PROGRESS IN THE DEVELOPMENT OF MULTICOMPONENT REACTIONS

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PROGRESS IN THE DEVELOPMENT OF MULTICOMPONENT REACTIONS

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Multicomponent reactions (MCRs) are processes in which three or more reactants are combined in one pot to form products that display structural features from each reactant. For this reason, MCRs provide rapid access to chemically diverse structures in an operationally simple manner. MCRs that produce drug-like structures are particularly useful in pharmaceutical development.

As part of our ongoing effort to improve and expand synthetically useful MCRs, *tert*-butylisonitrile was developed as an inexpensive, efficient, and readily available "convertible isonitrile", one whose post-condensation product (typically a carboxamide) can be converted to a variety of new functionalities. The process, which occurred under mild nonaqueous conditions, left carboxylic esters unaffected and transformed MCR amides into useful carboxylic acids for further synthetic elaboration. We further showed that *n*-butylisonitrile may provide a viable alternative to other convertible isonitriles for amide-to-ester transformations in Ugi reactions.

In another project, a simple and general synthesis of carbonimidic dichlorides from isonitriles was developed using sulfuryl choride at low temperature. Carbonimidic dihalides are found in several natural products and have been used as protecting groups for isonitriles. The method, which suppressed free radical chlorination, rapidly and

selectively furnished the corresponding carbonimidic dichlorides in excellent yields without further purification.

Published reports on the reaction of nitronates with thiols under strongly basic conditions to form thiohydroximate esters led to an investigation on the analogous reaction of nitronates with amines to afford the corresponding amidoximes, an important family of medicinally active compounds. During this investigation, the first example of an amidoxime-to-amidine transformation by nucleophilic addition of an amine and elimination of NH_2OH was discovered. The effect of metallating agent and amine substitution was also studied. Two generally useful sets of conditions were developed and applied to the preparation of a representative family of amidoximes.

This thesis also describes attempts to replace the intermediate iminium electrophile in the Ugi reaction with a thionium electrophile. In the course of that study, a rapid and gentle catalytic oxidation of isonitriles to isocyanates was serendipitously discovered. The new method proved to be simple and easy to use. It generated only volatile and innocuous byproducts, and represented a very mild, rapid, and environmentally acceptable procedure for preparing isocyanates from isonitriles.

BIOGRAPHICAL SKETCH

Hoang Van Le was born and raised in Vietnam. He developed a strong interest for mathematics and sciences when he was a student at Le Hong Phong High School for the Gifted in Ho Chi Minh City. In October 2003, the author emigrated to the United States with his parents and became a U.S. citizen five years later. In May 2008, he graduated from the University of California, Berkeley with a B.S. degree in chemistry. While at Berkeley, Hoang worked in the lab of Professor Kenneth Raymond, synthesizing dicationic linkers and investigating their stability in supramolecular systems. After graduation, the author entered the graduate program at Cornell University and pursued a Ph.D. in organic chemistry under the guidance of Professor Bruce Ganem. Hoang has accepted an offer to join the lab of Professor Richard Silverman at Northwestern University as a postdoctoral researcher starting August 2013.

To my beloved parents, Ngoc Le, Anh Nguyen,

and brother, Hung Le,

and friends

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My wonderful friends, including Jimmy John, Sean Conte, Michael Coleman, Laura Tomasevich, Sonia Thangavelu, Swapna Lekkala, Joanna Tan and Jun Liang, have enriched my experience at Cornell and made it a very rewarding time. I especially need to thank my best friend Jimmy for being such a good listener whenever I vented my frustrations from time to time.

I also owe much thanks to my undergraduate advisor, Professor Kenneth Raymond at the University of California, Berkeley. His generosity, patience, and enthusiasm for science fostered a positive environment where I learned how to do research for the first time. While in his lab, I was fortunate to work with many wonderful

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Last, but certainly not least, I would like to thank my parents and brother for always being there for me. Their unconditional love and encouragement are the backbone of my achievements. I greatly appreciate my uncle, Dang Le, and his family for their sponsorship of my family into the United States where I have received world-class education. I am fortunate to have incredible grandparents whom I look up to as role models, and many amazing uncles and aunts, both in Vietnam and in the U.S., who have always believed in me. I am thankful for their love.

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CHAPTER 1

Introduction

1.1 Background

Multicomponent reactions (MCRs) are chemical reactions in which three or more starting materials combine to form a product.[1] Most or all of the atoms from the reactants contribute to the newly formed product. The structure of the final product is often very complex as it displays the features of each input. Many MCRs produce heterocyclic rings and/or drug-like structures that are often present in pharmaceutical agents. MCRs are ideal tools for building large collections of structurally diverse compounds. Many bioactive compounds and pharmaceutical drugs have been discovered by combinatorial chemistry through screening such collections.[2]

Used primarily by pharmaceutical companies, combinatorial chemistry describes a number of laboratory techniques that make it possible to synthesize large collections of related compounds in a single process.[3] This process is often carried out in a preprogramed and computer-controlled sequence. Combinatorial chemistry uses either solid-phase synthesis or solution-phase synthesis to generate these chemical libraries. Solid-phase synthesis uses resin beads as a means to bind the chemicals before doing the chemistry. The products are purified by washing away excess reagents and by-products after each reaction step.

Two commonly used techniques in solid-phase synthesis are mix-and-split synthesis and parallel synthesis. The mix-and-split technique was first used by Merrifield in 1963 to synthesize a library of peptides.[4] A sample of resin beads was split equally into portions. Each portion was then coupled with a different starting amino acid. The amino acid-bound beads were mixed thoroughly and then split again into portions. Each new portion was then reacted with a second set of amino acids to give a complete set of

possible outcomes of dimers. The cycle of mixing and splitting was repeated with more sets of amino acids to generate a library of peptides. The mix-and-split technique can also be used to synthesize libraries of other organic compounds. The parallel synthesis technique was developed by Geysen *et al.* in 1984 to synthesize an array of peptides using plastic rods that were coated with the solid support.[5] By immersing the rods into the solutions of different amino acids in a stepwise process, they were able to synthesize an array of 96 different peptides.

While solid-phase synthesis is very easy to conduct, it can generally only produce small quantities of products.[6,7] The adaptation of the reaction conditions that are normally used in solution synthesis for solid-phase synthesis also takes time. Solution-phase synthesis can produce a much larger chemical library than solid-phase synthesis, making it the method of choice for many chemists. Solution-phase synthesis can also use a broader range of reactions; thus, it can produce a much more diverse chemical library.

Although combinatorial chemistry uses a variety of laboratory techniques to generate large chemical libraries, the synthetic approach still involves conventionally linear processes. To shorten the time and improve the efficiency in creating libraries of complex structures, combinatorial chemists have been using MCRs in both solid-phase synthesis and solution-phase synthesis.[8] Multicomponent reactions represent an obvious advantage over conventional synthetic approaches in generating these large chemical libraries. By combining many inputs and forming several new bonds in a one-pot procedure, a MCR provides rapid access to chemically diverse structures in an operationally simple manner. New distinct molecules are produced by simply changing any one of the inputs.[6] Moreover, MCRs often occur with high atom economy, which

increases both synthetic efficiency (by reducing time, labor, cost, and chemical waste generation) and molecular complexity. As synthetic chemists pay increasing attention to efficient and environmentally benign routes of synthesis, the use of MCRs has grown more attractive in creating large chemical libraries.

Figure 1.1 depicts some of the most well-known examples of MCRs. In 1850, Strecker reported the synthesis of amino acids through the condensation of aldehydes, ammonia, and hydrogen cyanide, which has been widely recognized as the first MCR.[9] In 1912, Mannich reported that the reaction of non-enolizable aldehydes, amines, and enolizable ketones produced aminocarbonyls.[10] The first MCR involving an isonitrile was reported by Passerini in 1921, taking advantage of the unique divalent nature of the isonitrile carbon.[11] In the Passerini reaction, α-acyloxyamides were formed through the condensation of carbonyl compounds, carboxylic acids, and isonitriles. In 1959, Ugi reported that the reaction of carbonyl compounds, amines, carboxylic acids, and isonitriles generated α-aminoacyl amides.[12] In 1882, Hantzsch reported that an aldehyde, 2 equivalents of a β-ketoester, and ammonia combined to give a dihydropyridine derivative.[13] A subsequent oxidation would lead to a corresponding pyridine. In 1890, Hantzsch reported the synthesis of substituted pyrroles through the condensation of primary amines, β-ketoesters, and α-haloketones.[14] In 1891, Biginelli reported that the reaction of aldehydes, ureas, and β-ketoesters generated 3,4-dihydropyrimidin-2(1H)-ones.[15] Reported by Bergs in 1929 and improved by Bucherer in 1934, the Bucherer-Bergs reaction is the condensation of aldehydes or ketones with potassium cyanide and ammonium carbonate to give hydantoins.[16,17] Of particular interest, the Hantzsch dihydropyridine synthesis, the Hantzsch pyrrole synthesis, the Biginelli reaction, and the

Bucherer-Bergs reaction produced heterocyclic compounds that are often featured in pharmaceutical products.

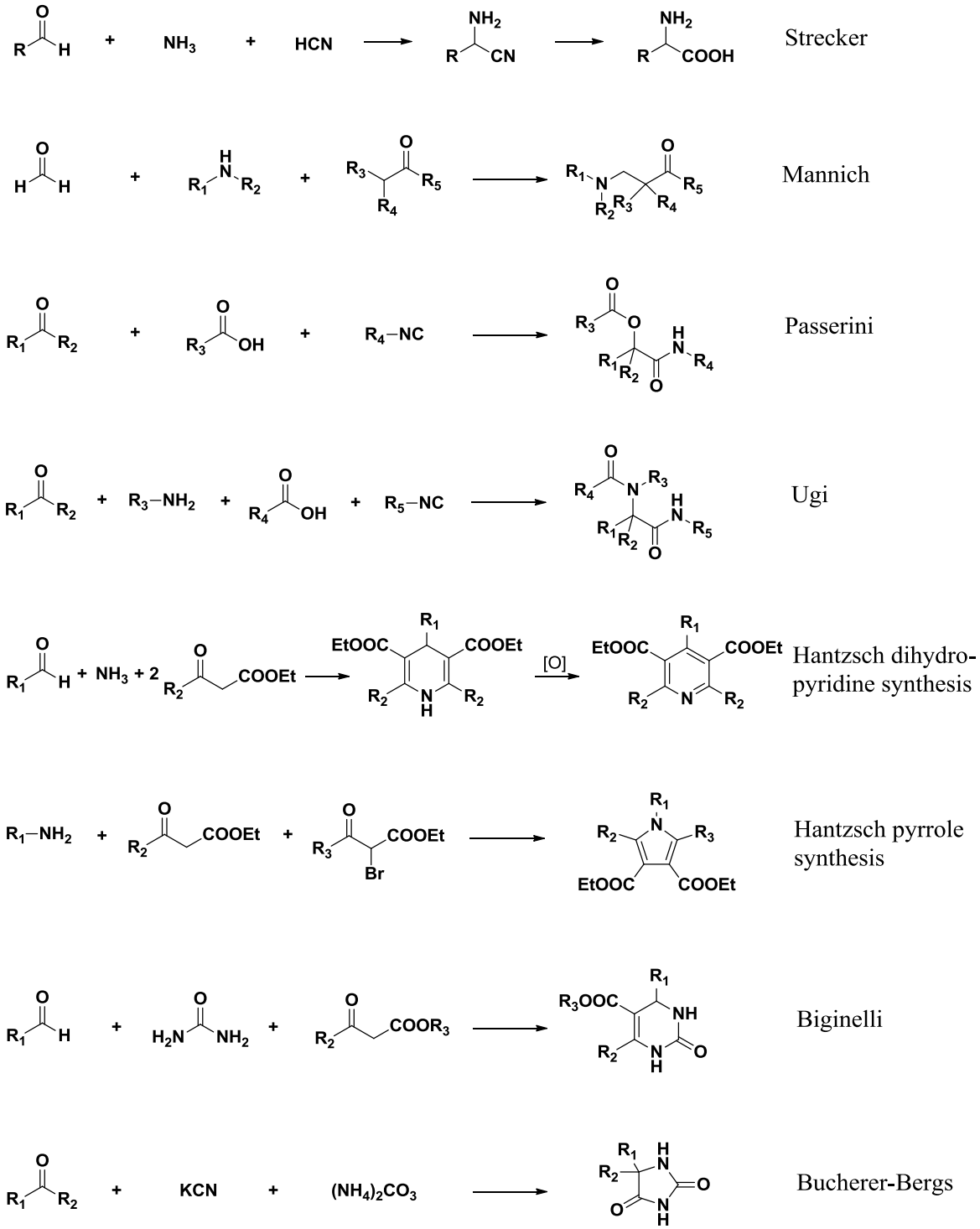


Figure 1.1 Examples of Some Well-Known MCRs.

Because many MCRs produce heterocyclic rings and/or drug-like structures, MCRs have also been used in the synthesis of many drugs. For example, the Hantzsch dihydropyridine synthesis has been used to synthesize many different substituted 1,4-dihydropyridines (1,4-DHPs), which are well known in pharmacology as L-type calcium channel blockers.[18] Many 1,4-DHPs, such as amlodipine, felodipine, nicardipine, and nifedipine, have been used in treatment of angina and hypertension (Figure 1.2). Recent generations of 1,4-DHPs display antianginal, anticancer, antidiabetic, bronchodilating, neurotropic, and other pharmacological activities.

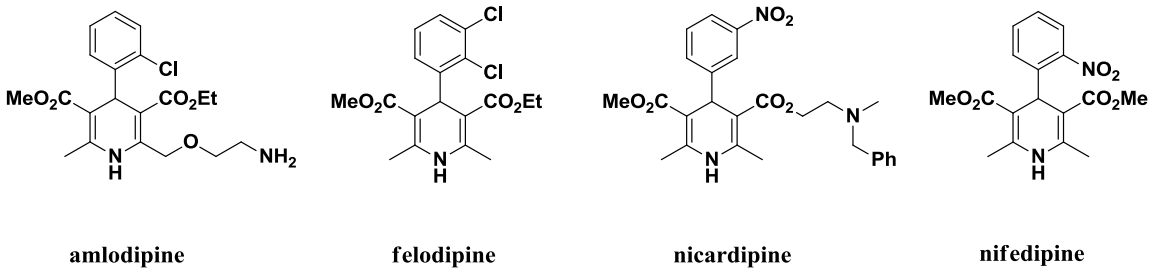
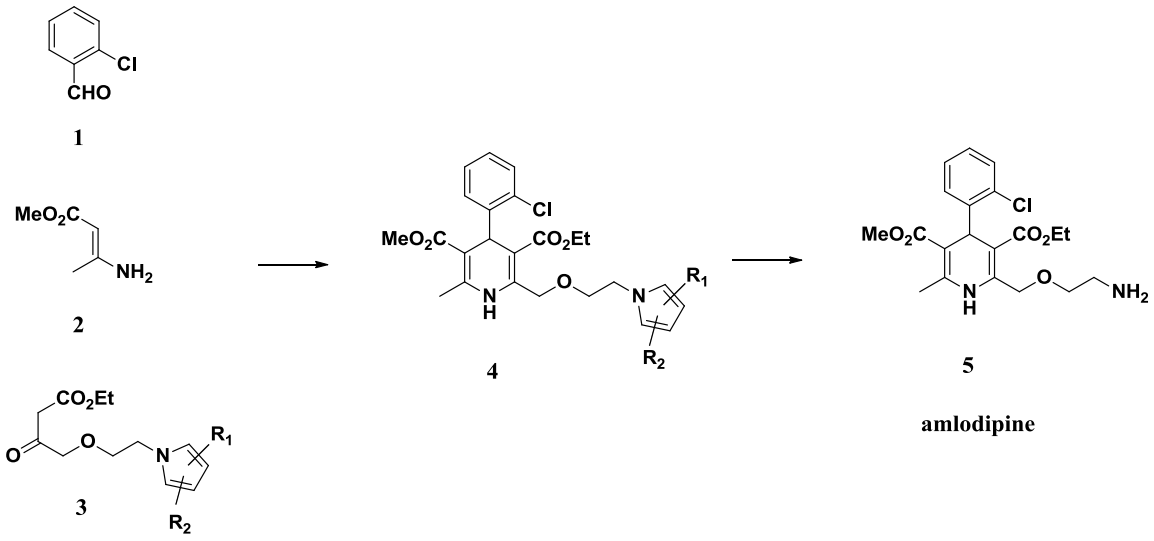


Figure 1.2 Some Well-Known Drugs in the 1,4-DHP Family.[18]

Amlodipine **5**, for example, was recently produced using the Hantzsch dihydropyridine synthesis in a U.S. patent (Scheme 1.1).[19] The Hantzsch dihydropyridine product **4** was formed by the condensation of 2-chlorobenzaldehyde **1**, methyl (E)-3-aminocrotonate **2**, and ethyl-3-oxidanylidene-4-(2-pyrrol-1-ylethoxy)butanoate **3**. Subsequent removal of the amine protective group afforded amlodipine **5** in 90% overall yield.



Scheme 1.1[19]

The Biginelli reaction has been used to synthesize many different substituted 3,4-dihydropyrimidinones (3,4-DHPMs), which are well-known in pharmacology as calcium channel blockers and have shown antiviral, antiinflammatory, antibacterial, anticarcinogenic, antihypertensive, and antagonist activities.[20] A typical 3,4-DHPM **6** might be constructed from the condensation of an aryl aldehyde **7**, a β-ketoester **8**, and a urea or thiourea **9** (Figure 1.3).[20–23] Examples of 3,4-DHPMs include SQ 32547 and SWO2, which have been discovered as potent antihypertensive agents, and monastrol, which is known as the only mitotic kinesin Eg5 inhibitor (Figure 1.4).[23] Mitotic kinesin Eg5 is a motor protein that plays an essential role in cell division. Monastrol is currently under investigation for its anticancer activity.

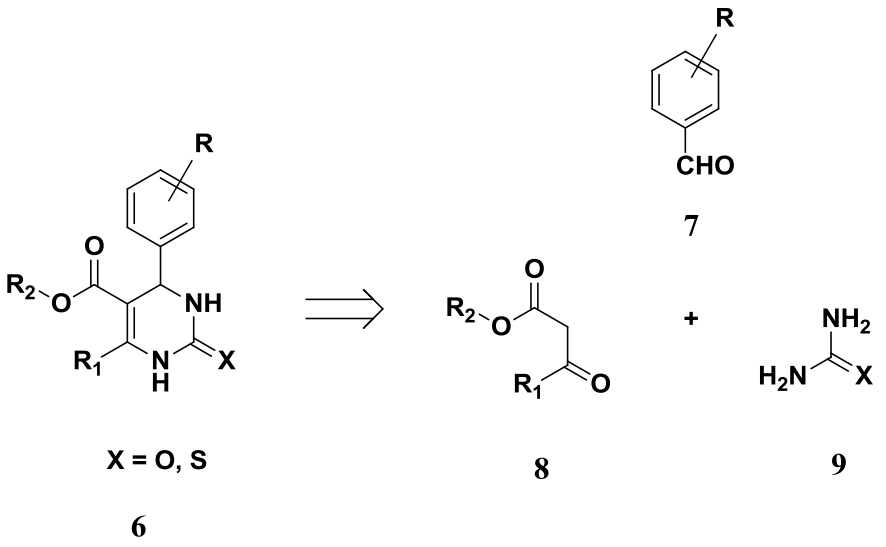


Figure 1.3 The Biginelli Synthesis of a Typical 3,4-DHPM **6**.[20–23]

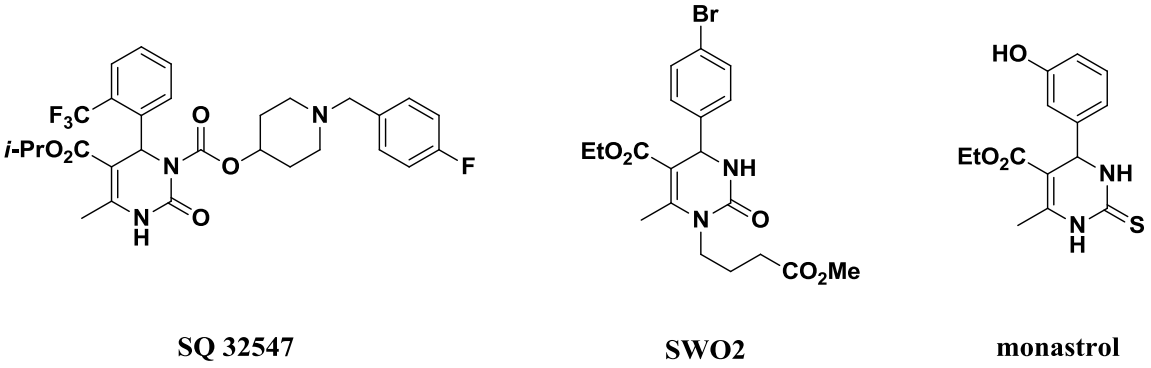
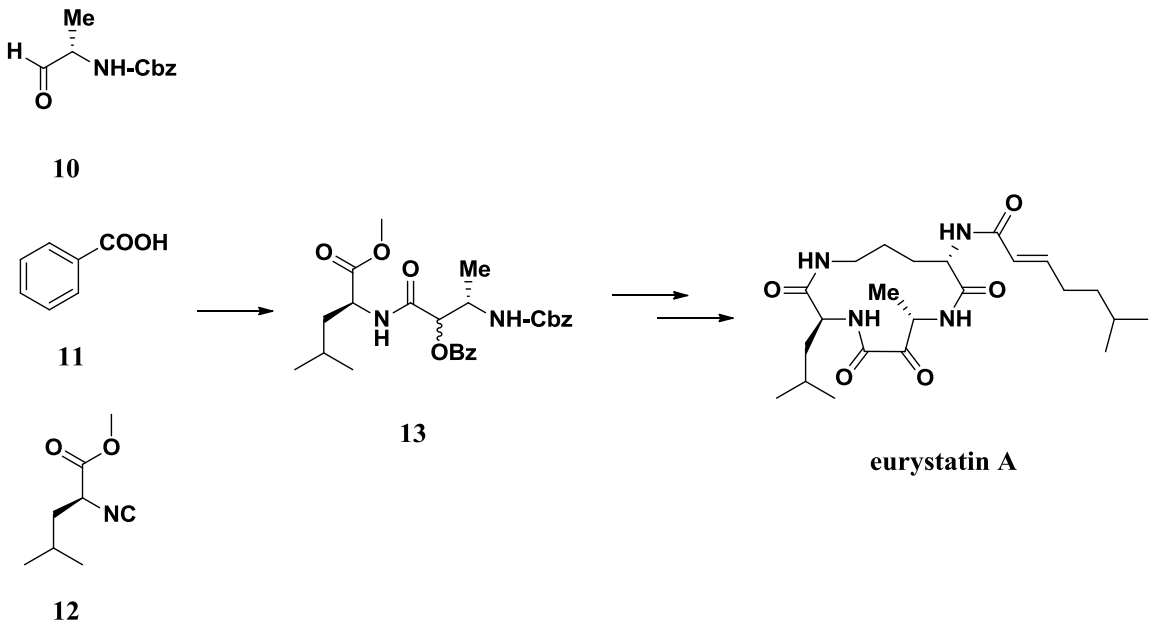


Figure 1.4 Some Well-Known Drugs in the 3,4-DHPM Family.[23]

Since its discovery, the Passerini reaction has been widely used in the synthesis of many drugs and bioactive compounds. For example, Schmidt and Weinbrenner used a Passerini reaction as the first step in their synthesis of eurystatin A (Scheme 1.2).[24] Eurystatin A has been reported to inhibit the activity of prolyl endopeptidase (PEP). The Passerini product **13** was formed by the condensation of aldehyde **10**, benzoic acid **11**, and isonitrile **12**. Subsequent modification afforded eurystatin A.



Scheme 1.2[24]

Kalinski *et al.* recently used a 2-component Passerini to synthesize bicalutamide **14** (Figure 1.5).[25] Bicalutamide is an oral anti-androgen drug that is used in the treatment of prostate cancer and hirsutism.[26,27] Peak sales for bicalutamide (2006) were $1.5 billion.[28] Bicalutamide **14** was constructed by the combination of the aldehyde **15** and the isonitrile **16** using a Lewis acid as a promoter.

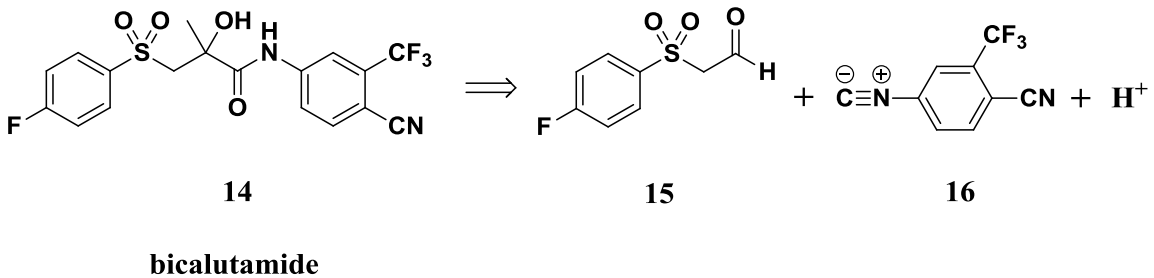
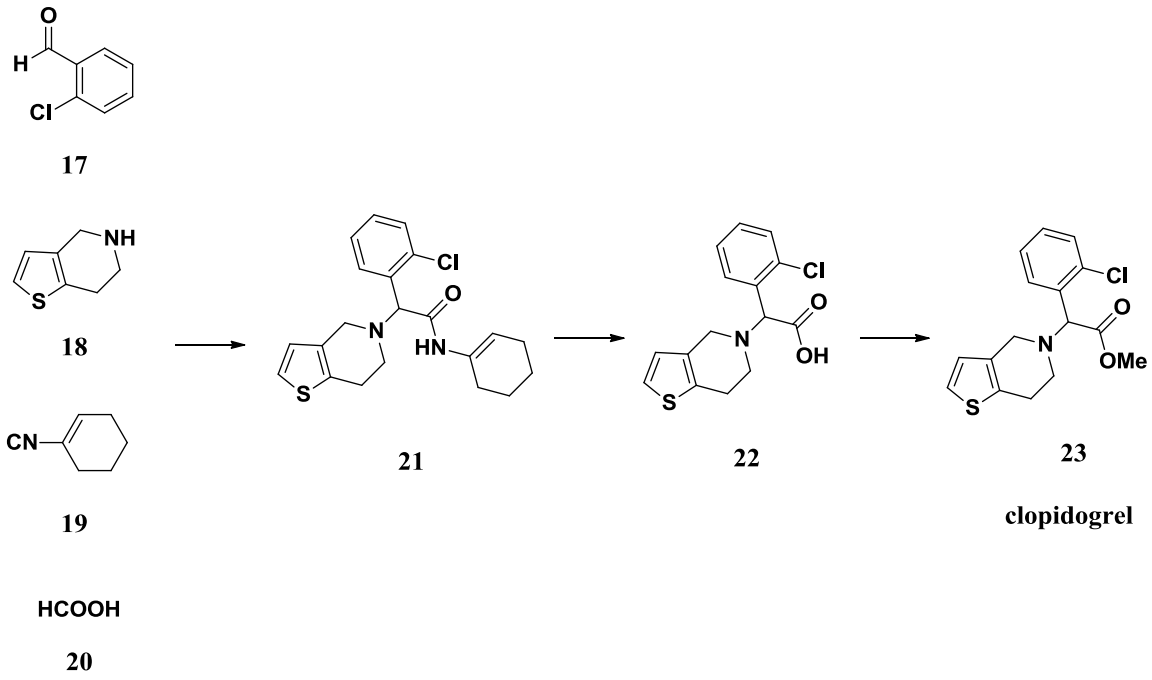


Figure 1.5 A 2-Component Passerini Synthesis of Bicalutamide.

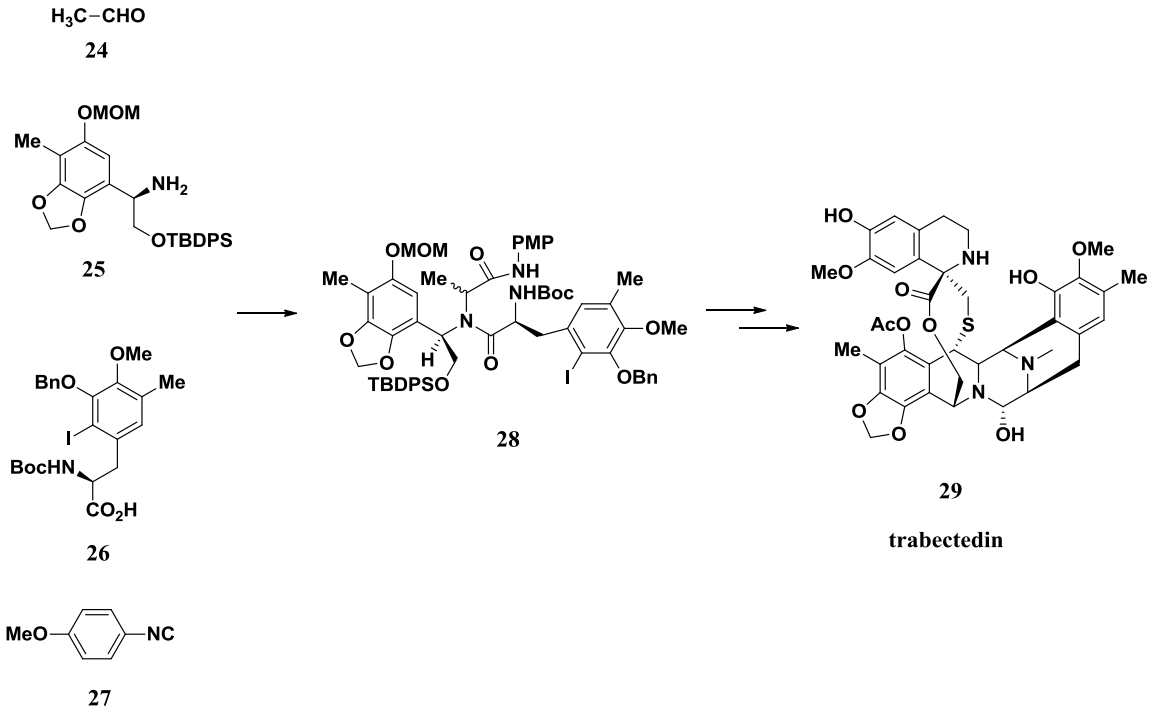
Similar to the Passerini reaction, the Ugi reaction has also been widely used in the synthesis of many drugs and bioactive compounds since its discovery. For example, Kalinski *et al.* used a 3-component Ugi reaction to synthesize clopidogrel **23** (Scheme 1.3).[25] Clopidogrel is an oral antiplatelet agent that is used to inhibit blood clots in many diseases. In 2005, clopidogrel was the world's second-highest-selling drug. The Ugi product **21** was formed by the condensation of 2-chlorobenzaldehyde **17**, 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **18**, 1-isocyanocyclohexene (Armstrong isonitrile) **19**, and formic acid **20**. Subsequent hydrolysis of the amide in **21** and esterification of carboxylic acid **22** afforded clopidogrel **23** in high yield.



Scheme 1.3[25]

The Ugi reaction was recently used by Fukuyama *et al.* as the first step in the synthesis of trabectedin, also known as ecteinascidin 743 or ET-743 (Scheme 1.4).[29]

Trabectedin is a very potent antitumor agent that is used in treatment of soft tissue sarcoma and ovarian cancer.[30,31] It is also in phase II trials for treating breast cancer and paediatric tumors.[32] The Ugi product **28** was formed by the condensation of acetaldehyde **24**, the amine **25**, carboxylic acid **26**, and *p*-methoxyphenyl isonitrile **27**. Subsequent modification afforded trabectedin **29**.



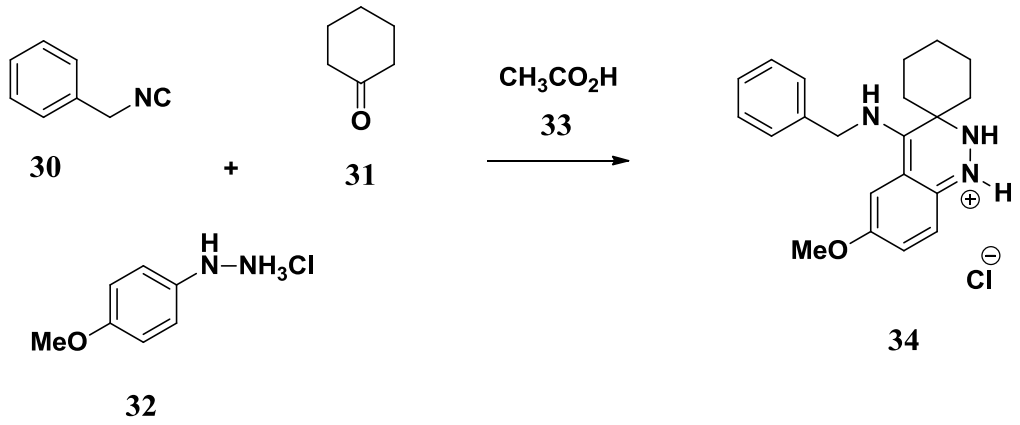
Scheme 1.4[29]

1.2 Improving Known MCRs and Evolving New MCRs

MCRs offer rapid access to chemically diverse structures that have heterocyclic rings and/or drug-like features. For these and other reasons, the use of MCRs in the discovery process of new drugs and bioactive compounds has intensified lately.[33]

Numerous research groups are now focusing on MCR design and development, and important advances in MCRs have been discovered either by chance or by design.

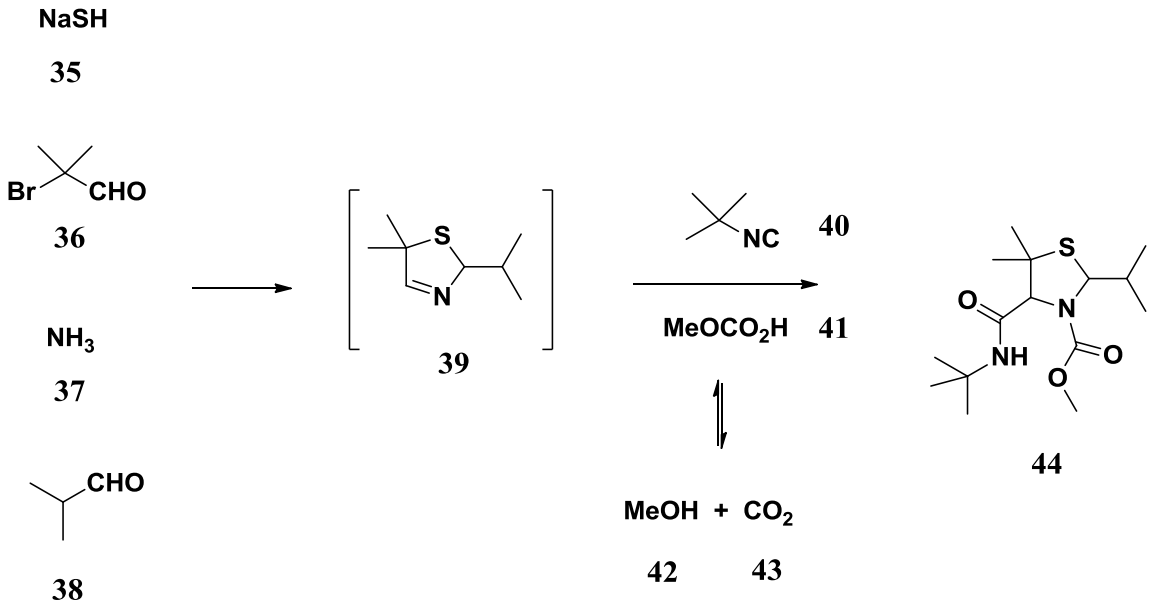
One example of the discovery of new MCRs by chance is illustrated by the work of Lacke and Webber.[34] After selecting 10 starting materials with different functional groups, the compounds were mixed in all possible combinations of 2 to 10 components. Overall, 1013 reactions were carried out using an automated robotic system. HPLC-MS was employed to identify new peaks that were different from the reactants. Ultimately, the team "rediscovered" the Ugi reaction and also identified a new MCR that furnished 2,3-dihydrocinnoline **34** by the condensation of benzylisonitrile **30**, cyclohexanone **31**, and 4-methoxyphenyl hydrazine **32** (Scheme 1.5).



Scheme 1.5[33]

One example of the discovery of new MCRs by design is the union of two or more known MCRs. This concept was first described by Dömling and Ugi in 1993.[35] They also reported the first seven-component reaction by combining the Asinger reaction and the Ugi reaction (Scheme 1.6). The intermediate **39** of the Asinger four-component

reaction was formed by the condensation of sodium hydrosulfide **35**, 1-bromo-2,2-dimethylacetaldehyde **36**, ammonia **37**, and isobutyric aldehyde **38**. This intermediate **39** contained a Schiff base, which was the starting point for a subsequent Ugi reaction with *tert*-butylisonitrile **40** and methoxycarboxylic acid **41**. Methoxycarboxylic acid **41** was thus generated from methanol **42** and carbon dioxide **43**. The final product of this seven-component reaction was thiazolidine **44**.



