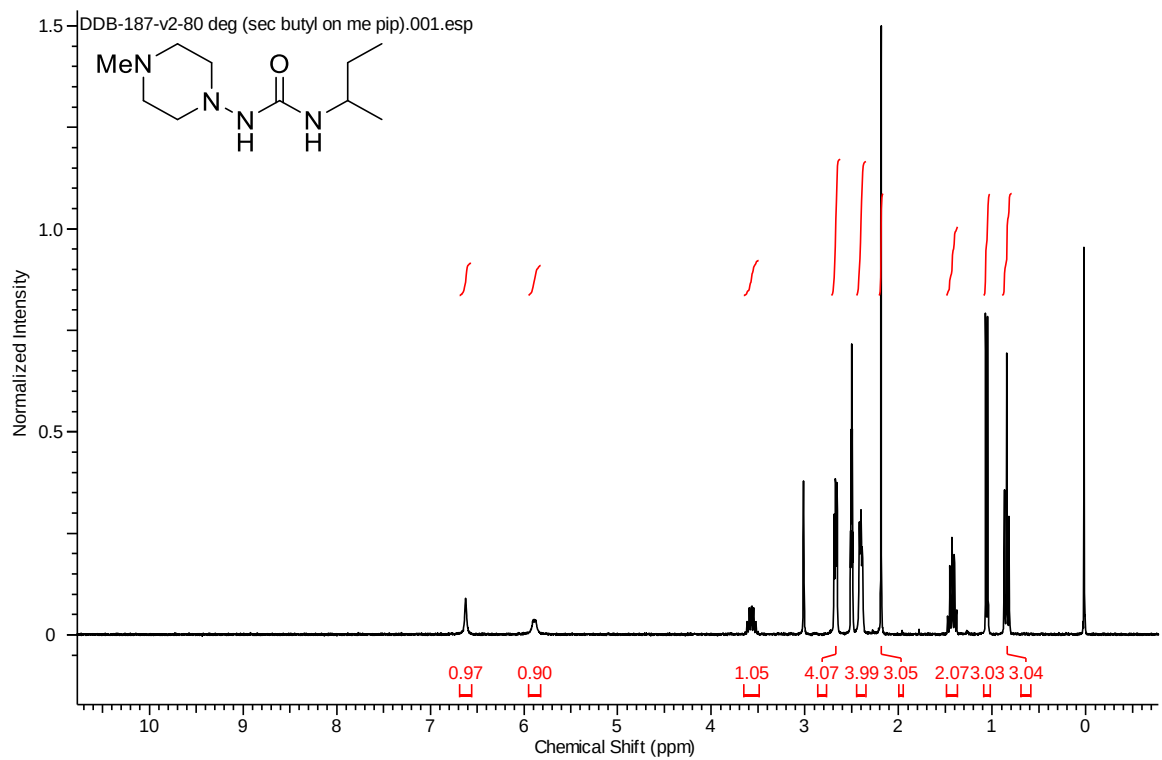


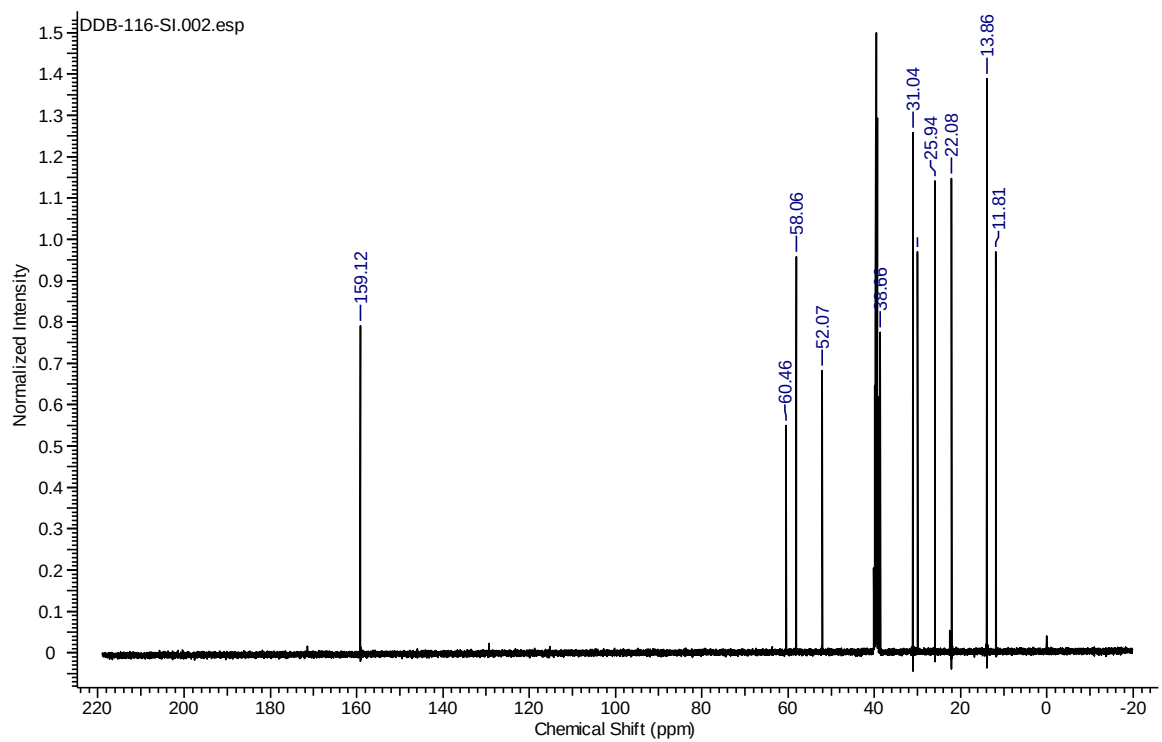
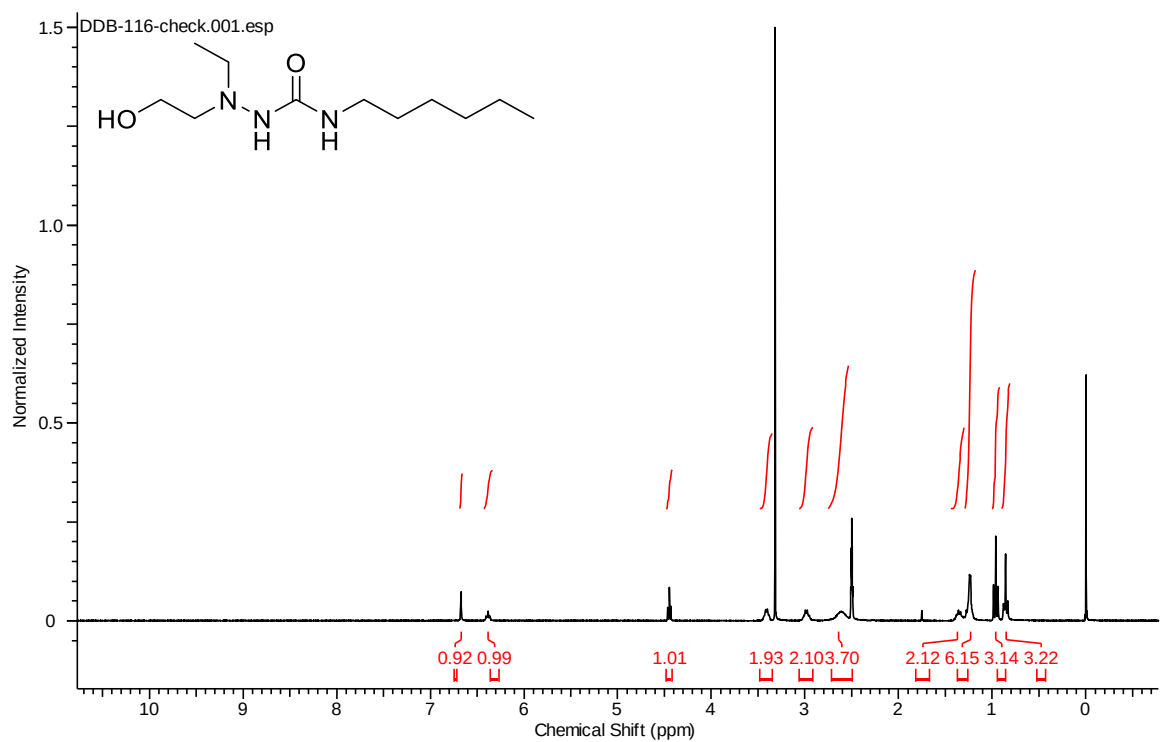


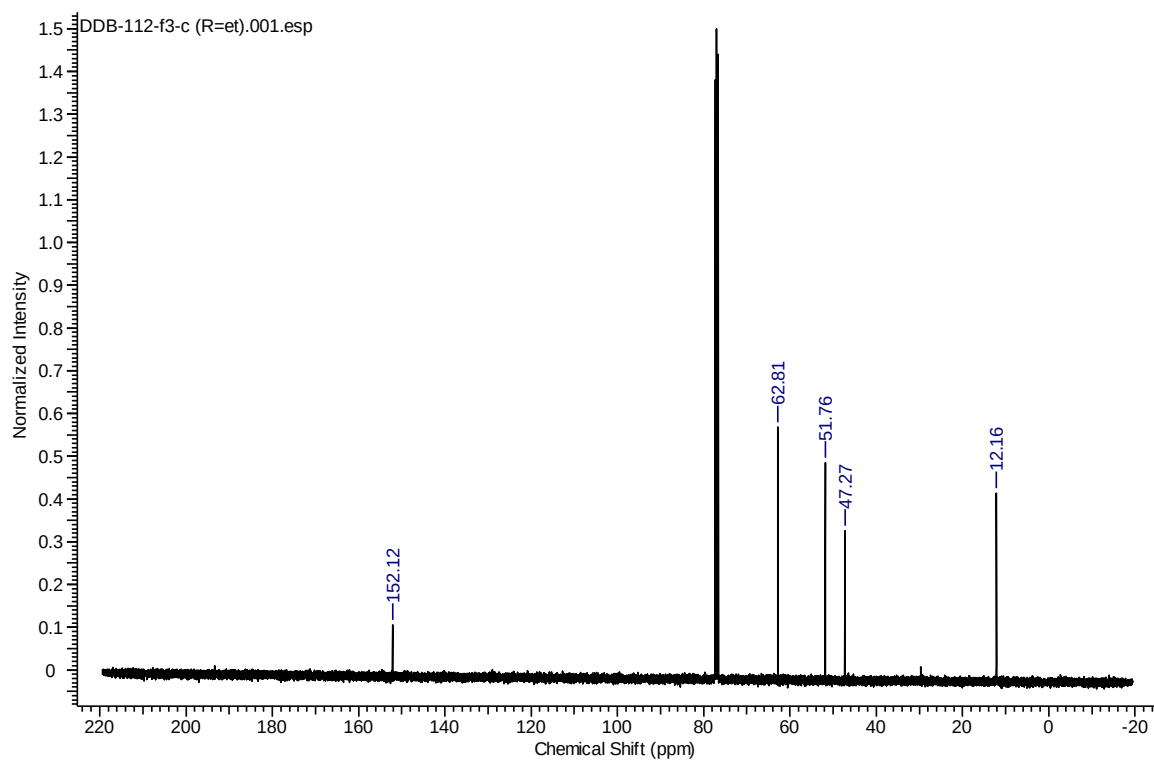
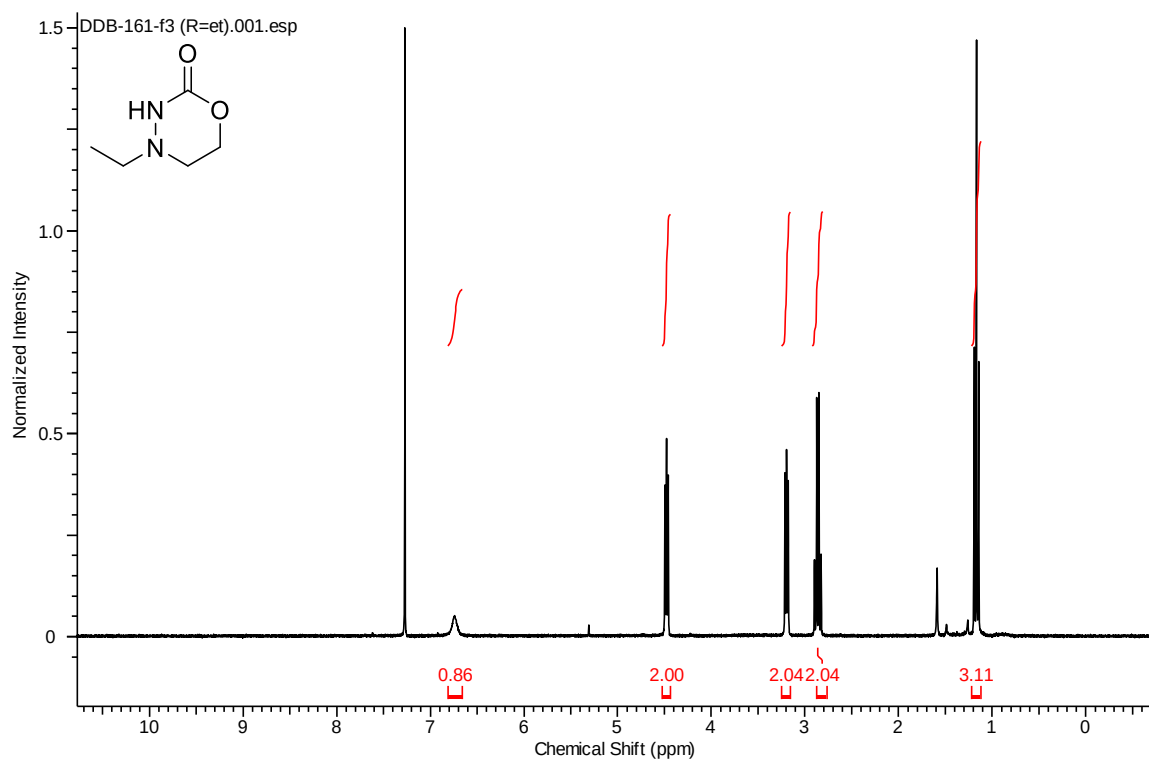


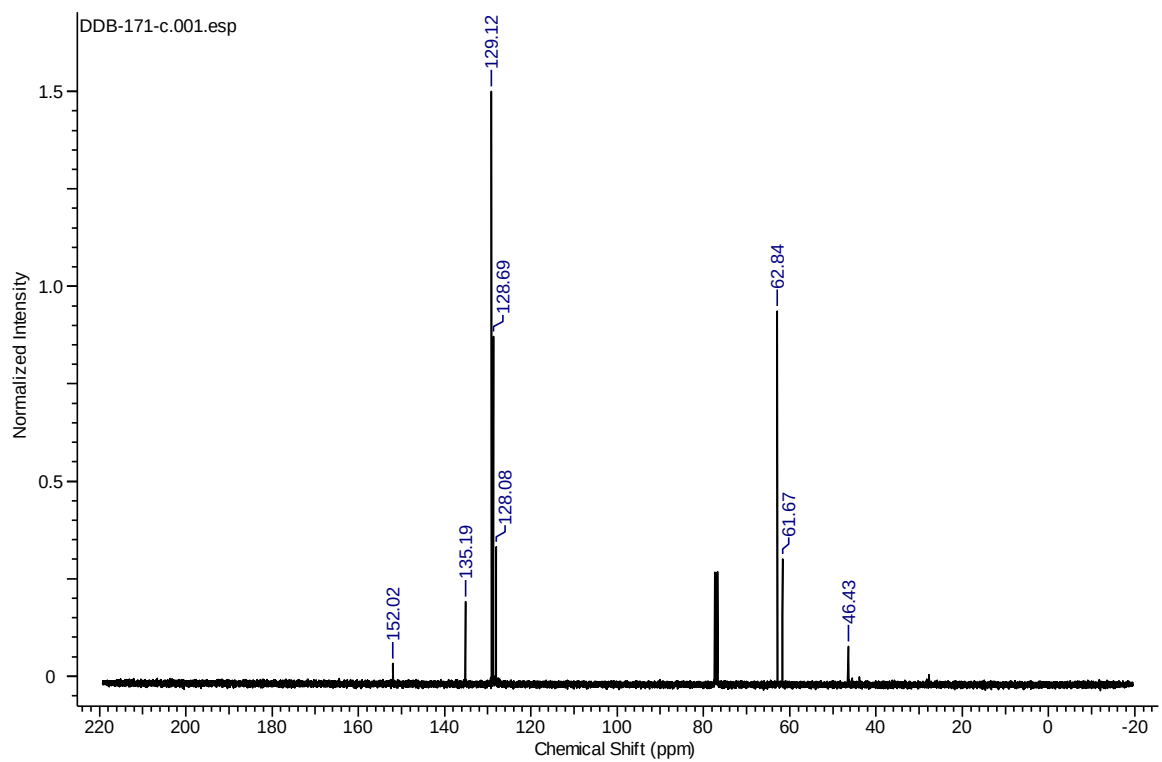
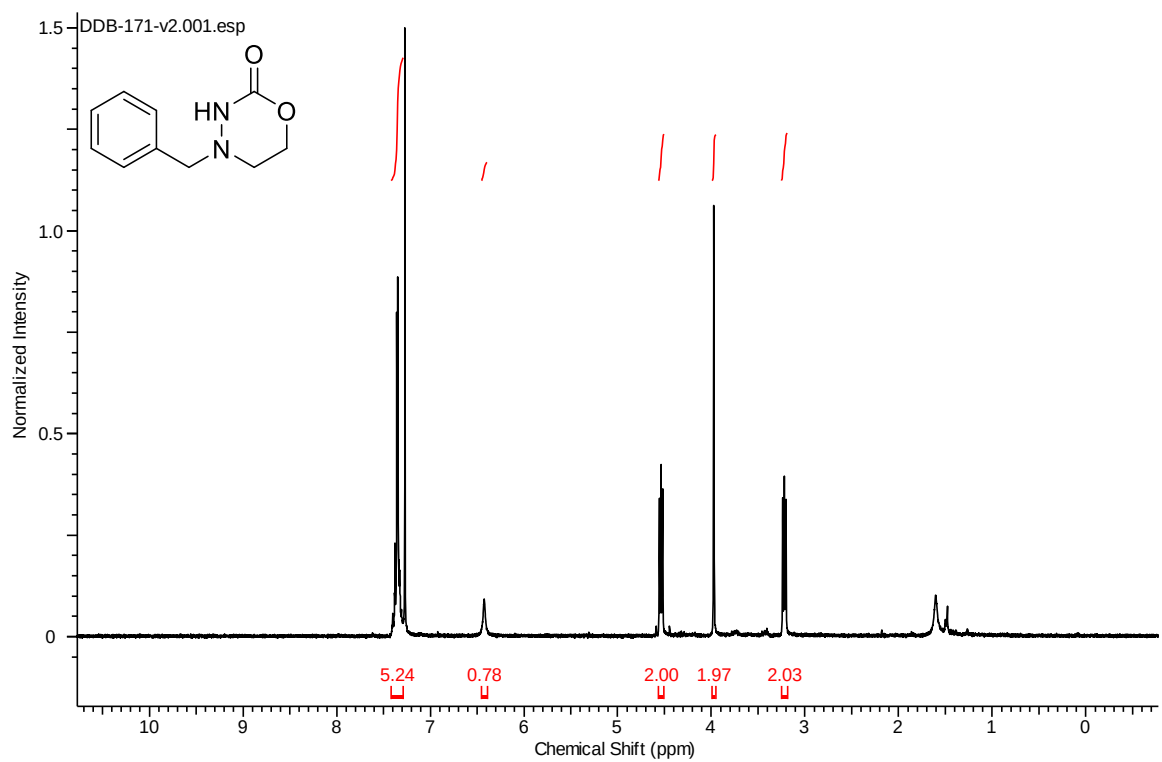


