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Synthesis of Pyridines and Pyrazines Using Intramolecular Hydroamination

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Synthesis of Pyridines and Pyrazines Using Intramolecular Hydroamination

by

Toni Rizk

A Thesis Submitted to the Faculty of Graduate and

Postdoctoral Studies in Partial Fulfillment of the

Requirements for the Master's Degree in Chemistry

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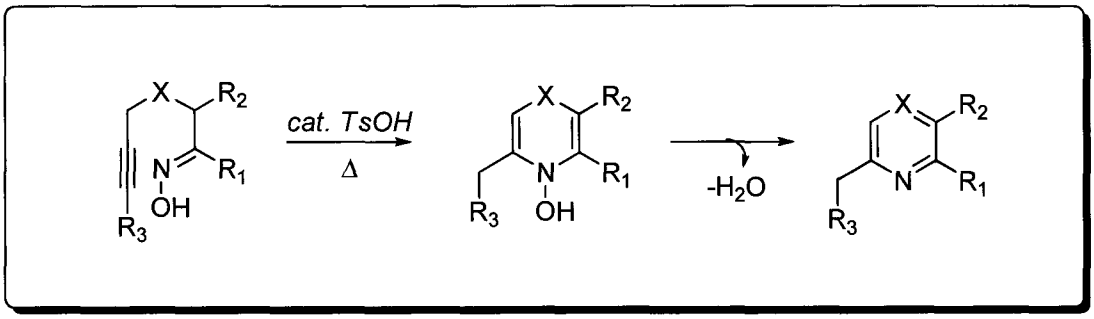
Abstract



Despite recent progress, the scope and efficiency of intramolecular hydroamination has not yet reached its full synthetic potential. In particular, cyclizations to form 6-membered rings and applications in the synthesis of aromatic nitrogen heterocycles remain rare, despite the potential to access a variety of medicinally relevant heterocycles. The intramolecular hydroamination of alkynes presented offers a general approach to such nitrogen heterocycles from appropriately substituted acyclic precursors, in which the oxime functionality allows for a milder cyclization event and allows subsequently for the installation of one additional unsaturation (via loss of H_2O). The discovery and optimization of an acid-catalyzed, hydroamination-isomerization-aromatization route for the synthesis of pyridines and pyrazines will be presented and discussed.

"Live your life each day as you would climb a mountain. An occasional glance towards the summit keeps the goal in mind, but many beautiful scenes are to be observed from each new vintage point."

- *Harold B. Melchart*

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First and foremost I would like to thank my professor and supervisor Dr. André Beauchemin for his continuous support throughout my two years as a graduate student and his admirable enthusiasm for chemistry. Anytime I needed guidance, I knew I could always walk into his office and he would listen gracefully and offer his best advice. I am forever grateful for the opportunity and experience you have given me – I have without a doubt gained irreplaceable memories being a member of this research group, thank you.

I'd equally like to thank all the members of my lab group, past and present; we've really become a family in the past years and I wish you all well. Jenn, I'll never forget our catalysis centre days; Isa, my fume hood neighbour - always there to help and answer questions; Joseph, throwing hilarious lines back and forth was a blast; Pam, I love all the nicknames we've created; Hao, thank you for providing us with many many laughs; Frank, your cheerful attitude was always enlightening, I wish you all the best - you deserve great things; Joffré, I'll never forget that thick (but amazing) French accent; Peter, what can I say to you other then F-72 for life!; Ashley, always smiling and fun to be around; Chris, many memories I won't forget (QOMSBOC); Melissa, you're just starting out and I hope you get as good an experience in the lab as I did; and last but not least – Roveda, I don't even know where to start, we've become good friends - good luck with everything.

Finally, I'd like to deeply thank Mom, Dad, Jess and Ashley for your continued support and encouragement at times where I just could not see the light. I know you

really had no idea what I was talking about when I came home cheering because my reaction worked! Thank you for caring and pretending like you knew what I was saying.

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List of Abbreviations

Ac	acetate
aq.	aqueous
Bn	benzyl
br	broad
Boc_2O	*tert*-butoxycarbonyl anhydride
cat.	catalytic or catalyst
Cy	cyclohexyl
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron ionization
equiv.	equivalents
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
Et_3N	triethylamine
HRMS	high resolution mass spectrometry

IR	infrared
i-PrOH	isopropanol
i-Pr	isopropyl
J	coupling constant
La	lanthanide
LDA	lithiumdiisopropylamide
m	multiplet
M^+	molecular ion
Me	methyl
mp	melting point
MS	molecular sieves
n-Bu	*n*-butyl
n-Buli	*n*-butyllithium
NMR	nuclear magnetic resonance
Nuc	nucleophile
PG	protecting group
Ph	phenyl
Pyr	pyridine
PPh_3	triphenylphosphine
p-TsOH	*para*-toluenesulfonic acid
q	quartet
quant.	quantitative yield
Rf	retention factor
s	singlet

SM	starting material
SO_3-Pyr	sulfur trioxide pyridine complex
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilyl
TMSCN	trimethylsilyl cyanide
Ts	*para*-toluenesulfonyl

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Introduction

1.1. Pyridines and Unsaturated Nitrogen Heterocycles

Ever since the very first isolation of benzene in 1825 by Faraday,[1] the concept of aromatic compounds has set a new challenge for organic chemists. As Hückel described the laws of aromaticity in 1931,[2] benzene set the bar for a new class of organic molecules. Not surprisingly, further discovery into this new class of compounds led to the higher understanding of their energies, related reactivity, and possibilities for diversification. Since Faraday's discovery, aromatic molecules have been manipulated and discovered in many different applications allowing for a spectrum of compounds with varying ring sizes, functionalities, and heteroatomic substitutions. The latter category raises much attention as it has proven to be quite complex and infer great synthetic applicability.

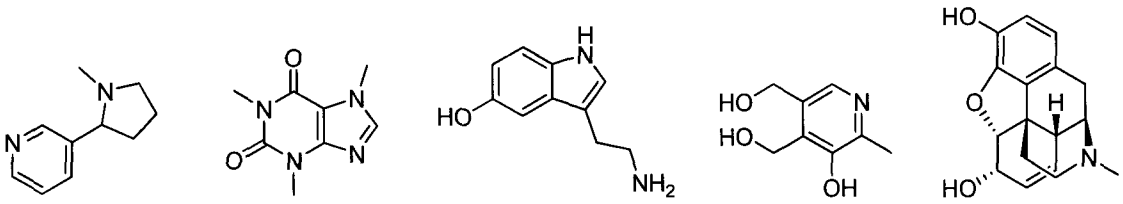


Figure 1.1. *Selected bioactive heterocyclic structures*

(1) Faraday, M. *Phil. Trans. R. Soc. Lond.* **1825**, *115*, 440.
(2) Hückel, E. *Z. für Physik* **1931**, *70*, 204.

Amazingly, in the more than 20 million known chemical compounds that are registered, nearly half contain heterocyclic systems.[3] Drug discovery is forever changing as new bioactive compounds are discovered, and with that, the study of heterocyclic compounds gains even more importance. Where would the world be without the discovery of the structures of nicotine, caffeine, serotonin, heroin, morphine, DNA, hemoglobin, chlorophyll? In this extremely broad spectrum of aromatic alkaloids, it has been shown that pyridines are among the most important in terms of drug content, natural products, and are generally an essential part of many biological systems and processes.

Recently, Carey surveyed 128 drug candidate molecules and was able to show that 95% of these molecules contained at least one nitrogen atom.[4] In detail, 113 of these 128 molecules were aromatic heterocycles whereby 24% contained a pyridine moiety, 16% contained a quinazoline moiety and 7% contained pyrimidines – illustrating that in total, 56% of the studied molecules contain at least one 6-membered (also called an electron deficient) ring system.

In order to be able to synthesize a fully unsaturated heterocyclic compound, one must understand that oxidation state management is primordial. This is because aromatic heterocycles are at a high oxidation level - as a result, this must be accounted for when trying to synthesize them from acyclic precursors. As an example, when synthesizing 6-membered aromatic heterocycles (such as pyridines or pyrazines), 3 oxidation state

(3) Duggers, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Proc. Res. Dev.* **2005**, *9*, 253.
(4) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

adjustments must be built into the precursor for the compound to have potential to aromatize post-cyclization. In order to classify and understand the oxidation state, the aromatic heterocyclic series can be separated into two categories.

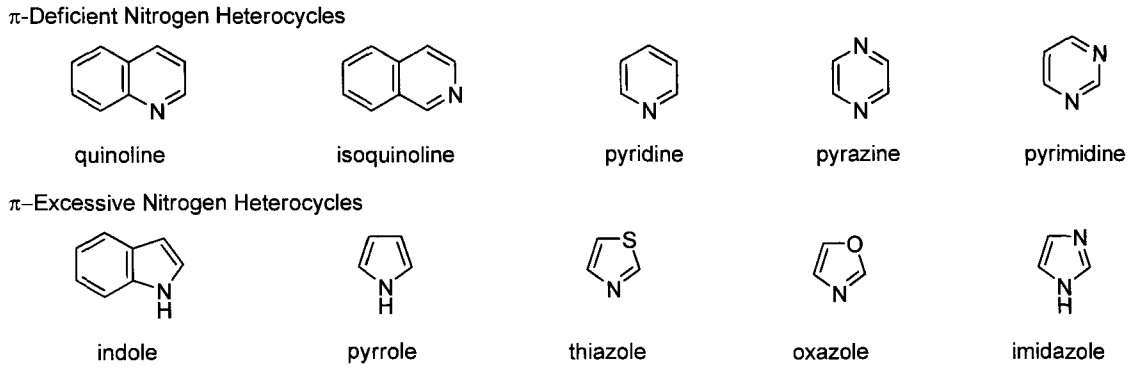


Figure 1.2. *π-deficient and π-excessive nitrogen heterocycles*

The first is the group of π-deficient systems which comprise of 6-membered heterocycles such as quinolines, isoquinolines, pyridines and pyrazines and require precursors at 3 oxidation levels relative to saturated analogs. The second is the group of π-excessive systems which generally comprise of 5-membered heterocycles such as indoles, pyrroles, thiazoles and imidazoles requiring precursors at only 2 oxidation levels relative to saturated analogs.

Historically, forming these heterocyclic organic building blocks required robust methodologies with unconventional requirements and are usually low yielding. With that said, there is an ever-growing interest in the creation of methodologies for formation of aromatic heterocycles to add to the literature. Modern methods for formation of aromatic heterocycles vary quite significantly and include metal-catalysis,

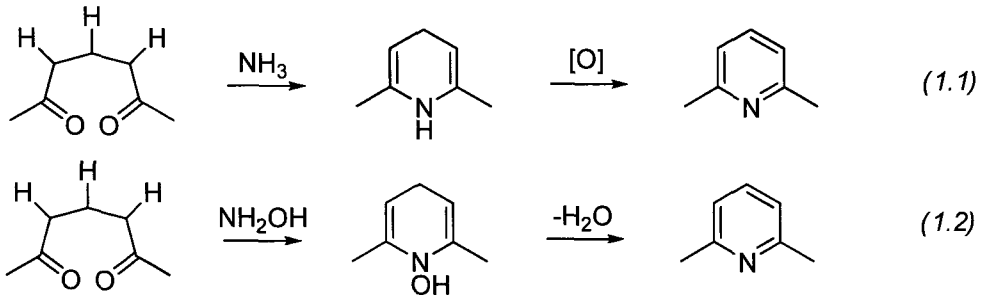
acid-catalysis as well as completely non-catalyzed methods. Since the beginning of this discussion, we've established the abundance and importance of the pyridine ring amongst all other unsaturated heterocycles. The following section outlines these systems, specifically.

1.2. Synthesis of Pyridines and Pyrazines

In past years, methods for formation of nitrogen containing aromatic molecules are quite numerous; from the classic routes to the more modern ones. Classic and modern routes towards pyridines and pyrazines are elaborated below.

1.2.1. Classic Pyridine Syntheses

The most classic method for formation of pyridine rings is likely the condensation of 1,5-diones with ammonia. However, once the ammonia is added, it can be seen that there is nothing built into the precursor to complete the aromatization step which yields a dihydropyridine intermediate. To account for this, an extra step is taken whereby an oxidant is introduced into the reaction in order to aromatize the molecule.[5]



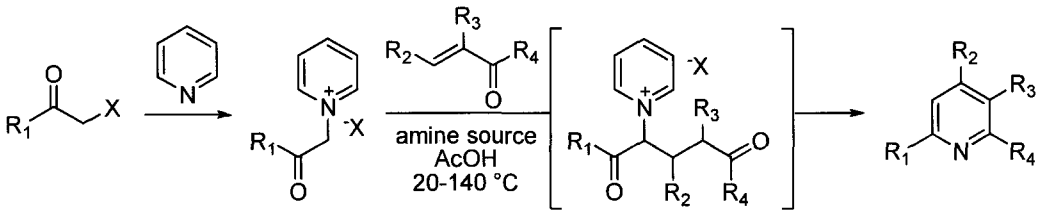
(1.1)

(1.2)

(5) Li, J.-J. "*Name Reaction in Heterocyclic Chemistry*" John Wiley & Sons, Hoboken, New Jersey, **2005**, 303.

Other variations that opt to remove this oxidation step will use hydroxylamines as their nitrogen source (instead of ammonia) which is a much more practical source of nitrogen which allows elimination of water to account for the final oxidation state adjustment.[6] Although these methods are conceptually simple, disadvantages mainly concern the difficulty in synthesizing the starting material, which makes this method less common.

Shortly thereafter the discover of the last condensation, Kröhnke *et al.* revealed an efficient method to synthesize pyridines using an *in situ* formation of a 1,5-dicarbonyl scaffold.[7,8] It generally involves the reaction of α-haloketones with pyridine to form acylmethylpyridinium salts which are subsequently condensed with α,β-unsaturated ketones and a source of amine. This method is now referred to as the Kröhnke pyridine synthesis.

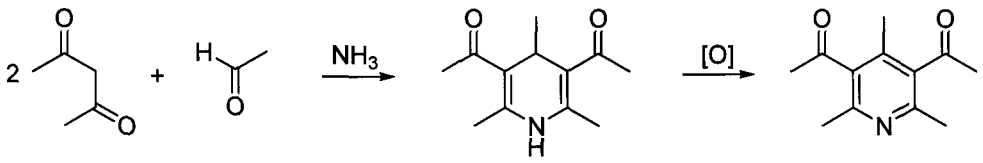


(1.3)

A much more common method is the Hantzsch dihydropyridine synthesis.[9] As the name suggests, this method also leads primarily to a dihydropyridine which is usually

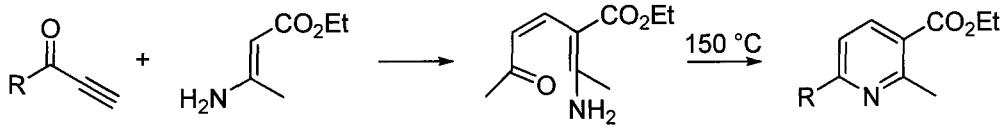
(6) a) Knoevenagel, E. *Justus Liebigs Ann. Chem.*, **1894,** *281,* 25. (b) Stobbe, H.; Vollard, H., *Chem. Ber.*, **1902,** 55, 3973.
(7) Zecher, W., Kröhnke, F. *Chem. Ber.* **1961**, *94*, 690.
(8) Kurti, L.; Czakò, B. *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, **2005**, 254
(9) Bossart, F., Meyer, H., Wehinger, E. *Angew. Chem., Int. Ed.* **1981**, *20,* 762.

further oxidized to the aromatic species. This method consist of the condensation of an aldehyde, two equivalents of a 1,3-dicarbonyl and ammonia, followed by the oxidation.



(1.4)

Another interesting approach is the Bohlmann-Rahtz synthesis which incorporates a condensation of alkynes and enamines using two sets of reaction conditions.[10] As seen below, it starts with the condensation at a mild temperature to give the intermediate which is aromatized through loss of water at higher temperatures (120-160°C). Recent modifications to the Bohlmann-Rahtz reaction employ microwave technology whereby this reaction can be completed in 20 minutes in DMSO at 170°C to generate the pyridine ring.[11]

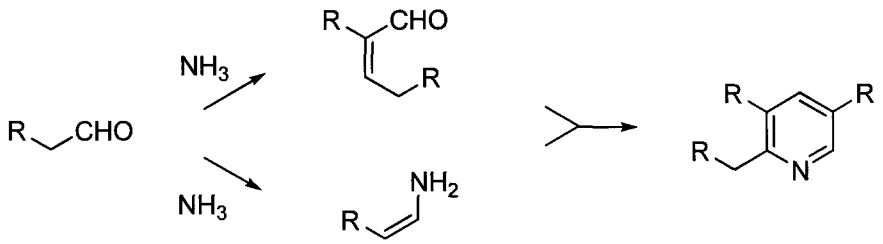


(1.5)

An equally historically important method is the Chichibabin pyridine synthesis which was first discovered in 1905.[12] It simply involves heating an aldehyde and ammonia at 300-400°C to produce the corresponding 2,3,5-trisubstituted pyridines. Here, the ammonia is said to serve as the nitrogen source for the pyridine ring and acts as a base

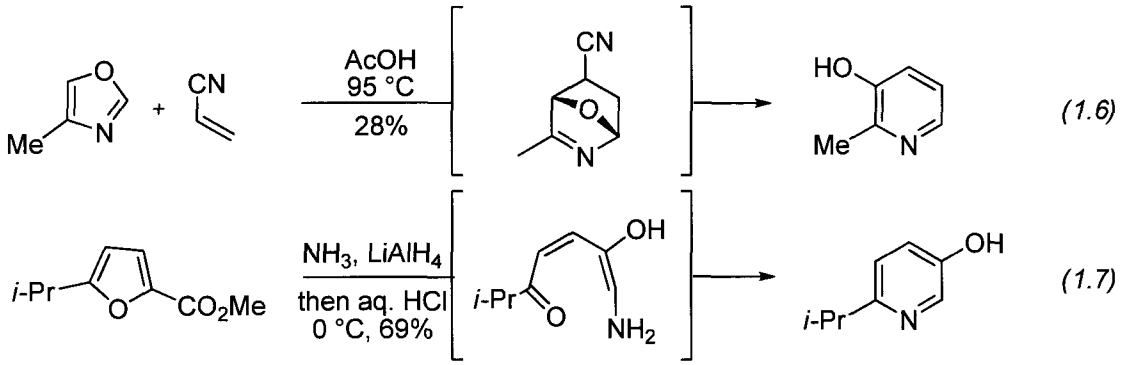
(10) Li, J.-J. *Name Reaction In Heterocyclic Chemistry*, John Wiley & Sons, Hoboken, New Jersey, **2005**, 308.
(11) Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331.
(12) Sprung, M. M. *Chem. Rev.* **1940**, *40*, 297.

to catalyze an aldol reaction between two molecules of aldehyde.[13] The aldol reaction forms the enal and the enamine which undergo a Michael addition prior to the cyclization (as seen in scheme 1.1).[14]



Scheme 1.1. *Chichibabin pyridine synthesis*

Pyridines have also been synthesized from heterocyclic starting materials such as oxazoles (through cycloadditions),[15] and furans (through ring openings).[16] Although not the most efficient reactions to for pyridines, they prove to be interesting heterocyclic transformations.

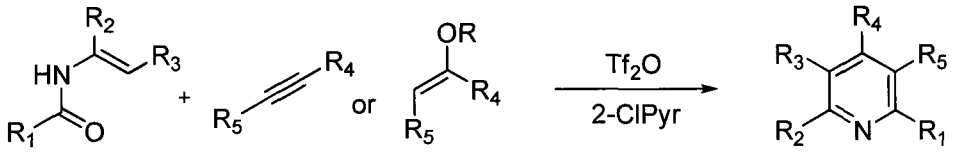


(13) a) Frank, R. L.; Seven, R. P. *J. Am. Chem. Soc.* **1949**, *71*, 2629. (b) Frank, R. L.; Riener, E. F. *J. Am. Chem. Soc.* **1950**, *72*, 4182. (c) Farley, C. P.; Eliel, E. L. *J. Am. Chem. Soc.* **1956**, *78*, 3477.
(14) Li, J.-J. *Name Reaction in Heterocyclic Chemistry*, John Wiley & Sons, Hoboken, New Jersey, **2005**, 309.
(15) Naito, T.; Yoshikawa, T.; Ishikawa, F.; Isoda, S.; Omura, Y.; Takamura, I. *Chem. Pharm. Bull,* **1965,** *13,* 869.
(16) Clauson-Kaas, N.; Petersen, J. B.; Sorensen, G. O.; Olsen, G.; Jansen, G. *Acta Chem. Scand.,* **1965,** *19,* 1146.

As mentioned, classic routes for formation of pyridine rings are quite numerous, but many will lead to lower yields or require slightly more demanding conditions.

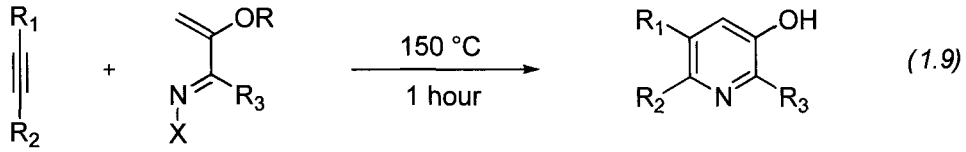
1.2.2. Modern Pyridine Syntheses

To account for this, there are now several methods discovered in recent years for formation of pyridines which use newer technologies. A few illustrative examples will be provided below. In 2007, Movassaghi *et al.* illustrated a simple and direct method for formation of fully substituted pyridine rings using one amide moiety and one alkyne or alkene moiety (eq. 1.8).[17] The method is shown to be compatible with many different functional groups such as methoxy groups, silicon-based groups, heterocycles, ethers, amides.



(1.8)

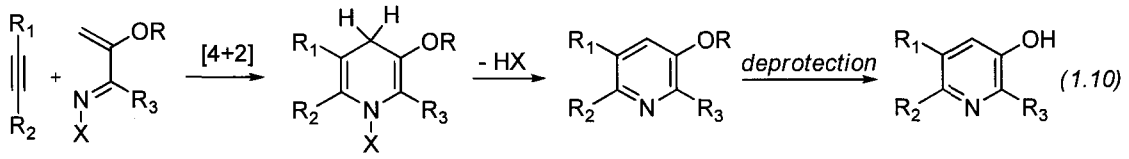
Another discovery in 2007 by Arndt *et al.* used the Diels-Alder reaction to assemble 3-hydroxypyridines.[18] The method requires 150 °C and a 1 hour reaction time.



(1.9)

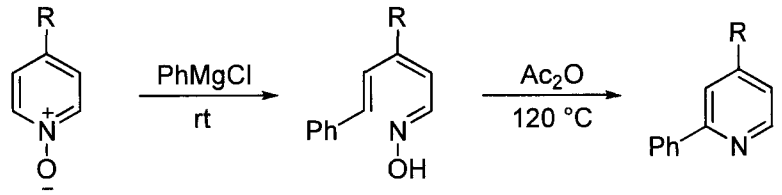
(17) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096.
(18) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205.

The mechanistic rationale here is a 4+2 hetero Diels-Alder cycloaddition to yield the dihydropyridine which is followed by the loss of an appropriately placed leaving group (X) on the nitrogen atom. At this stage, the protecting group is removed to yield the desired 3-hydroxypyridine.



(1.10)

An interesting recent discovery by Olsson *et al.* uses pyridine *N*-oxides to access a variety of substituted pyridines.[19] Starting from a selected Grignard reagent, a ring opening event leads to an oxime intermediate which is then cyclized and aromatized using acetic anhydride.



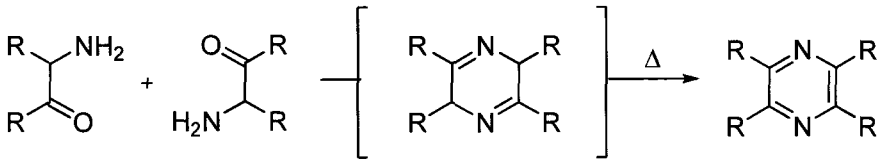
(1.11)

1.2.3. Selected Pyrazine Syntheses

A final important category of unsaturated heterocycles are pyrazines. There are interesting approaches for the synthesis of pyrazines which include the Staedel-Rugheimer pyrazine synthesis which involves the condensation of two equivalents of

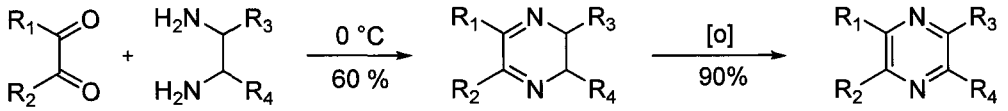
(19) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335.

aminoketone (which are typically prepared *in situ* from 2-haloketones) followed by an oxidation.[20]



(1.12)

Variations of this method were quickly established whereby the starting aminoketone is smodified with the use of sulfonyl nitrogen protecting groups,[21] or α-aminoesters.[22] Other methods allow the double condensation of 1,2-dicarbonyls with 1,2-diamines, yielding a dihydropyrazine species whereby a further oxidation is required.[23,24]



(1.13)

From the selected pyridine and pyrazine syntheses, we can see that the final unsaturations required for aromatization are typically obtained either from removal of a leaving group or water from a dihydropyridine or dihydropyrazine core or a subsequent oxidation of the aforementioned intermediates.

(20) Staedel, W.; Rügheimer, L. *Ber.* **1876**, *9*, 563.
(21) Gastaldi, G. *Gazz. Chim. Ital.* **1921**, *51*, 233.
(22) Selected reviews: a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.
(23) Flament, I.; Stoll, M. *HeIv. Chim. Acta* **1967**, *50*, 1754.
(24) Rothkopf, H. W.; Wohrle, D.; Muller, R.; Kossmehl, G. *Chem. Ber.* **1975**, *108*, 875.

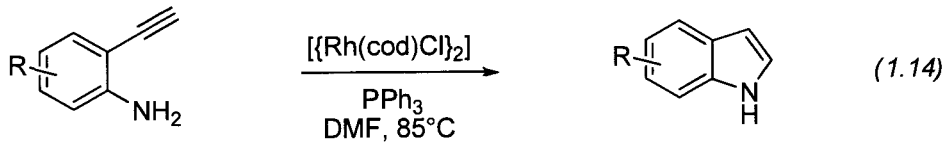
1.3. Aromatic Nitrogen Heterocycles via π-Bond Amination

There now exists a large array of methodologies that allow access to a variety of nitrogen-containing heterocycles using π-bond amination which comprises of the addition of a nitrogen atom across a π system. With that said, there are several reported metal- and acid-catalyzed methodologies where π-bond aminations allow access to saturated and unsaturated heterocycles.[25] Within this category, hydroamination is an important tool for the introduction of a carbon-nitrogen bond. However, the use of hydroamination has been rather focused on the synthesis of saturated and 5-membered aromatic heterocycles. This means using this tool to access aromatic systems is still limited to π-excessive aromatic heterocycles where the formation of π-deficient molecules is extremely rare. Let us examine two types of π-bond aminations that allow access to aromatic systems; transition metal- or electrophile-catalyzed aminations and hydroaminations.

1.3.1. Routes Involving Metal and Electrophile-Catalyzed Aminations

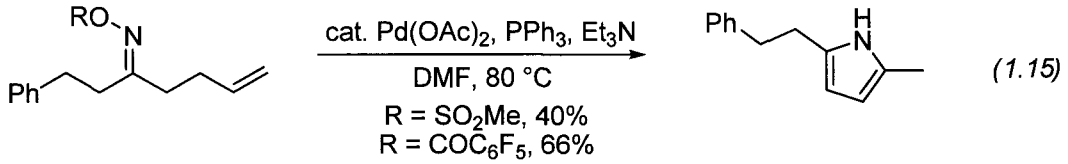
The first noteworthy amination method to discuss was reported by Trost *et al.* in 2007 where it was observed that an intramolecular oxidative amination allows the formation of 5-membered nitrogen heterocycles (indoles) whereby an amine is reacted with a tethered alkyne in a 5-endo fashion.[26]

(25) Selected reviews: a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.
(26) Trost, B. M.; McClory, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2074.



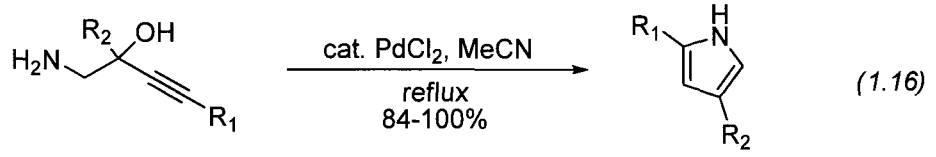
(1.14)

Extensions of this methodology for formation of pyrroles are equally as abundant. Narasaka and coworkers recently showed that using α,β-unsaturated *O*-sulfoximes, a palladium catalyst and triethylamine, pyrroles can be synthesized with modest yields.[27] When changing the nature of the imine to a more potent leaving group (important for the aromatization step), they quickly saw an increase in the reaction yield.



(1.15)

Interestingly enough, the first case reported whereby the formation of pyrroles was effected using alkynes was in 1981 by Utimoto who also used a palladium (II) complex to effectively cyclize and aromatize the molecules with excellent yields.

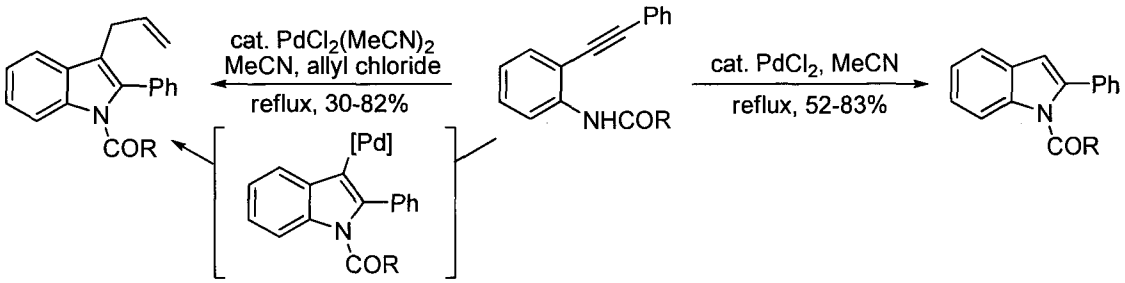


(1.16)

What is interesting here is the exploration of alkynylamides (Scheme 1.2), an obvious extension to alkynylamines. In fact, Utimoto was able to elaborate the effectiveness of

(27) Narasaka, K. *Pure Appl. Chem.* **2002**, *74*, 143.

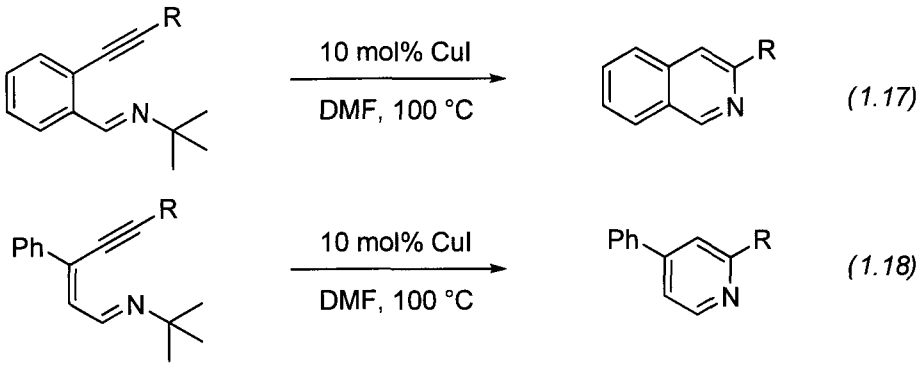
these substrates by employing palladium-catalyzed cyclizations to form indoles.[28] The use of palladium leads to an indole-intermediate species having a metal at the 3-position, which can undergo further cross coupling reactions. In effect, Utimoto showed that when allyl chloride was introduced in the reaction mixture, 3-allyl-2-alkylindoles are formed.



Scheme 1.2. *The use of palladium for tandem reactivity*

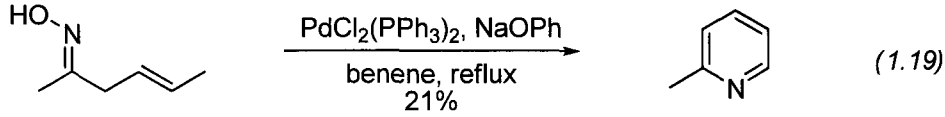
What can be observed through these examples is the abundance of literature for formation of π-excessive aromatic nitrogen ring systems. There are, however, a very limited number of examples that allow efficient access to π-deficient heterocycles using π-bond amination whereby an amine or imine is reacted with an alkyne. For example, this reactivity was seen using the following method where three unsaturations were strategically built into the starting material allowing access to isoquinolines (eq. 1.17) and pyridines (eq. 1.18) using catalytic amounts of copper.[29]

(28) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799.
(29) a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Zeni, G.; Larock, R. C. *Chem Rev.* **2004**, *104*, 2285.



The slight drawback here (concerning the formation of pyridines) is that the products are limited to always containing a phenyl ring (or another stabilizing substituent) in the 4-position because of the risk of having the central olefin isomerize whereby the required *Z* geometry will no longer be available. The engineering of this methodology requires the olefin in order to fulfill the required level of oxidation states without having cyclization halt at a dihydropyridine intermediate.

In contrast, Murahashi *et al.* elaborated a simpler method to access the desired oxidation state required for formation of the pyridine ring – an oxime. In detail, the use of an alkene provided one oxidation state adjustment, and the two other requirements were accessed from the tethered oxime functionality (through loss of H_2O post-cyclization).[30]

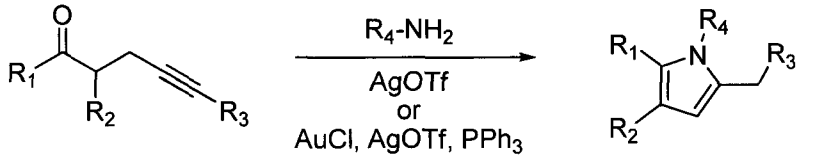


(30) Maeda, K.; Hosokawa, T.; Murahashi, S.-I.; Moritani, I. *Tetrahedron Lett.* **1973**, *14*, 5075.

Although in low yield, this method shows the efficiency of the oxime as it allows a cyclization and further elimination of water to provide an unsaturation that could not be accounted for using the imines in Larock's proposed routes. Further, this allows the removal of the central olefin that confines the pyridine products to a *para*-substituted phenyl ring.

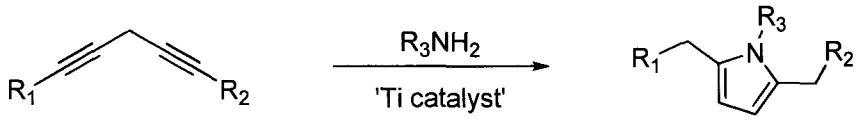
1.3.2. Routes Involving Hydroamination

Dake *et al.* took advantage of a different type of π-bond amination (hydroamination) and were able to start with ketones and amines in order to have a tandem amination-cyclization onto the alkyne using silver triflate or a combination of gold chloride, silver triflate and triphenylphosphine.[31]



(1.20)

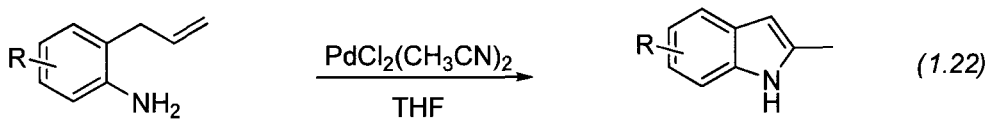
Next, this method proves to be quite interesting as it incorporates intermolecular hydroamination followed by intramolecular hydroamination to cyclize and aromatize the pyrrole ring. Starting from a di-yne system, an amine source, and a titanium catalyst, the Odom group was able to successfully form pyrrole rings in one step.[32]



(1.21)

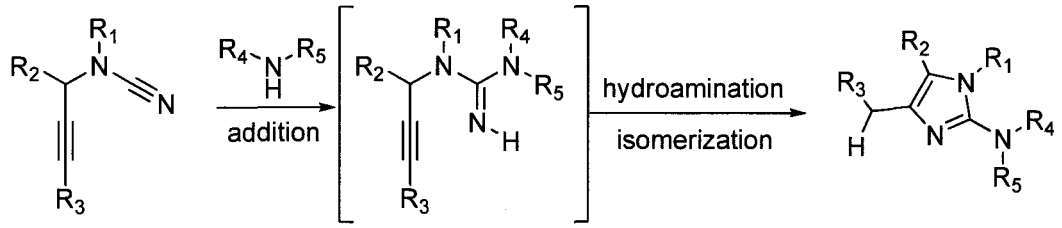
(31) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525.
(32) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957.

Next, the Hegedus group showed a similar procedure whereby an amine was reacted with an alkene but this time in a 5-exo manner to provide a series of 2-methyl indoles.[33]



(1.22)

A very recent method developed by Looper *et al.* elaborates an interesting alkyne hydroamination-based method to form imidazoles using lanthanide catalysis.[34] This method uses a nitrile bond as an electrophilic site of attack to form an imine *in situ* to infer a cyclization onto the alkyne.

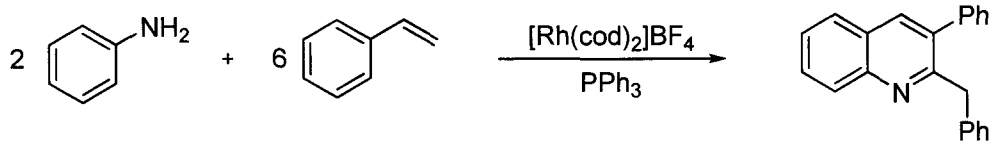


(1.23)

Throughout these examples it is clear that effectively attaining pyridines through hydroamination is a challenge yet to be resolved. In fact, the only known hydroamination to form any π-deficient aromatic system is presented by Beller *et al.* whereby quinolines are synthesized using anilines and styrenes.[35] Here, the use of a

(33) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674.
(34) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 3116.
(35) Beller, M.; Thiel, O. R.; Trauthwien, H.; Hartung, C. G. *Chem. Eur. J.* **2000**, *6*, 2513.

metal-catalyst to assist with the hydroamination is mandatory, and still, the final quinoline products are quite specific.



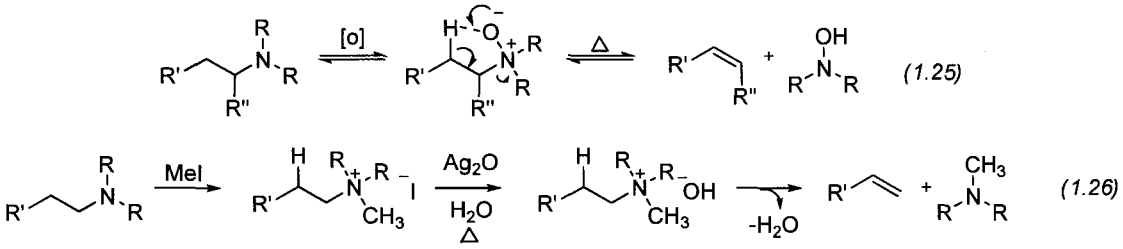
(1.24)

1.4. The Carbon-Nitrogen Bond

As we discussed earlier, the abundance of the nitrogen atom surpasses that of any other heteroatom as we saw that the most abundant moieties in drug candidate molecules were pyridine, quinazoline, pyrimidines, all exclusively nitrogen-bearing heterocycles. This in fact shows the importance and the high reactivity of the nitrogen atom. It differs from other atoms as it provides an efficient way to connect 3 chemical bonds and still be basic enough to make a fourth link (albeit slightly more difficult) through its non-bonding lone pair. An even more important factor in making this the main target atom is the abundance of the carbon-nitrogen bond. Recently, Ripin *et al.* surveyed 1039 chemical reactions and discovered that the formation of the C-N bond comprised 15% of those performed industrial organic reactions.[36] Ripin elaborated that the major C-N bond forming reactions are S_N2 (23.1%), S_NAr (19.4%), reductive amination (46.3%), and heterocyclic formation (21.6%). This interesting statistic affirms the importance and abundance of C-N bond forming reactions for synthesis of saturated and unsaturated heterocycles. Within these important categories exists many novel C-N bond forming reactions such as the Mitsunobu reaction,[37] the Mannich

(36) Duggers, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Proc. Res. Dev.* **2005**, *9*, 253.
(37) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Japan* **1967**, *40*, 2380.

reaction,[38] the Buckwald-Hartwig amination reaction,[39] and the Ritter reaction.[40] Other equally important reactions start from a C-N bond and lead to a different but synthetically useful adduct such as that seen in the Gabriel synthesis,[41] the Hofmann elimination,[42] or the Cope elimination.[43] Let us veer our attention towards the latter to further understand its synthetic capability.



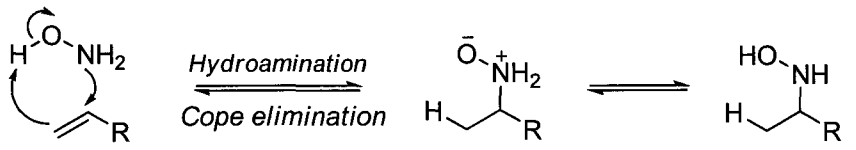
Scheme 1.3. *Cope elimination (top) and Hofmann elimination (bottom)*

1.5. Hydroamination

In 1949, Arthur C. Cope discovered that by heating trialkylamine-*N*-oxides having β-hydrogens, an olefin and *N,N*-dialkylhydroxylamine are formed. They showed that these *N*-oxide compounds can fairly easily be obtained through oxidation of the parent tertiary amine using hydrogen peroxide or other oxidizing agents such as *meta*-chloroperoxybenzoic acid (*m*CPBA). In fact, the Cope elimination is an alternative to the Hofmann elimination where the latter requires the creation of a tertiary amine by

(38) Mannich, C.; Krosche, W. *Archiv der Pharmazie* **1912**, *250*, 647.
(39) a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (b) Louise, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
(40) a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.
(41) Gabriel, S. *Ber.* **1887**, *20*, 2224.
(42) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (3rd ed.),* **1985**, New York: Wiley.
(43) Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656.

use of excess methyl iodide, silver oxide, water and heat.[44] Both methods allow the formation of olefins and the corresponding amines but it is only the Cope elimination that permits a 5-membered cyclic transition state inferring controlled syn elimination. What makes the Cope elimination even more interesting is its reversibility. The reverse Cope elimination is essentially the very opposite of the former reaction where a hydroxylamine is reacted on an olefin to create a new C-N bond. This methodology can now be applied to a variety of systems including cyclic and acyclic, or alkenes and alkynes. The more modern name given to the reverse Cope elimination is *the Cope-type hydroamination* and this approach is the focus of the Beauchemin research group. This branch of hydroamination differs from standard hydroamination as it utilizes hydroxylamine as a bifunctional reagent that can donate electron density to act as a nucleophile as well as receive electron density by donating a proton.

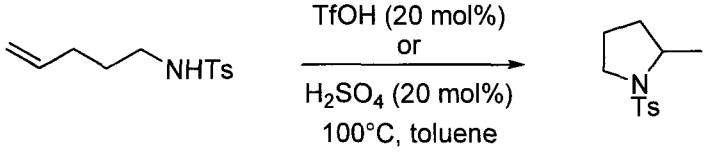


(1.27)

What makes hydroxylamines even more interesting is their ability to undergo a concerted mechanism, permitting these types of reactions to have lower transition states and undergo metal-free additions. In order to understand this concerted mechanism, it is important to consider the basic hydroamination reaction, typically performed with amines.

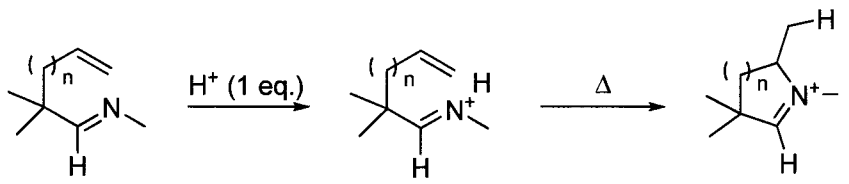
(44) Hofmann, A. W. *Ann. Chem. Pharm.* **1851**, *78*, 253.

The hydroamination reaction is in fact one of the most desirable C-N bond forming reactions. It is a very atom economical method for creation of a C-N bond by reaction of an N-H bond across a C=C double or C≡C triple bond of an alkene or alkyne. The atom economy of this reaction comes from its ability to undergo clean, virtually waste free reactivity. Conversely, hydroamination faces many noteworthy challenges in order to obtain the desired reactivity. Firstly, the reaction is said to be nearly thermodynamically neutral. In other words, the energies of the starting materials and products are nearly identical. With that said, the activation energy barrier required for this reaction to proceed is typically raised due to the repulsion between the lone pair on the nitrogen atom and the electron rich nature of the given substrate (π bonds). In most cases where activation energy is the limiting step of the reaction, catalytic conditions are typically employed. In the case of amines as the nitrogen sources for hydroamination reactions, the bifunctionality of the reagent (that is observed with hydroxylamines) is no longer available, and the activation energy barrier is too high for thermal conditions to be applicable. Due to this, catalysis has become an important branch of hydroamination and is the near exclusive focus of newly developed methodologies. Unfortunately, this leads to other important challenges that need to be overcome before catalyzed hydroamination can be rendered completely efficient. Catalysis for hydroamination has been explored with acids, lanthanides, and transition metals.



(1.28)

With acid and lanthanide catalysis, functional group compatibility becomes questionable which reasonably decreases the scope and applicability of the reaction. Hartwig's method for hydroamination (shown above) of protected amines under strongly acidic conditions to render the corresponding pyrrolidines.[45] Although this method seems efficient, it can be observed (as expected) that the scope of the reaction is limited to highly robust functional groups such as phenyl rings and nitro groups. Recently, a discovery by Bertrand *et al.* elucidated a method to cyclize 5- and 6-membered rings using alkene "hydroiminumation" of imines using acid.[46]



(1.29)

Transition metal catalysis has also shown to be quite useful and broadly applicable but is known majorly for alkynes - as reactions of alkenes typically feature cyclization reactions (often only 5-membered ring formation is reported). In fact, titanium and zirconium are usually the more common metal complexes chosen for hydroaminations. Recently, the use of gold to catalyze alkyne hydroamination has shown to be a very efficient process.[47,48]

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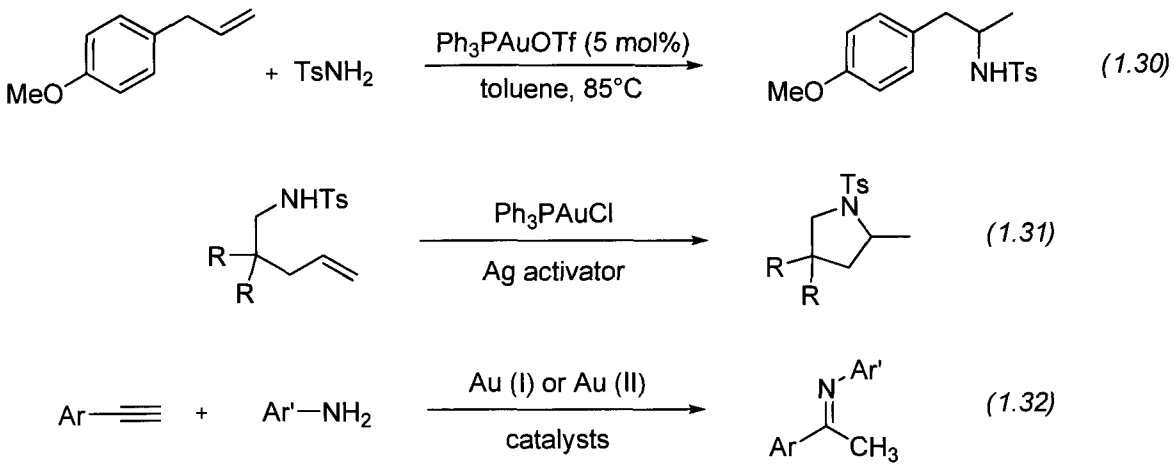
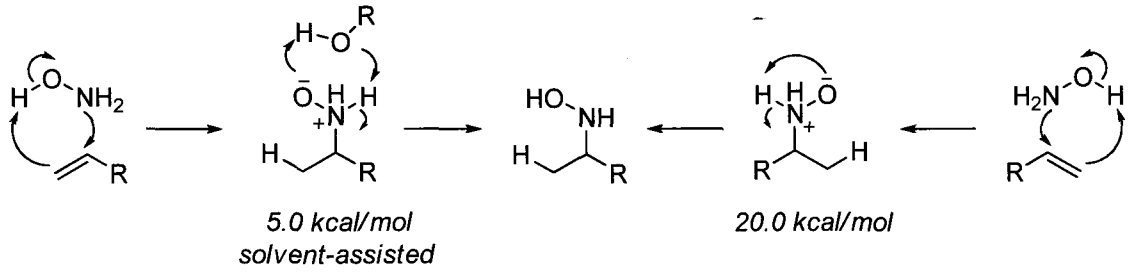
(45) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.
(46) a) Jazzar, R.; Drewhurst, R.D.; Bourg, J.-B.; Donnadieu, B.; Canac, Y.; Bertrand, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2899. (b) Jazzar, R.; Bourg, J.-B.; Drewhurst, R.D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492.
(47) Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1744.
(48) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661.



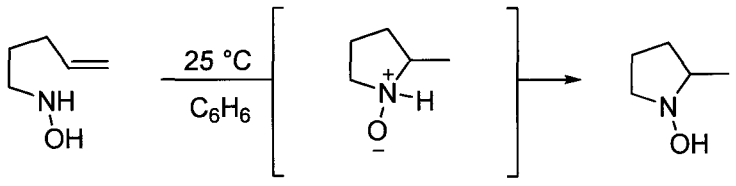
Conditions for the inter- and intramolecular hydroaminations of alkenes and alkynes using gold have shown great success.[49,50] However, transition metal catalysis is still very substrate specific where no general routes exist rendering these reactions less versatile, not to mention the cost of materials associated with catalysis. The use of hydroxylamines instead of amines in the Cope-type hydroamination, as mentioned earlier, provides the possibility for a concerted mechanism where the activation energy barrier is lowered. Consequently, this allows for a reaction that does not require further activation from metal catalysts and can simply occur using thermal or even neutral conditions. Intermolecular reactivity with hydroxylamines has been proven by the Beauchemin lab to occur at fairly mild conditions preferably in protic solvents. The group has reported that protic solvents, notably isopropanol, help mediate the proton transfer step in the transition state of the Cope-type hydroamination. This was supported by DFT computational calculations where it was shown that a solvent-

(49) Zhang, J.; Yang, C.-G.; He., C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.
(50) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

assisted (or bimolecular) proton transfer step requires 5.0 kcal/mol whereas a non-assisted proton transfer step required a fourfold increase in energy.[51]



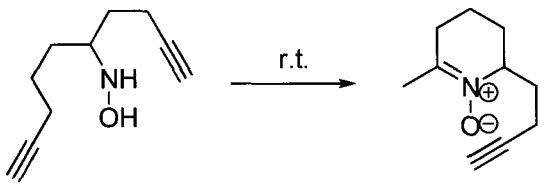
Intramolecular Cope-type hydroamination, on the other hand, has been thoroughly studied and has seemingly taken precedence over intermolecular reactivity in the literature. If one recalls earlier we discussed that while using amines, the cyclization event could not occur without the use of trifluoromethanesulfonic acid (TfOH) or sulfuric acid (H_2SO_4). Works by House, Ciganek, Oppolzer, and Holmes illustrate the synthetic possibility of the reverse Cope elimination whereby simply using hydroxylamine instead of amines can have a twofold positive effect on the reaction.[52,53,54,55] Firstly it permits the removal of any acid catalyst from the reaction, and also allows the reaction to proceed at room temperature.



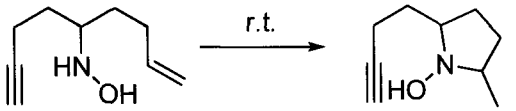
(1.33)

(51) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S., *Angew. Chem., Int. Ed.* **2008**, *47*, 1410.
(52) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.
(53) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007.
(54) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.
(55) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *Tetrahedron Lett.*, **1992**, *33*, 7421.

Experiments demonstrated the relative reactivity of intramolecular Cope-type hydroamination. For alkene hydroamination, the formation of 5-membered rings is most facile; with increased difficulty as ring size was increased. This statement does not hold for terminal alkyne hydroamination as 5-membered rings are said to be difficult to form, whereas the one carbon homologues are known to cyclize at or below room temperature.



(1.34)



(1.35)

Holmes and coworkers proved this statement by creating a non-biased system (eq. 1.34) whereby a hydroxylamine could cyclize to form either a five or six-membered ring using a terminal alkyne. His experiments showed that at room temperature, the six-membered ring formed preferentially, leaving a nitrone species with a tethered alkyne.[55,56] Holmes equally prepared a similar system (eq. 1.35) where a hydroxylamine, an alkyne and alkene were placed in on the same chain, allowing possibility for formation of a five-membered ring through either of the provided unsaturations. Not surprisingly, the 5-membered ring was formed through the alkene, leaving the alkyne unreacted – truly demonstrating that the alkene is the favoured site

(56) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc. Perkin. Trans.* **1994**, *1*, 3379.

of attack to close a 5-membered ring. Furthermore, the latter displays the difficulty for formation of 5-membered rings using alkynes. Regardless, the Cope-type hydroamination presents a potentially versatile method for cyclizing heterocyclic rings and has further possibility to aromatize in order to obtain unsaturated compounds.

1.6. Aim of the Project

Since our goals in terms of heterocyclic synthesis were in fact to access π-deficient systems (specifically pyridines and pyrazines), we wanted hydroamination to be the key tool in the process. What is important to note is that there is not a single method in literature that allows access to pyridines or pyrazines using metal-free hydroamination.

In order access these π-deficient heterocycles, the two requirements are primarily to attain a cyclization forming the desired 6-membered ring, which must be followed by an aromatization. The latter step must be made possible by the pre-cyclized precursor being at the correct oxidation state. A great advantage in using the Cope-type hydroamination as our cyclization tool is that we utilize hydroxylamines which provide metal-free access to the required nitrogen atom and – after the cyclization – can release H_2O to account for an oxidation state adjustment during aromatization. As we discussed earlier, in order for our precursors to be able to be in the correct oxidation state for the aromatization sequence of a 6-membered ring to occur, we must account for three unsaturations. Likewise, the simpler variant - the 5-membered ring – requires only two oxidation state adjustments built into the precursors as only two unsaturations need to be provided for aromaticity. Since the latter seemed like the simpler problem, we decided to primarily attempt the formation of pyrroles.

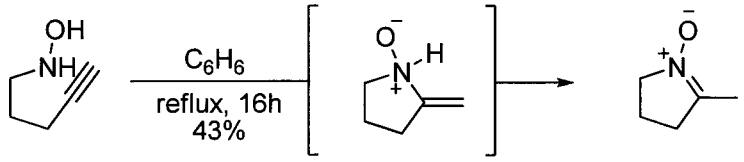
2

Formation of 5-Membered Azacycles

2.1. Introduction

In keeping with starting with a much more simplistic system whereby only two oxidation state adjustments must be made to access aromatic products, we decided to attempt the formation of pyrrole rings. These targets seemed simple to form and would yield pharmaceutically valuable products.

The work by Holmes *et al.* showed that with this type of scaffold, the hydroamination leads to a 5-membered nitrone.[55] As mentioned earlier, formation of 5-membered rings using alkyne hydroamination is difficult and requires sufficient energy for a cyclization event to occur efficiently. Holmes demonstrated that the difficulty of this cyclization leads only to a modest yield of the corresponding nitrone, likely via an *N*-oxide intermediate.