Scheme 1.6[7,35]

Our laboratory has been applying logical strategies to improve known MCRs and evolve new MCRs.[36] In order to be a useful lead compound for pharmaceutical development, a MCR product needs to possess a drug-like (i.e., natural product-like) structure. Because there are only a handful of MCRs that satisfy this criterion, most MCRs are not useful in drug discovery. The strategies that drive our research goals have aimed to find practical and useful MCRs for drug discovery.

One approach to improve known MCRs takes advantage of detailed knowledge of the MCR reaction mechanisms, and applies retrosynthetic analysis to the intermediates in a logic-based approach. Once a new independent route to an intermediate is identified, it is carefully evaluated against our goal. Such a finding would constitute a new route to the final product through new starting materials and reactions. As one illustration of MCR improvement, Figure 1.6 depicts a typical four-component reaction that combines the inputs A, B, C, and D, each representing a family of compounds. Assuming the overall transformation proceeds via symbolic intermediates [A, D] and [A, D, C], which are depicted as the blue line and blue triangle, respectively, one may then apply retrosynthetic analysis to the intermediate [A, D], for example, and identify an independent route to the intermediate [A, D] from Q + R + S. Such a finding would thus constitute a new five-component route to the final product [A, B, C, D] by combining Q + R + S with B and C. Besides producing the final product from a more diverse set of reactants, this new five-component route also would enhance the dimensionality of the reaction and broaden the potential size of chemical libraries. For example, Simoneau pointed out that a four-component reaction with 10 inputs each would theoretically produce a chemical library of 10,000 compounds, while a five-component reaction with 10 inputs each would theoretically produce a chemical library of 100,000 compounds.[6] The diversity of the chemical libraries would also increase as they incorporate structural diversity from five, instead of four, reactants.

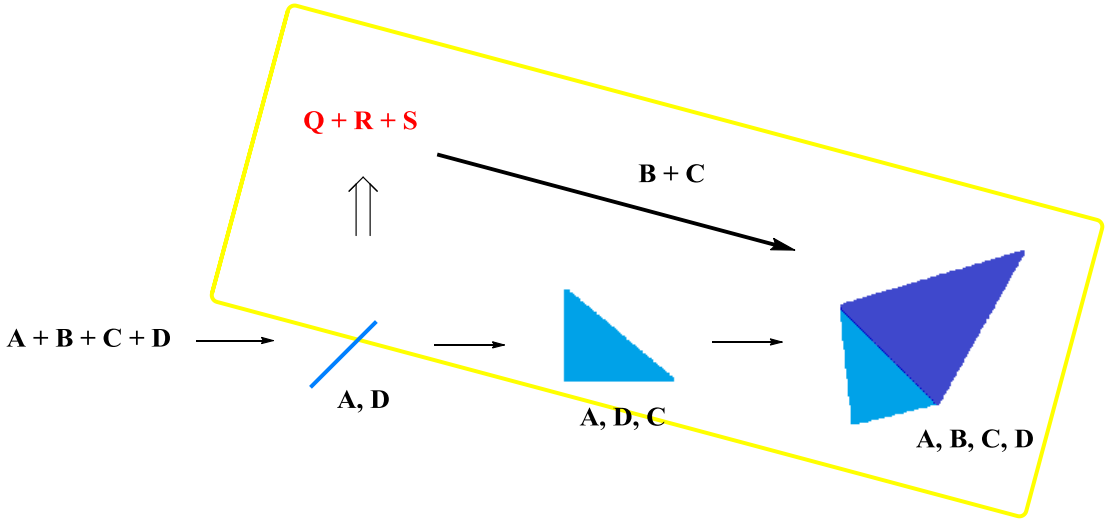


Figure 1.6 Improving Known MCRs by Retrosynthetic Analysis.[36]

To evolve new MCRs, our group has developed a logic-based approach called the single reactant replacement (SRR) approach.[36] In this approach, careful analysis of the reaction mechanism is conducted to identify the key reactivity element (KRE) of each reactant in a known MCR. For example, a reactant might serve as an electrophile, or base, or chelating agent, or hydrogen bond donor, just to name a few possible KREs. Once the KRE has been identified, the chemist might replace one reactant with another input having the same KRE. This new input could carry an additional orthogonal reactivity element that might ultimately direct the reaction, either during or after, to a different outcome. As one illustration of this approach, Figure 1.7 depicts a three-component reaction that combines the inputs A, B, and C, each representing a family of compounds. If one replaces A with a different input W that shares the same KRE with A, one might direct the reaction to the formation of a new chemical structure that is different from the product of the parent MCR. The SRR approach is iterative and can then be reapplied to one of the other inputs to evolve the reaction to a second generation and so

on. Ideally, the difference in the structures of the final products would increase after each iteration. Gradually, a new MCR would be evolved and would be distinct from its predecessors. The SRR approach would thus further expand the repertoire of MCRs in building chemical libraries.

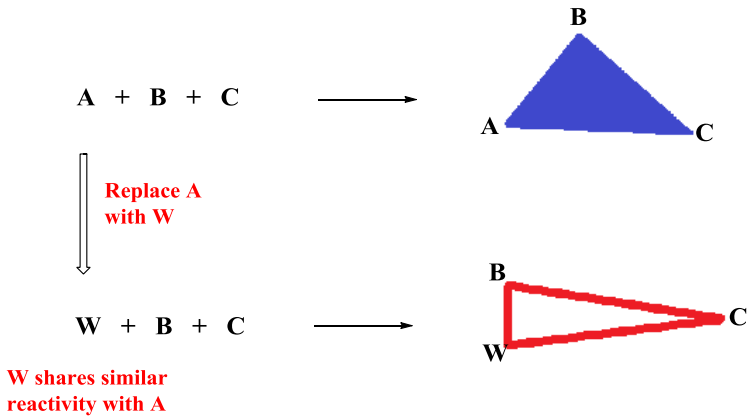
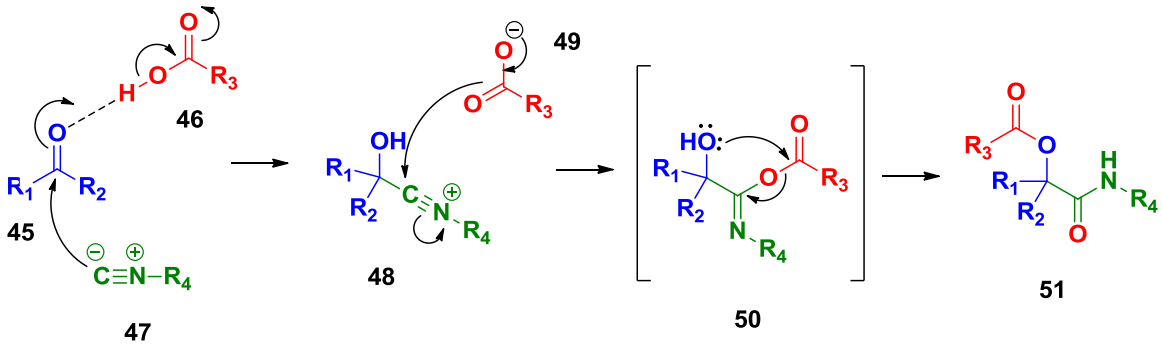


Figure 1.7 Developing New MCRs by the Single Reactant Replacement Approach.[36]

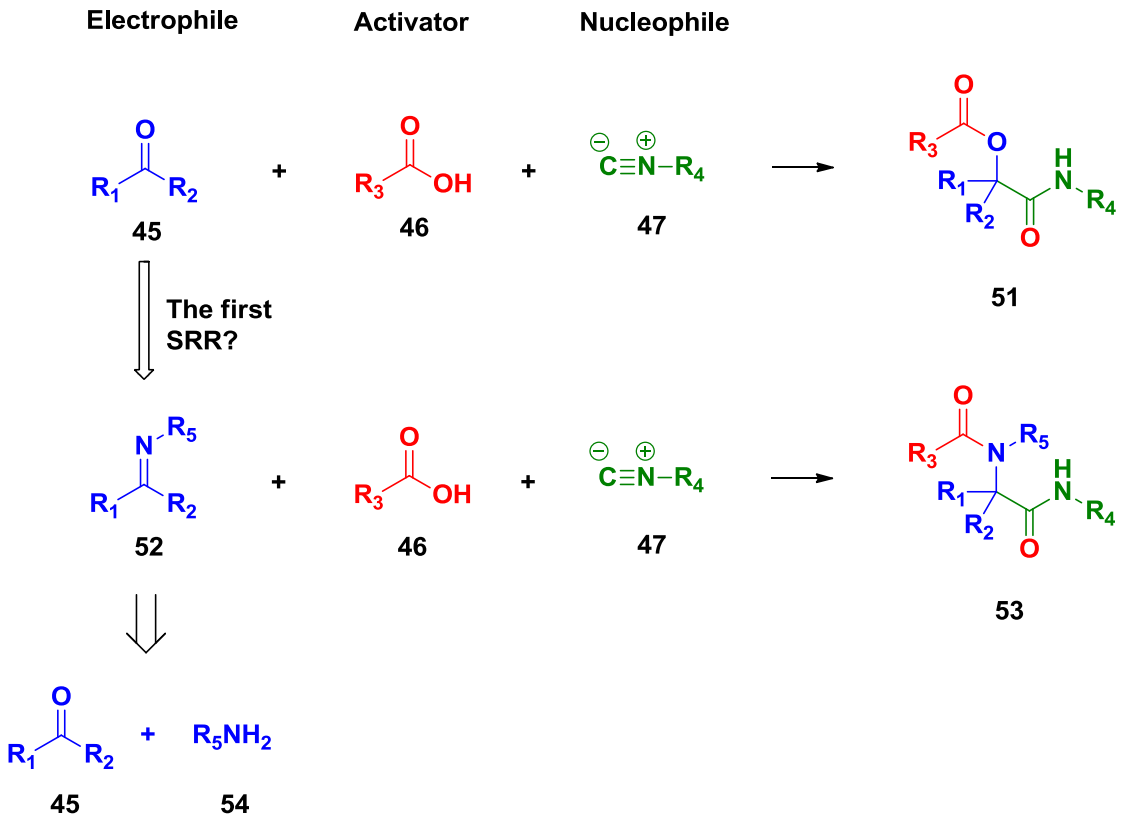
An early example of the SRR approach can be seen in the development by Ivar Ugi of a new MCR based on the Passerini reaction, where the functional similarities between simple carbonyl compounds and their corresponding imines were exploited by Ugi. As shown in Figure 1.1, in the Passerini reaction, an α-acyloxyamide was formed through the condensation of either an aldehyde or a ketone, a carboxylic acid, and an isonitrile.[11] The accepted mechanism for the Passerini reaction is depicted in Scheme 1.7. The carbonyl **45** is activated by the carboxylic acid **46** via hydrogen bonding. Nucleophilic addition of the isonitrile **47** to the activated carbonyl affords the nitrilium ion **48**. A second nucleophilic addition of the carboxylate anion **49** to this intermediate

leads to the alcohol **50**. The final step is a Mumm rearrangement, which transfers the R_3 acyl group to the alcohol oxygen, affording the final product **51**.



Scheme 1.7

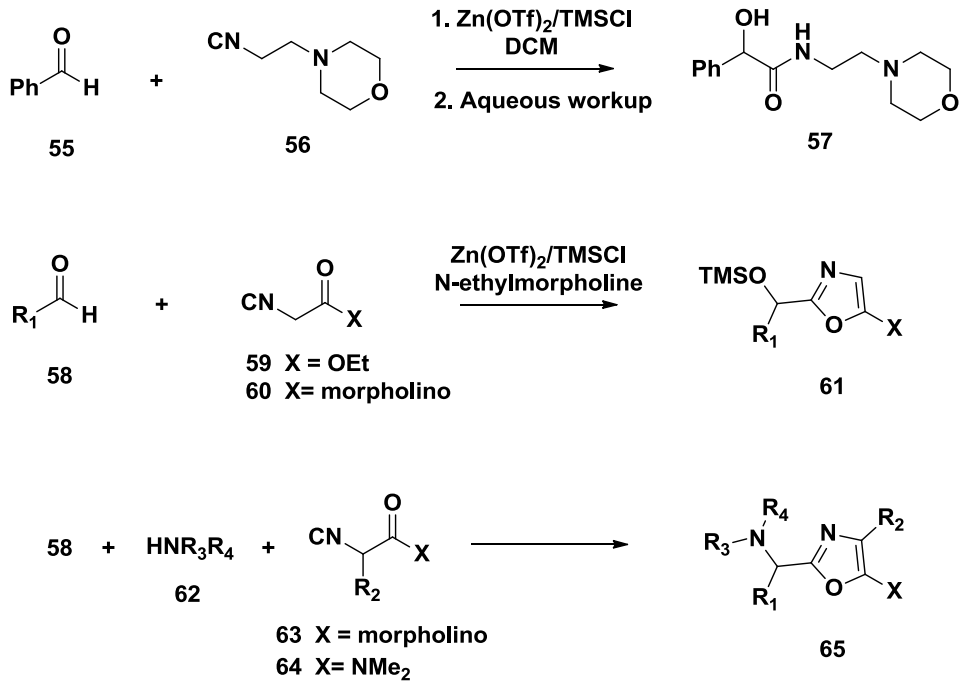
After careful analysis of the Passerini reaction mechanism and the functional roles of each reactant, Ugi recognized that an imine might play a role similar to the carbonyl in the Passerini reaction. In a 1962 article that reported his research on the α-addition of immonium ions and anions to isonitriles, Ugi noted that: "Had Passerini been conversant with present day views on reaction mechanisms while studying the reaction which now bears his name, he would probably have added ammonia or the primary amines, to his three starting materials and thereby discovered the α-amino alkylation of isonitriles and acids."[37] Effectively, Ugi was practicing the SRR approach when he replaced the carbonyl component **45** in the Passerini with a comparable electrophilic imine **52** (Scheme 1.8). The α-aminoacyl amide product **53** would be formed through the condensation of the imine **52** with a carboxylic acid **46** and an isonitrile **47** in a similar mechanistic pathway.



Scheme 1.8

Following in Ugi's footsteps and guided by the SRR approach, our laboratory has evolved several MCRs. In one example, the carboxylic acid component of the Passerini reaction was replaced with a Lewis acid such as TMSOTf.[38] The resulting silylation of the carbonyl component (benzaldehyde) in the presence of isonitrile **56** led to α-hydroxyamide **57** in good yield after aqueous workup (Scheme 1.9). In another variant, isonitriles that contain good donor groups, such as ethyl isocyanoacetate **59** or 2-morpholinoethyl isonitrile **60** afforded ethoxyoxazoles or morpholinooxazoles **61** via neighboring group participation. The iterative aspect of the SRR approach was investigated by subsequently replacing the aldehydes **58** in the oxazole-forming reaction with the corresponding "iminium" species, which were made by premixing **58** with either

morpholine or dimethylamine **62**. Bis-aminooxazoles **65** were obtained in good yields without the need for Lewis acid promoters. These reactions could be useful in finding drug lead compounds as many medicinally significant natural products bear substituted oxazole motifs.[39,40]

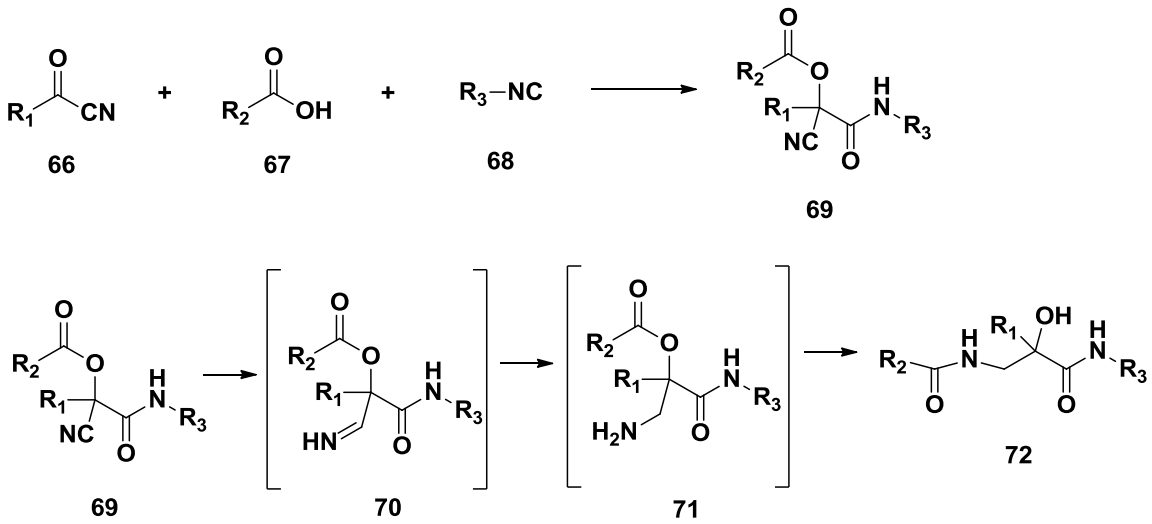


Scheme 1.9[38]

Guided by the SRR approach, Oaksmith *et al.* in our group replaced the carbonyl component in the Passerini with an acylnitrile to test the effect of embedding an orthogonal reactivity element within the carbonyl component.[41] The α-acyloxy-α-cyanoamide **69** was formed in good yield by the condensation of an acylnitrile **66**, a carboxylic acid **67**, and an isonitrile **68** (Scheme 1.10). The α-acyloxy-α-cyanoamide **69** was then directed to a different outcome by a simple catalytic hydrogenation. The nucleophilic amine group released in **71** triggered a rearrangement that produced β-amino acid diamide **72** as the final product. This two-stage process could be performed in one

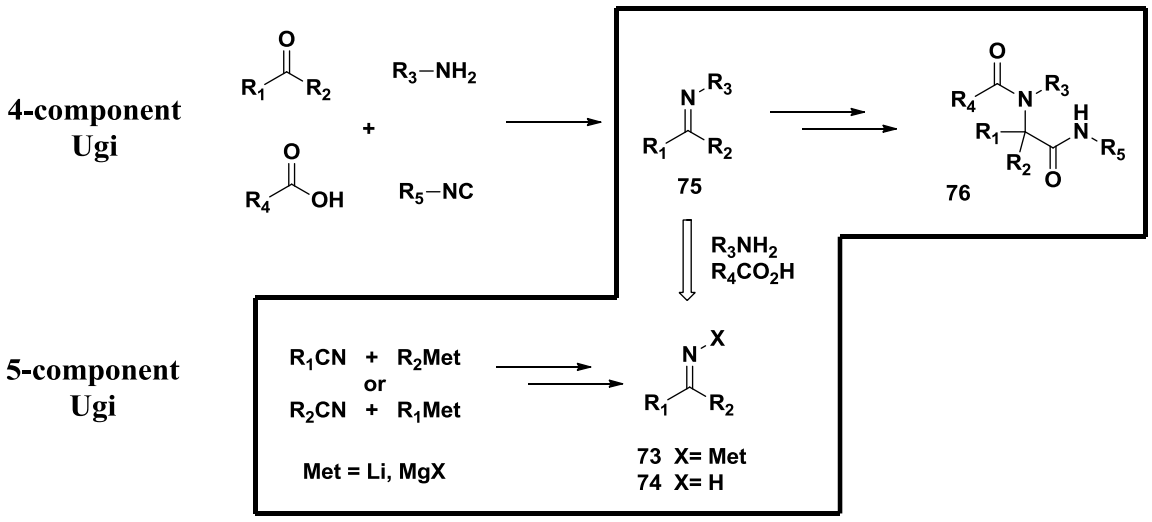
pot without isolating the α-acyloxy-α-cyanoamide **69**. Interestingly, the β-amino acid diamide or β-peptide motif is found in many medicinally significant natural products.[42,43]

Through post-condensation modification, our group was also successful in directing the α-acyloxy-α-cyanoamide **69** to 1,3-oxazoles or tetrazoles.[44] This production was achieved by reacting **69** with diazomalonic esters or alkyl azides.



Scheme 1.10[41]

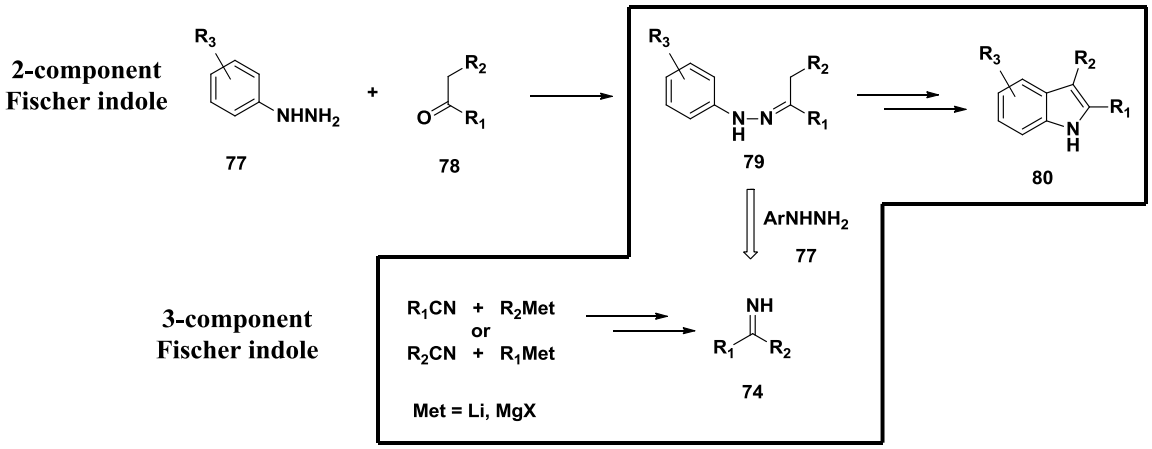
Through careful analysis on the Ugi reaction mechanism and the functional roles of each reactant in the overall process, Simoneau *et al.* applied retrosynthetic analysis to the imine species **73** and identified an alternative route to the imine, leading to the development of a new 5-component Ugi reaction (Scheme 1.11).[45] The key step in this process involves addition of organometallic reagents to nitriles. Simoneau *et al.* demonstrated that N-substituted imines **75** could be formed by the condensation of N-unsubstituted ketimines **74** and primary amines R_3NH_2. This new finding led to a successful development of a new 5-component Ugi reaction.



Scheme 1.11[36]

As mentioned earlier, increasing the dimensionality of MCRs increases the potential size of the chemical library exponentially. Since there are only a few MCRs that are currently useful in drug discovery, our group wondered if a useful 2-component reaction could be transformed into a MCR. Appropriate 2-component reactions for this approach must not be elementary reactions; i.e. they must involve at least one intermediate that could be subjected to retrosynthetic analysis. The well-known Fischer indole reaction served as a good case in point (Scheme 1.12).[46] In the Fischer indole sythesis, an arylhydrazine **77** combines with an enolizable ketone **78** to form the hydrazone **79**. This hydrazone **79** undergoes a series of acid-catalyzed tautomerizations, rearrangements, and eliminations to produce the final substituted indoles **80**. After performing a careful analysis on the mechanism of this reaction, Simoneau *et al.* recognized that the initial arylhydrazone **79** might alternatively be prepared by the reaction of arylhydrazine **77** with N-unsubstituted ketimine **74**. Following the approach described earlier, imine **74** might arise from the nucleophilic addition of organometallic

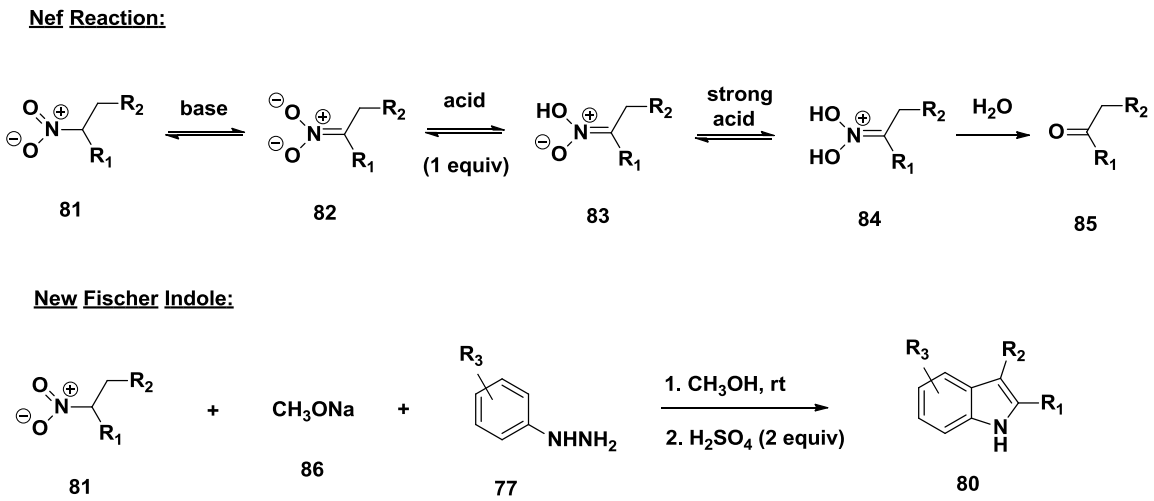
reagents to nitriles. A new 3-component Fischer indole was thus successfully demonstrated by combining organometallic reagents, nitriles, and arylhydrazines. In effect, the useful and well-known 2-component Fischer indole reaction "evolved" into a new 3-component reaction.



Scheme 1.12[36]

Another independent route to arylhydrazones like **79** was developed by Simoneau *et al.* by focusing on the properties of nitroalkanes.[47] When treated with base, a nitroalkane **81** gives rise to a nitronate anion **82**. When treated with strong acid, the nitronate anion **82** is protonated first to the aci-nitro species **83** and then to the iminium species **84**. Upon hydrolysis, the iminium species **84** forms the carbonyl product **85**. In theory, any of the intermediates **82**-**84** might give rise to the formation arylhydrazone **79**. In reality, phenylhydrazine failed to react with nitronate **82**. However, Simoneau *et al.* observed that a mixture of nitroalkane **81**, sodium methoxide **86** and arylhydrazine **77,** upon mild acidification and heating, produced the substituted indole **80** in good yield.

This finding offered another convenient access to the substituted indole motif that is found in many medicinally significant natural products.[48,49]



Scheme 1.13[36]

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CHAPTER 2

A Practical and Inexpensive 'Convertible' Isonitrile for Use in Multicomponent Reactions

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Tetrahedron Letters **2011**, *52*, 2209–2211

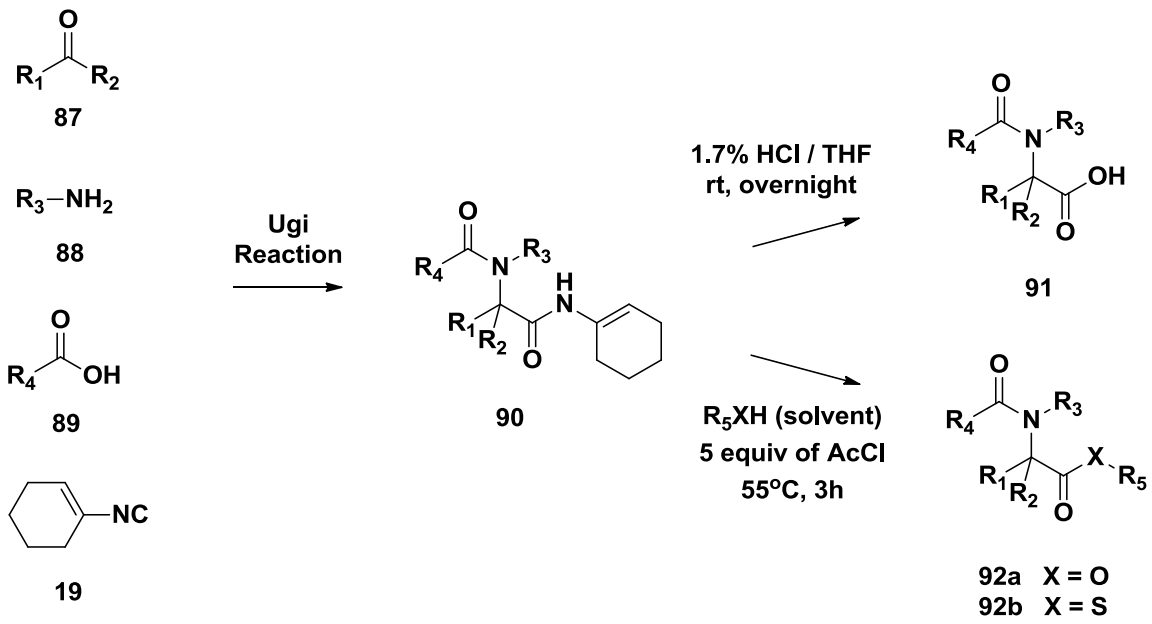
2.1 Background

The use of multicomponent reactions (MCRs) to generate complex small molecule arrays continues to play an important role in drug discovery and development.[1,2] By concurrently forming several new bonds in a one-pot procedure and with high atom economy, MCRs provide rapid access to chemically diverse structures in an operationally simple manner. Recently, the ability to perform iterative[3] as well as higher-order[4] MCRs has significantly increased the molecular complexity that can be obtained in chemical libraries.

Isonitriles are key components in the design and development of many MCRs.[5,6] Isonitriles contain a unique divalent carbon atom, allowing them to take part in a broad range of chemical reactions involving both nucleophiles and electrophiles. MCRs using isonitriles as one component are very versatile,[5,7] as can be seen in the Passerini and the Ugi reactions. In each case, the isonitrile input creates a secondary carboxamide group in the product. Because amides have low reactivity, mild methods for converting such amides into carboxylic acids or esters would enhance the utility of MCR products. The newly converted carboxylic acid or ester could, for example, become an input in another MCR or participate in other chemical transformations to diversify the chemical libraries or to synthesize specific targets.

To date, several "convertible" isonitriles have been developed. The most well-known and commonly-used "convertible" isonitrile is 1-cyclohexenylisonitrile **19**, which was developed by Armstrong and demonstrates excellent utility in the Ugi reaction (Scheme 2.1).[8,9] The use of **19** leads to a cyclohexenamide group in the Ugi product **90**. Subsequent hydrolysis of the cyclohexenamide in acidic environment leads to a

carboxylic acid product **91**, whereas reaction of the cyclohexenamide in neat alcohol or thiol affords an ester **92a** or thioester product **92b**, respectively.

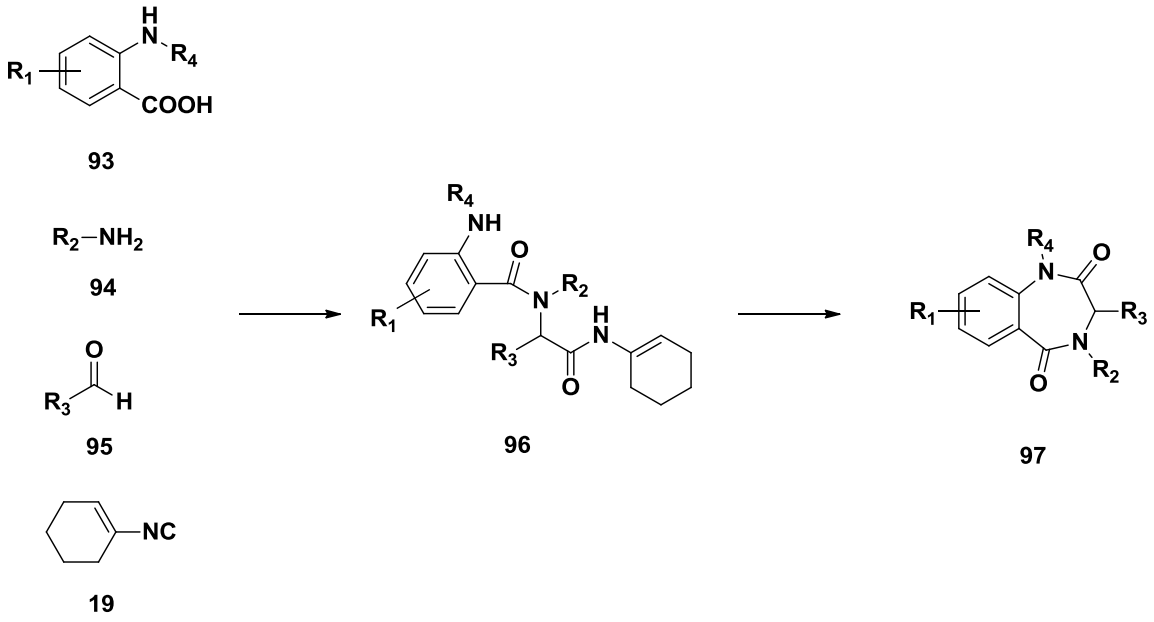


Scheme 2.1[8]

1-Cyclohexenylisonitrile has been widely used in the synthesis of many pharmaceutical agents and bioactive compounds. For example, Kalinski *et al.* recently used **19** in their synthesis of the oral antiplatelet agent clopidogrel (Scheme 1.3).[10]

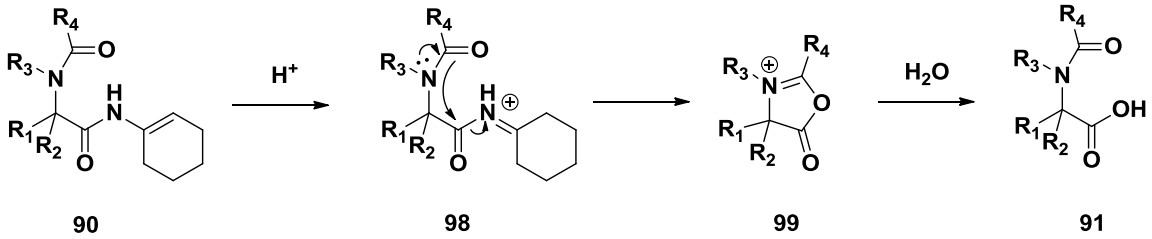
Keating and Armstrong used 1-cyclohexenylisonitrile in a remarkable two-step synthesis of diverse 1,4-benzodiazepine-2,5-diones (BZDs), which have been identified as platelet aggregation inhibiting mimics of the arginine-glycine-aspartic acid (RGD) peptide sequence and have shown anticonvulsant, anxiolytic, and antitumor activities.[11] The Ugi product **96** was formed by the condensation of **19** with anthranilic acid **93**,

amine **94**, and aldehyde **95**. Subsequent methanolysis using methanolic HCl and cyclization afforded 1,4-benzodiazepine-2,5-dione **97** (Scheme 2.2).



Scheme 2.2[11,12]

The accepted mechanism for the conversion of Ugi products derived from isonitrile **19** to carboxylic acids or esters is depicted in Scheme 2.3.[8] Protonation of **90** leads to the N-acyliminium species **98**. With the participation of the α-acylamino group, **98** cyclizes and eliminates to give the munchnone **99**. Subsequent ring opening by water or alcohol gives rise to the acid or ester product, respectively. It is known that the electron rich α-acylamino group plays an essential role in the formation of the munchnone **99**.[13] If the Ugi products do not contain an α-acylamino group or instead contain an α-formylamino group, no cyclization to the munchnone **99** occurs.



Scheme 2.3[8]

The synthesis of 1-cyclohexenylisonitrile is quite laborious, and it is difficult to prepare in quantities larger than a few hundred milligrams.[13,14] In addition to exhibiting vile odor, isonitrile **19** is unstable on storage and decomposes even when stored under argon at -30 °C.

Besides isonitrile **19**, several other "convertible" isonitriles have also been developed, including (β-isocyanoethyl)alkylcarbonates **100-103** developed by Ugi,[13] and various fragrant oxazole- and benzoxazole-derived isonitriles **104-112** developed by Pirrung[14] (Figure 2.1). While these isonitriles have all demonstrated utility in the Ugi reaction, none has been shown to be "convertible" in α-acyloxyamide (i.e., Passerini) products. Moreover isonitriles whose amides convert into esters create a new selectivity problem in Passerini reaction products, which already contain hydrolyzable ester functionality.