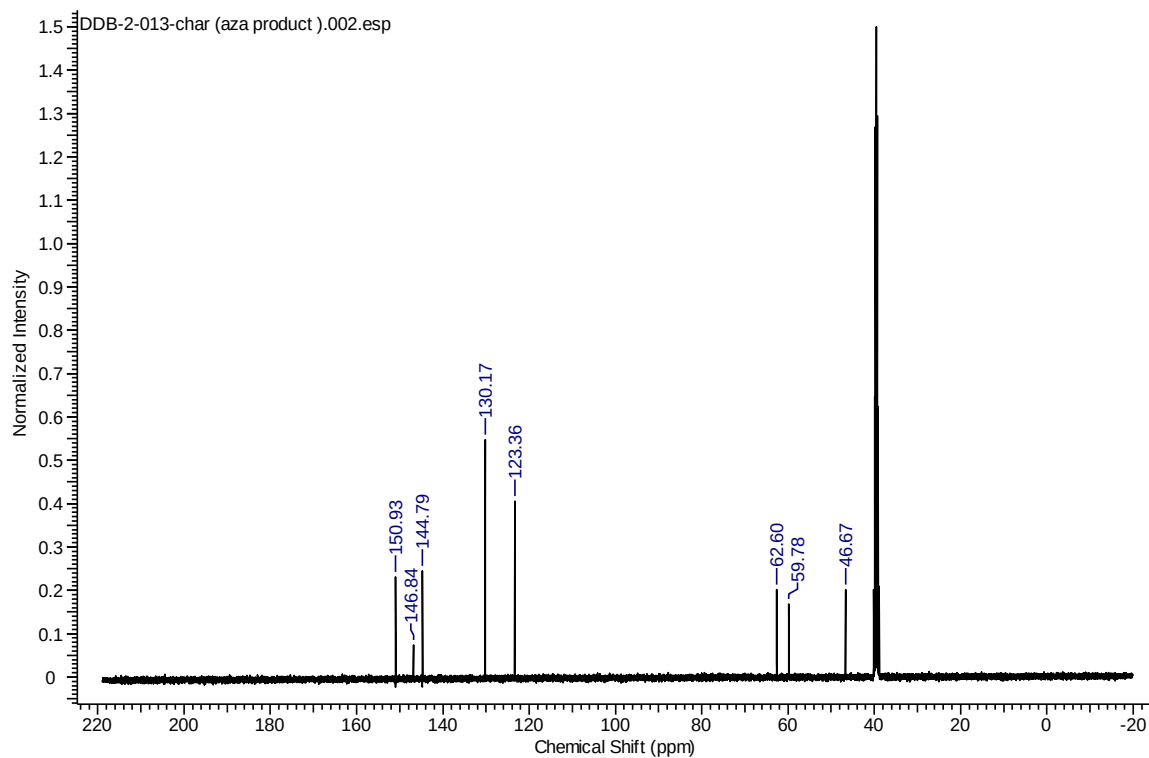
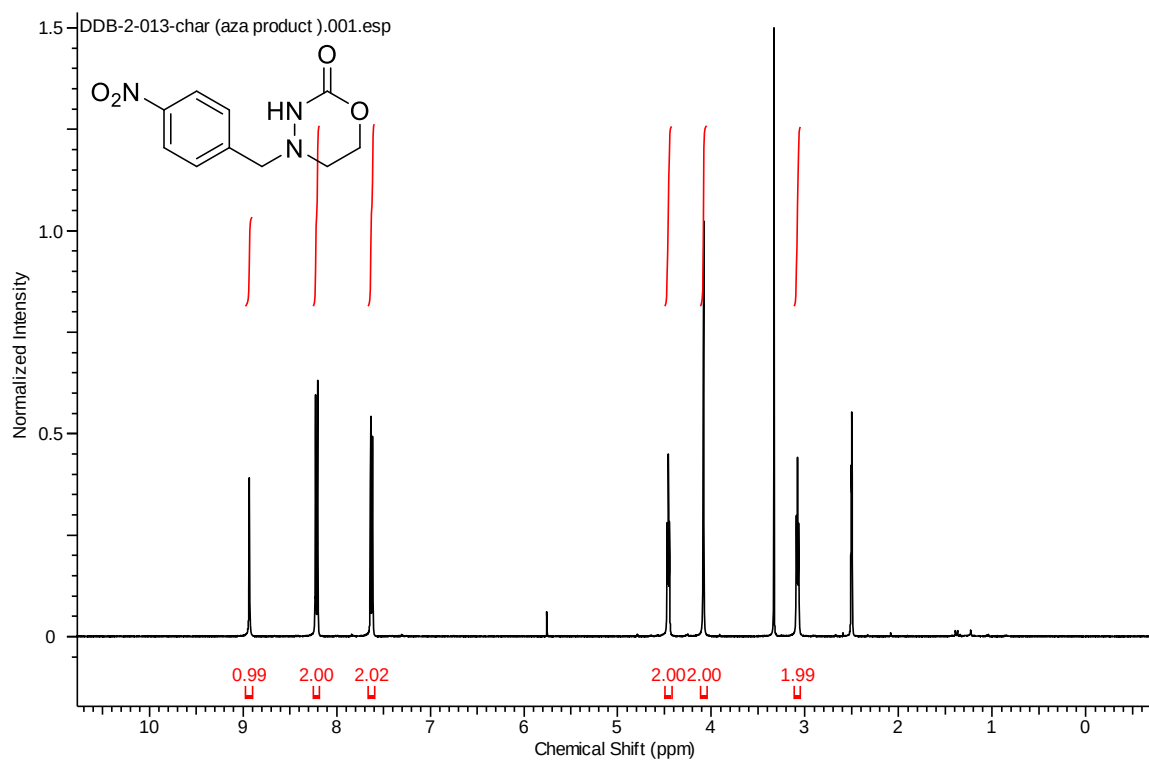


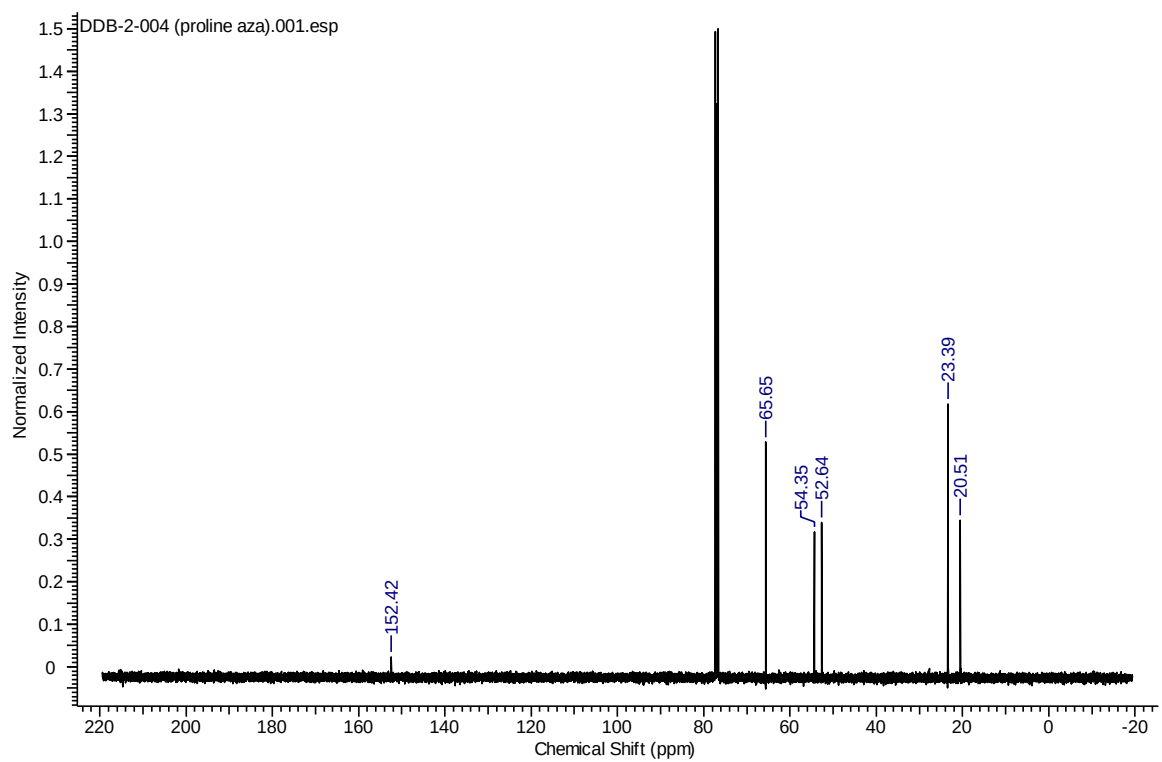
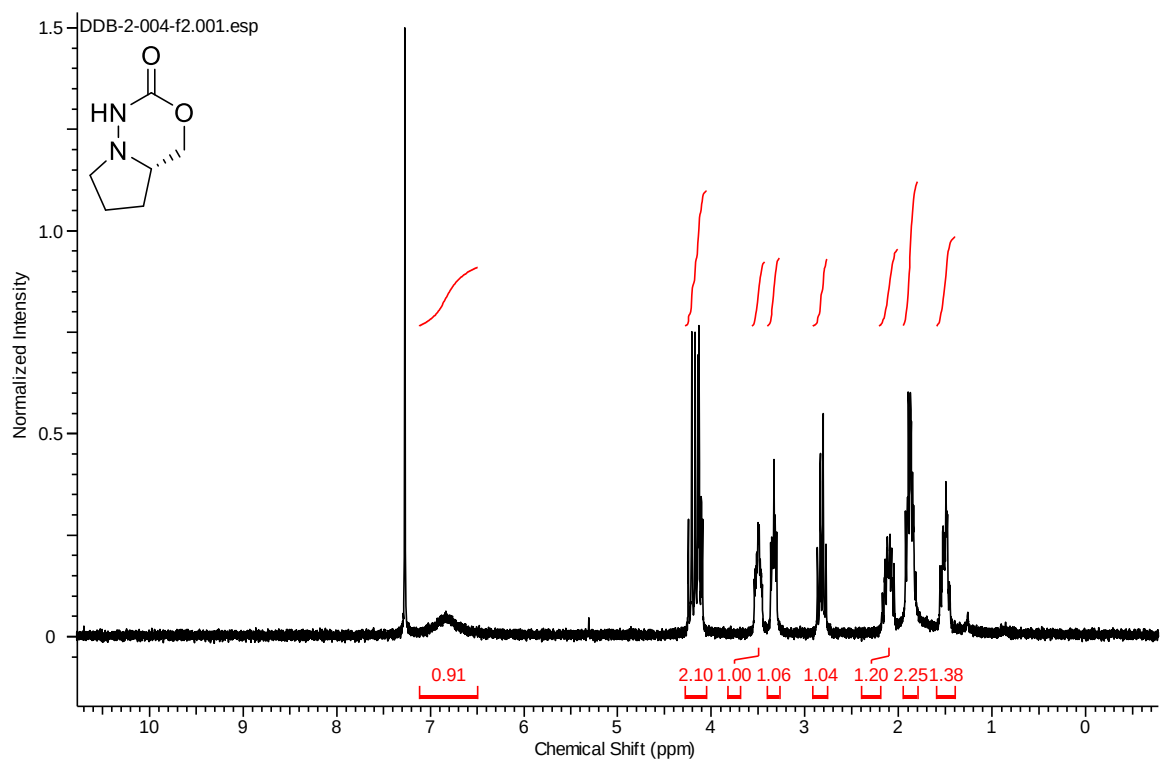


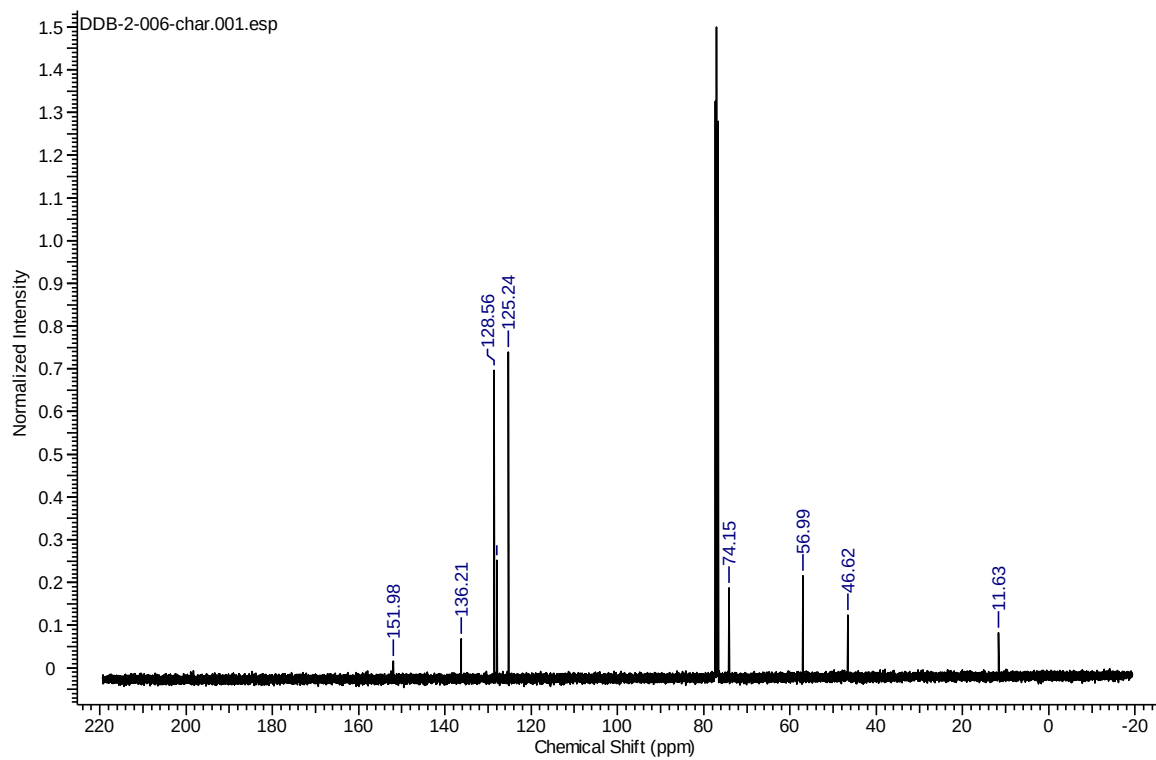
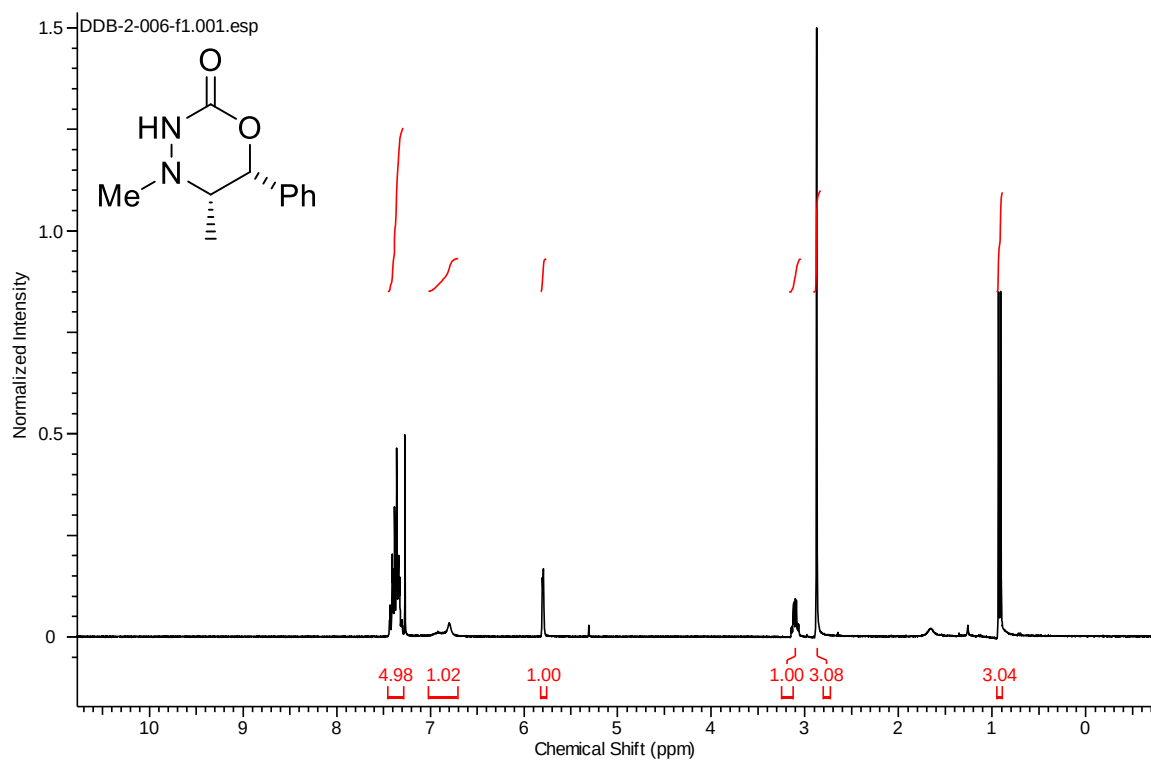