2.1 **2.2** **2.3** *(2.1)*

2.2. Goals

With the use of hydroxylamines, a five-carbon chain, and a terminal alkyne, we hypothesized the formation of pyrrole rings to still be a viable process. We postulated that the nitrone obtained from a five-membered ring formation could be an intermediate, which could then aromatize to provide the desired aromatic product. Theoretically, this is achievable because, as mentioned, the nitrone intermediate is at the same oxidation sate as the desired aromatic adduct.

2.2 **2.3** **2.4** **2.5** *(2.2)*

In order to be able to achieve the proposed difficult aromatization sequence, we considered two possibilities. First, we wanted to provide the nitrone intermediate with different conditions which could favour a more facile cyclization-aromatization sequence. Second, we wanted to explore a related sequence that could avoid forming a stable nitrone intermediate altogether.

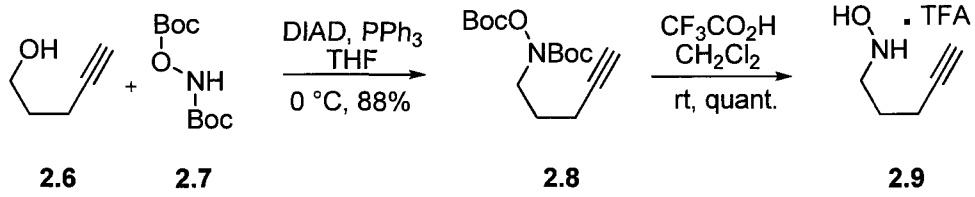
2.3. Approaches Towards Developing Ideal Reaction Conditions

In order to benefit and exploit the available oxidation state coming from such precursors, we reasoned that varying the reaction conditions could induce the nitrone to eliminate water and form the desired pyrrole. Holmes reported that the cyclization of 5-membered rings proceeded in benzene at reflux to give a 43% yield.[55] This shows that under these conditions, the reaction stops at a stable intermediate, the nitrone.

With that, we reasoned it was best to work at more elevated temperatures as this will allow the high activation energy to be surpassed and push the nitrone intermediate to the stable aromatic product.

2.3.1. Preparation of Starting Materials

The ideal substrate to primarily synthesize was 4-pentyn-1-hydroxylamine, which began with the Mitsunobu reaction of 4-pentyn-1-ol with a di-boc-protected hydroxylamine, providing the bis-boc adduct in excellent yields. Simple deprotection using trifluoroacetic acid yielded the desired hydroxylamine in 2 steps.[57]

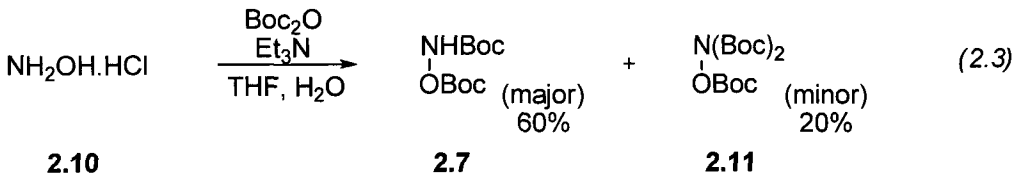


2.6 **2.7** **2.8** **2.9**

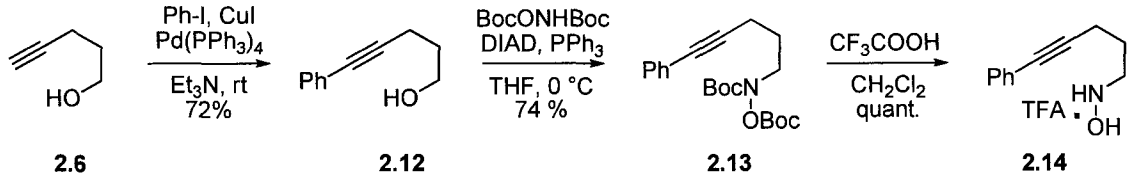
Scheme 2.1. *Forward synthesis for preparation of hydroxylamine starting material*

The preparation of the boc-protected hydroxylamine used in the Mitsunobu reaction was quite sensitive as the reaction with di-*tert*-butyl dicarbonate (Boc_2O) contained the possibility for formation of a tri-Boc adduct – an unreactive species. Nonetheless, its synthesis involved the reaction of hydroxylamine hydrochloride with di-*tert*-butyl dicarbonate under basic conditions.[58]

(57) Tao, T.; Alemany, L. B.; Parry, R. J. *Org Lett.* **2003**, *5*, 1213.
(58) Knight, D. W.; Leese. M. P. *Tetrahedron Lett.* **2001**, *42*, 2593.



Due to suspected volatility issues, we decided to equally synthesize a similar compound whereby the terminal alkyne would be substituted with a phenyl ring. This was achieved by simple Sonogashira cross coupling of phenyl iodide with 4-pentyn-1-ol.[59] At this stage, the alcohol underwent a similar Mitsunobu reaction (followed by TFA deprotection) to provide the phenyl-substituted hydroxylamine.[60]



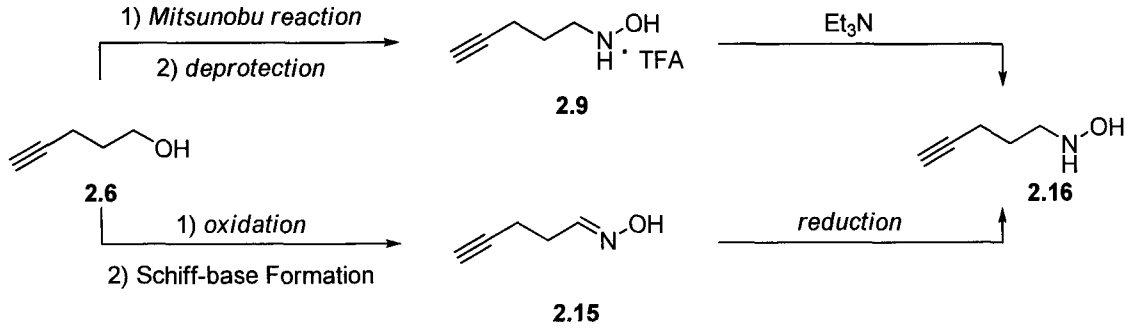
Scheme 2.2. *Sequence for formation of alkyne-substituted hydroxylamine*

2.3.2. Results and Discussion

The inherent problem of volatility was frequently an issue with these reactions, be it when handling the hydroxylamine starting material or the pyrrole final product. To synthesize the hydroxylamine starting material, we had the choice between two main routes; a Mitsunobu-deprotection pathway and an oxidation-Schiff-base formation-reduction pathway. We chose the former to avoid issues with volatility. Indeed, deprotection with trifluoroacetic acid provides the hydroxylamine as a trifluoroacetic

(59) Carson, J. R.; Almond, H. R.; Brannan, M. D.; Carmosin, R. J.; Flaim, S. F.; Gill, A.; Gleason, M. M.; Keely, S. L.; Ludovici, D. W.; Pitis, P. M.; Rebarchak, M. C.; Villani F. J. *J. Med. Chem.* **1988**, *31*, 630.
(60) Tao, T.; Alemany, L. B.; Parry, R. J. *Org Lett.* **2003**, *5*, 1213.

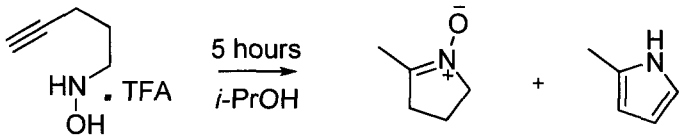
acid (TFA) salt, a non-volatile species. If the second synthetic route is chosen, a reduction of the oxime (which would be the product of an oxidation-amination) would lead to the free hydroxylamine, which is volatile.



Scheme 2.3. *Two routes to access desired hydroxylamine*

With the starting materials in hand, we decided to immediately subject 4-pentyn-1-hydroxylamine to various reaction conditions, outlined in Table 2.1. Initial attempts involved the use of isopropanol as solvent, as it would facilitate the Cope-type hydroamination process, and possibly provide polar and hydrogen-bonding media favouring the aromatization.

Table 2.1. *Cyclization-Aromatization Sequence Results*



2.9 **2.3** **2.5**

Entry	Temperature (°C)	Additive (3.0 equiv.)	Product Observed	NMR Yield (%) [c]
1	180	Et_3N	**2.3**	53
2	180	-	**2.3**	51
3	180	Et_3N[a]	**2.3**	- [d]
			2.5	5
4	183[b]	Et_3N	**2.3**	- [d]
			2.5	4
5	190[b]	Et_3N	**2.3**	- [d]
			2.5	5
6	140[b]	Et_3N	**2.3**	- [d]
7	100[b]	Et_3N	**2.3**	- [d]

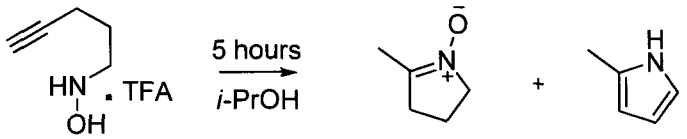
[a] Used prior to reaction. [b] Reaction in microwave. [c] NMR yield determined using styrene as an internal standard. [d] NMR yield not determined when nitrone presence detected.

Since the early stages of our studies we postulated that the TFA salts binding to the hydroxylamine starting material (which arise from the synthetic route) would interfere with the reactivity due to irreversible protonation of the required nitrogen atom. We thought to correct this by addition of triethylamine (Et_3N) whereby *in situ* formation of the free would lead to a desired cyclization-aromatization sequence. This only led to formation of nitrone, results previously reported by Holmes – allowing us to conclude that excess base does not favour aromatization. As a control experiment, we examined if the use of the hydroxylamine as its TFA salt would encourage the aromatization, due to possible counter ion effects (Table 2.1, entry 2). However we saw only nitrone formation and no difference in terms of reactivity. Finally, we decided to do a basic triethylamine workup prior to the cyclization. This provided the desired free

hydroxylamine with weaker yields (likely due to volatility), but nonetheless a neutral species. Surprisingly, this lead to traces of the desired pyrrole product - observed through NMR analysis. However, the results were not reproducible, nor isolable.

In keeping with this result, we decided to try more forcing conditions by heating the compound at 183 °C in the microwave (Table 2.1, entry 4). Unfortunately, this again lead only to traces of the desired product. When increasing the microwave temperature (Table 2.1, entry 5), similar results arose. Further, when the temperature was decreased to 140 °C or 100 °C, the reaction was completely halted and only the nitrone was observed by NMR.

Table 2.2. *Effect of Additives on the Cyclization*



2.9 **2.3** **2.5**

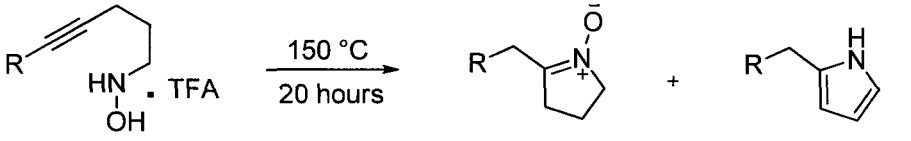
Entry	Temperature (°C)	Additive (3.0 equiv.)	Product Observed[a]
1	180	Et_3N	**2.3**
2	180	$Et_3N + H_2O$	**2.3**
3	180	H_2O	**2.3**
4	140	AcOH	**2.3**

[a] NMR yield not determined when nitrone presence detected.

Lastly, we examined if an additive can have a positive effect on the cyclization. Table 2.2 illustrates that basic, neutral, and acidic additives lead only to the nitrone product.

At this stage, we decided to examine if volatility was a dictating factor not allowing us to observe any pyrrole final product. In order to test this, we explored the cyclization of a phenyl-substituted alkyne which would yield a 2-benzylpyrrole – a non-volatile species. This control experiment seemed as though it could give an insight as to the relative volatility of the products. However, this system is slightly biased - as mentioned earlier; Holmes *et al.* explained that alkyne substitution substantially reduced the rate of cyclization.[55]

Table 2.3. *Cyclizations with Alkyne Substitution*



2.16

R = H; 2.3
R = Ph; 2.17

R = H; 2.5
R = Ph; 2.18

Entry	Substrate (R)	Solvent	Product Observed[a]
1	H	*i*-PrOH	**2.3**
2	Ph	*i*-PrOH	**2.17**
3	H	C_6H_6	**2.3**
4	Ph	C_6H_6	**2.17**
5	Ph	CH_3CN	**2.17**
6	Ph	$PhCF_3$	**2.17**
7	H	Pyridine	**2.5** [b]
8	Ph	Pyridine	**2.17**

[a] NMR yield not determined when nitrone presence detected. [b] Only Traces of desired product observed by ^{1}H NMR Analysis.

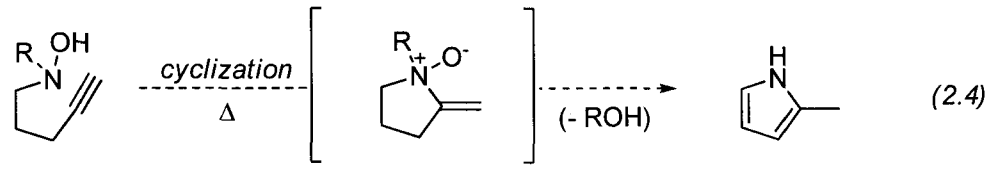
While substituting the alkyne, we decided to equally scan a variety of solvents to see if alcoholic solvents were not ideal candidates for this sequence. Reactions with other non-alcoholic solvents (benzene, acetonitrile, α,α,α–trifluorotoleuene) led to no encouraging results. Finally, when pyridine was used as a solvent (Table 2.3, entry 7)

with a terminal alkynyl hydroxylamine, only traces of product was observed. A direct comparison with the phenyl-substituted alkynyl starting material (Table 2.3, entry 8) led to no conversion to a pyrrole. When looking for further answers as to why the aromatization would not initiate, we questioned the efficiency of the actual cyclization. Recall that the original research by Holmes reported only 43% yield of the nitrone. This indicates that the cyclization is very difficult and not very efficient, which does not leave much room for error during the aromatization step.

After a number of optimization trials led us to the same unwanted result: the five-membered nitrone. Speculating that the stability of the nitrone is such that it would prevent aromatization under most reaction conditions, we turned our attention to alternative strategies.

2.4. Development of a Sequence

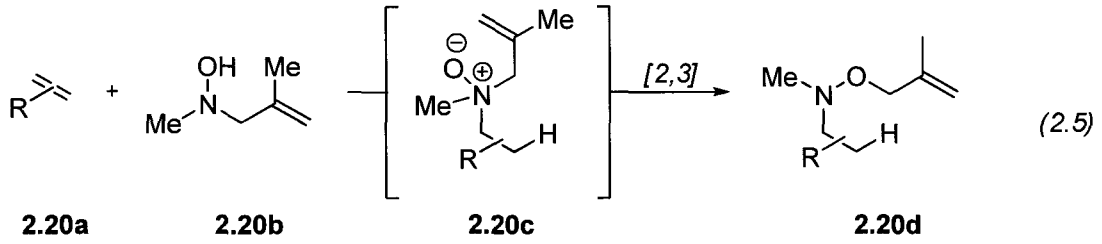
Since the nitrone appears to be too stable, we postulated that if we were to prevent its formation, a modified sequence would allow for aromatization. To do this, we wanted to substitute the hydroxylamine starting material as only primary hydroxylamines (R=H) can lead to the nitrone intermediate. Once cyclized, other reaction intermediates would be formed in order to help the induction of aromatization.



2.19 **2.19a** **2.5** *(2.4)*

2.4.1. Hydroamination/Meisenheimer Rearrangement

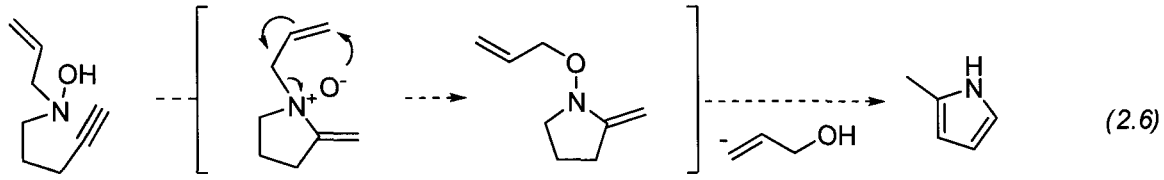
Towards the end, we looked at a recent hydroamination/Meisenheimer rearrangement developed in the Beauchemin lab.[61] This tandem sequence utilizes allylhydroxylamines and allows the formation of neutral hydroamination product from the *N*-Oxide intermediate without the need for a proton shuttle. This work illustrated much efficiency with alkenes and encouraging intermolecular reactivity had been observed with alkynes.



2.20a **2.20b** **2.20c** **2.20d** *(2.5)*

We decided to exploit this reactivity and attempted to apply it to the intramolecular hydroamination of alkynes. Our hypothesis for this reaction was to have a hydroamination step followed by the Meisenheimer rearrangement to yield an intermediate bearing an N-O-allyl bond. Further, we then postulated the final desired unsaturation (required for aromatization) can be gained through elimination of allyl alcohol

(61) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874.

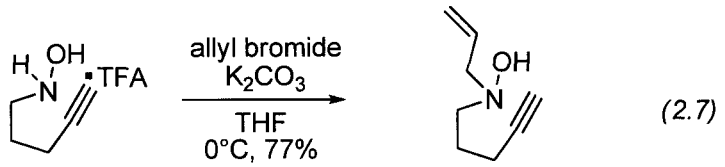


(2.6)

2.21 **2.22** **2.23** **2.5**

2.4.2. Preparation of Starting Materials

This allylic functionality was introduced by the reaction of 4-pentyn-1-hydroxylamine trifluoroacetic acid with allyl bromide under basic conditions.

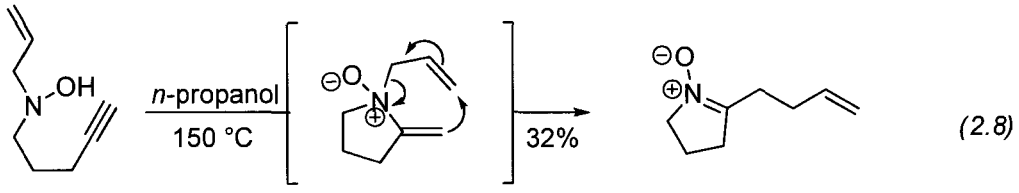


(2.7)

2.9 **2.21**

2.4.3. Results and Discussion

Once the starting material was built, we decided to heat the hydroxylamine and see if the desired hydroamination/Meisenheimer rearrangement/aromatization sequence would take place. Testing this hypothesis revealed that, again, the reaction did not proceed to form the desired aromatic adduct.

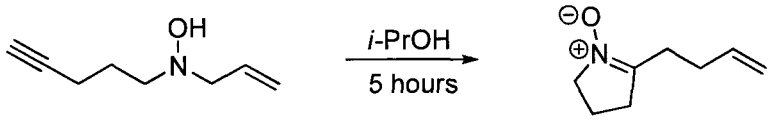


(2.8)

2.21 **2.22** **2.24**

Instead, we discovered a different type of rearrangement that occurred succeeding the hydroamination – a [3,3] rearrangement. Interestingly, the exo-olefin formed after the hydroamination allowed for an aza-[3,3] rearrangement. Cyclization of the hydroxylamine at 150°C in isopropanol (such that the concentration of hydroxylamine was 0.1M) gave a 32% NMR yield of product **2.24**.

Table 2.4. Optimization of Hydroamination/[3,3] rearrangement



2.21 **2.24**

Entry	Temperature (°C)	Concentration [M]	NMR Yield (%)[a]
1	150	0.1	32
2	150	0.05	36
3	125	0.05	34
4 [b]	120	0.03	44
5 [b]	100	0.025	50
6 [b]	80	0.025	45
7 [b]	100	0.01	50

[a] NMR yield determined using styrene as an internal standard. [b] In *n*-propanol.

After minor optimization, we discovered the hydroamination/[3,3] rearrangement occurs best at lower temperatures (Table 2.4, entry 5) and in highly dilute conditions. Further, we discovered that *n*-propanol has a beneficial effect on the cyclization as it allows increased yields at lower temperatures. Unfortunately, these results did not show any promise as further efforts to increase the yield of the reaction were unsuccessful (Table 2.4, entry 6-7).

2.5. Conclusion

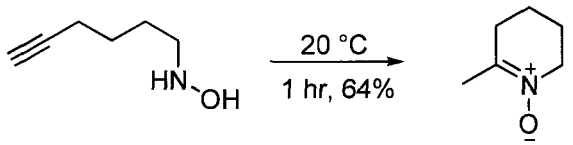
After all attempts at forming pyrroles shown above, it was concluded that the reaction thermodynamics were not favouring this cyclization, only leading to a known thermodynamic sink – the nitrone. Looking at the general trends for alkyne-hydroxylamine cyclizations, it is important to remember that formation of 5-membered rings with alkynes is not favoured and is in fact more difficult then forming 6-membered rings – likely the cause of the more modest yields of any of the nitrone species. This conclusion began our research on hydroamination to form 6-membered unsaturated heterocycles.

3

Formation of 6-Membered Aromatic Azacycles

3.1. Introduction

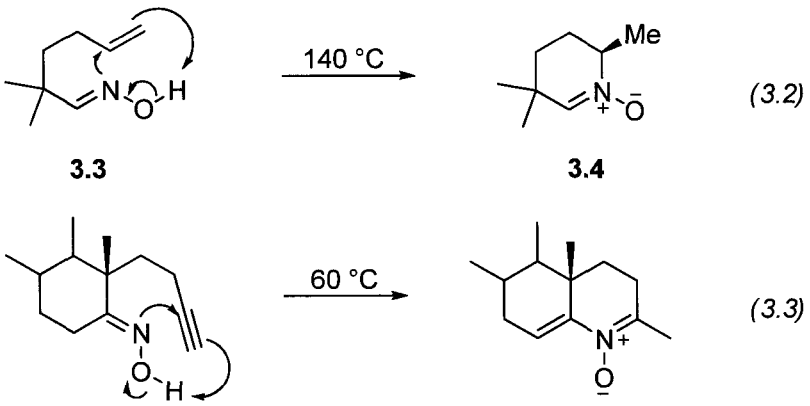
The work by Holmes *et al.* truly illustrated the ease of Cope-type hydroaminations when it comes to 6-membered ring cyclizations onto alkynes. In order to be able to access these favourable reaction thermodynamics and still have possibility to form an aromatic adduct – pyridines and pyrazines in this case – the cyclization must be engineered to occur on a substrate in a higher oxidation state. Literature for the formation of 6-membered rings through alkyne hydroamination has been shown to occur at room temperature subsequently forming the corresponding piperidine ring as a nitrone.[55] Previous cyclizations of this type, however, provide no possibility for aromatization due to a missing oxidation state adjustment.



3.1 **3.2** *(3.1)*

In order to access pyridines and pyrazines – π–deficient 6-membered rings – using a hydroamination route, we had to primarily build the correct scaffold in the correct oxidation state. To avoid issues associated with using enynes as precursors – such as substrate synthesis and possible alkene isomerization – we became interested in the

hydroamination reactivity of oximes reported by the Grigg and Pradhan groups.[62,63] They were able to successfully cyclize 6-membered rings through oxime hydroamination of alkenes and alkynes – referred to as an Aza-Protio Transfer (APT). In fact, Cope-type hydroaminations using oximes have been thoroughly studied with alkenes (eq. 3.2) and alkynes (eq. 3.3).[64]



3.3 **3.4** *(3.2)*

3.5 **3.6** *(3.3)*

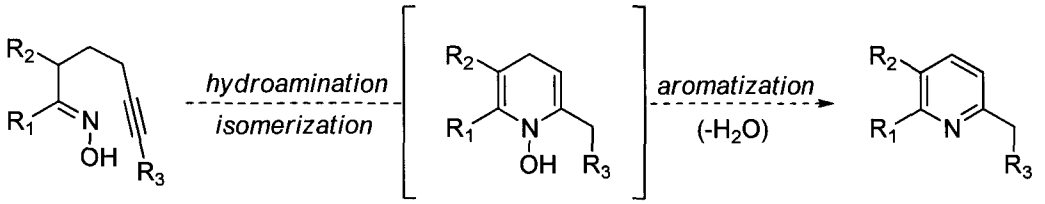
Through Grigg and Pradhan's experiments, it was shown that alkenes require much more energy then alkynes in order to cyclize with oximes,[65] following the same trends as hydroxylamines. It seemed quite intriguing that these workers did not stumble upon the formation of pyridine during hydroaminations of alkynes in subsequent investigations as it is clear that the presented nitrones are in the correct oxidation state for an aromatization event to occur. In fact, this could not be observed in the above

(62) a) Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991** *41*, 8297. (b) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929. (c) Grigg, R.; Myers, P.; Somasunderam, S.; Sridharan, V. *Tetrahedron* **1992**, *48*, 9135.
(63) a) Pradhan, S. K.; Akamanchi, K. G.; Divakaran, P. P.; Pradhan, P. M. *Heterocycles* **1989**, *28*, 813. (b) Pradhan, S. K.; Akamanchi, K. G.; Divakaranl, P. P. *Tetrahedron Lett.* **1982**, *24*, 5017.
(64) Davidson, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, 52, 11601 (and references therein).
(65) Grigg, R.; Perrior, T. R.; Sexton, G. J.; Surendrakumar, S.; Suzuki, T. *J. Chem. Soc. Chem. Commun.* **1993**, 372.

example (eq. 3.3), as the angular methyl group prevents aromatization. Nevertheless, this cyclization reactivity validates an important part of the reactivity proposed below and suggests that related approaches could be used for the synthesis of pyridines and associated heterocycles.

3.2. Goals

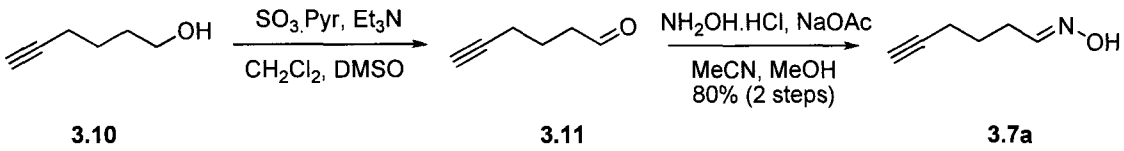
In light of the discussed Aza-Protio Transfer reactivity of oximes and the known selectivity for formation of 6-membered rings using hydroamination of alkynes, we decided to endeavour the formation of pyridines using these tools. Our postulated approach was an initial hydroamination reaction of the oxime moiety with the tethered alkyne leading to a cyclization which - after an isomerization event - would lead to a dihydropyridine intermediate. Under the correct conditions, we reasoned an aromatization sequence (via release of H_2O) could then lead to the desired unsaturated product. Indeed, dihydropyridine intermediates have been shown to aromatize under thermal conditions.[66]



3.7 **3.8** **3.9** *(3.4)*

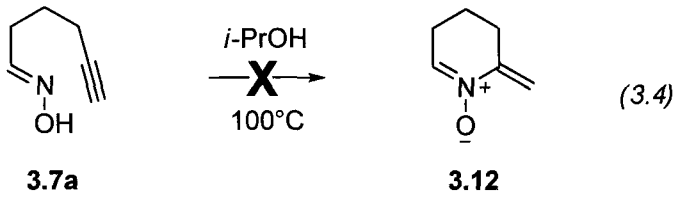
(66) a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry,* 4th ed.; Blackwell: Oxford, UK, **2000**. b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, Wiley-VCH: Weinheim, **2003**. c) Katrizky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed, Pergamon: Amsterdam, **2000**.

To test basic thermal reactivity, we decided to heat hex-5-ynal oxime in protic conditions to see if such a sequence can be observed. We prepared one substrate simply by Parikh-Doering oxidation of 5-hexyn-1-ol followed by standard oxime formation.

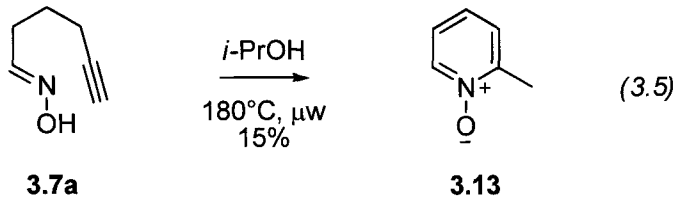


Scheme 3.1. *Sequence for formation of 5-hexynal oxime*

When heated at 100 °C, no reactivity was observed. This seemed unusual as all only starting material was observed through TLC and NMR analysis. Looking more closely at reported literature, we realized that these cyclizations were biased by a Thorpe-Ingold effect causing the oxime to be closer in space to the alkene – consequently facilitating substrate cyclization. With that in mind, we decided to significantly increase the temperature (180°C). When doing this, we observed a 15% conversion of the 2-picoline *N*-oxide adduct.



(3.4)

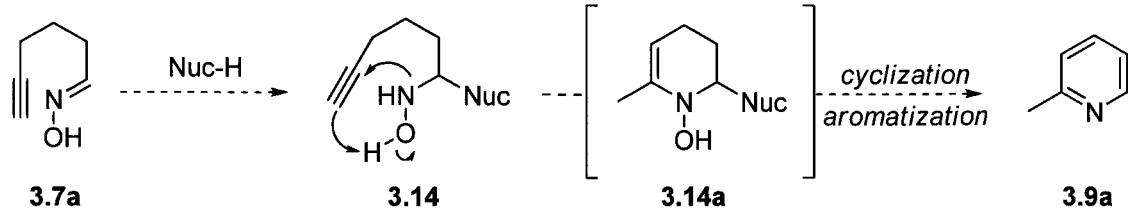


(3.5)

These results indicated that at low temperatures, the reagent could not undergo a hydroamination, but at high temperatures an auto-oxidation pathway is likely the cause of the oxidation of the desired product. It seemed as though a milder method able to exploit the available oxidation state of an oxime had to be found. At this point, due to the difficulty of the cyclization we were attempting, we reasoned that two solutions were possible. First, we wanted to explore the option of an *in situ* formation of a hydroxylamine intermediate since a more facile cyclization would be expected - based on Holmes' work. A second possibility would be to find a catalyst for the cyclization process.

3.3. Approaches Involving a Transient Nucleophile

When thinking about the oxime functionality, we considered that it could be electrophilic enough under appropriate conditions to undergo an attack from a weak nucleophile, yielding an α-substituted hydroxylamine. Since Holmes showed that 6-membered rings form efficiently at room temperature when hydroxylamines and alkynes are reacted together (eq. 3.1), we postulated that our newly formed hydroxylamine therefore facilitate the desired cyclization. Once cyclized, we further postulated that this weak nucleophilic group (CN for example) could act as a leaving group, accounting for the final desired unsaturation to aromatize to the desired pyridine product.

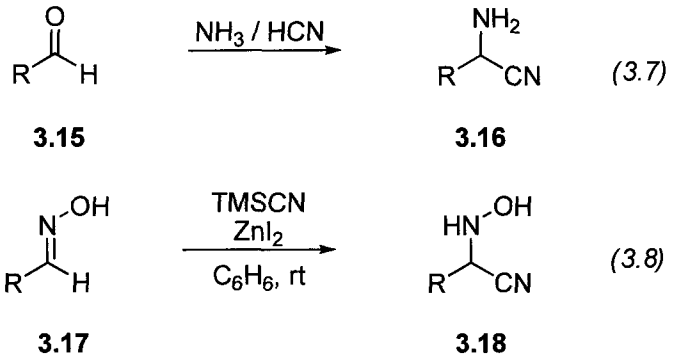


3.7a **3.14** **3.14a** **3.9a**

Scheme 3.2. *Use of a transient nucleophile to promote a cyclization/aromatization*

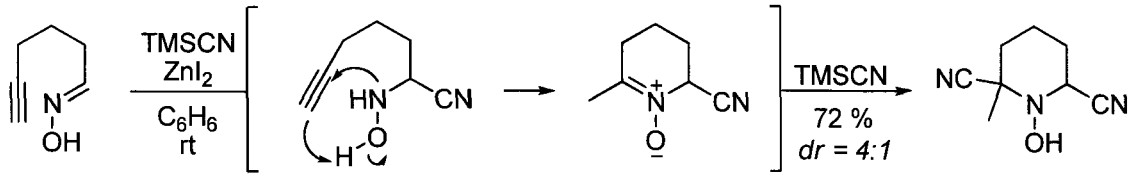
3.3.1. The Strecker Reaction

With that, it was intriguing to consider the Strecker reaction.[67] The Strecker reaction is a common method for preparation of α-aminonitriles from aldehydes and amines, which in turn can be useful for formation of amino acids.[68]



This reaction has been shown to be efficient to form α-hydroxylaminonitriles from oximes. Indeed, Ojima *et al.* demonstrated that with the use of ZnI_2 and TMSCN, the desired product can be formed at room temperature.[69] We decided to take this methodology and apply it to our six-membered alkyne system. Basing ourselves on Ojima's work, it seemed likely that one would form a cyclized nitrone bearing the newly added cyano group under the reaction conditions. However, we observed that as soon as the α-hydroxylaminonitrile compound was formed, not only did the expected cyclization event take place, the intermediate nitrone then used a second equivalent of TMSCN to form an α-hydroxymethylpiperidine-2,6-dicarbonitrile ring.

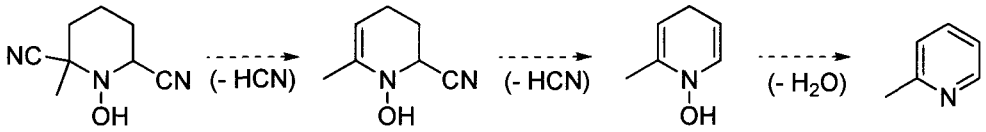
(67) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(68) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795.
(69) Ojima, I.; Inaba, S.; Nakatsugawa, K. *Chem. Lett.* **1975**, 331.



3.7a **3.19** **3.20** **3.21**

Scheme 3.3. *Formation of a bis-cyano piperidine ring*

This product provided us with enough information to affirm that a tandem Strecker/hydroamination sequence took place. What makes this sequence even more interesting is the fact that this newly formed bis-cyano piperidine ring is still in the correct oxidation state for aromatization by release of two molecules of hydrogen cyanide (HCN) one molecule of water (eq. 3.10).

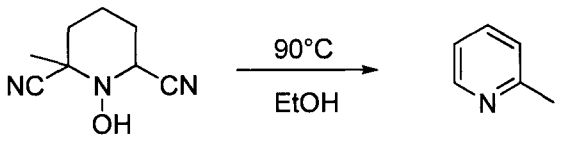


3.21 **3.22** **3.8a** **3.9a** *(3.10)*

3.3.2. Results for the Aromatization of the Intermediate

With an efficient approach to cyclize product **3.21**, we decided to explore thermal conditions to perform the aromatization. We decided to survey this in the presence of a base as 2 equivalents of HCN would be generated in the reaction.

Table 3.1. *Aromatization Attempts in the Presence of a Base*



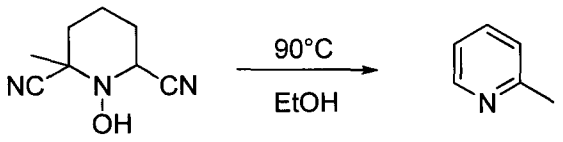
3.21 **3.9a**

Entry	Base (4.0 equiv.)	Reaction Time (h)	NMR Yield (%) [a]
1	DBU	24	20
2	Hünig's Base	24	0
3	K_2CO_3	24	20
4	Imidazole	24	0
5	Et_3N	24	0
6	$CsCO_3$	24	3
7	DBU [b]	12	15
8	K_2CO_3 [b]	5	3

[a] NMR yield determined using styrene as internal standard. [b] Reaction in microwave reactor.

As seen in the base scan, potassium carbonate and DBU provided the best conversions for the aromatization sequence. We then decided to examine the effects of varying solvents with both DBU and K_2CO_3.

Table 3.2. *Solvent Scan*



3.21 **3.9a**

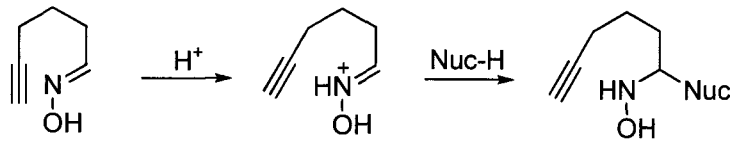
Entry	Solvent [0.1M]	Base (4.0 equiv.)	NMR Yield (%) [a]
1	EtOH	DBU	20
2	$CDCl_3$	DBU	10
3	*i*-PrOH	DBU	13
4	MeCN	DBU	0
5	MeOH	DBU	9
6	EtOH	K_2CO_3	20
7	CH_2Cl_2	K_2CO_3	0
8	Acetone	K_2CO_3	8
9	H_2O	K_2CO_3	0
10	MeCN	K_2CO_3	0

[a] NMR yield determined using styrene as internal standard.

After many trials, it seemed as though the threshold was hit at 20% NMR yield in ethanol and DBU (or K_2CO_3). These results led us to speculate that the adducts formed were too stable, proving to be a liability for the subsequent aromatization process. As such, optimization with weaker nucleophiles was explored in parallel.

3.3.3. Varying the Nucleophile

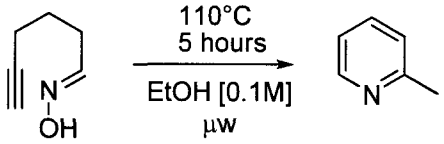
Once establishing the presented problems with the Strecker-based hydroamination sequence, we attempted to screen a variety of different nucleophiles that could react similarly. In other words, we attempted to create a system where an acid could protonate the oxime nitrogen and have a nucleophile attack the oxime carbon to generate a hydroxylamine intermediate.



3.7a **3.23** **3.14** *(3.11)*

With this strategy, the identity of the nucleophile can vary and possibly offer better outcomes then the cyanide nucleophile did in terms of leaving group potency. Once at the hydroxylamine stage, just like with the Strecker reaction, the free hydroxylamine could cyclize and form the desired adduct. Table 3.3 shows the conditions of the screening process in detail.

Table 3.3. *Acid and Nucleophile Scan*



3.7a **3.9a**

Entry	Acid (1.0 equiv.)	Nucleophile (2.5 equiv.)	NMR Yield (%) [a]
1	AcOH	-	0
2	TFA	Et_2NH	0
3	TFA	DMAP	0
4	TFA	$(i\text{-}Pr)_2NH$	0
5	-	$NH_2OH.HCl$	traces
6	-	$NH_2OH.HCl$ [b]	traces
7	TFA	-	5
8	-	NH_4Cl [c]	traces

[a] NMR yield determined using styrene as internal standard. [b] Reaction at 140°C.
[c] Reaction length: 22 hours

What can be observed is that all of the entries where an acid and a nucleophile were used resulted in no conversion. Entry 7, however, showed that when only

trifluoroacetic acid was added, a clean reaction seemed to be occurring where only starting material and product was observed by TLC and by NMR. These encouraging results were very tempting to explore.

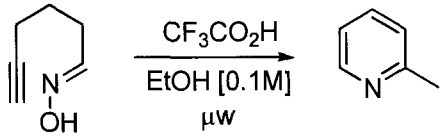
3.4. Development of an Acid-Catalyzed Sequence to Access Pyridines

The control experiment with trifluoroacetic acid clearly indicating that an acid-catalyzed process was possible, further optimization was required.

3.4.1. Optimization

With that said, we first opted to examine if higher temperatures, longer reaction times and more acid would lead to better results (Table 3.4). The primary conditions were set in ethanol as this is an easily accessible, practical solvent.

Table 3.4. *Effect of Time and Temperature on Cyclization*



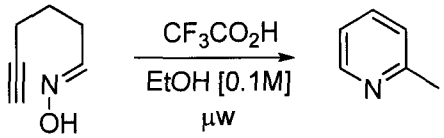
3.7a **3.9a**

Entry	Temperature (°C)	TFA equiv.	Time (hours)	NMR Yield (%) [a]
1	100	5.0	5	5
2	100	5.0	24	35
3	120	5.0	24	60
4	120	5.0	72 [b]	55
5	150	5.0	12	81
6	120	0	72 [b]	0

[a] NMR yield determined using styrene as internal standard. [b] Reaction in sealed tube.

First, we see that reaction time has a significant effect on the efficiency of the sequence (entries 1-2) as we invoke a five-fold increase in reaction time. In addition, reaction temperature allowed faster reactions which led to better yields. This is specifically displayed whereby a primary increase of 20 °C (entry 3) provided nearly a two-fold increase in yield and a further increase of 30 °C (entry 5) allowed a yield increase of 20% with reduced reaction time, nonetheless. Finally, comparison of entries 4 and 6 highlight that acid is essential for this cyclization-aromatization sequence.

Table 3.5. *Effect of Acid Equivalents on Cyclization*



3.7a **3.9a**

Entry	Temperature (°C)	TFA (equiv)	Time (hours)	NMR Yield (%) [a]
1	120	0	12	0
2	120	0.5	12	20
3	120	1.0	12	35
4	120	5.0	12	45
5	120	10	12	60

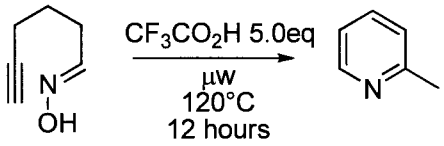
[a] NMR yield determined using styrene as internal standard.

Thus, the reaction also showed dependency on concentration of the acid medium. Results (Table 3.5) showed that the best conversions arose from higher amounts of CF_3COOH in solution. In fact, the experiments using 0.5 equivalents of acid gave only 20% conversion versus the same reaction with 5.0 equivalents where a 45% conversion was observed. With 10 equivalents of acid, the reaction was only slightly more efficient, likely due to the competing reversible protonation of the oxime functionality

(protonation of the oxime would prevent cyclization).[70] Due to practical reasons, only 5 equivalents were used for further optimization.

With that, we then decided to scan a series of solvents in order to verify if ethanol was in fact the ideal candidate for this hydroamination-aromatization sequence (Table 3.6). The main criterion in our choice of solvents was that of a low boiling point, due to the predicted volatility of the desired pyridine products. Table 3.6 shows alcoholic and oxygenated solvents are optimal for this reaction.

Table 3.6. *Solvent Scan for Hydroamination-Aromatization Sequence*



3.7a **3.9a**

Entry	Solvent [0.1M]	NMR Yield (%) [a]
1	EtOH	45
2	THF	53
3	C_6H_6	20
4	MeCN	3
5	$CHCl_3$	16
6	MeOH	30
7	***i*-PrOH**	**60**
8	dioxane	36
9	CF_3CH_2OH	43
10	*n*-PrOH	38

[a] NMR yield determined using styrene as internal standard.

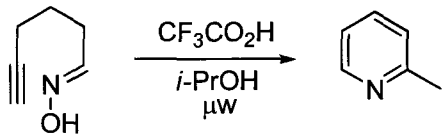
However, by TLC analysis, the alcoholic solvents gave the cleanest reactions, rendering them the most efficient. It also seemed as though the more hindered the

(70) An alternative explanation could be a more rapid Fisher esterification to provide CF_3CO_2Et, which would inherently lead to lower concentrations of TFA as the reaction proceeds.

solvent was, the better the observed reactivity. Methanol (Table 3.6, entry 6), the least hindered of the alcohols gave the lowest yield of 30 % followed by ethanol (Table 3.6, entry 1) and *n*-propanol (Table 3.6, entry 10) with 45 % and 38 %, respectively. Finally, the most hindered - isopropanol (Table 3.6, entry 7) - showed much promise with a 60 % NMR yield and further became the solvent of choice for the sequence. We thought to also try larger solvents (such as *n*-butanol) but the boiling point became an issue for further purification and the reactions were not carried through.

The final stages of optimization remaining were to simply establish which temperature would be optimal. By establishing that 5.0 equivalents of acid were sufficient for reactivity, we opted to increase reaction temperature.

Table 3.7. *Temperature and Acid Dependency*



3.7a **3.9a**

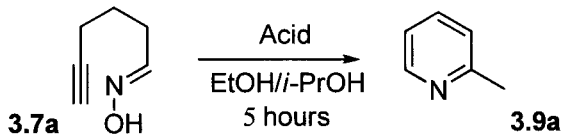
Entry	Temperature (°C)	TFA equiv.	Time (hours)	NMR Yield (%) [a]
1	120	5.0	12	45 [b]
2	120	10	12	60 [b]
3	150	5.0	12	81
4	160	5.0	5	80
5	160	10.0	5	85

[a] Conversion determined using styrene as internal standard. [b] Reaction in EtOH.

Temperature dependency was also clearly an important issue. At 120°C, the highest conversions were recorded at extremely long heating times, which are generally not

practical. A closer look (Table 3.7) showed that a slight increase in the temperature was the most important factor as an increase of 10 °C (Table 3.7, entries 3-4) allowed us to reduce the reaction times by 2.4 times and obtain essentially identical yields. Once increased to 160°C, yields in the 80-90 % range were recorded. Here, the stability and robustness of oximes is really demonstrated. Further, at higher temperatures (now evaluated for complete conversion) the increase in acid (Table 3.7, entries 4-5) only slightly increases (5%) the overall yield of the reaction, rendering an increased amount of acid necessary, but not most important past 5.0 equivalents. The latter result also suggested that trifluoroacetic acid may not be the ideal additive candidate for the cyclization. We therefore decided to look at other acids and selected optimization data is shown in Table 3.8.

Table 3.8. *Pyridine Formation Acid Scan*



3.7a **3.9a**

Entry	Acid	Equivalents	Temperature (°C)	NMR Yield (%) [a]
1	AcOH	5.0	120	0
2	CF_3CO_2H [b]	5.0	120	45
3	CCl_3CO_2H [b]	5.0	120	37
4	TsOH	5.0	120	traces
5	TsOH	1.25	160	12
6	TsOH	0.8	160	20
7	TsOH	0.1	160	82
8	TsOH	0.02	160	99
9	TsOH	0.01	160	95
10	TsOH	0.02	150	90
11	TfOH	0.1	160	45

[a] Conversion determined using styrene as internal standard. [b] Reaction time: 12 hours.

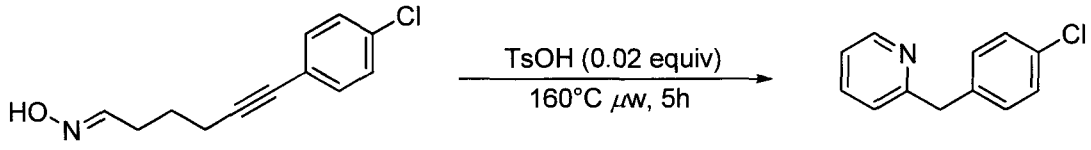
In order to verify the ideal acid additive, we explored different candidates that vary in strength according to their PKa values (Table 3.8). Using acetic acid (AcOH, pKa 4.76), no formation of product was observed. This led us to believe that acetic acid was too weak of an acid and that a stronger acid must be used in order to perform the reaction. Entry 3 shows the use of trichloroacetic acid, one that is very similar to trifluoroacetic acid in acid strength and allowed us to test if varying the acid counter ion would change the reaction outcome. The 37% conversion shows a very small difference with the original CF_3CO_2H conditions.

The next acid that was tested was *p*-toluenesulfonic acid (TsOH, PKa -7) due to its large availability and its ease of use. Here, a different trend is examined. At 5.0 equivalents of TsOH only traces of the desired product was observed. This acid likely halted the reaction due to irreversible protonation of the oxime, which – as mentioned earlier - would prevent cyclization. We then decided to examine what the effects of a near-stoichiometric amount of TsOH (Table 3.8, entry 5) would be. Interestingly, increased reactivity was recorded. When further lowering the acid loading to a sub-stoichiometric amount (Table 3.8, entry 6) the trend was consistent, giving an NMR yield of 20%. Next, catalytic amounts of 10 mol% were tested and a significant improvement was seen in the isolated yield of the desired product. The next step was to keep reducing the catalyst loading until a maximum yield was achieved. This was in fact seen at 2 mol% catalyst loading as we were pleased to observe an NMR yield of 99% with a 95% isolated yield. Surprisingly, when the loading was reduced to 1 mol %, the conversion dropped slightly to 95% (Table 3.8, entry 9). Even though this was not a significant decrease, we decided to remain at 0.02 equivalents.

In order to verify the efficiency of an even stronger acid while keeping a similar counter ion as TsOH, we decided to examine how trifluoromethanesulfonic acid (TfOH) would behave. At 0.1 equivalents of TfOH, we observed a conversion of 45 % almost half of what was observed with 0.1 equivalents of TsOH. Therefore, TsOH was selected as the acid of choice for subsequent experiments.

Next, we turned our attention to the development of alternative reaction conditions to allow efficient cyclization of challenging substrates – such as those where the alkyne is no longer terminal. Table 3.9 details a solvent scan performed on a typical benzylpyridine precursor and shows that isopropanol is not the ideal solvent for these more difficult cyclizations. However, the reaction in chlorobenzene (PhCl) gives a yield that is more than doubled from the original conditions.

Table 3.9. *Solvent Scan for Difficult Cyclizations*



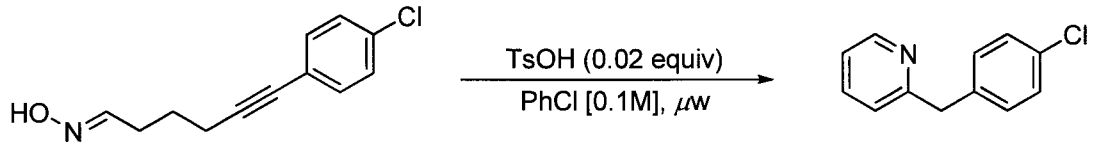
3.7h **3.9h**

Entry	Solvent [0.1M]	NMR Yield (%) [a]
1	*i*-PrOH	26
2	THF	39
3	$PhCF_3$	45
4	$CHCl_3$	48
5	**PhCl**	**54**
6	CF_3CH_2OH	5

[a] NMR yield determined using 1,4-dimethoxybenzene as internal standard.

By increasing the temperature slightly to 180°C and increasing the reaction time to 8 hours, we observed that we can get clean reactions (by TLC analysis) and very good isolated yields.

Table 3.10. *Temperature and Time Optimization for Difficult Cyclizations*



3.7h **3.9h**

Entry	Time (hours)	Temperature (°C)	NMR Yield (%) [a]
1	5	160	54
2	8	180	83
3	10	180	82

[a] NMR yield determined using 1,4-dimethoxybenzene as internal standard

We hypothesize that the new solvent choice works best at 180°C because at such high temperatures, isopropanol could behave as a nucleophile and attack the oxime moiety which could then lead to degradation. When using non-nucleophilic solvent such as chlorobenzene, this side-reaction is not possible, causing the increase in yield. Another hypothesis could be acid-catalyzed formation of a sulfonate (i.e. a fisher-type esterification).

3.4.2. Reaction Scope

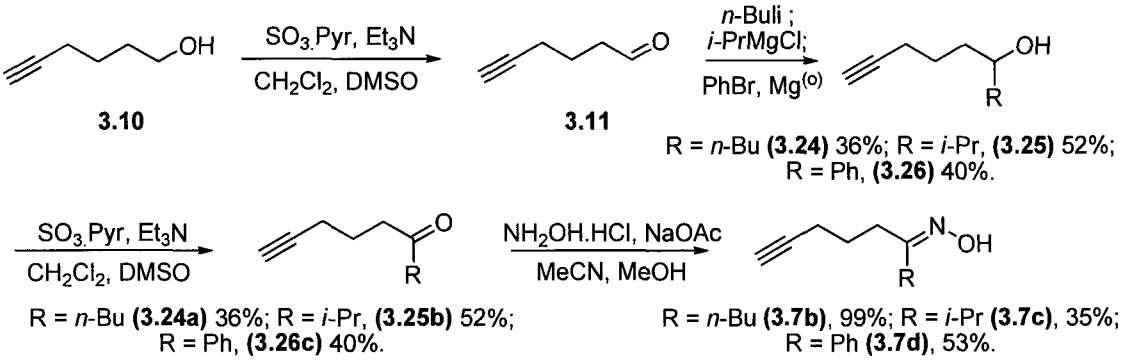
With that, the two sets of conditions for the oxime hydroamination to form pyridines were set. Conditions A (for less difficult cyclizations) used a 2 mol% catalyst loading

of TsOH at 160°C for 5 hours in the microwave. Conditions B (for more difficult cyclizations) used a 2 mol% catalyst loading of TsOH at 180°C for 8 hours in the microwave. To determine the reaction scope of the acid-catalyzed sequence, a variety of substrates were required. Their preparation is discussed in the following section.

3.4.2.1. Preparation of Pyridine Starting Materials

3.4.2.1.1 Ketoximes

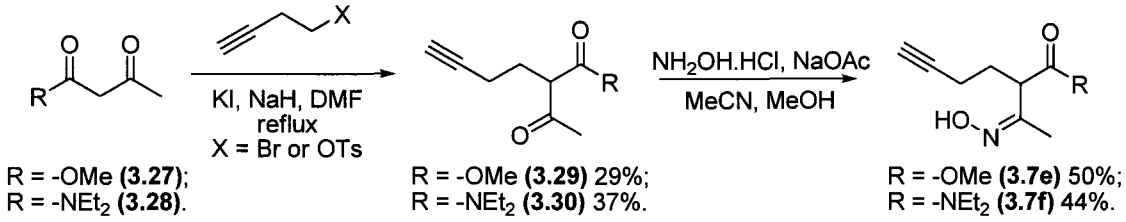
The three ketoximes we synthesized comprised of substituting the proton at the aldoxime position to *n*-butyl, isopropyl, and phenyl substituents. This was performed starting with hex-5-yn-1-ol whereby a Parikh-Doering oxidation. The corresponding crude aldehyde was subjected to a carbon-nucleophile; *n*-Buli for addition of the *n*-butyl group, isopropylmagnesium chloride for addition of the isopropyl group, and phenylmagnesium bromide for the addition of the phenyl group. The nucleophilic addition yields the corresponding alcohol which is then further oxidized and converted to yield the desired oxime under standard conditions.



Scheme 3.4. *Formation of ketoximes 3.7b, 3.7c and 3.7d*

3.4.2.1.2. Oximes with Ester and Amide Functionalities

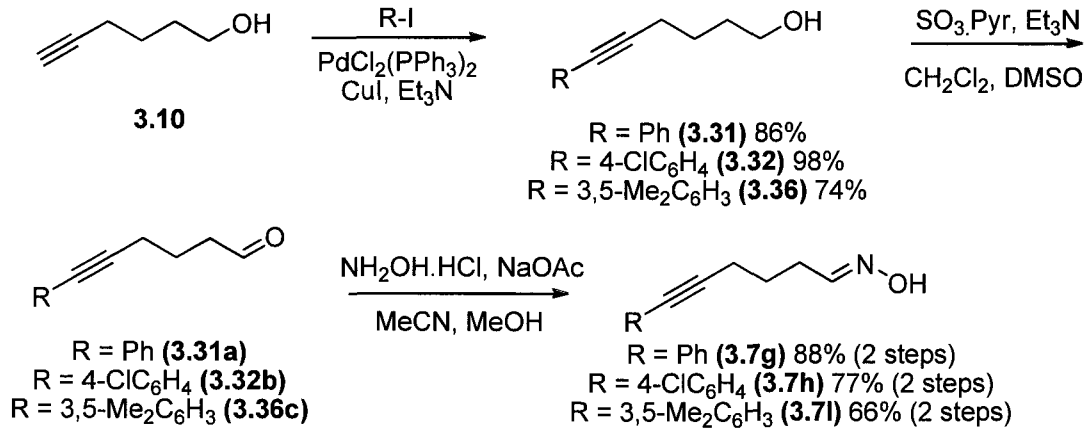
These precursors were synthesized by alkylation of methyl 3-oxobutanoate and *N,N*-diethyl-3-oxobutanamide, respectively – followed by standard oxime formation.