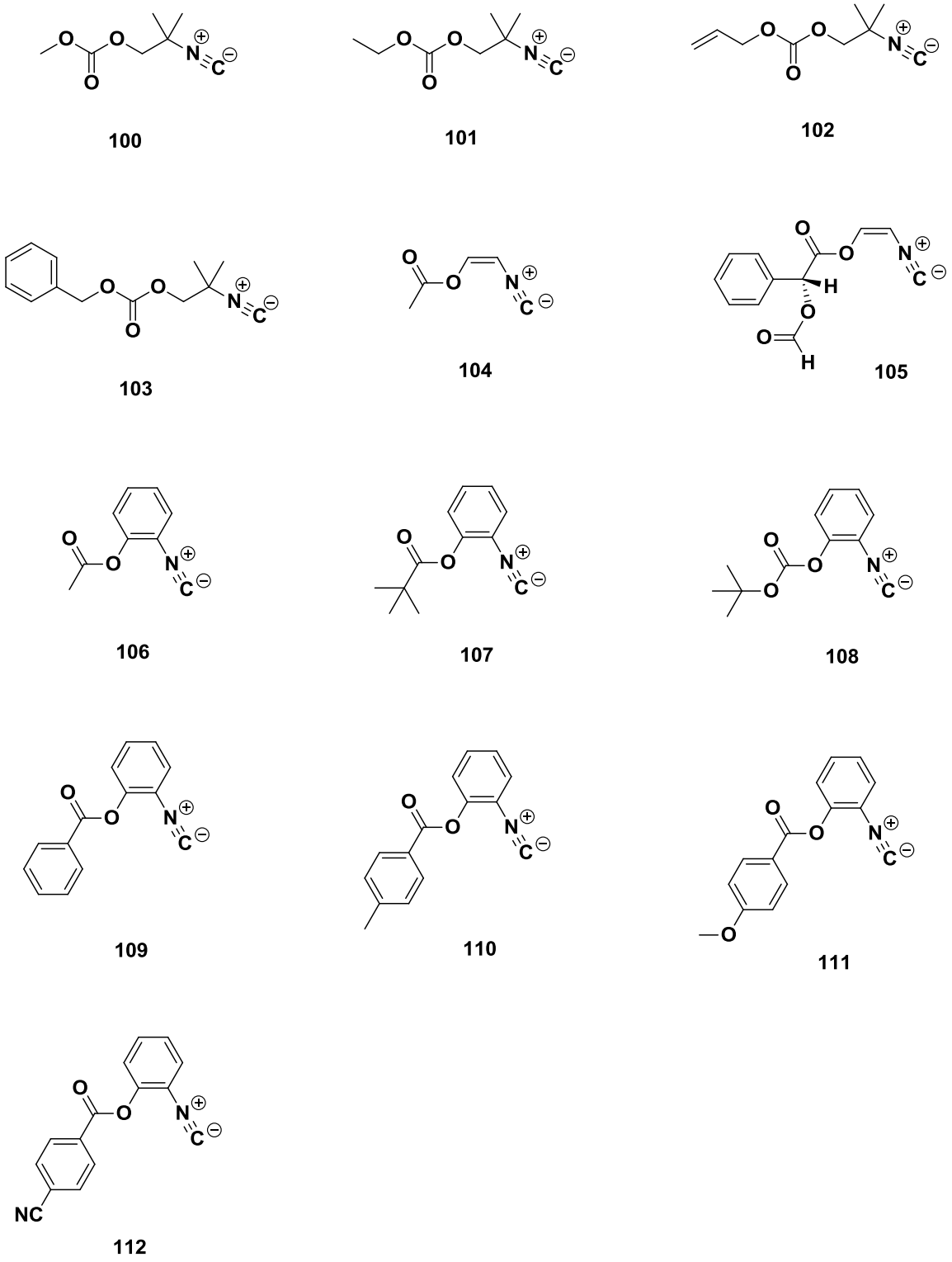
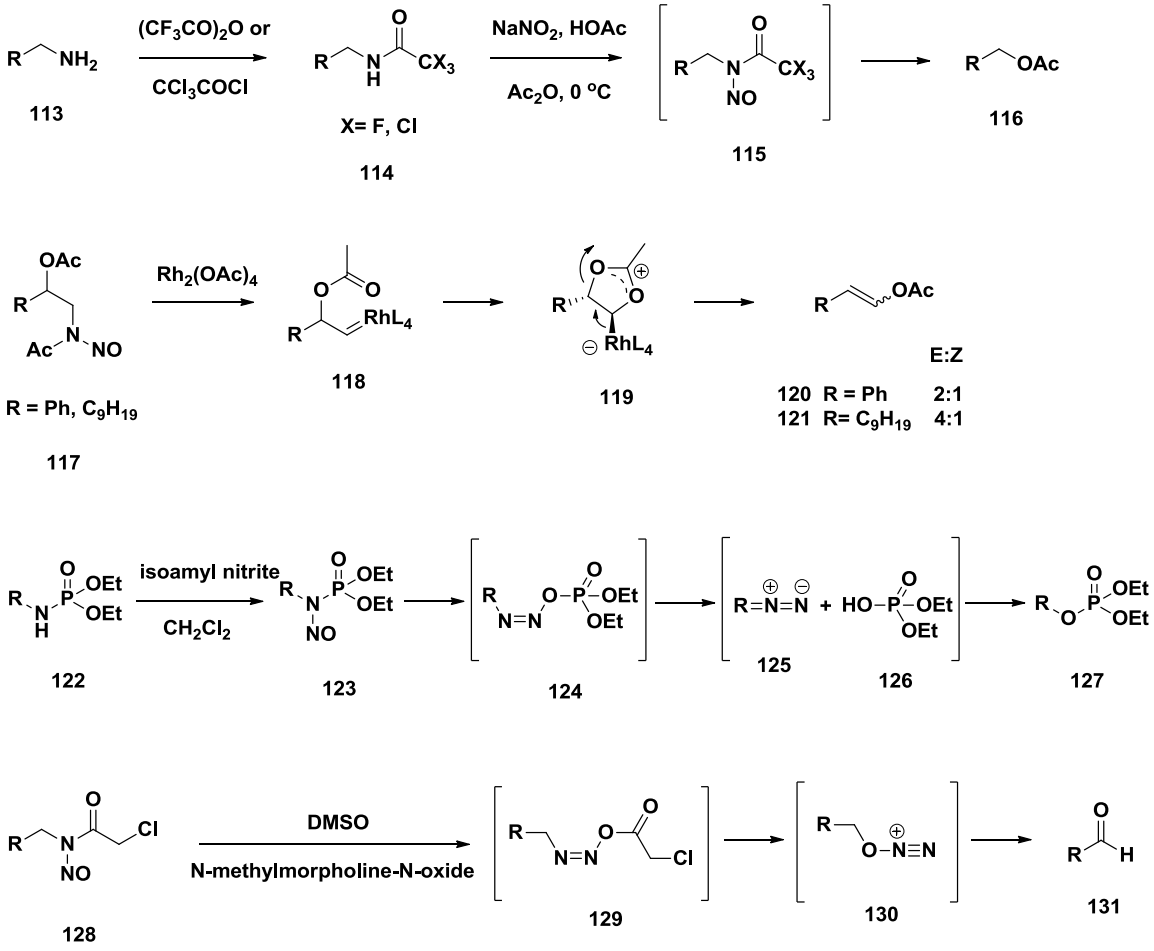


Figure 2.1 Some "Convertible" Isonitriles for MCRs

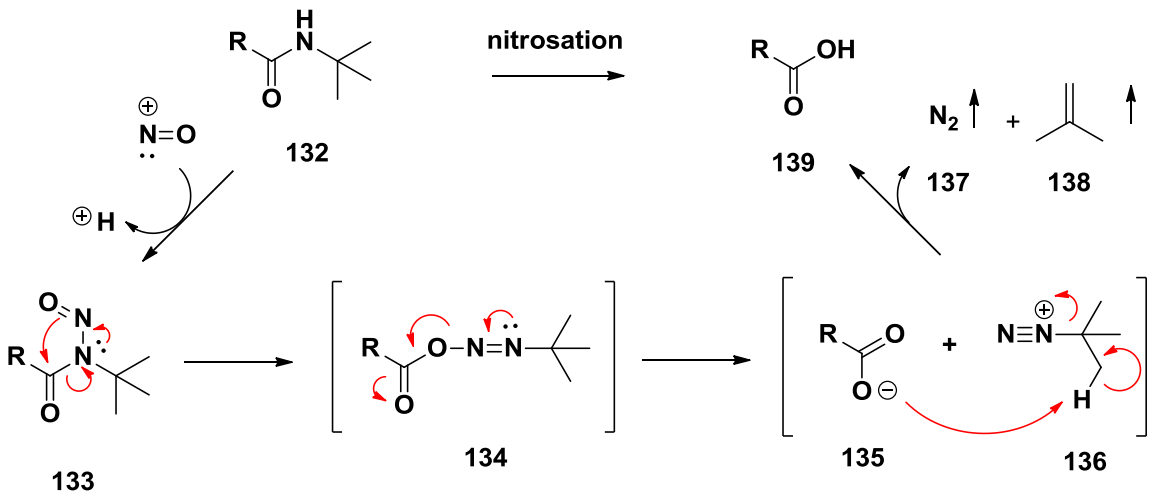
We recognized that *tert*-butylisonitrile might serve as a useful convertible isonitrile in Passerini and related reactions. Among its many advantages, including low cost and commercial availability, *tert*-butylisonitrile gives rise in MCRs to N-*tert*-butylamides, whose characteristic NMR singlet simplifies the analysis of multicomponent reaction products. We now demonstrate that nitrosation of various N-*tert*-butylamides affords carboxylic acids under non-hydrolytic conditions.

The nitrosation of secondary carboxamides and thermal transformations of the derived N-alkyl-N-nitrosamides, first investigated systematically by White,[15,16] have been the subject of extensive mechanistic study over the past half-century, including recent theoretical calculations.[17] N-Alkyl-N-nitrosamides undergo a highly solvent-dependent thermal rearrangement at 80–100°C via diazenes to products derived either from diazoalkane or carbocation intermediates. By controlling and/or intercepting such intermediates, our laboratory several years ago developed several new synthetic transformations of amines via their derived nitrosamides to alcohols, phosphotriesters alkenes, alkynes, enol acetates, and aldehydes (Scheme 2.4).[18–21]



Scheme 2.4[18–21]

Building on those earlier findings, we reasoned that upon rearrangement of N-nitroso-N-*tert*-butylamides **133** to **134**, the subsequent dissociation should strongly favor the carbocationic pathway shown in Scheme 2.5, thus achieving a mild amide-to-acid conversion while releasing innocuous gaseous byproducts nitrogen **137** and isobutene **138**.



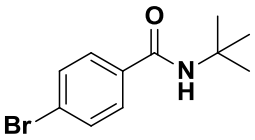
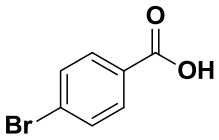
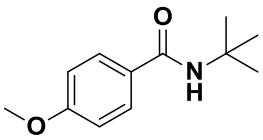
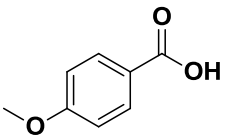
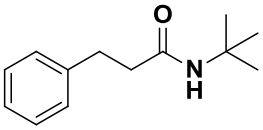
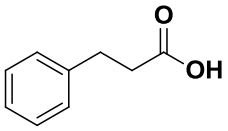
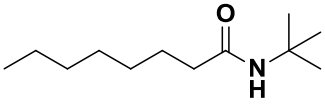
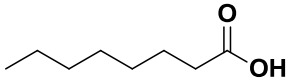
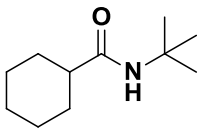
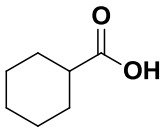
Scheme 2.5

In support of this hypothesis, the nitrosation of N-cyclohexylamides has been reported in the literature to afford modest yields of carboxylic acids,[16] but to the best of our knowledge nitrosation of secondary amides bearing tertiary alkyl substituents has not been described. The dealkylation of N-*tert*-butylamides **132** to acids **139** has only been achieved non-oxidatively using strong acids.[22–24]

2.2 Results and Discussion

To test this hypothesis, a series of simple N-*tert*-butylamides were nitrosated using $NaNO_2$ in 1:2 acetic acid/acetic anhydride (Method A) as first described by White. The results, shown in Table 2.1, established that nitrosation and rearrangement proceeded under mild conditions to afford the desired carboxylic acids in excellent yield.

Table 2.1 Nitrosation/Rearrangement of *tert*-Butylamides Leading to Carboxylic Acids [a]

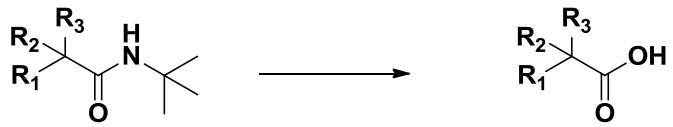
N-tert-butylamide	Carboxylic Acid	% Yield [b]
 **140**	 **141**	**92**
 **142**	 **143**	**99**
 **144**	 **145**	**92**
 **146**	 **147**	**65** [c]
 **148**	 **149**	**66** [c]

[a] Conditions: 2 x 10 equiv $NaNO_2$; 1:2 acetic acid/acetic anhydride, 0 °C, 3 h; then stirring 16 h at rt followed by concentration and partitioning between diethyl ether and aq $NaHCO_3$.

[b] Reported yields were corrected for small quantities (2–8%) of recovered starting material.

[c] Control workups established that ca. 25% of this volatile product was lost by rotary evaporation during workup.

Next a representative group of α-acyloxyamides **150a-e** (Scheme 2.6) was prepared using the Passerini three-component reaction following standard procedures for reacting the appropriate carbonyl compound, carboxylic acid, and *tert*-butylisonitrile.[25]



150 **151**

(a) R_1= Ph, R_2= H, R_3= OAc

(b) R_1= $PhCH_2CH_2$, R_2= H; R_3= OAc

(c) R_1= $PhCH_2CH_2$, R_2= H; R_3= OBz

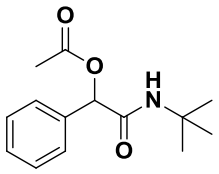
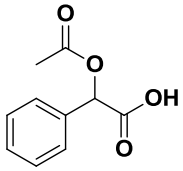
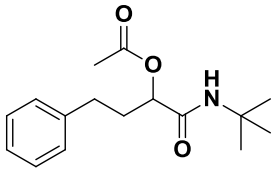
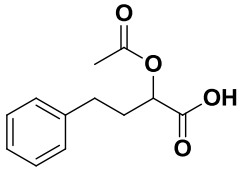
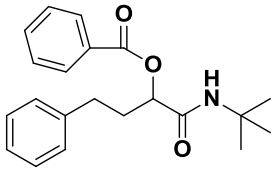
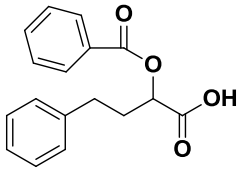
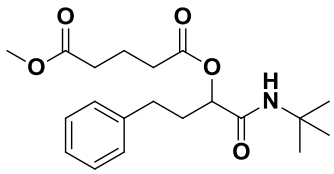
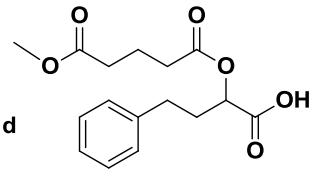
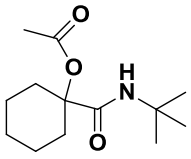
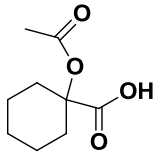
(d) R_1= $PhCH_2CH_2$, R_2= H; R_3= $OCO(CH_2)_3CO_2CH_3$

(e) R_1,R_2= $(CH_2)_5$; R_3= OAc

Scheme 2.6

Initially, nitrosation of **150a-e** was performed using Method A, which afforded variable results. The more sterically hindered Passerini compounds **150c-e** reacted sluggishly, but cleanly, using Method A, with recovered starting materials being the only other products. Superior results were obtained using the more reactive nitrosating reagent N_2O_4 with sodium acetate in CCl_4 (Method B). Much higher yields and complete conversion were achieved with amides **150c-e** (Table 2.2).

Table 2.2 Conversion of Passerini Compounds **150** to Carboxylic Acids

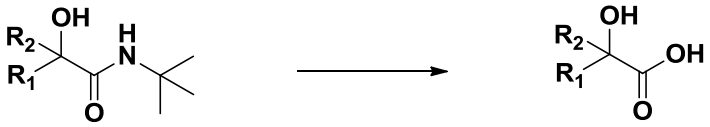
3-Component Passerini N-tert-butylamide		Carboxylic Acid		% Yield (Method)
150a		151a		79 (A)
150b		151b		95 (A)
150c		151c		52 (A) 81 (B)
150d		151d		63 (A) 95 (B)
150e		151e		33 (A) 89 (B)

- Method A: 2 x 10 equiv $NaNO_2$; 1:2 acetic acid/acetic anhydride, 0 °C, 3 h; then stirring 16 h at rt followed by concentration and partitioning between diethyl ether and aq $NaHCO_3$.

- Method B: gaseous N_2O_4 bubbled (~2 bubbles/sec) for 5 min; CCl_4, 0 °C, 3 h; then stirring 16 h at rt followed by concentration and partitioning between diethyl ether and aq $NaHCO_3$.

Of particular interest was the fact that the *tert*-butylamides in **150a-e** were transformed into the corresponding carboxylic acids **151a-e** without affecting the carboxylic esters present in each substrate. Notably **150d**, which incorporates two ester groups (one of which is sterically uncongested), was transformed into acid-diester **151d** in excellent yield (Method B), thus highlighting the non-hydrolytic nature of this transformation.

Next a series of α-hydroxy-N-*tert*-butylamides **152a-c** was prepared by a recently reported variation of the Passerini two-component reaction using boric acid as the Brønsted acid (Scheme 2.7).[26]



152 **153**

(a) R_1, R_2 = $(CH_2)_5$

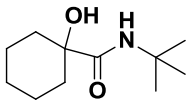
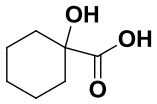
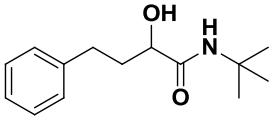
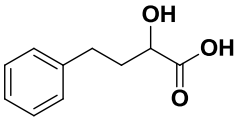
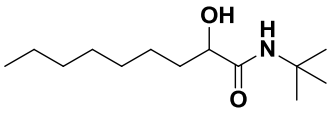
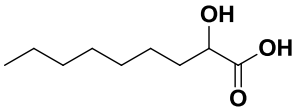
(b) R_1 = $PhCH_2CH_2$, R_2 = H

(c) R_1 = $CH_3(CH_2)_6$, R_2 = H

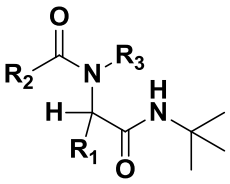
Scheme 2.7

Method A was not compatible with these α-hydroxy-N-*tert*-butylamides. When **152a** was nitrosated under those conditions, acetylation of the free alcohol group afforded acetoxyacid **151e** as the major product. However, Method B furnished the desired hydroxyacids **153a-c** in modest to high yield (Table 2.3).

Table 2.3 Conversion of α-Hydroxy-N-*tert*-Butylamides to Carboxylic Acids

2-Component Passerini N-tert-butylamide		Carboxylic Acid		% Yield (Method)
152a		153a		60 (B)
152b		153b		90 (B)
152c		153c		89 (B)

tert-Butylisonitrile has been widely used in Ugi four-component condensations, thus it was of interest to learn whether the derived secondary/tertiary diamides could be "converted" into the corresponding amidoacids. A test series of diamides was prepared (Figure 2.2) using *tert*-butylisonitrile following the standard Ugi protocol in methanol.[9] Somewhat surprisingly, we observed no nitrosation of diamide **154a** using Method A conditions. To test whether steric effects at the tertiary amide group were a factor, diamides **154b** and **154c** were also subjected to Method A conditions, and in each case, starting material was recovered nearly quantitatively. Diamides **154d-e** behaved similarly.



154

(a) R_1= $PhCH_2CH_2$, R_2= Ph, R_3= Bn

(b) R_1= $PhCH_2CH_2$, R_2= CH_3, R_3= Bn

(c) R_1= $PhCH_2CH_2$, R_2= CH_3, R_3= CH_3

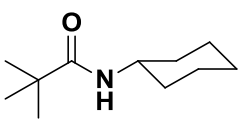
(d) R_1= $PhCH_2CH_2$, R_2= Ph, R_3= n-Bu

(e) R_1= Ph, R_2= Ph, R_3= Bn

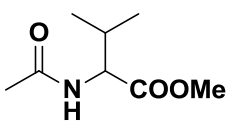
Figure 2.2 A Representative Group of Diamides

Nitrosations of **154a-e** using the more potent nitrosating agent N_2O_4 (Method B) were also unpromising, affording at best trace quantities of acids along with (mostly) unreacted diamides and several uncharacterized byproducts.

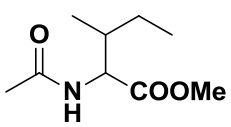
Difficulties in nitrosating N-cyclohexyl- and other sterically hindered amides have previously been reported by Vilarrasa *et al.* (Figure 2.3).[27] When compounds **155-157** were treated with N_2O_4 / NaOAc, no amounts of N-nitrosated products were detected. Substitution of pyridine for NaOAc had been previously shown to improve the nitrosation of some moderately hindered peptide bonds.[28,29] However, when this substitution was applied for compounds **155-157**, no significant improvement was observed.[27]



155



156

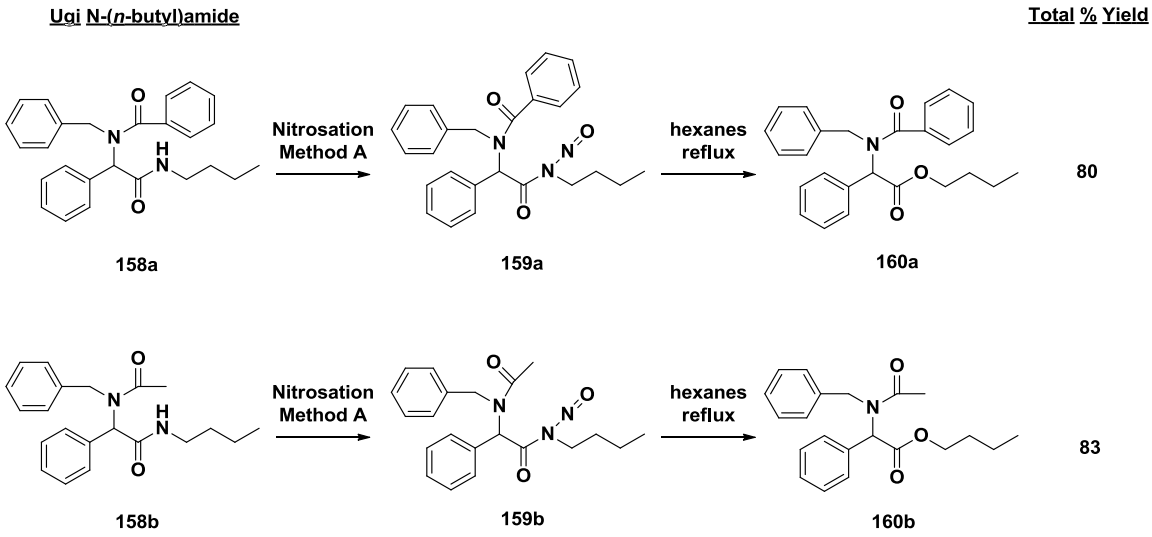


157

Figure 2.3 Some Sterically Hindered Amides[27]

The resistance of Ugi amides **154a-e** to nitrosation made it possible to selectively deprotect a Passerini *tert*-butylamide in the presence of an Ugi *tert*-butylamide. Nitrosation of a 1:1 mixture of **150b** and **154e** using Method A afforded **151b** in 54% yield (96% based on recovered **150b**). Compound **154e** was recovered quantitatively.

Hulme *et al.* recently reported an alternative use of *n*-butylisonitrile, expedited with microwaves, as a convertible isonitrile for heterocycle synthesis.[30] Therefore, it was of interest to determine whether *n*-butylisonitrile might serve as a convertible isonitrile for Ugi reactions by enabling an amide-to-ester conversion of the corresponding N-(*n*-butyl)amide product. Two test diamides **158a-b** were prepared (Scheme 2.8) using *n*-butylisonitrile following the standard Ugi protocol in methanol.[9] Ugi compounds **158a-b** underwent smooth nitrosation using Method A to afford the corresponding N-nitrosoamides **159a-b** following the standard workup. Upon heating to reflux in hexanes, the desired *n*-butylesters **160a** and **160b** were produced in 80% and 83% overall yield, respectively. This finding offered another convenient access to the α-amino ester motif that is found in many pharmaceutical agents and bioactive compounds, including the oral antiplatelet agent clopidogrel **23**,[10] the general anaesthetic agent for large animals carfentanil **161**,[31] the fungicide metalaxyl **162**,[32] the herbicide benzoylprop-ethyl **163**,[33] and the lipoprotein(a) assembly inhibitor **164**[34] (Figure 2.4).



Scheme 2.8

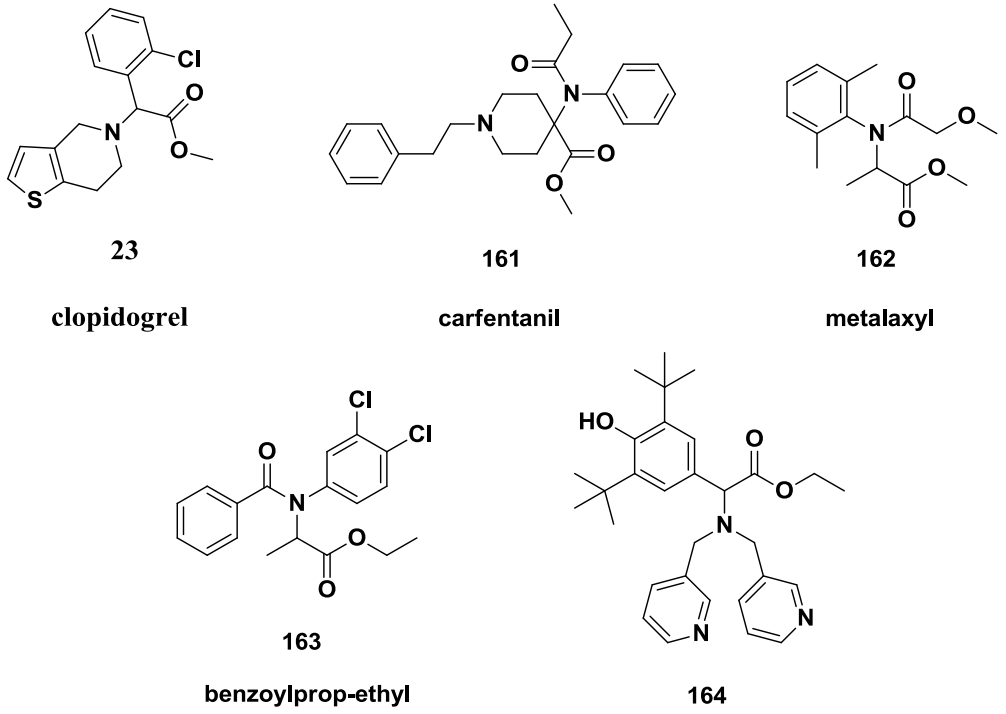


Figure 2.4 Some Pharmaceutical Agents Containing α-Amino Ester Motif

In summary, the studies presented herein demonstrate that *tert*-butylisonitrile can serve as an inexpensive, efficient, and readily available "convertible isonitrile" in Passerini and related multicomponent reactions. To the best of our knowledge, *tert*-butylisonitrile is the first isonitrile whose amide-to-acid "conversion" is compatible with preexisting ester functionality in MCR products. We further show that *n*-butylisonitrile may provide a viable alternative to other convertible isonitriles for amide-to-ester transformations in Ugi MCR products.

2.3 Experimental Procedures

General Procedures

^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker ARX300, Varian Mercury-300, Varian Inova-400, or Varian Inova-500 spectrometer using $CDCl_3$ with 0.05% v/v TMS as solvent. Spectra were recorded in δ (ppm) and were referenced to TMS (0.00 ppm for ^{1}H NMR) and $CDCl_3$ (77.23 ppm for ^{13}C NMR). IR spectra were obtained on a Mattson Instruments Galaxy Series FT-IR spectrometer and were recorded in wavenumbers (cm^{-1}). Melting points were measured using a Thomas Hoover Uni-melt capillary melting point apparatus. Mass spectra were measured at the Life Sciences Core Laboratories Center using ABI/MDS Sciex 4000 Q Trap or Waters Synapt HDMS. Chemicals were obtained from Aldrich, Fluka, Fisher, or Mallinckrodt and used as received unless specified.

Preparation of α-Acyloxy-N-(tert-Butyl)amides

A literature procedure for the Passerini 3-component reaction was followed.[25]

Preparation of α-Hydroxy-N-(tert-Butyl)amides

A literature procedure for the Passerini 2-component reaction was followed.[26]

Preparation of α-Acylamino-N-(tert-Butyl)amides and α-Acylamino-N-(n-Butyl)amides

A literature procedure for the Ugi reaction was followed.[9]

Nitrosation Using Method A

The carboxamide (0.25 mmol) was dissolved in 1:2 acetic acid:acetic anhydride (2.5 mL) in a 25 mL round-bottom flask (RBF). After cooling the solution to 0 ^{o}C, $NaNO_2$ (2.5 mmol, 10 equiv) was added in one portion. The resulting suspension was stirred vigorously at 0 ^{o}C for 30 min, then another portion of $NaNO_2$ (2.5 mmol) was added. The suspension was stirred vigorously at 0 ^{o}C for another 2.5 h. The ice bath was removed and the reaction mixture was stirred vigorously at rt for 16 h, then concentrated using a rotary evaporator and neutralized by slow addition of saturated $NaHCO_3$ to pH 8. The aqueous phase was extracted with ether (4 x 10 mL), then cooled to 0 ^{o}C and carefully acidified with ice-cold 1*M* HCl solution to pH 2 and immediately extracted with ether (4 x 15 mL). The combined ether layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired product.

Nitrosation Using Method B

The carboxamide (0.25 mmol) was dissolved in CCl_4 (2.5 mL) in a 25 mL round-bottom flask. The solution was cooled to 0^{o} C, then NaOAc (0.75 mmol) was added. Stiring was stopped while gaseous N_2O_4 was bubbled into the cold suspension using a 5" disposable pipette (~2 bubbles/sec) for 5 min. The mixture was stirred vigorously for 3 h at 0 ^{o}C, then for 16 h at rt. The bulk of solvent was removed using a rotary evaporator

and the product isolated as in Method A. (For compounds **152a-c**, the acidified aqueous layer was saturated with NaCl before ether extraction to maximize the yield).

^{1}H NMR, ^{13}C NMR, IR, MS and Other Physical Characterization Data for New Products

NOTE - Passerini **152a** and acid **151e** are known but their spectral data are not available on databases; therefore, copies of their ^{1}H NMR spectra are also provided.

*Passerini **150b***: Recrystallized with hexane to afford a white crystal (63%, m.p. 93 ^{o}C). IR (CH_2Cl_2) 3315(m), 2967(m), 2932(m), 1742(s), 1667(s), 1529(m); ESI-MS (CH_3OH) 278.14 (M+H), 300.13 (M+Na).

*Passerini **150c***: Recrystallized with ethyl ether to afford a white crystal (22%, m.p. 130-131 ^{o}C). IR (CH_2Cl_2) 3332(s), 3061(m), 2965(s), 1716(s), 1660(s), 1539(s); ESI-MS (CH_3OH) 340.16 (M+H), 362.15 (M+Na).

*Passerini **150d***: Purified with 1:3 ethyl acetate:hexane (R_f=0.3) to afford a white solid (47%, m.p. 63-64 ^{o}C). IR (CH_2Cl_2) 3324(m), 2966(s), 1740(s), 1674(s), 1529(s); ESI-MS (CH_3OH) 363.8 (M+H), 385.5 (M+Na).

*Passerini **150e***: Recrystallized with hexane to afford a white crystal (59%, m.p. 110.5-111 ^{o}C). IR (CH_2Cl_2) 3363(m), 2941(s), 1734(s), 1662(s), 1522(s); ESI-MS (CH_3OH) 242.14 (M+H), 264.14 (M+Na).

*Passerini **152c***: Purified with 1:3 ethyl acetate:hexane (R_f=0.2) to afford clear oil (42%): IR 3384(s), 2925(s), 2857(m), 1655(s), 1530(s); ESI-MS (CH_3OH) 230.4 (M+H), 252.4 (M+Na).

*Acid **151c***: general procedure afforded a yellow solid m.p. 100-101 ^{o}C: IR (CH_2Cl_2) 3028(m), 2931(m), 1723(s), 1602(m); ESI-MS (CH_3OH) 283.08 (M-H).

*Acid **151d***: general procedure afforded a yellow oil: IR (CH_2Cl_2) 3467(m), 3027(m), 2955(m), 1739(s); ESI-MS (CH_3OH) 309.4 (M+H), 331.4 (M+Na).

*Ugi **154a*****:** Purified with 1:3 ethyl acetate:hexane (R_f=0.3) to afford a clear sticky gel (43%): IR (CH_2Cl_2) 3414(s), 3062(m), 2965(m), 1680(s), 1623(s), 1514(m); ESI-MS (CH_3OH) 429 (M+H), 451.5 (M+Na).

*Ugi **154b*****:** Purified with 1:3 ethyl acetate:hexane (R_f=0.2) to afford a clear sticky gel (28%): IR (CH_2Cl_2) 3321(m), 3062(m), 2967(m), 1678(s), 1635(s), 1543(m); ESI-MS (CH_3OH) 367.4 (M+H), 389.5 (M+Na).

*Ugi **154c*****:** Purified with ethyl acetate (R_f=0.4) to afford a clear sticky gel (22%): IR (CH_2Cl_2) 3315(m), 3026(m), 2966(s), 1678(s), 1634(s), 1541(m); ESI-MS (CH_3OH) 291.4 (M+H), 313.4 (M+Na).

*Ugi **154d*****:** Purified with 1:3 ethyl acetate:hexane (R_f=0.3) to afford a light yellow gel (16%): IR 3312(m), 3026(m), 2961(s), 2872(m), 1683(s), 1617(s), 1540(m); ESI-MS (CH_3OH) 395.2562 (M+H).

*Ugi **154e*****:** Purified with 2:3 ethyl acetate:hexane (R_f=0.3) to afford a white solid (84%, m.p. 60-62 ^oC): IR (CH_2Cl_2) 3316(m), 3062(m), 2968(m), 1683(s), 1627(s), 1547(m); ESI-MS (CH_3OH) 401.5 (M+H), 423.5 (M+Na).

*Ugi **158a*****:** Purified with 2:3 ethyl acetate:hexane (R_f=0.2) to afford a white solid (69%, m.p. 113-113.5 ^oC): IR (CH_2Cl_2) 3296(s), 3061(m), 2957(m), 1656(s), 1632(s), 1560(m); ESI-MS (CH_3OH) 401.5 (M+H), 423.5 (M+Na).

*Ugi **158b*****:** Recrystallized with toluence to afford a white crystal (29%, m.p. 116-117^oC): IR (CH_2Cl_2) 3297(s), 3087(m), 2960(m), 1682(s), 1626(s), 1560(m); ESI-MS (CH_3OH) 339.4 (M+H), 361.4 (M+Na).

*Ester **160a***: general procedure afforded yellow oil: IR 3062(m), 2959(s), 1743(s), 1647(s); ESI-MS (CH_3OH) 402.5 (M+H), 424.5 (M+Na).

*Ester **160b***: general procedure afforded yellow oil: IR 3063(m), 2959(s), 1739(s), 1654(s). ESI-MS (CH_3OH) 340.4 (M+H), 362.4 (M+Na).