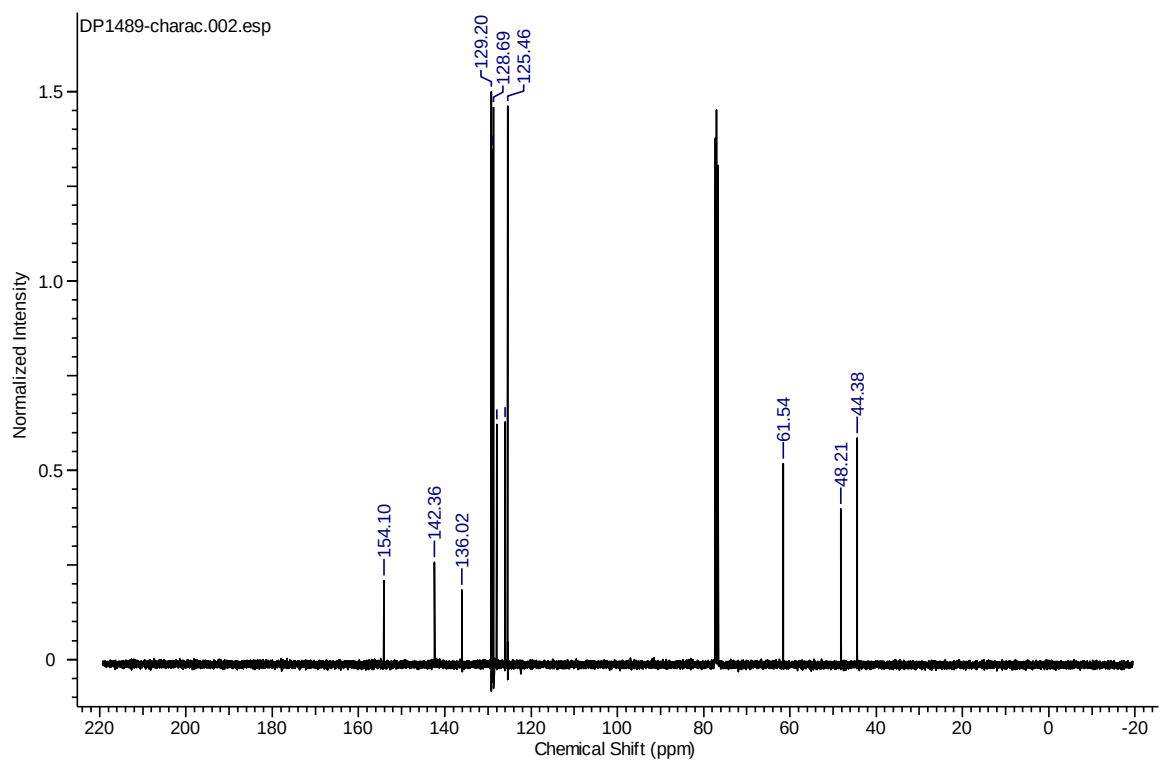
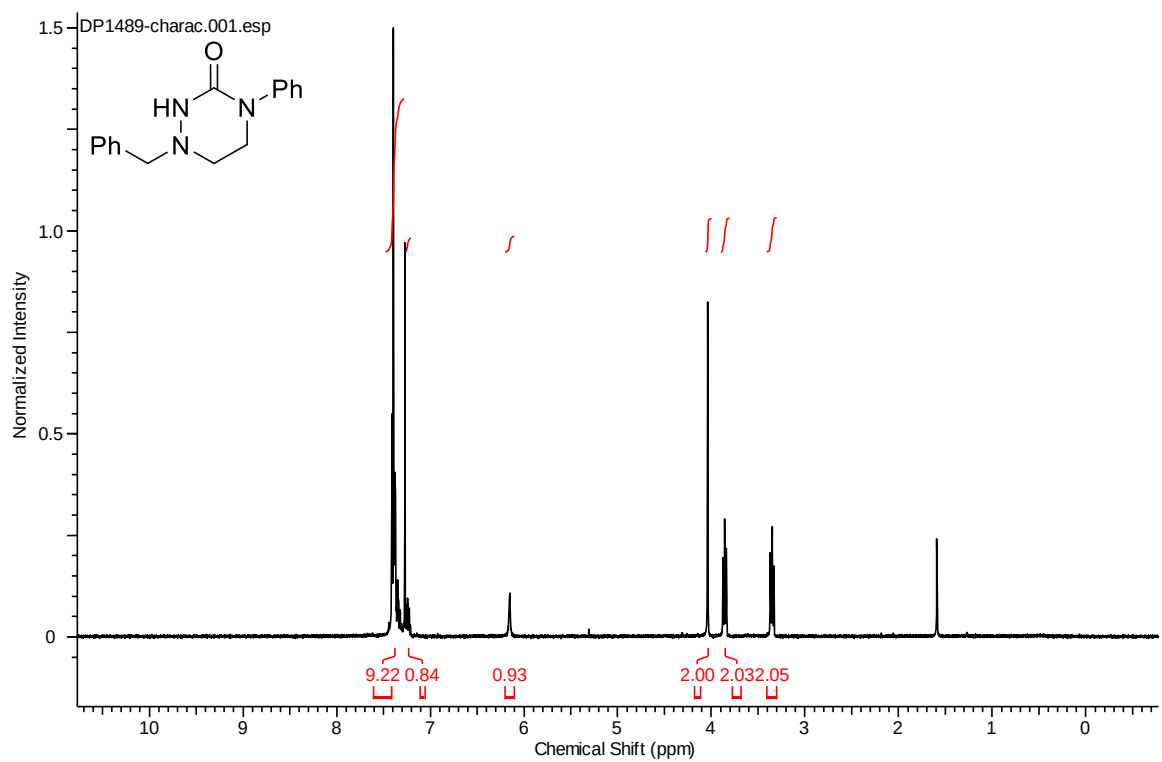


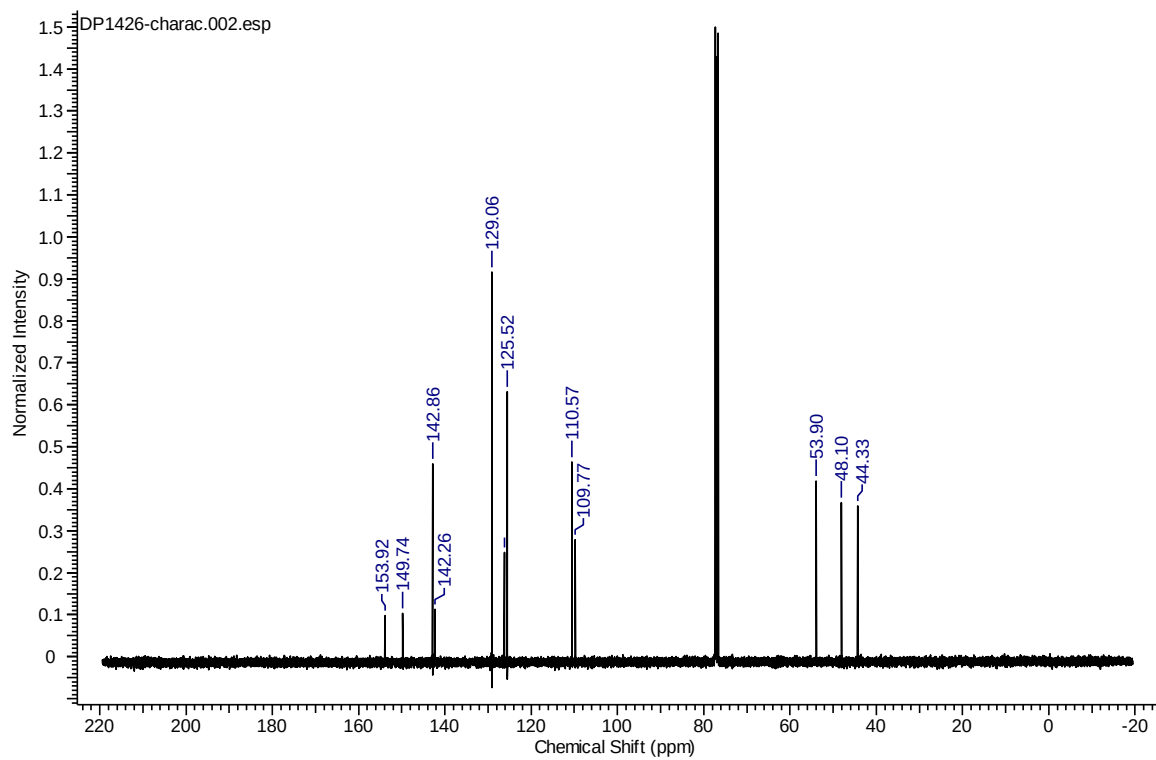
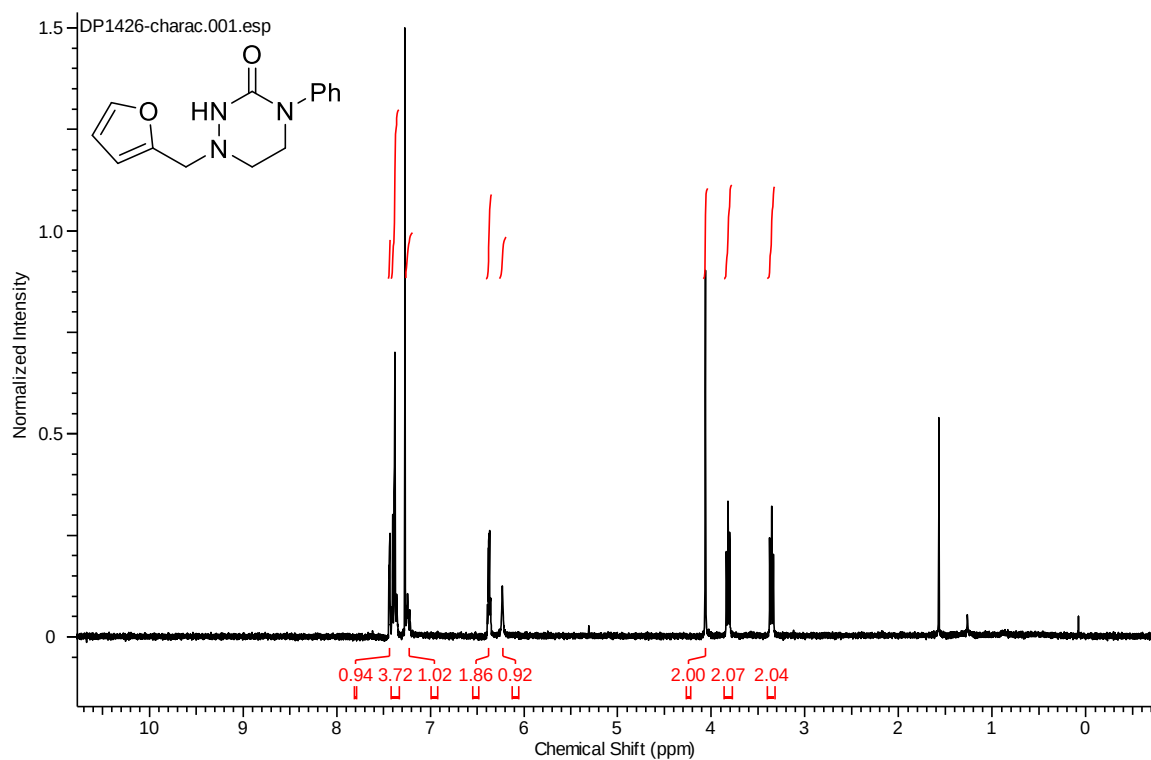


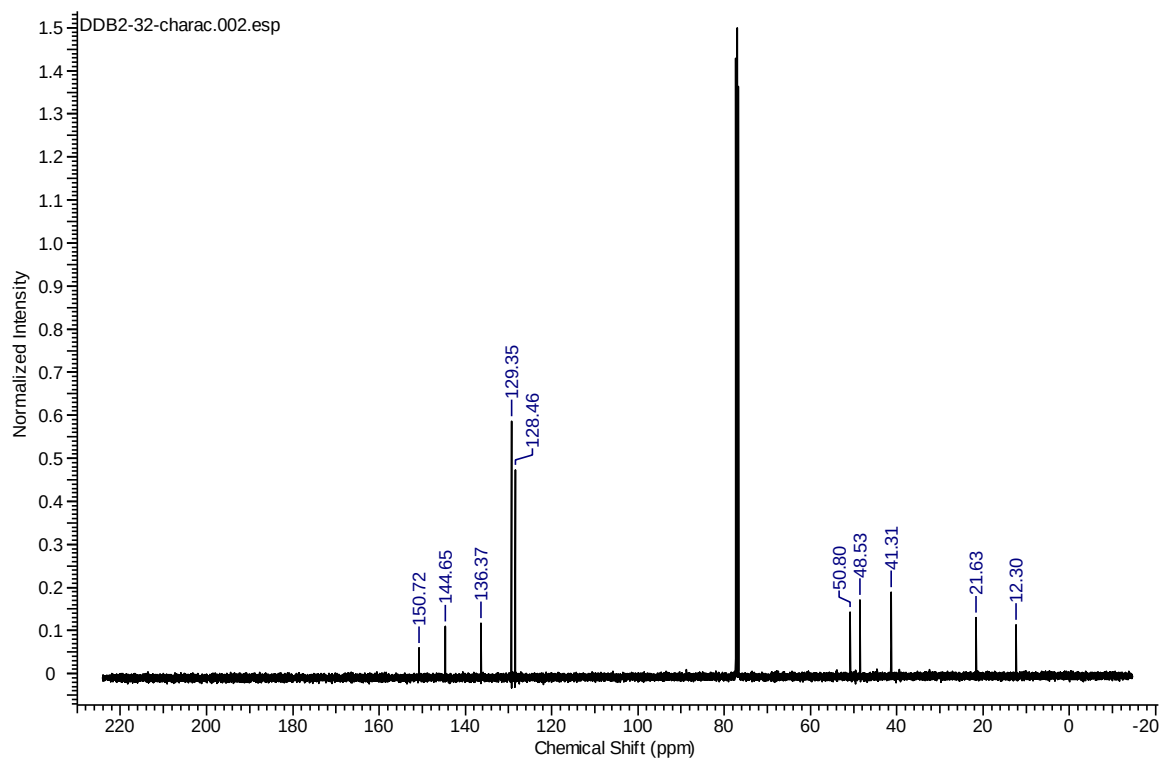
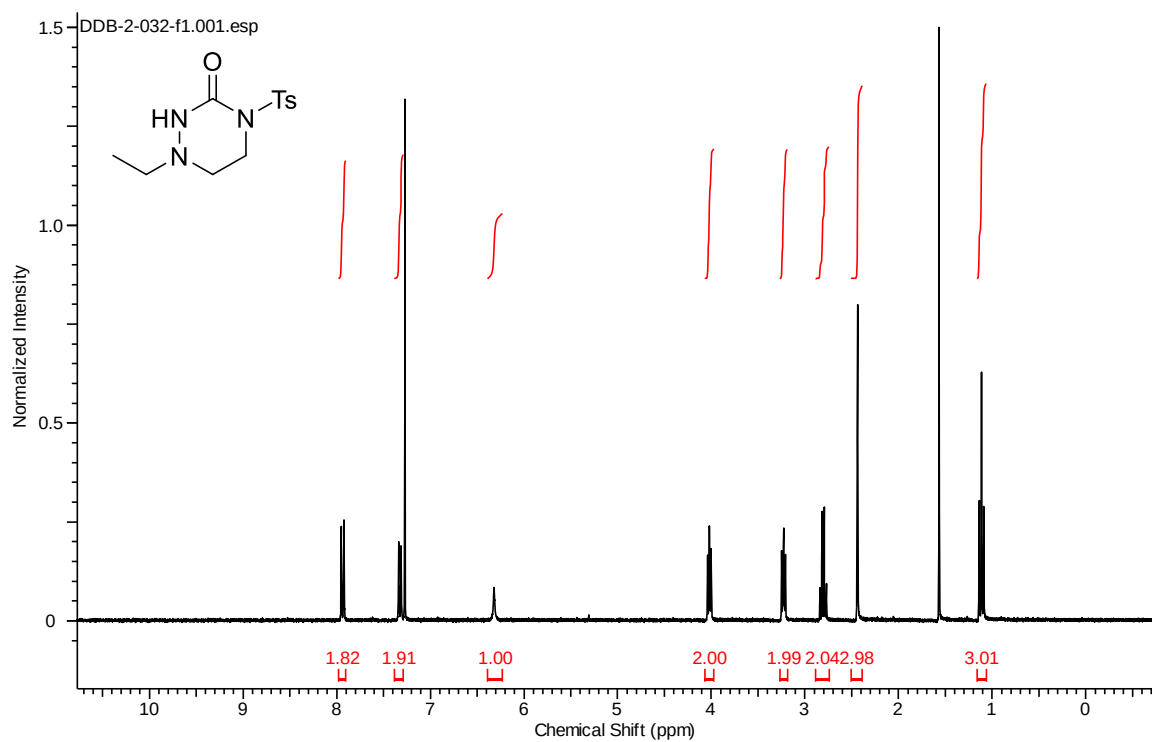


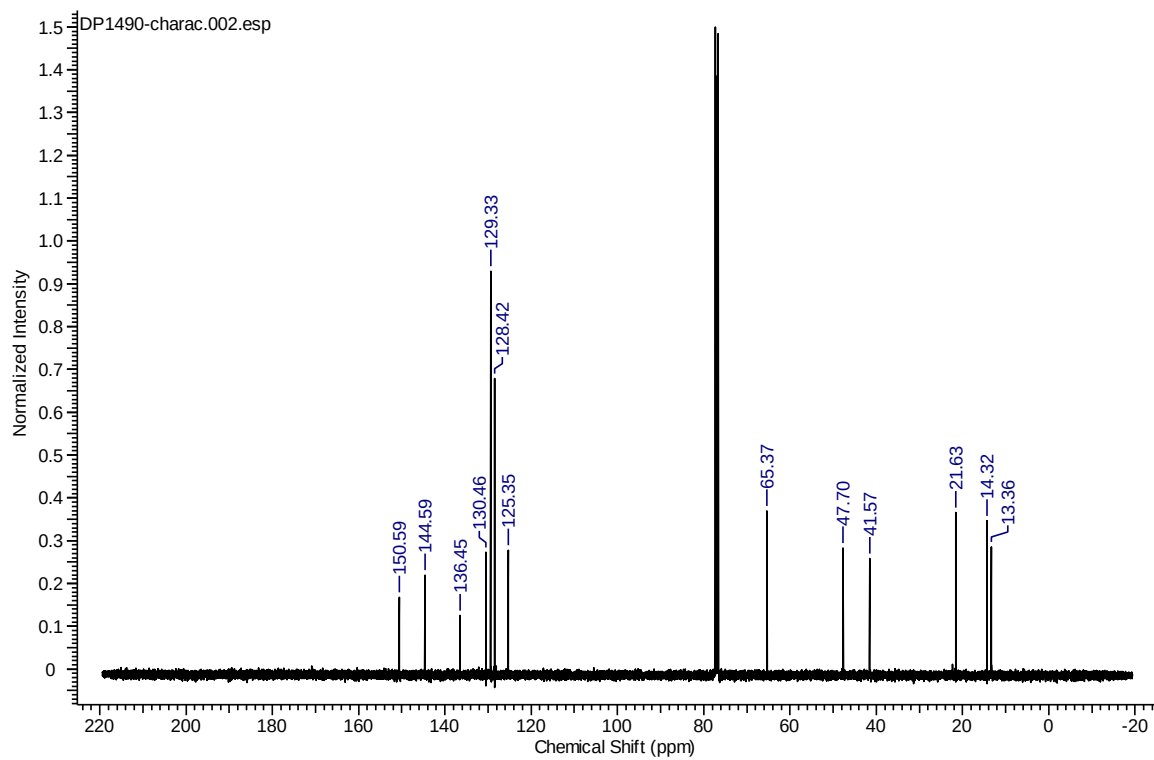
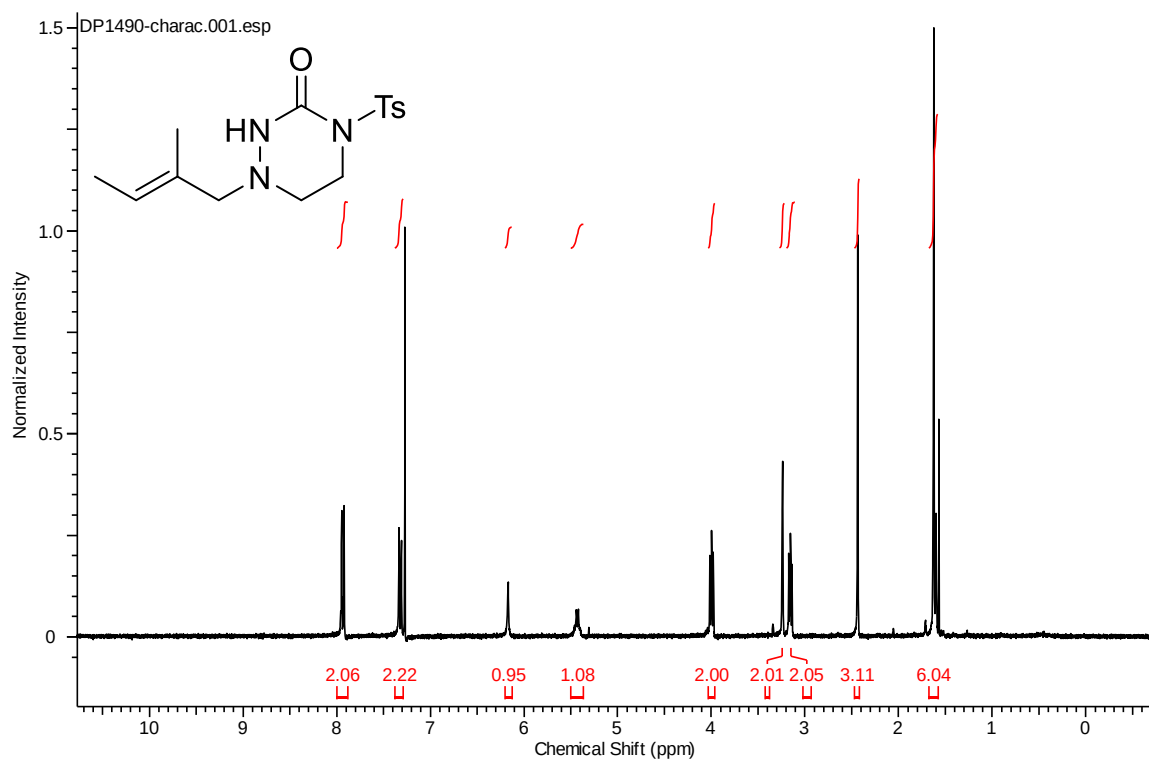


