New Reactivity Involving *N*-Isothiocyanates: Aminothiocarbonylation and [3+2] Cycloadditions to Form Molecules Containing NNCS Motifs

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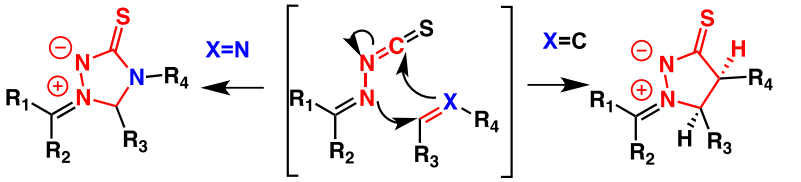
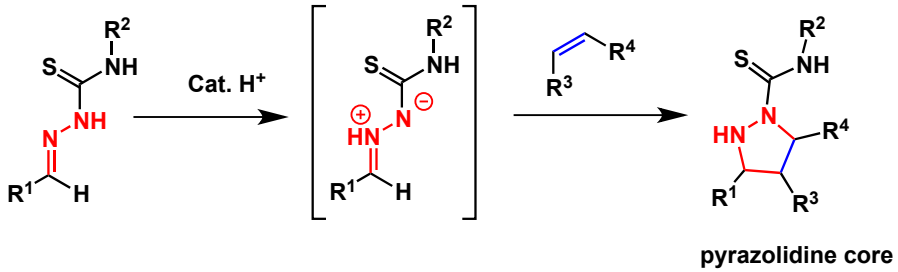
Abstract

Nitrogen-containing heterocycles are of vital importance for the pharmaceutical and agrochemical industries. The Beauchemin group has been studying rare, amphoteric nitrogen-substituted isocyanates over the past years, and showed that their [3+2] alkene cycloaddition and cascade reactions provide access to a variety of NNCO containing heterocyclic compounds. This triggered interest into the reactivity of the parent *N*-isothiocyanates, which are also rare, and led to the discovery of aminothiocarbonylation reactions. The products formed are azomethine imines which contain a cyclic β-aminothiocarbonyl motif, thus providing a cycloaddition route to these useful dipoles from simple starting materials. Such aminothiocarbonylation reactions were developed with both alkenes and imines as substrates.



Apart from cyclic azomethine imine formations, efforts have also been made toward forming the acyclic azomethine imines as intermediates. These intermediates undergo [3+2] cycloaddition to form thiocarbamoyl pyrazolidine derivatives, and a preliminary substrate scope for this new intermolecular reactivity is presented.



Other preliminary results include an unexpected Chugaev type reactivity. Collectively, these results show that *N*-isothiocyanates hold significant potential for the development of new reactivity.

Dedication

Indu Vidayarathna

Thank you for opening the doors to the world of chemistry.

I hope you get better soon.

Acknowledgements

First and foremost, I would like to thank my supervisor André Beauchemin for giving me the opportunity to join the group. It has been two great years in my life where I learned a tremendous amount of chemistry and many more things which would come handy in life. André, you were a great example of a person who has so much passion for what you do and I do appreciate all the time you take out of your busy day to discuss chemistry with us. I find myself very lucky to have a supervisor like you and thank you so much for your support, understanding and inspiration.

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List of Abbreviations

AcOH	Acetic acid
MeCN	Acetonitrile
β	Beta
$CHCl_3$	Chloroform
δ	Chemical shift in parts per million
CS_2	Carbon disulfide
°C	Degrees Celsius
DFT	Density functional theory
DBU	1,8-diazabicycloundec-7-ene
dr	Diastereomeric Ratio
DMSO	Dimethyl sulfoxide
EI	Electron impact
ESI	Electrospray ionization
ee	Enantiomeric excess
Equiv.	Equivalents
EtOH	Ethanol
EtOAc	Ethyl Acetate
g	Gram
Δ	Heat or Reflux
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol

Hz	Hertz
HRMS	High-resolution mass spectrometry
HOMO	Highest Occupied Molecular Orbital
H_2S	Hydrogen Sulfide
h	Hours
NH_2OH	Hydroxylamine
IR	Infrared
i-Pr	isopropyl
LR	Lawesson's reagent
PbS	Lead Sulfide
LG	Leaving group
LUMO	Lowest Unoccupied Molecular Orbital
MeOH	Methanol
Me	Methyl
µw	Microwave
MW	Microwave
mL	Millilitres
mmol	Millimoles
M	Moles per Litre
m	Multiplet
mmHg	Millimeter of mercury
NMR	Nuclear magnetic resonance

Nuc	Nucleophile
ppm	Parts per million
Ph	Phenyl
PG	Protecting group
qa	Quartet
rt	Room Temperature
$PhCF_3$	Trifluorotoluene
R	Generic group
TsCl	Tosyl chloride
AgO	Silver Oxide
s	Singlet
NaH	Sodium hydride
THF	Tetrahydrofuran
Boc	*tert*- butoxycarbonyl
TLC	Thin layer chromatography
Et_3N	Triethylamine
t	Triplet
UV	Ultraviolet
H^+	Generic acid

Chapter 1: Introduction

1.1 Cycloaddition Reactions Using Amphoteric Molecules

Cycloaddition reactions are popular among organic chemists for their atom and step economy. While [3+2] dipolar cycloadditions of 1,3-dipoles are well established, using amphoteric molecules to carry out cycloadditions is an alternative strategy to synthesize heterocycles. The Beauchemin group is particularly interested in synthesizing nitrogen-containing heterocycles using new methods. In the following sections of this chapter, the use of amphoteric molecules with a β-aminocarbonyl (N-N-C=O) motif functionality and their sulfur analogues, in such cycloaddition reactions are described.

1.1.1 Related Amphoteric Molecules

Molecules which contain both nucleophilic and electrophilic centers are known as amphoteric molecules. Amphoteric molecules are of significant interest because they are capable of forming multiple bonds in a single transformation and have been found to perform high yielding reactions, often with high chemoselectivity.[1] In an amphoteric molecule, two functional groups that are usually considered as incompatible are present, for example α-aminoaldehydes typically require protection of the nitrogen atom to avoid dimerization and other side-reactions.[2] However, by controlling the availability of these functional groups, they can provide useful reactivity involving these two reactive functional groups.

1 (a) Baktharaman, S.; Hili, R.; Yudin, A. K. *Aldrichimica Acta* **2008**, *41*, 109. Also for reviews see; (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron Lett.* **2002**, *58*, 2253. (c) Lazny, R.; Nodzewska, A. *Chem. Rev*. **2010**, *110*, 1386.

2 Yudin, A. K. *Chem. Heterocycl. Compd.* **2012**, *48*, 191.

1.1.1.1 Hydrazones and Semicarbazones

Hydrazones are used as reagents in many organic synthetic applications due to their stability as well as their easy accessibility. Pioneering work by Baldwin and coworkers showed that substituted hydrazones display ambient nucleophilic reactivity.[3] Also, *N,N'*-dialkylhydrazones are characterized by an ambiphilic behaviour at the azomethine carbon. These types of hydrazones, in reactions with nucleophiles, showed imine-like reactivity and with electrophiles showed aza enamine like reactivity (**Figure 1a**).[1c] According to a review by Fernandez, the C=N-N structure provides different reactivity patterns with numerous nucleophile and electrophile partners (**Figure 1b**).[4] These types of hydrazones were investigated in forming C-N and C-C bonds.

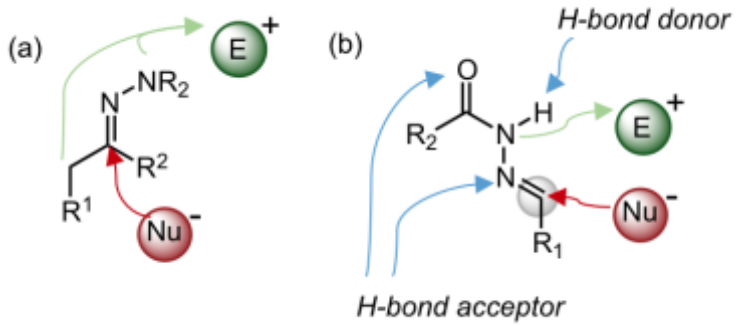


Figure 1: Amphoteric features of a hydrazine and a semicarbazone

3 (a) Baldwin, J. E.; Adlington, R. M.; Newington, I. M. *J. Chem. Soc., Chem. Commun.* **1986**, *2*, 176. (b) Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Kolhe, J. N.; Perry, M. W.; Jain, A. U. *Tetrahedron Lett.* **1986**, *42*, 4223.

4 Gracia, R.; Matador, E.; Monge, D.; Lassaletta, J. M.; Fernandez, R. *Chem. Eur. J.* **2016**, *22*, 13430.

Semicarbazones, are a sub-type of hydrazones, can be accessed by reacting hydrazones with isocyanates.[5] Another method of synthesizing them is to condense ketone/aldehyde with a carbazate.[6] The amphoteric character on a semicarbazone is shown in **Figure 1b**. A different type of reactivity for semicarbazone is due to the presence of two heteroatoms on each side of the carbonyl group: the thermal cleavage of the semicarbazones can proceed to form nitrogen-substituted isocyanates (**Figure 2**). *N*-Isocyanates are known amphoteric molecules, used in cycloaddition reactions.[7]

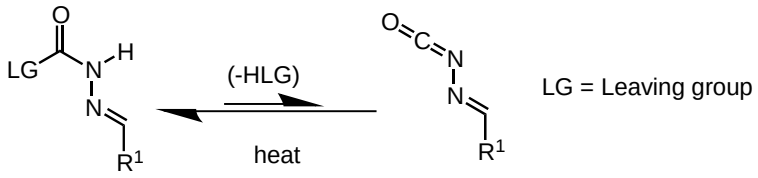


Figure 2: *N*-Isocyanate formation from a semicarbazone

1.1.1.2 *N*-Isocyanates

N-Isocyanates are a rare class of amphoteric molecules and often show a tendency toward dimerization.[8] Controlled generation of *N*-isocyanates has been achieved through blocking (masking) groups on isocyanates. A recent review by Vincent-Rocan and Beauchemin discusses the synthesis and reactivity of these isocyanates.[9] *N*-Isocyanates can notably engage in [3+2] cycloaddition reactions. Two important classes of *N*-isocyanates are amino-isocyanates and imino-isocyanates. *N*-Isocyanates containing a nucleophilic nitrogen (sp^3 hybridized) are

5 Suni, M.; Nair, V. A.; Joshua, C. *Tetrahedron Lett.* **2001**, *57*, 2003. (b) Hassan, A. A.; Shawky, A. M. *J. Heterocycl. Chem.* **2011**, *48*, 495.

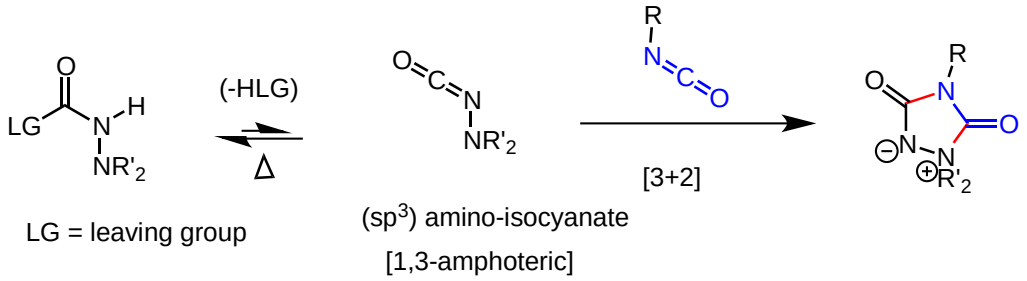
6 Alam, M. S.; Liu, L.; Lee, Y.-E.; Lee, D.-U. *Chem. Pharm. Bull .* **2011**, *59*, 568.

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

8 (a) Reichen, W. *Chem. Rev.* **1978**, *78*, 569. (b) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem.* **2011**, *15*, 1745.

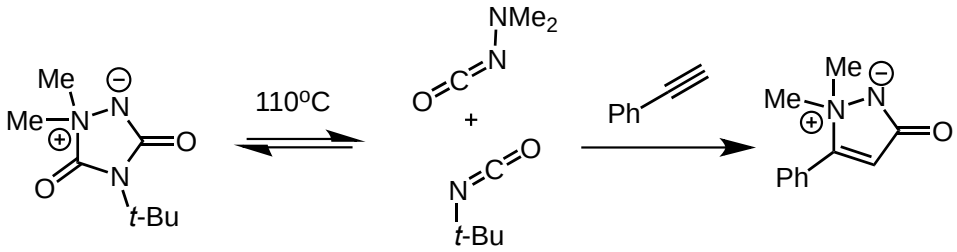
9 Vincent Rocan, J.-F.; Beauchemin, A. M. *Synthesis* **2016**, *48*, 3625.

amino-isocyanate. Amino-isocyanates can react with alkyl and aryl isocyanates to give 5-membered heterocyclic products (**Scheme 1**).



Scheme 1: Isocyanate generation and cycloaddition reaction of amino-isocyanates

Interestingly, Lockley and Lwowski found out that alkynes can also act as a cycloaddition partners with amino-isocyanates (**Scheme 2**).[10] The solubility of the aminimide was controlled by performing the reaction in a non-polar solvent, leading to a low concentration the amino-isocyanate upon formation by a retro- [3+2] reaction. This strategy minimized the dimerization of the amino-isocyanate, a fast competing side-reaction, and allowed formation of the desired

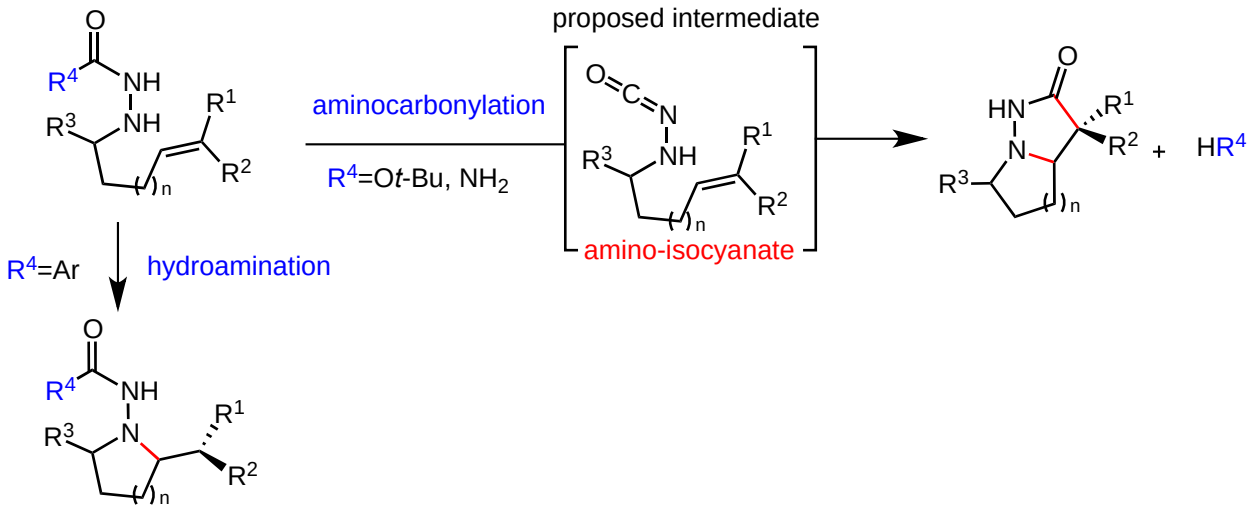


cycloaddition product.

Scheme 2: Alkynes as dipolarophiles in [3+2] cycloaddition with amino-isocyanates

10 Lockley, W. J. S.; Lwowski, W. *Tetrahedron Lett.* **1974**, *48*, 4263.

The Beauchemin group became interested in alkene aminocarbonylation and *N*-isocyanates with an observation of a byproduct formation while exploring hydroamination reactions. The unexpected aminocarbonylation product was obtained when the hydroamination reaction was conducted with a Boc-protected hydrazide (**Scheme 3**).[11]



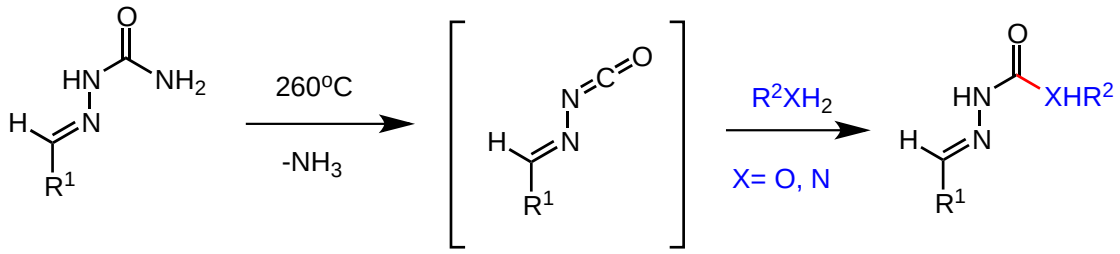
Scheme 3: Difference in reactivity observed changing the R⁴ group on hydrazine

Amino-isocyanates gave promising results for intramolecular reactions, although intermolecular reactivity was limited. This led the group to explore another type of *N*-isocyanates, imino-isocyanates.[12] Compared to amino-isocyanates, imino-isocyanates showed less propensity towards dimerization. Such imino-isocyanates are rare compared to amino-isocyanates, therefore,

11 (a) Clavette, C. Synthesis of beta-Aminocarbonyl Compounds and Hydrazine Derivatives Using Amino- and Imino-Isocyanates, PhD Thesis, University of Ottawa, 2015. (b) Roveda, J. G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc*. **2009**, *131*, 8740.

12 (a) Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074. (b) Vincent Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, *7*, 315. (c) Derasp, J. S.; Vincent Rocan, J.-F.; Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 658.

their reactivity had not been studied in detail.[13] Larsen and Jakobsen introduced the blocking group method to access imino-isocyanates.[14] Studies followed, for example, work showing that the isocyanate generated can react with alcohols and amines (**Scheme 4**).[15]



Scheme 4: Imino-isocyanate formation as an intermediate

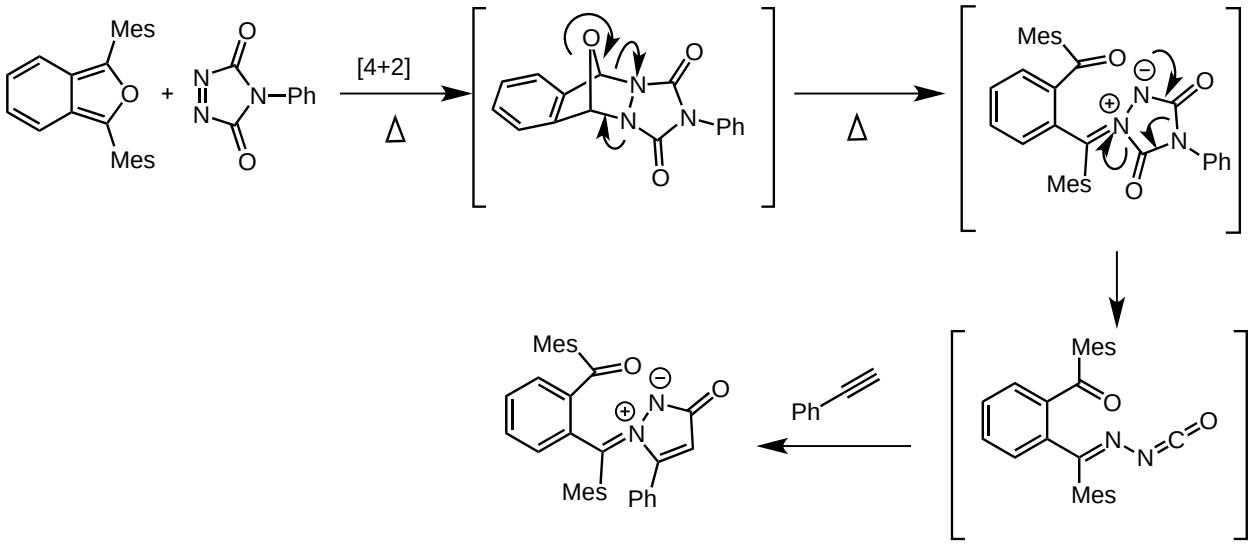
Jones reported in 1982 the generation of an imino-isocyanate by performing a [3+2] cycloaddition/ retro-cycloaddition sequence on a hindered benzofuran in boiling toluene (**Scheme 5**).[16] He reported formation of an azomethine imine product using phenylacetylene. Similar azomethine imine product formations were also observed with norbornene, styrene and 1,5-cyclooctadiene. However, there were no yields provided for the reaction.

13 (a) Wentrup, C.; Finnerty, J. J.; Koch, R. *Curr. Org. Chem*. **2011**, *15*, 1745. (b) Reichen, W. *Chem. Rev*. **1978**, *78*, 569. (c) Vincent Rocan, J.-F.; Beauchemin, A. M. *Synthesis* **2016**, *48*, 3625.

14 Larsen, C.; Jakobsen, P. Acta *Chem. Scand*. **1970**, *24*, 1445.

15 Shah, S. N.; Chudgar, N. K. *Molecules* **2000**, *5*, 657.

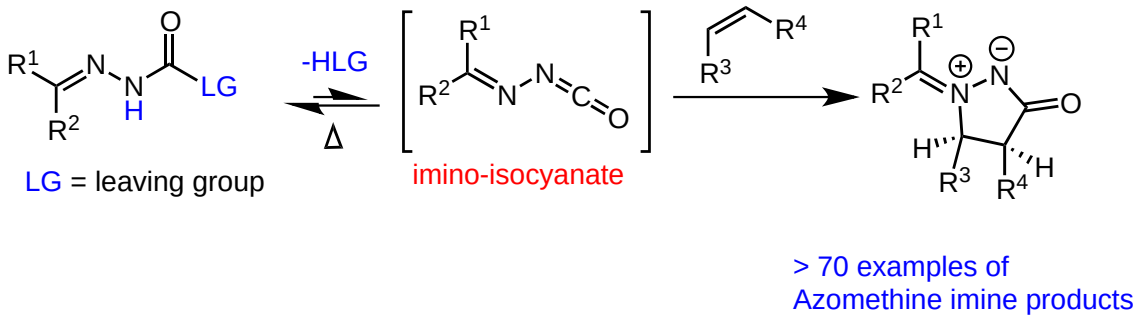
16 Jones, D. W. J. *Chem. Soc. Chem. Commun*. **1982**, 766.



Scheme 5: Cycloaddition reaction of imino-isocyanates with phenylacetylene

Following Jones' synthesis, our group began exploring the intermolecular cycloaddition reactions of imino-isocyanates. In contrast to Jones, the strategy was to use a blocking (masking) group on the isocyanate precursor, which allow a controlled release of imino-isocyanate and facile synthesis of the reagent (**Scheme 6**).[17]

17 (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M.*J. Am. Chem. Soc.* **2012**, *134,* 16111. (b) Gan, W.; Moon, P.; Clavette, C.; DasNeves, N.; Markiewicz, T.;Toderian, A.; Beauchemin, A. M.*Org. Lett.* **2013**, *15,* 1890. (c) Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, A. M. *Org. Lett.* **2015**, *17,* 3612. (d) Garland, K.; Gan, W.; Depatie-Sicard, C.; Beauchemin, A. M. *Org. Lett.* **2013**, *15*, 4074. (e) Clavette, C.; Vincent Rocan, J.-F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2013**, *52,* 12705. (f) Vincent-Rocan, J.-F.; Clavette, C.; Leckett, K.; Beauchemin, A. M. *Chem. - Eur. J.* **2015,** *21*, 3886. (g) Vincent-Rocan, J.-F.; Derasp, J. S.; Beauchemin, A. M. *Chem. Commun.* **2015,** *51,* 16405. (h) Ivanovich, R. A.; Vincent-Rocan, J.-F.; Elkaeed, E. B.; Beauchemin, A. M. *Org. Lett.* **2015**, *17,* 4898. (i) Vincent Rocan, J.-F.; Ivanovich, R. A.; Clavette, C.; Leckett, K.; Bejjani, J.; Beauchemin, A. M. *Chem. Sci.* **2016**, *7*, 315.



Scheme 6: Intermolecular [3+2] cycloaddition of alkenes with imino-isocyanates

[3+2] Cycloadditions of imino-isocyanates with alkenes yielded cyclic azomethine imine products. DFT calculations support the following pathway: the HOMO of the alkene interacting with the LUMO of the imino-isocyanate which acts as the dominant interaction. In fact, DFT calculations showed that the reaction proceeds through an asynchronous transition state.[18] The forming bond length between the alkene and carbonyl carbon was short compared to the forming bond between the alkene and the nitrogen atom.[19] This finding was consistent with experimental results since compounds produced showed generally high chemoselectivity and high Markonikov regioselectivity.

18 (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M.*J. Am. Chem. Soc.* **2012**, *134,* 16111. (b) Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, *A. M. Org. Lett.* **2015**, *17*, 3612.

19 Bongers, A. L. Intermolecular [3+2] Cycloadditions of Imino-isocyanates to Acess β-Amino Carbonyl Compounds, Ph. D. Thesis, University of Ottawa, 2016.

1.1.1.3 Azomethine Imines

Azomethine imines are another example of an amphoteric molecule containing a 1,3-dipole. There are three main categories of azomethine imines with NNCO motifs that present in the literature:

1) *N,N'*-cyclic, 2) acyclic and 3) *C,N*-cyclic azomethine imines (**Figure 3**).

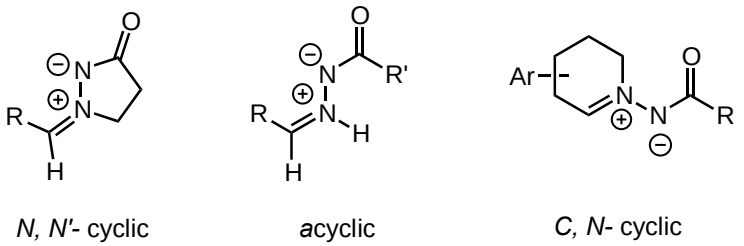
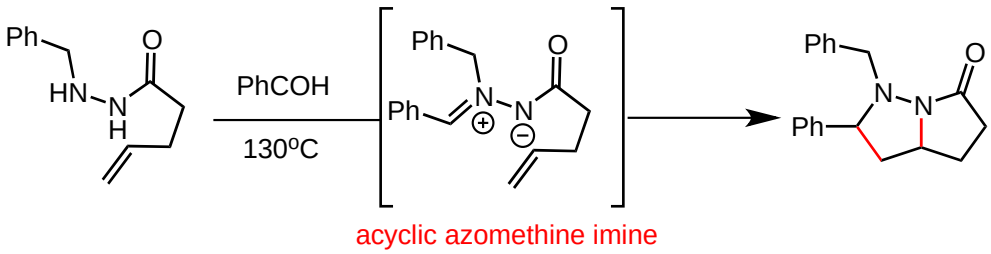


Figure 3: Classes of azomethine imines

Among various reactivity, reactions of azomethine imines with alkenes have broad applicability in heterocyclic synthesis.[20] This can result in bicyclic heterocycles including two nitrogen atoms in their structure (**Scheme 7**).[21]

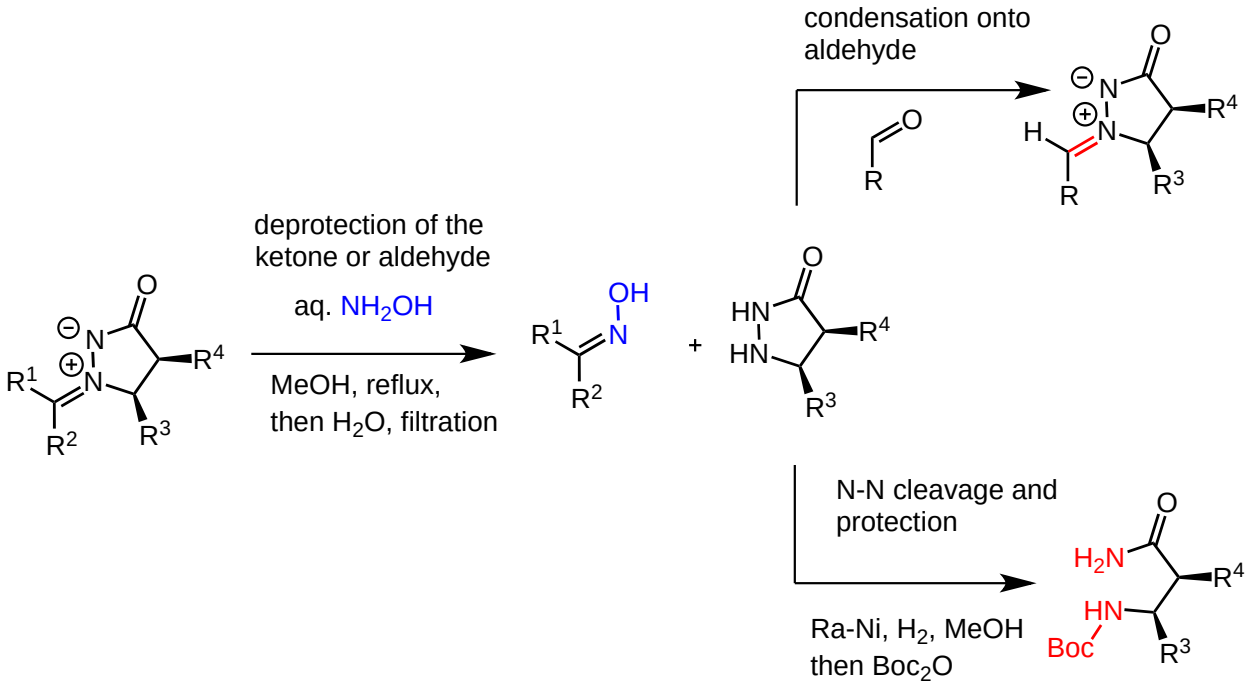


Scheme 7: Polycyclic heterocycle synthesis via an acyclic azomethine imine intermediate

20 Schantl, J. G. *Azomethine Imines, Science of Synthesis* **2004**, *27*, 731-824.

21 Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10.

As shown in **Scheme 6**, our group was able to obtain over 70 examples of *N, N'*-cyclic azomethine imines from various alkenes and imino-isocyanates. This allowed access to many complex β-aminocarbonyl containing azomethine imine molecules starting from semicarbazones and readily available alkenes. Also, few derivatization methods of azomethine imines were illustrated to access a variety of β-aminocarbonyl compounds (**Scheme 8**).[22]

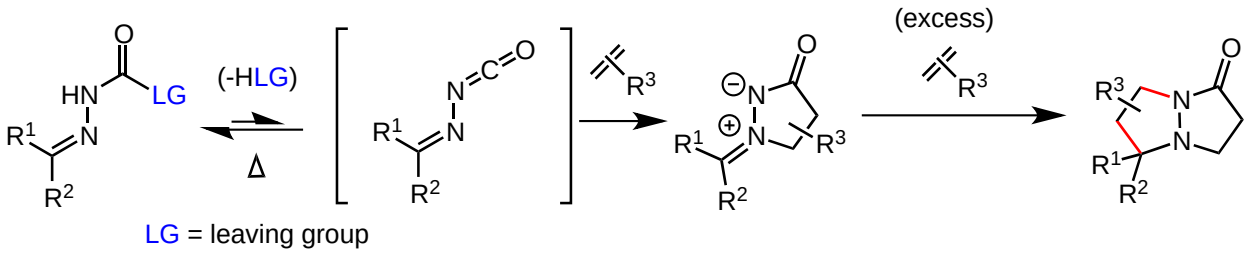


Scheme 8: Derivatization of azomethine imines

With their amphoteric character, azomethine imines can perform cycloaddition reactions. Initial studies on alkene aminocarbonylation focused on preventing such 1,3-dipolar cycloadditions of azomethine imines in the optimization. The use of symmetrical ketones and increasing the steric bulk of the hydrazones simplified the reaction as well as prevented side reactions. However, when

22 (a) Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134,* 16111. (b) Lavergne, K.; Bongers, A.; Betit, L.; Beauchemin, *A. M. Org. Lett.* **2015**, *17*, 3612. (c) L. Betit, M. Sc. Thesis, University of Ottawa, 2015.

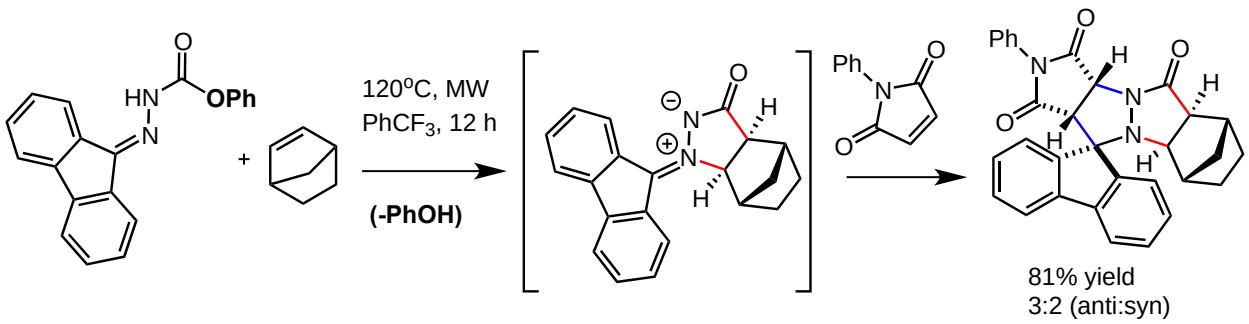
using excess alkenes, the aldhydrazones showed a propensity for criss-cross cycloaddition processes (**Scheme 9**).[23]



Scheme 9: Alkene aminothiocarboylation and 1,3-dipolar cycloaddition of azomethine imines with excess alkene

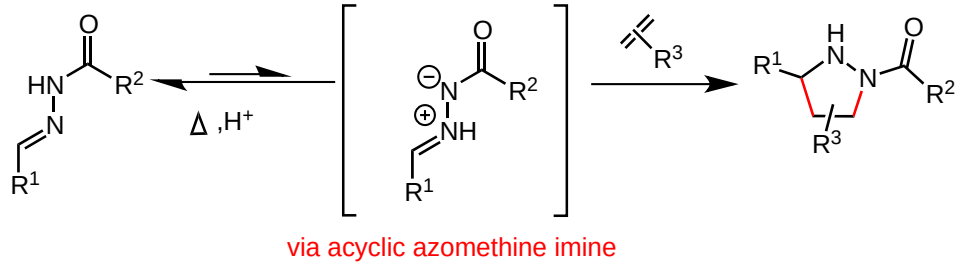
However, more control is possible. In 2012, Clavette *et al.* reported an intermolecular 1,3-cycloaddition reaction with an azomethine imine intermediate formed in situ as shown in **Scheme 10**. This reaction used two different alkenes which showed two different reactivities to selectively form the azomethine imine with norbornene, which is the more electron-rich alkene (norbornene as a reagent for azomethine imine synthesis will be discussed in **Chapter 1**). Then the formed product, azomethine imine, underwent a 1,3-dipolar cycloaddition reaction with the electron-poor *N*-phenylmaleimide. In **Chapter 4,** 1,3-cycloaddition reactivity with azomethine imines will be further discussed.

23 Rádl, S. *Aldrichimica Acta* **1997**, *30*, 97.



Scheme 10: Intermolecular 1,3-cycloaddition reaction with *N*-phenylmaleimide using an azomethine imine formed in-situ

Acyclic azomethine imines are synthesized in situ and can perform intermolecular cycloadditions with an electron-deficient dipolarophile. Acyclic azomethine imines are scarce in the literature and can be accessed through heating a semicarbazone with an acid (**Scheme 11**).[24]



Scheme 11: In situ generation of acyclic azomethine imine and [3+2] cycloaddition with an alkene

As discussed above briefly, our group was able to successfully form β-aminocarbonyl compounds embedded in heterocycle containing the NNCO motif. Then the interest was directed towards forming heterocycles with a β-aminothiocarbonyl motif. The idea was to see the reactivity difference by introducing a thiocarbonyl instead of the carbonyl. The following section will focus on discussing the cycloaddition reactions of NNCS motif.

24 Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2015**, *13*, 8596.

1.2 NNCS Motifs - Isolation and Reactivity of Isothiocyanates

1.2.1 Importance of NNCS Motif

The NNCS motif is present in many interesting compounds showing different biological properties (**Figure 4**).[25] For example, Elesclomol shown below is a novel potent oxidative stress inducer that elicits pro-apoptosis events among tumor cells.[26e]

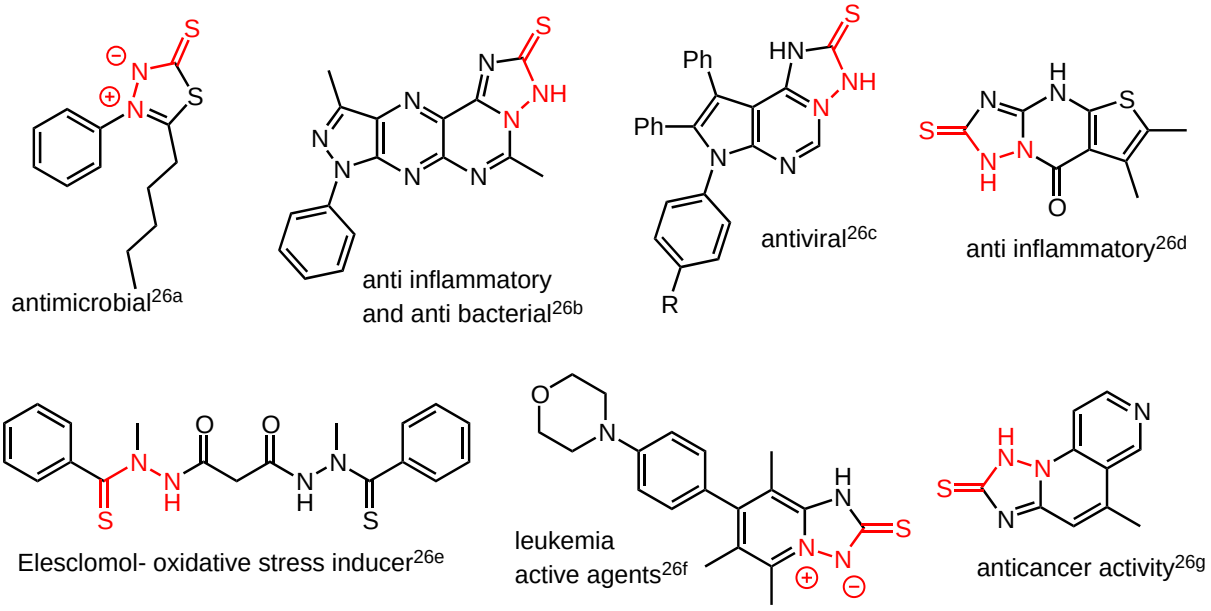


Figure 4: NNCS motifs in biologically active compounds

However, synthetic routes accessing these motifs through *N*-isothiocyanate intermediates are rare. As discussed earlier it is possible to access more complex NNCO motifs using *N*-isocyanates.

25 Navarro, S. L.; Lampe, J. W.; *Food Funct.* **2011**, *2*, 579.

26 (a) Beyaert, R.; Marynen, P.; Baens, T.; Heyninck, K. **2009**, WO 2009065897. (b) Abdel, M.; Shawkat, A.; El-Emary, T. I.; El-Kashef, Hussein, S. *Chem. Pharm. Bull.* **2016**, *64,* 476. (c) Mohamed, M. S.; Abd El-Hameed, R. H.; Sayed, A. I.; Soror, S. H. *Arch. Pharm. Chem. Life Sci*. **2015**, *348,* 1. (d) Ashour, H. M.; Shaaban, O. G.; Rizk, O. H.; El-Ashmawy, I. M. *Eur. J. Med. Chem.* **2013,** *62,* 341-351. (e) Nagai, M.; Vo N. H.; Shin, O. L,; Chimmanamada, D. I. T.; Chu, J,; Beaudette-Zlatanova, B. C.; Lu, R.; Blackman, R. K,; Barsoum, J.; Koya, K.; Wada, Y.; *Free Radic Biol. Med.* **2012**, *52*, 2142. (f) Katritzky, A. R.; Girgis, A. S.; Slavov, S.; Tala, S. R.; Stoyanova, S.; *Eur. J. Med. Chem.* **2010**, *45*, 5183

However, there are only a few reports on using isothiocyanates to access NNCS motifs. Our group was interested in using isothiocyanates in parallel to the studies conducted on *N*-isocyanates to further explore their use as amphoteric intermediates.

1.2.2 Importance of Isothiocyanates

In direct analogy to the reactivity presented in the previous section, the use of *N*-isothiocyanates to access NNCS compounds will be discussed in this thesis. Different types of isothiocyanates such as *C*-isothiocyanates, amino-isothiocyanates and imino-isothiocyanates can be used as partners to form various NCS-containing motifs (**Figure 5**).

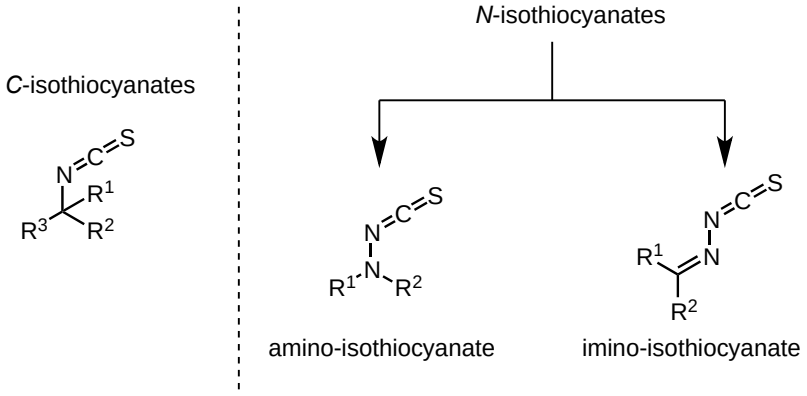
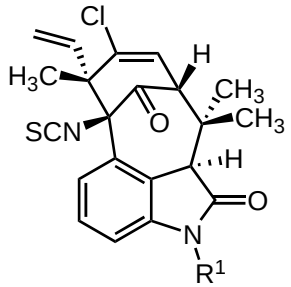


Figure 5: Structures of different Isothiocyanates

C-Isothiocyanates have gotten attention from various research groups' interest, and around 1600 derivatives are commercially available. They are also present in natural products. For example, Moore and co-workers have isolated a series of fascinating welwitindolinones from green algae and those include *C*-isothiocyanate precursors (**Figure 6**). They exhibited significant biological activities represented by the ability to reverse P-glycoprotein mediated multidrug resistance in

human cancer cells.[27] Studies have been conducted on isothiocyanates in order to examine the hypothesis made on the relationship between cancer prevention and isothiocyanate intake of a person. Among many studies, one of the experiments was a controlled study on breast cancer which was conducted by Fowke *et al.* in 2003. The study showed women with the highest quartile of isothiocyanate excretion had a twofold decreased risk for developing breast cancer.[28] In a review in 2011, Lampe states "Evidence suggests that isothiocyanates exert their effect through a variety of distinct but interconnected signaling pathways important for inhibiting carcinogenesis, including those involve in detoxification, inflammation, apoptosis, and cell cycle and epigenetic regulation, among others".[29]



R^1= H; *N*-Methylwelwitindolinone *C*-isothiocyanate

R^1= CH_3; Welwitindolinone *C*-isothiocyanate

Figure 6: Isolated *C*-isothiocyanate precursors from green algae

As discussed, isothiocyanates show interesting links with natural products and for the cycloaddition reactions we were more interested in exploring the synthesis and reactivity of *N*-isothiocyanates. Presented below is an overview of the work published on these reactive intermediates.

27 Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47,* 241.

28 Fowke, J. H.; Qi, D.; Bradlow, H. L.; Shu, X. O.; Gao, Y. T.; Cheng, J. R.; Jin, F.; Zheng, W. *Steroids* **2003**, *68*, 65.

29 Navarro, S. L.; Li, F.; Lampe, J. W, *Food Funct.* **2011**, *2,* 579.

1.2.3 Synthesis of *N*-isothiocyanates

McElhinney reported the first *N*-isothiocyanate formation in 1966. He proposed a mechanism with amino-isothiocyanate intermediate during the formation of thiosemicarbazides (**Scheme 12a**).[30] Around the same time, Anthoni *et al.* were able to observe the amino-isothiocyanate formation using IR spectroscopy at -78 °C.[31] They also observed that usually, these isothiocyanates dimerize within a few seconds at room temperature.[32] The isothiocyanate shown in **Scheme 12b** was formed through an unmasking process, where the imidazole is the leaving group.