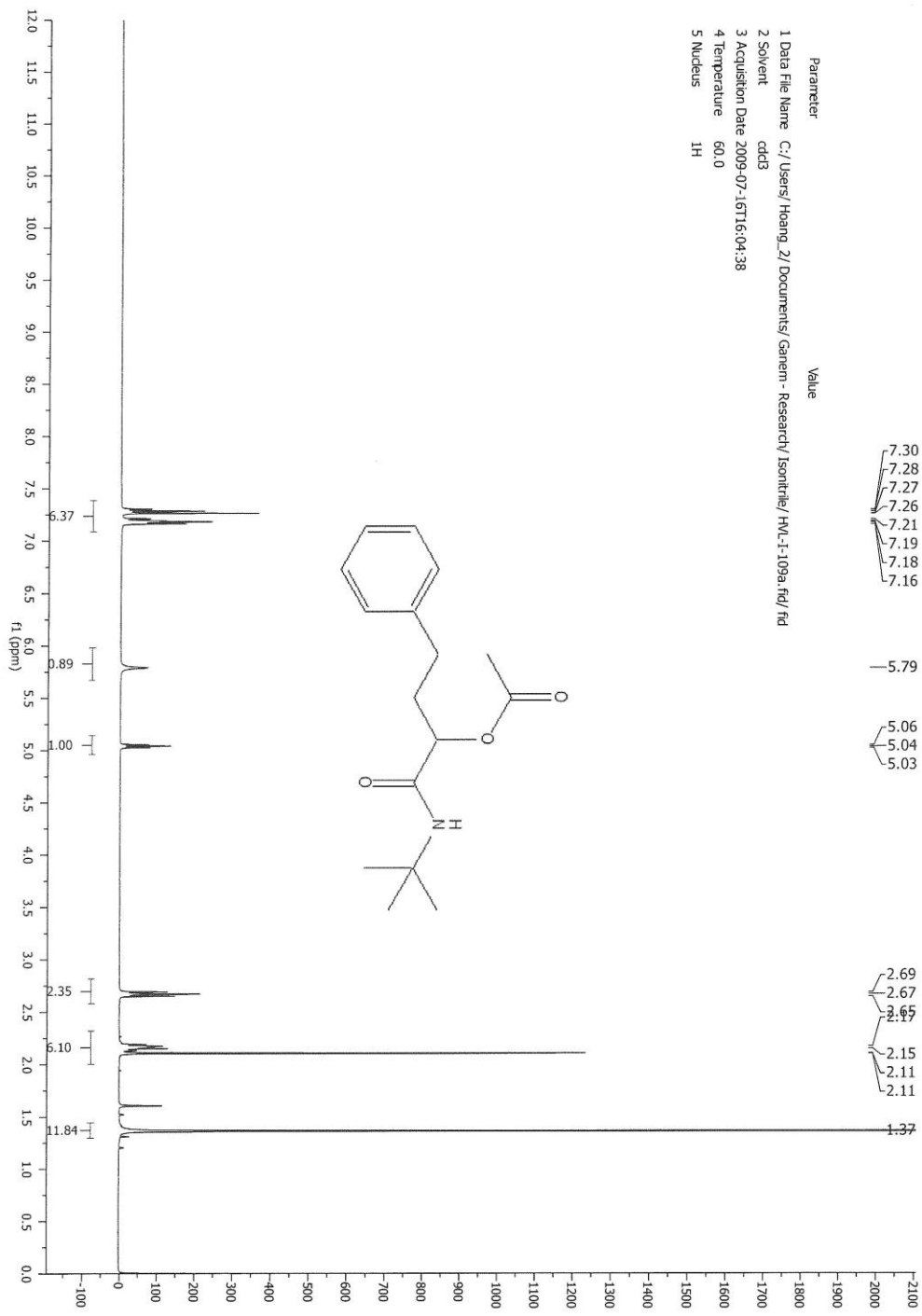


Figure 2.5 ^{1}H NMR Spectrum of Passerini **150b**

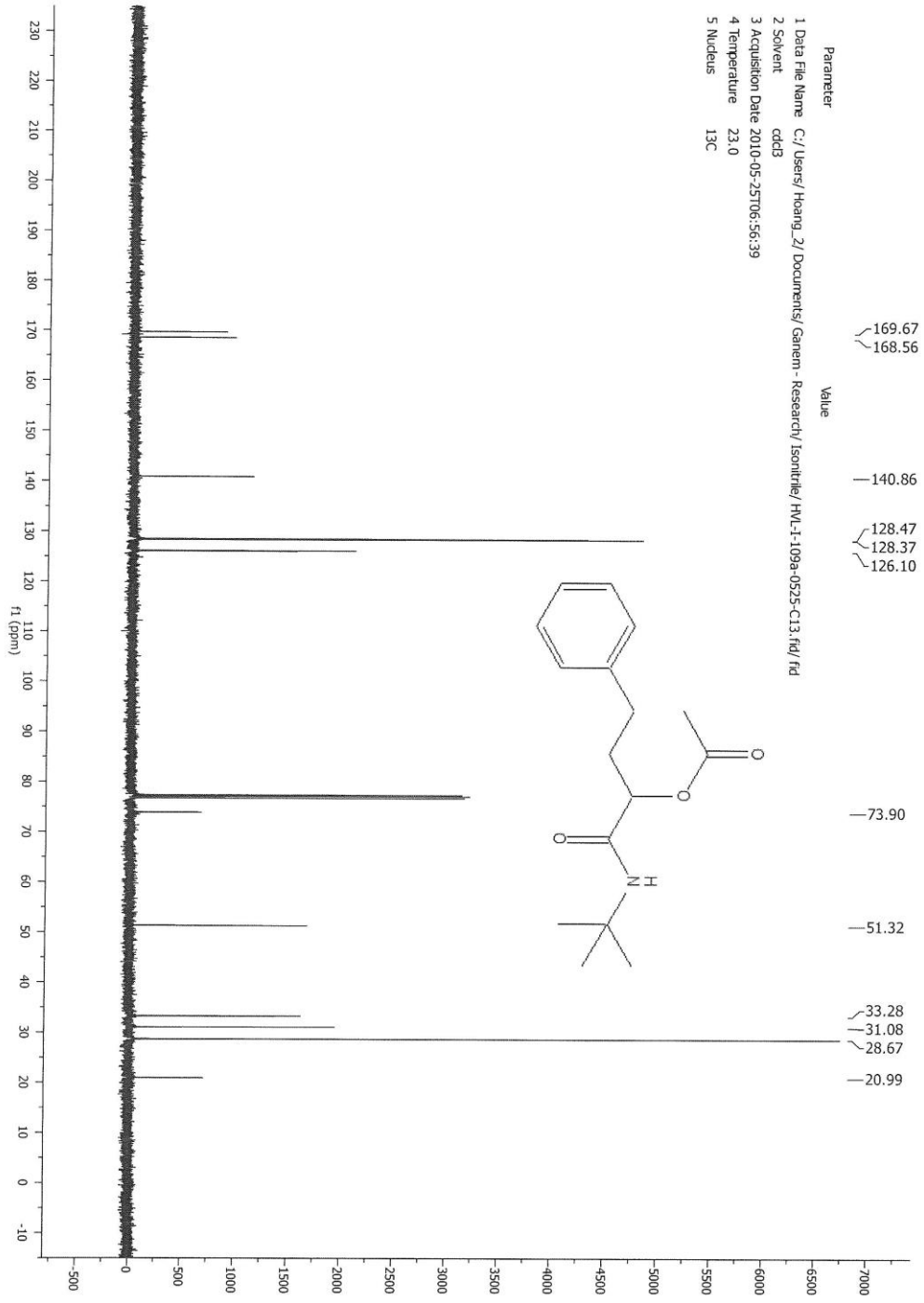


Figure 2.6 ^{13}C NMR Spectrum of Passerini **150b**

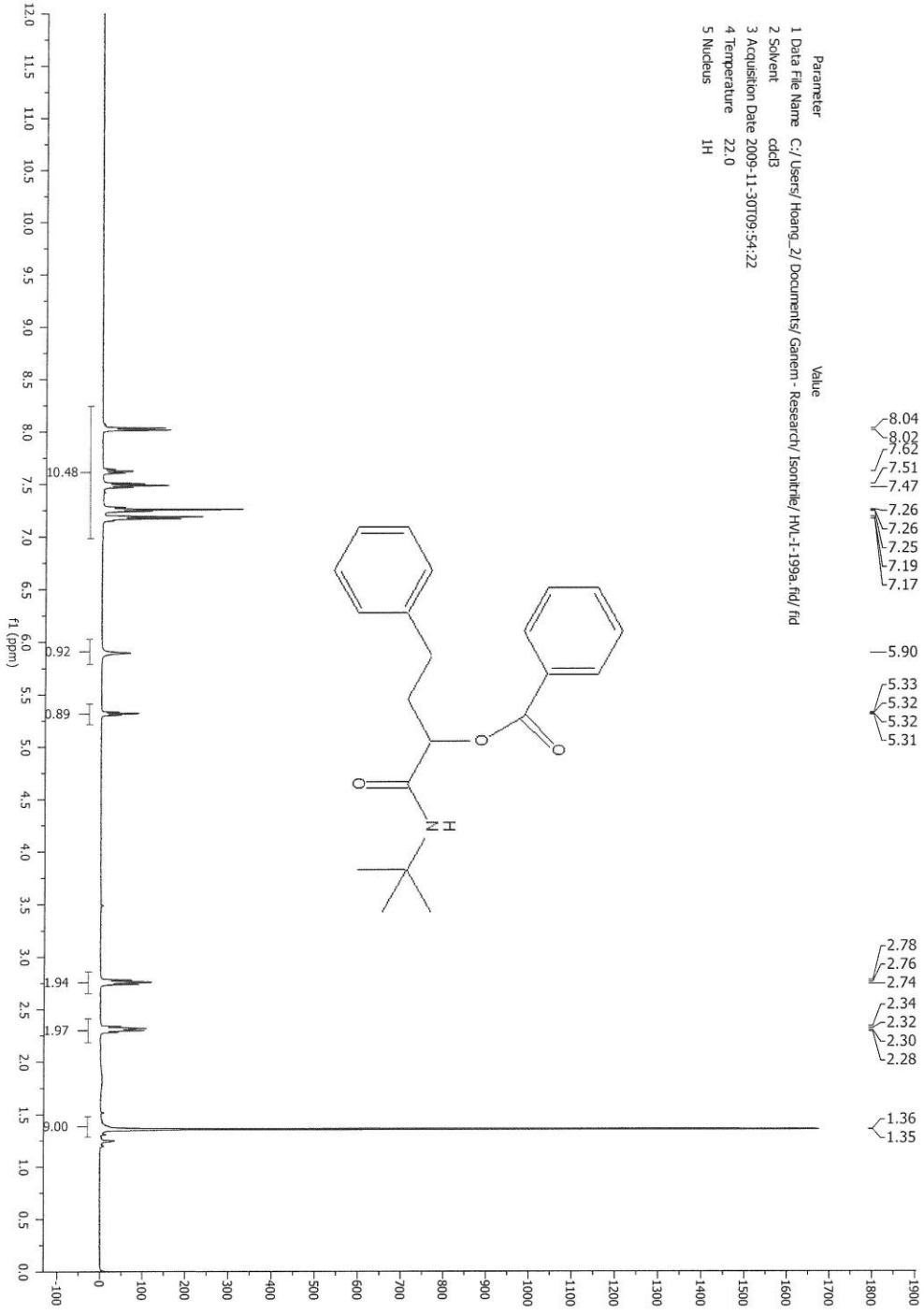


Figure 2.7 ^{1}H NMR Spectrum of Passerini **150c**

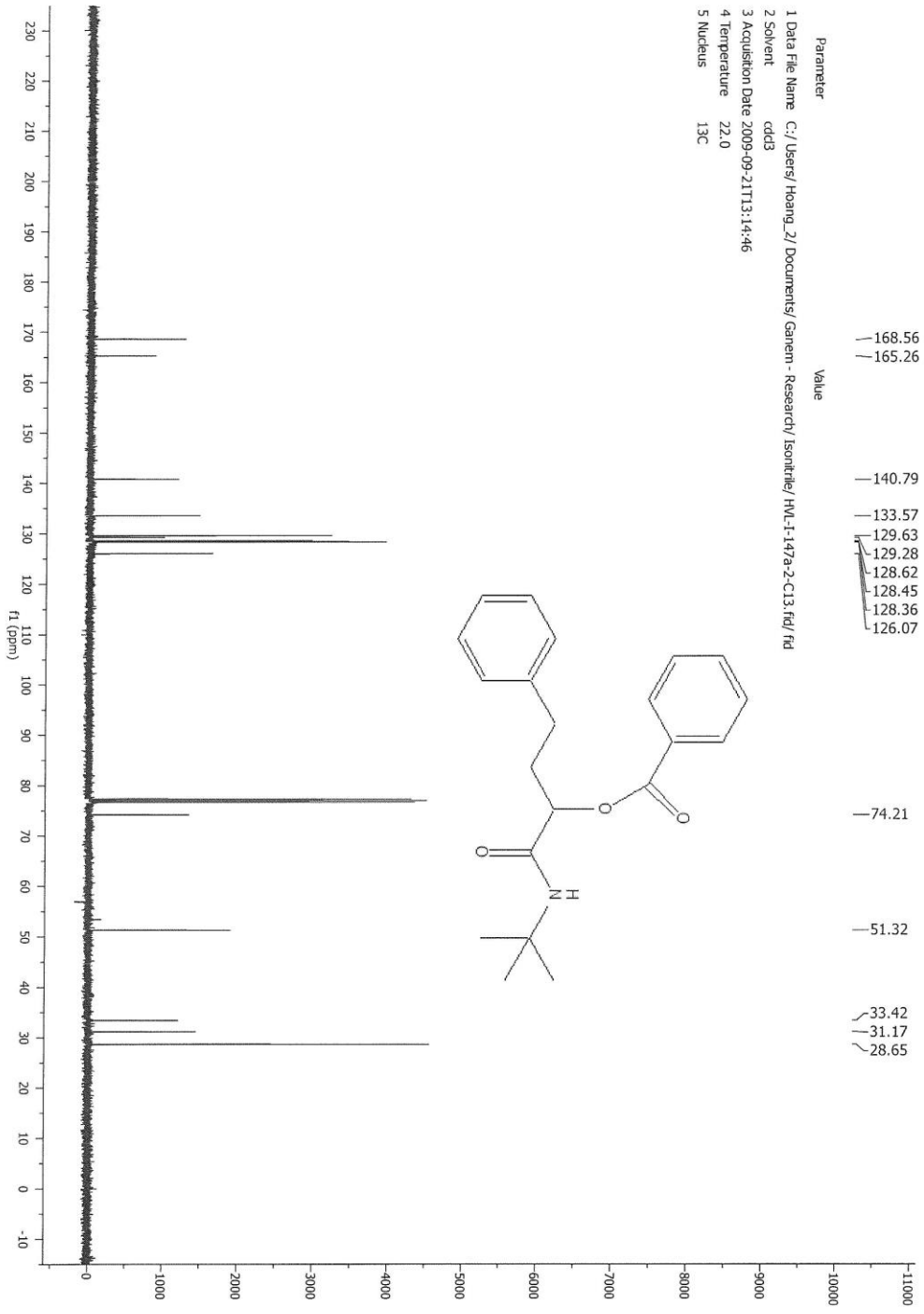


Figure 2.8 ^{13}C NMR Spectrum of Passerini **150c**

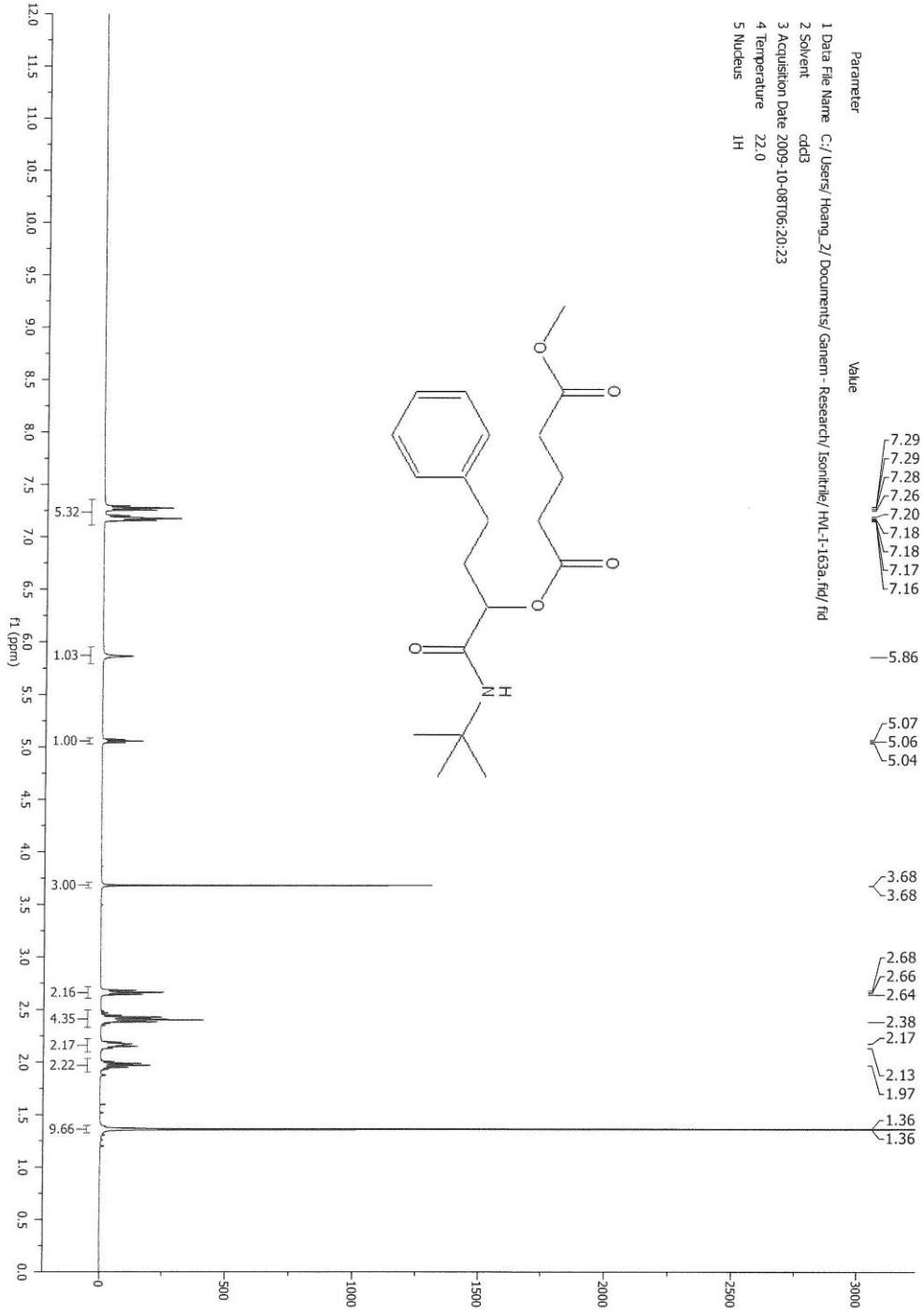


Figure 2.9 ^{1}H NMR Spectrum of Passerini **150d**

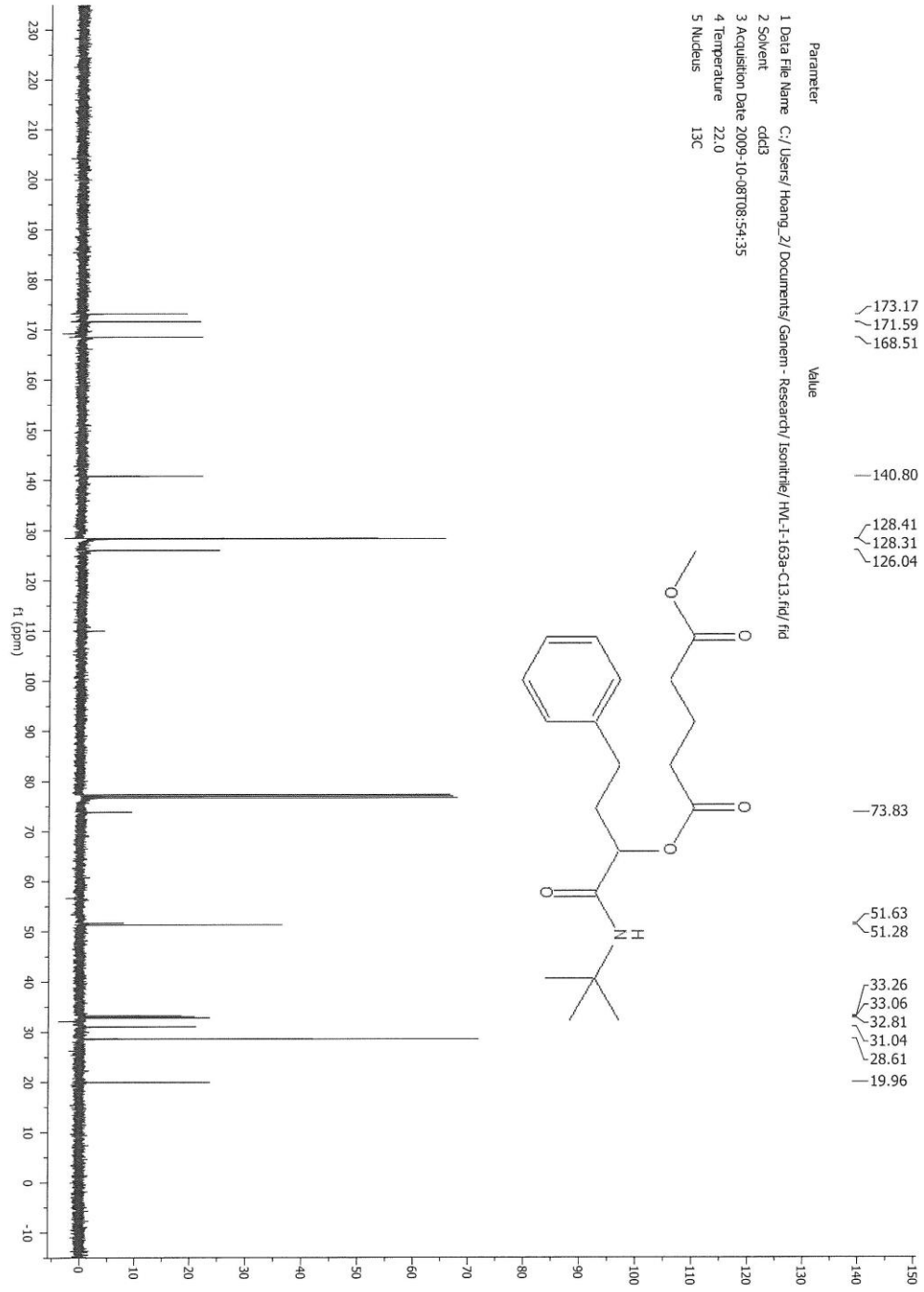


Figure 2.10 ^{13}C NMR Spectrum of Passerini **150d**

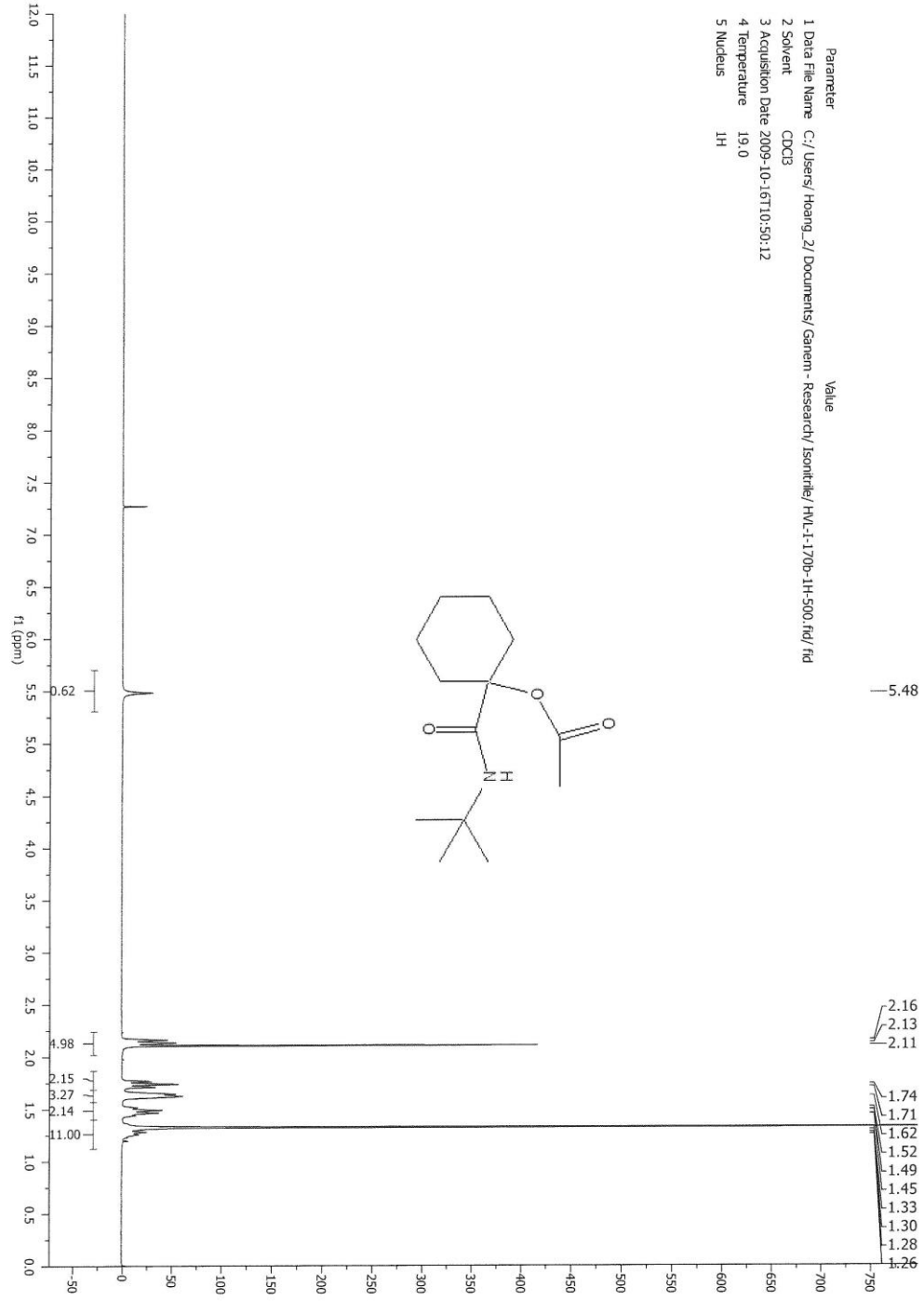


Figure 2.11 ^{1}H NMR Spectrum of Passerini **150e**

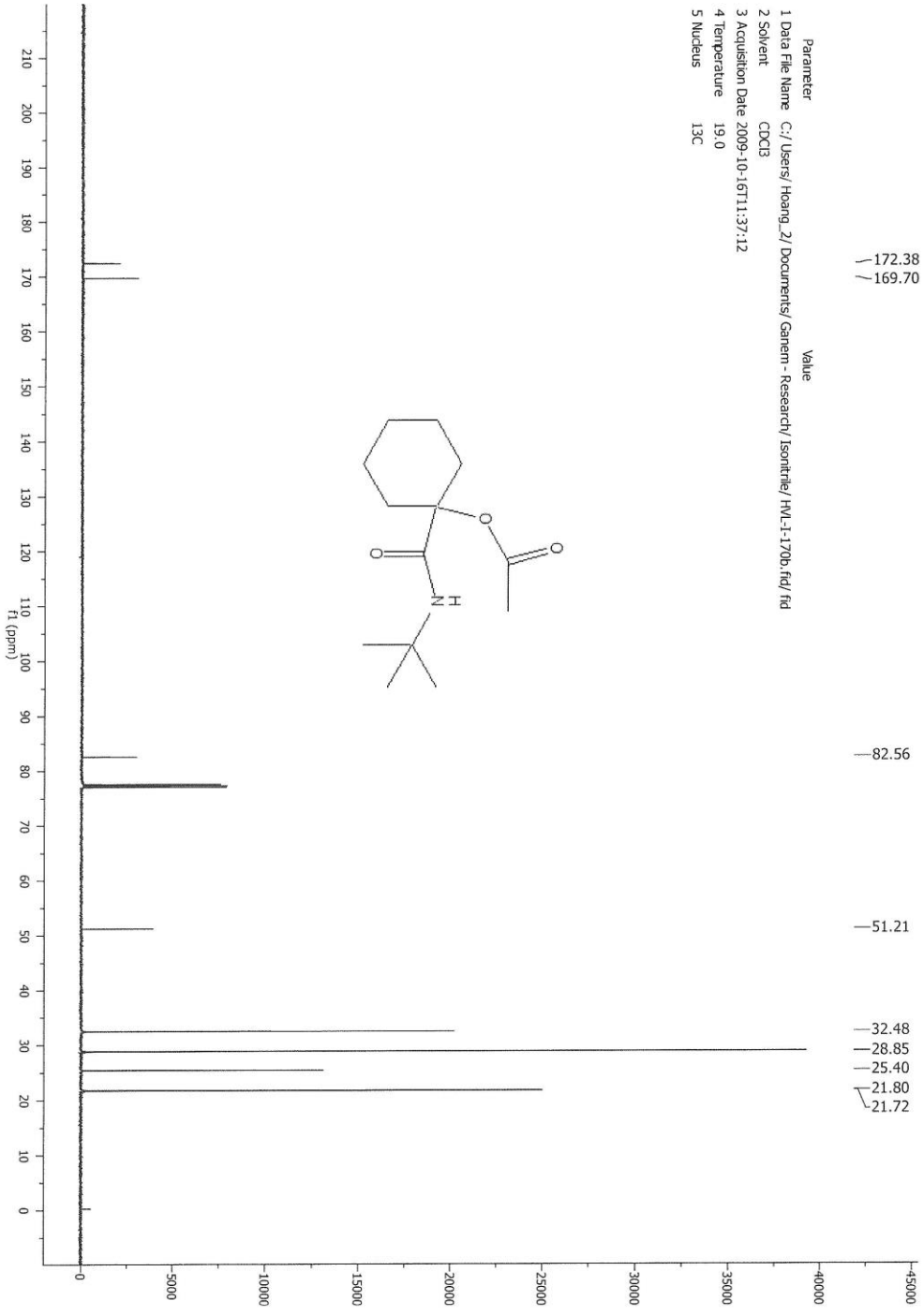


Figure 2.12 ^{13}C NMR Spectrum of Passerini **150e**

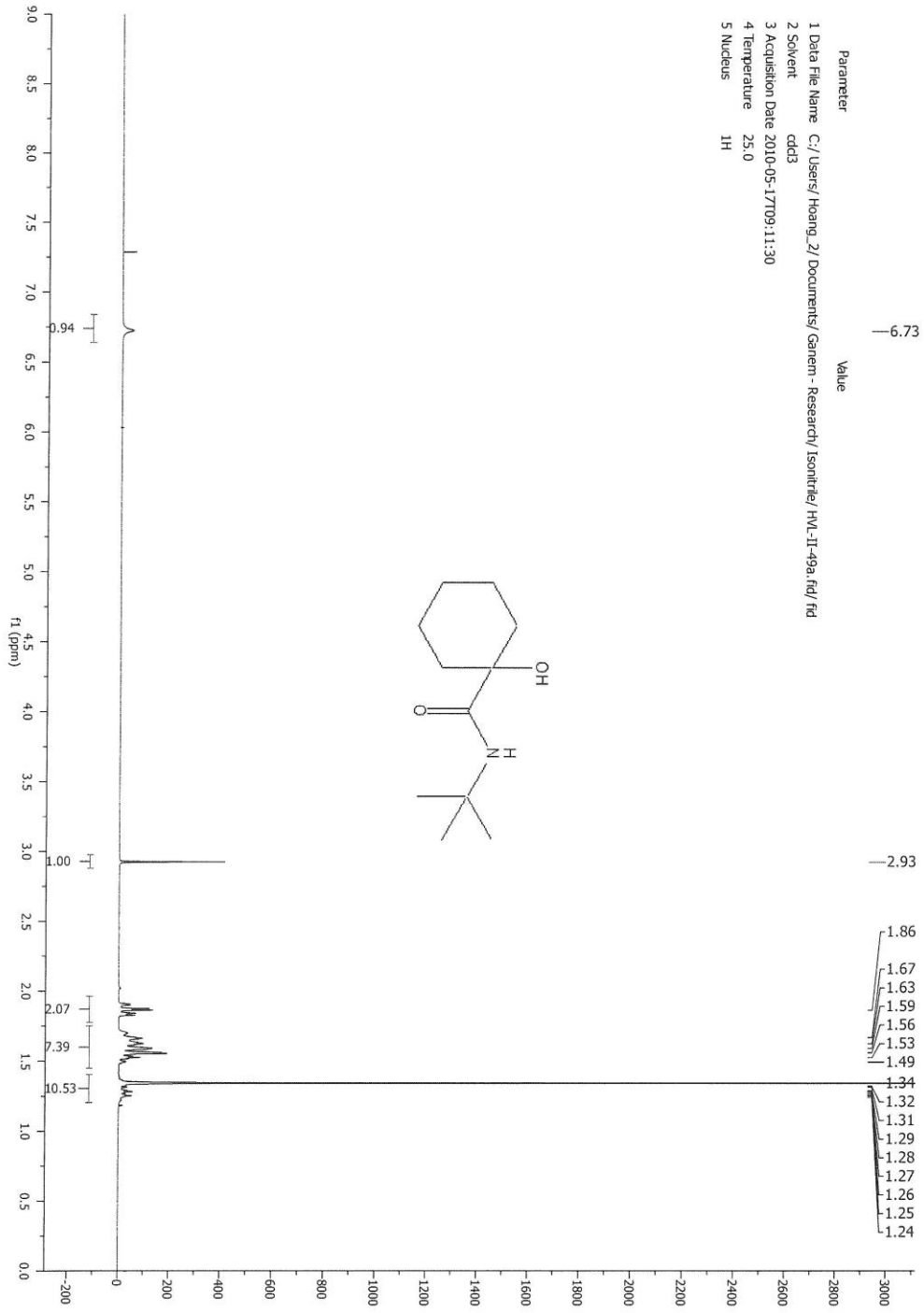


Figure 2.13 ^{1}H NMR Spectrum of Passerini **152a**

