

Synthesis of Azomethine Imines via Alkene Aminocarbonylation and their Derivatization into Pyrazolones

By

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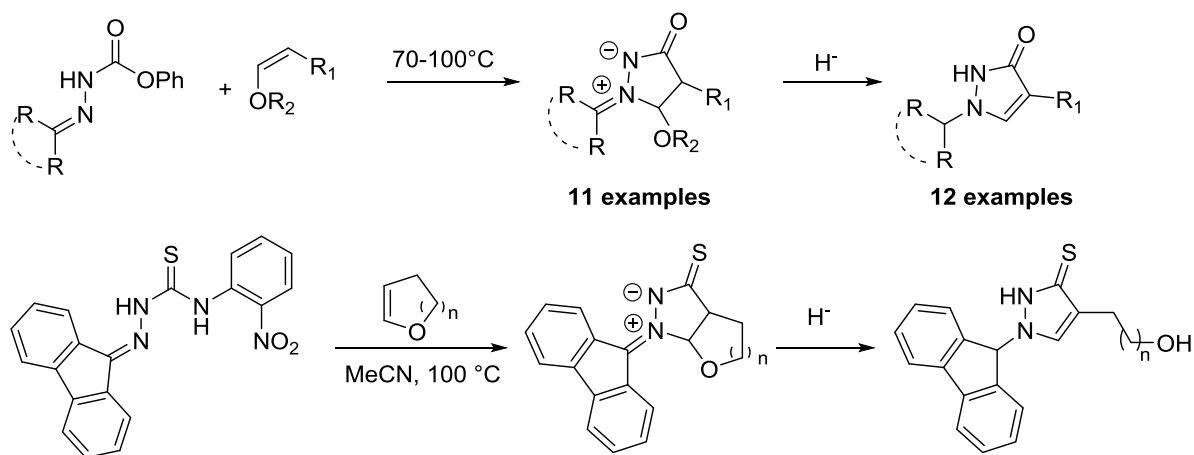
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Abstract

Nitrogen-containing heterocyclic compounds are very important to the pharmaceutical and agrochemical industries, among others. Over the past few years, the Beauchemin group has been exploring reactivity of *N*-substituted isocyanates and as part of this has developed a metal-free alkene aminocarbonylation process relying on imino-isocyanates to form azomethine imines. The azomethine imines formed are interesting since they contain a cyclic β -aminocarbonyl motif.

Catalysis of this reaction using basic additives allowed milder reaction conditions with electron-rich C=C bonds such as enol ethers. Efforts have also been made towards the derivatization of these azomethine imines into useful products. It was discovered that upon reduction and aromatization of azomethine imines, pyrazolones could be obtained. This is providing a novel modular approach to these compounds, which have relevance in pharmaceuticals and agrochemicals. This reactivity was extended to include imino-isothiocyanates.



Aknowledgments

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List of Abbreviations

AcOH	Acetic acid
MeCN	Acetonitrile
α	Alpha
Bn	Benzyl
β	Beta
Calcd	Calculated
CO	Carbon monoxide
δ	Chemical shift
PhCl	Chlorobenzene
J	Coupling constant
$^{\circ}\text{C}$	Degrees celcius
DFT	Density functional theory
DNA	Deoxyribonucleic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
d	Doublet
EI	Electron impact
ESI	Electrospray ionization
ee	Enantiomeric excess
Equiv.	Equivalentents
EtOH	Ethanol
EtOAc	Ethyl Acetate
g	Gram
Hz	Hertz
HRMS	High-resolution mass spectrometry
h	Hours
IR	Infrared
<i>i</i> -Pr	isopropyl
LR	Lawesson's reagent
LG	Leaving group
MHz	Megahertz
MeOH	Methanol
μw	Microwave
mL	Millilitres
mmol	Milimoles
min	Minutes
M	Moles per Litre
m	Multiplet
NMR	Nuclear magnetic resonance
Nuc	Nucleophile
pTsOH	para toluene sulfonic acid
ppm	Parts per million
Ph	Phenyl

PG	Protecting group
q	Quartet
R _f	Retention value
RNA	Ribonucleic acid
rt	Room Temperature
s	Singlet
SPRIX	Spirobis(isoxazoline)
Boc	<i>tert</i> -butoxycarbonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl
Et ₃ N	Triethylamine
TFT	Trifluorotoluene
t	Triplet
UV	Ultraviolet

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Chapter 1: Alkene Aminocarbonylation in Heterocyclic Synthesis

Heterocyclic compounds are of paramount importance in many regards. They are present in small as well as large and complex molecules and have broad applications. Heterocycles can be separated in two categories. The first group is composed of aromatic heterocycles that are usually five or six membered rings, and polycyclic systems are also common. DNA / RNA bases (purines and pyrimidines) are nitrogen containing aromatic heterocycles in their simplest form. Amino acids such as histidine (imidazole) and tryptophan (indole) also have aromatic heterocycles in their side chains (**Figure 1.1**).

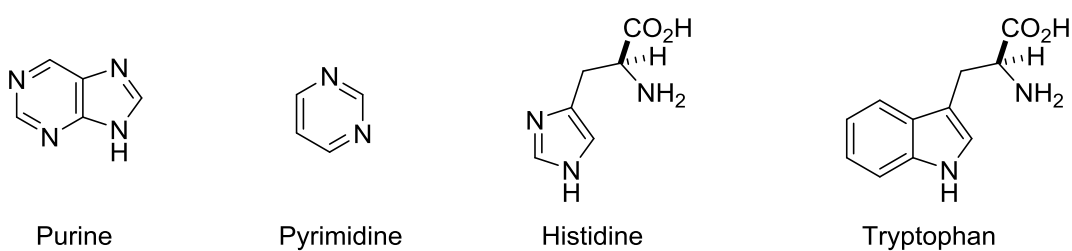


Figure 1.1 Aromatic heterocycles

The second category contains aliphatic heterocycles which include cores as small as three membered rings. As opposed to aromatic heterocycles, aliphatic molecules often react in a similar fashion to their acyclic analogues and have at least one sp^3 atom which allows for stereochemistry. Examples of aliphatic heterocycles are aziridines, β -lactams, pyrrolidines and piperidines (**Figure 1.2**).

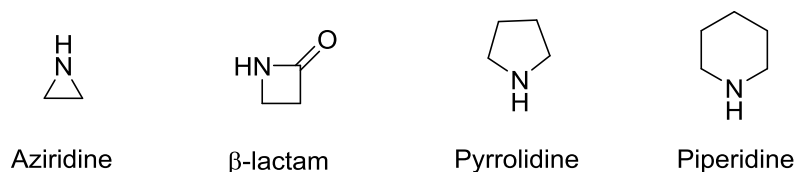


Figure 1.2. Aliphatic heterocycles

Heterocyclic cores can be found in many natural products such as vitamins (B_1 , B_2 , B_3 and B_6), substances produced by plants called alkaloids,¹ macrocycles from the marine environment² and

¹ Cordell, G. A. *The alkaloids*,; *Chemistry and Biology*; Elsevier, 2013, pp. 1-348

² For key examples a) Anderson, R. J.; Faulkner, D. J.; Chu-Heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492. b) Copp, B. R.; Ireland, C. M.; Barrows, L. R. *J. Org. Chem.* **1991**, *56*, 4596.

flavonoids which occur in flower pigments among others.³ Heterocycles are also found in a wide variety of biologically active synthetic compounds such as pharmaceuticals and agrochemicals (Figure 1.3).

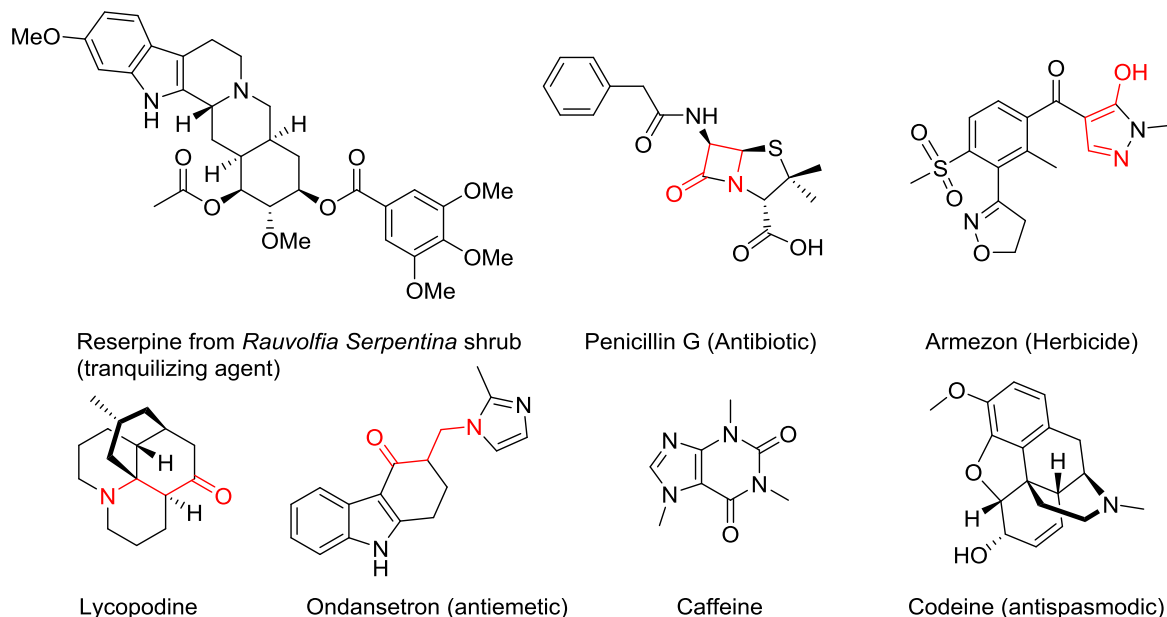


Figure 1.3 Heterocycles in natural products and biologically active compounds

Apart from their occurrence in natural products and pharmaceuticals, heterocycles are also found in materials, polymers for example, many agrochemicals and even in things we consume everyday such as coffee (caffeine).⁴ It then becomes clear why so many researchers have devoted their time on understanding these types of molecules and why so much effort has been put into developing methods to build heterocyclic cores.

A motif that is of particular interest to the Beauchemin group is β -aminocarboxyls because of their interesting applications. β -Aminocarboxyls are present in β -peptides, assembled using β -aminoacids that mimic the function of α -amino acids but have the advantage of being more resistant to proteolytic degradation due to the extra methylene group.⁵ Relevant examples of

³ Morita, N.; Arisawa, M. *Heterocycles* **1976**, *4*, 373.

⁴ Pozharskii, A. F.; Soldalnikov, A.; Katritzky, A. R., *Heterocycles in life and society: An introduction to heterocyclic chemistry and biochemistry and the role of heterocycles in science, technology, medicine and agriculture*, **2011**, Wiley and sons, 396p. (chapter 7 and 8).

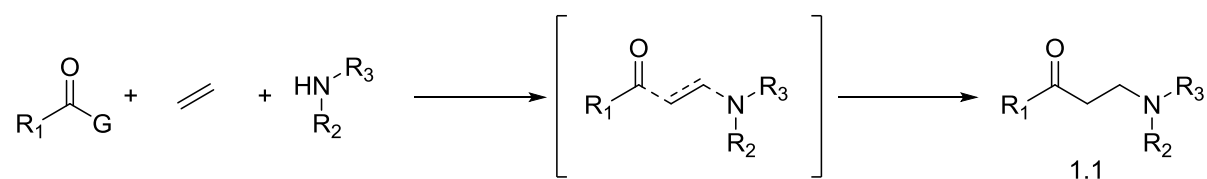
⁵ a) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913. (b) Hintermann, T.; Seebach, D. *Chimia* **1997**, *51*, 244. (c) Seebach, D.; Abele, S.; Schreiber, J. V.; Martinoni, B.; Nussbaum, A. K.; Schild, H.; Schulz, H.;

heterocycles bearing a β -aminocarbonyl motif are Penicillin G, Armezon, Lycopodine and Odansetron.

1.1 Aminocarbonylation

β -Aminocarbonyl derivatives can be synthesized using an array of methods such as reductive amination,⁶ Arndt-Eistert homologation,⁷ and cycloadditions.⁸ Perhaps the two most successful methods to form β -aminocarbonyls are the Mannich reaction and conjugate addition of amines.^{9,10} All of these methods afford the desired motif, but can have drawbacks: limited scope due to starting material unavailability and steric hindrance, lengthy synthesis of starting materials, and the use of toxic and wasteful reagents.

An alternative and complementary method to synthesize β -aminocarbonyls is alkene aminocarbonylation. Aminocarbonylation is defined here as the addition of a carbonyl and an amine across a double bond (**Scheme 1.1**). This method allows for the use of simple and readily available alkenes to generate molecular complexity as well as forming C-C and C-N bonds simultaneously. Not only does it have the advantage of being inexpensive compared to other methods, it is also atom and step economical.



Scheme 1.1 Alkene aminocarbonylation for the synthesis of β -aminocarbonyls

Over the past few years, the Beauchemin group has targeted the synthesis of β -aminocarbonyls and reported that the motif could be obtained as a cyclic azomethine imine using alkene

Hennecke, H.; Woessner, R.; Bitsch, F. *Chimia* **1998**, *52*, 734.

⁶ Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *12*, 6907.

⁷ Podlech, J.; Seebach, D. *Angew. Chem. Int. Ed.* **1995**, *34*, 471.

⁸ Sustmann, R.; Rogge, M.; Nuchter, U.; Bandmann, H. *Chem. Ber.* **1992**, *125*, 1647. (b)

Snowden, R. L.; Brauchli, R.; Wust, M. *Helv. Chim. Acta.* **1990**, *73*, 640.

⁹ a) Loh, T-P.; Liung, S.B.K.W.; Tan, K-L.; Wei, L-L. *Tetrahedron*, **2000**, *56*, 3227. b) Manabe, K.; Mori, Y.;

Kobayashi, S. *Tetrahedron*, **2001**, *57*, 2537. c) Cordova, A.; Barbas, C. F.; *Tetrahedron Lett.* **2002**, *43*, 7749.

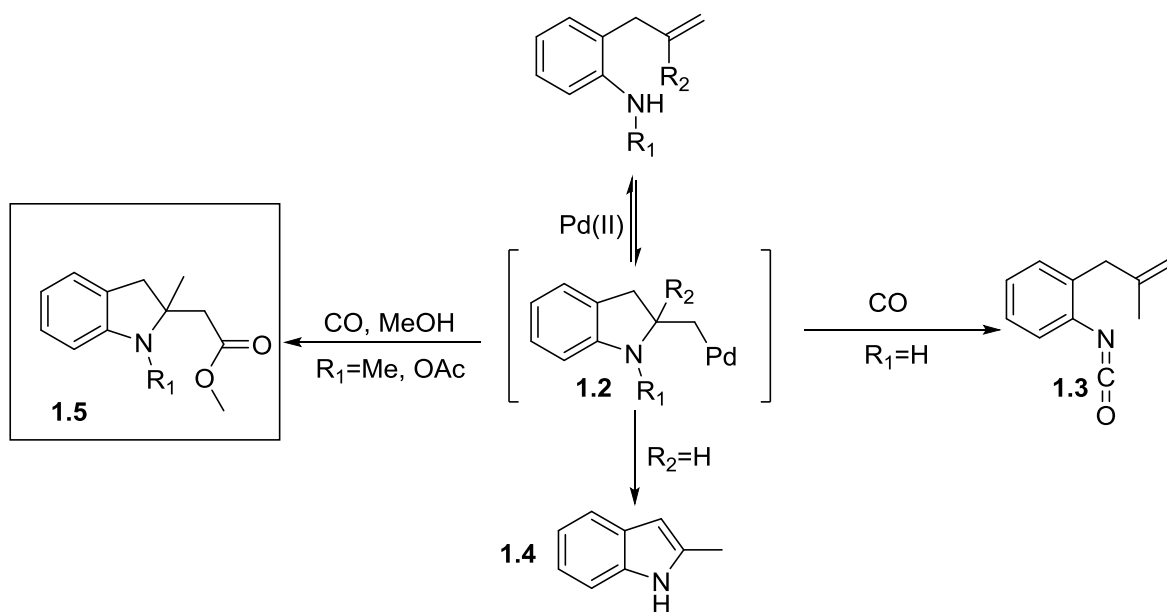
¹⁰ Khan, T. A.; Parvin, T.; Sarifuddin, G.; Choudhury, L. H. *Tetrahedron Lett.* **2007**, *48*, 3805.

aminocarbonylation with *N*-substituted isocyanates, which will be discussed at a later point (Section 1.2).

1.1.1 Metal Catalyzed Aminocarbonylation in Heterocyclic synthesis

Examples of alkene aminocarbonylation being used in heterocyclic synthesis are scarce. The first reports were mostly intramolecular, involved the use of transition metals and carbon monoxide, and showed very limited applicability.

One of the first reports on alkene aminocarbonylation for the synthesis of heterocyclic molecules was by Hegedus and his group in 1980.¹¹ In their publication, they used palladium assisted cyclizations to form heterocycles using alkenyl amine derivatives and carbon monoxide. Since alkenes and amines readily form complexes with palladium, the first step in their approach is the formation of an alkylpalladium (II) complex (**1.2**). This palladium (II) species is then reactive enough to undergo several transformations creating a challenge in controlling the outcome of the reaction. The authors have identified two side reactions that must be avoided in order to achieve the desired cyclization (formation of **1.5**, **Scheme 1.2**).

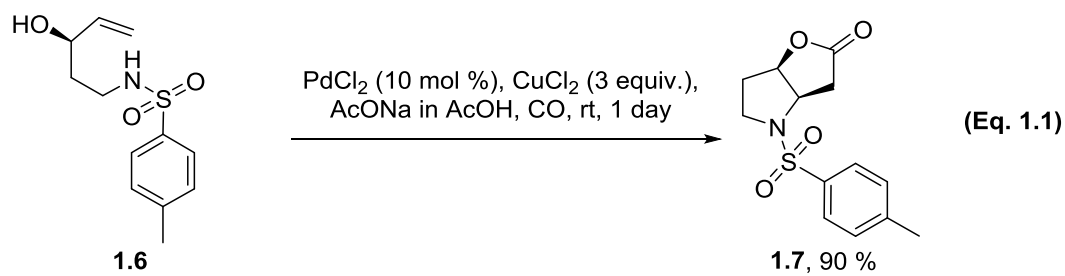


Scheme 1.2 Palladium assisted cyclization of alkenyl amines and insertion of carbon monoxide

¹¹ Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

Their first observation was direct carbonylation of the nitrogen to give isocyanate **1.3** at low temperature. To prevent this from happening, substituents must be installed on the nitrogen, such as methyl and acetate groups. The second by-product they observed was indole **C** resulting from β -hydride elimination in cases where β -hydrogens were present. Since this pathway is favored at higher temperatures, mild reaction conditions (-78 to -10 °C) must be used to avoid competition between elimination and the desired cyclization. Therefore, if both these precautions are taken, cyclization to product **1.5** through insertion of carbon monoxide in the alkylpalladium complex occurs in modest to good yields (21-75 %). Even though this is one of the first examples of aminocarbonylation affording heterocycles, it has a very limited reaction scope.

Tamaru, Yoshida and their group have also made important contributions in this field. Similarly to Hegedus, they have reported in 1985 an intramolecular aminocarbonylation of alkenyl amines and carbon monoxide using palladium as a catalyst.¹² This method allows for a slightly broader reaction scope but requires an allylic hydroxyl group. This has the advantage of being a diastereoselective reaction, but the use of excess copper chloride as a reoxidant and an acid additive are required (Equation 1.1).¹³

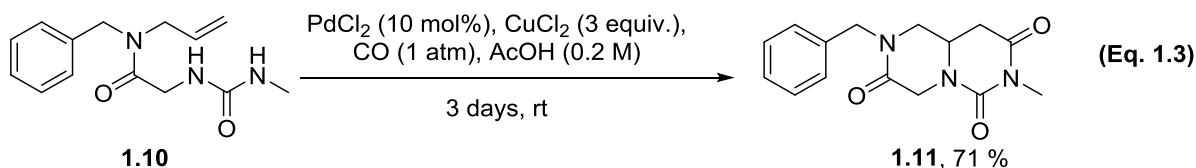
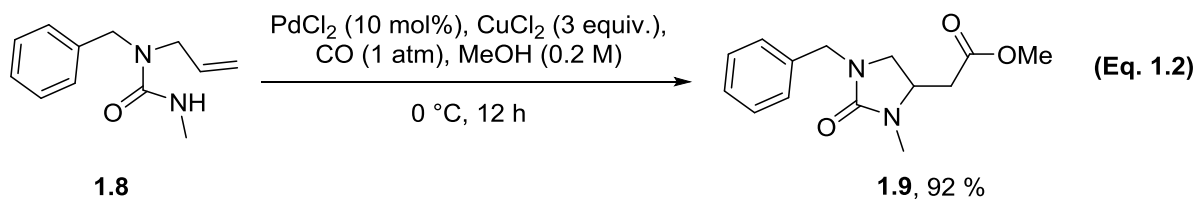


A few years later, they expanded the scope to include aminocarbonylation of ureas and carbamates (Equations 1.2 and 1.3).¹⁴

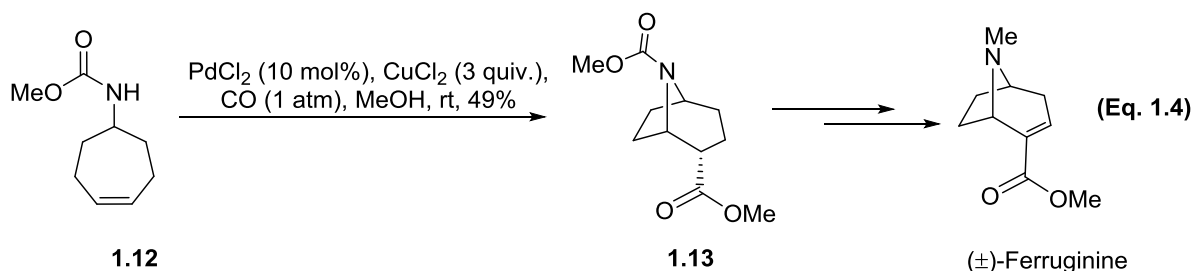
¹² Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Yoshida, Z. *Tetrahedron Lett.* **1985** 26, 4479.

¹³ Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, 53, 5731.

¹⁴ Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, 110, 3994.



This allowed for the formation of both five and six membered nitrogen containing heterocycles. It must be noted that this chemistry is limited by the requirement for an electron withdrawing group on the nitrogen in order for the cyclization to occur. Nonetheless, this methodology developed by Tamaru and Yoshida allowed access to a variety of heterocycles, and has also been shown to be synthetically useful in the synthesis of natural products. For example, the synthesis of the alkaloid Ferruginine reported by the Lee group where palladium catalyzed intramolecular aminocarbonylation constitutes the key step in their synthetic pathway (**Equation 1.4**).¹⁵



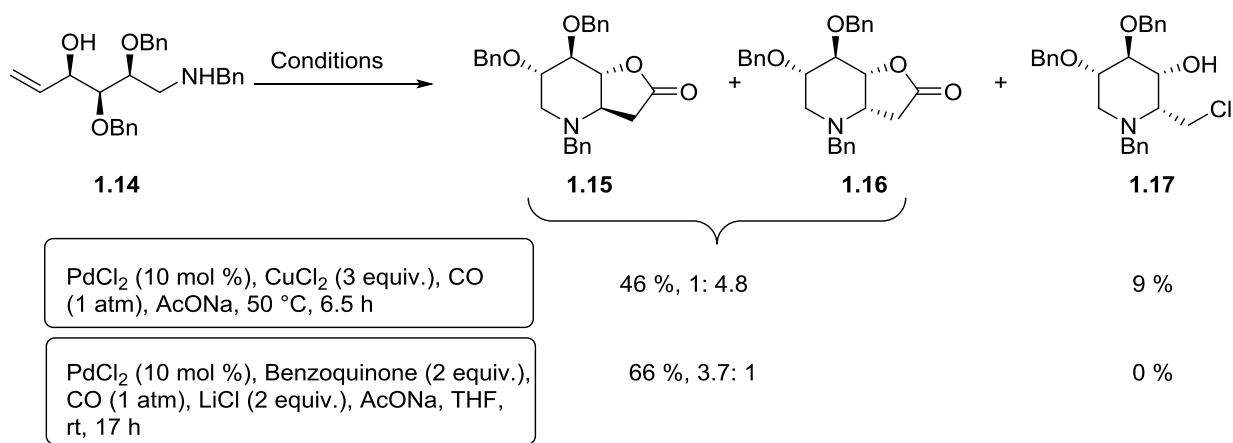
In a very similar fashion, another alkaloid with interesting biological properties, Anatoxin-a, was synthesized using aminocarbonylation.¹⁶ In 2000, Liptaj reported the synthesis of C-6 homologues of 1-deoxynojirimycin and 1-deoxy-L-idonojirimycin which are glycosidase inhibitors.¹⁷ The challenge for their synthesis was the formation of a six membered ring without using an electron withdrawing group on the nitrogen while maintaining good diastereoselectivity. Under the standard conditions described earlier and using a benzyl protecting group on the nitrogen, the desired products were

¹⁵ Ham, W.-H.; Jung, Y.H.; Lee, K; Oh, C.-Y.; Lee, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 3247.

¹⁶ Oh, C.-Y.; Kim, K.-S.; Ham, W.-H. *Tetrahedron Lett.* **1998**, *39*, 2133.

¹⁷ Szolcsanyi, P.; Gracza, T.; Koman, M.; Pronayova, N.; Liptaj, T. *Tetrahedron Asym.* **2000**, *11*, 2579.

not formed. However, when increasing the temperature to 50 °C, they observed the formation of 3 products: cis-fused lactone **1.15** and trans-fused lactone **1.16** in a ratio of 1:4.8, as well as the product of an aminochlorination **1.17** (Scheme 1.3). While optimizing the reaction conditions, they discovered that by using a non-chlorinating oxidant such as benzoquinone, the aminocarbonylation could still occur without any formation of chlorinated by products.

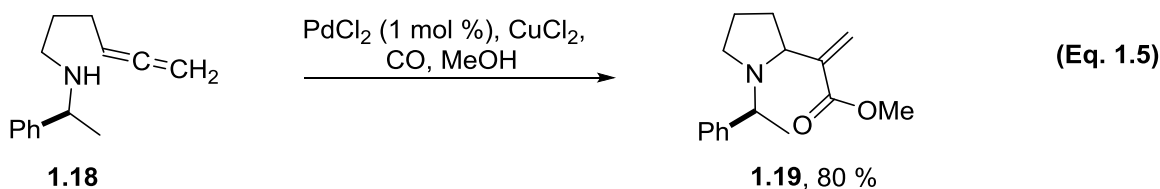


Scheme 1.3 Aminocarbonylation in the synthesis of C-6 homologues of 1-deoxynojirimycin and 1-deoxy-L-idonojirimycin

Even though both sets of conditions gave incomplete conversions and low yields, they were able to get some control over the outcome of the reaction. Standard conditions favored formation of trans-fused lactone **2** whereas using non-chlorinating conditions favored the formation of cis-fused lactone **1**. Once both products were in hand, completion of the synthesis of both glycosidase inhibitors was possible by reductive opening of the lactones followed by removal of benzyl groups. This is the first example of palladium catalyzed aminocarbonylation that does not require electron withdrawing groups on the nitrogen and that can access both diastereoisomers of the resulting lactone although with limited selectivity.

There are also a few examples of aminocarbonylation with allenes. In 1991, Gallagher reported the use of aminocarbonylation on an allene (Equation 1.5) to access Pumiliotoxin 251D, an alkaloid that has the ability to activate voltage dependent sodium channels.¹⁸

¹⁸ Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. J. *Am. Chem. Soc.* **1991**, *113*, 2652.



What makes allenes interesting and synthetically useful reagents for aminocarbonylation is that the corresponding product contains an alkenyl group, which is reactive enough to undergo other transformations, as is shown in the synthesis of Pumiliotoxin. Another thing to notice is that the synthesis begins with enantiopure starting material. The idea was that the stereochemistry on the starting material might be able to control the stereoselectivity of the cyclization since it has been reported previously that cyclization could happen with good diastereocontrol using metals such as silver and mercury.¹⁹ Unfortunately, no diastereoselectivity was observed regardless of the range of conditions used.

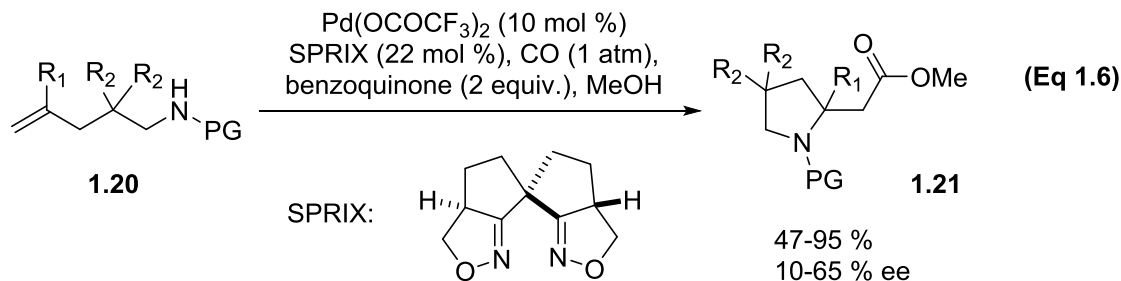
Up to the late 1990's, most aminocarbonylation reactions used palladium catalysts with very simple ligands and enantioselective processes were rare. Because most natural products or pharmaceutical targets have stereochemistry, efforts have been made towards the development of enantioselective aminocarbonylation by the Sasai group.

The Sasai group focused on optimizing the ligands on the metal center to achieve enantioselectivity in the cyclization. They were inspired by the fact that Wacker type cyclizations of alkenyl alcohols could be accomplished with stereocontrol. The ligand used in those studies is a spirobis(isoxazoline) (SPRIX) that has a chiral spirocyclic-backbone.²⁰ First they examined the possibility of using such a catalyst system for aminocarbonylation with alkenyl amines. Using standard aminocarbonylation conditions with non-chlorinating oxidant and a SPRIX ligand, they were able to synthesize cyclic β -aminocarbonyl motifs in good to excellent yields at room temperature. Using low temperatures (-40 to -20 °C), long reaction times, and a chiral ligand they achieved the first enantioselective intramolecular aminocarbonylation of alkenyl amines (**Equation 1.6**).²¹

¹⁹ Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. J. *Chem. Soc., Chem. Comm.* **1989**, 1073.

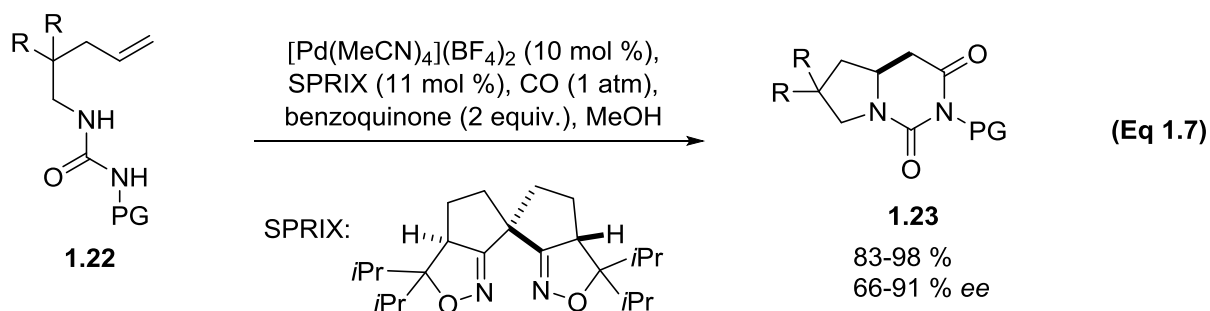
²⁰ a) Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, *1*, 1795. b) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907.

²¹ Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711.



Using this process, enantiomeric excess of up to 65 % was obtained. The limitations of this method are similar to the others available in that it requires an electron withdrawing protecting group on the nitrogen (PG =Ts) to get good yields.

Over the years, Sasai and his group continued to explore SPRIX type ligands. In doing so, they have been able to expand the enantioselective aminocarbonylation to alkenyl ureas (**Equation 1.7**).²²



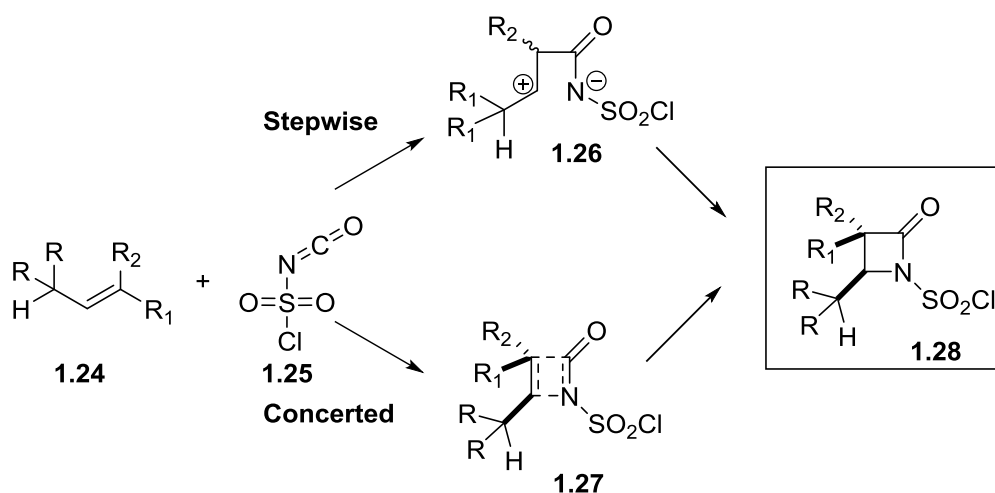
The authors found that when the substituents on the spiro core are small, the reaction occurred in good yields but the enantioselectivity was poor. In order to achieve good yields and high enantioselectivity, the use of a bulkier chiral ligand, for example bearing isopropyl groups, was required. They also observed that low temperature, long reaction time, and low concentrations were needed for high enantioselectivity. Alkyl and ester substituents on the alkenyl amine are well tolerated in terms of yield, however enantioselectivity was poor. Even though the scope for these reactions is limited, this chemistry remains the first example of enantioselective alkene aminocarbonylation.

²² Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J Org. Chem.* **2009**, *74*, 9274.

1.1.2 Alkene Aminocarbonylation with Chlorosulfonyl Isocyanate

All examples presented above use a palladium catalyst to form five or six membered rings from alkenyl amines, allenes, or ureas. These reactions are mostly limited to electron withdrawing groups on the nitrogen and also intramolecular systems, there are very few examples of intermolecular and metal free aminocarbonylation. The [2 + 2] cycloaddition of chlorosulfonyl isocyanate with double bonds is one of those few examples (**Scheme 1.4**). This reactivity is very well known and affords β -lactams that are of particular interest to the pharmaceutical industry.

There have been a few proposals as to the mechanism for this reaction. According to Graf and coworkers, the first step is the addition of the olefin onto the isocyanate to form a zwitterionic species.²³ This intermediate can then react along two different pathways. The first route is the desired cyclization to the β -lactam. The second competitive pathway is elimination when beta-hydrogens are available. The other possible mechanism is a concerted [2+2] cycloaddition as proposed by Moriconi.²⁴ This mechanism is supported by the observation that the reaction is typically stereospecific, meaning that the configuration of the olefin is retained in the cycloadduct.



Scheme 1.4 [2 + 2]cycloaddition of chlorosulfonyl isocyanate and olefins

The rate of the cycloaddition is highly dependent on the polarity of the solvent and the nucleophilicity of the olefin. The reaction works well with a variety of olefins, cyclic, acyclic, dienes

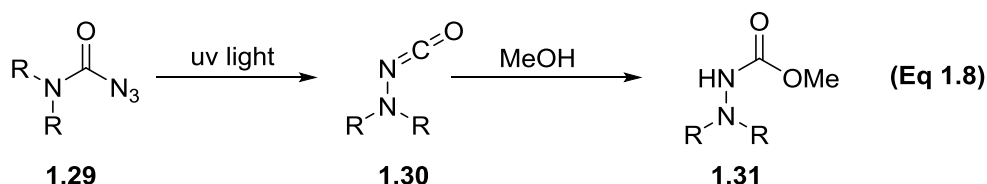
²³ Graf, R.; *Justus Liebigs Ann. Chem.* **1963**, 111, 661.

²⁴ Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, 36, 2841.

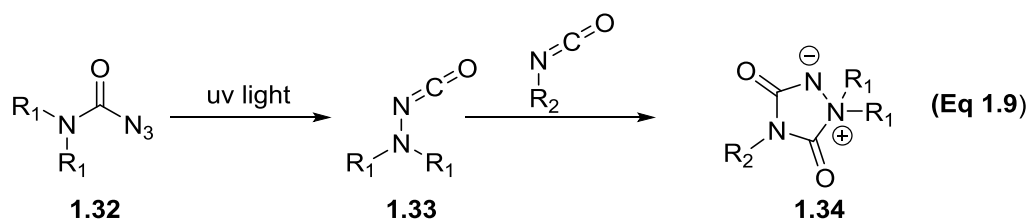
and allenes.²⁵ The main problem with this aminocarbonylation is the toxicity of the reagents used. Chlorosulfonyl isocyanates are very reactive but they are also highly toxic. Isocyanates in general are highly toxic and represent serious health risks if they are not handled correctly.²⁶ As a result, blocked isocyanates have been developed and the isocyanates can be released *in situ* when needed. This technique is used routinely in the application of isocyanate based coatings.²⁷

1.2 N-Substituted Isocyanates

There are many examples of isocyanate reactivity in the literature. However, reports on the formation and reactivity of nitrogen substituted isocyanates are very rare. One of the first reports was by Lwowski *et al.* in 1964, where they report the formation and reaction of amino-isocyanates (Equation 1.8).²⁸



It was found that starting with carbamoyl azides, photolysis could induce a Curtius rearrangement to the amino-isocyanate, followed by solvolysis. The same year, Wadsworth reported the use of phosphoramidate anions to generate amino-isocyanates that then react with themselves to form dimers.²⁹ N-Substituted isocyanates have interesting reactivity, since they have both an electrophilic carbon and nucleophilic nitrogen. Because of their amphoteric nature, N-substituted isocyanates tend to react with themselves or other isocyanates to form dimers or aminimides (Equation 1.9).³⁰



²⁵ Bestian, H. *Pure App. Chem* **1971**, 27, 611.

²⁶ Meredith, S. K.; Bugler, J.; Clarke, R. L. *Occupational Environment Medicine* **2000**, 57, 830–836.

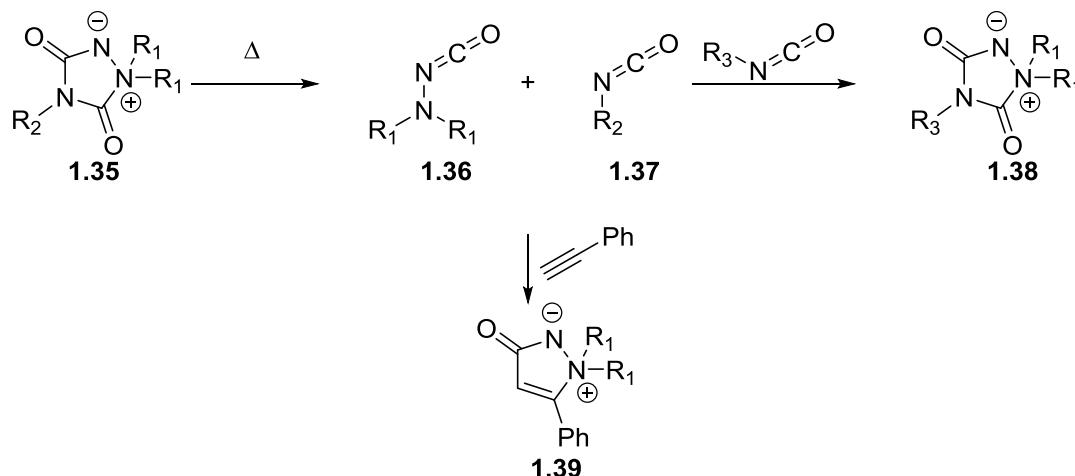
²⁷ Wicks, D. A.; Wicks, Z. W. Jr. *Prog. Org. Coat.* **1999**, 36, 148.

²⁸ Lwowski, W.; DeMauriac, R.; Mattingly, T. M.; Scheiffle, E. *Tetrahedron Lett.* **1964**, 3285.

²⁹ Wadsworth, W. S.; Emmons, W. D., *J. Org. Chem.* **1964**, 29, 2816.

³⁰ Lunow, L.; Murray, R. A.; de Mauriac, R. A.; Lwowski, W. *Tetrahedron Lett.* **1971**, 12, 425.

Upon heating the aminimide can open to release amino-isocyanates, and having bulky groups such as *tert*-butyl (R_1 or R_2) helps the process significantly.³¹ The released amino-isocyanates can then react with new isocyanates or with other π systems such as alkynes (**Scheme 1.5**).³²



Scheme 1.5 Formation of amino-isocyanates from aminimides and their trapping

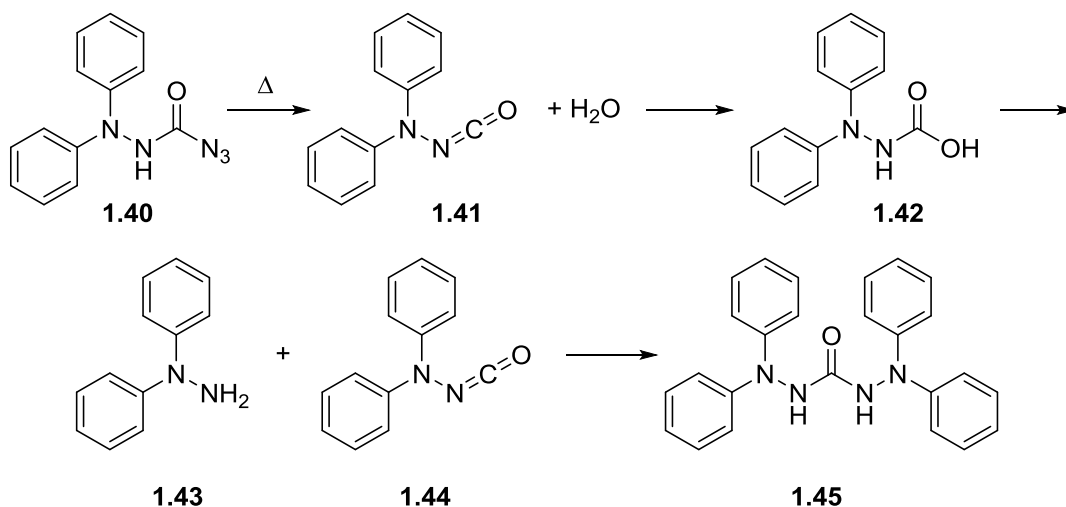
In order to successfully trap the amino-isocyanate with an alkyne, this cycloaddition must be faster than the competing dimerization. This can be achieved by using low concentrations of substrate.

Amino-isocyanates are very reactive intermediates, therefore certain precautions must be taken in order to prevent their decomposition. One concern is that water can act as a nucleophile on amino-isocyanates, making it very susceptible to decarboxylation. The hydrazine formed can then react with another amino-isocyanate to yield a carbazide (**Scheme 1.6**).³³

³¹ Lockley, W. J. S.; Ramakrishnan, V. T.; Lwowski, W. *Tetrahedron Lett.* **1974**, 2621.

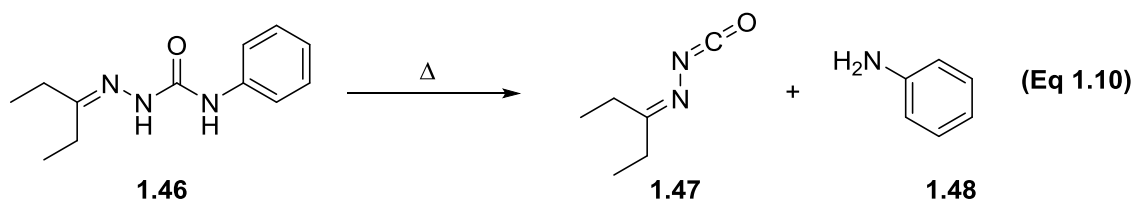
³² Lockley, W. J. S.; Lwowski, W. *Tetrahedron Lett.* **1974**, 4263.

³³ a) Reichen, W. *Chem. Rev.* **1978**, 78, 569. b) Merkle, M.; Stolle, R. *J. Prakt. Chem.* **1928**, 227, 275.



Scheme 1.6 Decarboxylation of amino-isocyanates

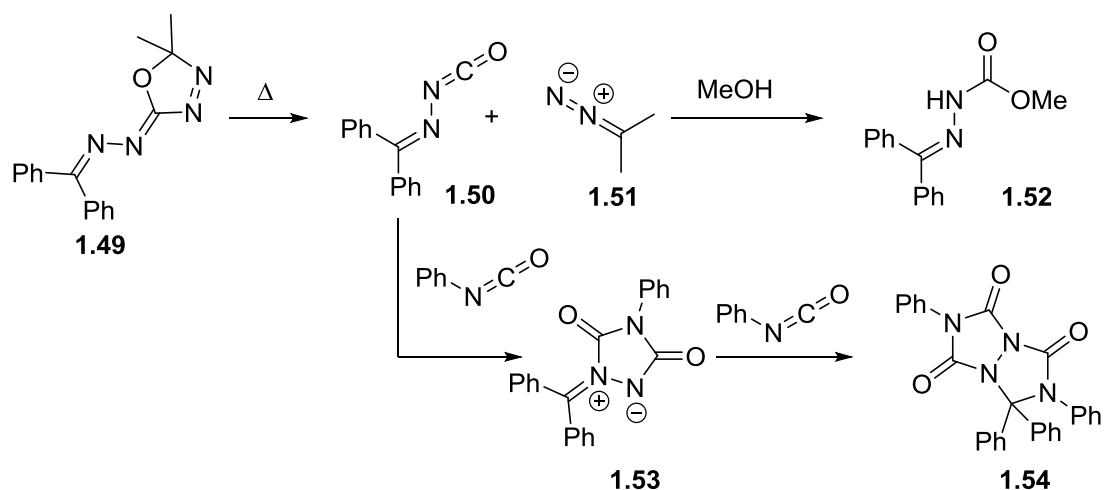
Another type of *N*-substituted isocyanates is imino-isocyanates, which have even less literature precedence. In 1969, Jacobsen was able to detect the formation of an imino-isocyanate by mass spectrometry by heating a semi-carbazide (**Equation 1.10**).³⁴



In 1976, Workentin discovered that imino-isocyanates are generated upon heating of oxadiazolines.³⁵ Detailed studies revealed that the imino-isocyanates generated under the reaction conditions can be trapped by some nucleophiles, such as methanol to form benzophenone methyl carbamate **1.52**. They can also react with other isocyanates similarly to what has been shown with amino-isocyanates. However, in this case the 1,3-dipolar product **1.53** is formed and, in presence of excess isocyanate, will undergo another cycloaddition to **1.54** (**Scheme 1.7**). This was the first example of reactivity of imino-isocyanates.

³⁴ Larsen, C.; Jacobsen, P. *Acta Chem. Scand.* **1969**, 23, 324.

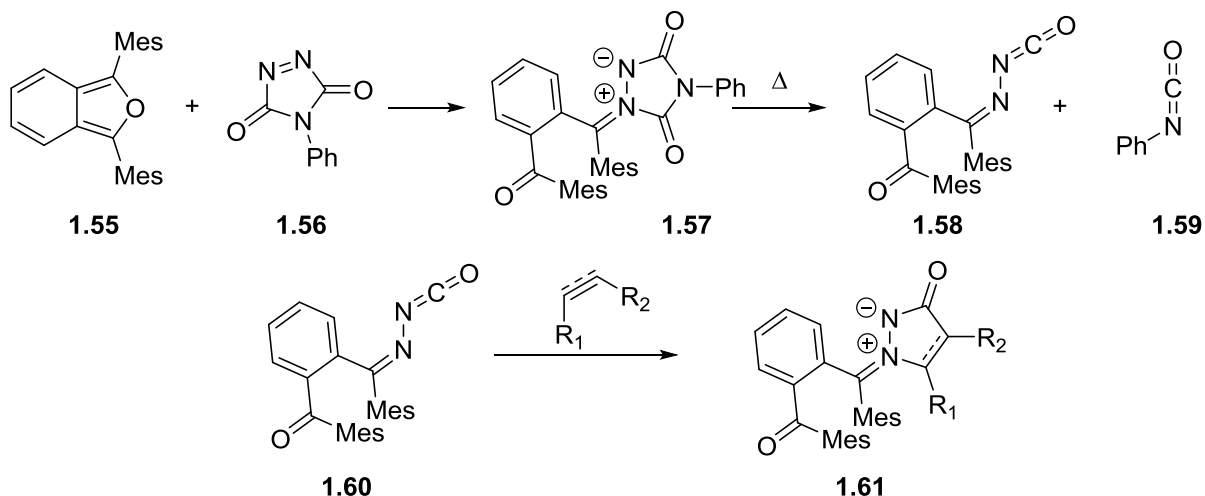
³⁵ Ramakrishnan, K.; Fulton, J. B.; Workentin, J. *Tetrahedron* **1976**, 32, 2685.



Scheme 1.7 Formation and reactivity of imino-isocyanates generated from oxadiazolines

A few years later, Jones showed that the dipolar product generated from what the authors refer to as a foiled Diels-Alder reaction could be heated to decompose into an imino-isocyanate (**Scheme 1.8**).³⁶ Initially, it was expected that the dipolar product would undergo a dipolar cycloaddition when heated in presence of alkenes or alkynes. However, what they observed was the formation of different cycloadducts that would come from the formation of the imino-isocyanate which then reacts with alkenes (*N*-phenylmaleimide, styrene, cyclooctadiene and norbornadiene) or alkynes (phenylacetylene) give azomethine imines (**Scheme 1.8**). This was the very first report of alkene aminocarbonylation with imino-isocyanates, unfortunately no yields were reported in this publication.

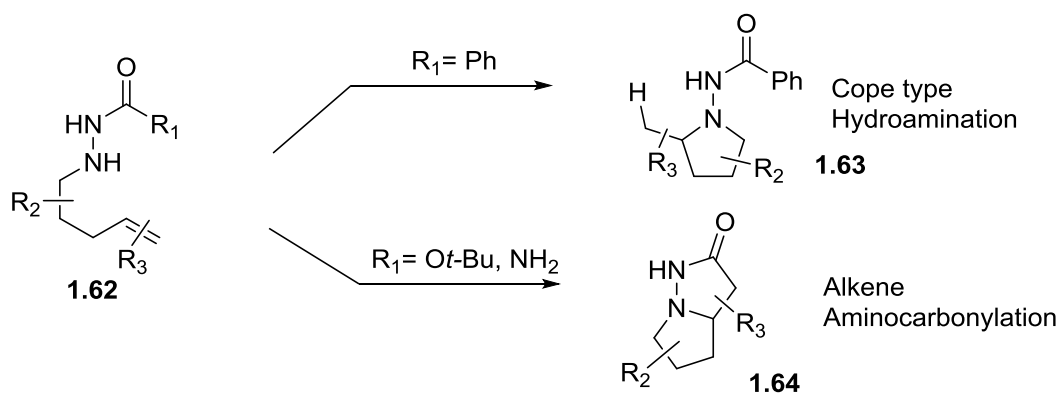
³⁶ Jones, D. W. *J. Chem. Soc., Chem. Comm.* **1982**, 13, 766.



Scheme 1.8 Cycloaddition of an imino-isocyanate with alkenes and alkynes

It wasn't until very recently that amino- and imino-isocyanates started being developed as synthetic tools. In 2009, the Beauchemin group discovered that hydrazides could be used as blocked *N*-substituted isocyanates and have since been exploring the reactivity of these species since then.

While studying the Cope-type hydroamination of benzoic hydrazides and carbazates, it was observed that when a leaving group (as R_1) is present, the reaction goes through a different pathway, i.e. alkene aminocarbonylation rather than hydroamination (**Scheme 1.9**).³⁷

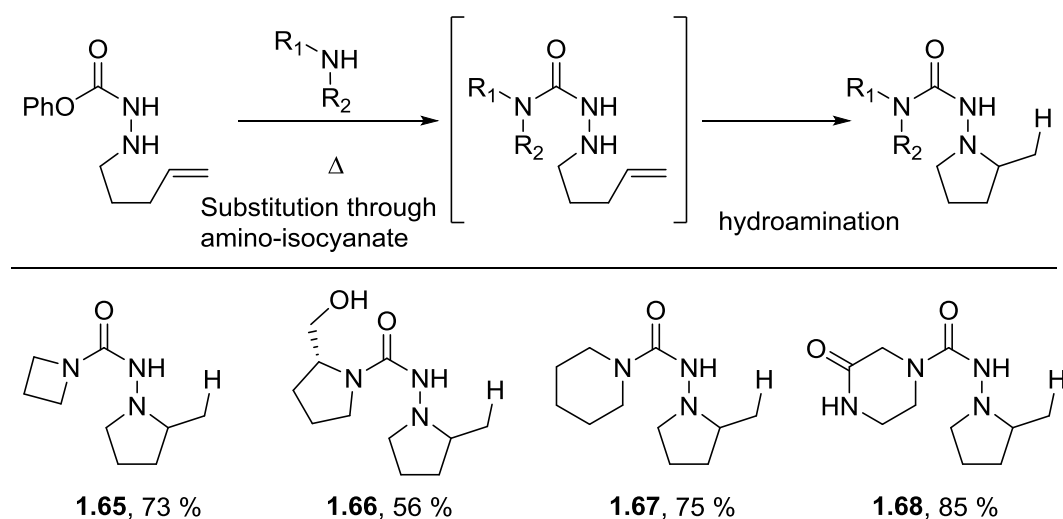


Scheme 1.9 Cope type hydroamination vs. alkene aminocarbonylation

³⁷ Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

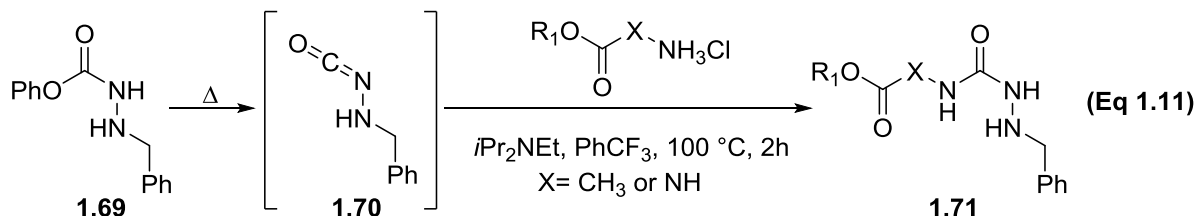
A preliminary substrate scope was conducted and showed that substitution on the alkene was tolerated and that the reaction was stereospecific. These observations combined with the fact that high temperatures were used suggested an amino-isocyanate was involved as an intermediate.