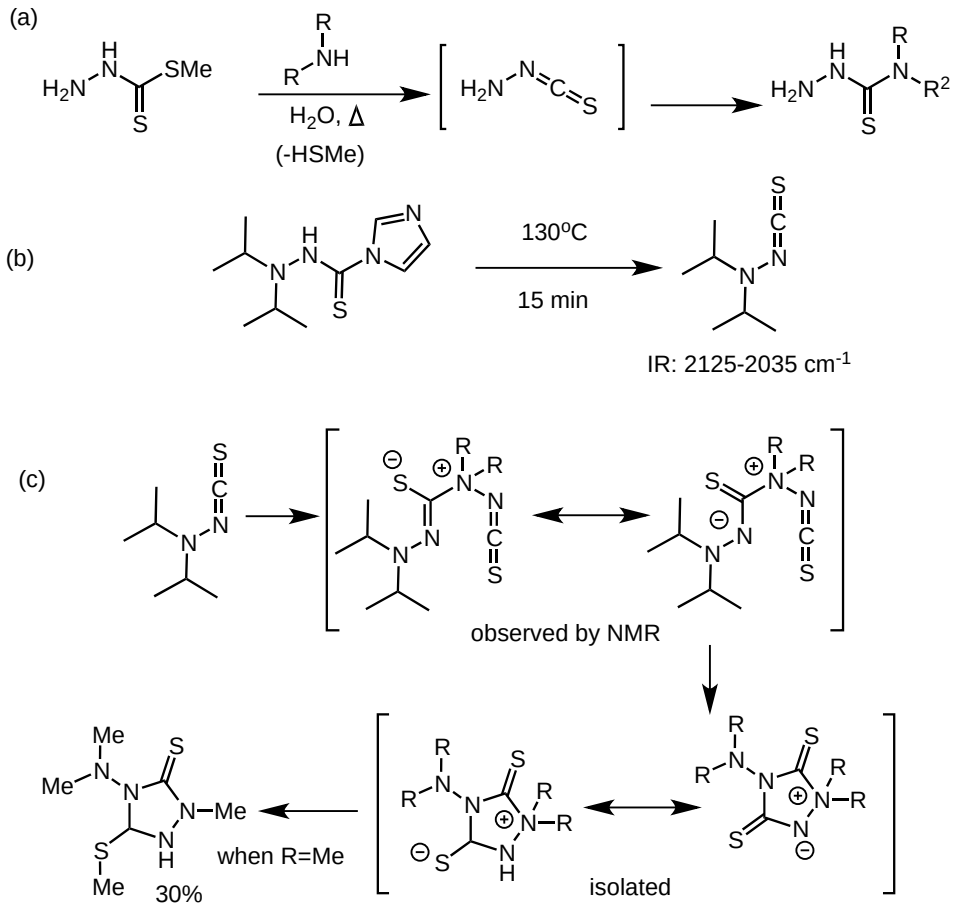
They were able to identify the isolated isothiocyanate using IR spectroscopy and the NCS stretch was at 2125 and 2035 cm^{-1}.[33] Also, with an important note, they were able to isolate the dimerized product and proposed a mechanism for the dimerization as indicated in **Scheme 12c**.

30 (a) McElhinney, R. S. *J. Chem. Soc.* **1966**, 950. (b) El-Hewhi, Z.; Taeger, E.; Funge, F. *J. Prakt. Chem*. **1962**, *18*, 275. (c) Delépine, M. *Bull. Soc. Chim. Fr.* **1902,** 587. (d) Delépine, M.; Schving, P. *Bull. Soc. Chim. Fr*. **1910**, 896. (e) Aubert, P.; Knott, E. B.; Williams, L. A. *J. Chem. Soc.* **1951**, 2188. (f) Knott, E. B. *J. Chem. Soc.* **1956**, 1644.

31 Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1966**, *20,* 1714.

32 Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1968**, *22*, 309.

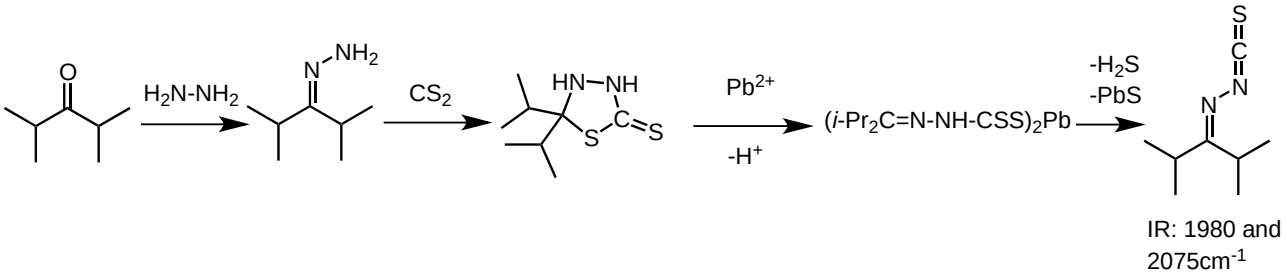
33 Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1967**, *21,* 2061.



Scheme 12: Amino-isothiocyanate formation and dimerization (a) Thiosemicarbazone formation through proposed *N*-isothiocyanate intermediate (b) Isolation of the amino-isothiocyanate (c) Dimerization of the amino-isothiocyanate at room temperature (R=*i*Pr)

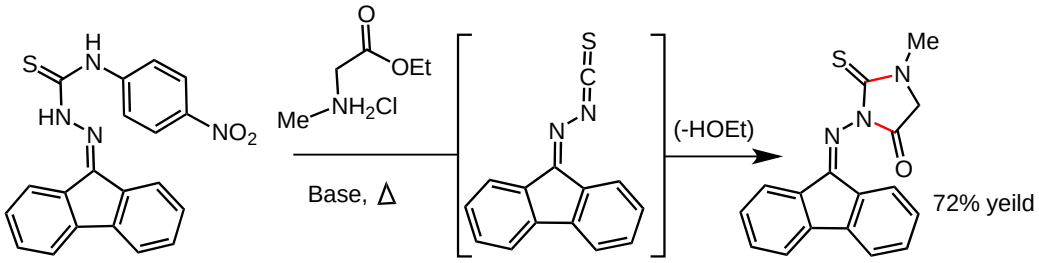
Imino-isothiocyanate formation using high-temperature conditions with different leaving groups of thiosemicarbazides were reported. Anthoni and Berg were able to isolate and characterize the imino-isothiocyanate monomer for the first time using lead salts as precursors with isopropyl semicarbazones (**Scheme 13**).[34]

34 Anthoni, U.; Berg, C. *Acta Chem. Scand.* **1969**, *23*, 3602.



Scheme 13: Imino-isothiocyanate formation through lead salts

A cascade reaction involving imino-isothiocyanate was reported by Vincent-Rocan from our group in 2015.[35] In this reaction, an in situ-formed imino-isothiocyanate reacted with a secondary amine, resulting in a thiosemicarbazone that then cyclized to yield the aminothiohydantoin product shown in **Scheme 14**.



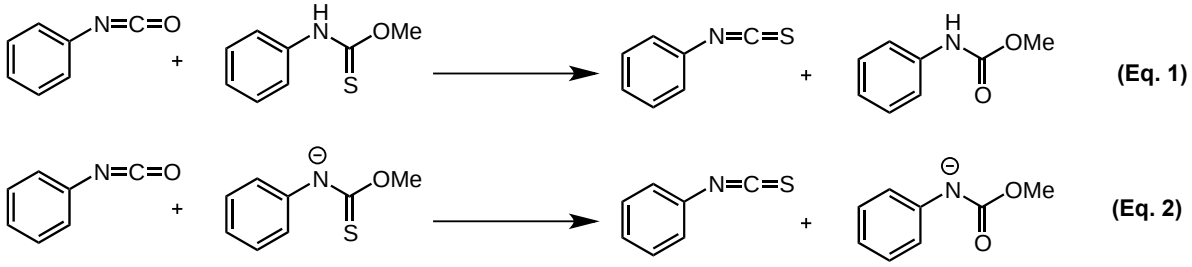
Scheme 14: Cascade reaction for formation of aminothiohydantoin via imino-isothiocyanate intermediate

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

1.2.4 Reactivity of Isothiocyanates vs Isocyanates

In 2009, Wilberg and coworkers investigated the reactivity difference in *C*-isocyanates versus *C*-isothiocyanates using experimental as well as computational studies.[36] At 0°C the reaction rate of PhNCO with pure ethanol as the nucleophile was approximately around 50 000 times more rapid than the analogues reaction with PhNCS. This corresponds to a difference in activation free energy of 6 kcal/mol. Energy differences were also calculated as shown in **Table 1** for the transfer of methanol and methoxide ion.

Table 1: Energies (kcal/mol) of transfer reactions



Reaction	ΔH	ΔG
Eq. 1	-9.9	-10.3
Eq. 2	0.7	-1.5

As indicated in **Table 1**, methanol had a large preference for addition to PhNCO versus PhNCS, which was similar to observed experimental data. However, the results shown for **Equation 2** methoxide ion had a small preference for addition to PhNCO vs PhNCS. Results obtained were explained using Hirshfeld charges as illustrated in **Figure 7.**

36 Wiberg, K. B.; Wang, Y.-G.; Miller, S. J.; Puchlopek, A. L.; Bailey, W. F.; Fair, J. D. *J. Org. Chem.* **2009**, *74*, 3659.

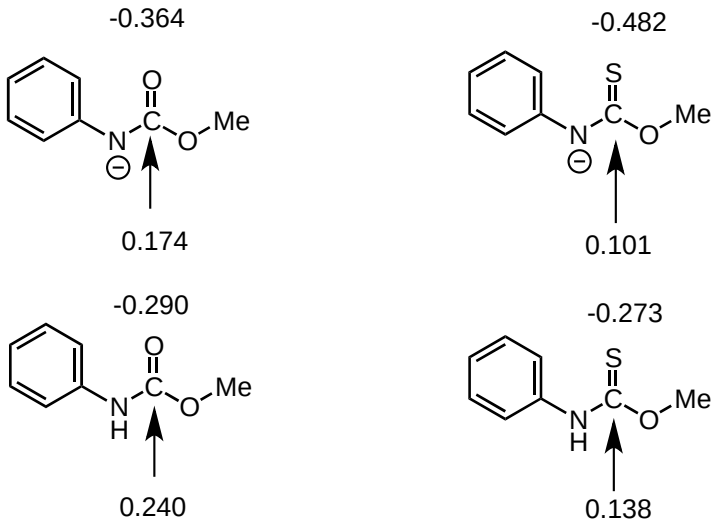


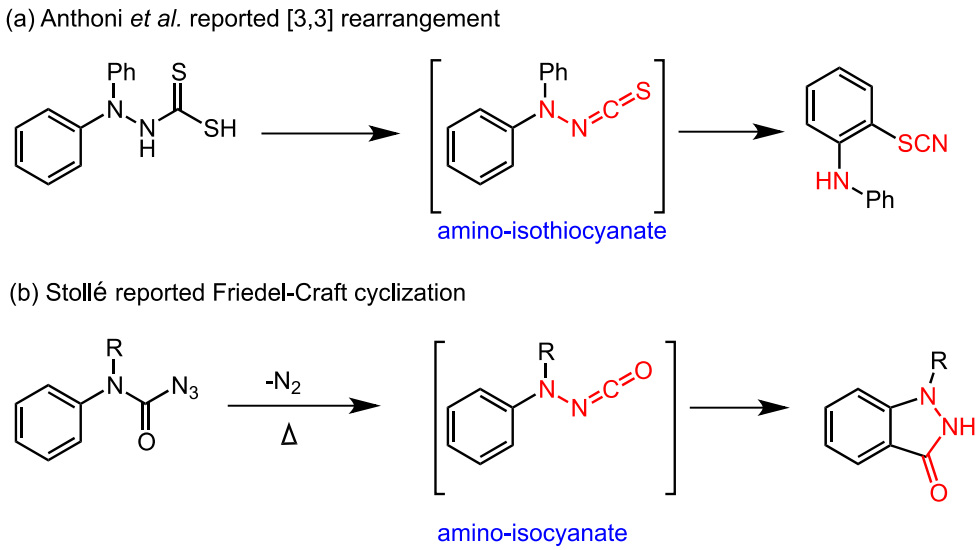
Figure 7: Hirshfeld charges for isocyanate and isothiocyanate derivatives in substitution reactions

The product of methoxide addition to PhNCS was found to lead to a larger partial negative charge on sulfur than on the carbonyl oxygen (**Figure 7**, top row). Therefore, the negative charge is stabilized by the sulfur atom, which accounts for the near thermo-neutrality of the reaction shown in **Equation 2**. The greater acidity of H_2S compared to H_2O as well as higher pK_a of enol compounds compared to the enethiol analogues supports that sulfur is better able to bear a negative charge than oxygen.[37]

Moreover, the fact that the addition products of isothiocyanates should be more stable compared to isocyanates led to the research project in using *N*-isothiocyanates as intermediates for azomethine imine formation (See **Chapter 2**).

37 Sklenak, S.; Apeloig, Y.; Rappoport, Z. *J. Chem. Soc.* **2000**, *2,* 2269.

After being able to isolate and characterize *N*-isothiocyanates, there are few studies that have reported the reactivity of these amphoteric molecules. Anthoni *et al.* in 1967 reported a [3,3] rearrangement via amino-isothiocyanate intermediate.[38] Interestingly, a different reactivity for similar conditions was observed by Stollé with in situ generated amino-isocyanate. Indeed, the amino-isocyanate formed an intramolecular Friedel-Crafts cyclization product (**Scheme 15**).[39]



Scheme 15: Divergent reactivity of amino-isothiocyanate vs amino-isocyanate

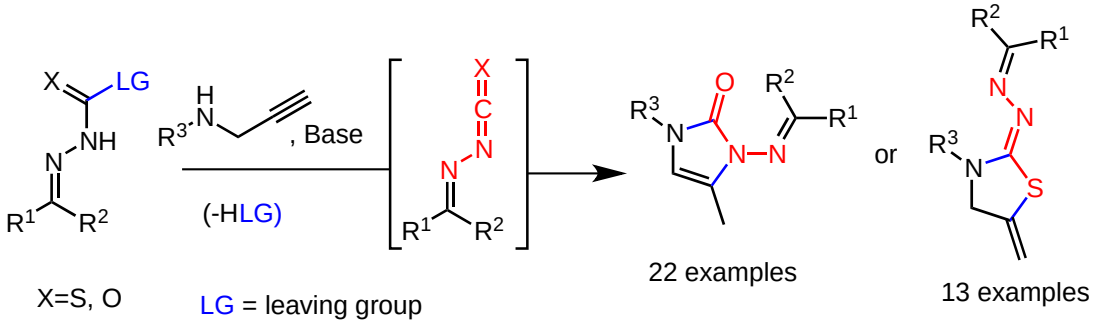
In 2015, Vincent-Rocan and Derasp from our group also reported divergent reactivity of imino-isocyanates and imino-isothiocyanates. Imidazolones and thiazolidines were formed as products under similar conditions, respectively (**Scheme 16**).[40] This result can be explained using the Hirshfeld charges we discussed above, where with the *N*-isothiocyanate, the negative charge is more stabilized on sulfur atom. Therefore, once the propargyl amine attack on the *N*-isothiocyanate,

38 Anthoni, U.; Larsen, C.; Nielsen. P. H. *Acta Chem. Scand.* **1967**, *21,* 1201.

39 (a) Stollé, R. *J. Prakt. Chem.* **1927**, *116,* 192. (b) Stollé, R. *J. Prakt. Chem.* **1928**, *117*, 185.

40 Vincent-Rocan, J.-F. ; Derasp, J. S.; Beauchemin, A. M. *Chem. Commun.* **2015**, *51,* 16405.

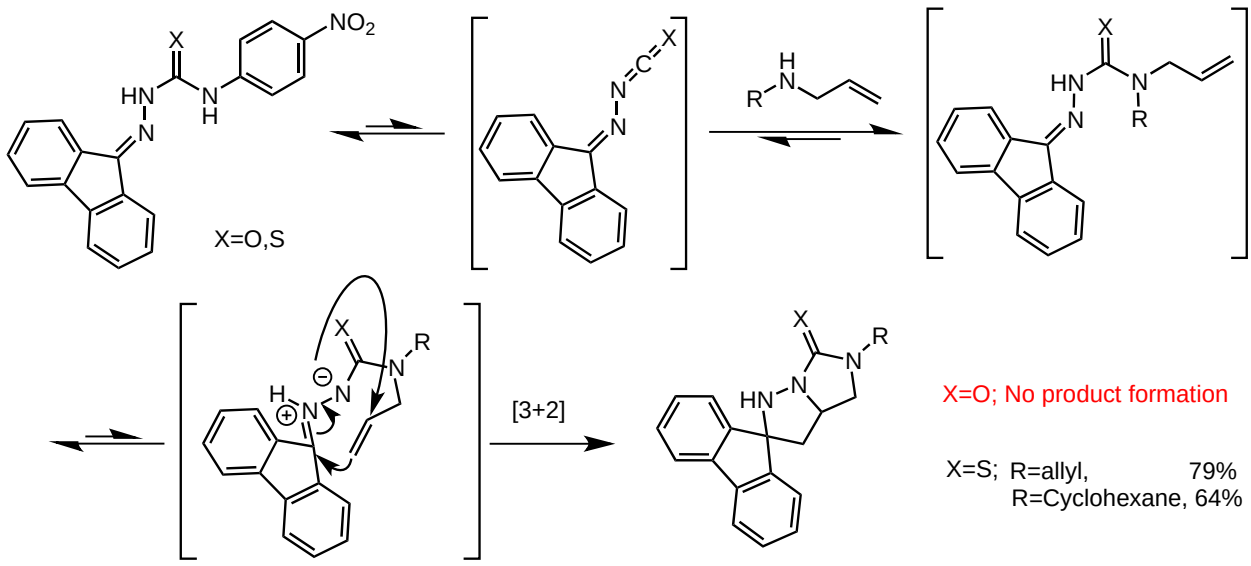
sulfur becomes the nucleophile. This can also be explained through the Hard and Soft principle[41], in that cyclization of the soft sulfur atom is favored on the soft alkyne. Again, on the *N*-isocyanate the negative charge is softer on the nitrogen atom, and consequently, this is the nucleophile providing two different reactivities for the reaction.



Scheme 16: Divergent reactivity of the imino-isocyanate and imino-isothiocyanate

In the same publication, a cascade reaction proceeding through the formation of acyclic azomethine imine intermediate was reported. This intermediate undergoes a [3+2] cycloaddition, which was only observed with *N*-isothiocyanate precursor (**Scheme 17**). This chemistry was unprecedented in the literature of azomethine imines and highlighted the differences in reactivity between the use of imino-isocyanate and imino-isothiocyanate precursors, and the increased stability of the dipole intermediate possessing the thiocarbonyl motif.

41 (a) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (b) Pearson. R. G. *J. Chem. Educ.* **1968**, *45*, 643.

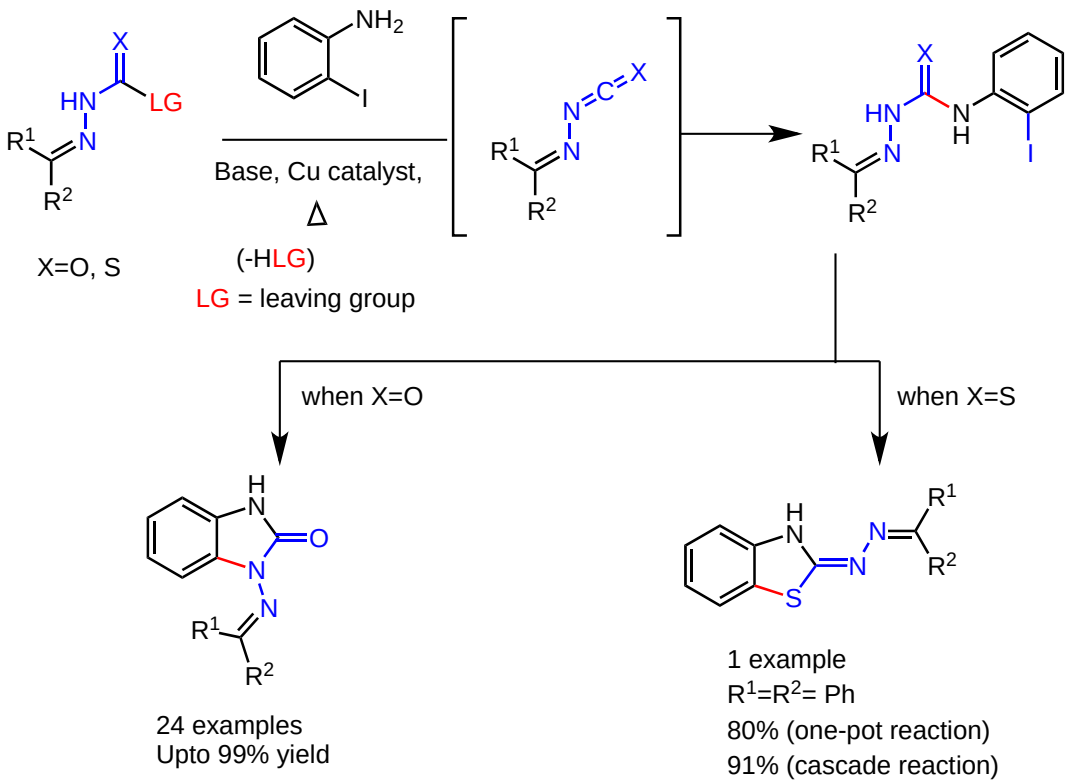


Scheme 17: Acyclic thioxo-azomethine imine intermediate performing intramolecular 1,3-dipolar cycloadditions

Recently, An from our group observed different reactivity with a masked *N*-isothiocyanate substrate compared to a masked *N*-isocyanate substrate in a copper-catalyzed cascade cyclization reaction. She was conducting base-catalyzed substitution reactions with a 2-iodoaniline precursor and then intramolecular copper-catalyzed coupling to synthesize 1-aminobenzimidazolones (**Scheme 18**).[42] However, with the sulfur analogue, similar to negative charge stabilization pattern we discussed for **Scheme 16**, An reported the formation of a heterocycle where sulfur participated as a coupling partner.[43] In contrast, with the *N*-isocyanate precursor coupling involved the nitrogen atom, and yielded a different product (the imidazolone).

42 An, J.; Alper, H.; Beauchemin, A. M. *Org. Lett.* **2016**, *18*, 3482.

43 A slower, uncatalyzed reaction was observed to give the benzothiazole ring system in modest yield under similar reaction conditions. See footnote 18 of reference 42.



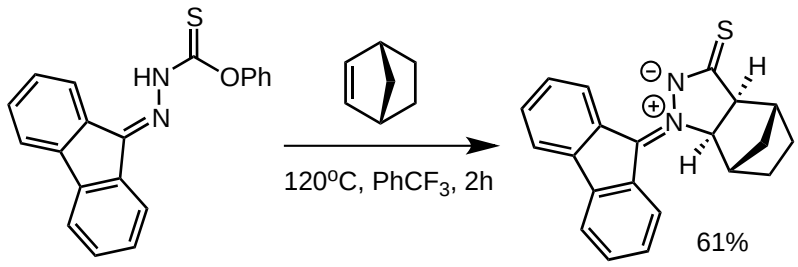
Scheme 18: Divergent pathways for product formation with the use of *N*-isocyanate and *N*-isothiocyanate precursors

Our group was interested in exploring aminothiocarbonylation particularly due to: 1) The inspiration from the successful azomethine imine formation through *N*-isocyanates, 2) *N*-isothiocyanate showing divergent reactivity compared to *N*-isocyanates and 3) The scarcity of reports on the reactivity of the *N*-isothiocyanates.

1.3 NNCS Motifs – Preliminary Results for Alkene Aminothiocarbonylation

1.3.1 Fluorenone Based Precursor Formation

N-Isothiocyanate formation was an interest in the group and Dr. Gan first introduced fluorenone based precursor shown in **Scheme 19** but never developed the reaction further since the precursor was difficult to form, and early experiments suggested a reduced reactivity compared to the parent *N*-isocyanate.[44]

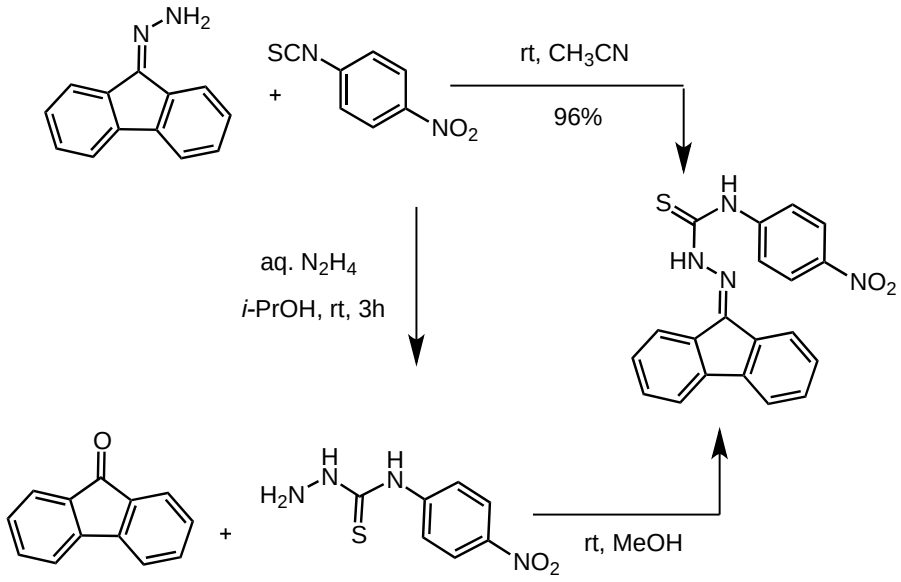


Scheme 19: Initial aminothiocarbonylation result by Dr. Gan

The use of the fluorenyl group on the hydrazone added steric bulk and helped to avoid byproduct formation with an excess alkene. Also, this reagent likely provides increased stabilization through resonance, thus forming more stable azomethine imines.

44 Clavette, C.; Gan, W.; Markiewicz, T.; Toderian, A.; Beauchemin, A. M. **2013**, *Patent:* WO2013/67646 A1.

To address the issue of difficult formation of the *N*-isothiocyanate precursor, Vincent-Rocan then developed a precursor with an aniline as the leaving group.[45] This precursor can be accessed by two general synthetic pathways. Either the reaction of the NH_2-hydrazone onto the *para*-nitroisothiocyanate or using *para*-nitroaniline based thiosemicarbazate with fluorenone (**Scheme 20**).[46]



Scheme 20: Synthesis of fluorenone hydrazone precursor with *para*-nitroaniline instead of phenol

With this fluorenone precursor, Alyssa Perozzo, a former undergraduate student from the Beauchemin group, was able to get results for alkene aminothiocarbonylation as following (**Figure 8**). While encouraging, there were few issues with these results: First, use of HFIP as a solvent was not the best option since it is too expensive to be an acceptable solvent. Second, only NMR yields were provided and both isolated yields and characterization data were needed for these

45 Vincent-Rocan, *N*-Isocyanates: Versatile Intermediates in Heterocyclic Synthesis, Ph.D. Thesis, University of Ottawa, 2016.

46 Bongers, A.; Ranasinghe, I.; Lemire, P.; Vincent-Rocan, J.-F.; Perozzo, A.; Beauchemin, A. M. *Org. Lett,* **2016**, *18*, 3778.

compounds. Third, the reactions were difficult to reproduce (Attempted alkenes are listed in the supporting information section).

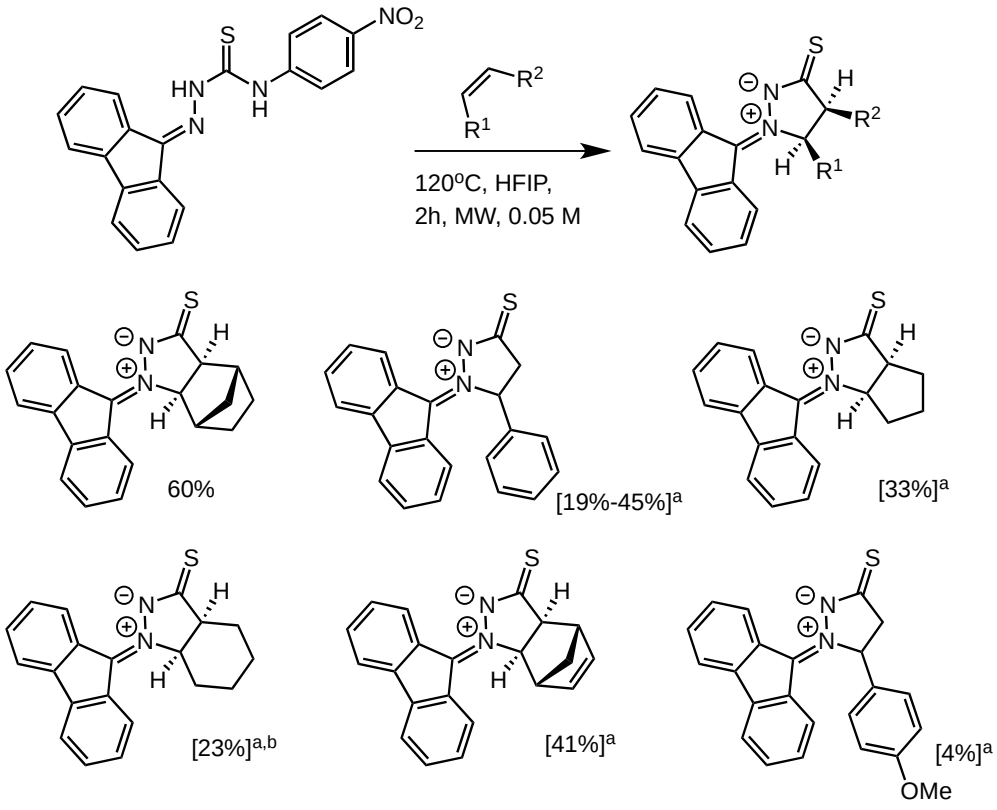


Figure 8: Preliminary results on alkene aminothiocarbonylations. [a]NMR yields were obtaiend

1.3.2 Enol Ether Aminothiocarbonylation

With the improved *N*-isothiocyanate precursor, alkene aminothiocarbonylation with enol ethers was explored by Ms. Lavergne from our group. The desired products were obtained in moderate yields and the dihydrofuran adduct was successfully isolated in 57% yield and characterized (**Figure 9**).[47] It should be emphasized that a slightly different reagent was used for these cycloadditions.

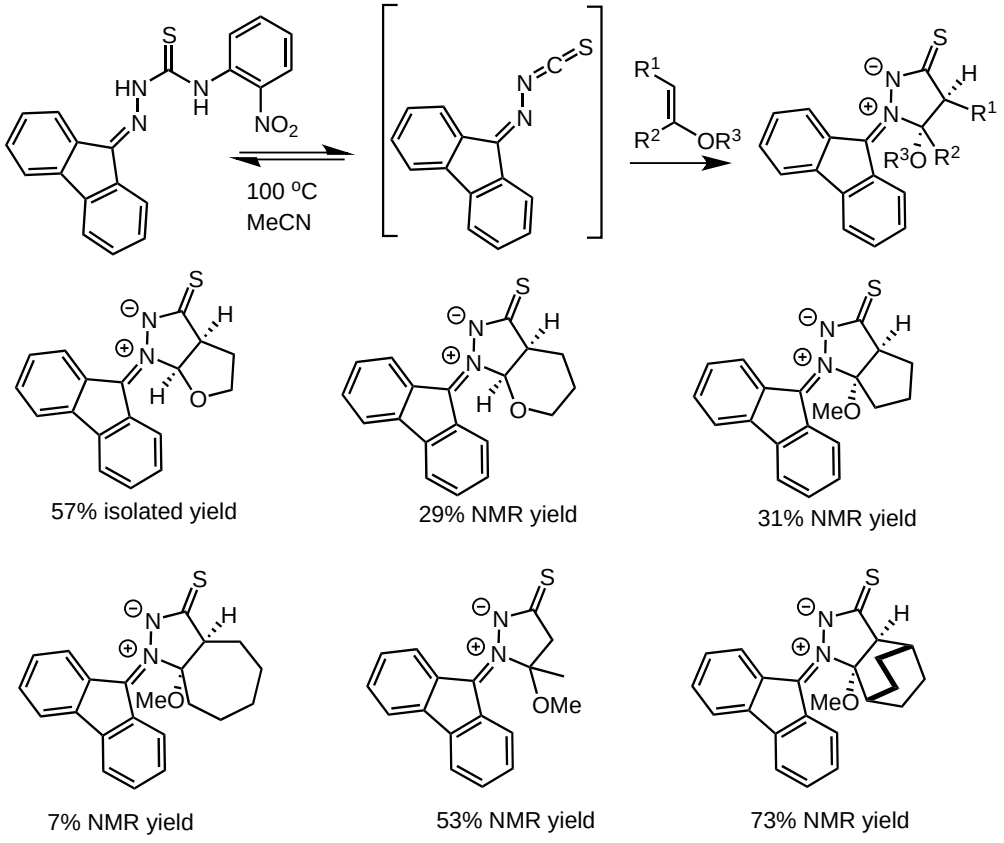
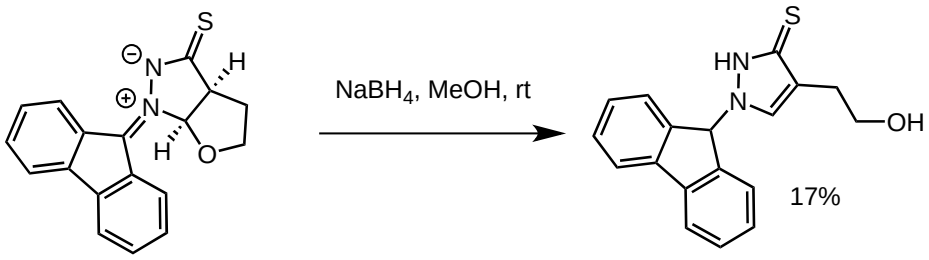


Figure 9: Scope of thioxo-azomethine imines with enol ethers

47 Lavergne, K. Synthesis of Azomethine imines via Alkene Aminocarbonylation and their Derivatization into Pyrazolones, M.Sc. Thesis, University of Ottawa, 2014.

1.3.3 Derivatization of Thioxo-azomethine Imines

Lavergne was able to reduce the thioxo-azomethine imine using sodium borohydride to obtain the desired products in 17% yield after an acidic work up (**Scheme 21**).[48]



Scheme 21: Reduction of the thioxo-azomethine imine yielding the desired thiopyrazolone product

In conclusion for this chapter, as discussed, many studies have reported in using amphoteric molecules to form heterocyclic molecules through cycloaddition reactions. Our group has reported new synthetic pathways in synthesizing β-aminocarbonyl motifs through *N*-isocyanates. The divergent reactivity observed between *N*-isothiocyanates and *N*-isocyanates as well as the success observed in synthesizing β-aminocarbonyl motifs encouraged our group to further study *N*-isothiocyanates and develop their aminothiocarbonylation reactivity.

48 Lavergne, K. Synthesis of Azomethine imines via Alkene Aminocarbonylation and their Derivatization into Pyrazolones, M.Sc. Thesis, University of Ottawa, 2014.

1.4 Research Objectives

N-Substituted isothiocyanates and their reactivity have only been reported rarely in the literature, and all prior work has been introduced earlier in this chapter. The research presented in this thesis centers around thioxo-azomethine imines and the use of *N*-isothiocyanates in new cycloaddition reactions, thus providing a new synthetic route to form nitrogen-containing heterocycles with a β-aminothiocarbonyl motif. Improvement in aminothiocarbonylation reactions, different unprecedented reactivity observed with *N*-isothiocyanates and imines will also be discussed in this thesis.

Chapter 2: Aminothiocarbonylation

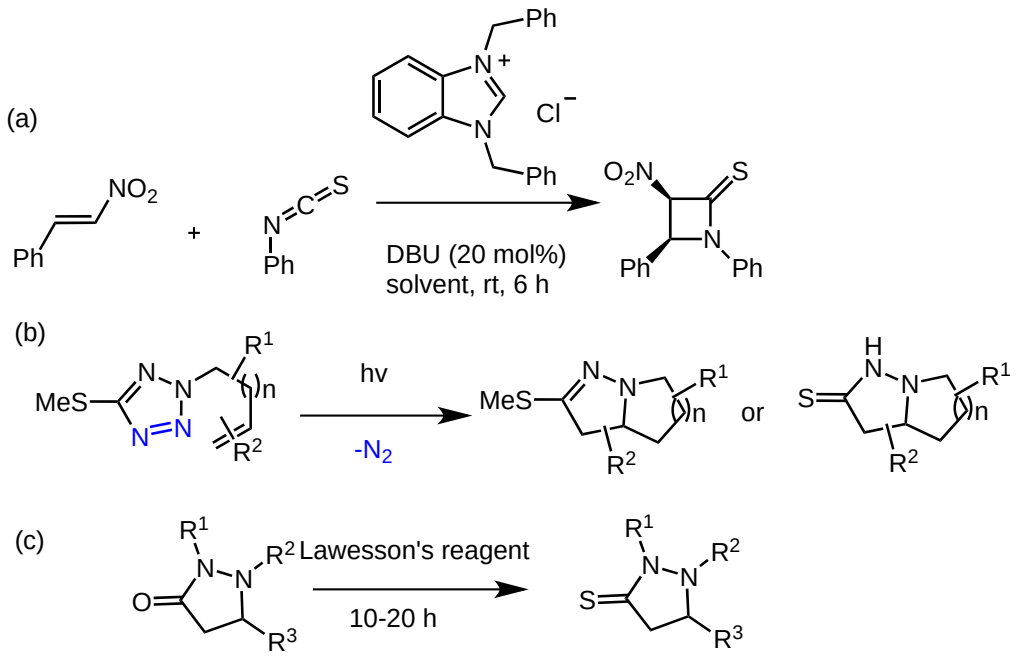
2.1 Introduction to Aminothiocarbonylation

2.1.1 Alkenes as Substrates

Alkenes are readily available substrates and amination reactions of alkenes still have important limitations. There are only two reports on alkene aminothiocarbonylation reactions, which involve the addition of a nitrogen atom and of a thiocarbonyl across an olefin. First is a formal [2+2] cycloaddition of aryl isothiocyanates and nitroolefins to form β-thiolactams (**Scheme 22a**).[49a] Second is a synthesis of polycyclic pyrazoline via photo-induced intramolecular nitrile imine-alkene 1,3-dipolar cycloaddition reported by Pla *et al.* in 2014 (**Scheme 22b**).[49b] A common method of forming such NNCS motifs is to use Lawesson's reagent to transform the carbonyl precursor into a thiocarbonyl (**Scheme 22c**).[50] The use of this method and issues will be discussed later in this chapter.

49 (a) Awasthi, C.; Yadav, L. D. S. *Synlett* **2010**, 1783–1788. (b) Pla, D.; Tan, D. S.; Gin, D. Y. *Chem. Sci.* **2014**, *5*, 2407– 2415.

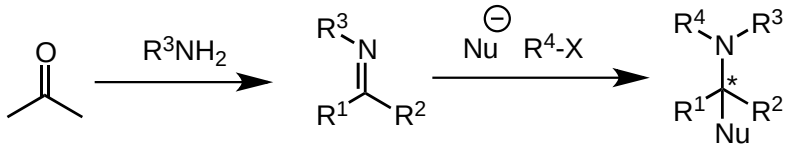
50 Dorn, H.; Kreher, T. *Heterocycles*, **1994**, *38*, 2171.



Scheme 22: (a) and (b) Addition of the alkene double bond across the nitrogen and C=S bond (c) Installation of thiocarbonyl in place of carbonyl

2.1.2 Imines as Substrates

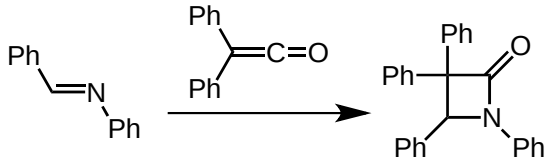
Imines are readily accessed through a simple condensation reaction between an amine and a ketone. These are common building blocks employed in the synthesis of nitrogen-containing compounds and are often used to form chiral amines starting from unsymmetrical imines (**Scheme 23**).[51]



Scheme 23: Synthesis of imine followed by nucleophilic attack on carbon to access chiral compounds

51 Staudinger, H.; Liebigs, J. *Ann. Chem.* **1907**, *356*, 51.

The reaction of imines with ketenes was discovered more than 100 years ago, long before the utility of the products in medicinal chemistry was recognized. Hermann Staudinger found in 1907 that isocyanates react with imines in [2+2] cycloadditions, producing the first synthetic β-lactams (**Scheme 24**).[52]



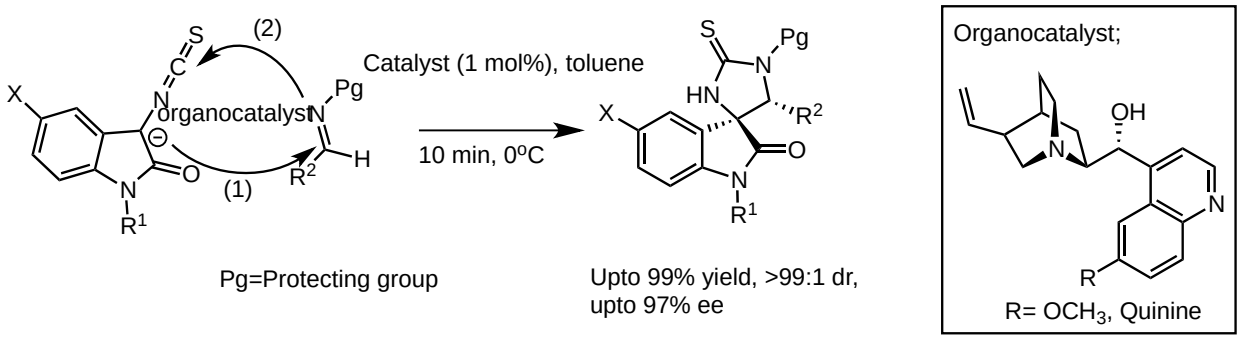
Scheme 24: Synthesis of β-lactams with imines and ketenes

There are no reports on the reaction of *N*-isothiocyanates with imines, but many reports on Mannich type cyclization reaction with isothiocyanato indoles and imines (**Scheme 25**).[53] These compounds were in high demand at the time since they were widely present in alkaloid natural products and are biologically active compounds.[54]

52 Kobayashi, S.; Ishltani, H. *Chem. Rev.* **1999,** *99,* 1069.

53 Yuan, W.-C.; Han, W.-Y.; Chen, Y.-Z.; Cui, B.-D.; Xu, X.-Y. In *Recent Advances in Organocatalysis*; Karame, I.; Srour, H., Ed.; InTech, 2016; pp 33–56.

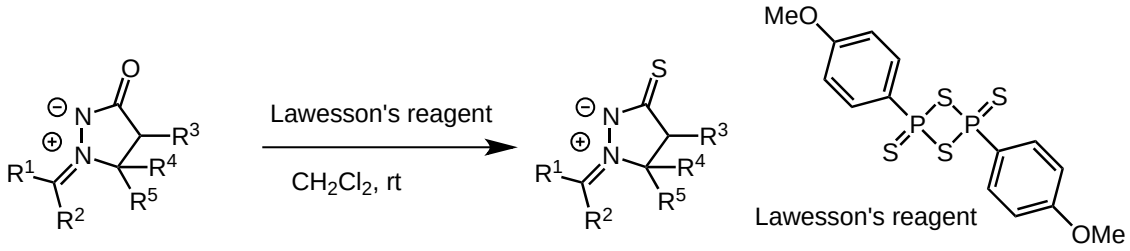
54 (a) Bai, M.; Cui, B. D.; Zuo, J.; Zhao, J.; You, Y.; Chen, Y.; Xu, X.; Zhang, X.; Yuan, W. *Tetrahedron* **2015,** *71,* 949. (b) Kato, S.; Yoshino, T.; Shibasaki, M.; Kanai, M.; Matsunaga, S. *Angew. Chem. Int. Ed.* **2012,** *51,* 7007.



Scheme 25: Reaction of isothiocyanato oxindoles and imines via (1) Mannich reaction and (2) cyclization process

2.1.3 Thioxo-azomethine Imines

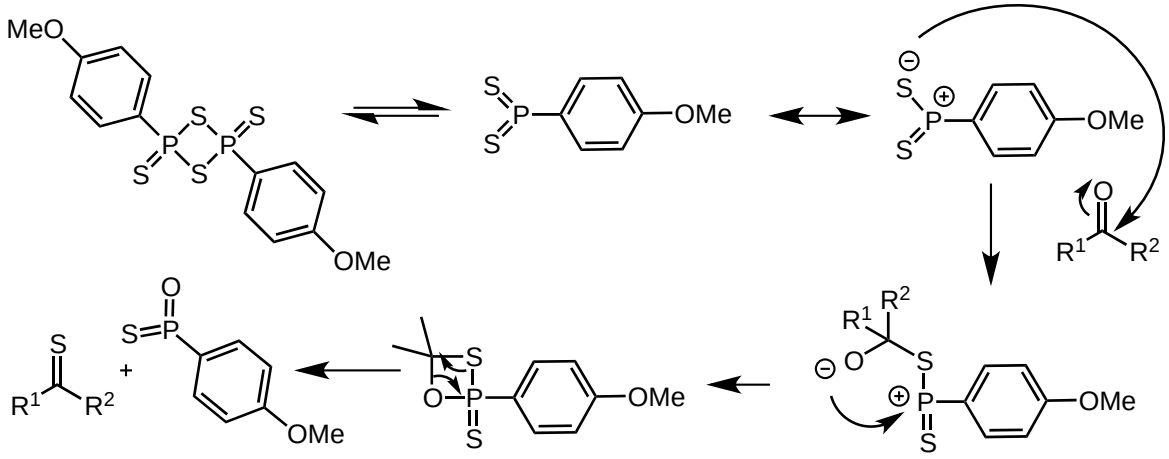
Dorn and Kreher first synthesized the thioxo-azomethine imine analogues in 1994. They were able to introduce the thiocarbonyl using Lawesson's reagent as shown in **Scheme 26**.[55]



Scheme 26: Converting carbonyl to thiocarbonyl to synthesize thioxo-azomethine imines using Lawesson's reagent

55 Dorn, H.; Kreher, T. *Heterocycles*, **1994**, *38*, 2171.

In the proposed mechanism for the thionation, the Lawesson's reagent is in equilibrium with a highly reactive dithiophosphine ylide. This ylide can react analogous to Wittig reaction with the carbonyl containing compounds to form the corresponding thiocarbonyl compound (**Scheme 27**).[56]



Scheme 27: Mechanism for the thionation reaction using Lawesson's reagent

Dorn and Kreher were able to obtain a variety of cyclic thioxo azomethine imines by transforming carbonyl into thiocarbonyl derivatives (**Figure 10**), providing a method to form sulfur analogues which were not accessible before. There were practical difficulties in using this reagent such as unpleasant odor. However, it was the only method of synthesizing thioxo-azomethine imines at the time. Given the scarcity of alkene aminocarbonylation reactions and the fact that sulfur analogues of azomethine imines can only be accessed indirectly, we decided to further develop the alkene aminothiocarbonylation using amphoteric *N*-isothiocyanates.