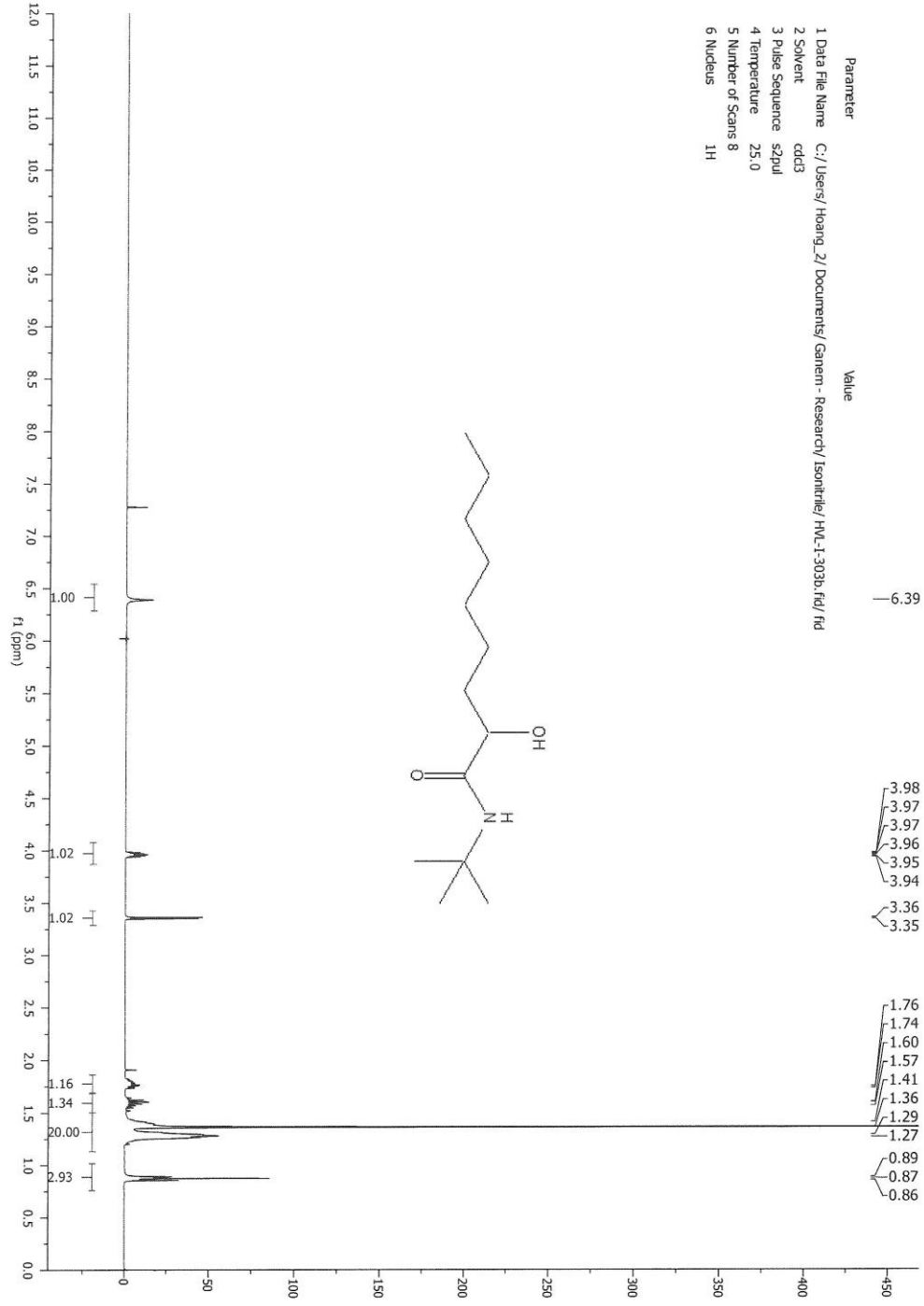


Figure 2.14 ^{1}H NMR Spectrum of Passerini **152c**

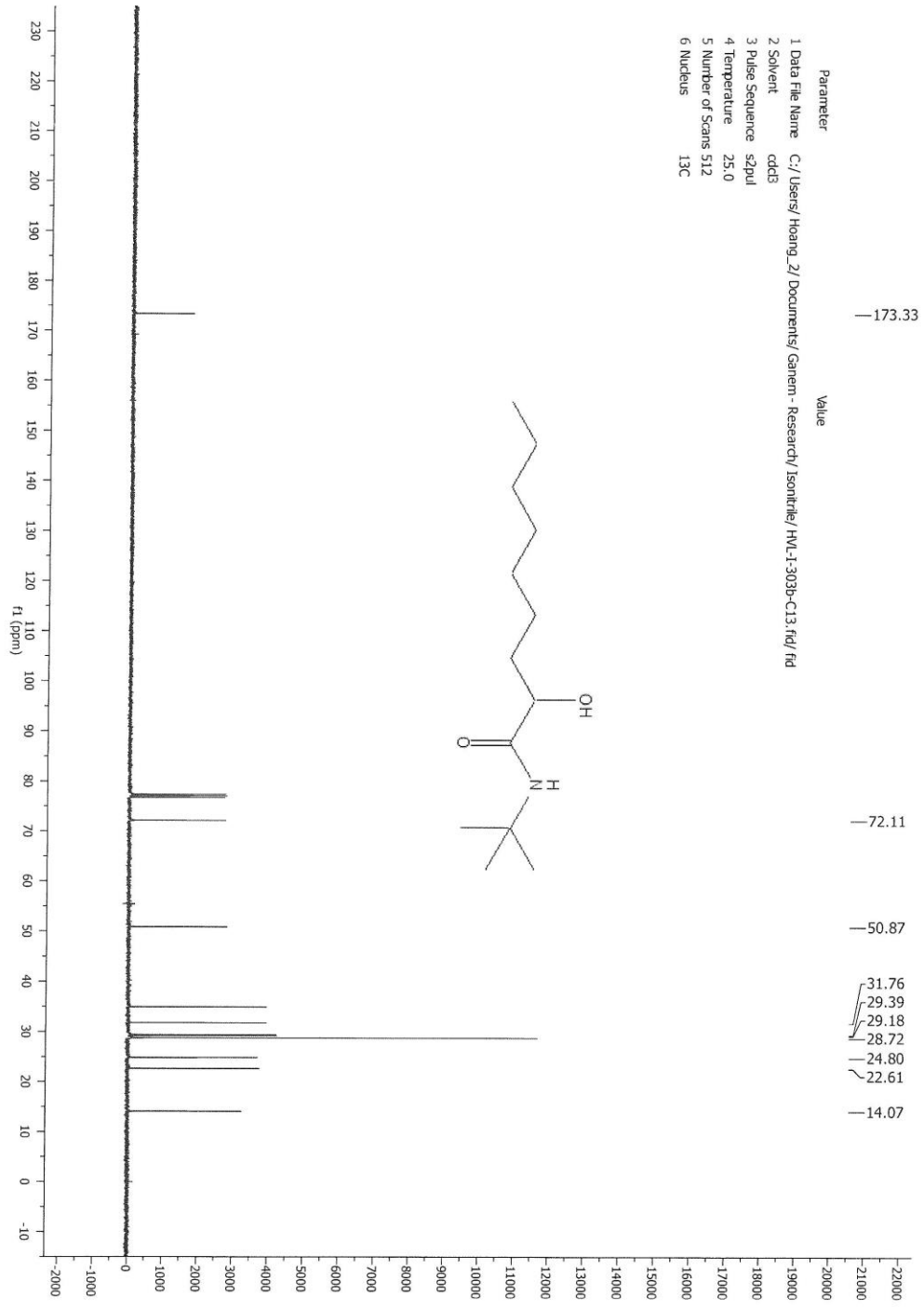


Figure 2.15 ^{13}C NMR Spectrum of Passerini **152c**

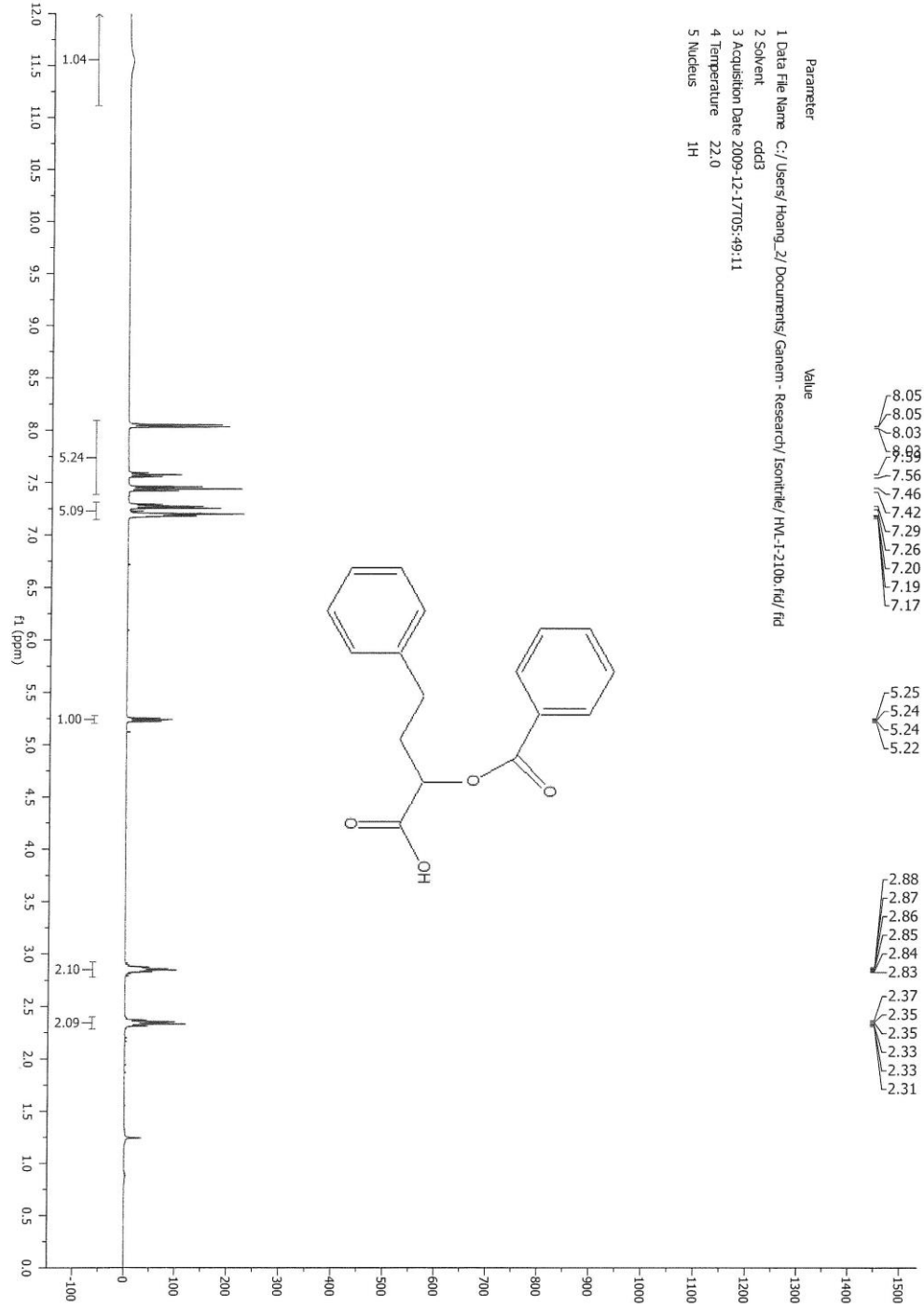


Figure 2.16 ^{1}H NMR Spectrum of Acid **151c**

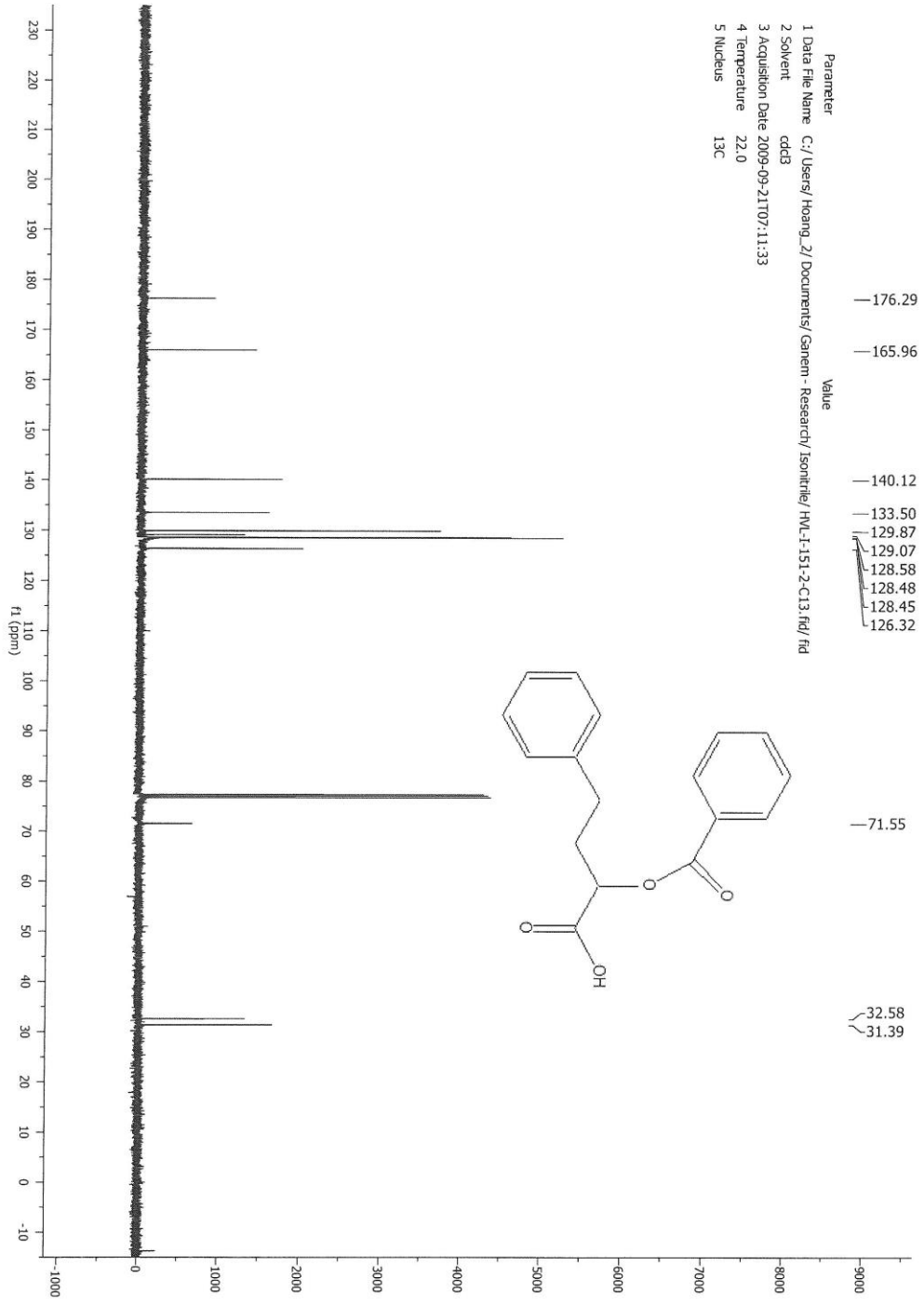


Figure 2.17 ^{13}C NMR Spectrum of Acid **151c**

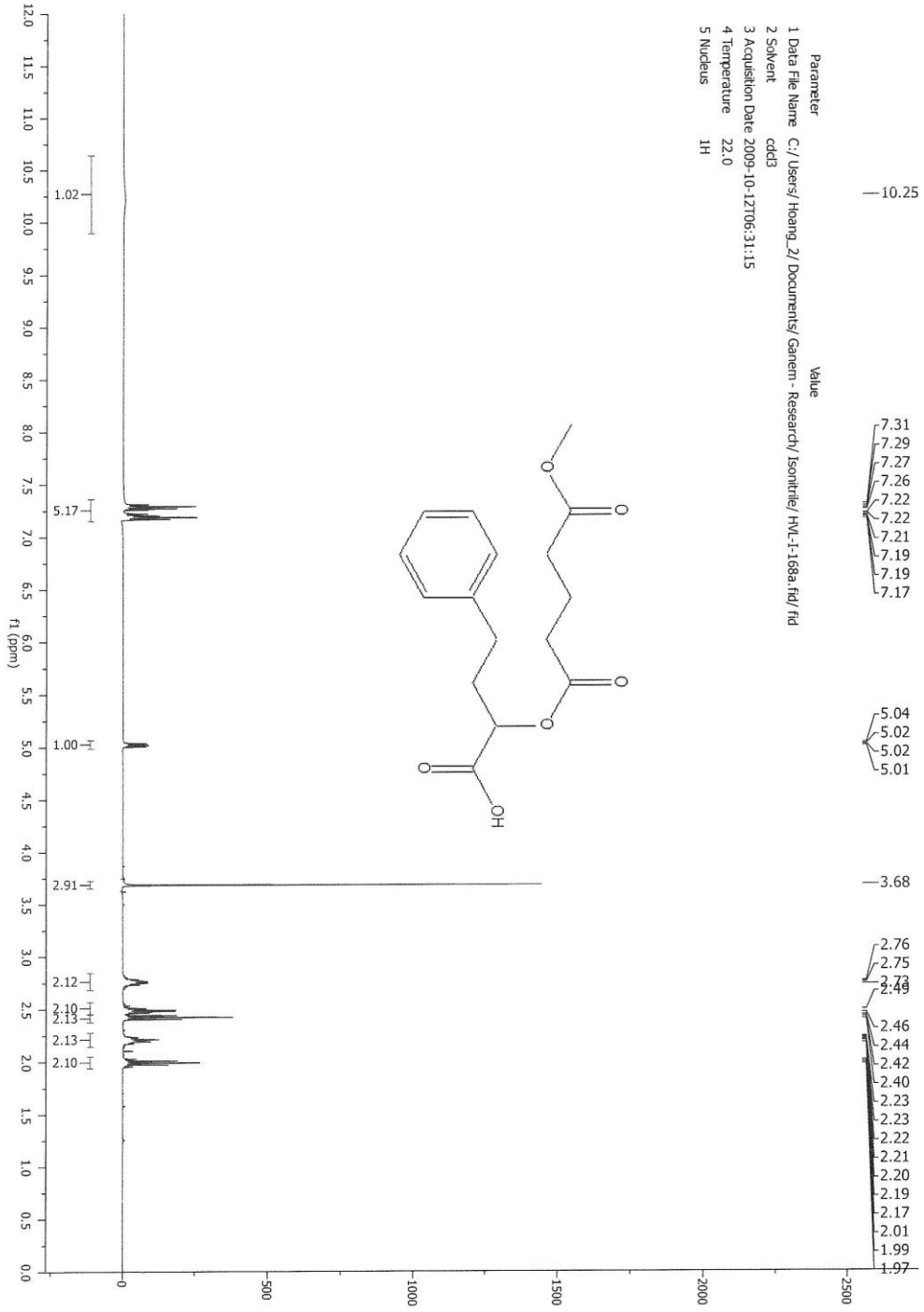


Figure 2.18 ^{1}H NMR Spectrum of Acid **151d**

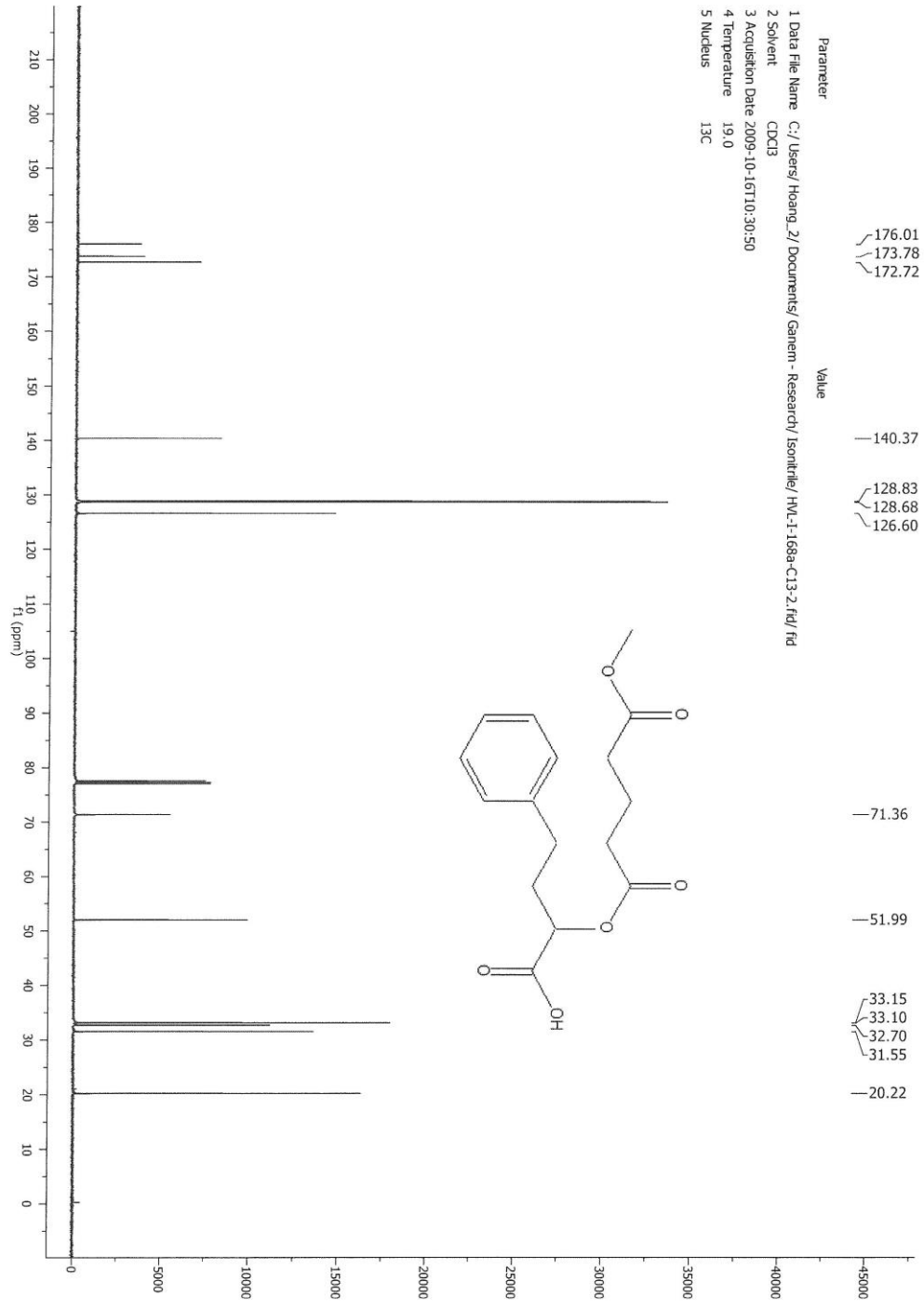


Figure 2.19 ^{13}C NMR Spectrum of Acid **151d**

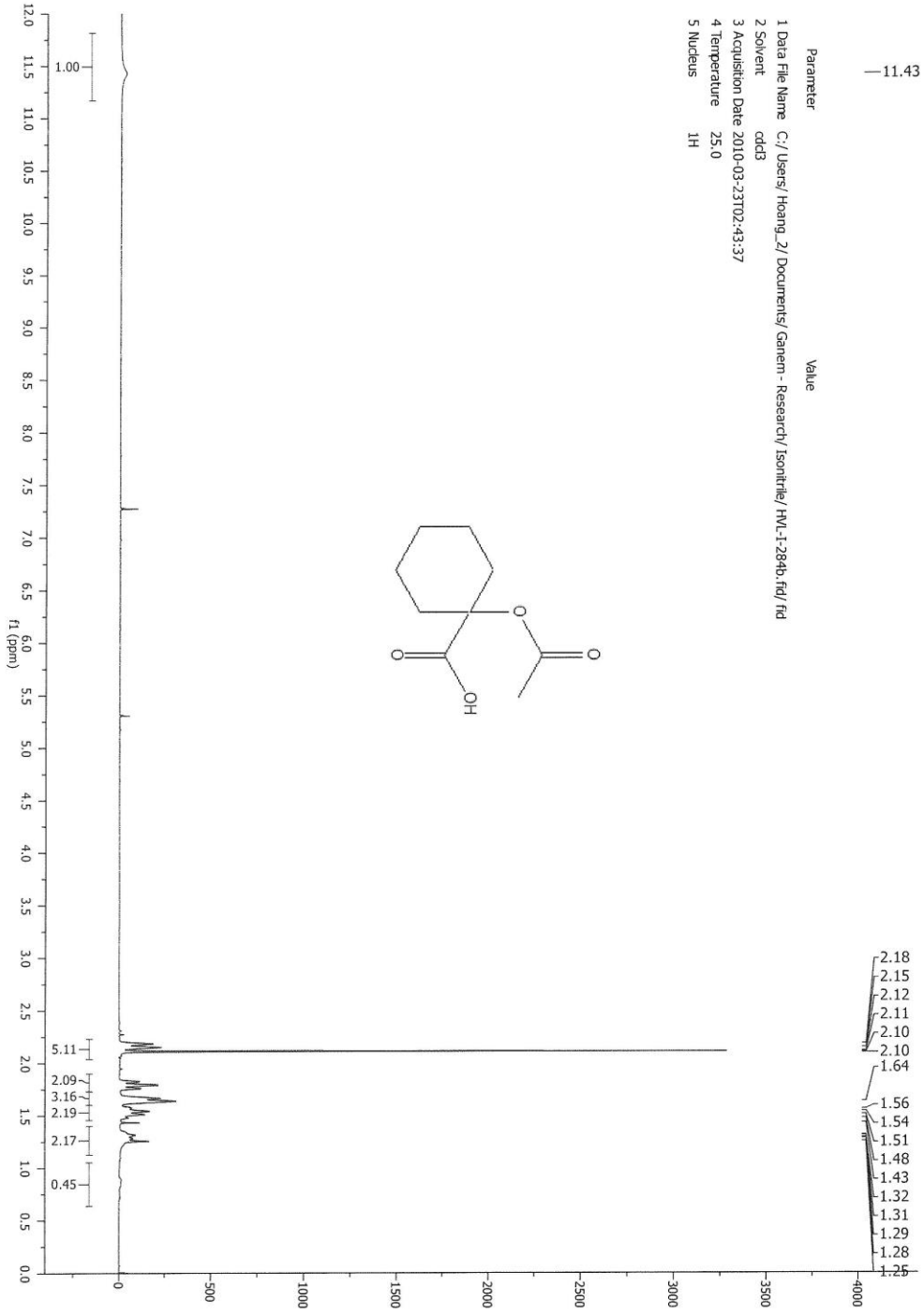


Figure 2.20 ^{1}H NMR Spectrum of Acid **151e**

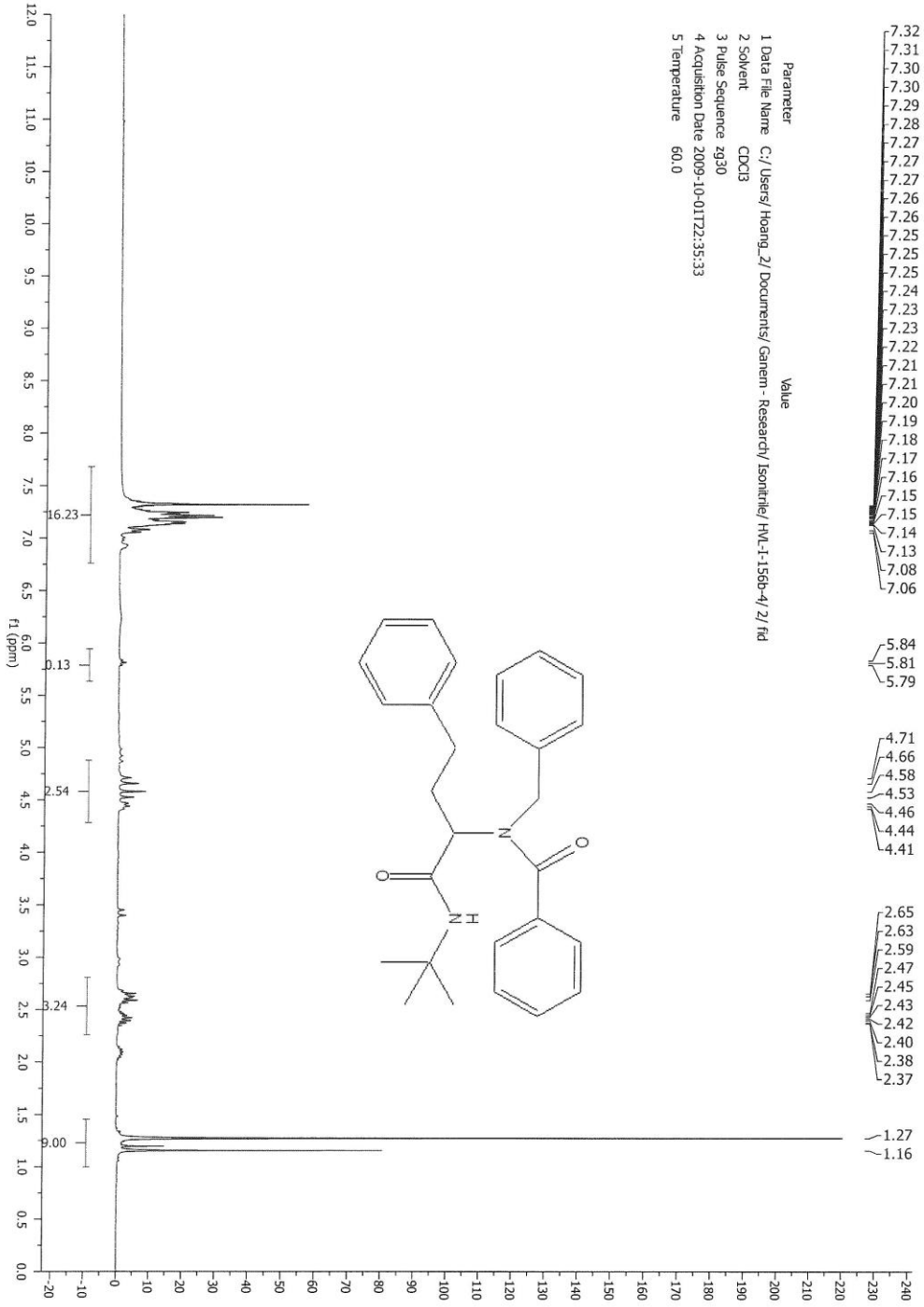
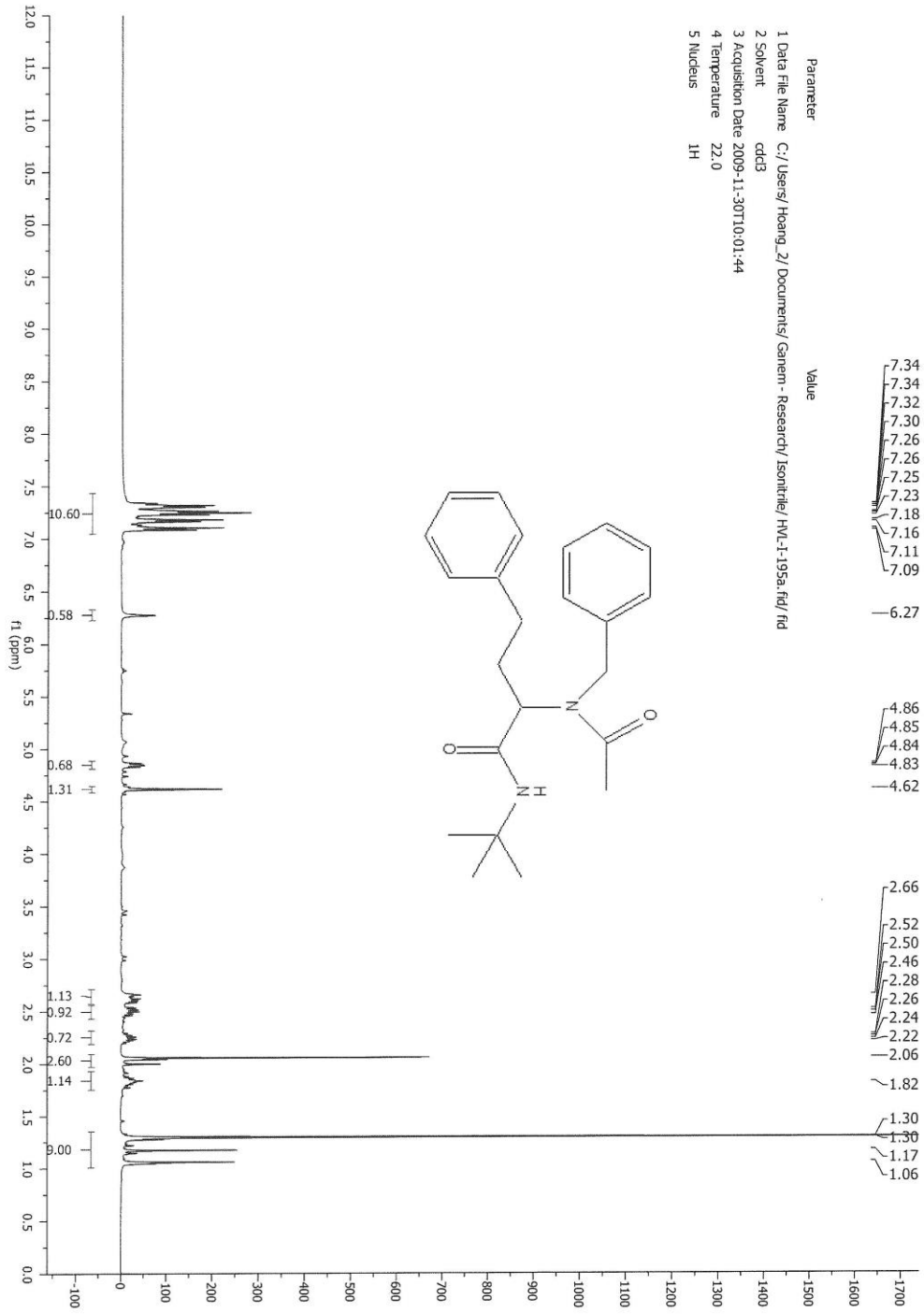


Figure 2.21 ^{1}H NMR Spectrum of Ugi **154a**



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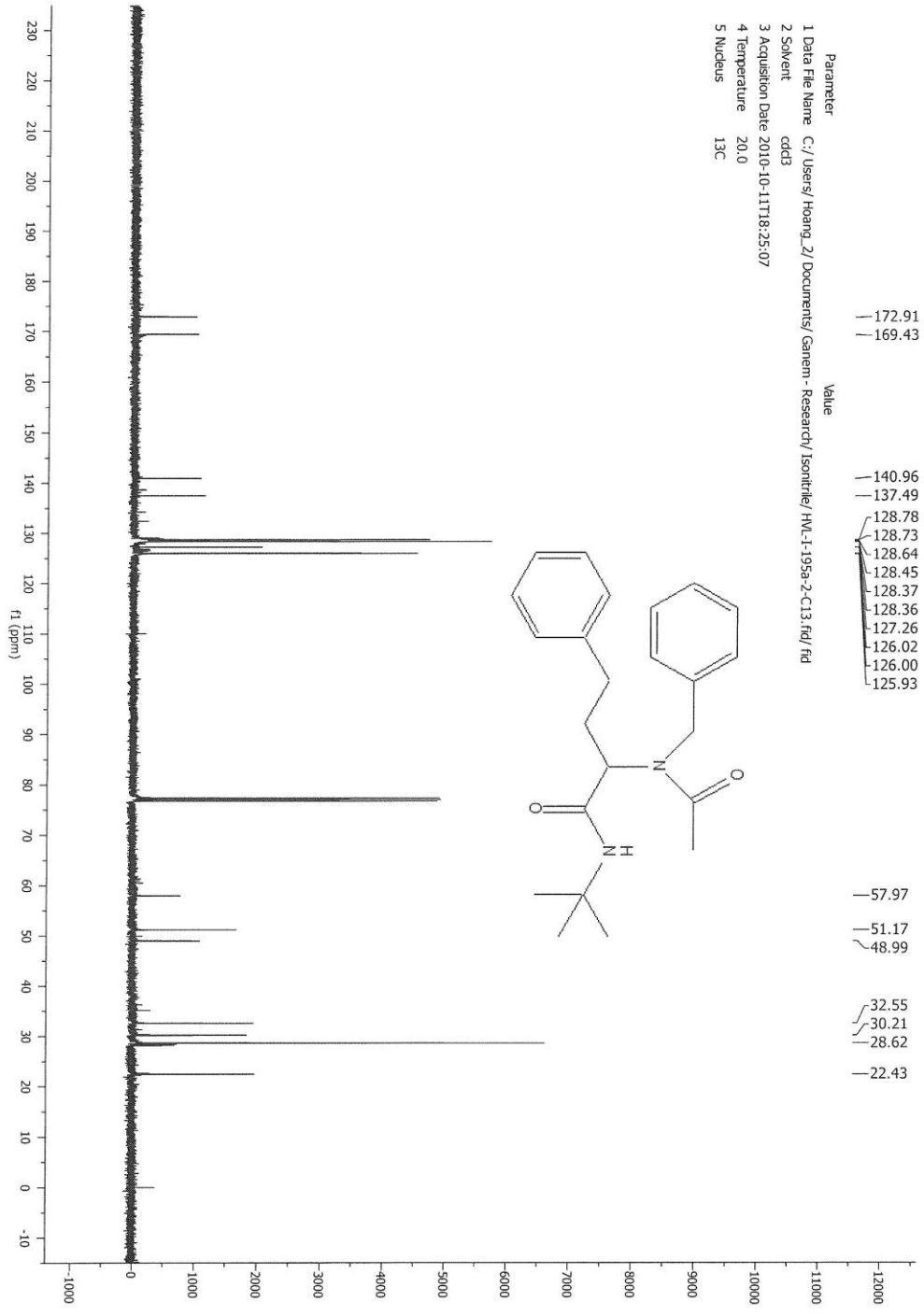