Continuing with amino-isocyanates, the Beauchemin group has since greatly expanded the scope of reactions possible with these intermediates. First, it was shown that secondary amines such as pyrrolidine can act as good nucleophiles to trap amino-isocyanates that are generated thermally. A cascade substitution/hydroamination was then developed using this knowledge. The substitution with an amine occurs first, followed by hydroamination occurring afterwards (**Scheme 1.10**).³⁸



Scheme 1.10 Substitution/hydroamination cascade and sample of reaction scope

The substitution chemistry was then expanded to include amino esters giving rise to azadipeptides units which are important to the medicinal industry (**Equation 1.11**).³⁹

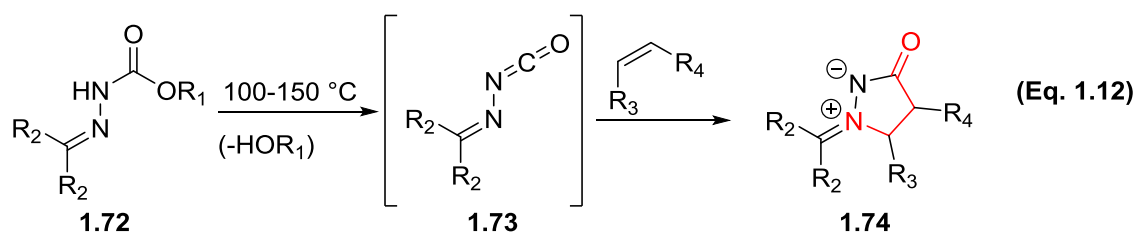


³⁸ Clavette, C.; Vincent-Rocan, J.-F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12705.

³⁹ Vlieghe, P.; Lisowski, V.; Martinez, J.; Khrestchatsky, M. *Drug Discovery Today*, **2010**, *15*, 40.

1.3 Alkene aminocarbonylation with imino-isocyanates

As mentioned earlier, there aren't many examples of formation and reactivity of imino-isocyanates. The Beauchemin group was inspired by the work of Jones and previous findings on amino-isocyanates to develop an intermolecular metal-free alkene aminocarbonylation reaction using imino-isocyanates. Hydrazones are used as imino-isocyanate precursors which react with a wide variety of alkenes. Indeed, the Beauchemin group showed that upon heating hydrazones, imino-isocyanates form by ejection of a leaving group, and then undergo a [3+2] cycloaddition to give *N,N'*-cyclic azomethine imines (**Equation 1.12**).⁴⁰ *N,N'*-Cyclic azomethine imines are interesting heterocycles that are generally stable enough to be isolated, but sufficiently reactive to be useful synthetic tools containing the β -aminocarbonyl motif (shown in red). For example, they can be derivatized into β -amino amides and further to β -amino esters and acids which are present in many biologically active compounds.^{41,42}



First, the effect of different substituents on the hydrazone was studied. It was found that having a better leaving group such as phenol or thiophenol (rather than *tert*-butyl alcohol) increased the yield of product at lower temperatures (100 °C vs. 150 °C). It was also found that the size of R₂ is important to prevent side reactions. When R₂ is small, low yields were obtained even with full consumption of the starting materials, suggesting by-product formation. Apart from the possible dimerization of imino-isocyanates, another competing side reaction is a subsequent dipolar cycloaddition between the azomethine imine product and the excess alkene present in solution.⁴³ Hydrazones derived from bulky ketones (diisopropyl ketone or fluorenone) were found to not undergo this side reaction.

⁴⁰ Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S.I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111.

⁴¹ a) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625. b) Li, L.-C.; Ren, J.; Liao, T.-G.; Jiang, J.-X.; Zhu, H.-J. *Eur. J. Org. Chem.* **2007**, 1026.

⁴² Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366.

⁴³ Hori, M.; Sakakura, A.; Ishihara, K. *J. Am. Chem. Soc.* **2014**, *136*, 13198.

The scope of the reaction was further extended to hydrazones derived from unsymmetrical ketones, and aldehydes (albeit with slightly lower yields for aldehydes).⁴⁴ A wide variety of alkenes are well tolerated for the reaction with most of these hydrazones, including electron poor, electron rich, aromatic, and aliphatic groups, however electron rich olefins show better reactivity. The reaction is highly Markovnikov selective and is thought to be a concerted asynchronous process as supported by DFT calculations and retention of alkene stereochemistry in the final product. There are currently more than 100 examples of alkene aminocarbonylation with imino-isocyanates and selected examples of the scope are presented in **Figure 1.4**.

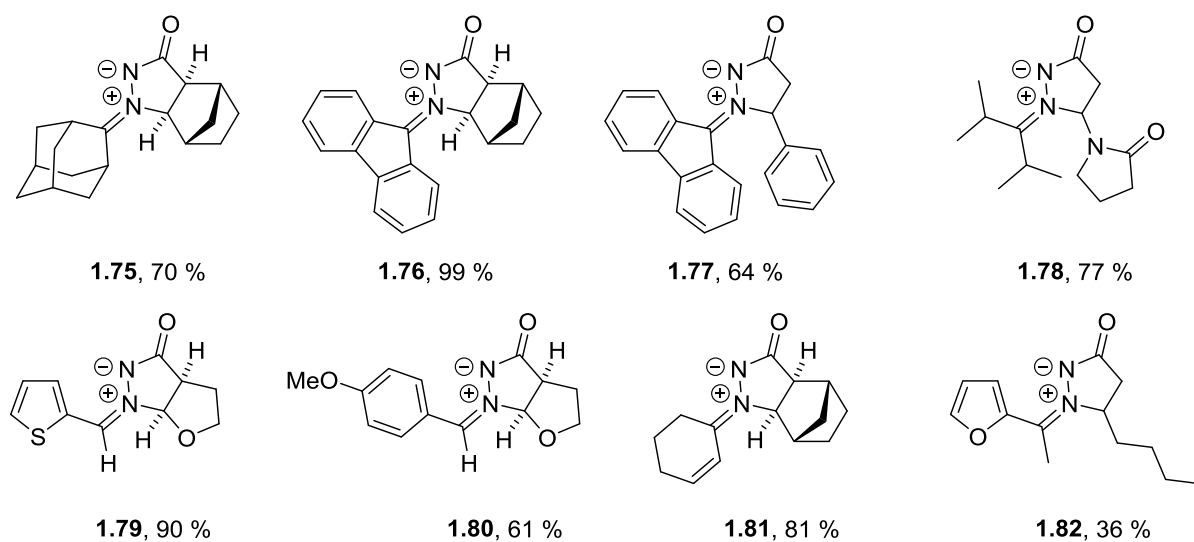


Figure 1.4 Sample scope of alkene aminocarbonylation with imino-isocyanates

1.3.1 Investigation into base catalysis

Although this azomethine imine synthesis is quite general and has extended the diversity *N,N'*-cyclic azomethine imines available, it still usually requires high temperatures and a large excess of alkene. As part of my Honours research, I have worked on achieving milder reaction conditions. The reaction studied goes through two steps: 1) formation of the imino-isocyanate and 2) alkene aminocarbonylation, as depicted in equation **1.12**.

The rate determining step, either imino-isocyanate formation or aminocarbonylation, is thought to be highly substrate and temperature dependent. At typical reaction temperatures, aminocarbonylation is considered the limiting step. Because the formation of the imino-isocyanate

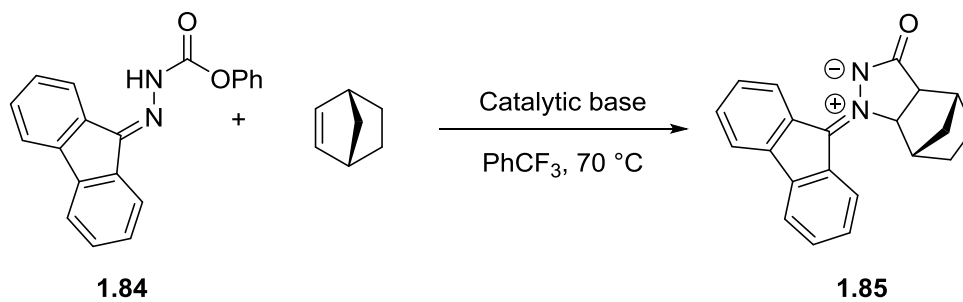
⁴⁴ Gan, W.; Moon, P. J.; Clavette, C.; Das Neves, N.; Markiewicz, T.; Toderian, A. B.; Beuchemin, A. M. *Org. Lett.* **2013**, *15*, 1890.



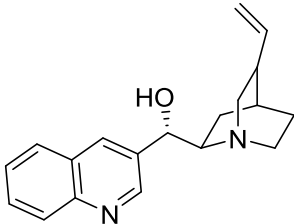
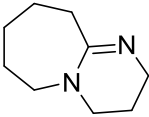
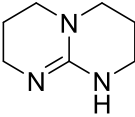
occurs thermally, low reaction temperature could make this step rate determining, but only if aminocarbonylation is facile at that same low temperature. Therefore, we investigated catalysis for the formation of the imino-isocyanate with reactions at lower temperatures with very reactive alkenes.

The investigation was conducted the fluorenone-derived hydrazone with PhOH as the leaving group. Norbornene was chosen as the alkene because it is strained and electron rich, and consequently very reactive in this system. The assumption that the rate limiting step was the formation of the imino-isocyanate was then made. It has to be noted that the mechanism for the formation imino-isocyanates is still not fully understood. We proposed that base might help the formation of the imino-isocyanates by removal of the NH proton. Hence, nitrogen containing bases were screened using lower temperature (70 °C) than previously reported (100 to 150 °C). It was found that many tertiary amine bases could increase the yield of product at a loading of 30 mol % **(Table 1.1)**.⁴⁵

⁴⁵ Lavergne, K. Investigation into Catalytic Intermolecular Aminocarbonylation of Alkenes with Imino-isocyanates. Honours Thesis, University of Ottawa, 2012.

Table 1.1 Effect of nitrogen containing bases on alkene aminocarbonylation

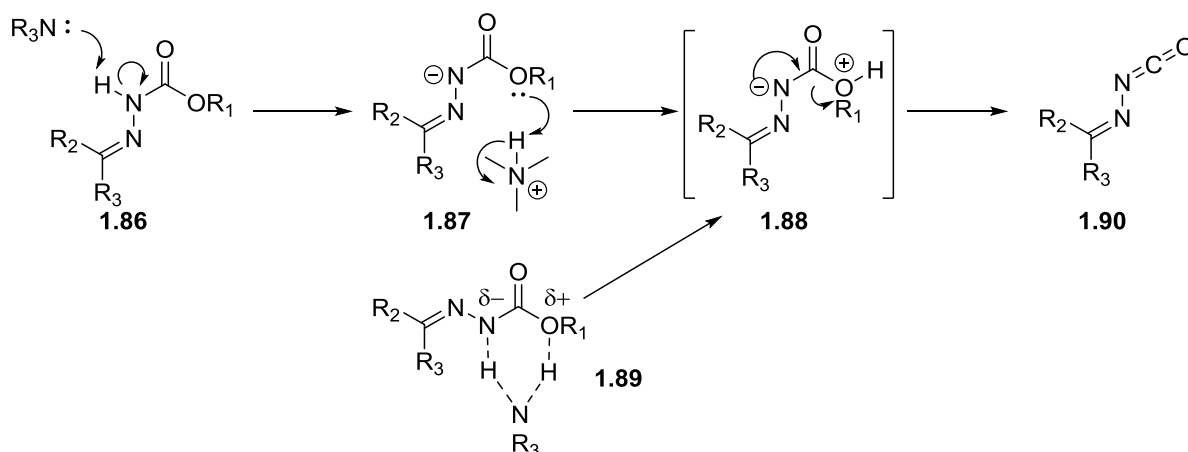


Entry	Base (3 or 30 mol %)	NMR yield (30 mol %)	NMR yield (3 mol %)	pK _a (DMSO)
1	-	16-22	-	-
2		28	14-21	5.25
3		49	44	8.82
4		50	36	9.92
5	Et ₃ N	26	52	10.75
6		16	52	12
7		20	47	21

a) Entries were made on a 50-100 mg scale. The reactions were run with the hydrazones dissolved in PhCF₃ (0.05 M) and 10 equivalents of norbornene. Heated in an oil bath at 70 °C for 2 h. b) The NMR yields were taken using 1,3,5-trimethoxybenzene as the internal standard. c) pK_a of ammonium ion.

In most cases (entry 4-7) it was observed that the yields increased when the loading of base was decreased to 3 mol %. This is in accordance with a slower release of the imino-isocyanate in solution, therefore diminishing side reactions. 1,8-Diazabicycloundec-7-ene (DBU) (entry 6) and triethylamine (entry 5) proved to be the best candidates as they doubled the yield when compared to the control. It was also noted that the concentration could be increased from 0.05 M to 0.1 M without any impact on the efficiency of the reaction.

Based on work done by Booker-Milburn, it was proposed that the base triggers a proton transfer from the nitrogen to the leaving group, facilitating its ejection either in a stepwise or concerted fashion (**Scheme 1.11**).⁴⁶



Scheme 1.11 Proposed step-wise or concerted mechanism for formation of imino-isocyanate

This was the first example of base catalyzed imino-isocyanate formation. The applicability and generality of this approach remained unexplored.

1.4 Project Objectives

Following this work, one of the objectives for this project was to see if the base catalysis described above could be extended to other electron-rich alkenes, such as enol ethers and to gain better understanding of the mechanism of the imino-isocyanate formation. The other objective is to transform the azomethine imines into useful heterocycles such as pyrazolones.

⁴⁶ Hutchby, M.; Houlden, C. E.; Gair Ford, J., Tyler, S. N. G., Gagné, M. R., Lloyd-Jones, G. C., Booker-Milburn, K. *I. Angew. Chem., Int. Ed.* **2009**, *48*, 1830.

Chapter 2: Development of Mild Alkene Aminocarbonylation

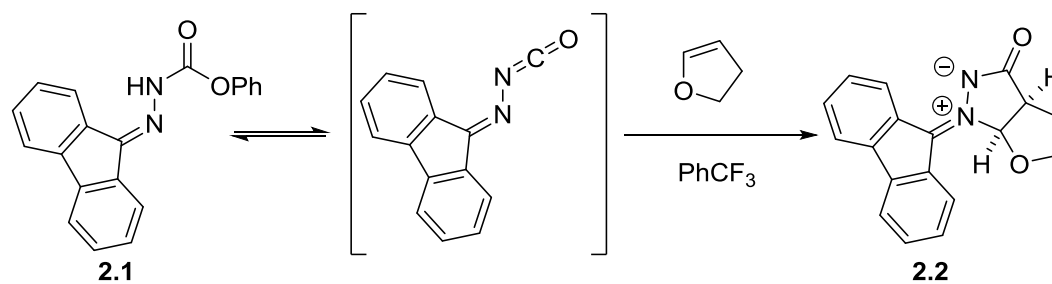
The alkene aminocarbonylation methodology developed in our lab has allowed the synthesis of structurally diverse azomethine imines starting from alkenes and hydrazones as blocked imino-isocyanates. Previous results using tertiary amine bases showed for the first time that base catalysis is possible for the formation of imino-isocyanates. The main goal of this part of the project is to determine if base the catalysis can be extended to other electron rich alkenes, and form useful products from the unusual azomethine imines derived from enol ethers.

2.1 Base Catalysis: Optimization Using Dihydrofuran

Based on preliminary results with base catalysis, we hypothesized that using reactive and electron rich alkenes such as enol ethers will make the formation of the imino-isocyanate the rate determining step. Enol ethers are also sensitive to decomposition at high temperatures, which might explain the lower yields obtained using previously reported conditions at higher temperatures.

Dihydrofuran and other enol ethers seemed to be perfect candidates to study base catalysis of imino-isocyanate formation. Fluorenone hydrazone was chosen since the steric bulk usually prevents side reactions, it displays optimal reactivity in alkene aminocarbonylation, and its synthesis and purification are straightforward.

The first step was to determine reaction conditions for which the control reaction shows limited product formation. It was found that when heating at 70 °C for 2 hours without the use of any base, only 24 % of the desired product was observed (**Table 2.1**, entry 2). Once the comparison point was established, the reaction was repeated with 3 mol % of the three bases that worked best in the past: 1,8-diazabicycloundec-7-ene (DBU), triethylamine (Et₃N), and 1,4-diazabicyclo[2.2.2]octane (DABCO). From these first experiments, it was clear that basic additives have a positive effect on the the reaction with dihydrofuran. All three bases seem to have very similar effects on the reactivity and resulted in 65 % (entry 4), 61 % (entry 5) and 68 % (entry 6) isolated yields respectively. Not only were the yields three fold higher than the control, but they are also higher than the yield obtained under previously reported conditions (entry 1). Another common factor between all three reactions was that little or no starting material was left, suggesting side reactions. In the end, triethylamine (Et₃N) was used as the base for further optimization, because of positive results obtained with norbornene and because it is readily available and inexpensive.

Table 2.1 Optimization of alkene aminocarbonylation with base additives^a

Entry	Time (h)	Temp. (°C)	Base	Equiv. hydrazone	Equiv. alkene	Yield ^b (%)
1 ^c	2	100	None	1	10	57
2 ^c	2	70	None	1	2	24
3	2	70	None	2	2	31
4	2	70	DBU	1	2	65
5	2	70	DABCO	1	2	61
6	2	70	Et ₃ N	1	2	68
7	2	70	Et ₃ N	1	1.5	68
8	2	70	Et ₃ N	1	1	78
9	2	70	Et ₃ N	1.5	1	88
10	2.5	70	Et ₃ N	1.5	1	>95

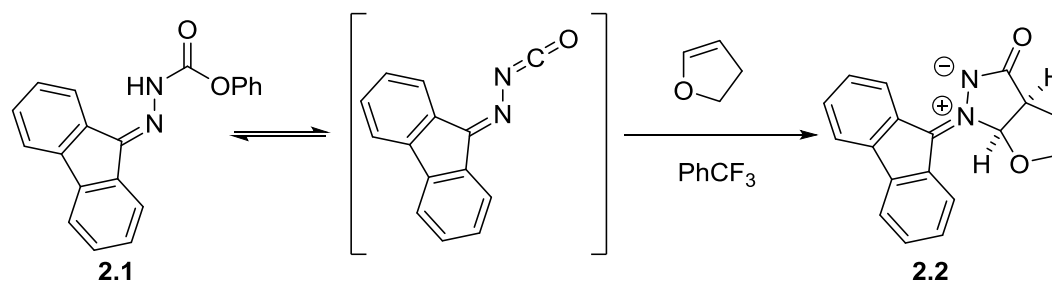
a) Conditions: Hydrazone, alkene, base (3 mol %) and PhCF₃ (0.1 M) were added to an oven dried vial, purged with inert gas and heated in oil bath of microwave reactor. **b)** Isolated yields. **c)** 0.05 M

Because it is assumed that the formation of the imino-isocyanate is the rate limiting step, having the alkene as the limiting reagent would make sense. In this case, the hydrazone should be in slight excess to favor the formation of the imino-isocyanate. First, the equivalents of alkene were lowered from 2.0 to 1.5, resulting in no improvement. When the alkene and hydrazone were present in a 1 to 1 ratio, the yield went up to 78 % (entry 8). When the alkene was made as the limiting reagent, the yield increased to 88 % (entry 9). Unexpectedly, increasing the time by just 30 minutes increased the yield for the reaction to almost quantitative by NMR, and 95 % yield of isolated product was obtained. While speculative, the important difference in reaction efficiency is consistent with a competitive side reaction of the hydrazone component.

Because Et₃N was very efficient to promote imino-isocyanate formation at 70 °C, it might be able to work at even lower temperatures (**Table 2.2**). A control reaction was performed at 50 °C for 2.25 hours and only traces of the azomethine imine were observed (entry 1). When 3 mol % of Et₃N was

added, 48 % yield (entry 2) of the desired product was found by NMR. Further increasing reaction time to 6 hours increased the yield up to 60 % (entry 3) and increasing the concentration from 0.1M to 0.25 M increased the yield up to 72 % (entry 4).

Table 2.2 Base catalysis at 50°C^a



Entry	Time (h)	Temp. (°C)	Base	Equiv. hydrazone	Equiv. alkene	Yield ^b (%)
1	2.25	50	None	1.5	1	<5
2	2.25	50	Et_3N	1.5	1	48
3	6	50	Et_3N	1.5	1	60
4 ^c	6	50	Et_3N	1.5	1	72 ^d

a) Conditions: Hydrazone, alkene, base (3 mol %) and PhCF_3 (0.1 M) were added to an oven dried vial, purged with inert gas and heated in oil bath of microwave reactor. **b)** NMR yields **c)** 0.25 M **d)** Isolated yield

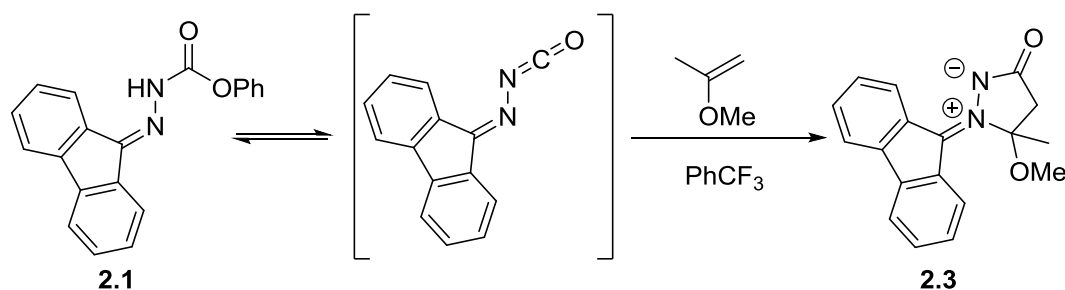
Unfortunately, at room temperature no reaction at all was observed even with larger amounts of base, suggesting that aminocarbonylation is now rate limiting. What can be concluded from this is that the fluorenone derived hydrazone with phenol as a leaving group can form the corresponding imino-isocyanate at a temperature as low as 50 °C in the presence of 3 mol % of Et_3N . We were able to show that the yields could be significantly improved using base catalysis with alkenes such as norbornene and dihydrofuran at 70 °C.

2.2 Extension of scope for base catalysis

We then wanted to know if the aminocarbonylation reactivity could be extended to other commercially available enol ethers. We felt that base catalysis could provide an advantage, since enol ethers can degrade even under mildly acidic reaction conditions. The next alkene targeted was 2-methoxypropene, which was challenging due to its high volatility and reactivity (**Table 2.3**). Because aminocarbonylation with this alkene was never performed before, uncatalyzed conditions

were first tried to get calibration on its reactivity. As expected, no azomethine imine was observed (entry 1). A control was established at 70 °C with no base giving a 23 % NMR yield (entry 2).

Table 2.3 Alkene aminocarbonylation of methoxypropene and effect of basic additives^a

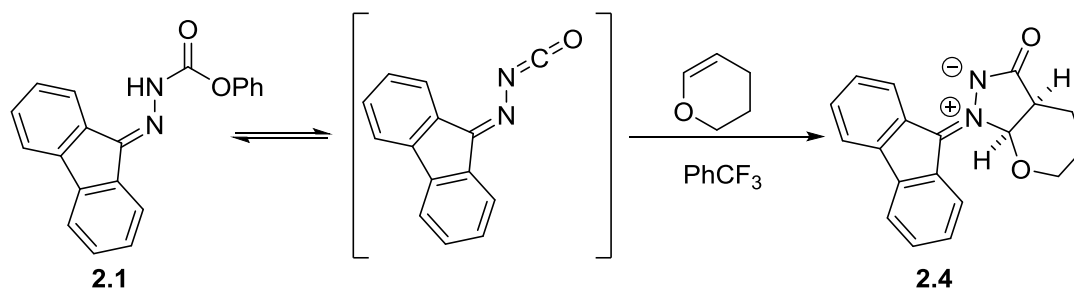


Entry	Time (h)	Temp. (°C)	Base	Equiv. hydrazone	Equiv. alkene	Yield ^b (%)
1	2	100	None	1	5	-
2	2	70	None	1	2	23
3	2	70	Et ₃ N	1	2	78
4	3	70	Et ₃ N	1.5	1	69

a) Conditions: Hydrazone, alkene, base (3 mol %) and PhCF₃ (0.1 M) were added to an oven dried vial, purged with inert gas and heated in oil bath of microwave reactor. **b)** Isolated yield

When 3 mol % of Et₃N was added, the yield increased to 78 % (entry 3). However, as the alkene became the limiting reagent the yield decreased slightly to 69 % (entry 4). At first this result seemed unusual but after considering the volatile nature of the alkene, it was thought that there might be a significant part of it in the gas phase of the sealed vial, unable to react with the imino-isocyanate. It also is important to note that the azomethine imine produced is not stable in chloroform and readily decomposes.

Our attention was then focused on dihydropyran (**Table 2.4**) in order to probe the reactivity needed for base catalysis to be useful. In other words, for which alkenes does the rate determining step switch to the aminocarbonylation rather than the formation of the imino-isocyanate. This would hopefully help us get better insight into this reaction. The control reaction was performed as before to give 20 % NMR yield (entry 1). In this case, when Et₃N was added, the yield of the reaction did increase but not significantly (entry 2). When increasing the temperature to 80 °C, the yield with addition of base was comparable to the yield in the absence of base (52 %, entry 3 and 56 %, entry 4). This suggests that at this temperature, the formation of the imino-isocyanate occurs thermally.

Table 2.4 Effect of basic additives on alkene aminocarbonylation with dihydropyran^a

Entry	Time (h)	Temp. (°C)	Base	Equiv. hydrazone	Equiv. alkene	Yield (%)
1	2.5	70	None	1.5	1	20
2	2.5	70	Et ₃ N	1.5	1	38
3	2.5	80	None	1.5	1	52
4	2.5	80	Et ₃ N	1.5	1	56
5 ^b	3	100	None	1	10	77
6 ^b	3	100	None	1.5	1	84
7 ^b	3	100	Et ₃ N	1.5	1	87

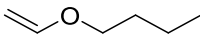
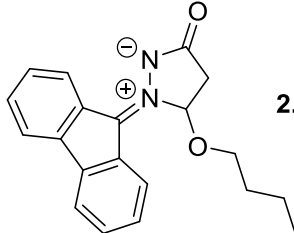
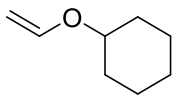
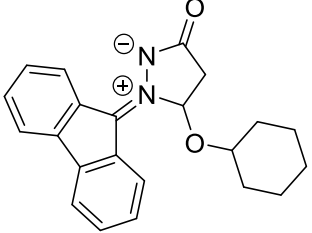
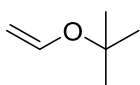
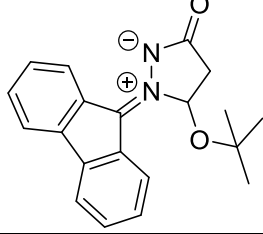

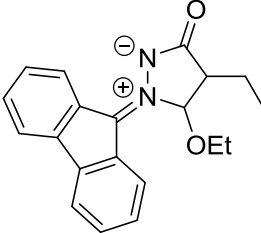
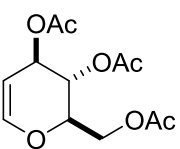
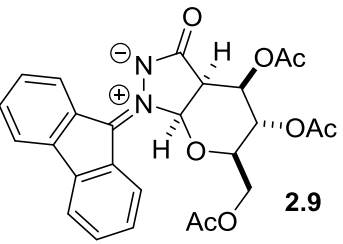
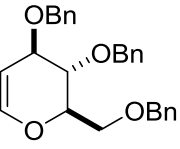
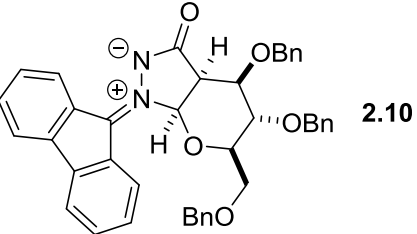
a) Conditions: Hydrazone, alkene, base (3 mol %) and PhCF₃ (0.1 M) were added to an oven dried vial, purged with inert gas and heated in oil bath of microwave reactor. **b)** Isolated yield

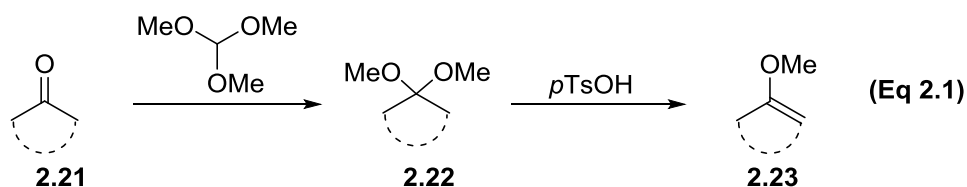
The reaction was then carried out at 100 °C with Et₃N using the alkene as limiting reagent. Surprisingly, the yield was slightly higher than previously reported (77 %, entry 5 and 87 %, entry 7). However, when the same reaction was run without base, a comparable yield of 84 % was obtained (entry 6). This suggested that the base is not required for imino-isocyanate formation, but it also does cause reaction inhibition at this temperature.

2.3 Alkene Aminocarbonylation with enol ethers

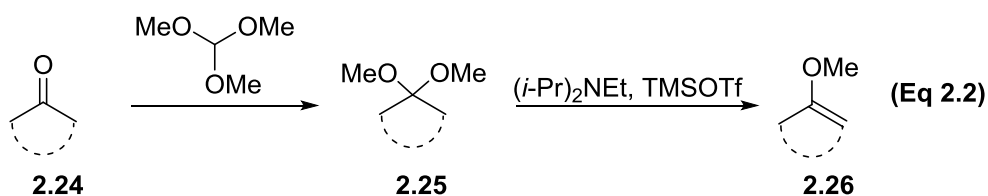
Other commercially available acyclic and cyclic enol ethers were then probed. All the alkenes depicted in **Table 2.5** afforded desired product. Aminocarbonylation with an acetyl-protected glucal (entry 7) have poor yields even at high temperatures. *tert*-Butyl vinyl ether gave the desired azomethine imine in moderate yield at 70 °C whereas no product was observed at 100 °C (entries 4 and 5). This suggests that, at higher temperature, decomposition was possible or that the cycloaddition is sensitive to steric hindrance.

Table 2.5 Alkene aminocarbonylation with commercially available enol ethers^a

Entry	Alkene	Azomethine imine	Equiv. hydrazone	Equiv. alkene	Temp. (°C)	Yield ^b (%)
1 ^c 2 ^c			1.5 1	1 10	70 100	68 75
3			1.5	1	70	72
4 5			1.5 1.5	1 1	70 100	41 -
6 ^{c,d}			1	2	100	70
7			1	2	100	16
8 ^c			1.5	1	100	76



Another method that was found in the literature involved a two-step synthesis to enol ethers.⁴⁸ First, the acetal is synthesized and isolated using the same conditions as described above. Then elimination is accomplished using *N,N*-diisopropylethylamine and TMSOTf (Equation 2.2).



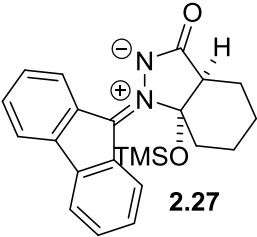
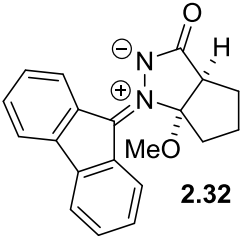
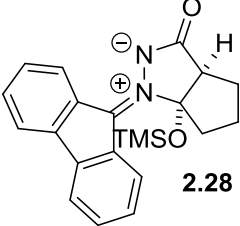
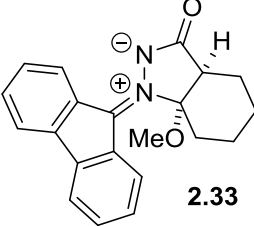
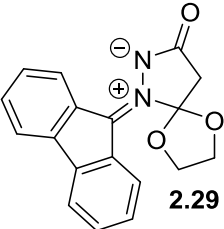
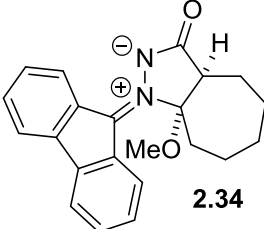
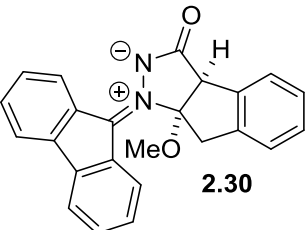
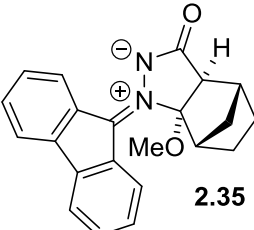
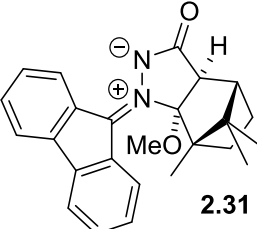
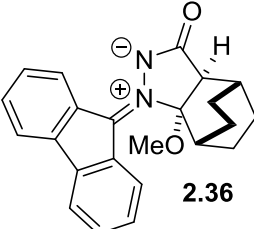
This method proved to be reliable and was used whenever the other method failed. As mentioned earlier, **2.20** has never been reported in the literature, and the parent ketone is not commercially available but can be synthesized following the literature (see supporting information). The synthesis of enol ether **2.20** required a total of 5 steps which are outlined in the experimental procedures. It has to be noted that the compound was not fully characterized since purification was difficult, and the crude mixture was used as-is for the alkene aminocarbonylation reaction.

After synthesizing all these enol ethers, they were tested as alkene aminocarbonylation reagents (Table 2.6). TMS protected enol ethers **2.11**, **2.12** and **2.13** did not form any desired product but showed degradation of the enol ether. Enol ether **2.14** proved to be unreactive towards aminocarbonylation, most likely due to steric hindrance. Camphor derived enol ether showed limited reactivity, however the product was unstable therefore isolation was not possible.

Fortunately, enol ethers **2.16** to **2.20** yielded the desired azomethine imines when the reactions were heated to 100 °C. Base catalysis was not possible for these alkenes. Cyclic 5-membered methyl enol ether **2.15** gave moderate yield of 63 % of the azomethine imine. Increasing the ring size to six-membered showed poor reactivity, but the product was nonetheless isolated in 25 % yield. This result was expected since it follows the trends observed in Table 2.2 and 2.4. Further increasing the ring size to seven restored some reactivity and the azomethine imine was isolated in a 57 % yield.

⁴⁸ References for procedures can be found in the supporting information.

Table 2.6 Alkene aminocarbonylation with prepared enol ethers^a

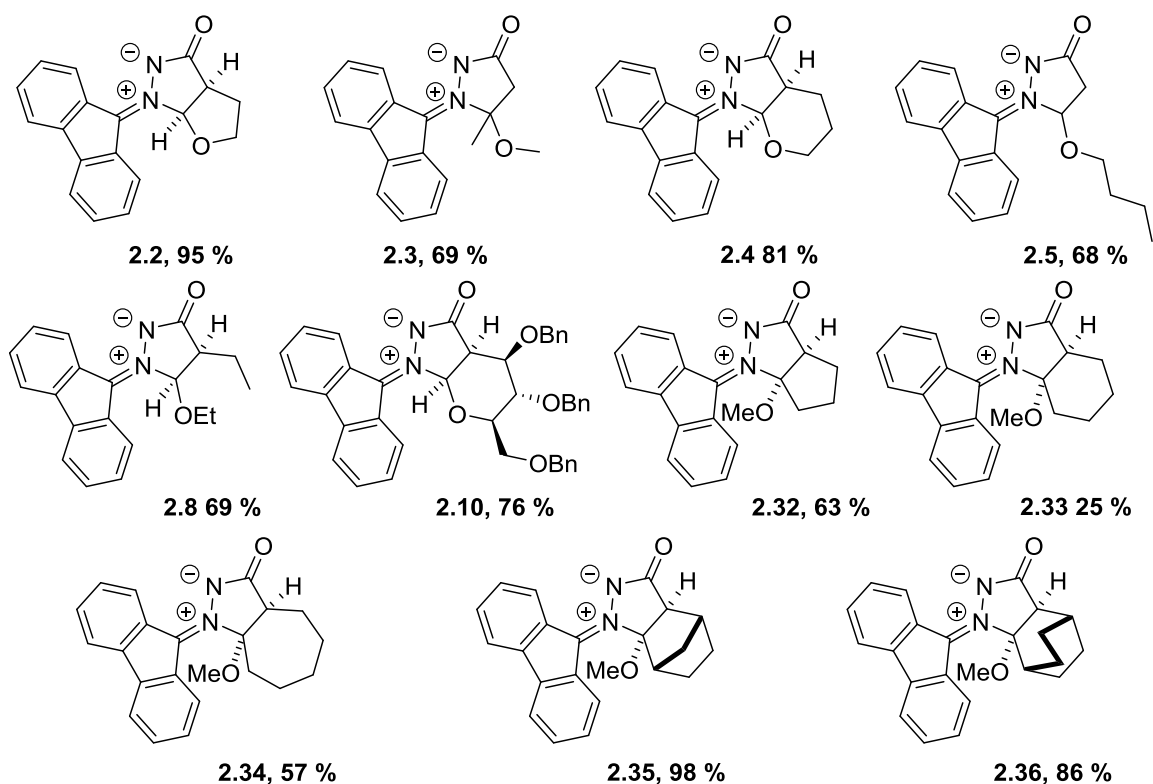
Entry	Alkene	Azomethine imine	Yield (%) ^b	Entry	alkene	Azomethine imines	Yield (%) ^b
1	2.11	 2.27	0	6	2.16	 2.32	63
2	2.12	 2.28	0	7	2.17	 2.33	25
3	2.13	 2.29	0	8	2.18	 2.34	57
4	2.14	 2.30	0	9 ^c	2.19	 2.35	98
5	2.15	 2.31	0	10	2.20	 2.36	86

a) Conditions: Hydrazone, alkene, base (3 mol %) and PhCF₃ (0.1 M) were added to an oven dried vial, purged with inert gas and heated in oil bath of microwave reactor at 100 °C. **b)** Isolated yields. **c)** Reaction performed by Amanda Bongers

Moving on to bicyclic enol ethers **2.19** and **2.20**, it was expected that the reactivity would improve because they are strained, and the cycloaddition would release some strain. Indeed, **2.19** proved to be extremely reactive. Regardless of whether the hydrazone or the enol ether was limiting, the yield

was quantitative after 1 hour at 100 °C (by Amanda Bongers). This substrate would probably have been amenable to base catalysis, but since the azomethine imine was obtained quantitatively, no further optimization was done. The crude enol ether **2.20** was also very reactive, 86 % of the corresponding azomethine imine was isolated using 2 equivalents of the enol ether.

The azomethine imines presented in **Table 2.6** are interesting because of their complexity, offering bicyclic as well as tricyclic cores. They are also functionalized, which gives them potential for further transformations. In total, eight new azomethine imines were synthesized with enol ethers and the yields of three previously reported azomethine imines were improved. A summary of those results is presented in **Scheme 2.1**.



Scheme 2.1 Scope of alkene aminocarbonylation with enol ethers

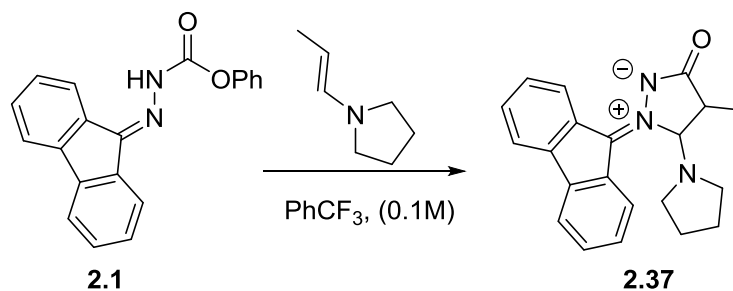
These results have not only allowed the extension of the scope of azomethine imines and the improvement of some yields by base catalysis, it has also provided a better understanding of the reaction. We have learned that for the fluorenone hydrazone, the formation of the imino-isocyanate is thermally favored at temperatures higher than 70 °C and that only very few alkenes are reactive enough in aminocarbonylation to make formation of the imino-isocyanate rate determining.

2.4 Alkene aminocarbonylation with enamines

With all these results in hand, we wanted to know if base catalysis could be extended to other electron rich alkenes such as enamines. Enamines would give, similarly to enol ethers, functionalized azomethine imines that could be used for further transformations.

To test this hypothesis, 1-propenyl-pyrrolidine was used with the fluorenone derived hydrazone. First, previously reported conditions (3 h, 100 °C) were used. No aminocarbonylation product was observed by NMR, however there were several byproducts seen by TLC and all starting materials had been consumed. Then, lower temperatures were tested (2 h, 70 °C) (**Table 2.7**) and this time no azomethine imine was formed, but also no significant byproducts.

Table 2.7 Aminocarbonylation with 1-propenyl-pyrrolidine^a



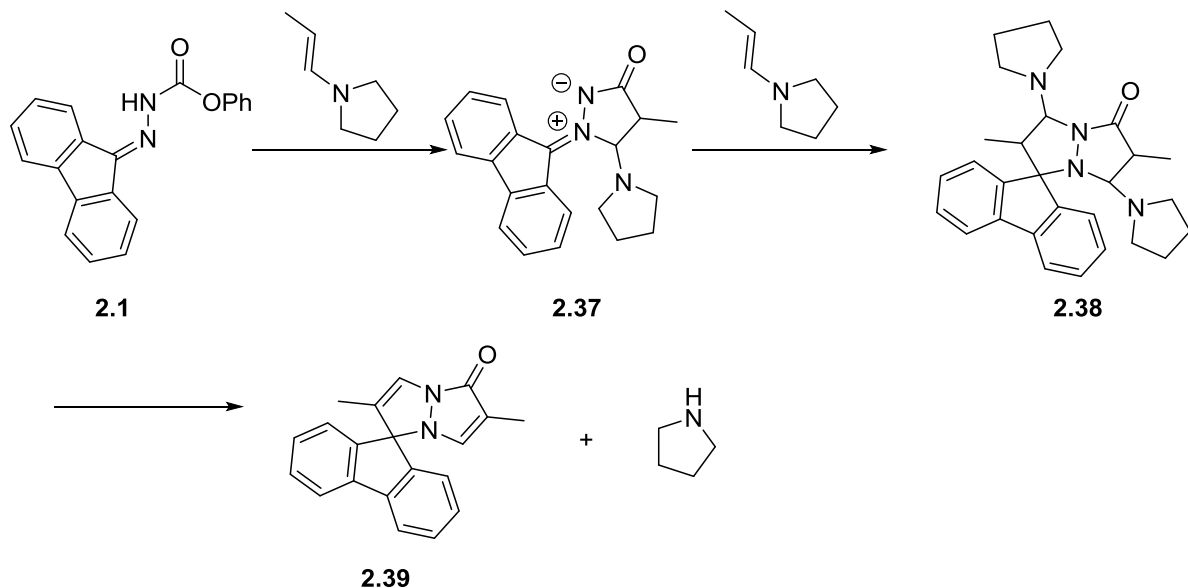
Entry	Time (h)	Temp. (°C)	Equiv. hydrazone	Equiv. alkene	Yield (%) ^b
1	3	100	1.2	1	-
2	2	70	1.5	1	-

a) Conditions: Hydrazone, enamine (1 equiv.) and PhCF₃ (0.1 M) were added to an oven dried microwave vial, purged with inert gas and heated in a wax bath for 2-3 hours. b) NMR yield

At this point, identification of the products from different side reactions was conducted. The main spot observable by TLC from the reaction performed at 100°C was isolated by flash column chromatography. The spot was less polar than the starting hydrazone. Once the compound was isolated, it was analyzed by proton NMR and by mass spectrometry.

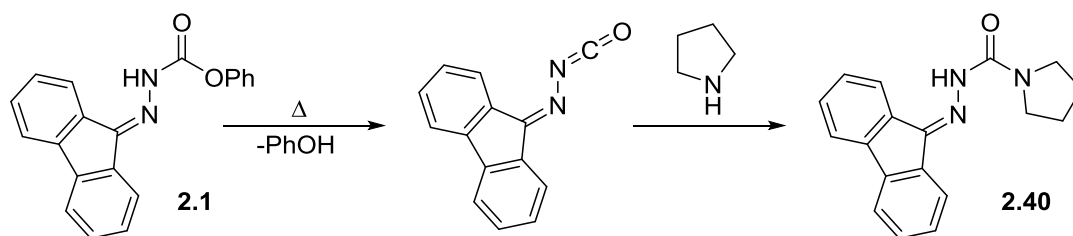
By NMR, the less polar compound did not have any signals for the pyrrolidine and showed two slightly deshielded singlets, each integrating for 3 protons in the aliphatic region. In the crude reaction mixture proton NMR, one equivalent of phenol was present but the aromatic region was still very similar to the starting hydrazone. Based on these observations, it was proposed that aminocarbonylation does occur, but that the azomethine imine generated underwent a dipolar

cycloaddition with another molecule of 1-propenyl pyrrolidine. Then, elimination of both pyrrolidine molecules would occur, aromatization being the driving force, to give the bicyclic double adduct (**Scheme 2.2**).



Scheme 2.2 Proposed double cycloaddition/double elimination by product formation

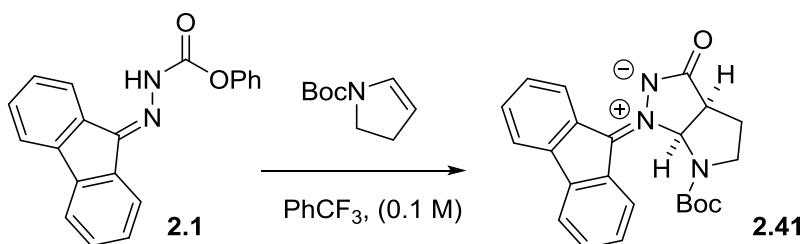
There was only one equivalent of the enamine and half of it was being used by the second cycloaddition. Therefore, a lot of hydrazone was left in the mixture. However, the elimination released pyrrolidine which is a great nucleophile. It has been shown previously that substitution with pyrrolidine occur readily on hydrazones, therefore another byproduct is the pyrrolidine substituted hydrazone (**Scheme 2.3**). The new hydrazone is much more stable as pyrrolidine is not a good leaving group, and consequently the imino-isocyanate does not form easily. Both the newly formed hydrazone and the double cycloaddition/double elimination product were successfully identified by mass spectrometry.



Scheme 2.3 Substitution of phenol for pyrrolidine

A less electron rich cyclic enamine such as 1-Boc-2,3-dihydropyrrole was then used to present the second cycloaddition. First the reaction was conducted at 100 °C, but no azomethine was formed. When performing the reaction at 70 °C and 3 mol % of triethylamine, a 60 % yield of azomethine imine was observed by crude NMR (**Table 2.8**).

Table 2.8 Aminocarbonylation with 1-Boc-2,3-dihydropyrrole^a



Entry	Time (h)	Temp. (°C)	Base (3 mol %)	Equiv. hydrazone	Equiv. alkene	Yield (%) ^b
1	3	100	None	1	2	-
2	2	70	Et ₃ N	1	2	60

a) Conditions: Hydrazone, enamine (2 equiv.) and PhCF₃ (0.1 M) were added to an oven dried microwave vial, purged with inert gas and heated in a wax bath for 2-3 hours. b) NMR yield.

The azomethine imine formed is very unstable. The purification was attempted by quick flash column chromatography but the characterization was impossible due to fast decomposition to a bright orange product that could not be identified. In the case of enamines, base catalysis seems possible, however the azomethine imines formed are either undergo a dipolar cycloaddition with the enamine or decompose readily.

2.5 Exploration of base catalysis on intramolecular aminocarbonylation reactions

Our group has mainly focused its attention on intermolecular aminocarbonylation because examples were rare in the literature. However, we have a few unpublished examples of intramolecular aminocarbonylation with imino-isocyanates, and these reactions require high temperatures. Therefore it was natural to explore the possibility of using base catalysis to achieve the transformation under milder reaction conditions.

The substrate chosen for these experiments (**Figure 2.2**) contains a pentenyl chain, a methyl group on the other side of the imine nitrogen and phenol as the leaving group.

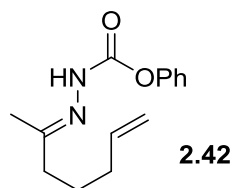
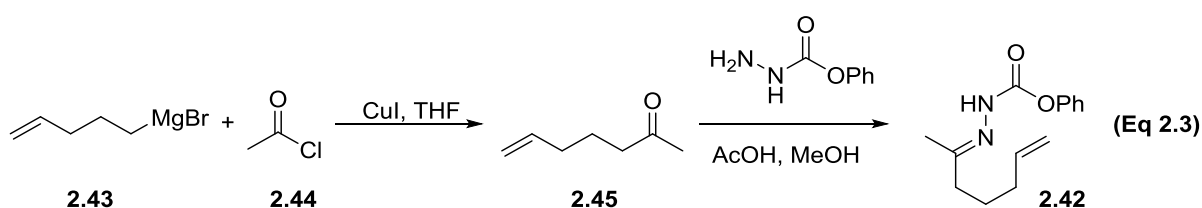
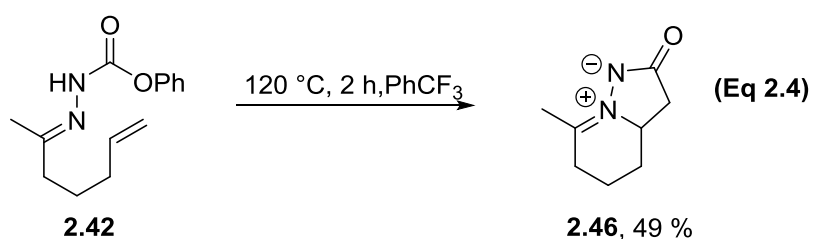


Figure 2.2 Hydrazone chosen for intramolecular aminocarbonylation

This hydrazone has an aliphatic chain long enough to allow aminocarbonylation and would form a 5-6 bicyclic product. The hydrazone was prepared starting with a Grignard reaction with acetyl chloride to form the corresponding ketone, followed by condensation onto *O*-phenyl carbazate (Equation 2.3).⁴⁹



The condensation on the ketone was difficult and the hydrazone was only obtained in 22 % yield on small and large scale reactions, but enough material was obtained to continue. The hydrazone was subjected to 120 °C in the microwave reactor for three hours and gave only 49 % to 67 % NMR yield of the corresponding azomethine imine (Equation 2.4).



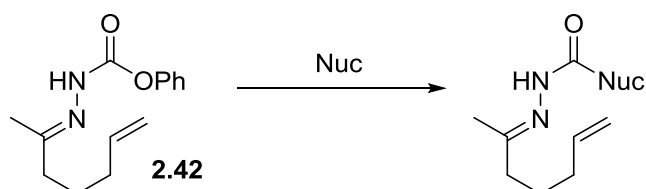
The same reaction was carried out at 50 °C with Et₃N for six hours. No aminocarbonylation product was formed, however a full equivalent of phenol was produced. The byproduct formed was extremely similar to the starting material by proton NMR. Heating up to 80 °C gave the same result.

⁴⁹ Gribkiv, D. V.; Hultzs, K. C.; Hampel, F. J. *Am. Chem. Soc.* **2006**, *128*, 3748.

A small solvent scan was conducted at 50 °C to see if it would impact the outcome of the reaction. Chlorobenzene gave only byproduct formation whereas the hydrazone remained unreacted in toluene and methanol.

Then the effect of leaving groups was evaluated. Studies by a previous member of our group, Ms. Keira Garland, showed that having hexylamine as a leaving group facilitated the formation of the imino-isocyanates in certain cases.⁵⁰ Substitution with hexylamine was attempted following known procedures. The product was observed by NMR, but isolation was surprisingly unsuccessful, giving a mixture of the desired hydrazone and nucleophile. The same results were obtained with diisopropyl amine as the nucleophile. Substitution with thiophenol gave the desired hydrazone albeit in low yield (**Table 2.9**).

Table 2.9 Synthesis of hydrazones by substitution with nucleophiles^a



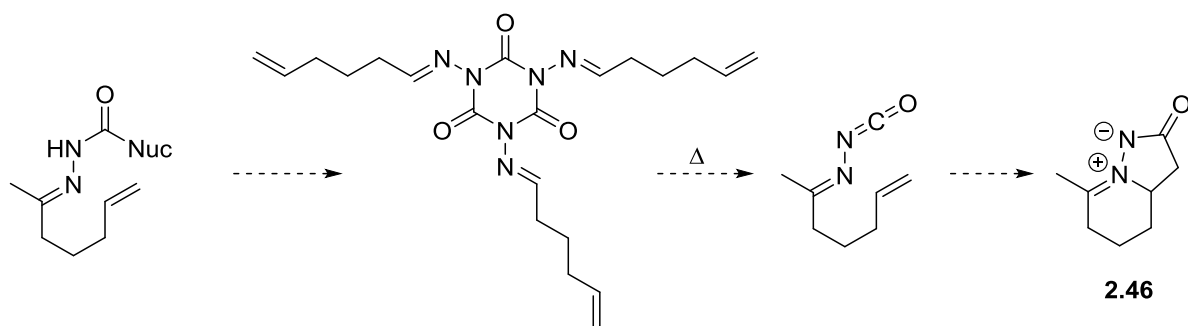
Entry	Nucleophile	Temp. (°C)	Time (h)	Yield (%) ^b
1 (2.47)	Hexylamine	Rt	0.3	-
2 (2.48)	<i>i</i> -Pr ₂ NH	rt-60	1	-
3 (2.49)	Thiophenol	150	0.15	33

a) Conditions: Hydrazone, nucleophile (2-5 equiv.) and trifluorotoluene (0.2 M) were added to an oven dried microwave vial. b) Isolated yields

Aminocarbonylation was attempted on thiophenol substituted hydrazone increasing the temperature 150 °C. No azomethine imine was observed at any point by TLC, only byproduct was formed. Identification of the byproduct formed was then necessary in order to gain a better understanding of what was going on.

⁵⁰ Keira Garland, A Practical Approach to Semicarbazone and Hydrazone Derivatives via Imino-Isocyanates, M.Sc. Thesis, University of Ottawa, 2014.

It is well documented that dimerization of *N*-substituted isocyanates is possible. As described by Lwowski, low concentrations are required to trap the isocyanate and avoid formation of dimers, trimers, and polymers.⁵¹ Based on this, the first hypothesis was that the byproduct was a trimer of the imino-isocyanate. This seemed reasonable since the trimer would look very similar to the hydrazone by NMR. It is also known that, depending on the substituents, the oligomers of *N*-substituted isocyanates can decompose back to the isocyanate upon heating. Therefore, if we were really in the presence of the trimer, we should be able to heat it up and potentially observe aminocarbonylation reactivity (**Scheme 2.4**).



Scheme 2.4 Trimerization of imino-isocyanate

Unfortunately, the byproduct is very stable and no reaction was observed. After careful analysis of the proton NMR, there seems to be broad bands that could correspond to N-H protons, which is not in accordance with the structure proposed above. The mass obtained by high resolution electron impact also did not match. To better probe what was going on, we studied the acetophenone derived hydrazone. The advantage of using this hydrazone is that it doesn't contain a reactive alkene. The hydrazone was heated to 80 °C in the presence of 10 mol % of Et₃N. Formation of a byproduct was observed with ejection of a full equivalent of phenol. Again, the proton NMR spectrum was nearly identical to the starting material. Because the byproduct formed was crystalline, the compound was submitted for X-ray crystallography (**Figure 2.3**)

⁵¹ Lockley, W. J. S.; Lwowski, W., *Tetrahedron Lett.* **1974**, *15*, 4266.