56 Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, *13*, 1929.

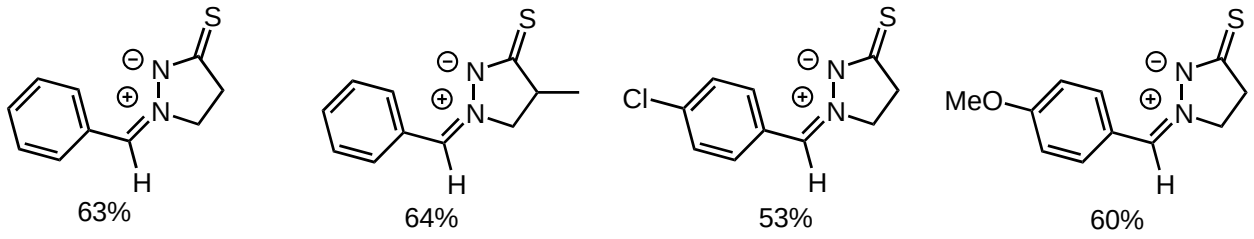


Figure 10: Selected scope of the thioxo-azomethine imines

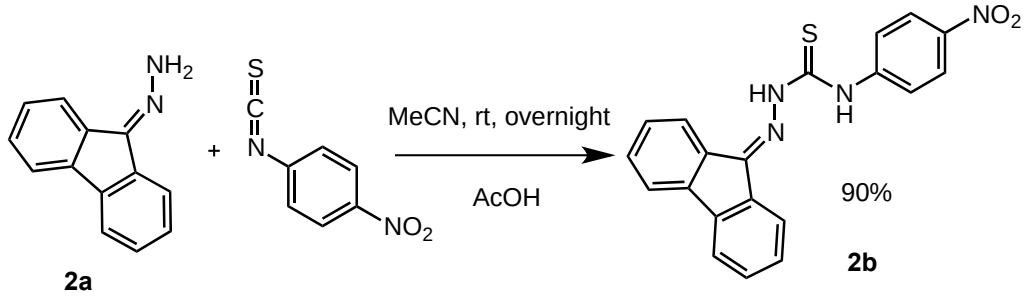
2.1.4 Project Objectives

As indicated in **Chapter 1**, some encouraging preliminary results for alkene aminothiocarbonylation had been obtained with activated alkenes by previous group members. Our hypothesis was that optimization would result in a more broadly applicable transformation.

2.2 Results and Discussion

2.2.1 Alkene Aminothiocarbonylation

As indicated in **Chapter 1**, the fluorenone-derived thiosemicarbazone was shown to react efficiently with norbornene by Jean-François Vincent-Rocan, a former member of the Beauchemin group. Due to the steric hindrance, these precursors avoid side reactions, and further of dipolar cycloadditions of the azomethine imine products with the excess alkene present under the reaction conditions (**Scheme 9** & **10**, **Chapter 1**).[57] These type of dipolar cycloaddition byproducts were not observed in the aminothiocarbonylation reactions. The use of *N*-isothiocyanate precursor **2b** also favors product formation through resonance stabilization of the azomethine imine. Thiosemicarbazones were used as imino-isothiocyanate precursors which were synthesized using *para*-nitroisothiocyanate and fluorenone hydrazones such as 2a (**Scheme 28**).[58]



Scheme 28: Synthesis of thiosemicarbazone reagent 2b

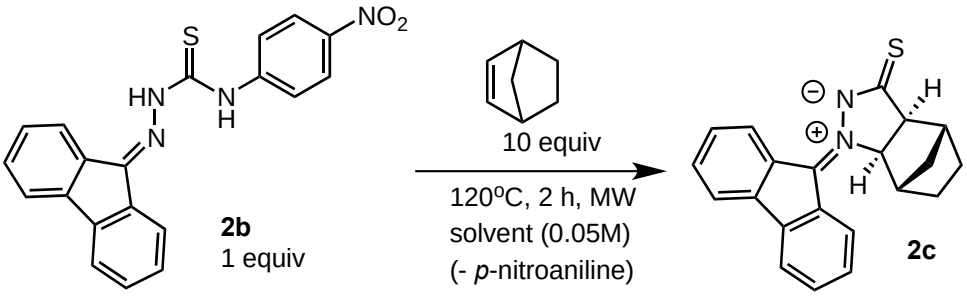
Synthesizing the *O*-phenyl leaving group precursor for thiosemicarbazones was not successful. The precursor **2b** required temperature of 120°C for the formation of the *N*-isothiocyanate (**Figure 8** in **Chapter 1**). To begin with the reinvestigation of this reactivity, a solvent scan was conducted for

57 Clavette, C.; Vincent-Rocan, J.-F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2013**, *52,* 12705.

58 Bongers, A.; Ranasinghe, I.; Lemire, P.; Vincent-Rocan, J.-F.; Perozzo, A.; Beauchemin, A. M. *Org. Lett.* **2016,** *18*, 3778.

the reaction of thiosemicarbazone (**2b**) with norbornene (**Table 2**). Norbornene is a strained, electron-rich olefin which has proven to be very reactive in alkene aminocarbonylation reactions involving *N*-isocyanates.[59]

Table 2: Solvent scan of norbornene aminothiocarbonylation with 1a[a]



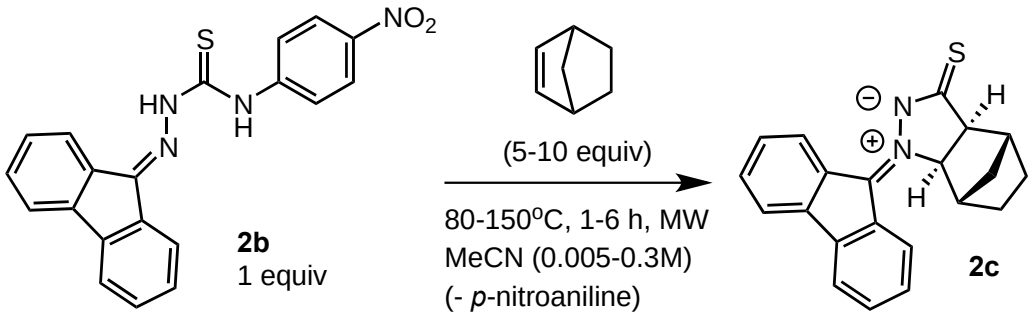
Entry	Solvent	**2a** NMR yield[b] (%)
1	$CHCl_3$	76
2	Acetone	89
3	HFIP	93
4	*i*-PrOH	57
5	t-amyl alcohol	72
6	THF	92
7	MeCN	95-98
8	MeCN[c](wet)	83
9	DMSO	62

[a]Conditions: 1a (1.0 equiv.), norbornene (10 equiv.), and solvent (0.03 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated by microwave irradiation to 120 °C for 2 hours. [b]NMR yields were taken using 1,3,5-trimethoxybenzene as the internal standard in deuterated chloroform. [c]1 drop of H_2O added.

59 Bongers, A.; Ranasinghe, I.; Lemire, P.; Vincent-Rocan, J.-F.; Perozzo, A.; Beauchemin, A. M. *Org. Lett.* **2016,** *18*, 3778.

MeCN and HFIP gave comparably better NMR yields and also the reaction proved to be moisture sensitive (**Table 2**, entries 7-8)**.** As discussed in the introduction, HFIP is expensive, which is not a good option of a solvent. Thus, further optimization used MeCN as the solvent, and a survey of the effect of temperature and concentration was also conducted in dry MeCN (**Table 3**)**.** Increasing the concentration of the solution resulted in a decrease in yield while increasing the amount of alkene present led to higher yields.

Table 3: Condition optimization of 2b with norbornene to yield 2c[a]

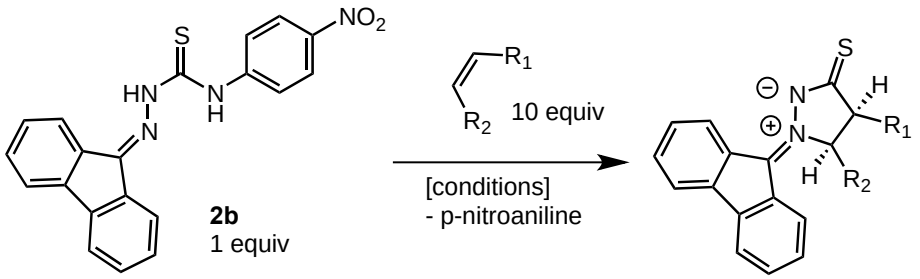


Entry	Conc.	Equiv	Temperature	Time	PNA[c] conversion	**2a** NMR yield[b] (%)
10	0.05	10	120	2h	99	92
11	0.15	10	120	2h	61	59
12	0.3	10	120	2h	61	46
13	0.005	10	120	2h	99	86
14	0.05	10	80	6h	32	30
15	0.05	10	150	1h	65	32
16	0.05	5	120	2h	92	57
17	0.05	15	120	2h	99	98

[a]Conditions: Thiosemicarbazide **1a** (1.0 equiv.), norbornene (5-15 equiv.), and solvent (0.005-0.3 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated (by microwave irradiation). [b]NMR yields are given using 1,3,5-trimethoxybenzene as the internal standard in deuterated chloroform. [c]*Para*-nitroaniline is abbreviated as PNA.

With the optimized conditions the reaction was tested with a variety of alkenes (**Table 4**).

Table 4: Exploratory scope of unreactive alkenes in aminothiocarbonylation with 2b[a]



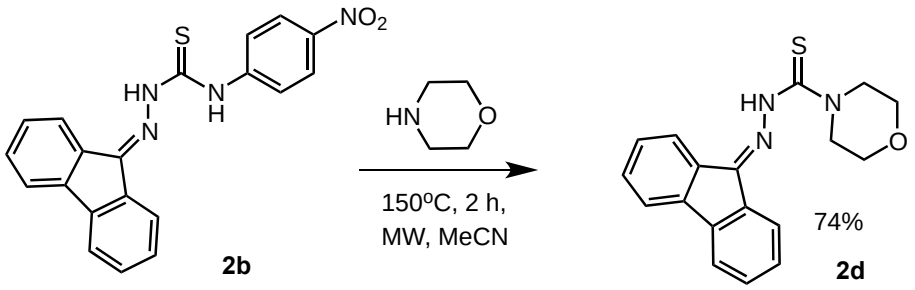
Entry	R_1, R_2	Solvent	Time (h)	Temp. (°C)	Yield (%)[b]
1	H, Ph	MeCN	17	100	23-45
2	H, Ph	HFIP	17	100	11
3	H, Ph	MeCN	2	120	19
4	H, 4-$MeOC_6H_4$	MeCN	5	100	5
5	-$(CH_2)_3$-	MeCN	3	120	24
6[c]	-$(CH_2)_3$-	MeCN	3	120	5
7	-$(CH_2)_3$-	HFIP	4	120	27
8	H, $CH_2Si(Me)_3$	MeCN	3	120	14
9	H, $CH_2Si(Me)_3$	HFIP	2	120	-
10	H, 2-pyrrolidinone	MeCN	2	120	-
11	H, 2-pyrrolidinone	MeCN	10	120	-
12	H, ferrocene	MeCN	2	120	-

[a]Conditions: Thiosemicarbazide **1a** (1.0 equiv.), alkene (10 equiv.), and solvent (0.05 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated (by microwave irradiation). NMR yields are given. [b]NMR yields were taken using 1,3,5-trimethoxybenzene as the internal standard in deuterated chloroform. [c]Added AgO (10mol%) as an additive.

Styrene as an alkene was observed by Perozzo to give products in 45% NMR yield, which is a result that we were not able to reproduce despite being under the same reaction conditions. Using more electron-rich styrene derivatives led to lower yields (Entry 4). With cyclopentene, the NMR yield was only 24% (Entry 5). AgO was added as an additive in entry 6 since it has been shown to complex with thiocarbonyl[60] and the idea was to see if it could improve the product formation. The decrease in yield obtained could be potentially due to the coordination that could happen with the products, so that it could increase the byproduct formation. Unfortunately, alkenes such as allyl TMS, vinyl pyridinone, vinyl ferrocene were not successful for the reaction (Entry 8-12). In addition, the low yields and high polarity of the products made the isolation very difficult. These preliminary results suggest that *N*-isothiocyanates are less reactive than *N*-isocyanates in their reactions with alkenes.

60 Examples of silver complex with thiocarbonyl; (a) Altaf, M.; Stoeckli-Evans, H.; Cuin, A.; Sato, D. N.; Pavan, F. R.; Leite, C. Q. F.; Ahmad, S.; Bouakka, M.; Mimouni, M.; Khardli, F. Z.; Hadda, T. B. *Polyhedron* **2013**, *62*, 138. (b) Lin, I. W.-S.; Lok, C.-N.; Yan, K.; Che, C.-M. *Chem. Commun.* **2013**, *49*, 3297.

Lavergne developed conditions to achieve base catalysis for the aminocarbonylation reaction, by using 3 mol% Et_3N.[61] The same concept was attempted for the aminothiocarbonylation reaction using *N*-methyl morpholine as the leaving group. Morpholine, a secondary amine was used in this case as the leaving group. This was explored since a hypothesis to rationalize the lower reactivity was that the presence of the *p*-nitroaniline substituent could have resulted in *p*-nitrophenyl isothiocyanate formation and degradation of the reagent.[62] To avoid this potential issue precursor **2d** was synthesized using **2a** by substituting *para*-nitroaniline to morpholine (**Scheme 29**). Similar types of substitution reactions have been studied by Garland and colleagues from the Beauchemin group.[63]



Scheme 29: Substitution reaction of *p*-nitroaniline with morpholine

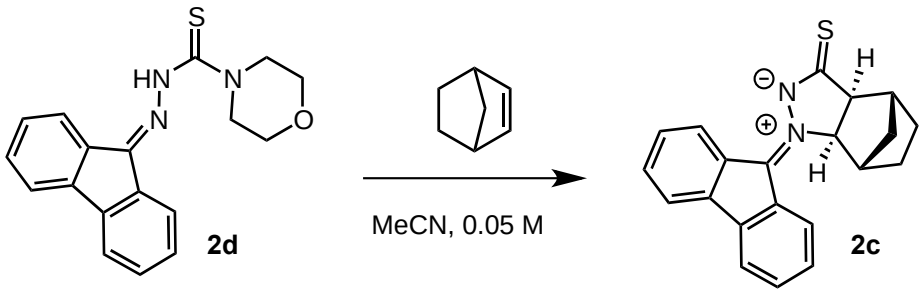
The reactivity of this potential aminothiocarbonylation reagent was then explored using norbornene, as shown in **Table 5**.

61 (a) Lavergne, K. ; Bongers, A.; Betit, L.; Beauchemin, A. M. *Org. Lett.* **2015,** *17,* 3612. (b) Lavergne, K. Synthesis of Azomethine imines via Alkene Aminocarbonylation and their Derivatization into Pyrazolones, M.Sc. Thesis, University of Ottawa, 2014.

62 Larsen, C. H.; Anthioni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1969,** *23,* 332.

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

Table 5: Attempt of base/ acid catalysis for aminothiocarbonylation[a]



Entry	base/ acid	Alkene (equiv)	Time (h)	Temp. (°C)	Yield (%)[b]
1	none	10	6	100	0
2	none	10	1	150	35
3	none	10	1	175	15
4	Et_3N	10	6	100	6
5	Et_3N	10	10	100	<2
6	Et_3N	10	1	150	17
7	Et_3N	2	1	150	0
8	4-Methyl morpholine	10	6	100	4
9	DBU	10	10	100	0
10	AcOH	10	6	100	5

[a]Conditions: Thiosemicarbazide **2d** (1.0 equiv.), alkene (2 or 10 equiv.), and solvent (0.05 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated (by microwave irradiation). [b]NMR yields are taken using 1,3,5-trimethoxybenzene as the internal standard in deuterated chloroform.

As shown above, only modest results were achieved. Comparing entries 1 and 4, with the background reaction no yield was observed. But when using Et_3N for same conditions the NMR yield was 6%. However, running the reaction for a longer time (Entry 5) decreased the yield. With high temperatures, such as 150°C, the background reaction was 35% and when using bases or acids the yield decreased (Entry 2 and 6). Also, different bases such as *N*-methyl morpholine and stronger bases such as DBU were tested which weren't successful. Unfortunately, the results obtained do not provide enough evidence to support base or acid catalysis for the reaction and suggest there could be an inhibitory effect.

Since norbornene showed good reactivity towards *N*-isocyanates other strained alkenes were tested to delineate the scope of the reaction. The results are presented in **Figure 11**. Optimized conditions[a] were used (as mentioned in the footnote of **Figure 11**).

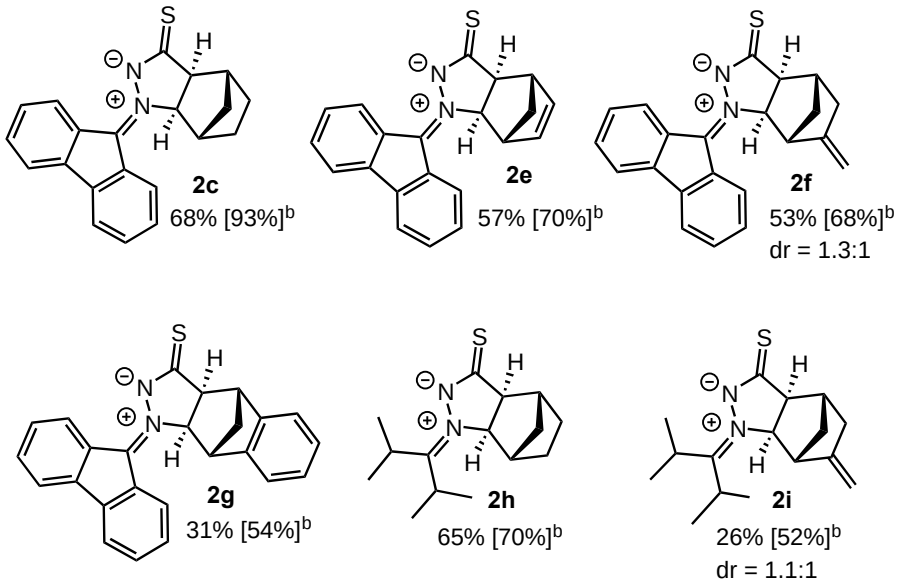


Figure 11: Scope of aminothiocarbonylation with stained norbornene analogues.[a]

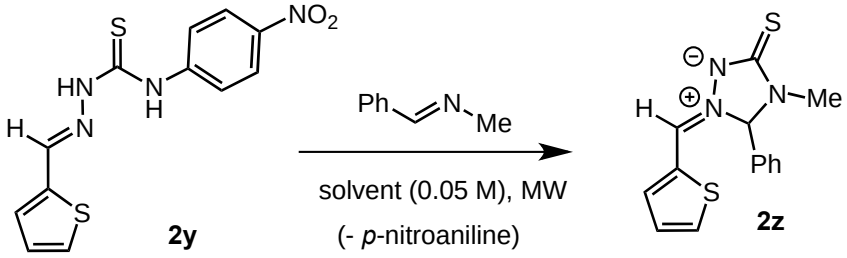
[a]Conditions: 120°C (microwave irradiation), 2 h, MeCN (0.05 M), 10 equiv. of alkene. Isolated yields are provided. [b]NMR yields with 1,3,5-trimethoxybenzene internal standard.

As shown above, variable yields were obtained with a variety of strained alkenes of relatively similar structures. The best yields were obtained with norbornene derivatives from moderate to excellent NMR yields such as **2c**. Considerably higher NMR yields compared to the isolated yields can be explained with the high polarity of these compounds as well as the degradation which occurs during the purification by flash column chromatography. These results combined with the results obtained by Lavergne with electron-rich enol ethers suggests that the frontier molecular orbital interactions during the [3+2] cycloadditions involve the HOMO of the alkene with the LUMO of the *N*-isothiocyanate and that this reaction has only limited synthetic potential.

2.2.2 Imine Aminothiocarbonylation

As an alternative to alkenes, imines were tested in the reaction with the objective of forming azomethine imines containing triazole thione core (**Eq. 2.3**). Optimization was conducted by Phillipe Lemire, a colleague from our group (**Table 6**).[64]

Table 6: Optimization of imine aminothiocarbonylation[a]



Entry	Imine (equiv)	Solvent	Time (h)	Temp. (°C)	Yield (%)[b]
1	2	$PhCF_3$	2	120	5
2	2	$PhCF_3$	2	140	7
3	2	MeCN	2	120	34
4	2	MeCN	0.5	120	66
5	2	MeCN	0.5	100	17
6	0.67	MeCN	0.5	120	69 (53[c])

[a]Conditions: Thiosemicarbazide **2y** (1.0 equiv.), imine (2 or 0.67 equiv.), and solvent (0.05 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated (by microwave irradiation). [b]NMR yields are taken using 1,3,5-trimethoxybenzene as the internal standard in deuterated chloroform. [c]Isolated yield given in parenthesis.

64 Bongers, A.; Ranasinghe, I.; Lemire, P.; Vincent-Rocan, J-F.; Perozzo, A.; Beauchemin, A. M. *Org. Lett.* **2016,** *18*, 3778.

The optimization efforts showed that imine as the limiting reagent increased the yield (Entry 6). Also, this showed that the yield is better for shorter reactions. However, the reaction to go to completion with the fluorenone precursor required 2 hours. The results obtained under the optimized reaction conditions are shown in **Figure 12**.

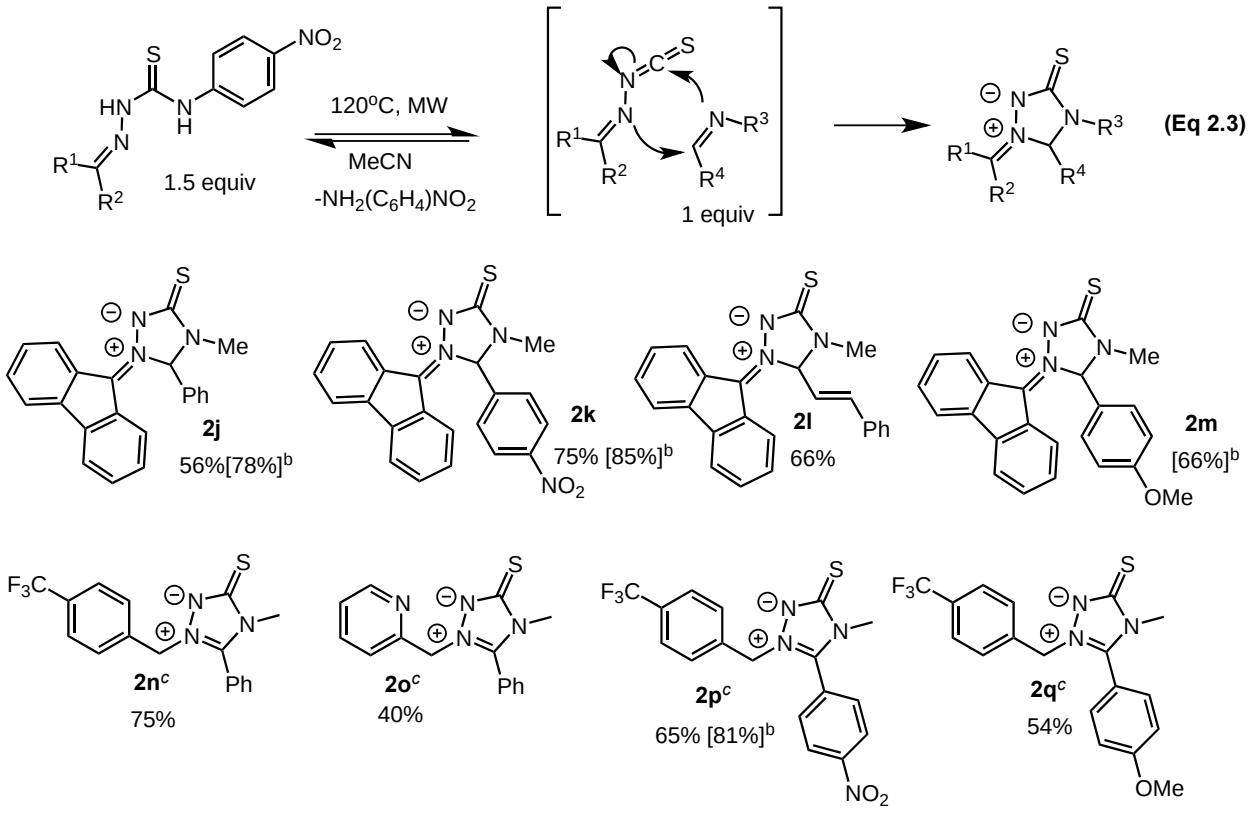


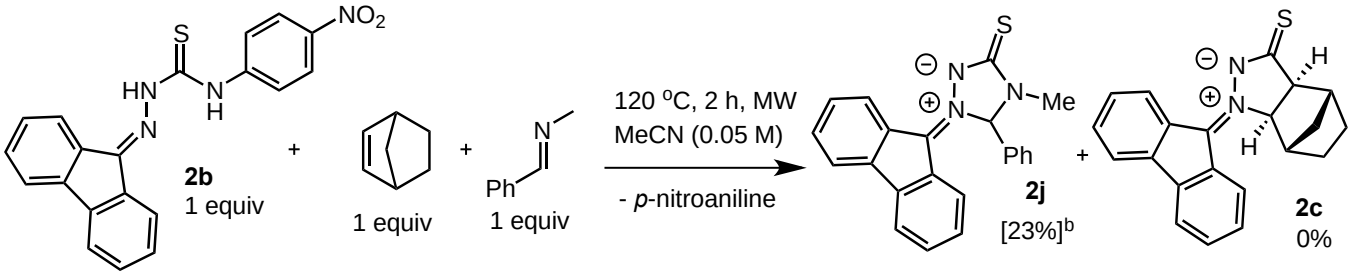
Figure 12: Scope of the intermolecular C=N aminothiocarbonylation of aldimines. [b]NMR yields with 1,3,5-trimethoxybenzene as internal standard. Isolated yields were provided for except 2m. Compounds 2j, 2n-2q were formed & isolated by Lemire. [c]Reaction time 30 min.

Higher reactivity for the aminothiocarbonylation reaction was observed with imines compared to alkenes. Electron-poor imines with fluorenone thiosemicarbazone provided the desired product in 85% NMR yield. A pattern observed is that using electron-poor imines typically leads to higher yields of the desired products. This could be due to the product stabilization with the electron-

withdrawing effect, by preventing ring opening of the azomethine imine. Higher yields were also obtained when using the fluorenone-derived reagent. This could be due to the stabilization of the charges from the resonance of the fluorenyl group. Finally, Lemire observed when using electron-poor substrates (**2o-2q**), that isomerization[65] occurs to form the aromatic azomethine imines. The aromatization of the cycloaddition product is under further experimentation in the group.

2.2.3 Alkene vs Imine Competition Reaction

A competition reaction was conducted with 1 equivalent of **2b**, norbornene and *N*-methyl phenylimine, heated in the microwave for 2 hours at 120 °C (**Scheme 30**). Only the imine product was observed in 23% NMR yield. This was expected since the reaction required 10 equivalents of alkene while 2 or 3 equivalents of the imine are typically used under the optimized reaction conditions. Hence this competition reaction provides a proof that the imines are more reactive than alkenes.

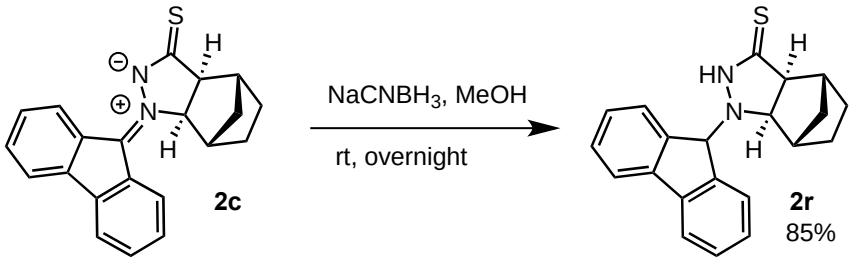


Scheme 30: Competition reaction of alkene vs imine

65 (a) Evans, G. W.; Milligan, B. *Aust. J. Chem.* **1967**, *20*, 1779. (b) Kubota, S.; Uda, M. *Chem. Pharm. Bull*. **1973**, *21*, 1342.

2.2.4 Derivatization of Azomethine Imines

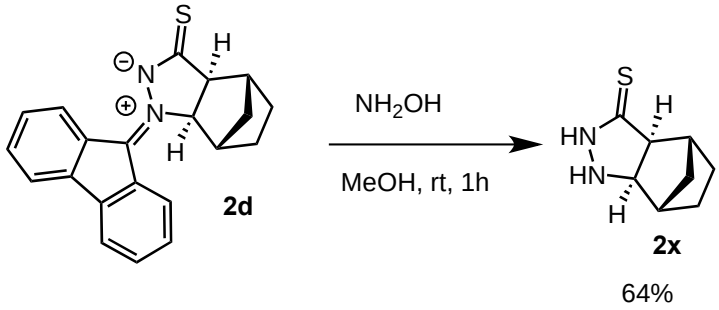
A thioxo-azomethine imine could be transformed into the reduced derivative using the mild reducing agent $NaCNBH_3$, providing product **2r** in high isolated yield under mild conditions (**Scheme 31**).



Scheme 31: Reducing the azomethine imine

When **2r** was subjected to KO*t*Bu in methanol, just stirring for one hour produced the azomethine imine **2c** in 10% NMR yield. This could be due to the O_2 in the air acting as an oxidant to regenerate the azomethine imine.

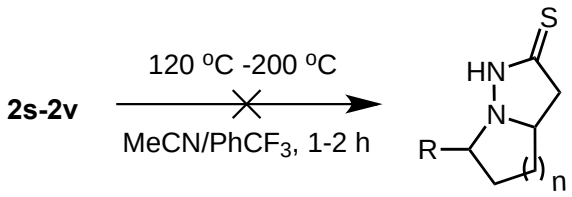
The carbon-nitrogen bond was also cleaved to deprotect the fluorenone using hydroxylamine as a nucleophile (**Scheme 32**). Within 1 hour the reaction was completed at room temperature. Using a water/ methanol solvent mixture, the fluorenone oxime crystalized and this allowed isolation of the product of interest in 64% yield after filtration.



Scheme 32: Deprotection of the fluorenone to obtain thiopyrazolones

2.2.5 Intramolecular Aminothiocarbonylation

Our group was also able to achieve intramolecular aminocarbonylation reactions in which *N*-isocyanates react with terminal alkenes in [3+2] cycloadditions that do not require external reagents or catalysts.[66] The attempt of applying the similar concept with *N*-isothiocyanate intermediates was not successful (**Scheme 33**). The reaction was tried with different chain lengths which could form 5-membered as well as 6-membered cycles also with both hydrazone and hydrazine *N*-isothiocyanate precursors (**Figure 13**).



Scheme 33: Attempted intramolecular reactions at high temperatures and with two different solvents for 1-2 hours

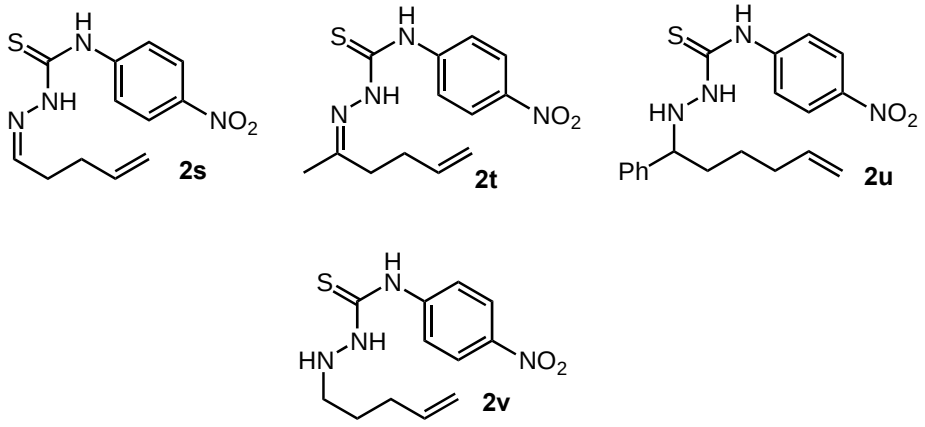


Figure 13: Substrates used for the intramolecular aminothiocarbonylation attempts

66 Ivanovich, R. A.; Clavette, C.; Vincent-Rocan, J.-F.; Roveda, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Eur. J.* **2016,** *22,* 7906.

In conclusion for this chapter, alkene and imine aminothiocarbonylation allowed accessing the sulfur analogues of azomethine imines in a single reaction. Optimization of the alkene aminothiocarbonylation reaction gave the opportunity to obtain a moderate yielding scope with strained alkenes. Imines were better substrates for the cycloaddition reaction and found to be more reactive compared to alkenes. Mild derivatization reactions were also achieved. The scarcity of these sulfur analogues and synthetic pathways as well as divergent reactivity observed in the synthesis of *N*-isocyanate vs *N*-isothiocyanate products calls for further exploration. Future work, such as DFT calculations and computational studies would be an asset to provide more information.

Chapter 3: Other reactivity of Isothiocyanates and Thiosemicarbazones

3.1 Introduction to Other Reactivity of Isothiocyanates

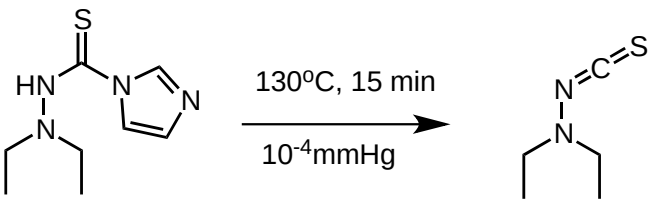
In this chapter, other results on different reactivities and different aspects of the project will be presented: 1) Attempts in forming and isolating imino-isothiocyanates, 2) The work performed on synthesizing isothiocyanates from amines and 3) New reactivity observed with a secondary amine, an elimination reaction will be discussed.

3.1.1 Formation, Reactivity, and Isolation of Amino- and Imino-isothiocyanates

As discussed in the introduction, McElhinney first reported the formation of isothiocyanates as intermediates in 1966.[67] In the same year, Anthoni, Larsen, and Nielsen reported the formation of dialkylamino-isothiocyanates (**Scheme 34**).[68] Anthoni and coworkers observed the decomposition of the thiocarbazoylamidazoles to species exhibiting the properties of a monomeric *N*-isothiocyanatoamines. The experiment was performed in a setup which connected the reaction mixture to a vacuum system capable of achieving a pressure of 10^{-4} mmHg. The experimental system was also connected to a cold finger to trap volatile products, and they were able to isolate the isothiocyanate by heating the thiosemicarbazone at 130°C for 15 minutes. Anthoni and coworkers were interested in this new group of compounds, *N*-isothiocyanates, and further investigated their properties.

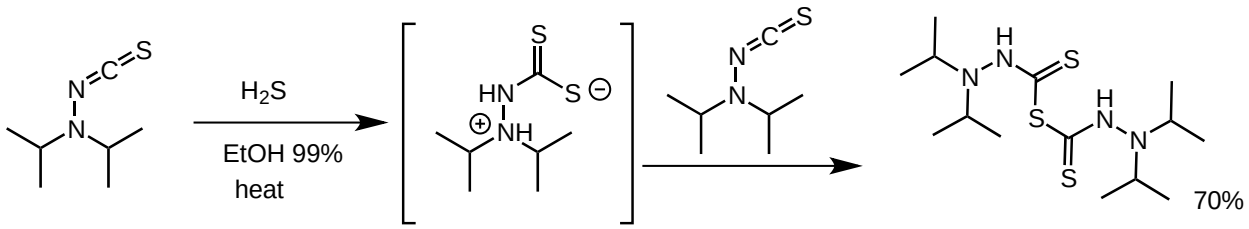
67 McElhinney, R. S. *J. Chem. Soc.* **1966**, 950.

68 Anthoni, U.; Larsen, C. H.; Nielsen, P. H. *Acta Chem. Scand.* **1966**, *20,* 1714.



Scheme 34: Amino-isothiocyanate formation

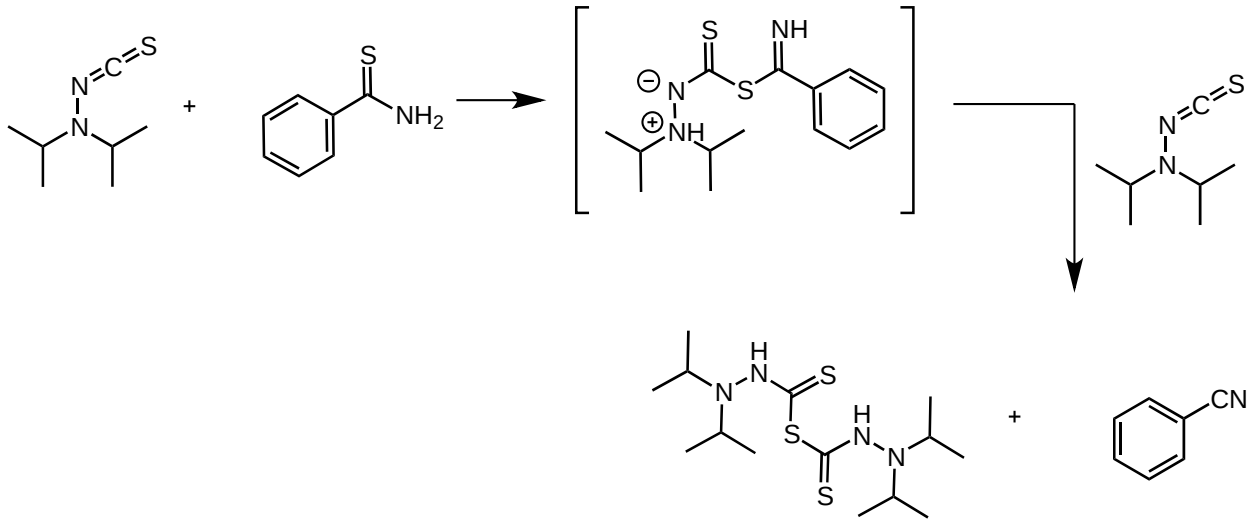
Anthoni and co-workers examined the reaction between the *N*-isothiocyanatodiisopropylamine and hydrogen sulfide. They proposed reaction going through the intermediate shown in **Scheme 35** to obtain the dimerized product.



Scheme 35: Hydrazine derived isothiocyanate reaction with hydrogen sulfide

Next, Anthoni and co-workers investigated the reactivity of the *N*-isothiocyanatodiisopropylamine with thiobenzamide (**Scheme 36**) to observe the same crystalline product as in **Scheme 35** as well as the corresponding nitrile products. The nitriles were identified by IR spectroscopy in solution. The formation of nitrile products could be due to the negative charge being stable on sulfur, as we discussed in **Chapter 1**, which makes the sulfur atom a good nucleophile.[69] This would result in the formation of a C-S bond with the *N*-isothiocyanate. The intermediate formed would have ultimately cleaved the thioamide C-S bond to give the nitrile as a byproduct.

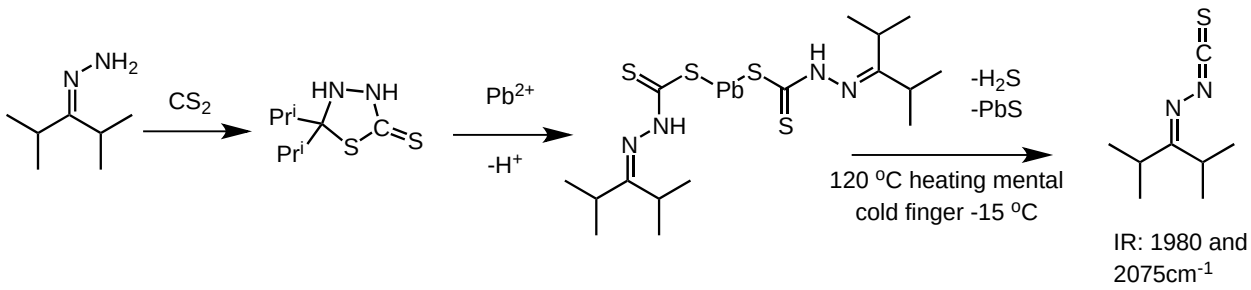
69 Ormazábal-Toledo, R.; Castro, E. A.; Santos, J. G.; Millán, D.; Cañete, A.; Contreras, R.; Campodónico, P. R. *J. Phys. Org. Chem.* **2012**, *25*, 1359.



Scheme 36: Isothiocyanates with thioamides to form nitriles and disulfide

Anthoni and Berg were also able to perform a study to investigate the imino-isothiocyanate formation. They used a different approach to synthesize the imino-isothiocyanates from hydrazones than amino-isothiocyanates. The reaction of hydrazones with carbon disulfide lead to 5,5-dialkyl-1,3,4-thiadiaolidine-2-thione (**Scheme 37**)**.** They also studied the ring opening of these compounds with lead acetate to form salts and dithiocarbonic esters. Using lead acetate, a lead salt was formed as a yellow precipitate, and this crude mixture was subjected to vacuum conditions similar to those used in **Scheme 34**. The reaction temperature was 120 °C and the cold finger receiver was chilled at −15 °C with methanol and ice mixture to avoid condensation of H_2S. They were able to observe imino-isothiocyanate formation via IR spectroscopy and NMR.[70]

70 Anthoni, U.; Berg, C. *Acta Chem. Scand.* **1969**, *23,* 3602.



Scheme 37: Imino-isothiocyanate synthesis via a lead salt compound

Since the C=N bond is in conjugation with the N=C=S group, lower IR stretches were obtained when compared to amino-isothiocyanates described above. Analysis of the imino-isothiocyanates by NMR was used to identify the unsymmetrical isopropyl groups in the imino-isothiocyanate. The complete dimerization of the isocyanate occurs in 15 minutes upon standing at room temperature. Moderate stability was examined when dissolved in an inert solvent, and the imino-isothiocyanate was able to be stored under liquid nitrogen.

As we will be discussing later in this chapter, efforts were given to synthesize and isolate imino-isothiocyanates according to the literature.

3.1.2 Isothiocyanate Formation from Amines

Isothiocyanates, as briefly discussed in **Chapter 1** of this thesis, are abundant natural compounds found in many cruciferous vegetables. Naturally occurring isothiocyanates have shown potential medical applications including chemo-preventive activity.[71] Due to the potential medical application, many research groups were interested in developing synthesis routes to convert readily available amines into isothiocyanate analogues since the 20th century. Most of the reports used thiophosgene, but due to the high toxicity and incompatibility of this reagent with many functional groups, this pathway is limited for general use (**Scheme 38a**).[72]

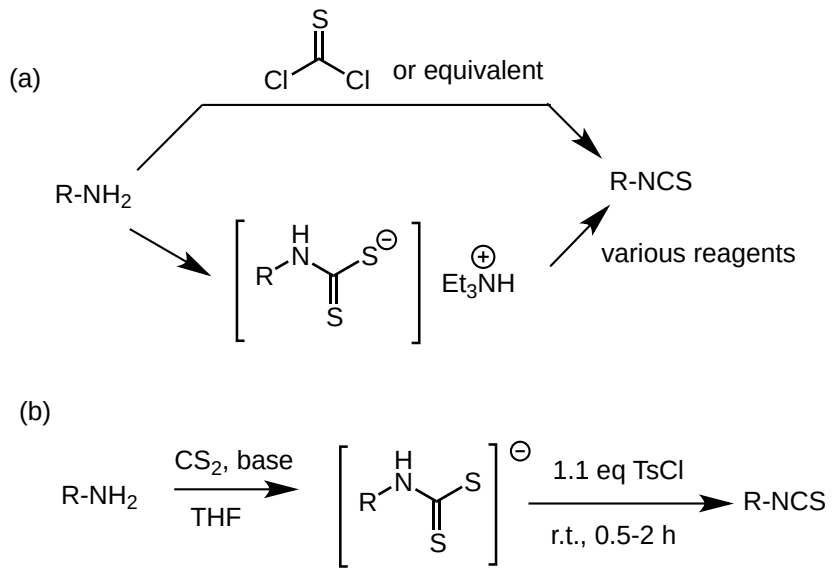
An alternative approach to isothiocyanate formation is reagent promoted decomposition of dithiocarbamic acid salts. The dithiocarbamic acid is accessed in situ by treatment of an amine with carbon disulfide in the presence of a base such as triethylamine. Converting the dithiocarbamic acids into salts were performed usually under harsh conditions such as phosgene, ethyl chloroformate with hydroxide, cyanogen chloride, etc.[73] Dolman and Wong were able to perform the reaction under much milder conditions by using tosyl chloride in the desulfurization process (**Scheme 38b**).[74] Electron-deficient amines needed stronger bases to do the deprotonation.

71 (a) Fahey, J. W.; Zalcmann, A. T.; Talalay, P. *Phytochemistry* **2001**, *56,* 5. (b) Nakamura, Y.; Miyoshi, N. *Biosci., Biotechnol., Biochem.* **2010**, *74,* 242.

72 Dyer, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54,* 777.

73 (a) Hodgkin, J. E.; Ettlinger, M. G. *J. Org. Chem.* **1956**, *21,* 404. (b) Hodgkin, J. E.; Reeves, W. P. *J. Org. Chem.* **1964**, *29,* 3098.