Figure 2.23 ^{13}C NMR Spectrum of Ugi **154b**

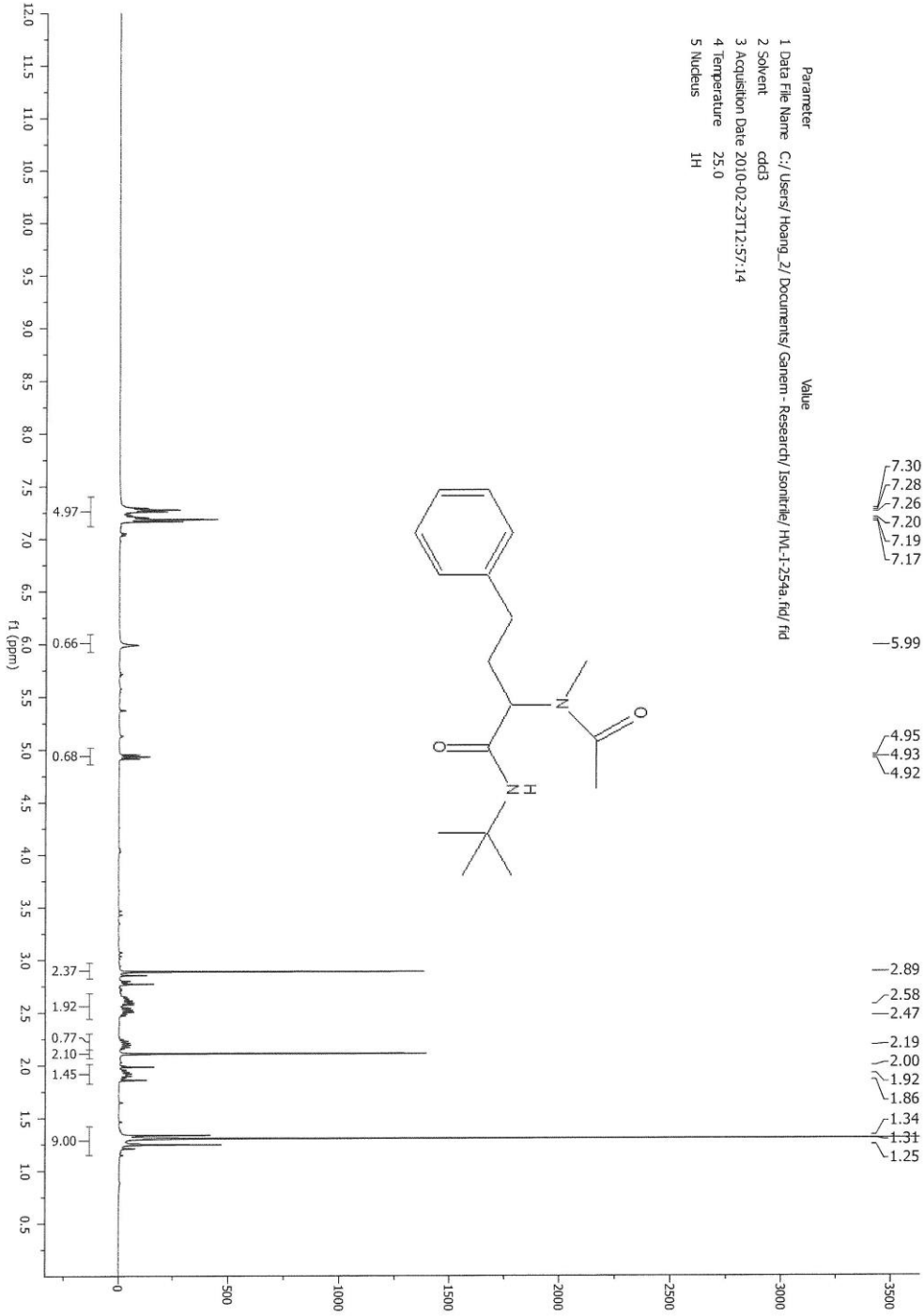

Figure 2.24 ^{1}H NMR Spectrum of Ugi **154c**

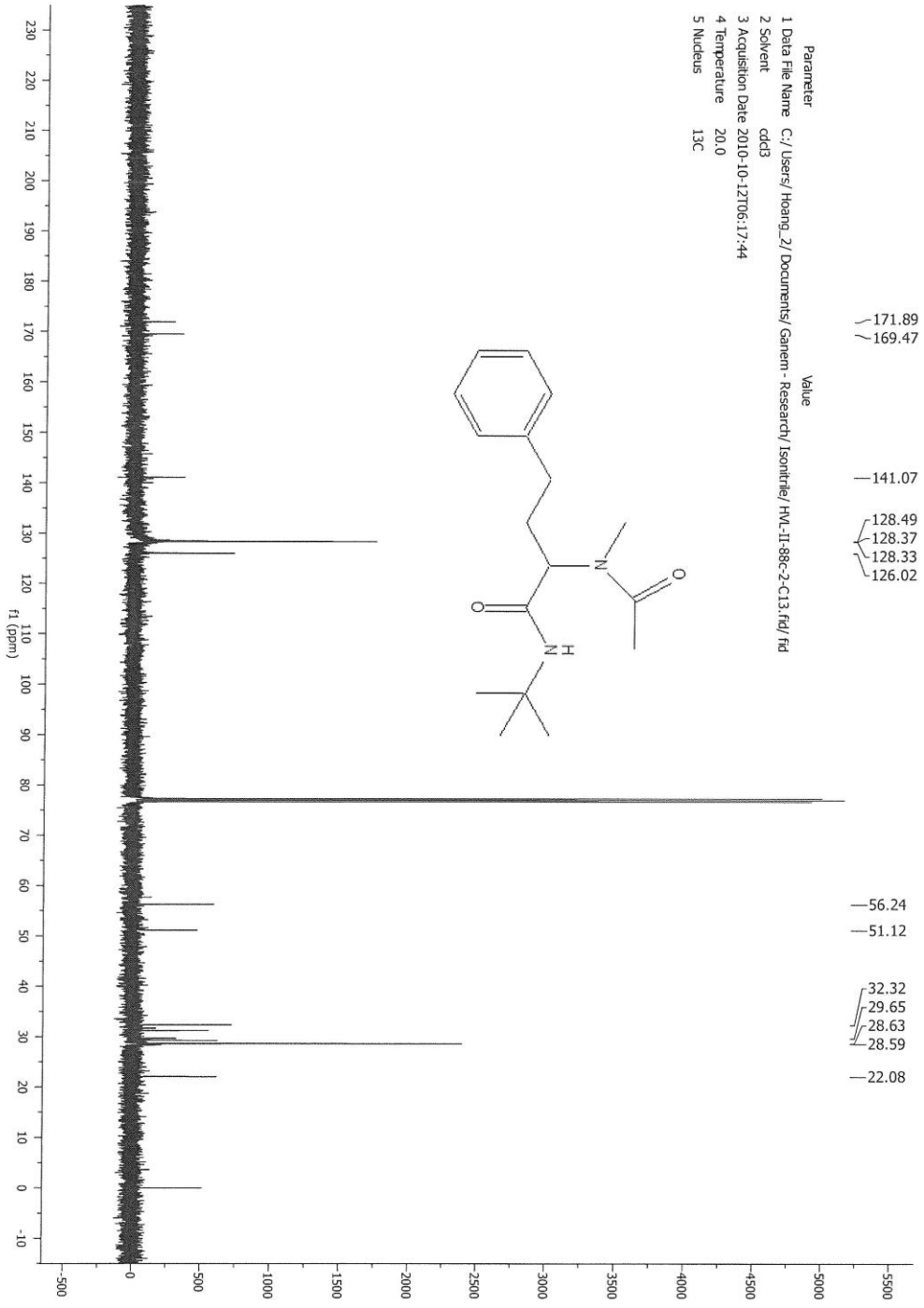

Figure 2.25 ^{13}C NMR Spectrum of Ugi **154c**

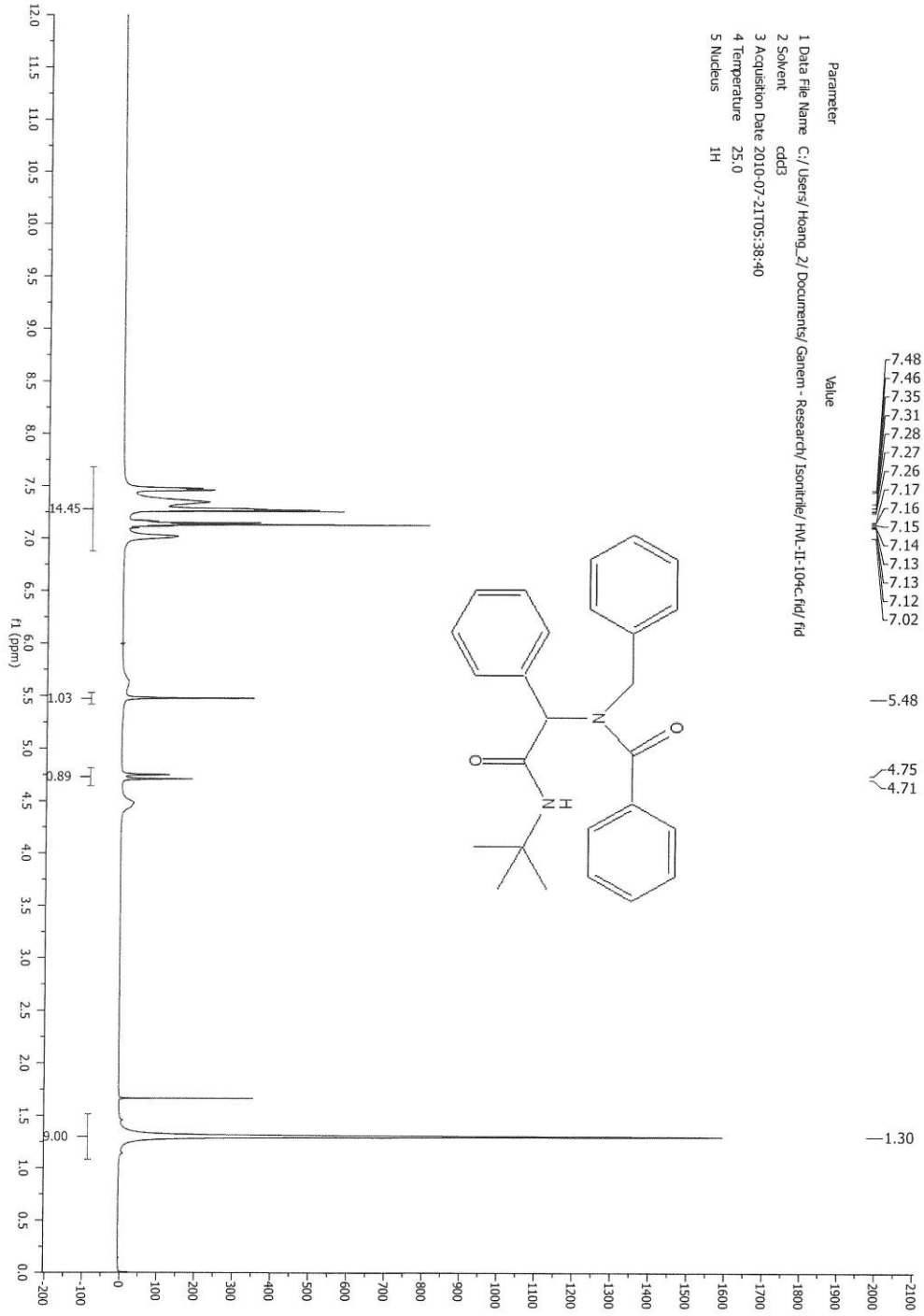

Figure 2.26 ^{1}H NMR Spectrum of Ugi **154e**

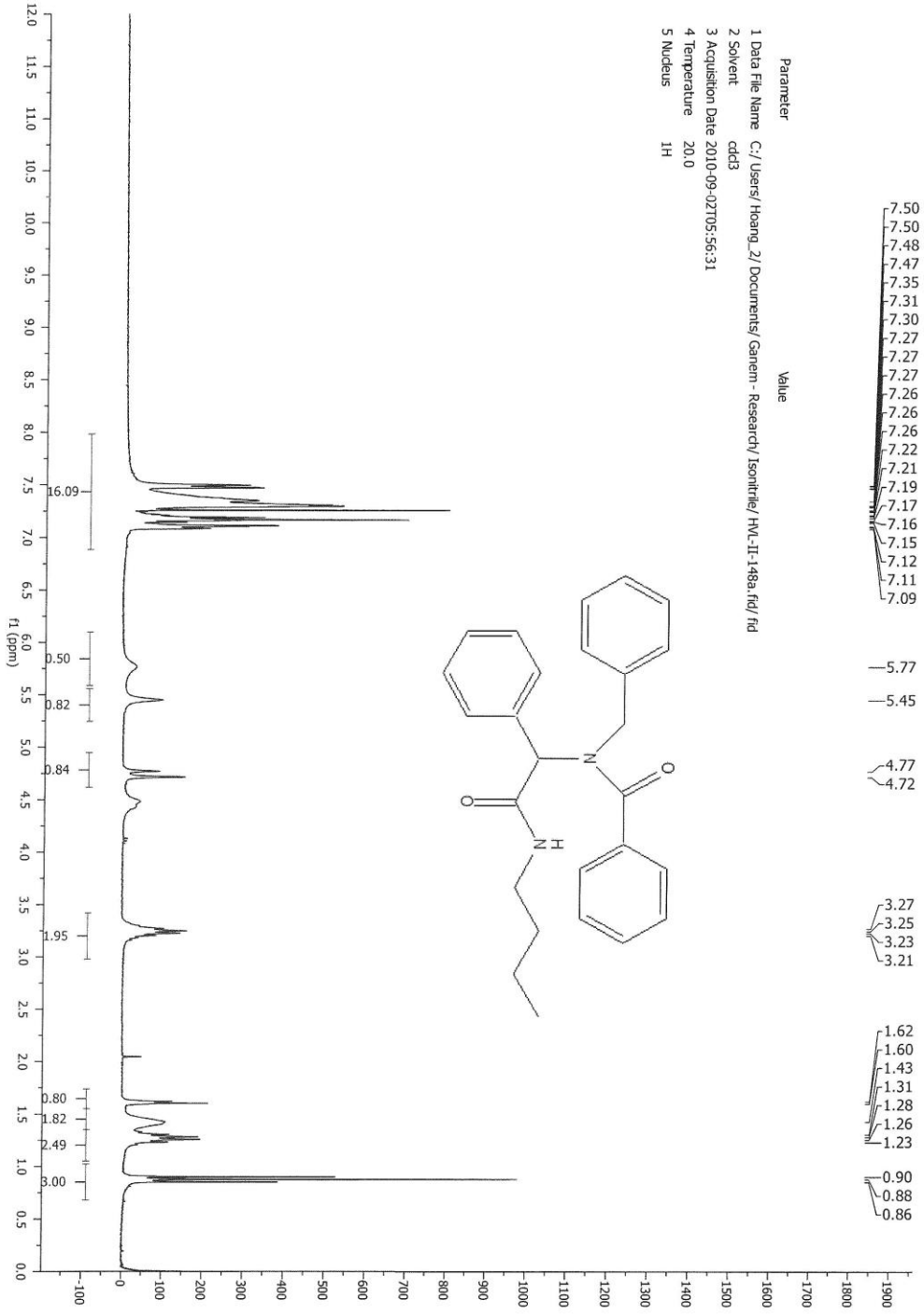

Figure 2.27 ^{1}H NMR Spectrum of Ugi **158a**

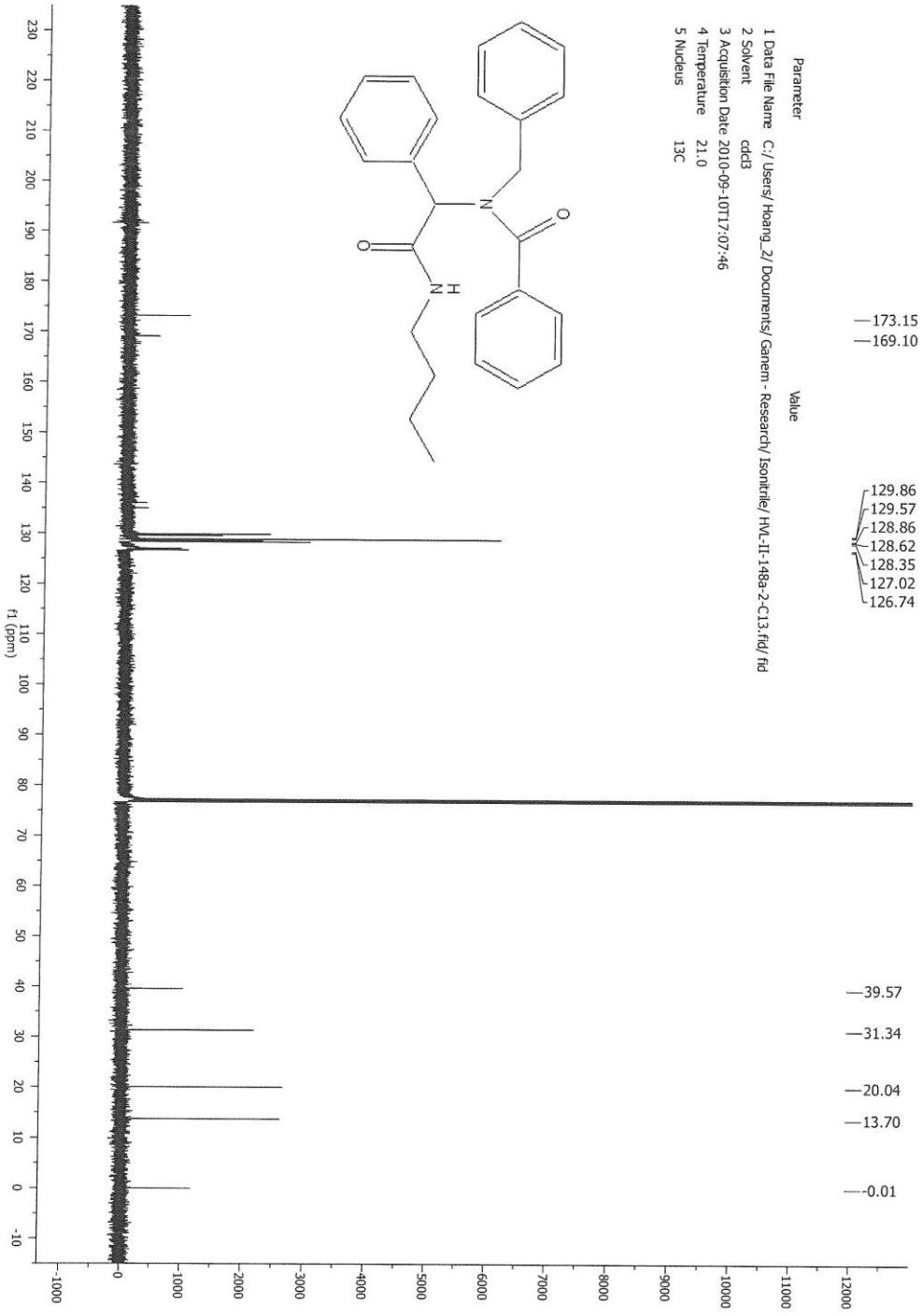

Figure 2.28 ^{13}C NMR Spectrum of Ugi **158a**

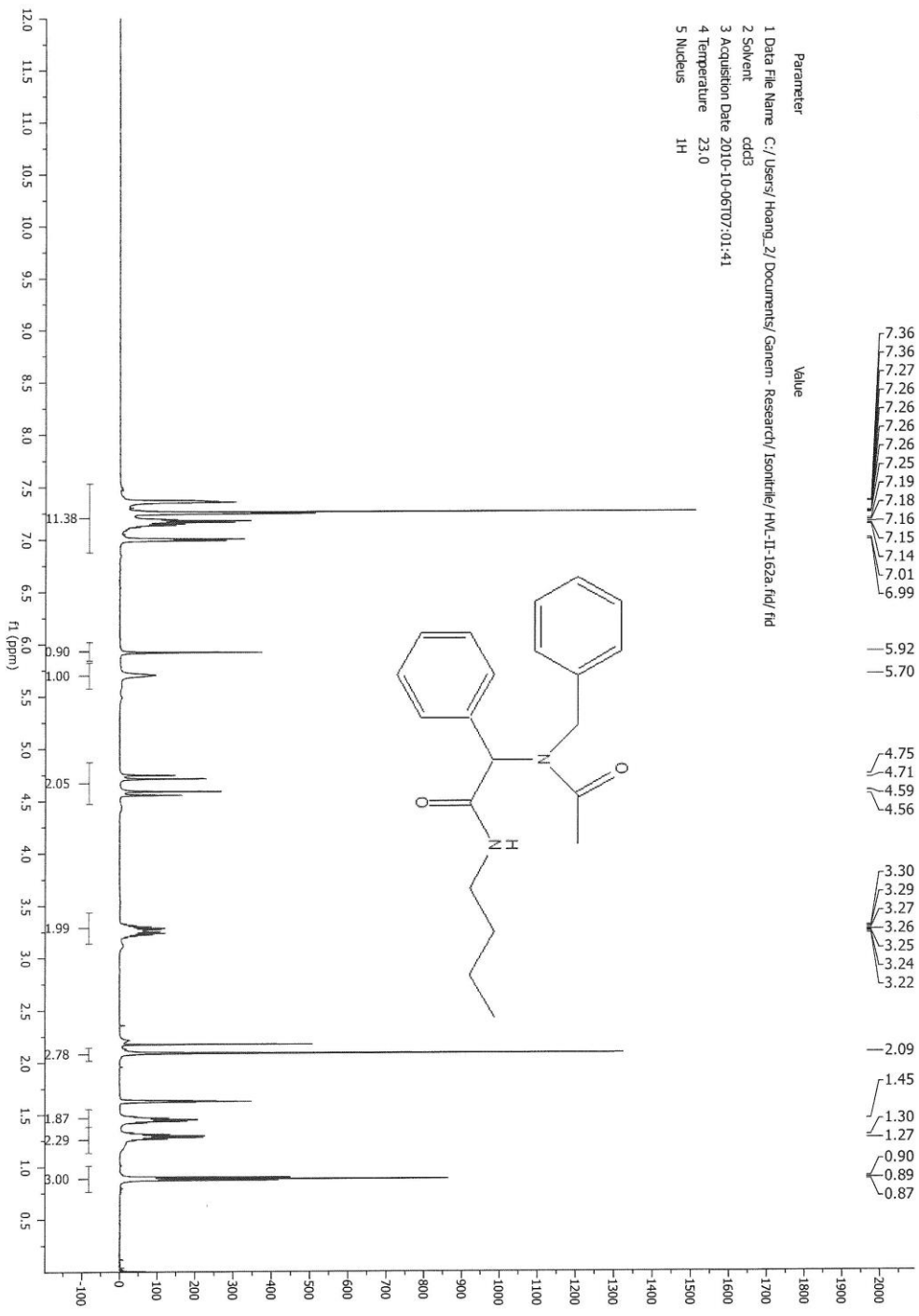

Figure 2.29 ^{1}H NMR Spectrum of Ugi **158b**

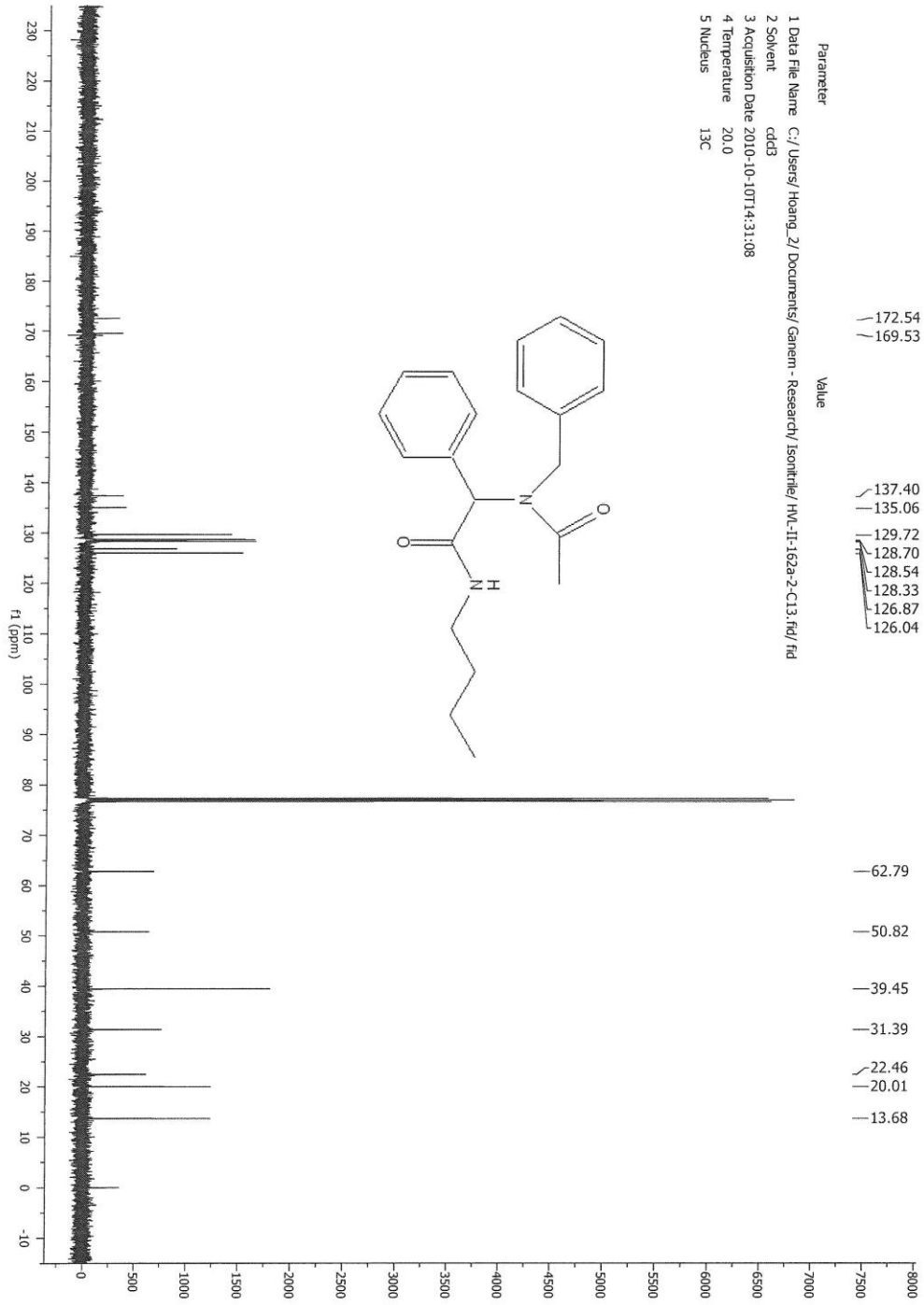

Figure 2.30 ^{13}C NMR Spectrum of Ugi **158b**

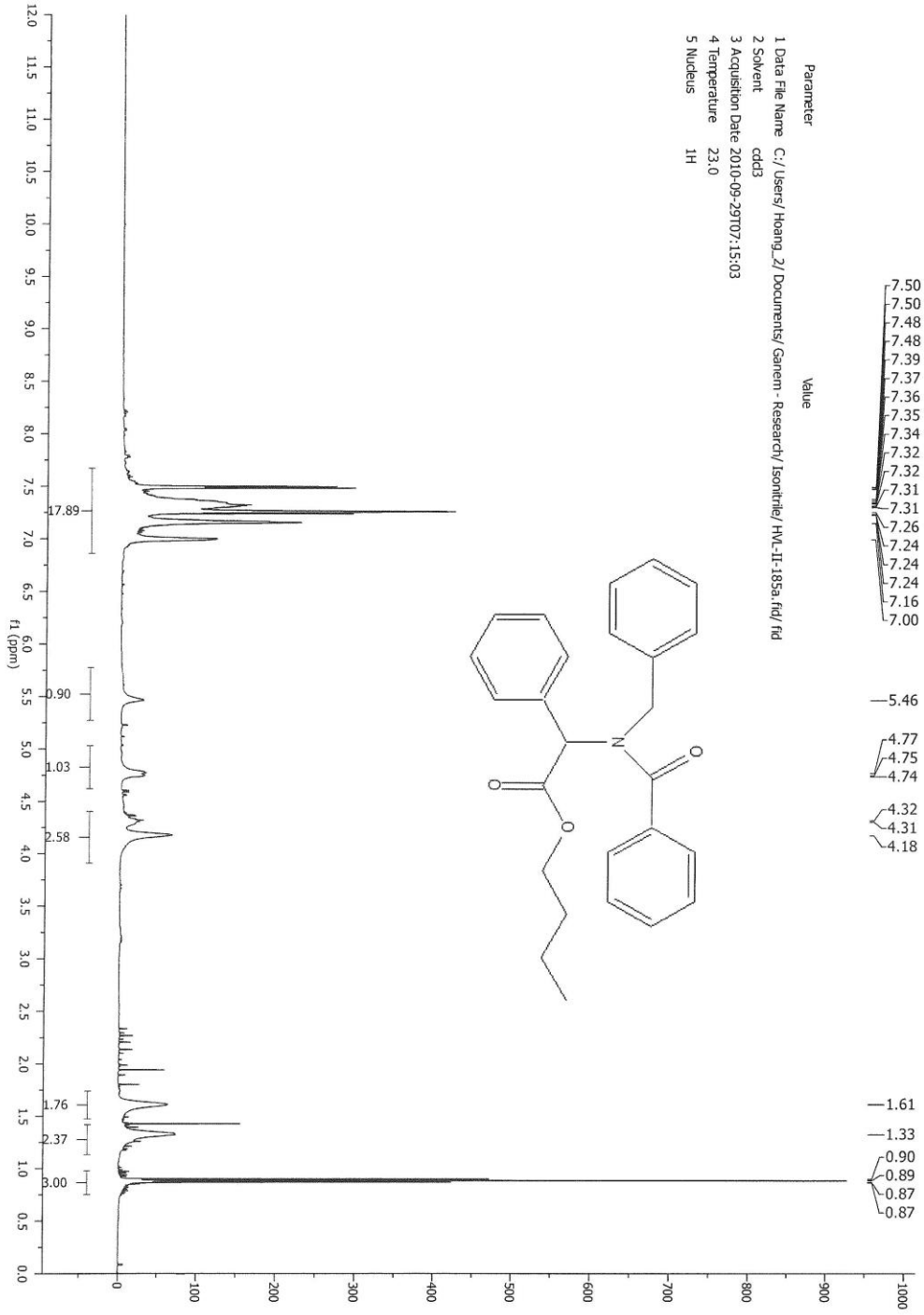

Figure 2.31 ^{1}H NMR Spectrum of Ester **160a**

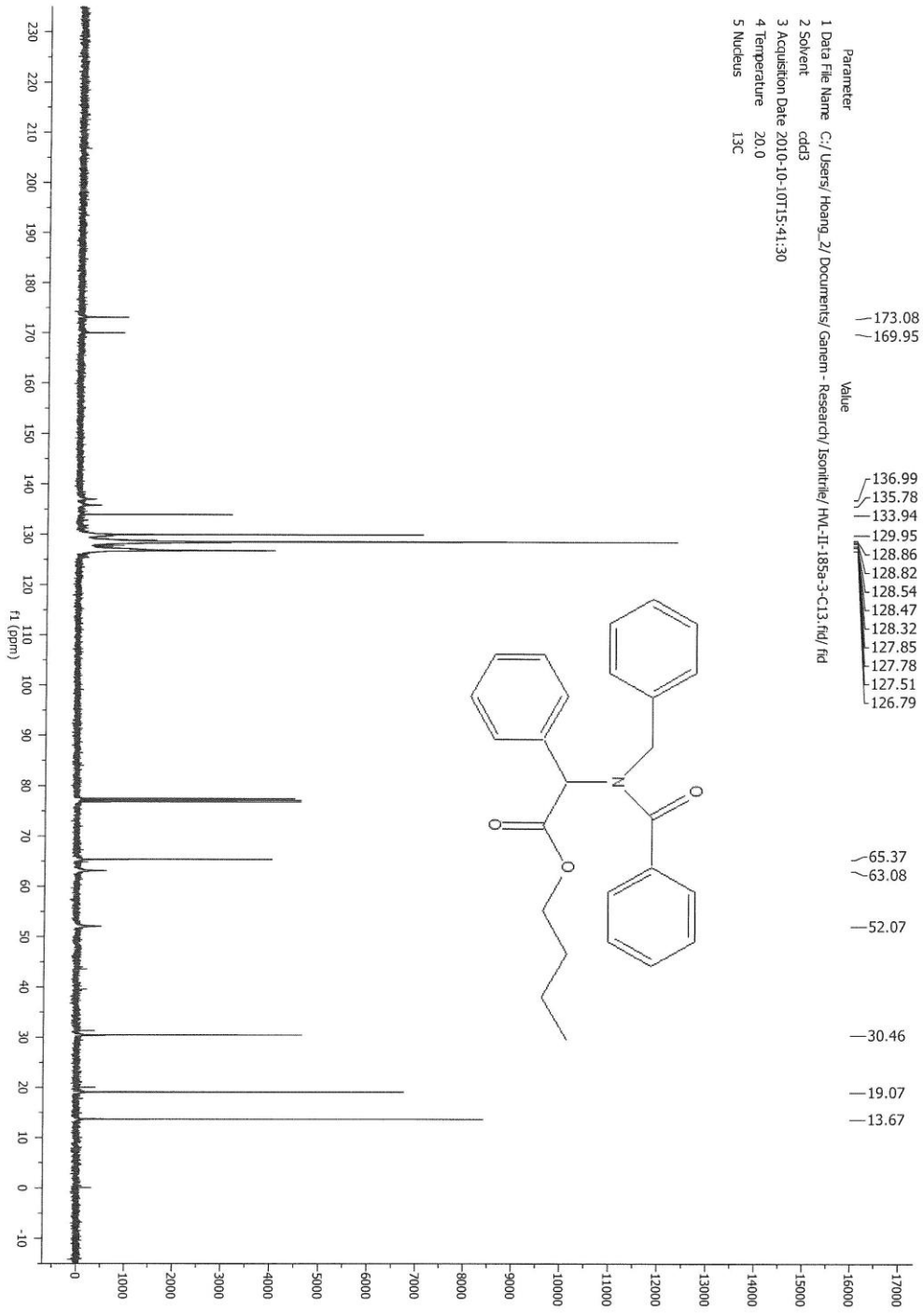

Figure 2.32 ^{13}C NMR Spectrum of Ester **160a**

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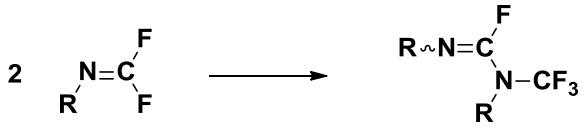
CHAPTER 3

A Simple, General Synthesis of Carbonimidic Dichlorides

3.1 Background

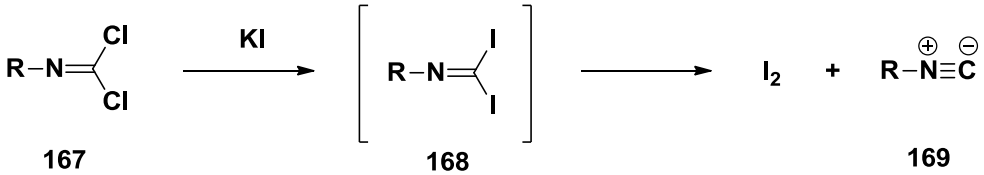
Carbonimidic dihalides (also known as isonitrile dihalides), which have the general structure R−N=CX_2 (where X typically = Br or Cl), have recently attracted attention not only as protecting groups for isonitriles,[1] but also as building blocks for more complex molecular architectures.[2]

Carbonimidic dibromides and carbonimidic dichlorides are generally stable at room temperature,[3] while several types of carbonimidic difluorides dimerize at ambient temperature (Scheme 3.1).[4] Carbonimidic diiodides are virtually unknown because they are not stable and dissociate into iodine and the corresponding isonitriles (Scheme 3.2).[3] This characteristic has been used to easily transform a carbonimidic dihalide such as **167** into the corresponding isonitrile **169** by reacting it with potassium iodide.



165 **166**

Scheme 3.1

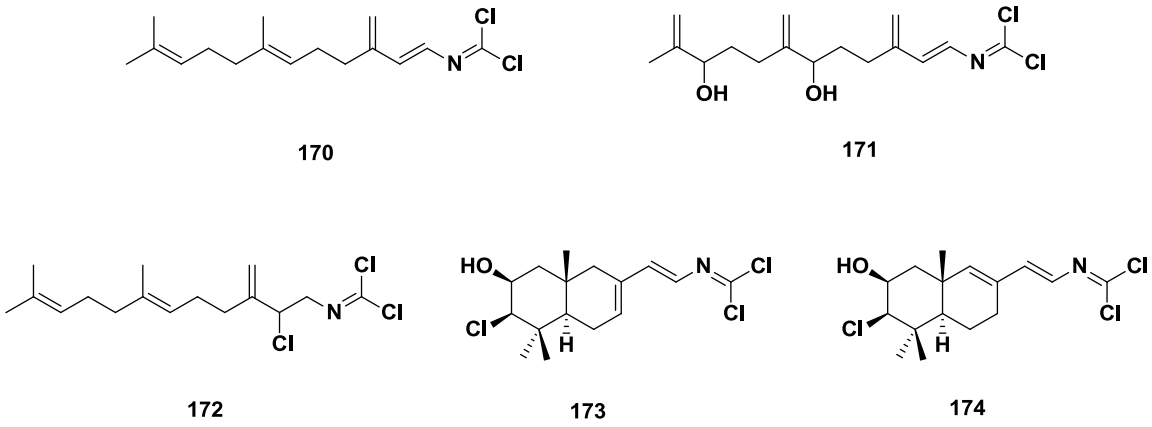


167 **168** **169**

Scheme 3.2[3]

Carbonimidic dihalides have a strong, unpleasant odor, though not as unpleasant as that of isonitriles.[5] The vapors of carbonimidic dihalides cause extreme irritation to the eyes and may lead to temporary loss of vision.

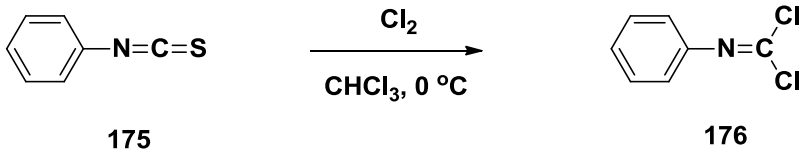
Carbonimidic dihalides can be found in many natural products. For example, König *et al.* recently isolated five sesquiterpene carbonimidic dichlorides **170-174** from the Australian sponge *Ulosa spongia* (Figure 3.1).[6]



170 **171** **172** **173** **174**

Figure 3.1 Some Sesquiterpene Carbonimidic Dichlorides Isolated from the Australian Sponge *Ulosa Spongia*[6]

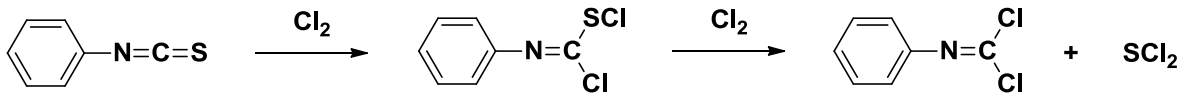
The first carbonimidic dihalide was synthesized by Sell and Zierold in 1874 when they obtained phenylcarbonimidic dichloride **176** from the reaction of phenyl-isothiocyanate **175** and chlorine in chloroform at 0 ^{o}C (Scheme 3.3).[7,8] This method proved to be general.[8,9] Nef later observed that the reaction reported by Sell and Zierold also contained chlorination products of the benzene ring.[8,10] However, when carbon tetrachloride was used as the solvent, the reaction gave no chlorination products of the ring.