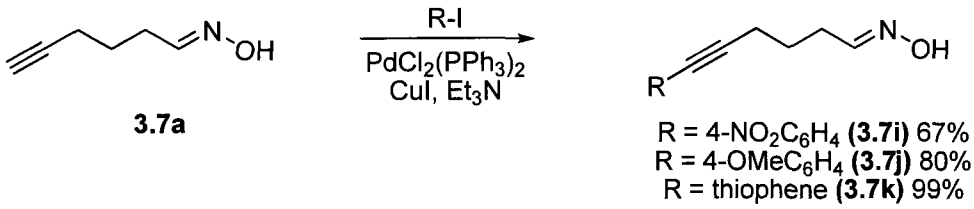
Scheme 3.5. *Formation of compounds 3.7e and 3.7f*

3.4.2.1.3. Benzylpyridine Precursors

We were then interested in alkyne substitution, in particular to form benzylpyridines. We employed a general Sonogashira cross coupling reaction onto 5-hexyn-1-ol which gave the phenyl-coupled alcohols in excellent yields.[71] Next, a standard Parikh-Doering oxidation led to the corresponding aldehydes, which were then subjected to standard amination methods to furnish the oximes.



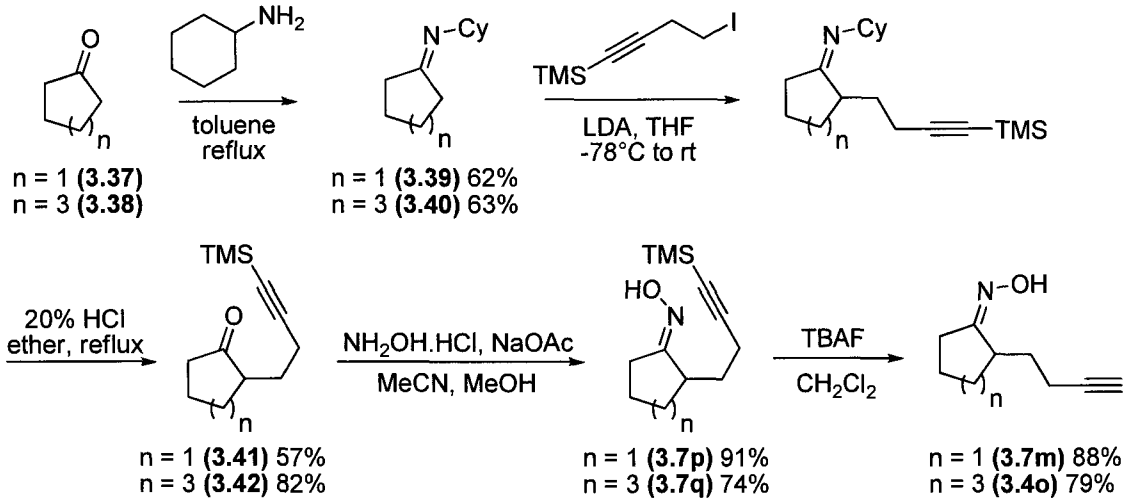
(71) Lin, G.; Yang, C.; Liu, R. *J. Org. Chem.* **2007**, *72*, 6753.



Scheme 3.6. *Formation of the starting materials of 2-benzylpyridine precursors*

3.4.2.1.4. Bicyclic Pyridine Precursors

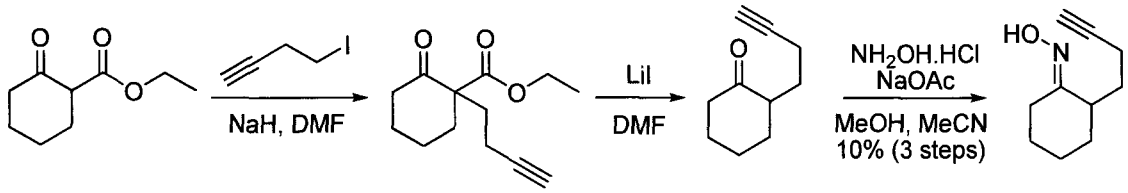
The 5- and 7-membered ring systems were synthesized identically whereby an initial cycloimine formation (using cyclohexylamine) lead to an adduct that could provide a stable enolate for alkylation.[72] Using LDA, the cycloimine was alkylated with (4-iodobut-1-ynyl)trimethylsilane and refluxed in presence of aqueous acid to provide the alkylated ketone.[73] At this stage, a standard amination furnished the desired TMS-substituted oxime. To access the terminal alkynes, a simple reaction with TBAF was performed.



Scheme 3.7. *Sequence for formation of 5- and 7-membered bicyclic systems*

(72) Tietze, L. F.; Wünsch, J. R. *Synthesis* **1990**, 985.
(73) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541.

The 6-membered ring equivalent was synthesized under slightly different conditions. Here, we attempted to use a substrate where the proton to be abstracted was slightly more acidic. Using ethyl 2-oxocyclohexanecarboxylate, we were able to alkylate to form compound **3.48**, which was then exposed to a Krapcho decarboxylation rendering the desired ketone.[74] The ketone was then aminated using standard conditions to yield the corresponding oxime.



3.47 **3.48** **3.49** **3.7n**

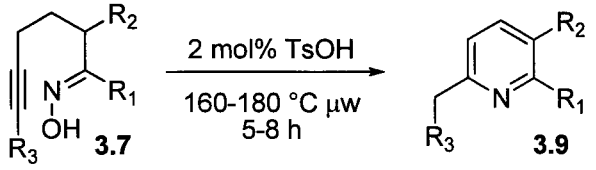
Scheme 3.8. *Sequence for formation of the 6-membered precursor*

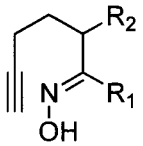
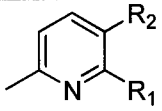
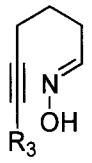
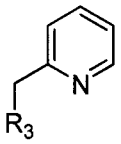
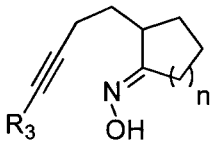
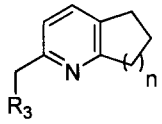
3.4.3. Results and Discussion

Table 3.11 shows the substrate scope for pyridine synthesis using the two sets of reaction conditions.

(74) Beaufils, F.; Dénès, F.; Becattini, B.; Renaud, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 5273.

Table 3.11. *Pyridine Substrate Scope*



Entry	Substrate	Conditions [a]	Product	NMR Yield (%) [b]	Isolated yield (%)
					
1	R_1, R_2 = H (**3.7a**)	A	**3.9a**	99	95
2	R_1 = *n*-Bu, R_2 = H (**3.7b**)	A	**3.9b**	90	94
3	R_1 = *i*-Pr, R_2 = H (**3.7c**)	A	**3.9c**	65	55
4	R_1 = Ph, R_2 = H (**3.7d**)	A	**3.9d**	60	50
5	"	B	**3.9d**	>99	99
6	R_1=Me, R_2=CO_2Me (**3.7e**)	A	**3.9e**	78	72
7	R_1=Me, R_2=$CONEt_2$ (**3.7f**)	A	**3.9f**	71	68
					
8	R_3 = Ph (**3.7g**)	A[c]	**3.9g**	-	45
9	"	B	**3.9g**	-	81
10	R_3 = 4-ClC_6H_4 (**3.7h**)	B	**3.9h**	-	83
11	R_3 = 4-$NO_2C_6H_4$ (**3.7i**)	B	**3.9i**	-	91
12	R_3 = 4-$OMeC_6H_4$ (**3.7j**)	B	**3.9j**	24	-
13[75]	R_3 =  (**3.7k**)	B	**3.9k**	15	-
14	R_3 = 3,5-$Me_2C_6H_3$ (**3.7l**)	B	**3.9l**	-	61
					
15	n = 1, R_3 = H (**3.7m**)	A	**3.9m**	75	77
16	n = 2, R_3 = H (**3.7n**)	A	**3.9n**	91	90
17	n = 3, R_3 = H (**3.7o**)	A	**3.9o**	78	74
18	n = 1, R_3 = $SiMe_3$ (**3.7p**)	A	R_3 =H (**3.9m**)	94	92
19	n = 3, R_3 = $SiMe_3$ (**3.7q**)	A	R_3 =H (**3.9o**)	68	63

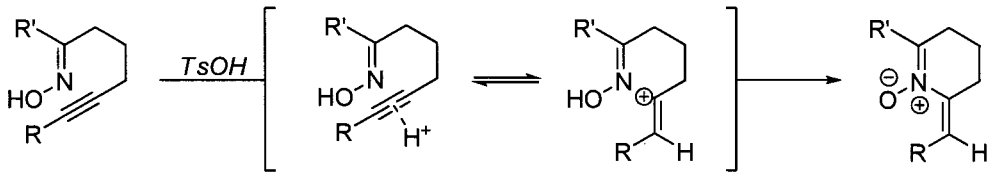
[a] Conditions: A: in *i*-PrOH (0.1M) at 160 °C for 5 h (microwave reactor, μw); B: in PhCl (0.1M) at 180 °C for 8 h (μw). [b] NMR yield determined using styrene as internal standard. [c] at 180 °C.

(75) The author would like to thank undergraduate student *E. Bilodeau* for synthesizing this compound.

At this stage, we decided to validate the methodology by varying the substitutions at different positions on the ring. As already discussed, entry 1 was the substrate (5-hexynal oxime) used for all previous optimization for formation of 2-picoline to give a 99% NMR conversion and 95% isolated yield. Next, we decided to test how different ketoximes will react under these conditions. As seen in Table 3.11, simple ketoximes generally react less efficiently then simple alodoximes, but nonetheless gave moderate yields (entries 2-5). Next, we wanted to explore the possibility of functionalizing the pyridine ring. In detail, we were able to form pyridine rings bearing an ester (entry 6) and amide (entry 7) functionality, both of which formed the trisubstituted end-product in good yields. We then wanted to explore the effect of bulky alkyne substitution, notably phenyl rings which would provide access to benzylpyridine end-products. We quickly discovered that these substrates containing electron-donating groups (entries 12-13) thus creating a strong activating effect on the phenyl ring lead only to degradation (explaining the poor NMR yields reported). Conversely, substrates containing electron-withdrawing groups (entry 11) - where the phenyl ring is strongly deactivated - increase the reaction efficiency. In cases where the ring is not significantly activated or deactivated (entries 8-10 and 14), good yields are reported. Finally, we wanted to be able to access pyridine rings in bicyclic systems. As hoped, we were able to form 5 to 7-membered bicyclic structures with good yields for terminal alkynes (entries 15-17) as well as substrates where the precursors bear a terminal silyl group (entries 18-19).

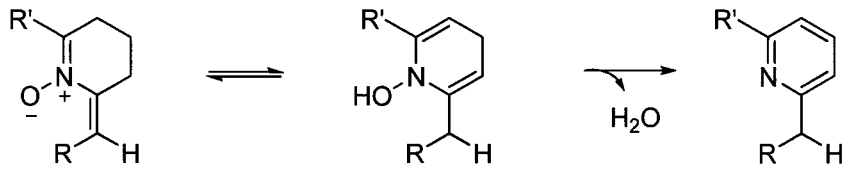
Since our hydroamination is acid-catalyzed, we hypothesize that this cyclization goes through a Ritter-type pathway which involves either an initial protonation of the alkyne

(to form **3.50b**) or direct cyclization on the π-complex (**3.50a**). At this stage the alkyne could either remain coordinated to the proton in a dative fashion or create an olefinic tertiary carbocation which is then subsequently trapped with the tethered oxime.



3.7 **3.50a** **3.50b** **3.51** *(3.12)*

Equation 3.12 shows precisely why both the alkyne and oxime moieties were specifically chosen. As we have discussed earlier, in order for the nitrone intermediate to aromatize to the desired unsaturated heterocycle, it must be at the correct oxidation level. Observing the nitrone, we can see that post-cyclization there are 2 unsaturations built-in to the ring that can be utilized to form the product as well as the weak N-O bond that can be broken to release H_2O and provide the final unsaturation.



3.51 **3.52** **3.7** *(3.13)*

When we decided to examine the efficiency of ketoxime cyclizations, we discovered a decrease in reactivity for the more hindered systems (entries 3-5). Brought forth by the rigidity of the carbon-nitrogen double bond, oximes naturally exist in two

geometrically isomeric forms; the *E* or *anti* isomer and the *Z* or *syn* isomer.[76] In solution, they can quickly isomerize until the proper thermodynamic equilibrium is met.

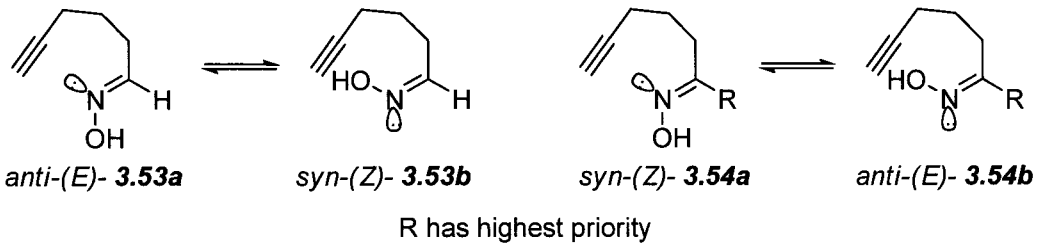


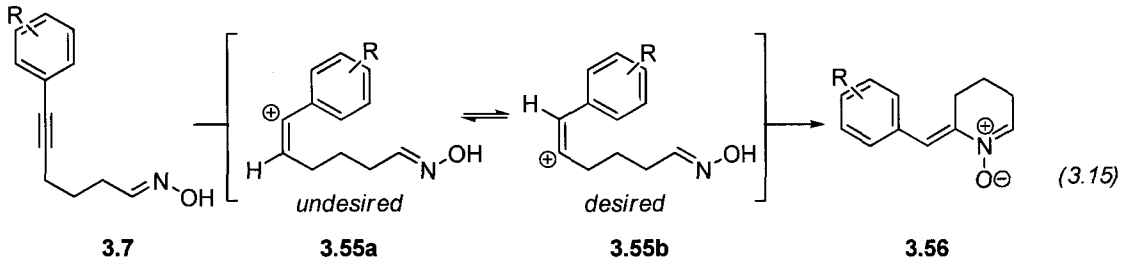
Figure 3.1. Aldo*xime and ketoxime isomerization*

In fact, their isomerization is usually halted once a thermodynamic equilibrium between the two isomers is established, at which point the more favourable isomer will be the major component of the mixture. Looking at figure 3.1, we can see that in order to get the correct reactivity, the nitrogen lone pair has to be aligned facing the alkyne π bonds. Thus, only one of the two oxime isomers allows for this correct orientation and for reactivity to be observed. Interestingly, it has been observed that the isomerization of oximes can be induced by acid (H+ ions),[77] base (OH- ions), thermolysis, irradiation, and a solvent - which may in fact be a key contributor in allowing the oximes to assume the correct geometry in our cyclizations.[78] Further, we hypothesized that aldoximes would give better results then ketoximes due to the intrinsic hindrance that extra substitution would cause. This added hindrance would influence the

(76) Rappoport, Z.; Liebman, J. F. *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids, Part 1* **2009**, John Wiley & Sons Inc, New York, 392.
(77) Nsikabaka, S.; Harb, W.; Ruiz-Lopez, M. F. *J. Mol. Struct.* **2006**, *764*, 161.
(78) Kwon, J.-W.; Armburst, K. L. *J. Pharm. Biomed. Anal.* **2005**, *37*, 643.

ketoxime to prefer the *anti* orientation (with respect to the R group) whereby reactivity is slowed down. This rationale is consistent with the reactivity trends observed.

Another aspect of the reaction scope to discuss is the reactivity to access benzyl pyridines. As expected, conditions B were necessary, likely due to the increased alkyne stability and to the propensity of the aryl substituent to favour an unproductive pathway.



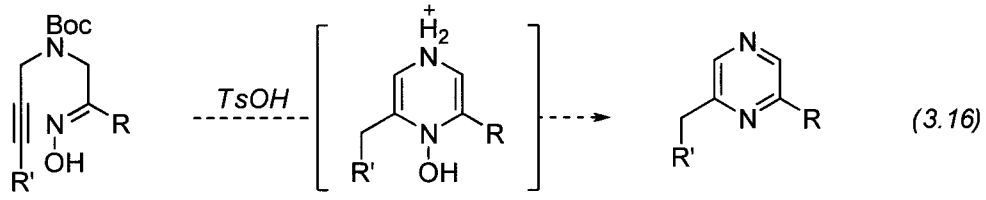
3.7 **3.55a** **3.55b** **3.56** *(3.15)*

When attempted using conditions A, entry 8 resulted in a modest yield of 45%. Upon resubmission to conditions B, the yield significantly increased further justifying the need for a second set of conditions. With that, we were able to conclude that substituents that are weak phenyl ring-activators or deactivators work well under conditions B.

3.5. A Similar Approach to Pyrazines

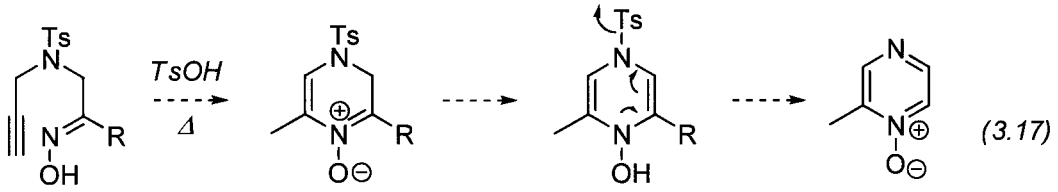
At this stage, we realized our substrate scope for pyridines was quite developed and showed that the method is applicable for many different substitution patterns. We wanted to see if the same conditions could be used in order to allow access to

pyrazines. We hypothesized that by simply changing carbon 3 in our oxime precursors to a nitrogen atom, the cyclization could proceed.



3.57 **3.57a** **3.58** *(3.16)*

The first difference that can be noticed with this cyclization is that we now have a more basic nitrogen atom in our precursors – likely complicating substrate synthesis as secondary amines are difficult to handle when not protected with an electron-withdrawing group. Consequently, we decided to introduce a *tert*-butyl carbamate (Boc) group for two main reasons. Firstly, as mentioned, the use of this electron-withdrawing group will allow a more simplistic approach to access the cyclization precursors. Second, we hypothesize that the Boc protecting group will likely cleave immediately under our reaction conditions prior to cyclization. Other viable nitrogen protecting groups (such as *p*-toluenesulfonyl), would not offer such possibilities.



3.59 **3.61** **3.62** **3.63** *(3.17)*

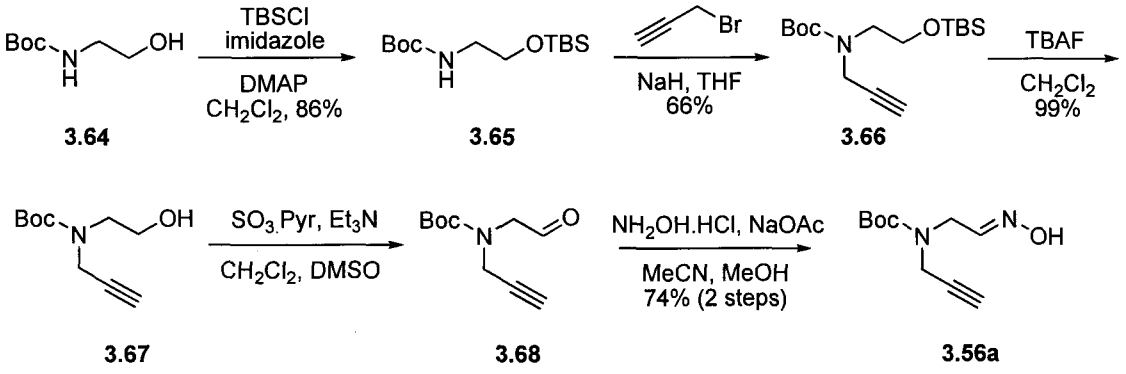
The use of a *p*-toluenesulfonyl group would afford us with an extra undesired oxidation state adjustment which would lead to complications during removal of water for aromatization. Consequently, the extra unsaturation no longer allows the formation of the pyrazine ring – instead will cause the formation of a pyrazine *N*-oxide product.

3.5.1. Reaction scope

To explore if this hydroamination-based sequence could be extended to pyrazine derivatives, we embarked on the synthesis of various precursors and explored their reactivity to form pyrazines. In the attempt at maintaining broadly applicable reaction conditions, we decided to try and use the same conditions for the pyrazines as for the pyridine cyclizations.

3.5.1.1. Preparation of pyrazine starting materials

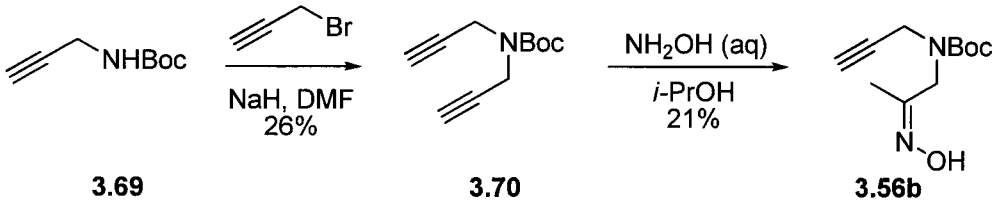
With that, we synthesized our first oxime precursor in hopes of forming the simplest pyrazine our method could allow; 2-methylpyrazine. This first substrate (entry 1, table 3.12) was prepared according to the sequence outlined in Scheme 3.9.



Scheme 3.9. *Synthetic sequence for preparation of precursor 3.56a*

In detail, starting with the boc-protected aminoalcohol, a standard TBS protection lead to the silyl-protected intermediate. Intermediate **3.65** was then alkylated under basic conditions using propargyl bromide affording the corresponding propargyl amine. The silyl group was then removed using TBAF to uncover the resulting alcohol in near quantitative yields.[79] The alcohol then underwent the standard Parikh-Doering oxidation, followed by an amination to render the desired oxime starting material.

Next, to synthesize a ketoxime precursor we alkylated boc-protected propargylamine using propargyl bromide to furnish the *tert*-butyl diprop-2-ynylcarbamate.[80] The latter was then an ideal candidate to test an intermolecular hydroamination in order to provide access to the desired oxime.[81] The reaction of compound **3.70** with aqueous hydroxylamine gave a modest yield of 21%, but nonetheless provided the desired oxime precursor, **3.56b**.

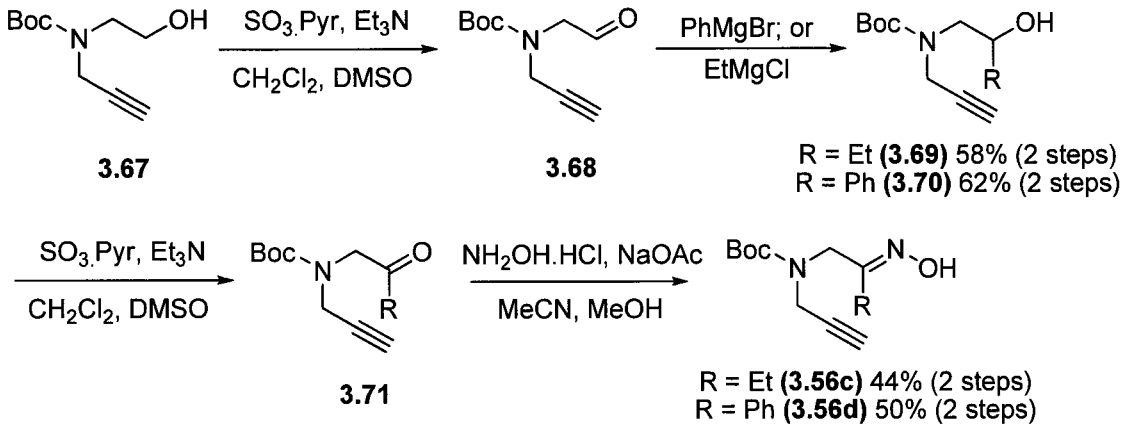


Scheme 3.10. *Preparation of precursor 3.56b*

To gain access to other ketoximes, we decided to expose aldehyde **3.68** to a Grignard addition of phenylmagnesium bromide and ethylmagnesium chloride, respectively.

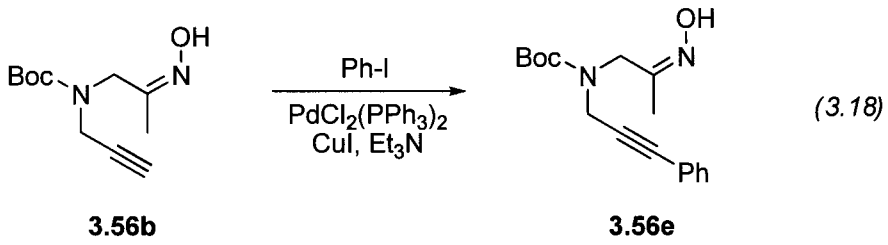
(79) Molander, G. A.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622.
(80) Boger, D. L.; Lee, J. K.; Goldberg, J.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 1467.
(81) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

This provided the corresponding alcohols which were then oxidized and aminated under standard conditions.



Scheme 3.11. *Preparing pyrazine precursors 3.56c and 3.56d*

Lastly, we decided to synthesize a compound whereby the alkyne would not be terminal. The synthesis of *tert*-butyl 2-(hydroxyimino)propyl(3-phenylprop-2-ynyl)carbamate proceeded as a standard Sonagashira cross coupling reaction whereby oxime **3.56b** was reacted with iodobenzene to provide the corresponding oxime, **3.56e.**

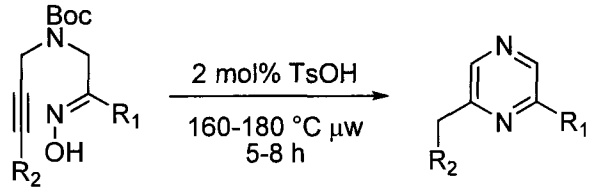


(3.18)

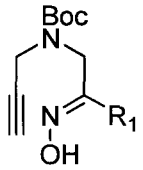
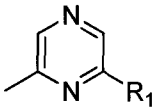
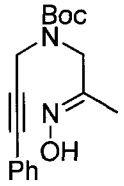
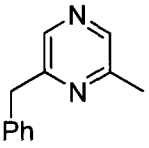
3.5.2. Results and Discussion

Table 3.12 shows the substrate scope for pyrazine synthesis using the two sets of reaction conditions, identical to that developed for the pyridine series.

Table 3.12. *Pyrazine Substrate Scope*



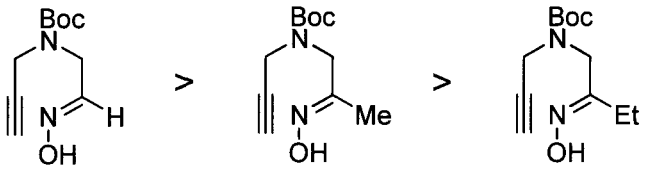
3.56 **3.58**

Entry	Substrate	Conditions [a]	Product	NMR Yield (%) [b]	Isolated yield (%)
					
1	R_1 = H (**3.56a**)	A	**3.58a**	67	-
2	R_1 = Me (**3.56b**)	A	**3.58b**	80	75
3	R_1 = Et (**3.56c**)	A	**3.58c**	89	81
4	R_1 = Ph (**3.56d**)	A	**3.58d**	35	-
5	"	B	**3.58d**	50	45
6	 **(3.56e)**	B	 **(3.58e)**	55	51

[a] Conditions: A: in *i*-PrOH (0.1M) at 160 °C for 5 h (microwave reactor, μw); B: in PhCl (0.1M) at 180 °C for 8 h (μw). [b] NMR yield determined using styrene as internal standard.

Unlike with the formation of 2-methylpyridine, (Table 3.11, entry 1) the reaction did not give a quantitative NMR yield. Instead we only observed a 67% conversion. Surprisingly, when adding a methyl group at the oxime carbon (rendering a methylketoxime) and submitting this to our reaction conditions, we recorded an increase in the NMR yield to 80%. Further, when increasing the carbon count by

replacing the methyl group with an ethyl group, we saw a additional increase of the NMR yield to 89%. This trend (Figure 3.2) suggests that the pyrazine precursors are much more susceptible to degradation and, generally, the oximes are more sensitive in this system. Recall that earlier we discussed the possibility of an oxime having sufficient electrophilicity to be susceptible to attack by a nucleophile. Comparing the pyrazine oxime precursors to those of pyridines, we can see that the added electron-withdrawing group is possibly further increasing the electrophilicity of the oxime, subsequently causing a general increase in sensitivity. With that said, it seemed understandable that the larger the substitution at the ketoxime position (such as the ethyl substitution), the more masked and protected that oxime will be; making it less likely to be sensitive and decompose.



3.56a **3.56b** **3.56c**

Figure 3.2. *Observed sensitivity trend with pyrazine precursors*

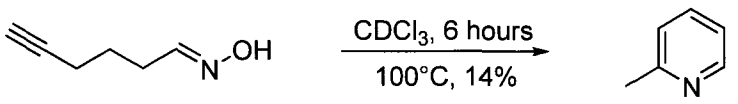
To take this one step further, we decided it was important to verify what the effects of adding a phenyl group at the ketoxime position would have on the yield of the reaction. When running the reaction with the standard conditions, we saw a large decrease in the NMR yield of the reaction to 35%. This information was valid and matched well with our pyridine results as adding the phenyl ring at this position should favour the *E* oxime isomer, while the *Z* isomer is required for cyclization. When this was observed, we decided to try test conditions B and we saw a slight increase in the NMR yield to

45%. The increase from one set of conditions to the other was not as significant as with pyridines, but it was nonetheless an improvement and helped us understand and illustrate the difficulty and sensitivity of these cyclizations.

Knowing this information, when attempting to cyclize entry 6, we decided to immediately use conditions B as it was obvious that this cyclization was more demanding – as discussed earlier, due to the stability of the phenyl-substituted alkyne. This cyclization proceeded well and gave the expected product in a modest yield of 51%.

3.6. Mechanistic insight

To gain understanding of these reactions, we wanted to know which step of our cyclization-aromatization sequence was the slowest, or rate limiting. We reasoned there could be two possibilities here; the first is the actual hydroamination (the cyclization) which can be caused by the intrinsic increased difficulty that the oxime brings forth, as proposed by Grigg.[82] The second is the aromatization step, which is seen to require slightly elevated temperatures for the dihydropyridine intermediate to undergo aromatization. In order to help answer this question, we decided to run a reaction at a lower temperature and see if any intermediate could be observed.



3.7a **3.9a** *(3.19)*

(82) Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991** *41*, 8297.

We hypothesized that if at lower temperatures, we would only see the intermediate in the reaction, this would strongly indicate that the hydroamination step is very fast, but aromatizing the intermediate is slow. On the other hand, if we were to only see starting material and product, this indicates that the hydroamination step is rate limiting as there would be little or no observable intermediate. To test our hypothesis, we decided to heat 5-hexynal oxime in $CDCl_3$ (allowing us to monitor the reaction without solvent evaporation) at 100°C for 6 hours. Once completed, we examined the reaction by TLC and NMR (with internal standard) analysis. Qualitatively, the TLC showed a very clean reaction whereby starting material and some product were observed. Quantitatively, the NMR experiment showed that all of the mass balance could be accounted for with starting material and product. Accordingly, we did not observe any intermediates or degradation products in the NMR spectrum. This suggests that once formed, the intermediate quickly aromatizes to the desired products – providing evidence that the actual cyclization (hydroamination) is the slow step in the reaction.

4

Conclusions

4.1. General Conclusions and Future Directions

The aforementioned project allowed the investigation and discovery of a novel intramolecular hydroamination-isomerization-aromatization sequence which allows the efficient formation of pyridines and pyrazines from simple oxime precursors. Preliminary results of this study suggested that the method is limited to less hindered oxime starting materials, but was quickly rectified by establishment of a different set of reaction conditions. Further, we were able to synthesize 13 different pyridine structures showing compatibility with various substitutions and functionalities. In contrast, the methodology is limited by functionalities bearing high electron-donating capabilities that can conjugate with the alkyne. Finally, the development of this methodology is really the beginning of a chapter of the use of hydroamination to form π-deficient heterocycles whereby the use of more potent imines, metal catalysts and tandem sequences has the potential to lead to even more encouraging results.

4.2 Claims to Original Research

1. Developed the first Strecker/Hydroamination sequence for formation of functionalized piperidine ring systems.

2. Successfully established the first methodology that allows the generation of a variety of pyridine rings using two different sets of conditions.

3. Showed the broad applicability of this methodology as this was elaborated to the formation of pyrazine rings using the same set of conditions.

4. Conducted experiments to identify the rate limiting step of the cyclization-aromatization sequence.

4.2.1. Publication from This Work

Rizk, T.; Bilodeau, E.; Beauchemin, A. M. "Synthesis of Pyridines and Pyrazines Using an Intramolecular Hydroamination-Based Sequence." *Angew. Chem., Int. Ed.* **2009**, *48*, 8325. (Highlighted in Synfacts)

4.2.2. Oral Presentation

Rizk, T.; Beauchemin, A. M "*Synthèse de pyridines et pyrazines par une méthode d'hydroamination intramoléculaire*" Symposium Association francophone pour le savoir (ACFAS), Ottawa, ON, May 14, 2009.

4.2.3. Poster Presentations

Rizk, T.; Beauchemin, A. M. "*Synthesis of Unsaturated Heterocycles via Intramolecular Hydroamination*",

1. June 8, 2009, 31st Spring Organic Synthesis Symposium, University of Ottawa, Ontario, Canada.
2. November 8, 2008, Quebec Ontario Minisymposium in Biological and Organic Chemistry, University of Toronto, Ontario, Canada.
3. October 3, 2008, AstraZeneca R&D Chemistry Symposium, Montreal, Québec, Canada.
4. June 16, 2008, 30th Spring Organic Synthesis Symposium, University of Ottawa, Ontario, Canada.
5. May 15, 2008, Ottawa-Carleton Chemistry Institute, University of Ottawa, Ontario, Canada.

5

Experimental

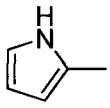
General Information. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm), unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on aluminum, cut to size. Visualization was accomplished with UV light followed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

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 MHz and 400 MHz spectrometers at ambient temperature, unless otherwise indicated. Spectral data was reported in ppm using solvent as the reference ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm or DMSO-d_6 at 2.50 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.43 for ^{13}C NMR). ^{1}H NMR data was reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet), integration and coupling constant(s) in Hz. Infrared (IR) spectra were obtained with neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carleton Mass Spectrometry Centre.

Materials. Unless otherwise noted, all commercial materials were purchased from commercial sources and used without further purification. Solvents used were freshly distilled prior to use unless otherwise noted: THF and ether over sodium; benzene, triethylamine, dichloromethane, isopropanol over calcium hydride; α,α,α-trifluorotoluene over phosphorous pentoxide; pyridine and acetonitrile over molecular sieves.

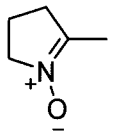
General Procedure for 5-Membered Ring Cyclization (Table 2.1, 2.2)

Typical Experimental Procedure: An oven-dried 10 mL sealed tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynyl hydroxylamine (1.00 equiv), the additive (3.00 equiv.) and solvent (see tables 2.1 and 2.2 for details) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a screw cap and heated (see tables 2.1 and 2.2 for details). The reaction solution was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene as an internal standard. The unpurified material was then again concentrated under reduced pressure and directly purified by silica gel chromatography to give the corresponding products.

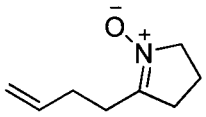


2-Methyl-1H-pyrrole (Table 2.1, entry 3-5; Table 2.3, entry 7, 2.5). Synthesized according to the general procedure for 5-membered ring cyclization using

hydroxylamine **2.9** (0.049 g, 0.230 mmol) and triethylamine (0.0961 mL, 0.690 mmol). The reaction mixture was concentrated and gave an NMR yield of 4-5 % using styrene as an internal standard. The spectral data is in agreement with literature.[83]



5-Methyl-3,4-dihydro-*2H*-pyrrole 1-oxide (Table 2.1, entry 1, 2.3). Synthesized according to the general procedure for 5-membered ring cyclization using hydroxylamine **2.9** (0.0707 g, 0.332 mmol) and triethylamine (0.139 mL, 0.995 mmol). The reaction mixture was concentrated and isolated using flash chromatography (10% MeOH in CH_2Cl_2). The title compound was obtained as a brown liquid (0.0167 g, 51 % yield). TLC R_f 0.33 in 10 % MeOH in CH_2Cl_2. The spectral data is in agreement with previously reported literature data.[84]

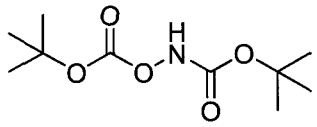


5-(But-3-enyl)-3,4-dihydro-2H-pyrrole 1-oxide (Table 2.4, entry 1-7, 2.24). An oven-dried 45 mL sealed tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynyl hydroxylamine 2.21 (0.0731 g, 0.525 mmol), *n*-propanol (21 mL) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a screw cap and heated for 5 hours at 100 °C. The reaction solution

(83) Fukui, H.; Shimokawa, S.; Shoma. J. *Mol. Phys.* **1970**, *18*, 217.
(84) Ali, S. A.; Wazeer, M. I. M. *Tetrahedron* **1993**, *49*, 4339.

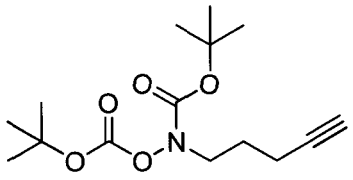
was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene as an internal standard. The reaction mixture was then concentrated and isolated using flash chromatography (10 % MeOH in CH_2Cl_2). The title compound was obtained as a brown liquid (0.0365 g, 50 % yield). TLC R_f 0.35 in 10 % MeOH in CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (tdd, J = 16.70, 10.22, 6.36 Hz, 1H), 5.07 (dd, J = 17.14, 1.53 Hz, 1H), 5.01 (dd, J = 10.24, 1.23 Hz, 1H), 4.05-3.94 (m, 2H), 2.71 (t, J = 7.44 Hz, 2H), 2.61 (t, J = 7.50 Hz, 2H), 2.30 (td, J = 13.72, 6.85 Hz, 2H), 2.08 (td, J = 15.20, 7.77 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.6 (C), 136.7 (CH), 115.8 (CH_2), 62.2 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 16.7 (CH_2); IR (film) 3303, 2925, 1610 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{13}NO$ $[M]^+$: 139.0997. Found 139.0988.

Preparation of Substrates (Table 2.1-2.2)

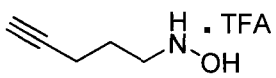


***N,O*-Di-*tert*-butoxycarbonyl-hydroxylamine (2.7).** To a cold solution of hydroxylamine hydrochloride (2.00 g, 28.8 mmol) in THF:water (1:1, 120 mL) containing triethylamine (8.00 mL, 57.6 mmol), di-*tert*-butyl-dicarbonate (12.6 g, 57.6 mmol) was added. The mixture was warmed to room temperature and stirred for 8 hours. The solvent was removed *in vacuo*, the residue extracted with methylene chloride (3 x 20 mL), and the combined extracts were dried over sodium sulfate. After filtration, the solvent was removed, and the residue was purified by flash column chromatography on silica gel using 2 % EtOAc/hexanes to yield 4.0 g (60%) of the

product as a white solid. The spectral data is in agreement with previously reported literature data.[85]

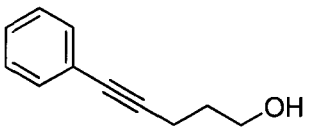


***N,O*-Di-*tert*-butoxycarbonyl-pent-4-yn-1-hydroxylamine (2.8).** Prepared by a modification of Parry's procedure.[86] To a cold solution of *N,O*-di-*tert*-butoxycarbonyl-hydroxylamine (2.78 g, 11.9 mmol), pent-4-yn-1-ol (1.10 mL, 11.9 mmol), and triphenylphosphine (9.37 g, 35.7 mmol) in anhydrous THF (119 mL), diisopropyl azodicarboxylate (6.93 mL, 35.7 mmol) was added. The mixture was then stirred at 0°C for 4 hours. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel with 10% EtOAc/hexanes to yield 3.15 g (88%) of the product as a clear colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67-3.61 (m, 2H), 2.23 (dt, J = 7.02, 2.46 Hz, 2H), 1.91 (t, J = 2.58 Hz, 1H), 1.76 (tt, J = 6.94, 6.91 Hz, 2H), 1.47 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.7 (C), 152.1 (C), 84.7 (s), 83.1 (CH), 82.2 (C), 68.8 (CH), 48.9 (CH_2), 28.0 (CH_3), 27.5 (CH_3), 26.0 (CH_2), 15.6 (CH_2); IR (film) 3295, 2981, 2936, 1784, 1720 cm^{-1}; HRMS (EI): Exact mass calcd for C_5H_9NO [M^+ - 2 Boc groups]: 99.0684. Found 99.0694.



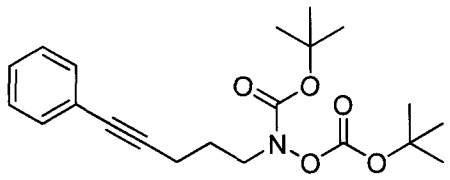
(85) Knight, D. W.; Leese. M. P. *Tetrahedron Lett.* **2001**, *42*, 2593.
(86) Tao, T.; Alemany, L. B.; Parry, R. J. *Org Lett.* **2003**, *5*, 1213.

Pent-4-yn-1-hydroxylamine-TFA salt (Table 2.1, entry 1-7; Table 2.2, entry 1-4; Table 2.3, entry 1, 2.9). A solution of *N,O*-di-*t*-butoxycarbonyl-pent-4-yn-1-hydroxylamine (2.65 g, 8.86 mmol) in trifluoroacetic acid (8.7 mL) and methylene chloride (35 mL) was stirred at room temperature for 2 hours. The solvent was removed, and the residue was dried *in vacuo* to yield 2.99 g (158 %) of the product as an orange-brown oil.^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (t, J = 7.10 Hz, 2H), 2.41 (dt, J = 6.80, 2.64 Hz, 2H), 2.11 (t, J = 2.65 Hz, 1H), 2.07-1.97 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 81.4 (C), 70.9 (CH), 50.5 (CH_2), 22.0 (CH_2), 15.7 (CH_2); IR (film) 3583, 3302, 2914, 2849; HRMS (EI): Exact mass calcd for C_5H_9NO $[M]^+$: 99.0684. Found 99.07064.

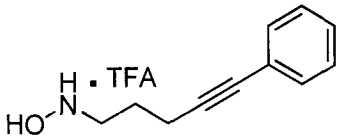


5-Phenyl-pent-4-yn-1-ol (2.12). $Pd(PPh_3)_4$ (0.0750 g, 0.130 mmol) and CuI (0.0250 g, 0.260 mmol) were added to the solution of iodobenzene (1.45 mL, 13.0 mmol) and pent-4-yn-1-ol (0.600 mL, 6.49 mmol) in triethylamine (9.10 mL, 64.9 mmol) and THF (3 mL) under argon. The reaction mixture was stirred at room temperature for 12 h. The mixture was then filtered and the filtrate was concentrated under reduced pressure. The product was purified by flash column chromatography using 30 % EtOAc in hexanes to yield the desired alcohol (0.749 g, 72% yield). The spectral data is in agreement with previously reported literature data.[87]

(87) Carson, J. R.; Almond, H. R.; Brannan, M. D.; Carmosin, R. J.; Flaim, S. F.; Gill, A.; Gleason, M. M.; Keely, S. L.; Ludovici, D. W.; Pitis, P. M.; Rebarchak, M. C.; Villani F. J *J. Med. Chem.* **1988**, *31*, 630.



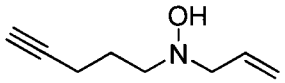
***N,O*-Di-*tert*-butoxycarbonyl-5-phenyl-pent-4-yn-1-hydroxylamine (2.13).** Prepared by a modification of Parry's procedure.[88] To a cold solution of *N,O*-di-*tert*-butoxycarbonyl-hydroxylamine (1.29 g, 8.07 mmol), 5-phenyl-pent-4-yn-1-ol (1.88 mL, 11.9 mmol), and triphenylphosphine (6.93 g, 24.2 mmol) in anhydrous THF (119 mL), diisopropyl azodicarboxylate (4.69 mL, 24.2 mmol) was added. The mixture was then stirred at 0°C for 4 hours. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel with 10 % EtOAc in hexanes to yield 2.05g (74%) of the product as a clear colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 3.75 (t, J = 7.08 Hz, 2H), 2.51 (t, J = 7.10 Hz, 2H), 1.91 (pent, J = 7.12 Hz, 2H), 1.52 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.8 (C), 152.3 (C), 131.6 (CH), 128.2 (CH), 127.6 (CH), 123.8 (C), 88.9 (C), 84.8 (C), 81.2 (C), 49.3 (CH_2), 28.1 (CH_3), 27.6 (CH_3), 26.4 (CH_2), 16.8 (CH_2); IR (film) 3587, 2986, 2933, 1786, 1716 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{13}NO$ [M^+ – 2 Boc groups]: 175.0997. Found 175.1510.



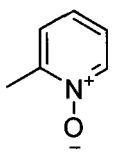
5-Phenyl-pent-4-yn-1-hydroxylamine-TFA salt (Table 2.3, entry 2-8, 2.14). A solution of *N,O*-di-*tert*-butoxycarbonyl-pent-4-yn-1-hydroxylamine (0.390 g, 1.04 mmol) in trifluoroacetic acid (0.865 mL) and methylene chloride (3.46 mL) was stirred

(88) Tao, T.; Alemany, L. B.; Parry, R. J. *Org Lett.* **2003**, *5*, 1213.

at room temperature for 2 hours. The solvent was removed, and the residue was dried *in vacuo* to yield 0.358 g (119%) of the product as a orange-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 3.52 (t, J = 6.99 Hz, 2H), 2.63 (t, J = 6.51 Hz, 2H), 2.11 (p, J = 6.76 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.6 (CH), 128.4 (CH), 128.4 (CH), 86.4 (C), 83.4 (C), 51.5 (CH_2), 22.1 (CH_2), 16.8 (CH_2); IR (film) 3587, 2921, 2857 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{13}NO$ $[M]^+$: 175.0997. Found 175.0994.



***N*-Allyl-pent-4-yn-1-hydroxylamine (Table 2.4, entry 1-7, 2.21).** To a solution of pent-4-yn-1-hydroxylamine trifluoroacetic acid (0.130 g, 0.608 mmol) and potassium carbonate (0.252 g, 3.04 mmol) in anhydrous THF (2.43 mL) was added allyl bromide (0.263 mL, 3.04 mmol). The mixture was stirred at room temperature for 4 hours. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel with 40% EtOAc in hexanes to yield 0.0655 g (77 %) of the product as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (tdd, J = 16.77, 10.24, 6.49 Hz, 1H), 5.24 (ddd, J = 17.92, 3.51, 1.80 Hz, 1H), 5.21-5.17 (m, 1H), 3.35 (td, J = 6.49, 1.23 Hz, 2H), 2.79-2.73 (m, 2H), 2.27 (dt, J = 7.06, 2.65 Hz, 2H), 1.95 (t, J = 2.66 Hz, 1H), 1.83 (p, J = 7.11 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 133.8 (CH_2), 118.6 (CH), 84.1 (C), 68.5 (CH), 63.9 (CH_2), 58.3 (CH_2), 26.1 (CH_2), 16.2 (CH_2); IR (film) 3598, 2965, 2892 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{13}NO$ $[M]^+$:139.09971. Found 139.0945.

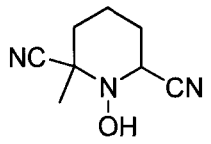


2-Methylpyridine 1-oxide (3.13). An oven-dried 2-5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The oxime **3.7a** (0.0500 g, 0.450 mmol, 1.00 equiv) and isopropanol (such that the concentration of the alkynyl oxime was 0.1 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated at 180°C for 5 hours. The reaction mixture was concentrated and gave an NMR yield of 15% using styrene as an internal standard. The spectral data is in agreement with literature.[89]

Procedure for Aromatization Optimization (Tables 3.1-3.2)

Typical experimental procedure: An oven-dried 10 mL sealed tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. 1-Hydroxy-2-methylpiperidine-2,6-dicarbonitrile **3.21** (0.0500 g, 0.211 mmol, 1.00 equiv), the base and the solvent (4.22 mL, see tables for more details) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a screw cap and heated for 24 hours at 90 °C. The reaction solution was cooled to ambient temperature, acidified using trifluoroacetic acid (1.0 equiv), concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard.

(89) Dyumaev, K. M.; Vinogradova, N. P.; Lokhov, R. E.; Elinson, G. S. *Chem. Het. Comp.* **2004**, *9*, 888.



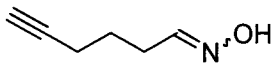
1-Hydroxy-2-methylpiperidine-2,6-dicarbonitrile (Table 3.1, entry 1-8; Table 3.2, entry 1-10, 3.21). Prepared by a modification of Ojima's procedure.[90] To a flame-dried 25 mL RBF equipped with a magnetic stir bar was added ZnI_2 (0.144 g, 0.450 mmol), Hex-5-ynal oxime (0.500 g, 4.50 mmol), benzene (45 mL), and TMSCN (1.40 mL, 11.2 mmol) sequentially. The mixture was stirred at room temperature for 36 hours. Once completed, reaction mixture was concentrated. The mixture was then dissolved in methanol (10 mL) and a 10% HCl solution was added (10 mL). The mixture was stirred at room temperature for 30 minutes and dissolved in dichloromethane (30 mL). To the mixture was added $NaHCO_3$ (15 mL) and the organic extracts were washed with water, brine, dried and concentrated to afford an orange liquid as a crude product. The crude was then purified by flash chromatography on silica gel with 20% EtOAc/hexanes to afford the title compound as a yellow oil (0.768 g, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.92 (s, 1H), 3.83 (dd, J = 12.3, 3.26 Hz, 1H), 2.24-2.15 (m, 1H), 2.03 (m, 1H), 1.92 (ddd, J = 17.7, 12.9, 5.56 Hz, 1H), 1.81-1.64 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ. 118.2 (C), 117.7 (C), 62.28 (C), 56.4 (CH), 36.0 (CH2), 29.2 (CH2), 25.1 (CH3), 19.4 (CH2); IR (film) 3345, 2252, 2241 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{13}NO$ [M+]: 165.0902. Found 165.0906. (major stereoisomer)

^{1}H NMR (400 MHz, Acetone-d_6) δ ppm 8.70 (br, 1H), 4.40 (br, 1H), 3.07 (br, 1H), 2.13-2.04 (m, 1H), 1.98-1.93 (m, 1.22H), 1.75-1.73 (m, 3.43H), 1.55 (s, 3H); ^{13}C NMR (400 MHz, Acetone-d6) δ 121.0 (C), 118.6 (C), 61.0 (C), 56.0 (CH), 38.0 (CH2), 31.3

(90) Ojima, I.; Inaba, S.; Nakatsugawa, K. *Chem. Lett.* **1975**, 331.

(CH2) 30.1 (CH3), 19.2 (CH2); IR (film) 3342, 2251, 2244 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{13}NO$ [M+]: 165.0902. Found 165.0905. (minor stereoisomer)

Preparation of Substrates (Tables 3.1-3.2)



Hex-5-ynal oxime. A flame-dried flask was charged with CH_2Cl_2 (84 mL), Et_3N (8.40 mL, 59.2 mmol), DMSO (4.20 mL, 59.2 mmol) and alcohol (18.4 mmol) at 0°C. After 5 min of stirring, pyridine sulfur trioxide complex (8.83 g, 55.5 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted three times with dichloromethane. The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. To the crude aldehyde was added methanol (35.3 mL) and acetonitrile (3.53 mL) under argon. Then, sodium acetate (4.35 g, 53.0 mmol) and hydroxylamine hydrochloride (1.35 g, 19.4 mmol) were added sequentially at room temperature and stirred for 1 hour. Upon completion, the reaction mixture was added to water and brine. The aqueous phase was extracted 3 times with ether. $NaHCO_3$ was then added to the combined organic extracts and the organic phase was washed with water, brine, dried and concentrated. The crude product was then purified by flash column chromatography on silica gel to yield the product. The crude was purified by flash chromatography on silica gel (25 % EtOAc in hexanes). The title compound was obtained a white solid (mp = 99 – 100 °C) (1.56 g, 79 % yield). TLC R_f 0.33 in 25% EtOAc in hexanes; ^1H NMR (400 MHz, $CDCl_3$) (mixture of oxime isomers) δ ppm 7.45 (t, J = 5.86, 1H), 2.47 (br, 1.31H), 2.34 (dt, J =

7.58, 7.44, 5.92 Hz, 2.12H), 2.26 (dt, J = 6.99, 6.96, 2.60 Hz, 3.28H), 1.98 (dt, J = 2.64, 1.21 Hz, 1.61H), 1.75 (m, 3.40H), 1.25 (br, 0.79H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 151.4 (CH), 83.4 (C), 69.1 (CH), 28.4 (CH2), 25.2 (CH2), 17.9 (CH2); IR (film) 3274, 2901, 1668, 1448, 1416, 1329, 1305 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_9N_1O_1$ $[M]^+$: 111. 0684. Found: 111.0656.

Procedure for the Alkyne Cyclizations (Tables 3.3 – 3.9)

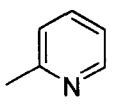
Typical experimental procedure: An oven-dried 2-5 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The oxime **3.7a** (0.0500 g, 0.450 mmol, 1.00 equiv), the acid, the additive and solvent (see tables for details) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated (see tables for heating times and temperatures). The reaction solution was cooled to ambient temperature, further acidified using trifluoroacetic acid (1.0 equiv), concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard.

General Procedure for the Alkyne Cyclizations - Pyridines (Table 3.11)

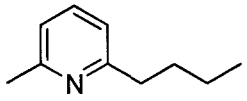
General Procedure A : An oven-dried 5-20 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynyl oxime (1.00 equiv), *p*-toluenesulfonic acid (0.02 equiv) and isopropanol (such that the concentration of the alkynyl oxime was 0.1 M) were added to the sealed tube,

while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 5 hours at 160 °C. The reaction solution was cooled to ambient temperature, further acidified using trifluoroacetic acid (1.0 equiv), concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure, cooled to 0 °C, basified using triethylamine (1.5 equiv) and directly purified by silica gel chromatography to give the corresponding products.

General Procedure B : An oven-dried 5-20 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynyl oxime (1.00 equiv), *p*-toluenesulfonic acid (0.02 equiv) and chlorobenzene (such that the concentration of the alkynyl oxime was 0.1 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 8 hours at 180 °C. The reaction solution was cooled to ambient temperature, further acidified using trifluoroacetic acid (1.0 equiv), concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure, cooled to 0 °C, basified using triethylamine (1.5 equiv) and directly purified by silica gel chromatography to give the corresponding products.