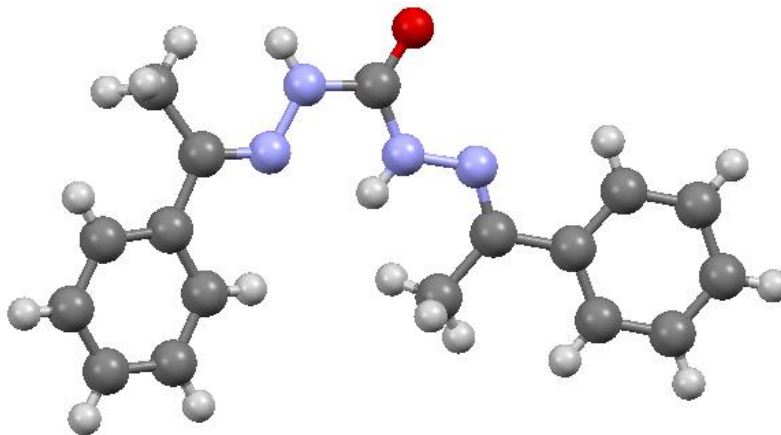
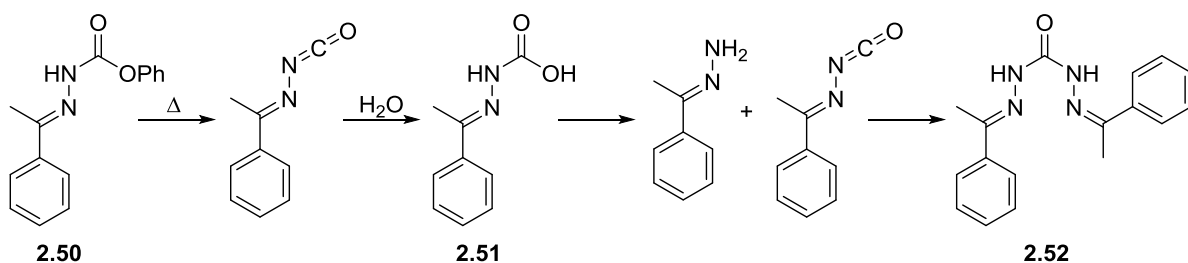


Figure 2.3 X-ray of by product

This X-ray structure shows that the byproduct is in fact a dihydrazone. This was somewhat surprising, but looking back to **Scheme 1.6** it should have been expected. The byproduct formation might occur through decarboxylation of the imino-isocyanate in the presence of trace water, releasing a free NH_2 hydrazone that can act as a nucleophile on another molecule of imino-isocyanate (**Scheme 2.5**). The NMR and mass spectra of these byproducts matches with the proposed dihydrazone structure.



Scheme 2.5 Proposed reaction sequence for formation of dihydrazone

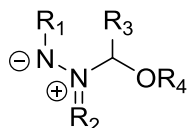
The formation of this product is surprising since dry solvents from a solvent system were used and the reactions are performed under inert atmosphere. Adding molecular sieves to the mixture did not solve the issue, suggesting a different pathway might be involved.

2.6 Conclusions for Chapter 2

In this part, it was shown that base catalysis could be extended to a few very reactive enol ethers. Even if nitrogen-containing bases are not assisting in the reaction, they are well tolerated in the

system. The rate determining step, either imino-isocyanate formation or aminocarbonylation, is highly substrate and temperature dependant. As a general rule, aminocarbonylation is the limiting step unless the reaction is performed at low temperature with very reactive alkenes.

The motif created using aminocarbonylation of enol ether is very difficult to obtain using other methods. The only other method described in the literature dates to 1982 and involves the reaction of hexafluoroacetone azine with enol ethers.⁵² Therefore, the scope of azomethine imines derived from enol ethers was significantly expanded.



These azomethine imines are functionalized and could be used to synthesize other interesting heterocycles such as pyrazolones, which will be discussed in **Chapter 3**. Aminocarbonylation with enamines has the potential to be catalyzed by basic additives, however the azomethine imines formed are either very reactive or decompose readily. Further optimization would be needed to achieve the products in good yields. *In situ* reduction and aromatization of azomethine imines to access corresponding pyrazolones is the next stage of this project. Finally, while studying intramolecular aminocarbonylation, it was shown that some hydrazones form a dihydrazone as the major product, preventing the intramolecular reaction.

⁵² Burger, K.; Hein, F. *Liebigs Ann. Chem.* **1982**, *5*, 853.

Chapter 3: Synthesis of Pyrazolones

3.1 Introduction

Pyrazolones are nitrogen containing aromatic heterocycles that are important to several industries, for example they are found in many pharmaceuticals,⁵³ agrochemicals⁵⁴ as well as in dyes and pigments (Figure 3.1).⁵⁵ Pyrazolones have possible isomers, 3-pyrazolone and 5-pyrazolone, and both are found in biologically active compounds.

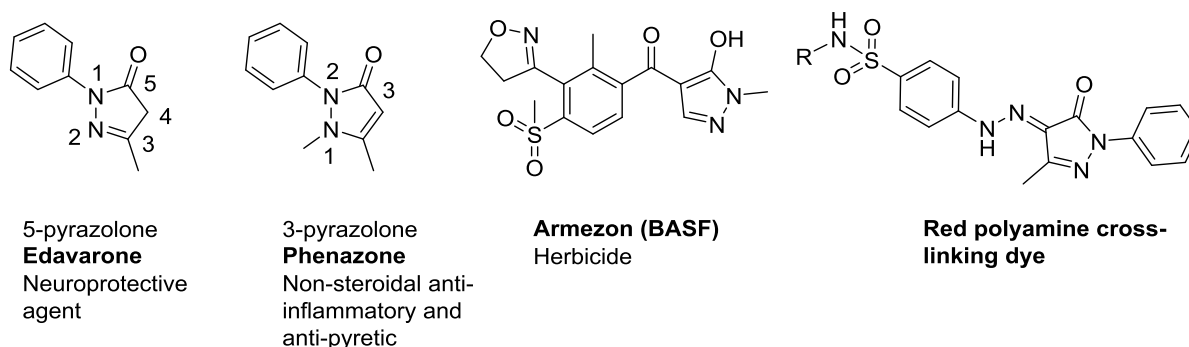


Figure 3.1 Pyrazolones in the industry

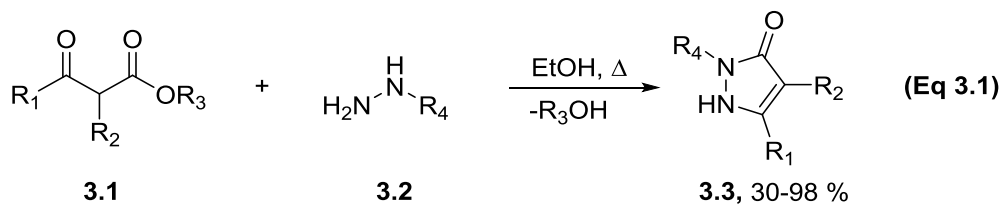
There are many synthetic approaches to 3-pyrazolones, but all involve the reaction of a hydrazine with a β -keto ester or equivalent, to form a hydrazone or hydrazide as the key intermediate. These methods have very similar disconnections and thus lack diversity in the synthesis of 3-pyrazolones. However, a lot of work has been done on derivatization of pyrazolones, for example functionalization on the different positions of the cycle. The next few pages will overview the key methods available for the synthesis of pyrazolones.

⁵³ a) Bondock, S.; Rabie, R.; Etman, H. A.; Fadda, A. A. *Eur. J. Med. Chem.* **2008**, *43*, 2122. b) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 450. c) Brogden, R. N. *Drug* **1986**, *32*, 60. d) Kawai, H.; Nakai, H.; Suga, M.; Yuki, S.; Watanabe, T.; Saito, K. I. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 921. e) Watanabe, T.; Yuki, S.; Egawa, M.; Nishi, H. *J. Pharmacol. Exp. Ther.* **1994**, 268. f) Volz, M.; Kellner, H. M. *Br. J. Clin. Pharmacol.* **1980**, *10*, 299. g) Laleu, B.; Gaggini, F.; Orchard, M.; Fioraso-Cartier, L.; Cagnon, L.; Houngninou-Molango, S.; Gradia, A.; Duboux, G.; Merlot, C.; Heitz, F.; Szyndralewicz, C.; Page, P. *J. Med. Chem.* **2010**, *53*, 7715.

⁵⁴ a) Maser, H.; Boehner, B.; Forey, W.; Eur. Patent. Appli. EP 268554; *Chem. Abstr.* **1988**, *110*, 2387 9. b) Kazuo, y.; Akira, M.; Norihiko, M.; Toshiro, M.; Kazutaka, A.; Shigera, I. *Pestic. Sci.* **1999**, *55*, 161.

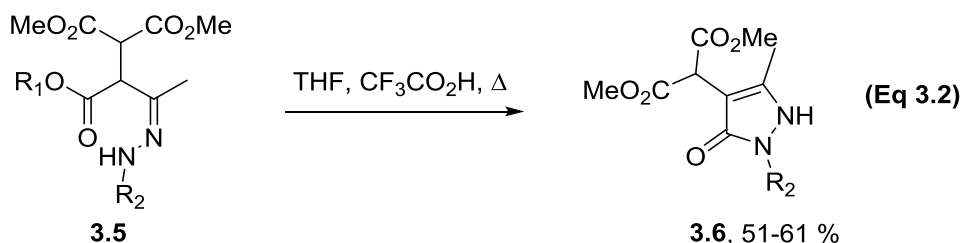
⁵⁵ a) Li, Y.; Zhang, S.; Yang, J.; Jiang, S.; Li, Q. *Dyes Pigm.* **2008**, *76*, 508. b) Metwally, A. A.; Khalifa, M.E.; Amer, F. A. *Dyes Pigm.* **2008**, *76*, 379.

The most widely used method to synthesize these aromatic heterocycles is the condensation of hydrazines onto β -keto esters (**Equation 3.1**).⁵⁶



This method works well with hydrazine hydrates and substituted or heterocyclic hydrazines. The reaction typically requires high temperature, in some cases up to 180 °C. Most reactions also require acidic additives, however there are also several examples using basic additives. In this regard, the array of conditions available is useful when sensitive substrates are involved.

There are also many alternatives to β -keto esters. For example, 3-pyrazolones can be synthesized by cyclization of hydrazones (**Equation 3.2**).⁵⁷ However, the hydrazone is merely an intermediate from the reaction between hydrazines and β -keto esters and the high temperature requirement is still present.

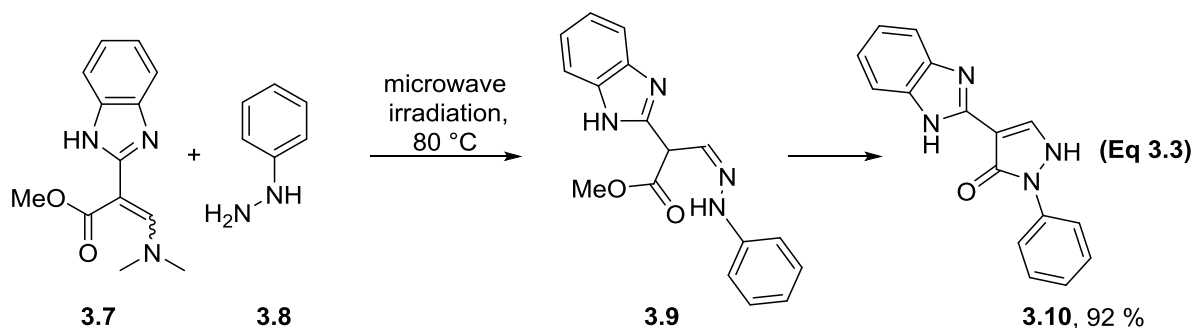


Similar cyclizations can also occur with β -enaminoesters (**Equation 3.3**).⁵⁸ First, conjugate addition of the hydrazide on the β -enaminoester occurs, followed by loss of dimethylamine. The authors refer to this as an aza-annulation. The corresponding hydrazones are formed as key intermediates and react as described above.

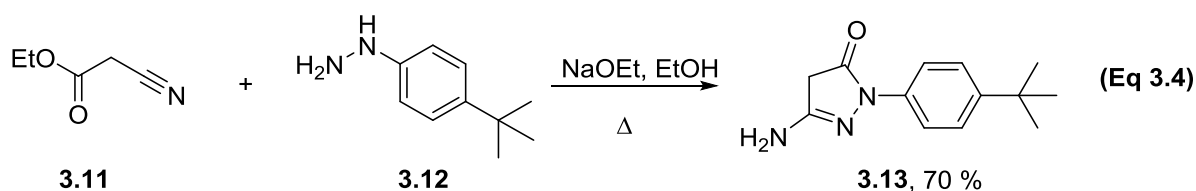
⁵⁶ Varvounis, G., Pyrazol-3-ones: Part IV: Synthesis and Applications. *Advances in Heterocyclic Chemistry*. Alan R. Katritzky. Elsevier, **2009**; vol. 98; pp. 1-328.

⁵⁷ Attanasi, O. A.; Gescentini, L. D.; Favi, G.; Filipone, P.; Paolino, M. F.; Santeusano, S. *Synthesis*, **2002**, 1546.

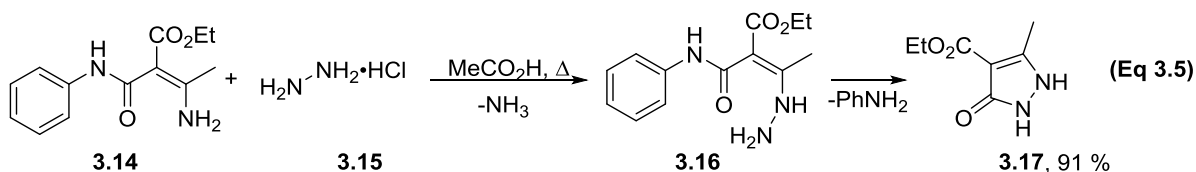
⁵⁸ Meddad, N.; Rahmouni, M.; Derdour, A.; Bazureau, J. P.; Hamelin, J. *Synthesis*, **2001**, 581.



Cyanoesters are also suitable partners for condensation with hydrazines to form 5-pyrazolones. The resulting hydrazone can cyclize in a similar way as described earlier to form 3-pyrazolones. This reaction is generally conducted in basic medium (**Equation 3.4**).⁵⁹



The reaction between hydrazines and α,β -unsaturated esters can also form 5-pyrazolones by initial conjugate addition of the hydrazine on the ester and elimination followed by cyclization (**Equation 3.5**).⁶⁰ There are only a few examples of this in the literature.



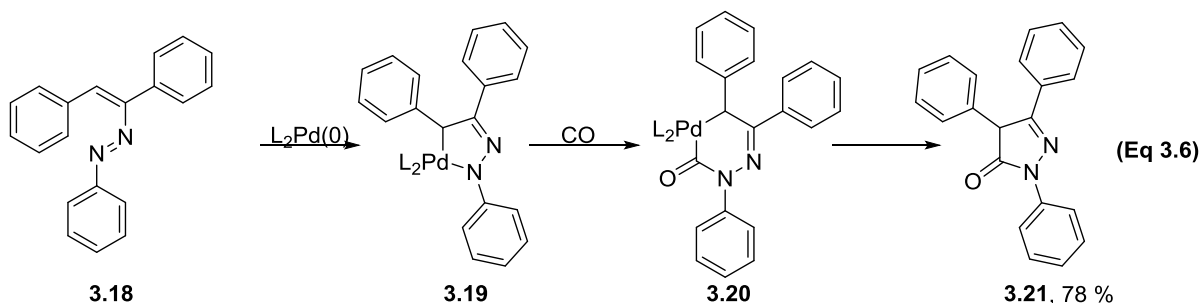
There are many more different examples of pyrazolone synthesis that have different starting points but all involve the formation of a hydrazone or hydrazone as the key intermediate. The main limitation of these methods comes from the synthesis of the starting materials; installing substituents on β -ketoesters can be difficult and often requires many steps. In the case of hydrazines, the main problem is the installation of different substituents on one of the nitrogens

⁵⁹ Duffy, K. J.; Darcy, M. G.; Delorme, E.; Dillon, S. B.; Eppley, D. F.; Erikson-Miller, C.; Giampa, L.; Hopson, C. B.; Huang, Y.; Keenan, R. M.; Lamb, P.; Leong, L.; Miller, S. G.; Liu, S.; Price, A. T.; Rosen, J.; Shah, R.; Shaw, T. N.; Smith, H.; Stark, K. C.; Tian, S.-S.; Tyree, C.; Wiggall, K. J.; Zhang, L.; Luengo, J. I. *J. Med. Chem.* **2001**, *44*, 3730.

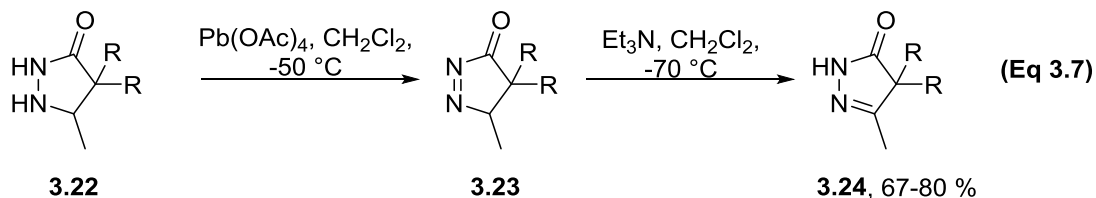
⁶⁰ Jung, J. C.; Watkins, E. B.; Avery, M. A. *Synth. Commun.* **2002**, *32*, 3767.

with regioselectivity. All of the above methods have very similar disconnections and thus lack diversity in the synthesis of pyrazolones.

There are other alternative routes to synthesize the pyrazolone motif. A good example of this would be palladium-catalyzed carbonylation of 1,2-diazabutadienes using carbon monoxide (**Equation 3.6**).⁶¹ However, there is only one example of this in the literature and it is limited to one substrate.



5-Pyrazolones can be formed by the oxidation of pyrazolidinones usually with lead tetraacetate. Isomerization to the 5-pyrazolone can easily be induced in the presence of base such as triethylamine (**Equation 2.7**).⁶²

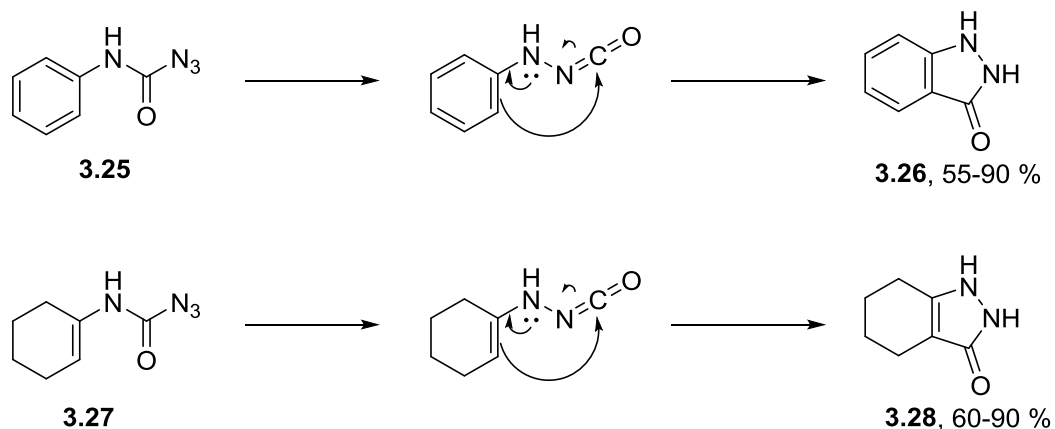


Lastly, Chupp reported in 1971 that pyrazolones can be obtained by cyclization of electron rich π -bonds and amino-isocyanates, which is of particular interest to the Beauchemin group.⁶³ This work showed that aryl or alkenyl carbamoyl azides form amino-isocyanates through a Curtius rearrangement. In the absence of a reagent to trap the isocyanate, the adjacent π -electrons attack the amino-isocyanate to form a pyrazolone upon tautomerization (**Scheme 3.1**).

⁶¹ Boeckman, R. K.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651.

⁶² Nagata, W.; Kamata, S. *J. Chem. Soc.* **1970**, 540.

⁶³ Chupp, J. P. *J. Heterocycl. Chem.* **1971**, *8*, 557.



Scheme 3.1 Synthesis of pyrazolones from aryl and alkenyl carbamoyl azides

The oxidation and Curtius approaches to access the heterocyclic core provide different disconnections. However, the scope for both these reactions is limited to very specific substrates.

From this review of the literature there is clearly a lack of diversity in the synthesis of the pyrazolone heterocyclic core. The method that is most widely used is the condensation of hydrazines onto β -ketoesters, which offers many different reaction conditions. On the other hand, the reactions involve the use of high temperatures, acidic or basic additives, and hydrazines that can sometimes be sensitive. It can also be difficult to selectively install substituents on the hydrazines, and the synthesis of substituted β -keto esters and derivatives can be lengthy. Other methods such as palladium-catalyzed carbonylation of 1,2-diazabutadienes, oxidation of pyrazolidinones, and cyclization of amino-isocyanates that are used to synthesize pyrazolones have a very limited scope. Thus complex and diversified pyrazolones are typically only available upon derivatization of simpler pyrazolones.

3.1.1 Project Objectives

As shown above, there are not many different ways to synthesize diversified pyrazolone cores using different building blocks. We sought to develop a general, mild method to synthesize the heterocyclic motif with a totally different disconnection. This could be valuable especially when the methods described above fail or are unpractical, for example due to hydrazine sensitivity, or lack of chemoselectivity. The goal of this project was to use the functionalized azomethine imines prepared in **Chapter 2** to synthesize pyrazolones.

3.2. Results and Discussion

3.2.1 Synthesis of pyrazolones via azomethine imines

Azomethine imines share a cyclic core with pyrazolones as well as pyrazolidinones, they differ by their oxidation states. Based on previous studies on using $\text{NNC}=\text{O}$ building blocks, it was envisioned that nitrogen-substituted isocyanates could be used to synthesize pyrazolones from alkenes via azomethine imines. This approach would be different from previously reported methods since simple and readily available alkenes would be used to generate the heterocycle. The imino-isocyanates can easily be obtained from their corresponding hydrazones, which act as blocked *N*-substituted isocyanates. It is already established by the Beauchemin group that a wide variety of azomethine imines can be obtained by alkene aminocarbonylation with imino-isocyanates. Accessing pyrazolones would first involve building the heterocyclic core by synthesizing corresponding azomethine imines. Then, the azomethine imine could be reduced to a pyrazolidinone followed by the aromatization of the cyclic core to form the pyrazolone (**Figure 3.2**).

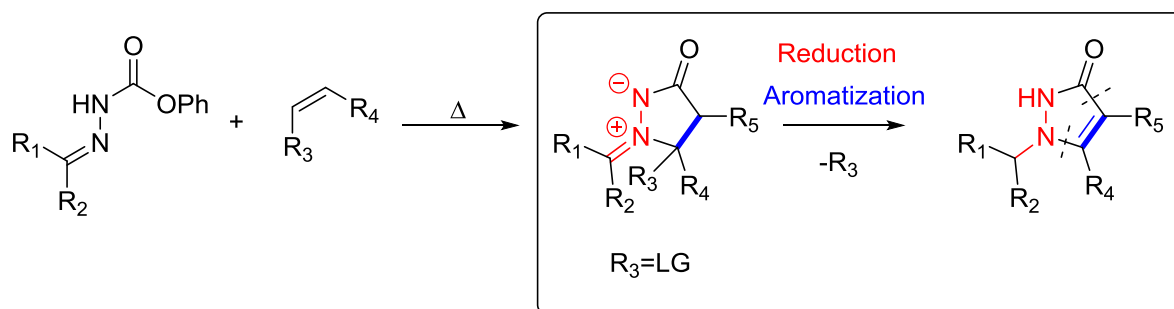


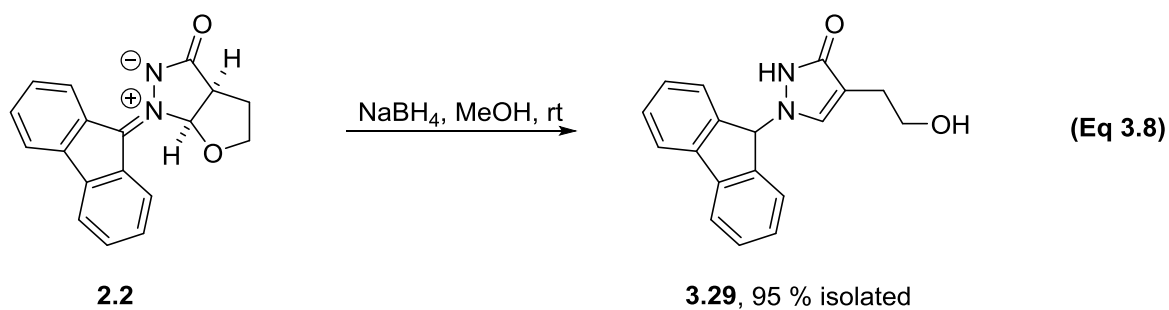
Figure 3.2 Proposed reduction and aromatization of azomethine imines to pyrazolones

It is well precedented that azomethine imines can be reduced to pyrazolidinones using simple reducing agents such as sodium borohydride.⁶⁴ We imagined that having R_3 as a leaving group we could aromatize the ring to access pyrazolones. The azomethine imines synthesized from enol ethers seemed perfect to achieve the desired transformation. The advantage of this approach is that we already know that enol ethers have excellent reactivity in alkene aminocarbonylation when fluorenone derived hydrazone is used.

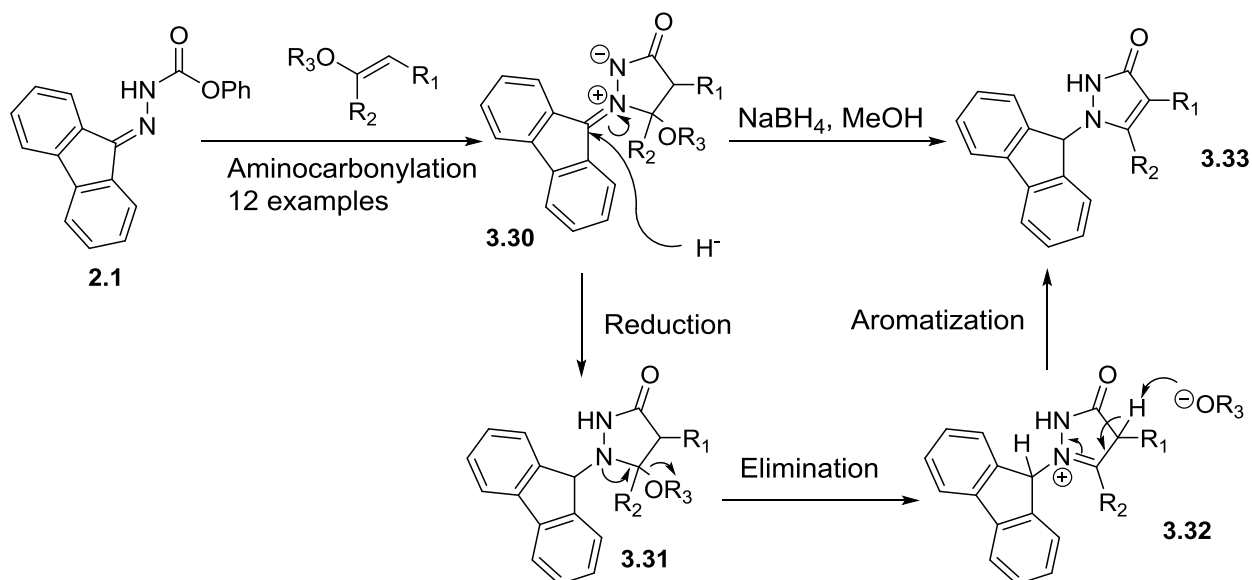
With this in mind, the reduction/aromatization was first attempted on an azomethine imine derived from dihydrofuran, using sodium borohydride as a reducing agent in methanol at room

⁶⁴ Suarez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244.

temperature. As soon as the reducing agent was introduced into the mixture, the solution turned from bright yellow to off-white. The transformation was complete in approximately 10 minutes with full consumption of the starting material and conversion to only one product. Analysis by NMR and mass spectrometry confirmed that desired pyrazolone was indeed synthesized in near quantitative yield (**Equation 3.8**).



The proposed mechanism for the formation of pyrazolones from azomethine imines is shown in **Scheme 3.2**. The reduction of the azomethine imine derived from an enol ether give a pyrazolidinone. This would lead to the restoration of electron density on the nitrogen, which would then be able to induce ejection of an alkoxide. The intermediate formed could then aromatize rapidly, the driving force of this reaction being the aromatization.

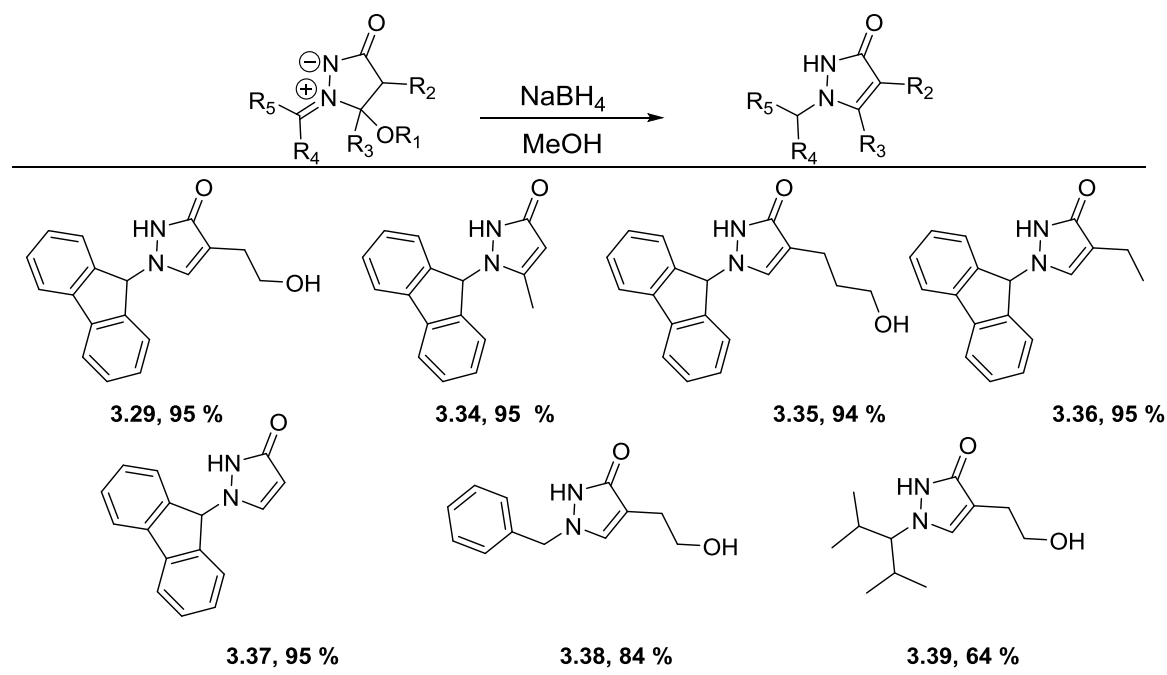


Scheme 3.2 Proposed mechanism for the synthesis of pyrazolones from azomethine imines

With this promising results in hand, other substrates were then derivatized into pyrazolones, first starting with the azomethine imines prepared in **Chapter 2 (Scheme 2.1)**. It was found that

formation of pyrazolones from the azomethine imines derived from acyclic and simple cyclic enol ethers provided the desired pyrazolones in near quantitative yields (**Scheme 3.4**). It is important to mention that the reaction is typically complete in less than 30 minutes. This is most likely due to fast reduction and a favorable aromatization.

Table 3.1 Derivatization of cyclic and bicyclic azomethine imines into pyrazolones^a



a) Conditions: azomethine imine, NaBH_4 (10 equiv.) and MeOH (0.05 M) were added to a round bottom flask and stirred at room temperature until gas evolution stopped

An interesting entry is **3.36** since it required 4 hours to reach completion. The explanation for this result might come from the isomeric structure of the azomethine imine. By NMR, this substrate had a ratio of 1:16 of the *syn:anti* isomers.

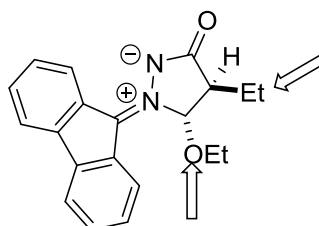
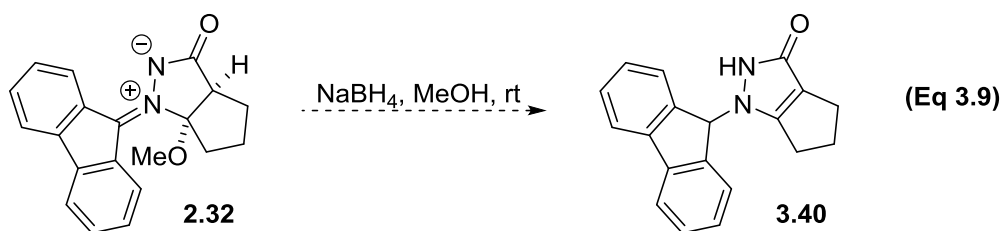


Figure 3.3 Thermodynamic isomer after alkene aminocarbonylation

This means that the ethyl group is *anti* to the leaving group (**Figure 3.3**). In all the other examples, the side chain was *syn* to the leaving group. This leads to an eclipsed conformation which destabilizes this isomer and favors a fast aromatization. The longer reaction time could then potentially be explained the loss of this destabilizing interaction, leading to less favorable and slower aromatization.

Derivatization of azomethine imines bearing different substituents on the nitrogen atom was then conducted. When the protecting group was a benzyl (**3.38**), 84 % of the pyrazolone was obtained whereas when diisopropyl (**3.39**) was used, 64 % was obtained. It must be noted that in the case of **3f**, the isolation of the azomethine imine was difficult, so reduction/aromatization was performed on the crude mixture. The isolated yield of the pyrazolone was determined based on the NMR yield of the alkene aminocarbonylation. These conditions were then applied to more complex substrates, such as the azomethine imines derived from enol ethers that were not commercially available. The first attempt (**Equation 3.9**) gave unexpected results.



The reaction went to full conversion with a clean crude NMR. When the compound was submitted for mass spectrometry, it was found that it was actually a mixture of two products that differed by 2 Daltons. Because there was an excess of reducing agent in the reaction mixture it was proposed that the pyrazolone and the corresponding pyrazolidinone were produced (**Figure 3.4**).

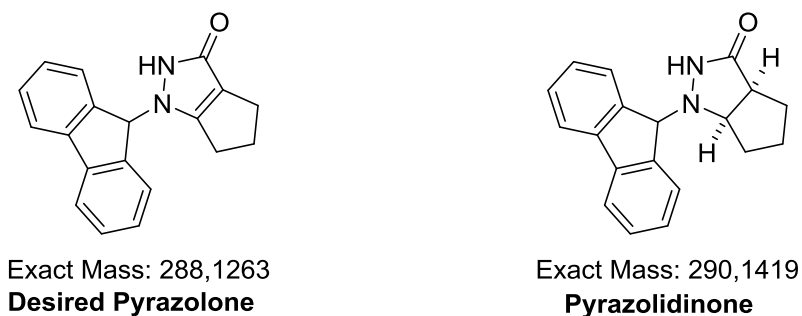
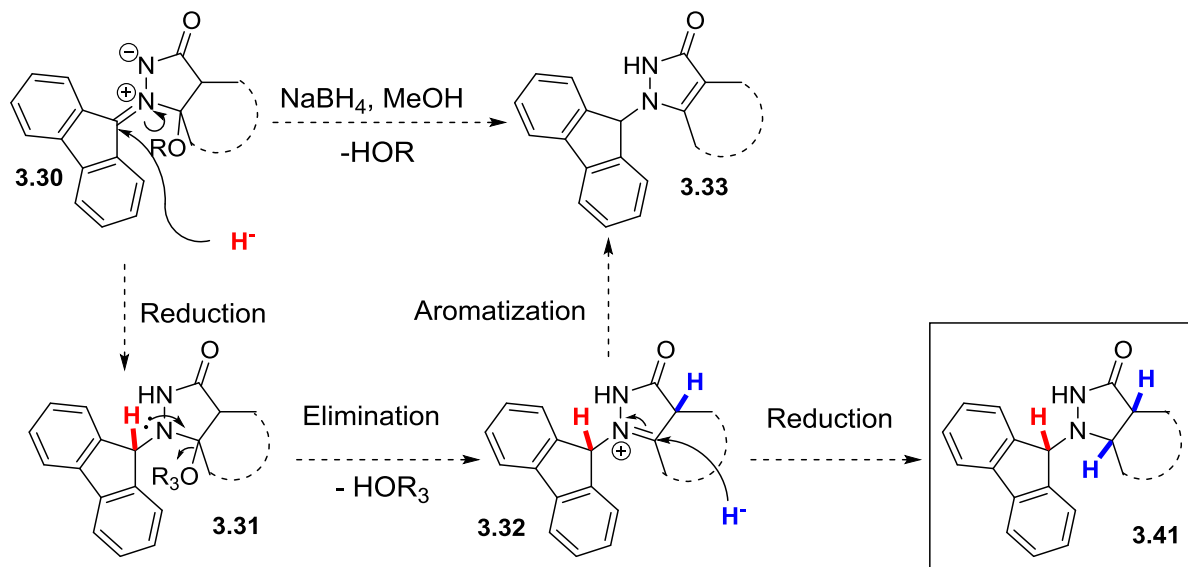


Figure 3.4 Proposed pyrazolone and pyrazolidinone formed under reducing conditions

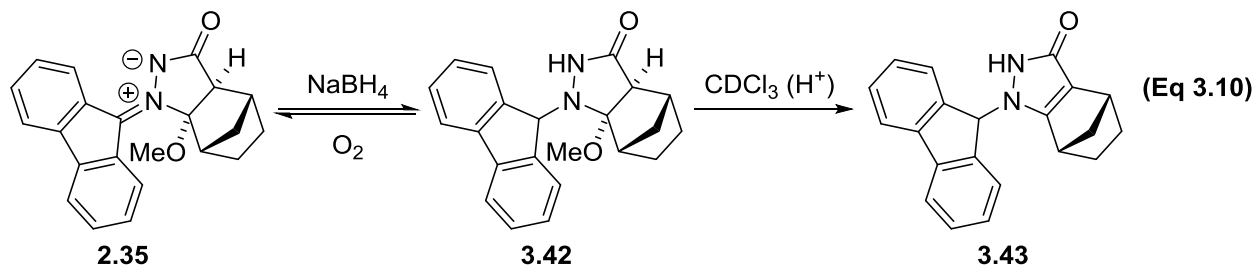
This was very surprising because in the previous examples, the aromatization seemed to be the driving force for this transformation. This result then implies that once the reduction and elimination have occurred, a second reduction occurs. This may be rationalized by the fact that even though aromatization is energetically favored, the pyrazolone formed is strained (**Scheme 3.3**). Furthermore, the aromatic stabilization energy is not as important in cycles containing multiple heteroatoms.



Scheme 3.3 Proposed pathway for the formation of pyrazolidinone

Different reaction conditions were then investigated to avoid this side reaction. First, milder reducing agents such as NaCNBH_3 and $\text{NaBH}(\text{OAc})_3$ were used, but no reaction was observed. Decreasing the equivalents of NaBH_4 to only one still led to formation of undesired doubly reduced pyrazolidinone **3.31**.

The temperature was lowered to 0 and $-20\text{ }^\circ\text{C}$. In this case, the reaction seemed to go to full conversion to the intermediate pyrazolidinone (**3.31**), which was supported by the fact that it quickly re-oxidized to the azomethine imine in the presence of air. Interestingly, when the same product was dissolved in deuterated chloroform the solution turned from yellow to off-white within seconds and a pyrazolone was observed by NMR (**Equation 3.10**). Based on these observations, pyrazolidinone **3.31** was proposed as an intermediate. This intermediate has since been observed by NMR. Several acidic additives were investigated at lower temperatures based on the hypothesis that the slightly acidic nature of chloroform induced the formation of pyrazolones.



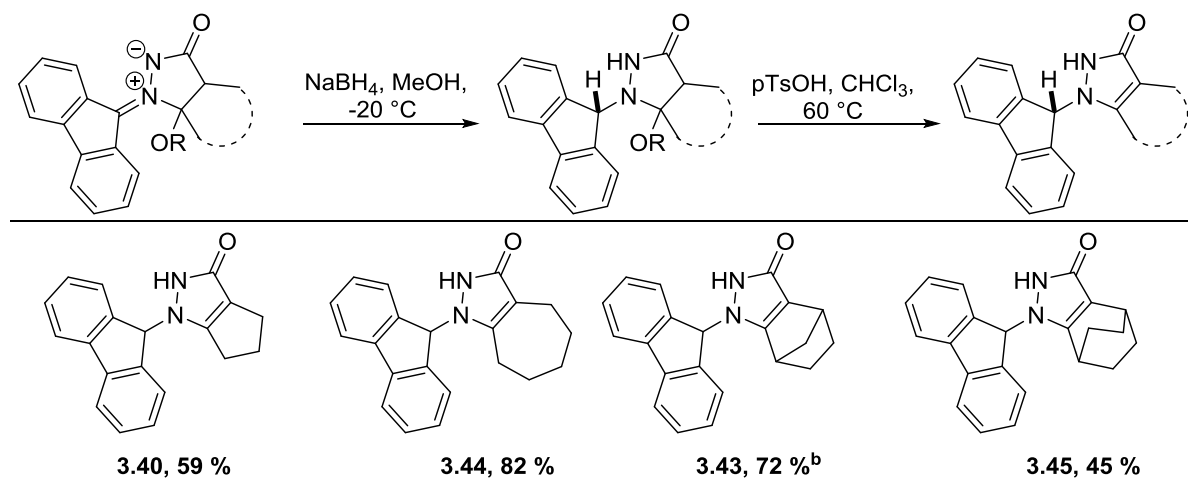
First, hydrochloric acid was used instead of ammonium chloride in the quenching of the excess sodium borohydride. The desired product was obtained, but another salt was also obtained and isolation was difficult. Dowex-H⁺ resin, which is slightly acidic, was added to the reaction mixture after the reduction was complete. At first glance this seemed like the perfect solution since 72 % of the pyrazolone was observed by NMR. The isolation of the pyrazolone required filtration through celite several times as well as treatment with triethylamine. Even though this method gave the desired product on small scale, it would not be practical on larger scale.

The next few trials were slightly different as they were performed in two steps. First the reduction was conducted at low temperatures to give pyrazolidinone **3.42**, which was then isolated before being subjected to acidic conditions. Using acetic acid did not give the desired pyrazolone, however re-oxidation of pyrazolidinone **3.42** to the azomethine imine was observed. When **3.42** was dissolved in chloroform and a catalytic amount of *p*-TsOH was added, 95 % conversion to the pyrazolone was observed at room temperature over 16 hours. It was found that by heating to 60 °C, the reaction time could be decreased to only 3 hours. The isolation also only required simple extraction and trituration. This sequence was then chosen as the alternative conditions when double reduction becomes a problem. This work was done in collaboration with Amanda Bongers.

The following explanation for these results was proposed. As mentioned before, using low temperatures allows the reaction to stop at pyrazolidinone **3.42**. The reducing agent is quenched with a mild aqueous acid and removed by extraction. The subsequent addition of a catalytic amount of acid allows the elimination to occur, followed by aromatization without the presence of any reducing agents and avoiding altogether a second reduction. It must be noted that the initial work-up and addition of acid must be rapid in order to avoid re-oxidation to the azomethine imine. Using these conditions, four pyrazolones were synthesized in modest to good yields (**Scheme 3.6**). The

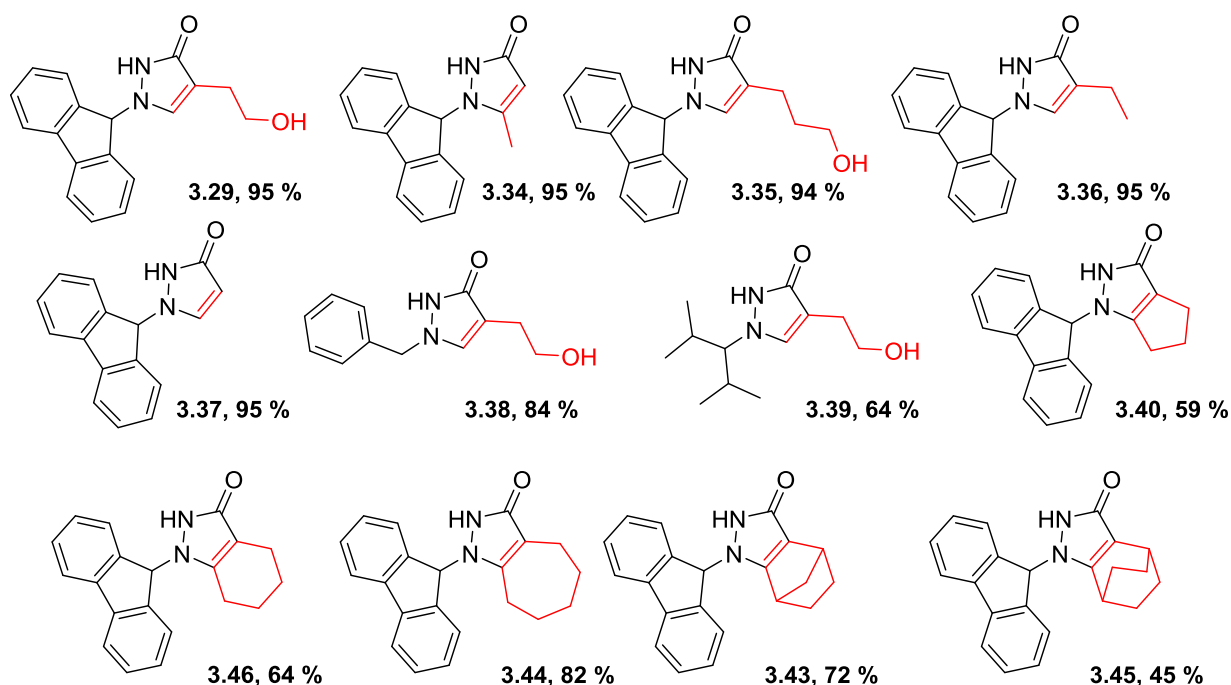
step wise route requires careful execution, however accessing those complex pyrazolones would be very difficult with other available methods.

Table 3.2 Two-step sequence for the synthesis of bicyclic and tricyclic pyrazolones^a



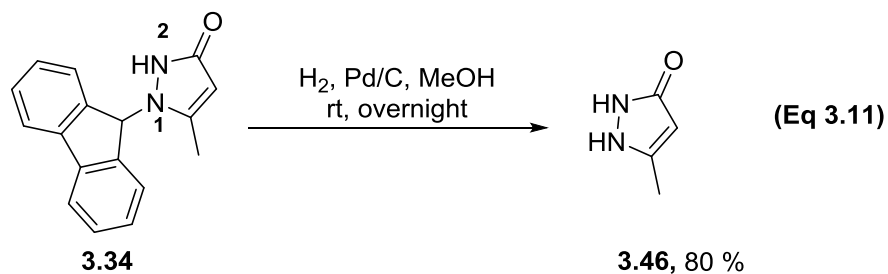
- a) Conditions: azomethine imine, NaBH_4 (10 equiv.) and MeOH (0.05 M) were added to a round bottom flask and stirred at -20 to $0\text{ }^\circ\text{C}$ until gas evolution stopped, NH_4Cl quench; then $p\text{-TsOH}$ (0.5 mol %), CHCl_3 (0.05 M), $60\text{ }^\circ\text{C}$, 3 h. b) Result by Amanda Bongers

Using both sets of conditions, the scope of pyrazolones derived from azomethine imines was expanded and the results are summarized in **Scheme 3.4**. In total, 11 new pyrazolones were synthesized in modest to excellent yields bearing substituents at the 4 and 5 positions, and with different nitrogen “protecting groups” such as fluorenyl, benzyl and diisopropyl.



Scheme 3.4 Full scope of pyrazolones synthesized from azomethine imines

The next step in this project was to access unprotected (NH-NH) pyrazolones. The fluorenone derived hydrazone was initially used since it displays excellent reactivity in alkene aminocarbonylation. Furthermore, once the azomethine imine is reduced, we are left with a fluorenyl which can be removed with standard deprotection conditions using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).⁶⁵ However, it was thought that the fluorenyl protecting group could be removed using simpler and more reliable conditions. Because the C-N bond is doubly benzylic, the cleavage of the C-N bond was successfully accomplished with hydrogen gas and palladium on carbon in good yield (80 %) (**Equation 3.11**).



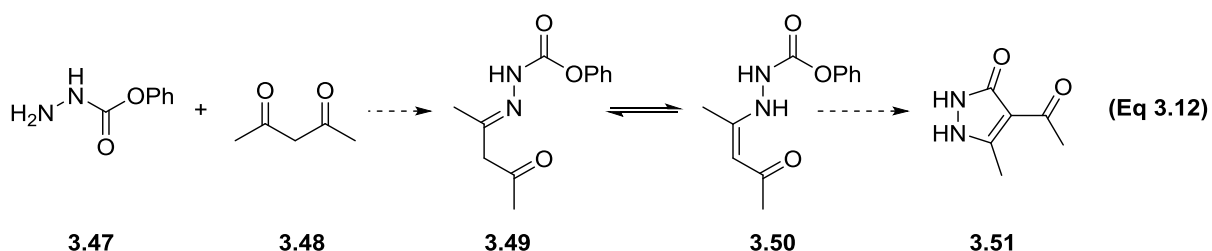
⁶⁵ Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650.

There are many examples of functionalization of pyrazolones on N2 when a protecting group is present on N1.⁶⁶ Having a protecting group such as fluorenyl also allows access to pyrazolones with substituents on N1, N2, or both nitrogens since it can be easily removed under mild conditions.

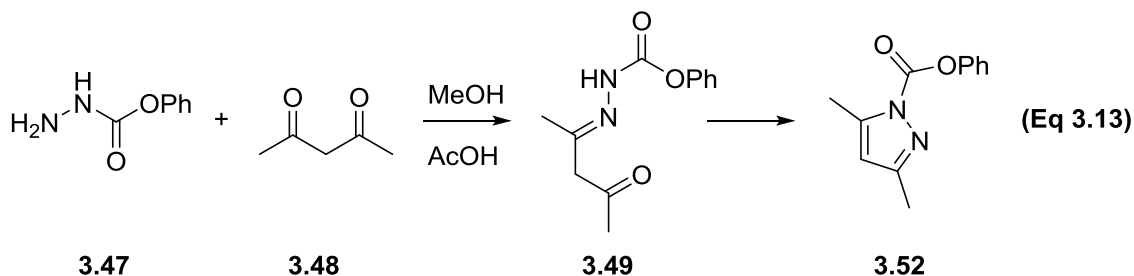
This new method affords a novel route to pyrazolones from azomethine imines taking advantage of a generally facile aminocarbonylation between enol ethers and imino-isocyanates. This process is complementary to other methods available as it uses a completely different disconnection and could be valuable to access structurally diverse set of pyrazolones.

3.2.2 Synthesis of Pyrazolones from hydrazones and hydrazides

Other methods to synthesize pyrazolones using *N*-substituted isocyanates were then envisioned. Inspired by Chupp's work (**Scheme 3.1**), it was thought that pyrazolones could be accessed through cyclization of hydrazones and hydrazides similarly to what has been described in the **section 3.1**. It was proposed that upon condensation of a diketone such as acetylacetone onto *O*-phenyl carbazate, the hydrazone formed might be in equilibrium with the enamine due to the acidity of the β -hydrogens. This intermediate could then cyclize in a similar fashion to Chupp's system (**Equation 3.12**).

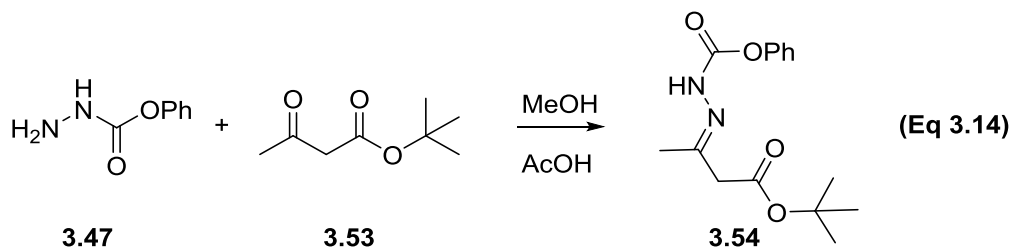


Unfortunately, the product obtained from the condensation is not stable and undergoes a second condensation to form a pyrazole (**Equation 3.13**).

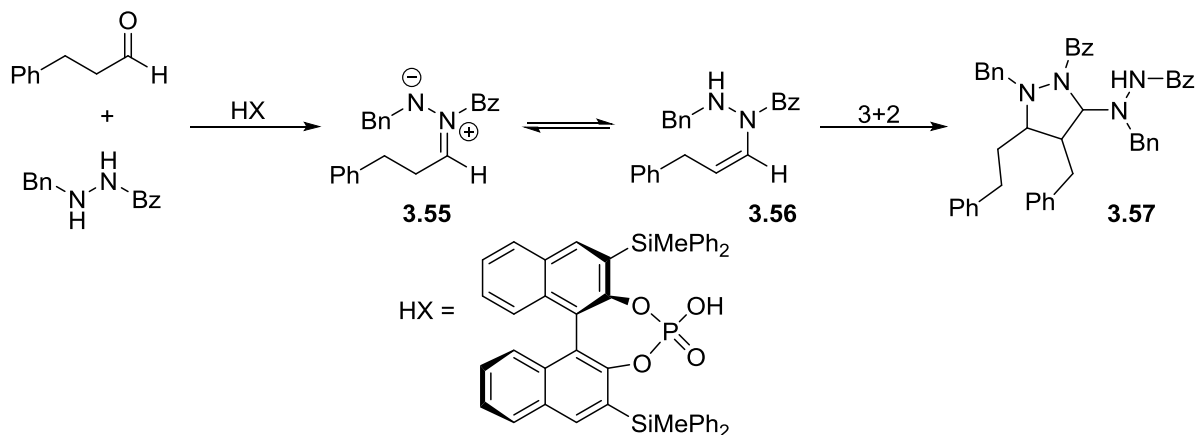


⁶⁶ (a) Rujtes, F. P. J. T.; Udding, J. H.; Hiemstra, H.; Speckman, W. N. *Heterocycles*, **1992**, *33*, 81. (b) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. (c) Sibi, M. P.; Manyem, S.; Palencia, H. *J. Am. Chem. Soc.* **2006**, *128*, 13660.

To prevent the pyrazole formation, a β -ketoester was used. Condensation of O-phenyl carbazate with *tert*-butyl acetoacetate gave the desired hydrazone in 81 % yield (**Equation 3.14**). Unfortunately, even heating up to 150 °C did not give the desired pyrazolone.