175 176

Scheme 3.3

The chlorination of phenylisothiocyanate **175** was discovered by Zumach *et al.* to proceed in two steps (Scheme 3.4).[9] An N-(chloro-chlorothiomethylene)carbonamide **177** was first formed by addition of chlorine in a strongly exothermic reaction. Further chlorination led to the elimination of sulfur dichloride to afford phenylcarbonimidic dichloride **176**. No heat evolution was observed in the second step. The comparable addition of bromine to phenylisothiocyanate **175** was investigated by Freund but did not afford phenylcarbonimidic dibromide; only bromine adducts were observed.[9,11]

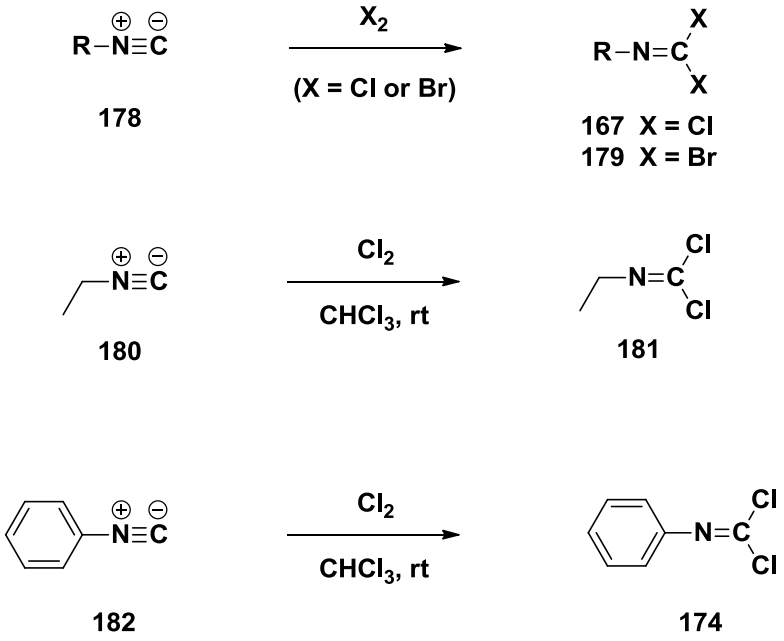


175 177 176

Scheme 3.4

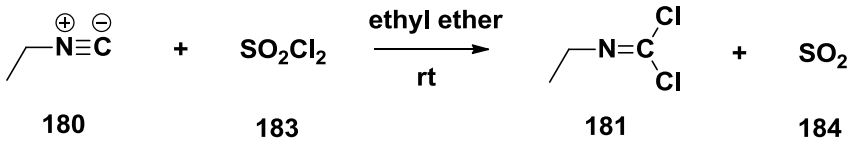
Another method of synthesis of carbonimidic dihalides is the addition of halogen to isonitriles (Scheme 3.5).[8,9] The addition of chlorine to isonitriles was first reported by Nef in 1892. When ethylisonitrile **180** and phenylisonitrile **182** were treated with chlorine in chloroform at room temperature, ethylcarbonimidic dichloride **181** and phenyl-

carbonimidic dichloride **174** were obtained, respectively. Likewise, the comparable addition of bromine to isonitriles **178** afforded carbonimidic dibromides **179**.



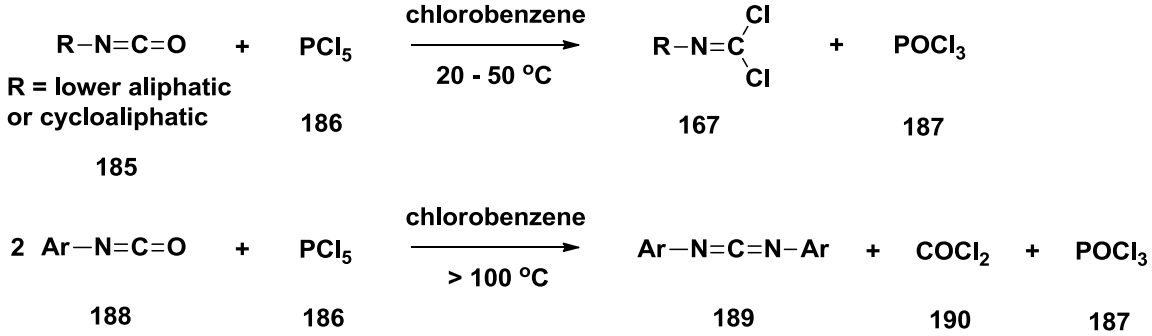
Scheme 3.5

Sulfuryl chloride can also be used as the chlorinating agent instead of chlorine in the synthesis of carbonimidic dichlorides from isonitriles.[8] This replacement was first done by Nef when he obtained ethylcarbonimidic dichloride **181** from the reaction between ethylisonitrile **180** and sulfuryl chloride **183** in ethyl ether at room temperature (Scheme 3.6). However, this method of synthesis of carbonimidic dichlorides has received little attention and to the best of our knowledge, no further studies have been conducted.



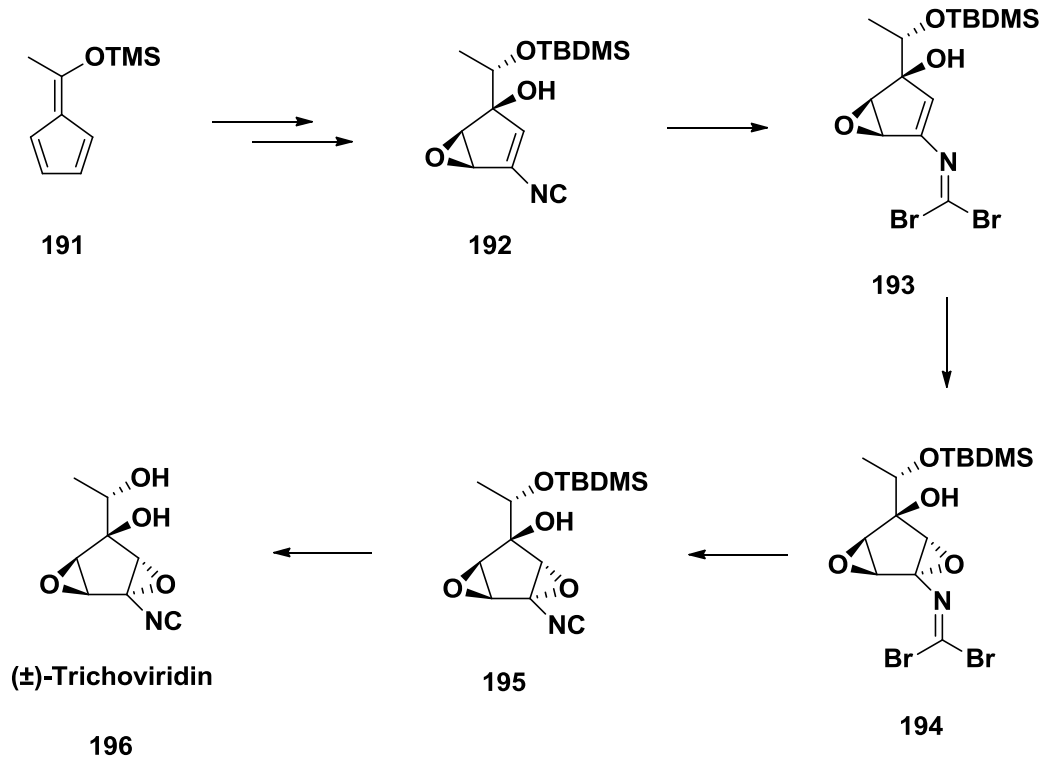
Scheme 3.6[8]

Carbonimidic dichlorides can also be obtained from the reaction of isocyanates and phosphorus pentachloride (Scheme 3.7).[9] When lower aliphatic and cycloaliphatic isocyanates **185** were treated with 1 equiv of phosphorus pentachloride **186** in chlorobenzene at 20 to 50 °C, the corresponding carbonimidic dichlorides **167** were obtained in good yields. When long-chain aliphatic isocyanates were treated with the same reaction conditions, side-chain chlorination concurrently occurred. Aromatic isocyanates **188** only reacted with phosphorus pentachloride **186** at temperatures above 100 ^{o}C. The corresponding carbonimidic dichlorides were obtained only in low yield. The main products were carbodiimides **189**.



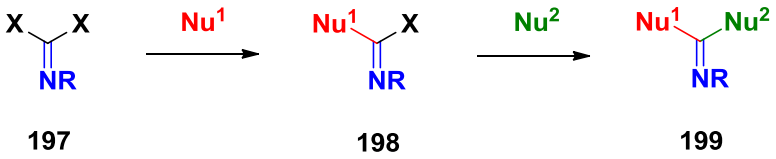
Scheme 3.7

Carbonimidic dihalides have been used as protecting groups for isonitriles, and they can be easily converted back to the parent isonitriles by reacting them with iodide, triethylphosphine, $LiAlH_4$, or electrochemical reduction.[1] For example, Baldwin *et al.* turned the isonitrile **192** into the corresponding carbonimidic dibromide **193** to protect the isonitrile functionality from the epoxidation conditions in their total synthesis of the antibiotic (±)-trichoviridin **196**, a naturally occurring epoxy-isonitrile (Scheme 3.8).[12]



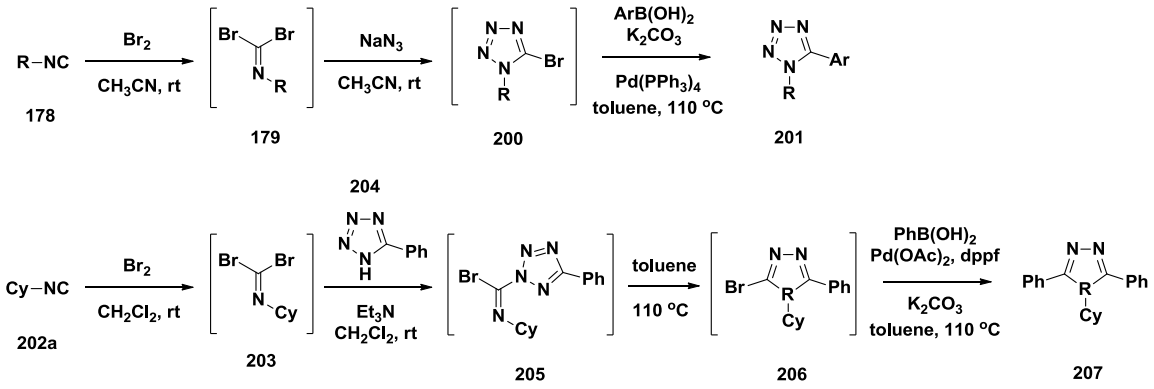
Scheme 3.8

Activated by two halogen atoms, the C=N double bond in carbonimidic dihalides could be subjected to two nucleophilic additions, possibly in sequential manner (Scheme 3.9).[2] This unusual characteristic of carbonimidic dihalides has led to their use as building blocks for more complex molecular architectures.



Scheme 3.9[2]

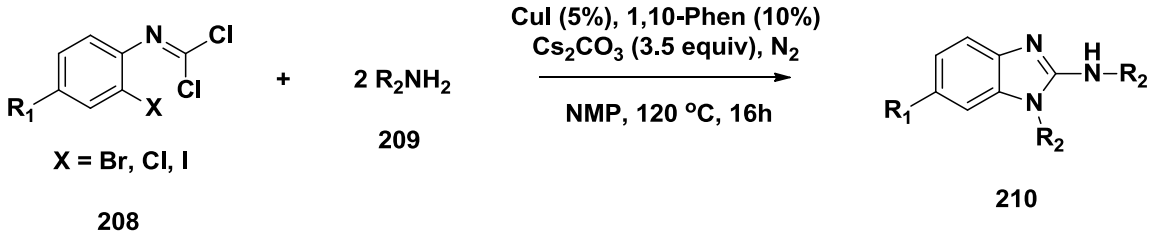
El Kaim *et al.* recently used carbonimidic dibromides in their 3-component strategy to afford tetrazole and triazole scaffolds (Scheme 3.10).[2] Tetrazoles **201** were synthesized by the addition of sodium azide to carbonimidic dibromides **179**, followed by electrocyclization and a Suzuki coupling. Triazole **207** was synthesized by the addition of tetrazole **204** to carbonimidic dibromide **203**, followed by Huisgen rearrangement and a Suzuki coupling.



Scheme 3.10[2]

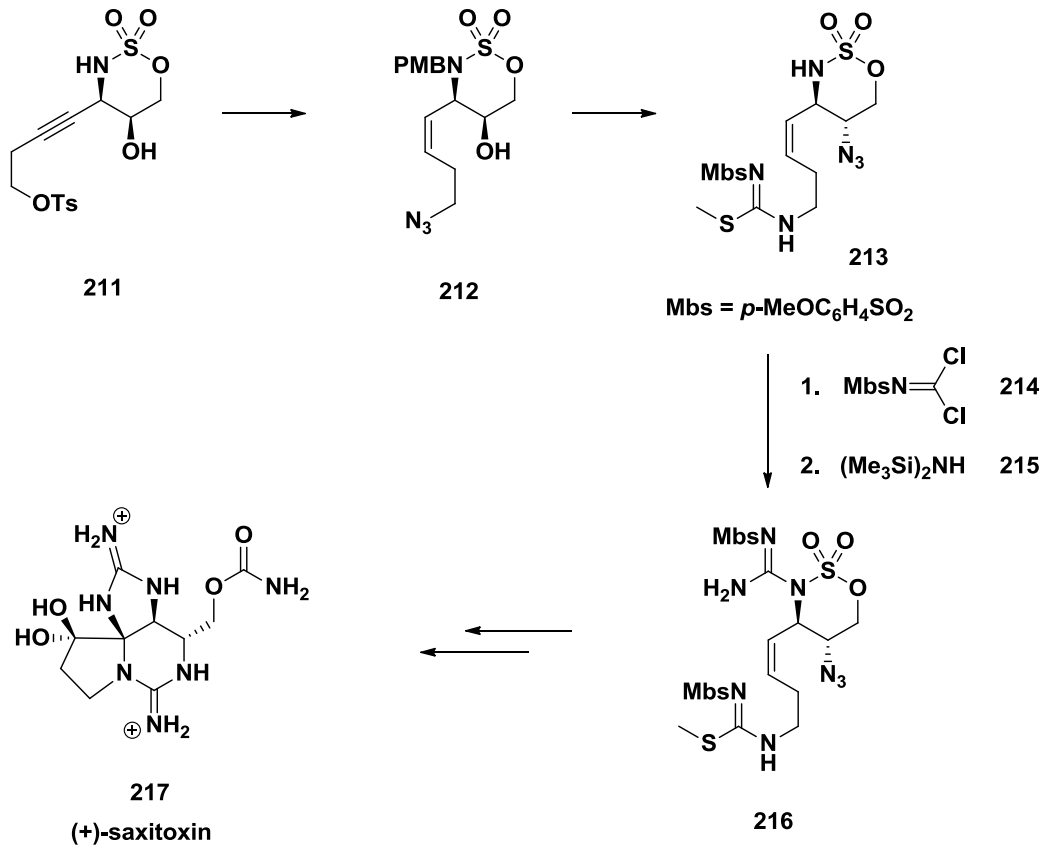
Yu *et al.* recently developed a one-pot method for the synthesis of 2-amino-benzimidazoles from carbonimidic dichlorides and amines (Scheme 3.11).[13] Such benzimidazoles display significant biological activity and compose the core structure of

many commercial drugs such as vermox, fenbendazole, nocodazole, and mizolastine. The copper-catalyzed condensation of carbonimidic dichlorides **208** and 2 equiv of amines **209** formed 2-aminobenzimidazoles **210**.



Scheme 3.11[13]

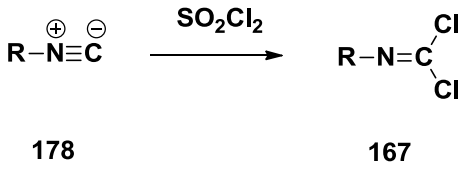
Du Bois *et al.* recently used a carbonimidic dichloride in their total synthesis of a paralytic agent (+)-saxitoxin associated with oceanic red tides (Scheme 3.12).[14] Compound **216** was formed by the condensation of carbonimidic dichloride **214**, amine **213**, and amine **215**. Subsequent modification afforded (+)-saxitoxin **217**.



Scheme 3.12

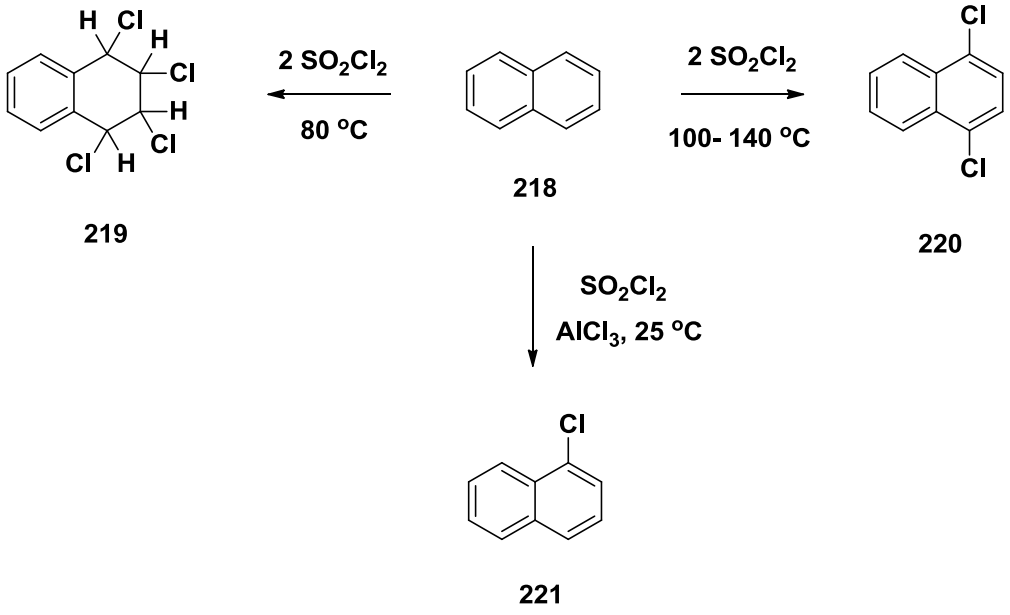
Carbonimidic dibromides can usually be prepared by simple addition of elemental bromine to the isonitrile. However, the comparable addition of elemental chlorine (Cl_2) to isonitriles is not a generally useful reaction with alkylisonitriles, since free-radical processes generally produce alkyl chloride byproducts resulting from C–H substitution.[9]

Here we report that the chlorination of isonitriles **178** using sulfuryl chloride rapidly and selectively furnishes the corresponding carbonimidic dichlorides **167** (Scheme 3.13). Besides being readily available, inexpensive, and quite convenient to use, sulfuryl chloride is also easy to purify and manipulate in small quantities for benchtop experimentation.



Scheme 3.13

Sulfuryl chloride has long been known as both an excellent chlorinating and sulfonylating agent for aromatic compounds, depending on the choice of experimental conditions.[15] Both addition and substitution processes have been observed. For example, naphthalene **218** can be made to react with sulfuryl chloride in different reaction conditions to afford different chlorinated products (Scheme 3.14). At 80 ^{o}C, 1,2,3,4-tetrachloro-1,2,3,4-tetrahydronaphthalene **219** is collected as the main product, whereas at 100-140 ^{o}C, 1,4-dichloronaphthalene **220** is obtained as the main product. When aluminum chloride is used as a catalyst at room temperature, the reaction affords 1-chloro-naphthalene **221**.

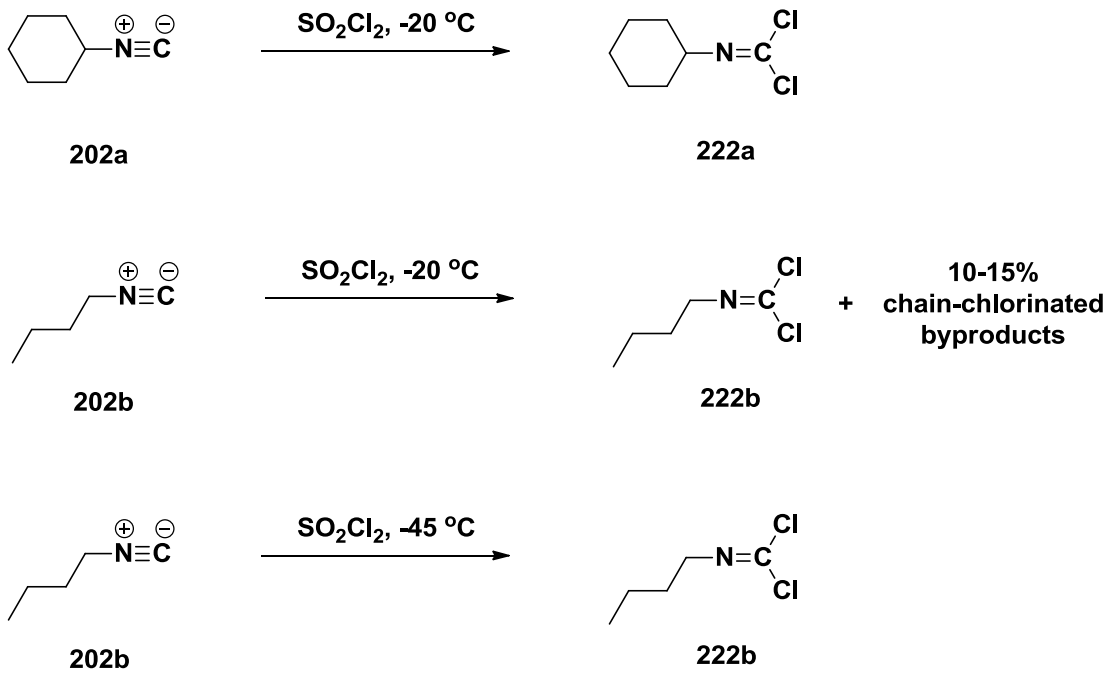


Scheme 3.14[15]

Sulfuryl chloride also produces chlorination of aliphatic hydrocarbons under ionic conditions using Lewis acid catalysts, or under free radical conditions in the presence of a suitable catalyst (peroxides) or light.[15] However, in the absence of such free radical initiators, aliphatic chlorination can largely be suppressed at low temperatures. This exquisite control of product outcomes, as summarized in a recent review,[16] has led to a resurgence of interest in sulfuryl chloride on the part of academic and industrial researchers.[17,18]

3.2 Results and Discussion

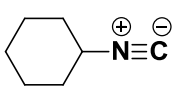
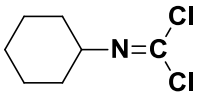
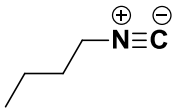
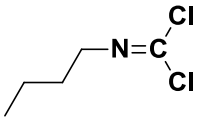
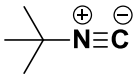
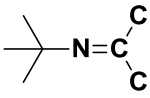
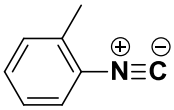
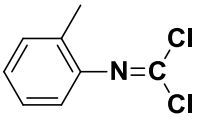
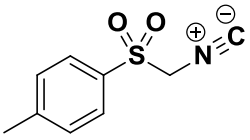
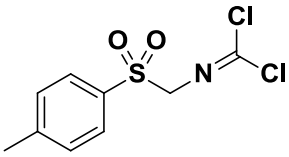
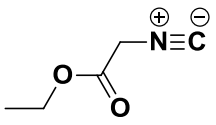
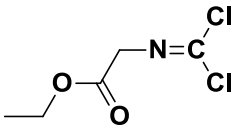
Using cyclohexylisonitrile **202a** as a test case, neat SO_2Cl_2 (1 equiv) was added dropwise to a stirred $CHCl_3$ solution (1.0 M) of the isonitrile at -20 ºC under nitrogen, and the reaction mixture was warmed to room temperature (15–30 min total reaction time) (Scheme 3.15). The desired carbonimidic dichloride **222a** was obtained in nearly quantitative yield and exhibited the expected 9:6:1 ratio of M:M+2:M+4 peaks characteristic of two chlorine atoms in the structure. Applying the same procedure to *n*-butylisonitrile **202b** led to product **222b** contaminated with 10–15% chain-chlorinated byproducts. However, by lowering the reaction temperature to -45 ºC and pre-diluting the SO_2Cl_2 with $CHCl_3$, **222b** was obtained ca 95% pure. The latter reaction condition was thus chosen as the preferred method for the synthesis of carbonimic dichlorides from isonitriles.



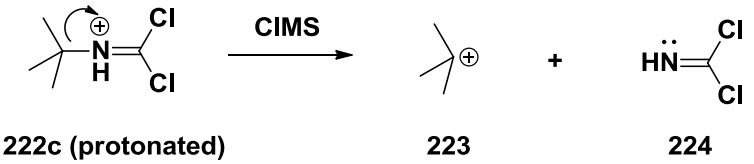
Scheme 3.15

Chlorinations of representative isonitriles **202a–f** using SO_2Cl_2 at -45 ºC are summarized in Table 3.1 and illustrate the broad scope and efficiency of the method. Both aliphatic and aromatic isonitriles were readily converted into the corresponding dichlorides in excellent yield. Although carbonimidic dichlorides **222a–e** have previously been synthesized (as referenced in Table 3.1), very little spectroscopic or physical characterization (other than IR and mp) data were provided in earlier publications. All products **222a–f** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and either chemical ionization mass spectrometry (CIMS) or electron impact mass spectrometry (EIMS). The product carbonimidic dichlorides could be stored neat at -20 ºC for up to 4–5 days without appreciable decomposition, but NMR samples deteriorated appreciably upon standing at room temperature after 1–2 days.

Table 3.1 Synthesis of Isonitrile Dichlorides Using Sulfuryl Chloride

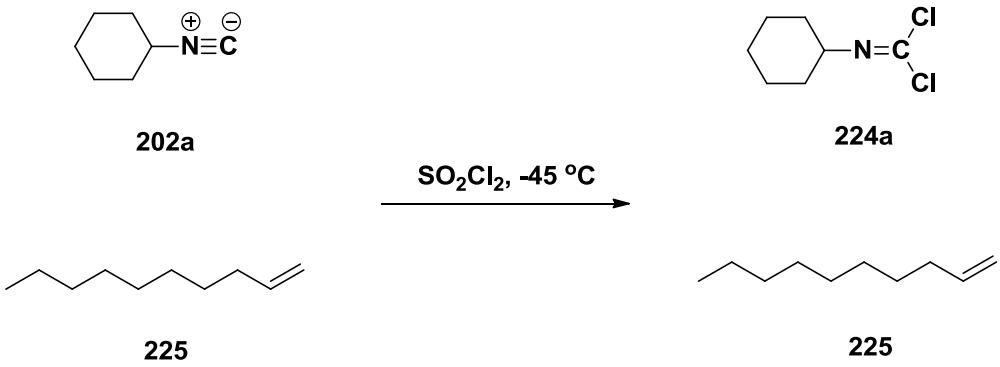
Isonitrile	Isonitrile Dichlorides	% Yield	Lit. Reference
		99	19
202a	222a		
		80	20, 21, 22
202b	222b		
		90	21
202c	222c		
		98	20, 21, 23, 24
202d	222d		
		97	25
202e	222e		
		98	
202f	222f		

When dichloride **222c** was analyzed using CIMS, no parent ions could be detected, likely because of the facile fragmentation of protonated **222c** shown in Scheme 3.16. However the EIMS spectrum of **222c** revealed the expected M, M+2 and M+4 pattern of parent ions, as well as characteristic fragment ions resulting from both α-cleavage and inductive cleavage pathways.



222c (protonated) **223** **224**

Scheme 3.16



202a **224a**

225 **225**

Scheme 3.17

Data in Table 3.1 confirm that the reaction is compatible with other functionality, including carboxylic esters. Moreover, no aromatic chlorination products were detected. In a competition experiment between cyclohexylisonitrile **202a** and 1-decene **225**, dichloride **222a** was formed exclusively (94%) and 1-decene **225** was returned

unchanged, indicating high selectivity for chlorine addition to the isonitrile in the presence of an alkene (Scheme 3.17). Furthermore, isonitriles **202d–f** selectively underwent addition in preference to substitution, even in the presence of activated methyl and methylene groups, such as CH_3–Ar in **202d**, –SO_2CH_2– in **202e**, and –CH_2CO_2Et in **202f**.

3.3 Experimental Procedures

Representative Procedure for the Chlorination of Isonitriles Using SO_2Cl_2

A magnetically-stirred $CHCl_3$ solution of isonitrile (0.7– 1.0 mmol) under N_2 in an oven-dried 25 mL round-bottom flask was cooled in a dry ice-$CHCl_3$ bath to -45 ºC. A solution of freshly distilled SO_2Cl_2 (1 equiv) in $CHCl_3$ (1 M) was added dropwise via microsyringe over 10 min. The resulting solution was stirred for 10 min, then allowed to warm to rt. The desired product was obtained by concentrating the solution on a rotary evaporator and briefly exposing the residual oil to a vacuum line (0.1–0.25 torr, 1–2 min) to remove last traces of solvent. The product carbonimidic dichlorides were characterized without further purification.

^{1}H NMR, ^{13}C NMR, IR, and MS for Dichloride Products

*Cyclohexylcarbonimidic Dichloride **222a***: ^{1}H NMR δ 3.52–3.58 (m, 1 H), 1.22–1.88 (m, 10 H); ^{13}C NMR δ 121.7, 63.9, 32.2, 25.4, 24.2; IR (cm^{-1}) 1644; CIMS *m/z* 180 (MH^+), 182 (MH^++2), 184 (MH^++4).

*n-Butylcarbonimidic Dichloride **222b***: ^{1}H NMR δ 3.49 (t, 2 H, *J* = 6.9 Hz), 1.59–1.65 (m, 2 H), 1.36–1.40 (m, 2 H), 0.94 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 123.4, 54.6, 31.3, 20.3, 13.6; IR (cm^{-1}) 1654; CIMS *m/z* 154 (MH^+), 156 (MH^++2), 158 (MH^++4).

tert-Butylcarbonimidic Dichloride ***222c***: ^{1}H NMR δ 1.39 (s, 9 H); ^{13}C NMR δ 116.4, 59.9, 28.5; IR (cm^{-1}) 1648; EIMS *m/z* 153 (M^{+}), 155 (M^{+}+2), 157 (M^{+}+4); 138, 140, 142 (loss of CH_3); 57 (base peak).

(2-Methylphenyl)carbonimidic Dichloride ***222d***: ^{1}H NMR δ 7.25–7.17 (m, 3 H), 7.13 (td, 1 H, *J* = 7.5, 1.4 Hz), 6.82 (dd, 1 H, *J* = 7.8, 1.3 Hz), 2.17 (s, 3H); ^{13}C NMR δ 144.5, 130.6, 128.4, 126.4, 125.9, 118.9, 17.6; IR (cm^{-1}) 1647; CIMS (electron impact, *m/z*): 188 (MH^{+}), 190 (MH^{+}+2), 192 (MH^{+}+4).

{[(4-Methylphenyl)sulfonyl]methyl}carbonimidic Dichloride ***222e***: ^{1}H NMR δ 7.83 (d, 1 H, *J* = 8.3 Hz), 7.39 (d, 1 H, *J* = 8.0 Hz), 4.79 (s, 2 H), 2.47 (s, 3 H); ^{13}C NMR δ 145.7, 134.0, 129.9, 129.0, 128.8, 73.9, 21.7; IR (cm^{-1}) 1650; CIMS *m/z* 266 (MH^{+}), 268 (MH^{+}+2), 270 (MH^{+}+4).

Ethyl[(dichloromethylidene)amino]acetate ***222f***: ^{1}H NMR δ 4.29 (s, 2 H), 4.26 (q, 2 H, *J* = 7.2 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 167.3, 129.9, 61.7, 55.6, 44.1, 14.1; IR (cm^{-1}) 1662; CIMS *m/z* 184 (MH^{+}), 186 (MH^{+}+2), 188 (MH^{+}+4).