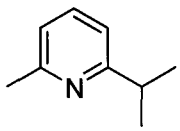


2-Methylpyridine (Table 3.11, entry 1, 3.9a). Synthesized according to general procedure A using oxime **3.7a** (0.0500 g, 0.450 mmol). The reaction mixture was concentrated and isolated using flash chromatography (75 % ether in pentane). The title compound was obtained as a yellow liquid (0.0398 g, 95 % yield). TLC R_f 0.33 in 70 % ether in hexanes. The spectral data is in agreement with previously reported literature data.[91]

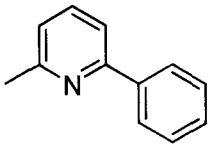


2-Butyl-6-methylpyridine (Table 3.11, entry 2, 3.9b). Synthesized according to general procedure A using oxime **3.7b** (0.175 g, 1.05 mmol). The reaction mixture was concentrated and isolated using flash chromatography (15 % ether in pentane). The title compound was obtained as a clear colourless oil (0.147 g, 94 % yield). TLC R_f 0.71 in 50 % ether in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 (t, J = 7.65, 1H), 6.93 (dd, J = 7.66, 2.79 Hz, 2H), 2.78-2.70 (m, 2H), 2.52 (s, 3H), 1.75-1.58 (m, 2H), 1.38 (qd, J = 14.73, 7.36 Hz, 2H), 0.92 (t, J = 7.35 Hz, 3H); ^{13}C NMR (400MHz, $CDCl_3$) δ ppm 162.1, 157.8, 136.6, 120.4, 119.6, 38.4, 32.5, 24.7, 22.7, 14.1; IR (film) 3264, 2960, 2858, 1463 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{15}N$ $[M]^+$: 149.1204. Found: 149.1185.

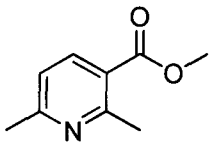
(91) Klei, E.; Teuben, J. H. *J. Organomet. Chem.* **1981**, *214*, 53.



2-Isopropyl-6-methylpyridine (Table 3.11, entry 3, 3.9c). Synthesized according to general procedure A using oxime **3.7c** (0.0640 g, 0.418 mmol). The reaction mixture was concentrated and isolated using flash chromatography (5 % ether in pentane). The title compound was obtained as a pale yellow oil (0.0302 g, 55 % yield). TLC R_f 0.88 in 15 % EtOAc in hexanes. The spectral data is in agreement with previously reported spectral data.[92]



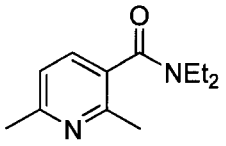
2-Methyl-6-phenylpyridine (Table 3.11, entry 4-5, 3.9d). Synthesized according to general procedure B using oxime **3.7d** (0.0750 g, 0.400 mmol). The reaction mixture was concentrated and isolated using flash chromatography (20 % ether in pentane). The title compound was obtained as a yellow liquid (0.0669 g, 99 % yield). TLC R_f 0.59 in 15 % EtOAc in hexanes. The spectral data is in agreement with literature.[93]



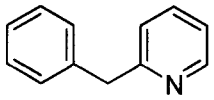
Methyl 2,6-dimethylnicotinate (Table 3.11, entry 6, 3.9e). Synthesized according to general procedure A using oxime **3.7e** (0.0500 g, 0.273 mmol). The reaction mixture was concentrated and isolated using flash chromatography (90 % ether in pentane).

(92) Jun, J-G.; Shin, H. S. *Tetrahedron. Lett.* **1992**, *33*, 4593.
(93) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551.

The title compound was obtained as a pale yellow oil (0.0326 g, 72 % yield). TLC R_f 0.63 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[94]



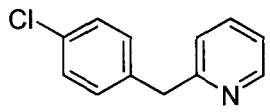
***N,N*-Diethyl-2,6-dimethylnicotinamide (Table 3.11, entry 7, 3.9f)**. Synthesized according to general procedure A using oxime **3.7f** (0.0750 g, 0.334 mmol). The reaction mixture was concentrated and isolated using flash chromatography (8 % MeOH in CH_2Cl_2). The title compound was obtained as a yellow oil (0.0469 g, 68 % yield). TLC R_f 0.11 in 100 % EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.36 (d, *J* = 7.77 Hz, 1H), 7.00 (d, *J* = 7.77 Hz, 1H), 3.81-3.29 (m, 2H), 3.12 (q, *J* = 7.09 Hz, 2H), 2.53 (s, 3H), 2.47 (s, 3H), 1.25 (t, *J* = 7.13 Hz, 3H), 1.02 (t, *J* = 7.12, 3H); ^{13}C NMR (300 MHz, CDCl3) δ ppm 169.4, 158.1, 153.4, 133.8, 129.3, 120.2, 42.7, 38.9, 24.4, 22.0, 14.0, 12.7; IR (film) 2979, 2937, 2876, 1629, 1588, 1421, 1288 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{18}N_2O_1$ $[M]^+$: 206.1419. Found: 206.1394.



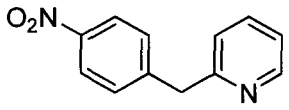
2-Benzylpyridine (Table 3.11, entry 8-9, 3.9g). Synthesized according to general procedure B using oxime **3.7g** (0.075 g, 0.40 mmol). The reaction mixture was concentrated and isolated using flash chromatography (25 % ether in pentane). The

(94) Karthikeyan, G.; Paramasivan, T. P. *Can. J. Chem.* **2005**, *83*, 1746.

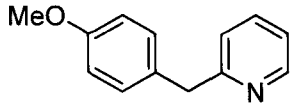
title compound was obtained as a pale yellow oil (0.0549 g, 81 % yield). TLC R_f 0.60 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[95]



2-(4-Chlorobenzyl)pyridine (Table 3.11, entry 10, 3.9h). Synthesized according to general procedure B using oxime **3.7h** (0.100 g, 0.451 mmol). The reaction mixture was concentrated and isolated using flash chromatography (50 % ether in pentane). The title compound was obtained as a yellow oil (0.0759 g, 83 % yield). TLC R_f 0.43 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[96]

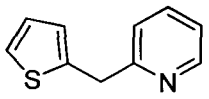


2-(4-Nitrobenzyl)pyridine (Table 3.11, entry 11, 3.9i). Synthesized according to general procedure B using oxime **3.7i** (0.100 g, 0.431 mmol). The reaction mixture was concentrated and isolated using flash chromatography (50 % EtOAc in hexanes). The title compound was obtained as a yellow oil (0.0839 g, 91 % yield). TLC R_f 0.38 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[97]

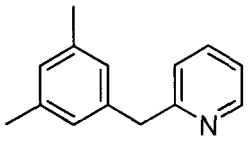


(95) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 2643.
(96) Wakabayashi, S.; Ishida, M.; Takeda, T.; Oae, S. *Tetrahedron. Lett.* **1988**, *29*, 4441.
(97) Florio, S.; Lorusso, P.; Luisi, R.; Granito, C.; Ronzini, L.; Troisi, L. *Eur. J. Org. Chem.* **2004**, 2118.

2-(4-Methoxybenzyl)pyridine (Table 3.11, entry 12, 3.9j). Synthesized according to general procedure B using oxime **3.7j** (0.100 g, 0.460 mmol). The reaction mixture was concentrated and gave an NMR yield of 24% using styrene as an internal standard.

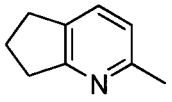


2-(Thiophen-2-ylmethyl)pyridine (Table 3.11, entry 13, 3.9k). Synthesized according to general procedure B using oxime **3.7k** (0.100 g, 0.517 mmol). The reaction mixture was concentrated and gave an NMR yield of 15% using styrene as an internal standard.

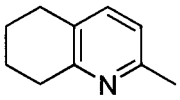


2-(3,5-Dimethylbenzyl)pyridine (Table 3.11, entry 14, 3.9l). A) Synthesized according to general procedure B using oxime **3.7l** (0.100 g, 0.464 mmol). The reaction mixture was concentrated and isolated using flash chromatography (35 % ether in pentane). The title compound was obtained as a yellow oil (0.0562 g, 61 % yield). TLC R_f 0.7 in 50 % EtOAc in hexanes. B) Synthesized according to general procedure B using oxime **1j** (0.450 g, 1.96 mmol). The reaction mixture was concentrated and isolated using flash chromatography (35 % ether in pentane). The title compound was obtained as a yellow oil (0.213 g, 55 % yield). TLC R_f 0.7 in 50 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.55 (d, J = 4.83 Hz, 1H), 7.57 (dt, J = 7.76, 1.74 Hz, 1H), 7.12 (dd, J = 10.34, 5.12 Hz, 2H), 6.88 (d, J = 8.94 Hz, 3H), 4.09 (s, 2H), 2.28 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 161.2, 149.2,

139.3, 138.0, 136.5, 128.0, 126.9, 123.1, 121.1, 44.6, 21.2; IR (film) 3010, 2917, 2861, 1678, 1665, 1569, 1473, 1433 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{15}N_1$ $[M]^+$: 197.1204. Found: 197.1192.

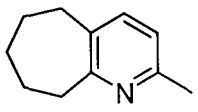


2-Methyl-6,7-dihydro-5*H*-cyclopenta[b]pyridine (Table 3.11, entry 15, 3.9m). Synthesized according to general procedure A using oxime **3.7m** (0.0750 g, 0.496 mmol). The reaction mixture was concentrated and isolated using flash chromatography (90 % ether in pentane). The title compound was obtained as a clear colourless oil (0.0512 g, 77 % yield). TLC R_f 0.33 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[98]

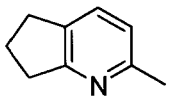


2-Methyl-5,6,7,8-tetrahydroquinoline (Table 3.11, entry 16, 3.9n). Synthesized according to general procedure A using oxime **3.7n** (0.0360 g, 0.218 mmol). The reaction mixture was concentrated and isolated using flash chromatography (80 % ether in pentane). The title compound was obtained as a pale yellow oil (0.0289 g, 90 % yield). TLC R_f 0.33 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[99]

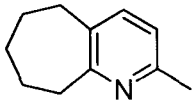
(98) Rougeot, E.; Moskowitz, H.; Miocque, M. *J. Het. Chem.* **1983**, *20*, 1407.
(99) Boruah, C. R.; Ahmed, S.; Sharma, U.; Sandhu, J. S. *J. Org. Chem.* **2000**, *65*, 922.



2-Methyl-6,7,8,9-tetrahydro-*5H*-cyclohepta[b]pyridine (Table 3.11, entry 17, 3.9o). Synthesized according to general procedure A using oxime **3.7o** (0.0850 g, 0.475 mmol). The reaction mixture was concentrated and isolated using flash chromatography (50 % ether in pentane). The title compound was obtained as a pale yellow oil (0.0567 g, 74 % yield). TLC R_f 0.45 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[100]



2-Methyl-6,7-dihydro-*5H*-cyclopenta[b]pyridine (Table 3.11, entry 18, 3.9m). Synthesized according to general procedure A using oxime **3.7p** (0.0700 g, 0.313 mmol). The reaction mixture was concentrated and isolated using flash chromatography (90 % ether in pentane). The title compound was obtained as a clear colourless oil (0.0382 g, 92 % yield). TLC R_f 0.33 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[98]



2-Methyl-6,7,8,9-tetrahydro-*5H*-cyclohepta[b]pyridine (Table 3.11, entry 19, 3.9o). Synthesized according to general procedure A using oxime **3.7q** (0.0750 g, 0.299 mmol). The reaction mixture was concentrated and isolated using flash chromatography (50 % ether in pentane). The title compound was obtained as a pale

(100) Epsztajn, J.; Hahn, W. E.; Tosik, B. K. *Rocz. Chem.* **1970**, *44*, 431.

yellow oil (0.0303 g, 63 % yield). TLC R_f 0.45 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[100]

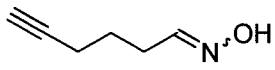
Preparation of Substrates (Table 3.11, entries 1-19, 3.7a-q)

General Procedure for the Formation of Oximes from Alcohols(C) or Ketones(D)

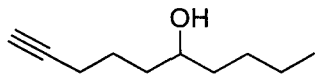
General Procedure C: A flame-dried flask was charged with CH_2Cl_2 (84 mL), Et_3N (8.40 mL, 59.2 mmol), DMSO (4.20 mL, 59.2 mmol) and alcohol (18.4 mmol) at 0°C. After 5 min of stirring, pyridine sulfur trioxide complex (8.83 g, 55.5 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted three times with dichloromethane. The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. To the crude aldehyde was added methanol (35.3 mL) and acetonitrile (3.53 mL) under argon. Then, sodium acetate (4.35 g, 53.0 mmol) and hydroxylamine hydrochloride (1.35 g, 19.4 mmol) were added sequentially at room temperature and stirred for 1 hour. Upon completion, the reaction mixture was added to water and brine. The aqueous phase was extracted 3 times with ether. $NaHCO_3$ was then added to the combined organic extracts and the organic phase was washed with water, brine, dried and concentrated. The crude product was then purified by flash column chromatography on silica gel to yield the product.

General Procedure D: To the ketone (18.4 mmol) was added methanol (35.3 mL) and acetonitrile (3.53 mL) under argon. Then, sodium acetate (4.35 g, 53.0 mmol) and

hydroxylamine hydrochloride (1.35 g, 19.4 mmol) were added sequentially at room temperature and stirred for 1 to 2 hours. Upon completion, the reaction mixture was added to water and brine. The aqueous phase was extracted 3 times with ether. $NaHCO_3$ was then added to the combined organic extracts and the organic phase was washed with water, brine, dried and concentrated. The crude product was then purified by flash column chromatography on silica gel to yield the product.

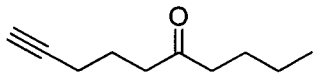


Hex-5-ynal oxime (Table 3.3, entry 1-8; Table 3.4, entry 1-6; Table 3.5, entry 1-5; Table 3.6, entry 1-10; Table 3.7, entry 1-5; Table 3.8, entry 1-11; Table 3.11, entry 1; 3.7a). Synthesized according to general procedure C using hex-5-yn-1-ol (2.00 mL, 18.4 mmol). The crude was purified by flash chromatography on silica gel (25 % EtOAc in hexanes). The title compound was obtained a white solid (mp = 99 – 100 °C) (1.56 g, 79 % yield). TLC R_f 0.33 in 25% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of oxime isomers) δ ppm 7.45 (t, *J* = 5.86, 1H), 2.47 (br, 1.31H), 2.34 (dt, *J* = 7.58, 7.44, 5.92 Hz, 2.12H), 2.26 (dt, *J* = 6.99, 6.96, 2.60 Hz, 3.28H), 1.98 (dt, *J* = 2.64, 1.21 Hz, 1.61H), 1.75 (m, 3.40H), 1.25 (br, 0.79H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 151.4 (CH), 83.4 (C), 69.1 (CH), 28.4 (CH2), 25.2 (CH2), 17.9 (CH2); IR (film) 3274, 2901, 1668, 1448, 1416, 1329, 1305 cm^{-1}; HRMS (EI): Exact mass calcd for $C_6H_9N_1O_1$ $[M]^+$: 111. 0684. Found: 111.0656.

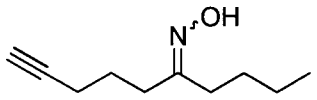


Dec-9-yn-5-ol (3.24). A flame-dried flask was charged with CH_2Cl_2 (42 mL), Et_3N (4.20 mL, 30.2 mmol), DMSO (2.10 mL, 29.6 mmol) and hex-5-yn-1-ol (1.00 mL, 9.22 mmol) at 0 °C. After 5 min of stirring, pyridine sulfur trioxide complex (4.42 g, 27.8 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted with dichloromethane (3 times). The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. *n*-BuLi (11.0 mL, 18.4 mmol) was added to dry THF (188 mL) and the resulting mixture cooled to -78 °C. The freshly prepared aldehyde was slowly added and the mixture was stirred for 2 hours while its temperature reaches 23 °C. Methanol (45 mL) was the added to quench excess *n*-BuLi and all was concentrated. The residue was dissolved in 10 % HCl (20 mL) and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give a red-yellow oil as a crude which was then purified with flash column chromatography (15 % EtOAc in hexanes) to give 0.510 g (36 %) of the alcohol as a clear colourless oil. TLC R_f 0.28 in 20% EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 3.62 (d, *J* = 3.09 Hz, 1H), 2.22 (dt, *J* = 6.59, 2.55 Hz, 2H), 1.95 (t, *J* = 2.58 Hz, 1H), 1.75-1.58 (m, 3H), 1.58-1.50 (m, 2H), 1.50-1.40 (m, 2H), 1.40-1.23 (m, 4H), 0.90 (t, *J* = 6.94 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 84.8 (C), 71.9 (CH), 68.9 (CH), 37.7 (CH2), 36.8 (CH2), 28.2 (CH2), 25.0 (CH2), 23.1 (CH2), 18.8 (CH2), 14.5 (CH3); IR (film) 3306, 2930, 2873 cm^{-1}; LRMS m/z (relative intensity): 184.0844 (9.3 %),

167.0827 (36.6 %), 142.9930 (5.7 %), 123.0912 (13.8 %), 87.0705 (25.6 %), 68.0508 (23.6 %), 57.0709 (100 %).



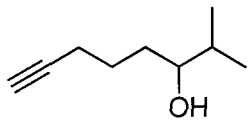
Dec-9-yn-5-one (3.24a). A flame-dried flask was charged with CH_2Cl_2 (14.8 mL), Et_3N (1.47 mL, 10.6 mmol), DMSO (0.739 mL, 10.4 mmol) and dec-9-yn-5-ol (0.500 g, 3.24 mmol) at 0°C. After 5 min of stirring, pyridine sulfur trioxide complex (1.55 g, 9.76 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted with dichloromethane (3 times). Organic extracts were washed with water, brine, dried and concentrated. The crude was purified using flash column chromatography (7 % EtOAc in hexanes) to afford 0.120 g (24 %) of the ketone as a clear colourless oil. The spectral data is in agreement with literature.[101]



Dec-9-yn-5-one oxime (Table 3.11, entry 2, 3.7b). To dec-9-yn-5-one was added methanol (1.45 mL) and acetonitrile (0.145 mL) under argon. Then, sodium acetate (0.177 g, 2.17 mmol) and hydroxylamine hydrochloride (0.0552 g, 0.795 mmol) were added at room temperature and stirred for 2 hours. Upon completion, the reaction mixture was added to water, and brine was added. The aqueous phase was extracted 3 times with ether. $NaHCO_3$ was then added to the organic extracts and the organic phase was then washed with water then brine, dried and concentrated to afford a pale yellow

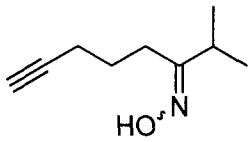
(101) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2006**, *128*, 6499.

oil as a crude product. The crude was then purified by flash chromatography on silica gel with 25 % EtOAc in hexanes to yield 0.120 g (99 %) of the product as a clear colourless oil. TLC R_f 0.11 in 10 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of oxime isomers) δ ppm 8.52 (br, 1H), 2.44 (dd, *J* = 9.20, 6.74 Hz, 1H), 2.38-2.29 (m, 2H), 2.28-2.14 (m, 3.5H), 1.98 (td, *J* = 4.55, 2.65 Hz, 1H), 1.82-1.68 (m, 2.3H), 1.50 (td, *J* = 15.08, 7.09 Hz, 2.2H), 1.35 (pd, *J* = 14.53, 7.26, 7.18 Hz, 2.2H), 0.92 (dt, *J* = 7.20, 4.36 Hz, 3.26H)); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 161.11 (C), *161.08 (C), 83.8 (C), *83.7 (C), 68.85 (CH), *68.81 (CH), 34.0 (CH2), *32.9 (CH2), 28.3 (CH2), *27.8 (CH2), 27.5 (CH2), *26.8 (CH2), 24.9, (CH2), *24.6 (CH2), 22.9 (CH2), *22.4 (CH2), 18.7 (CH2), *18.0 (CH2), 13.83 (CH3), *13.80 (CH3); IR (film) 3306, 3116, 2960, 2930, 2869, 1459, 1436, 957, 635 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{17}NO$ $[M]^+$: 167.1310. Found: 167.1287.



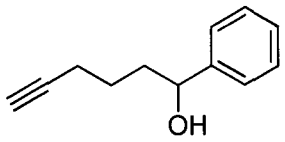
2-Methyloct-7-yn-3-ol (3.25). A flame-dried flask was charged with CH_2Cl_2 (42mL), Et_3N (4.20 mL, 30.2 mmol), DMSO (2.10 mL, 29.6 mmol) and hex-5-yn-1-ol (1.00 mL, 9.22 mmol) at 0 °C. After 5 min of stirring, pyridine sulfur trioxide complex (4.42 g, 27.8 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted with dichloromethane (3 times). The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. A THF (23 mL) solution of the crude aldehyde was treated with isopropylmagnesium chloride (2 M solution in THF, 23.0 mL, 46.1 mmol) at 0 °C. Once added, the ice bath

was removed and the mixture was stirred at room temperature. Upon completion, the reaction medium was diluted with 50 mL of ether and quenched with 50 mL of sat. NH_4Cl. The aqueous layer was extracted twice with ether and the organic phase was washed with brine, dried and concentrated. The crude was then purified using a 10 % EtOAc in hexanes column to afford 0.667 g (52 %) of the alcohol as a clear colourless oil. TLC R_f 0.58 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.36 (m, 1H), 2.22 (dt, *J* = 6.75, 2.56 Hz, 2H), 1.94 (t, *J* = 2.60 Hz, 1H), 1.82-1.48 (m, 5H), 1.46 (m, 2H), 0.90 (dd, *J* = 6.80, 2.27 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 84.4 (C), 68.4 (CH), 33.6 (CH), 33.1 (CH2), 24.9 (CH2), 18.8 (CH2), 18.4 (CH2), 17.1 (CH2); IR (film) 3310, 2899, 2877 cm^{-1}; HRMS (EI): Exact mass calcd for C_9H_6O $[M]^+$: 140.1201. Found: 140.1189.



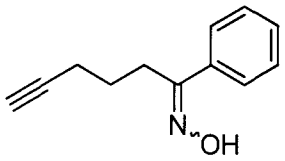
2-Methyloct-7-yn-3-one oxime (Table 3.11, entry 3, 3.7c). Prepared according to general procedure C using 2-methyloct-7-yn-3-ol (0.667 g, 4.75 mmol). The crude product was then purified by flash chromatography on silica gel with 15 % EtOAc in hexanes to yield 0.235 g (35 %) of the product as a clear colourless oil. TLC R_f 0.43 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of oxime isomers) δ ppm 7.95 (br) 3.43 (td, *J* = 14.12, 7.09 Hz), 2.50 (td, *J* = 13.80, 6.94 Hz, 1H), 2.44-2.35 (m, 2H), 2.26 (ddd, *J* = 9.62, 5.62, 2.11 Hz), 1.99 (t, *J* = 2.65 Hz, 1H), 1.97-1.96 (m), 1.88-1.70 (m), 1.60 (s), 1.11 (d, *J* = 6.89 Hz, 6H), 1.08 (d, *J* = 7.06 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 164.6 (C), *164.3 (C), 83.8

(C), *83.7 (C), *68.9 (CH), 68.8 (CH), 33.7 (CH), *28.6 (CH2), *26.3 (CH), 25.9 (CH2), 24.7 (CH2), 19.9 (CH3), 18.8 (CH2), *18.0 (CH2); IR (film) 3299, 3019, 2920, 2791, 1447, 955, 648 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{15}NO$ $[M]^+$: 153.1154. Found: 153.1114.

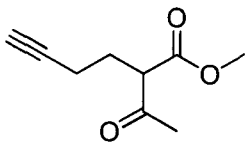


1-Phenylhex-5-yn-1-ol (3.26). A flame-dried flask was charged with CH_2Cl_2 (42 mL), Et_3N (4.20 mL, 30.2 mmol), DMSO (2.10 mL, 29.6 mmol) and 5-hexyn-1-ol (1.00 mL, 9.22 mmol) at 0 °C. After 5 min of stirring, pyridine sulfur trioxide complex (4.42 g, 27.8 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted with dichloromethane (3 times). The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. Magnesium turnings (0.426 g, 17.6 mmol) were mixed with Et_2O (8.8 mL) and bromobenzene (1.39 mL, 13.2 mmol) in ether (6.6 mL) was slowly added. The reaction mixture was stirred for 1 hour at rt then refluxed for 30 minutes. This Grignard reagent was then slowly added to a solution of the aldehyde in ether (8.8 mL) and the mixture was refluxed for 2 hours. Ice (5.0 g) was added and the resulting suspension was dissolved with HCl (2 M). The organic layer was separated, washed with aq. $NaHSO_3$, aq. $NaHCO_3$, water, dried ($MgSO_4$), concentrated and purified by flash column chromatography (20 % EtOAc in hexanes) to afford 0.644 g (40 %) of the desired

alcohol as a clear colourless oil. TLC R_f 0.38 in 30 % EtOAc in hexanes. The spectral data is in agreement with literature.[102]



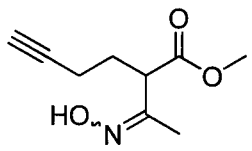
1-Phenylhex-5-yn-1-one oxime (Table 3.11, entry 4-5, 3.7d). Prepared according to general procedure C using 1-phenylhex-5-yn-1-ol (0.600 g, 3.44 mmol). The crude product was then purified by flash chromatography on silica gel with 20 % EtOAc in hexanes to yield 0.341 g (53 %) of the product as a pale yellow oil. TLC R_f 0.25 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of oxime isomers) δ ppm 7.88-7.47 (m, 2H), 7.49-7.30 (m, 3H), 2.99-2.86 (m, 2H), 2.28 (dt, *J* = 7.04, 2.56 Hz, 2H), 2.00 (t, *J* = 2.61 Hz, 1H), 1.83 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 159.1 (C), 135.3 (C), 129.4 (CH), 128.6 (CH), 126.3 (CH), 83.7 (C), 68.9 (CH), 25.3 (CH2), 25.2 (CH2), 18.6 (CH2); IR (film) 3295, 3055, 2930, 2865, 1455, 1303, 919 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{13}NO$ $[M]^+$: 187.0997. Found: 187.0924.



Methyl 2-acetylhex-5-ynoate (3.29). To KI (0.320 g, 1.93 mmol), NaH (60% dispersion in mineral oil, 0.170 g, 4.25 mmol), DMF (3.86 mL) and THF (3.86 mL) was added methyl acetoacetate dropwise (0.500 mL, 4.63 mmol). Homopropargyl

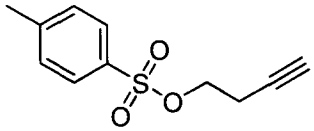
(102) Inaba, K.; Takaya, J.; Iwasawa, N. *Chem. Lett.* **2007**, *36*, 474.

bromide (0.362 mL, 3.86 mmol) was then added in one portion. The solution was refluxed for 24 hours then cooled to room temperature. The mixture was diluted with ether and washed successively with 10 % HCl (3 times), brine, dried and concentrated. The crude material was purified using flash column chromatography (10 % EtOAc in hexanes) to afford 0.186 g (29 %) as a clear colourless oil. TLC R_f 0.78 in 50 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.05-3.43 (m, 4H), 2.29 (s, 3H), 2.27 (dd, *J* = 6.68, 2.62 Hz, 2H), 2.08 (dt, *J* = 7.20, 2.60 Hz, 2H), 2.02 (t, *J* = 2.64 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 202.5 (C), 169.7 (C), 82.5 (C), 69.8 (CH), 57.6 (CH), 52.5 (CH3), 29.4 (CH3), 26.4 (CH2), 16.3 (CH2); IR (film) 3295, 2960, 2922, 2850, 1740, 1713, 1698, 1436, 1364, 1147 cm^{-1}; LRMS m/z (relative intensity): 116.0462 (29.2 %), 101.0231 (6.00 %), 87.0419 (55.0 %), 55.0195 (33.0 %), 43.0183 (100 %).

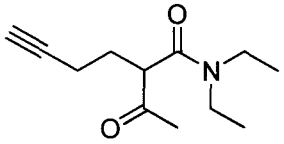


Methyl 2-(1-(hydroxyimino)ethyl)hex-5-ynoate (Table 3.11, entry 6, 3.7e). Prepared according to general procedure D using methyl 2-acetylhex-5-ynoate (0.186 g, 1.11mmol). The crude product was then purified by flash chromatography on silica gel with 30 % EtOAc in hexanes to yield 0.101 g (50 %) of the product as a clear colourless oil. TLC R_f 0.61 in 50 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of oxime isomers) δ ppm 8.80 (br, 1H), 3.70 (s, 3H), 3.47 (t, *J* = 7.38 Hz, 1H), 2.21 (td, *J* = 6.08, 4.74 Hz, 2H), 2.17-2.06 (m, 1H), 1.99 (m, 1H), 1.89 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 171.8 (C), 155.0 (C), 82.6 (C), 69.6 (CH). 52.3

(CH), 49.9 (CH3), 27.6 (CH2), 16.3 (CH2), 11.9 (CH3); IR (film) 3454, 3283, 2952, 2914, 2858, 1732, 1701, 1698 1436, 1158 cm^{-1}; HRMS (EI): Exact mass calcd for $C_9H_{13}NO_3$ $[M]^+$: 183.0895. Found: 183.0015.



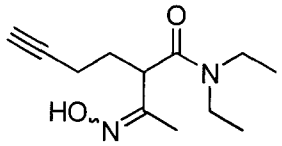
But-3-ynyl 4-methylbenzenesulfonate. A flask was charged with a stir bar, *p*-toluene sulfonyl chloride (7.56 g, 39.6 mmol), triethylamine (11.1 mL, 79.3 mmol) and CH_2Cl_2 (7.6 mL) under argon at 0 °C. A solution of 4-butyn-1-ol (2.00 mL, 26.4 mmol) in CH_2Cl_2 (11.4 mL) was then added and stirred in an ice bath for 1 hour. The reaction mixture was raised to room temperature and let stir for 16 hours. The reaction was then cooled in an ice bath and 1 M HCl (11.4 mL) was added and let stir for 5 minutes. The solution was then extracted 3 times with CH_2Cl_2 and the combined organic layers were washed with saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was isolated using flash column chromatography (20 % EtOAc in hexanes) to afford 4.83 g (82 %) as a clear colourless oil. The spectral data is in agreement with literature.[103]



2-Acetyl-*N*,*N*-diethylhex-5-ynamide (3.30). To KI (0.555 g, 3.34 mmol), NaH (60 % dispersion in mineral oil, 0.294 g, 7.35 mmol), DMF (6.7 mL) and THF (6.7 mL) was

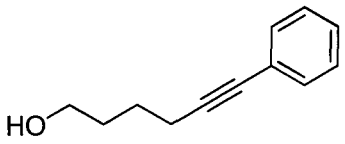
(103) Coogan, M. P.; Stanton, L. S.; Walther, T. *J. Organomet. Chem.* **2003**, *677*, 125.

added *N,N*-diethylacetoacetamide dropwise (0.970 mL, 8.35 mmol). But-3-ynyl 4-methylbenzenesulfonate (1.50 g, 6.69 mmol) was then added in one portion. The solution was refluxed for 24 hours then cooled to room temperature. The mixture was diluted with ether and washed successively with 10 % HCl (3 times), brine, dried and concentrated. The crude material was purified using flash column chromatography (10 % EtOAc in hexanes) to afford 0.520 g (37 %) as a clear colourless oil. TLC R_f 0.66 in 50 % EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.79 (t, *J* = 6.91 Hz, 1H), 3.51-3.25 (m, 4H), 2.34-2.23 (m, 1H), 2.20 (ddd, *J* = 8.06, 5.62, 2.60 Hz, 1H), 2.15 (s, 3H), 2.10 (dd, *J* = 13.20, 6.10 Hz, 1H), 2.07-1.99 (m, 1H), 1.98 (br, 1H), 1.21 (t, *J* = 7.13 Hz, 3H), 1.11 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 204.4 (C), 167.8 (C), 83.1 (C), 69.6 (CH), 55.9 (CH), 42.2 (CH2), 40.7 (CH2), 27.7 (CH2), 27.4 (CH3), 16.5 (CH2), 14.4 (CH3), 12.8 (CH3); IR (film) 3291, 3249, 2975, 2937, 2876, 1723, 1637, 1478, 1447, 1433, 1360, 1136 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{19}NO_2$ $[M]^+$: 209.1416. Found: 209.1399.



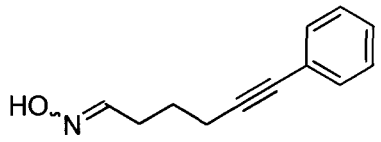
***N,N*-Diethyl-2-(1-(hydroxyimino)ethyl)hex-5-ynamide (Table 3.11, entry 7, 3.7f).** Prepared according to general procedure D using methyl 2-acetyl-*N,N*-diethylhex-5-ynamide (0.400 g, 1.91 mmol). The crude product was then purified by flash chromatography on silica gel with 40 % EtOAc in hexanes to yield 0.189 g (44 %) of the product as yellow powder (mp = 110.2-112.1 °C, ethanol). TLC R_f 0.45 in 50 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers)

8.19 (br, 1H), 3.70 (t, J = 7.02 Hz, 1H), 3.51 (qt, J = 14.14, 7.17, 7.11 Hz, 2H), 3.34-3.12 (m, 2H), 2.26-2.08 (m, 3H), 1.97 (m, 1H), 1.86 (s, 3H), 1.84-1.75 (m, 1H), 1.16 (t, J = 7.11 Hz, 3H), 1.09 (t, J = 7.08 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 169.0 (C), 156.9 (C), 83.5 (C), 69.2 (CH), 46.9 (CH), 41.8 (CH2), 40.7 (CH2), 28.5 (CH2), 16.2 (CH2), 14.3 (CH3), 12.9 (CH3), 10.5 (CH3); IR (film) 3264, 2968, 2914, 2842, 1637, 1618, 1607, 1447, 949 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{20}N_2O_2$ $[M]^+$: 224.1525. Found: 224.1503.

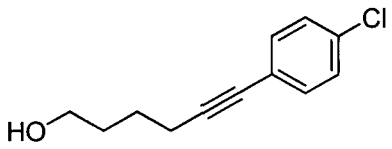


6-Phenylhex-5-yn-1-ol (3.31). Prepared by a modification of Liu's procedure.[71] To a Et_3N (30 mL) solution of iodobenzene (1.37 mL, 12.2 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.0858 g, 0.122 mmol) and CuI (0.0465 g, 0.244 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition of 5-hexyn-1-ol (1.00 g, 10.2 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude alcohol was then purified using flash column chromatography (15 % EtOAc in hexanes) to afford 1.52 g (86 %) of the alcohol as a clear colourless oil. TLC R_f 0.3 in 25 % EtOAc in hexanes. The spectral data is in agreement with literature.[104]

(104) Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270.

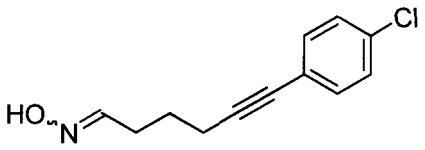


6-Phenylhex-5-ynal oxime (Table 3.11, entry 8-9, 3.7g). Prepared according to general procedure C using 6-phenylhex-5-yn-1-ol (1.15 g, 6.60 mmol). The crude product was then purified by flash chromatography on silica gel (20% EtOAc in hexanes) to yield 0.980 g (88 %) of the oxime as a clear colourless oil. TLC R_f 0.38 in 30 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 9.09 (br, 1H), 7.52 (t, *J* = 5.93 Hz, 0.25H), 7.43 (dd, *J* = 6.37, 2.83 Hz, 2H), 7.30 (dd, *J* = 5.51, 3.23 Hz, 3H), 6.83 (t, *J* = 4.63, 4.63 Hz, 0.75H), 2.59 (dd, *J* = 13.13, 7.48 Hz, 1.5H), 2.50 (t, *J* = 7.04 Hz, 2H), 2.43 (dd, *J* = 13.90, 7.17 Hz, 0.5H), 1.85 (p, *J* = 7.32 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm *151.8 (CH), 151.3 (CH), *131.50 (CH), 131.53 (CH), 128.2 (CH), *127.6 (CH), 123.7 (C), 89.0 (C), *88.9 (C), 81.41 (C), *81.37 (C), 28.6 (CH2), 25.5 (CH2), *25.2 (CH2), *24.4 (CH2), *19.2 (CH2), 18.8 (CH2); IR (film) 3249, 3101, 2934, 1598, 1490, 1442, 931 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{13}N_1O_1$ $[M]^+$: 187.0997. Found: 187.1045.



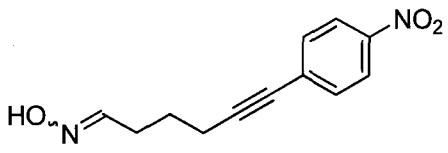
6-(4-Chlorophenyl)hex-5-yn-1-ol (3.32). Prepared by a modification of Liu's procedure.[71] To a Et_3N (30 mL) solution of 1-chloro-4-iodobenzene (1.25 mL, 11.5 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.0809 g, 0.115 mmol) and CuI (0.0439 g, 0.230 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition

of 5-hexyn-1-ol (1.13 g, 11.5 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude alcohol was then purified using flash column chromatography (15 % EtOAc in hexanes) to afford 2.35 g (98 %) of the alcohol as a pale yellow oil. TLC R_f 0.28 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.28 (q, *J* = 8.70 Hz, 4H), 3.71 (t, *J* = 5.54 Hz, 2H), 2.45 (t, *J* = 6.62 Hz, 2H), 1.83-1.60 (m, 4H), 1.43 (br, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 133.5 (C), 132.7 (CH), 128.5 (CH), 122.3 (C), 90.9 (C), 79.9 (C), 62.4 (CH2), 31.8 (CH2), 24.9 (CH2), 19.2 (CH2); IR (film) 3352, 2941, 2865, 1490, 1091, 1014, 827 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{12}OCl$ $[M]^+$: 208.0655 Found: 208.0699



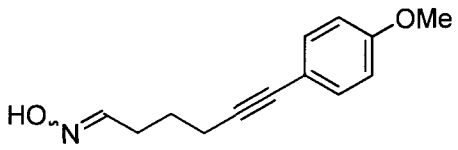
6-(4-Chlorophenyl)hex-5-ynal oxime (Table 3.9, entry 1-6; Table 3.10, entry 1-3; Table 3.11, entry 10, 3.7h). Prepared according to general procedure C using 6-(4-chlorophenyl)hex-5-yn-1-ol (2.35 g, 11.3 mmol). The crude product was then purified by flash chromatography on silica gel with 20 % EtOAc in hexanes to yield 1.90 g (77 %) of the product as small white needles (mp = 131-132 °C, toluene). TLC R_f 0.15 in 20 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 8.09 (br, 0.5H), 7.67 (br, 0.5H), 7.48 (t, *J* = 5.90 Hz, 0.17H), 7.37-7.19 (m, 4H), 6.79 (t, *J* = 5.49 Hz, 1H), 2.55 (dt, *J* = 7.60, 5.61 Hz, 2H), 2.47 (t, *J* = 7.05 Hz, 2.3H), 2.43-2.32 (m, 0.4H), 1.82 (p, *J* = 7.26, 2.4H); ^{13}C NMR (300 MHz, $CDCl_3$)

δ ppm 152.0 (CH), 133.6 (C), 132.8 (CH), 128.5 (CH), 122.2 (C), 90.1 (C), 80.3 (C), 25.2 (CH2), 24.3 (CH2), 19.3 (CH2); IR (film) 3203, 3099, 2941, 2869, 1490, 1449, 1397, 1332, 1089, 827 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{12}NOCl$ $[M]^+$: 221.0607. Found: 221.0664.

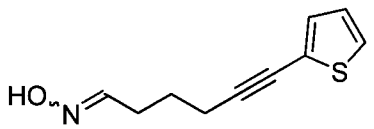


6-(4-Nitrophenyl)hex-5-ynal oxime (Table 3.11, entry 11, 3.7*i*). Prepared by a modification of Liu's procedure.[71] To a Et_3N (30 mL) solution of 1-iodo-4-nitrobenzene (0.806 g, 3.239 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.0190 g, 0.0270 mmol) and CuI (0.0103 g, 0.0540 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition of hex-5-ynal oxime (0.30 g, 2.7 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude product was then purified using flash column chromatography (30 % EtOAc in hexanes) to afford 0.42 g (67 %) of the oxime as orange needles (mp = 120.4 – 121.2 °C, ethanol). TLC R_f 0.38 in 35 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 8.54 (br, 0.5H), 8.24-8.01 (m, 2H), 7.61-7.43 (m, 2H), 6.82 (br, 0.5H), 2.66-2.46 (m, 3H), 2.40 (dd, *J* = 13.51, 6.43 Hz, 1H), 1.85 (p, *J* = 7.02 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm * denotes minor isomer 151.2 (CH), 146.9 (C), 132.4 (CH), 130.9 (C), 123.6 (CH), 92.3 (C), *80.1 (C) 80.2 (C), 28.8 (CH2), *25.3 (CH2), 25.1 (CH2), 24.9 (CH),

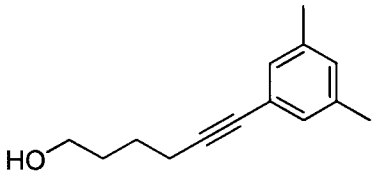
*19.9 (CH2), 19.6 (CH2), *19.2 (CH2); IR (film) 3210, 1593, 1535, 1513, 1342cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{12}N_2O_3$ [M]$^+$: 232.0848. Found: 232.0839.



6-(4-Methoxyphenyl)hex-5-ynal oxime (Table 3.11, entry 12, 3.7j). Prepared by a modification of Liu's procedure.[71] To a Et_3N (5.29 mL) solution of 1-iodo-4-methoxybenzene (0.505 g, 2.16 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.0126 g, 0.0180 mmol) and CuI (0.00529 g, 0.0360 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition of hex-5-ynal oxime (0.200 g, 1.80 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude product was then purified using flash column chromatography (35 % EtOAc in hexanes) to afford 0.314 g (80 %) of the oxime as a pale yellow oil. TLC R_f 0.45 in 50 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 9.84-9.00 (m, 1H), 7.58-7.33 (m, 2H), 6.83 (d, J = 7.97 Hz, 2H), 3.81 (s, 3H), 2.65-2.39 (m, 4H), 1.82 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 159.5 (CH), 133.3 (CH), 116.3 (C), 114.2 (CH), 87.8 (C), 81.5 (C), 77.9 (CH2), 77.5 (CH2), 77.1 (CH2), 55.7 (CH2), 29.1 (CH2), 26.1 (CH2), 25.8 (CH2), 24.9 (CH2), 19.7 (CH2), 19.3 (CH2); IR (film) 3222, 2949, 2903, 2869, 2842, 1606, 1565, 1463, 1290, 1246 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{15}N_1O_2$ [M]$^+$: 217.1103. Found: 217.1094.



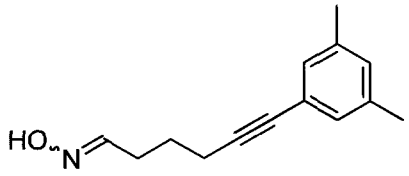
6-(Thiophen-2-yl)hex-5-ynal oxime (Table 3.11, entry 13, 3.7k). Prepared by a modification of Liu's procedure.[71] To a Et_3N (5.30 mL) solution of 2-iodothiophene (0.888 g, 3.24 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.0190 g, 0.0270 mmol) and CuI (0.0103 g, 0.0540 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition of hex-5-ynal oxime (0.300 g, 2.70 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude product was then purified using flash column chromatography (30 % EtOAc in hexanes) to afford 0.517 g (99 %) of the oxime as a yellow oil. TLC R_f 0.30 in 30 % EtOAc in hexanes.[105]



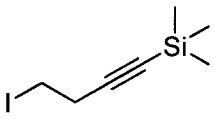
6-(3,5-Dimethylphenyl)hex-5-yn-1-ol (3.36). Prepared by a modification of Liu's procedure.[71] To a Et_3N (54 mL) solution of iodoxylene (3.19 mL, 22.1 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.162 g, 0.184 mmol) and CuI (0.0702 g, 0.369 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition of 5-hexyn-1-ol (2.00 mL, 18.4 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude alcohol was then

(105) The author would like to thank undergraduate student *E. Bilodeau* for synthesizing this compound.

purified using flash column chromatography (30 % EtOAc in hexanes) to afford 2.75 g (74 %) of the alcohol as a yellow-orange oil). TLC R_f 0.3 in 30 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.04 (s, 2H), 6.91 (s, 1H), 3.68 (t, *J* = 6.12 Hz, 2H), 2.44 (t, *J* = 6.55 Hz, 2H), 2.28 (s, 6H), 1.71 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 137.6 (C), 129.3 (CH), 129.1 (CH), 123.3 (C), 89.0 (C), 81.0 (C), 62.1 (CH), 31.7 (CH2), 24.9 (CH2), 20.9 (CH3), 19.0 (CH2); IR (film) 3572, 3408, 3036, 2926, 2869, 2226, 1603, 1462, 1056, 846 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{18}O$ [M]$^+$: 202.1358. Found: 202.1334.

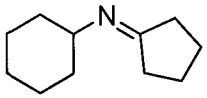


6-(3,5-Dimethylphenyl)hex-5-ynal oxime (Table 3.11, entry 14, 3.7l). Prepared according to general procedure C using 6-(3,5-dimethylphenyl)hex-5-yn-1-ol (2.75 g, 13.6 mmol). The crude product was then purified by flash chromatography on silica gel with 20% EtOAc in hexanes to yield 1.93 g (66 %) of the product as a pale yellow oil). TLC R_f 0.31 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 8.28-7.66 (br, 0.5H), 7.49 (t, *J* = 5.90 Hz, 0.5H), 7.03 (s, 2H), 6.91 (s, 1H), 2.55 (br, 1H), 2.47 (t, *J* = 6.95 Hz, 2H), 2.44-2.35 (m, 1H), 2.27 (s, 6H), 1.82 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 151.5 (CH), 137.7 (C), 129.6 (CH), 129.2 (CH), 123.2 (C), 88.1 (C), 81.7 (C), *81.6 (C), 28.6 (CH2), 25.6 (CH2), *25.3 (CH2), 21.1 (CH3), *19.2 (CH2), 18.9 (CH2); IR (film) 3275, 3112, 2922, 2865, 1599, 1451, 923, 847 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{17}NO$ [M]$^+$: 215.1310. Found: 215.1287.

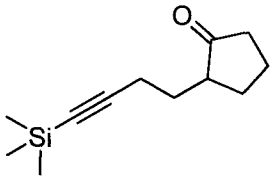


4-(Trimethylsilyl)but-3-yn-1-ol. *N*-Butyllithium (2.44 M in hexane, 11.4 mL, 27.7 mmol) was added dropwise via cannula over 20 minutes to a stirred solution of 3-butyn-1-ol (1.00 mL, 13.2 mmol) in THF (41.3 mL) at -78 °C. The mixture was stirred at -78 °C for 1 hour, then chlorotrimethylsilane (4.10 mL, 32.0 mmol) was added dropwise over 5 minutes and the mixture was stirred at -78 °C for 30 minutes. The mixture was allowed to warm to 0 °C over 1 hour, then quenched by cautious addition of water (15 mL) and allowed to warm to room temperature. The separated aqueous phase was extracted with diethyl ether (2 × 15 mL) and the combined organic extracts were concentrated *in vacuo*. The residue was dissolved in diethyl ether (30 mL) and washed sequentially with 2 M hydrochloric acid (15 mL), a saturated aqueous solution of NaHCO3 (2 × 30 mL), and brine (30 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. Triphenylphosphine (3.98 g, 15.2 mmol) and imidazole (1.72 g, 25.2 mmol) were added to a stirred solution of the residue in dichloromethane (63 mL) and the mixture was then cooled to 0 °C. Iodine (3.86 g, 15.2 mmol) was added in portions over 10 minutes and the resulting mixture was stirred at room temp for 1 hour. The mixture was diluted with water (40 mL) and the separated aqueous phase was extracted with pentane (2 × 15 mL). The combined organic extracts were washed with brine (30 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica (100 % petroleum ether) to give the iodide (2.27 g, 69 %) as a clear colourless oil. The spectral data is in agreement with literature.[106]

(106) Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, 3917.

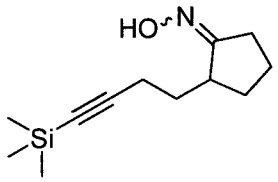


***N*-Cyclopentylidenecyclohexanamine (3.39).** Cyclopentanone (2.00 mL, 22.6 mmol), aminocyclohexane (2.84 mL, 24.9 mmol) and dry toluene (4.52 mL) were refluxed for 20 hours in a dean-stark apparatus. After cooling to room temp, the volatiles are removed *in vacuo* and the residual ketimine is purified by distillation (bp 108-111 °C/9 Torr) to provide the desired ketimine (2.3 g, 62 %) as a pale yellow oil. The spectral data is in agreement with literature.[72]

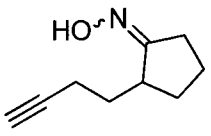


2-(4-(Trimethylsilyl)but-3-ynyl)cyclopentanone (3.41). A solution of LDA prepared from 1.18 mL of freshly distilled diisopropylamine (8.32 mmol) and 3.87 mL of *n*-butyllithium (2.25 M in hexane, 8.70 mmol) in 8.3 mL of THF was cooled to -78 °C. *N*-Cyclopentylidenecyclo-hexanamine (1.25 g, 7.56 mmol) was then added dropwise. The reaction was allowed to warm to 0 °C slowly. It was then recooled to -78 °C, and 4-iodo-1-trimethylsilylbut-1-yne (2.00 g, 7.94 mmol) was added. The reaction was allowed to warm to room temperature slowly and stirred overnight. The solvents were partially removed, and the residue was taken up in 12 mL of ether and 7.7 mL of 2 M aqueous hydrochloric acid and heated to reflux. After 8 h, the layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were extracted with saturated, aqueous sodium bicarbonate solution (2 x 10 mL) and brine (2 x 10 mL) and dried. Removal of solvents *in vacuo* yielded a brown liquid.

Flash column chromatography (10 % ether in pentane) gave the titled compound as a yellow liquid (0.9 g, 57 %). The spectral data is in agreement with literature.[73]

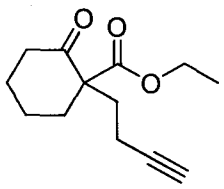


2-(4-(Trimethylsilyl)but-3-ynyl)cyclopentanone oxime (Table 3.11, entry 18, 3.7p). Prepared according to general procedure D using 2-(4-(trimethylsilyl)but-3-ynyl)cyclopentanone (0.900 g, 4.32 mmol). The crude product was then purified by flash chromatography on silica gel with 35 % ether in pentane to yield 0.87 g (91 %) of the product as a pale yellow oil. TLC R_f 0.25 in 30 % ether in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 9.09 (br, 1H), 2.71-2.49 (m, 2H), 2.43 (dd, J = 9.99, 8.62 Hz, 1H), 2.35-2.22 (m, 2H), 2.10-1.76 (m, 3H), 1.73-1.46 (m, 2H), 1.46-1.28 (m, 1H), 0.12 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 168.5 (C), 106.7 (C), 84.8 (C), 42.2 (CH), 31.5 (CH2), 31.0 (CH2), 27.2 (CH2), 22.4 (CH2), 18.1 (CH2), 0.076 (CH3); IR (film) 3317, 2968, 2873, 2173, 1679, 1443, 1409, 1246, 1041, 839cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{21}NOSi$ $[M]^+$: 223.3867. Found: 223.1364.



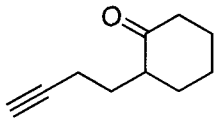
2-(But-3-ynyl)cyclopentanone oxime (Table 3.11, entry 15, 3.7m). To a solution of 2-(4-(trimethylsilyl)but-3-ynyl)cyclopentanone oxime (0.230 g, 1.03 mmol) in CH_2Cl_2 (2.6 mL) was added TBAF (1.29 mL of a 1.0 M solution in THF, 1.29 mmol) at rt. The

reaction mixture was stirred for 3 hours, diluted with ether and extracted 3 times, washed with NH_4Cl, water, brine, then dried and concentrated. Purification by flash column chromatography (35 % ether in pentane) provided 0.136 g (88 %) of the desired product as a clear colourless oil. TLC R_f 0.29 in 20 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 9.00 (br, 1H), 2.61 (ddd, *J* = 12.45, 11.55, 5.46 Hz, 2H), 2.49-2.36 (m, 1H), 2.36-2.17 (m, 2H), 2.10-1.97 (m, 1H), 1.97-1.90 (m, 2H), 1.90-1.76 (m, 1H), 1.74-1.47 (m, 2H), 1.37 (tt, *J* = 11.90, 9.24 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δppm168.5 (C), 83.9 (C), 68.6 (CH), 42.0 (CH), 31.5 (CH2), 30.8 (CH2), 27.2 (CH2), 22.4 (CH2), 16.6 (CH2); IR (film) 3295, 2957, 2868, 1672, 1440, 1432, 1197, 961, 923, 639 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{11}NO$ $[M]^+$: 151.0997. Found: 151.0979.

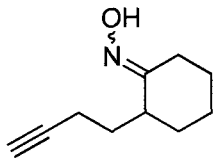


Ethyl 1-(but-3-ynyl)-2-oxocyclohexanecarboxylate (3.48). Prepared by a modification of Renaud's procedure.[74] To a suspension of NaH (0.586 g, 14.7 mmol, 60% dispersion in mineral oil) in DMF (12.3 mL) was added dropwise at 0 °C a solution of 2-oxo-cyclohexanecarboxylic acid ethyl ester (1.95 mL, 12.2 mmol) in DMF (12.3 mL). The cold bath was removed and the reaction mixture stirred at room temperature for 1.5 h. A solution of 4-iodo-but-1-yne (2.20 g, 12.2 mmol) in DMF (12.3 mL) was added dropwise at room temperature and the reaction mixture was stirred for 12 h. The reaction was treated with 1 N HCl. Ether (20 mL) was added and the aqueous layer extracted with ether (4 x). The combined organic layers were washed

with diluted HCl (1 N), brine (2 x), dried over Na_2SO_4, and the solvent removed under reduced pressure. Product was used crude for the next reaction.

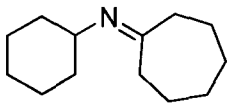


2-(But-3-ynyl)cyclohexanone (3.49). To a solution of crude ethyl 1-(but-3-ynyl)-2-oxocyclohexanecarboxylate in DMF (16.3 mL) was added LiI (8.18 g, 61.1 mmol). The reaction mixture was stirred at 150 °C for 1.5 h. After completion, the reaction mixture was cooled to room temperature and treated with 1 N HCl. Ether (20 mL) was added and the aqueous layer extracted (4 x). The combined organic layers were washed with 1 N HCl, brine (2 x), dried over Na_2SO_4, and the solvent removed under reduced pressure. Product was used crude for the next reaction.

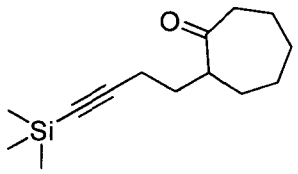


2-(But-3-ynyl)cyclohexanone oxime (Table 3.11, entry 16, 3.7n). Prepared according to general procedure D using crude 2-(but-3-ynyl)cyclohexanone. The product was then purified by flash chromatography on silica gel (20 % EtOAc in hexanes) to yield 0.176 g (10 % over 3 steps) of the product as a clear colourless oil. TLC R_f 0.67 in 50 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 8.17 (br, 1H), 3.83-3.37 (br, 1H), 2.35-2.06 (m, 4H), 1.97 (t, J = 2.44 Hz, 1H), 1.95-1.83 (m, 2H), 1.82-1.66 (m, 2H), 1.59 (d, J = 6.36 Hz, 3H), 1.43 (td, J = 13.51, 8.11 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm *162.3 (C),

160.8 (C), 84.4 (C), 68.1 (CH), 32.1 (CH2), *31.9 (CH), 30.1 (CH2), *29.9 (CH2), 28.6 (CH2), 26.8 (CH2), *26.8 (CH2), *25.8 (CH2), 25.6 (CH2), *24.4 (CH2), *20.7 (CH2), 16.6 (CH2); IR (film) 3298, 2933, 2861, 1653, 1451 1242, 965 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{15}NO$ $[M]^+$: 165.1154. Found: 165.1143.