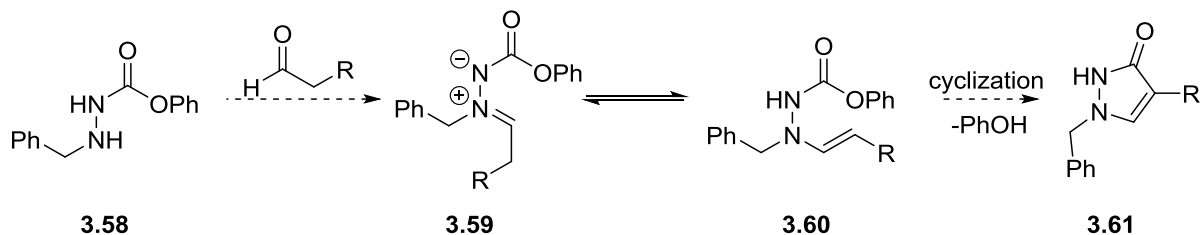
Following this work, a different approach was taken to potentially access pyrazolones. In 2011, Maruoka and coworkers showed that it was possible to form acyclic azomethine imines in-situ from the condensation of aldehydes onto hydrazines using acid catalysts.⁶⁷ In some cases the authors observed a product that could come from the isomerisation of the acyclic azomethine imine followed by a [3+2] cycloaddition (**Scheme 3.5**).



Scheme 3.5 Formation of azomethine imines, tautomerization and resulting cycloaddition

Based on work done by Maruoka as well as Tsuge, it was envisioned that condensation of a simple ketone on a hydrazide might be possible. This would give an azomethine imine that could be in equilibrium with the corresponding enamine and would possibly yield cyclization to the pyrazolone (**Scheme 3.6**).

⁶⁷ Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nature Chem.* **2011**, *3*, 642.

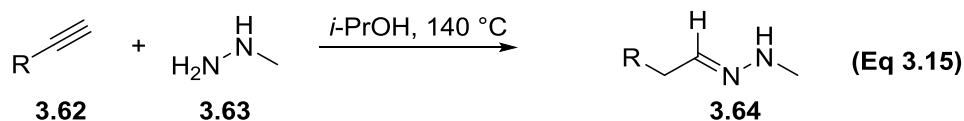


Scheme 3.6 Proposed route to pyrazolones via cyclization of hydrazides

To test this idea, benzyl protected hydrazide was chosen to mimic Maruoka's substrate. The first aldehyde used was butyraldehyde because it is simple and contains a methylene group that could allow formation of the enamine. First, both hydrazide and aldehyde were refluxed in toluene. Triethylamine was added to the reaction mixture because Tsuge reported that it could inhibit dimerization of the azomethine imine.⁶⁸ The reaction was very messy and no azomethine imine or pyrazolone was observed.

Maruoka's conditions were then attempted using hydrocinnamaldehyde, first excluding the use of an acid catalyst. The aldehyde and hydrazide were stirred in trifluorotoluene from -20 °C to room temperature for up to 16 hours, but no product was formed. The same reaction was then run using diphenyl phosphate as a Bronsted acid catalyst, but again no reaction occurred. It was concluded that the condensation of a hydrazide with an aldehyde is too difficult to allow formation of the transient azomethine imine.

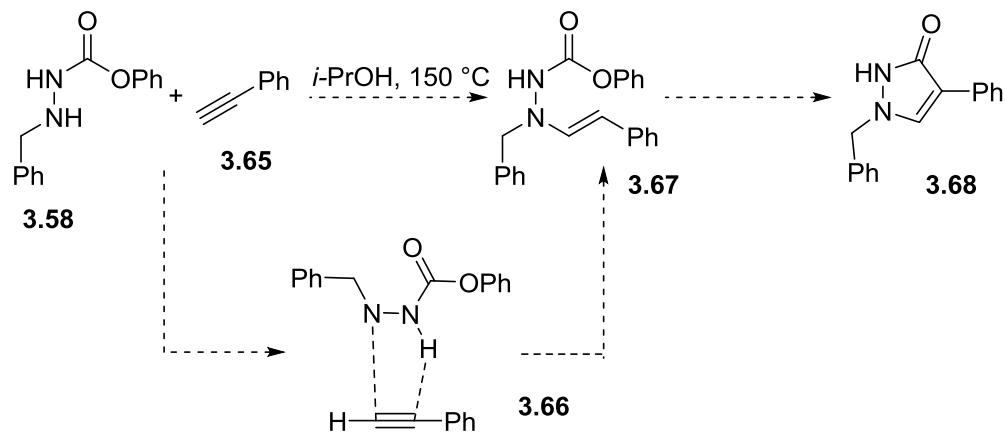
In 2008, the Beauchemin group reported intermolecular hydroamination of hydrazines with alkynes forming hydrazones (**Equation 3.15**).⁶⁹



Based on these results, it was hypothesized that at high temperature a hydrazide may undergo a hydroamination to form an enamine. This intermediate could then cyclize to the pyrazolone (**Scheme 3.7**).

⁶⁸ Kanemasa, S.; Tomoshige, N.; Wada, E. Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, 62, 3944.

⁶⁹ Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S.; Beauchemin, A. M. *Chem. Comm.* **2008**, 492.



Scheme 3.7 Proposed sequence for synthesis of pyrazolones from hydrazides and alkynes

When the hydrazide was heated in the presence of phenylacetylene, a polar product was formed. Analysis by NMR and mass spectrometry showed that the desired pyrazolone was not formed. Because high temperature was used, it was proposed that dimerization of the amino-isocyanate occurred (**Figure 3.5**). The structure was confirmed by proton and carbon NMR.

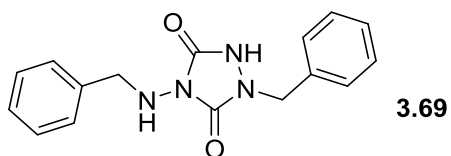


Figure 3.5 Proposed structure for dimerization of amino-isocyanate

3.2.3 Conclusions for Chapter 3

In this chapter, several pathways were investigated to synthesize pyrazolones. It was shown that pyrazolones can be synthesized from alkenes via azomethine imines. Azomethine imines derived from enol ethers are at the right oxidation state to allow nucleophile-induced aromatization to pyrazolones. A variety of pyrazolones were synthesized in modest to excellent yields. This new methodology provides a different disconnection to afford the heterocyclic core from simple alkenes and imino-isocyanates. It is complementary to methods already available, especially when sensitive hydrazines are required or regioselectivity is important.

Chapter 4: Alkene Aminothiocabonylation with Imino-isothiocyanates

4.1 Introduction

Sulfur incorporation in biologically active molecules is often used as a modification to study biological systems. For example, thioamides are often used as natural amino acid substitutions for the study of the role of protein backbones. They can be incorporated in the α -helix or β -turn without compromising the structure. It has also been reported that thioamide substitutions in the protein backbone confer resistance against proteolytic degradation, similarly to β -aminocarbonyls, due to “unnatural” nature of the “amide” linkage.⁷⁰

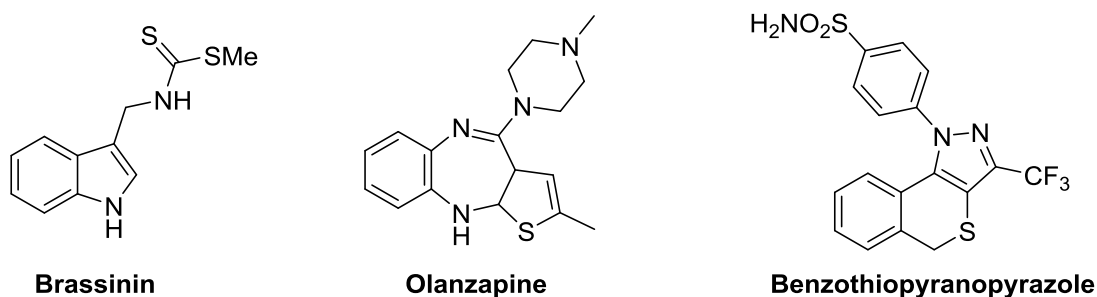


Figure 4.1 Relevant examples of sulfur containing compounds

Sulfur is also found in many heterocyclic compounds, which are present in a variety of pharmaceuticals. Brassinin is a phytoalexin that can be isolated from turnips. This toxin contains a dithiocarbamic acid group and is the defense mechanism of turnips against microorganism attacks (Figure 4.1). Olanzapine, which is an antipsychotic used to treat schizophrenia and bipolar disorder, is a good example. It was also shown that benzothiopyranopyrazoles have important biological activity. For example, they can act as interleukin-1 inhibitors.⁷¹ More importantly, benzothiopyranopyrazole depicted in Figure 4.1 is a COX-2 inhibitor, in other words a non steroidal anti-inflammatory. The advantage of this compound is the lack of gastric and renal toxicity.⁷²

In the Beauchemin group, we are interested in synthesizing thioxo-azomethine imines as well as thiopyrazolones due to their similarity to the oxygen analogues and lack literature precedents

⁷⁰ Batjargal, S.; Wang, Y. J.; Goldberg, J. M.; Wissner, R. F.; Petersson, E. J. *J. Am. Chem. Soc.* **2011**, *134*, 9172.

⁷¹ Parmar, N. J.; Parmar, B. D.; Sutariya, T. R.; Kant, R.; Gupta, V. K. *Tetrahedron Lett.* **2014**, *55*, 6060.

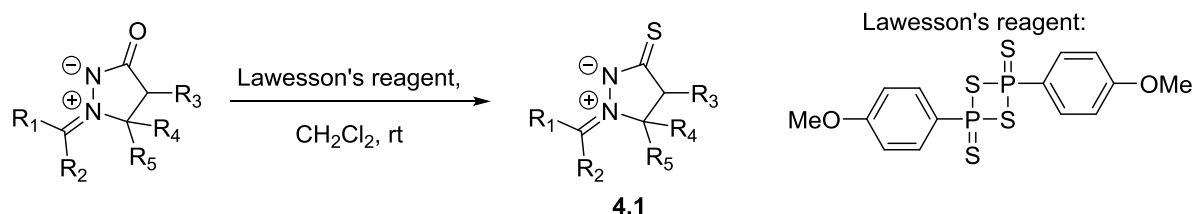
⁷² Bertenshaw, S. R.; Talley, J. J.; Rogier, D. J.; Graneto, M. J.; Kobolt, C. M.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2827.

surrounding an amino-thiocarbonylation. The different methods available to prepare these heterocycles will be discussed.

4.1.1 Synthesis of thioxo-azomethine imines

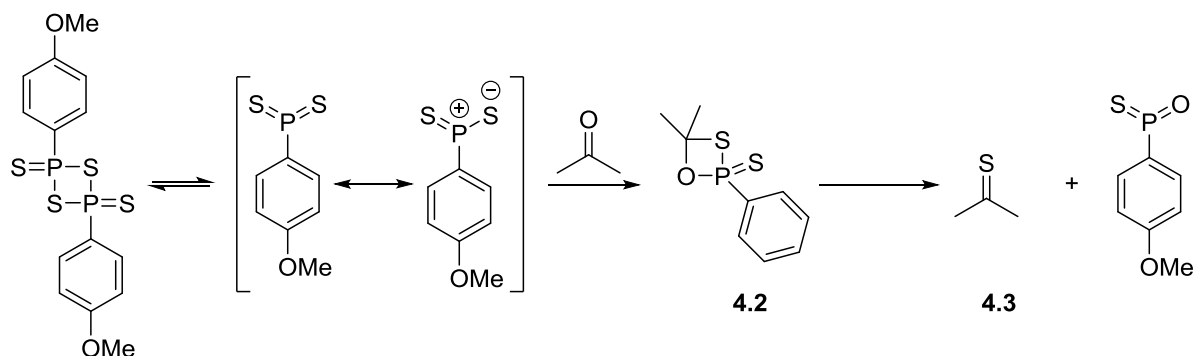
Thioxo-azomethine imines were first synthesized in 1994 by Dorn and Kreher.⁷³ Azomethine imines are reactive compounds, for this reason the authors decided to synthesize a sulfur analogue that they called thioxo-stabilized azomethine imines. These have been shown to have decreases electron density and more polarizability compared to their oxo analogues.

The synthesis of these heterocycles is accomplished via thionation of an oxo-azomethine imine using Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithiadiphosphenate-2,4-disulfide) as shown in **Scheme 4.1**. Unfortunately, no yields were provided in this publication.



Scheme 4.1 Synthesis of thioxo azomethine imines using Lawesson's reagent

It was proposed that the Lawesson's reagent is in equilibrium with the dithiophosphine ylides, which are very reactive. The ylide and carbonyl react together to form a thioxaphosphetane. This intermediate is not stable and rearranges to the thiocarbonyl (**Scheme 4.2**).⁷⁴



Scheme 4.2 Thionation reaction with the Lawesson's reagent using acetone as substrate

⁷³ Dorn, H.; Kreher, T. *Heterocycles*, **1994**, *38*, 2171.

⁷⁴ Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis*, **2003**, *13*, 1929.

The full scope of the reaction using this method is presented in **Figure 4.2**.

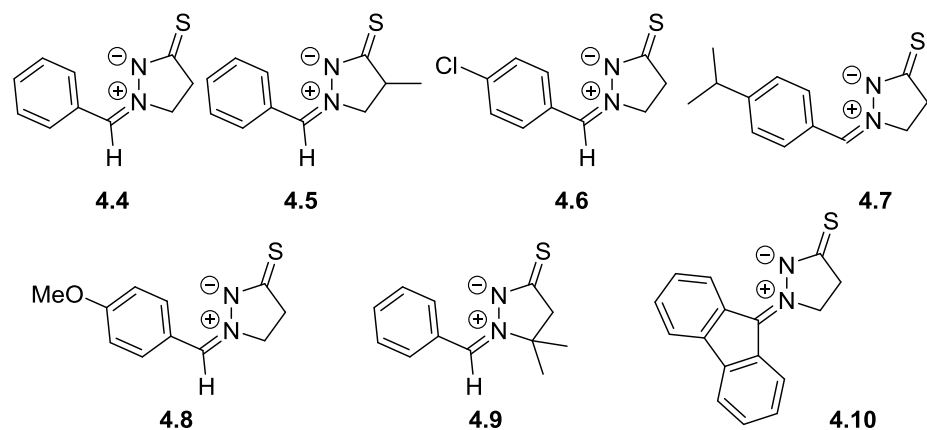
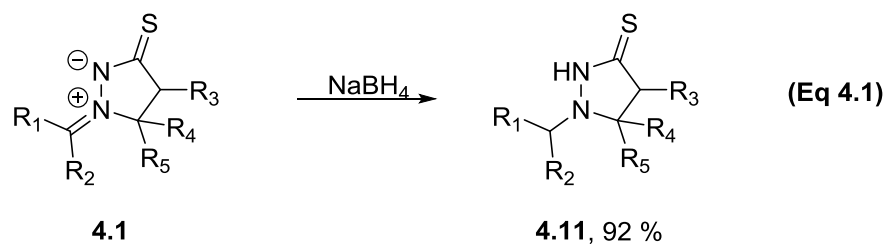


Figure 4.2 Full scope of thioxo-azomethine imines

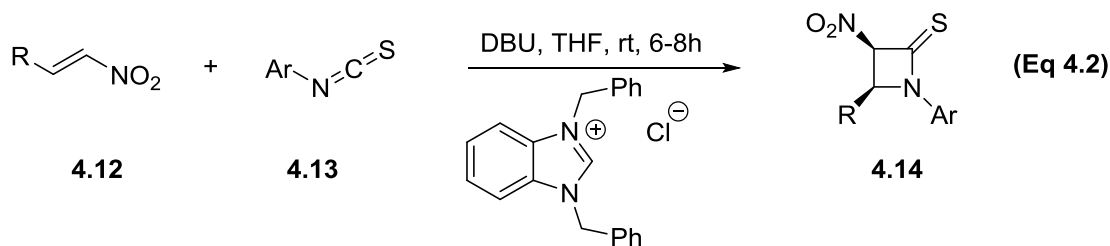
The authors have also shown that thioxo-azomethine imines can be derivatized. Indeed, it was possible to reduce them to thioxopyrazolidinones in 92 % yield using sodium borohydride (**Equation 4.1**).



Lawesson's reagent has allowed access to compounds that had not been synthesized before. However, this reagent has drawbacks. First, it has a strong unpleasant smell therefore special precautions have to be taken to clean glassware and purify products. It is also very moisture sensitive therefore reactions have to be conducted under inert atmosphere.

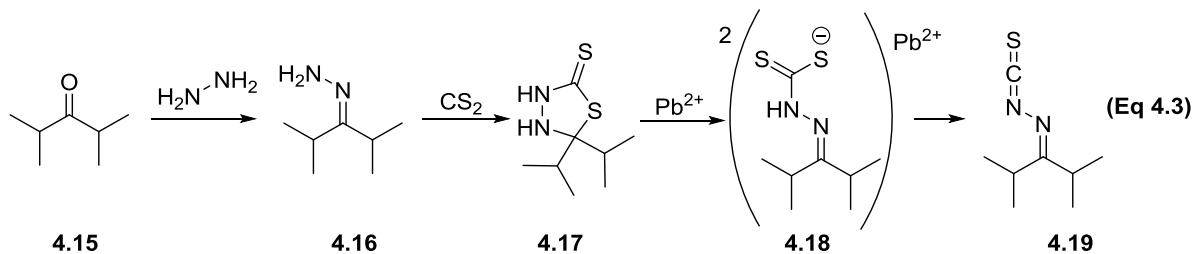
Even though the use of the Lawesson's reagent is impractical, it was nonetheless the only method to synthesize thioxo-azomethine imines at the time. We have been interested in expanding their alkene aminocarbonylation methodology to include imino-isothiocyanates. An interesting approach to this problem would be aminothiocabonylation for the same reasons as discussed in **Chapter 1 (Section 1.1)**. However, there are very few examples of aminothiocabonylation being used in heterocyclic synthesis. One of the few examples was by Yadav in 2010. They were able to perform

aminothi carbonylation with olefins and isothiocyanates to give β -thiolactams using carbene catalysis (**Equation 4.2**).⁷⁵



The reaction is typically high yielding and occurs under mild conditions. However, it only works with nitro-olefins and aryl isothiocyanates. This methodology is useful since there are a many commercially available isothiocyanates. As for the *O*-analogues, isothiocyanates have been studied in detail compared to *N*-substituted isothiocyanates. The Beauchemin group was interested in expanding their alkene aminocarbonylation methodology to include imino-isothiocyanates.

There are few examples of synthesis and reactivity of imino-isothiocyanates in the literature. In 1969, Berg showed that they could be obtained by thermal decomposition of lead bis-3-(diisopropylmethylene)-dithiocarbamates (**Equation 4.3**).⁷⁶

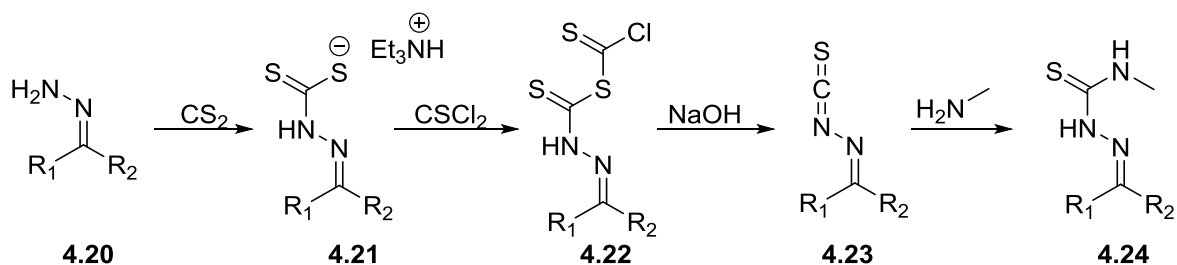


In 1974, Berg reported an alternative to his method that used triethylamine, carbon disulfide and thiophosgene (**Scheme 4.4**).⁷⁷ These reaction conditions are slightly milder but still require the use of toxic reagents. Berg also showed that imino-isothiocyanates could be trapped using nucleophiles such as methylamine to give thiosemicarbazones (**Scheme 4.3**).

⁷⁵ Yadav, L. D. S.; Awasthi, C. *Synlett* **2010**, 1783.

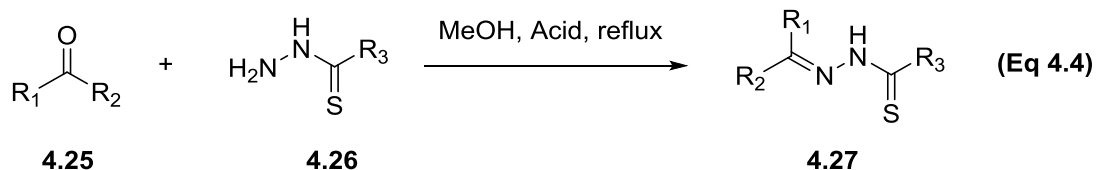
⁷⁶ Anthoni, U.; Berg, C. *Acta. Chem. Scand.* **1969**, *23*, 3602.

⁷⁷ Berg, C. *J. Chem. Soc., Chem. Comm.* **1974**, *4*, 122.



Scheme 4.3 Synthesis and reactivity of imino-isothiocyanates

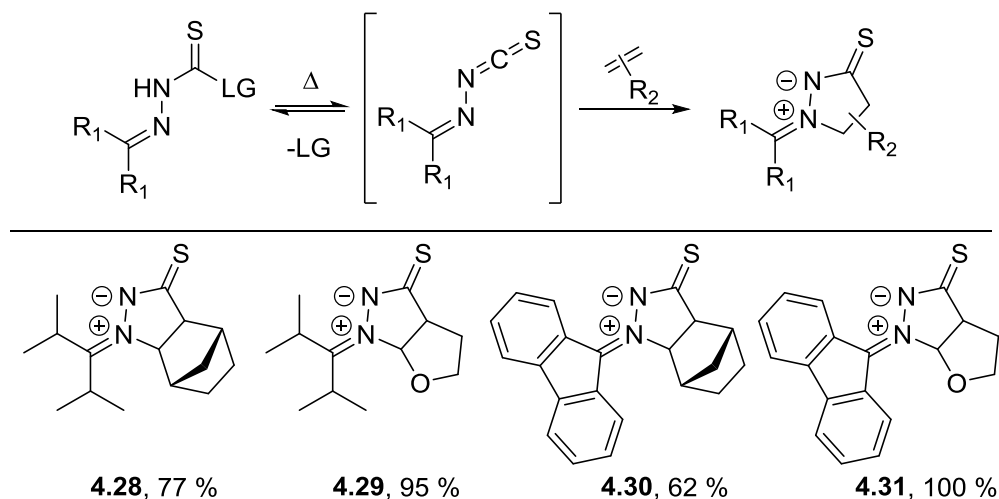
The Beauchemin group thought that imino-isothiocyanates could be accessed from thiocarbonylated hydrazones based on our studies on the *O*-analogues. Thiocarbonylated hydrazones are generally synthesized by condensation of the corresponding ketones and hydrazinethiocarbamates, which can be accomplished in good yields (**Equation 4.4**).⁷⁸



The problem with this approach is the synthesis of hydrazinethiocarbamates. There are some reports in the literature, however, the yields are very low and hard to reproduce. Nonetheless, in a recent patent, Dr. Gan has demonstrated that aminocarbonylation between imino-thioisocyanates and alkenes can occur at high temperature (**Scheme 4.4**).⁷⁹

⁷⁸ Hall, M. D.; Salam, N. K.; Hellawell, J. L.; Fales, H. M.; Kensler, C. B.; Ludwig, J. A.; Szakacs, G.; Hibbs, D. E.; Gottesman, M. M. *J. Med. Chem.* **2009**, *52*, 3191.

⁷⁹ Clavette, C.; Gan, W.; Markiewicz, T.; Toderian, A.; Beauchemin, A. M. **2013**, *Patent*: WO2013/67646 A1.



Scheme 4.4 Alkene aminothiocabonylation with imino-isothiocyanates

This method would not be very practical for synthetic purposes and would require further optimization.

4.1.2 Synthesis of thiopyrazolones

Similarly to thioxo-azomethine imines, there aren't many methods to synthesize thiopyrazolones. However, pyrazolones have been studied in more depth, especially analytically. For example, there are a few studies on the different tautomers of thiopyrazolones pioneered by Maquestiau.⁸⁰ Indeed, there are 3 possible isomers as represented in **Figure 4.3**.

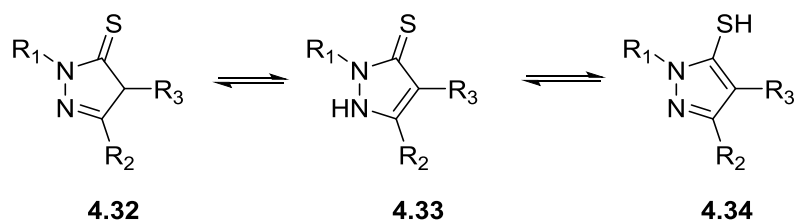
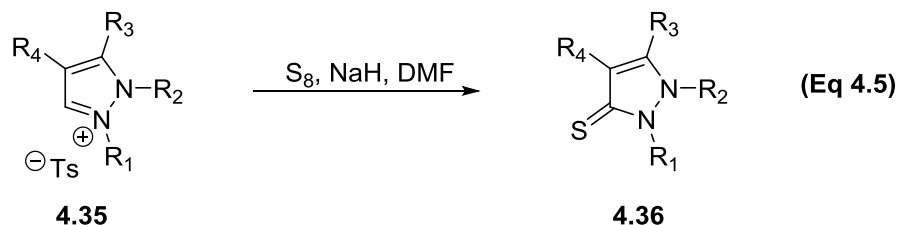


Figure 4.3 Isomers of thiopyrazolones

Maquestiau has been able to show that: tautomer **4.32** is never observed in solution, tautomer **4.33** and **4.34** are observed in aprotic solvent and only tautomer **4.33** is observed in protic solvents.

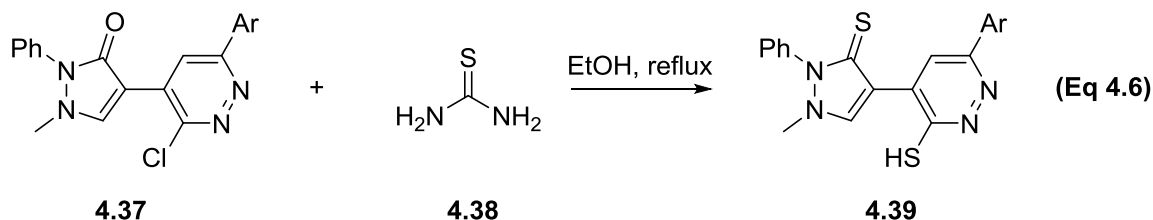
⁸⁰ Maquestiau, A.; Haverbeke, Y. V.; Vanovervelt, J.-C. *Bull. Soc. Chim. Belg.* **1977**, *86*, 949.

The first method to synthesize thiopyrazolones was reported in 1902 by Michaelis.⁸¹ In 1975, Begtrup reported the thiation of pyrazolium salts with elemental sulfur substitution of a chlorine by a sulphide or thiosulphate ion on *N,N'*-disubstituted chloropyrazolium salts (**Equation 4.5**).⁸²



This reaction requires the use of a very strong base, is limited to only a few substituents and gives modest to good yields.

In 1992, Sayed and coworkers were working on the synthesis of tetrahydropyridazinones in order to screen them for biological activity.⁸³ During the course of their synthesis, they got unexpected results when reacting a pyrazolone with a thiourea that led to the formation of an undesired thiopyrazolone (**Equation 4.6**). The mechanism for this transformation remains unclear. They were able to synthesize two thiopyrazolones using these conditions.



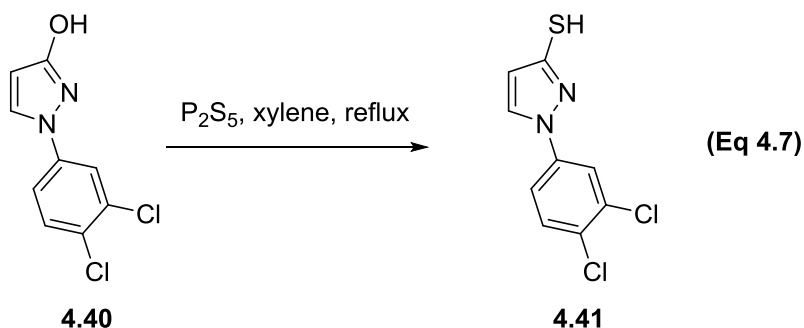
The most common method to prepare thiopyrazolones is by reaction of the corresponding pyrazolones with phosphorus pentasulfide (**Equation 4.7**).⁸⁴ Phosphorus pentasulfide is used to prepare the Lawesson's reagent and similarly to the Lawesson's reagent has a very unpleasant smell and special precautions must be taken when handling it.

⁸¹ Michaelis, A. *Annalen* **1902**, *1*, 320.

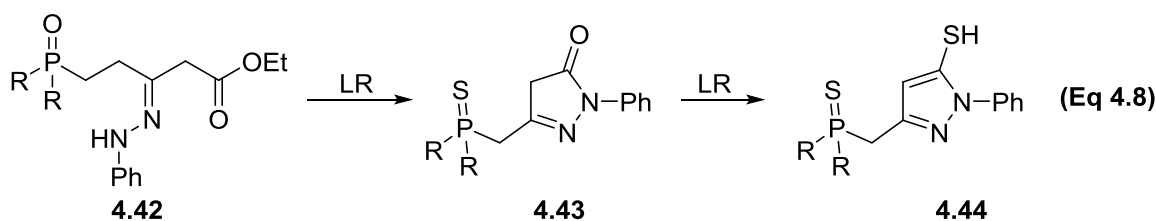
⁸² Begtrup, M. *J. Chem. Soc. Perkin I*, **1975**, 507.

⁸³ Sayed, G. H.; Shiba, S. A.; Radwan, A.; Mohamed, S. M.; Khalil, M. *Chinese J. Chem.* **1992**, *10*, 475.

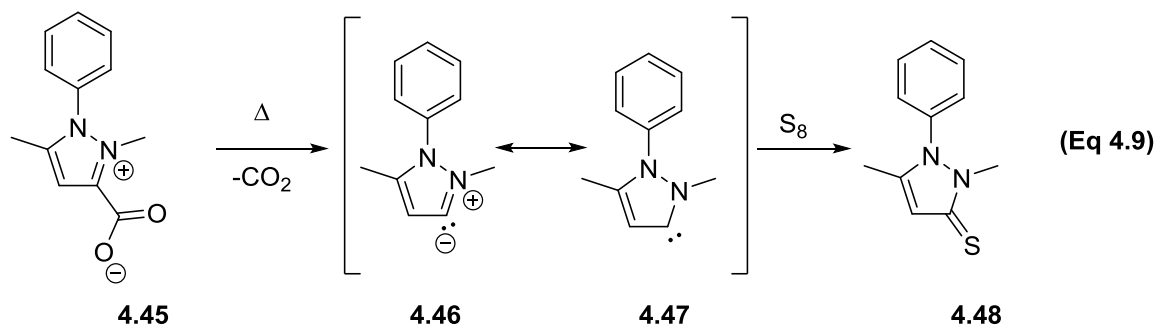
⁸⁴ Diaz, J. L.; Cuberes, R.; Berrocal, J.; Contijoch, M.; Christmann, U.; Fernandez, A.; Port, A.; Holenz, J.; Buschmann, H.; Laggner, C.; Serafini, M. T.; Burgueno, J.; Zamanillo, D.; Merlos, M.; Vela, J. M.; Almansa, C. *J. Med. Chem.* **2012**, *55*, 8211.



Lawesson's reagent can also be used as an alternative to phosphorus pentasulphide. In 2012, Jouil reported the synthesis of a thiopyrazolone from β -phosphoryl- β' -carbethoxyhydrazones using Lawesson's reagent (LR) (**Equation 4.8**).⁸⁵



In 2010, Dreger reported the synthesis of thiopyrazolones from carbenes.⁸⁶ First, the pyrazolium salt is prepared, followed by ester hydrolysis to obtain betaines. Upon heating, decarboxylation of the betaine occurs, generating a carbene species. The authors have found that the carbene they generated could be trapped using sulfur to form a thiopyrazolone in 72 % yield (**Equation 4.9**).



The advantage of octasulfur is that it is odorless. However, there is only one example of formation of thiopyrazolones using sulfur and is merely a modification to Begtrup's method (**Equation 4.5**).

⁸⁵ Chebil, E.; Jouil, S. *Lett. Org. Chem.* **2012**, *9*, 320.

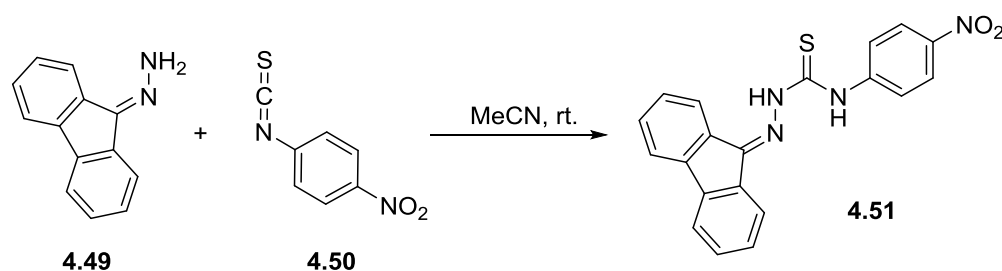
⁸⁶ Schmidt, A.; Munster, N.; Dreger, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2790.

4.1.3 Project objectives

The available literature on the synthesis of thioxo-azomethine imines and thiopyrazolones is very limited. In both cases, the most common methods use *O*-analogues of the desired target, and require smelly and toxic reagents to install the thiocarbonyl group. There are alternative methods, but they are limited to specific substrates. The goal of this project was to expand the scope of thioxo-azomethine imines using alkene aminothiocabonylation with imino-isothiocyanates. Lastly, the derivatization of the thioxo-azomethine imines into thiopyrazolones would be investigated.

4.2 Results and Discussion

As mentioned above, alkene aminothiocabonylation was reported in our group in 2013, but this method was not practical due to the difficulty in synthesizing thiocarbonylated hydrazone starting materials. This project was made possible by the work of a colleague on thiosemicarbazone derivatives. Jean-Francois Vincent-Rocan discovered that imino-isothiocyanates could be generated at 100 °C from thiosemicarbazones with nitro-aniline leaving groups. The synthesis of these compounds can be accomplished with a lot more ease than for thiocarbonylated hydrazones. Literature precedence shows that thiosemicarbazones can be obtained by reaction of a primary hydrazone with an isothiocyanate under mild conditions (**Scheme 4.5**).⁸⁷ The reagents required are commercially available and do not have smell or toxicity issues.



Scheme 4.5 Synthesis of thiosemicarbazones from hydrazones and isothiocyanates

4.2.1 Alkene aminothiocabonylation with thiosemicarbazones

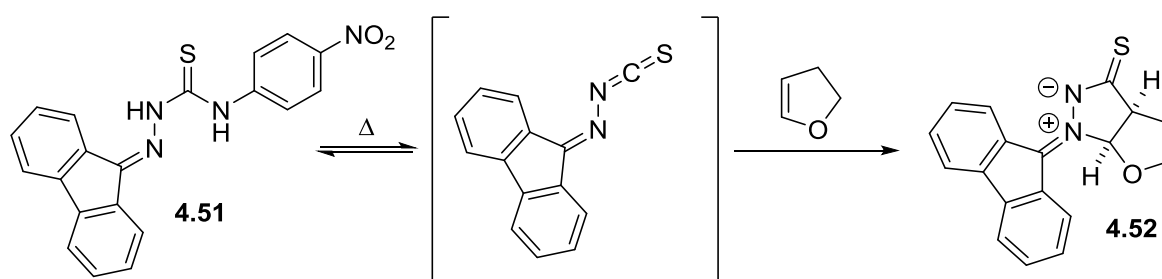
The thiosemicarbazone derived from fluorenone and with a para-nitroaniline leaving group (**Scheme 4.5**) was first tested because it was known that the imino-isothiocyanate could form at reasonable temperatures. Dihydrofuran (10 equivalents) was used to conduct these initial studies because of its excellent reactivity in the related alkene aminocarbonylation. Temperatures between 100 and 120 °C were used.

Unfortunately, the thiosemicarbazone derived from fluorenone was not soluble in many solvents even at high temperatures (**Table 4.1**). The starting material was not soluble at all in trifluorotoluene, therefore no product was observed. Even though the thiosemicarbazone was fully soluble in nitromethane, no thioxo-azomethine imine product was observed. The thiosemicarbazone was fully soluble in chlorobenzene at 120 °C, but surprisingly no product was

⁸⁷ Campagna, M.; Laborie, C.; Barbier, G.; Assan, R.; Milcent, R. *Eur. J. Med. Chem.* **1991**, *26*, 273.

observed. When the reaction was run in dioxane, 26 % NMR yield was obtained, whereas only 9 % NMR yield was obtained in chloroform. The best results were obtained when acetonitrile was used as a solvent. The semicarbazone had very poor solubility in acetonitrile at 120 °C, but 60 % isolated yield was obtained nonetheless.

Table 4.1 Optimization of aminothi carbonylation with dihydrofuran^a



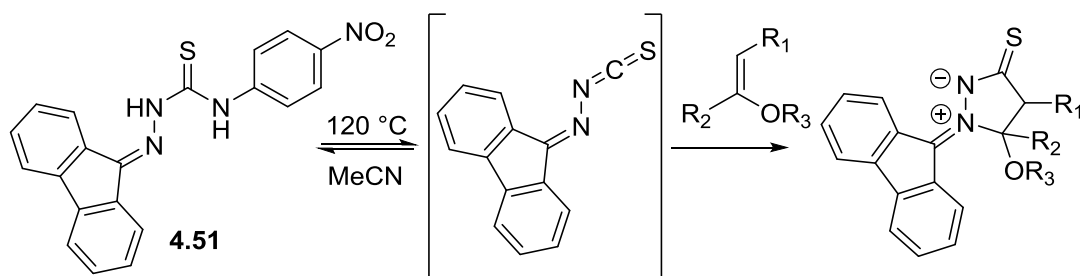
Entry	Solvent	Time (h)	Temp. (°C)	Yield (%) ^b
1	MeNO ₂	2	100	-
2	PhCF ₃	16	100	-
3	PhCl	2	120	-
4	dioxane	2	120	26
5	CHCl ₃	2	120	9
6	MeCN	1	120	56
7	MeCN	2	120	60 ^c

a) Conditions: thiosemicarbazone, alkene (10 equiv.) and solvent (0.05 M) were added to a sealed microwave vial and heated in the microwave reactor. b) NMR yields obtained using trimethoxybenzene as the internal standard c) Isolated yield

Acetonitrile was then chosen as the solvent for aminothi carbonylation of thiosemicarbazones with enol ethers and 120°C was required to allow reactivity. The lower yields obtained compared to the *O*-analogues could potentially be explained by the high temperatures required and the heat sensitivity of enol ethers. It must be noted that dry solvent is required in order for this reaction to occur. Isolation of thioxo-azomethine imines also proved difficult due to their affinity to silica gel and coelution of nitroaniline byproduct. Other enol ethers were then screened (**Table 4.2**). It was found that with dihydropyran, even when increasing the temperature up to 150 °C, no desired product was formed (entry 1). A decrease in yield was expected, but not complete loss of reactivity. Butenyl ethyl ether only gave 8 % NMR yield of the product (entry 3), and enol ether **2.32** only gave

31 % NMR yield (entry 4) of the corresponding thioxo-azomethine imine. In all these cases, it was nearly impossible to separate the thioxo-azomethine imines from *para*-nitroaniline by flash column chromatography. In all these reactions, unreacted starting material could be observed by TLC and NMR.

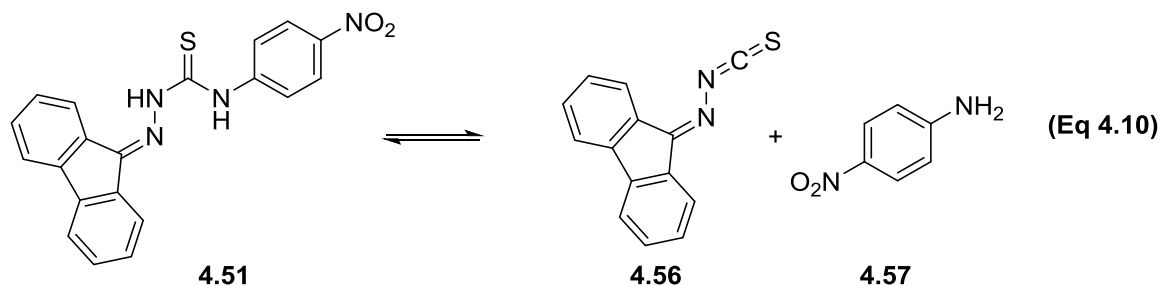
Table 4.2 Scope of enol ethers with thiosemicarbazone 4.51^a



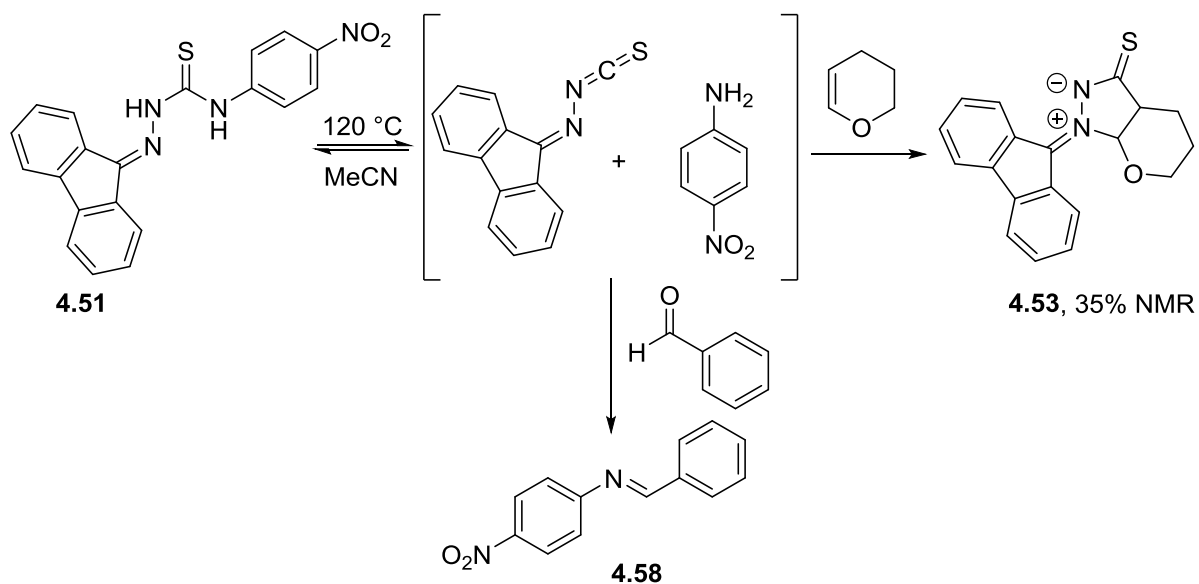
Entry	Enol ether	Additive	Thioxo azomethine imine	Yield (%) ^c
1		-		-
2 ^b		benzaldehyde		35
3		-		8
4		-		31
5 ^b		Benzaldehyde		23

a) Conditions: thiosemicarbazone, alkene (10 equiv.) and acetonitrile (0.05 M) were added to a sealed microwave vial and heated to 120 °C in the microwave reactor. b) 10 equivalents of benzaldehyde were added. c) NMR yields obtained using trimethoxybenzene as the internal standard.

Because the yields of product were so low, it was thought that the leaving group may be inhibiting alkene aminothiocabonylation reactivity. Upon formation of the imino-isothiocyanate *para*-nitroaniline is liberated. Therefore, it might be able to attack the imino-isothiocyanate, regenerating and pushing the equilibrium towards the thiosemicarbazone (**Equation 4.10**).



Following this, it was hypothesized that the equilibrium could be pushed towards the imino-isothiocyanate by trapping the *para*-nitroaniline as it formed. This could also make the isolation easier by decreasing the polarity of the aniline. Because anilines are known to react with aldehydes, benzaldehyde was added to the reaction mixture. This led to a slightly increased yield of 35 % (**Scheme 4.6**). However, this did not help in the reaction of enol ether **2.15**, in fact, the yield decreased (**Table 4.1**, entry 5). Furthermore, this did not solve the isolation issues.



Scheme 4.6 Alkene aminothiocabonylation in presence of aldehydes as additives

Three different thiosemicarbazones were then synthesized to probe the effect of the leaving group (**Figure 4.4**).

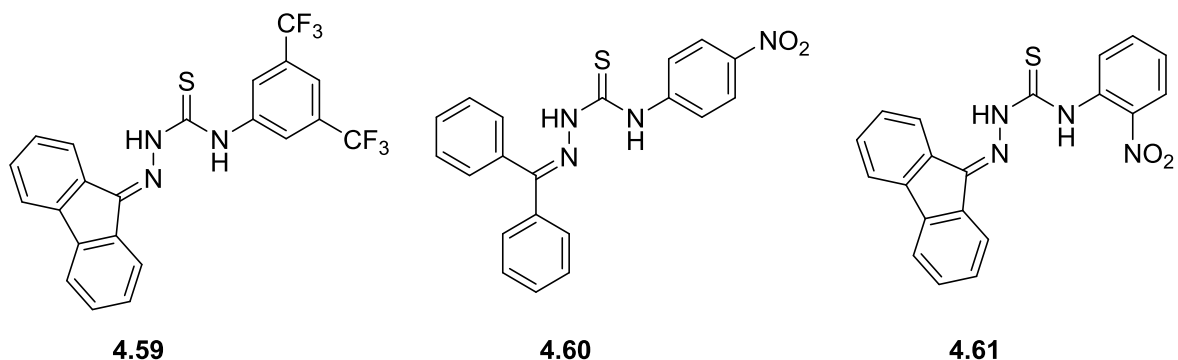


Figure 4.4 Alternative thiosemicarbazones

In the case of **4.59**, it was thought that adding different electron withdrawing substituents could have an effect on the outcome of the reaction. In the case of **4.60**, it was also thought that not having an extended aromatic system would increase solubility which could lead to better yields. Lastly with thiosemicarbazone **4.61**, it was thought that the electronics would be similar, but that the equilibrium would favor the imino-isothiocyanate due to steric and electronic reasons, since internal H-bonding might be possible. The results are summarized in **Table 4.3**.

When 3,5-bis(trifluoromethyl)aniline was used as a leaving group (**4.59**), only 24 % NMR yield of the thioxo-azomethine imine was observed, and no significant amount of starting material was left. The crude NMR was very messy, indicating side reactions. When **4.60** was heated at 100 °C, all reagents were soluble in acetonitrile, however no desired product was formed. A temperature of 100 °C was chosen since studies by Jane Nguyen showed that the corresponding imino-isothiocyanate could form at that temperature. Finally, when **4.61** was heated at 120 °C for 2h, 60 % of the desired product was observed by NMR. When the temperature was lowered to 100 °C, the yield went down to 53 % NMR yield, and when the reaction time was decreased to 1 hour, the yield increased to 65 % NMR yield. Generally, the reaction was cleaner than with the other thiosemicarbazones. This suggests that the thioxo-azomethine imine might not be stable under the reaction conditions. It also suggests that the formation of the imino-isothiocyanate is easier relatively to the others, most likely due to steric hindrance. Even though the yields have not been increased compared to thiosemicarbazone **4.51**, the thiosemicarbazone **4.61** allowed for similar yields using milder reaction conditions.

Table 4.3 Thiosemicarbazone optimization

The reaction scheme shows a thiosemicarbazone with a leaving group (LG) on the carbonyl carbon. Upon heating (Δ), it decomposes to a diazo intermediate (R-C(=N)-N=N-C=S). This intermediate then reacts with furan to form a bicyclic thiosemicarbazone-furan adduct.

Entry	Hydrazone	Time (h)	temp (°C)	Yield (%)
1		2	120	24
2		2	100	-
3		2	120	60
4		2	100	53
5		1	100	65

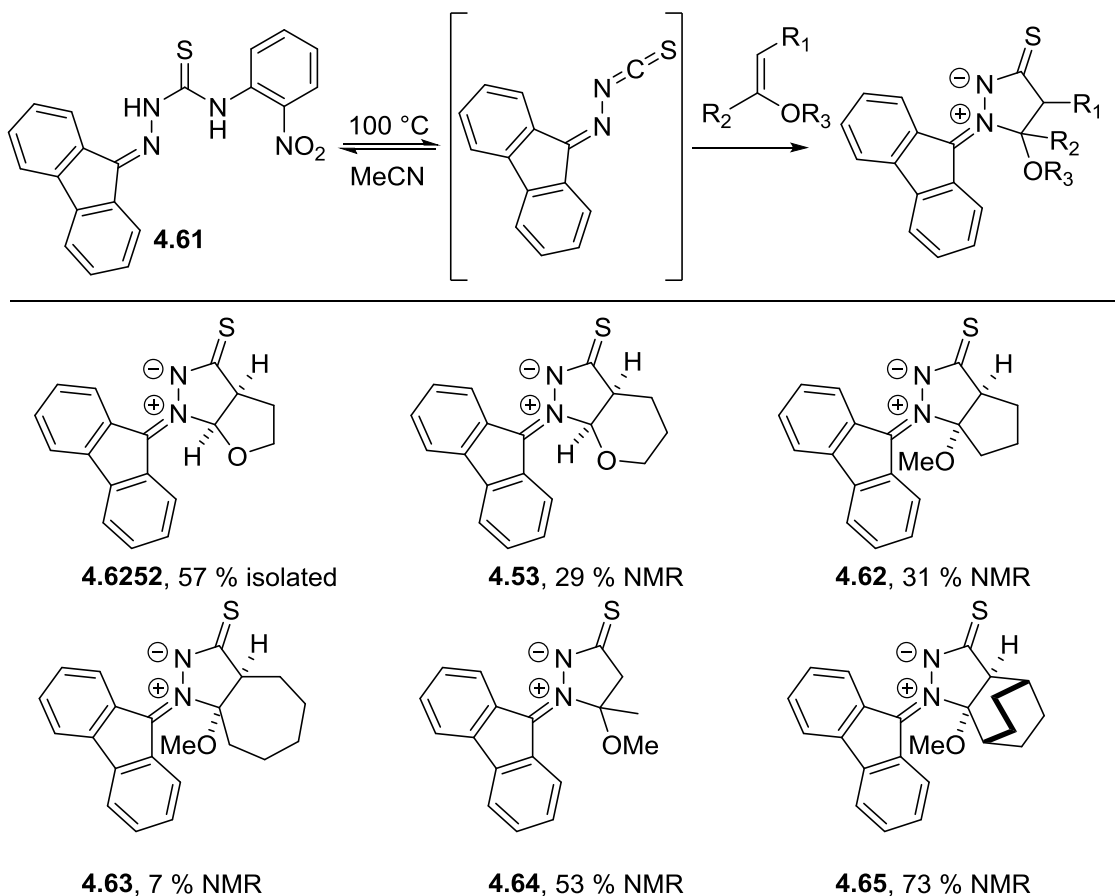
a) Conditions: thiosemicarbazone, alkene (10 equiv.) and acetonitrile (0.05 M) were added to a sealed microwave vial and heated in the microwave reactor. b) NMR yields obtained using trimethoxybenzene as the internal standard

With this thiosemicarbazone (**4.44**), the isolation was still difficult and the product was often obtained as a mixture with *ortho*-nitroaniline. Other purification methods were investigated to remove the nitroaniline from the mixture prior to column chromatography. When basic workups were attempted, decomposition of thioxo-azomethine imine was observed. After several trials, it was found that treating the silica gel with a 1 % solution of triethylamine helped by reducing the

affinity of nitroaniline and thioxo-azomethine imine to the silica. It was also found that dry loading the sample somewhat helped with the separation. These improvements allowed for the use of regularly sized columns relative to the reaction size and for better separation in some cases.

The scope of thioxo-azomethine imines was then probed using thiosemicarbazone **4.61** and a variety of enol ethers (**Scheme 4.7**). It was possible to isolate 57 % of the thioxo-azomethine dihydrofuran adduct. With dihydropyran, the resulting thioxo-azomethine imine was obtained in a maximum NMR yield of 29 %. Thioxo-azomethine imine derived from **2.16** also only gave 31 % NMR yield. Using enol ether **2.18**, an even lower yield of 7 % was obtained. On a more positive note, methoxypropene gave a modest yield of 53 % by NMR, and enol ether **2.20** gave a NMR yield of 73 %. Only one thioxo-azomethine imine was successfully isolated. All the other examples were isolated as mixtures of the desired product and *ortho*-nitroaniline.

Table 4.4 Preliminary scope of thioxo azomethine imines

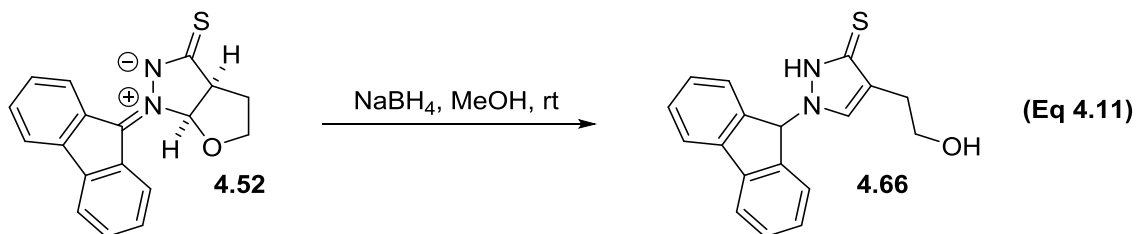


Enol ethers are not ideal substrates for aminothiocabonylation since they display limited reactivity. However, a better reagent could also increase the efficiency of this reaction. Studies on other types of alkenes are currently undergoing in the Beauchemin group.

4.2.2 Derivatization of thioxo azomethine imines

Since oxo-azomethine imines could be derivatized readily into pyrazolones, it was thought that the same could be accomplished with thioxo-azomethine imines.

When the thioxo-azomethine imine **4.52** was subjected to sodium borohydride, the solution slowly turned from bright red to orange. It must be noted that thioxo-azomethine imines are not very soluble in methanol but as the reduction occurs more and more entered in solution. The TLC and crude NMR were very encouraging as the reaction went to full conversion (**Equation 4.11**).



However, either a mixture of compounds or rotamers were observed by NMR as shown in **Figure 4.5**. Upon acidic workup, only the desired thiopyrazolone was obtained in 17 % yield.