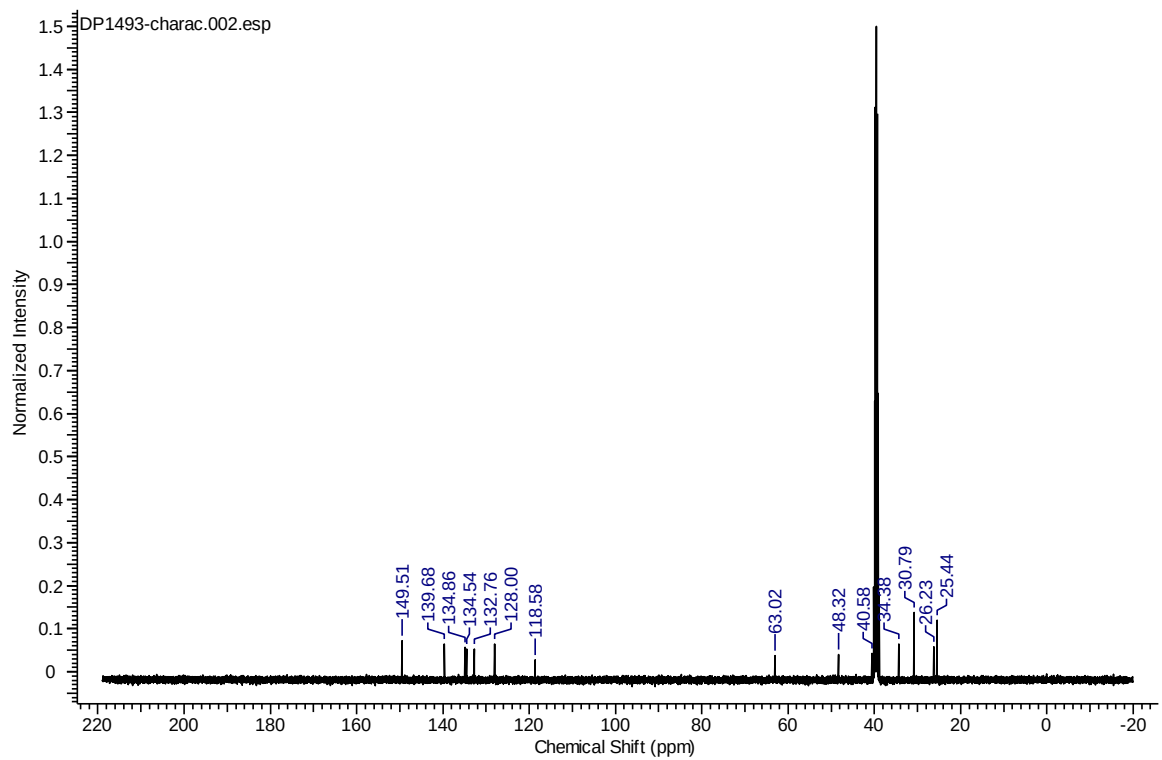
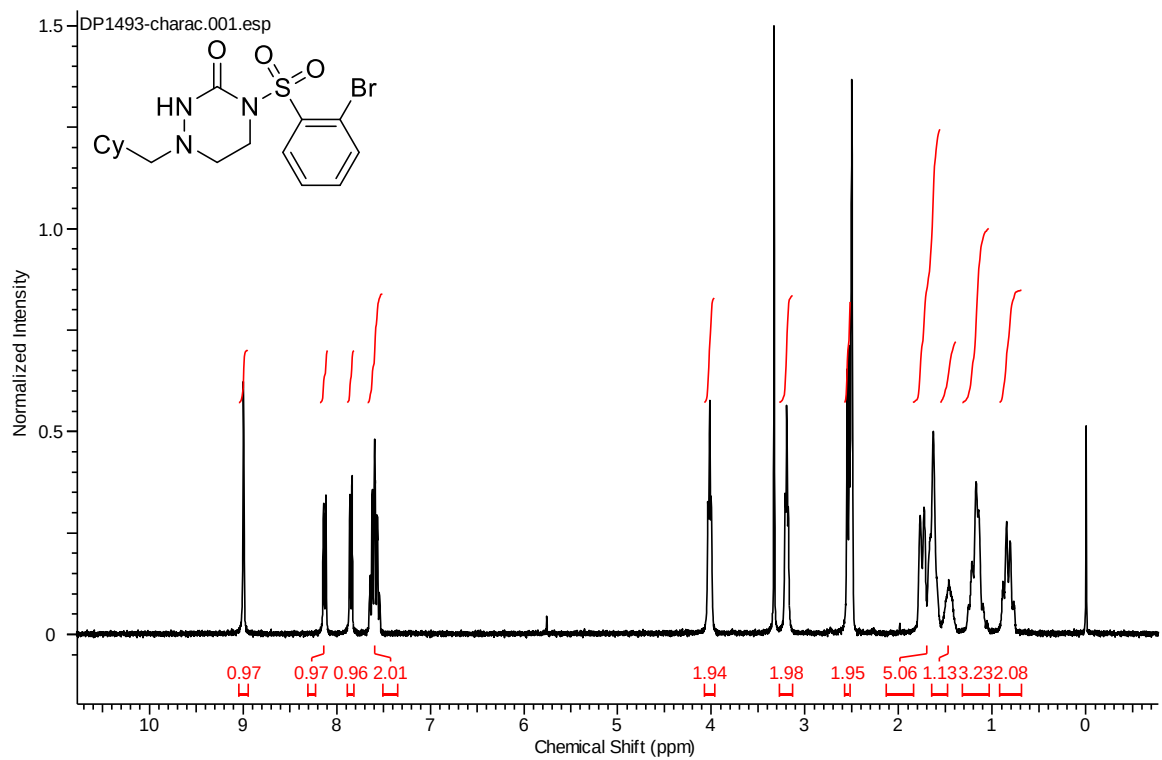


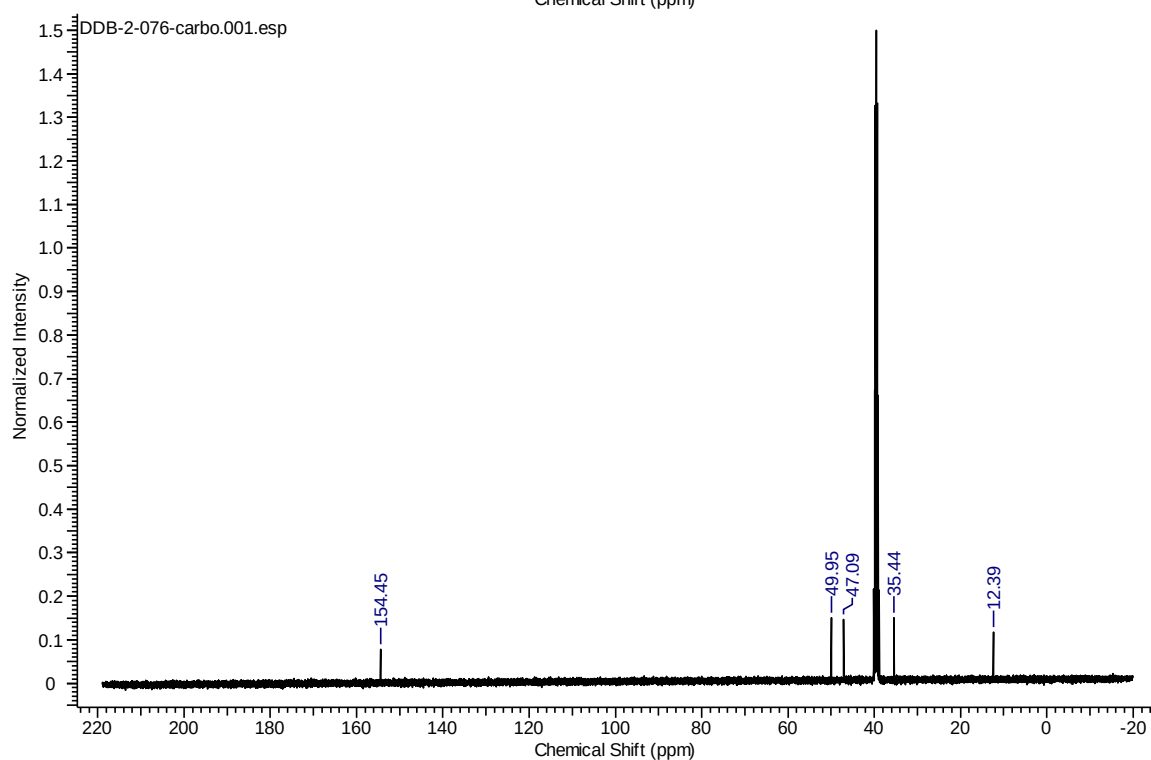
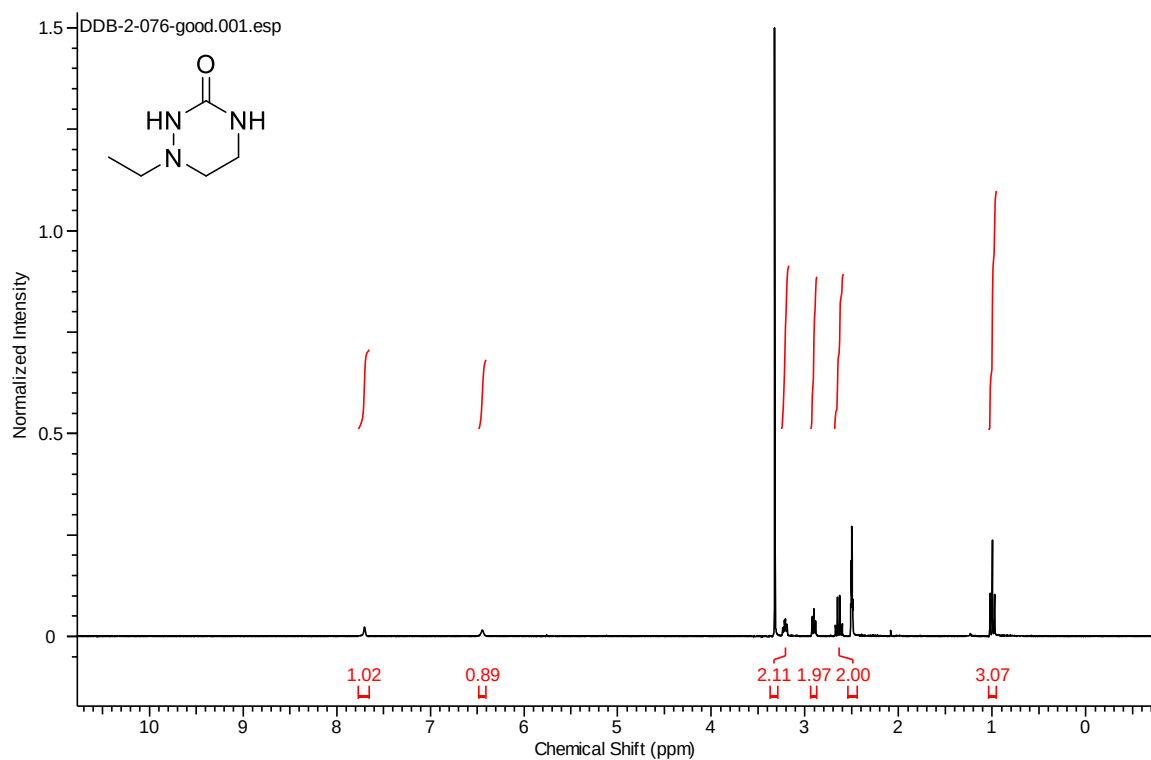


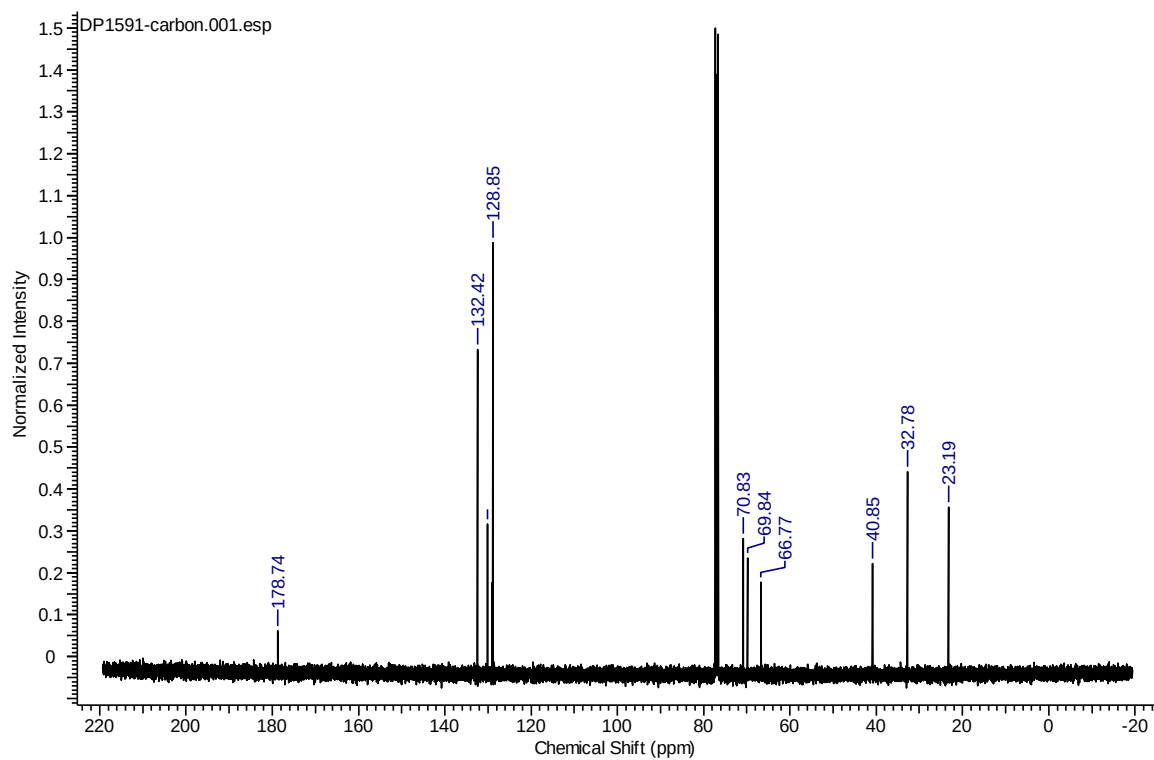
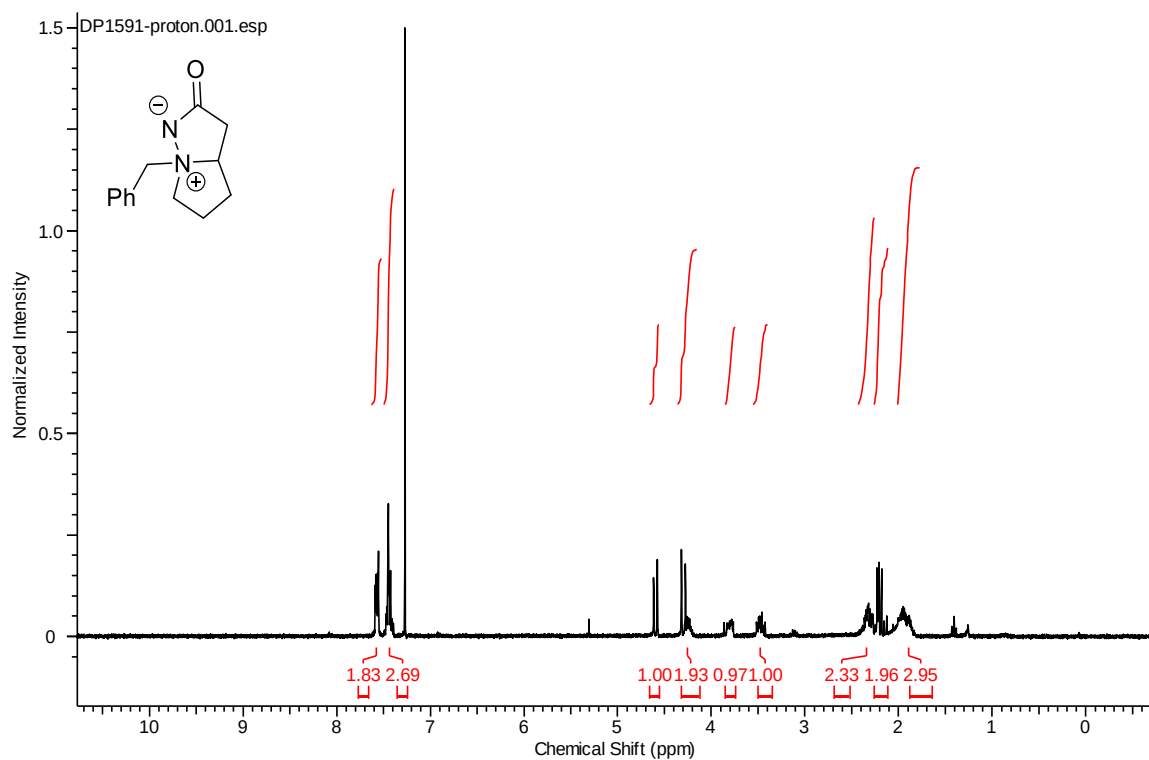