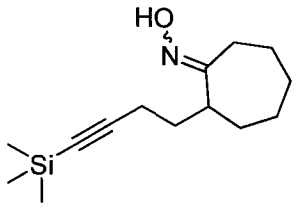


***N*-Cycloheptylidenecyclohexanamine (3.40).** Cycloheptanone (1.50 mL, 12.7 mmol), aminocyclohexane (1.60 mL, 14.0 mmol) and dry toluene (2.54 mL) were refluxed for 20 hours in a dean-stark apparatus. After cooling to room temp, the volatiles are removed *in vacuo* and the residual ketimine is purified by distillation (bp 93-100 °C/0.11 Torr) to provide the desired ketimine (1.55 g, 63 %) as a pale yellow oil. The spectral data is in agreement with literature.[72]



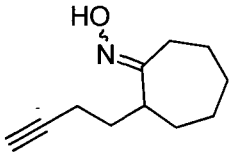
2-(4-(Trimethylsilyl)but-3-ynyl)cycloheptanone (3.42). Prepared by a modification of Trost's procedure.[73] A solution of LDA prepared from 1.09 mL of freshly distilled diisopropylamine (7.69 mmol) and 3.74 mL of *n*-butyllithium (2.15 M in hexane, 8.04 mmol) in 7.68 mL of THF was cooled to -78 °C. *N*-Cycloheptylidene-cyclohexanamine (1.35 g, 7.00 mmol) was then added dropwise. The reaction was allowed to warm to 0 °C slowly. It was then recooled to -78 °C, and 4-iodo-1-trimethylsilylbut-1-yne (1.85 g, 7.34 mmol) was added. The reaction was allowed to

warm to room temperature slowly and stirred overnight. The solvents were partially removed, and the residue was taken up in 11 mL of ether and 7.1 mL of 2 M aqueous hydrochloric acid and heated to reflux. After 8 h, the layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were extracted with saturated, aqueous sodium bicarbonate solution (2 x 10 mL) and brine (2 x 10 mL) and dried. Removal of solvents *in vacuo* yielded a brown liquid. Flash column chromatography (15 % ether in pentane) gave the titled compound as a pale yellow oil (1.36 g, 82 %). TLC R_f 0.78 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.72 (ddt, J = 10.38, 6.10, 3.13 Hz, 1H), 2.55-2.36 (m, 2H), 2.20 (t, J = 7.17 Hz, 2H), 2.00-1.73 (m, 5H), 1.71-1.56 (m, 1H), 1.54-1.37 (m, 2H), 1.37-1.15 (m, 2H), 0.11 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 215.4 (C), 106.6 (C), 85.1 (C), 50.3 (CH), 43.2 (CH2), 31.3 (CH2), 30.3 (CH2), 29.1 (CH2), 28.8 (CH2), 24.0 (CH2), 17.6 (CH2), 0.064 (CH3); IR (film) 2930, 2853, 2173, 1698, 1249, 842cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{24}OSi$ $[M]^+$: 236.1596. Found: 236.1570.



2-(4-(Trimethylsilyl)but-3-ynyl)cycloheptanone oxime (Table 3.11, entry 19, 3.7q). Prepared according to general procedure D using 2-(4-(trimethylsilyl)but-3-ynyl)cycloheptanone (1.36 g, 5.75 mmol). The crude product was then purified by flash chromatography on silica gel with 35 % ether in hexanes to yield 1.1 g (74 %) of the product as a clear colourless oil. TLC R_f 0.25 in 20 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 8.92 (br, 1H), 3.28 (tt, J =

12.91, 5.68 Hz, 0.7H), 2.83 (ddd, J = 13.43, 6.40, 2.47 Hz, 0.3H), 2.57-2.08 (m, 3H), 2.07-1.71 (m, 5H), 1.72-1.53 (m, 2H), 1.41-1.17 (m, 3H), 1.09 (dd, J = 22.23, 11.23 Hz, 1H), 0.13 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 165.9 (C), *164.4 (C), 107.4 (C), *107.3 (C), *84.3 (C), 84.4 (C), *43.2 (CH), 37.4 (CH), *31.9 (CH2), *31.9 (CH2), *32.3 (CH2), 32.2 (CH2), 31.2 (CH2), 30.8 (CH2), 30.7 (CH2), 30.6 (CH2), 29.3 (CH2), 26.7 (CH2), *26.4 (CH2), *25.3 (CH2), *17.9 (CH2), 17.8 (CH2), 0.129 (CH3), *0.099 (CH3); IR (film) 3234, 3089, 2933, 2854, 2175, 1456, 1448, 1249, 976, 801, 759, 641 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{25}NOSi$ $[M]^+$: 251.1705. Found: 251.1687.



2-(But-3-ynyl)cycloheptanone oxime (Table 3.11, entry 17, 3.7o). To a solution of 2-(4-(trimethylsilyl)but-3-ynyl)cycloheptanone oxime (0.525 g, 2.09 mmol) in CH_2Cl_2 (5.22 mL) was added TBAF (2.61 mL of a 1.0 M solution in THF, 2.61 mmol) at rt. The reaction mixture was stirred for 3 hours, diluted with ether and extracted 3 times, washed with NH_4Cl, water, brine, then dried and concentrated. Purification by flash column chromatography (35% ether in pentane) provided 0.297 g (79 %) of the desired product as a white solid (mp = 83.1 – 85 °C, ethanol). TLC R_f 0.32 in 25 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of oxime isomers) 9.10 (br, 1H), 2.98-2.65 (m, 1H), 2.61-2.38 (m, 1H), 2.30-2.08 (m, 2H), 2.03-1.86 (m, 3H), 1.87-1.39 (m, 6H), 1.24 (dd, J = 15.76, 8.05 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 164.2 (C), 84.1 (C), 68.4 (CH), 42.9 (CH), 32.6 (CH2), 32.6 (CH2), 30.7 (CH2), 26.2 (CH2),

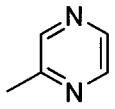
25.2 (CH2), 25.2 (CH2), 16.4; IR (film) 3298, 3222, 3066, 2930, 2854, 1652, 1451, 980, 953 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{17}NO$ $[M]^+$: 179.1310. Found: 179.1293.

General Procedure for the Alkyne Cyclizations - Pyrazines (Table 3.11)

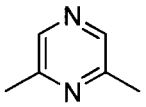
General Procedure A : An oven-dried 5-20 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynyl oxime (1.00 equiv), *p*-toluenesulfonic acid (0.02 equiv) and isopropanol (such that the concentration of the alkynyl oxime was 0.1 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for 5 hours at 160 °C. The reaction solution was cooled to ambient temperature, further acidified using *p*-toluenesulfonic acid (1.0 equiv), concentrated under reduced pressure and analyzed by ^1H NMR using styrene or 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure, cooled to 0°C, basified using triethylamine (1.5 equiv) and directly purified by silica gel chromatography to give the corresponding products.

General Procedure B : An oven-dried 5-20 mL microwave tube was charged with a stir bar, capped with a septum and purged with argon and an outlet for 5 minutes. The alkynyl oxime (1.00 equiv), *p*-toluenesulfonic acid (0.02 equiv) and chlorobenzene (such that the concentration of the alkynyl oxime was 0.1 M) were added to the sealed tube, while keeping it under an argon atmosphere. The septum was removed and the

tube was then quickly sealed with a microwave cap and heated for 8 hours at 180 °C. The reaction solution was cooled to ambient temperature, further acidified using *p*-toluenesulfonic acid (1.0 equiv), concentrated under reduced pressure and analyzed by ^{1}H NMR using styrene or 1,4-dimethoxybenzene as an internal standard. The unpurified material was then again concentrated under reduced pressure, cooled to 0°C, basified using triethylamine (1.5 equiv) and directly purified by silica gel chromatography to give the corresponding products.

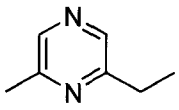


2-Methylpyrazine (Table 3.12, entry 1, 3.58a). Synthesized according to general procedure A using oxime **2a** (0.105 g, 0.494 mmol). The reaction mixture was concentrated and gave an NMR yield of 67% using 1,4-dimethoxybenzene as an internal standard. The spectral data is in agreement with literature.[107]

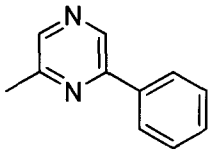


2,6-Dimethylpyrazine (Table 3.12, entry 2, 3.58b). Synthesized according to general procedure A using oxime **3.56b** (0.110 g, 0.486 mmol). The reaction mixture was concentrated and isolated using flash chromatography (80 % ether in pentane). The title compound was obtained as yellow crystals (0.0395 g, 75 % yield). TLC R_f 0.3 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[107]

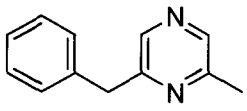
(107) Matsuo, M.; Matsumoto, S.; Kurihara, T.; Akita, Y.; Watanabe, T.; Ohta, A. *Org. Magn. Reson.* **1980**, *13*, 172.



2-Ethyl-6-methylpyrazine (Table 3.12, entry 3, 3.58c). Synthesized according to general procedure A using oxime **3.56c** (0.110 g, 0.456 mmol). The reaction mixture was concentrated and isolated using flash chromatography (30 % ether in pentane). The title compound was obtained as a pale yellow oil (0.0449 g, 81 % yield). TLC R_f 0.63 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[108]



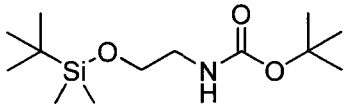
2-Methyl-6-phenylpyrazine (Table 3.12, entry 4-5, 3.58d). Synthesized according to general procedure B using oxime **3.56d** (0.125 g, 0.434 mmol). The reaction mixture was concentrated and isolated using flash chromatography (40 % ether in pentane). The title compound was obtained as a pale yellow oil (0.0335 g, 45 % yield). TLC R_f 0.37 in 50 % ether in hexanes. The spectral data is in agreement with literature.[107]



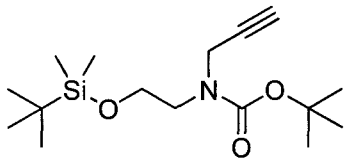
2-Benzyl-6-methylpyrazine (Table 3.12, entry 6, 3.58e). Synthesized according to general procedure B using oxime **3.56e** (0.0750 g, 0.248 mmol). The reaction mixture was concentrated and isolated using flash chromatography (50 % ether in pentane). The title compound was obtained as a pale yellow oil (0.0233 g, 51 % yield). TLC R_f 0.39 in 50 % EtOAc in hexanes. The spectral data is in agreement with literature.[108]108

(108) Bramwell, A. F.; Payne, L. S.; Riezebos, G.; Ward, P.; Wells, R. D. *J. Chem. Soc. (C)* **1971**, 1627

Preparation of Substrates (Table 3.11, entries 1-6, 4a-e)



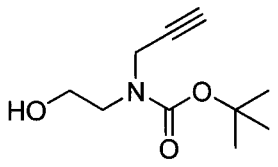
***tert*-Butyl 2-(*tert*-butyldimethylsilyloxy)ethylcarbamate (3.65).** To a solution of *N*-Boc-ethanolamine (5.36 g, 33.2 mmol) in CH_2Cl_2 (76 mL) was added TBSCl (5.51 g, 36.6 mmol), imidazole (3.40 g, 49.9 mmol) and DMAP (0.609 g, 4.99 mmol). The reaction was stirred at rt overnight then quenched with water. The mixture was extracted with CH_2Cl_2, then the combined organic layers were washed with water, a saturated aqueous solution of ammonium chloride, and then brine. The solution was dried with $MgSO_4$ and concentrated. The crude material was purified via column chromatography (30 % EtOAc in hexanes) to provide 7.85 g (86 %) as a clear colorless oil. The spectral data is in agreement with literature.[109]



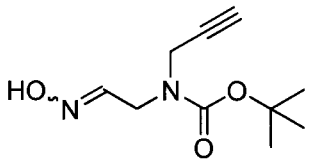
***tert*-Butyl 2-(tert-butyldimethylsilyloxy)ethyl(prop-2-ynyl)carbamate (3.66).** To a solution of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy)ethylcarbamate (7.48 g, 27.2 mmol) in THF (41 mL) was added NaH (1.63 g of a 60% dispersion in mineral oil, 40.7 mmol) in three portions at 0 °C. The suspension was then stirred for 1.5 h at rt and then cooled to 0 °C. To the reaction mixture was added propargyl bromide (10.1 mL of an

(109) Molander, G. A.; Cormier, E. P. *J. Org. Chem.* **2005**, *70*, 2622.

80 % wt solution in toluene, 67.9 mmol) at 0 °C. The reaction mixture was stirred overnight warming to rt, and then quenched with MeOH. Water was then added to the dark brown reaction mixture, followed by an aqueous workup. The crude material was then purified by column chromatography (5 % ether in hexanes) to afford 5.65 g (66 %). The spectral data is in agreement with literature.[109]

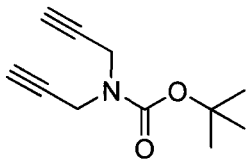


***tert*-Butyl 2-hydroxyethyl(prop-2-ynyl)carbamate (3.67).** To a solution of *tert*-butyl 2-(tert-butyldimethylsilyloxy)ethyl(prop-2-ynyl)carbamate (5.20 g, 16.6 mmol) in CH_2Cl_2 (83 mL) was added TBAF (20.0 mL of a 1.0 M solution in THF, 19.9 mmol) at rt. The reaction mixture was stirred overnight followed then quenched with an aqueous solution of NH_4Cl. Aqueous work up followed by column chromatography (40 % EtOAc in hexanes) provided 3.27 g (99 %) of the desired product as carbamate rotamers. The spectral data is in agreement with literature.[109]

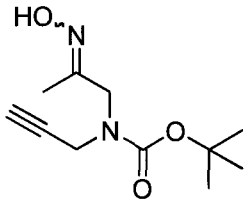


***tert*-Butyl 2-(hydroxyimino)ethyl(prop-2-ynyl)carbamate (Table 3.12, entry 1, 3.56a).** Prepared according to general procedure C using *tert*-butyl 2-hydroxyethyl(prop-2-ynyl)carbamate (0.900 g, 4.53 mmol). The crude product was then purified by flash chromatography on silica gel with 30 % EtOAc/hexanes to yield 0.713 g (74 %) of the product as a pale yellow oil. TLC R_f 0.41 in 30 % EtOAc in

hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers and oxime isomers) 8.75 (br, 1H), 7.38 (t, J = 5.29 Hz, 0.55H), 6.79 (br, 0.43H), 4.44-3.77 (m, 4H), 2.23 (br, 1H), 1.45 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) *denotes minor isomer δ ppm *154.8 (CH), *154.6 (CH), 150.2 (C), 147.2 (CH), 81.2 (C), 79.0 (C), *78.8 (C), *71.8 (CH), 72.0 (CH), *44.9 (CH2), 42.4 (CH2), *37.0 (CH2), 36.0 (CH2), 28.2 (CH3); IR (film) 3372, 3297, 2979, 2936, 1701, 1457, 1406, 1369, 1250, 1165, 1135, 994, 886, 774 cm^{-1}; LRMS m/z (relative intensity): 156.0528 (25.5 %), 139.0520 (24.4 %), 95.0606 (10.1 %), 57.0705 (100 %).

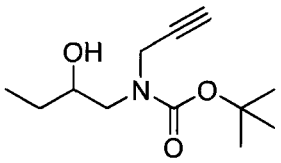


***tert*-Butyl diprop-2-ynylcarbamate (3.70).** A solution of *tert*-butyl prop-2-ynylcarbamate (3.83 g, 24.7 mmol) in 5.75 mL of DMF was treated portionwise (4 x) with 60 % NaH (1.20 g, 30.1 mmol) at 0 °C. After being stirred for 30 min at 25 °C, 4.48 mL of an 80% solution of propargyl bromide in xylene was added. The reaction mixture was stirred for an additional 5 h at 25 °C, and then quenched with the addition of ice-water. The mixture was extracted with Et_2O and the combined extracts were washed with brine, dried, and concentrated *in vacuo*. The crude product was purified using flash column chromatography (8 % EtOAc in hexanes) to afford 1.15 g (26 %) as a pale yellow oil. The spectral data is in agreement with literature.[80]



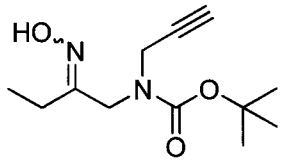
***tert*-Butyl 2-(hydroxyimino)propyl(prop-2-ynyl)carbamate (Table 3.12, entry 2, 3.56b).** Prepared by a modification of Beauchemin's procedure.[110] A 15 mL sealed tube was charged with a stir bar, a rubber septum and purged with argon. *tert*-Butyl diprop-2-ynylcarbamate (0.300 g, 1.55 mmol), aqueous hydroxylamine (0.143 mL, 2.33 mmol) and isopropanol (1.55 mL) were added in one portion. The mixture was heated at 100 °C overnight, concentrated and purified using flash column chromatography (20 % EtOAc in hexanes) to provide 0.0744 g (21 %) of the desired product as a clear colourless oil. TLC R_f 0.45 in 30 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers and oxime isomers) 9.06 (br, 1H), 4.34-3.82 (m, 1H), 2.20 (m, 1H), 1.85 (m, 3H), 1.45 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 156.6 (C), 154.9 (C), 154.8 (C), 154.7 (C), 80.9 (CH), 79.0 (C), *71.8 (C), 71.4 (C), *49.4 (CH2), 49.3 (CH2), *44.2 (CH2), *44.1 (CH2), *36.2 (CH2), 35.9 (CH2), *35.6 (CH2), 35.1 (CH2), 29.1 (CH3), 17.2 (CH3), *11.7 (CH3); IR (film) 3378, 3295, 2883, 2934, 1702, 1447, 1406, 1230, 1155 cm^{-1}; LRMS m/z (relative intensity): 170.0703 (31.5 %), 154.0716 (17.0 %), 153.0634 (100 %), 109.0752 (40.6 %), 73.0525 (52.7 %), 57.0699 (93.1 %).

(110) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

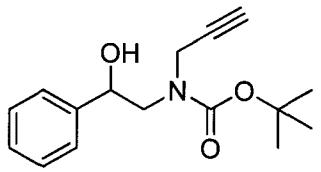


***tert*-Butyl 2-hydroxybutyl(prop-2-ynyl)carbamate (3.69).** A flame-dried flask was charged with CH_2Cl_2 (19 mL), Et_3N (1.91 mL, 13.7 mmol), DMSO (0.955 mL, 13.4 mmol) and *tert*-butyl 2-hydroxyethyl(prop-2-ynyl)carbamate (0.835 g, 4.19 mmol) at 0 °C. After 5 min of stirring, pyridine sulfur trioxide complex (2.08 g, 12.6 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted with dichloromethane (3 times). The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. A THF (10.5 mL) solution of the crude aldehyde was treated with ethylmagnesium chloride (2 M solution in diethyl ether, 10.5 mL, 21.0 mmol) at 0 °C. Once added, the ice bath was removed and the mixture was stirred at room temperature. Upon completion, the reaction medium was diluted with 20 mL of ether and quenched with 20 mL of sat. NH_4Cl. The aqueous layer was extracted twice with ether and organic phase was washed with brine, dried and concentrated. The crude was then purified using flash column chromatography (20 % EtOAc/Hexanes) to afford 0.552 g (58 %) of the alcohol as a clear colourless oil. TLC R_f 0.45 in 25 % EtOAc in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers) 4.06 (br, 2H), 3.73 (qd, J = 6.99, 5.54 Hz, 1H), 3.48-3.05 (m, 2H), 2.70 (br, 1H), 2.21 (t, J = 2.43 Hz, 1H), 1.50-1.40 (m, 11H), 0.94 (t, J = 7.44 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 156.1 (C), 80.8 (C), 79.7 (C), 72.3 (CH), 71.5 (CH), 53.0 (CH2), 38.2 (CH2), 28.2 (CH3), 27.8 (CH2), 9.78 (CH3); IR (film) 3450, 3311, 2975, 2934, 2880, 1683, 1461, 1412, 1368, 1249,

1169, 1142, 1064, 986, 873, 775 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{12}H_{21}N_1O_3$ $[M]^+$: 227.1521. Found: 227.1524.

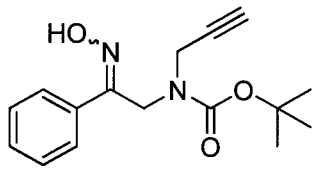


***tert*-Butyl 2-(hydroxyimino)butyl(prop-2-ynyl)carbamate (Table 3.12, entry 3, 3.56c).** Prepared according to general procedure C using *tert*-butyl 2-hydroxybutyl(prop-2-ynyl)carbamate (0.552 g, 2.43 mmol). The crude product was then purified by flash chromatography on silica gel with 20 % EtOAc/hexanes to yield 0.259 g (44 %) of the product as a clear colourless oil. TLC R_f 0.45 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers and oxime isomers) 4.31 (s, 1H), 4.16-3.86 (m, 3H), 2.34 (dd, *J* = 15.26, 7.65 Hz, 1H), 2.30-2.18 (m, 2H), 1.47 (s, 9H), 1.09 (t, *J* = 6.99 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 159.3 (C), *158.7 (C), 154.8 (C), 80.8 (C), 79.0 (C), 71.5 (CH), *47.8 (CH2), *47.5 (CH2), 43.0 (CH2), *42.4 (CH2), *37.5 (CH2), *37.0 (CH2), 35.7 (CH2), *35.5 (CH2), 28.2 (CH3), 24.8 (CH2), *24.3 (CH2), *19.4 (CH2), *19.1 (CH2), *9.9 (CH3), 9.8 (CH3); IR (film) 3382, 3296, 2977, 2937, 2884, 1700, 1456, 1406, 1368, 1250, 1165, 1125, 990, 934, 870, 772, 655 cm^{-1}; LRMS m/z (relative intensity): 167.0827 (36.6 %), 123.0912 (13.8 %), 87.0705 (25.6 %), 68.0508 (23.6 %), 57.0709 (100 %).

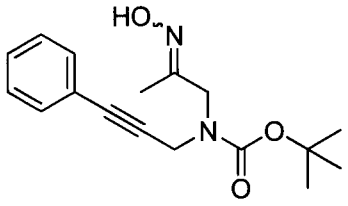


***tert*-Butyl 2-hydroxy-2-phenylethyl(prop-2-ynyl)carbamate (3.70).** A flame-dried flask was charged with CH_2Cl_2 (23 mL), Et_3N (2.30 mL, 16.4 mmol), DMSO (1.14 mL, 16.1 mmol) and *tert*-butyl 2-hydroxyethyl(prop-2-ynyl)carbamate (1.00 g, 5.02 mmol) at 0 °C. After 5 min of stirring, pyridine sulfur trioxide complex (2.40 g, 15.1 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was vigorously stirred for 2 hours, quenched by NH_4Cl addition and extracted with dichloromethane (3 times). The combined organic extracts were washed with water, brine, dried and concentrated to afford the crude aldehyde as a beige oil. A THF (12.5 mL) solution of the crude aldehyde was treated with phenylmagnesium bromide (3 M solution in diethyl ether, 8.36 mL, 25.1 mmol) at 0 °C. Once added, the ice bath was removed and the mixture was stirred at room temperature. Upon completion, the reaction medium was diluted with 20 mL of ether and quenched with 20 mL of sat. NH_4Cl. The aqueous layer was extracted twice with ether and organic phase was washed with brine, dried and concentrated. The crude was then purified using flash column chromatography (20 % EtOAc/Hexanes) to afford 0.860 g (62 %) of the alcohol as a pale yellow oil. TLC R_f 0.5 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers) 7.60-6.83 (m, 5H), 4.95 (s, 1H), 4.15-3.89 (m, 2H), 3.52 (s, 2H), 2.23 (t, J = 2.26 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 155.4 (C), *157.3 (C), 142.1 (C), 128.4 (CH), 127.4 (CH), 127.6 (CH), 125.8 (C), 81.2 (C), *81.1 (C), 80.2 (C), 74.4 (CH), *74.1 (CH), 71.8 (CH), 55.1 (CH2), *55.0 (CH2), 38.3 (CH2), *37.8 (CH2), 28.3 (CH3); IR

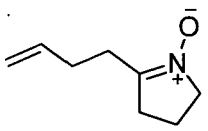
(film) 3447, 3296, 2978, 2934, 1679, 1456, 1411, 1368, 1249, 1166, 1129, 1061, 870, 756, 701.7 cm^{-1}; LRMS m/z (relative intensity): 202.0872 (6.4 %), 168.1027 (20.1 %), 107.0492 (68.2 %), 68.0484 (88.0 %), 57.0558 (100 %).



***tert*-Butyl 2-(hydroxyimino)-2-phenylethyl(prop-2-ynyl)carbamate (Table 3.12, entry 4-5, 3.56d).** Prepared according to general procedure C using *tert*-butyl 2-hydroxy-2-phenylethyl(prop-2-ynyl)carbamate (0.859 g, 3.12 mmol). The crude product was then purified by flash chromatography on silica gel with 20 % EtOAc/hexanes to yield 0.367 g (50 %) of the product as a clear colourless oil. TLC R_f 0.35 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers and oxime isomers) 9.34 (s, 1H), 7.79-7.27 (m, 5H), 4.79 (d, J = 32.47 Hz, 2H), 3.86 (d, J = 63.53 Hz, 2H), 2.31-2.02 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 156.6 (C), 155.0 (C), *154.9 (C), 133.7 (C), 133.6 (C), 129.3 (CH), 128.3 (CH), 127.0 (CH), *81.1 (C), 80.9 (C), 79.0 (C), 72.0 (CH), *71.4 (CH), *41.1 (CH2), 39.7 (CH2), 36.2 (CH2), 28.1 (CH3); IR (film) 3295, 2979, 1695, 1498, 1456, 1408, 1368, 1249, 1163, 1126, 976, 934, 870, 764, 696 cm^{-1}; LRMS m/z (relative intensity): 232.0843 (39.4 %), 215.0835 (42.4 %), 169.0763 (19.2 %), 135.0695 (59.4 %), 104.0501 (48.0 %), 57.0556 (100 %).



***tert*-Butyl 2-(hydroxyimino)propyl(3-phenylprop-2-ynyl)carbamate (Table 3.12, entry 6, 3.56e).** To a Et_3N (1.95 mL) solution of iodobenzene (0.0890 mL, 0.796 mmol) was added $Pd(PPh_3)_2Cl_2$ (0.00465 g, 0.00663 mmol) and CuI (0.00253 g, 0.0133 mmol) at room temperature, and the mixture was stirred for 5 minutes before addition of *tert*-butyl 2-(hydroxyimino)propyl(prop-2-ynyl)carbamate (0.150 g, 0.663 mmol). The resulting mixture was stirred for 12 hours, and the solvent was removed *in vacuo* and treated with a sat. $NaHCO_3$ solution. The solution was then extracted with ethyl acetate, washed with brine, and dried. The crude alcohol was then purified using flash column chromatography (30 % EtOAc in hexanes) to afford 0.160 g (80 %) of the desired product as a pale yellow oil. TLC R_f 0.21 in 30 % EtOAc in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ ppm (mixture of rotamers and oxime isomers) 7.34 (m, 5H), 4.43-4.02 (m, 1H), 4.48-3.92 (m, 4H), 1.95 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 154.8 (C), 154.9 (C), 131.7 (CH), 128.2 (CH), 122.8 (C), 84.5 (C), 83.4 (C), 80.8 (C), *49.6 (CH2), 49.5 (CH2), *44.2 (CH2), 37.9 (CH2), *36.9 (CH2), *36.8 (CH2), 28.3 (CH3), *17.3 (CH3), 11.7 (CH3); IR (film) 3378, 2976, 2926, 1703, 1682, 1490, 1456, 1404, 1368, 1248, 1165, 1125, 1030, 967, 915, 870, 757, 692 cm^{-1}; LRMS m/z (relative intensity): 246.1008 (34.0 %), 229.0531 (67.2 %), 201.1033 (20.4 %), 185.1062 (27.1 %), 144.0809 (20.0 %), 130.0653 (29.7 %), 115.0531 (100 %).



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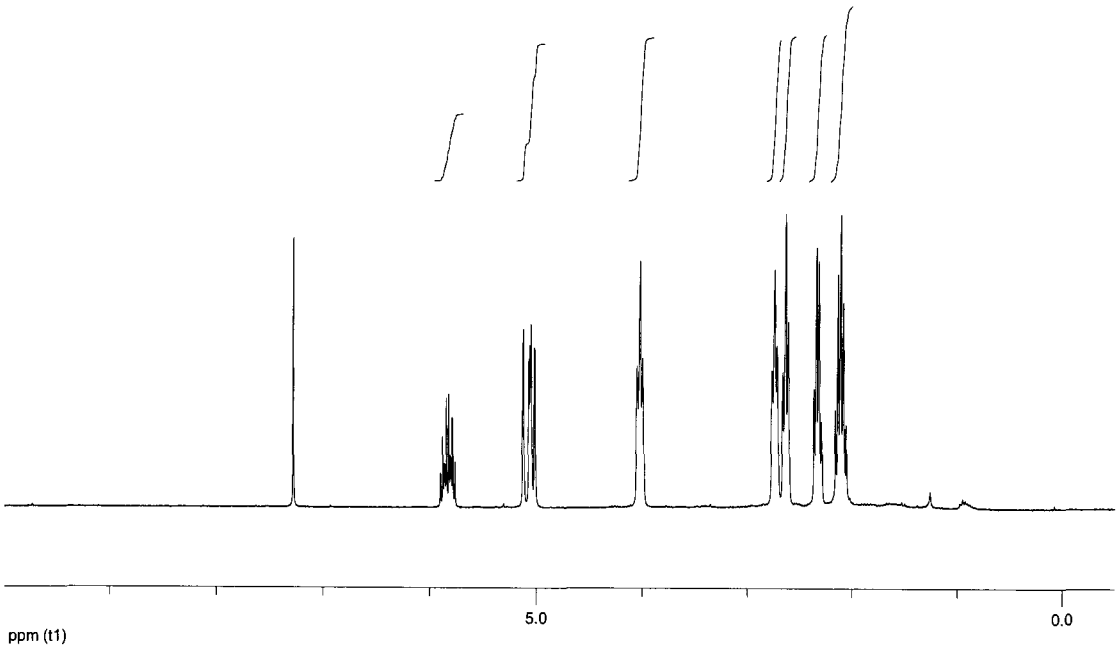

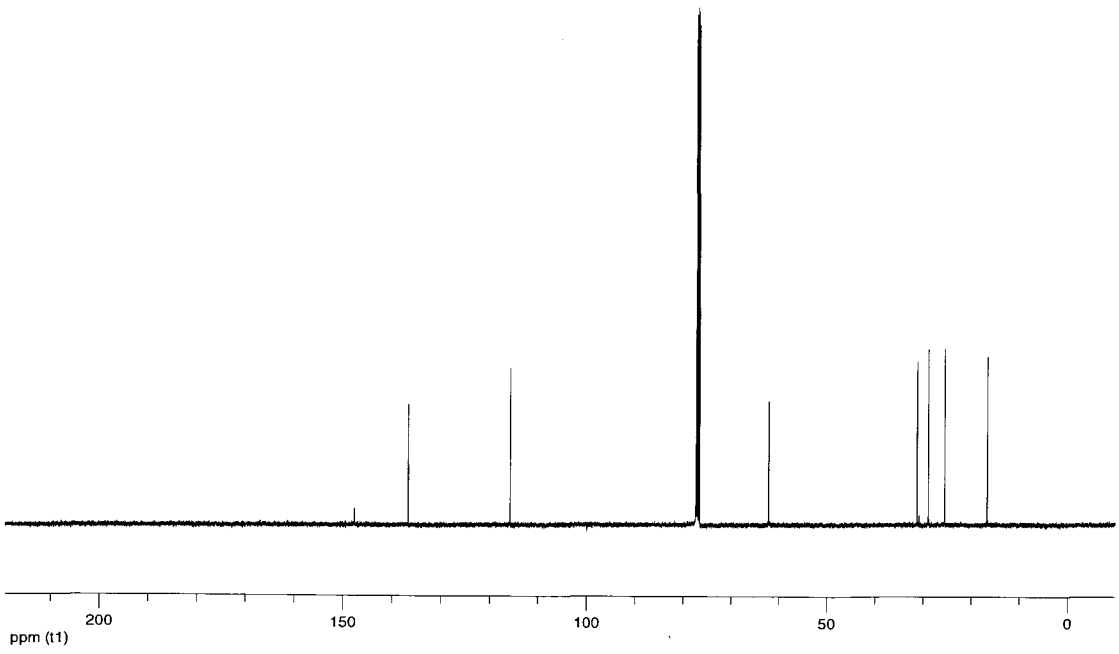

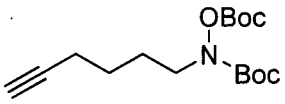

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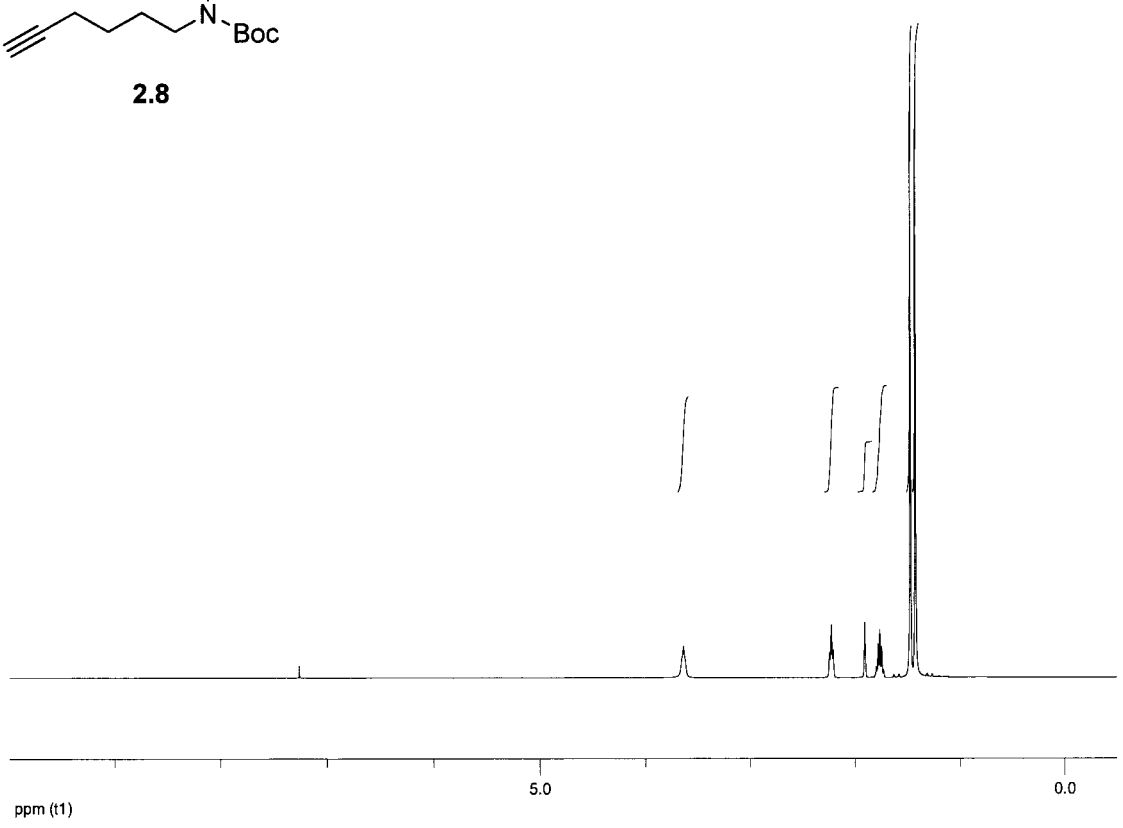

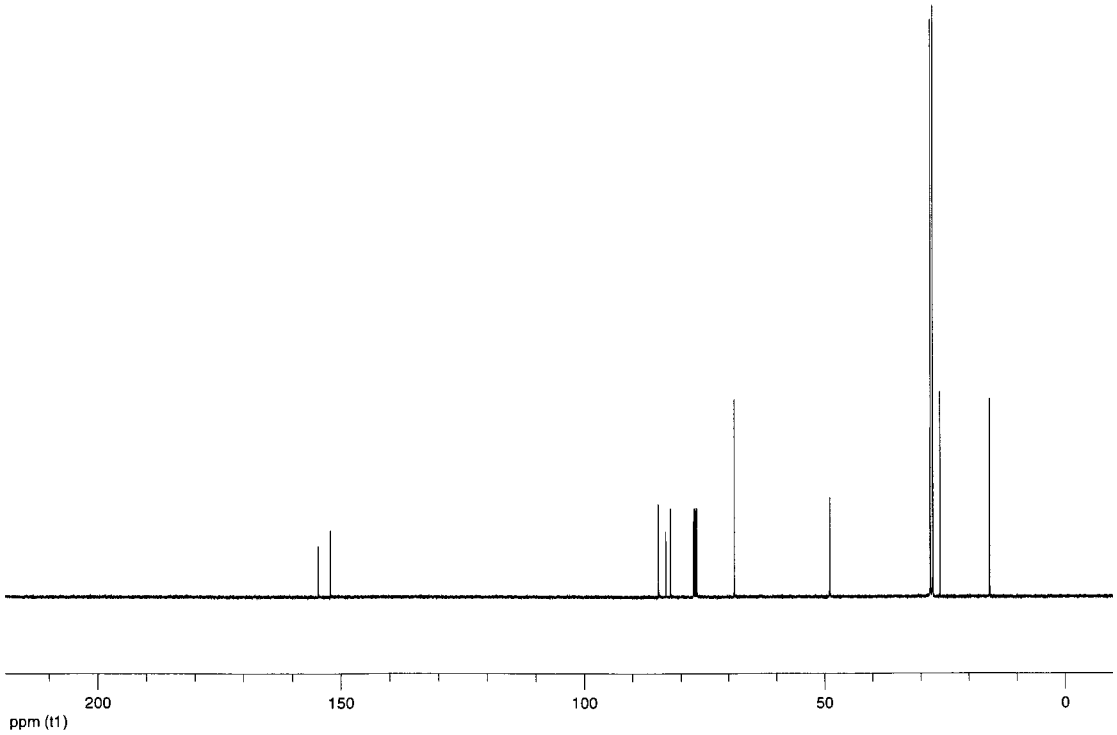

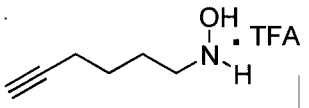

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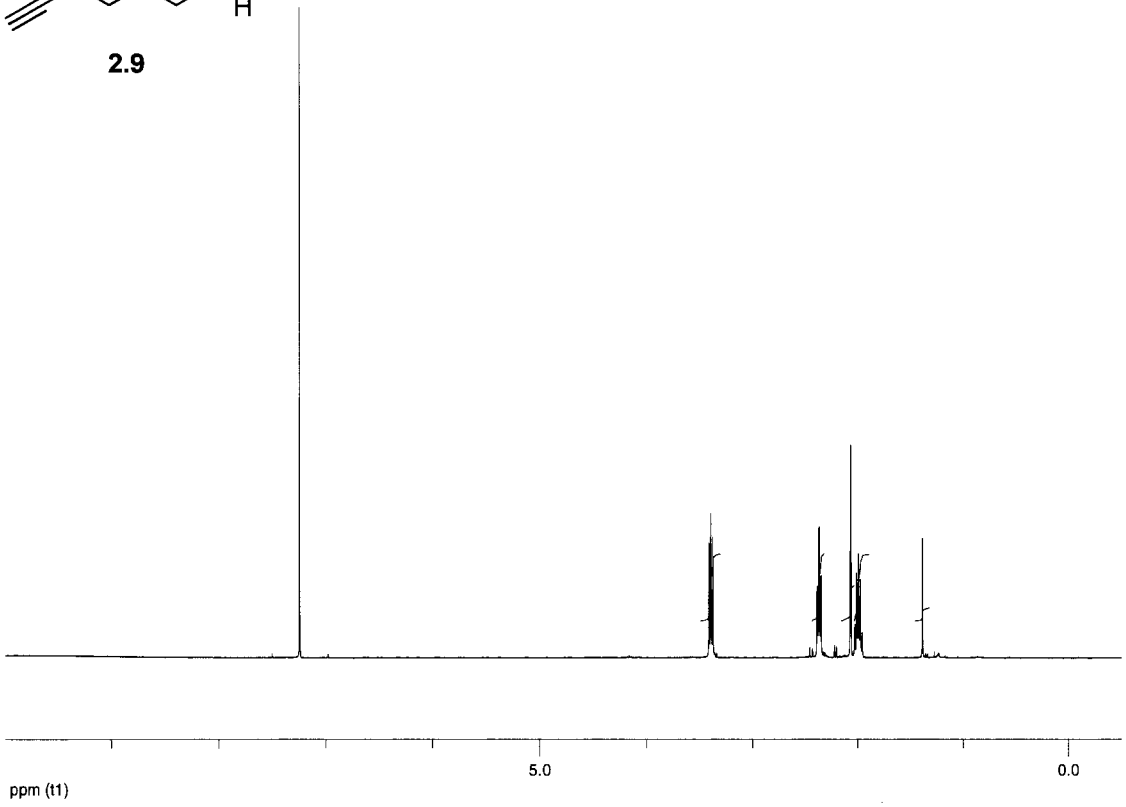

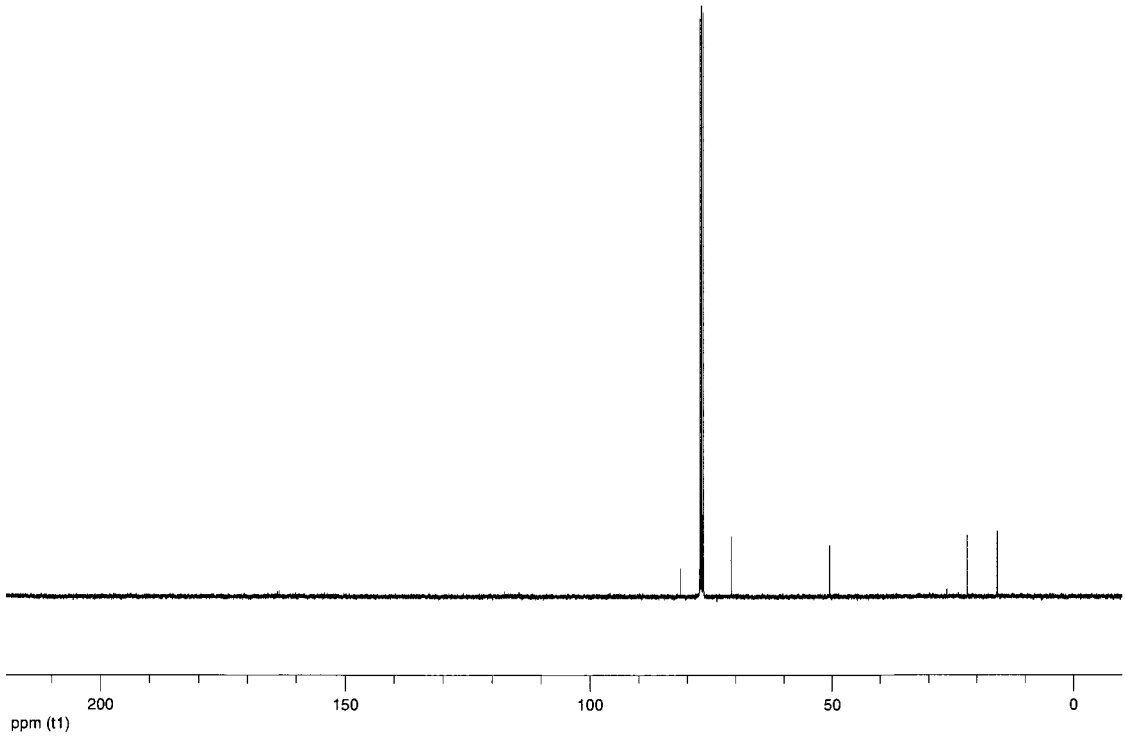

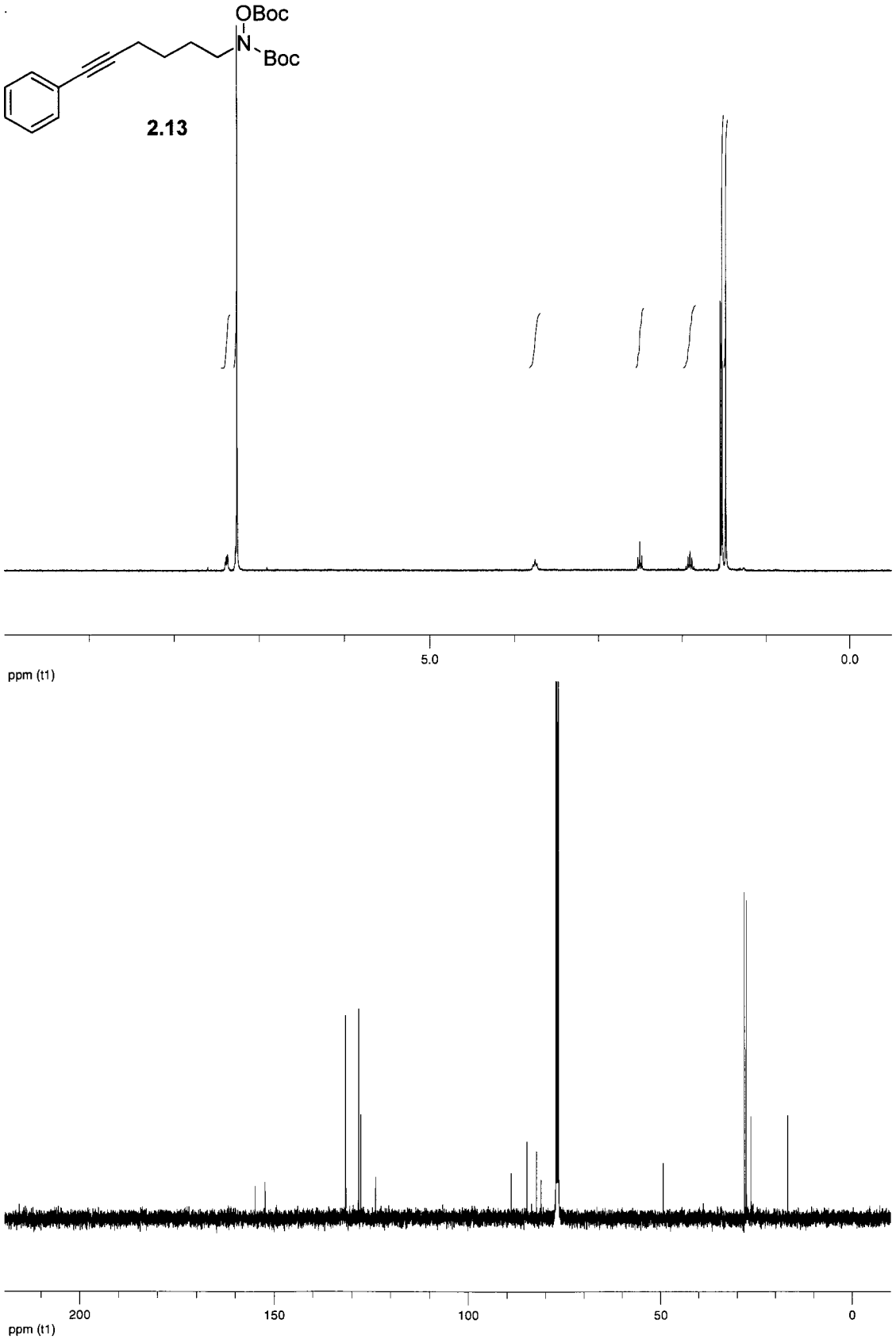
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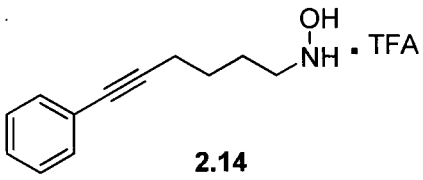

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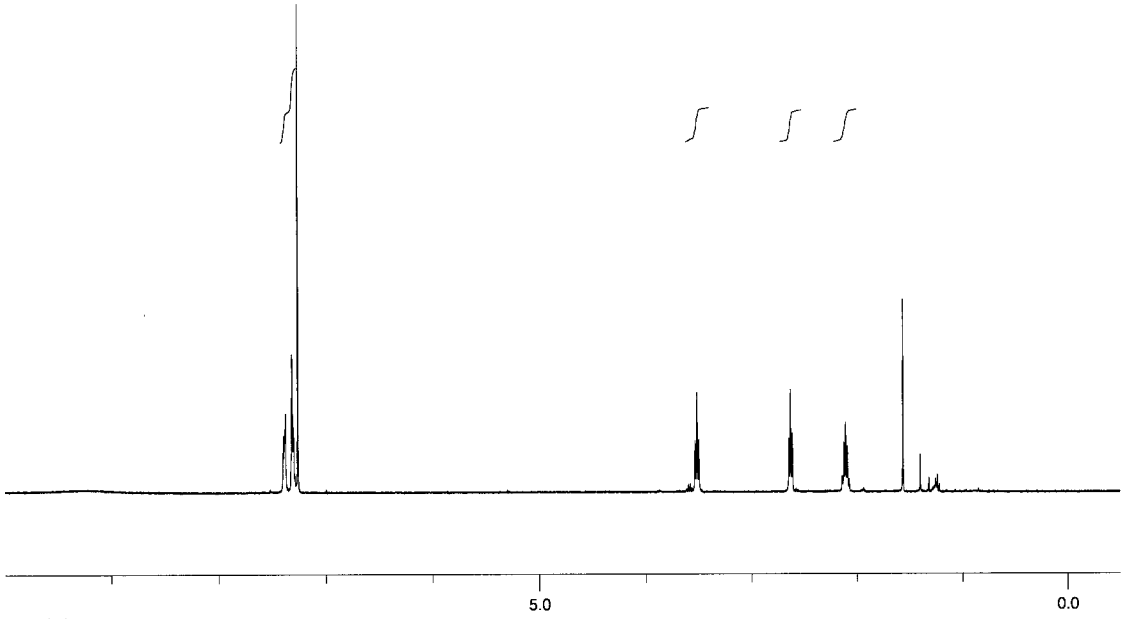

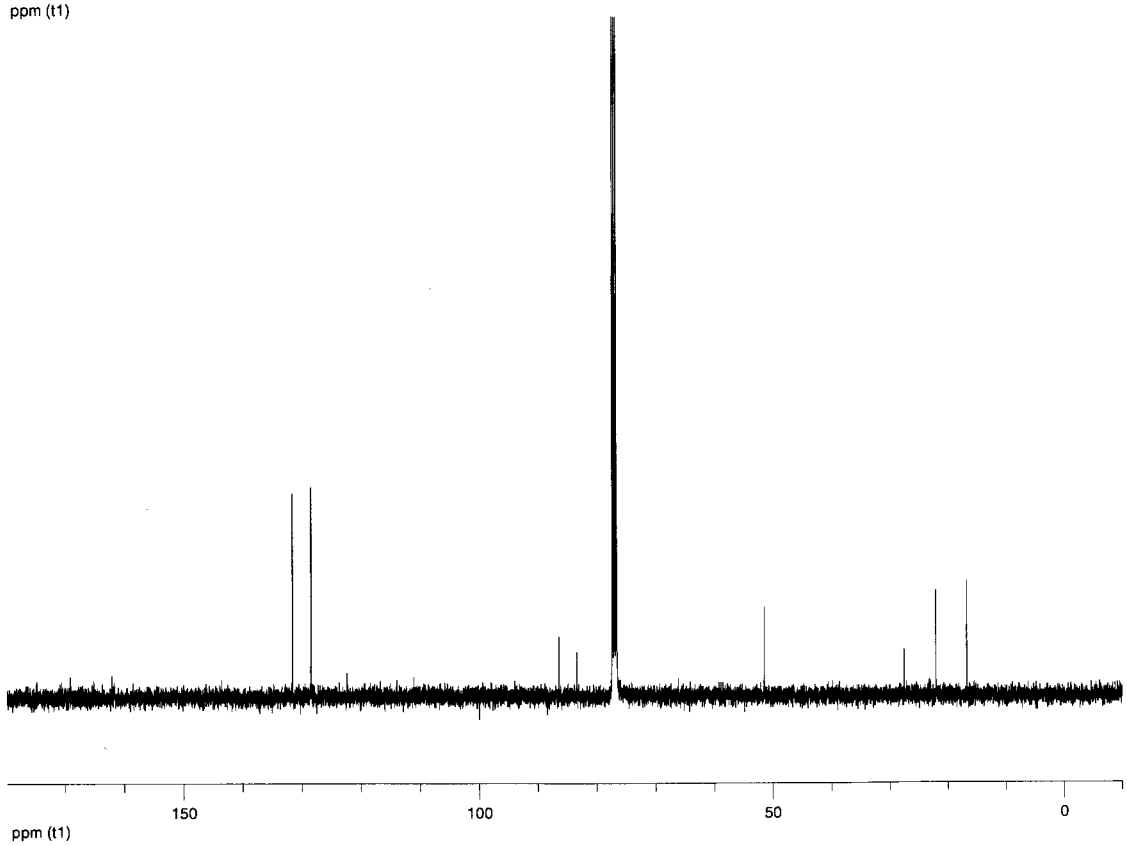

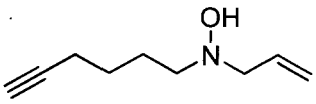

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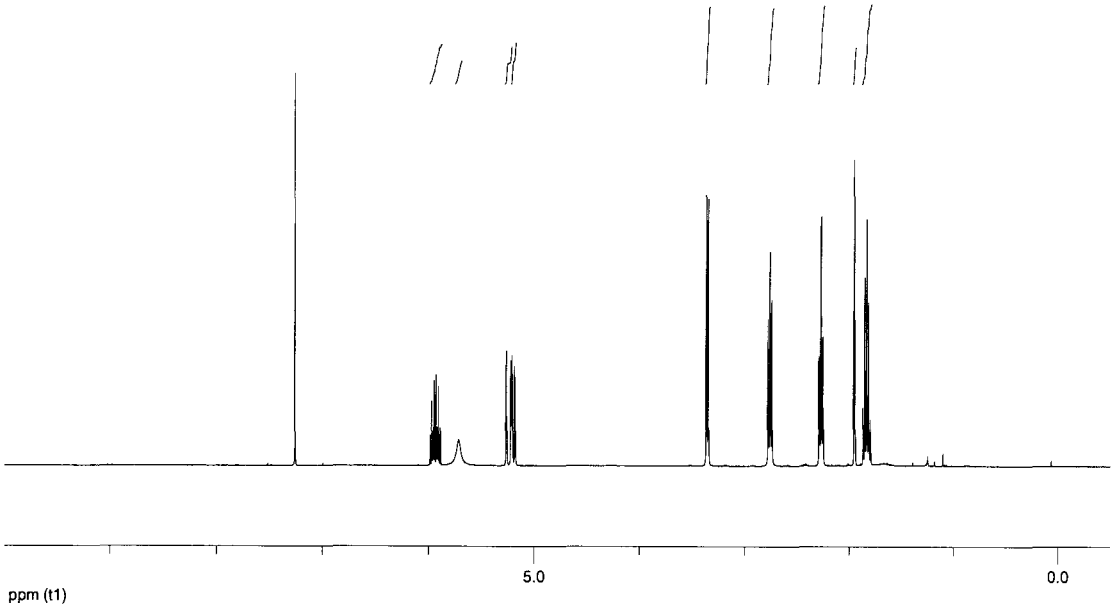