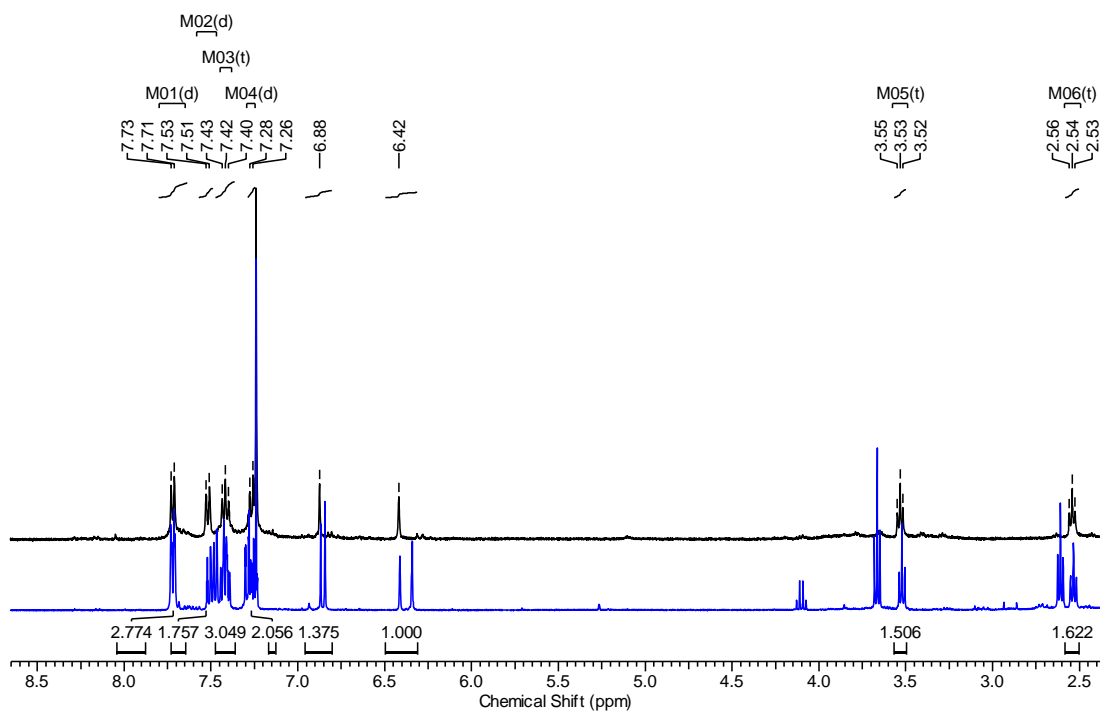
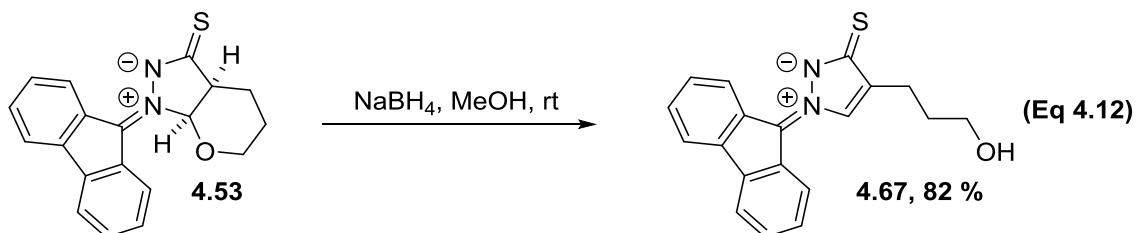


Figure 4.5 Comparative NMR of crude mixture and isolated thiopyrazolone

The same reaction was run with thioxo-azomethine imine **4.53** and the corresponding thiopyrazolone was obtained in 82 % yield (**Equation 4.12**).



It must be noted that the reaction was performed with crude **4.53**, as a mixture with *ortho*-nitroaniline and that the yield was based on the ratio of both after isolation. The thiopyrazolone could be purified without issue.

4.2.3 Conclusions for Chapter 4

We have been able to show that aminothiocabonylation with enol ethers and thiosemicarbazones is possible. It was found that acetonitrile was the best solvent for the reaction and that a nitroaniline leaving group with steric hindrance favored the formation of the imino-isothiocyanate. Only one thioxo-azomethine imine was successfully isolated (**4.52**). The other compounds

synthesized were isolated as a mixture with *para* or *ortho*-nitroaniline. Further optimization of the reaction and isolation procedures should be conducted. This method could be complementary to the only alternative by Dorn and Kreher's. Our method has the advantage of using simple alkenes to generate thioxo-azomethine imines and doesn't require the use of Lawesson's reagent.

Finally, it was shown that thioxo-azomethine imines can be transformed in thiopyrazolones using sodium borohydride. Only two examples could were shown, however this method affords a completely different approach and doesn't require the use of smelly or toxic reagent. Again, further optimization is necessary in order for this reactivity to be broadly applicable, but the preliminary work presented in this Chapter shows the potential of this approach

Claims to original research

- 1) Development of base catalysis for the formation of imino-isocyanates in alkene aminocarbonylation with selected enol ethers
- 2) Synthesis of new azomethine imines derived from enol ethers
- 3) Development of a novel route to pyrazolones from azomethine imines
- 4) Development of alkene aminothiocabonylation with imino-isothiocyanates and derivatization of thiooxoazomethine imines in thiopyrazolones.

Publications and presentations from this work

- 1) *Modular Synthesis of Pyrazolones using Alkene Aminocarbonylation*. Kaitlyn Lavergne, Amanda Boners, Lyanne Betit, André M. Beauchemin, *Org. Lett.* **2015**. *Manuscript in preparation*
- 2) Québec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (Ryerson 11/2014, Poster presentation): Alkene Aminocarbonylation: A Novel Route to Pyrazolones
- 3) Ottawa-Carleton Chemistry Institute (05/ 2014, oral presentation): Alkene Aminocarbonylation: a New Pyrazolone Synthesis
- 4) Québec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (Sherbrooke, 11/2013, Poster presentation): Investigation into Catalytic Intermolecular Aminocarbonylation of Alkenes with Imino-isocyanates and Derivatization into Pyrazolones
- 5) Canadian Society for Chemistry Conference and Exhibition (Québec, 05/2013, Poster presentation) Investigation into Catalytic Intermolecular Aminocarbonylation of Alkenes with Imino-isocyanates
- 6) Ottawa-Carleton Chemistry Institute (05/2013, Poster presentation): Investigation into Catalytic Intermolecular Aminocarbonylation of Alkenes with Imino-isocyanates
- 7) Oral presentation for Honours project thesis work: Investigation into Catalytic Intermolecular Aminocarbonylation of Alkenes with Imino-isocyanates

Chapter 5: Supporting Information

5.1 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 glass or aluminum backed plates, cut to size. Visualisation of the TLC plates was accomplished with UV light followed by staining in a potassium permanganate solution and heating.

^1H 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 solvent as the reference (CDCl_3 at 7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR; DMSO at 2.50 ppm for ^1H NMR and 39.5 ppm for ^{13}C NMR; MeOD at 3.31 ppm for ^1H NMR and 49.0 ppm for ^{13}C NMR; C_6D_6 at 7.16 ppm for ^1H NMR and 128.1 ppm for ^{13}C NMR). Data was reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), 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) or on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR, on a sodium chloride disk). 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.

5.2 Materials. Unless otherwise noted, all materials were purchased from commercial sources and used without further purification. Trifluorotoluene was freshly distilled or dried with 4Å molecular sieves before use.

5.3 Supporting Information for Chapter 2

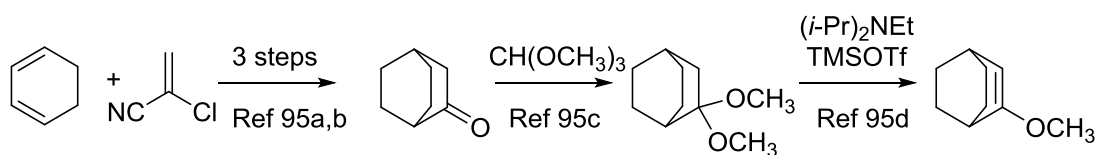
5.3.1 Preparation of enol ethers

Enol ethers **2.11**,⁸⁸ **2.12**,⁸⁹ **2.13**,⁹⁰ **2.14**,⁹¹ **2.15**, **2.17** and **2.19**,⁹² **2.16**,⁹³ and **2.18**⁹⁴ were synthesized according to literature procedures.

⁸⁸ Saraber, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1717.

⁸⁹ Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2756.

⁹⁰ Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Prieto, P. *Synth. Comm.* **1993**, *23*, 1935.



The enol ether **2.20** was prepared in 5 steps.⁹⁵ The corresponding ketone was synthesized following procedures from the literature. The corresponding acetal was synthesized using exo-bicyclo[2.2.2]oct-5-ene-2-al (2.00 g, 16.1 mmol), trimethyl orthoformate (2.10 mL, 19.3 mmol), 1 drop of hydrochloric acid and methanol (4.3 M). The solution was refluxed overnight and solvent was evaporated. The crude mixture was then dissolved in dichloromethane and *N,N*-diisopropylamine was added (0.52 mL, 3.06 mmol). The mixture was cooled to 0 °C. TMSOTf (0.5 mL, 2.76 mmol) was then added dropwise.^{5d} The solution was allowed to warm up to room temperature and stirred overnight. The solvent was evaporated and the product purified using a basic alumina plug. The crude enol ether **2.20** was obtained as a colorless oil containing 15 % acetal and 15 % *N,N*-diisopropylamine. It was used for alkene aminocarbonylation without purification.

5.3.2 Alkene aminocarbonylation with enol ethers

General procedure A (procedure used for Table 2.1, 2.2, 2.3, 2.4, 2.5, 2.6 and Scheme 2.1): To an oven dried vial was added the hydrazone phenyl 2-(9*H*-fluoren-9-ylidene)hydrazinecarboxylate **A**, phenyl 2-(2,4-dimethylpentan-3-ylidene)hydrazinecarboxylate **B** or phenyl 2-benzylidenehydrazinecarboxylate **C** (1.0-1.5 equiv.), trifluorotoluene (0.05-0.1 M), and the alkene (1.0-2.0 equiv.). For some reactions Et₃N (3 mol %) was added. The vial was then sealed and purged with argon for one minute. The reaction mixture was then heated for 3 hours at 70-100 °C. All heated reactions were performed using conventional oil or wax baths, unless otherwise noted. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude mixture was purified by column chromatography over silica gel.

⁹¹ Paquette, L. A.; Varadarajan, A.; Bay, E. *J. Am. Chem. Soc.* **1984**, *106*, 6702.

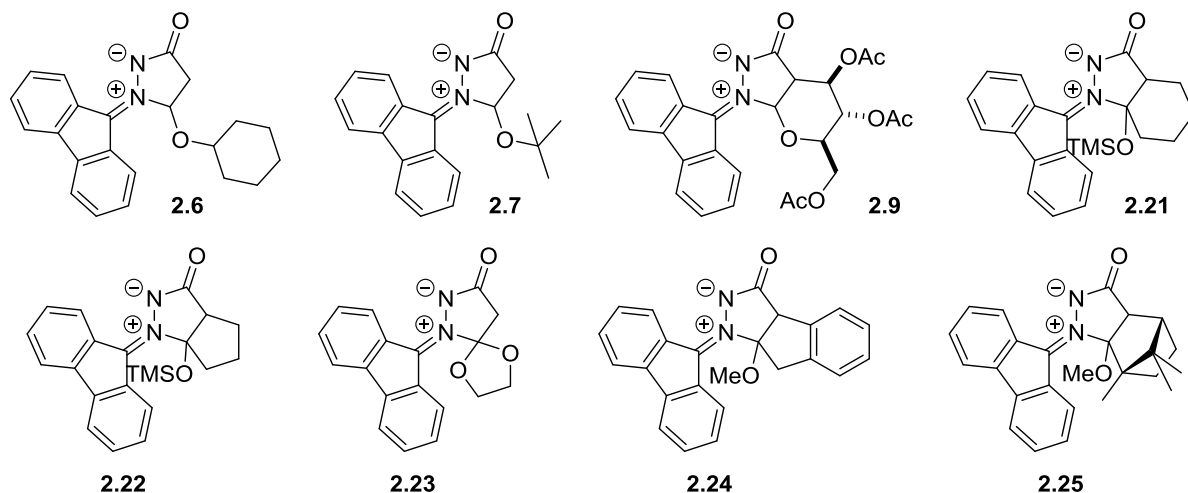
⁹² Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449.

⁹³ Peterson, P. E.; Stephanian, M. *J. Org. Chem.* **1988**, *53*, 1903.

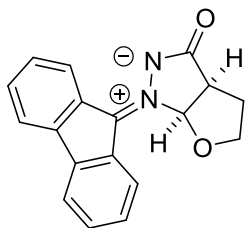
⁹⁴ Gassman, P.G.; Burns, S. J. *J. Org. Chem.* **1988**, *53*, 5574.

⁹⁵ Prepared in 5 steps : (a) Powers, D. C.; Leber, P. A.; Gallagher, S. S.; Higgs, A. T.; McCullough, L. A.; Baldwin, J. E. *J. Org. Chem.* **2007**, *72*, 187. (b) Baldwin, J. E.; Leber, P. A.; Powers, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 10020. (c) adapted from reference 94. d) Adapted from reference 92.

Note: the hydrazones **A**, **B** and **C** were synthesized according to a procedure taken from Leighton and coworkers.⁹⁶



Azomethine imines shown above were synthesized according to general procedure **A**, but no yield of desired products were obtained.

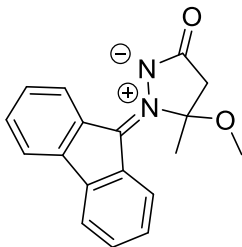


(±)-cis-1-[N'-(9H-Fluoren-9-ylidene)]-3-oxotetrahydro-1H-furo[2,3-c]pyrazolidine-1-ium-2-ide (2.2)

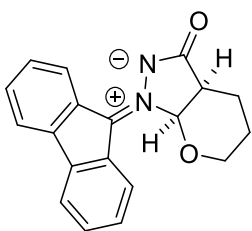
Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.487 g, 1.55 mmol), dihydrofuran (0.075 mL, 1.0 mmol), a solution of Et₃N in trifluorotoluene (0.03 M, 0.129 mL, 0.0310 mmol, 3 mol %) and trifluorotoluene (0.06 M). The reaction was heated to 70 °C for 2.5 hours in the microwave reactor. The desired product was obtained as a yellow solid (0.300 g, 95 % isolated yield). Spectral data was consistent with the literature.⁹⁷

⁹⁶ Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.

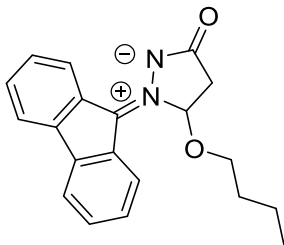
⁹⁷ Clavette, C.; Gan, W.; Bongers, A.; Markiewicz, T.; Toderian, A.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16111.



2-(9H-Fluoren-9-ylidene)-3-methoxy-3-methyl-5-oxopyrazolidin-2-ium-1-ide (2.3) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.321 g, 1.02 mmol), trifluorotoluene (0.1 M) and Et₃N (3 mol %). 2-Methoxypropene (0.0650 mL, 0.68 mmol) was added and the mixture was heated in the oil bath at 70 °C for 3 h. The crude mixture was purified by flash chromatography (1:3 EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as an orange solid (0.137 g, 69 % isolated yield). TLC R_f = 0.13 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, C₆D₆) δ 9.69 (d, *J* = 6.9 Hz, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 1.5 Hz, 2H), 7.14-6.89 (m, 4H), 2.79 (d, 17.3 Hz, 1H), 2.49 (s, 3H), 1.30 (d, *J* = 17.3 Hz, 1H), 1.98 (s, 3H) ¹³C NMR (75 MHz, DMSO-*d*₆) δ 179.9, 141.6, 140.0, 138.4, 132.7, 132.5, 131.5, 131.4, 129.3, 129.2, 128.9, 128.9, 121.3, 120.6, 109.0, 51.9, 38.7, 25.6. IR (film): 3700, 2950, 1670, 1608, 1506, 1448, 1411, 1365, 1296, 1201, 1170, 1118, 1081, 781, 730 cm⁻¹. HRMS (EI): Exact mass calcd for C₈₇H₁₆N₂O₂ [M⁺]: 292.1212, found: 292.1193.

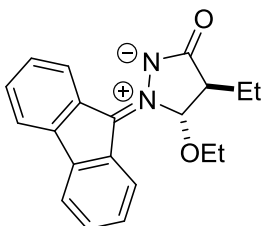


(±)-cis-1-[N'-(9H-Fluoren-9-ylidene)]-3-oxotetrahydropyrno[2,3-c]pyrazolidine-1-ium-2-ide (2.4) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.314 g, 0.999 mmol), dihydropyran (0.0609 mL, 0.668 mmol), Et₃N (3 mol %) and trifluorotoluene (0.1 M). The reaction was heated to 100 °C for 3 hours in an oil bath. The desired product was obtained as a yellow solid (0.164 g, 81 % isolated yield). Spectral data was consistent with the literature.⁵



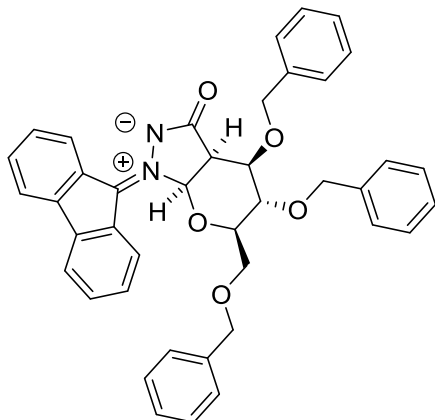
5-*n*-Butyloxy-1-[*N'*-(9*H*-Fluoren-9-ylidene)]-3-oxopyrazolidine-1-ium-2-ide (2.5)

Synthesized according to general procedure **A** using phenyl 2-(9*H*-fluoren-9-ylidene)hydrazinecarboxylate (0.315 g, 1.00 mmol), vinyl-*n*-butylether (0.0865 mL, 0.670 mmol), Et₃N (3 mol %) and trifluorotoluene (0.1 M). The reaction was heated to 70 °C for 3 hours in an oil bath. The desired product was obtained as a yellow solid (0.144 g, 68 % isolated yield). Spectral data was consistent with the literature.⁵

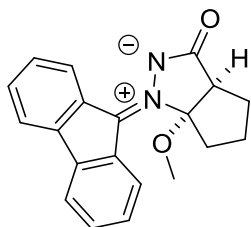


3-Ethoxy-4-ethyl-2-(9*H*-fluoren-9-ylidene)-5-oxopyrazolidin-2-ium-1-ide (2.8) (By Amanda Bongers)

Synthesized according to general procedure **A** using phenyl 2-(9*H*-fluoren-9-ylidene)hydrazinecarboxylate (0.314 g, 1.00 mmol), 1-butenyl ethyl ether (0.26 mL, 2.0 mmol) and trifluorotoluene (0.1 M). The reaction mixture was heated by microwave for 2 hours at 100 °C. The crude mixture was purified by flash chromatography (30 % EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as a bright yellow solid (0.224 g, 70 % isolated yield, 1:16 *syn/anti*). TLC R_f = 0.35 (*anti* isomer, EtOAc). ¹H NMR (*anti* isomer, 400 MHz, CDCl₃) δ 9.01 (d, *J* = 7.5 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 5 H), 7.64 (d, *J* = 7.4 Hz, 5 H), 7.67 (d, *J* = 7.4 Hz, 5 H), 7.49 - 7.41 (m, 11 H), 7.34 (td, *J* = 7.1, 12.5 Hz, 6 H), 7.35 (td, *J* = 8.2, 12.5 Hz, 6 H), 6.19 (d, *J* = 1.7 Hz, 4 H), 3.81 - 3.66 (m, 5 H), 3.44 (qd, *J* = 7.0, 8.9 Hz, 5 H), 2.87 (ddd, *J* = 1.8, 4.9, 8.6 Hz, 5 H), 2.13 - 1.92 (m, 4 H), 1.87 - 1.61 (m, 5 H), 1.15 (t, *J* = 7.0 Hz, 14 H), 1.09 (t, *J* = 7.4 Hz, 16 H). ¹³C NMR (*anti* isomer, 100 MHz, CDCl₃) δ 184.5, 141.8, 141.5, 140.5, 132.4, 131.6, 131.5, 131.4, 129.8, 129.1, 128.4, 126.8, 120.7, 119.8, 99.1, 59.8, 45.7, 23.6, 14.8, 11.4. IR (film); 2968, 2840, 1670, 1607, 1545, 1450, 1271, 1202, 1184, 1122, 1111, 1076, 777, 727 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₀H₂₀N₂O₂ [M]⁺: 320.1525. Found: 320.1501.

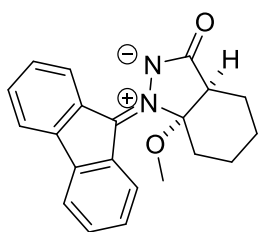


(4R,5S,6R)-4,5-is(Benzyloxy)-6-((benzyloxy)methyl)-1-(9H-fluoren-9-ylidene)-3-oxohexahydro-1H-pyrano[2,3-c]pyrazol-1-ium-2-ide (2.10) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.313 g, 0.997 mmol), tri-O-benzyl-D-glucal (0.277 g, 0.666 mmol), Et₃N (3 mol %) and trifluorotoluene (0.1 M). The reaction was heated to 100 °C for 3 hours in an oil bath. The crude mixture was purified by flash chromatography (10 % EtOAc: CH₂Cl₂ then 30 % EtOAc: CH₂Cl₂). The desired product was obtained as a yellow solid (0.324 g, 76 % isolated yield) TLC R_f = 0.38 (60 % EtOAc: Hexanes) ¹H NMR (300 MHz, CDCl₃) δ 8.99 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 11.8, 7.3 Hz, 3H), 7.45-7.26 (m, 13H), 7.16 (m, 3H), 7.02 (dd, *J* = 7.3, 1.9 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.68 (m, 3H), 4.54 (s, 1H), 4.36 (m, 1H), 4.27 (m, 2H), 3.82 (d, *J* = 8.3 Hz, 1H), 3.70 (m, 1H), 3.50 (d, *J* = 4.0 Hz, 2H), 3.48 (d, *J* = 8.0 Hz, 1H) ¹³C NMR (75 MHz, CDCl₃) δ 180.1, 142.4, 141.8, 140.6, 137.8, 137.7, 137.6, 132.5, 131.7, 131.5, 131.5, 129.8, 129.1, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 127.8, 127.4, 127.3, 127.2, 120.6, 119.7, 92.53, 74.6, 74.3, 73.1, 73.0, 71.6, 71.2, 69.4, 42.2. IR (film): 3849, 2920, 2380, 1733, 1662, 1608, 1558, 1506, 1452, 1272, 1118, 1085, 1026, 729, 698, 661 cm⁻¹. HRMS (EI): Exact mass calcd for C₄₁H₃₆N₂O₅: 636.2624. Not found. MS *m/z* (relative intensity) 91.1 (100 %), 164.1 (41 %), 253.1 (17 %),

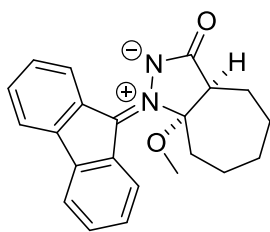


1-(9H-Fluoren-9-ylidene)-6a-methoxy-3-oxohexahydro-1H-cyclopenta[c]pyrazol-1-ium-2-ide (2.32) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.512 g, 1.63 mmol), methoxycyclopentene 2.15 (0.121 g, 1.11 mmol) and trifluorotoluene (0.1 M). The reaction mixture was heated for 3 hours at 100 °C in a wax

bath. The crude mixture was purified by flash chromatography (30 % EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as a yellow solid (0.224 g, 63 % isolated yield). TLC R_f = 0.14 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, CDCl₃) δ 9.15 (d, *J* = 7.4 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.44-7.31 (m, 3H), 7.26-7.21 (m, 1H), 3.32 (s, 3H), 2.90 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.38-2.25 (m, 2H), 2.11-2.01 (m, 1H), 1.89-1.84 (m, 1H), 1.63-1.53 (m, 1H). ¹³C NMR (75 MHz, C₆D₆) δ 182.9, 142.1, 136.9, 133.4, 132.4, 132.4, 131.7, 130.4, 130.2, 129.6, 128.2, 128.0, 127.8 (2C), 120.4, 119.6, 117.7, 52.4, 47.2, 39.3, 29.5, 23.9. IR (film): 3853, 3647, 3600, 2923, 1733, 1683, 1670, 1647, 1558, 1521, 1506, 1456, 1288, 1118, 1083, 995, 779, 730, 667 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₀H₁₈N₂O₂: 318.1368, found: 318.1370.

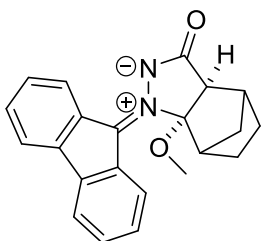


1-(9H-Fluoren-9-ylidene)-7a-methoxy-3-oxooctahydroindazol-1-ium-2-ide (2.33) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.336 g, 1.07 mmol), methoxycyclohexene **2.17** (0.0785 g, 0.701 mmol) and trifluorotoluene (0.1 M). The reaction mixture was heated for 3 h at 100 °C in a wax bath. The crude mixture was purified by flash chromatography (30 % EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as a yellow solid (0.0581 g, 25 % isolated yield). TLC R_f = 0.14 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, C₆D₆) δ 9.65 (m, 1H), 8.36 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.26 (m, 2H), 7.07-6.88 (m, 4H), 2.81 (s, 1H), 2.47 (s, 3H), 2.17-2.09 (m, 1H), 1.61-1.51 (1H), 1.25 (m, 4H), 1.10 (m, 2H). ¹³C NMR (75 MHz, C₆D₆) δ 180.7, 142.0, 139.7, 137.8, 133.4, 132.2, 131.3, 129.9, 129.8, 129.2, 128.3, 120.1, 119.1, 109.9, 50.5, 39.7, 32.8, 20.8, 20.1, 19.6. IR (film): 3600, 3750, 2929, 1728, 1683, 1647, 1558, 1517, 1506, 1309, 1259, 1195, 1118m 1083, 781, 731. HRMS (EI): Exact mass calcd for C₂₁H₂₀N₂O₂: 332.1525, found: 332.1513.

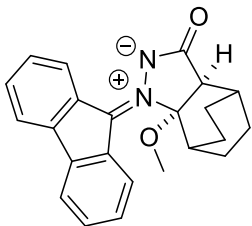


1-(9H-Fluoren-9-ylidene)-8a-methoxy-3-oxooctahydro-1H-cyclohepta[c]pyrazol-1-ium-2-ide (2.34) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-

ylidene)hydrazinecarboxylate (0.200 g, 0.637 mmol), methoxycycloheptene **2.18** (0.120 g, 0.954 mmol) and trifluorotoluene (0.1 M). The reaction solution was heated for 3 h at 100 °C in a wax bath. The crude mixture was purified by flash chromatography (30 % EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as a yellow solid (0.126 g, 57 % isolated yield). TLC R_f = 0.4 (10 % MeOH: EtOAc). ¹H NMR (300 MHz, C₆D₆) δ 9.75 (m, 1H), 8.42 (m, 1H), 7.31 (m, 2H), 7.14-6.95 (m, 4H) 2.95 (dd, *J* = 9.7, 4.4 Hz, 1H), 2.60 (s, 3H), 2.24-2.11 (m, 2H), 1.98-1.64 (m, 3H), 1.52-1.40 (m, 1H), 1.27-1.00 (m, 4H) MHz, C₆D₆) δ 181.2, 141.8, 139.3, 133.5, 132.0, 130.9, 130.1, 129.6, 129.1, 128.15, 127.8, 127.5, 119.9, 118.9, 113.8, 49.7, 45.6, 34.0, 30.1, 27.3, 25.8, 22.1, IR (film): 3886, 3749, 3676, 3525, 3000, 1733, 1683, 1647, 1554, 1506, 1298, 1126, 771, 734, 628. HRMS (EI): Exact mass calcd for C₂₂H₂₂N₂O₂: 346.1681, found: 346.1673.

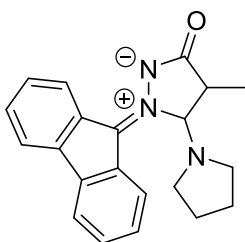


1-(9H-Fluoren-9-ylidene)-7a-methoxy-3-oxooctahydro-4,7-methanoindazol-1-ium-2-ide (2.35) (By Amanda Bongers) Synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.314 g, 0.999 mmol), 2-methoxybicyclo[2.2.1]hept-2-ene **2.19** (0.248 g, 2.00 mmol) and trifluorotoluene (0.1 M). The reaction mixture was heated for one hour at 100 °C. The crude mixture was purified by flash chromatography (30 % EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as a bright yellow solid (0.336 g, 98 % isolated yield). TLC R_f = 0.1 (Et₂O). ¹H NMR (400 MHz, CDCl₃) δ 9.17 (d, *J* = 7.8 Hz, 1 H), 8.32 (d, *J* = 8.0 Hz, 1 H), 7.70 - 7.51 (m, 2 H), 7.42 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1 H), 7.38 (ddd, *J* = 0.9, 7.5, 7.5 Hz, 1 H), 7.32 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1 H), 7.28 - 7.22 (ddd, *J* = 1.1, 7.5, 7.5 Hz, 1 H), 3.35 (s, 3 H), 3.26 (d, *J* = 3.4 Hz, 1 H), 2.82 (d, *J* = 4.0 Hz, 1 H), 2.67 (d, *J* = 2.1 Hz, 1 H), 2.15 - 1.93 (m, 1 H), 1.87 - 1.69 (m, 1 H), 1.68 - 1.42 (m, 3 H), 1.25 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 183.5, 142.2, 140.7, 140.2, 132.5, 132.3, 132.2, 131.1, 129.6, 129.1, 128.8, 128.0, 120.3, 119.4, 115.4, 53.5, 51.3, 43.8, 40.9, 34.4, 27.4, 21.8. IR (film); 2955, 1665, 1647, 1605, 1514, 1448, 1339, 1281, 1242, 1196, 1184, 1122, 1090, 995, 775, 731 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₂H₂₀N₂O₂ [M]⁺: 344.1525. Found: 344.1545.



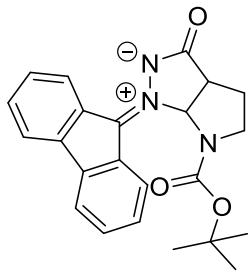
1-(9H-Fluoren-9-ylidene)-7a-methoxy-3-oxooctahydro-4,7-ethanoindazol-1-ium-2-ide (2.36) The azomethine imine **2.30** was synthesized according to general procedure **A** using phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate (0.0783 g, 0.249 mmol), crude enol ether **2.20** (0.0951 g, 0.688 mmol) and trifluorotoluene (0.1 M). The reaction mixture was heated for 3 h at 100 °C in a wax bath. The crude mixture was purified by flash chromatography (30 % EtOAc: CH₂Cl₂ then 10 % MeOH: EtOAc). The desired product was obtained as a yellow solid (0.0798 g, 86 % isolated yield). TLC R_f = 0.37 (10 % MeOH: EtOAc). ¹H NMR (300 MHz, C₆D₆) δ 9.24 (d, *J* = 7.9 Hz, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 6.6 Hz, 2H), 7.45-7.32 (m, 3H), 7.26-7.21 (m, 1H), 3.37 (s, 3H), 2.95 (2, *J* = 3.8 Hz, 1H), 2.83 (m, 1H), 2.49 (m, 1H), 2.14-2.02 (m, 1H) 1.72-1.61 (m, 4H), 1.44-1.36 (m, 2H), 1.26-1.18 (m, 3H) ¹³C NMR (75 MHz, C₆D₆) δ 183.6, 142.6, 140.3, 132.8, 132.6, 132.5, 131.4, 129.6, 129.3, 129.3, 128.1, 120.4, 119.4, 112.1, 50.6, 46.2, 30.1, 27.7, 23.9, 21.5, 20.5, 20.5. IR (film): 3820, 3649, 3573, 2943, 1730, 1679, 1652, 1635, 1558, 1506, 1456, 1338, 1288, 1126, 734 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₃H₂₂N₂O₂: 358.1681, found: 358.1682.

5.3.3 Alkene aminocarbonylation with enamines



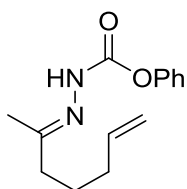
Phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate, 1-propenyl-pyrrolidine⁹⁸ and trifluorotoluene (0.1 M) were added to an oven dried microwave vial, purged with argon and heated in the microwave reactor for 2-3h at 70-100 °C. No desired aminocarbonylation products were obtained. Byproducts were identified as shown in **scheme 2.2** and **2.3**.

⁹⁸ Nagel, M.; Hans-Juergen, H. *Synlett* **2002**, 117.

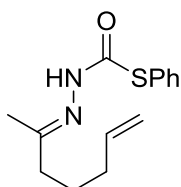


6-(*tert*-Butoxycarbonyl)-1-(9H-fluoren-9-ylidene)-3-oxohexahydro-1H-pyrrolo[2,3-c]pyrazol-1-ium-2-ide (2.41). phenyl 2-(9H-fluoren-9-ylidene)hydrazinecarboxylate, 1-boc-2,3-dihydropyrrole and trifluorotoluene (0.1 M) were added to an oven dried microwave vial, purged with argon and heated in a wax bath for 2-3h at 70-100 °C. 3 mol % of Et₃N were added to the reactions performed at 70 °C. No desired aminocarbonylation products were obtained at 100 °C. 60 % NMR yield was obtained when base catalysis was used, however the azomethine imine could not be isolated.

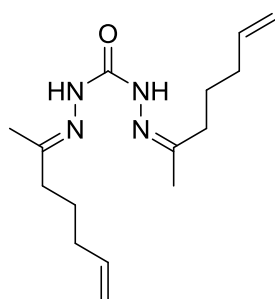
5.3.4 Intramolecular alkene aminocarbonylation



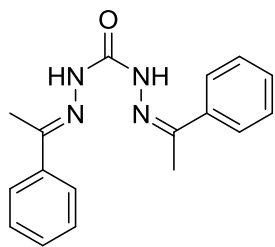
(E)-Phenyl 2-(hept-6-en-2-ylidene) hydrazinecarboxylate (2.42) To a round bottom flask was added *O*-phenyl carbazate (2.35 g, 20.9 mmol), ketone⁴⁹ (2.14 g, 14.1 mmol) and methanol (0.5M). The mixture was refluxed overnight in a wax bath. The crude mixture was purified by column chromatography (5 % EtOAc in CH₂Cl₂). The desired product was obtained as a white solid (0.997 g, 22 %). TLC R_f = 0.55 (20 % EtOAc: Hexanes). ¹H NMR (300 MHz, CDCl₃) δ 7.79 (s, 1H), 7.38 (m, 2H), 7.22 (m, 3H), 5.80 (m, 1H), 5.02 (m, 2H), 2.38 (m, 1H), 2.24 (m, 1H), 2.14 (m, 2H), 2.08 (s, 1H), 1.89 (s, 2H), 1.68 (m, 2H) ¹³C NMR (300 MHz, CDCl₃) δ 150.8, 138.0, 137.9, 137.3, 129.5, 129.4, 125.7, 115.4, 115.1, 42.9, 38.5, 33.3, 33.0, 29.1, 25.9, 24.3, 14.8 IR (film): 3195, 2345, 1720, 1490, 1197, 1022, 921.7. HRMS (EI): Exact mass calcd for C₁₄H₁₈N₂O₂[M⁺]:246.1368, found: 246.1369.



(E)-S-Phenyl 2-(hept-6-en-2-ylidene) hydrazinecarbothioate (2.49) To an oven dried microwave vial was added hydrazone (0.0481 g, 0.195 mmol), thiophenol (0.10 ml, 0.975 mmol) and PhCF₃ (0.5M). The reaction mixture was heated to 150 °C for 10 minutes. The crude mixture was purified by column chromatography (hexanes). The desired product was obtained as a white solid (0.0169 g, 33 %). TLC R_f = 0.55 (20 % EtOAc: Hexanes) ¹H NMR (300 MHz, CDCl₃) δ 8.82 (s, 1H), 7.55 (m, 2H), 7.40 (m, 3H), 5.77 (m, 1H), 5.04 (m, 2H), 2.34 (m, 2H), 2.15 (m, 2H), 2.06 (s, 1H), 1.79 (s, 3H), 1.71 (m, 2H) ¹³C NMR (300 MHz, CDCl₃) δ 138.6, 136.1, 136.1, 129.5, 129.3, 115.5, 38.5, 33.6, 25.6, 15.9. IR (film): 2927, 1728, 1674, 1490, 1477, 1440, 1203, 748, 688. HRMS (EI): Exact mass calcd for C₁₄H₁₈N₂OS[M⁺]: 262.1139 found: 153.1.



Hept-6-en-2-ylidene)-2-(hept-6-en-2-ylidene)hydrazine-1-carbohydrazide. To an oven dried microwave vial was added (E)-Phenyl 2-(hept-6-en-2-ylidene) hydrazinecarboxylate (0.0367 g, 0.149 mmol) imidazole (0.0656 g, 0.964 mmol) and trifluorotoluene (0.04 M). The vial was sealed and purged with argon. The reaction mixture was heated in a wax bath at 50 °C overnight. The crude mixture was purified by column chromatography (EtOAc). The product was obtained as a clear yellow oil. TLC R_f = 0.2 (EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 5.80 (m, 2H), 5.02 (m, 4H), 2.32 (m, 3H), 2.10 (m, 6H), 1.85 (s, 6H), 1.66 (dt, J= 15.1, 7.5 Hz, 4H). ¹³C NMR (300 MHz, CDCl₃) 152.8, 138.1, 137.2, 115.0, 33.6, 33.2, 24.2, 23.5, 14.9, δ HRMS (EI): Exact mass calcd for C₁₅H₂₆N₄O[M⁺]: 278.2106 found: 278.2106.



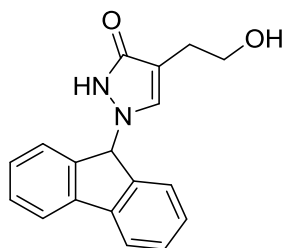
(E)-N'-((E)-1-Phenylethylidene)-2-(1-phenylethylidene)hydrazine-1-carbohydrazide (2.52). To an oven dried microwave vial was added (E)-phenyl 2-(1-phenylethylidene)hydrazinecarboxylate

(0.0997 g, 0.392 mmol) and trifluorotoluene (0.1M). The vial was sealed, purged with argon and heated to 80 °C for 2 hours. The crude mixture was purified by recrystallization in dichloromethane. The product was obtained as white crystals. TLC R_f = 0.15 (50 % EtOAc in hexanes). ^1H NMR (300 MHz, CDCl_3) δ 7.79 (m, 2H), 7.42 (m, 3H), 2.33 (s, 3H) ^{13}C NMR (300 MHz, CDCl_3) δ 152.6, 137.9, 129.3, 128.5, 128.3, 126.6, 126.2, 13.3. The structure of the product was confirmed by x-ray crystallography.

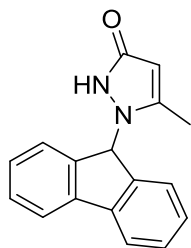
5.4 Supporting Information for Chapter 3

General Procedure B (Procedure used in Table 3.1 and Scheme 3.4): To a round bottom flask charged with a stir bar was added the azomethine imine (1 equiv.) and methanol (0.02-0.05 M). Sodium borohydride (1-6 equiv.) was added and the mixture was stirred at room temperature until full conversion by TLC. The reaction was quenched with aqueous NH_4Cl and extracted three times with CH_2Cl_2 . The combined organic layer was washed with brine, dried with Na_2SO_4 , and solvent was removed by evaporation to give the crude product. The product was purified using trituration with EtOAc if necessary.

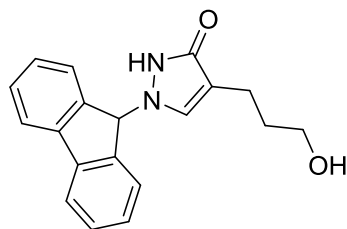
General Procedure C (Procedure used in Table 3.2 and Scheme 3.4): To a round bottom flask charged with a stir bar was added the azomethine imine (1 equiv.) and methanol (0.05 M). The reaction was cooled (-20 °C or 0 °C) and sodium borohydride (1 equiv.) was then added. The cooled mixture was stirred until full conversion by TLC. The reaction was quenched with aqueous NH_4Cl , extracted three times with CHCl_3 , and the combined organic layer was dried with Na_2SO_4 followed by filtration. Excess CHCl_3 was evaporated until the mixture concentration reached approximately 0.1 M. Catalytic *p*-TsOH was then added and the mixture was heated at 60 °C for 3 hours, then cooled to room temperature and partitioned with water. The organic layer was washed with brine, dried with Na_2SO_4 , and solvent was removed by evaporation to give the crude product. The product was purified by trituration with EtOAc.



1-(9H-Fluoren-9-yl)-4-(2-hydroxyethyl)-1H-pyrazol-3(2H)-one (3.29) Synthesized according to general procedure **B** using azomethine imine **2.2** (0.116 g, 0.398 mmol) in methanol (25 mL, 0.02 M). The solution was slightly heated until azomethine imine fully dissolved, then sodium borohydride (0.0602 g, 1.59 mmol) was added. The product was obtained as an off-white solid (0.114 g, >95 % isolated yield). TLC R_f = 0.26 (60 % EtOAc: Hexanes). ^1H NMR (300 MHz, CDCl_3) δ 7.73 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.29 (m, 2H), 6.72 (s, 1H), 6.11 (s, 1H), 3.73 (t, J = 5.8 Hz, 2H), 2.52 (t, J = 5.7 Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 160.5, 141.8, 140.6, 129.4, 128.4, 128.0, 125.4, 120.3, 103.5, 65.6, 62.1, 26.3. IR (film): 3820, 3689, 3647, 2925, 2354, 1730, 1683, 1652, 1635, 1558, 1506, 1448, 1319, 1149, 1045, 734, 686, 659, 624 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$ [M^+]: 292.1212, found: 292.1198.

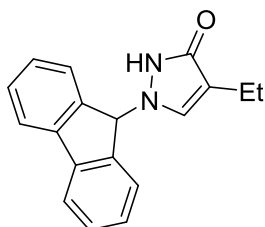


1-(9H-Fluoren-9-yl)-5-methyl-1H-pyrazol-3(2H)-one (3.34) Synthesized according to general procedure **B** using azomethine imine **2.3** (0.0435 g, 0.149 mmol) and sodium borohydride (0.0245 g, 0.647 mmol) in methanol (0.05 M). The product was obtained as an off-white solid (0.0371 g, 95 % isolated yield). TLC R_f = 0.47 (60 % EtOAc: Hexanes). ^1H NMR (300 MHz, DMSO) δ 9.48 (br s, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.39 (m, 2H), 7.25 (m, 4H), 6.30 (s, 1H), 5.33 (s, 1H), 2.25 (br s, 3H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 160.9, 144.1, 140.9, 140.5, 129.0, 128.1, 125.2, 120.7, 91.7, 62.6, 11.6. IR (film): 3629, 2364, 1922, 1728, 1652, 1554, 727 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_1$ [M^+]: 262.1106, found: 262.1116.

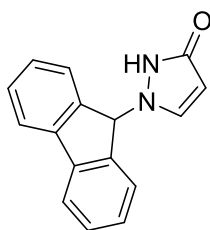


1-(9H-Fluoren-9-yl)-4-(3-hydroxypropyl)-1H-pyrazol-3(2H)-one (3.35) Synthesized according to general procedure **B** using azomethine imine **2.4** (0.0186 g, 0.0600 mmol) and sodium borohydride (0.0136 g, 0.36 mmol) in methanol (0.05 M). The product was obtained as an off-white solid (0.0169 g, 92 % isolated yield) TLC R_f = 0.26 (60 % EtOAc: Hexanes). ^1H NMR (300 MHz, CDCl_3) δ 7.75 (d, J =

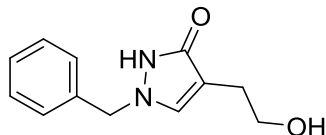
7.6 H, 2H), 7.59 (d, $J = 7.6$ Hz, 2H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.33 (m, 2H), 6.72 (s, 1H), 6.26 (s, 1H), 3.62 (t, $J = 5.9$ Hz, 2H), 2.41(t, $J = 7.0$ Hz, 2H), 1.70 (m, 1H) ^{13}C NMR (75 MHz, CDCl_3) δ 159.9, 141.4, 140.6, 129.5, 128.7, 128.1, 125.4, 120.3, 109.0, 65.4, 61.4, 32.1, 18.1 IR (film): 3637, 2920, 1730, 1683, 1652, 1558, 1521, 1506, 1448, 738 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ [M^+]: 306.1368, found: 306.140.



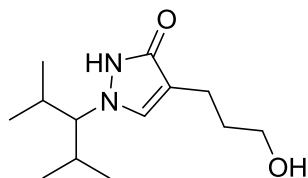
4-Ethyl-1-(9H-fluoren-9-yl)-1H-pyrazol-3(2H)-one (3.3) Synthesized according to general procedure **B** using azomethine imine **2.8** (0.160 g, 0.500 mmol) and sodium borohydride (0.080 g, 0.21 mmol) in methanol (0.05M). The mixture was stirred at room temperature for 4 hours. The product was isolated by silica gel chromatography (10 % Et_2O , 90 % CH_2Cl_2) to give a white solid (0.110 g, 80 %). TLC $R_f = 0.3$ (10 % Et_2O : CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 7.5$ Hz, 2 H), 7.65 - 7.51 (m, 2 H), 7.43 (t, $J = 7.3$ Hz, 2 H), 7.37 - 7.26 (m, 2 H), 6.59 (s, 1 H), 6.16 (s, 1 H), 2.28 (q, $J = 7.6$ Hz, 2 H), 1.04 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.4, 142.0, 140.5, 129.3, 127.9, 126.9, 125.5, 120.2, 108.7, 65.5, 15.7, 14.0. IR (film); 2929, 1724, 1602, 1526, 1448, 1300, 1175, 735 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$ [M^+]: 276.1263. Found: 276.1253.



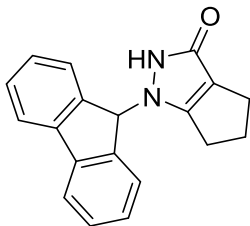
1-(9H-Fluoren-9-yl)-1H-pyrazol-3(2H)-one (3.36) Synthesized according to general procedure **B** using azomethine imine **2.5** (0.0602 g, 0.188 mmol) and sodium borohydride (0.0342 g, 0.904 mmol) in methanol (0.05 M). The product was obtained as an off-white solid (0.0462 g, 95 % isolated yield). TLC $R_f = 0.57$ (60 % EtOAc : Hexanes). ^1H NMR (300 MHz, CDCl_3) δ 7.74 (d, $J = 7.6$ Hz, 2H), 7.56 (m, 2H). 7.44 (t, $J = 7.4$ Hz, 2H), 7.31 (td, $J = 1.1$ Hz, 2H), 6.83 (d, $J = 2.6$ Hz, 1H), 6.18 (s, 1H), 5.61 (d, $J = 2.5$ Hz, 1H). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 162.2, 143.5, 140.53, 131.8, 129.3, 128.1, 125.3, 120.8, 91.2, 65.5. IR (film): 3865, 3811, 3867, 3647 2920, 1747, 1683, 1652, 1635, 1558, 1541, 1506, 1448, 1303, 1217, 1051, 1027, 738, 688, 617 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_1$ [M^+]: 248.0950, found: 248.0954.



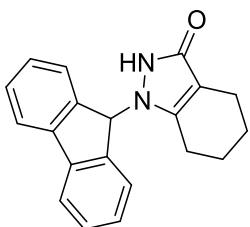
1-Benzyl-4-(2-hydroxyethyl)-1H-pyrazol-3(2H)-one (3.38) The azomethine imine was first synthesized according to general procedure **B** using hydrazone (0.318 g, 1.32 mmol), dihydrofuran (0.2 mL, 2.6 mmol), Et₃N (0.02 equiv.) and trifluorotoluene (0.1 M), heated for 3 hours at 100 °C in a wax bath. Then 0.0112 g of trimethoxybenzene internal standard was added and ¹H NMR showed 32 % yield. The crude mixture of the azomethine imine was dissolved in methanol then sodium borohydride (0.0854 g, 2.25 mmol) was added and the mixture was stirred at room temperature until full conversion. The product was obtained as a very viscous colorless oil (0.101 g, 84 % isolated yield, 35 % yield from hydrazone). TLC R_f = 0.17 (40 % EtOAc: Hexanes). ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.31 (m, 3H), 7.28-7.24 (m, 2H), 7.01 (s, 1H), 5.04 (s, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 2.63 (t, *J* = 5.6 Hz, 2H), (75 MHz, DMSO-*d*₆) δ 160.3, 136.0, 130.0, 128.8, 128.2, 127.9, 102.6, 63.0, 55.4, 26.2. IR (film): 3600, 3850, 2927, 1730, 1683, 1647, 1570, 1533, 1506, 1448, 1051, 1027, 730, 696, 648 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₂H₁₄N₂O₂ [M⁺]: 218.1055, found: 218.1075.



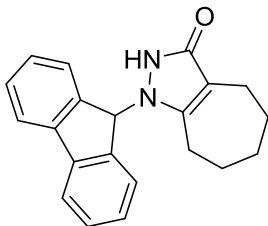
1-(2,4-Dimethylpentan-3-yl)-4-(2-hydroxyethyl)-1H-pyrazol-3(2H)-one (3.39) Synthesized according to general procedure **B** using azomethine imine (±)-*cis*-1-(2,4-dimethylpentan-3-ylidene)-3-oxo-tetrahydro-2H-pyro[2,3-*c*]pyrazolidine-1-ium-2-ide (0.110 g, 0.461 mmol) and sodium borohydride (0.0776 g, 2.02 mmol) in methanol (0.1 M). The product was obtained as a clear colorless oil (0.0932 g, 84 % isolated yield). TLC R_f = 0.37 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, CDCl₃) δ 6.86 (s, 1H), 3.60 (t, *J* = 5.0 Hz, 2H), 3.28 (t, *J* = 7.3 Hz, 1H), 2.48 (t, *J* = 6.8 Hz, 2H), 2.13 (dq, *J* = 13.5, 6.7 Hz, 2H), 7.76-7.72 (m, 2H), 0.86 (d, *J* = 6.7 Hz, 6H), 0.79 (d, *J* = 6.7 Hz, 6H) NMR (75 MHz, CDCl₃) δ 159.3, 129.5, 102.6, 73.9, 61.1, 33.0, 29.5, 20.4, 18.0, 17.7. IR (film): 3820, 3743, 3689, 2974, 1683, 1652, 1558, 1525, 1506, 1265, 725, 703, 669. HRMS (EI): Exact mass calcd for C₁₃H₂₄N₂O₂ [M⁺]: 240.1838, found: 240.1838.



1-(9H-Fluoren-9-yl)-1,2,5,6-tetrahydrocyclopenta[c]pyrazol-3(4H)-one (3.40) Synthesized according to general procedure **C** using azomethine imine **2.32** (0.0863 g, 0.274 mmol) in methanol (0.05 M), cooled to -20 °C. Sodium borohydride (0.0104 g, 0.275 mmol) was added and the mixture was stirred at -20 °C until bubbling stopped then quenched and extracted with CHCl₃ (3 x 5 mL). Catalytic *p*-TsOH was added to complete the aromatization. The product was obtained as a white solid (0.0530 g, 59 % isolated yield). TLC R_f = 0.26 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.54 (s, 1H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.39 (m, 4H), 7.30 (m, 2H), 6.12 (s, 1H), 2.30 (m, 4H), 2.19 (m, 2H) NMR (75 MHz, DMSO-*d*₆) δ 155.5, 151.7, 143.4, 140.5, 129.3, 128.2, 125.5, 120.7, 110.6, 64.4, 30.3, 24.3, 22.5 IR (film): 3851, 3647, 2970, 238, 1733, 1683, 1652, 1635, 1554, 1525, 1506, 1456, 1338, 742, 669 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₉H₁₆N₂O [M⁺]: 288.1263, found: 288.1251.

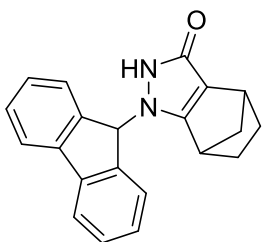


1-(9H-Fluoren-9-yl)-4,5,6,7-tetrahydro-1H-indazol-3(2H)-one (3.46) Synthesized according to general procedure **B** using azomethine imine **2.33** (0.0235 g, 0.0769 mmol) and sodium borohydride (0.0030 g, 0.068 mmol) in methanol (0.05 M). The product was obtained as an off-white solid (0.0137 g, 64 % isolated yield). TLC R_f = 0.51 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.29 (m, 2H), 6.28 (s, 1H), 2.30 (t, *J* = 6.0 Hz, 2H), 1.51 (m, 4H), 1.41 (m, 2H) NMR (75 MHz, CDCl₃) δ 157.9, 143.3, 139.9, 139.8, 128.3, 127.3, 124.5, 119.9, 100.1, 62.1, 22.3, 22.0, 20.9, 18.8 IR (film): 3849, 3676, 3627, 2920, 1733, 1683, 1652, 1558, 1539, 1506, 1448, 1299, 734 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₀H₁₈N₂O [M⁺]: 302.1419, found: 302.1428.



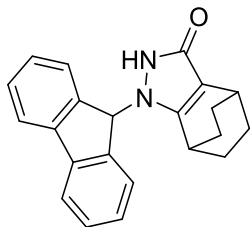
1-(9H-Fluoren-9-yl)-1,2,5,6,7,8-hexahydrocyclohepta[c]pyrazol-3(4H)-one (3.44)

Synthesized according to general procedure **C** using azomethine imine **2.34** (0.0863 g, 0.274 mmol) in methanol (0.05 M), cooled to -20 °C. Sodium borohydride (0.0030 g, 0.068 mmol) was added and the mixture was stirred at -20 °C until bubbling stopped then quenched and extracted with CHCl₃ (3x5 mL). Catalytic *p*-TsOH (0.0040 g, 0.021 mmol) was added to complete the aromatization. The product was obtained as a white solid (0.0309 g, 82 % isolated yield) TLC R_f = 0.54 (60 % EtOAc: Hexanes). ¹H NMR (300 MHz, DMSO-*d*₆) 9.35 (s, 1H), 7.82 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.22 (m, 4H), 6.36 (s, 1H), 3.07 (m, 2H), 2.29 (m, 2H), 1.80 (m, 3H), 1.52 (m, 3H) NMR (75 MHz, DMSO-*d*₆) δ 158.7, 144.5, 140.5, 128.9, 127.99, 125.0, 120.7, 105.1, 61.7, 31.8, 28.8, 26.4, 22.8 (2C), IR (film): 3853, 3743, 3637, 2920, 2846, 1730, 1679, 1652, 1558, 1506, 1456, 1313, 1222, 742 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₁H₂₀N₂O [M⁺]: 316.1576, found: 316.1576.

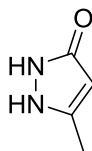


1-(9H-Fluoren-9-yl)-4,5,6,7-tetrahydro-1H-4,7-methanoindazol-3(2H)-one (3.43) Synthesized according to general procedure **C**. The azomethine imine **2.35** (0.0758 g, 0.220 mmol) in methanol (0.05 M) was cooled to 0 °C and sodium borohydride (0.0120 g, 0.317 mmol) was added. The mixture was stirred at 0 °C for one hour, then quenched and extracted with CHCl₃ (3x5 mL). Catalytic *p*-TsOH (0.0040 g, 0.021 mmol) was added to complete the aromatization. The product was purified by trituration in EtOAc to give a white solid (0.0501 g, 72 %). TLC R_f = 0.45 (Et₂O). ¹H NMR (400 MHz, CDCl₃) δ 7.76 - 7.71 (m, 2 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 7.4 Hz, 1 H), 7.47 - 7.40 (m, 2 H), 7.35 - 7.26 (m, 2 H), 6.12 (s, 1 H), 3.24 - 3.20 (m, 1 H), 2.03 - 1.98 (m, 1 H), 1.69 - 1.56 (m, 2 H), 1.39 - 1.30 (m, 1 H), 1.22-1.17 (m, 1 H), 1.13 - 1.05 (m, 1 H), 0.56 - 0.47 (m, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 155.6, 155.4, 142.9, 142.1, 140.7, 140.5, 129.4, 129.3, 128.2, 127.9, 125.7, 125.6, 120.2, 120.2,

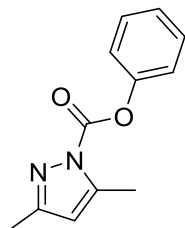
114.6, 65.0, 51.6, 40.0, 37.4, 28.1, 26.2. IR (film); 2962, 2635, 1526, 1452, 1284, 1261, 1176, 741, 696 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}]^+$: 314.1419. Found: 314.1422.