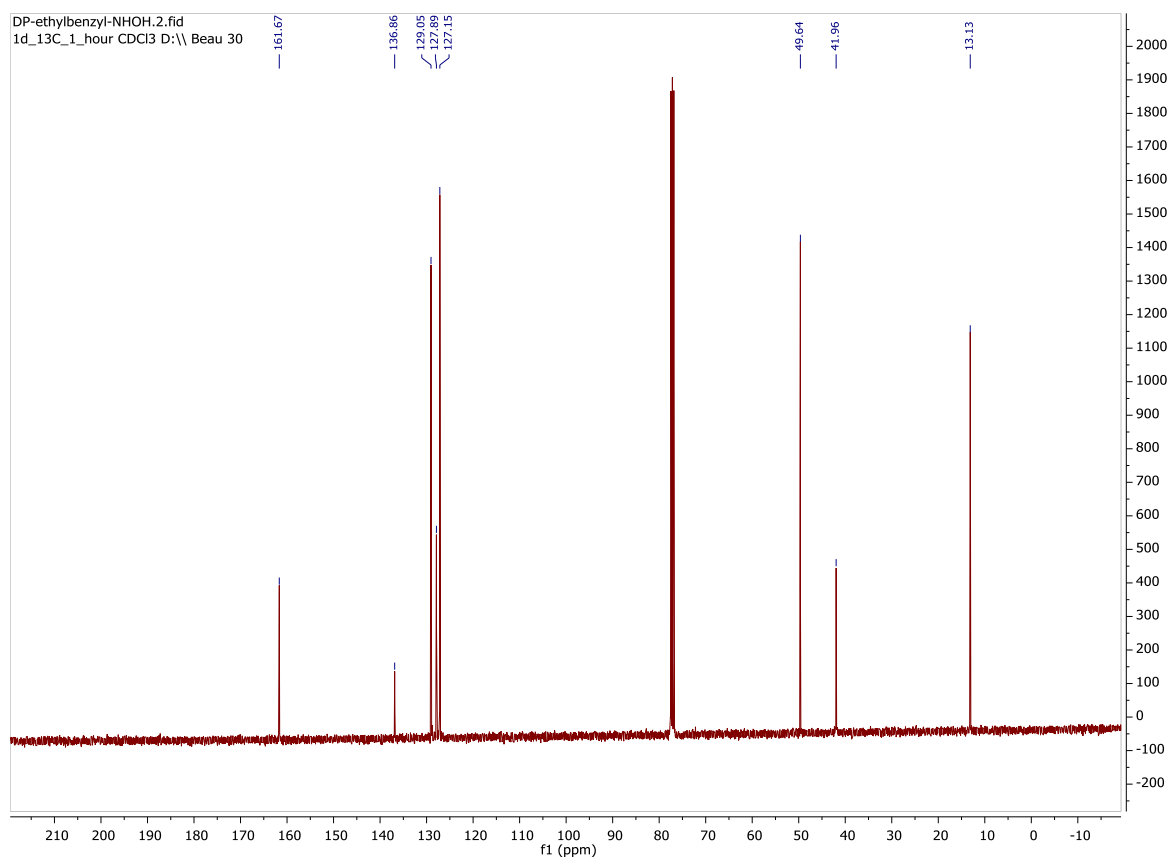
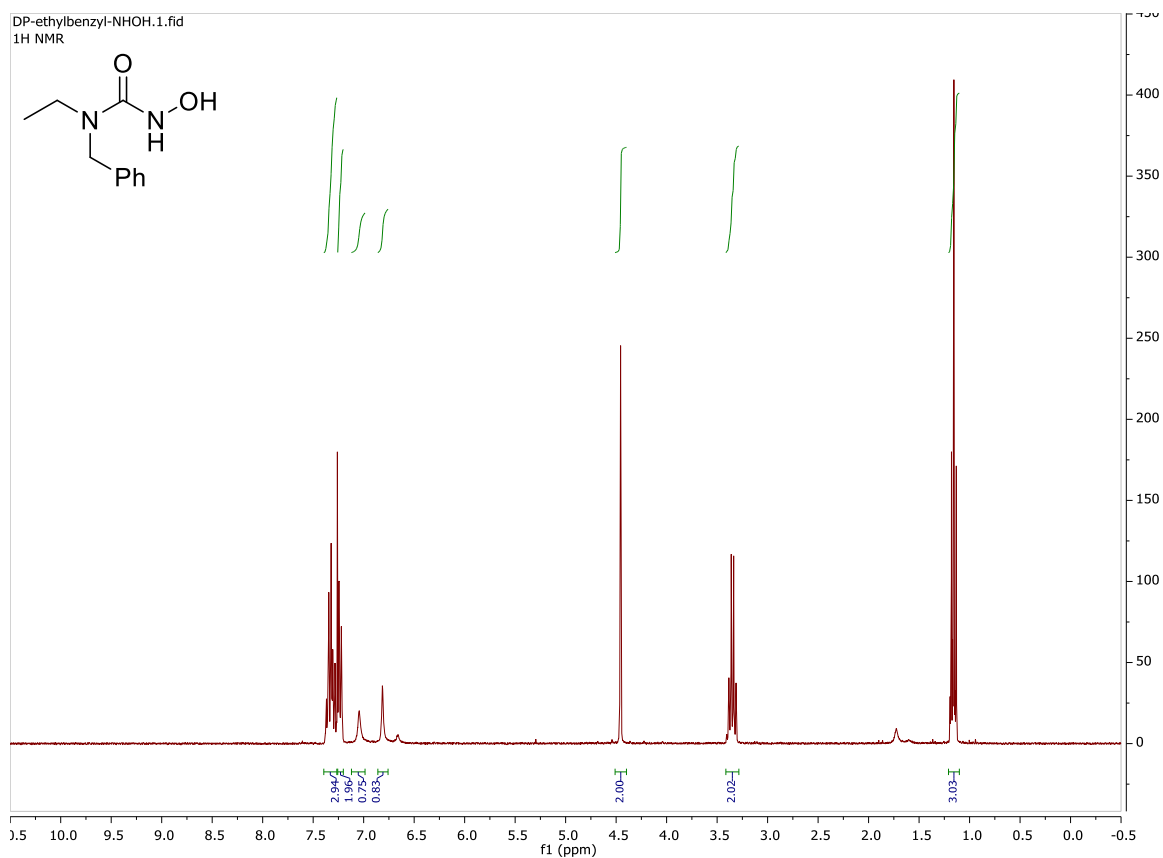


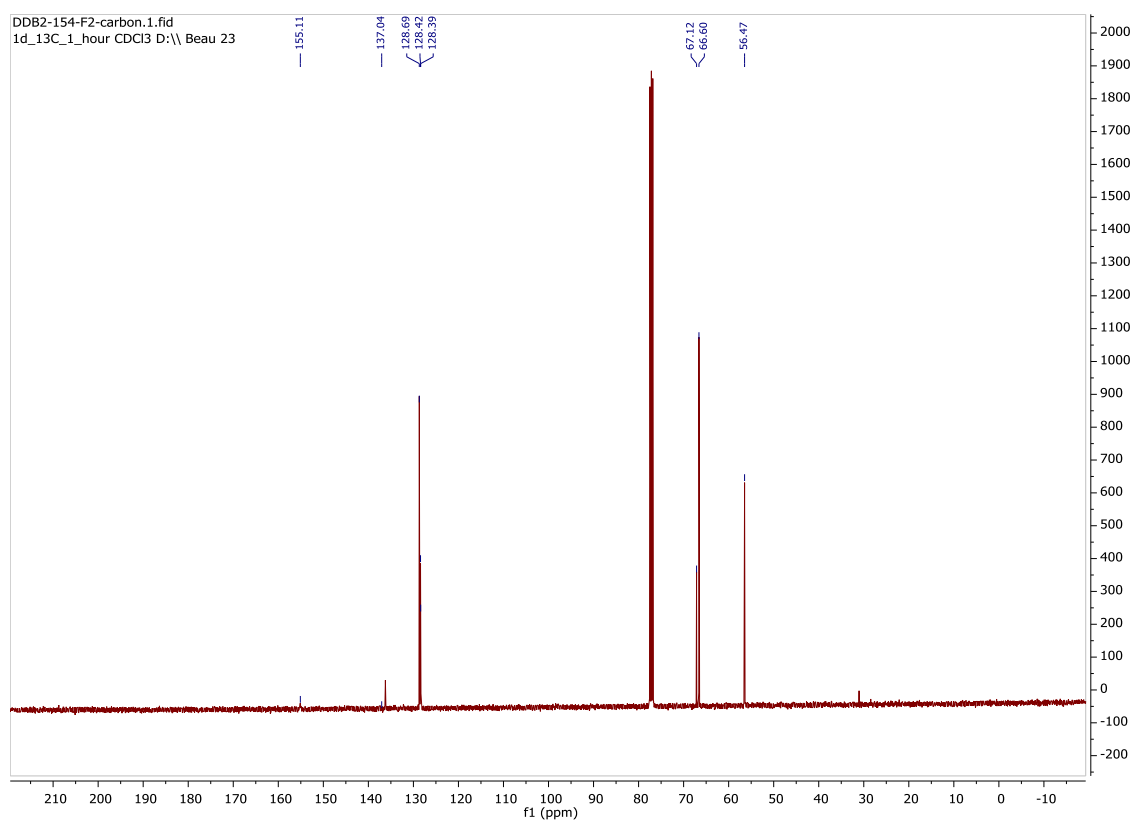
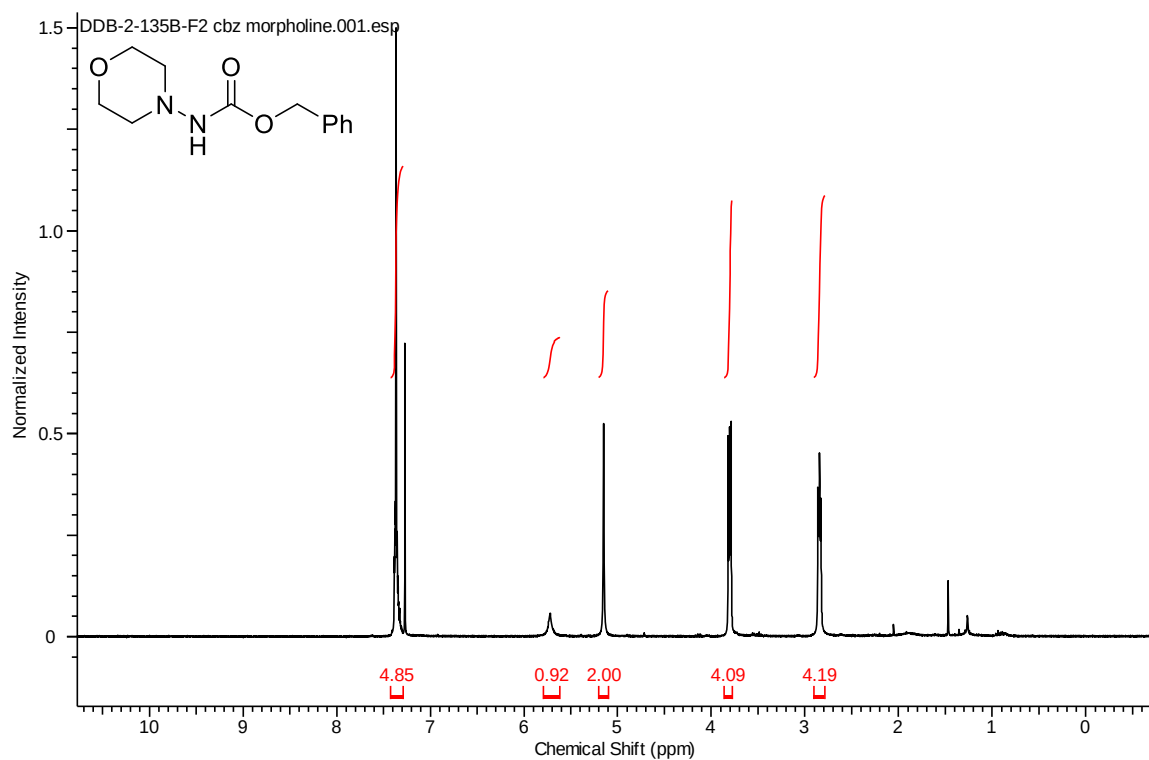


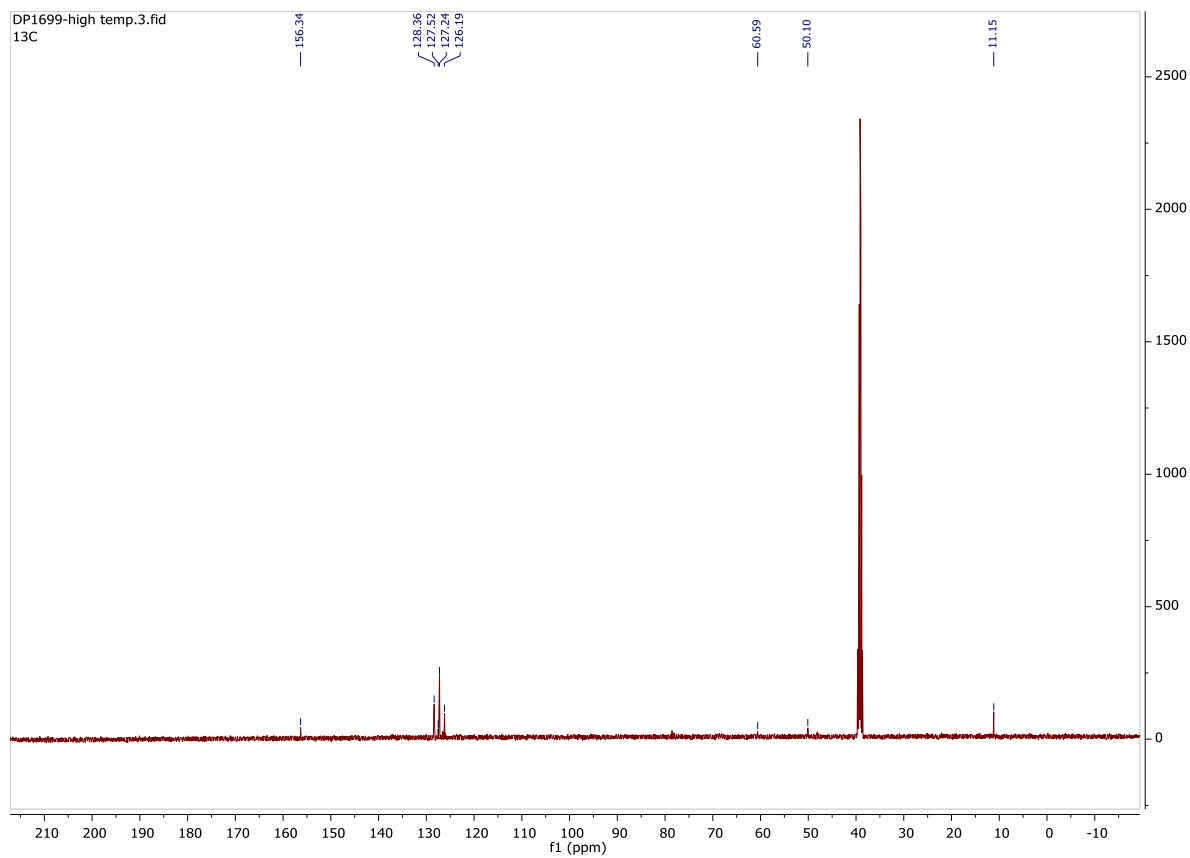
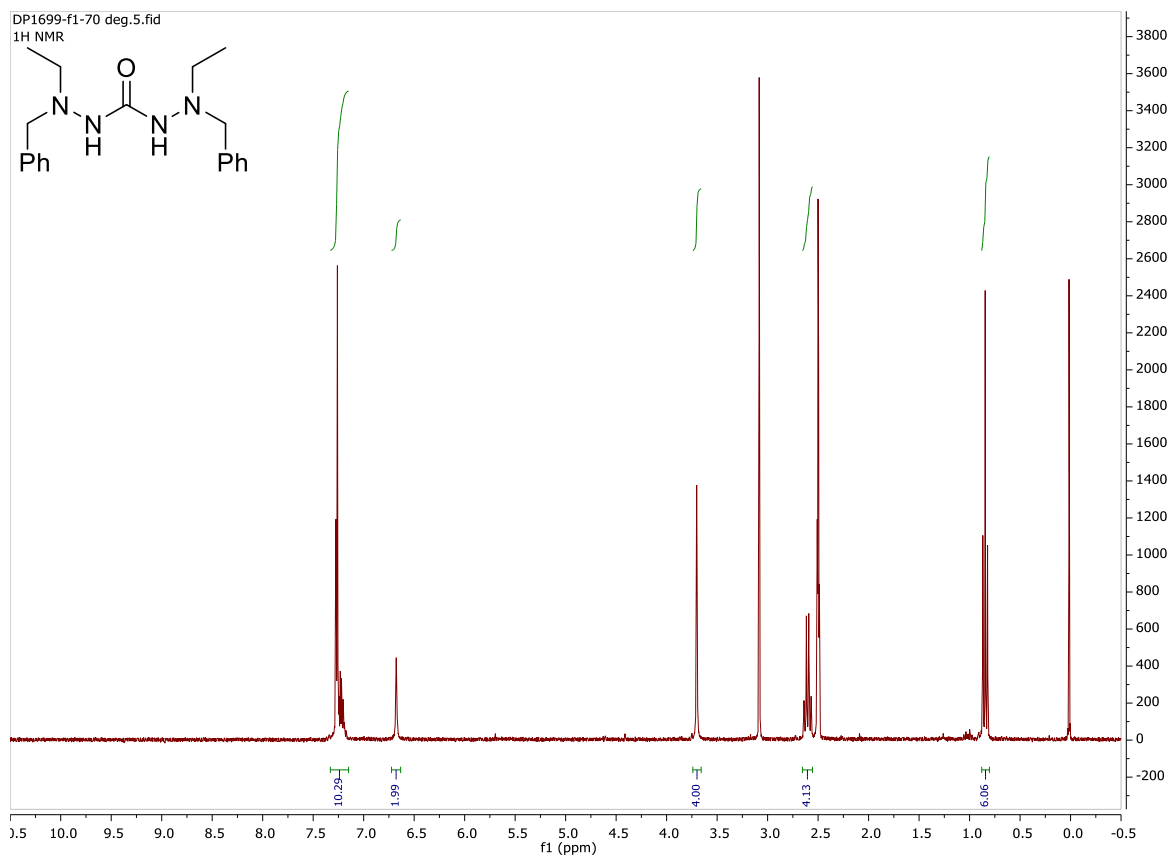