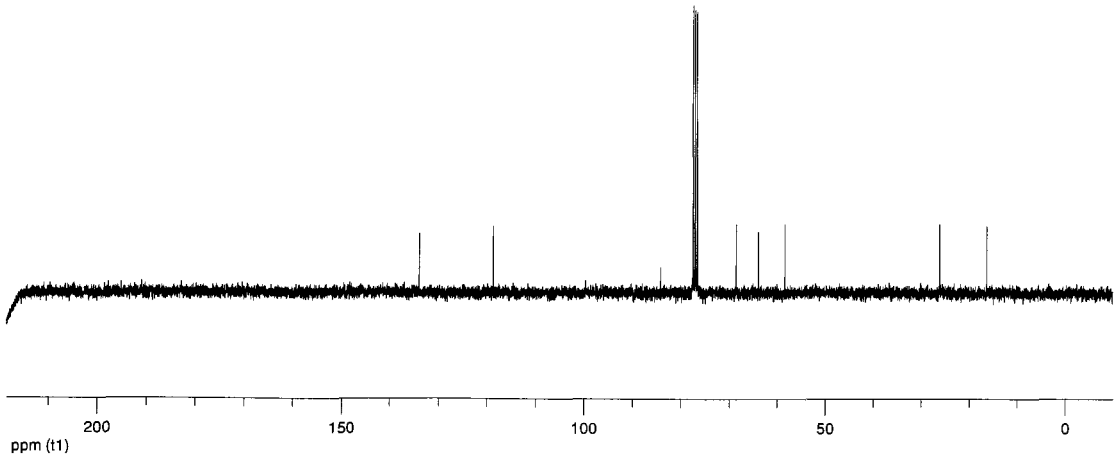

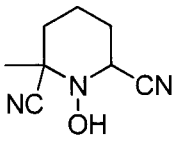

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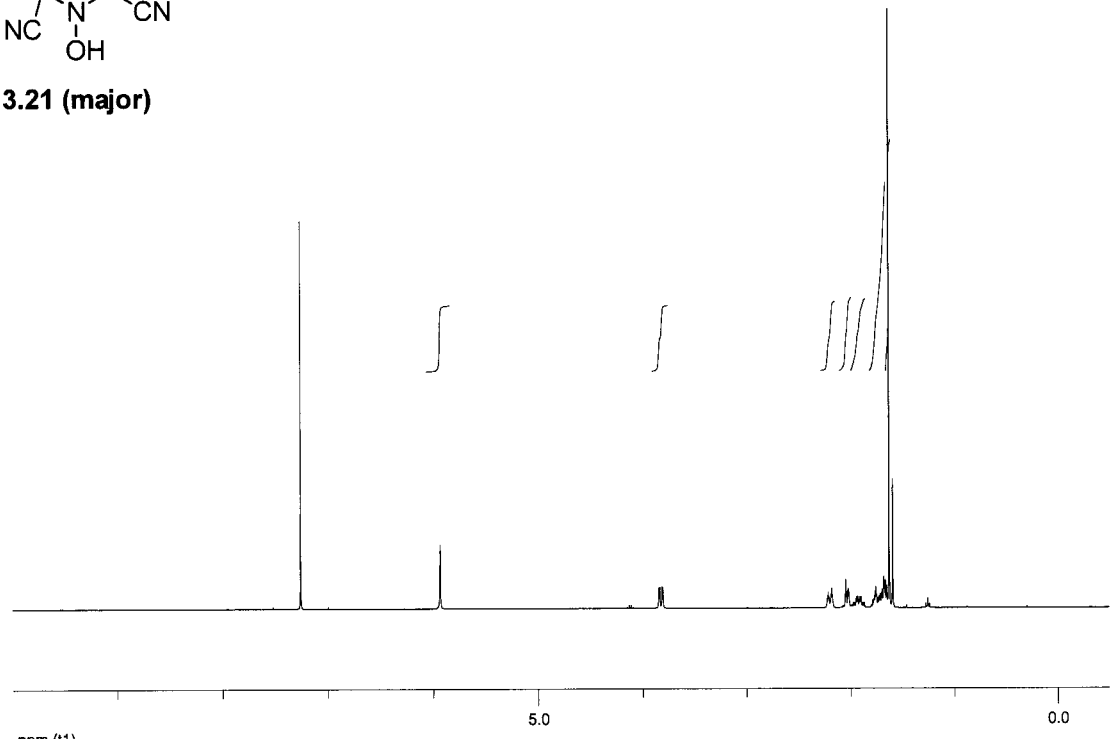

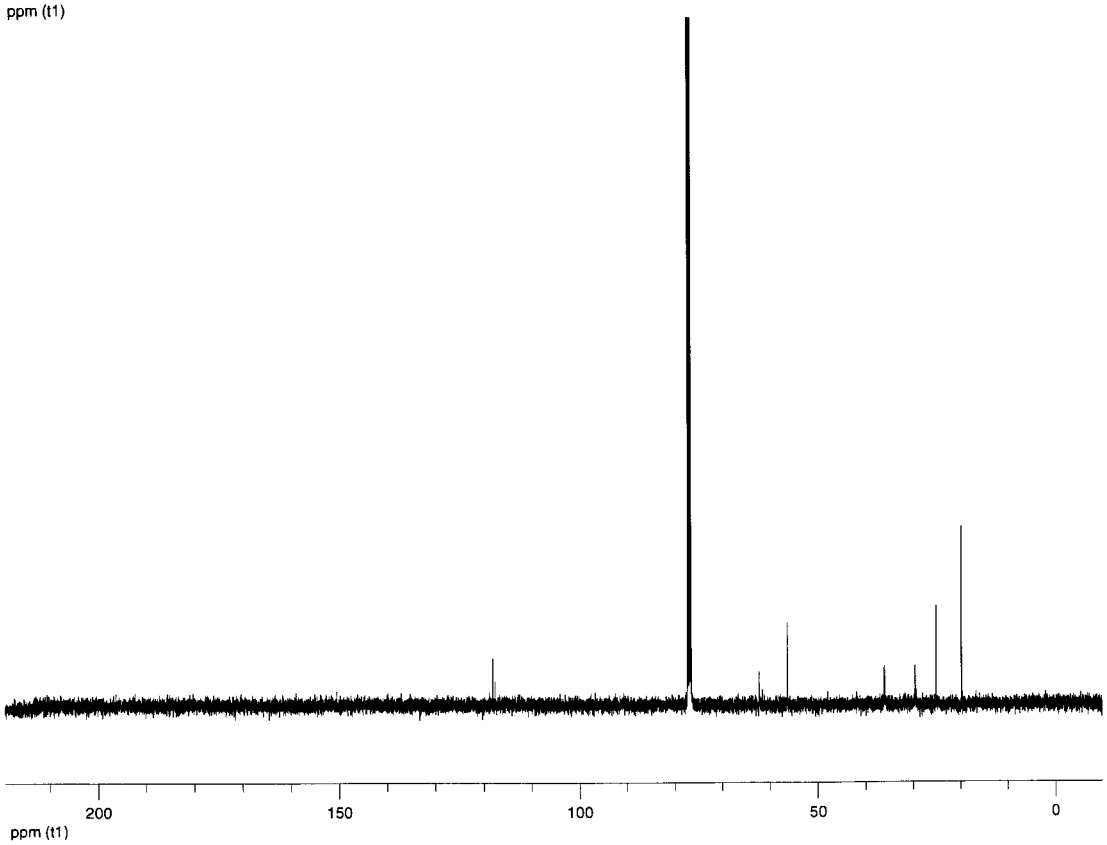

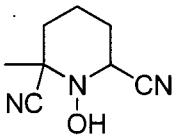

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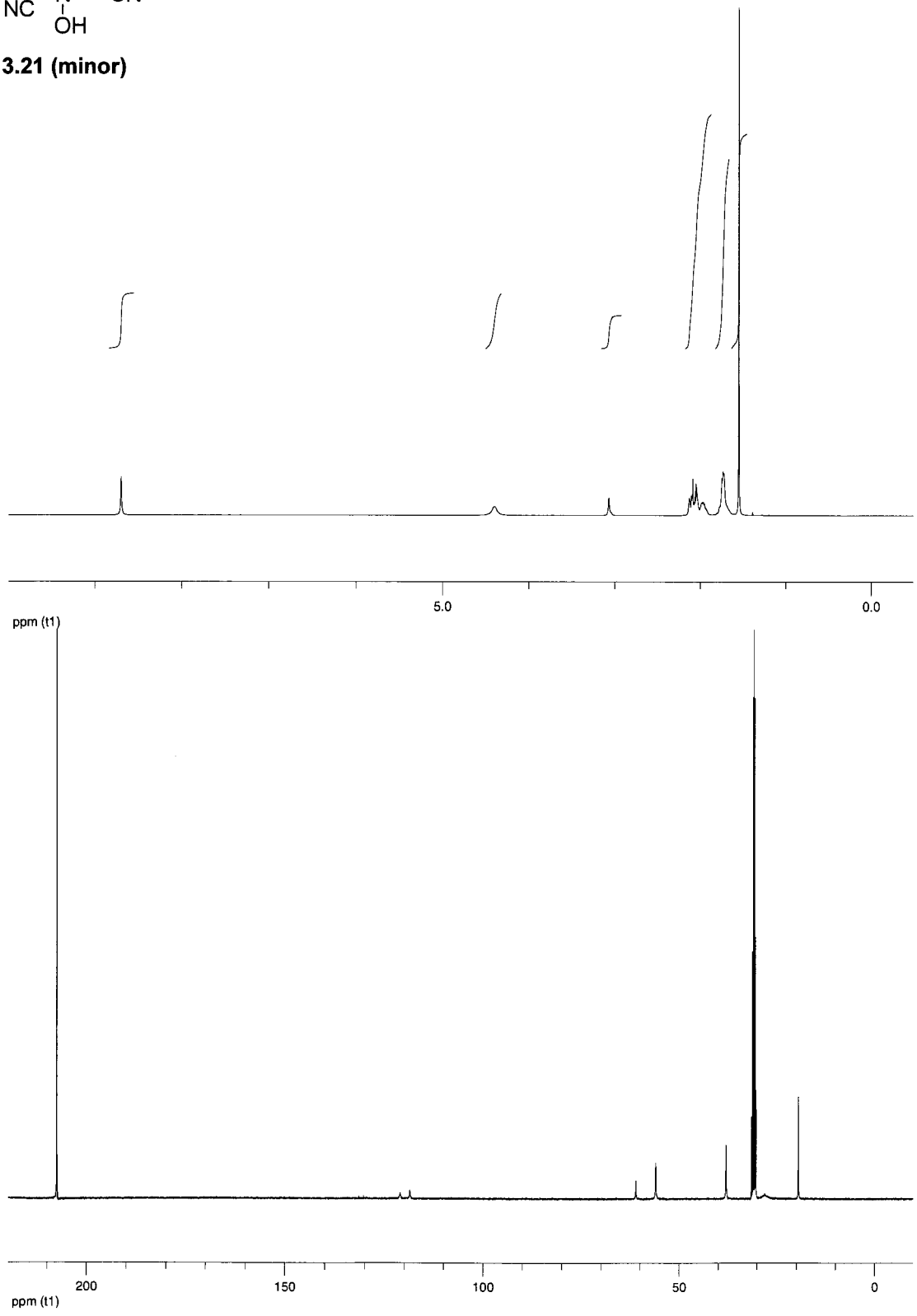

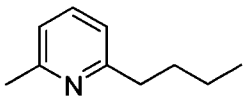

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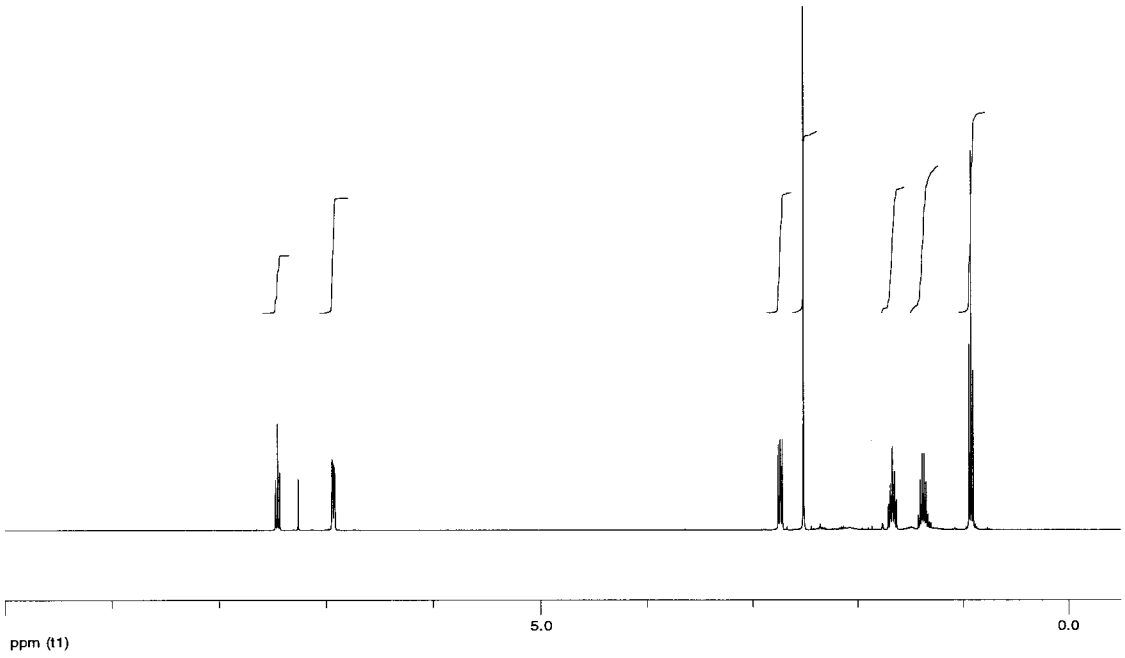

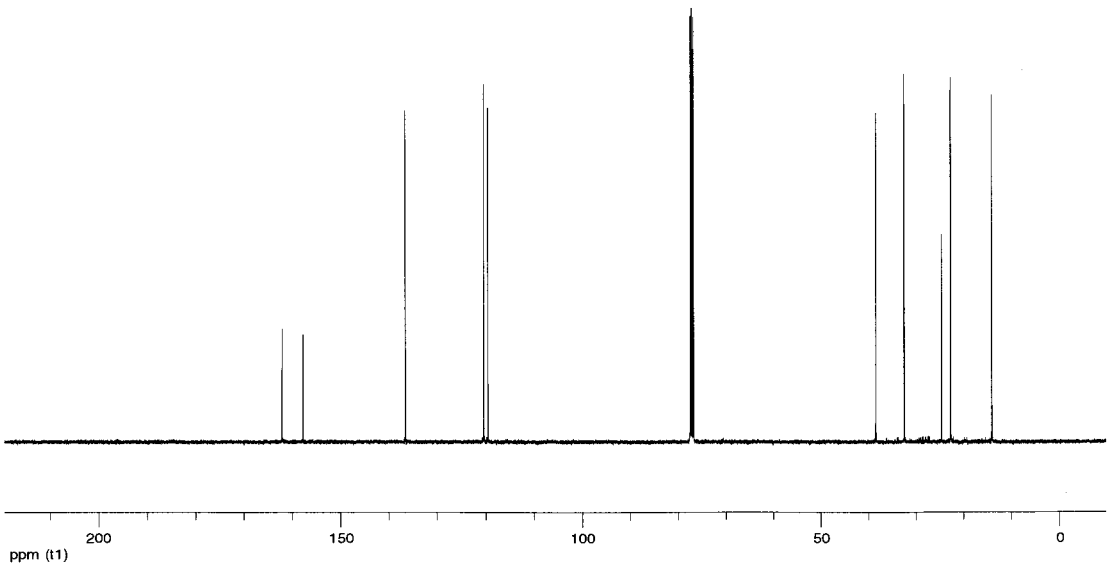

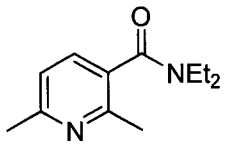

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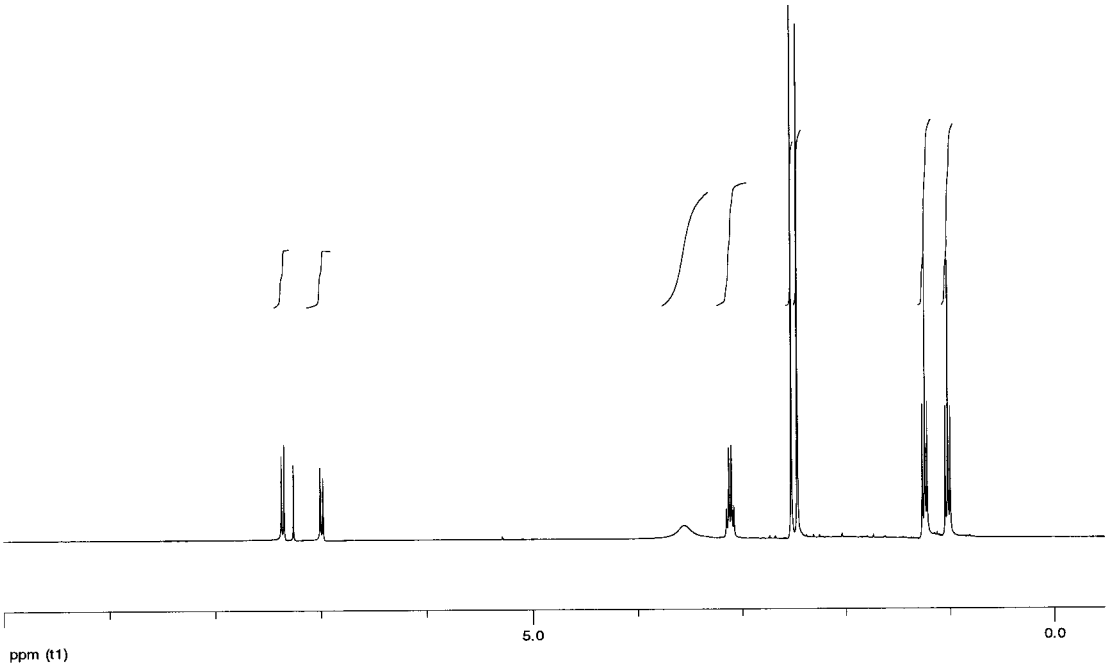

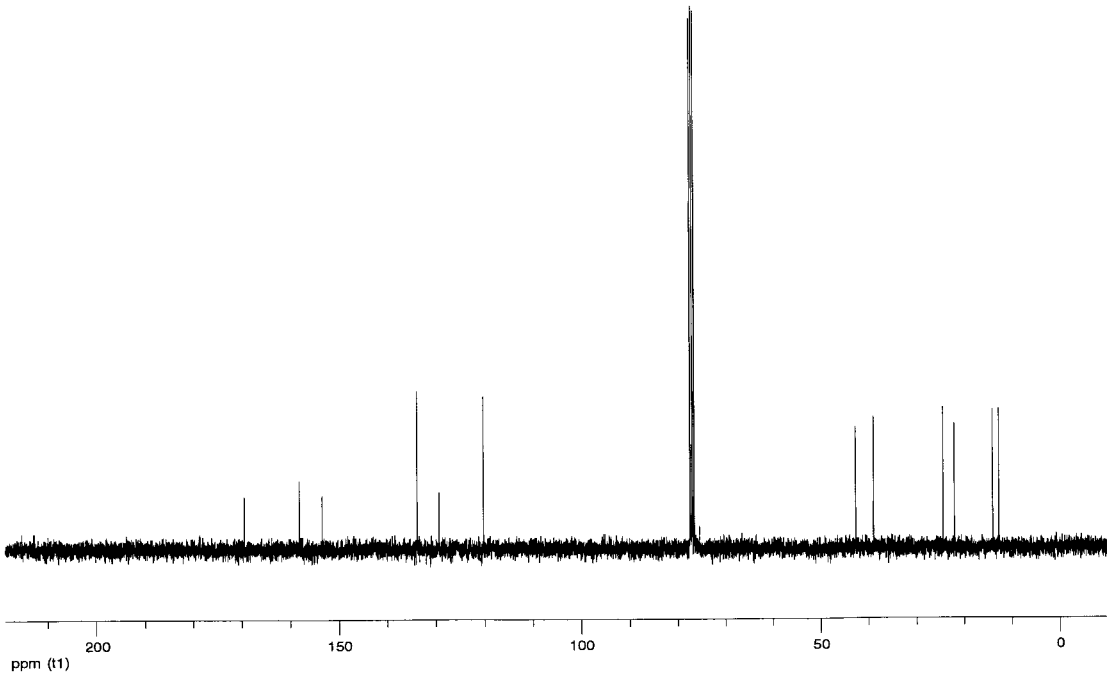

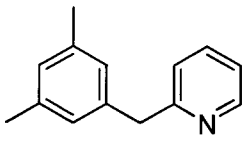

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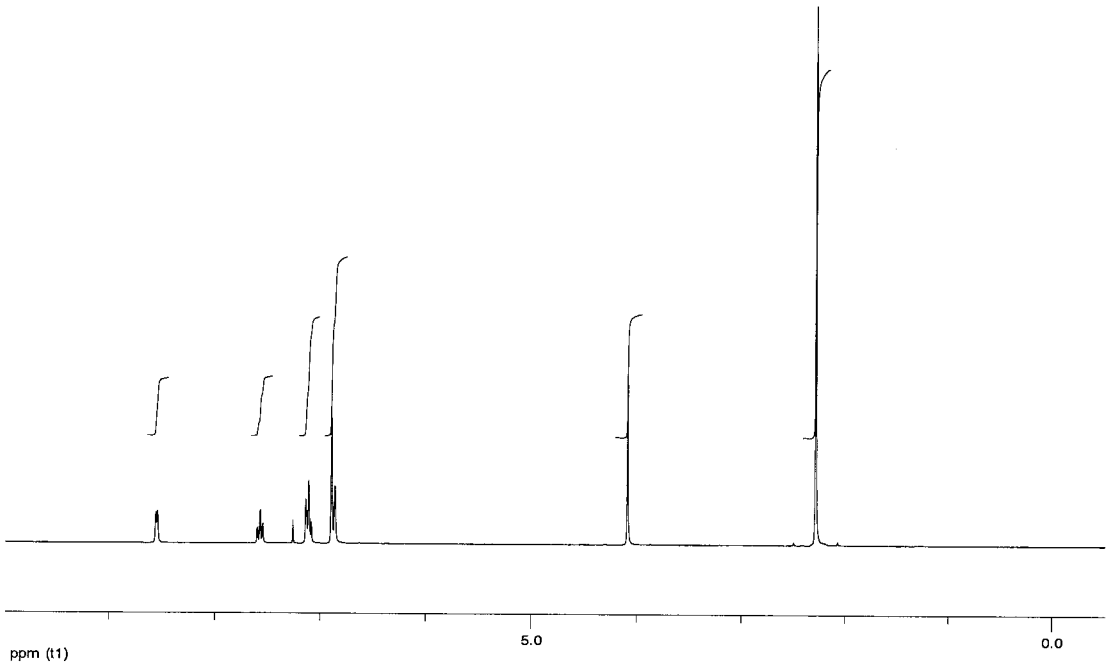

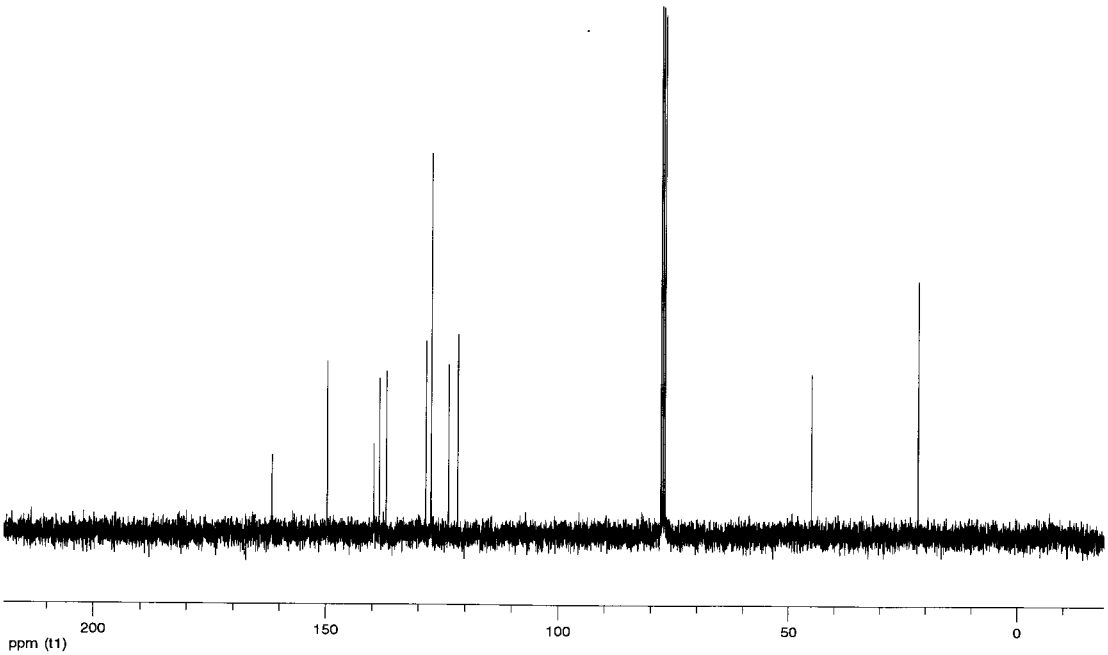

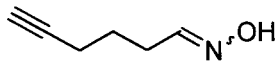

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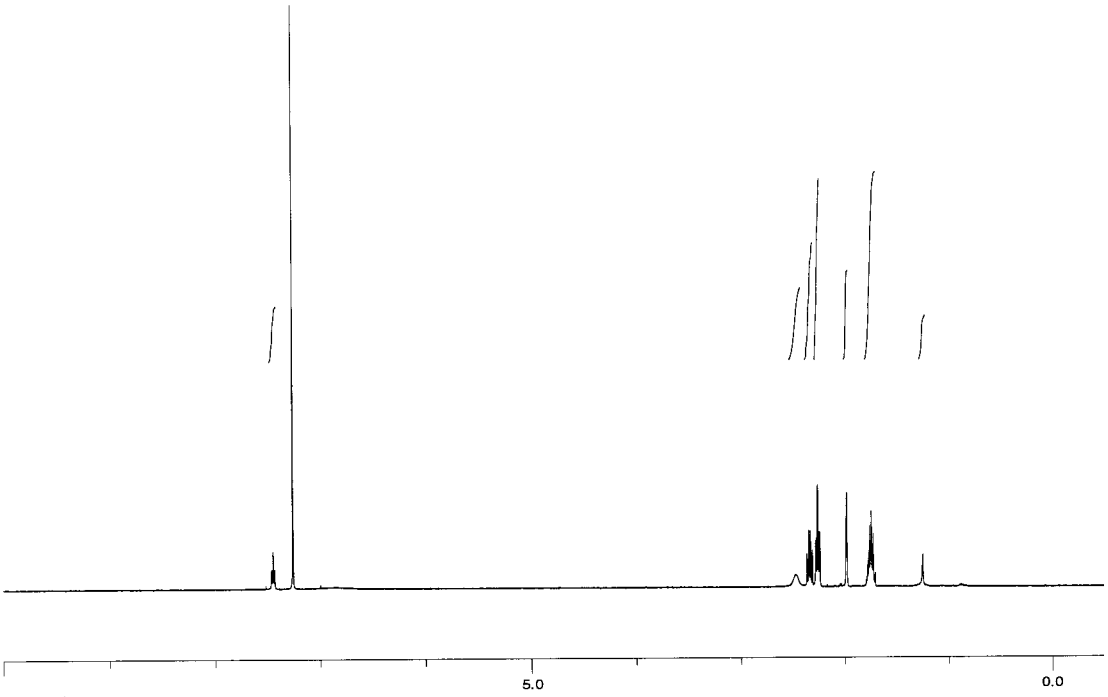

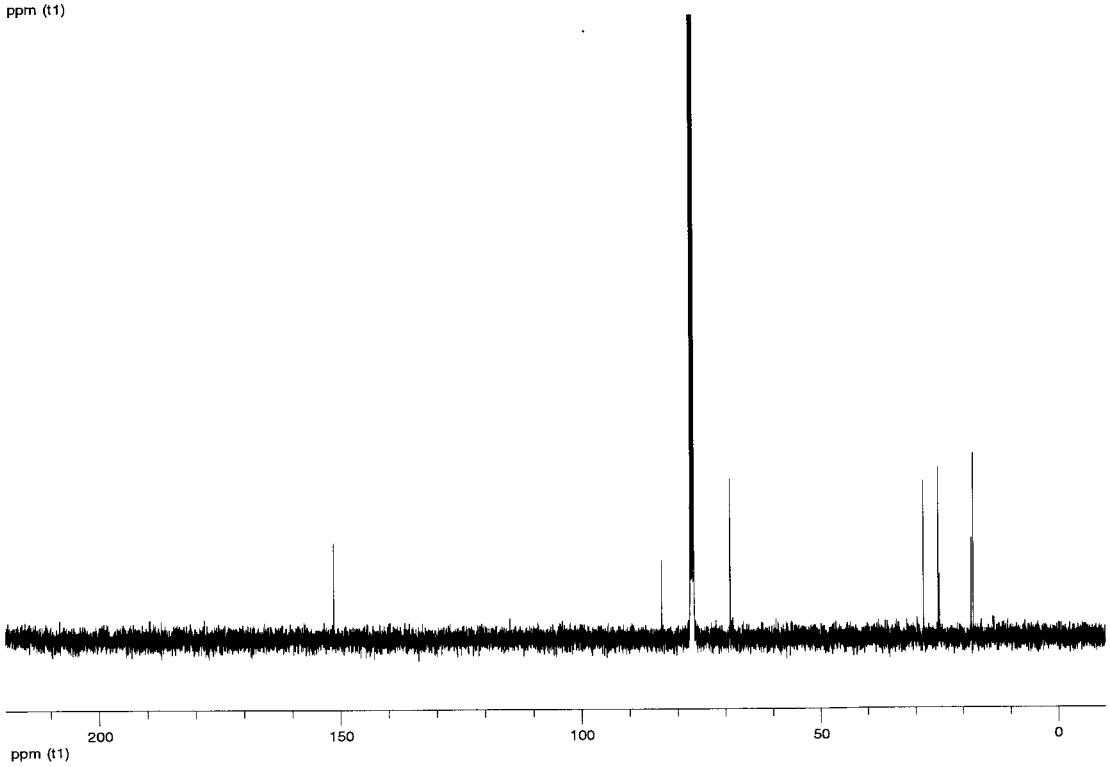

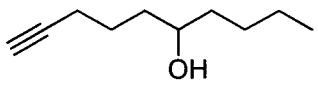

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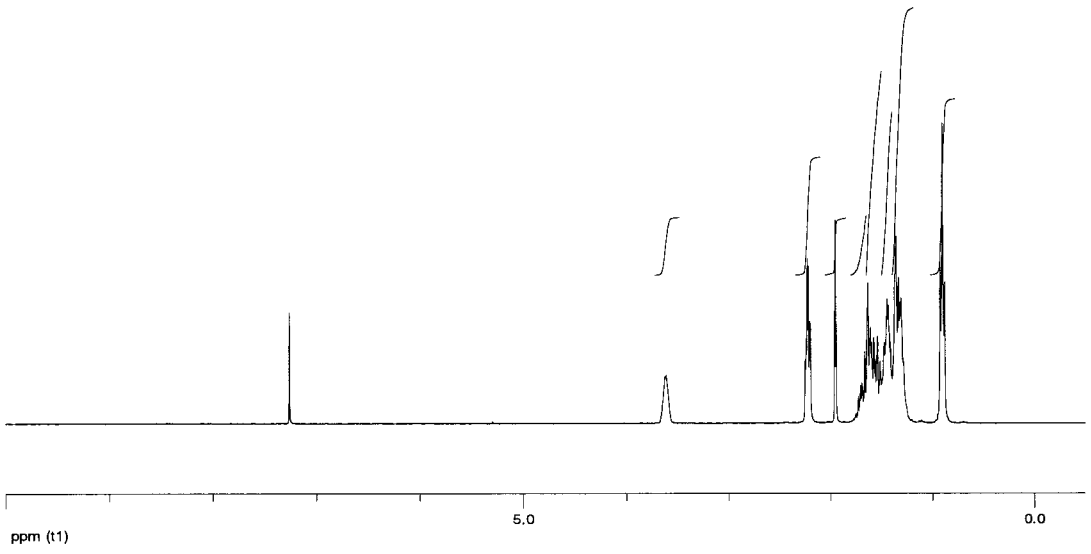

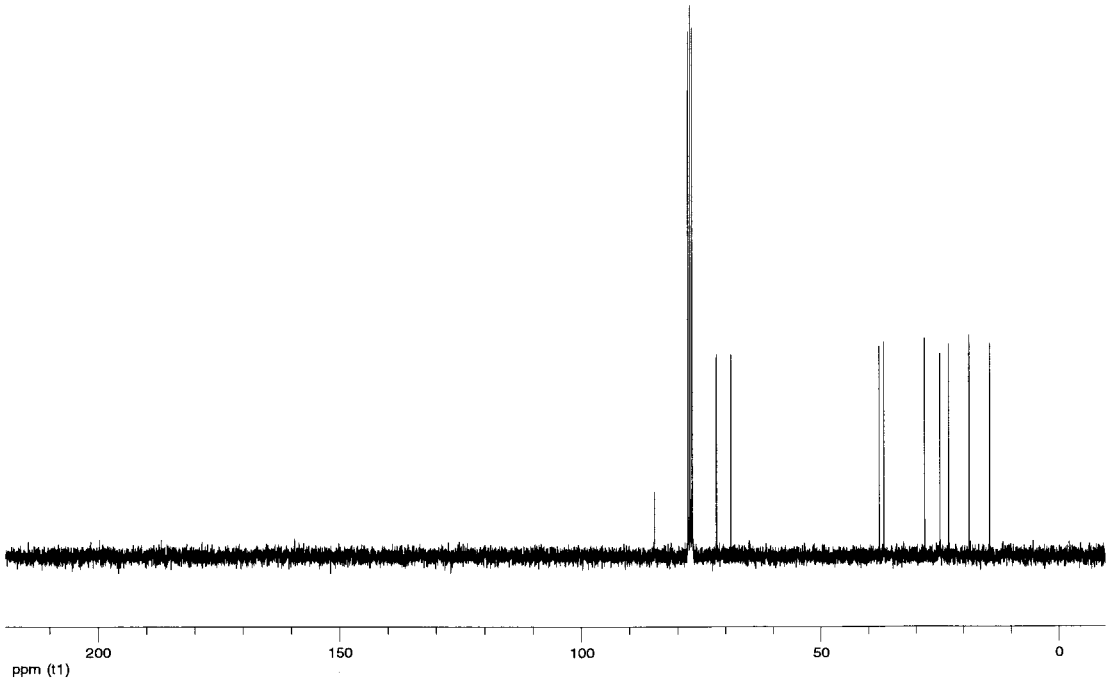

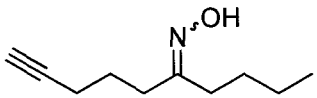

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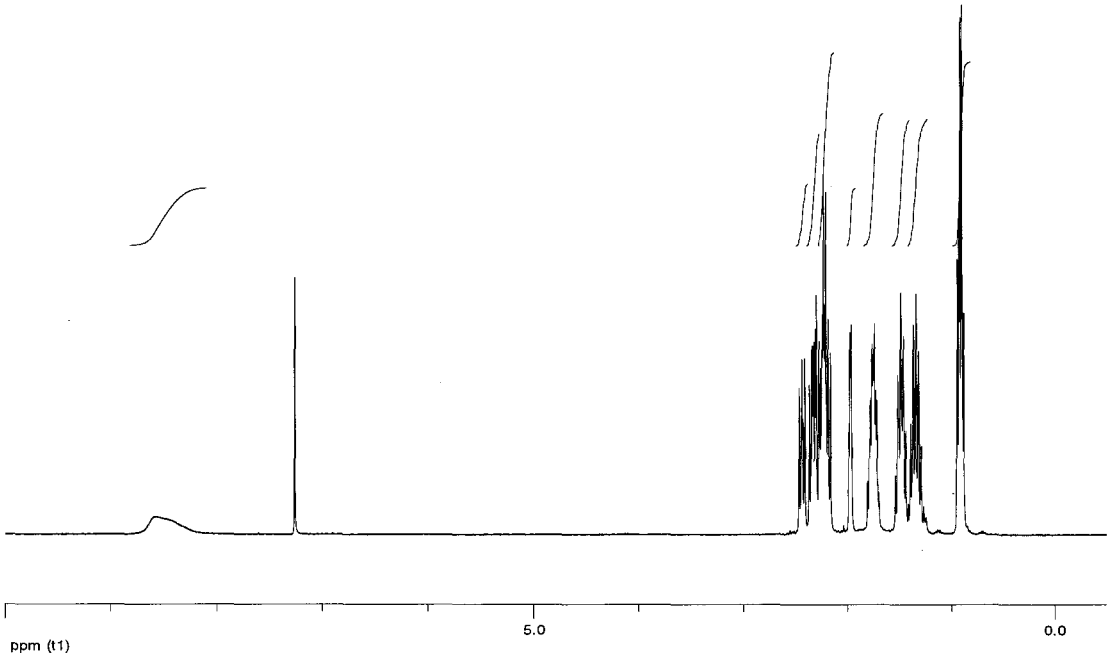

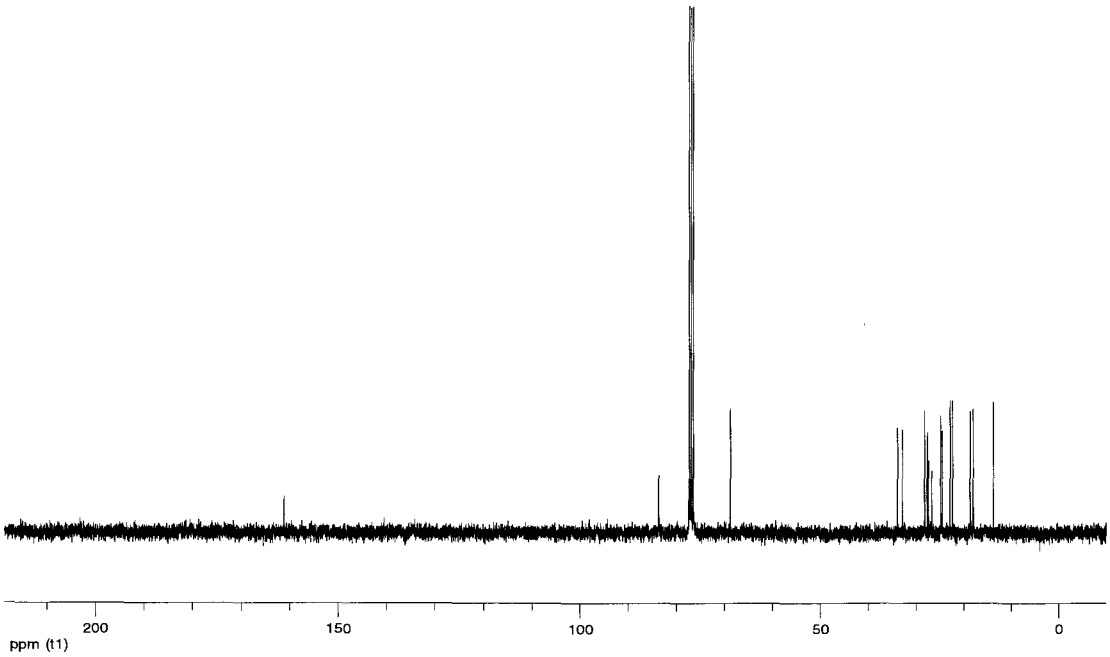

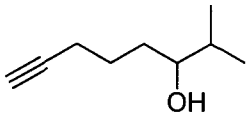

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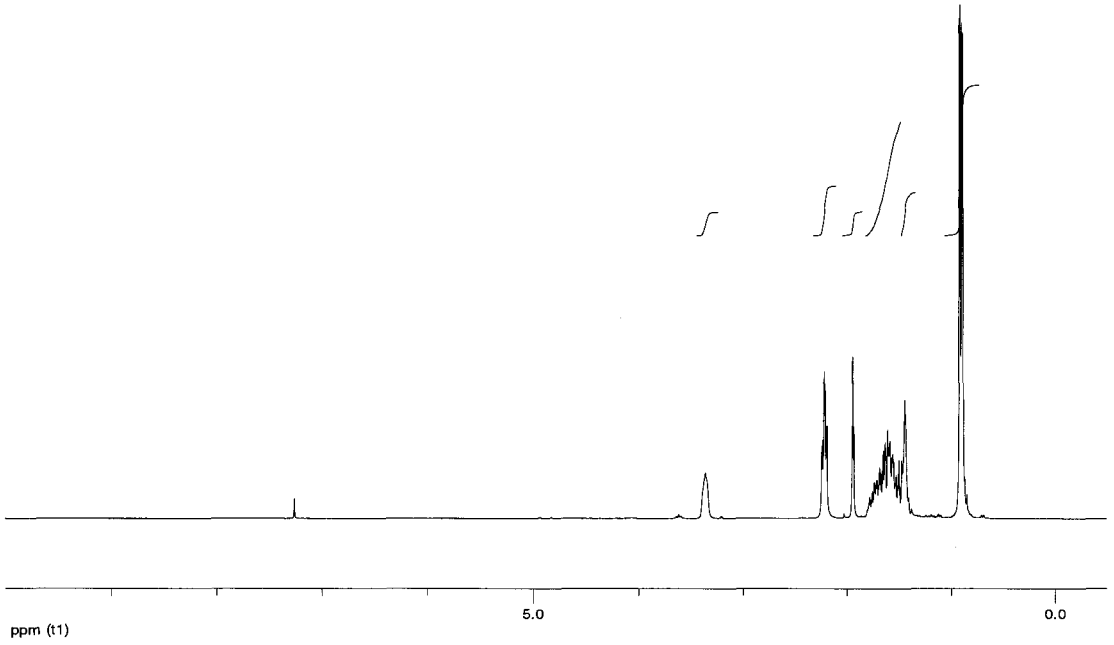

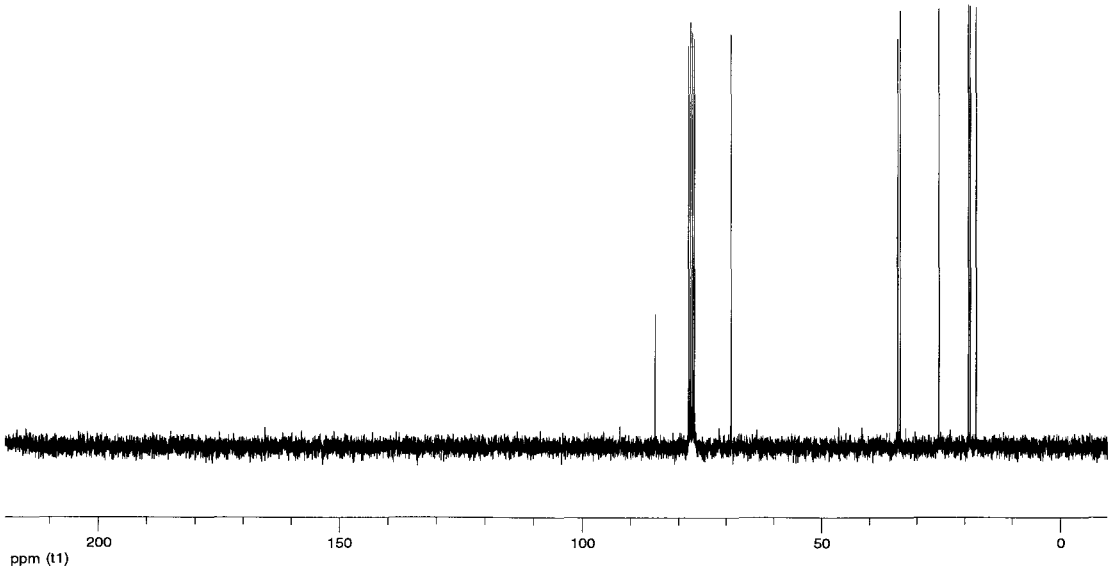

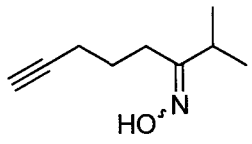

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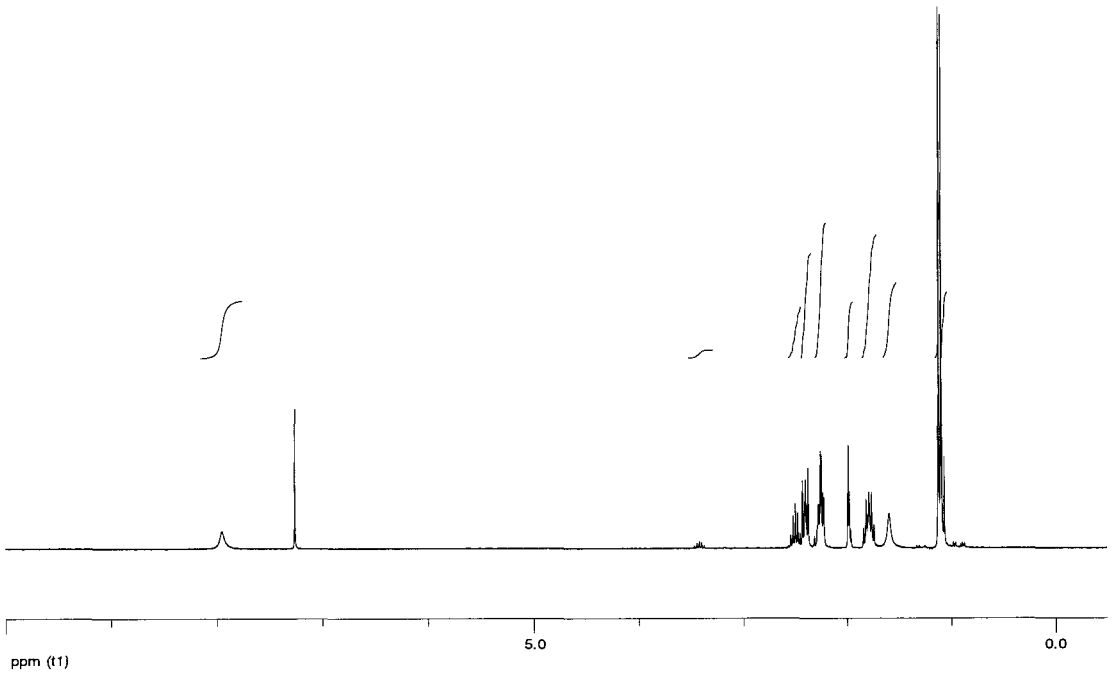

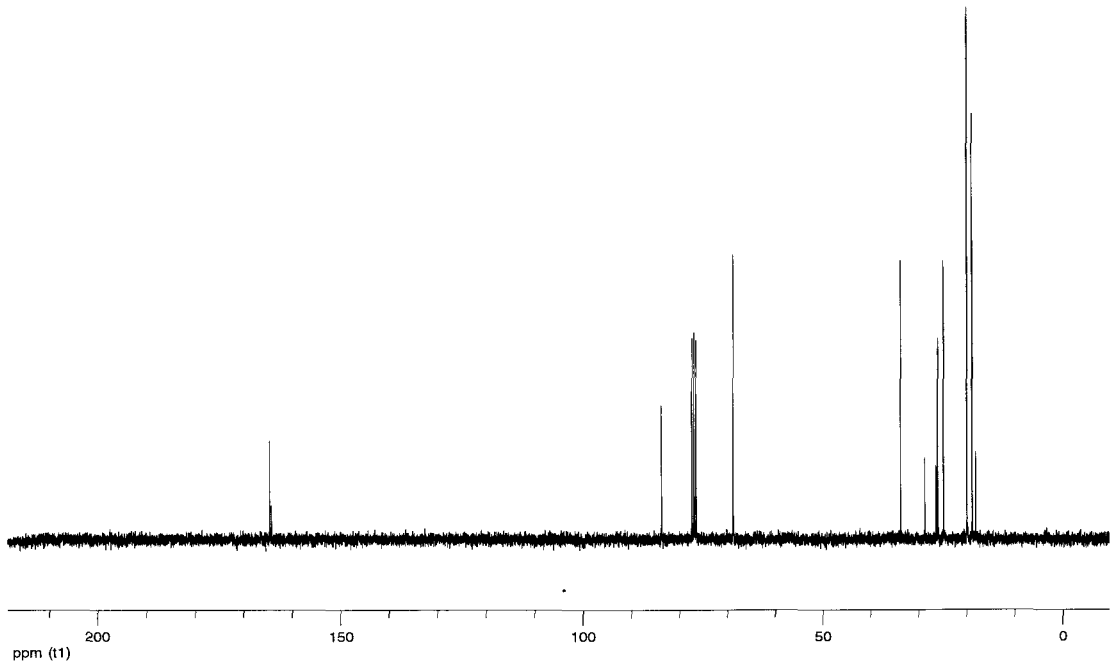

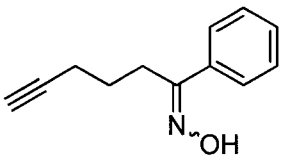

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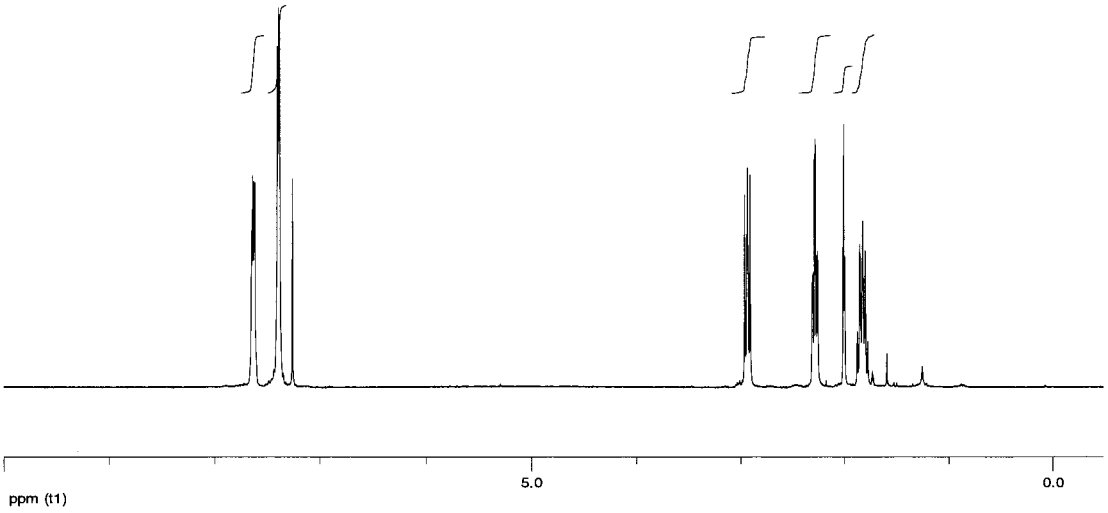

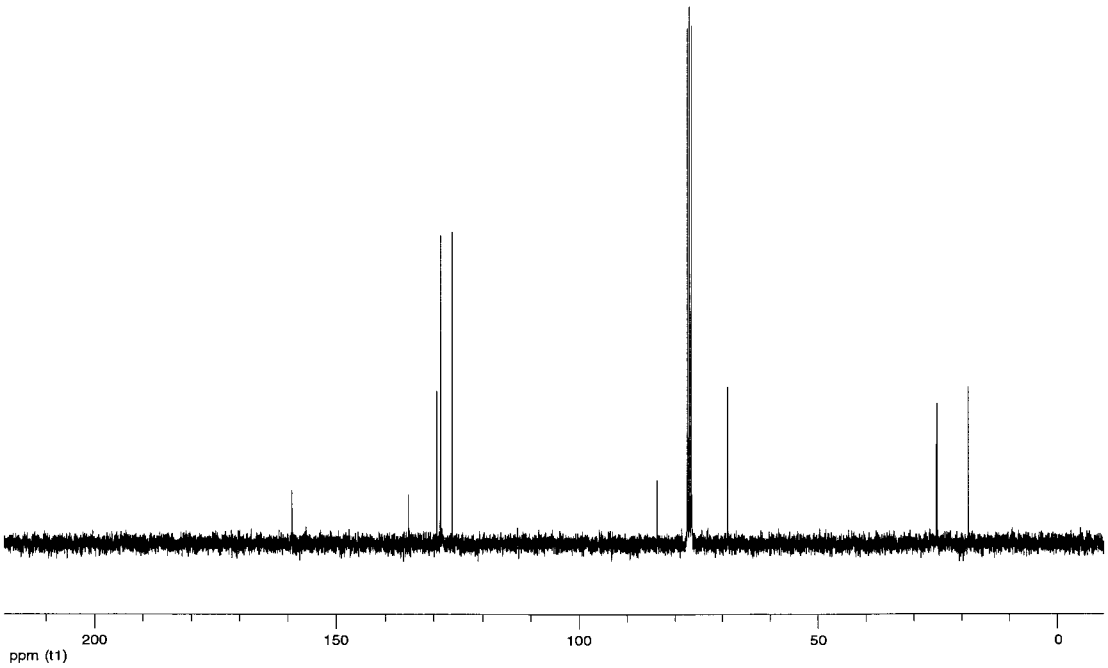

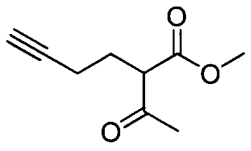

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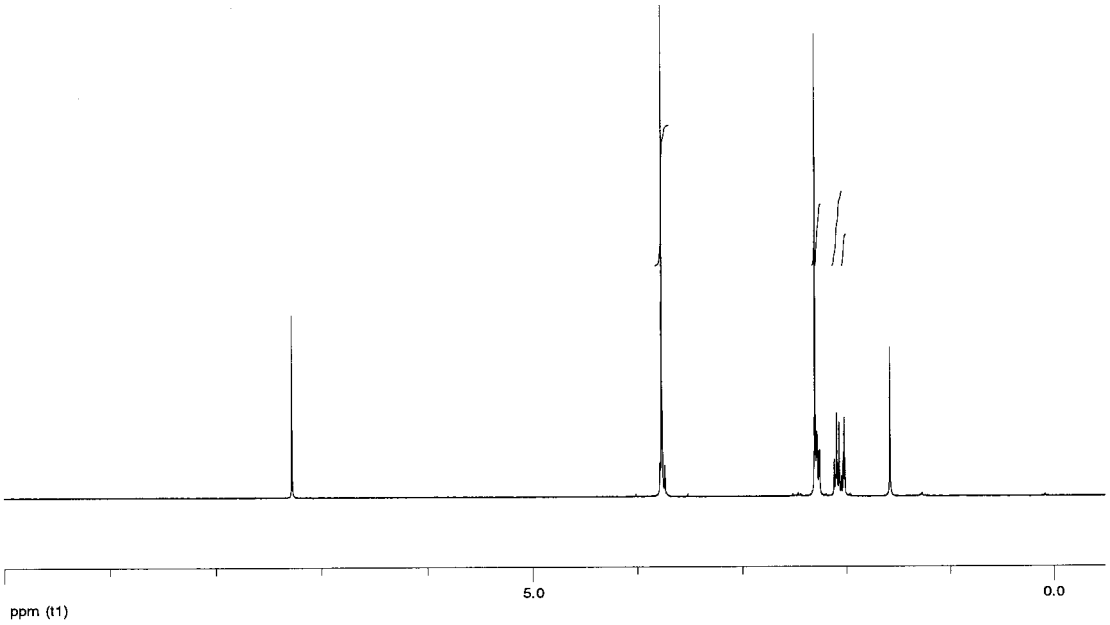