74 Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72,* 3969.74



Scheme 38: (a) Different methods of forming isothiocyanates from amines (b) Dolman's conditions to form isothiocyanates

The work identifying the challenges as well as synthesizing isothiocyanates from amines using Dolman's conditions will be discussed in the result section of this chapter. This method was a good alternative to access isothiocyanates that were not commercially available, including *N*-isothiocyanates, as well as expensive reagents.

3.1.3 Chugaev Elimination

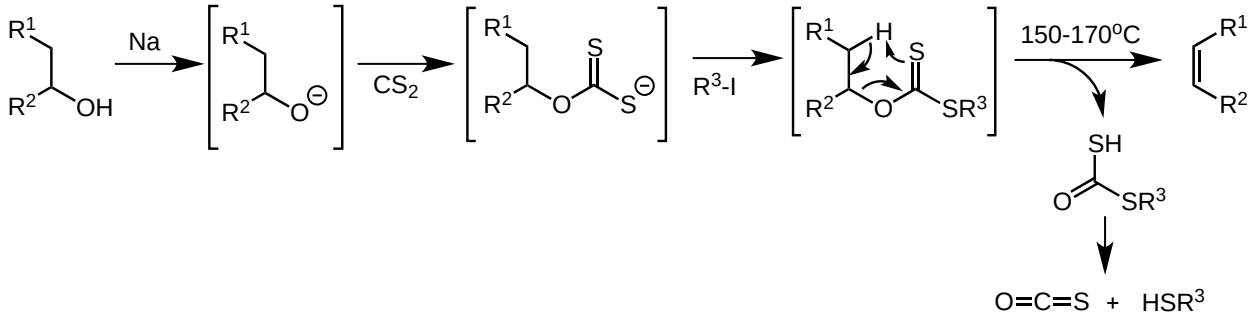
The Chugaev elimination reaction was first reported in 1899.[75] In this reaction sequence, alkoxide was produced as an intermediate after treating a corresponding alcohol with sodium. The alkoxide is then treated with carbon disulfide. Resulting adduct was alkylated to form a xanthate, which upon heating at 150-170 °C yielded an olefin. Also, there was unstable dithiocarbonate derivative formed as a byproduct which decomposed to carbon oxysulfide and alkylmercaptan.[76] Usually,

75 Chugaev, L. A. *Ber. Dtsch. Chem. Ges.* **1899**, *32,* 3332.

76 Majetich, G.; Irvin, T. C.; Thompson, S. B. *Tetrahedron Lett.* **2015**, *56,* 3326.

these elimination reactions required higher temperatures such as 200-600 °C which were not suitable for many substrates. Due to this, the Chugaev elimination got limited attention over time.

Barton[77] and Cram[78] proposed a concerted mechanism for the Chugaev elimination which involved a *syn*-β-hydrogen abstraction by the thiocarbonyl group of the xanthate (**Scheme 39**). Evidence for this pathway was provided by Bader and Bourns more than a decade later, based on carbon and sulfur isotope effects.[79]



Scheme 39: Proposed mechanism for Chugaev elimination

Our interest in this transformation arose when the unexpected formation of addition products indicating that a dealkylation process had occurred, leading to the hypothesis that a Chugaev type elimination reaction had occurred with products derived from *N*-isocyanates (check results section for more details).

77 Barton, D. H. R. *J. Chem. Soc.* **1949**, 2174.

78 Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71,* 3883.

79 Bader, R. F. W.; Bourns, A. N. *Can. J. Chem.* **1961**, *39,* 346.

3.1.4 Project Objectives

As indicated in the introduction above, known procedures were used in order to form imino-isothiocyanates and isothiocyanates. Imino-isothiocyanate formation was experimented using Anthoni and Berg conditions and isothiocyanate formation from amines were tested using Dolman's conditions. Another goal of this chapter is to present a new reactivity that we observed during thiosemicarbazone synthesis, which could be similar to Chugaev type elimination. The observations and the possible mechanism will be presented below.

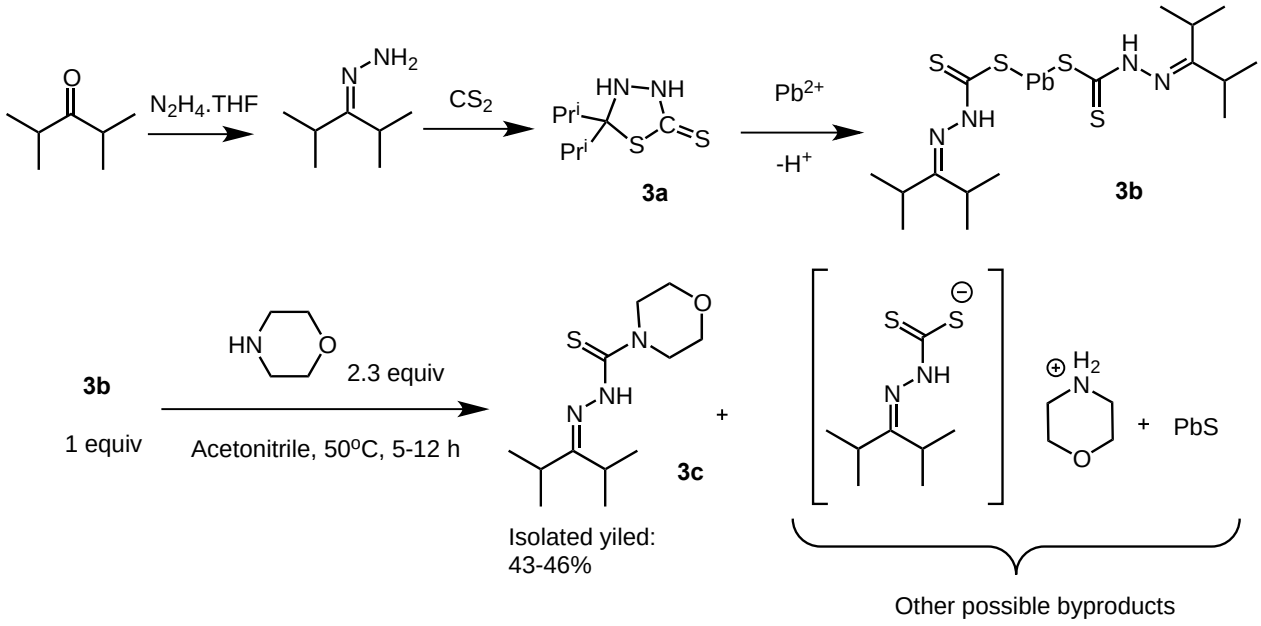
3.2 Results and Discussion

3.2.1 Imino-isothiocyanate Synthesis from Diispropyl Hydrazone

Imino-isothiocyanate formation was of high interest since it would allow synthesis of various thiosemicarbazone derivatives, with which we would be able to probe the cycloadditions discussed in **Chapter 2** and **Chapter 4**. Following the procedure for imino-isothiocyanate synthesis developed by Anthoni and Berg, a test was conducted to identify the formation of isothiocyanates (**Scheme 40**). The hydrazone precursor was first synthesized from diisopropyl ketone and hydrazine hydrate. The hydrazone was then subjected to carbon disulfide to yield the heterocycle **3a**, white crystalline needles. Next, aqueous lead acetate was added to **3a** to obtain the lead salts **3b**, used as a precursor to the imino-isothiocyanate. Isolation of the imino-isothiocyanate was attempted using the sublimation setup as reported by Anthoni and Berg. Unfortunately, this experiment wasn't successful. Compound **3b** was heated at 50 °C in MeCN for 5 hours with morpholine to identify the isothiocyanate release. The desired product **3c** was isolated by filtration through celite, and PbS was observed as a byproduct in this reaction. We assume that only one of

the isothiocyanate moieties in **3b** reacted favourably with morpholine, giving 43-46% yield of **3c**. After filtration, there was no trace of the second isothiocyanate moiety.

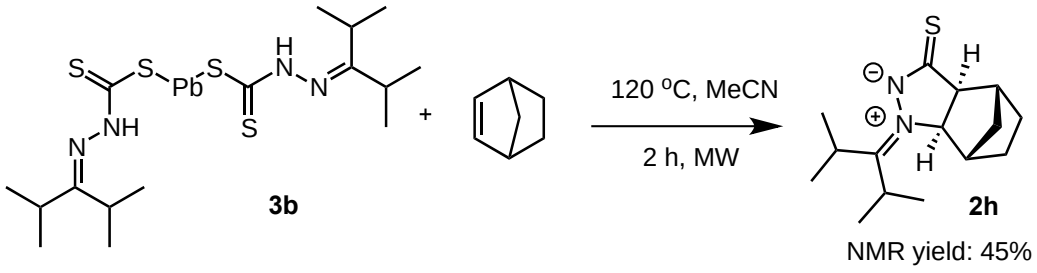
We could now access an imino-isothiocyanate precursor derived from diisopropyl hydrazone. We also tried using other hydrazones precursors, such as phenyl hydrazone, in forming the corresponding cyclized compounds like **3a**. But unfortunately, these reactions were not successful. We moved forward with precursor **3b** to explore cycloaddition reactivity of the imino-isothiocyanate.



Scheme 40: Synthesis of 3c via the lead precursor 3b

Then an alkene aminothiocarbonylation with the imino-isocyanate precursor **3d** was attempted. When **3b** was heated with norbornene at 70 °C for 5 hours, we observed a very messy crude mixture by NMR with no distinguishable product formation. Since that the isothiocyanate formation occur from compound **3b** at 50 °C reacting for 5 hours as indicated in **Scheme 40**, this indicated that norbornene is not reactive enough at 70 °C. However, when the reaction was repeated at 120 °C with 10 equivalents of norbornene, the product was observed in 45% NMR yield after two hours

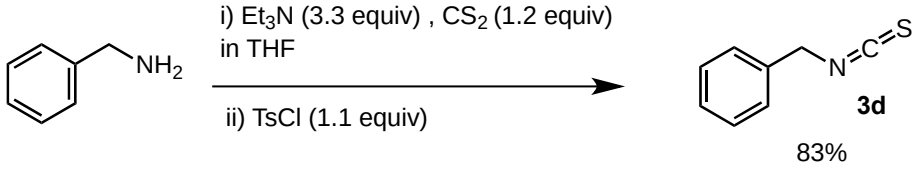
(**Scheme 41**). By comparison with the results presented in **Chapter 2**, this suggests that this method of generating the *N*-isothiocyanate is not as effective as the blocked isothiocyanate approach.



Scheme 41: Azomethine imine 2h formation using 3b as the precursor

3.2.2 Dolman's Conditions for Formation of Isothiocyanates

The Dolman's conditions[80] were successfully applied to obtain thiosemicarbazone by synthesizing isothiocyanates from amines, which would otherwise be commercially unavailable or expensive. Benzylamine was tested under the same conditions reported by Dolman to access the benzyl isothiocyanate **3d** (**Scheme 42**).

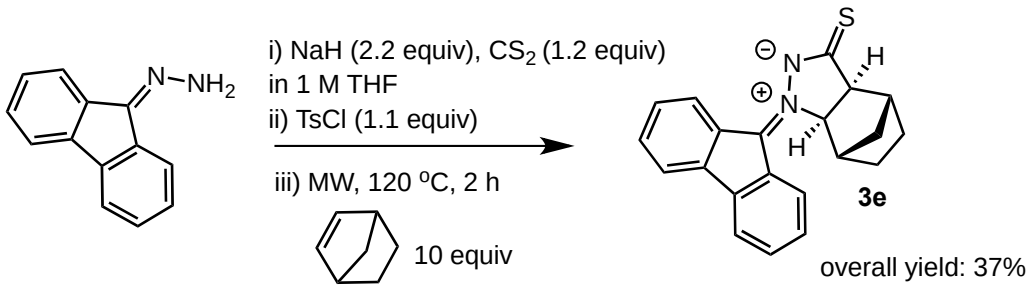


Scheme 42: Synthesis of isothiocyanate formation from amines

80 Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72,* 3969.

However, when fluorenone hydrazone was treated with same conditions, the desired salt (see **Scheme 38b**) were not observed. Addition of 2.2 equiv of NaH instead Et_3N successfully formed the salt. Then addition of TsCl to the mixture formed a crude solid. The crude mixture that formed was not soluble in THF or in DMSO. This indicated that the *N*-isothiocyanate is not in the mixture. The isothiocyanate could most probably be in a salt form, or it was in a protected form by reaction with an equivalent of hydrazone.

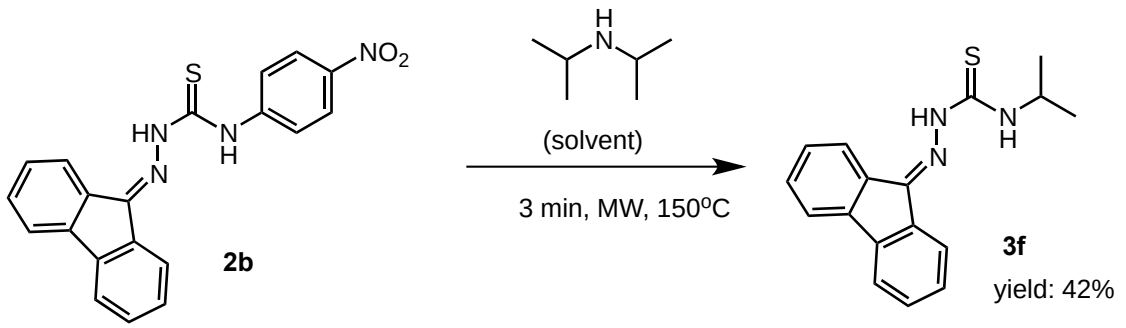
The crude mixture obtained after adding TsCl (**Scheme 43,** step ii) was then heated by microwave irradiation at 120 °C for 2 hours in MeCN, in the presence of excess norbornene. This reaction gave azomethine imine product **3e** in overall 37% yield from the fluorenone hydrazone.



Scheme 43: Azomethine imine formation via imino-isothiocyanate using Dolman's conditions

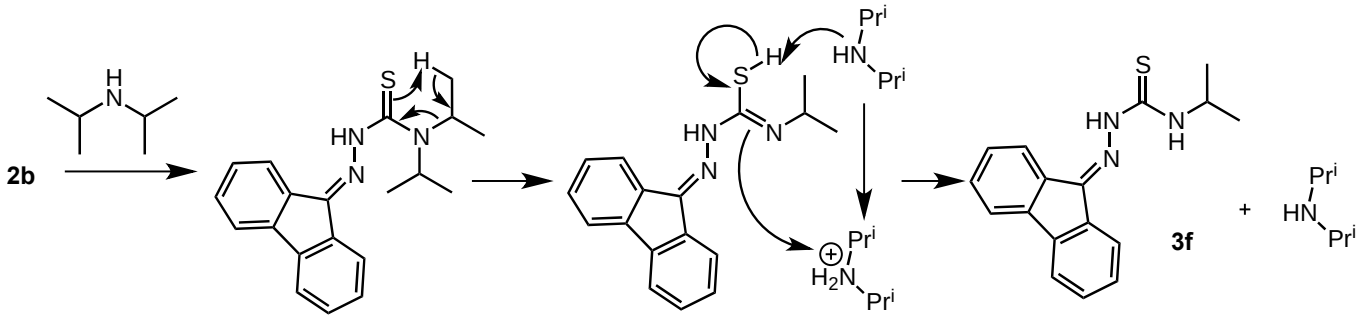
3.2.3 Observation of a Chugaev Related Elimination

In exploring the synthesis and reactions of imino-isothiocyanates, some new elimination reactivity was observed. This was first discovered when trying to substitute the *para*-nitroaniline group of semicarbazone **2b** with diisopropyl amine, and intriguingly the mono isopropyl amine product **3f** was isolated in 42% yield (**Scheme 44**).



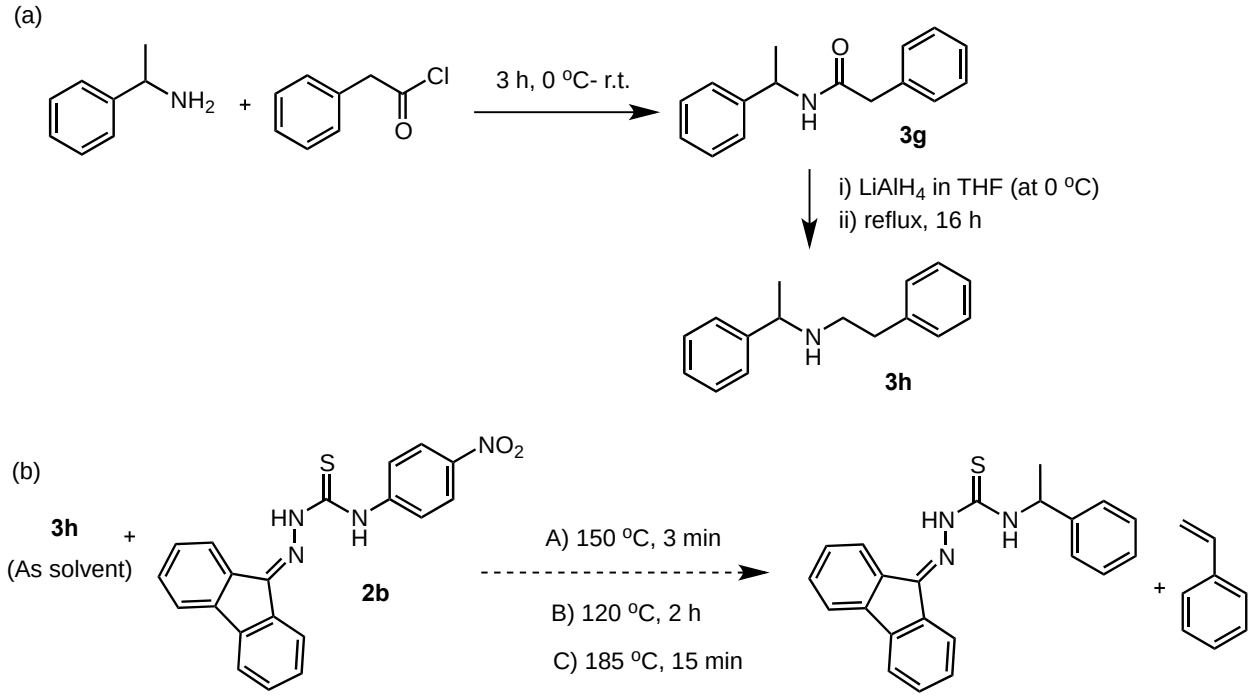
Scheme 44: Unusual synthesis of 3f with substitution of *para*-nitroaniline with diisopropyl amine

To the best of our knowledge, these types of secondary amine elimination reactions are unprecedented. We proposed a mechanism for this reaction that is related to the Chugaev elimination (**Scheme 45**). Propene has a boiling point of -47.6 °C, making it hard to detect as a leaving group.



Scheme 45: Proposed Chugaev-type related secondary amine elimination mechanism

To validate the proposed elimination mechanism, further experimentation was attempted. Substrate **3h** was synthesized from **3g**[81] through a known procedure by Sheldon and coworkers.[82] If the proposed pathway is occurring, it would result in eliminating styrene and substituting phenylethylamine to *para*-nitroaniline (**Scheme 46).** This would have been beneficial since we would have been able to detect styrene as a leaving group.



Scheme 46: (a) Synthesis of 3h via known methods in the literature. (b) Attempted substitution of 3h with thiosemicarbazone precursor 2b

The product formation for **Scheme 46b** was not identified. One of the problems with this method was to remove 2-phenylethyl-1-phenylethylamine (**3h**), it required a column purification. Column chromatography was not the best option since amines and hydrazine derivatives could be difficult

81 Lee, G. R.; Hyun, M. H. *Molecules* **2014,** *19,* 21386.

82 Serrano, L.; Jongejan, J. A.; Rantwijk, F.; Sheldon, R. A. *Tettrahedron Lett.* **2001,** *12,* 219.

to isolate by column chromatography. Since the products were not identified the mechanism of the observed reactivity is still not confirmed.

As a summary for this chapter; 1) Formation of the imino-isothiocyanates was confirmed even though the isolation attempt was not successful with the reported method by Anthoni and Berg. 2) Dolman's conditions were successfully applied in synthesizing isothiocyanates starting from amines. This method allowed access to isothiocyanates which would be either commercially unavailable or rather expensive to purchase. 3) Elimination reaction was identified forming an *N*-isocyanate addition product containing a primary amine substituent, starting from the *N,N*-diisopropylamine as a secondary amine. Further experimentation is needed to identify the mechanism as well as to explore the reaction.

Chapter 4: Acyclic Azomethine Imine Intermediates for [3+2] Cycloadditions

4.1 Introduction of Acyclic Azomethine Imines as Intermediates

4.1.1 Acyclic vs Cyclic Azomethine Imines

Acyclic azomethine imine intermediates, as introduced in **Chapter 1**, also are structurally similar to hydrazones and exhibit a rich reactivity as expected from their dipolar nature. In **Chapter 2**, we established an efficient method for the synthesis of cyclic azomethine imines from alkenes, using *N*-isothiocyanates as reactive amphoteric reagents formed in situ. In this Chapter, we will be focusing on other acyclic azomethine imines that can be formed from *N*-isothiocyanates, and their use as intermediates to generate cycloaddition products with a pyrazolidine core. Structural illustration for acyclic and cyclic azomethine imines are shown in **Figure 14**.

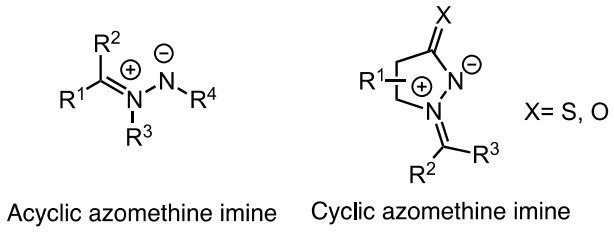


Figure 14: General illustration of an acyclic and a cyclic azomethine imine

4.1.2 Cyclic Azomethine Imine Reactivity

There are many examples in the literature reporting on cyclic azomethine imine reactivity.[83] A few of these examples have been discussed in **Chapter 1**. Two examples by the Beauchemin group for cyclic azomethine imine reactivity are shown in **Scheme 47**. Toderian and Clavette have formed a cyclic azomethine imine intermediate performing a subsequent [3+2] cycloaddition in an intramolecular fashion (**Scheme 47a**).[84] However, there are fewer examples of intermolecular acyclic azomethine imine reactivity that can be found in the literature.[85] One of these was by Clavette *et al.* where they developed a one-pot synthesis of [3+2] cycloaddition product via cyclic azomethine imine (**Scheme 47b**).[86]

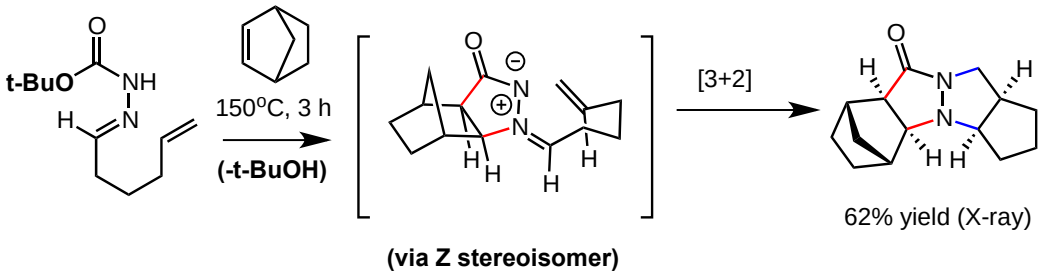
83 (a) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6324. (b) Shintani, R.; Soh, Y-T.; Hayashi, T. *Org. Lett.* **2010***, 12*, 4106. Review on azomethine imines: (c) Qiu, G.; Kuang, Y.; Wu, J. *Adv. Synth. Catal.* **2014**, *356*, 3483. (d) Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2015**, *13,* 8596. (e) Tšupova, S.; Mäeorg, U. *Heterocycles* **2014**, *88*, 129.

84 Gan, W.; Moon, P.; Clavette, C.; DasNeves, N.; Markiewicz, T.; Toderian, A.; Beauchemin, A. M. *Org. Lett.* **2013**, *15,* 1890.

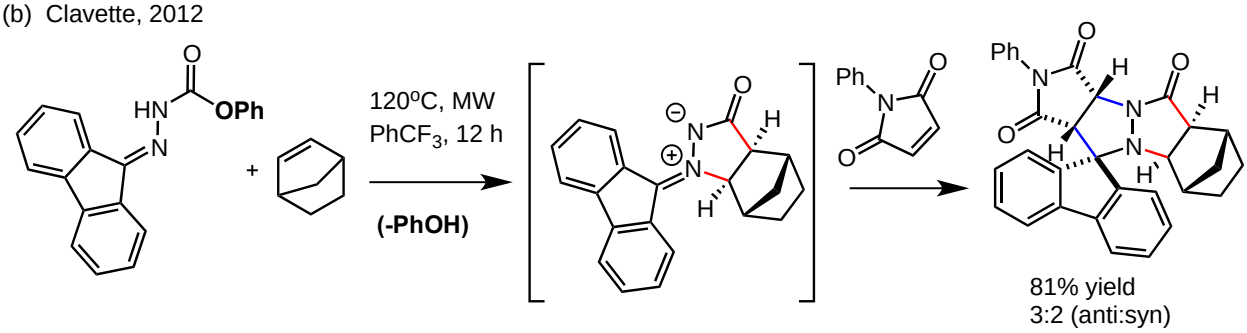
85 (a) Guerrand, H. D. S.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 7921 (b) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011,** *3,* 642 (c) For a review on acyclic azomethine imines see; Nájera, C.; Sansano, J. M.; Yus, M. *Org. Biomol. Chem.* **2015,** *13,* 8596.

86 Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134,* 16111.

(a) Toderian and Clavette, 2013



(b) Clavette, 2012

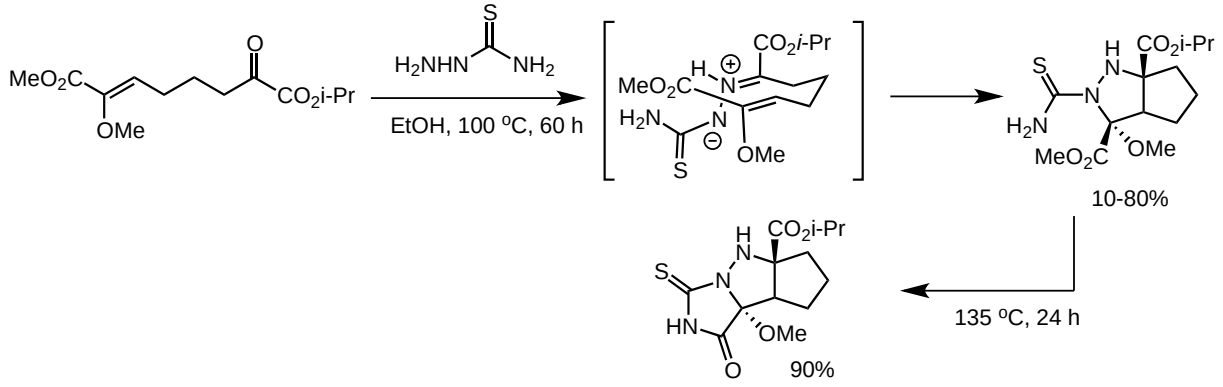


Scheme 47: Examples from the group for cyclic azomethine imine reactivity (a) Intramolecular [3+2] cycloaddition (b) Intermolecular [3+2] one pot synthesis

4.1.3 Acyclic Azomethine Imine Intermediates

4.1.3.1 Intramolecular Acyclic Azomethine Imine [3+2] Cycloadditions

Pioneering work on intramolecular acyclic azomethine imine intermediates bearing a thiocarbonyl group was performed by the Overman group, where they have shown the formation of pyrazolidine derivatives upon reacting thiosemicarbazide and α-methoxy-α, β-unsaturated ester (**Scheme 48**).[87] The intermediate azomethine imine is generated under heating, by condensation to form the thiosemicarbazone, followed by proton transfer. This intermediate then performed a [3+2] cycloaddition to give the *cis* cyclopentapyrazolidine as a single stereoisomer in variable yields. Overman explained that the irreproducibility observed could be due to the basic impurities in the unpurified ester. Trace of bases changing the yields made them explore the impact of adding acid or base for the catalysis of the reaction.

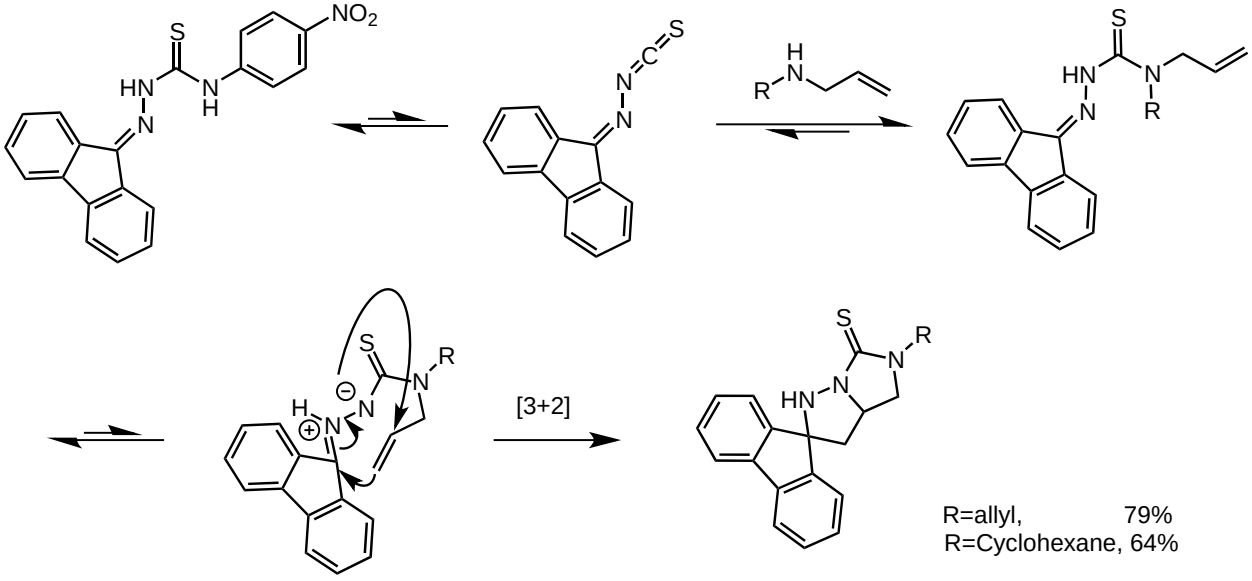


Scheme 48: Intramolecular [3+2] cycloaddition reaction of the azomethine imine intermediate

87 (a) Gergely, J.; Morgan J. B.; Overman, L. E. *J. Org. Chem.* **2006**, *71*, 9144. For more intramolecular azomethine imine work see; (b) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. (c) Katz, J. D.; Overman, L. E. *Tettrahedron Lett.* **2004**, *60*, 9559. (d) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7880.

The optimal additive was found to be citric acid and identified Fischer esterification byproducts when using ethanol as a solvent. Using *tert*-butyl alcohol avoided this complication. Also, increasing the temperature and the reaction time yielded the tricyclic thiohydantoin.

As discussed in **Chapter 1**, Vincent-Rocan and the Beauchemin group reported a cascade reaction where they proposed the formation of acyclic azomethine imine intermediate.[88] This intermediate undergoes a [3+2] cycloaddition, which was only observed with the *N*-isothiocyanate precursor. This chemistry was unprecedented in the literature of azomethine imines and highlighted the differences in reactivity between their carbonyl and thiocarbonyl precursors.

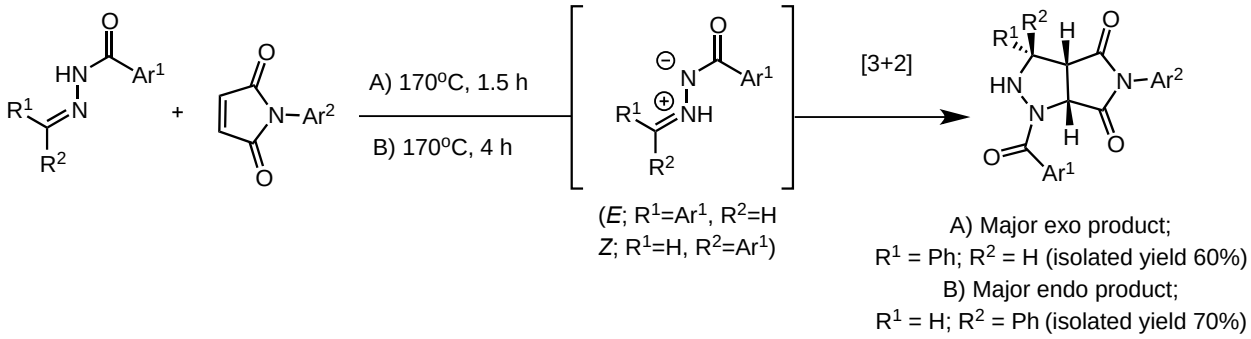


Scheme 49: Acyclic azomethine imine intermediate performing 1,3-dipolar cycloadditions with *N*-isothiocyanates as precursors

88 Vincent-Rocan, J. -F.; Derasp, J. S.; Beauchemin, A. M. *Chem. Commun.* **2015,** *51,* 16405.

4.1.3.2 Intermolecular Acyclic Azomethine Imine [3+2] Cycloadditions

A pioneering example on intermolecular cycloadditions with acyclic azomethine imine intermediates was reported by Ibrahim and coworkers.[89] They were able to form the products in a stereoselective manner using high temperatures. They first identified the formation of the kinetic product, which was converted to the thermodynamic product upon heating at 170 °C for a longer reaction time (**Scheme 50**).



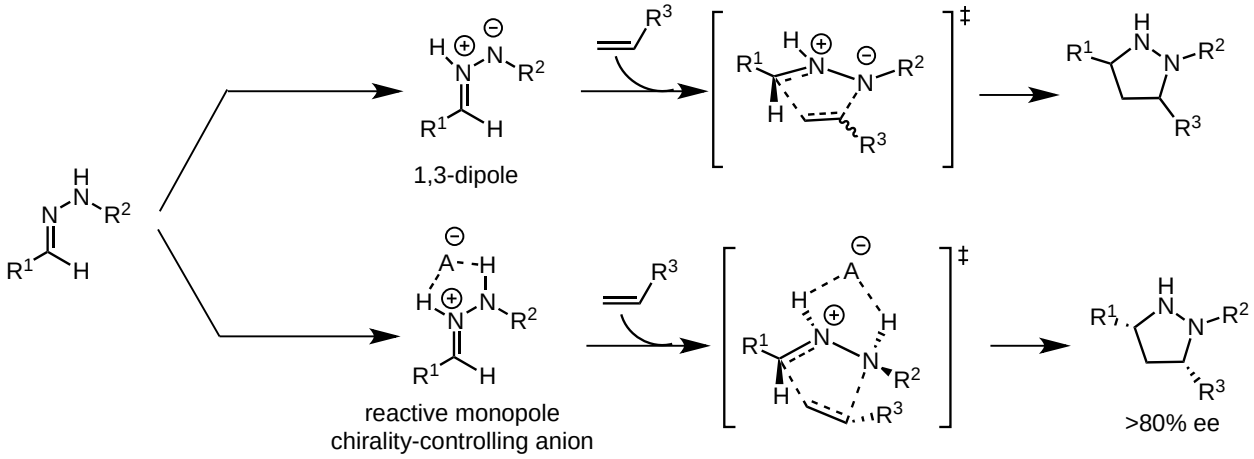
Scheme 50: Kinetic and thermodynamic product formation through acyclic azomethine imine intermediate

The mechanism of Brønsted acid (*N*-triflylphosphoramide) catalyzed asymmetric [3+2] cycloadditions was explored using DFT calculations.[90] Enantioselectivity was explained based on the most stable transition states in both catalyzed and uncatalyzed pathways. Protonation of the hydrazone by the Brønsted acid produced an ion pair complex, which became more reactive than the azomethine imine intermediate. A small distortion of this ion pair was required to reach the geometry present in the [3+2] cycloaddition transition state. Chiral *N*-triflylphosphoramide

89 Badawy, M. A.; El-Bahaie, S. A.; Kadry, A. M.; Ibrahim, Y. A. *Heterocycles* **1988**, *27*, 7.

90 Hong, X.; Küçuk, H. B.; Maji, M. S.; Yang, Y. F.; Rueping, M.; Houk, K. N. *J. Am. Chem. Soc*. **2014**, *136,* 13769.

efficiently yielded >80% ee of the desired *cis* compound (**Scheme 51**). This study illustrates the importance in using catalyzed pathways for azomethine imine intermediates and the reactivity moderation of using an acid.



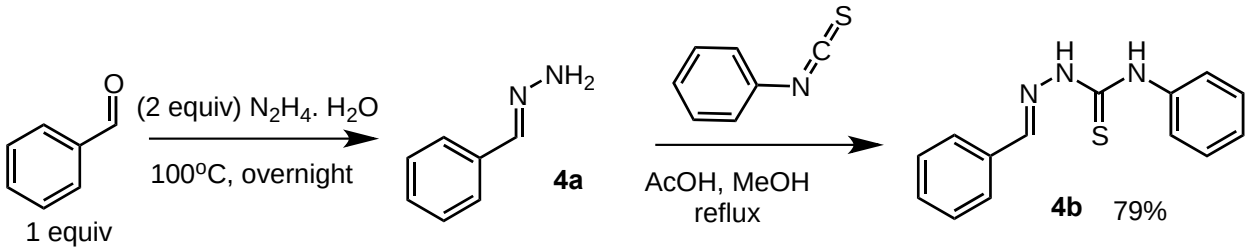
Scheme 51: Uncatalyzed and Brønsted acid catalyzed pathways

4.1.4 Project Objectives

With encouraging results shown in the introduction of this Chapter by the Beauchemin group, one objective of this project was to perform intermolecular 1,3-dipolar cycloadditions via the proposed acyclic azomethine imine intermediate. The second objective was to get a better understanding of the reactivity of acyclic azomethine imine intermediates which form in situ with *N*-isothiocyanate precursors.

4.2 Results and Discussion

1-Benzylidene-4-phenylthiosemicarbazide (**4b**) was synthesized to examine the cycloaddition property of *N*-isothiocyanate derived azomethine imine intermediates. This was accessed through benzyl hydrazone **4a**. Benzyl hydrazone was synthesized with a simple condensation of a benzaldehyde with hydrazine hydrate. Then the hydrazone was treated with phenyl isothiocyanate to synthesize **4b** (**Scheme 52**).

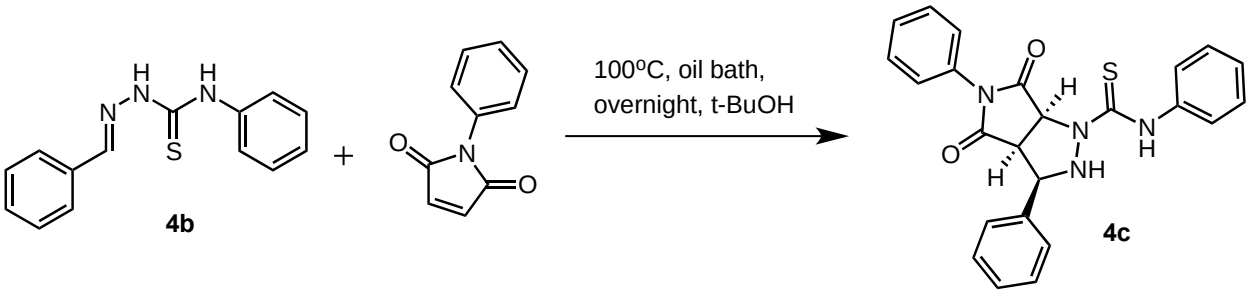


Scheme 52: Synthesis of starting material precursor 4b

Intramolecular reactions reported by Overman gave the best results when citric acid and *t*-BuOH were used. We decided to test similar reaction conditions on our system. *N*-Phenyl maleimide was used since it is known to be a good dipolarophile in [3+2] cycloaddition of azomethine imines, as reported in many publications (**Table 7**).[91]

91 For selected examples: (a) Koptelov, Y. B.; Sednev, M. V.; Kostikov, R. R. *Chem. Informationdienst* **2012**, *43*, 48. (b) Kirar, E. P. C. A.; Drev, M.; Mirnik, J.; Grošelj, U.; Golobič, A.; Dahmann, G.; Požgan, F.; Štefane, B.; Svete, J. *J. Org. Chem.* **2016**, *81*, 8920.

Table 7: Optimization of the reaction to synthesize 4c[a]

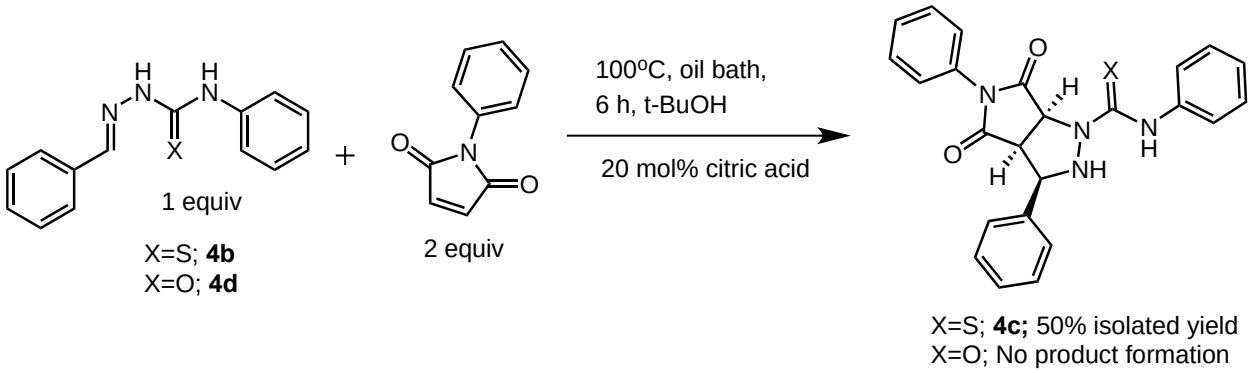


Entry #	Alkene (equiv)	Temperature	mmol	Time (h)	Citric acid	Yield[b]
1	10	100	1	12	1eq	70%
2	10	100	0.1	12	1eq	41%
3	10	100	0.1	12	0	<4%
4	10	100	0.1	12	20 mol%	47%
5	2	100	0.1	12	20 mol%	46%
6	1	100	0.1	12	20 mol%	40%
7	2	100	0.1	6	20 mol%	50%
8	2	150	0.1	6	20 mol%	45%

[a]Conditions: Precursor **4b**, alkene and solvent (0.03 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated with an oil bath. [b]Isolated yields are given.

With optimized conditions, 2 equivalents of alkene, 20 mol% citric acid as shown in entry 7 of **Table 7** gave the best isolated yield for 0.1 mmol scale. Semicarbazone precursor **4d**, the carbonyl analogue of the precursor **4b** was prepared by substituting O-*t*Bu (of t-butyl 3-benzylidenecarbazate) with aniline. Under the reaction conditions as in entry 7, the cycloaddition reaction was tested with precursor **4d** in order to probe the effect of the electron-withdrawing

group on the cycloaddition reactivity. No product formation was observed with **4d**. This is likely due to the lower stability of the azomethine imine intermediate with the carbonyl compared to the thiocarbonyl.

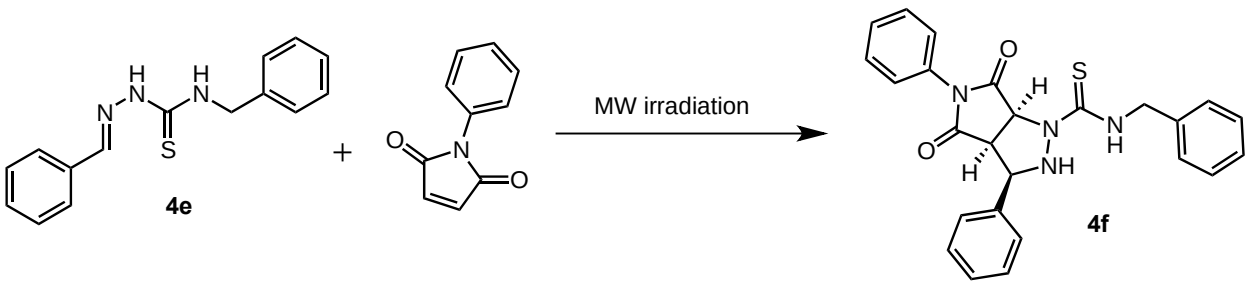


Scheme 53: Importance of using thiocarbonyl precursor for the reaction

Also, the reactions that were conducted with increased temperatures did not seem to have much effect on the yields obtained (**Table 7,** Entry 7 & 8). One possible explanation could be that degradation would occur via isothiocyanate formation.[92] The solution was to synthesize a precursor with a poor leaving group ability. Thus, thiosemicarbazone **4e** was synthesized via benzyl isothiocyanate (**3d**) formation with the Dolman's conditions as described in **Chapter 3**. As shown in **Table 8**, this precursor allowed the use of higher temperatures since it is less prone to form the isothiocyanate (Entry 4).