1-(9H-Fluoren-9-yl)-4,5,6,7-tetrahydro-1H-4,7-ethanoindazol-3(2H)-one (3.45) Synthesized according to general procedure **B** using azomethine imine **2.36** (0.0032 g, 0.0836 mmol) and sodium borohydride (0.0040 g, 0.105 mmol) in methanol (0.05 M). The product was obtained as an off-white solid (0.0122 g, 45 % isolated yield). TLC R_f = 0.22 (60 % EtOAc: Hexanes). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.42 (s, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 5.6 Hz, 2H), 7.30 (m, 2H), 7.06 (m, 1H), 6.34 (s, 1H), 2.99 (m, 2H), 1.59 (m, 4H), 1.15 (m, 4H) NMR (75 MHz, $\text{DMSO}-d_6$) δ 155.1, 147.8, 144.1, 140.4, 129.1, 128.1, 125.0, 120.7, 106.8, 63.5, 27.9, 27.5 (2C), 26.4 (2C), 26.2 IR (film): 3814, 3743, 3647, 2920, 1733, 1683, 1652, 1554, 1541, 1506, 1471, 742 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}$ $[\text{M}^+]$: 328.1576, found: 328.1556.

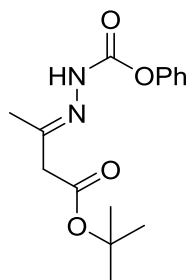


5-Methyl-1H-pyrazol-3(2H)-one (3.46) Pyrazolone **3.34** (0.0208 g, 0.0794 mmol) was dissolved in methanol (0.05 M) and Pd/C 10wt % (0.0084g, 0.0079 mmol) was added. The flask was put under an atmosphere of hydrogen and stirred at room temperature overnight. The mixture was filtered through celite and solvent was evaporated. The product was isolated by trituration with EtOAc to give a white solid (0.0062 g, 80 %). Spectral data was consistent with the literature.⁹⁹ HRMS (EI): Exact mass calcd for $\text{C}_4\text{H}_6\text{N}_2\text{O}$ $[\text{M}^+]$: 98.0480, found: 98.0480.



⁹⁹ Jung, J.-C.; Watkins, E. B.; Avery, M. A. *Tetrahedron* **2002**, *58*, 3639.

Phenyl 3,5-dimethylpyrazole-1-carboxylate (3.52). To an oven dried microwave vial was added *O*-phenyl carbazate (0.320 g, 2.11 mmol), acetylacetone (0.26 mL, 2.53 mmol) and methanol (0.5 M). The reaction mixture was refluxed for 2 hours. The product was isolated by flash chromatography using 20 % EtOAc in hexanes. The product was obtained as a white solid (0.164 g, 36 %). TLC R_f = 0.5 (50 % EtOAc: Hexanes). ^1H NMR (300 MHz, CDCl_3) δ 7.44 (m, 2H), 7.30 (m, 3H), 6.08 (s, 1H), 2.58 (d, J = 0.9 Hz, 3H), 2.35 (s, 3H). ^{13}C NMR (300 MHz, CDCl_3) δ 153.5, 150.4, 149.2, 145.6, 129.6, 129.5, 121.6, 111.3, 14.2, 13.9. HRMS (ESI): Exact mass calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$ [$\text{M}+\text{H}^+$]: 217.0898, found: 217.0305.



Phenyl 2-(4-(tert-butoxy)-4-oxobutan-2-ylidene) hydrazinecarboxylate (3.54). To a round bottom flask was added *O*-phenyl carbazate (0.497 g, 3.26 mmol), *tert*-butyl acetoacetate (1.10 mL, 6.52 mmol) and methanol (0.5M). The mixture was refluxed overnight in a wax bath. The crude mixture was purified by column chromatography (40 % EtOAc on Hexanes). The desired product was obtained as a clear oil (0.771 g, 81 %). TLC R_f = 0.20 (20 % EtOAc: Hexanes). ^1H NMR (300 MHz, CDCl_3) δ mixture of rotamers: 7.96 (s, 1H), 7.39 (m, 2H), 7.22 (m, 3H), 3.34 (m, 2H), 2.09 (m, 3H), 1.50 (m, 9H) ^{13}C NMR (300 MHz, CDCl_3) δ mixture of rotamers: 168.9, 150.6, 150.5, 129.4, 129.3, 125.8, 125.6, 121.5, 81.7, 45.5, 28.0, 27.9, 24.9, 15.4. IR (film): 3427, 2977, 1720, 1517, 1490, 1456, 1367, 1201, 1137, 1108, 1018, 734.8, 688.5. HRMS (EI): Exact mass calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4$ [M^+]: 292.1423 found: 292.1428

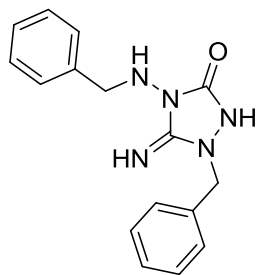
Phenyl 2-(4-(tert-butoxy)-4-oxobutan-2-ylidene) hydrazinecarboxylate was dissolved in chlorobenzene (0.1 M) and heated to 130-150 °C in a wax bath. No desired product was observed by NMR.

Screening of conditions for condensation aldehydes onto a hydrazide to form azomethine imines (Scheme 3.6):

Tsuge's conditions: To an oven dried microwave vial was added phenyl 2-benzylhydrazinecarboxylate, butyraldehyde (2 equiv.), toluene (0.3 M) and Et₃N (3 equiv.). The reaction mixture was refluxed overnight.

Conditions A adapted from Maruoka's paper: To an oven dried microwave vial was added 4Å molecular sieves and trifluorotoluene (0.1 M). The solution was cooled to -20 °C and phenyl 2-benzylhydrazinecarboxylate and hydrocinnamaldehyde (1.5 equiv.) were added. The reaction mixture was stirred at -20 °C for 20h.

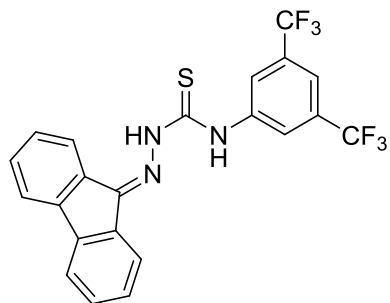
Conditions B adapted from Maruoka's paper: To an oven dried microwave vial was added 4Å molecular sieves, trifluorotoluene (0.1 M), phenyl 2-benzylhydrazinecarboxylate, hydrocinnamaldehyde (1.5 equiv.) and diphenyl phosphate were added. The reaction mixture was stirred at room temperature for 2h.



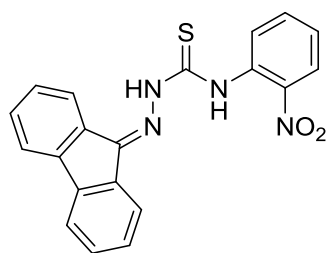
1-Benzyl-4-(benzylamino)-5-imino-1,2,4-triazolidin-3-one (3.69). To an oven dried microwave vial was added phenyl 2-benzylhydrazinecarboxylate²⁸ (0.153 g, 0.633 mmol), phenylacetylene (0.02 mL, 0.211 mmol) and isopropanol (0.5 M). The reaction mixture was heated at 150 °C for three hours in a wax bath. The product was isolated by trituration dichloromethane. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.3 (br s, 1H), 7.34 (m, 8H), 7.12 (m, 2H), 6.12 (t, *J* = 4.2 Hz, 1H), 4.53 (s, 2H), 4.10 (d, *J* = 4.1 Hz, 2H) ¹³C NMR (75 MHz, DMSO-*d*₆) δ 153.7, 153.2, 137.7, 135.8, 129.1, 129.0, 128.5, 128.5, 128.3, 127.7, 52.8, 49.7. Identified as main byproduct of the reaction.

5.5 Supporting Information for Chapter 4

5.5.1 Synthesis of thiosemicarbazones



***N*-(3,5-bis(Trifluoromethyl)phenyl)-2(9H-fluoren-9-ylidene) hydrazine carbothioamide (4.59).** To a round bottom flask was added fluorenone hydrazone (0.0310 g, 0.159 mmol), 2-nitrophenyl isothiocyanate (0.30 mL, 0.16 mmol) and acetonitrile (0.2 M). The mixture was stirred overnight at room temperature. Upon filtration, the product was obtained as a yellow solid (0.0587 g, 77 %). TLC $R_f = 0.58$. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 11.76 (s, 1H), 10.79 (s, 1H), 8.51 (s, 2H), 8.08 (t, $J = 7.0$ Hz 2H), 7.87 (m, 3H), 7.44 (m, 4H), ^{13}C NMR (300 MHz, $\text{DMSO-}d_6$) δ 178.4, 149.2, 142.1, 141.4, 140.3, 136.7, 132.3, 131.4, 131.0, 130.6, 130.2, 129.7, 129.6, 128.7, 128.6, 128.2, 125.8, 125.5, 123.4, 121.9, 121.2, 120.9. IR (film): 1670, 1539, 1471, 1212, 1164, 1128, 1105, 891, 7213. HRMS (EI): Exact mass calcd for $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$: 465.0734, found: 465.0755.

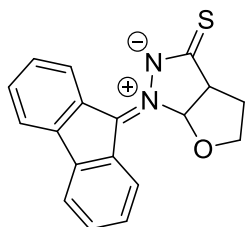


2-(9H-Fluoren-9-ylidene)-*N*-(2-nitrophenyl) hydrazine carbothioamide (4.61) To a round bottom flask was added fluorenone hydrazone (1.50 g, 7.73 mmol), 2-nitrophenyl isothiocyanate (1.39 g, 7.73 mmol) and acetonitrile (0.2 M). The mixture was stirred overnight at room temperature. Upon filtration, the product was obtained as a yellow solid (2.38 g, 82 %). TLC $R_f = 0.52$ ^1H NMR (300 MHz, DMSO) δ 11.79 (s, 1H), 11.39 (s, 1H), 8.4 (d, $J = 8.0$ Hz, 1H), 8.13 (m, 3H), 7.85 (m, 3H), 7.48 (m, 5H) ^{13}C NMR (300 MHz, DMSO) δ 178.4, 148.1, 143.1, 142.2, 140.3, 136.8, 134.6, 134.0, 132.3, 131.4, 129.5, 128.7, 128.7, 128.3, 126.8, 125.7, 122.9, 121.3, 120.9 IR (film): 1579, 1545, 1498, 1487, 1431, 1274, 1247, 1168, 1078, 781, 729. HRMS (EI): Exact mass calcd for $\text{C}_{20}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$:

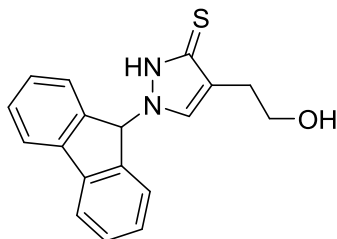
374.0837, not found. Key fragments identified by LRMS: 356.1, 236.04 (R=N-N=C=S), 178.1, 138.04 (*ortho*-nitroaniline).

5.5.2 Alkene aminothiocabonylation with enol ethers

General procedure D (Procedure used for Table 4.1, 4.2, 4.3 and Scheme 4.7): To an oven dried vial was added the thiosemicarbazone, trifluorotoluene (0.05 M), and the alkene (10 equiv.). The vial was then sealed and purged with argon for one minute. The reaction mixture was then heated for 1-2 hours at 100-120 °C. All heated reactions were performed using conventional oil or wax baths, unless otherwise noted. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude mixture was purified by column chromatography over silica gel.

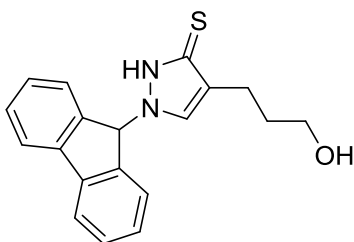


1-(9H-Fluoren-9-ylidene)-3-thioxohexahydrofuro[2,3-c]pyrazol-1-ium-2-ide (4.52) was synthesized according to general procedure **D**. Thiosemicarbazone **4.61** (0.0514 g, 0.137 mmol), dihydrofuran (0.10 mL, 1.37 mmol) and α,α,α -trifluorotoluene (0.05 M) were added to a microwave vial. The reaction mixture was heated up to 100 °C for 2h in a microwave reactor. The product was purified by flash chromatography (20 % EtOAc: Hexanes then 40 % EtOAc: Hexanes). The product was obtained as a red solid (0.0241 g, 57 %). Spectral data was consistent with the literature.



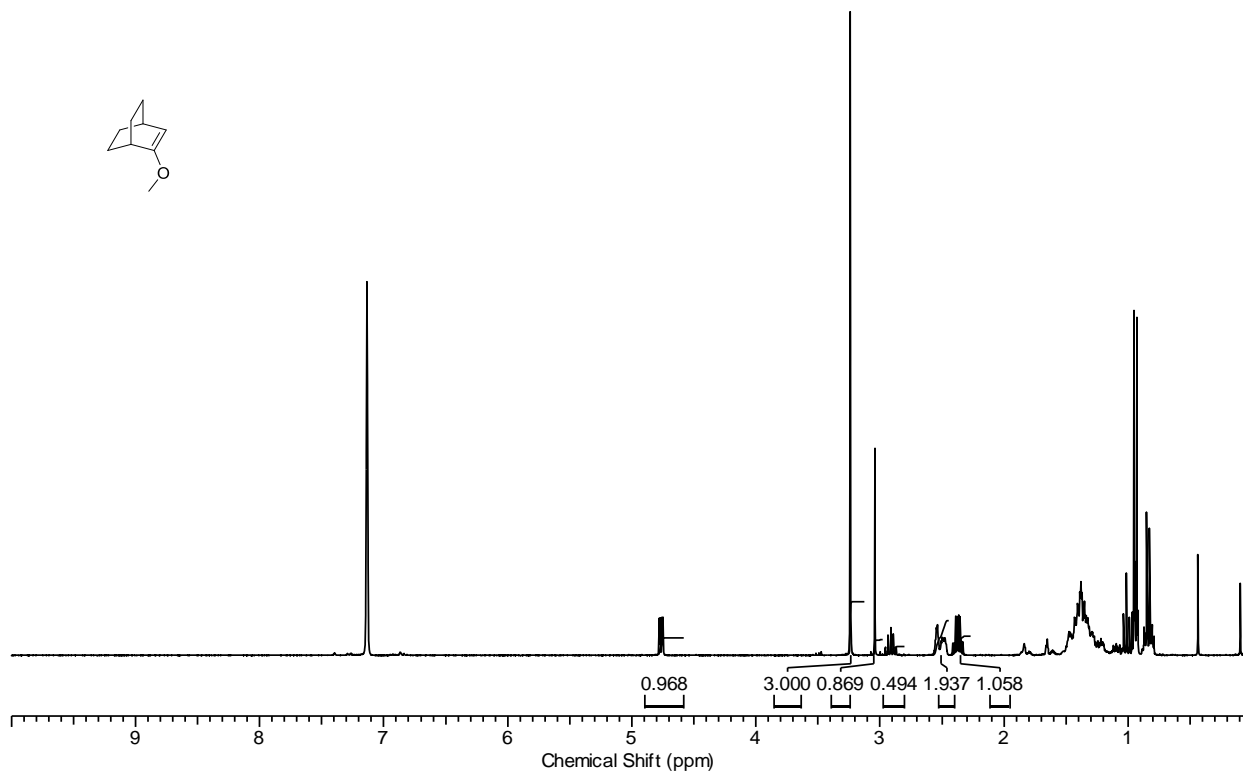
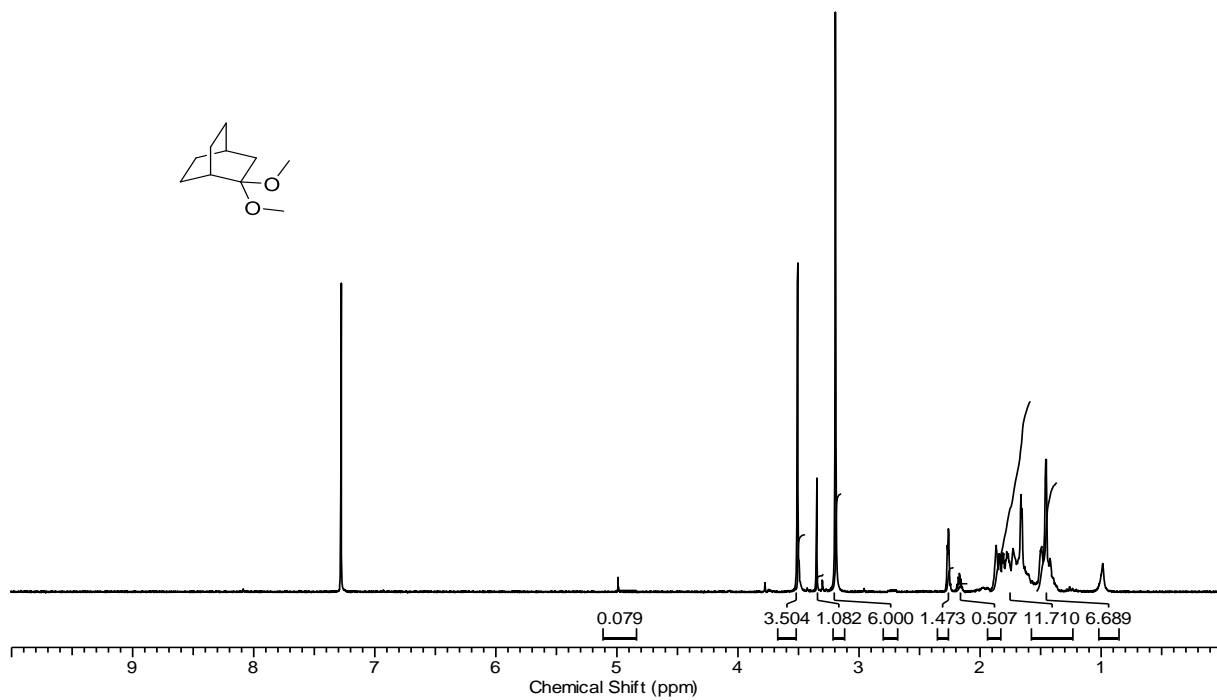
1-(9H-Fluoren-9-yl)-4-(2-hydroxyethyl)-1H-pyrazole-3(2H)-thione (4.66) Thioxo azomethine imine **4.52** (0.0241 g, 0.078 mmol), sodium borohydride (0.109 g, 0.28 mmol) and methanol were added to a round bottom flask and stirred at room temperature. The product was purified by workup with 1M HCL followed by flash column chromatography (40 % EtOAc in Hexanes, then EtOAc). The

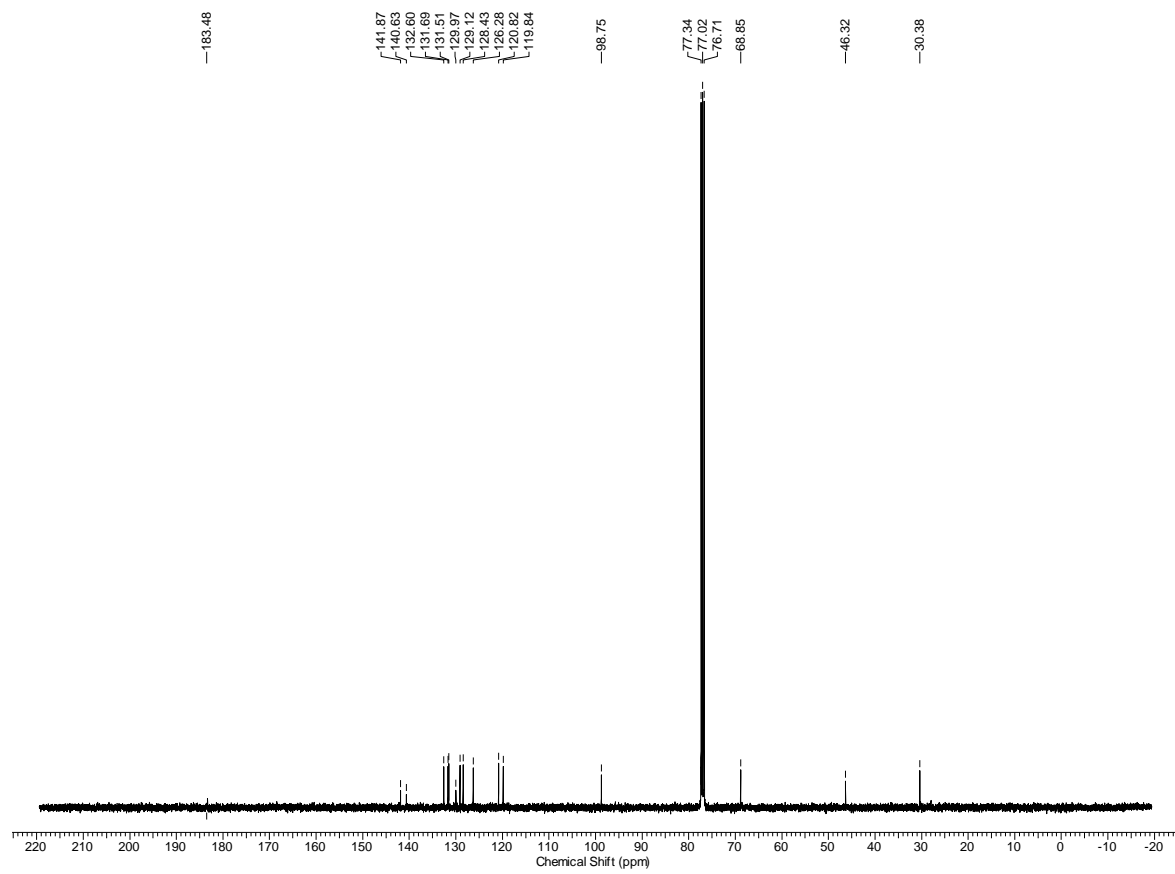
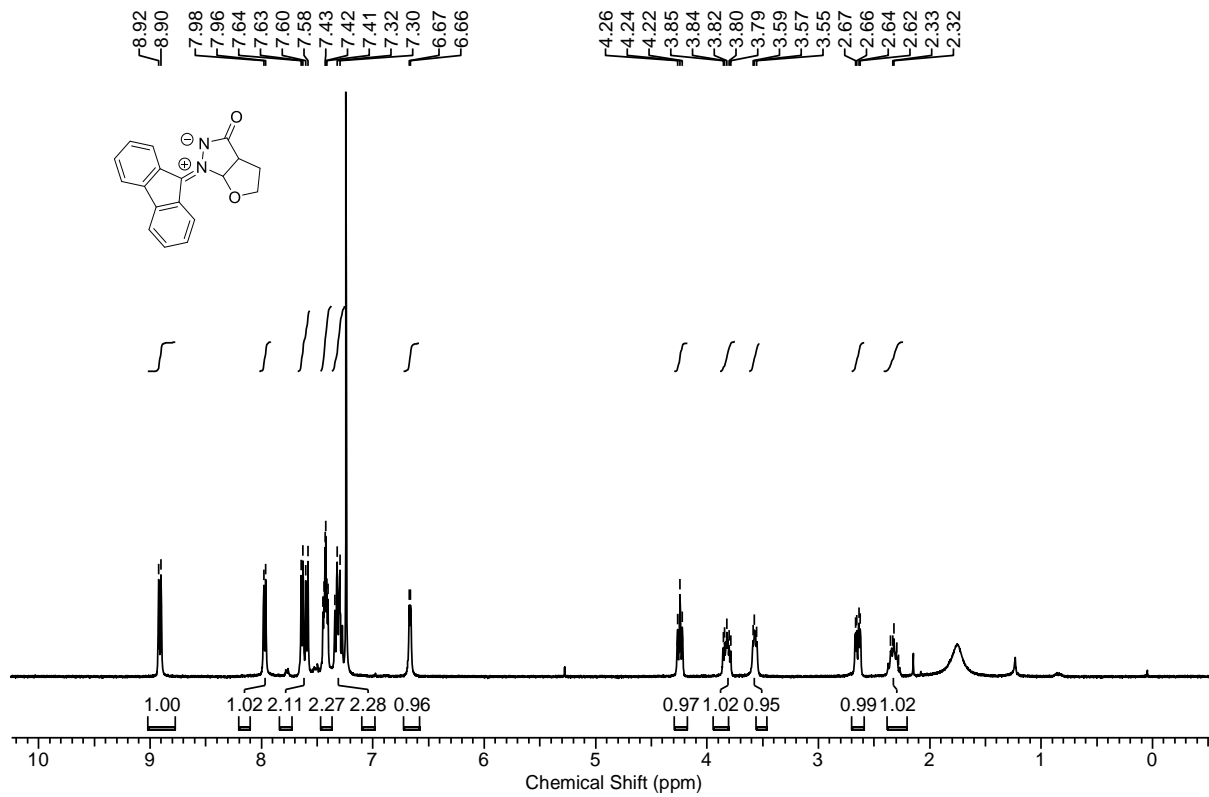
product was obtained as a yellow solid (0.0042 g, 17 %). ^1H NMR (300 MHz, CDCl_3) δ 7.72 (d, $J = 7.6$ Hz, 2H), 7.52 (d, $J = 7.3$ Hz, 2H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.26 (t, $J = 7.4$ Hz, 2H), 6.88 (s, 1H), 6.42 (s, 1H), 3.53 (t, $J = 6.4$ Hz, 2H), 2.54 (t, $J = 6.5$ Hz, 2H). A ^{13}C NMR could not be obtained due to limited amount of material obtained. HRMS (EI): Exact mass calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{OS}$ [M^+]: 308.0983, found: 308.0985

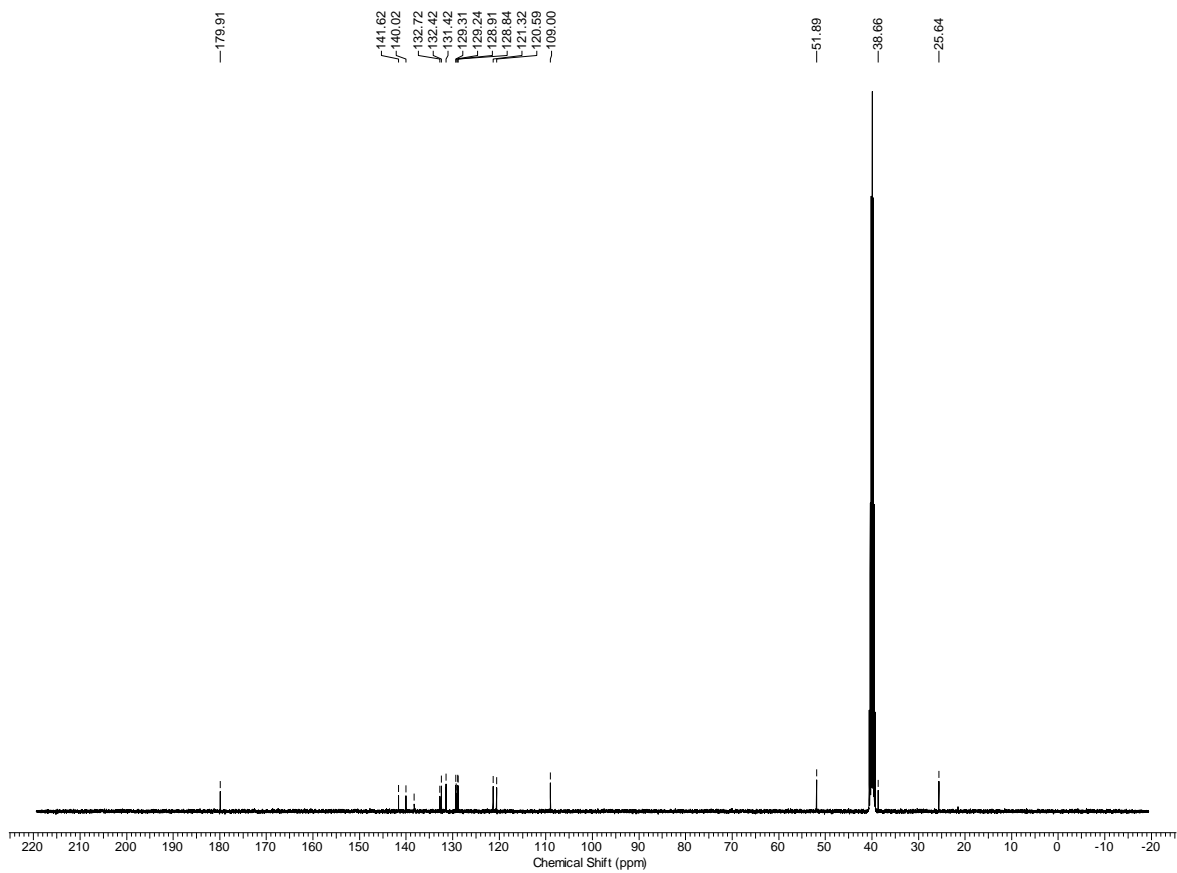
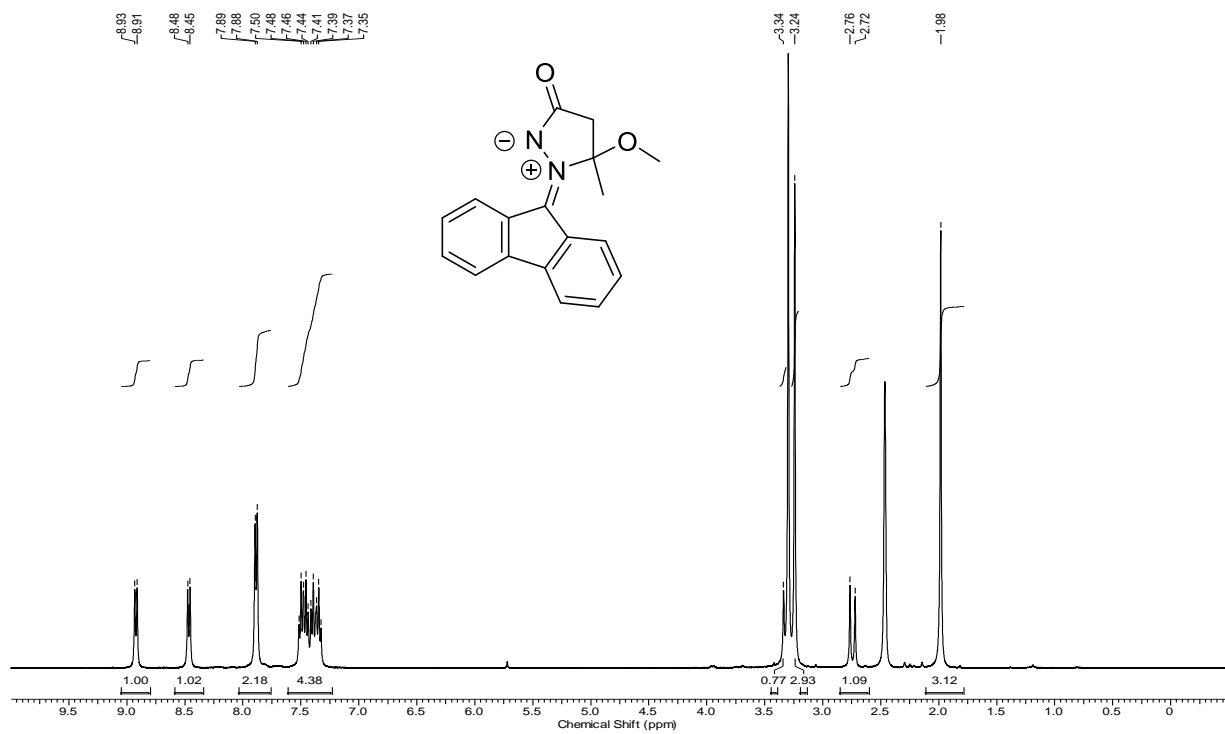


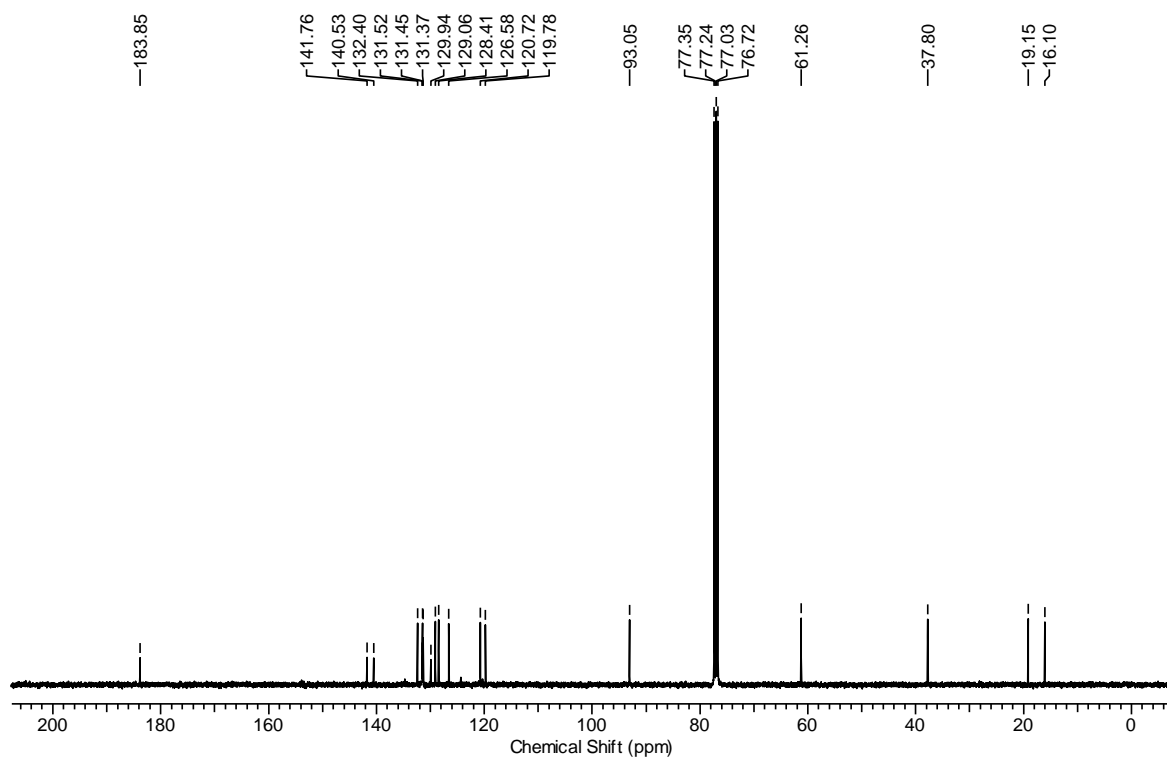
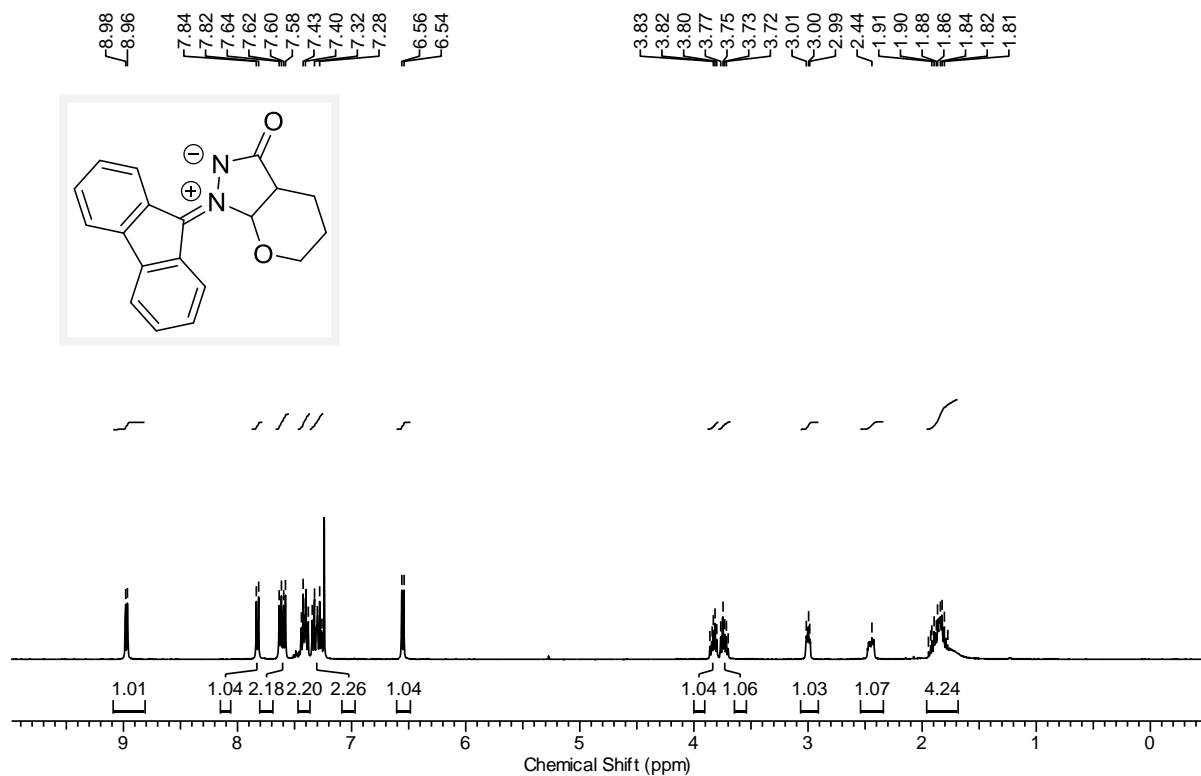
1-(9H-Fluoren-9-yl)-4-(3-hydroxypropyl)-1H-pyrazole-3(2H)-thione (4.67). Thiosemicarbazone **5d** (0.0573 g, 0.153mmol), Dihydrofuran (0.14 mL, 1.53 mmol), benzaldehyde (0.08 mL, 0.765 mmol) and α,α,α -trifluorotoluene (0.05 M) were added to a microwave vial. The reaction mixture was heated up to 100 °C for 2h in a microwave reactor. The product was purified by flash chromatography (20 % EtOAc: Hexanes then 40 % EtOAc: Hexanes) and obtained as a mixture of thioxo azomethine imine **4.53** (0.0198 g, 83 % purity) and nitroaniline. The mixture was dissolved in MeOH (0.05 M) and sodium borohydride (10 equiv.) was added. The product was purified by column chromatography (EtOAc). The product was obtained as an orange solid. (0.0135 g, 82 %). ^1H NMR (300 MHz, CDCl_3) δ 7.76 (d, $J = 7.5$ Hz, 2H), 7.55 (d, $J = 7.3$ Hz, 2H), 7.45 (t, $J = 7.4$ Hz, 2H), 7.30 (m, 2H), 6.80, s, 1H), 6.48 (s, 1H), 3.49 (m, 2H), 2.44 (m, 2H), 1.67 (m, 2H) ^{13}C NMR (100 MHz, CDCl_3) δ 144.3, 141.9, 140.6, 129.5, 128.1, 126.4, 125.5, 120.3, 66.8, 61.8, 33.0, 20.1 HRMS (EI): Exact mass calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{OS}$ [M^+]: 322.1139, found: 322.1118

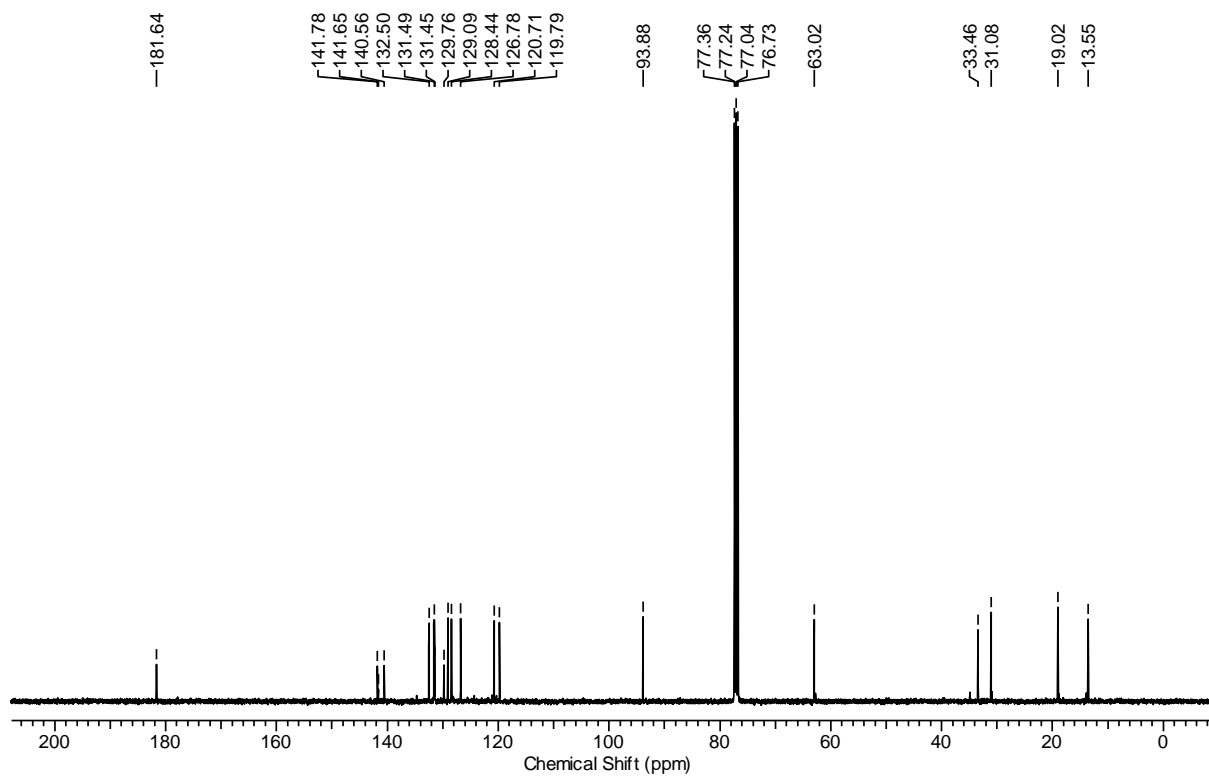
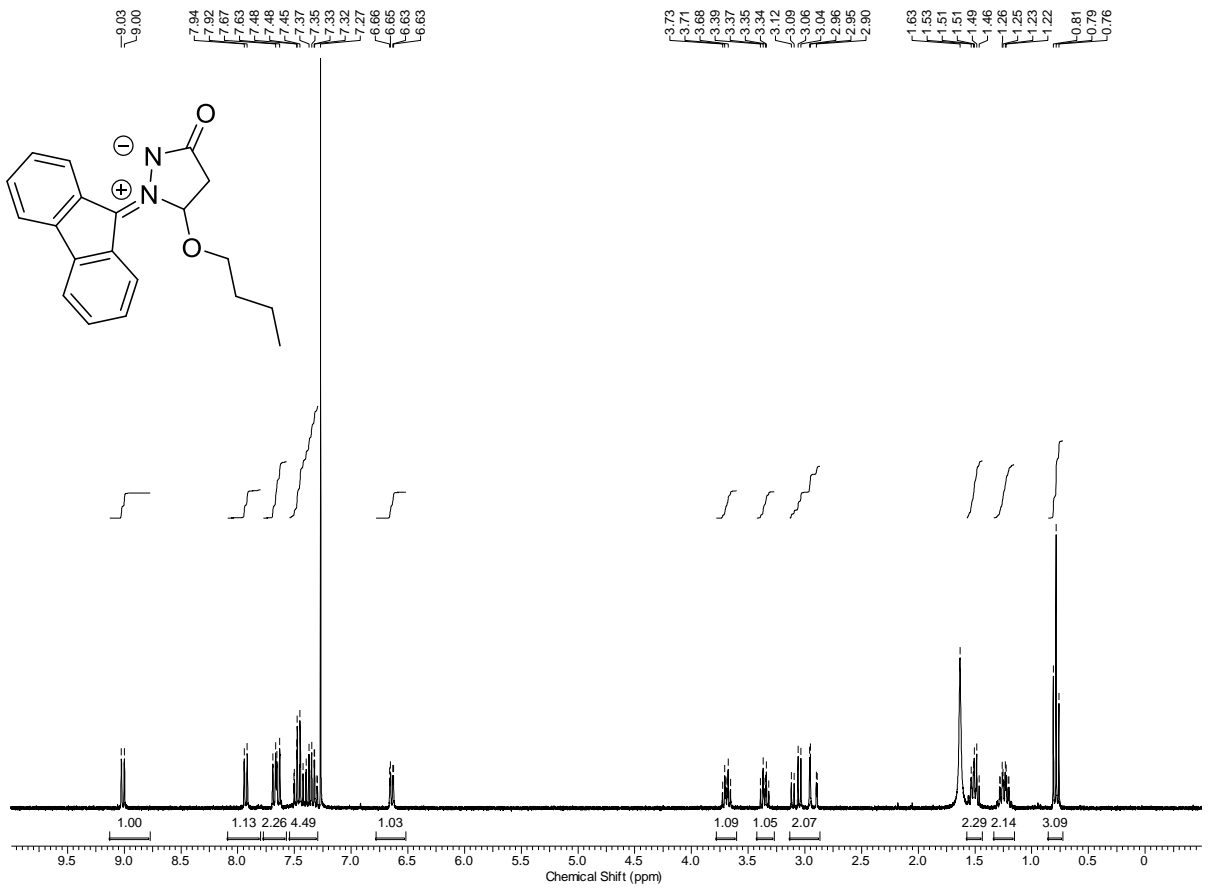
5.6 Spectra



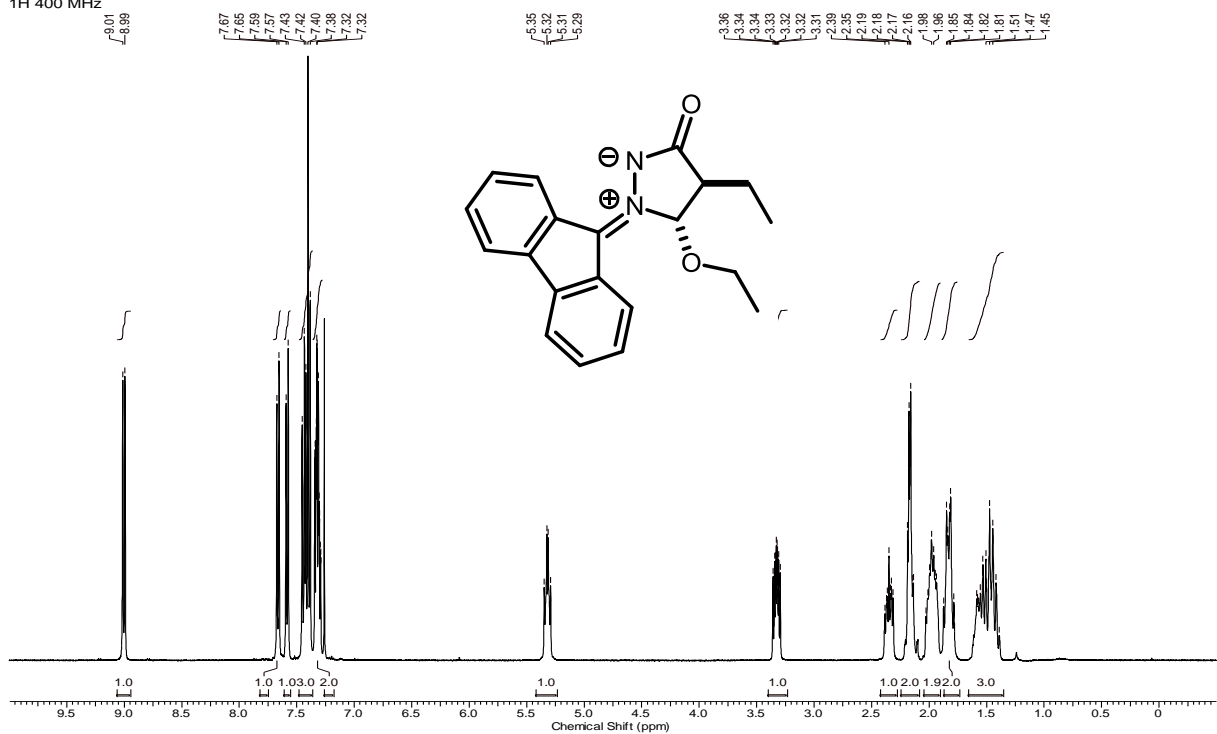




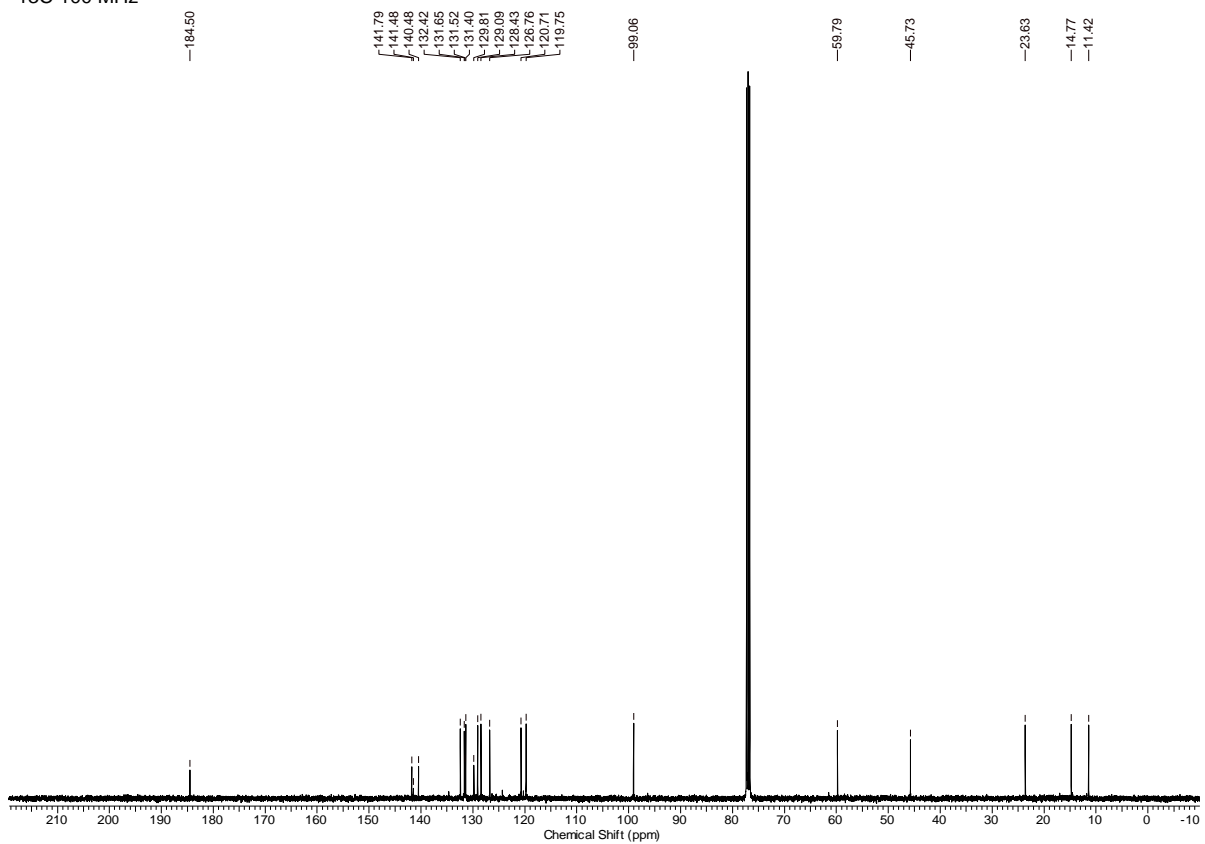


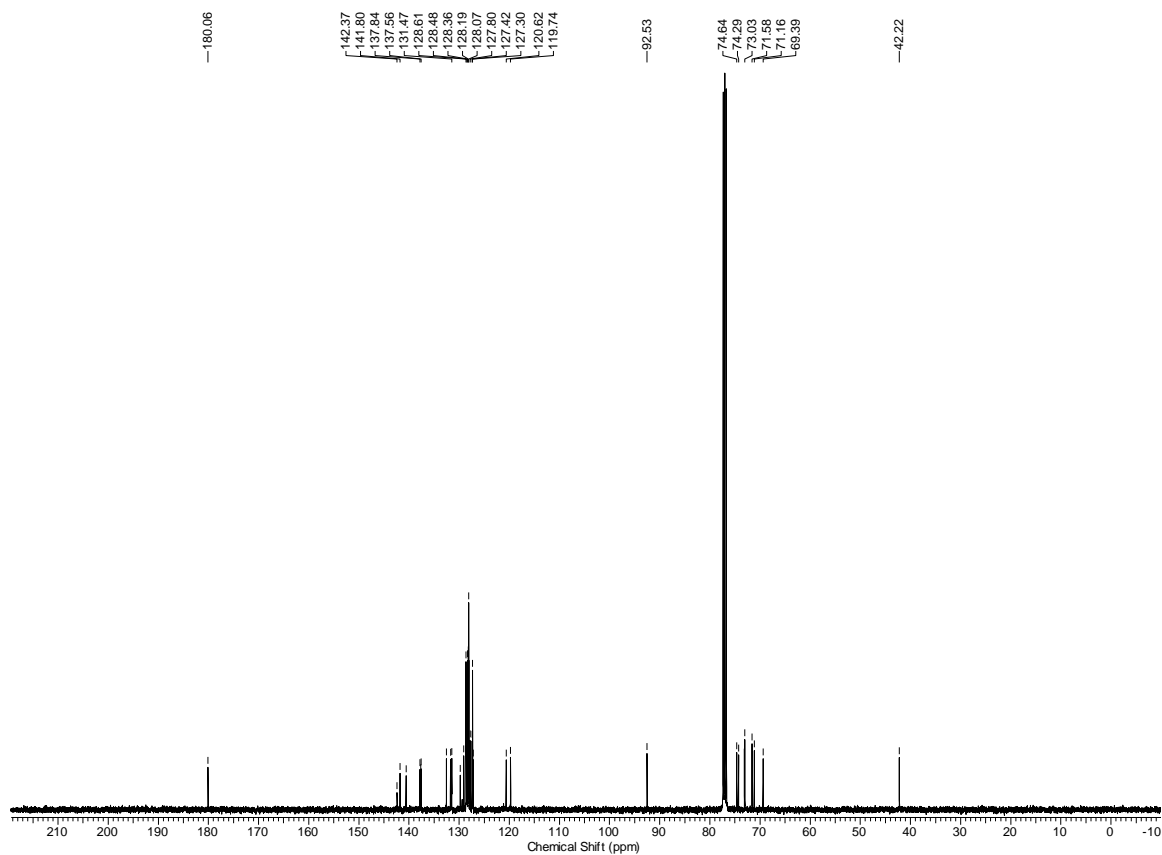
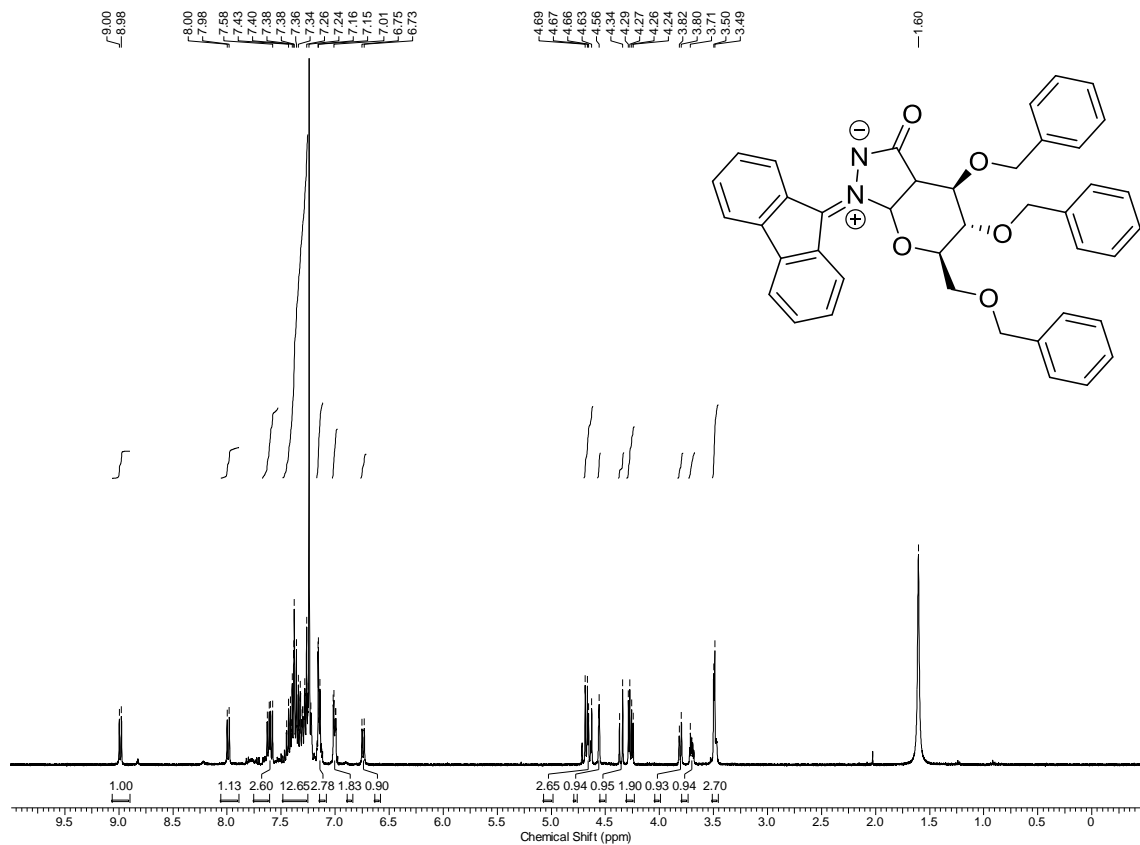