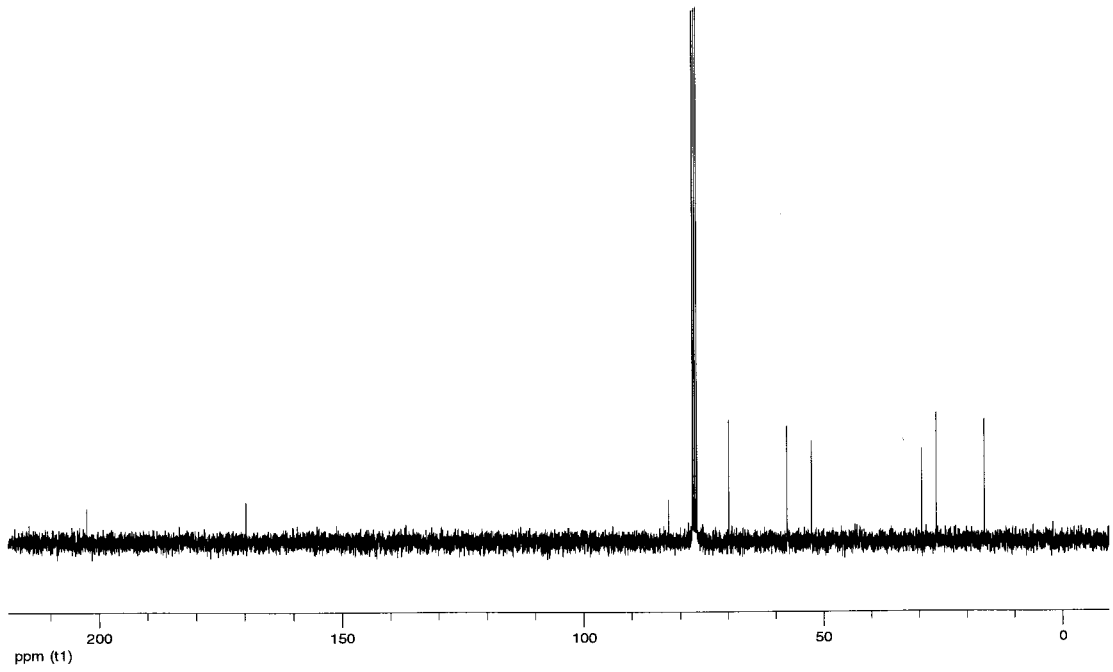

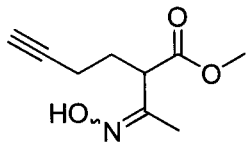

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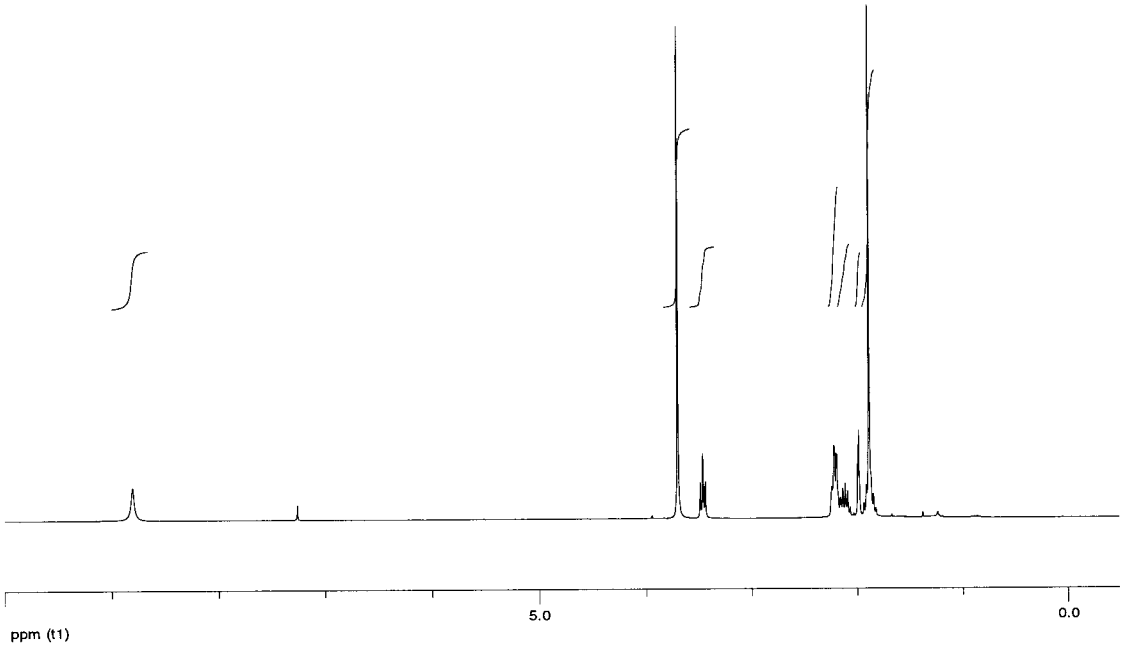

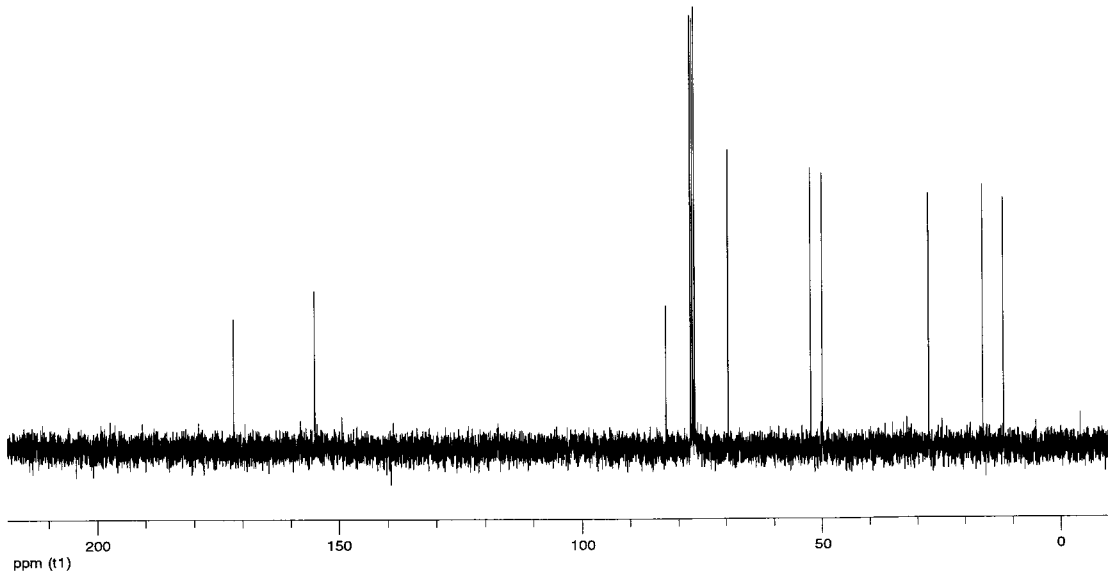

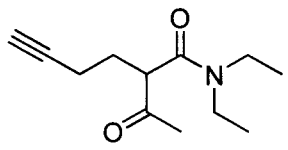

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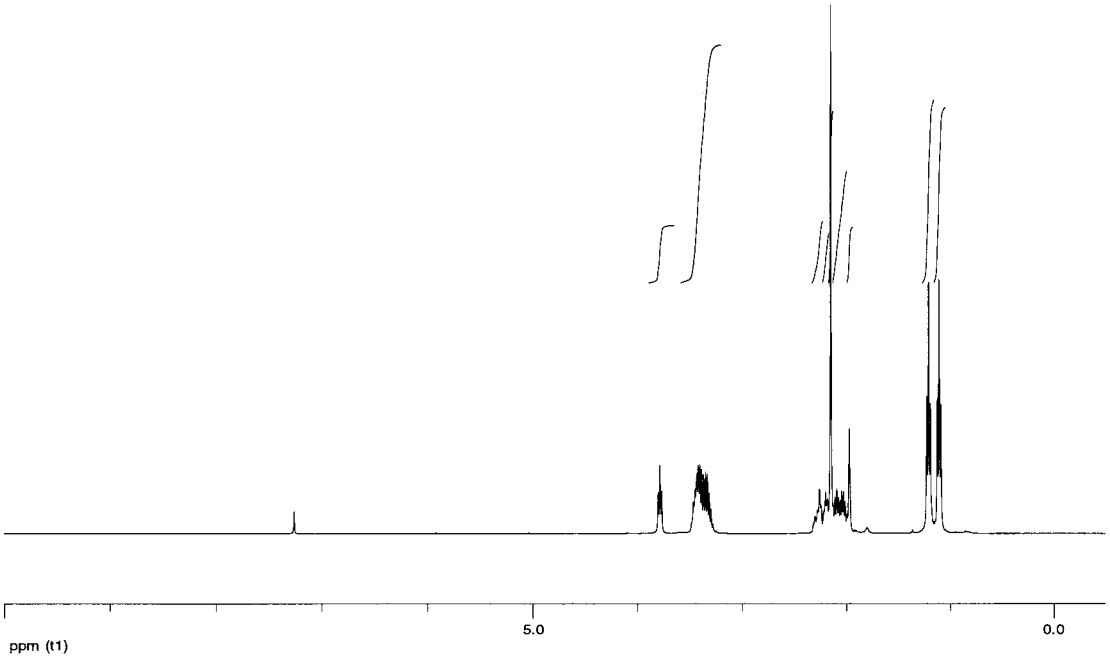

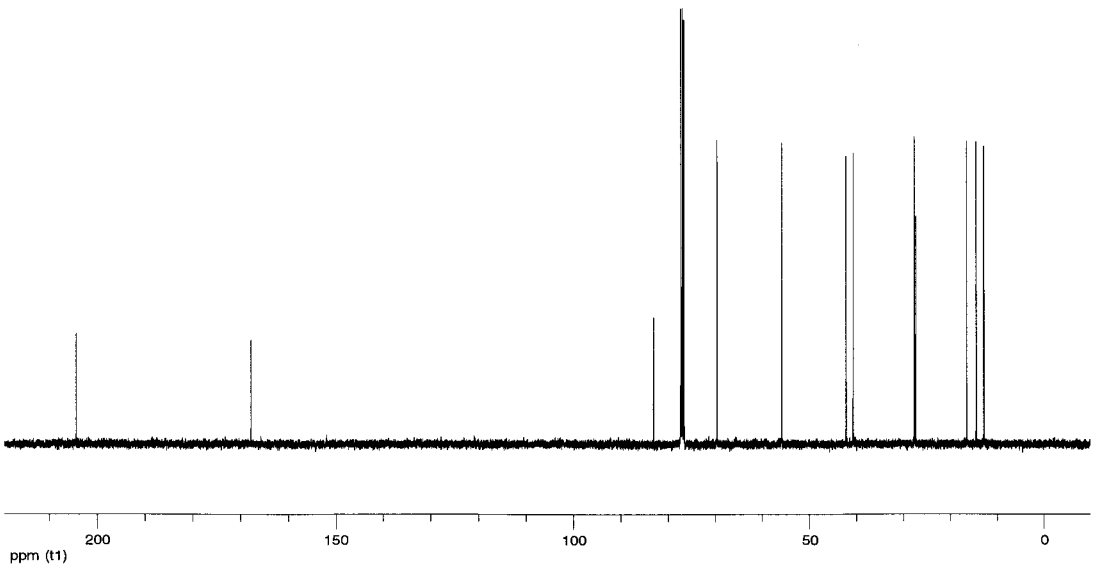

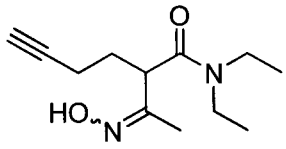

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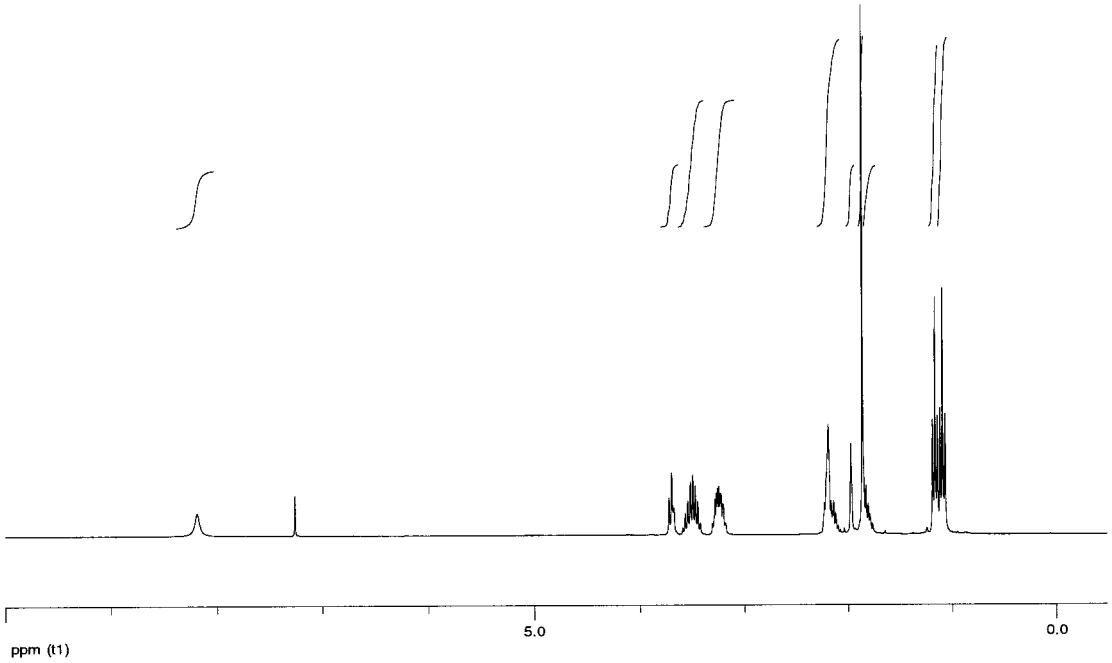

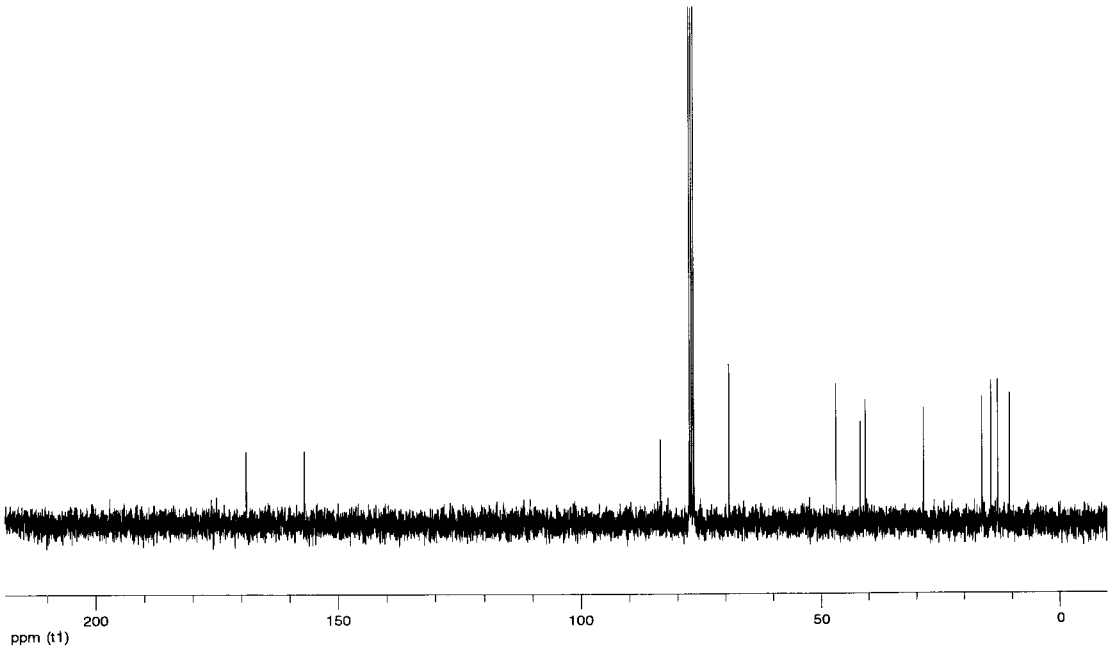

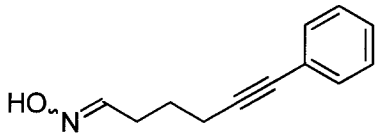

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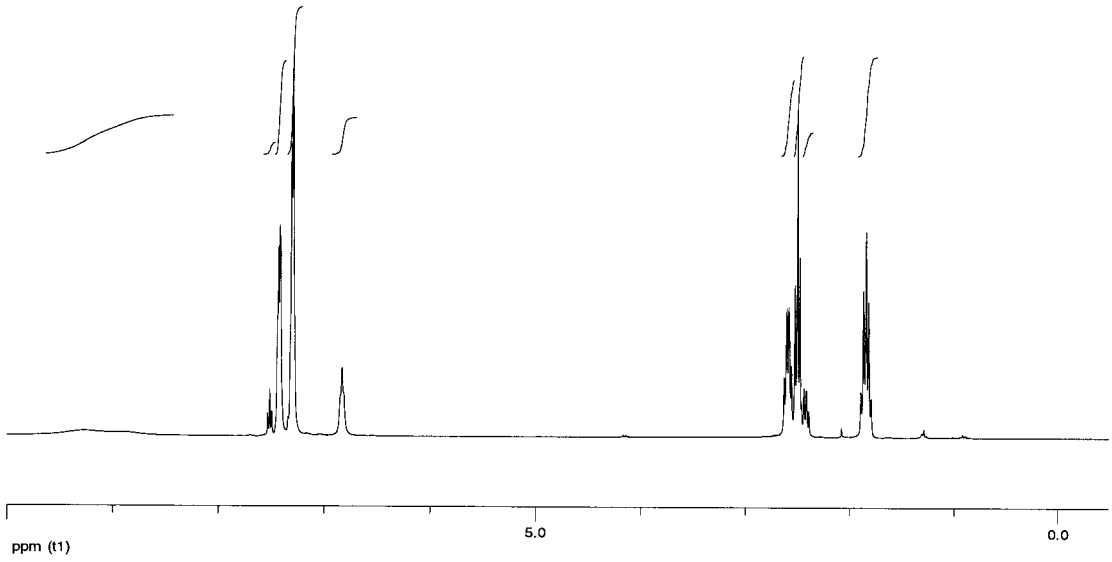

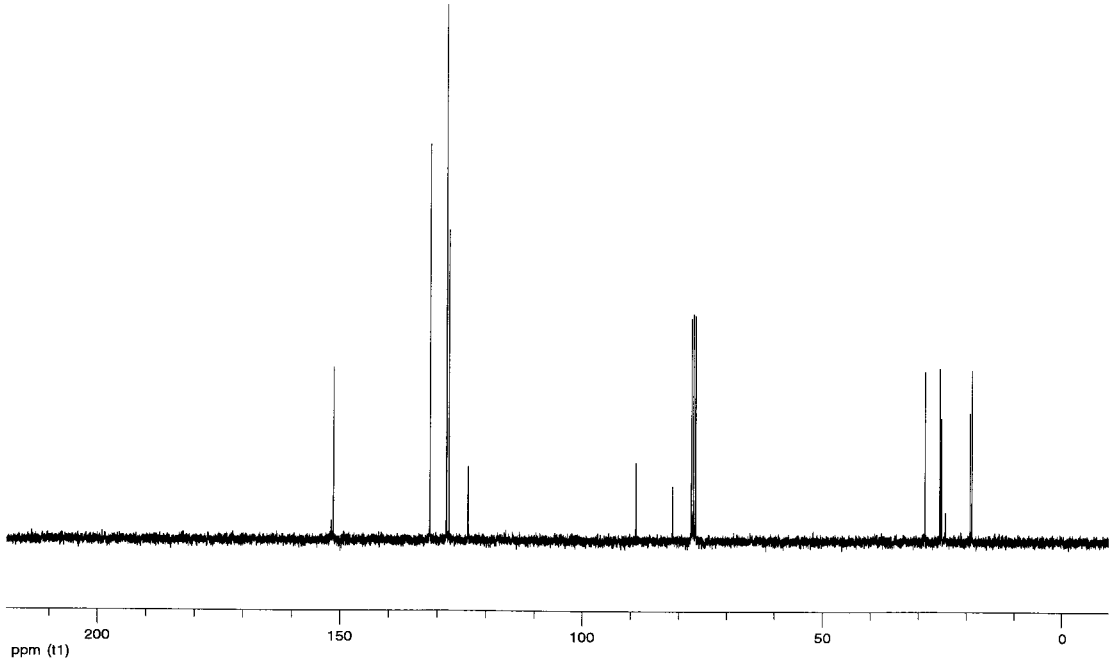

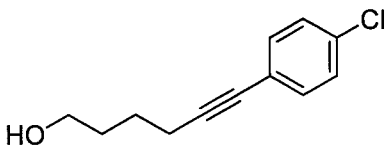

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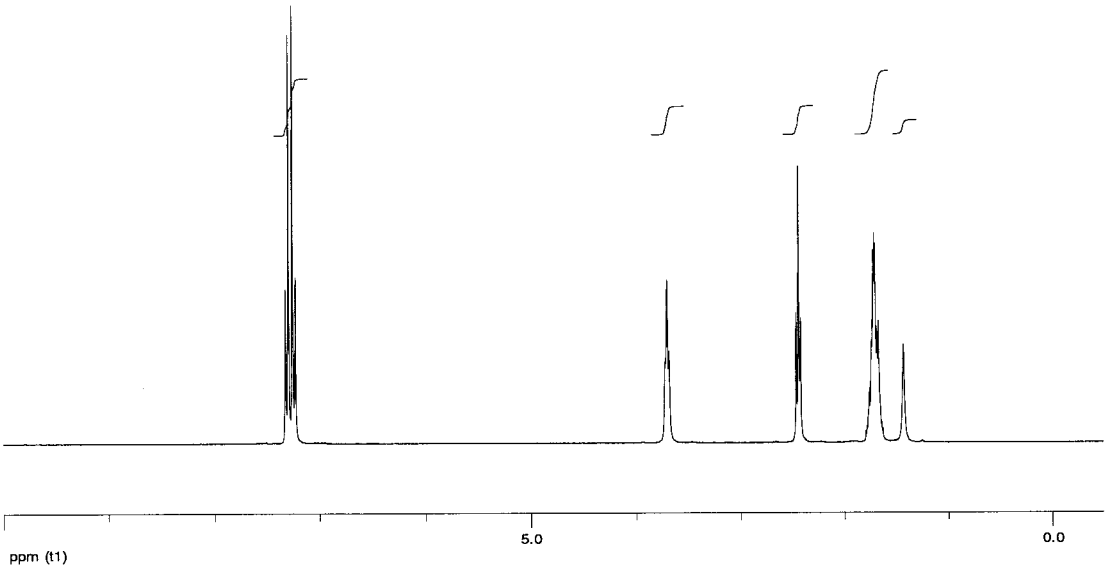

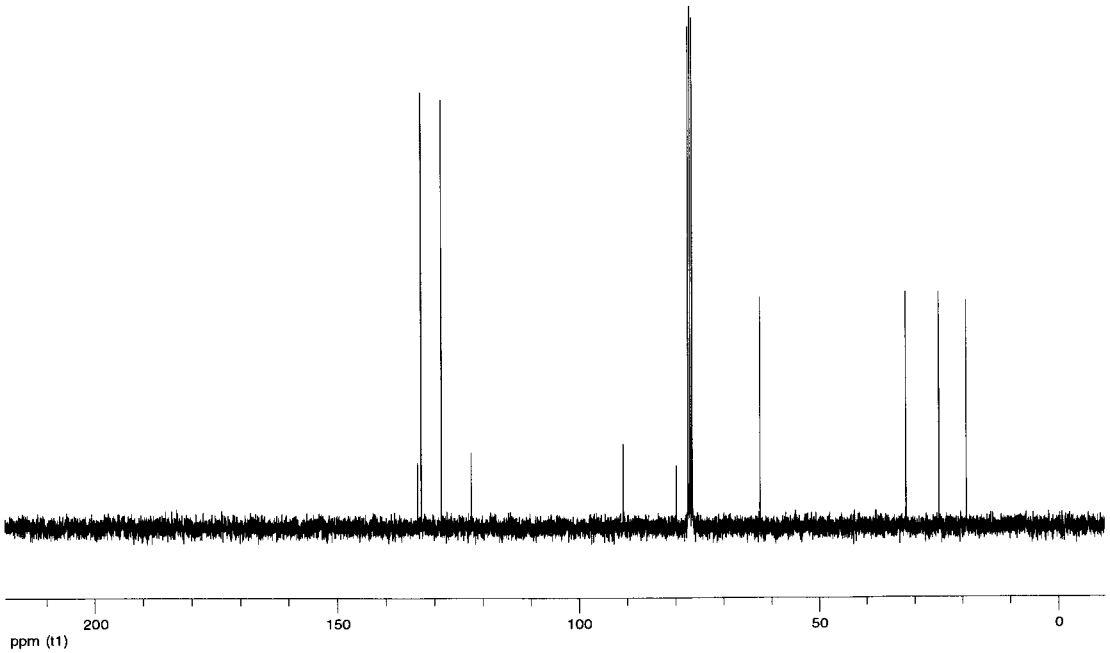

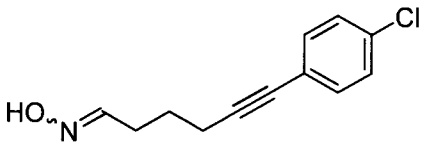

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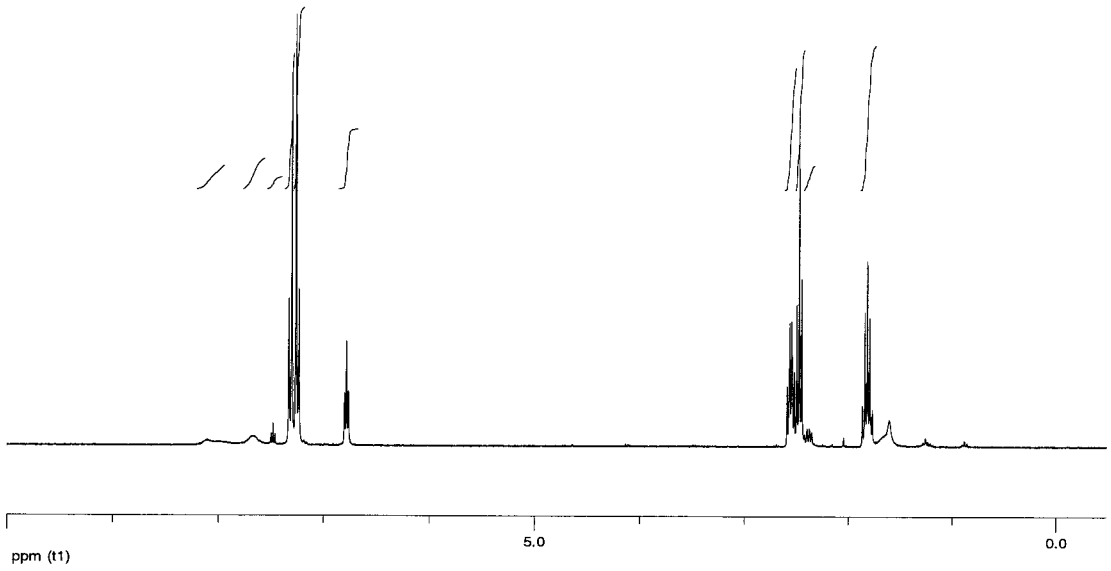

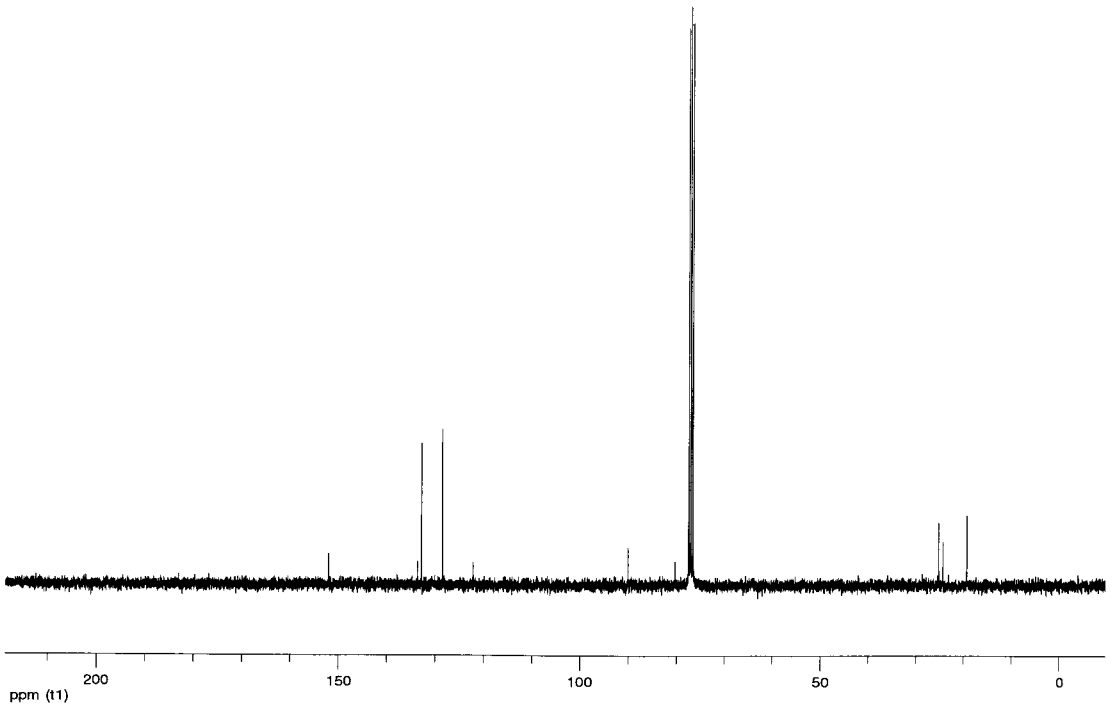

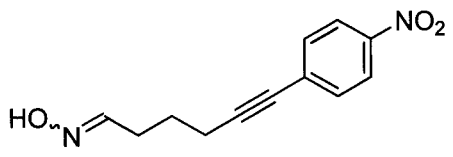

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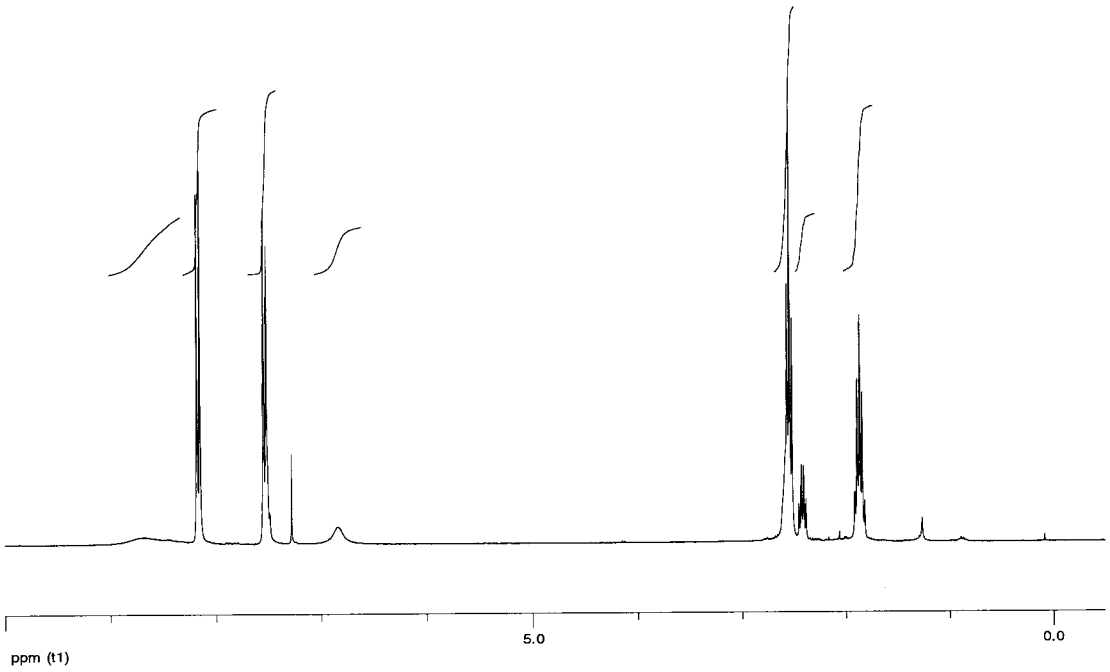

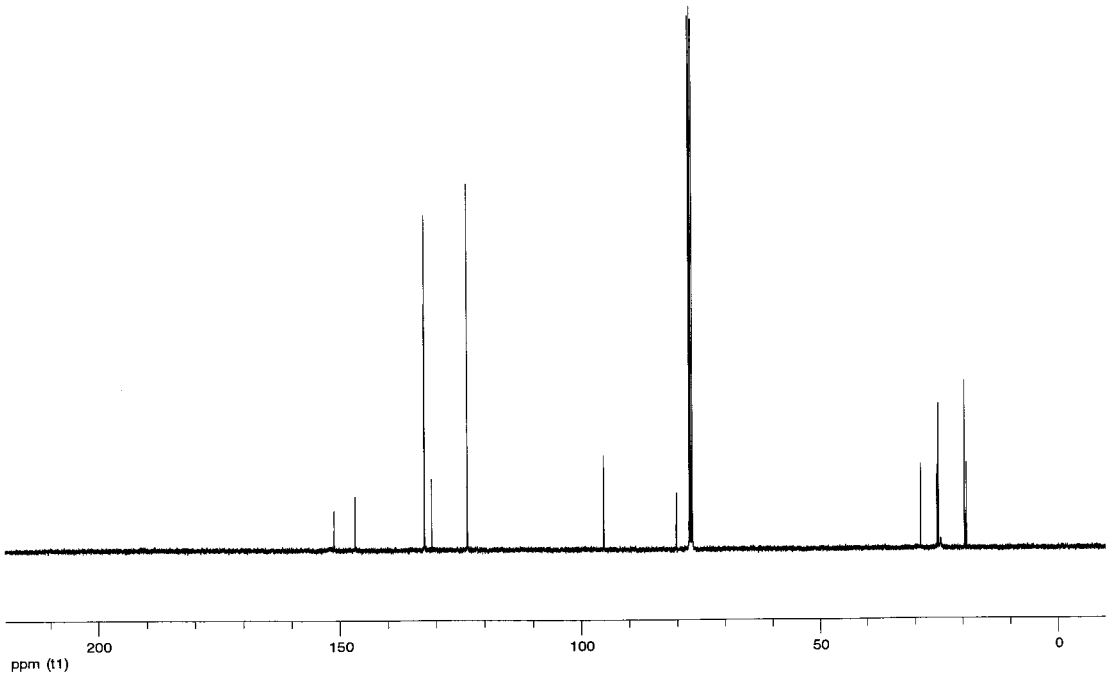

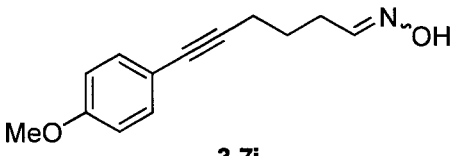

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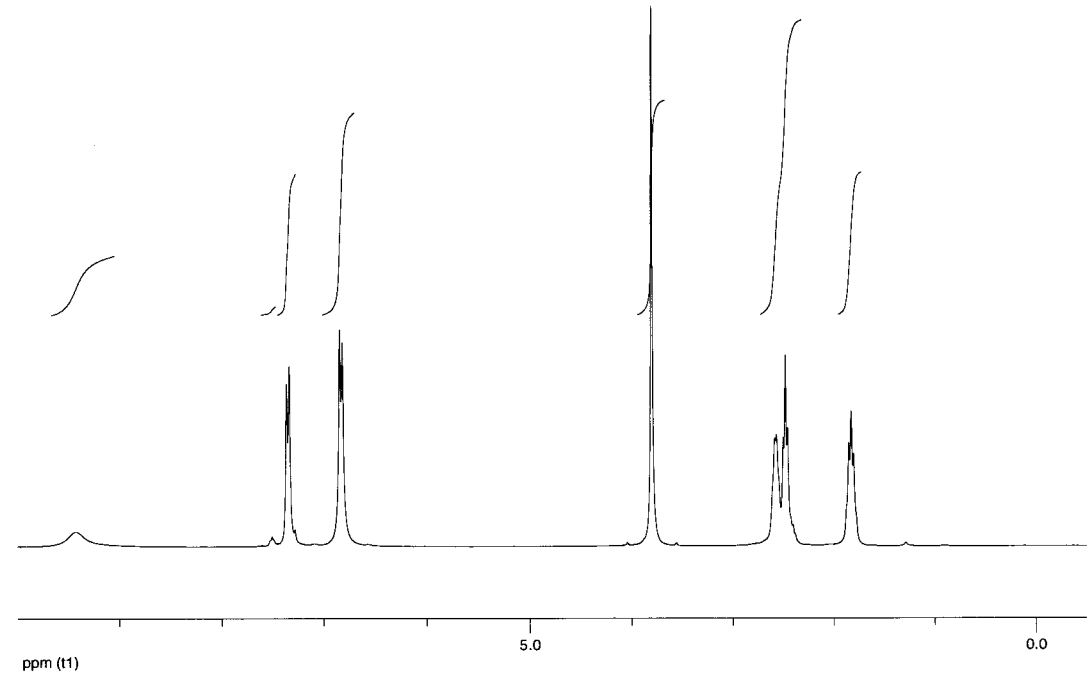

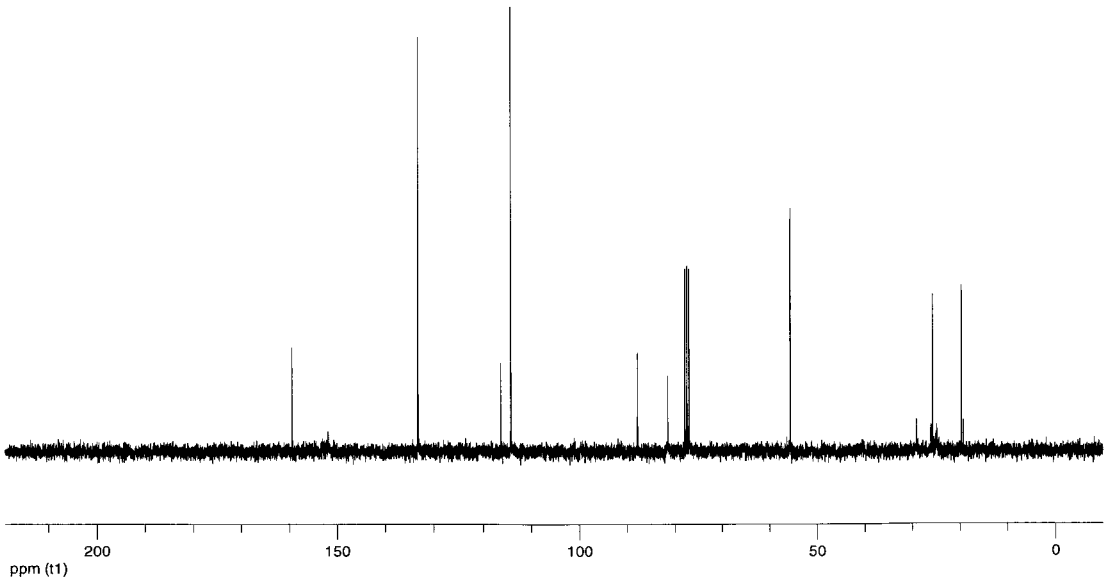

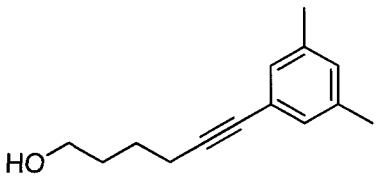

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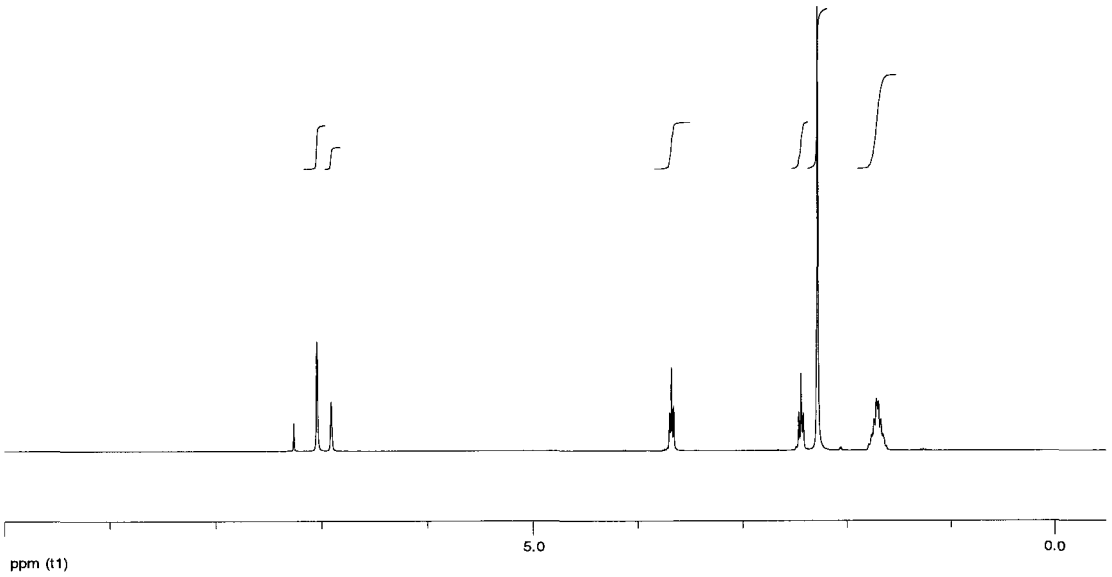

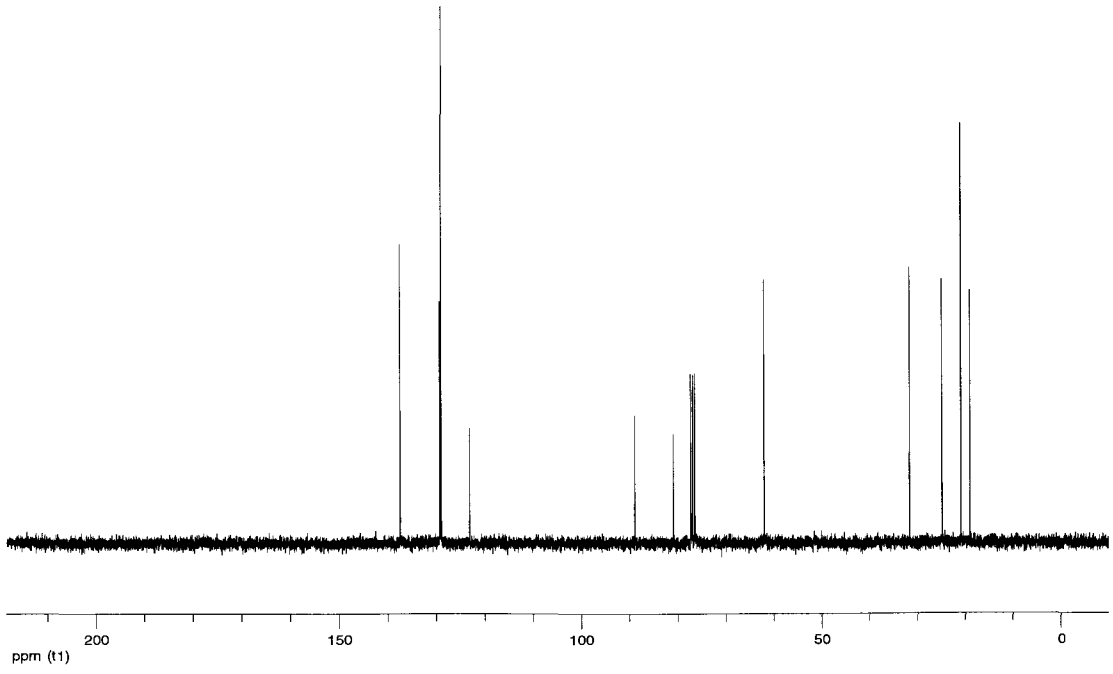

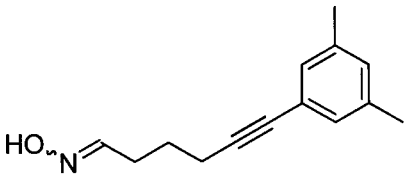

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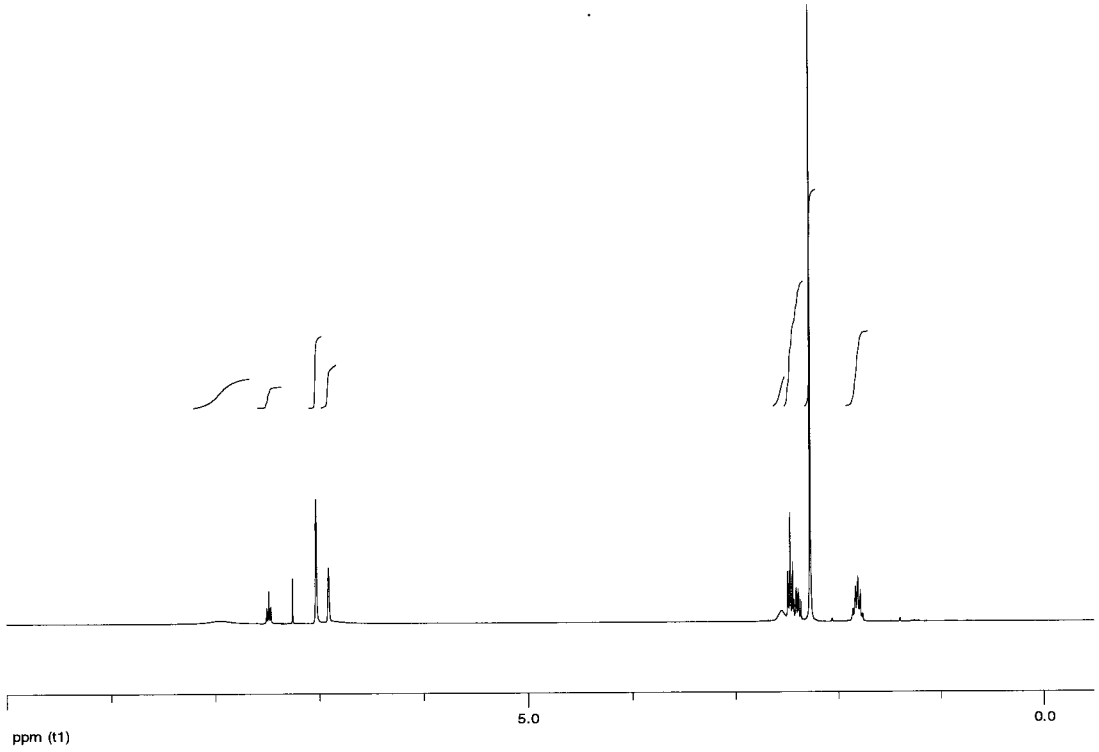

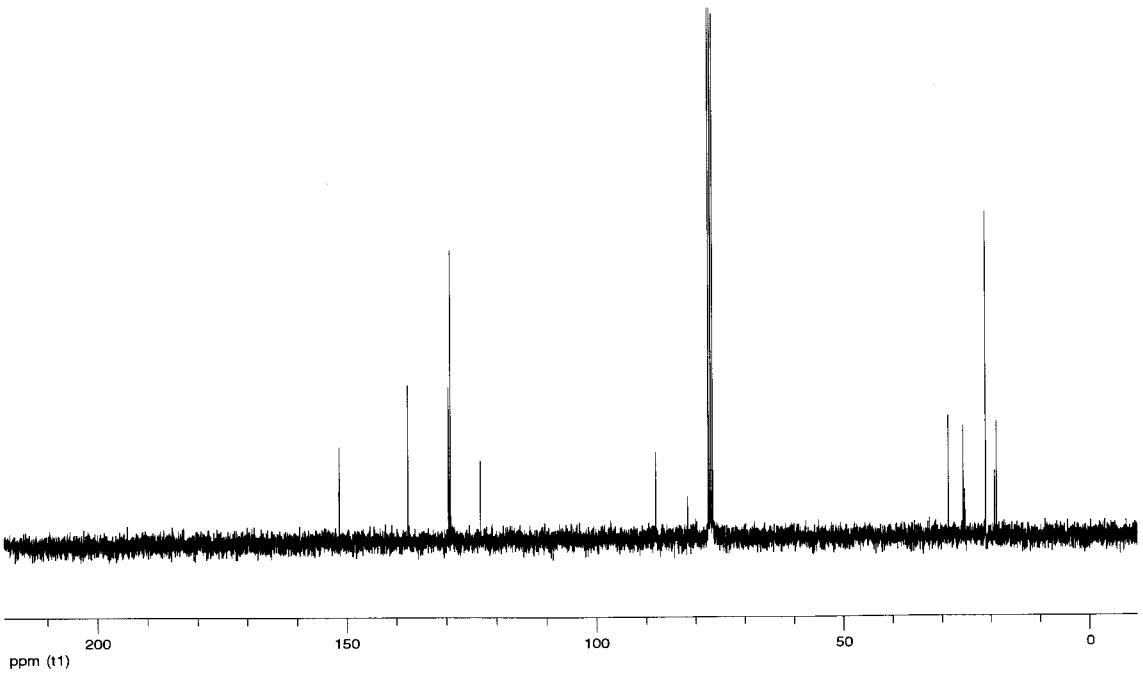

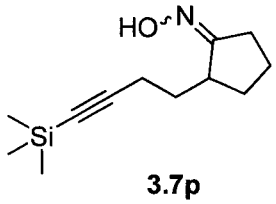

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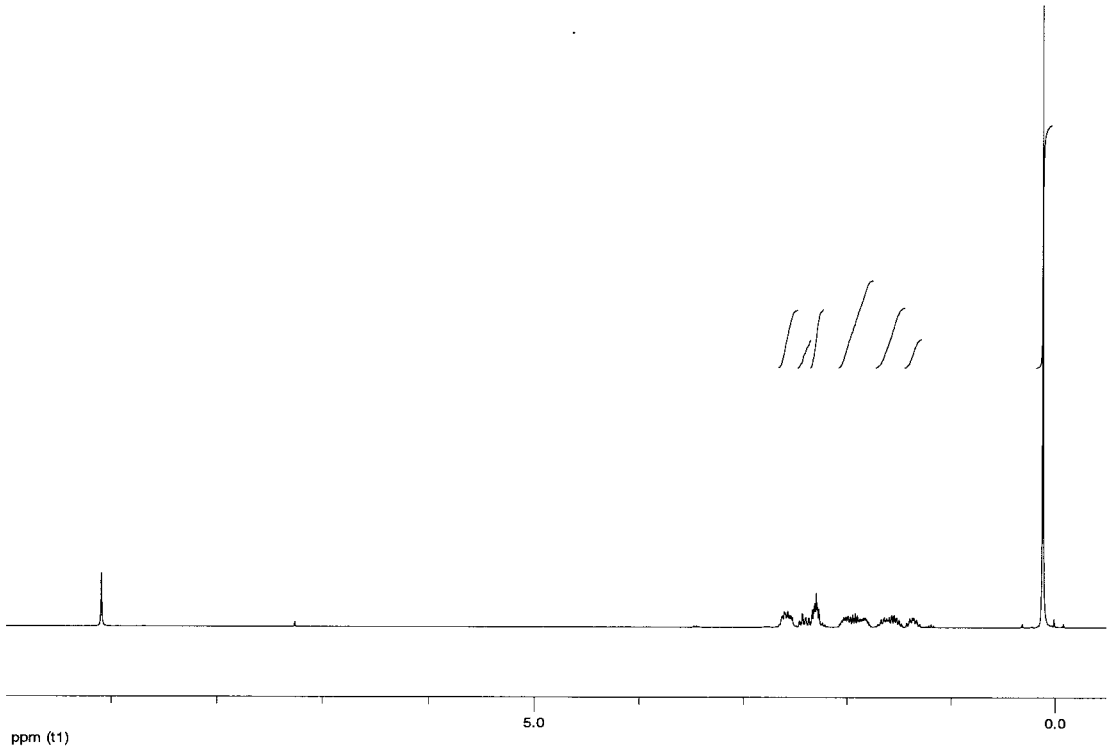

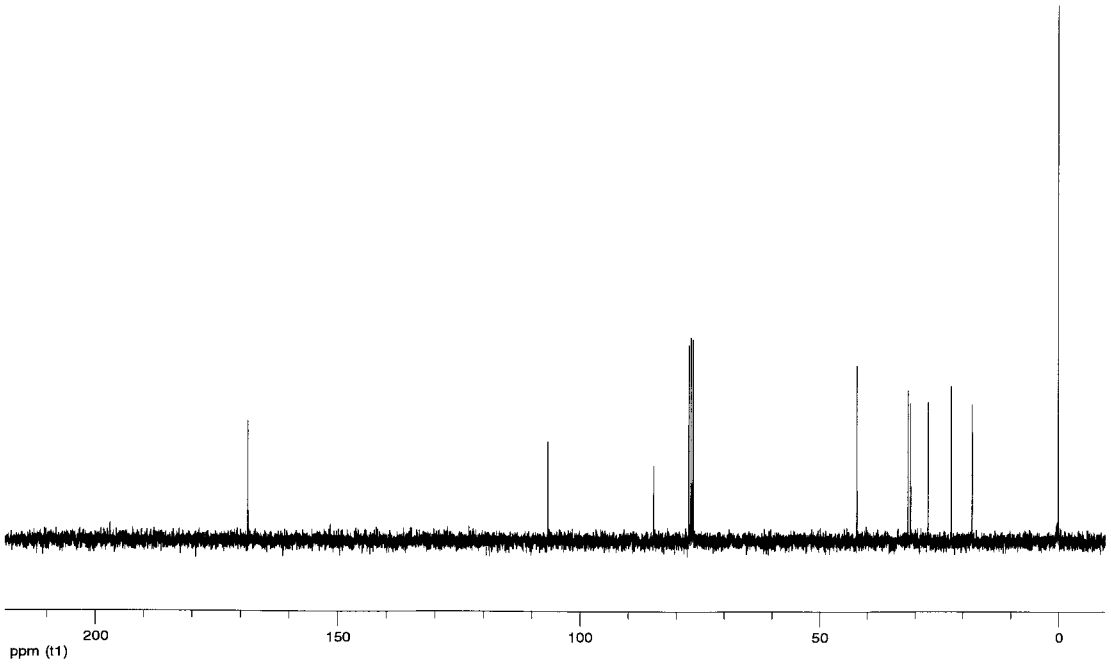

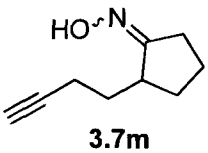

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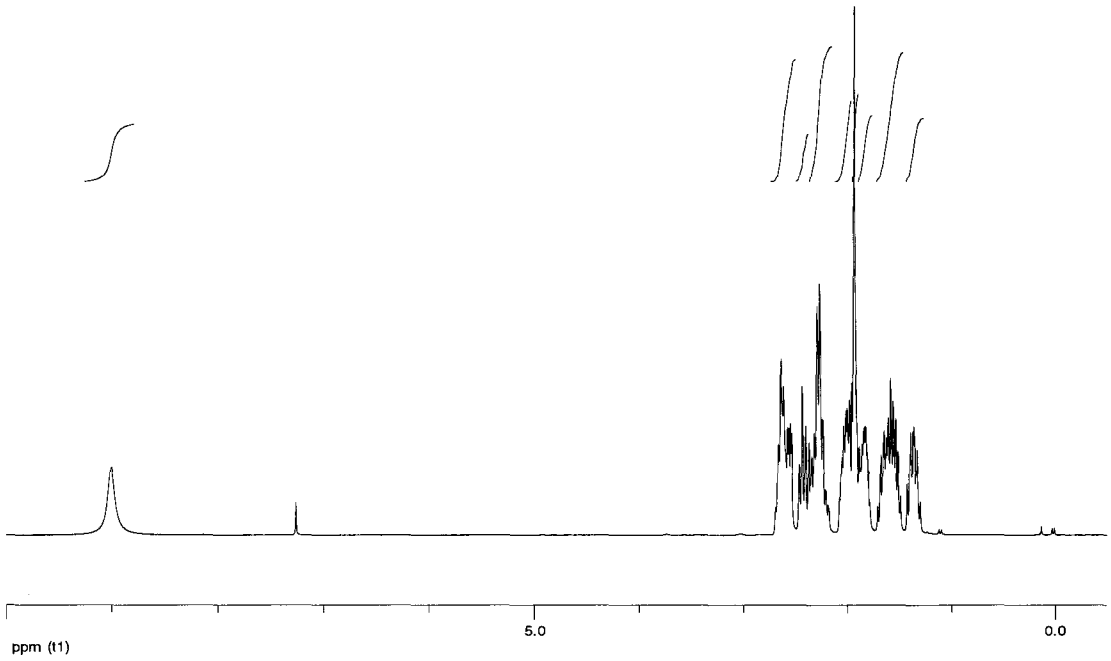