92 Larsen, C. H.; Anthioni, U.; Christophersen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1969,** *23,* 332.

Table 8: Optimization with precursor 4e[a]



Entry #	Temperature	Solvent	Time (h)	Citric acid	SM left	Yield[b]
1	120	*t*-BuOH	6	20 mol%	50%	50%
2	150	*t*-BuOH	6	20 mol%	<8%	83%
3	150	*t*-BuOH	6	10 mol%	12%	50%
4	180	*t*-BuOH	4	20 mol%	0%	52%
5	150	MeCN	6	20 mol%	19%	56%
6	150	Dioxane	6	20 mol%	56%	34%
7	150	*i*-PrOH	6	20 mol%	0%	80%
8	120	*i*-PrOH	4	20 mol%	30%	63%
9	120	THF	4	20 mol%	83%	15%
10	120	EtOH	4	20 mol%	5%	71%
11	120	$PhCF_3$	4	20 mol%	25%	65%
12	120	MeOH	4	20 mol%	23%	77%
13	120	TFE	4	20 mol%	2%	97%
14	120	DMSO-d_6	4	20 mol%	80%	8%

[a]Conditions: All these reactions were in 0.1 mmol scale. Precursor **4e** (1 equiv), alkene (2 equiv) and solvent (0.03 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated under microwave irradiation. [b]NMR yields were taken using 1,3,5-trimethoxybenzene as the internal standard in DMSO-d_6.

As shown above, different temperatures were first tested. At 120 °C in the presence of *t*-BuOH, the reaction mixture only contained product and starting material. Increasing temperature resulted in greater product formation but an unidentified byproduct was also formed. Higher yields were obtained in polar protic solvents. This could be due to the H-bond interactions that stabilize the transition state of the acyclic azomethine imine intermediate. This was further tested with using a solvent that is bearing a more acidic hydrogen than methanol in entry 13, giving the best results obtained.

Under the optimized conditions, the cycloaddition reaction was attempted with a number of alkenes (**Figure 15**). No cycloaddition products were observed with the alkenes shown in **Table 9**.

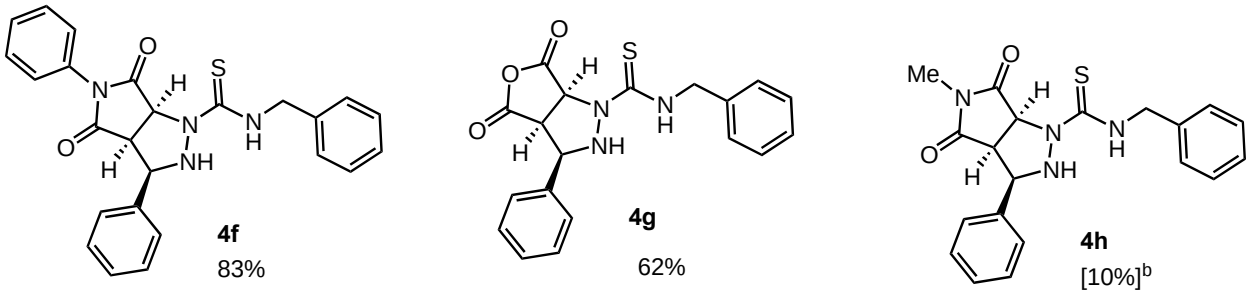


Figure 15: Scope of the reaction with isolated yields. bNMR yield is given

The stereochemistry for compound **4f** was determined with the use of *J* couplings (**Figure 16**) and 2D NMR (Supporting info).

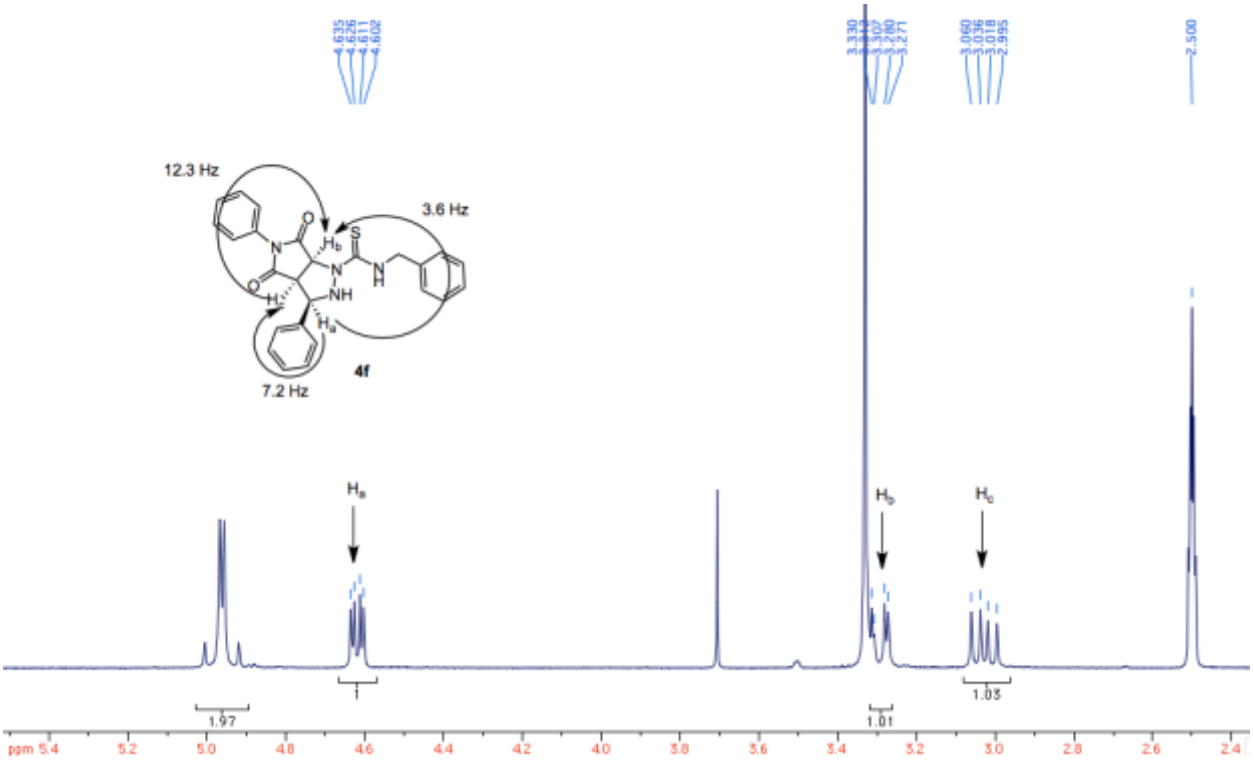
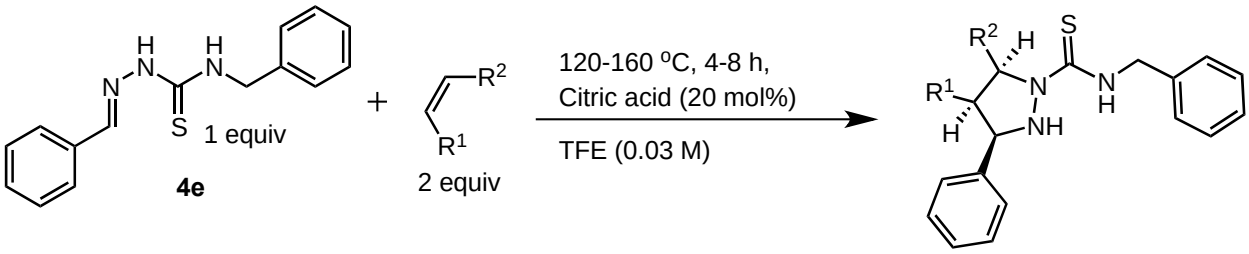


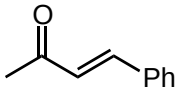
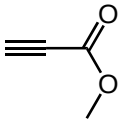
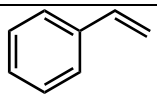
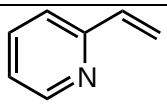
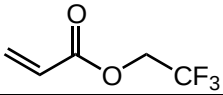
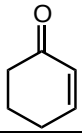
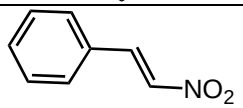
Figure 16: J-Coupling for the determination of stereochemistry of compound 4f

H_a was assigned for the most deshielded proton since it is next to a heteroatom and also next to an aromatic ring. H_b is next to a heteroatom so it is the middle set of peaks and leaving H_c to be the most shielded proton among this group. Since **4f** contained a fused two five-membered ring system, H_c and H_b protons are forced to be on the same side giving a coupling constant of 12.3 Hz. Also, H_b and H_a protons couple with each other through '*W* couplings'.

As shown in **Table 9**, the cycloaddition reaction was attempted with various alkenes according to the optimized conditions obtained for the synthesis of **4f**.

Table 9: Alkenes that were not successful in the reaction[a]



Alkene	Time	Temperature ° C	Starting material left %[b]	Comments
	A) 4 h B) 4 h	A) 120 B) 160	A) 90 B) 68	A) No other peaks B) Impurities present, no product formation identified
	A) 4 h B) 8 h	A) 120 B) 120	A) 95 B) 98	A) product like peaks, 5% B) No product formation
	4 h	120	83	No product formation
	4 h	120	ND[c]	Very messy NMR and was not able to purify
	4 h	120	95	No product formation
	4 h	120	77	No product formation
	4 h	120	90	No product formation
	4 h	120	83	No product formation
	4 h	120	76	No product formation

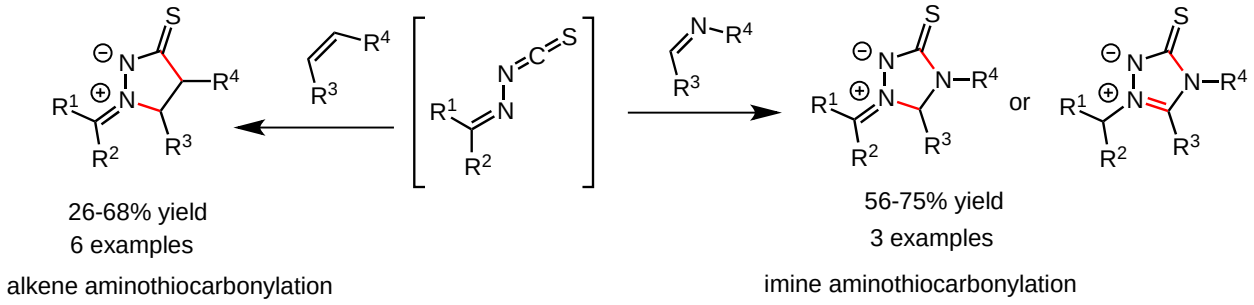
[a] Conditions: Thiosemicarbazide **4e** (1.0 equiv.), alkene (2 equiv.), and TFE (0.03 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated by microwave irradiation. [b]NMRs (To calculate SM left % and byproduct %) were taken using 1,3,5-trimethoxybenzene as the internal standard in deuterated dimethylsulfoxide. [c] Not determined.

In conclusion, we experimented an unprecedented intermolecular cycloaddition reaction of an acyclic thioxo-azomethine imine intermediate. The products were obtained in high diastereoselectivity, but currently, the reaction has a narrow substrate scope. Combined with the results obtained with cyclic azomethine imines, the reactivity arising from *N*-isothiocyanate precursors was highlighted again in this study. Additional experimentation is needed to improve the reaction conditions and extend the scope of the reaction to other alkenes.

Chapter 5: Conclusions

5.1 Summary and Future Work

Amphoteric *N*-isocyanate reagents were used in several types of reactivity. First, thioxo-azomethine imines were formed using cycloaddition reactions of readily available alkenes or imines. In this work, thiosemicarbazones were used as *N*-isothiocyanate precursors (**Scheme 54**). Unfortunately, alkenes showed limited reactivity toward the cycloaddition and the desired dipoles could only be obtained in acceptable yields when using strained alkenes. A large excess of alkene was used with thiosemicarbazones in order to achieve the best yields possible. In contrast, imines showed better reactivity and were able to achieve optimization with less than 1 equivalent of imine.



Scheme 54: Summarizing alkene and imine aminothiocarbonylation

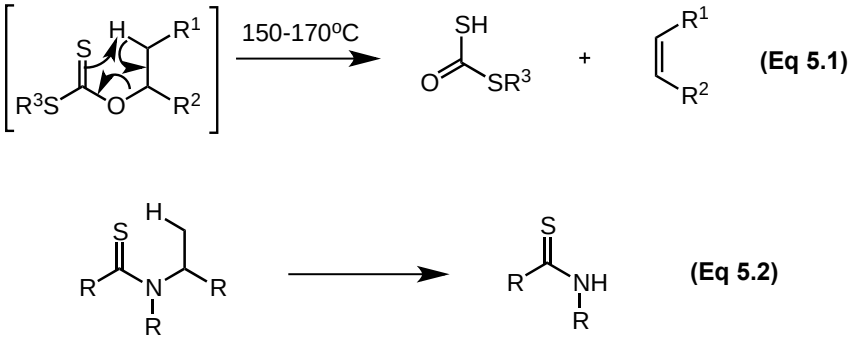
These thioxo-azomethine imine compounds were derivatized into their reduced or unprotected forms to achieve various thioxo-pyrazolone derivatives. Base catalysis was not successful with aminothiocarbonylation and in general reactivity, trends have shown that *N*-isocyanates are more reactive amphoteric reagents.[93] Further studies using DFT calculations to allow a detailed

93 Lavergne, K. Synthesis of Azomethine imines via Alkene Aminocarbonylation and their Derivatization into Pyrazolones, M.Sc. Thesis, University of Ottawa, 2014.

comparison of *N*-isocyanate versus *N*-isothiocyanate would be an interesting strategy to understand the differences in reactivity.

Imino-isothiocyanate formation and isolation were attempted using Anthoni and Berg conditions as well as Dolman's conditions. The imino-isothiocyanate formation was observed, but the isolation was not successful. The main issue with these compounds was that they tend to dimerize at room temperature.

The new reactivity observed in **Chapter 3** with NNCS motifs is appealing for further research exploring their chemistry. The mechanism proposed for the observed product is similar to the Chugaev elimination. This holds the potential of an unprecedented elimination reaction in forming protected primary amines from secondary amines (**Scheme 55**).[94]



Scheme 55: Eq 5.1) Proposed mechanism for Chugaev elimination Eq 5.2) Potential secondary amine elimination reaction

94 Calestani, G.; Capella, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Papa, R.; Zanardi, G. *Tetrahedron Lett.* **2001**, *57*, 7221. Dimitro rearrangement; (b) Sukumaran, P.; Rajasekharan, K. N. *Chem. Informationdienst* **2010**, *22*, 8.

As it was presented in **Chapter 4**, there are still challenges for broad applicability of azomethine imines in [3+2] cycloadditions. Interestingly, preliminary results suggest that thiosemicarbazones are superior precursors to allow the formation of the dipole in situ. However, further optimization is required in order for this unprecedented intermolecular reactivity to be broadly applicable, but the preliminary work presented in **Chapter 4** shows the potential of the reaction for cycloaddition of acyclic thioxo-azomethine imines (**Figure 17**).

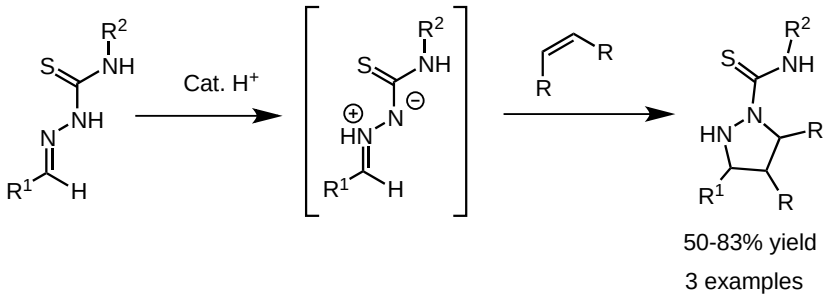


Figure 17: Cycloaddition of alkenes with acyclic azomethine intermediate

Chapter 6: Experimental Section

6.1 General Information

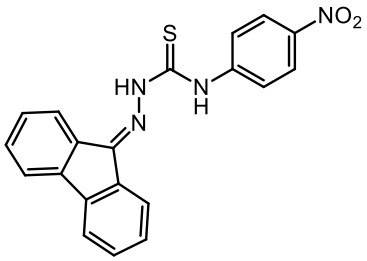
Purification of reaction products was carried out by flash column chromatography using SiliCycle silica gel (40-63 μm) unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum-backed plates, cut to size. Visualization of the TLC plates was accomplished with UV light followed by staining in a potassium permanganate vanillin or ninhydrin solution and heating. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AVANCE 300 MHz and 400 MHz spectrometers at ambient temperature. Spectral data was reported in ppm using a solvent as the reference ($CDCl_3$ at 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; DMSO-d_6 at 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). Data was reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app t = apparent triplet), coupling constants in Hz, and integration. Infrared (IR) spectra were obtained as neat thin films and were recorded on a Bruker EQUINOX 55 Fourier transform infrared spectrometer (FTIR). High-resolution mass spectroscopy (HRMS) was performed at the Ottawa-Carleton Mass Spectroscopy Centre on the Kratos Concept-11A mass spectrometer for Electron Impact (EI) and Waters Micromass Q-TOF I for electrospray ionization (ESI). Microwave reactions were performed using a Biotage Initiator Eight microwave reactor and Biotage microwave vials.

Materials. Unless otherwise noted, all materials purchased from commercial sources were used without further purification. Trifluorotoluene ($PhCF_3$) and acetonitrile (CH_3CN) were obtained from solvent purification system and stored in bottles charged with activated 4Å molecular sieves before use.

6.2 Supporting Information for Chapter 2

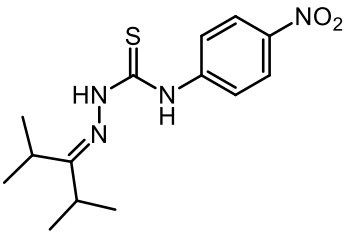
6.2.1 Synthesis and Characterization of Starting Material for Aminothiocarbonylation

2b 2-(9H-Fluoren-9-ylidene)-*N*-(4-nitrophenyl)hydrazine-1-carbothioamide



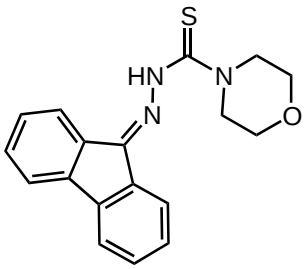
Fluorenone (19.4 g, 0.108 mol, 1 equiv), hydrazine hydrate (50-60% solution, 80 mL, 10 equiv) and EtOH (300 mL) were combined, acetic acid (2 mL) was added and the mixture stirred at reflux for 16 h. The mixture was cooled to room temperature and the hydrazone intermediate precipitated as yellow needles (16.0 g, 76%). This hydrazone intermediate (5.8 g, 30 mmol, 1 equiv), 4-nitrophenyl isothiocyanate (5.4 g, 30 mmol, 1 equiv), and MeOH (150 mL) were stirred for 16 h at room temperature. The precipitate was filtered and dried under vacuum, providing a yellow solid (10.2 g, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.78 (s, 1H), 8.28 (d, J = 9.2 Hz, 2H), 8.11 (dd, J = 9.6, 8.4 Hz, 4H), 7.91 (d, J = 7.2 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.56 (dd, J = 6.8, 6.8 Hz, 1H), 7.49-7.44 (m, 2H), 7.38 (dd, J = 8.4, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.0, 149.0, 145.7, 144.1, 142.1, 140.2, 136.7, 132.2, 131.3, 129.6, 128.6, 128.6, 128.6, 128.1, 126.8, 124.9, 124.3, 123.4, 121.2, 120.8. IR (ATR diamond) 3364, 3270, 3075, 1546, 1329, 1285, 1168, 759 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{20}H_{14}N_4O_2S$ [M]+· : 374.0837. Found: 374.0831.

2b[i] 2-(2,4-Dimethylpentan-3-ylidene)-*N*-(4-nitrophenyl)hydrazine-1-carbothioamide



2b[i] was prepared by Jean-François Vincent-Rocan. See the Reference article for the procedure.[95]

2d *N*'-(9*H*-fluoren-9-ylidene)morpholine-4-carbothiohydrazide



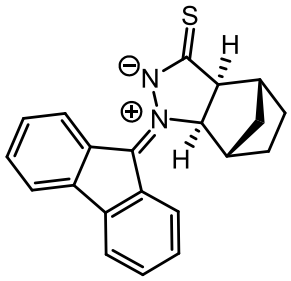
Fluorenone (0.659 g, 1.76 mmol, 1 equiv), morpholine (0.172 g, 1.94 mmol, 1.1 equiv), MeCN (20 ml) were combined. The mixture was heated (by microwave irradiation) to 150 °C for 2 hours. The crude mixture was cooled to 0 °C, filtered and purified by silica gel column chromatography (40% EtOAc, 60% Hexane) to give an orange solid (0.423 g, 74% yield). TLC R_f = 0.53 (100% EtOAc) ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, *J* = 7.5 Hz, 1 H), 7.83 (td, *J* = 0.9, 7.5 Hz, 1H), 7.67 (dt, *J* = 0.9, 8.7 Hz, 2H), 7.47 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.43-7.31 (m, 4H), 4.23 (br, 4H), 3.83 (t, *J* =5.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 141.3, 139.6, 132.1, 131.1, 131.0, 129.7, 128.6, 128.4, 128.4, 128.1, 121.1, 120.8, 120.6, 66.7. IR (ATR diamond) 1451, 1430, 1291, 1232, 1155, 1110, 898, 726 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{21}H_{18}N_2S$ [M]+: 323.1092. Found: 323.1190.

95 Bongers, A.; Ranasinghe, I.; Lemire, P.; Vincent-Rocan, J.-F.; Perozzo, A.; Beauchemin, A. M. *Org. Lett.* **2016,** *18*, 3778.

6.2.2 Alkene Aminothiocarbonylation

General procedure A Thiosemicarbazone **2b** or **2b**[i] (1.0 equiv.), alkene (10 equiv.), and MeCN (0.05 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated (by microwave irradiation) to 120 °C for 2 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (10% MeOH, 90% toluene), isolated yields are provided. Alkenes used were commercially available and Imines were prepared by known condensation methods following literature procedures[96]

2c (4R,7S)-1-(9H-fluoren-9-ylidene)-3-thioxooctahydro-4,7-methanoindazol-1-ium-2-ide

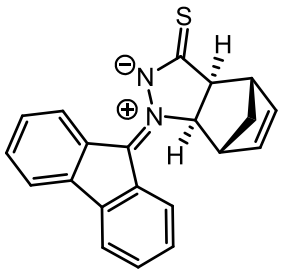


Synthesized according to **general procedure A** from **2b** (0.37 g, 0.98 mmol, 1 equiv) and norbornene (0.960 g, 10.2 mmol, 10 equiv). ^{1}H NMR of the crude mixture with 1,3,5-trimethoxybenzene internal standard showed 93% yield of **2b**, which was isolated to give a red dark solid (0.219 g, 68%). TLC R_f=0.42 (10% MeOH, 90% toluene) ^{1}H NMR (400 MHz, CDCl3) δ 8.89 (d, *J* = 7.6 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.46-7.37 (m, 3H), 7.33-7.29 (m, 1 H), 7.25-7.20 (m, 1 H), 4.83 (d, *J* = 6.4 Hz, 1 H), 3.38 (d, J = 6.8 Hz, 1 H), 2.95 (s, 1 H), 2.79 (s, 1 H), 1.72-1.70 (m, 2H), 1.51-1.48 (m, 2H), 1.43-1.40 (m, 1H), 1.20- 1.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 143.0, 141.9, 140.3, 132.9, 132.2, 132.1, 131.1, 129.4, 129.8, 128.4, 126.0, 121.3,

96 See individual entries for literature references.

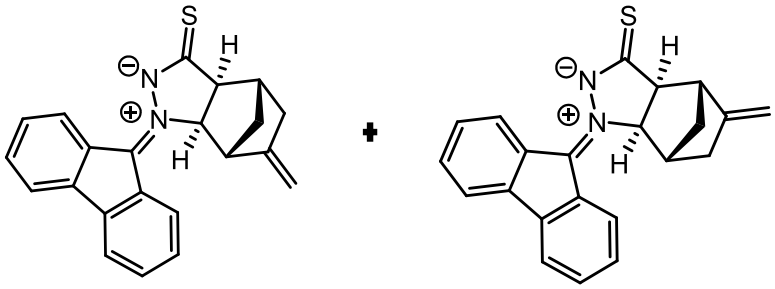
119.8, 74.5, 63.4, 43.0, 42.4, 32.1, 26.9, 25.5. IR (ATR diamond) 3061, 2965, 1771, 1448, 1352, 1095 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{21}H_{18}N_2S$ [M]+: 330.1190. Found: 130.1205.

2e(4S,7R)-1-(9H-fluoren-9-ylidene)-3-thioxo-1,3,3a,4,7,7a-hexahydro-4,7-methanoindazol-1-ium-2-ide



Synthesized according to **general procedure A** from **2b** (0.288 g, 0.77 mmol, 1 equiv) and norbornadiene (0.743 g, 8.07 mmol, 10 equiv). General column procedure gave 0.187 g of crystalline product which contained impurities. Further purification was performed on 0.025 g of product using preparative TLC R_f = 0.43 (10% MeOH, 90% toluene). Concentration in vacuo gave the product as a red solid containing 5 wt% dichloromethane (0.020 g, 57% corrected yield). This product was found to be unstable at room temperature over 24 hours. In addition, a reaction performed on a 0.58 mmol scale was analyzed by 1H NMR of the unpurified reaction mixture. Using 1,3,5-trimethoxybenzene as internal standard, NMR analysis indicated 88% yield for the reaction. TLC R_f =0.45 (10% MeOH, 90% toluene) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 7.61-7.61 (m, 2 H), 7.50-7.43 (m, 2H), 7.37-7.30 (m, 2H), 6.59-6.57 (m, 1H), 6.33-6.31 (m, 1H), 5.11 (d, *J* = 6.4 Hz, 1 H), 3.68 (d, *J* = 6.4 Hz, 1 H), 3.56 (s, 1 H), 3.48 (s, 1 H), 1.75-1.76-1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 143.2, 142.4, 140.5, 133.7, 133.1, 132.7, 132.4, 130.9, 129.8, 129.6, 128.5, 126.2, 124.3, 121.5, 119.9, 76.0, 63.4, 48.6, 48.2, 42.8. IR (ATR diamond) 3055, 2949, 2921, 2851, 1710, 1597, 1448, 1355 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{21}H_{16}N_2S$ [M]+: 328.1034. Found: 328.1031.

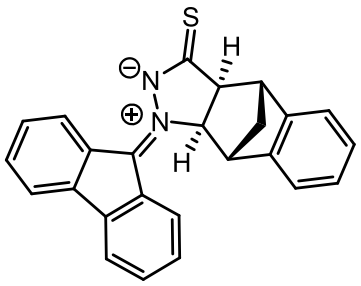
2f 1-(9H-fluoren-9-ylidene)-6-methylene-3-thioxooctahydro-4,7-methanoindazol-1-ium-2-ide



2f 1-(9H-fluoren-9-ylidene)-6-methylene-3-thioxooctahydro-4,7-methanoindazol-1-ium-2-ide

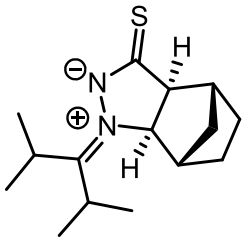
Synthesized according to **general procedure A**, from **2b** (0.360 g, 0.96 mmol, 1 equiv) and 5-methylenebicyclo- [2.2.1] hept-2-ene (0.70 mL, 9.87 mmol, 10 equiv). Mixture of regioisomers isolated in a ratio A:B = 1.3:1. Red solid (0.180 g, 53%). TLC R_f =0.51 (10% MeOH, 90% toluene) **Major isomer:** ^{1}H NMR (400 MHz, CDCl3) δ 8.92 (d, *J* = 7.6 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.61 (app t, *J* = 7.2 Hz, 1 H), 7.52-7.38 (m, 3H), 7.35-7.29 (m, 1H), 7.26 (app t, *J* = 7.6 Hz, 1 H), 5.23 (s, 1 H), 5.00 (s, 1 H), 4.90 (s, 1 H), 3.46 (d, *J* = 6.8 Hz, 1 H), 3.24 (s, 1 H), 3.10 (d, *J* = 3.6 Hz, 1 H), 2.42-2.31 (m, 1H), 2.21 (app t, *J* = 16.4 Hz, 1 H), 1.53 (app t, *J* = 9.6 Hz, 1 H), 1.37 (app t, *J* = 8.0 Hz, 1 H). **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 7.6 Hz, 1 H), 7.66 (d, J = 8.4 Hz, 1 H), 7.61 (app t, *J* = 7.2 Hz, 1 H), 7.52-7.38 (m, 3H), 7.35-7.29 (m, 1H), 7.26 (app t, *J* = 7.6 Hz, 1 H), 5.19 (s, 1 H), 4.91 (s, 1 H), 4.86 (s, 1 H), 3.49 (d, *J* = 6.8 Hz, 1 H), 3.38 (s, 1 H), 2.93 (d, J = 4.4 Hz, 1 H), 2.42-2.31 (m, 1H), 2.21 (app t, *J* = 16.4 Hz, 1 H), 1.53 (app t, *J* = 9.6 Hz, 1 H), 1.37 (app t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (mixture, 100 MHz, $CDCl_3$) δ 208.1, 207.0, 148.1, 147.4, 143.1, 142.0, 140.3, 133.1, 132.3, 132.2, 131.1, 129.6, 129.5, 128.5, 128.3, 126.1, 125.9, 121.4, 119.9, 108.1, 107.2, 74.1, 73.5, 63.1, 62.9, 50.9, 506, 43.4, 43.1, 35.6, 34.3, 32.6. IR (ATR diamond) 2970, 2199, 1660, 1351, 1309, 773 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{22}H_{18}N_2S$ [M]+: 342.1190. Found: 342.1198.

2g(4R,9R)-1-(9H-fluoren-9-ylidene)-3-thioxo-1,3,3a,4,9,9a-hexahydro-4,9-methanobenzo[f]indazol-1-ium-2-ide



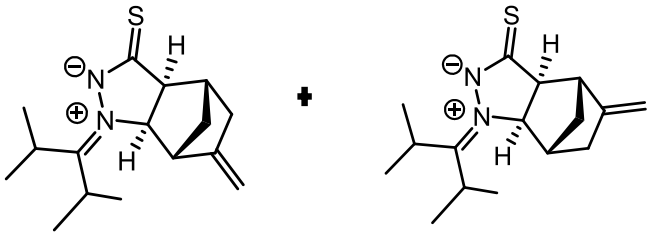
Synthesized according to **general procedure A**, from **2b** (0.037 g, 0.10 mmol, 1 equiv) and 1,4-dihydro-1,4-methanonaphthalene **7** (0.154 g, 1.08 mmol, 10 equiv). The product was isolated as a red solid. To remove residual grease, the product was dissolved into MeCN and extracted three times with hexane. (0.011 g, 31%). TLC R_f = 0.55 (10% MeOH, 90% toluene) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 7.6 Hz, 1 H), 8.02-8.00 (m, 1H), 7.96 (d, J = 7.6 Hz, 1 H), 7.83-7.80 (m, 1H), 7.65-7.61 (m, 3H), 7.57-7.55 (m, 1H), 7.49 (dd, J = 8.0, 1.2 Hz, 1H), 7.47-7.44 (m, 1H), 7.25-7.23 (m, 2H), 5.47 (d, J = 6.8 Hz, 1 H), 3.95 (s, 1 H), 3.78 (s, 1 H), 3.47 (d, J = 6.4 Hz, 1H), 1.85 (d, J = 10.4 Hz, 1 H), 1.77 (J = 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 147.4, 143.4, 142.8, 140.5, 133.3, 132.6, 131.1, 129.8, 129.7, 129.0, 128.5, 128.2, 127.9, 126.8, 126.3, 122.9, 121.6, 121.5, 120.0, 75.5, 64.2, 49.5, 49.4, 43.0. IR (ATR diamond) 3054, 2970, 2948, 1605, 1448, 1376, 1280 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{25}H_{18}N_2S$ [M]+: 378.1190. Found: 138.1190.

2h (4R,7S)-1-(2,4-dimethylpentan-3-ylidene)-3-thioxooctahydro-4,7-methanoindazol-1-ium-2-ide



Synthesized according to **general procedure A**, from **2b**[i] (0.030 g, 0.10 mmol, 1 equiv) and norbornene (0.114 g, 1.2 mmol, 10 equiv). The product was isolated as a brown solid (0.018 g, 65%). TLC R_f = 0.61 (10% MeOH, 90% CH2Cl2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, J = 9.6 Hz, 1 H), 3.13 (d, J = 9.6 Hz, 1 H), 3.05-2.96 (m, 1H), 2.95-2.89 (m, 2H), 2.39 (br. s, 1H), 1.65-1.52 (m, 2H), 1.38-1.15 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 72.3, 62.7, 43.4, 41.7, 34.3, 31.9, 30.8, 26.7, 25.5, 18.9, 18.1, 17.6. IR (ATR diamond) 2955, 2870, 1416, 1378, 1147, 1115, 1001 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{15}H_{24}N_2S$ [M]+: 264.1660. Found: 264.1614.

2i (3aS,4S,7R,7aR)-1-(2,4-dimethylpentan-3-ylidene)-6-methylene-3-thioxooctahydro-4,7-methanoindazol-1-ium-2-ide



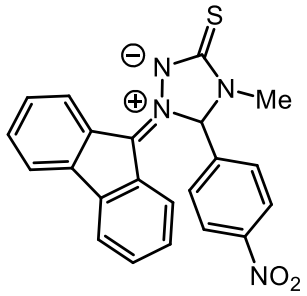
Synthesized according to **general procedure A**, from **2b**[i] (0.145 g, 0.49 mmol, 1 equiv) and 5-methylenebicyclo- [2.2.1] hept-2-ene (0.36 mL, 4.97 mmol, 10 equiv). Mixture of regioisomers isolated in a ratio A:B = 1.1:1. Brown solid (0.035 g, 26%). TLC R_f = 0.66 (10% MeOH, 90% CH_2Cl_2)

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (s, 1H), 4.86 (s, 1H), 4.26 (d, J = 7.2 Hz, 1 H), 3.22 (app t, J = 10.0 Hz, 1 H), 3.03-2.97 (m, 2H), 2.93-2.86 (m, 1H), 2.82 (s, 1H), 2.28-2.22 (m, 2H), 2.03 (app t, J = 12 Hz, 2 H), 1.36 (d, J = 6.8 Hz, 6 H), 1.31 (d, J = 6.8 Hz, 3 H), 1.22 (d, J = 1.6 Hz, 3 H). **Minor isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (s, 1H), 4.73 (s, 1H), 4.31 (d, J = 6.8 Hz, 1 H), 3.30 (s, 1H), 3.22 (app t, J = 10.0 Hz, 1 H), 3.03-2.97 (m, 1H), 2.93-2.86 (m, 1H), 2.50 ((d, J = 4.4 Hz, 1 H), 2.28-2.22 (m, 2H), 2.03 (app t, J = 12 Hz, 2 H), 1.39 (d, J = 6.8 Hz, 6 H), 1.28 (d, J = 6.8 Hz, 3 H), 1.24 (d, J = 1.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 201.2, 169.1, 148.3, 147.4, 147.3, 108.3, 106.5, 71.8, 71.6, 62.3, 52.3, 49.7, 44.0, 42.8, 35.6, 34.4, 34.3, 34.3, 32.5, 30.9, 30.8, 18.9, 18.9, 18.8, 18.1, 18.1, 17.6. IR (ATR diamond) 2970, 2199, 1660, 1351, 1309, 773 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{16}H_{24}N_2S$ [M]+: 276.1660. Found: 276.1661.

General Procedure B Thiosemicarbazone **2b** (1.5 equiv.), imine (1.0 equiv.), and MeCN (0.05 M) were combined in a dry vial, which was sealed and purged with argon. The mixture was heated (by microwave irradiation) to 120 °C for 2 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure (rotovap then 60 °C, 2 mmHg). The crude mixture was purified by silica gel column chromatography unless otherwise noted. Isolated yields are provided.

6.2.3 Imine Aminothiocarbonylation

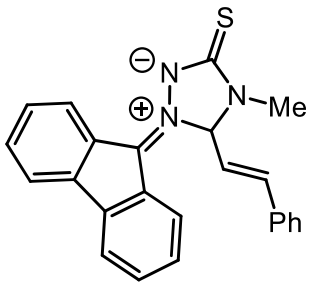
2k 2-(9H-fluoren-9-ylidene)-4-methyl-3-(4-nitrophenyl)-5-thioxo-1,2,4-triazolidin-2-ium-1-ide



4b. Synthesized according to **general procedure B**, from **2b** (0.058 g, 0.15 mmol, 1.5 equiv) and 4-nitrophenyl-N-methylmethanimine[97] (3b, 0.017 g, 0.10 mmol, 1.0 equiv), and $PhCF_3$ (4.0 mL). The reaction time was 2 h. The crude mixture was filtered, rinsing with with Et2O, and isolated by column chromatography using 10% MeOH, 90% toluene, providing a yellow solid (0.036 g, 75% yield). TLC R_f =0.23 (10% MeOH, 90% CH_2Cl_2) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 8.7 Hz, 2H), 8.26 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.49 (appt t, J = 7.2 Hz, 2H), 7.36 (ddd, J = 7.5 Hz, 7.5Hz, 1.2 Hz, 2H), 6.29 (s, 1H), 3.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) 170.2, 150.2, 148.4, 141.1, 140.9, 132.8, 130.1, 128.2, 128.1 125.8, 124.9, 121.0, 63.5, 32.6. IR (ATR diamond) 3040, 1514, 1332, 1193, 988 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{22}H_{16}N_4O_2S$ [M]+: 400.0994. Found: 400.0990.

97 Tanaka, S.-Y.; Tagashira, N.; Chiba, K.; Yasuda, M; Baba, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 6620.

2l (E)-2-(9H-fluoren-9-ylidene)-4-methyl-3-styryl-5-thioxo-1,2,4-triazolidin-2-ium-1-ide

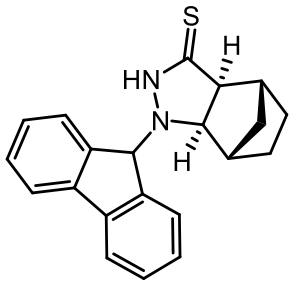


Synthesized according to **general procedure B**, from **2b** (0.258 g, 0.687 mmol, 1.5 equiv) and 3-(benzyldeneamino) propanenitrile[98] (0.0789 g, 0.543 mmol, 1 equiv), and $PhCF_3$ (16 mL). The reaction time was 2 h. The crude mixture was filtered, rinsing with Et2O, to isolate the product as the precipitate. Yellow solid (0.136 g, 66% yield). TLC R_f =0.20 (10% MeOH, 90% CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 7.5 Hz, 2 H), 7.54 (d, J = 7.5 Hz, 2 H), 7.45 (dd, J = 7.5, 7.5 Hz, 2 H), 7.38 - 7.18 (m, 5 H), 6.88 (d, J = 7.2 Hz, 2 H), 6.69 - 6.43 (m, 2 H), 5.74 (d, J = 16.6 Hz, 1 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) 170.9, 144.1, 141.4, 140.3, 139.9, 133.6, 130.7, 130.2, 128.9, 128.8, 127.2, 125.3, 120.6, 106.3, 66.7, 33.1. IR (ATR diamond) 3839, 3021, 2871, 1630, 1503, 1339, 1120, 959 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{24}H_{19}N_3S$ [M]+: 381.1299. Found: 381.1303.

98 Müller, W.; Feuerbach, D.; Nozulak, J.; Roy, B. L. *Substituted Pyrrolidine-2-ones*, **2010**, pg. 20 [0089] WO 2005/118535.

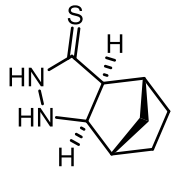
6.2.4 Derivatization of Azomethine Imine Products

2r (4R,7S)-1-(9H-fluoren-9-yl)hexahydro-1H-4,7-methanoindazole-3(2H)-thione



Azomethine imine **2c** (0.120 g, 0.36 mmol, 1 equiv) and NaCNBH3 (0.068 g, 1.10 mmol, 3 equiv) were combined in 1 mL of 2:1 MeOH: AcOH and stirred overnight at room temperature. The crude mixture was concentrated under reduced pressure then diluted with 10 mL of CH_2Cl_2. The organic layer was washed with brine, then concentrated to give the product as a green solid (0.102 g, 85%). TLC R_f = 0.46 (10% MeOH, 90% toluene) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.65 (m, 4H), 7.46-7.41 (m, 2H), 7.30-7.26 (m, 2H), 5.32 (s, 1H), 2.74 (d, *J* = 8.0 Hz, 1H), 2.65 (d, *J* = 3.6 Hz, 1H), 2.41 (d, *J* = 8.0 Hz, 1H), 1.94 (d, *J* = 4.4 Hz, 1H), 1.57 (d, *J* = 10.4 Hz, 1H), 1.46-1.37 (m, 1H), 1.27-1.11 (m, 3H), 1.04-0.98 (m, 1H), 0.60-0.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 141.9, 140.9, 140,9, 140.6, 129.1, 129.0, 128.1, 127.6, 126.1, 126.1, 120.1, 120.0, 69.1, 65.9, 63.2, 44.4, 42.4, 33.5, 27.3, 24.4. IR (ATR diamond) 3109, 2958, 2866, 1544, 1445, 1149 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{21}H_{20}N_2S$ [M]+ : 332.1347. Found: 332.1333.

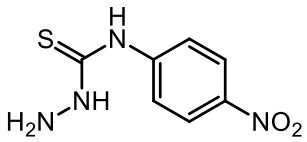
2x (4R,7S)-hexahydro-1H-4,7-methanoindazole-3(2H)-thione



Azomethine imine **2c** (0.091 g, 0.28 mmol, 1 equiv) hydroxylamine 50% wt H_2O (0.056 g, 0.84 mmol, 3 equiv) and MeOH (6 mL) were combined in a flask and stirred at room temperature for 1 h. The mixture was cooled to ambient temperature and the addition of 10 mL H_2O caused the fluorenone oxime to precipitate. The reaction mixture and filtered and the filtrate was concentrated under reduced pressure to give the product as a brown solid (0.030 g, 64%). TLC R_f = 0.38 (10% MeOH, 90% CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, *J* = 10.8 Hz, 1 H), 3.11 (d, *J* = 10.8 Hz, 1 H), 2.79 (d, *J* = 4.8 Hz, 1 H), 2.35 (d, *J* = 5.2 Hz, 1 H), 1.67-1.56 (m, 1H), 1.54- 1.43 (m, 2H), 1.35- 1.26 (m, 1H), 1.23 (d, *J* = 14.4 Hz, 1 H), 1.16-1.08 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 64.2, 63.4, 44.0, 42.1, 32.7, 27.4, 24.6. IR (ATR diamond) 3071, 1682, 1334, 1514, 1223, 941 cm^{-1}. HRMS (EI): Exact mass calculated for $C_8H_{12}N_2S$ [M]+: 168.0721. Found: 168.0712.

6.2.5 Intramolecular Aminothiocarbonylation Starting Material

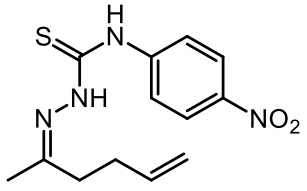
2y *N*-(4-nitrophenyl)hydrazinecarbothioamide



In a clean and dry round bottom flask equipped with a stir bar, hydrazine hydrate (1.25 equiv) was dissolved in i-PrOH (0.13 M). Under magnetic stirring, 4-nitrophenyl isothiocyanate (1 equiv) was added to the reaction mixture (0.10 M). The reaction mixture was left stirring at room temperature for 3 hours. The reaction mixture was filtered, and the collected thiosemicarbazide was dried under vacuum and used as is for the next step.

General Procedure C Ketone (1 equiv), hydrazinecarbathioamide **2y** (1 equiv), and MeOH (0.25M) were refluxed in a round bottom flask until the reaction goes to completion. Monitored starting material disappearance with TLCs. If the reactions were slow, added a drop of AcOH. Isolated yields are provided.

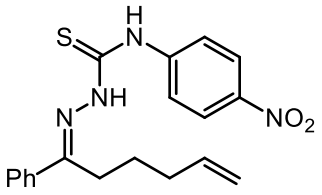
2t 2-(hex-5-en-2-yl)-*N*-(4-nitrophenyl)hydrazinecarbothioamide



Synthesized according to **general procedure C** from hex-5-en-2-one (0.235 g, 2.36 mmol, 1 equiv), **2y** (0.510 g, 2.40 mmol, 1 equiv), and 12 ml of MeOH. 1 drop of acetic acid was added after 3 hours. After 6 hours products were isolated as a yellow solid. (0.550 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

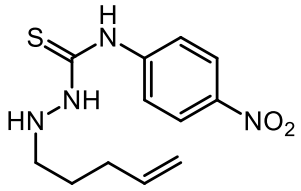
9.61 (s, 1H), 8.67 (s, 1 H), 8.21 (d, *J* = 9.2 Hz, 2 H), 7.99 (d, *J* = 8.8 Hz, 2 H),5.85-5.78 (m, 1H), 5.10-5.02 (m, 2 H), 2.46-2.35 (m, 4H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 175.3, 153.2, 143.9, 136.9, 136.1, 124.5, 122.1, 117.6, 115.7, 37.8, 30.0, 23.3, 16.1. IR (ATR diamond) 3236, 1594, 1479, 1192, 843, 748 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{13}H_{16}N_4O_2S$ [M]+: 292.0094. Found: 292.0985.