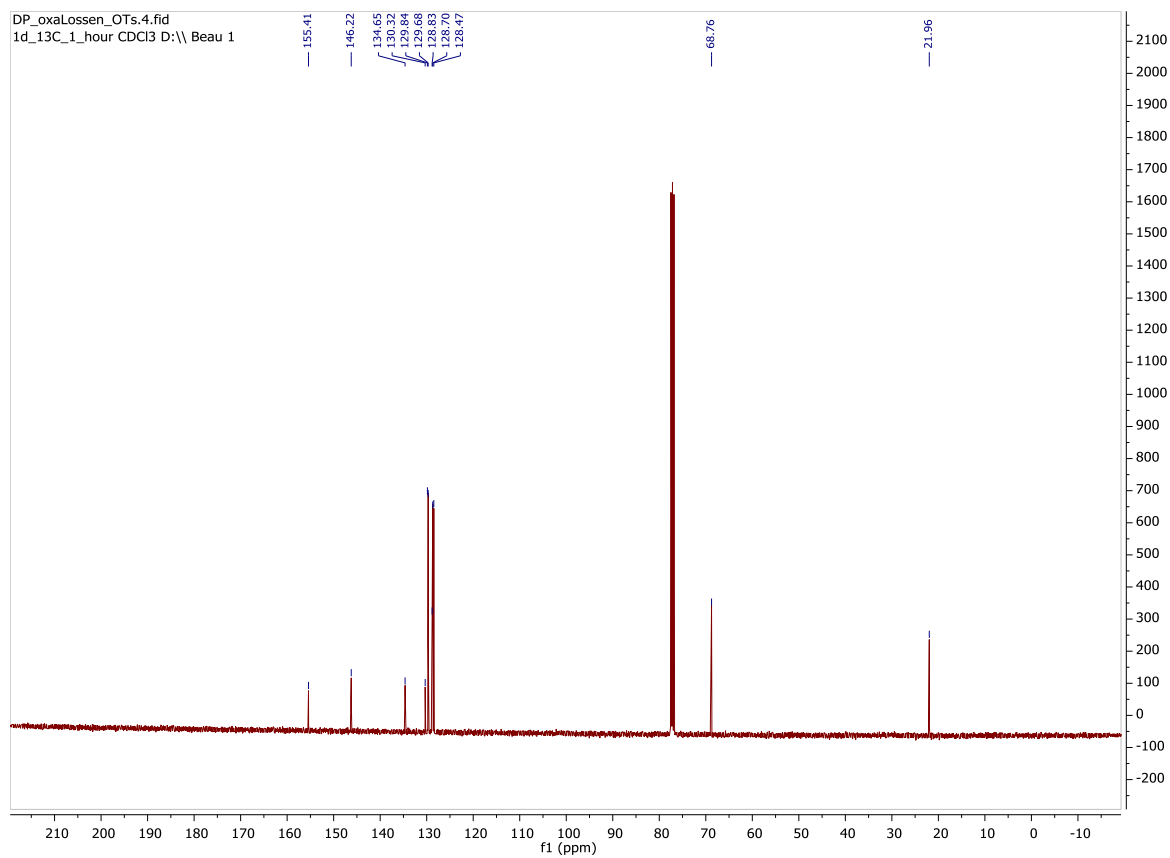
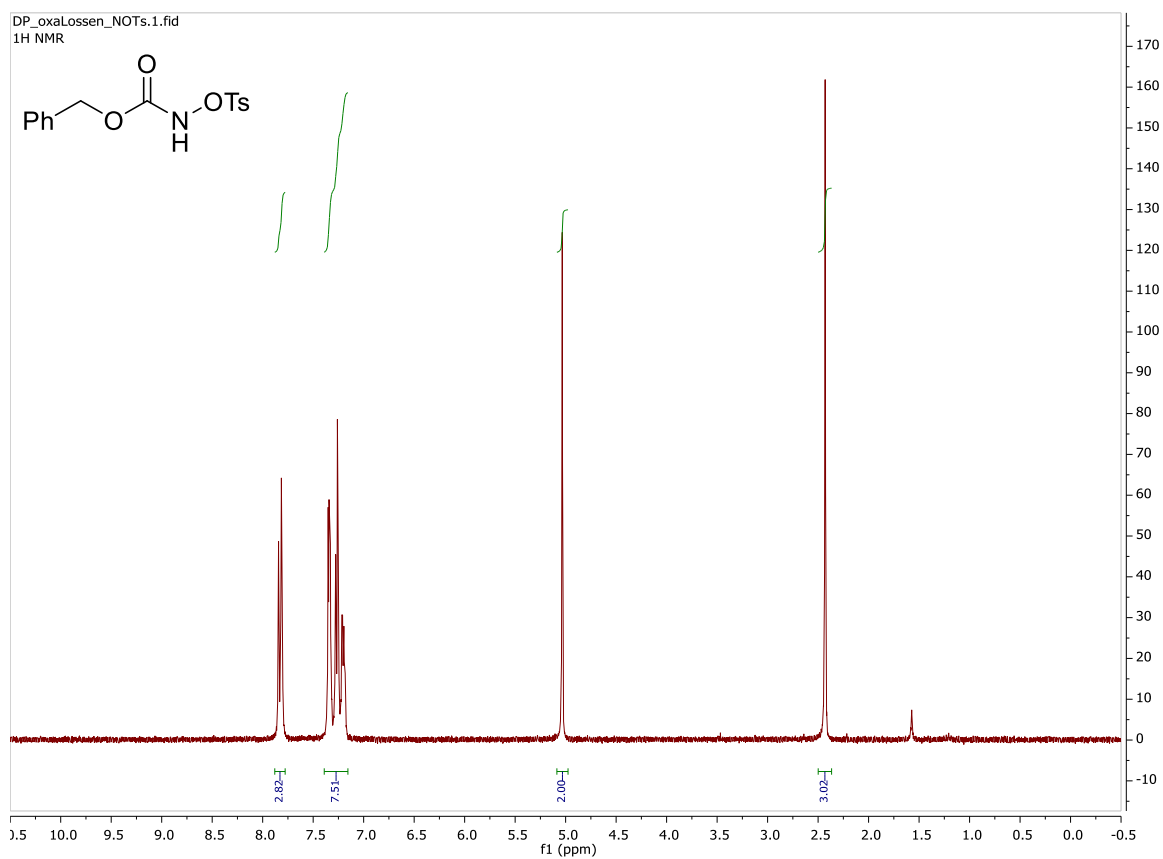


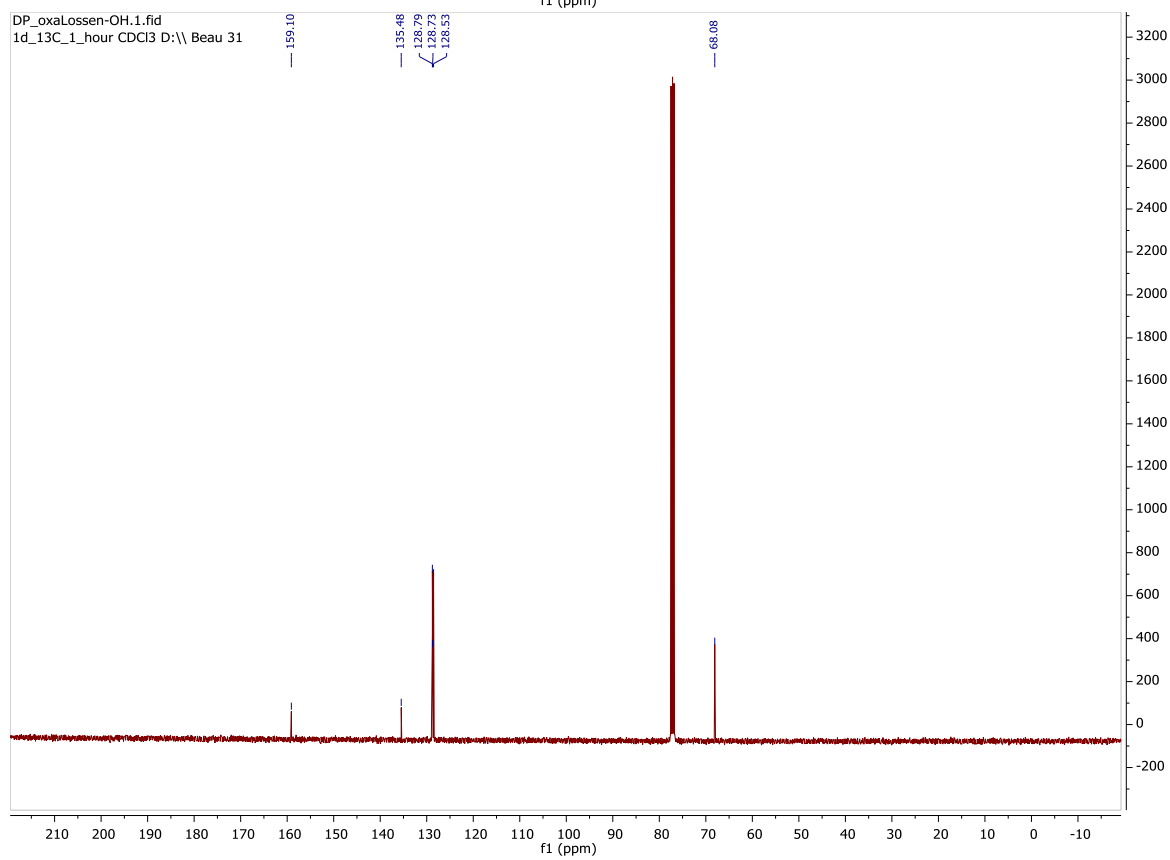
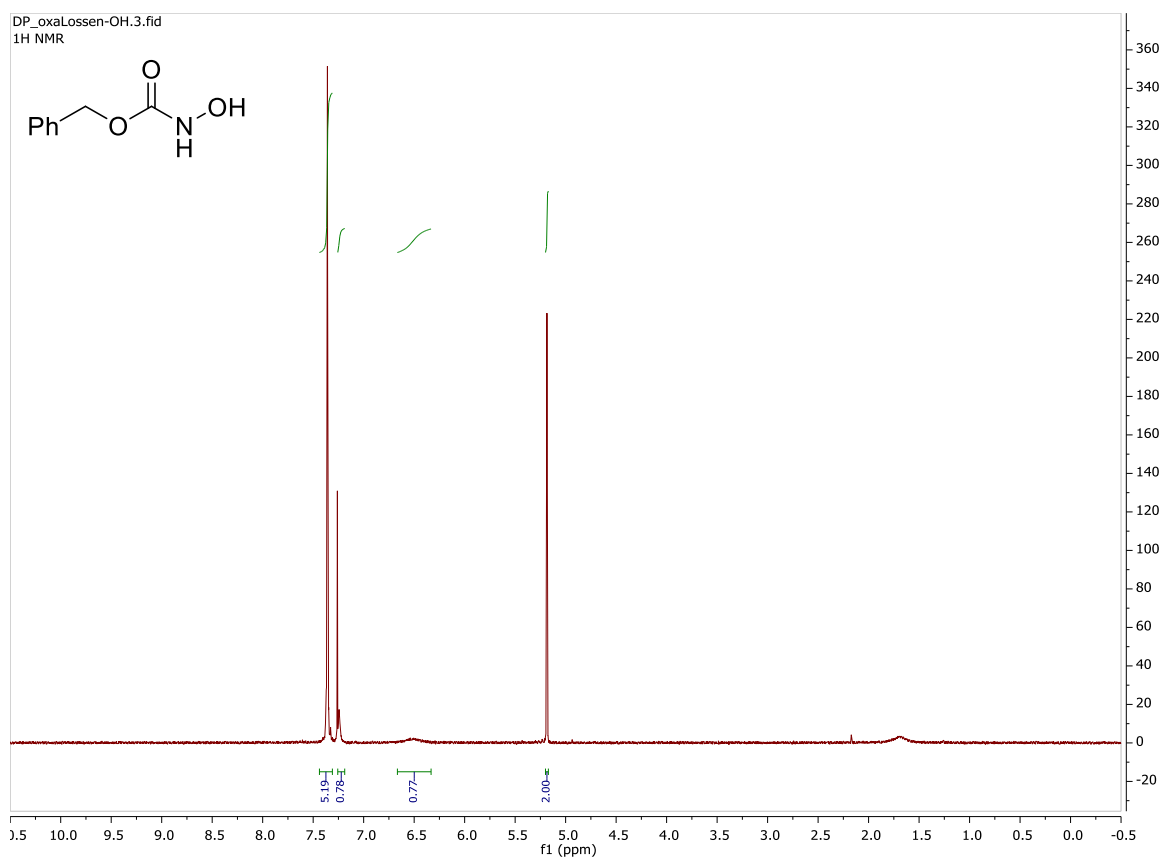


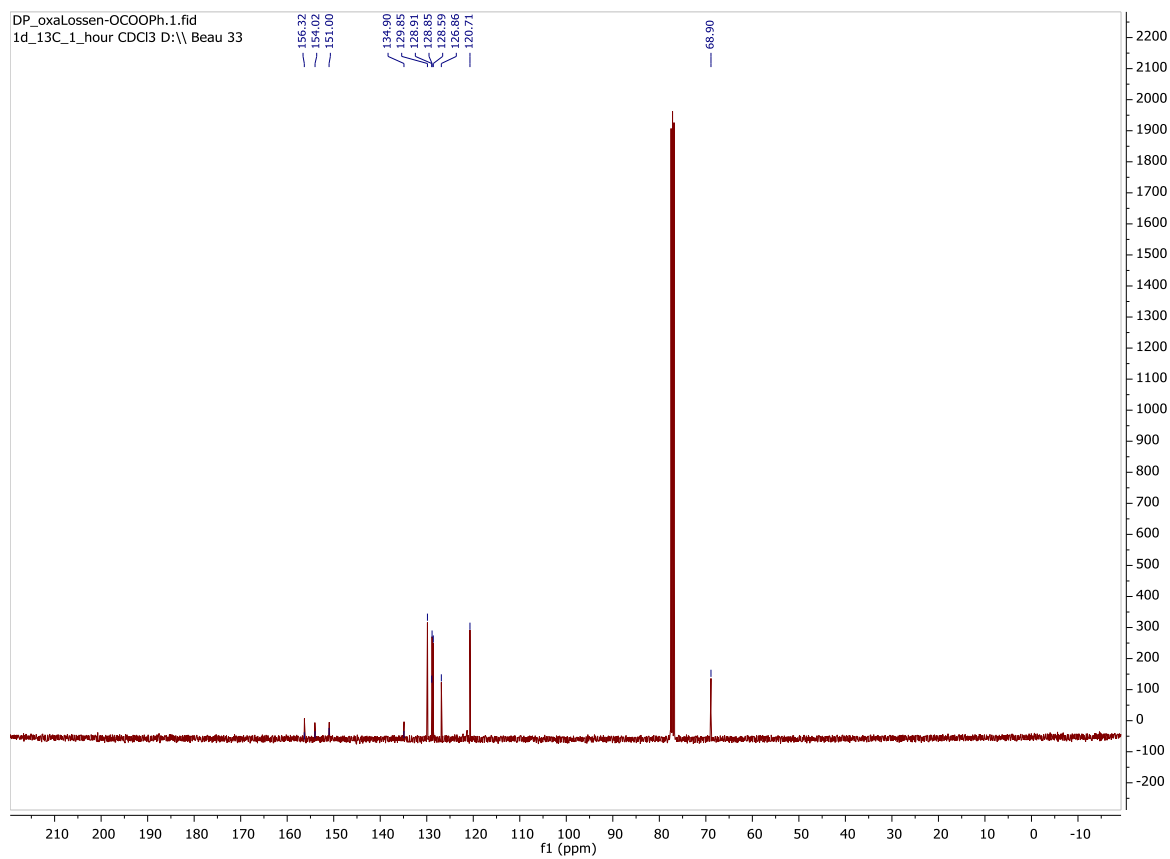
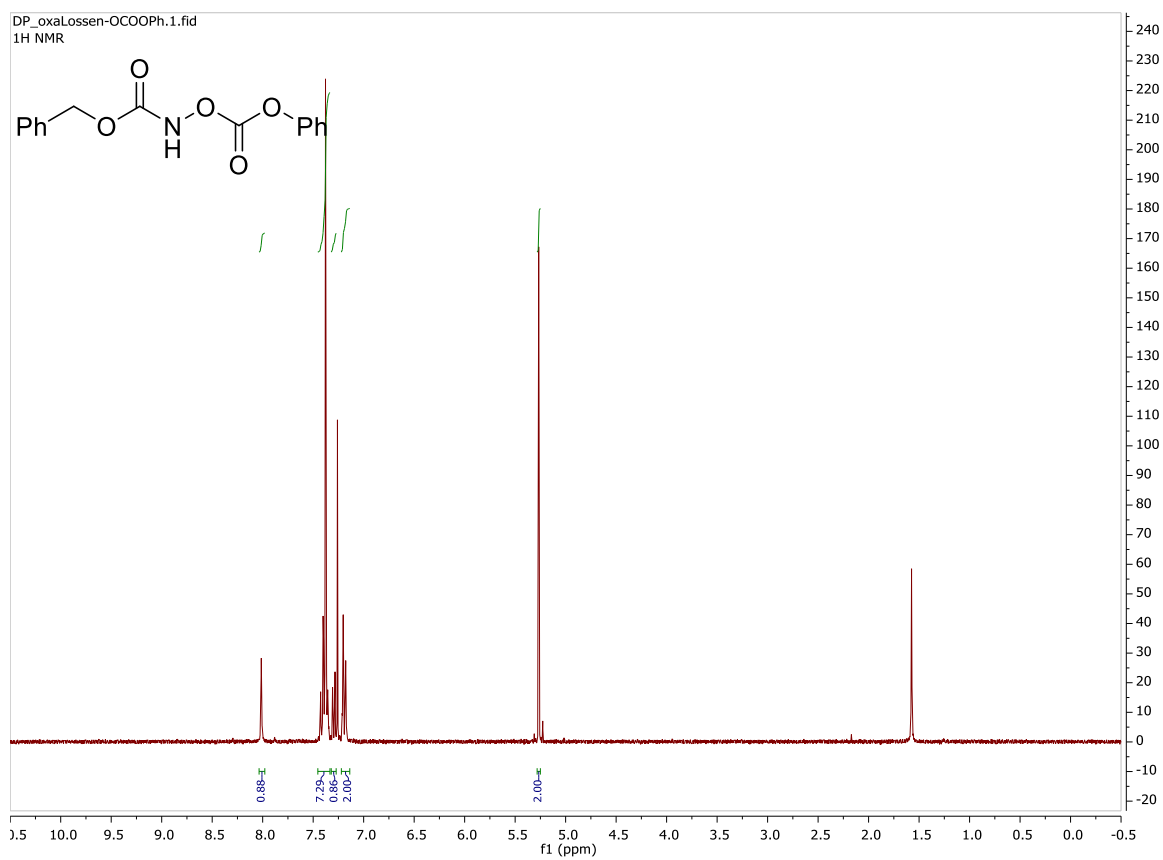