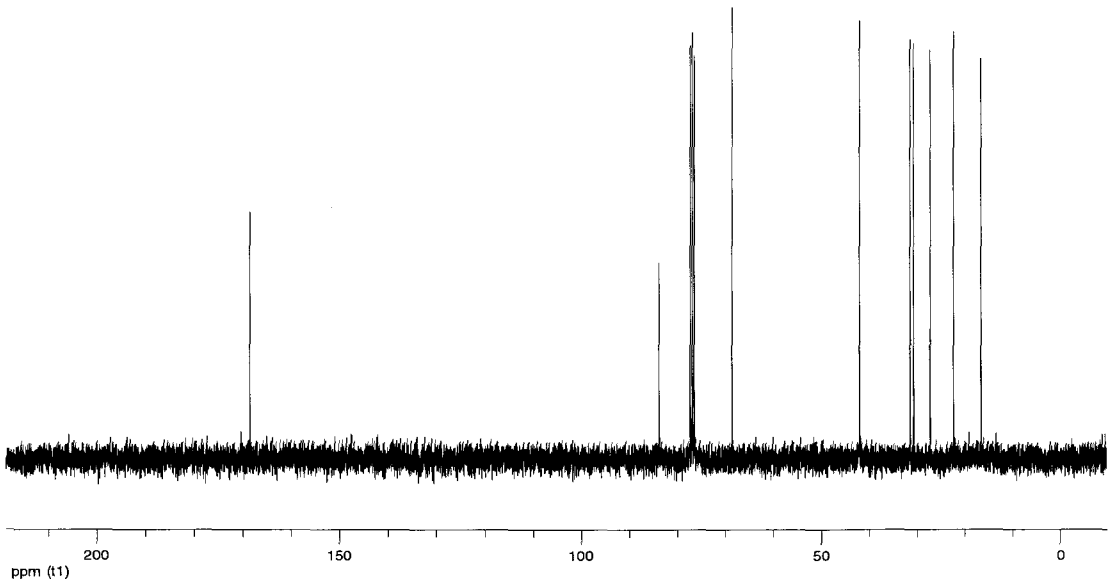

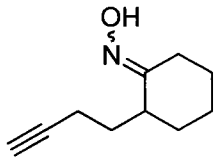

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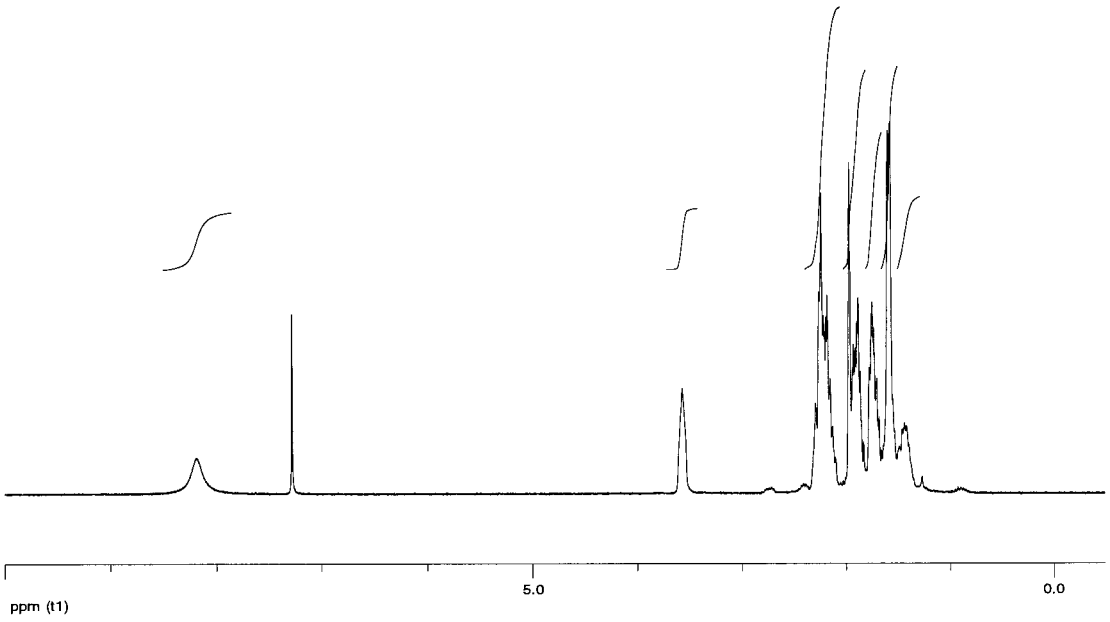

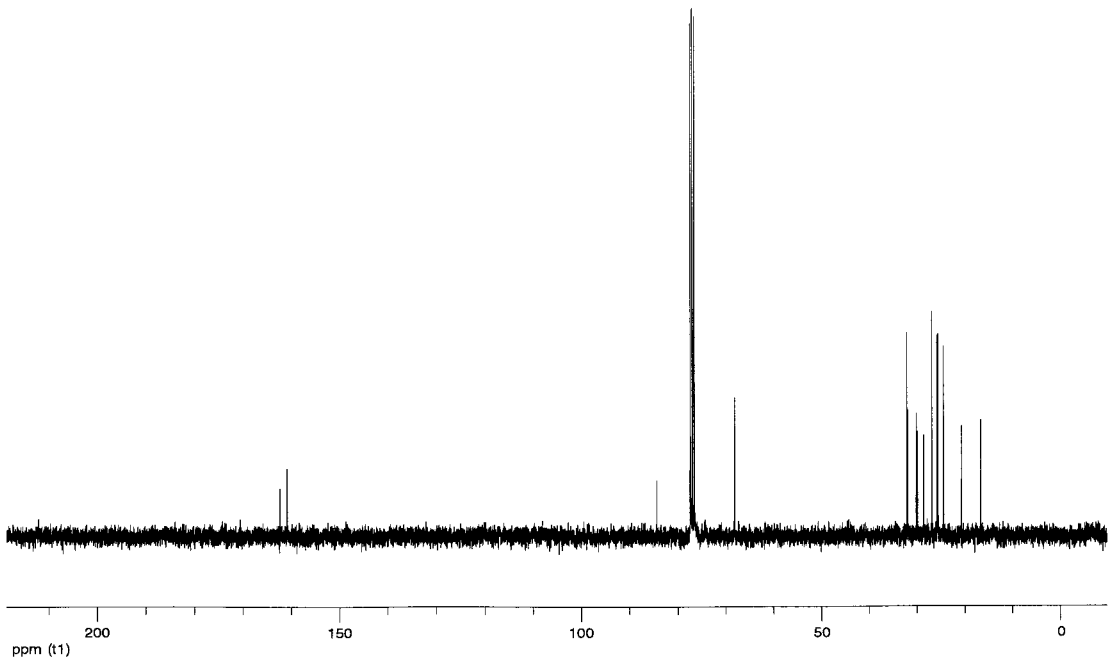

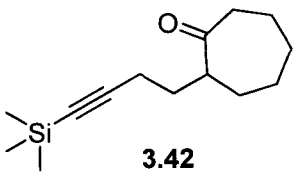

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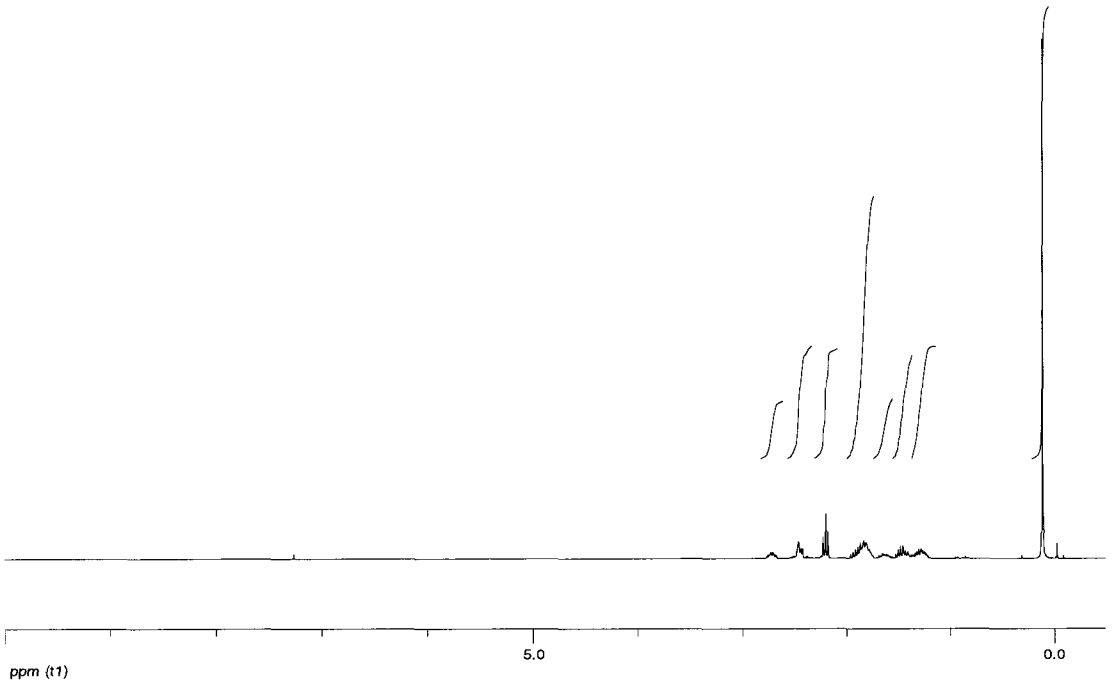

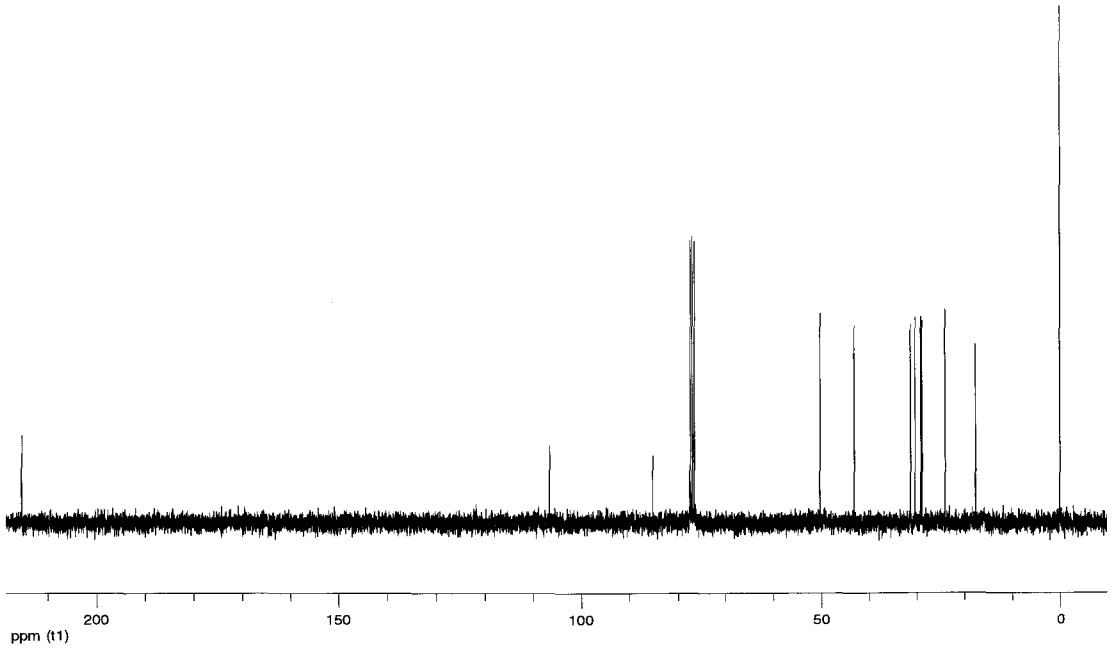

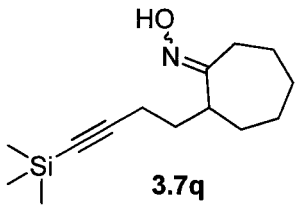

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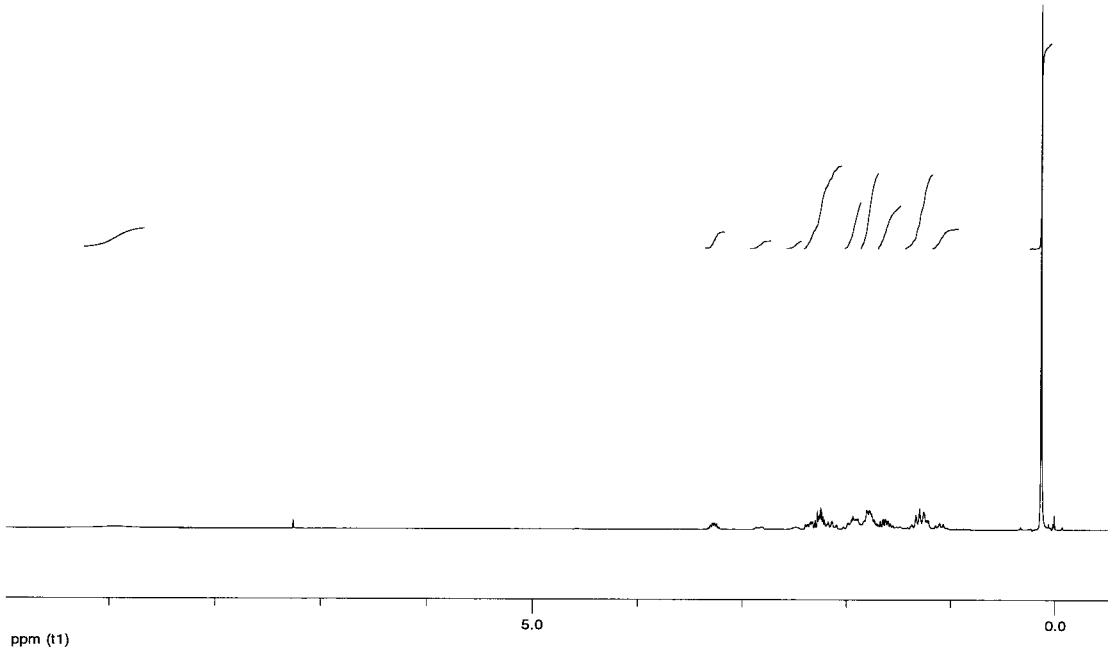

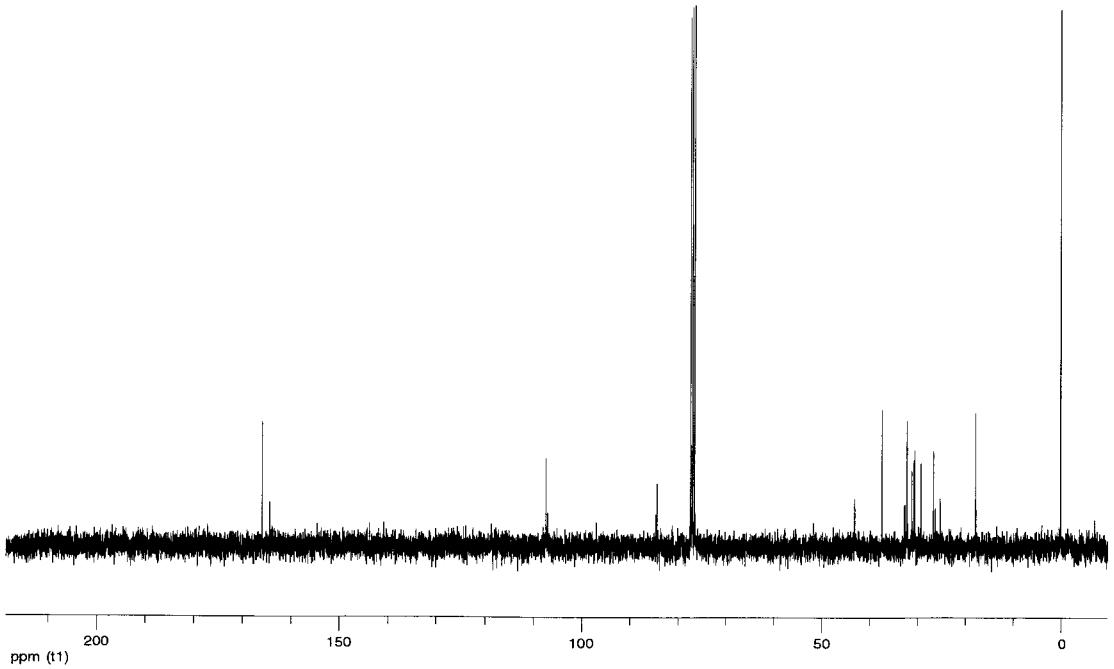

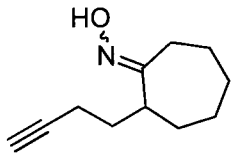

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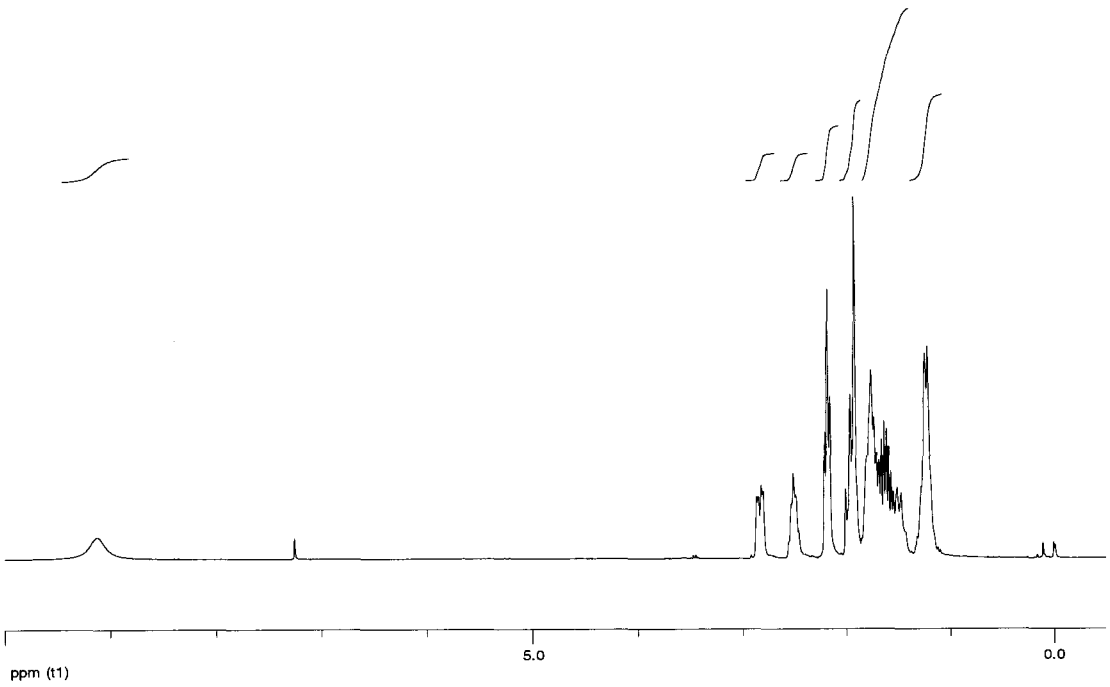

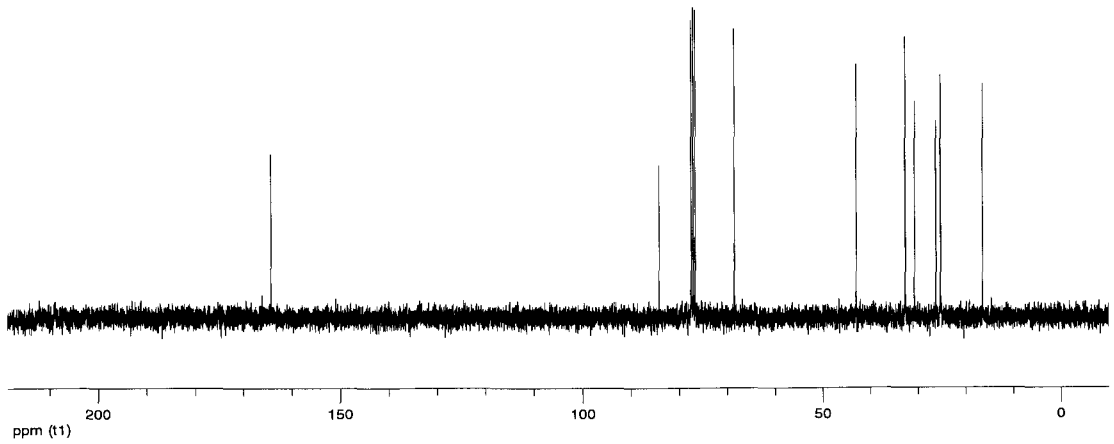

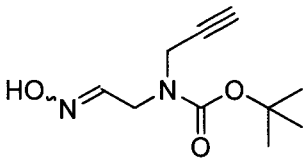

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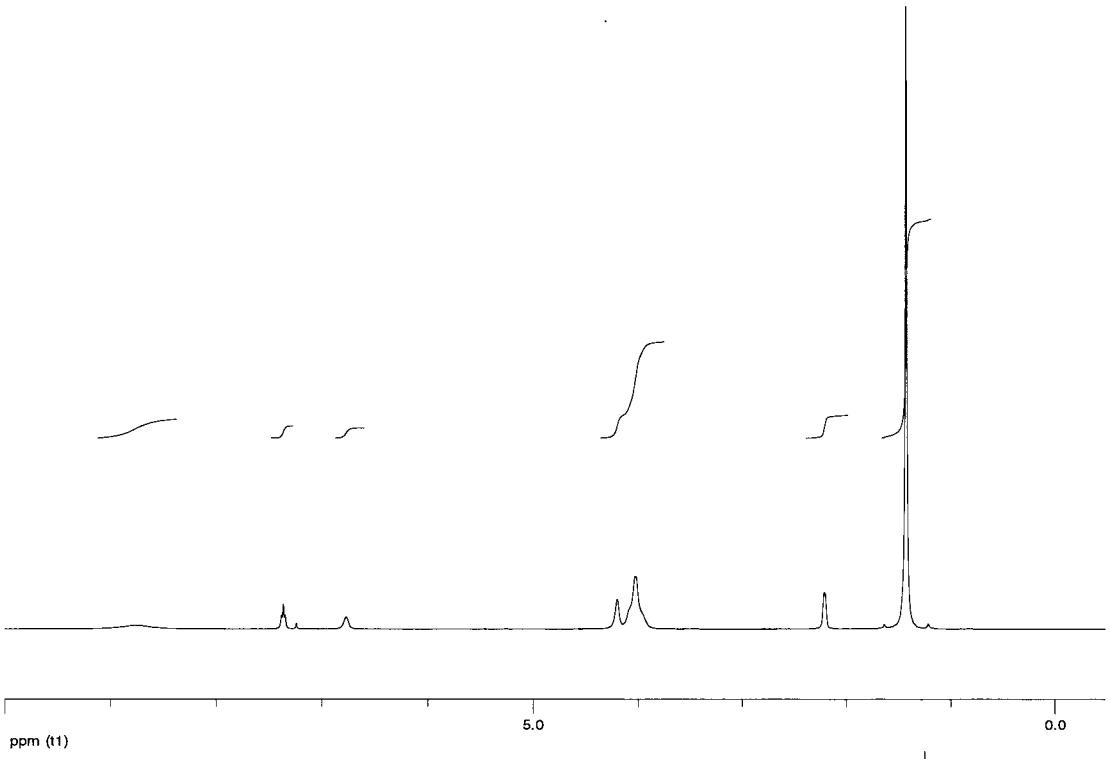

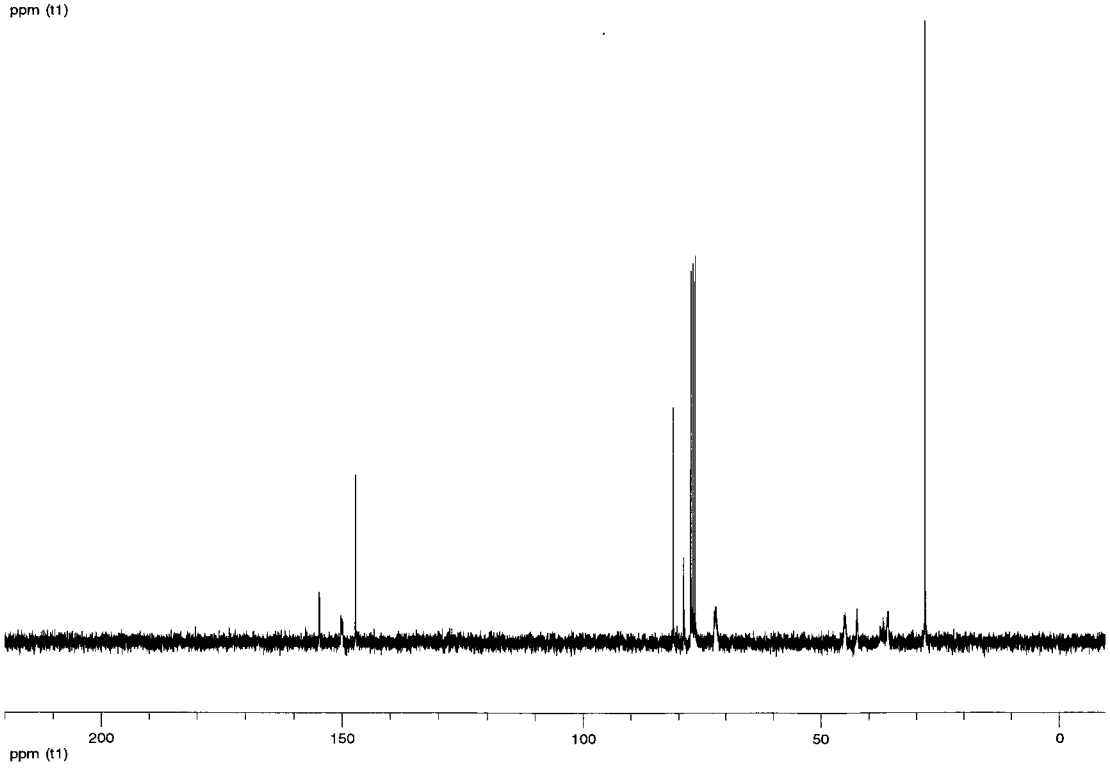

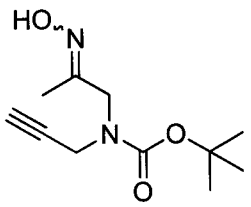

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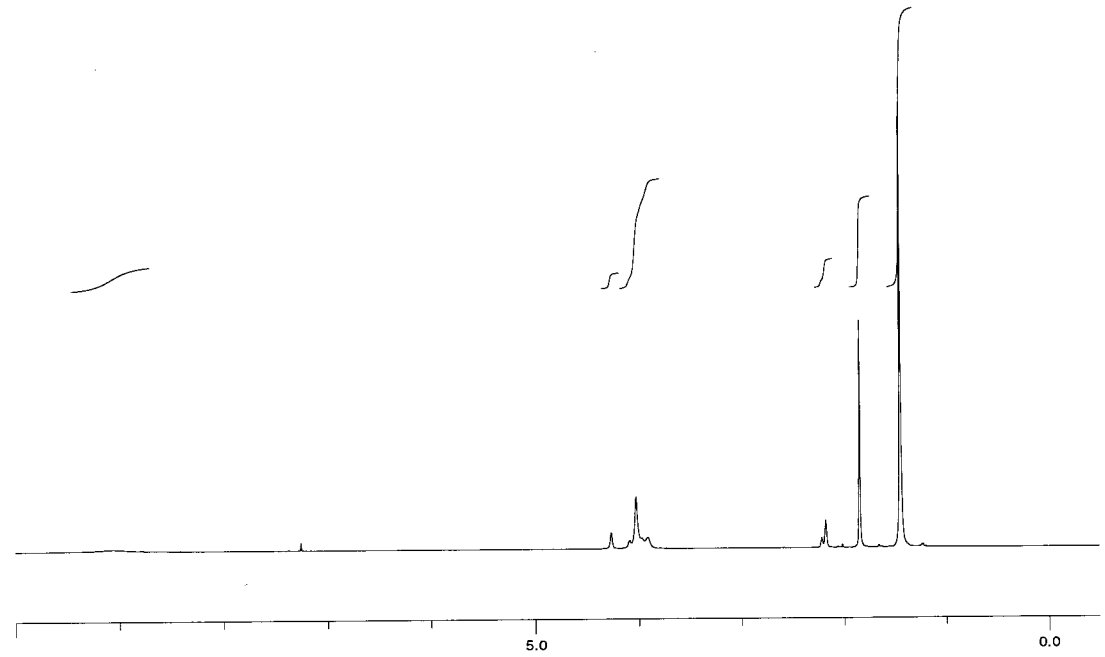

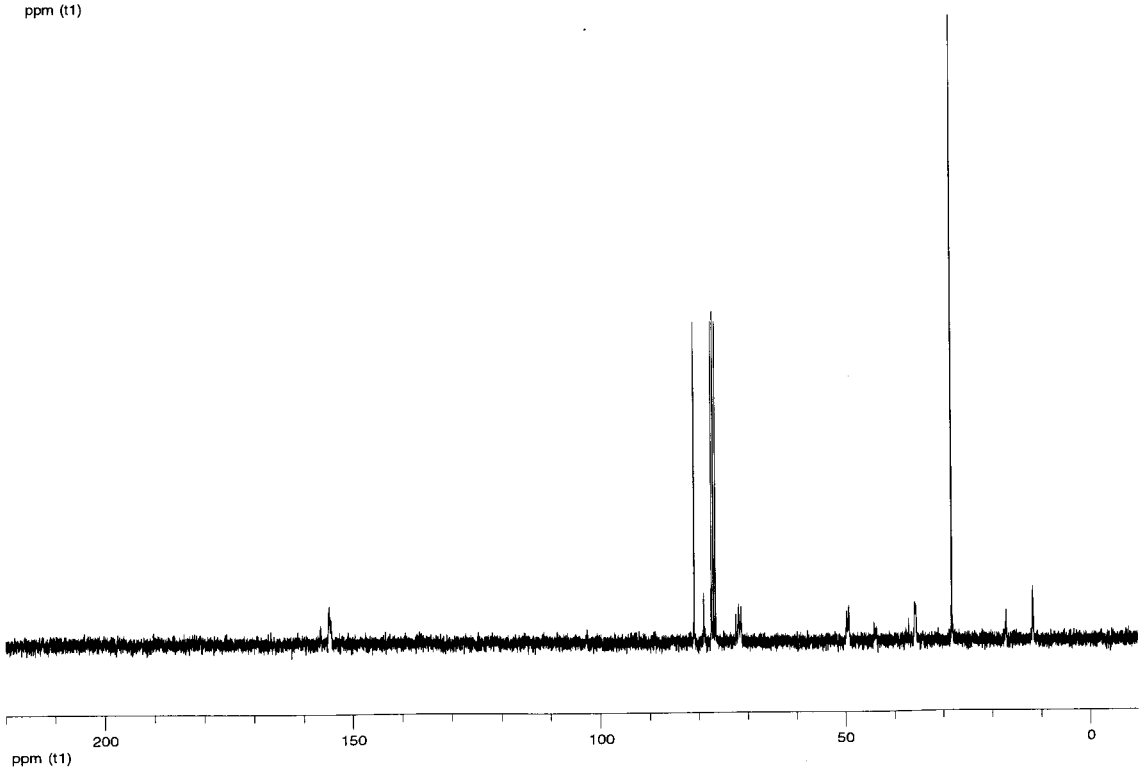

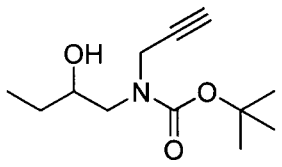

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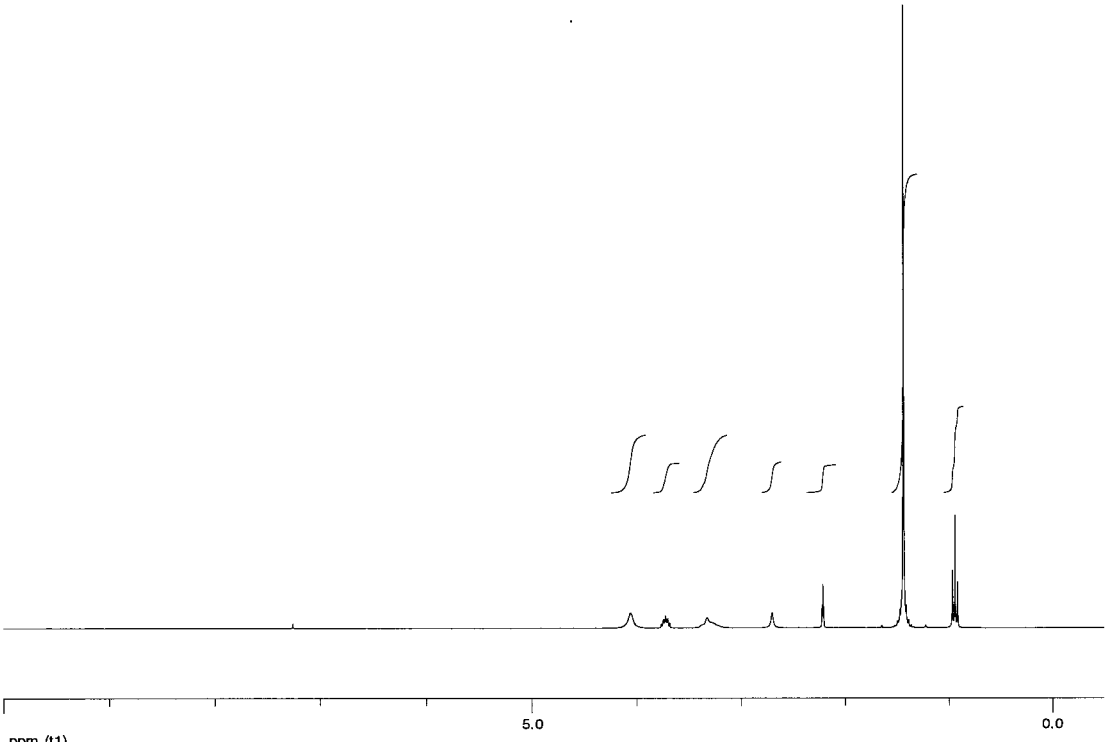

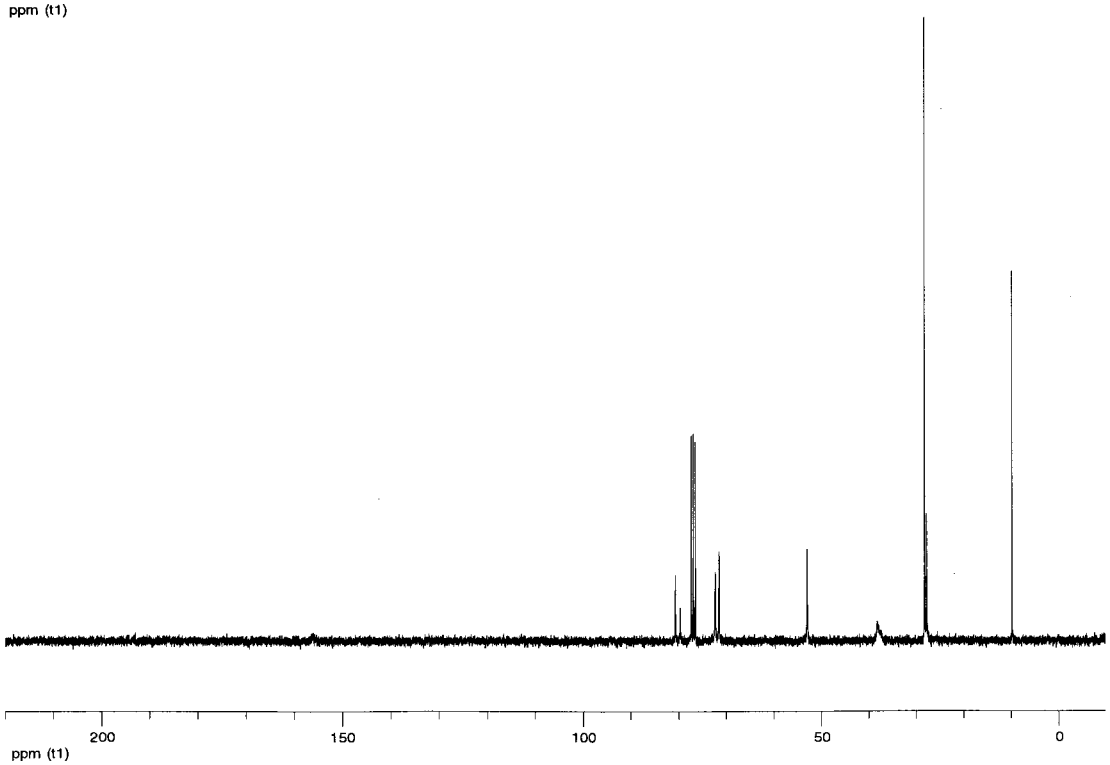

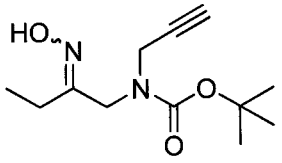

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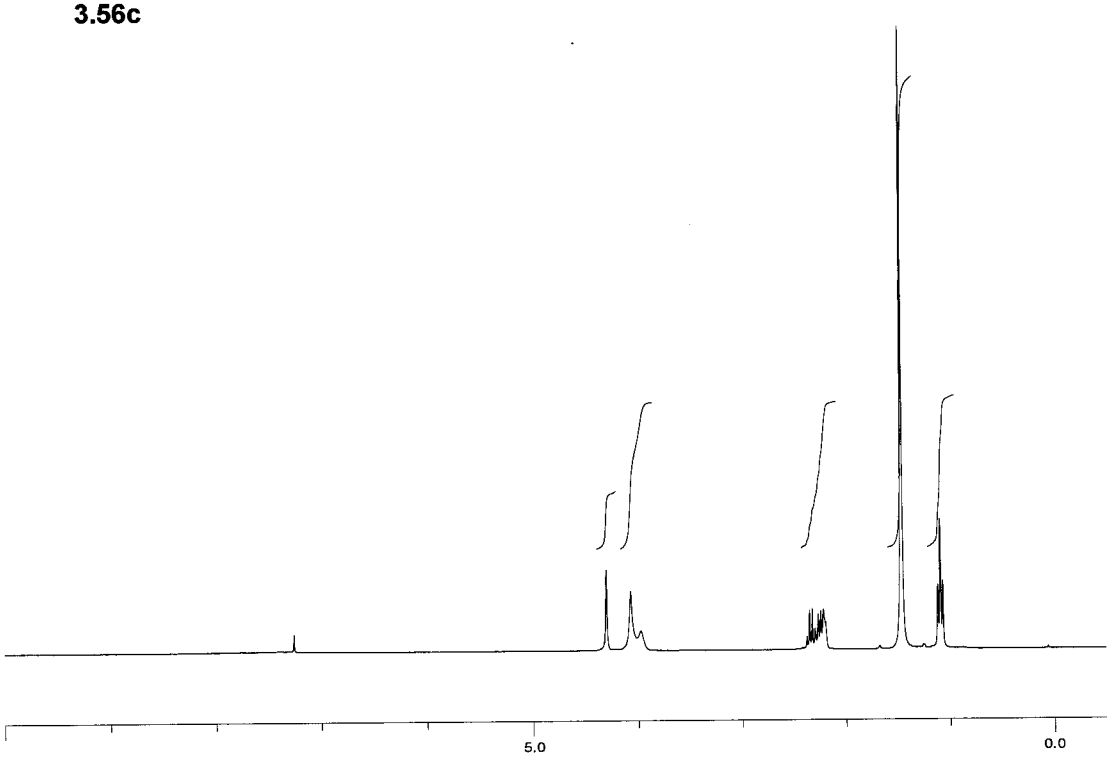

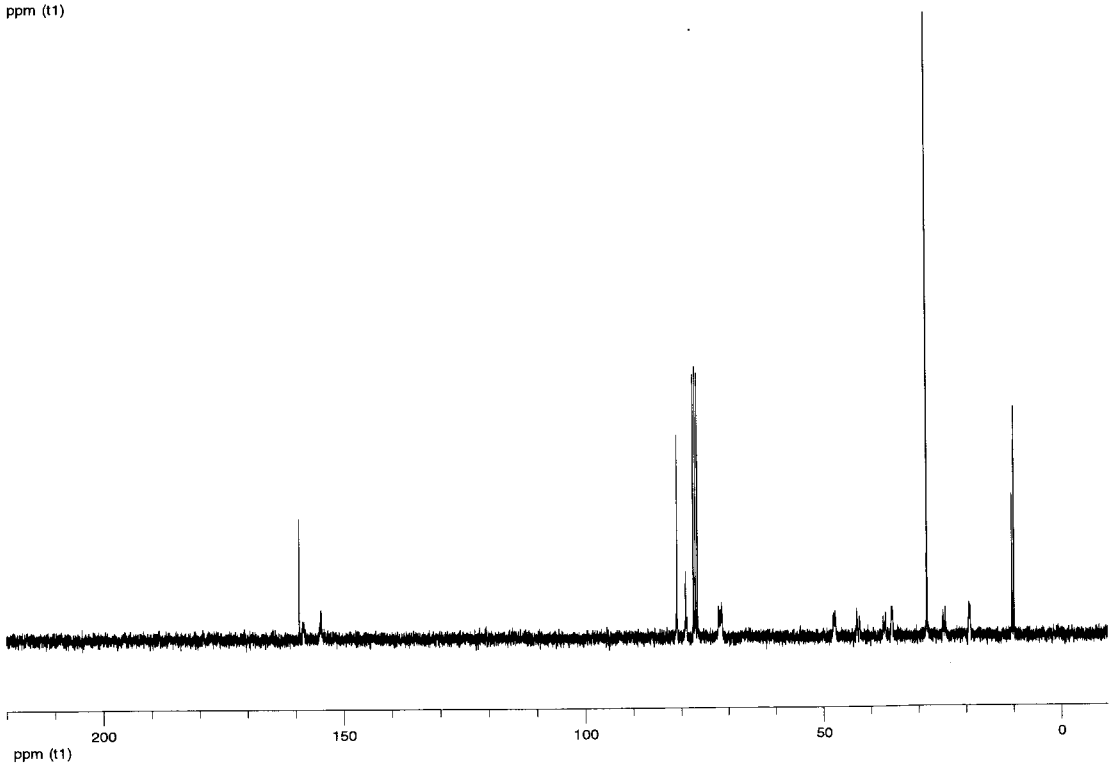

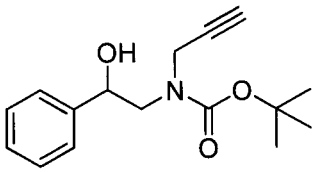

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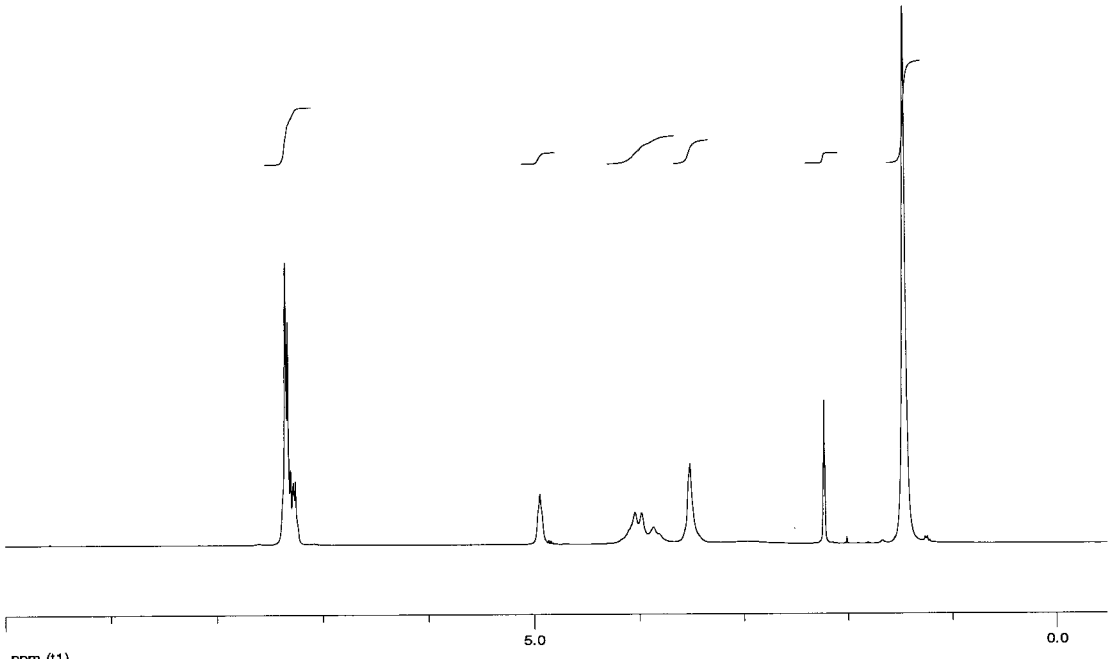

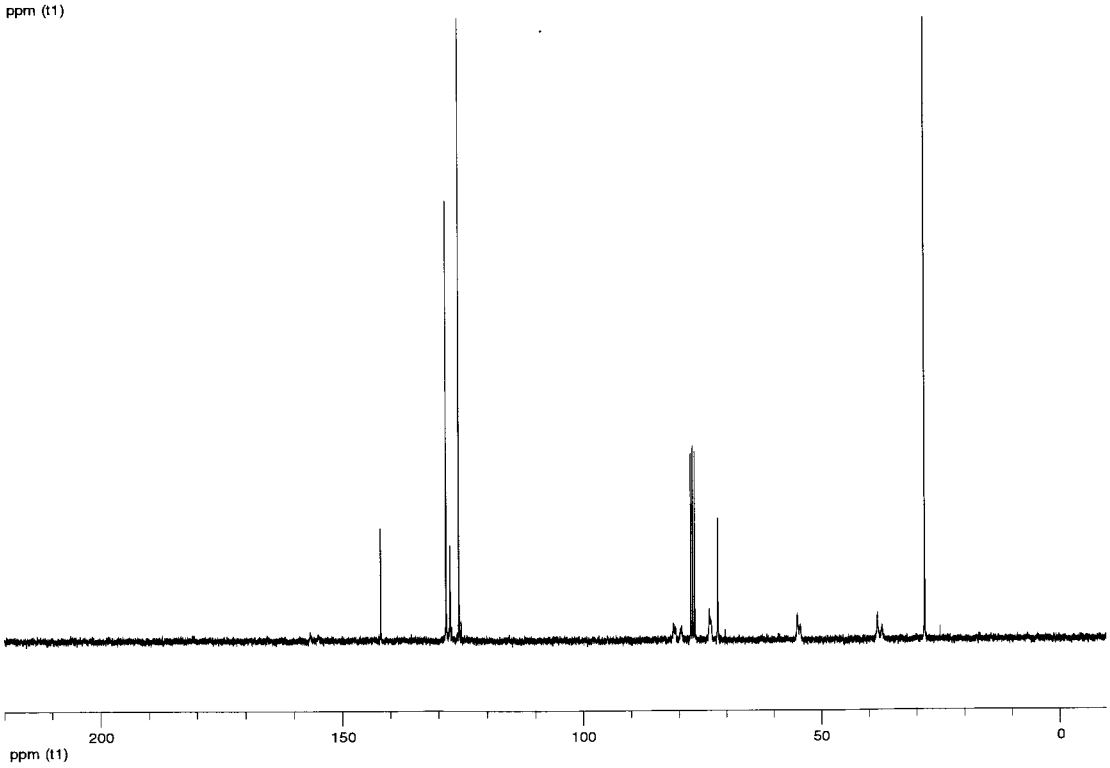

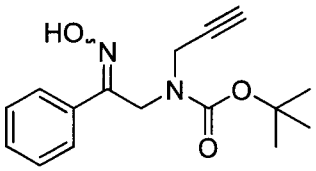

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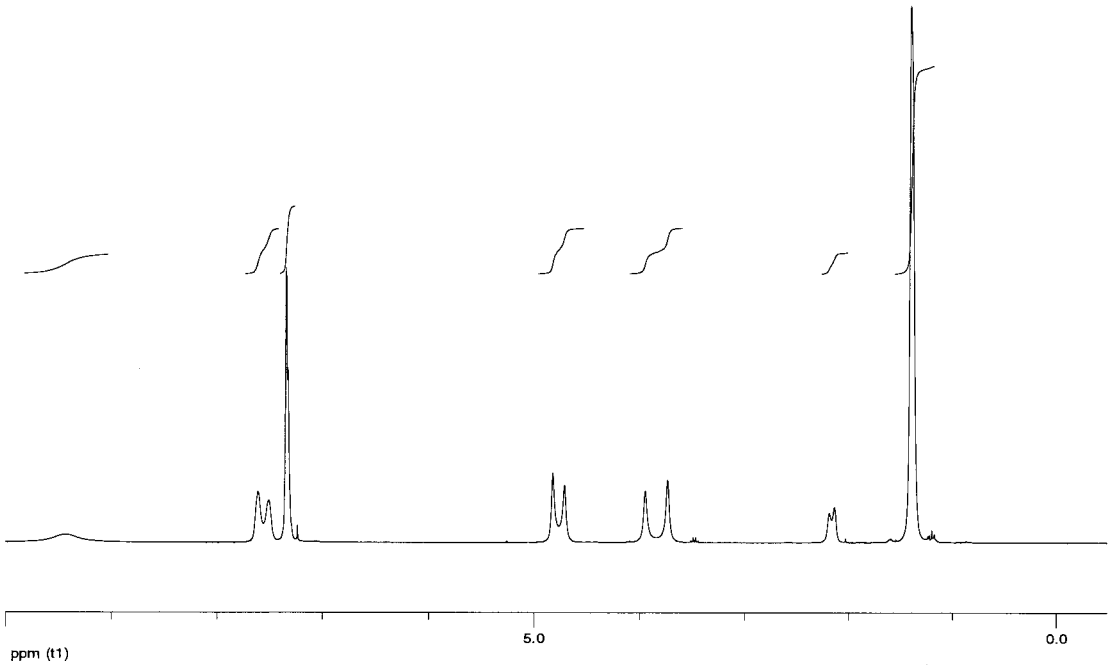

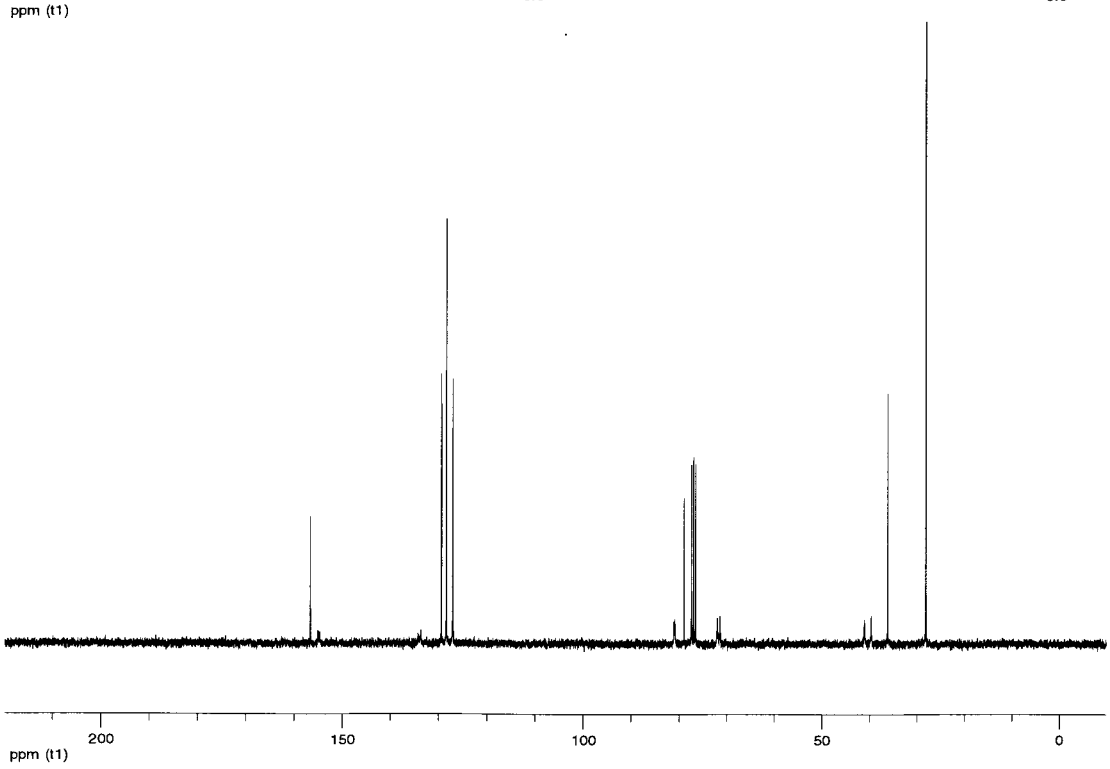

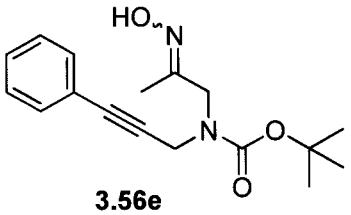

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