2u (E)-*N*-(4-nitrophenyl)-2-(1-phenylhex-5-en-1-ylidene)hydrazinecarbothioamide



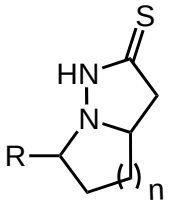
Synthesized according to **general procedure C**, from 1-phenylhex-5-en-1-one (0.188 g, 1 mmol, 1 equiv), thiosemicarbazone (0.222 g, 1 mmol, 1 equiv) and 4 ml of MeOH. Obtained white orange crystals. (0.286 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, *J* = 12.9 Hz, 2 H), 8.85 (d, 1H), 8.26 (d, *J* = 12.0 Hz, 2 H), 8.04 (t, *J* = 12.9 Hz, 2H), 7.73 (dd, *J* = 3.9, 3.3 Hz, 1H), 7.56-7.48 (m, 3H), 7.38 (d, *J* = 3.3 Hz, 1H), 5.91-5.75 (m, 1H), 5.17-5.00 (m, 1H), 2.78 (t, *J* = 8.1 Hz, 1H), 2.66 (t, *J* = 4.5 Hz, 1H), 2.24-2.12 (m, 2H), 1.77-1.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 179.6, 144.1, 143.9, 137.2, 124.5, 121.9, 115.8, 51.0, 31.0, 26.5. IR (ATR diamond) 3314, 3193, 1593, 1498, 1330, 910, 841, 745 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{19}H_{20}N_4O_2S$ [M]+: 368.1307. Found: 368.1201.

2v *N*-(4-nitrophenyl)-2-(pent-4-en-1-yl)hydrazinecarbothioamide



Synthesized **2s** according to **general procedure C**. Then **2v** was synthesized from **2s** (0.510 g, 1.82 mmol, 1 equiv), $NaCNBH_3$ (0.490 g, 7.8 mmol, 4 equiv), and 2:1 mixture of MeOH: AcOH was stirred overnight at room temperature. 5 ml of CH_2Cl_2 and NaOH until the mixture became pH 8 were added. Extracted the organic layer 3 times with CH_2Cl_2. Evaporated the solvent and further purified by silica gel column chromatography (5% EtOAc: 95% CH_2Cl_2) to obtain the isolated product. (0.380 g, 75%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.22 (d, *J* = 9.2 Hz, 2 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 7.88 (s, 1H), 5.84-5.73 (m, 1 H), 5.02 (t, *J* = 17.2 Hz, 2 H), 4.01 (s, 1 H), 2.96 (d, *J* = 0.4 Hz, 2 H), 2.17-2.14 (m, 2 H), 1.68-1.66 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) 179.6, 144.1, 143.9, 137.2, 124.5, 121.9, 115.8, 51.3, 31.0, 26.5. IR (ATR diamond) 3161, 1566, 1486, 1269, 1106, 748 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{12}H_{16}N_4O_2S$ [M]+: 280.0994. Found: 280.0023.

6.2.6 Experimental procedures conducted in attempt to form the cyclized product with 2s-2v (Scheme 33)

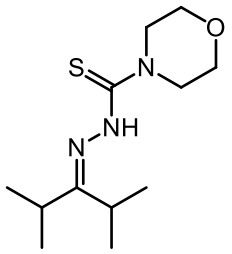


General Procedure: Hydrazinecarbothioamide with trifluorotoluene (0.03 M) was sealed in a μw vial and purged with argon. The mixture was heated (by microwave irradiation) 120-200 °C for 1-2 hours depending on starting material conversion. No products were determined with any of the reactions. With 120 °C always observed starting material and dimerization products were observed

in the NMR of the crude mixture when R=H. Degradation occur with high temperatures and longer time periods.

6.3 Supporting Information for Chapter 3

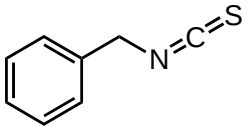
3c *N*'-(2,4-dimethylpentan-3-ylidene)morpholine-4-carbothiohydrazide



Lead bis[diisopropylmethylene]dithiocarbazate] **3b** was prepared according to referenced literature.[99] **3c** was synthesized from **3b** (0.054 g, 0.11 mmol, 1 equiv), morpholine (0.025 ml, 0.28 mmol, 3 equiv), and 3 ml of MeCN were combined in a sealed vial which was purged in argon and stirred at room temperature for 20 hours which turned yellow, grey and black gradually. The mixture was filtered through celite to obtain pure product (0.024 g, 46% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (br, 4H), 3.70-3.68 (m, 4H), 3.29-3.25 (m, 1 H), 2.87-2.83 (m, 1 H), 1.32 (d, *J* = 6.8 Hz, 6H), 1.26 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 183.3, 164.6, 66.8, 47.7, 32.3, 30.9, 20.5, 17.3. IR (ATR diamond) 2961, 2924, 2865, 2839, 1426, 1305, 1062, 998, 865, 799 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{12}H_{23}N_3OS$ [M]+: 257.1561. Found: 257.1522.

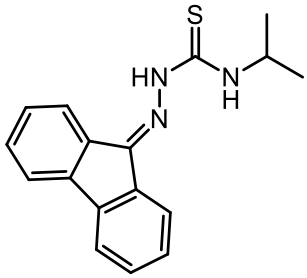
99 Anthoni, U.; Berg, C. *Acta Chem. Scand.* **1969,** *23,* 3602.

3d (Isothiocyanatomethyl)benzene



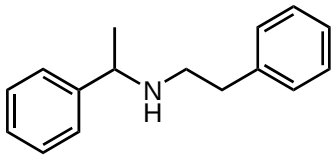
Synthesized according to Dolman's conditions with benzylamine (1.2 ml, 11 mmol, 1 equiv), Et_3N (4.5 ml, 36 mmol, 3.3 equiv), CS_2 (0.7 ml, 13 mmol, 1.2 equiv), TsCl, (2.3 g, 12 mmol, 1.1 equiv) in 10 ml of THF. Collected 1.36 g of colourless oil (1.36 g, 83%). TLC R_f =0.34 (100% Hexane) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.31 (m, 5H), 4.71 (s, 2H). This matches with the literature ^{1}H NMR data.[100]

3f 2-(9H-fluoren-9-ylidene)-*N*-isopropylhydrazinecarbothioamide



Thiosemicarbazone **2b** (0.347 g, 0.93 mmol, 1 equiv), diisopropylamine (20 ml, as solvent) was heated at 150°C by microwave irradiation for 3 minutes. product was isolated by column chromatography using 40% EtOAc: 60% Hexane solvent system. Obtained a brown solid. (0.114 g, 42%) TLC R_f = 0.54 (40% EtOAc: 60% Hexane) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 0.4 Hz, 1 H), 7.90 (d, J = 7.6 Hz, 1 H), 7.73 (dd, J = 7.6, 7.6 Hz, 2H), 7.62 (br, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.42-7.27 (m, 5H), 4.69-4.63 (m, 1H), 1.39 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) 176.6, 142.3, 139.8, 136.4, 131.5, 130.3, 129.5, 128.3, 128.1, 125.7, 121.5, 120.9, 120.0, 46.8, 22.4. IR (ATR diamond) 3274, 2966, 1592, 1428, 1294, 1000, 778 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{17}H_{17}N_3S$ $[M]^+$: 295.1143. Found: 295.1034.

100 Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72,* 3969.



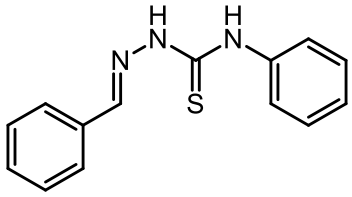
3h *N*-phenethyl-1-phenylethanamine

Synthesized according to a known procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 10H), 3.88 (q, *J* = 8.8 Hz, 1H), 2.91-2.81 (m, 4H), 1.45 (d, *J* = 8.8 Hz, 1H). Spectral data match with the literature ^{1}H NMR data.[101]

6.4 Supporting Information for Chapter 4

6.4.2 Starting Material Synthesis for Acyclic Azomethine Imines

4b (E)-2-benzylidene-N-phenylhydrazinecarbothioamide



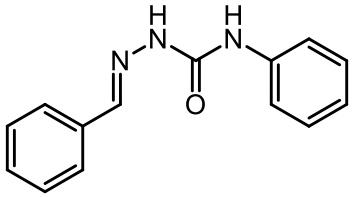
Benzaldehyde hydrzone[102] **4a** (2.30 g, 19.1mmol, 1 equiv), Phyenyl isothiocyanate (2.17 ml, 19.1 mmol, 1 equiv), AcOH (1 drop) and 50 ml MeOH were refluxed for 3 hours, obtained white crystalline product (3.86 g, 79% yield). TLC R_f=0.64 (100% CH_2Cl_2) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 10.11 (s, 1H), 8.18 (s, 1H), 7.91 (d, J = 3.6 Hz, 2 H), 7.58 (d, J = 7.6 Hz, 2 H), 7.42-7.37 (m, 5H), 7.22-7.20 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 176.5, 143.3, 139.5, 134.4, 130.5, 129.1,

101 100

102 Gan, W.; Moon, P.; Clavette, C.; DasNeves, N.; Markiewicz, T.; Toderian, A.; Beauchemin, A. M.*Org. Lett.* **2013**, *15,* 1890.

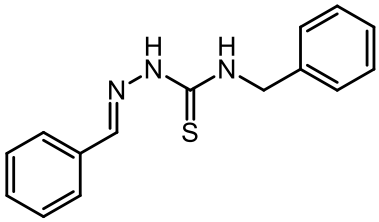
128.5, 128.1, 126.3, 125.7. IR (ATR diamond) 3096, 2990, 1503, 1188, 770 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{14}H_{13}N_3S$ $[M]^+$: 255.0832. Found: 255.0804.

4d (E)-2-benzylidene-N-phenylhydrazinecarboxamide



(Z)-*tert*-butyl 2-benzylidenehydrazinecarboxylate (from Wei Gan) (0.254 g, 1.15 mmol, 1 equiv), Aniline (0.221 g, 2.38 mmol, 2 equiv) heated at 120°C by microwave irradiation for 30 min in Trifluorotolune (3 ml). The product was isolated by column chromatography using 1:1 Hexane: CH_2Cl_2 to obtain the products as a white solid (0.168 g, 62%). TLC R_f = 0.62 (1:1 Hex: CH_2Cl_2) ^1H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, , J = 7.6 Hz, 2H), 7.31 (d, , J = 1.2 Hz, 1H), 7.29 (d, J = 1.2 Hz, 2H), 7.31 (dd, J = 3.6, 3.6 Hz, 2H), 6.72 (d, J = 7.6 Hz, 2H), 6.69 (dd, J = 3.6, 3.4 Hz, 1H), 6.12 (d, J = 8.0 Hz, 1H), 4.84-4.78 (m, 1H), 3.31 (dd, 13.2, 6.6 Hz, 1H), 2. 68 (dd, 13.2, 5.6 Hz, 1H) ^{13}C NMR (100 MHz, DMSO-d_6) 176.9, 174.7, 147.8, 135.1, 132.8, 129.3, 128.8, 127.4, 117.4, 113.3, 52.2, 36.7. IR (ATR diamond) 3367, 3080, 2948, 1678, 1498, 1280, 742 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{14}H_{13}N_3O$ $[M]^+$: 239.1058. Found: 239.1042.

4e (E)-N-benzyl-2-benzylidenehydrazinecarbothioamide

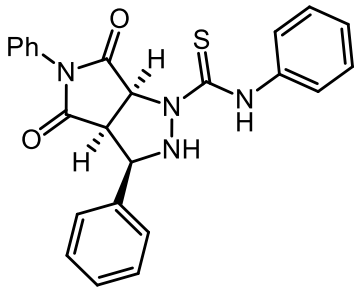


Benzyl isothiocyanate[103] (1.15 g, 7.8 mmol, 1 equiv), phenyl hydrazone (0.986 g, 7.8 mmol, 1 equiv), and 20 ml MeOH were refluxed for 3 hours, recrystallized in ether and hexane mixture to obtain white crystalline product (1.59 g, 59% yield). TLC R_f =0.64 (100% CH_2Cl_2) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 9.10 (s, 1H), 8.09 (s, 1H), 7.81 (dd, J = 4.0, 2.0 Hz, 2 H), 7.58 (dd, J = 2.4, 2.0 Hz, 3 H), 7.37-7.31 (m, 4H), 7.26-7.22 (m, 1H), 4.85 (d, J = 6.4 Hz, 2 H). ^{13}C NMR (100 MHz, DMSO-d_6) 178.0, 142.6, 139.9, 134.6, 130.3, 129.1, 128.6, 127.7, 127.1, 47.0. IR (ATR diamond) 3366, 3139, 2996, 1521, 1298, 1933, 752 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{15}H_{15}N_3O$ $[M]^+$: 269.0986. Found: 269.0946.

103 100

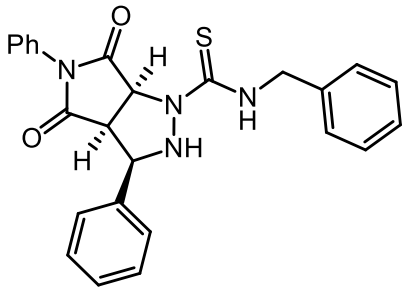
6.4.3 Cycloaddition Products via Acyclic Azomethine Imine Intermediates

4c (3R,6S)-4,6-dioxo-N,3,5-triphenylhexahydropyrrolo[3,4-c]pyrazole-1(2H)-carbothioamide



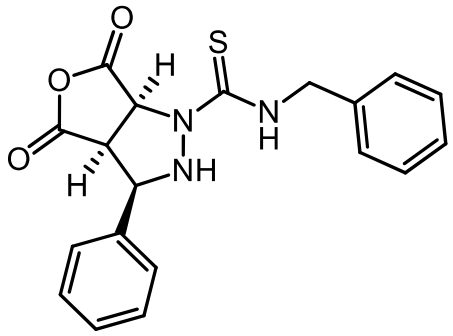
4b (0.256 mg, 1.00 mmol, 1 equiv), *N*-Phenyl maleimide (1.81 g, 10.4 mmol, 10 equiv), citric acid (0.193 g, 1.00 mmol, 1 equiv) was added to a vial which was sealed purged with argon. *t*-BuOH was added and reaction ran in oil bath at 100 °C overnight to obtain a white precipitate which was washed with ether to give the product as white solid. (0.298 g, 70%). TLC R_f = 0.33 (100% CH_2Cl_2) ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.28 (s, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 3.6 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.41-7.38 (m, 5H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.63 (dd, *J* = 3.9, 8.1 Hz, 1H), 3.31 (dd, *J* = 3.9, 16.8 Hz, 1H), 3.19 (dd, *J* = 8.1, 16.8 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.5, 168.3, 165.5, 158.1, 139.2, 135.7, 134.5, 131.2, 129.5, 129.2, 129.1, 128.7, 128.2, 123.9, 119.6, 43.2. IR (ATR diamond) 3346, 1715, 1579, 1246, 764 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{24}H_{20}N_4O_2S$ $[M]^+$: 428.1307. Found: 428.1280.

4f (3R,6S)-N-benzyl-4,6-dioxo-3,5-diphenylhexahydropyrrolo[3,4-c]pyrazole-1(2H)-carbothioamide



4e (0.120 mg, 0.44 mmol, 1 equiv), *N*-Phenyl maleimide (0.171g, 0.98 mmol, 2.2 equiv), citric acid (0.018 g, 0.09 mmol, 20 mol%) was added to a vial which was sealed purged with argon. trifluorotoluene (20 mL) was added and reaction ran in μw at 150°C for 6 hours to obtain a white precipitate which was washed with ether to give the product as white solid. (0.146 g, 74%). TLC R_f = 0.33 (100% CH_2Cl_2) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (d, *J* = 0.4 Hz, 2H), 8.42 (s, 1H), 7.73 (d, *J* = 2.8 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.41-7.25 (m, 9H), 7.03-7.00 (m, 1H), 4.95 (d, *J* = 4.0 Hz, 2H), 4.61 (dd, *J* = 12.3, 3.6 Hz, 1H), 3.29 (dd, *J* = 12.3, 3.6 Hz, 1H). 3.02 (dd, *J* = 7.2, 12.3 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.7, 168.2, 164.3, 158.2, 139.2, 136.4, 134.4, 131.2, 129.2, 128.9, 127.9, 123.8, 119.5, 93.3, 55.6, 46.2, 43.2, 39.2. IR (ATR diamond) 3289, 3028, 1710, 1540, 1181, 753 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{25}H_{22}N_4O_2S$ $[M]^+$: 442.5349. Found: 442.1434.

4g (3R,6S)-N-benzyl-4,6-dioxo-3-phenylhexahydro-1H-furo[3,4-c]pyrazole-1-carbothioamide



4e (0.269 mg, 1.00 mmol, 1 equiv), N-Phenyl maleimide (0.229 g, 2.30 mmol, 2.3 equiv), citric acid (0.050 g, 0.26 mmol, 26 mol%) was added to a vial which was sealed purged with argon. 20 ml of TFE was added and reaction ran in μw at 120°C for 4 hours to obtain a white precipitate which was isolated by column chromatography with 10% MeOH: CH_2Cl_2 solvent system. (0.180 g, 62%). TLC R_f = 0.34 (10% MeOH:CH_2Cl_2) ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.76 (s, 2H), 7.45-7.33 (m, 9H), 4.94 (s, 2H), 4.47 (s, 1H), 3.07-3.02 (m, 1H), 2.84-2.78 (m, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) 174.5, 172.4, 164.3, 158.1, 136.3, 134.5, 131.2, 129.3, 128.8, 128.2, 127.8, 123.1, 55.4, 46.2, 43.5, 40.5, 37.7. IR (ATR diamond) 3392, 3180, 1712, 1584, 1497, 1346, 1074, 860, 756 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{19}H_{17}N_3O_3S$ $[M]^+$: 367.0990. Found: 367.0789.

Appendix I

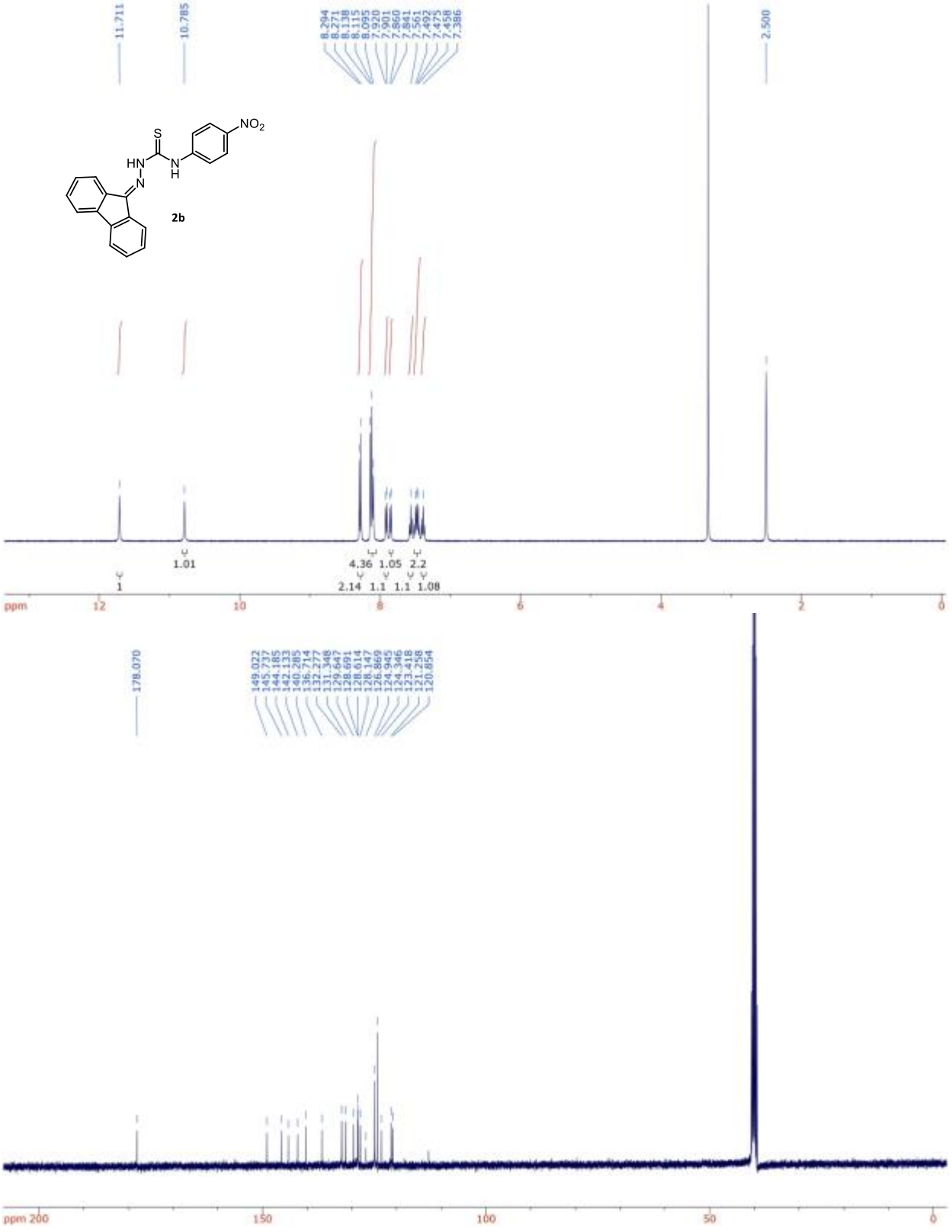
Claims to Original Research

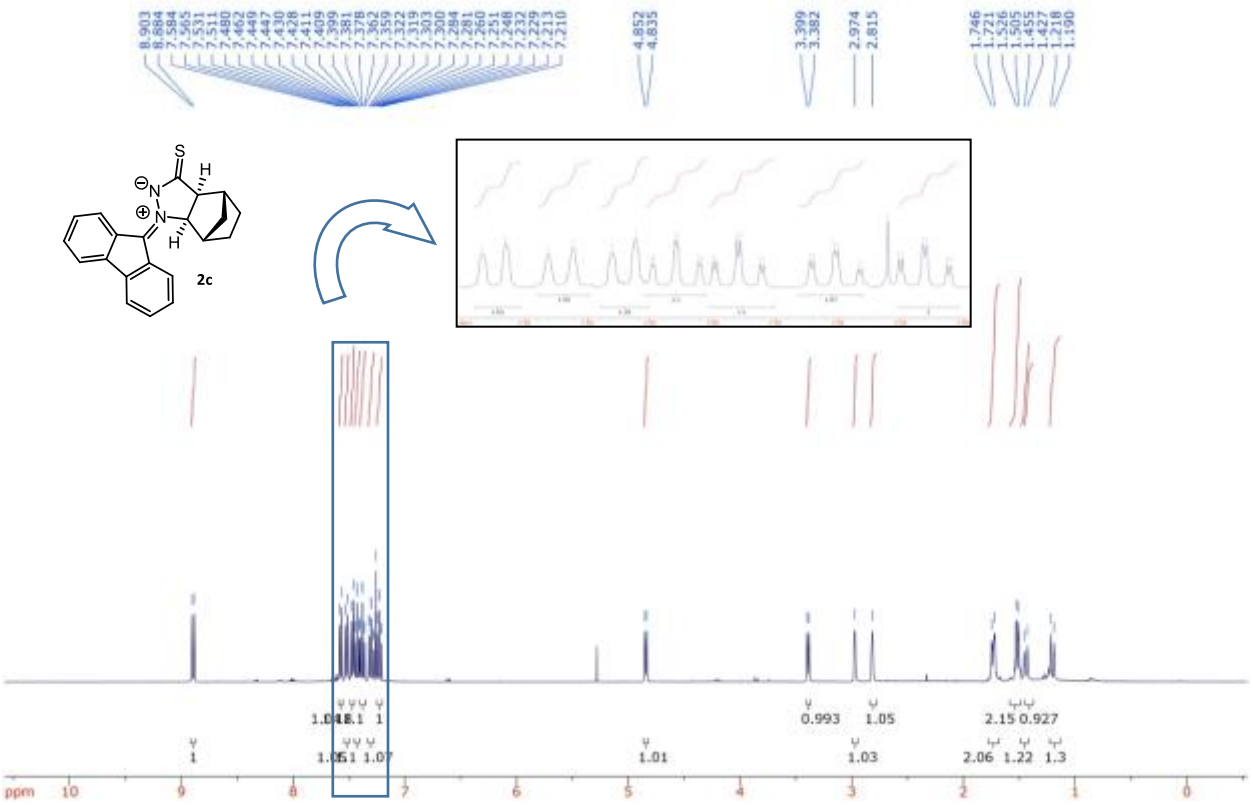
1) Synthesis of new azomethine imines derived from alkenes
2) Development of alkene and imine aminothiocarbonylation reactions
3) Synthesis of primary amino compounds from secondary amines (aza-Chugaev elimination reaction for secondary amines)
4) Development of cycloaddition reactions through acyclic azomethine imine intermediates

Publications and Presentations from This Work

1) *Synthesis of Cyclic Azomethine Imines by Cycloaddition Reactions of N-Isocyanates and N-Isothiocyanates,* Amanda Bongers, Indee Ranasinghe, Philippe Lemire, Alyssa Perozzo, Jean-François Vincent-Rocan, André M. Beauchemin, *Org. Lett.* **2016**, *18,* 3778.
2) Québec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (Waterloo 11/2016, Poster presentation): [3+2] Cycloadditions for the Synthesis of N-N-C=S Motifs, Amanda Bongers, Indee Ranasinghe, Philippe Lemire, Alyssa Perozzo, Jean-François Vincent-Rocan, André M. Beauchemin.
3) Synthesis Day Symposium (University of Ottawa, 06/2016, poster presentation): [3+2] Cycloadditions for the Synthesis of N-N-C=S Motifs, Amanda Bongers, Indee Ranasinghe, Philippe Lemire, Alyssa Perozzo, Jean-François Vincent-Rocan, André M. Beauchemin.

Appendix II – Spectra




8.903
8.884
7.584
7.565
7.531
7.511
7.480
7.462
7.449
7.447
7.430
7.428
7.411
7.409
7.399
7.381
7.378
7.362
7.359
7.322
7.319
7.303
7.300
7.284
7.281
7.260
7.251
7.248
7.232
7.229
7.213
7.210
4.852
4.835
3.399
3.382
2.974
2.815
1.746
1.721
1.526
1.505
1.455
1.427
1.218
1.190
S
H
N
N
H
2c
0.993
1.05
2.15
0.927
1
1.01
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1.3
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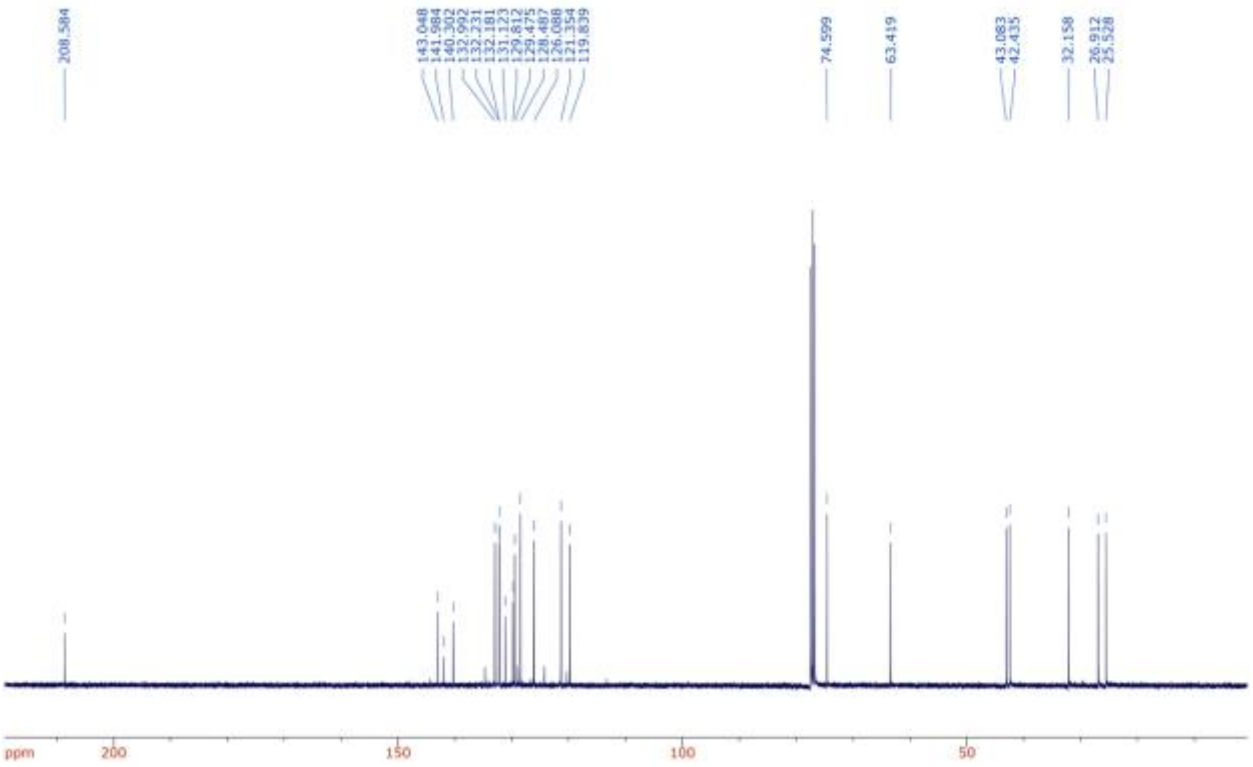
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126.088
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100
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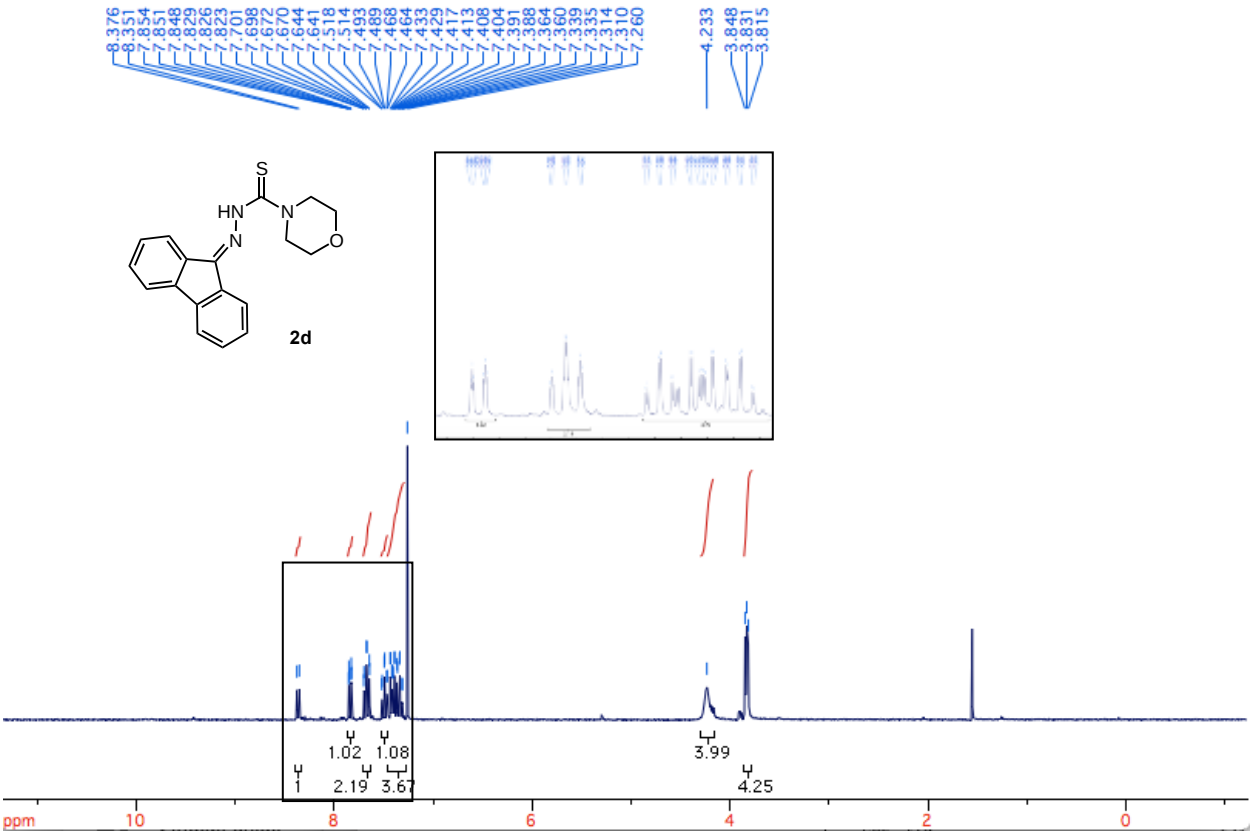
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7.670
7.644
7.641
7.518
7.514
7.493
7.489
7.468
7.464
7.433
7.429
7.417
7.413
7.408
7.404
7.391
7.388
7.364
7.360
7.339
7.335
7.314
7.310
7.260
4.233
3.848
3.831
3.815
S
HN
N
N
O
2d
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1.08
1
2.19
3.67
3.99
4.25
ppm
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8
6
4
2
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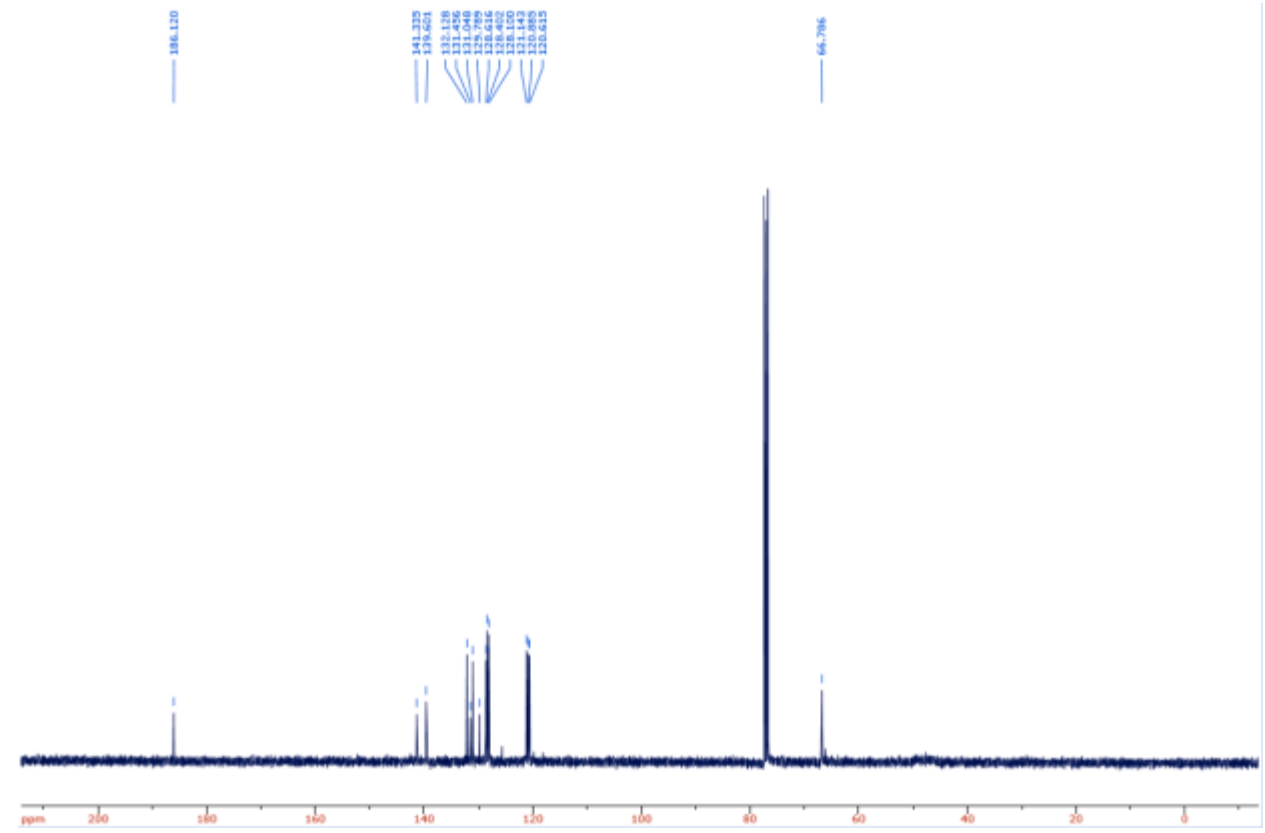
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141.225
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128.616
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120.615
66.796
ppm
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140
120
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80
60
40
20
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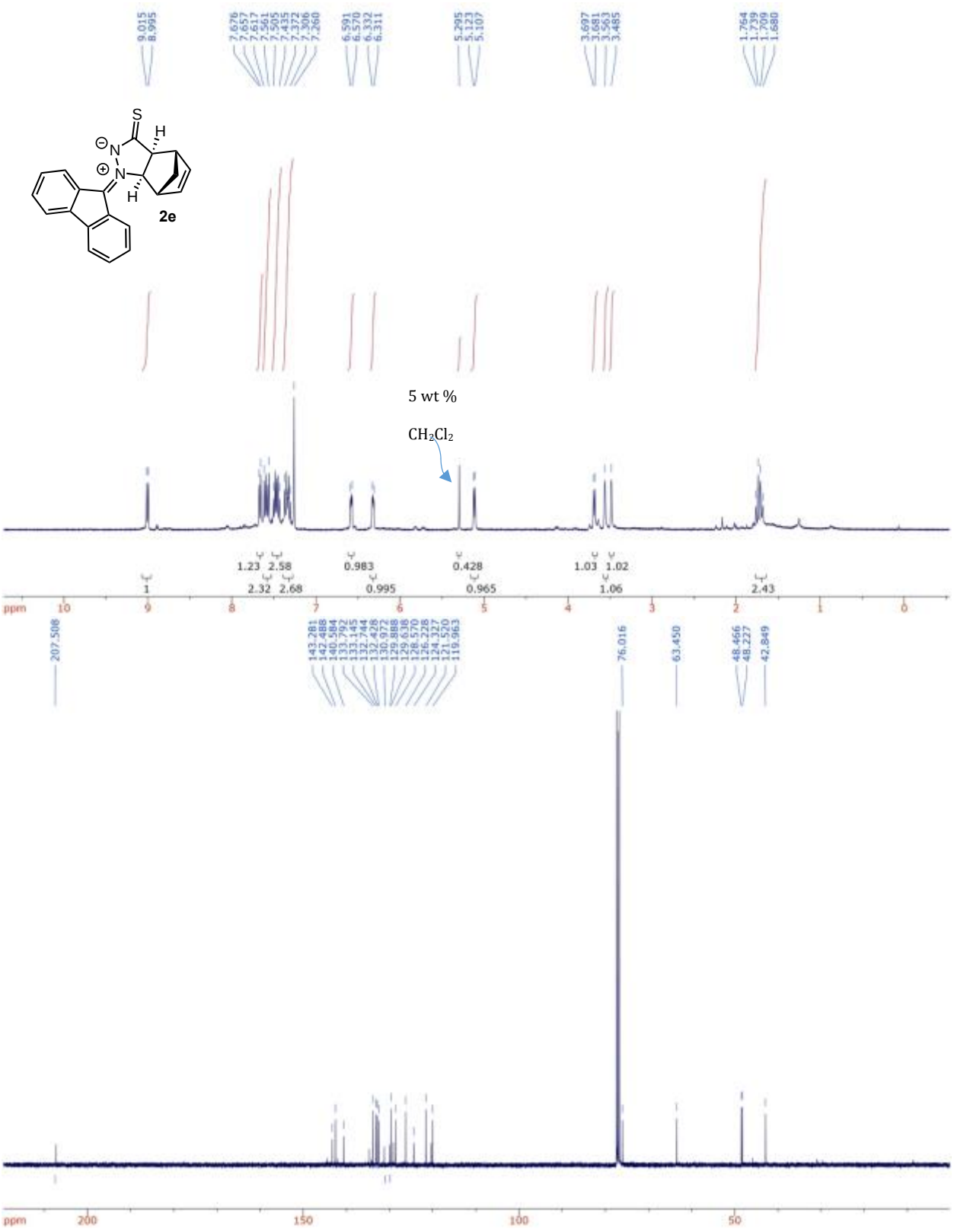
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8.995
7.676
7.657
7.617
7.561
7.505
7.435
7.372
7.306
7.260
6.591
6.570
6.332
6.311
5.295
5.123
5.107
3.697
3.681
3.563
3.485
1.764
1.739
1.709
1.680
S
H
N
N
H
2e
5 wt %
CH_2Cl_2
1.23
2.58
0.983
0.428
1.03
1.02
1
2.32
2.68
0.995
0.965
1.06
2.43
ppm
10
9
8
7
6
5
4
3
2
1
0
207.508
143.281
142.488
140.584
133.792
133.145
132.744
132.428
130.972
129.888
129.638
128.570
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150
100
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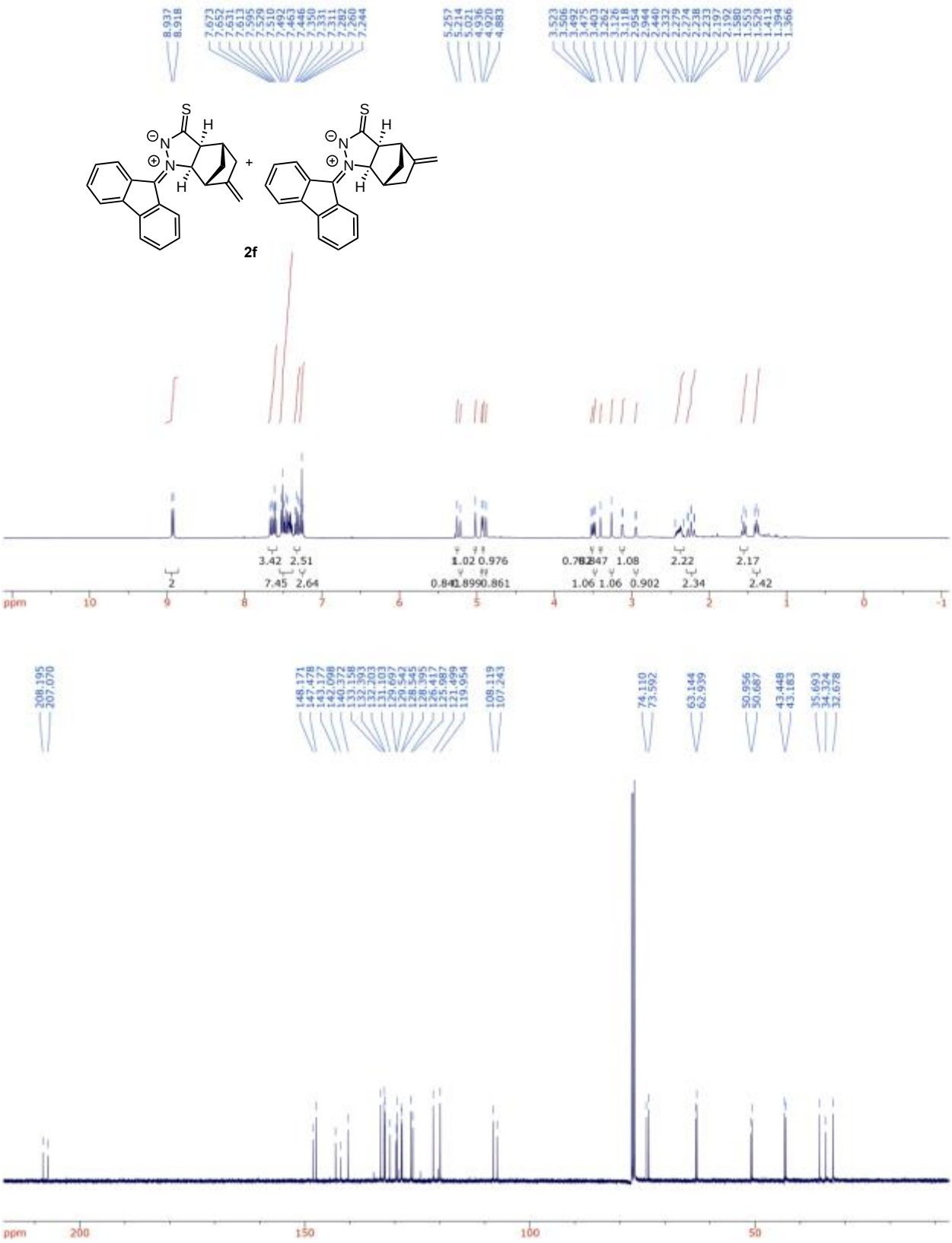
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7.673
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7.631
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7.595
7.529
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7.350
7.331
7.311
7.282
7.260
7.244
5.257
5.214
5.021
4.936
4.920
4.883
3.523
3.506
3.492
3.475
3.403
3.262
3.126
3.118
2.954
2.944
2.440
2.332
2.279
2.274
2.238
2.233
2.197
2.192
1.580
1.553
1.529
1.413
1.394
1.366
S
H
N
N
H
+
2f
3.42
2.51
1.02
0.976
1.08
2.22
2.17
2
7.45
2.64
1.06
1.06
0.902
2.34
2.42
ppm
208.195
207.070
148.171
147.478
143.177
142.098
140.372
133.158
132.393
132.203
131.103
129.697
129.542
128.545
128.395
126.417
125.987
121.499
119.954
108.119
107.243
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73.592
63.144
62.939
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50.687
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43.183
35.693
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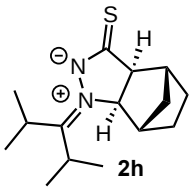
32.678
ppm