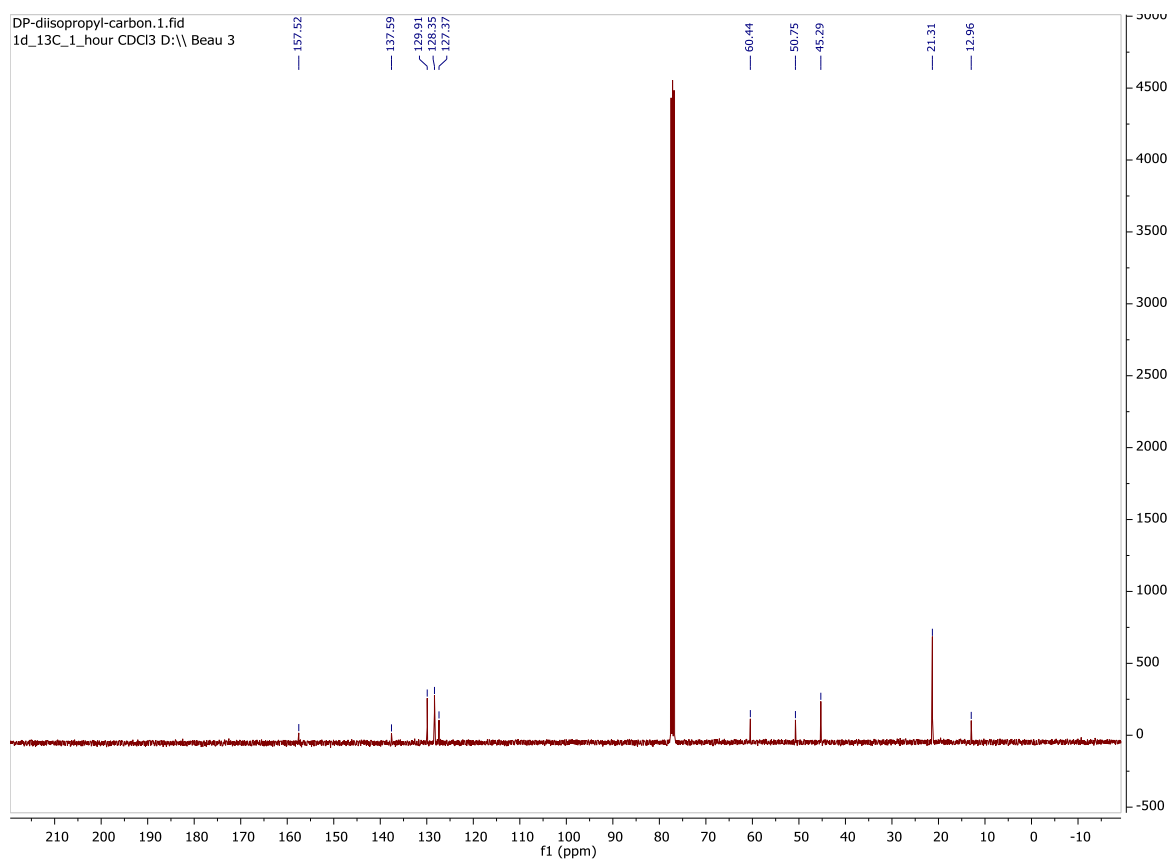
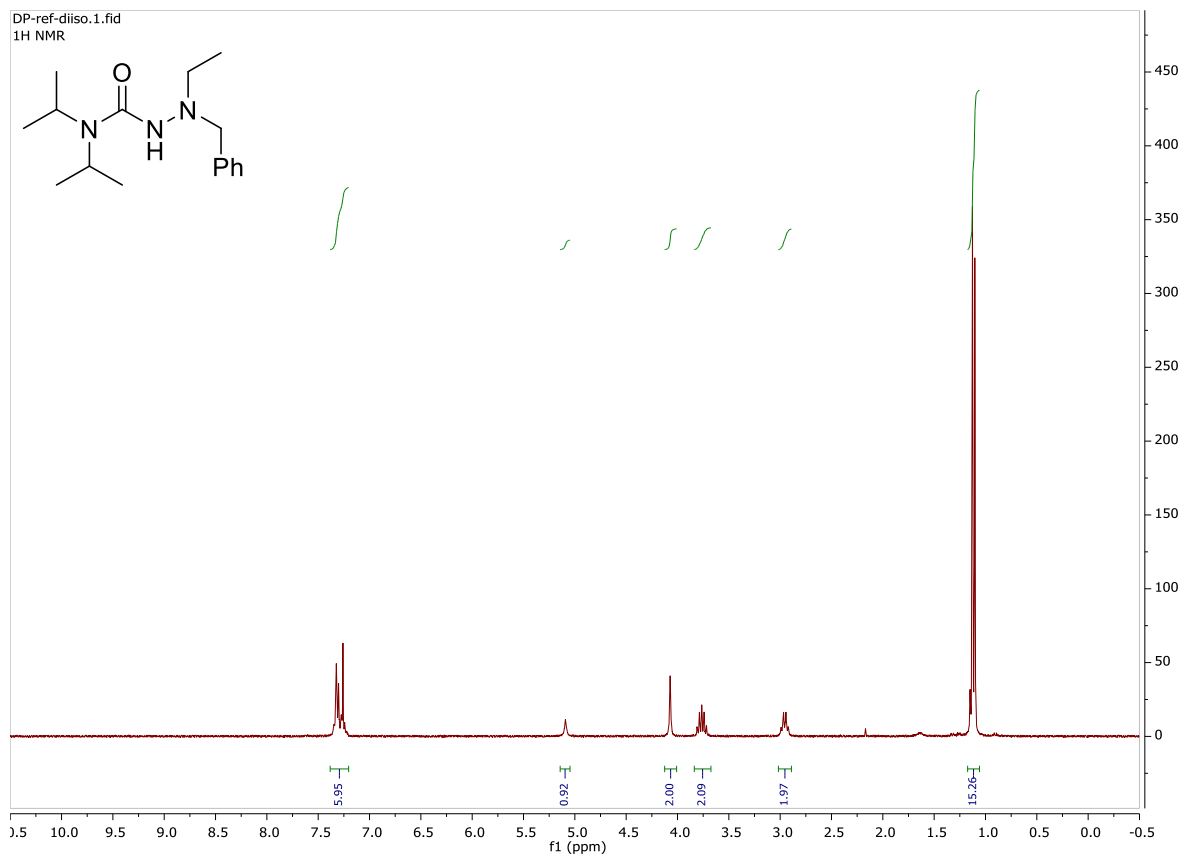


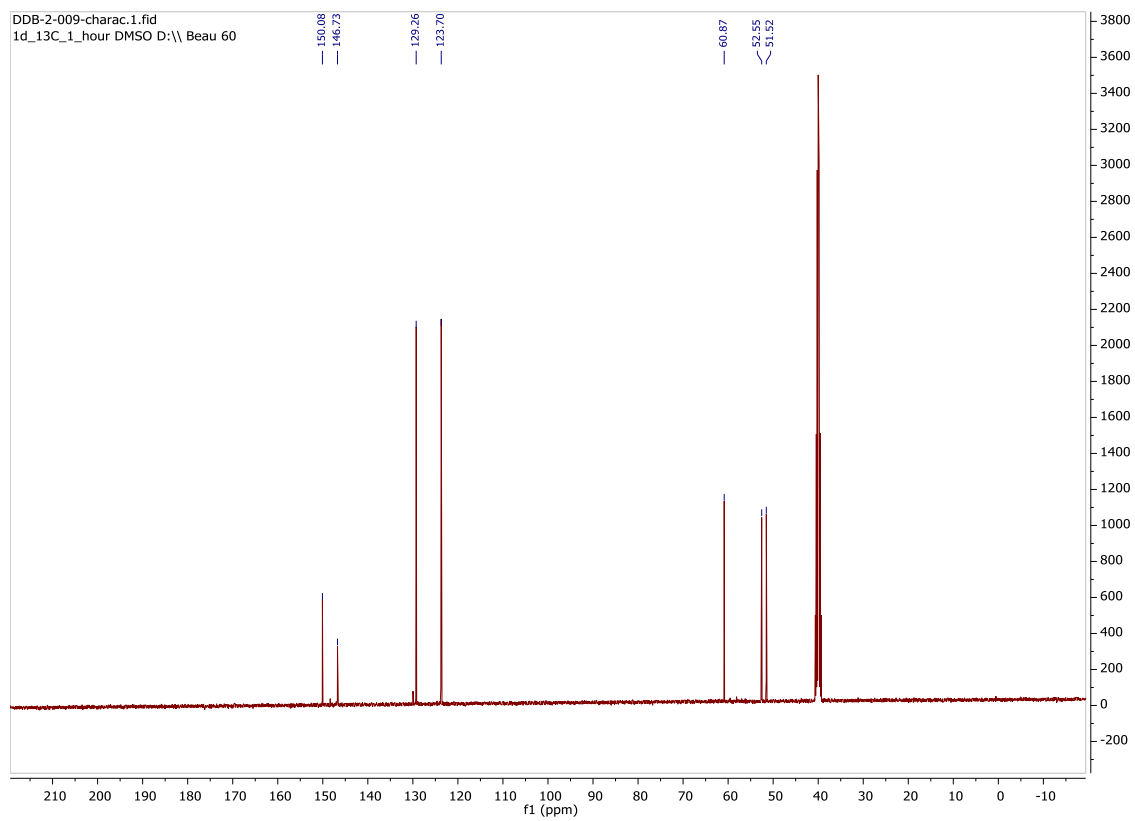
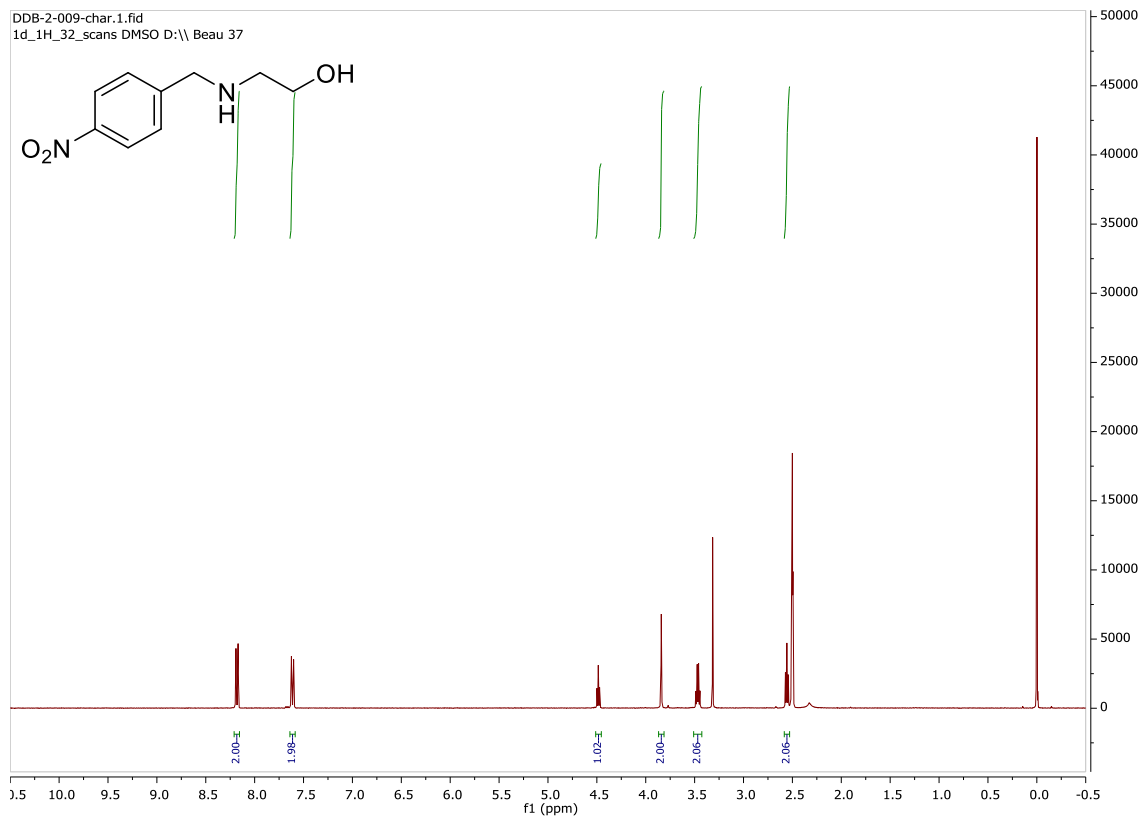


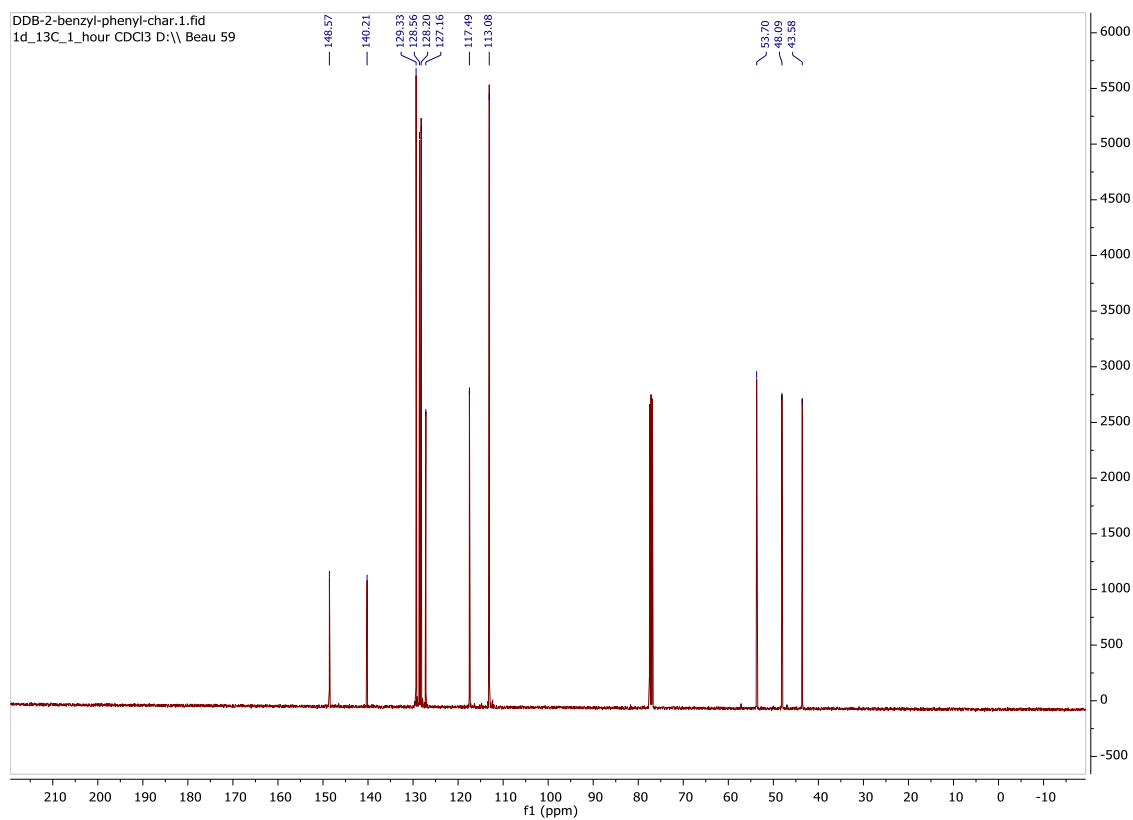
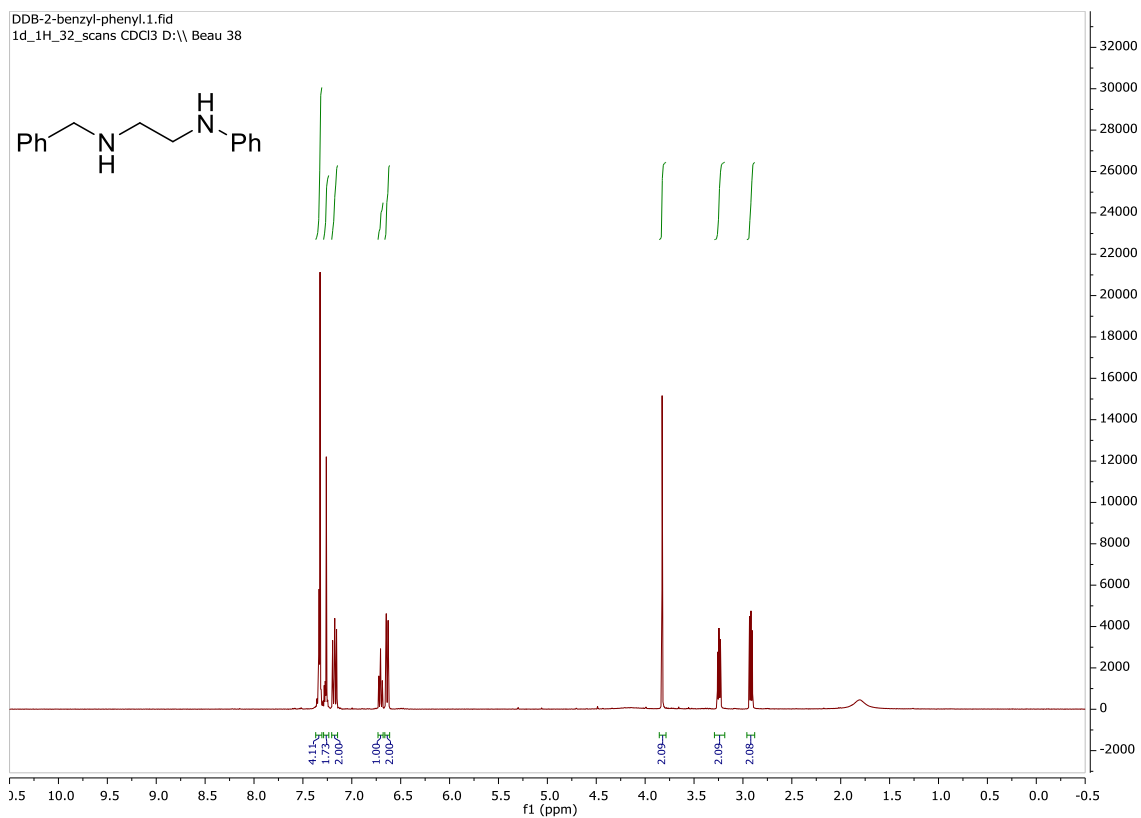


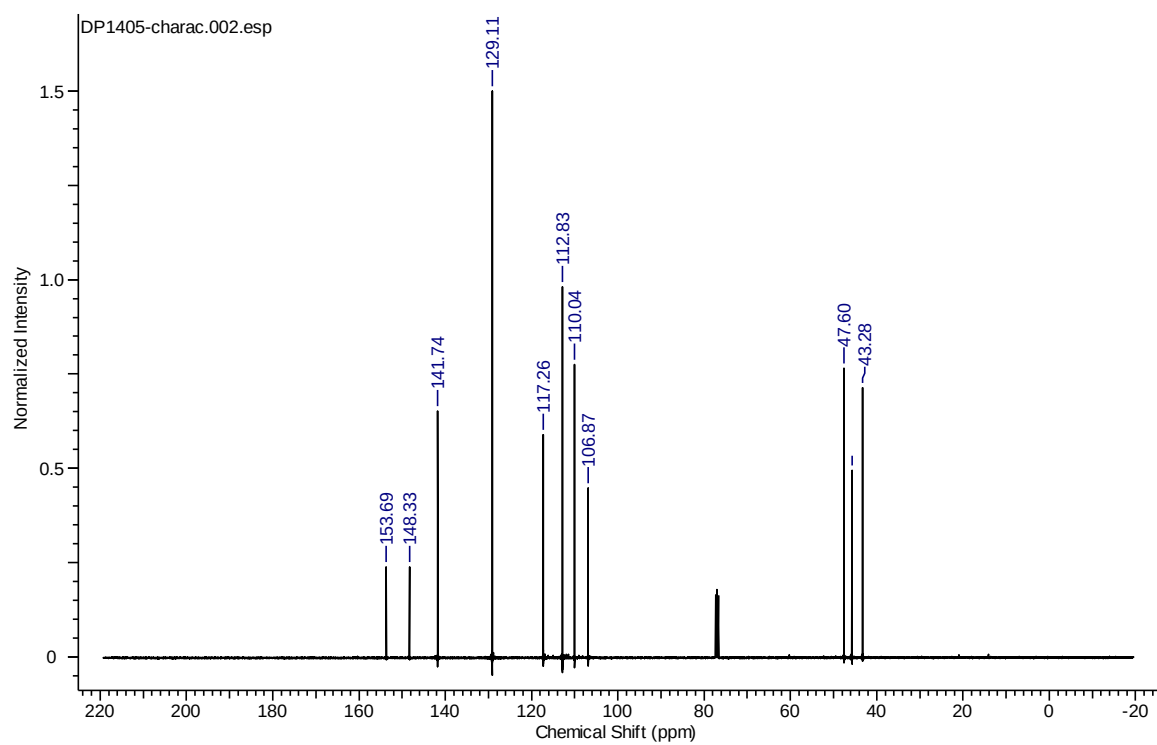
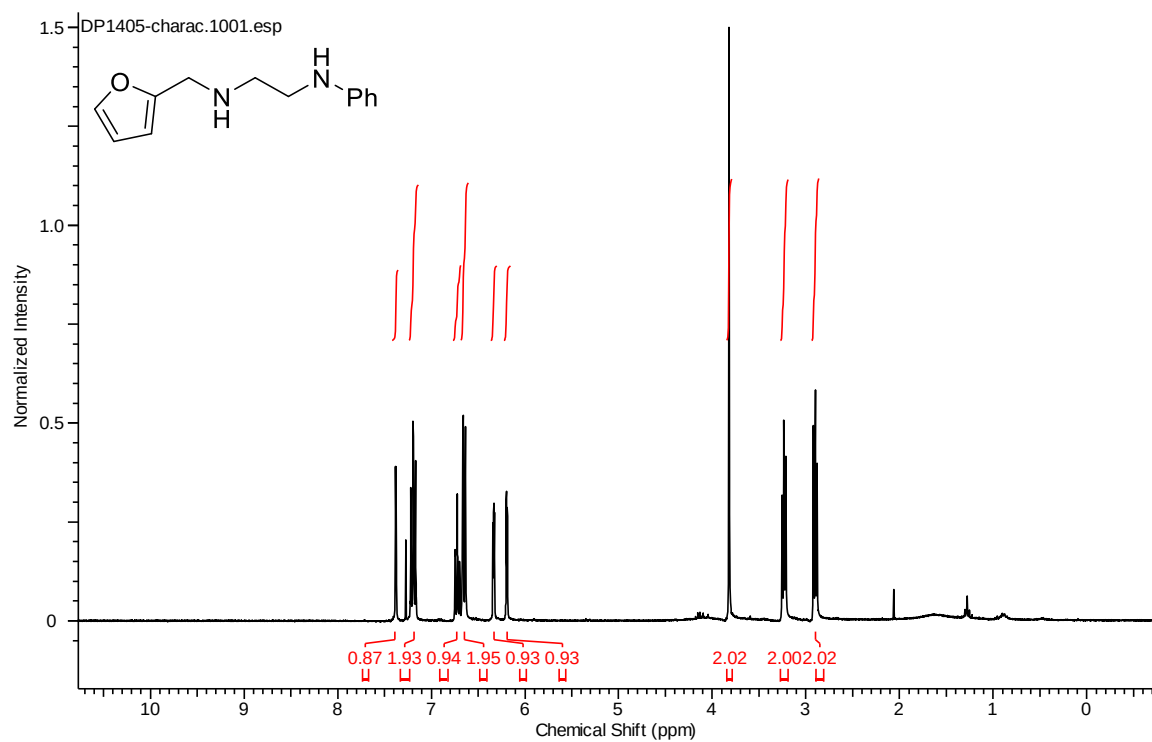