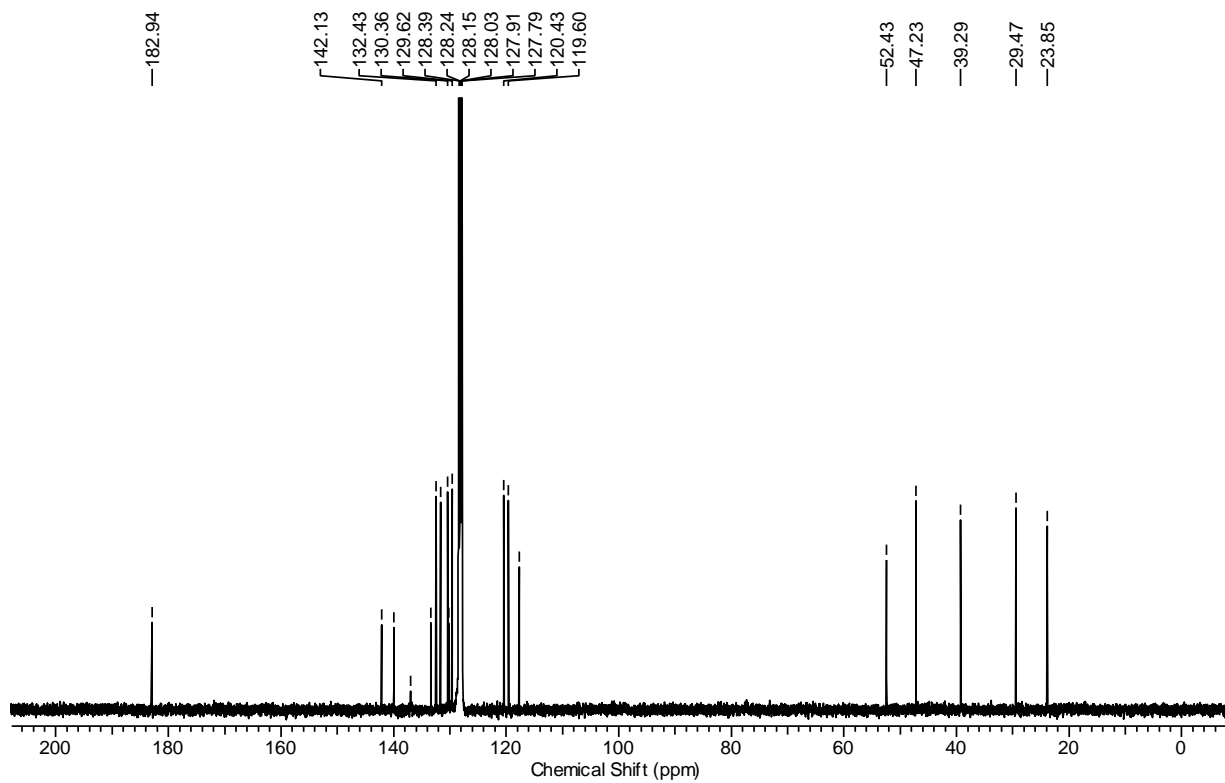
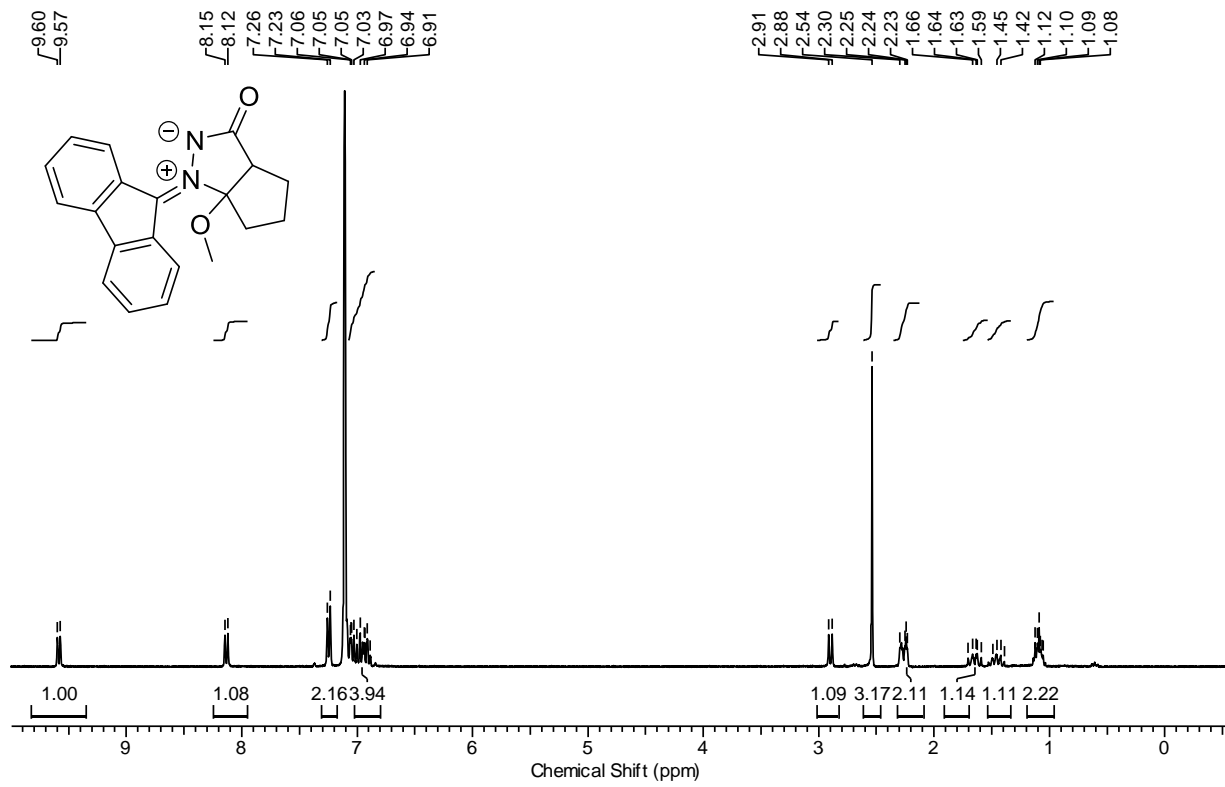
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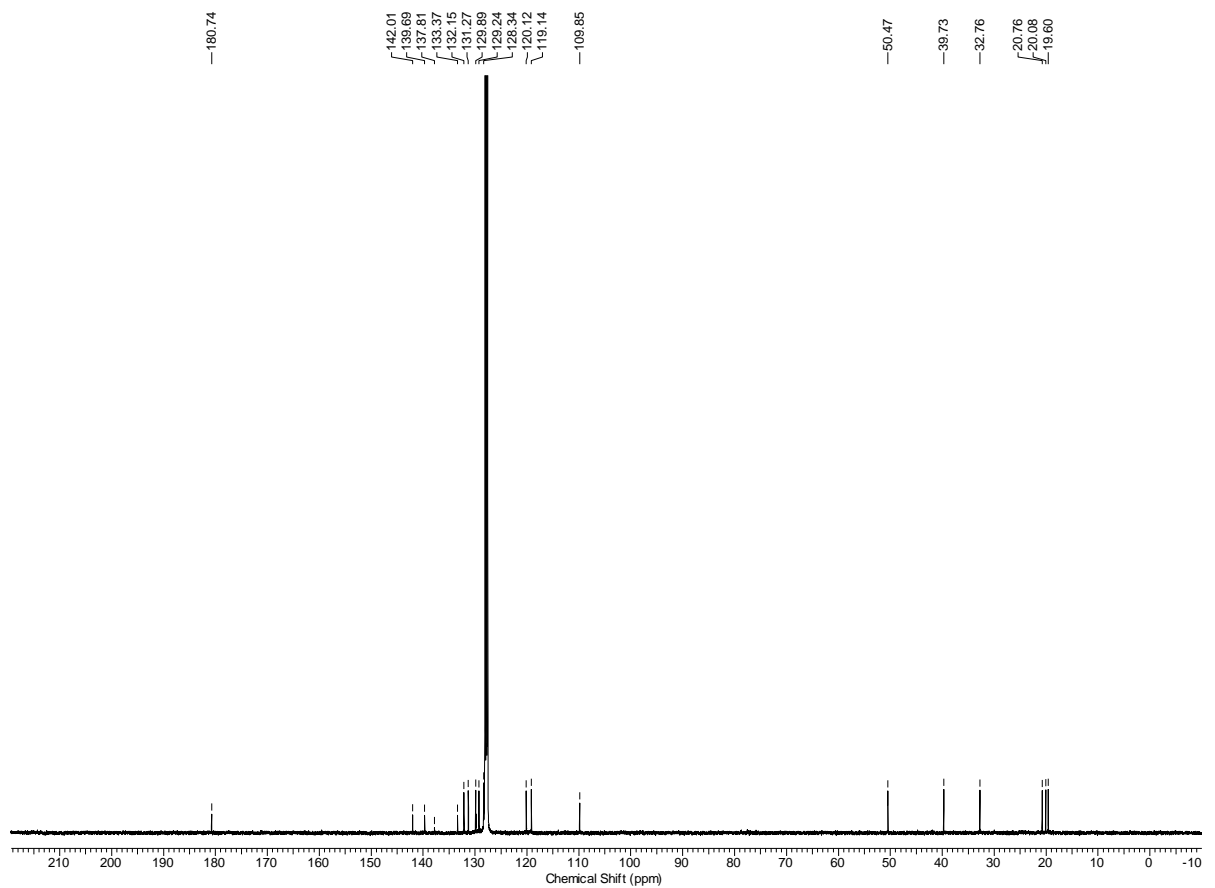
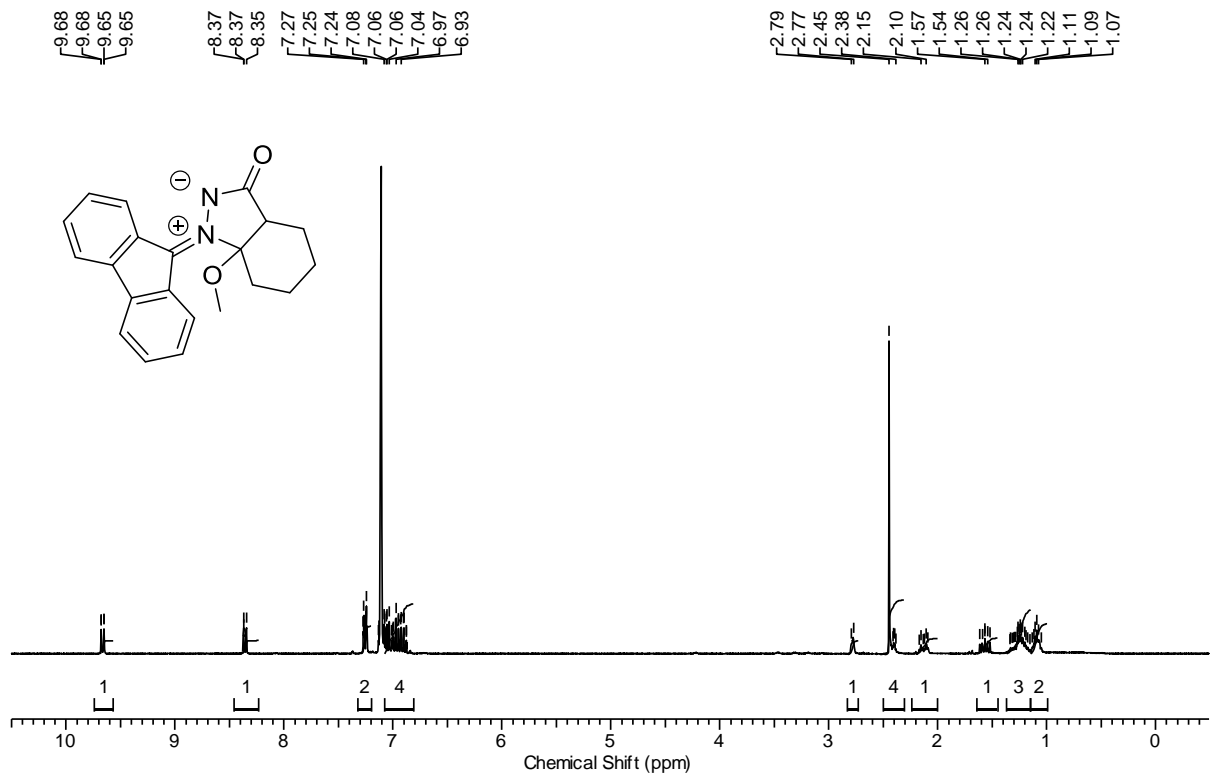


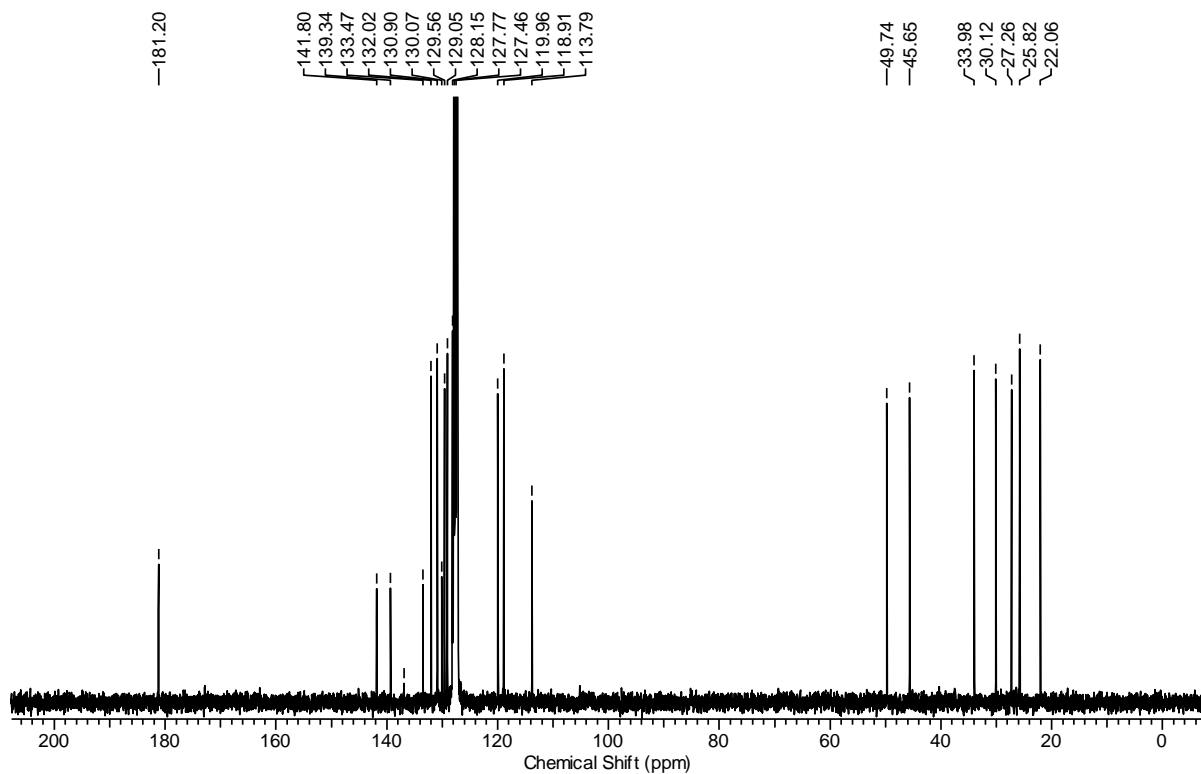
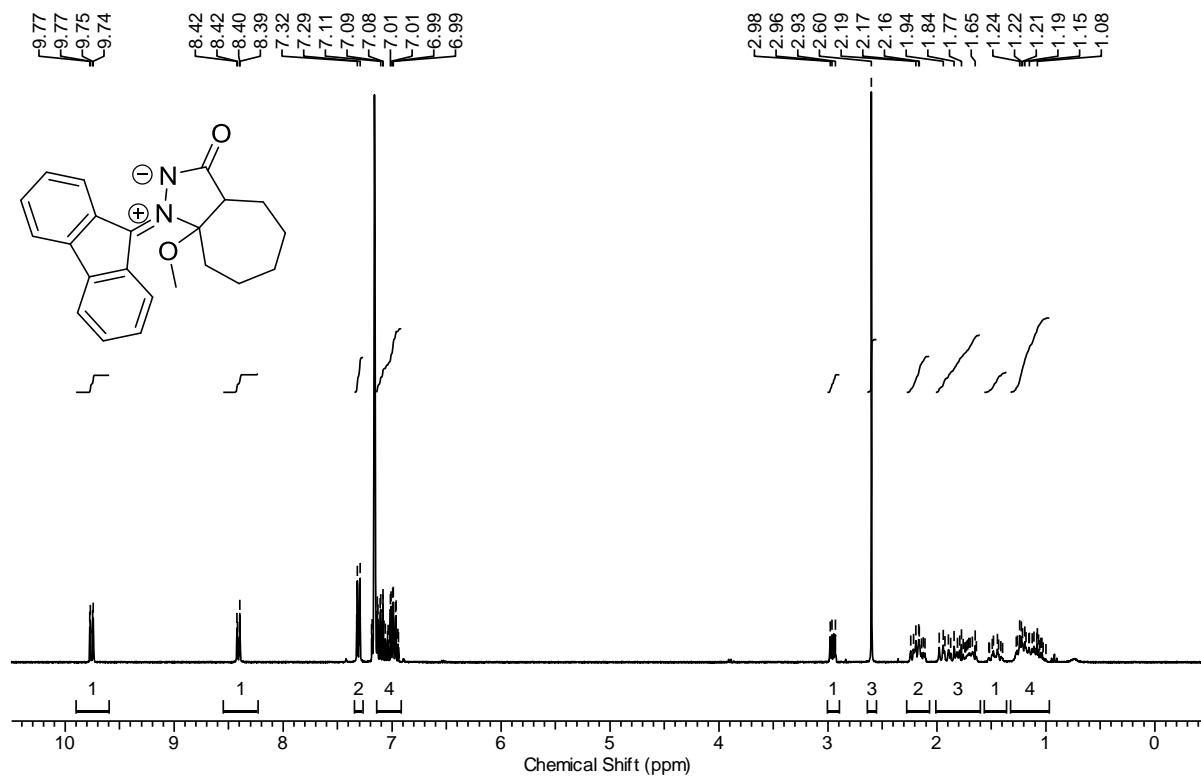
¹³C 100 MHz

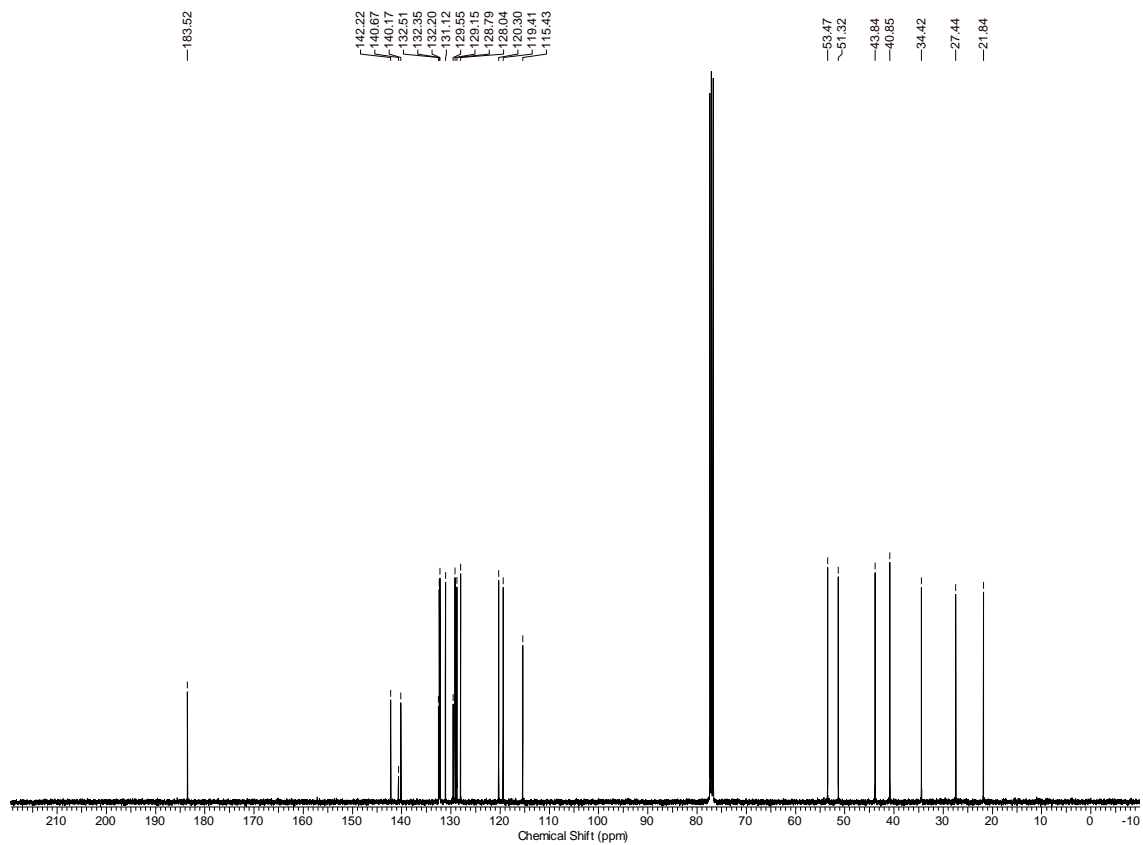


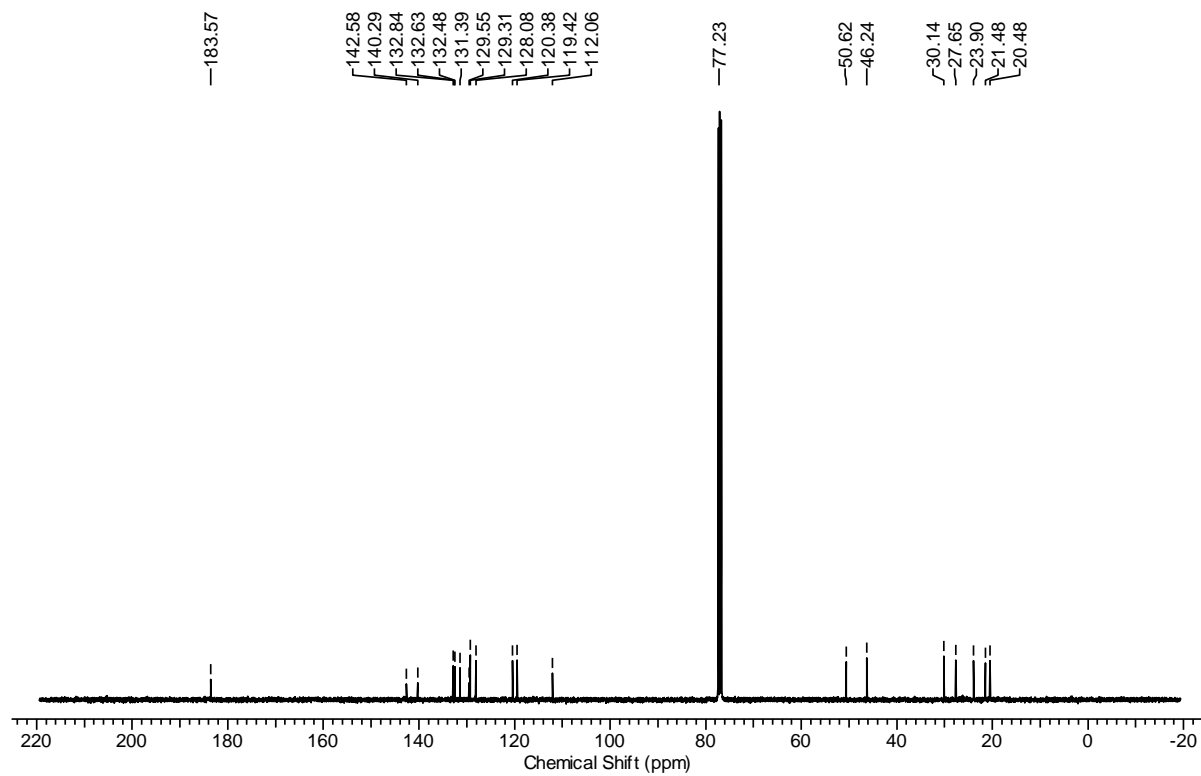
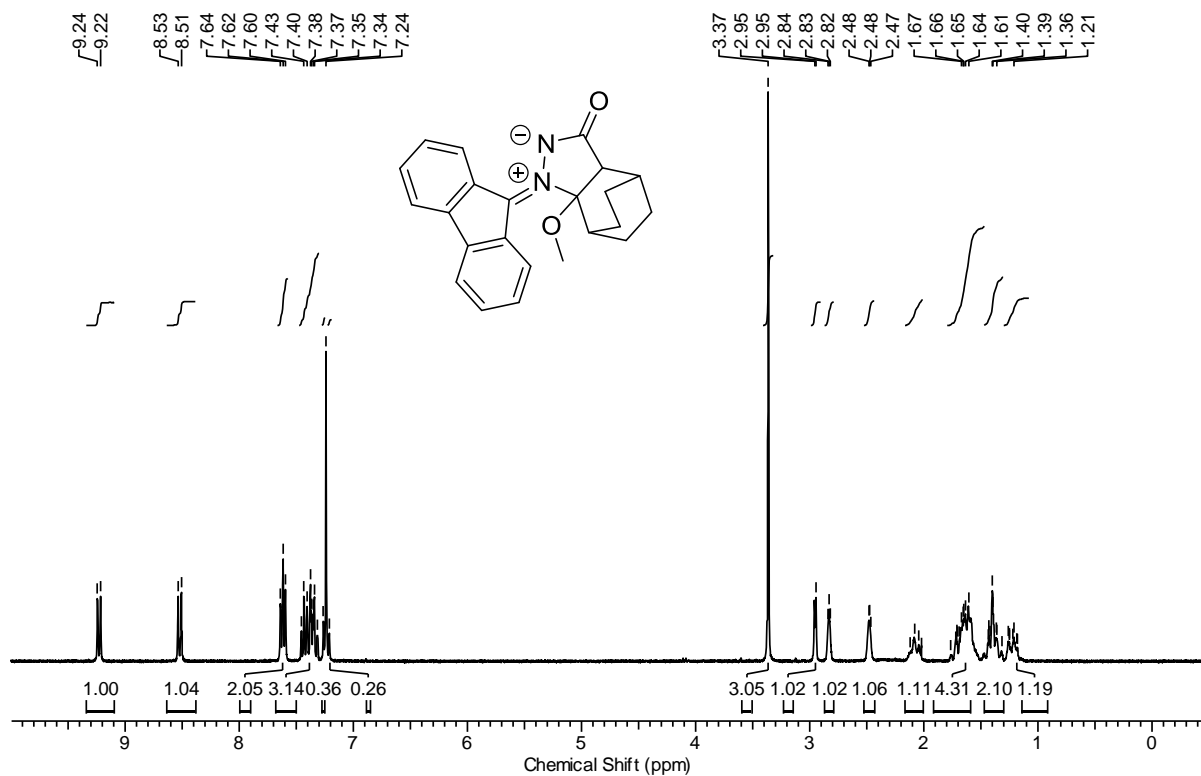


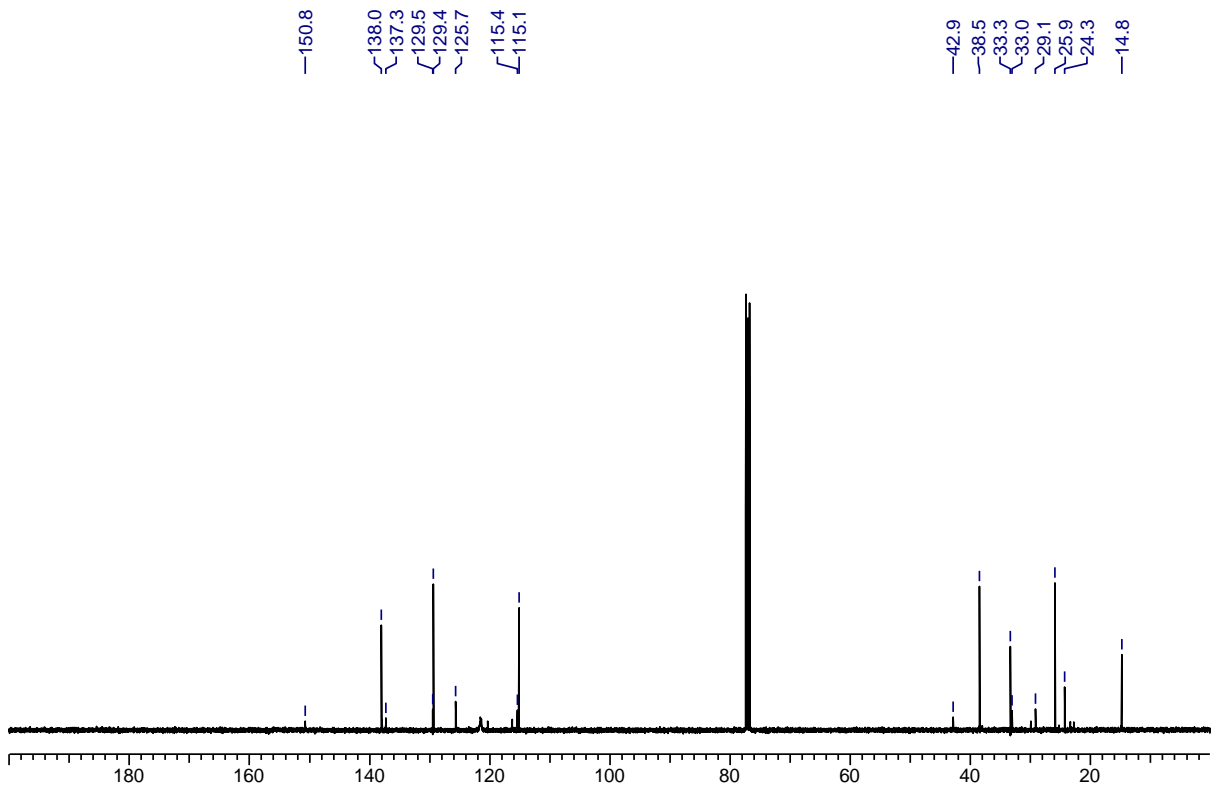
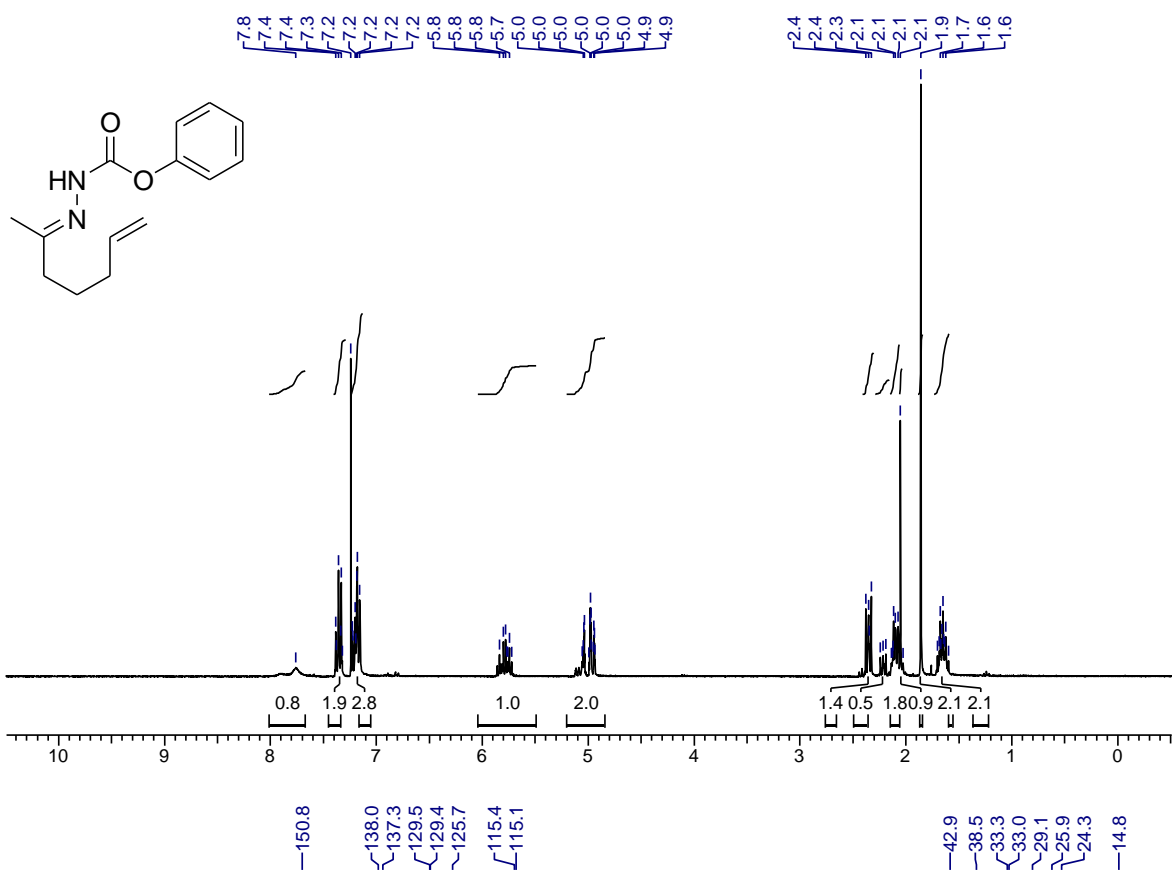


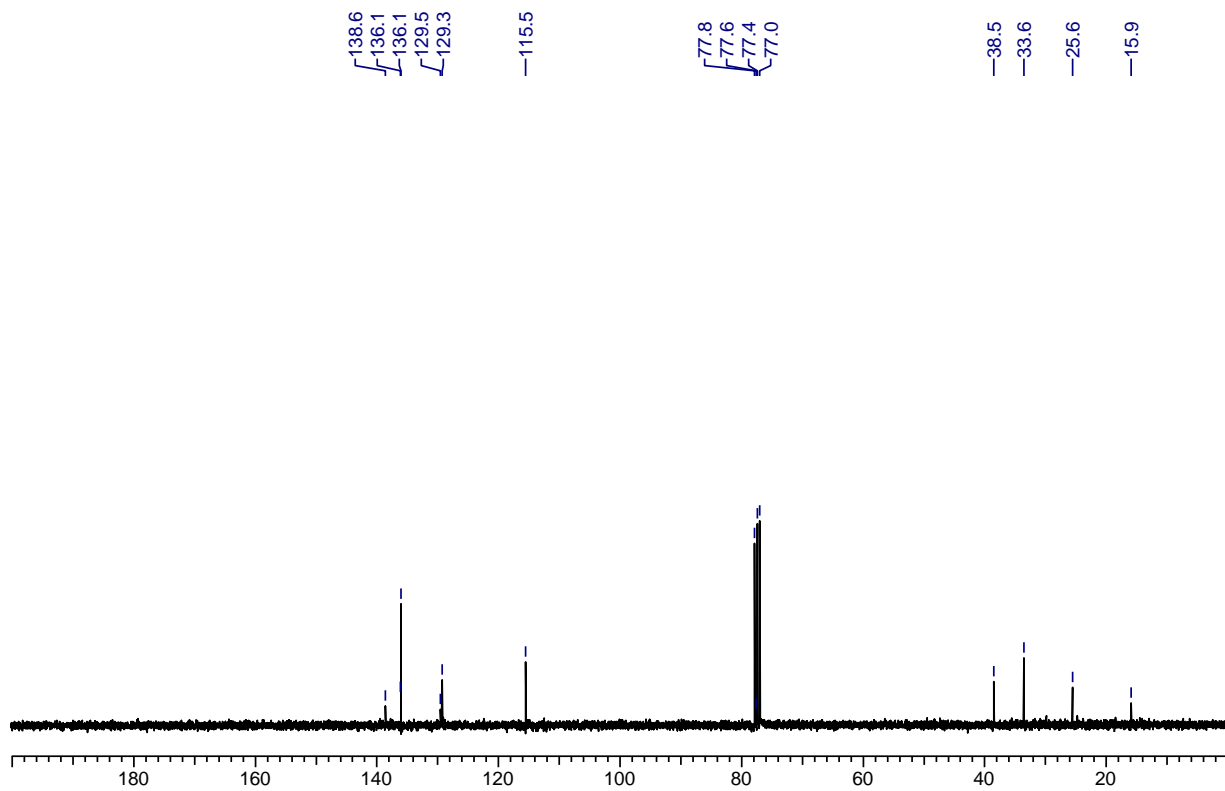
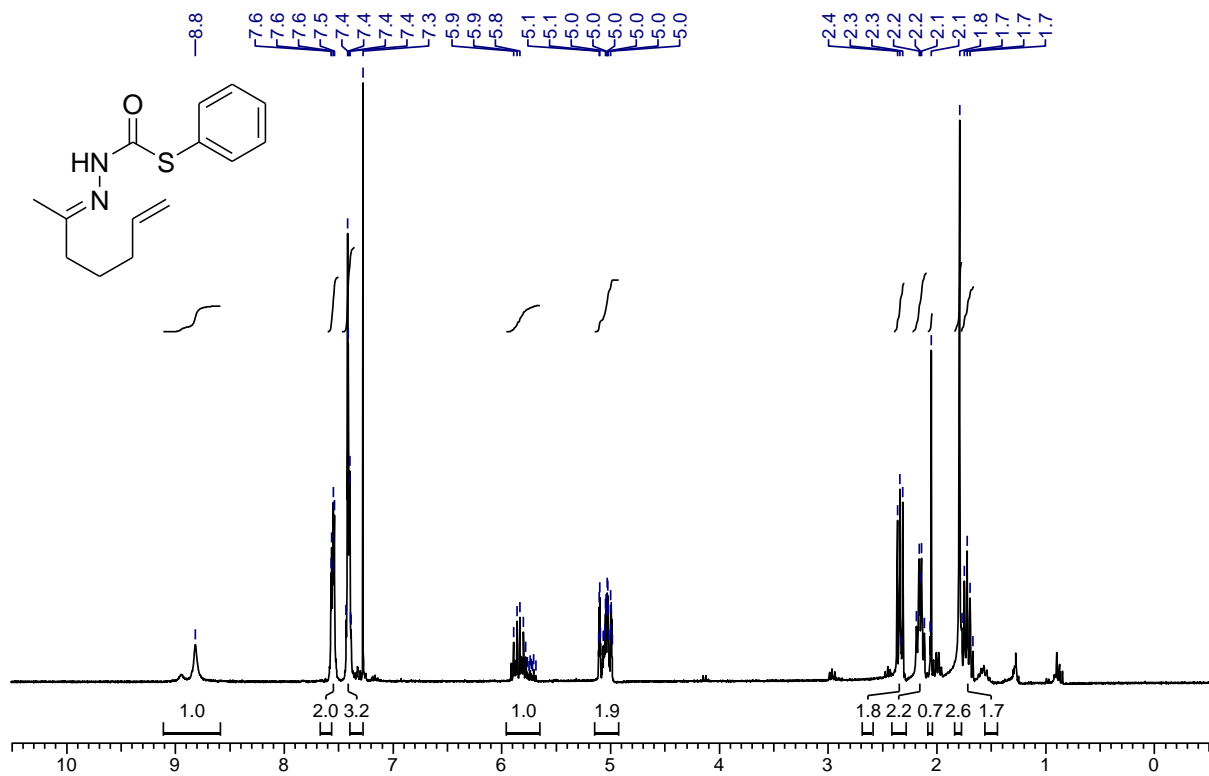


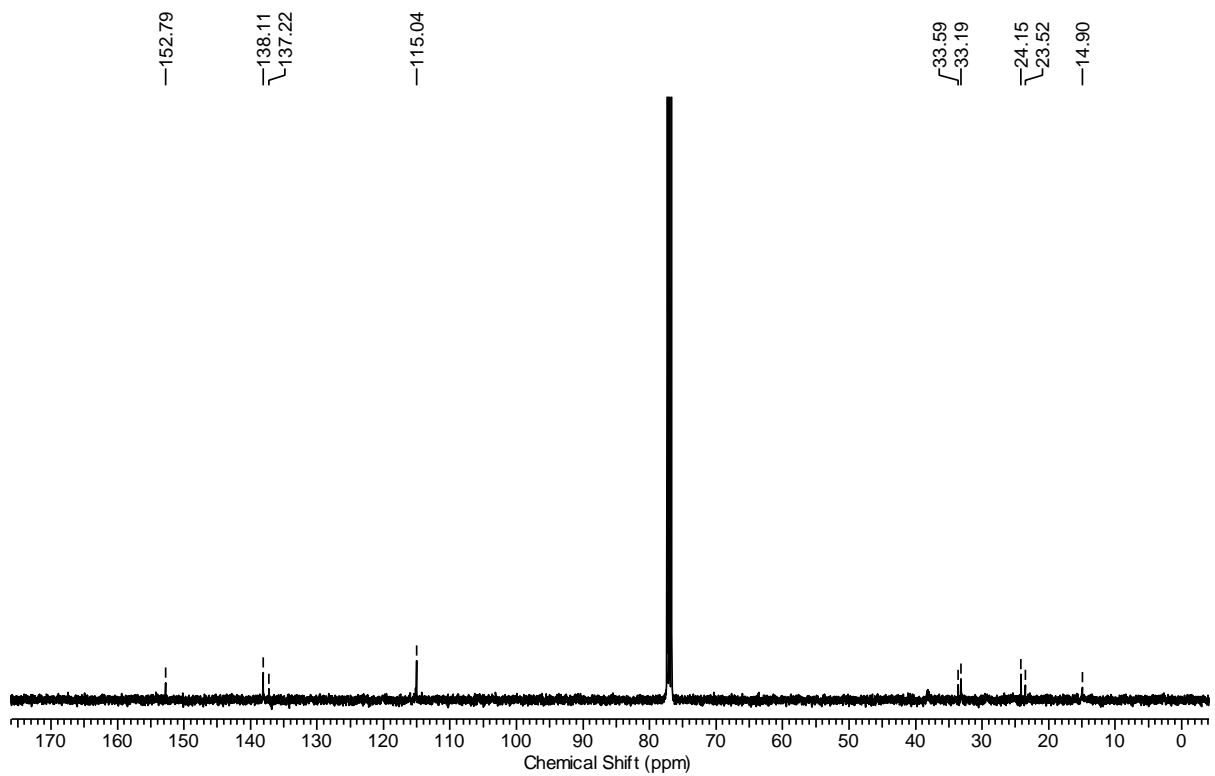
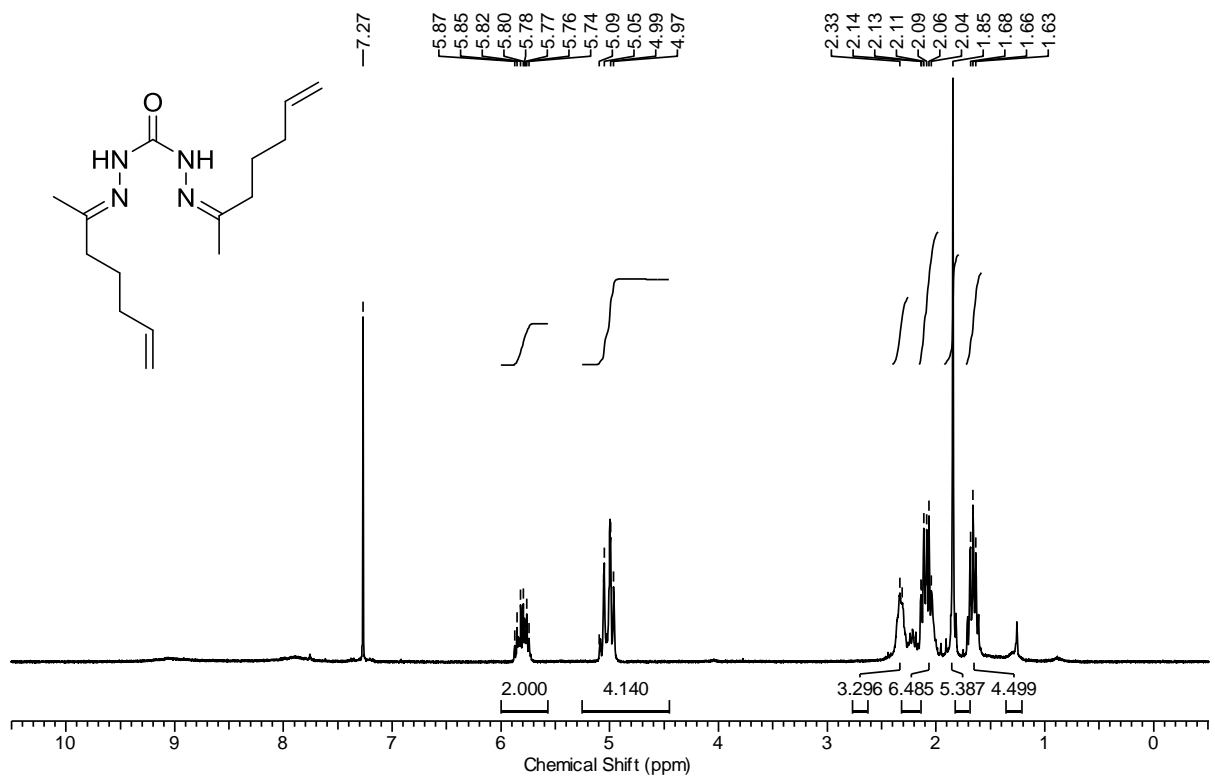


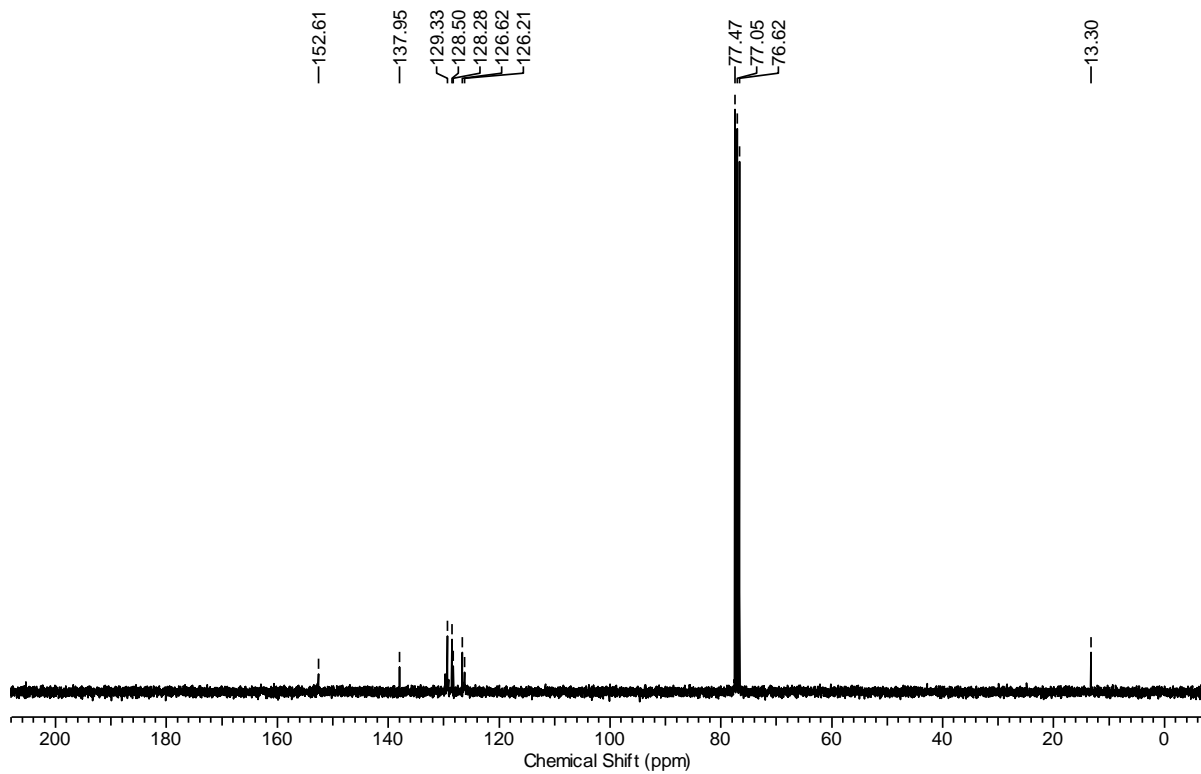
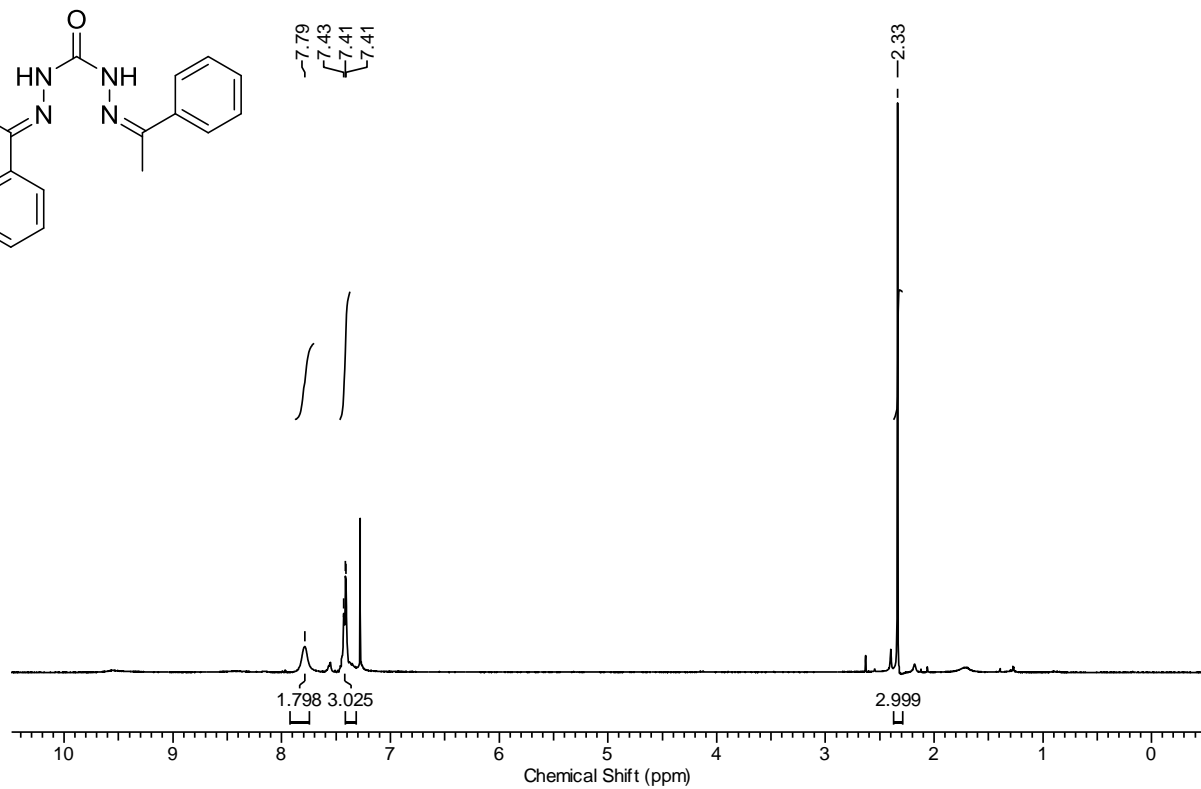
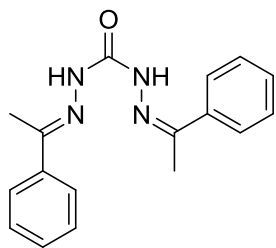