S
H
N
N
H

2h

7.260
4.213
4.189
3.140
3.116
3.056
2.968
2.906
2.398
1.612
1.412
1.389
1.367
1.298
1.275
1.238
1.216
1.172
1.135
1.03
1.92
2.23
5.24
1.36
1
1.07
1.01
6
3.76
ppm 10
9
8
7
6
5
4
3
2
1
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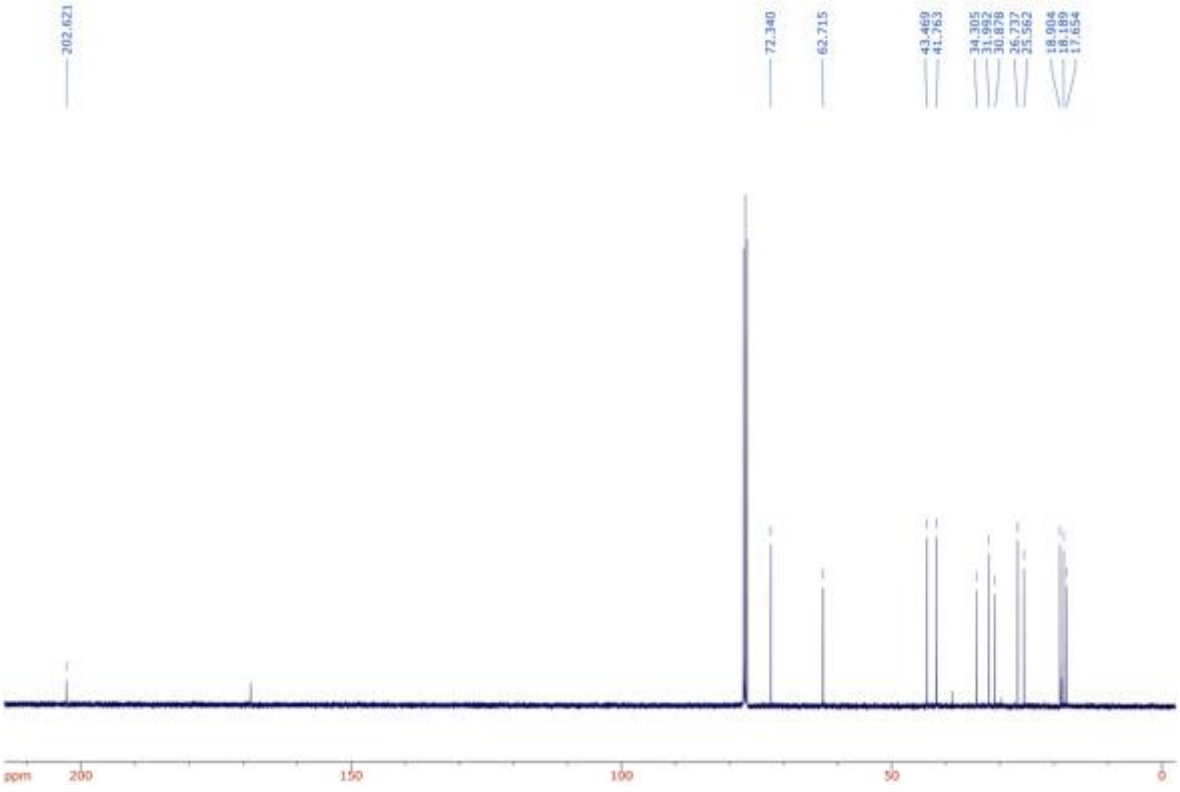
202.621
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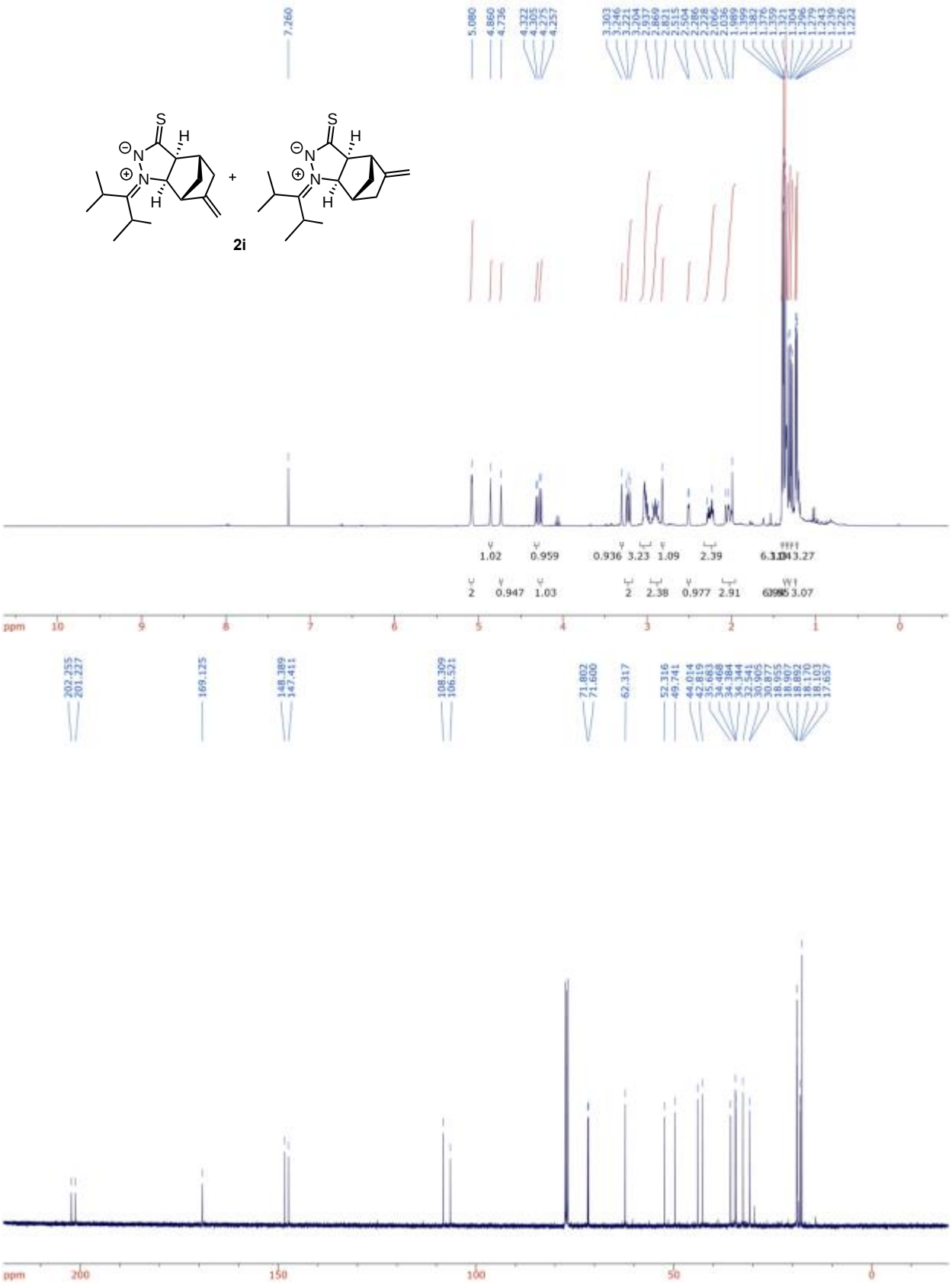
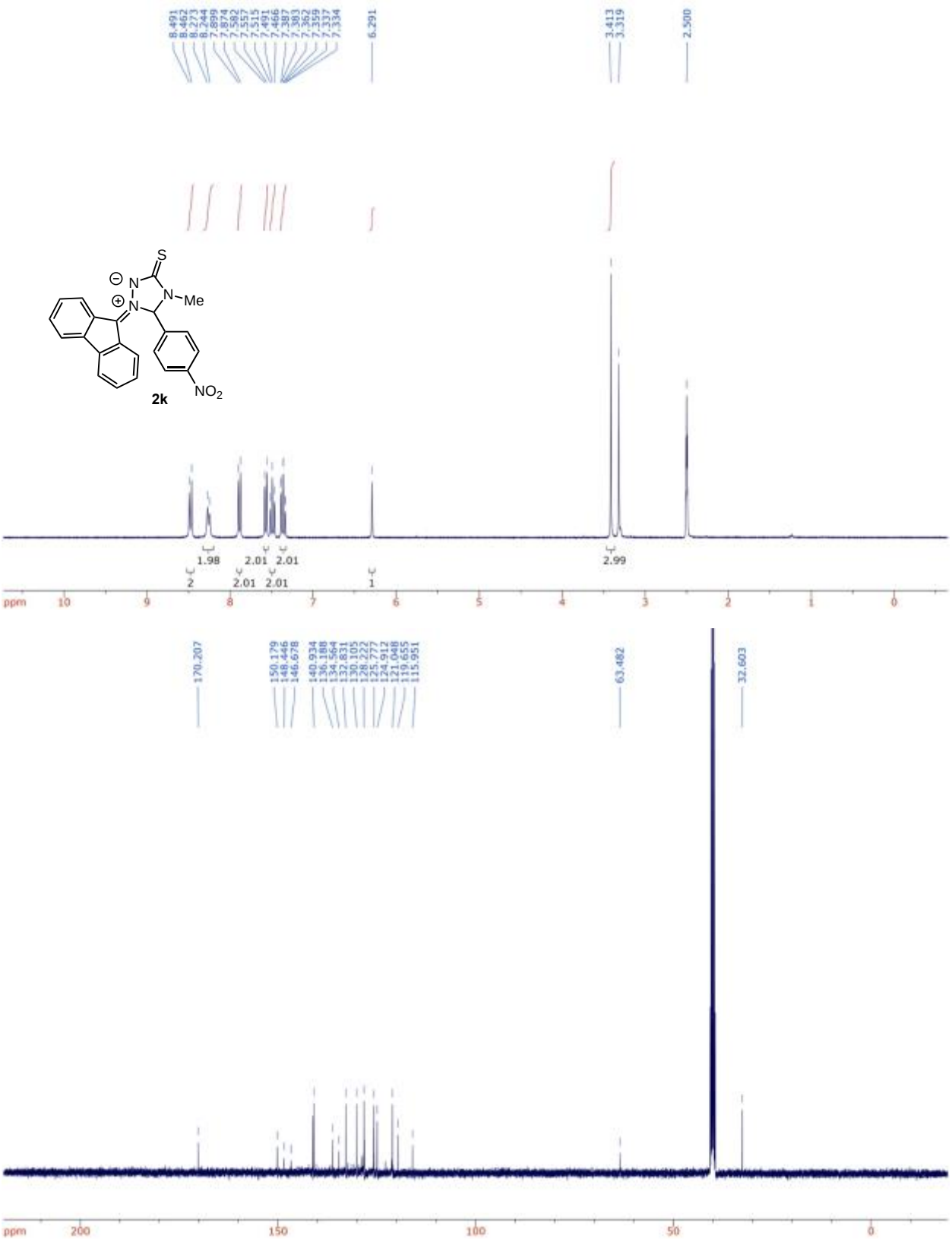
62.715
43.469
41.763
34.305
31.892
30.978
26.727
25.562
18.904
18.189
17.654
ppm
200
150
100
50
0


2i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8.462
8.273
8.244
7.899
7.874
7.582
7.557
7.515
7.491
7.466
7.387
7.383
7.362
7.359
7.337
7.334
6.291
3.413
3.319
2.500
S
N
N
Me
N
NO2
2k
1.98
2.01
2.01
2.99
2
2.01
2.01
1
ppm
10
9
8
7
6
5
4
3
2
1
0
170.207
150.179
148.446
146.678
140.934
136.188
134.564
132.831
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124.912
121.048
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50
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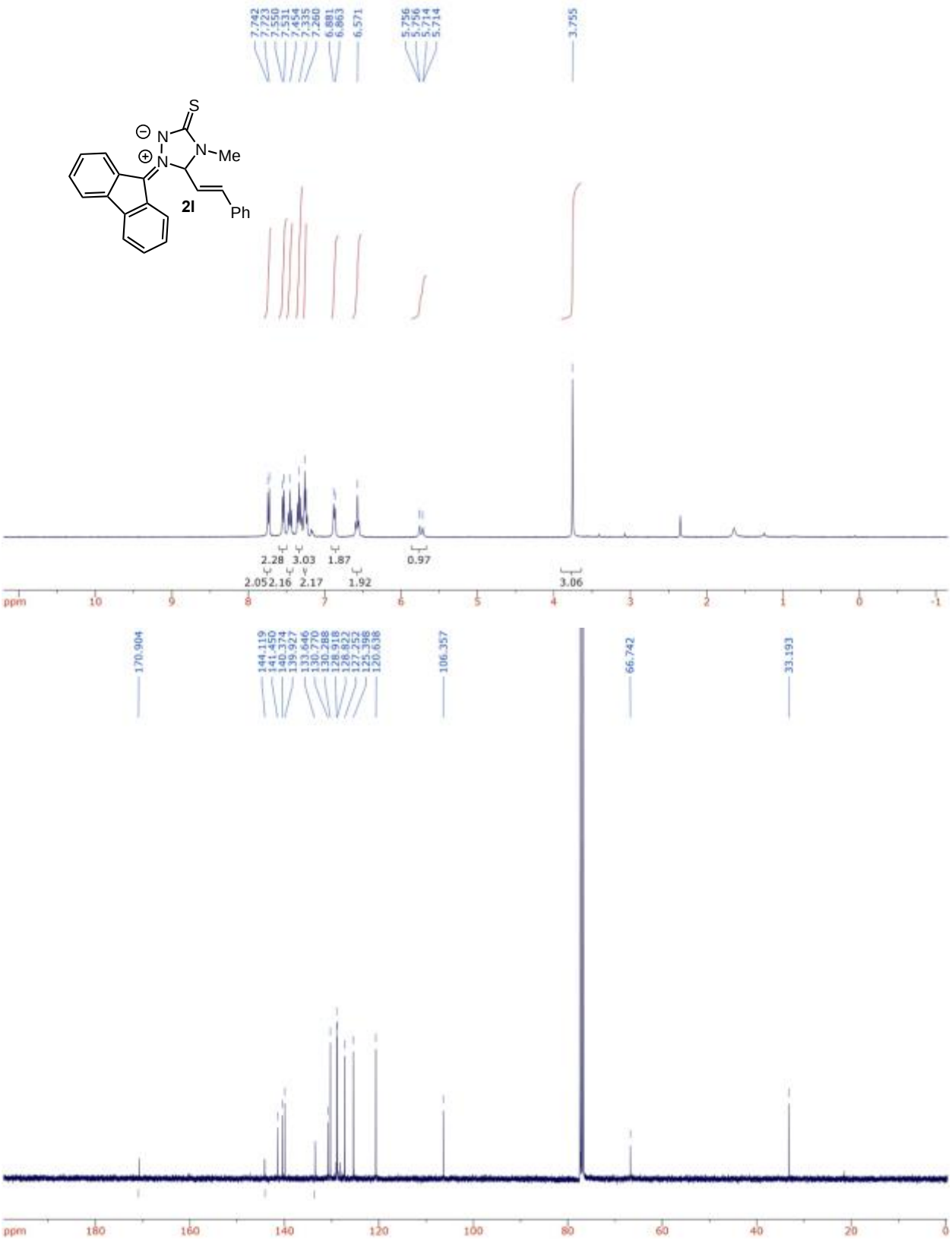
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7.723
7.550
7.531
7.454
7.335
7.260
6.881
6.863
6.571
5.756
5.756
5.714
5.714
3.755
S
N
N
N
Me
Ph
2l
2.28
3.03
1.87
0.97
2.05
2.16
2.17
1.92
3.06
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
170.904
144.119
141.450
140.374
139.927
133.646
130.770
130.288
128.918
128.822
127.592
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106.357
66.742
33.193
ppm
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140
120
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20
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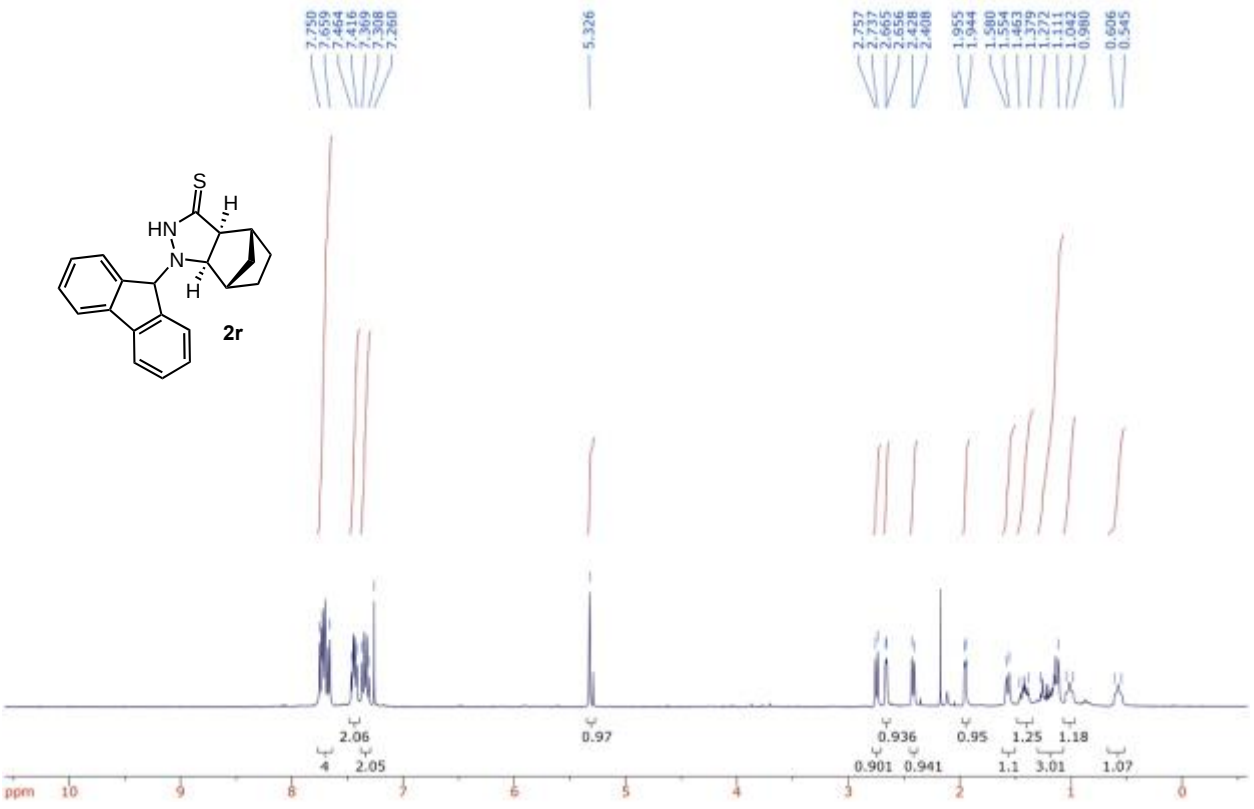
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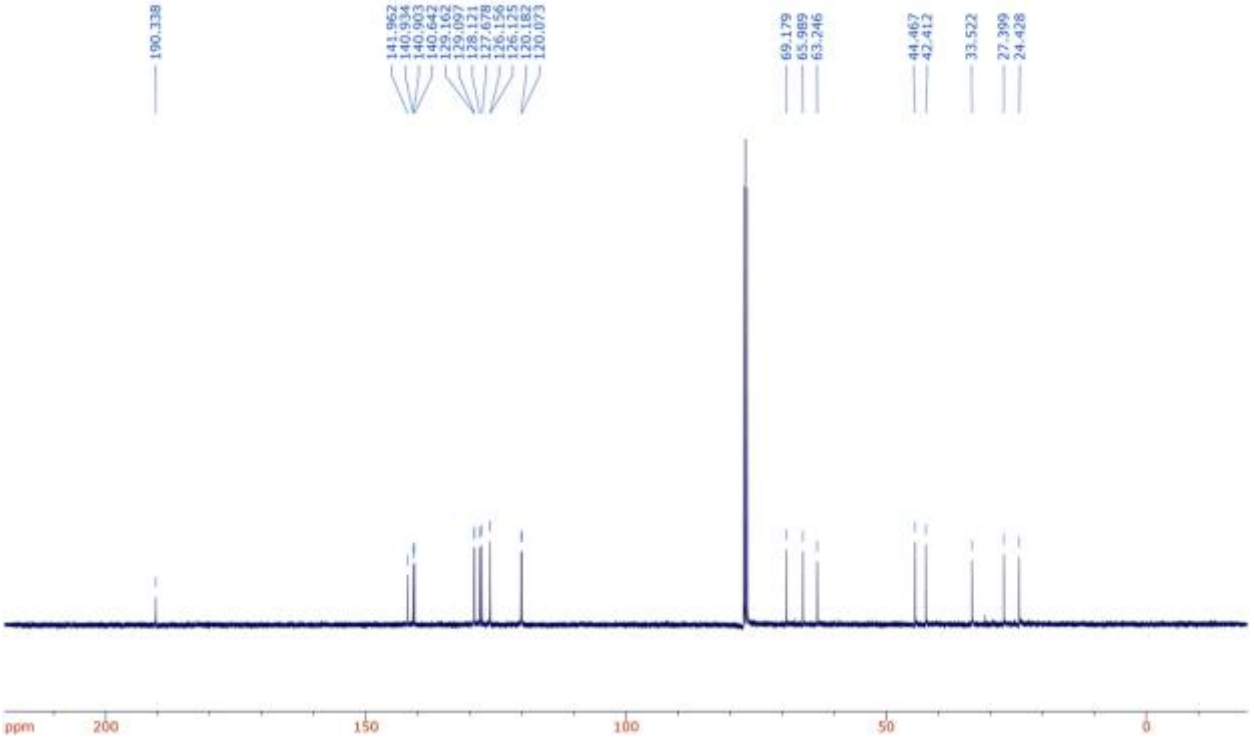
7.659
7.464
7.416
7.369
7.308
7.260
5.326
2.757
2.737
2.665
2.656
2.428
2.408
1.955
1.944
1.580
1.554
1.463
1.379
1.272
1.111
1.042
0.980
0.606
0.545
S
H
HN
N
H
2r
2.06
4
2.05
0.97
0.936
0.901
0.941
0.95
1.1
1.25
3.01
1.18
1.07
ppm
10
9
8
7
6
5
4
3
2
1
0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140.903
140.642
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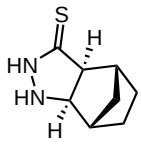
129.097
128.121
127.678
126.156
126.125
120.182
120.073
69.179
65.989
63.246
44.467
42.412
33.522
27.399
24.428
ppm
200
150
100
50
0


S
H
HN
HN
H

2x

7.260
3.742
3.715
3.126
3.099
2.785
2.773
2.355
2.342
1.676
1.622
1.582
1.569
1.544
1.503
1.492
1.475
1.458
1.433
1.397
1.356
1.316
1.315
1.269
1.250
1.214
1.165
1.081
0.942
0.91
0.918
0.916
2.13
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1.09
1.14
1.13
ppm 10
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8
7
6
5
4
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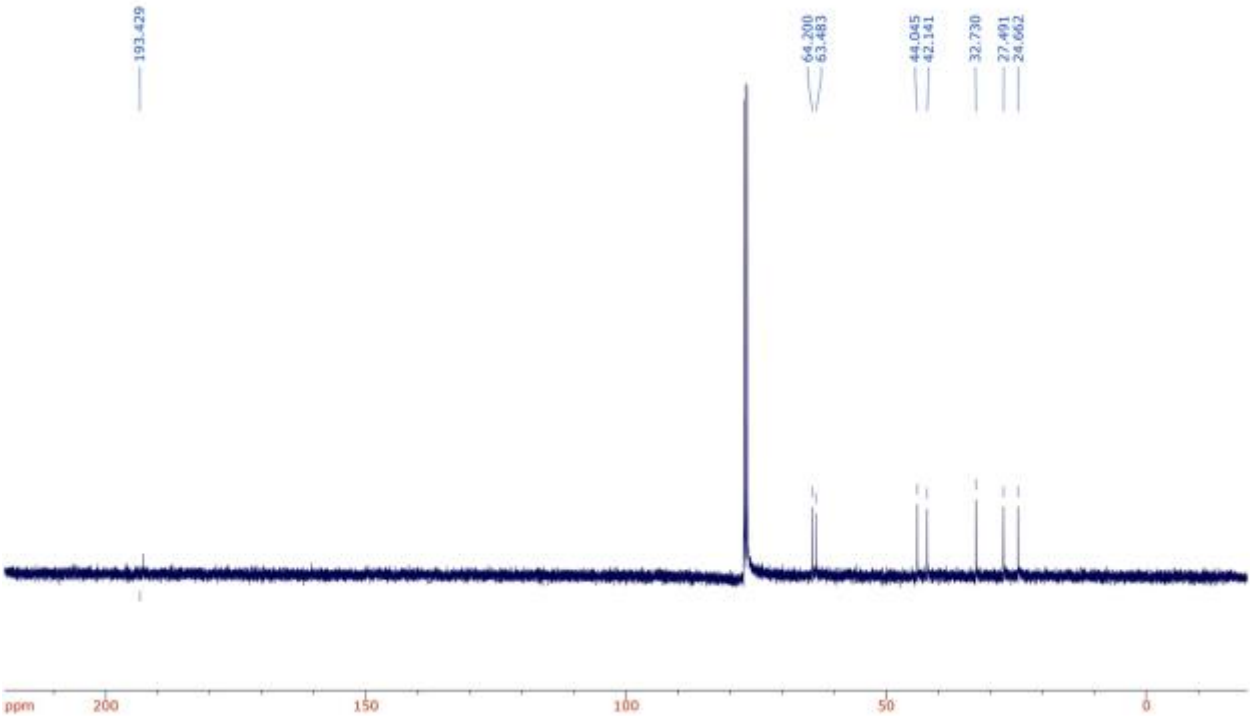
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24.662
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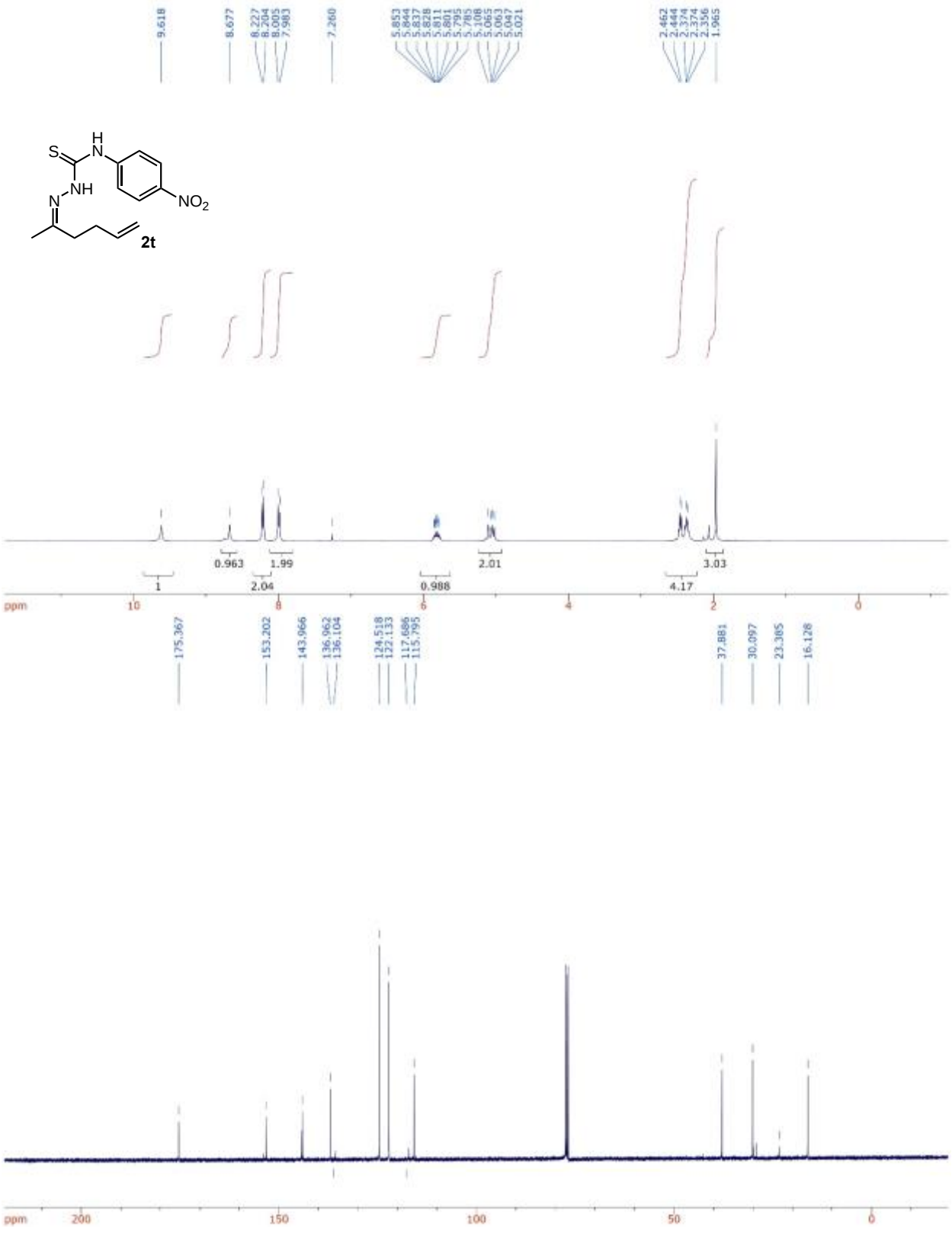
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7.260
5.853
5.844
5.837
5.828
5.811
5.801
5.795
5.785
5.108
5.065
5.063
5.047
5.021
2.462
2.444
2.374
2.374
2.356
1.965
S
H
N
NH
N
NO2
2t
0.963
1.99
2.01
3.03
1
2.04
0.988
4.17
ppm
10
8
6
4
2
0
175.367
153.202
143.966
136.962
136.104
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115.795
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100
50
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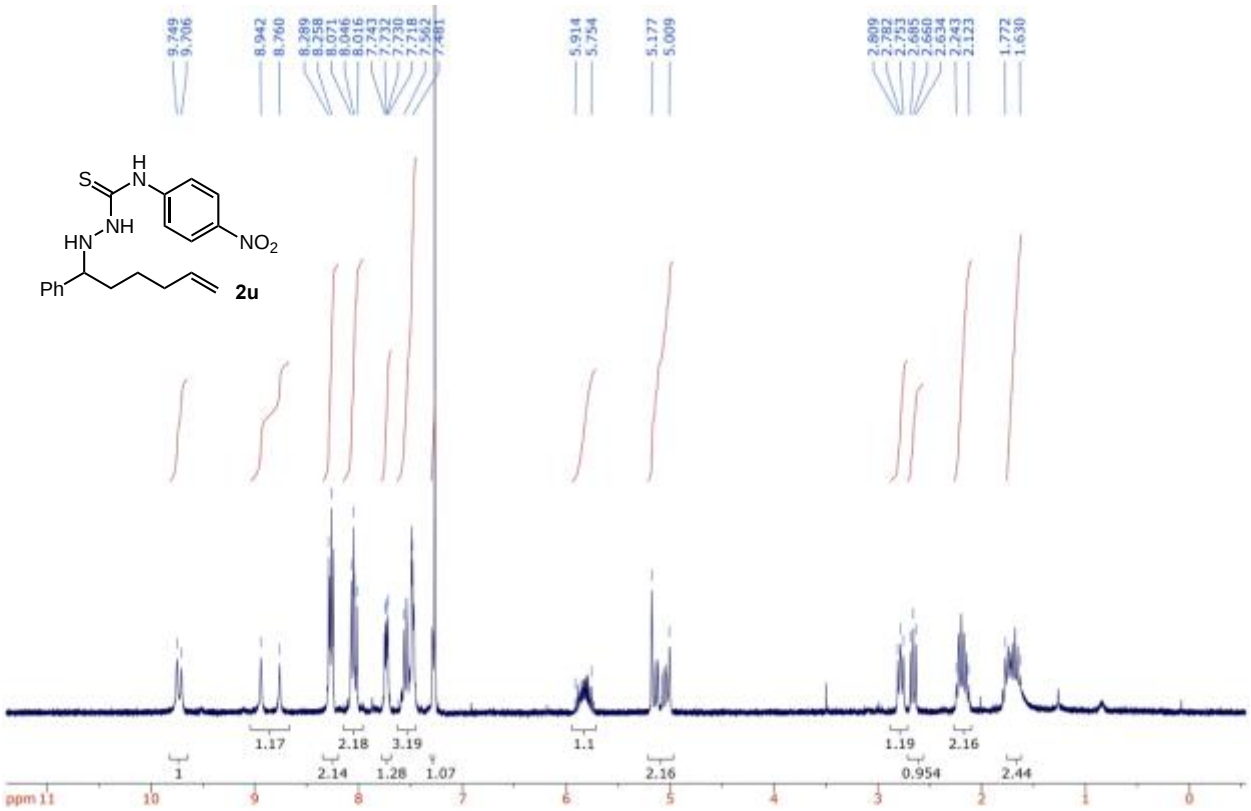
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8.760
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8.258
8.071
8.046
8.016
7.743
7.732
7.730
7.718
7.702
7.481
5.914
5.754
5.177
5.009
2.809
2.782
2.751
2.685
2.660
2.634
2.243
2.123
1.772
1.630
S
H
N
NH
HN
NO2
Ph
2u
1.17
2.18
3.19
1.1
1.19
2.16
1
2.14
1.28
1.07
2.16
0.954
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ppm 11
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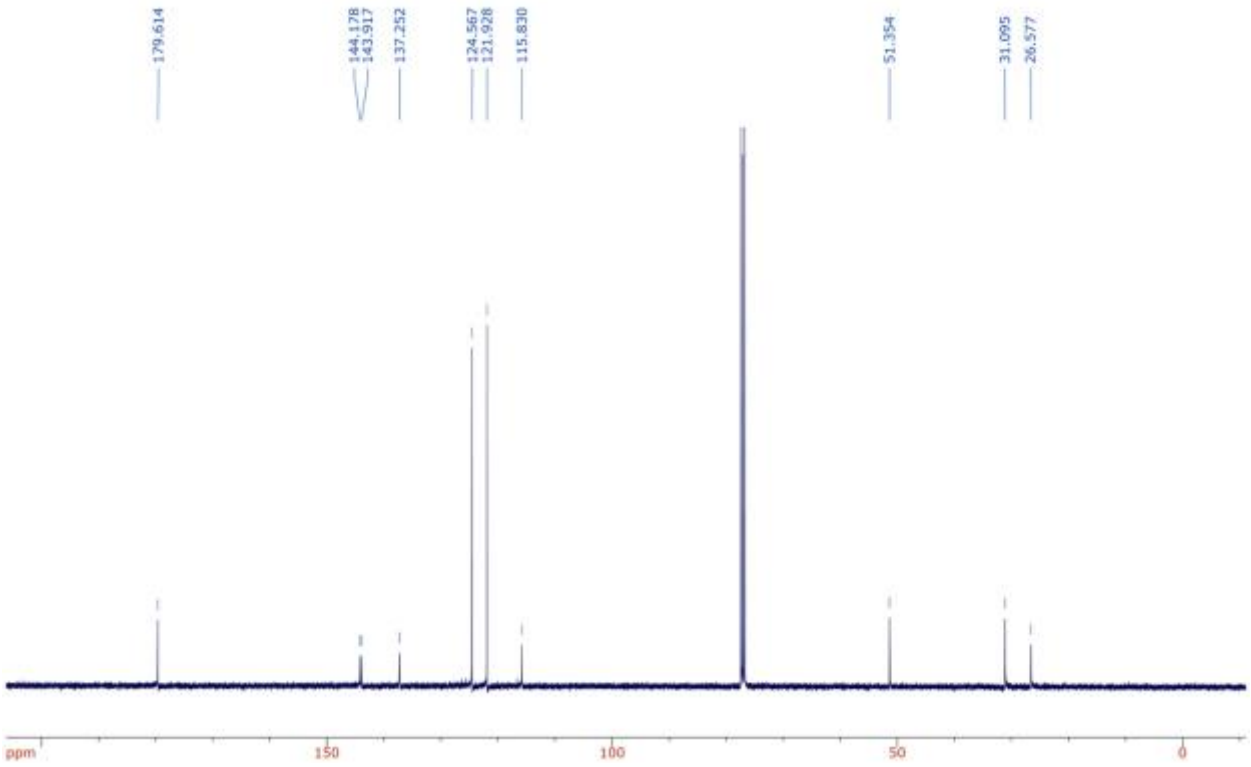
7
6
5
4
3
2
1
0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137.252
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121.928
115.830
51.354
31.095
26.577
ppm
150
100
50
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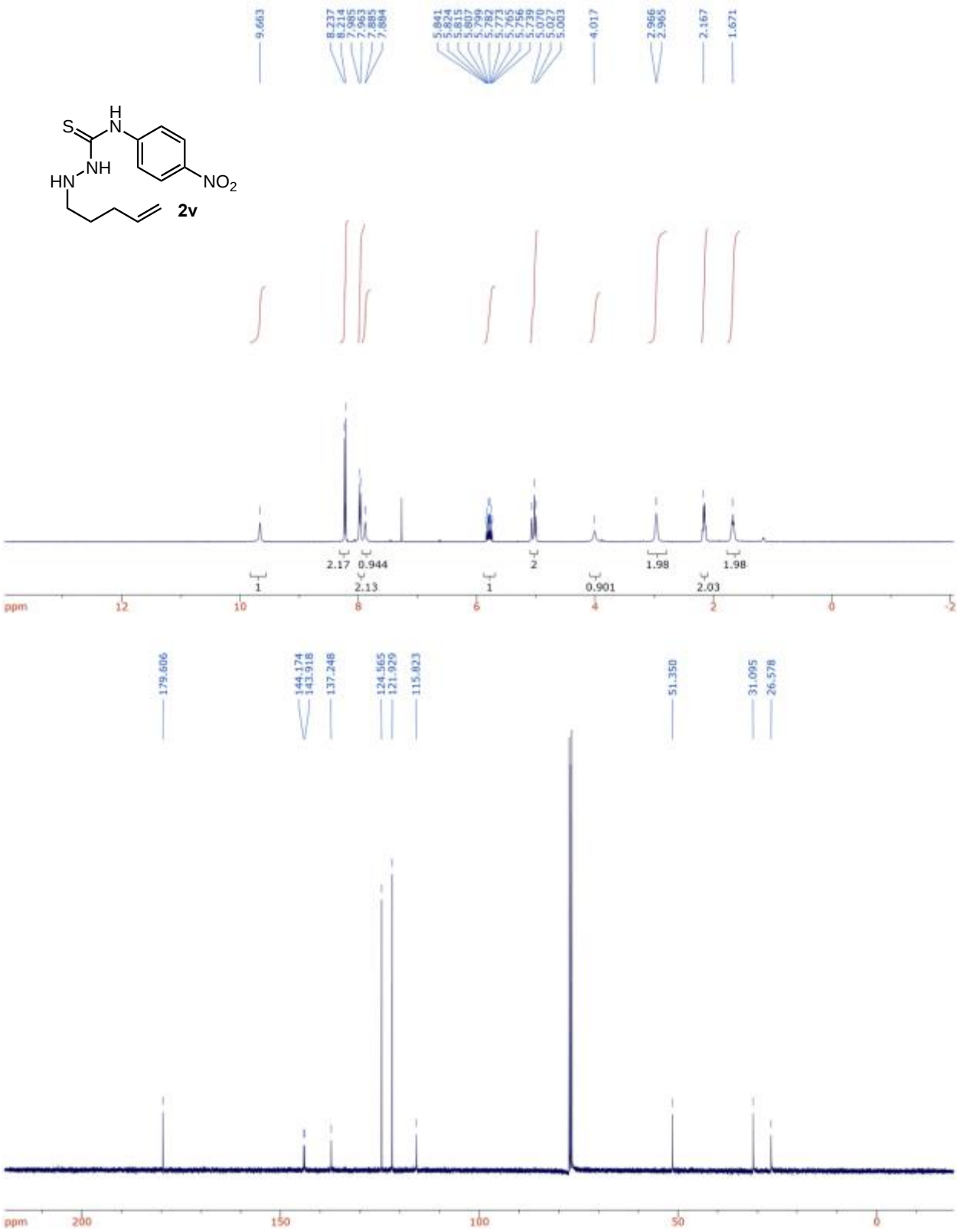
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7.963
7.885
7.884
5.841
5.824
5.815
5.807
5.799
5.782
5.773
5.765
5.756
5.739
5.070
5.027
5.003
4.017
2.966
2.965
2.167
1.671
S
H
N
NH
HN
NO2
2v
2.17
0.944
2
1.98
1.98
1
2.13
1
0.901
2.03
ppm
12
10
8
6
4
2
0
-2
179.606
144.174
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121.929
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100
50
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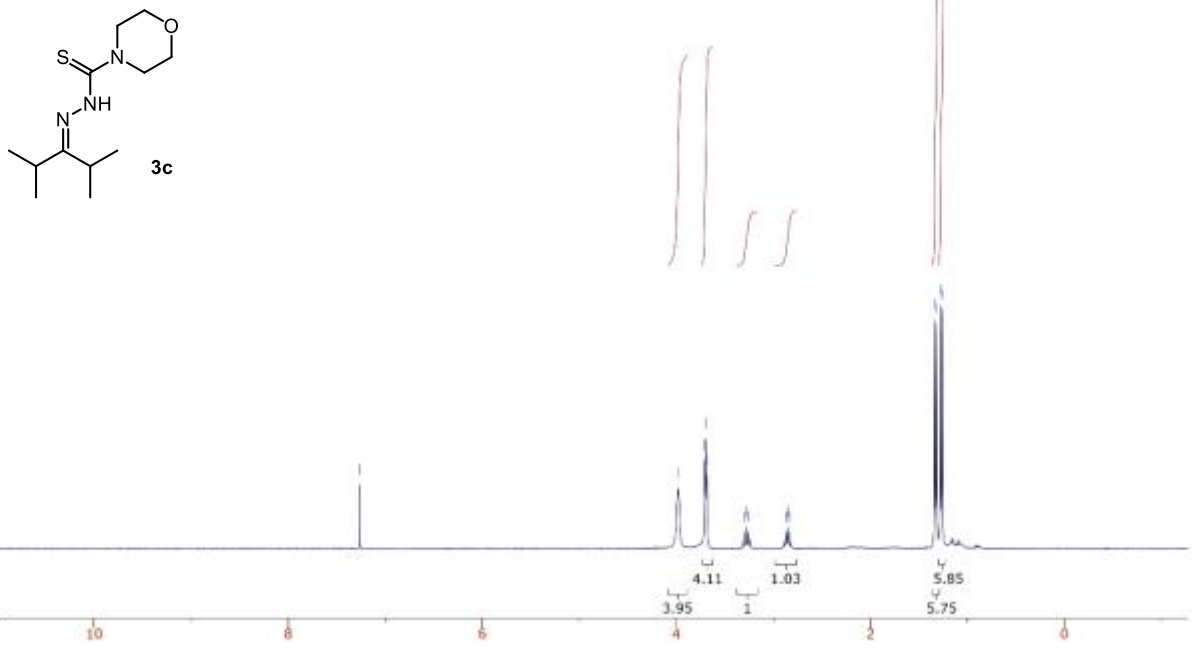
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3.697
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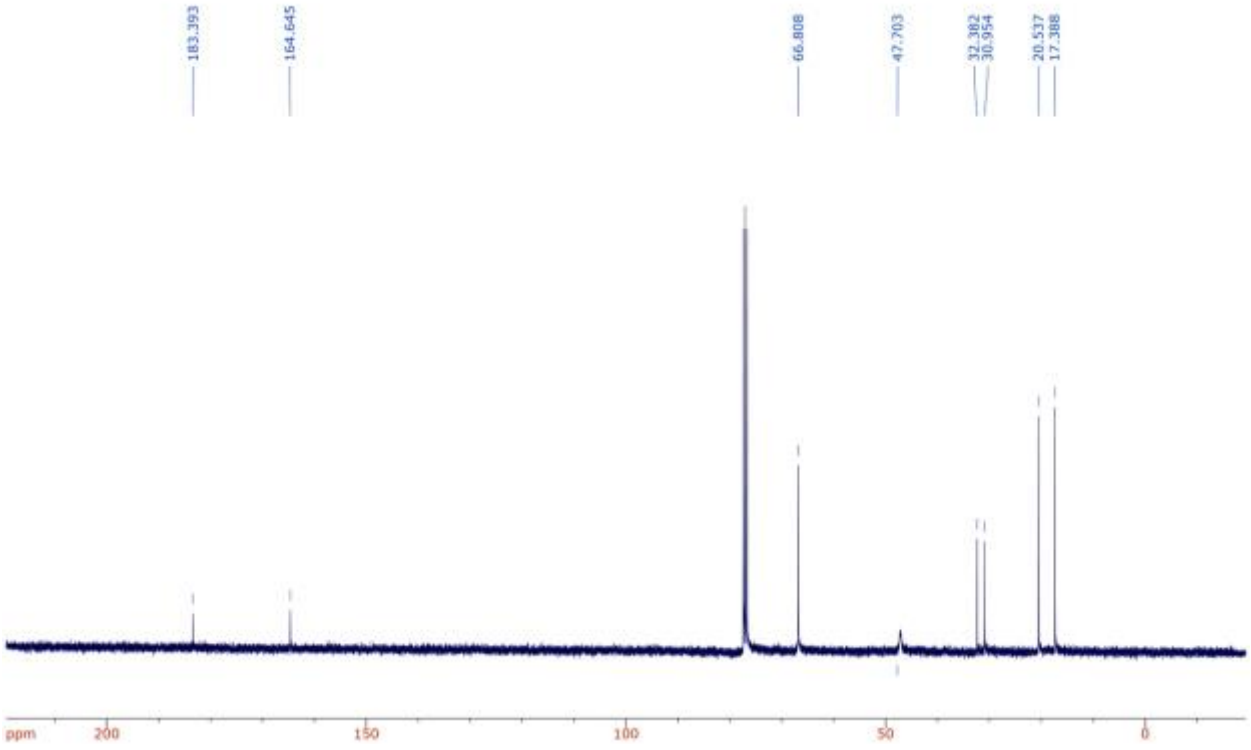
3.257
2.871
2.854
2.836
1.337
1.320
1.277
1.259
4.11
1.03
5.85
3.95
1
5.75
ppm
10
8
6
4
2
0