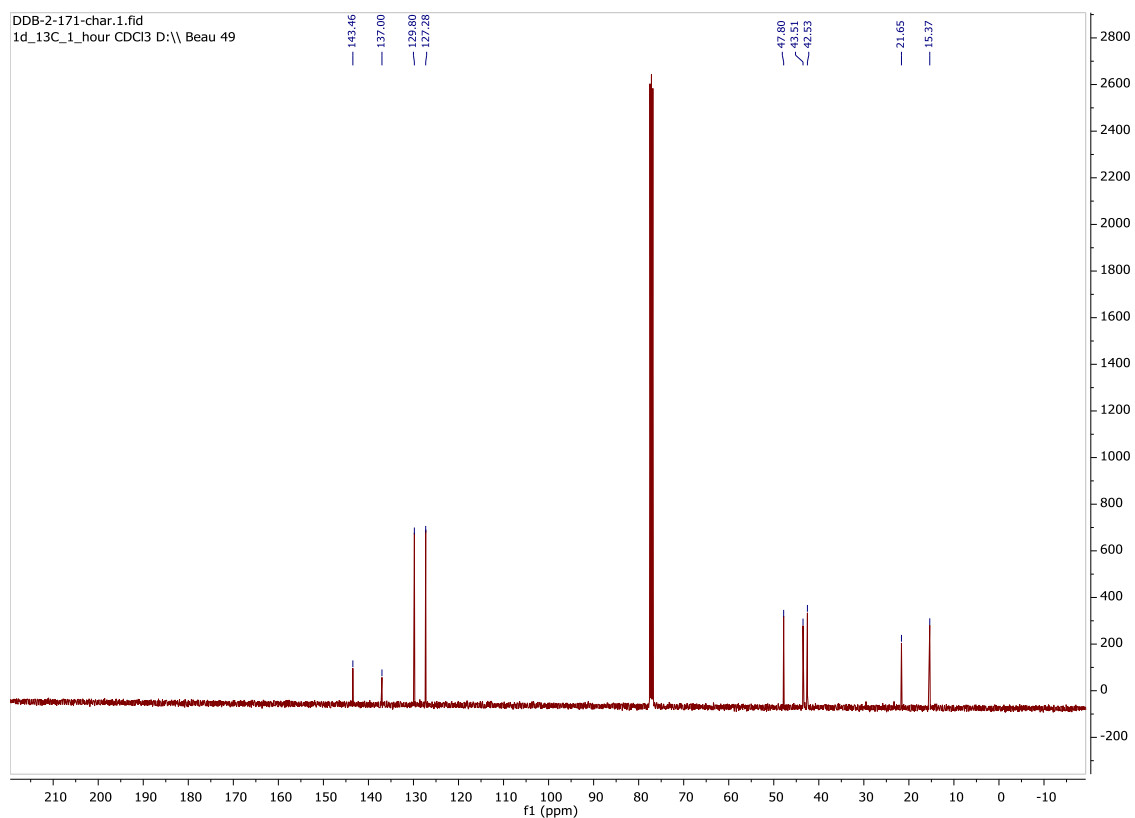
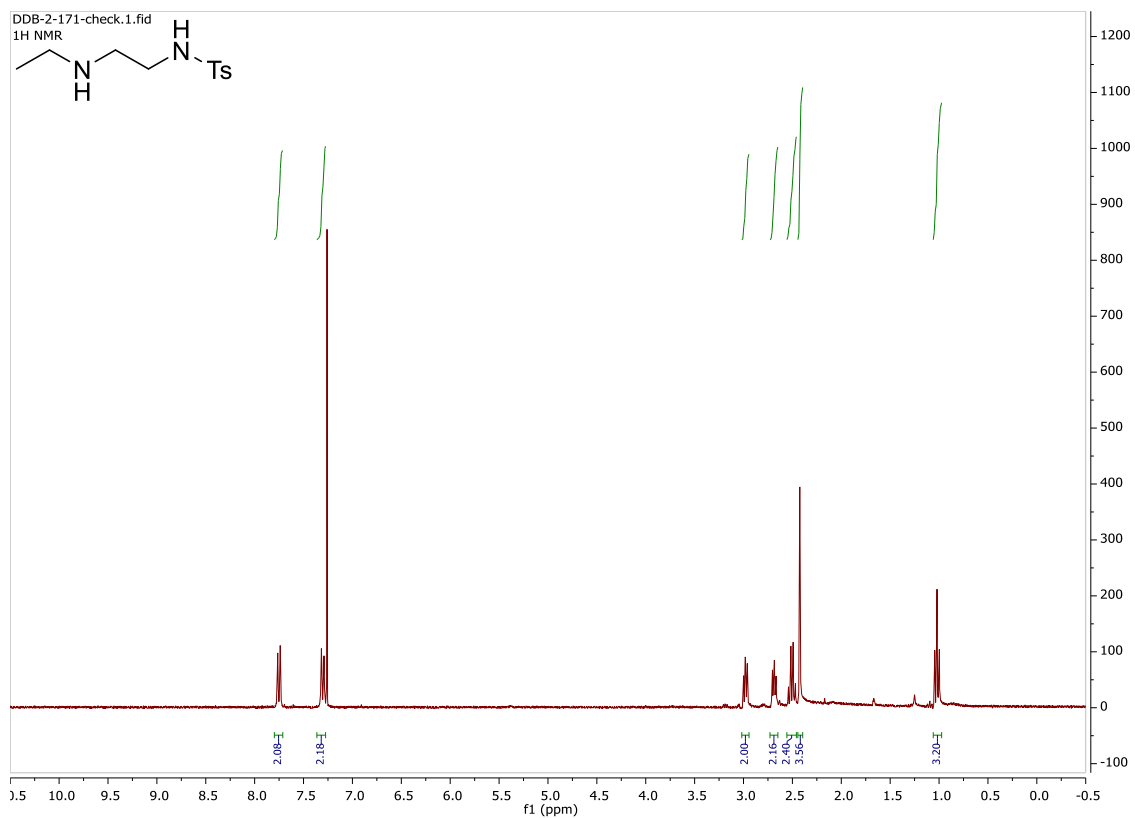


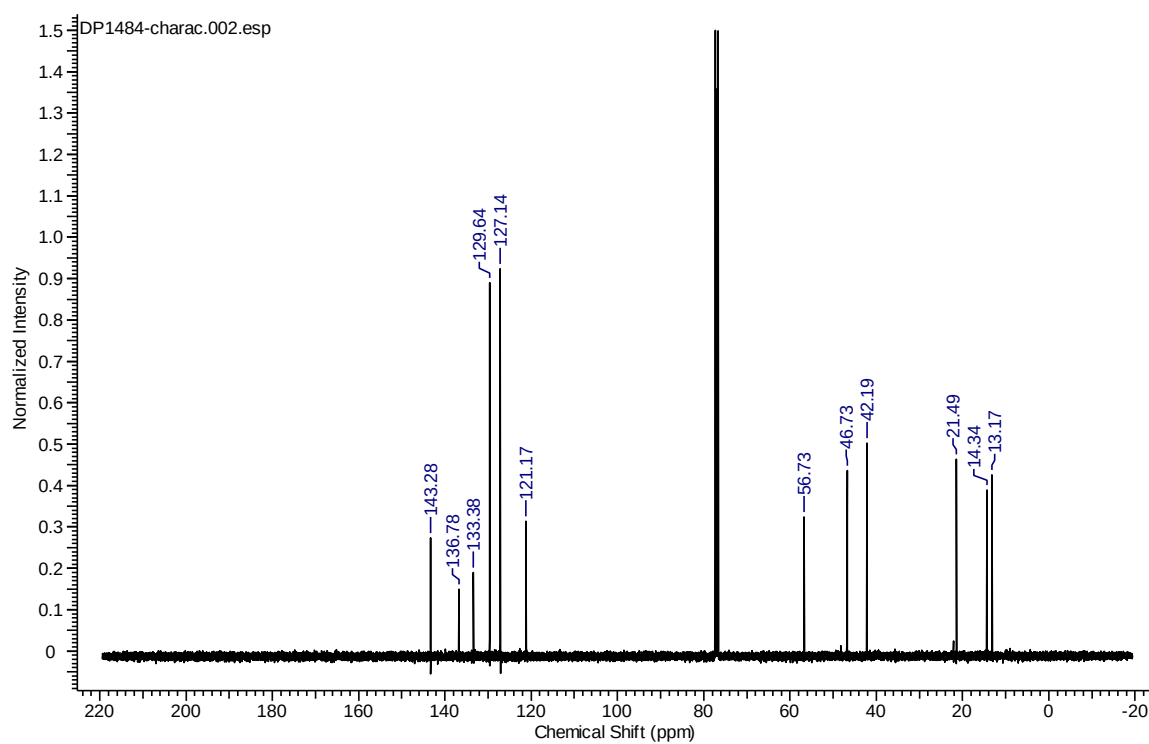
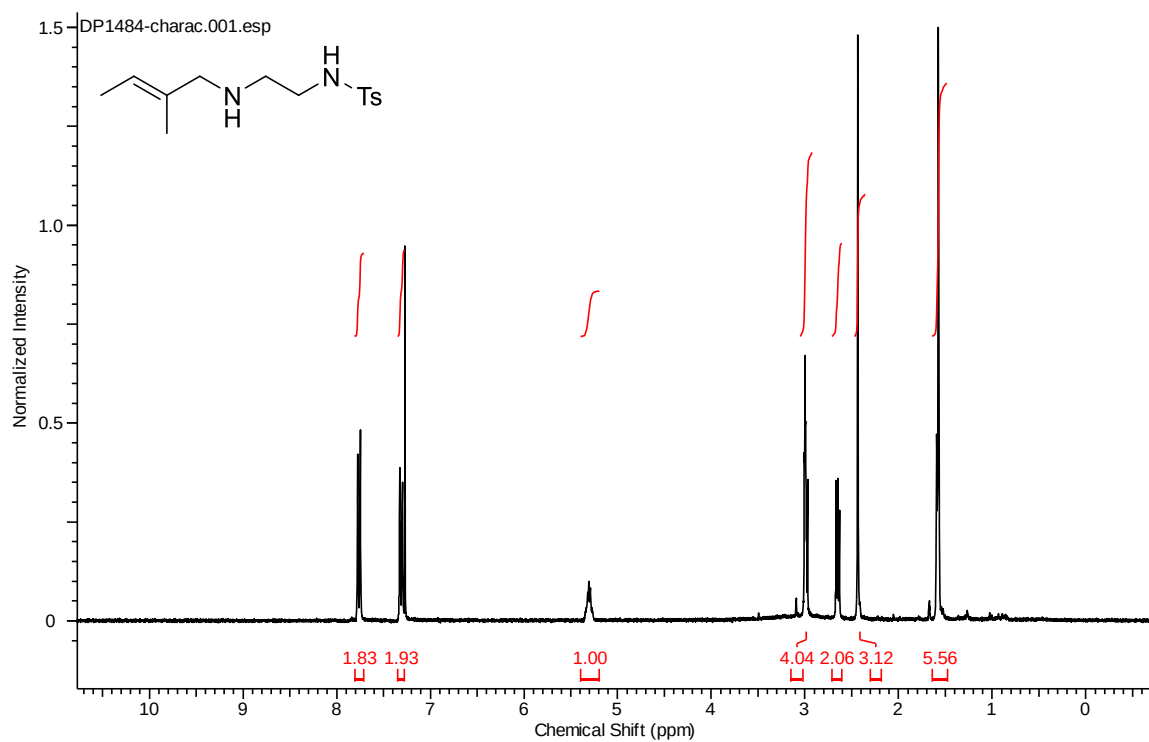


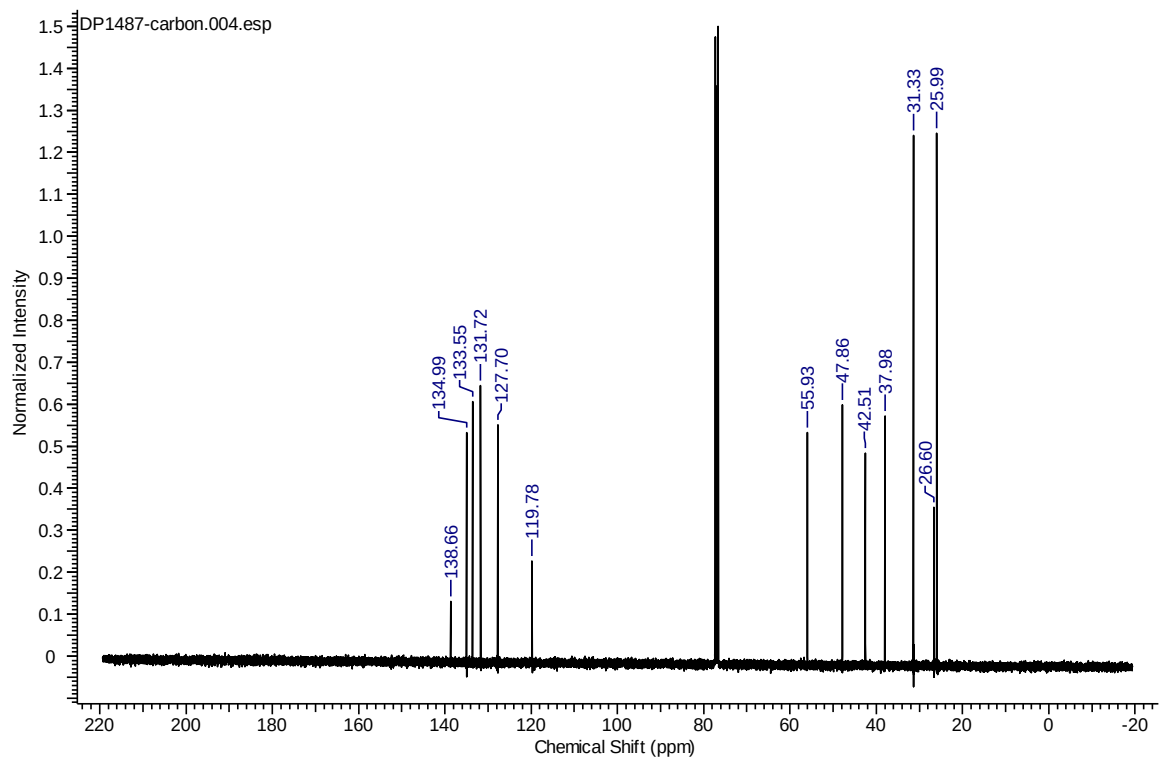
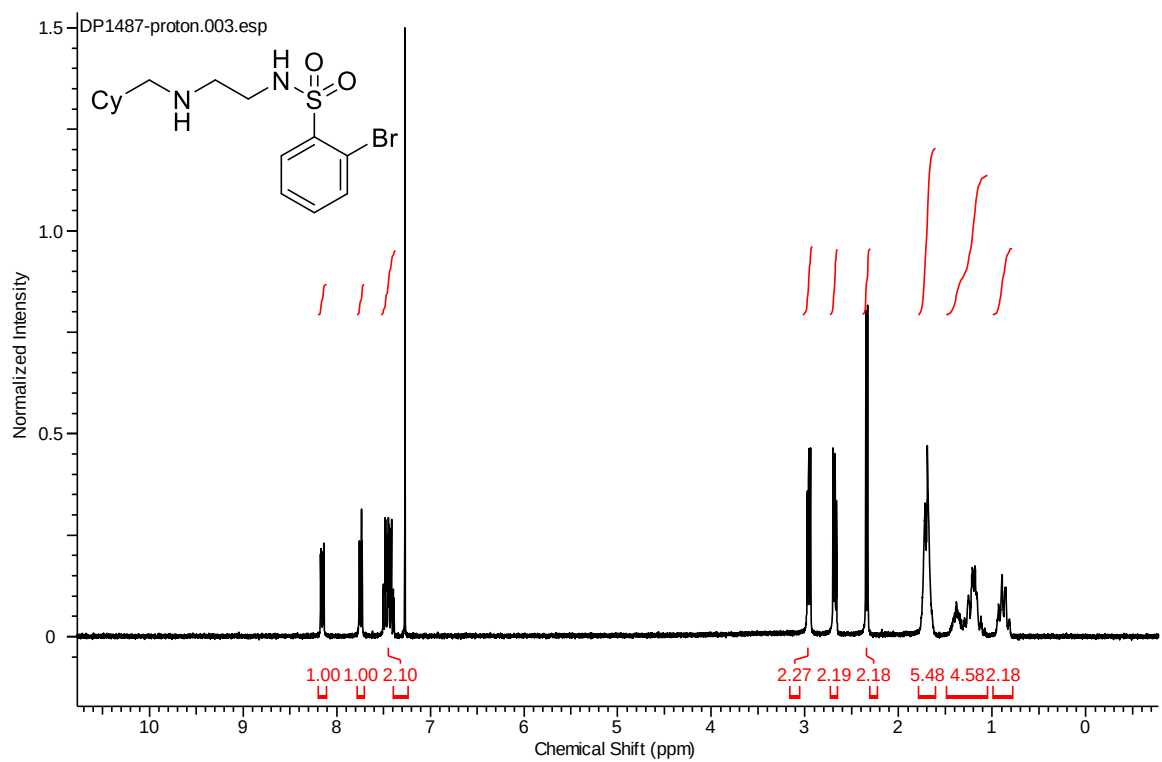












Spectra – Chapter 4