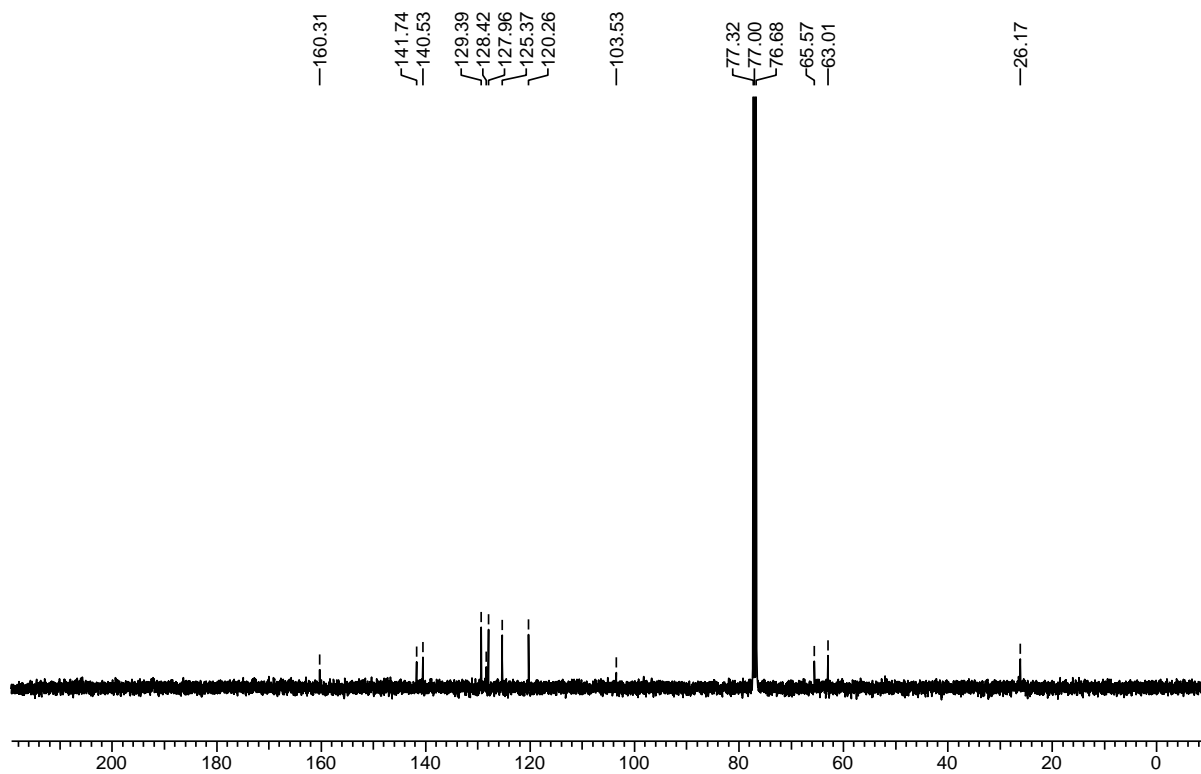
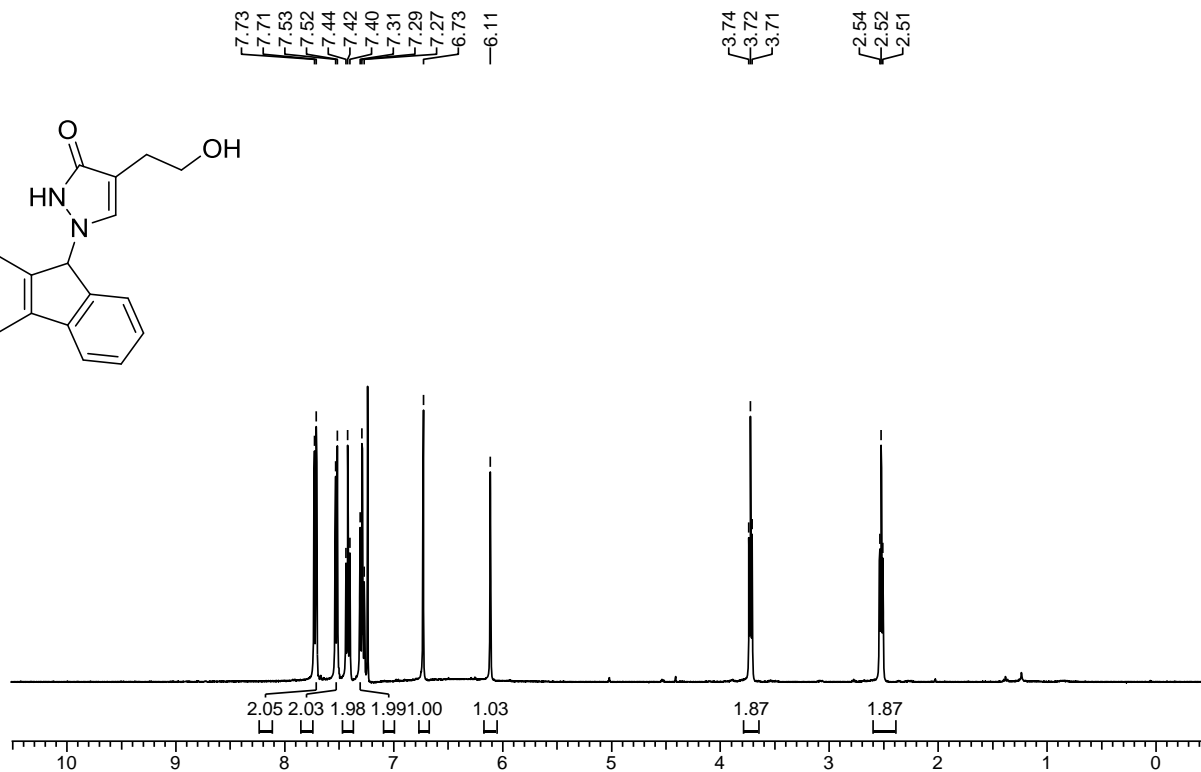
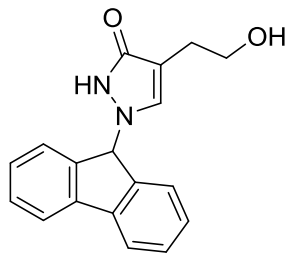


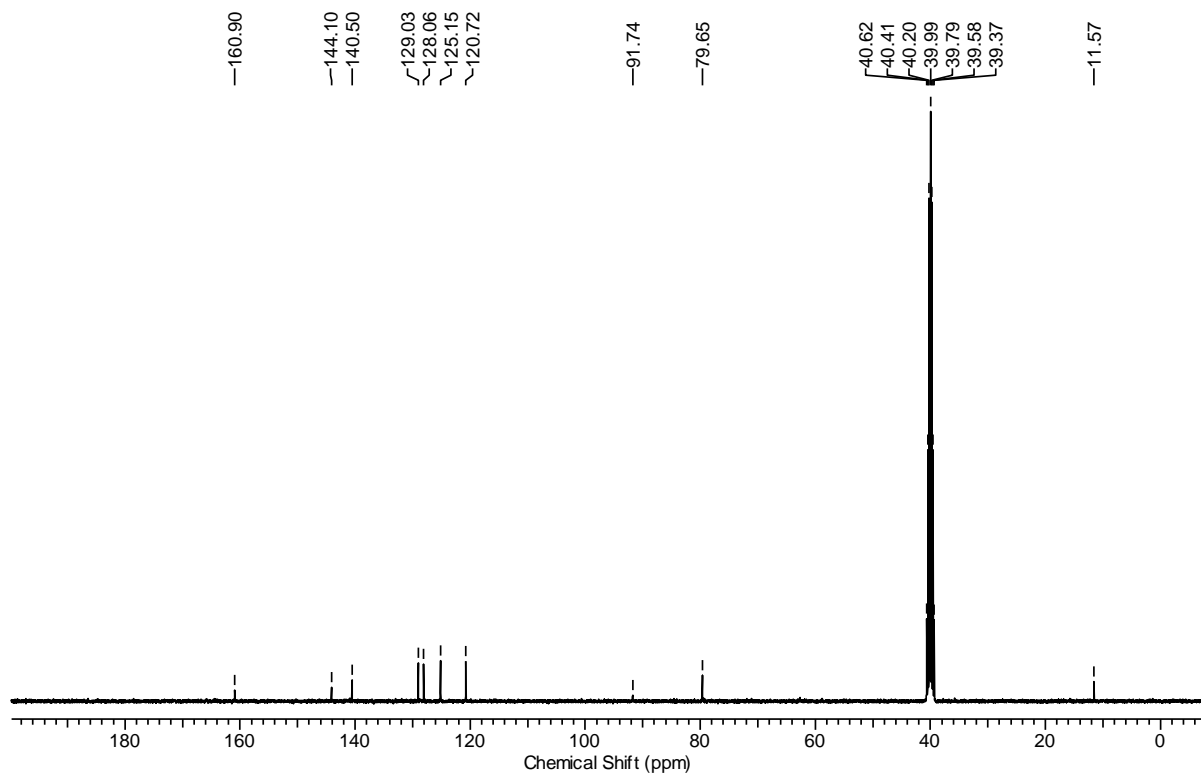
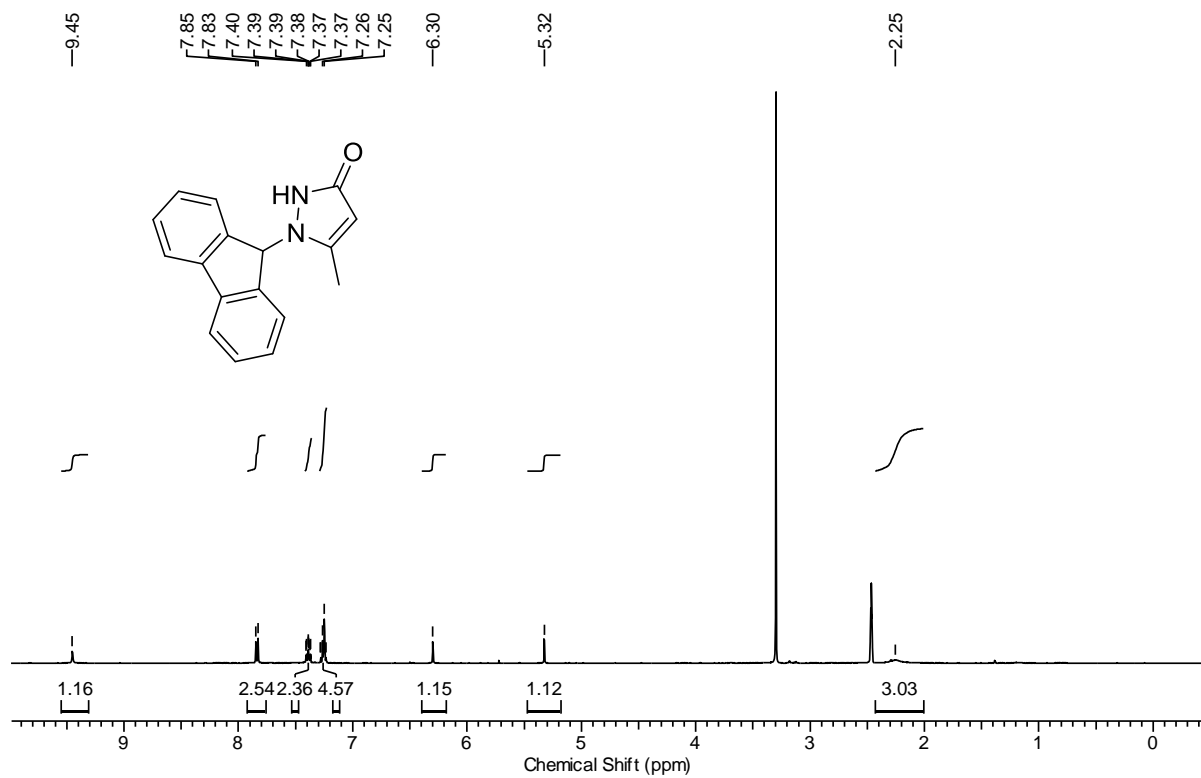


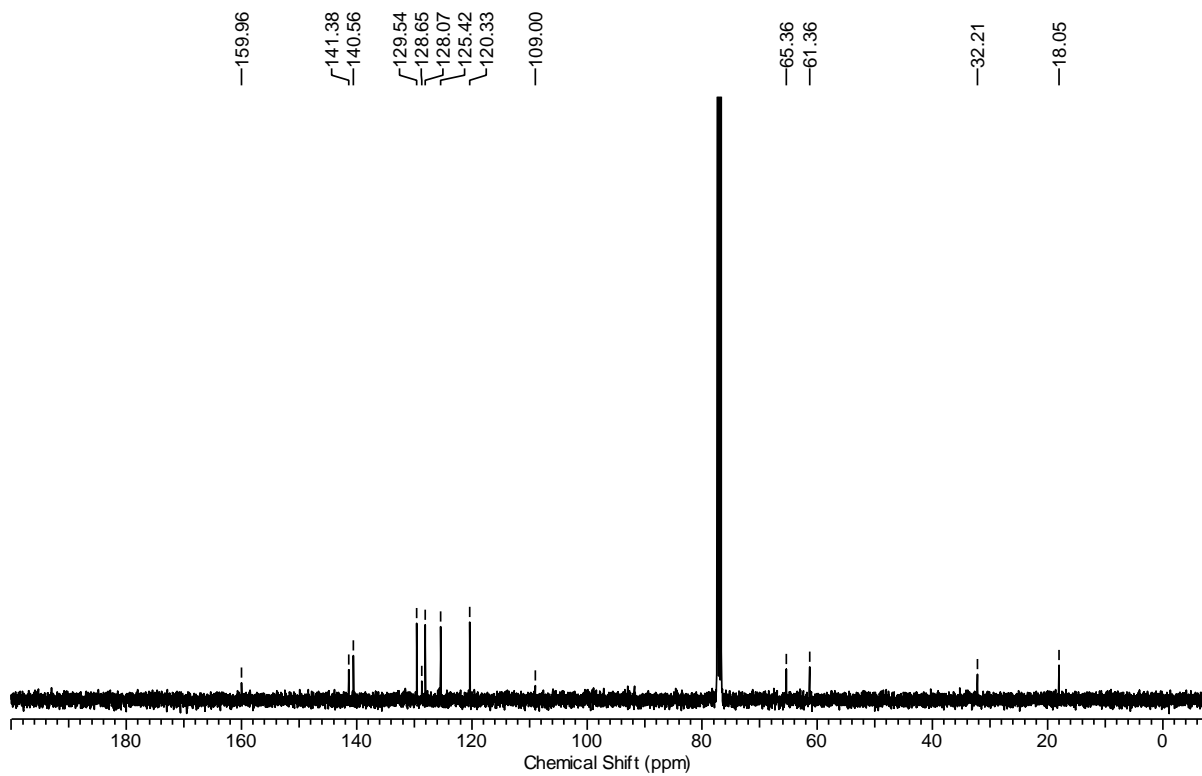
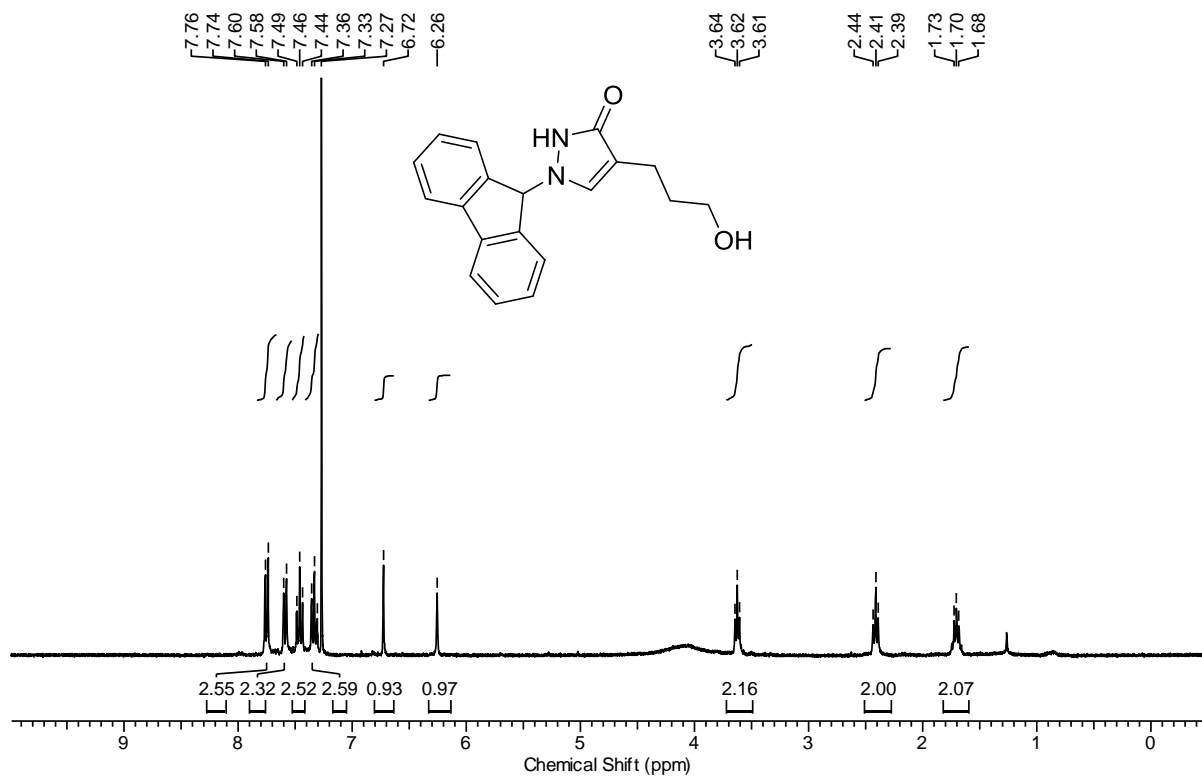




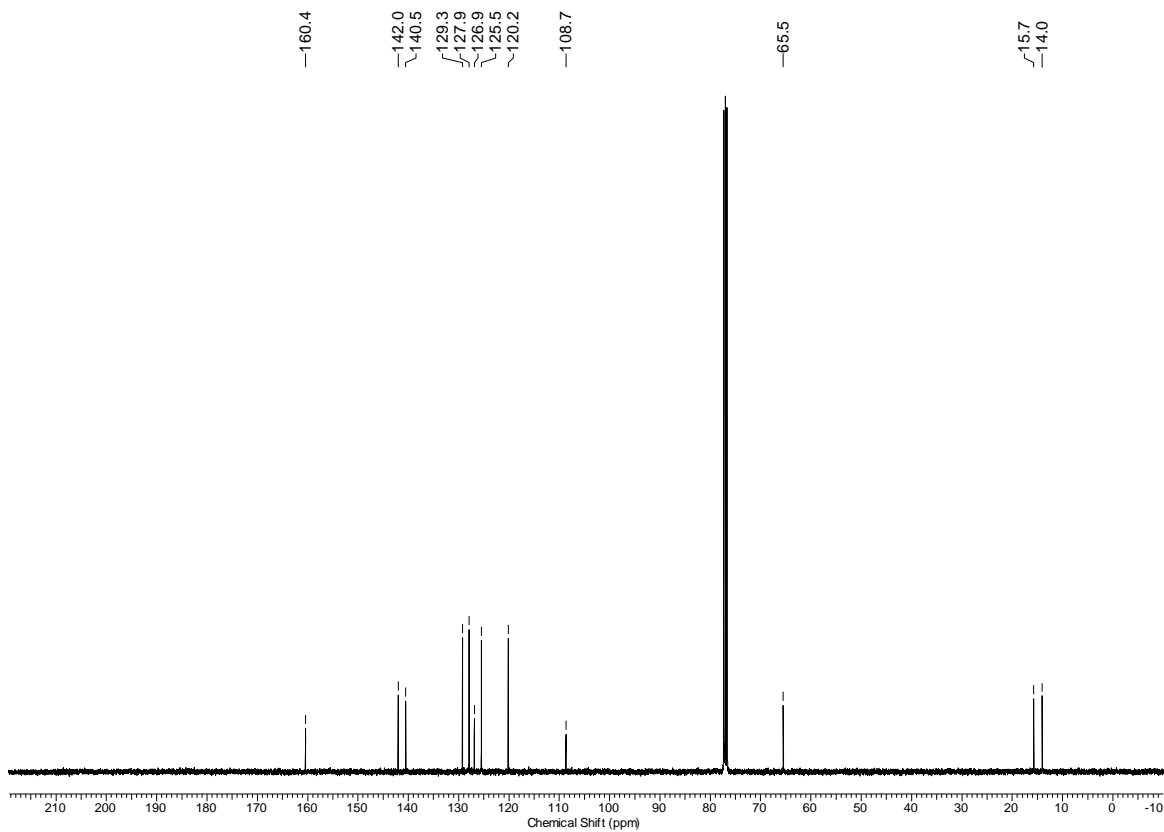
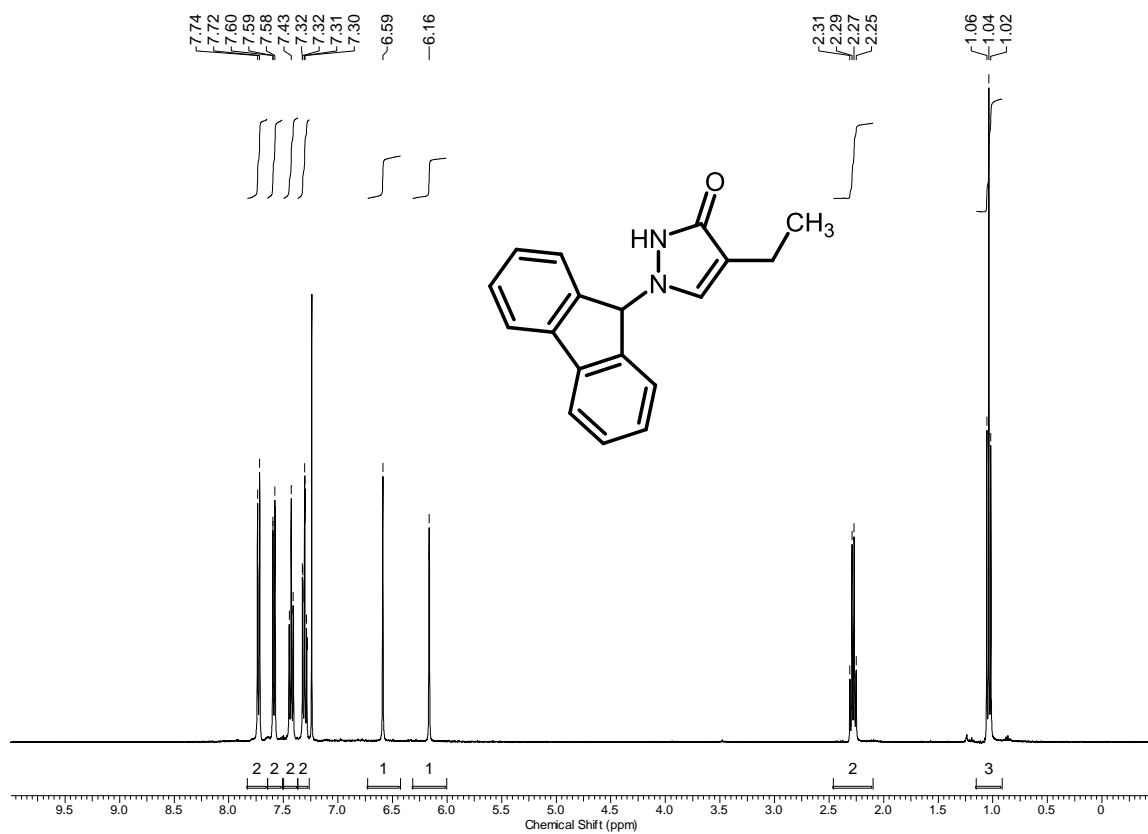


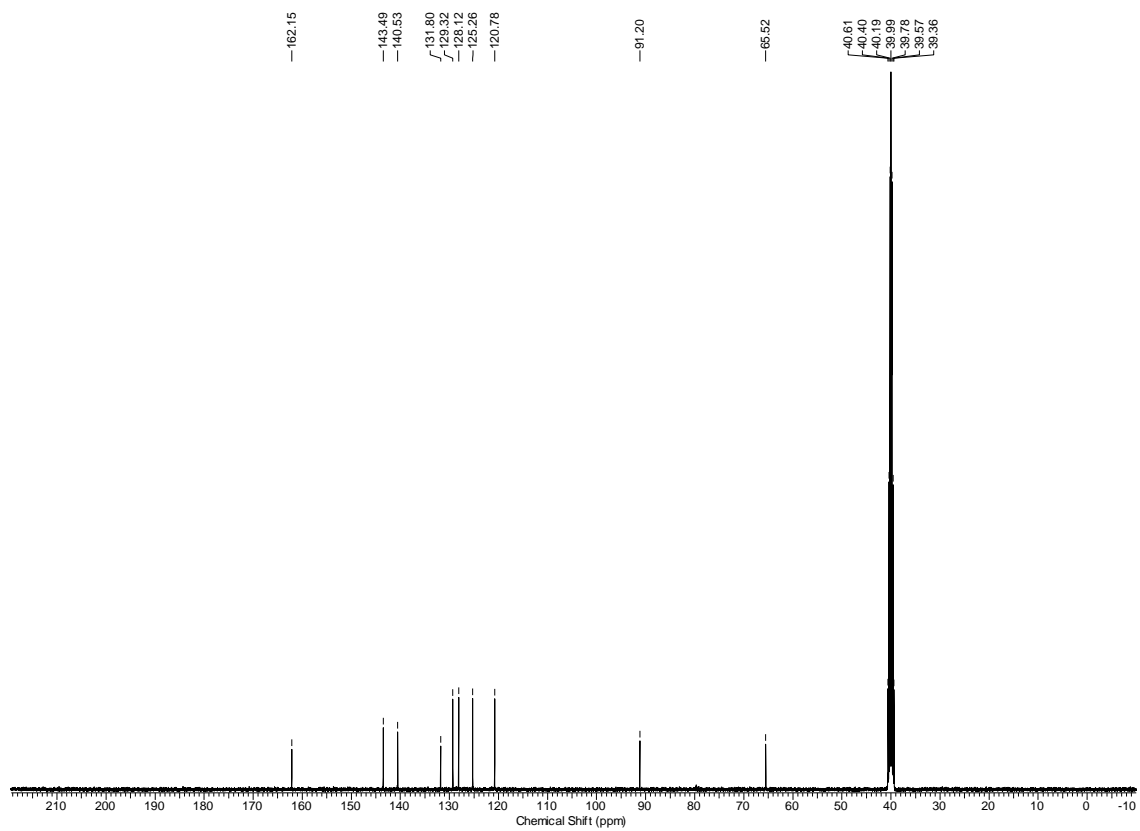
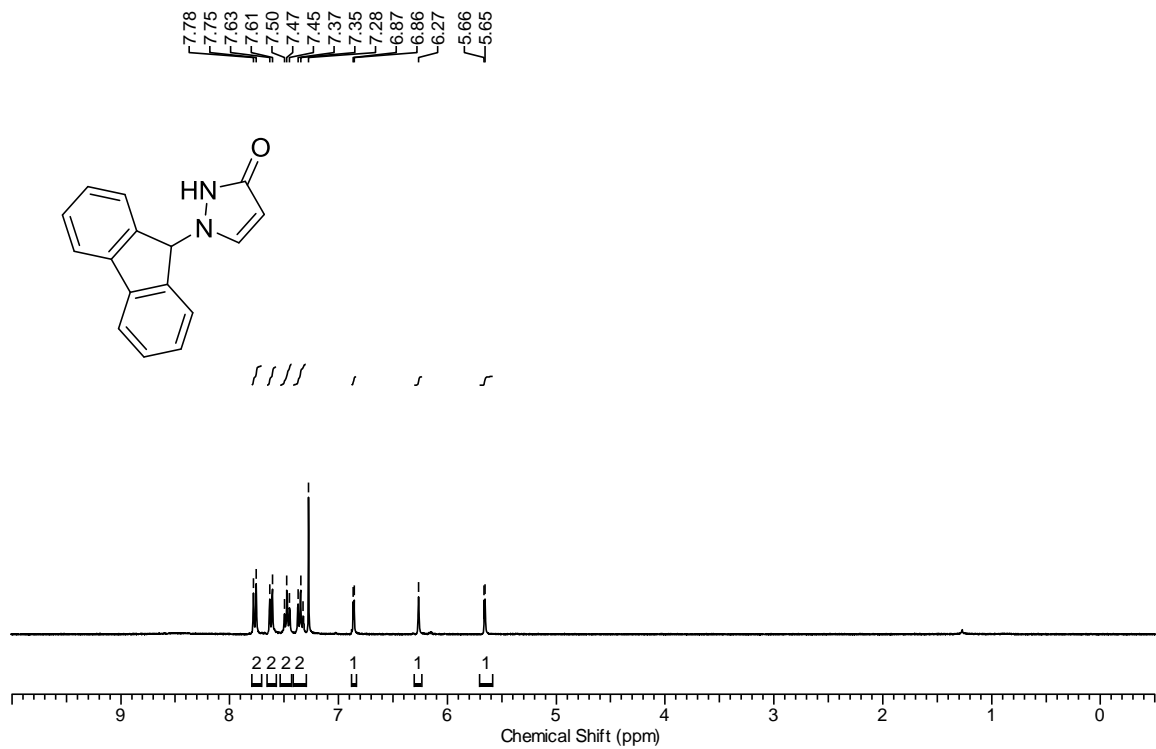


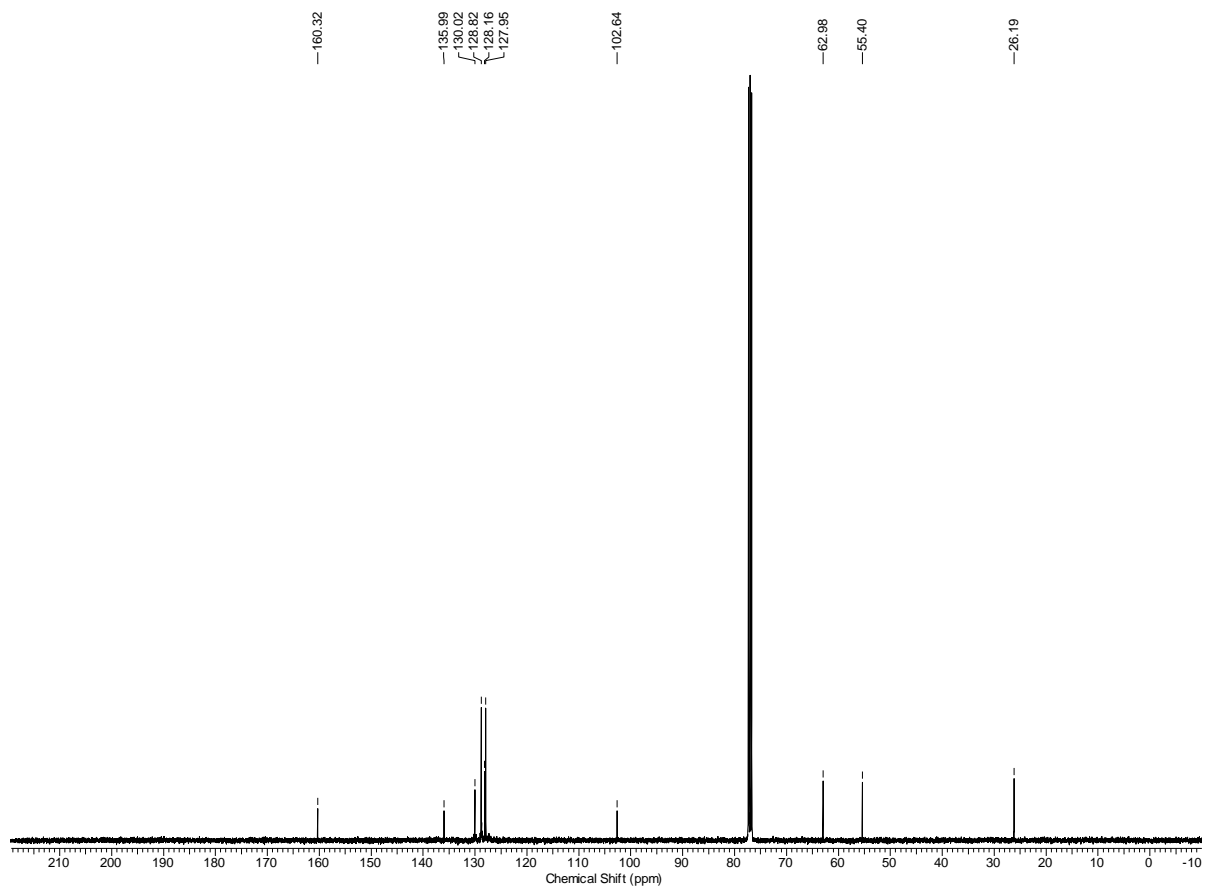
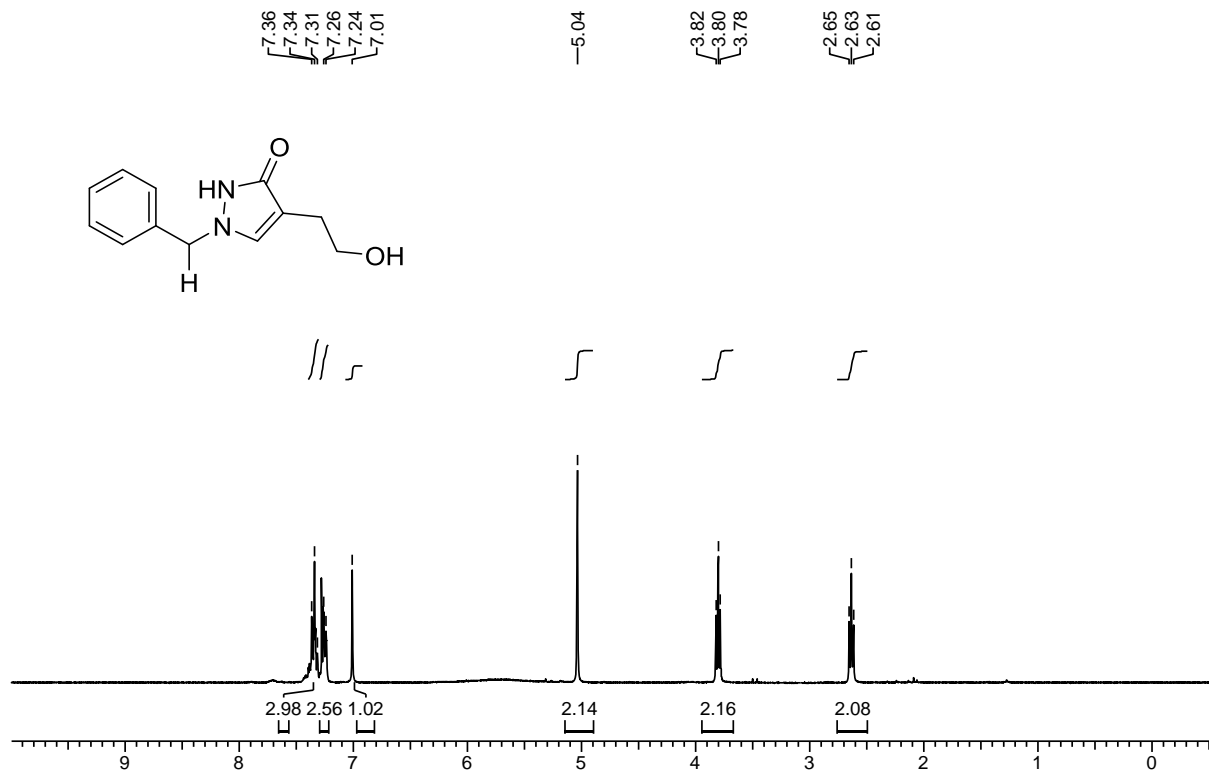


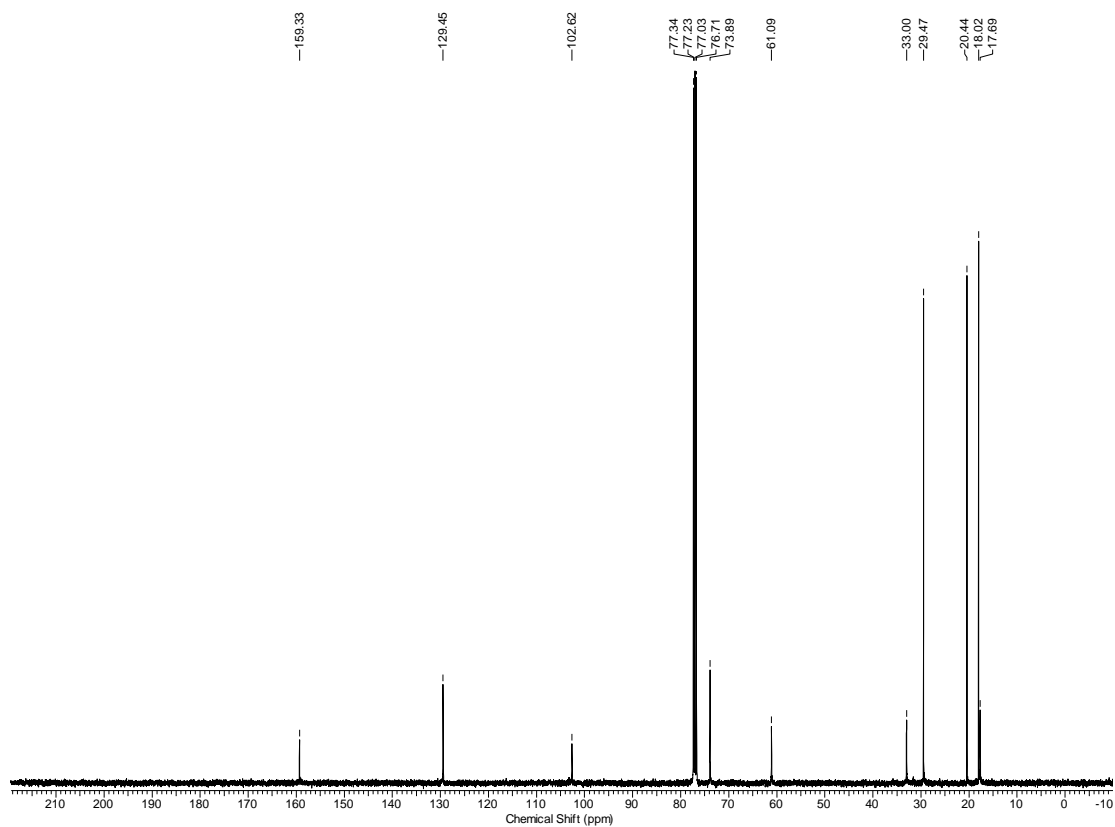
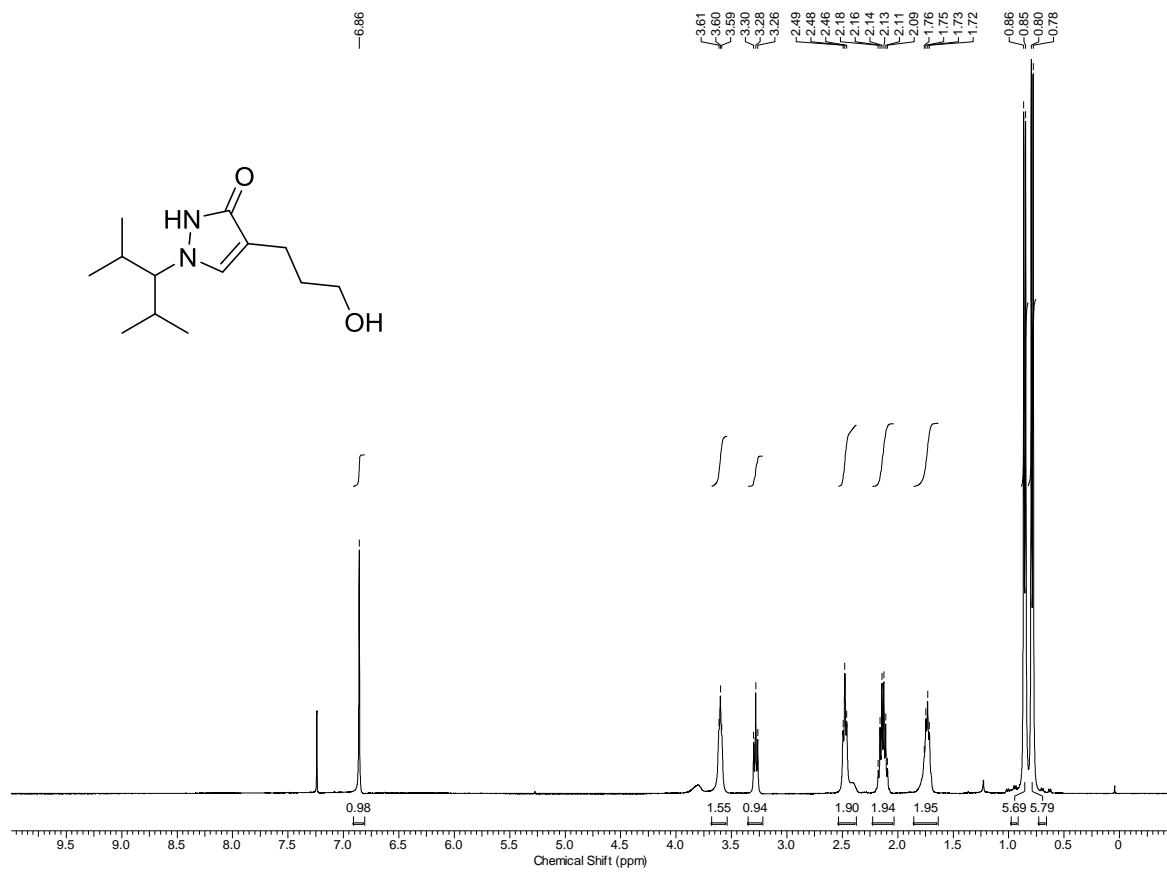


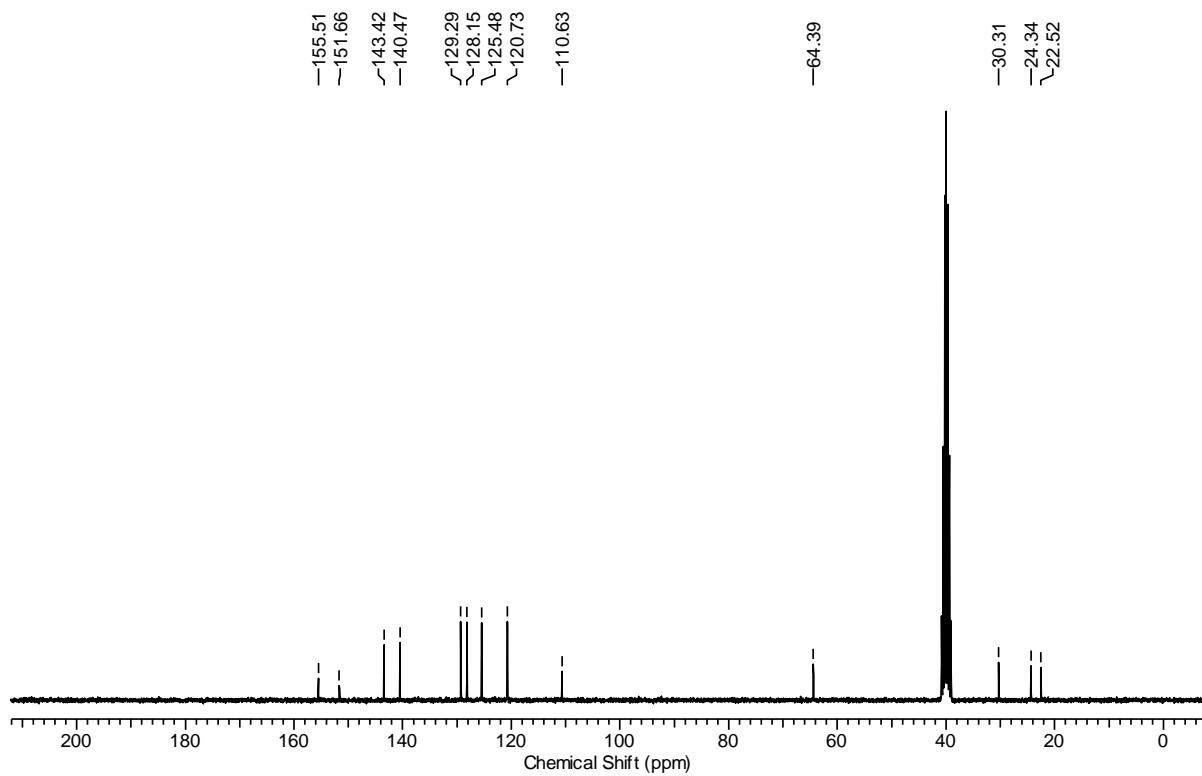
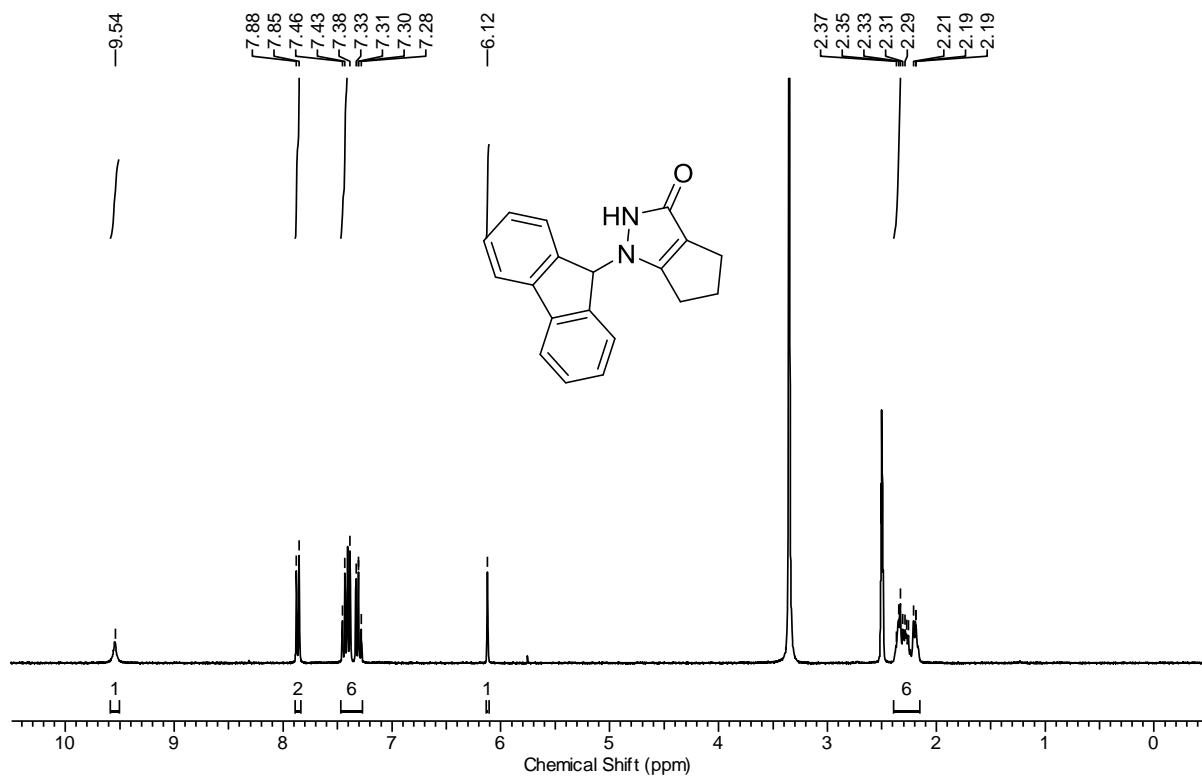
1H 400 MHz CDCl3

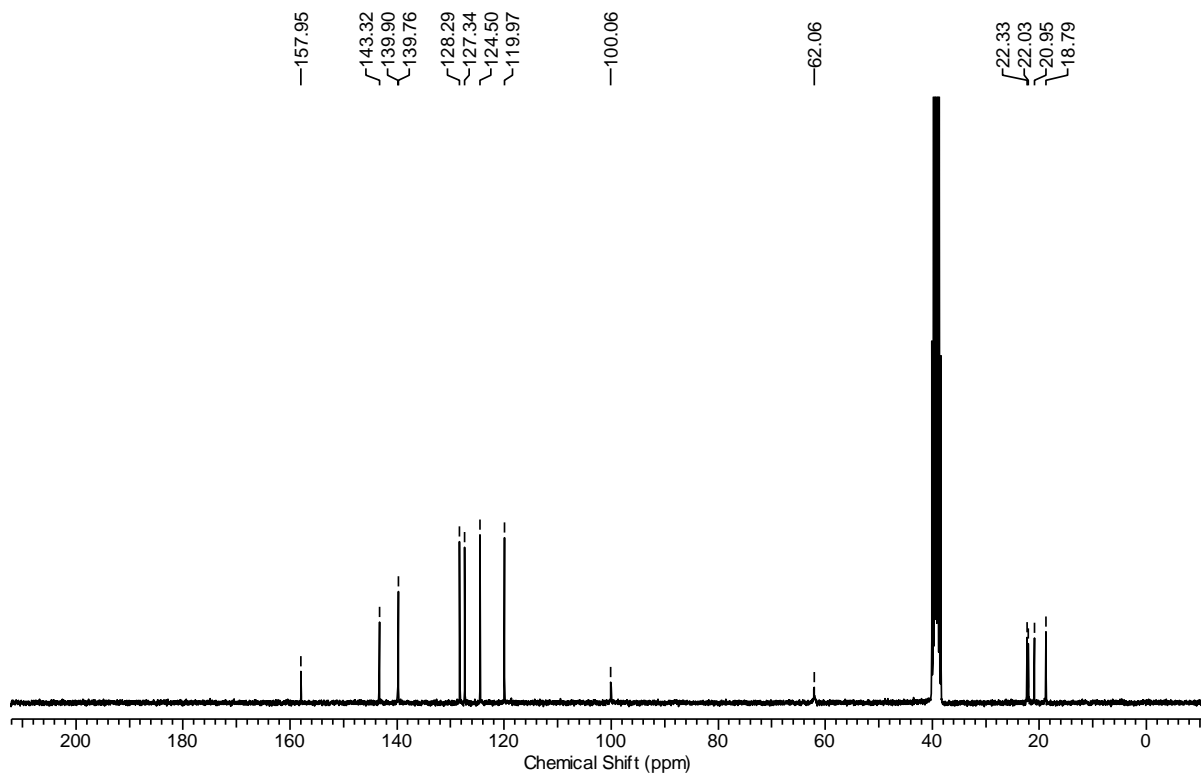
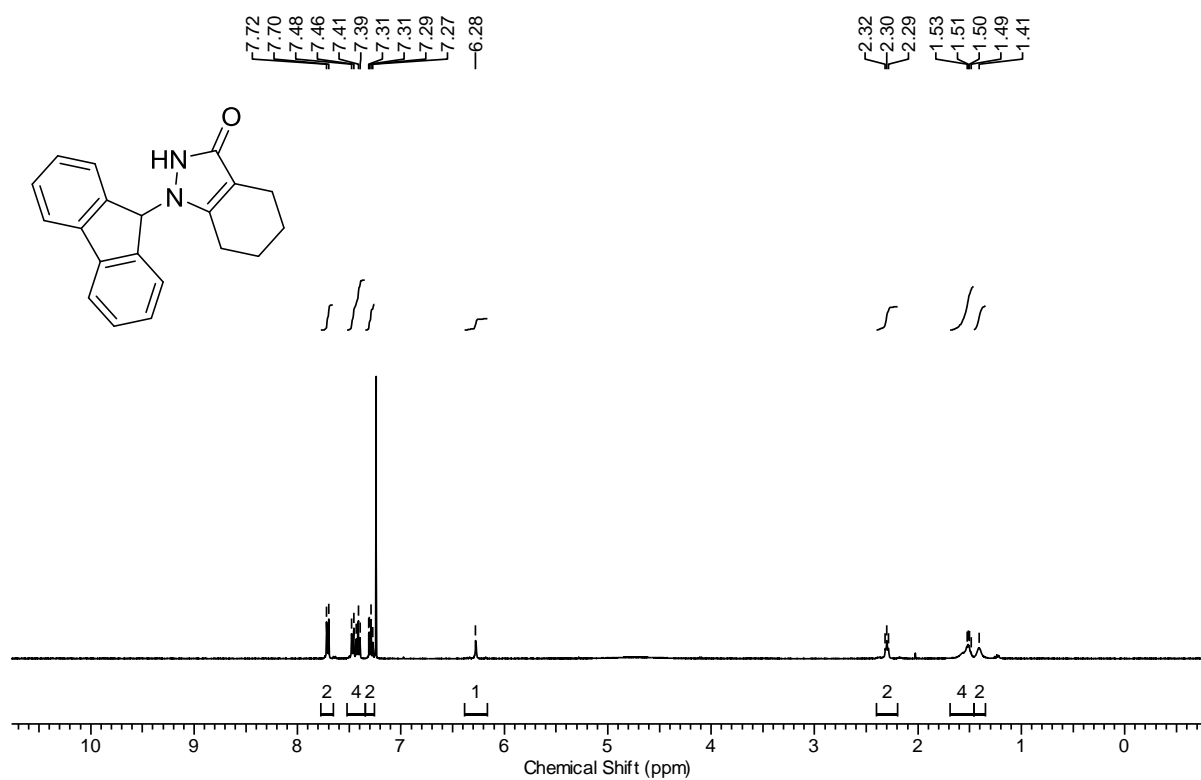


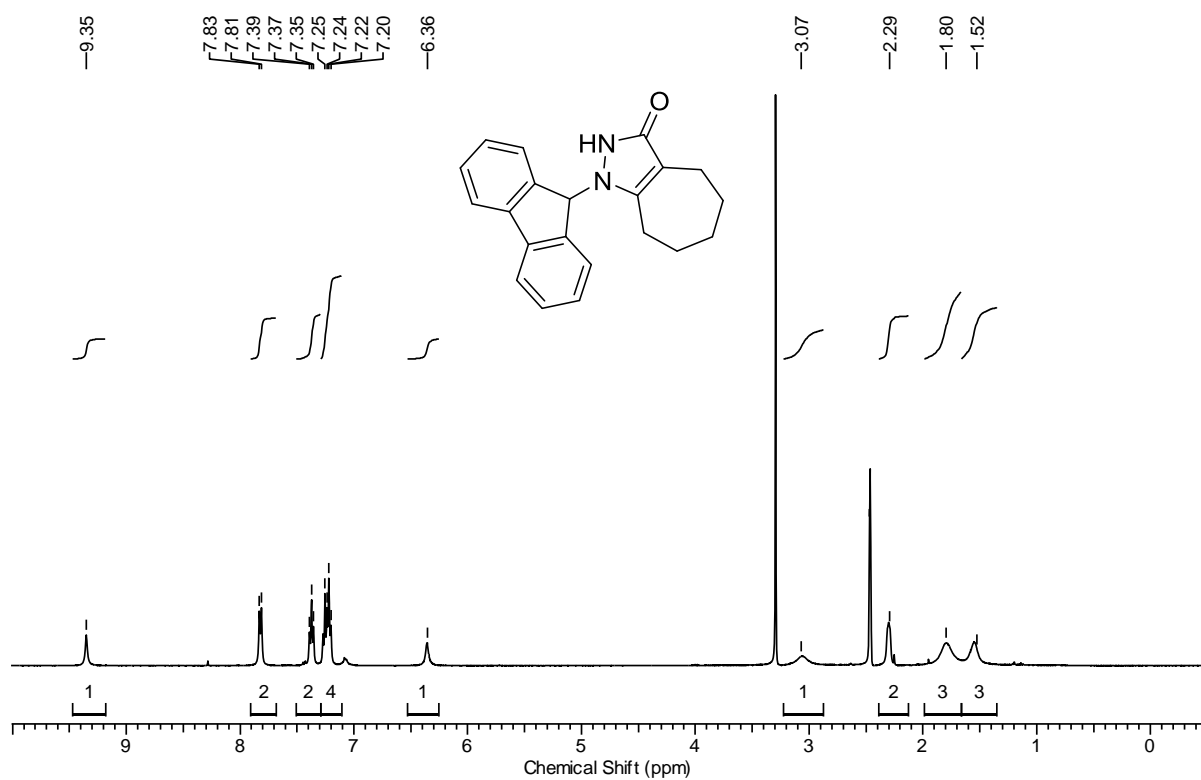












100 °C NMR