S
N
O
NH
N

3c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32.382
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17.388
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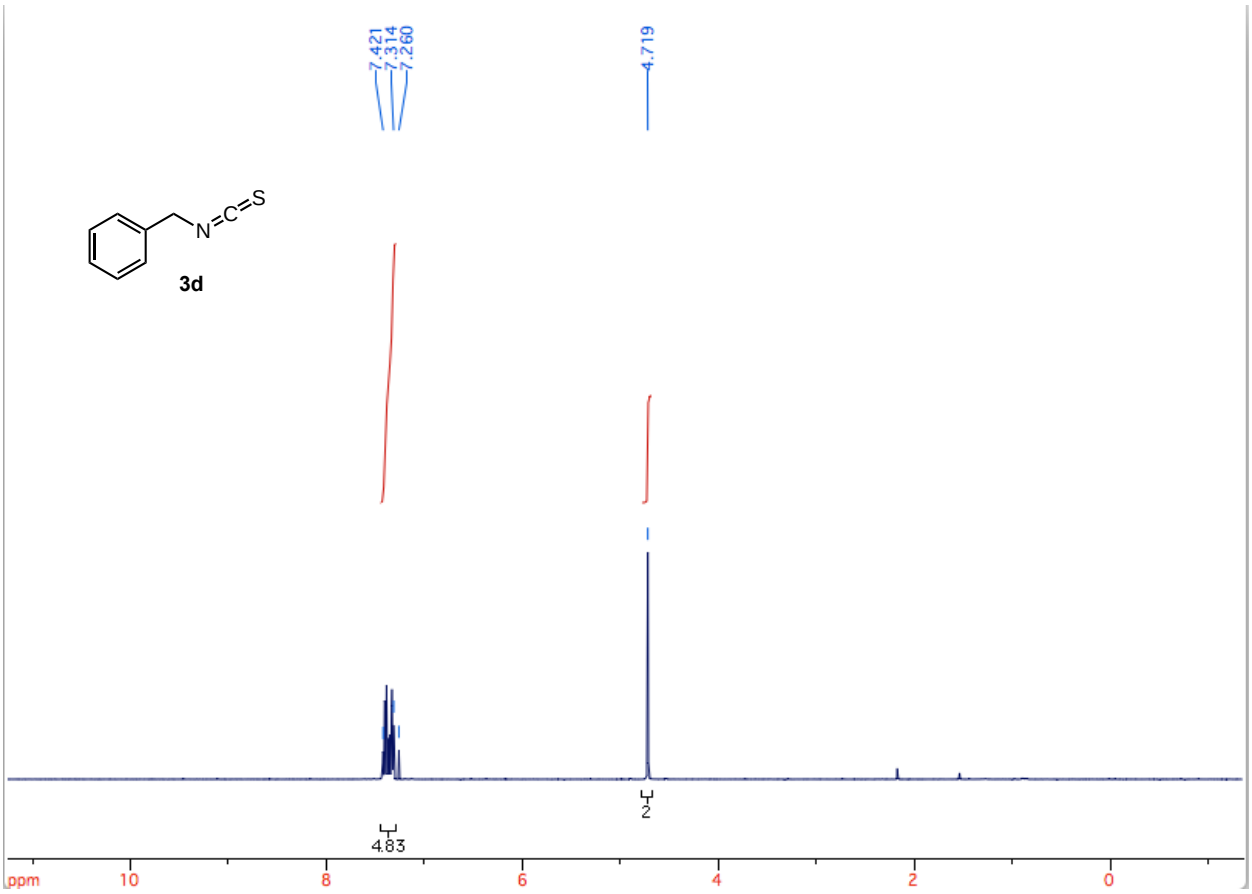
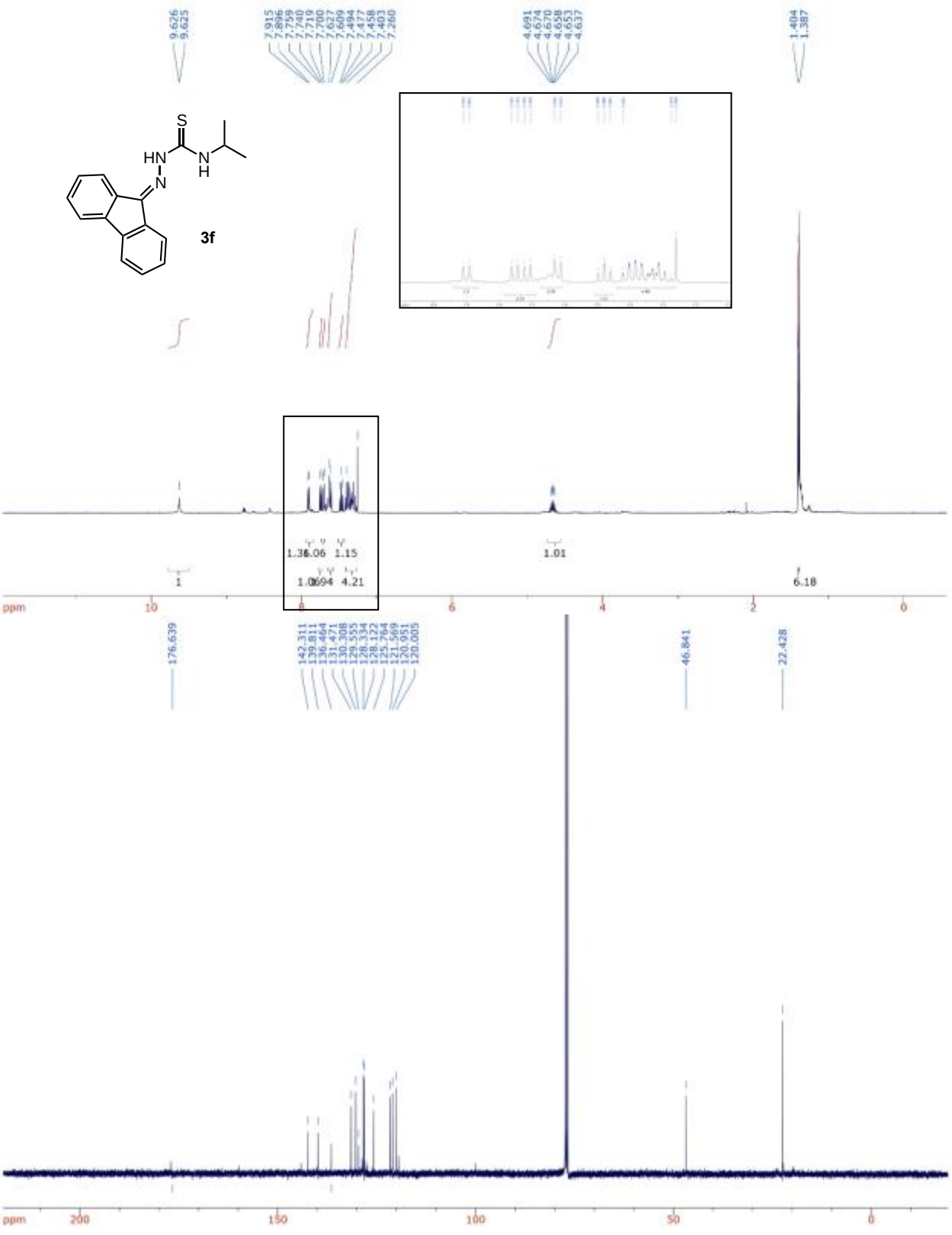
150
100
50
0


7.421
7.314
7.260
4.719
N=C=S
3d
4.83
2
ppm
10
8
6
4
2
0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9.625
7.915
7.896
7.759
7.740
7.719
7.700
7.627
7.609
7.494
7.477
7.458
7.403
7.260
4.691
4.674
4.670
4.658
4.653
4.637
1.404
1.387
S
HN
N
N
H
3f
1.36
1.06
1.15
1.01
1
1.08
0.94
4.21
6.18
ppm
10
8
6
4
2
0
176.639
142.311
139.811
139.464
131.471
130.308
129.555
128.334
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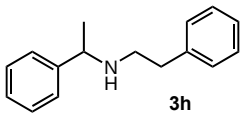
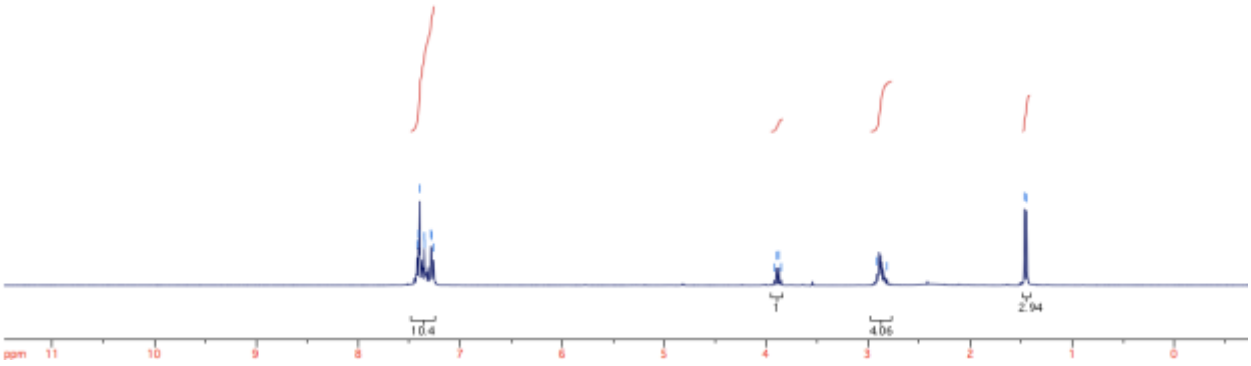
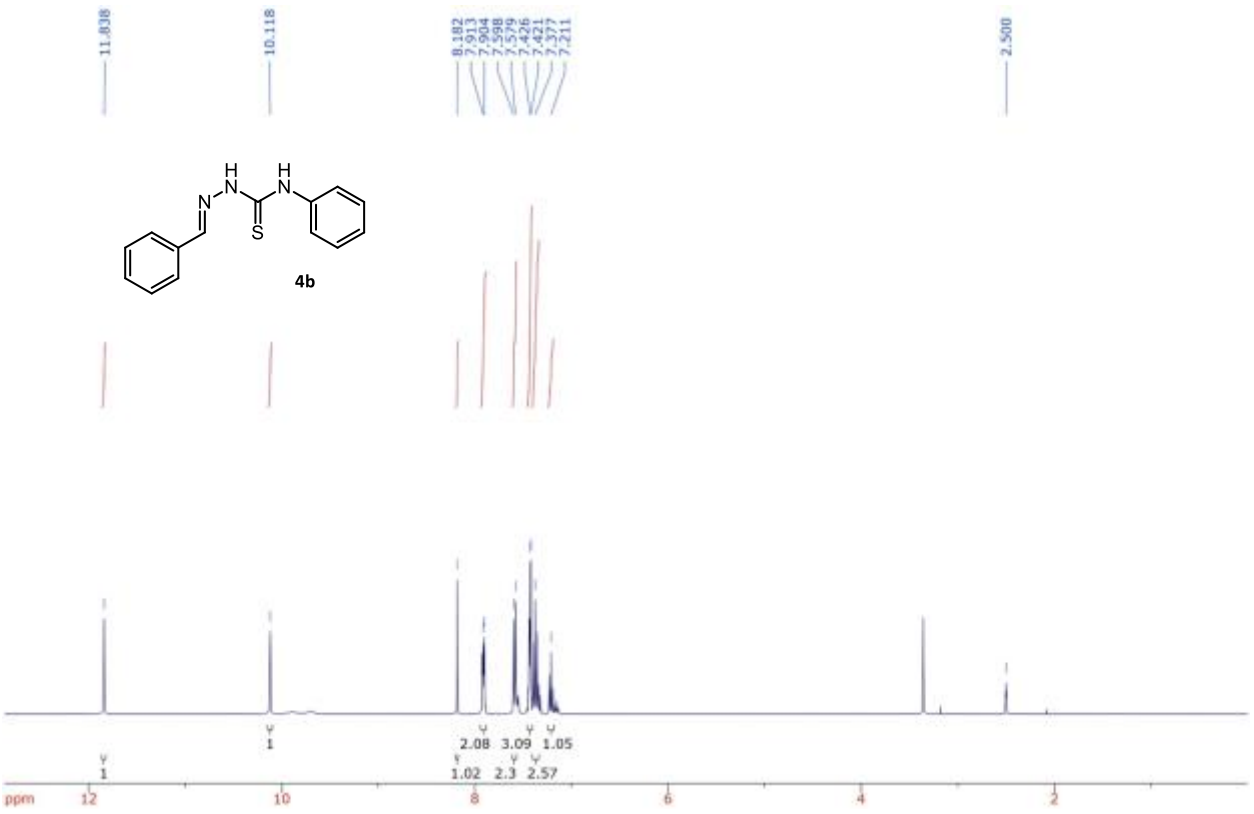
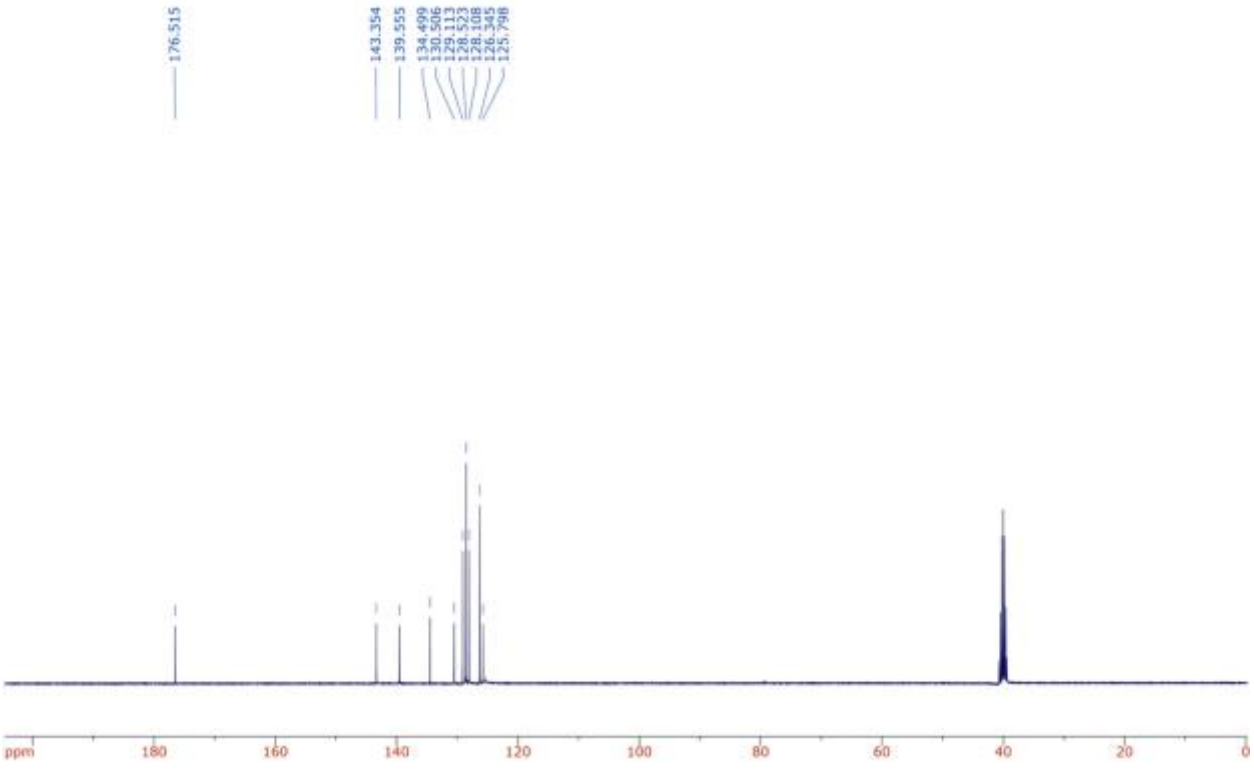
125.764
121.569
120.951
120.005
46.841
22.428
ppm
200
150
100
50
0



3h




11.838
10.118
8.182
7.913
7.904
7.598
7.579
7.426
7.421
7.377
7.211
2.500
4b
1
2.08
3.09
1.05
1
1.02
2.3
2.57
ppm
12
10
8
6
4
2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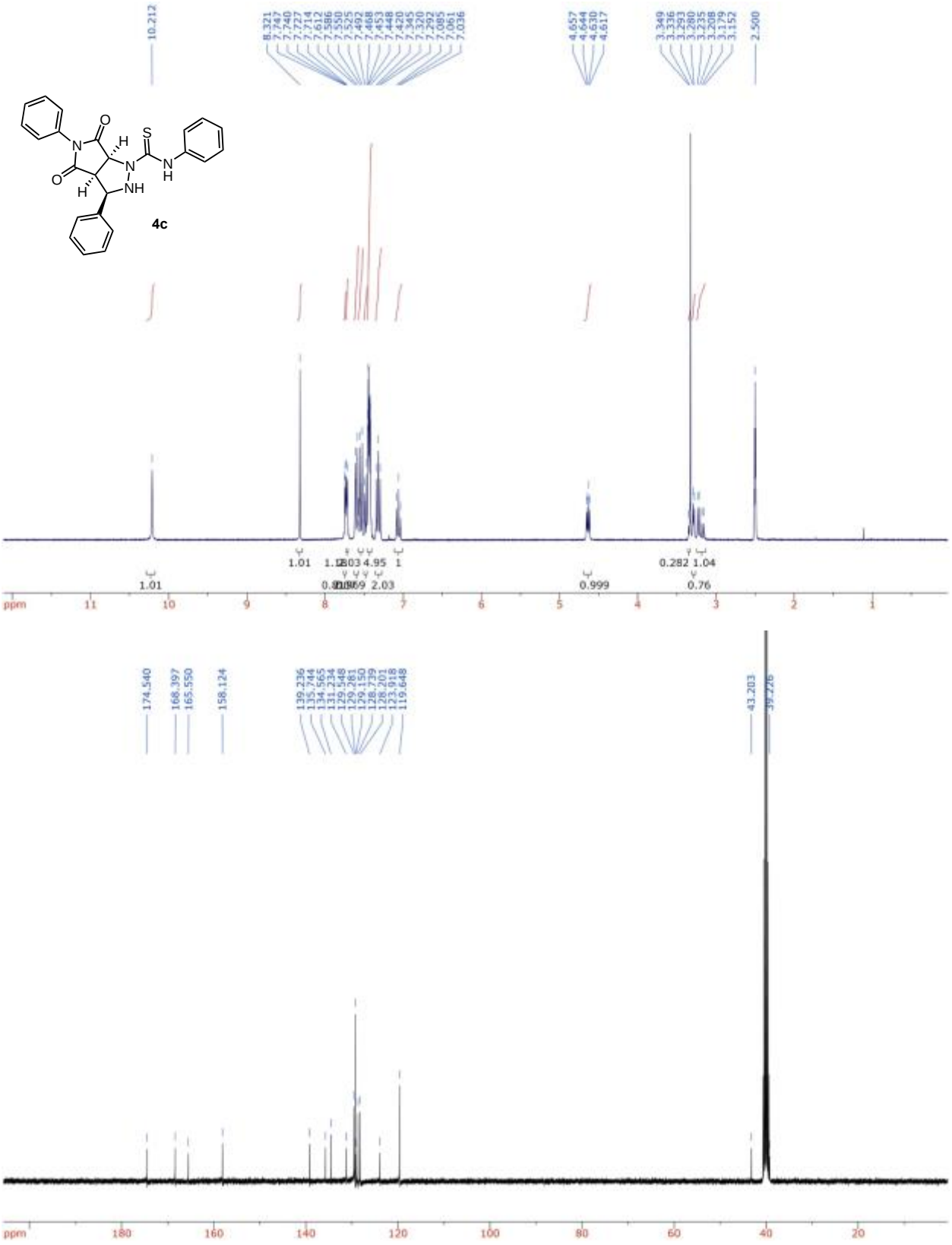
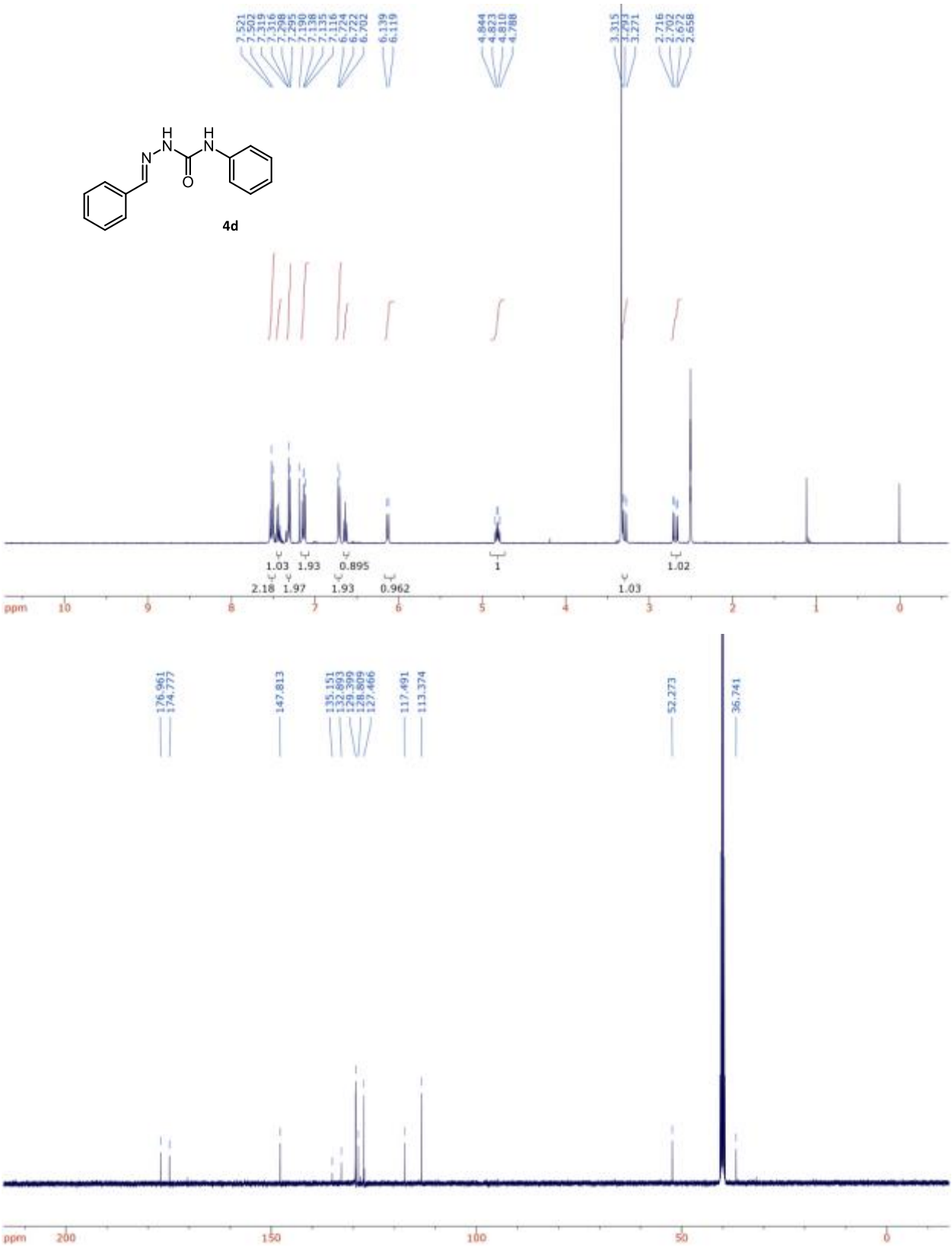
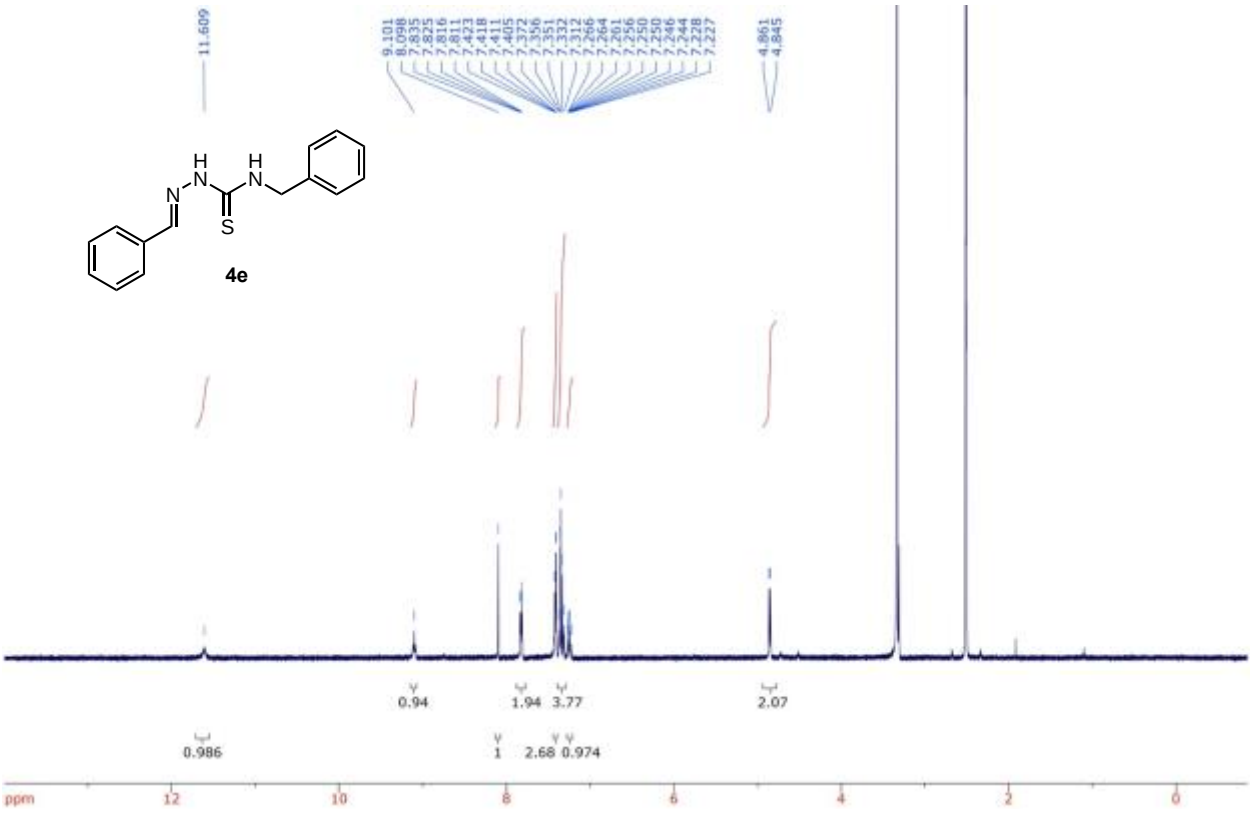
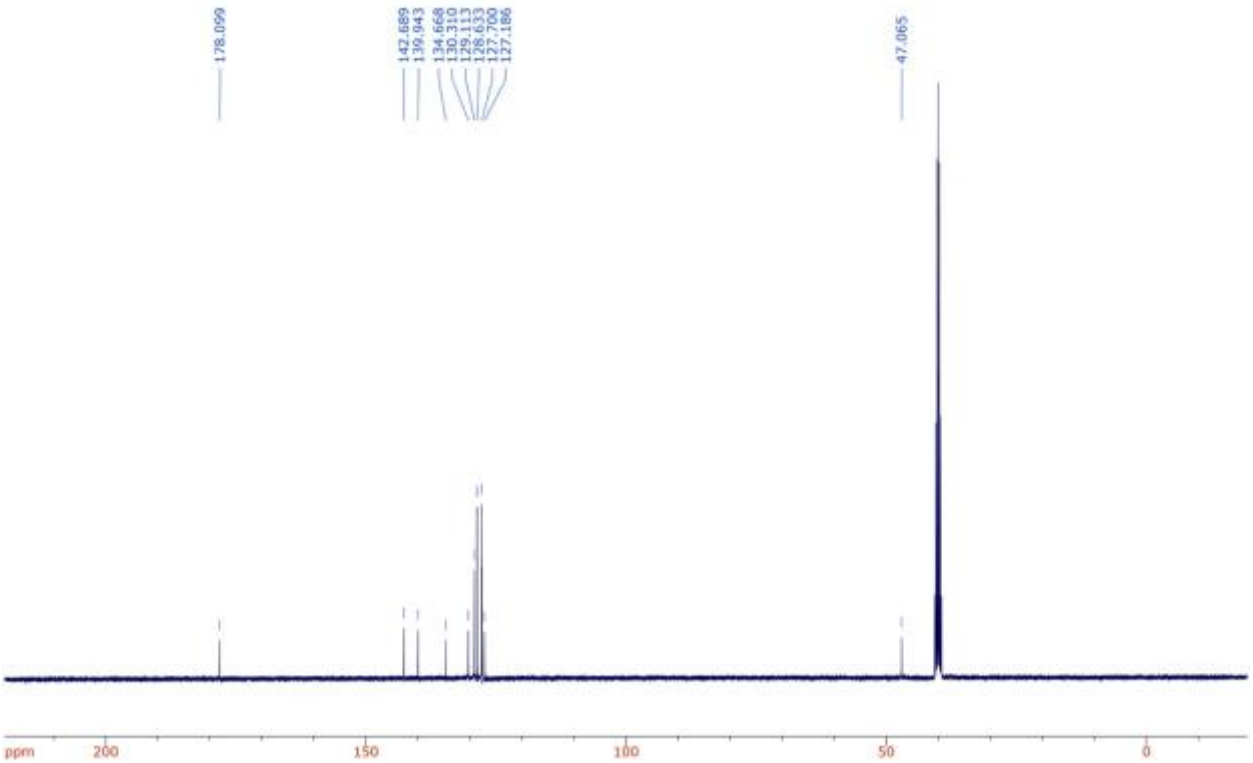
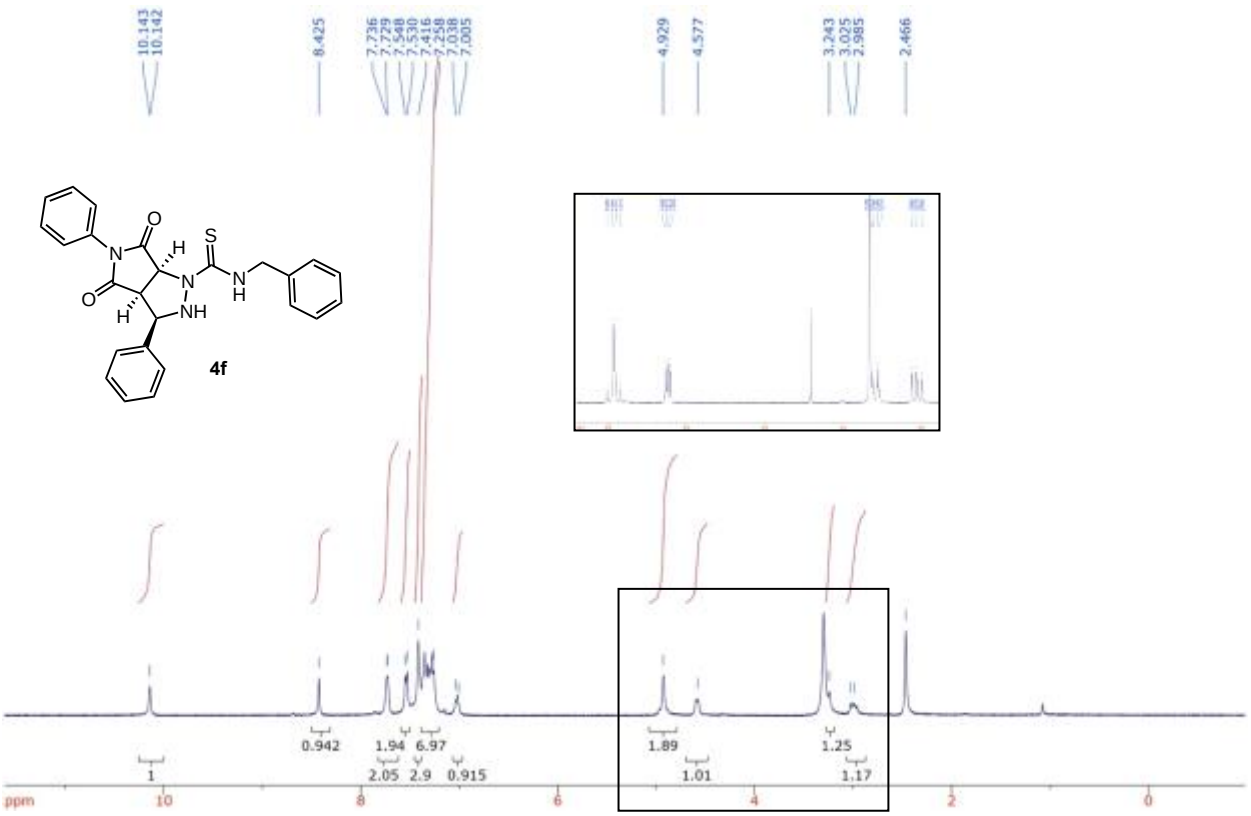
143.354
139.555
134.499
130.506
129.113
128.523
128.108
126.345
125.798
ppm
180
160
140
120
100
80
60
40
20
0

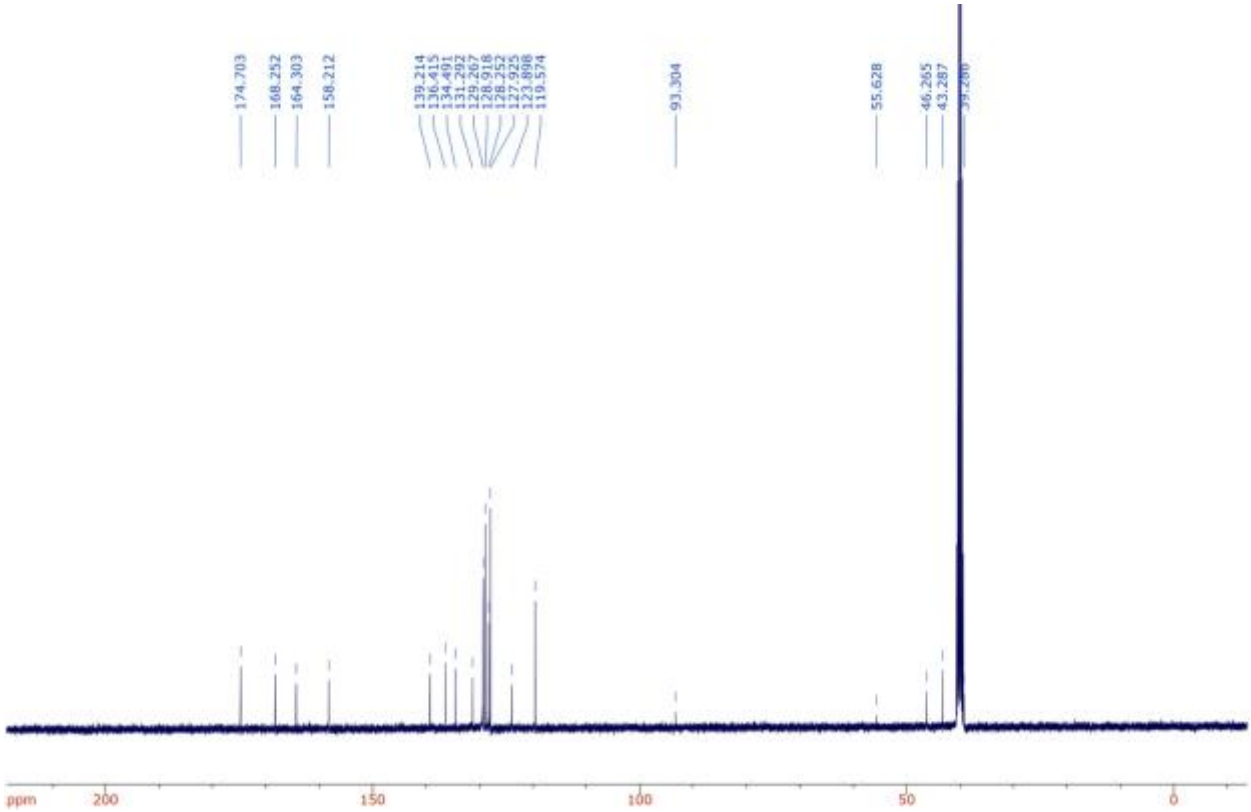

10.212
8.321
7.747
7.740
7.727
7.714
7.612
7.586
7.550
7.525
7.492
7.468
7.453
7.448
7.420
7.345
7.320
7.292
7.085
7.061
7.036
4.657
4.644
4.630
4.617
3.349
3.336
3.293
3.280
3.235
3.208
3.179
3.152
2.500
O
N
H
S
N
H
O
N
NH
H
4c
1.01
1.01
0.999
0.282
1.04
0.76
ppm
174.540
168.397
165.550
158.124
139.236
135.744
134.565
131.234
129.548
129.261
129.150
128.739
128.201
123.918
119.648
43.203
39.226
ppm


7.521
7.502
7.319
7.316
7.298
7.295
7.138
7.135
7.116
6.724
6.722
6.702
6.139
6.119
4.844
4.823
4.810
4.788
3.315
3.293
3.271
2.716
2.702
2.672
2.658
4d
1.03
1.93
0.895
1
1.02
2.18
1.97
1.93
0.962
1.03
ppm
176.961
174.777
147.813
135.151
132.893
129.399
128.809
127.466
117.491
113.374
52.273
36.741
ppm

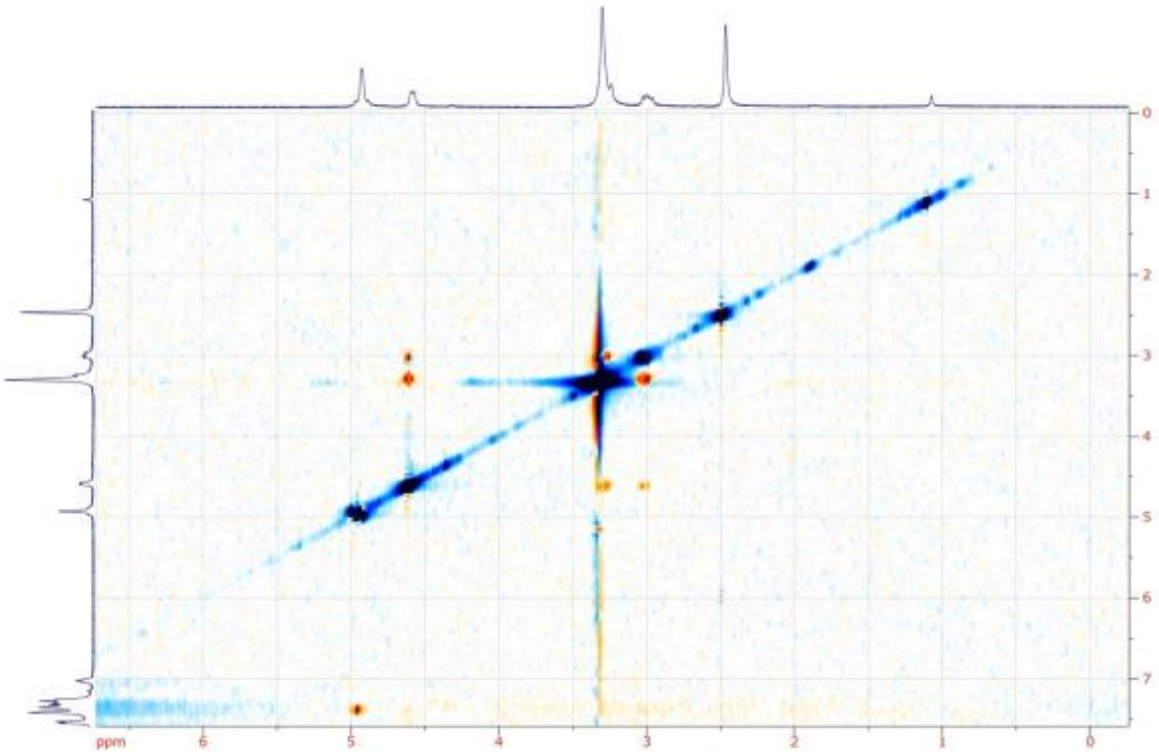

11.609
9.101
8.098
7.835
7.825
7.816
7.811
7.423
7.418
7.411
7.405
7.375
7.356
7.351
7.332
7.312
7.266
7.264
7.261
7.256
7.250
7.250
7.246
7.244
7.228
7.227
4.861
4.845
H
N
N
H
N
S
4e
0.94
1.94
3.77
2.07
0.986
1
2.68
0.974
ppm
12
10
8
6
4
2
0

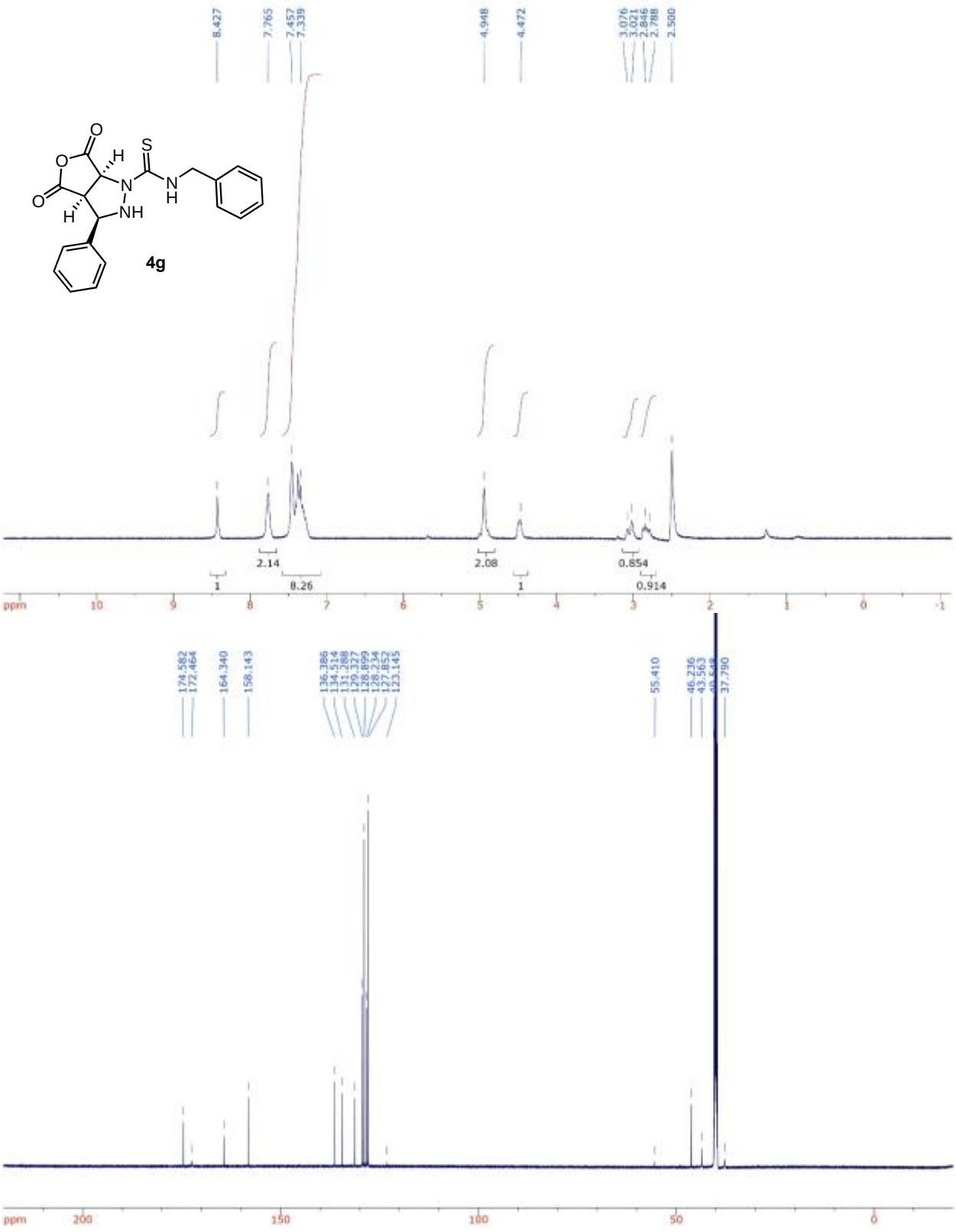

178.099
142.689
139.943
134.668
130.310
129.113
128.633
127.700
127.186
47.065
ppm
200
150
100
50
0


10.143
10.142
8.425
7.736
7.729
7.548
7.530
7.416
7.256
7.038
7.005
4.929
4.577
3.243
3.025
2.985
2.466
0.942
1.94
6.97
2.05
2.9
0.915
1.89
1.25
1.01
1.17
1
ppm
10
8
6
4
2
0


174.703
168.252
164.303
158.212
139.214
136.415
134.491
131.292
129.267
128.918
128.252
127.925
123.898
119.574
93.304
55.628
46.265
43.287
39.200
ppm
200
150
100
50
0

4f


ppm
6
5
4
3
2
1
0
0
1
2
3
4
5
6
7


8.427
7.765
7.457
7.339
4.948
4.472
3.076
3.021
2.846
2.788
2.500
O
O
O
H
S
N
N
H
NH
H
4g
2.14
8.26
2.08
1
0.854
0.914
ppm
10
9
8
7
6
5
4
3
2
1
0
-1
174.582
172.464
164.340
158.143
136.386
134.514
131.288
129.327
128.899
128.234
127.852
123.145
55.410
46.236
43.563
37.790
ppm
200
150
100
50
0