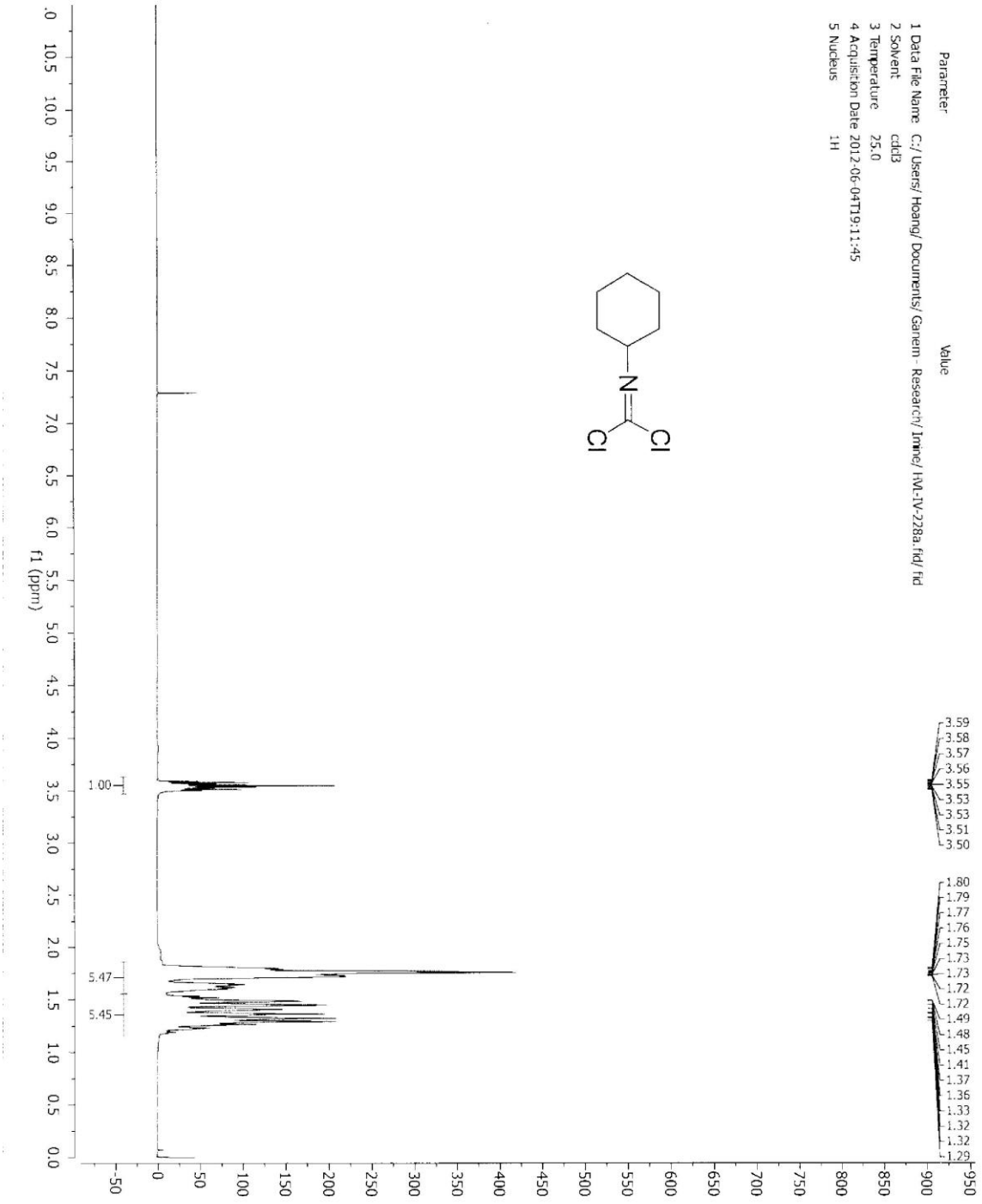


Figure 3.2 ^{1}H NMR Spectrum of Cyclohexylcarbonimidic Dichloride **222a**

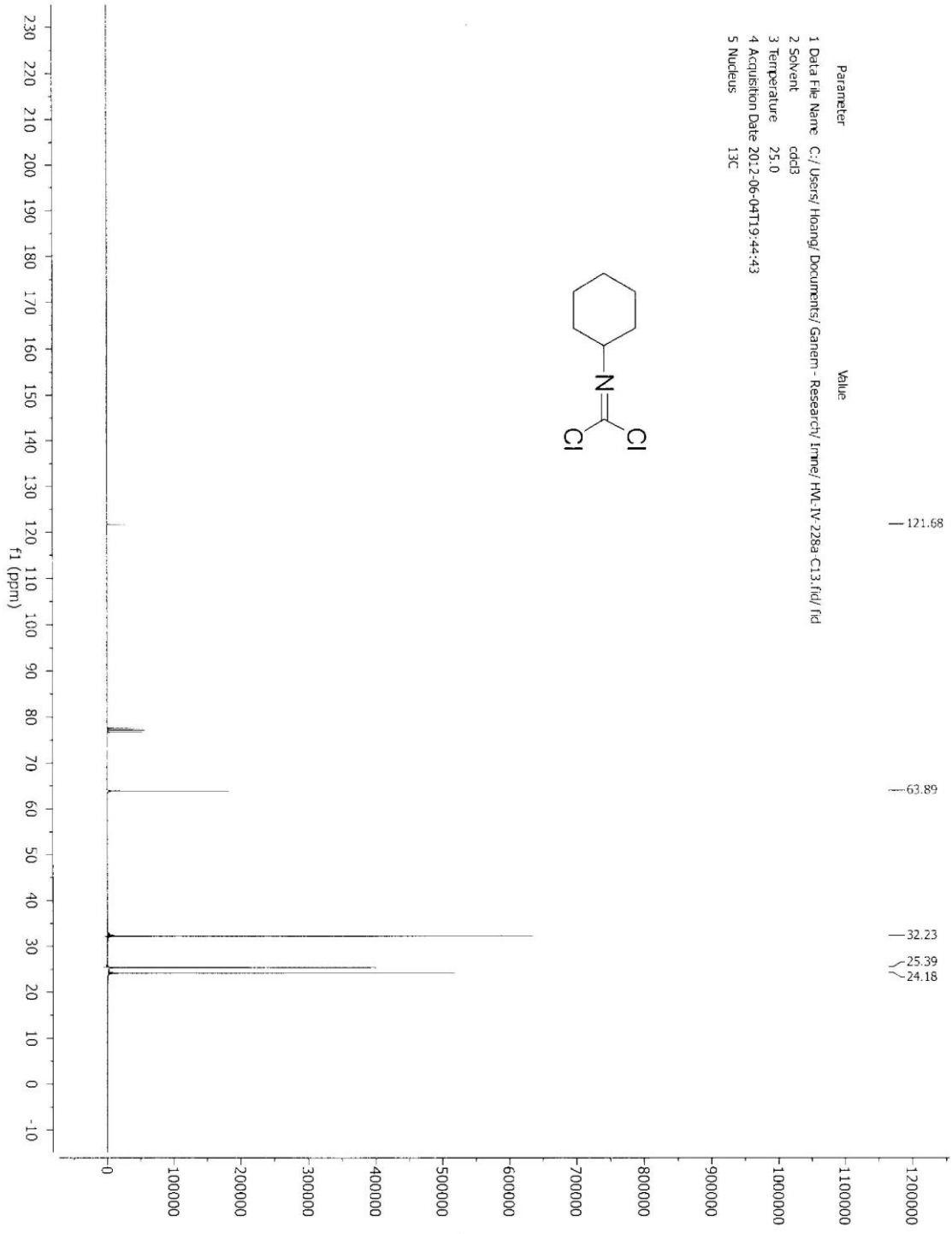


Figure 3.3 ^{13}C NMR Spectrum of Cyclohexylcarbonimidic Dichloride **222a**

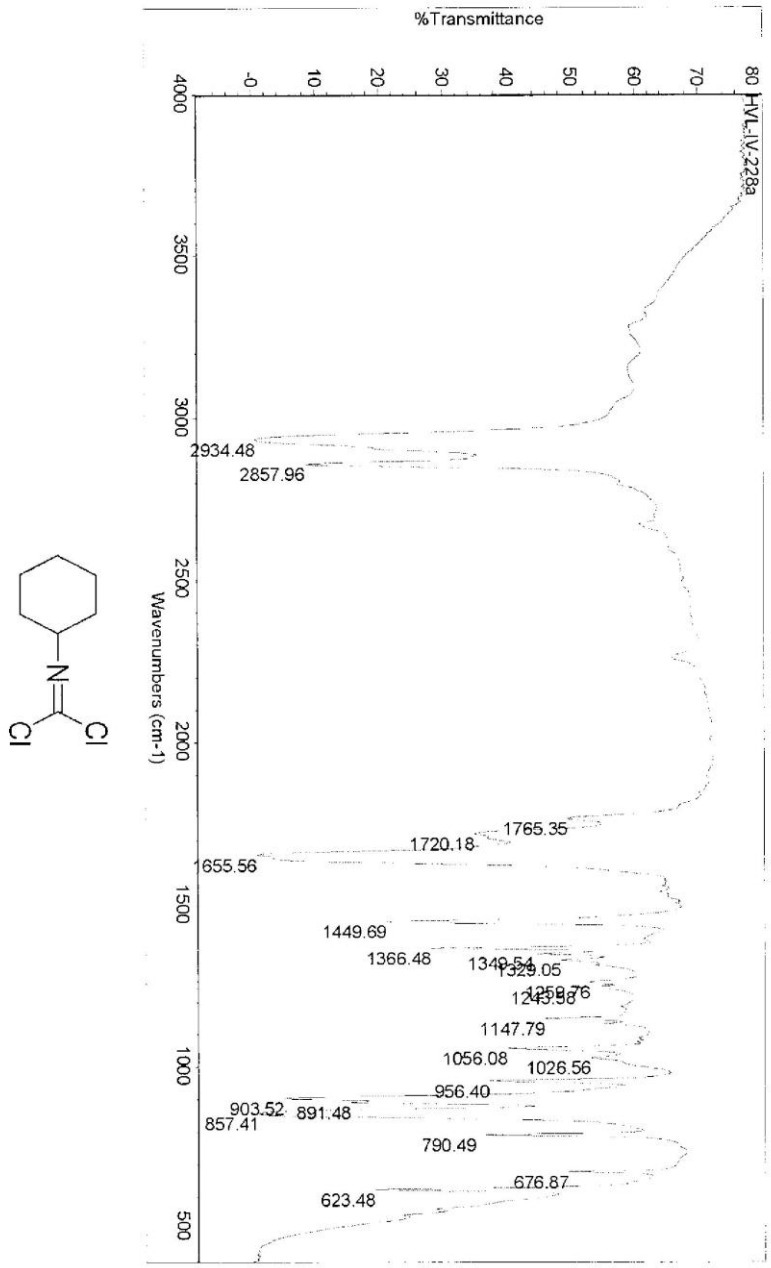


Figure 3.4 IR Spectrum of Cyclohexylcarbonimidic Dichloride **222a**

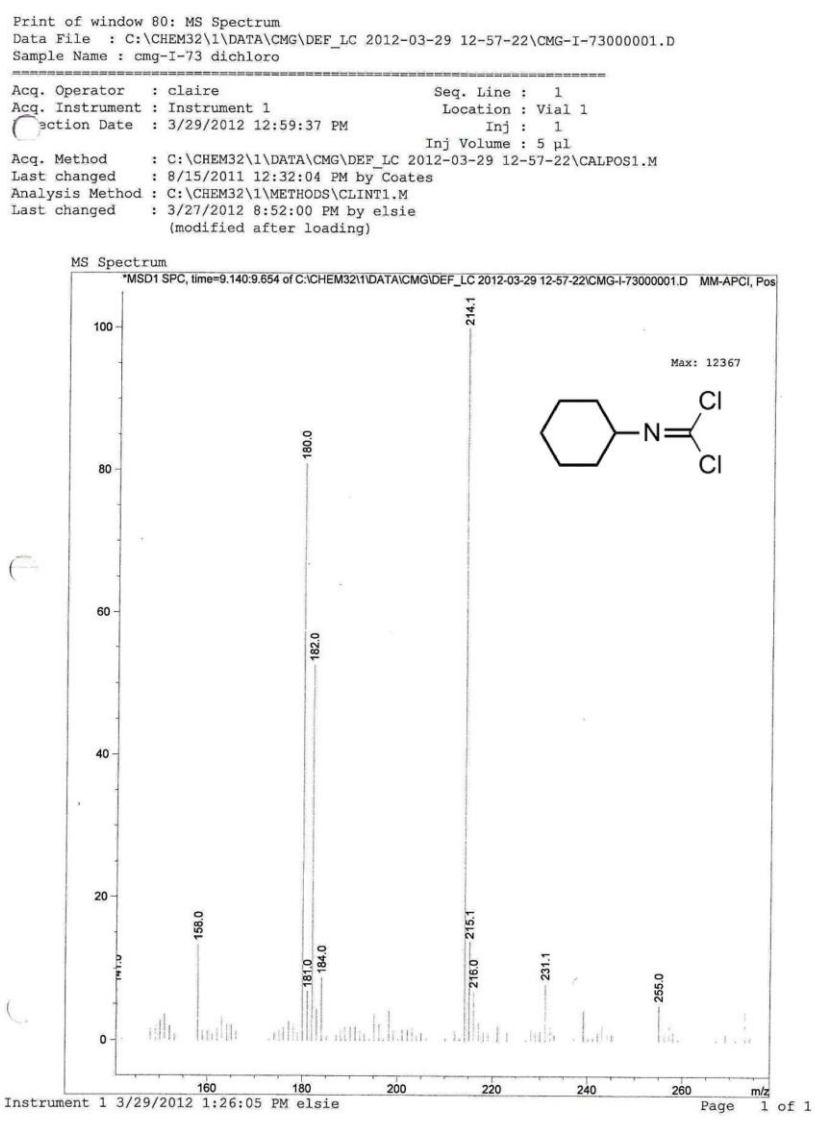


Figure 3.5 Mass Spectrum of Cyclohexylcarbonimidic Dichloride **222a**

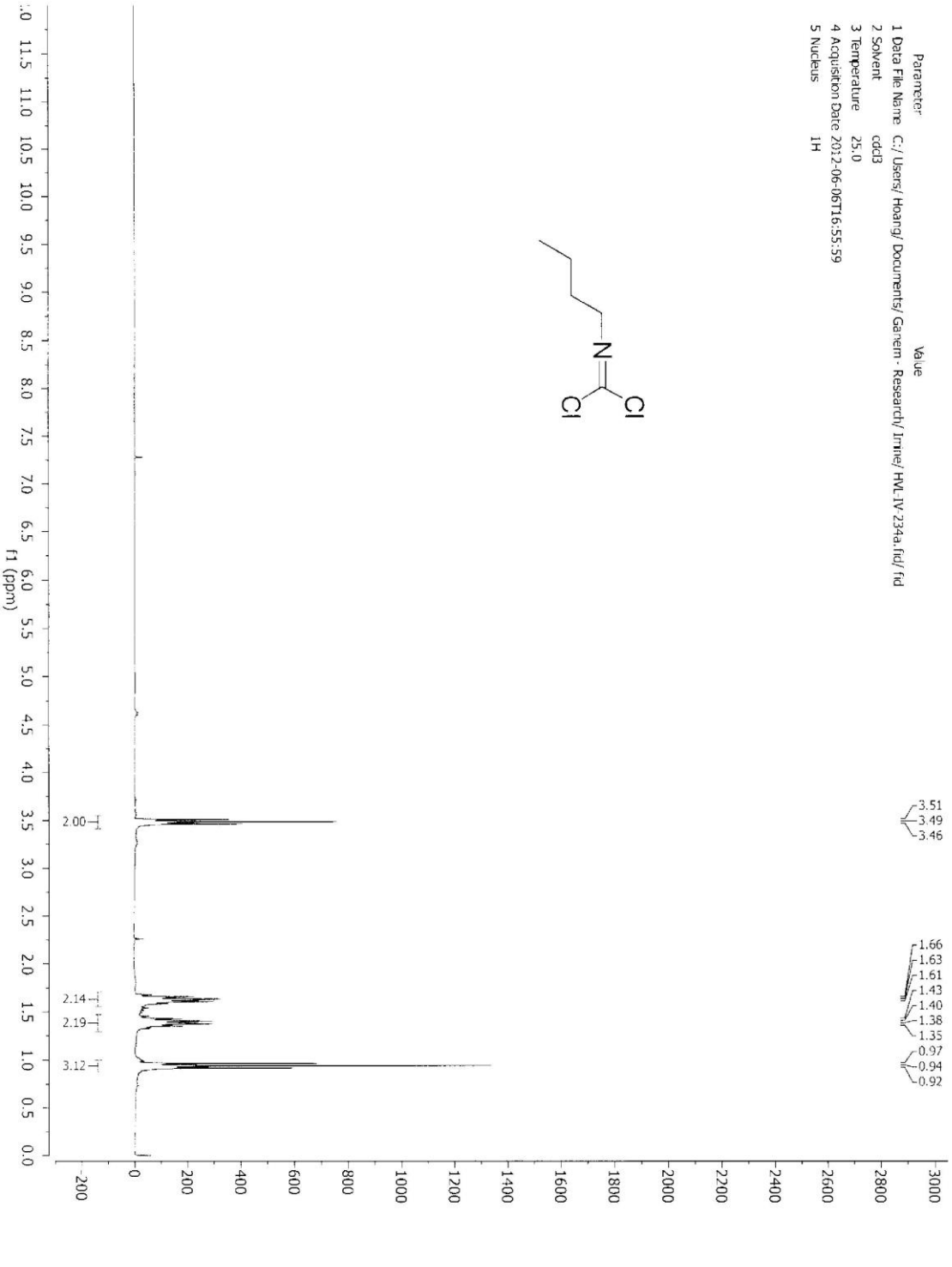


Figure 3.6 ^{1}H NMR Spectrum of *n*-Butylcarbonimidic Dichloride **222b**

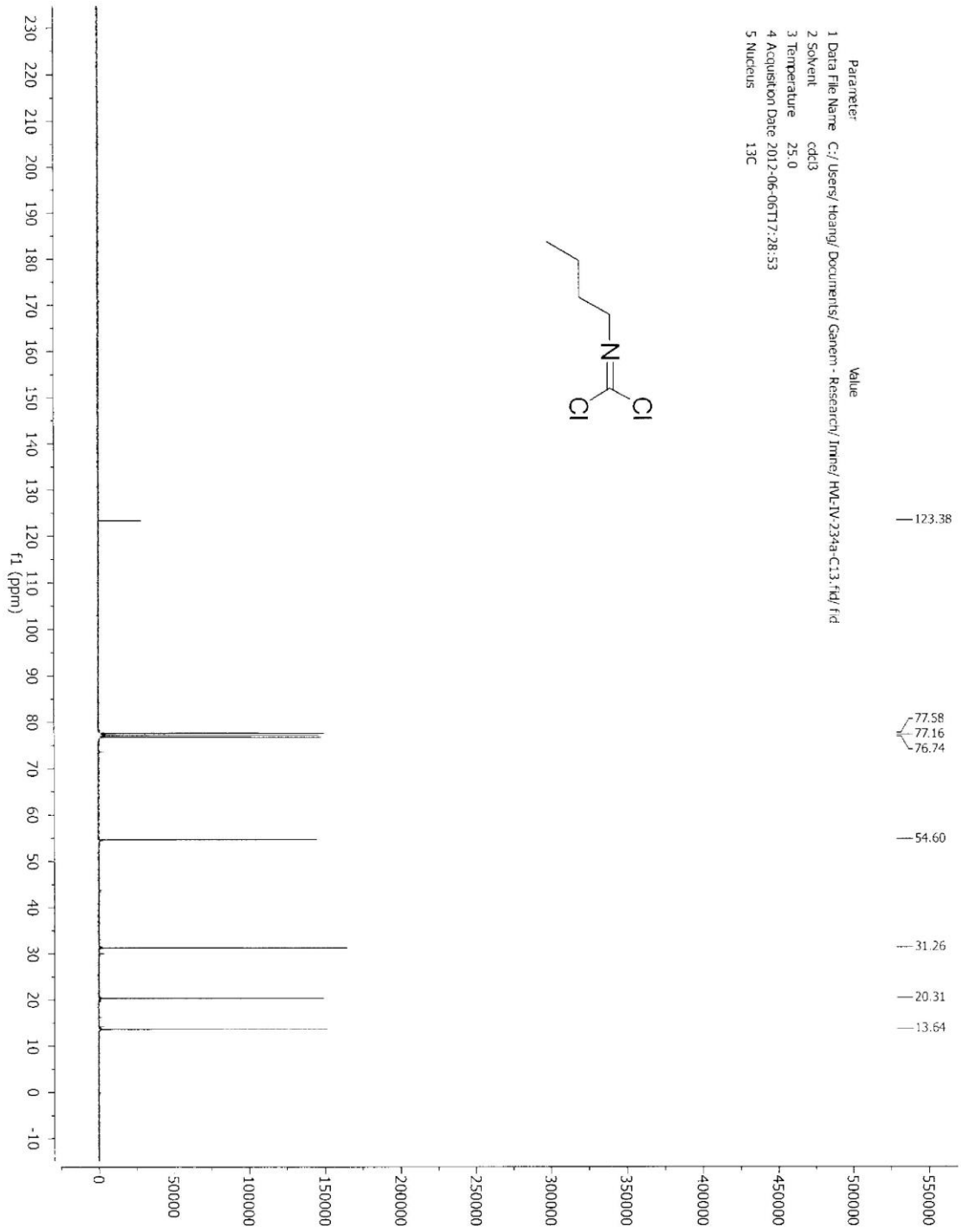


Figure 3.7 ^{13}C NMR Spectrum of *n*-Butylcarbonimidic Dichloride **222b**

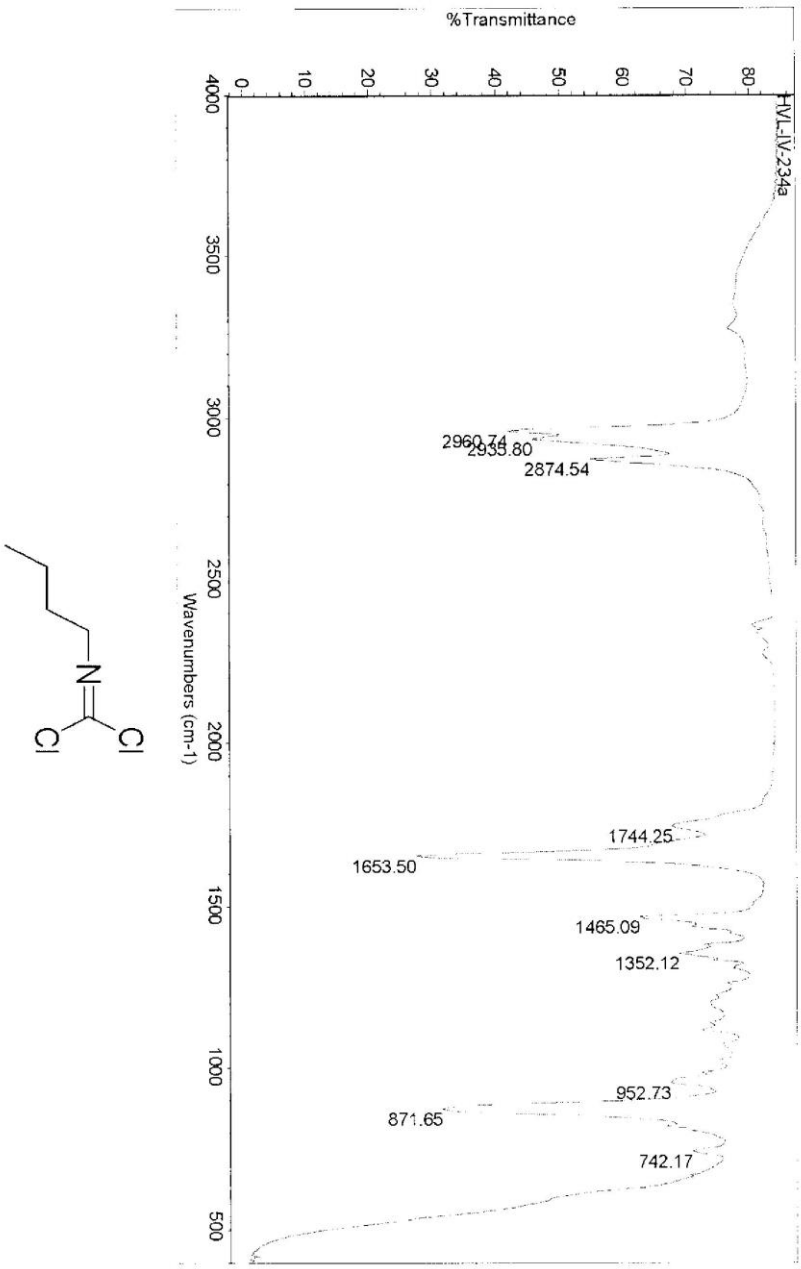


Figure 3.8 IR Spectrum of *n*-Butylcarbonimidic Dichloride **222b**

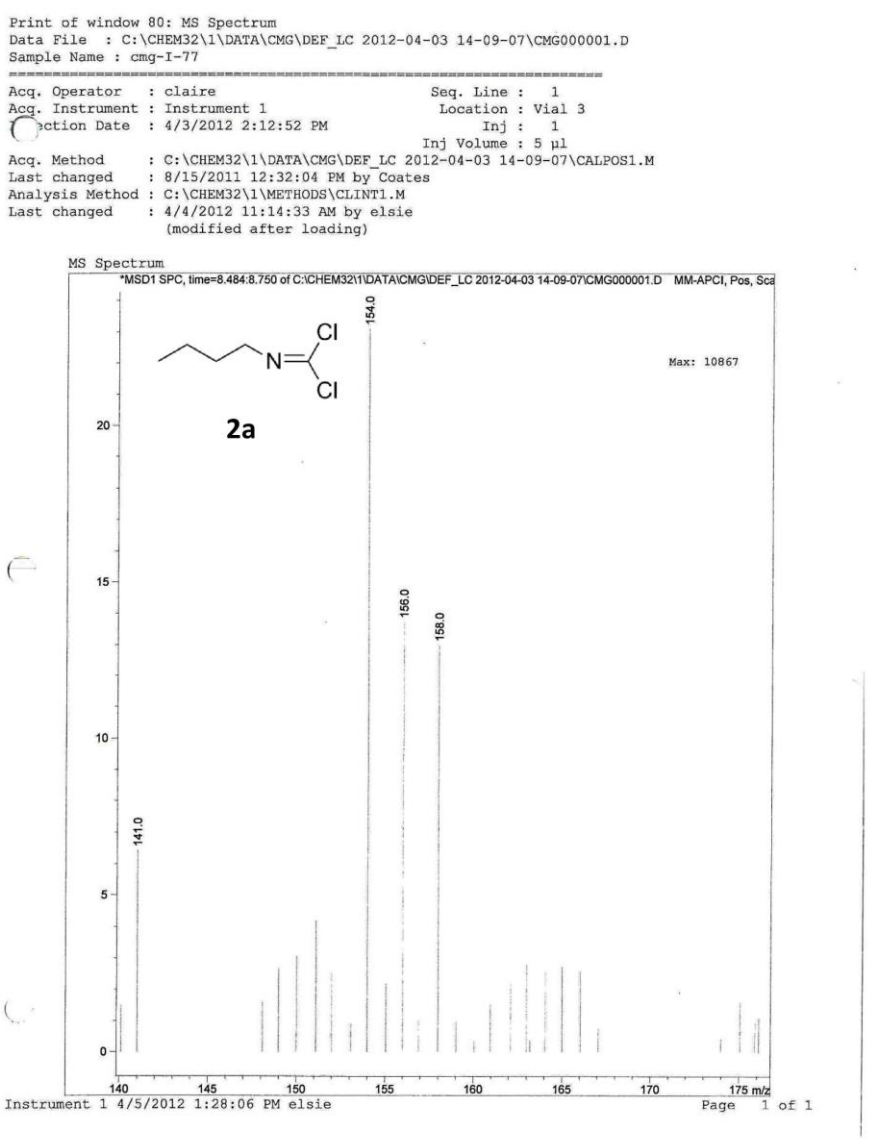


Figure 3.9 Mass Spectrum of *n*-Butylcarbonimidic Dichloride **222b**

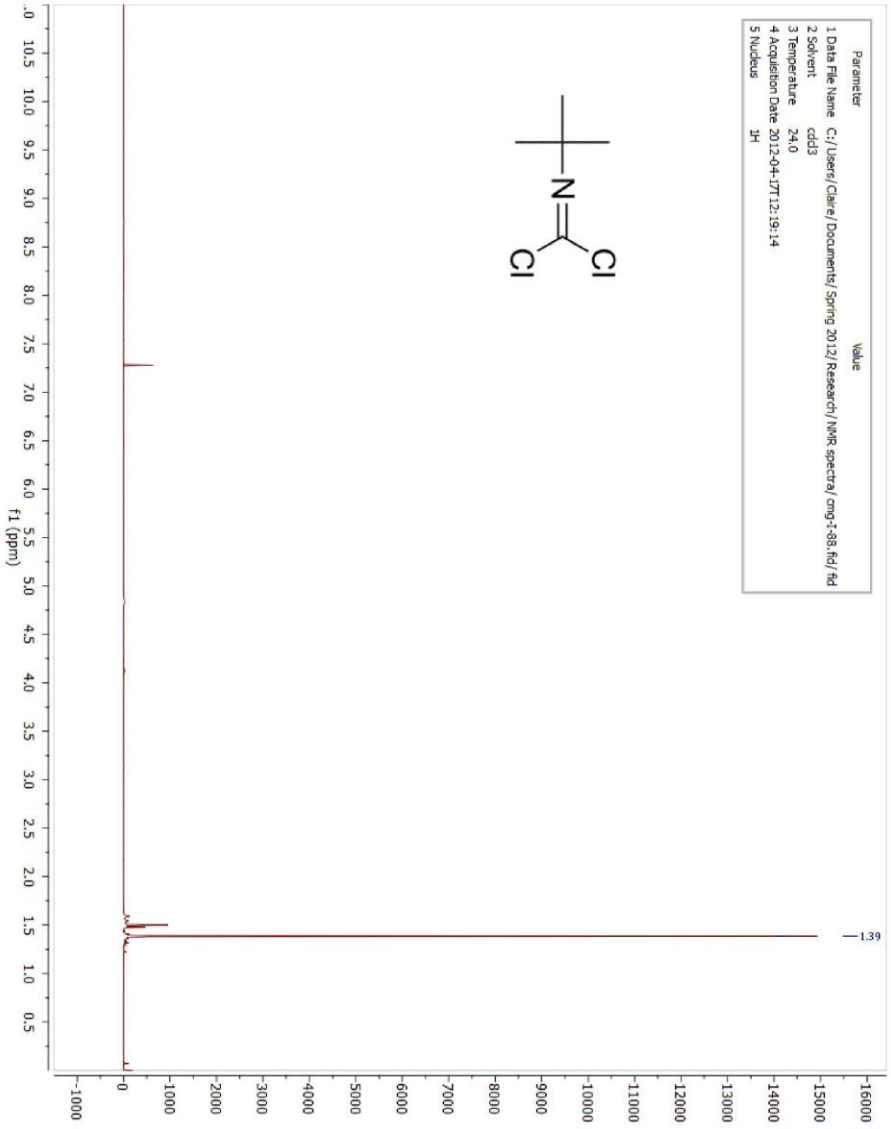


Figure 3.10 ^{1}H NMR Spectrum of *tert*-Butylcarbonimidic Dichloride **222c**

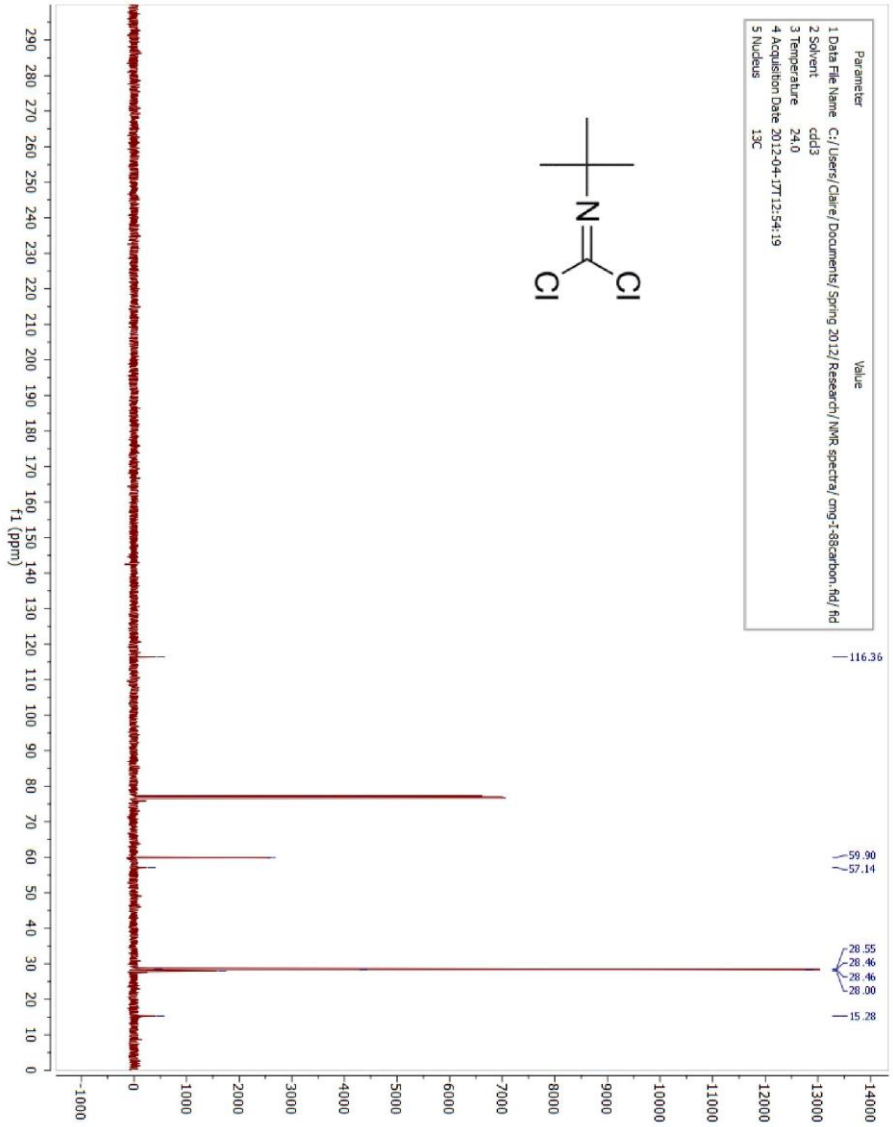


Figure 3.11 ^{13}C NMR Spectrum of *tert*-Butylcarbonimidic Dichloride **222c**

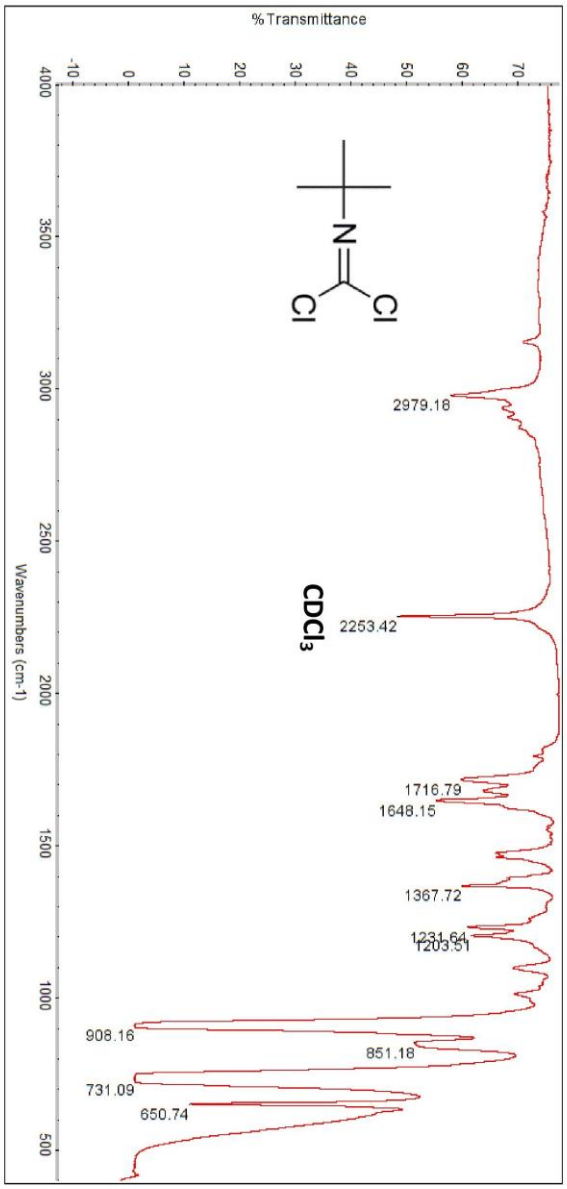


Figure 3.12 IR Spectrum of *tert*-Butylcarbonimidic Dichloride **222c**

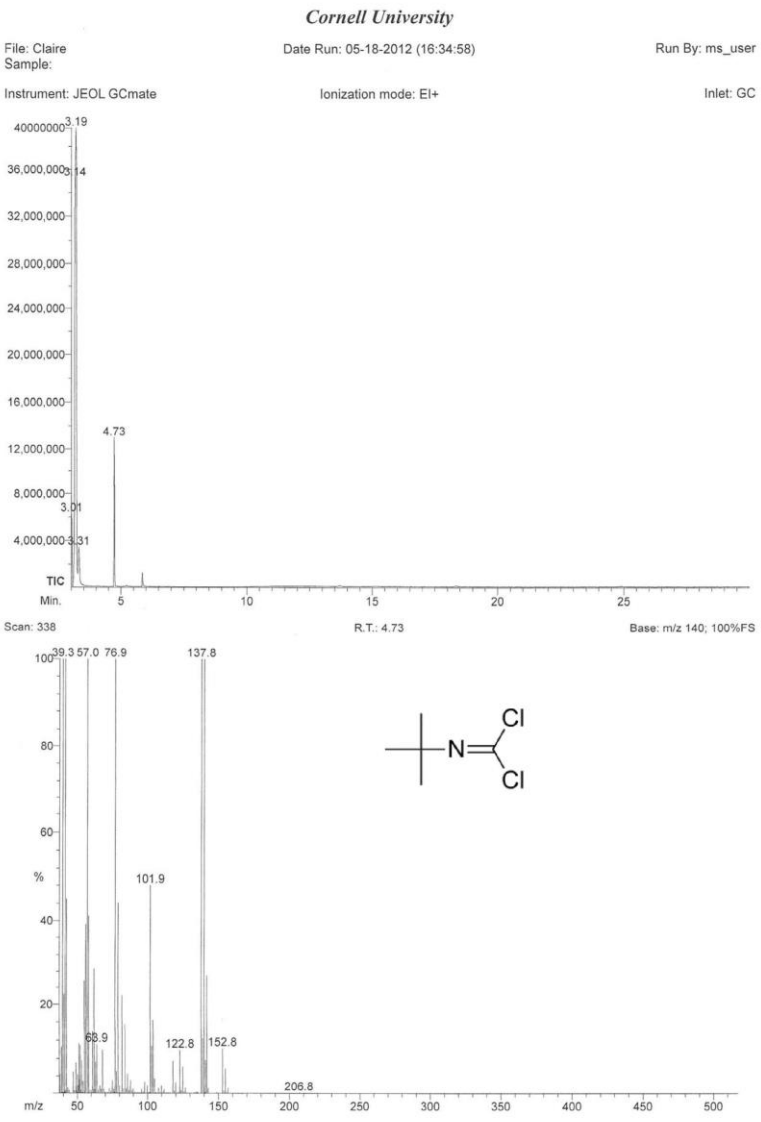


Figure 3.13 Mass Spectrum of *tert*-Butylcarbonimidic Dichloride **222c**

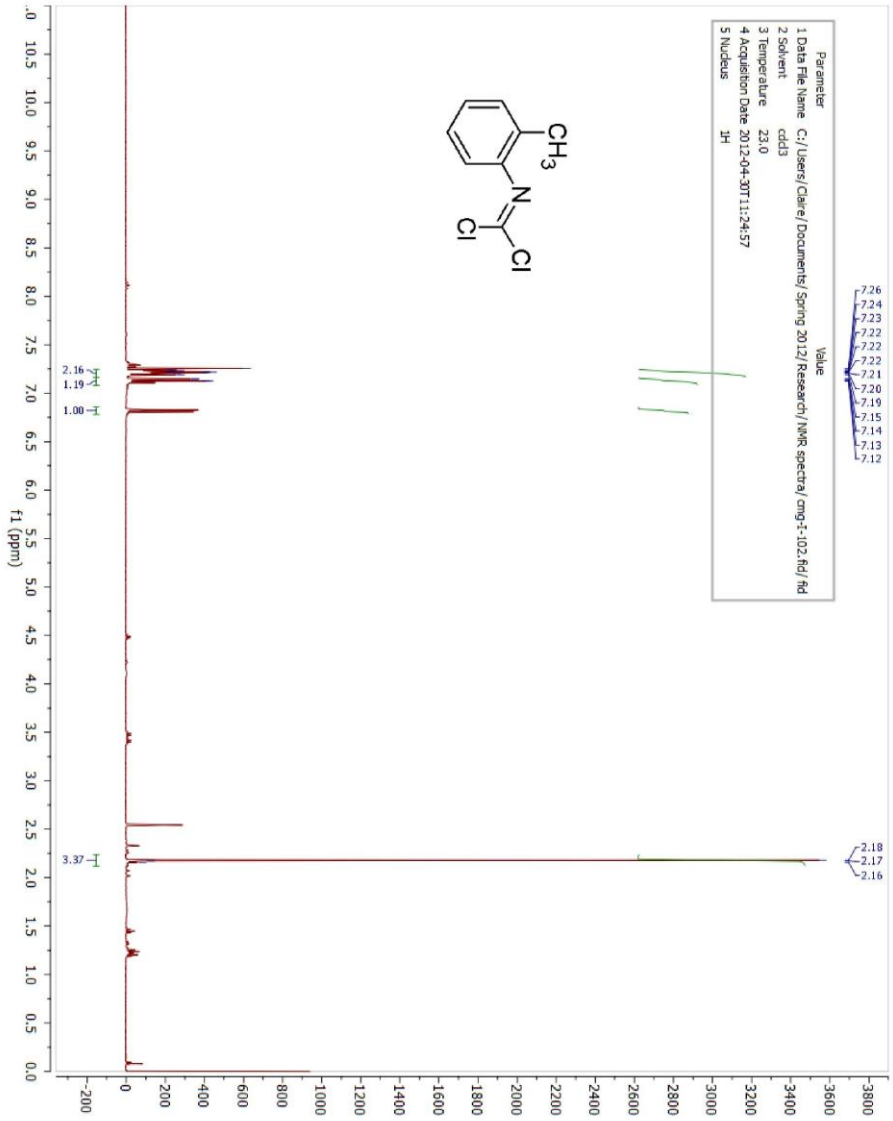


Figure 3.14 [1]H NMR Spectrum of (2-Methylphenyl)carbonimidic Dichloride **222d**

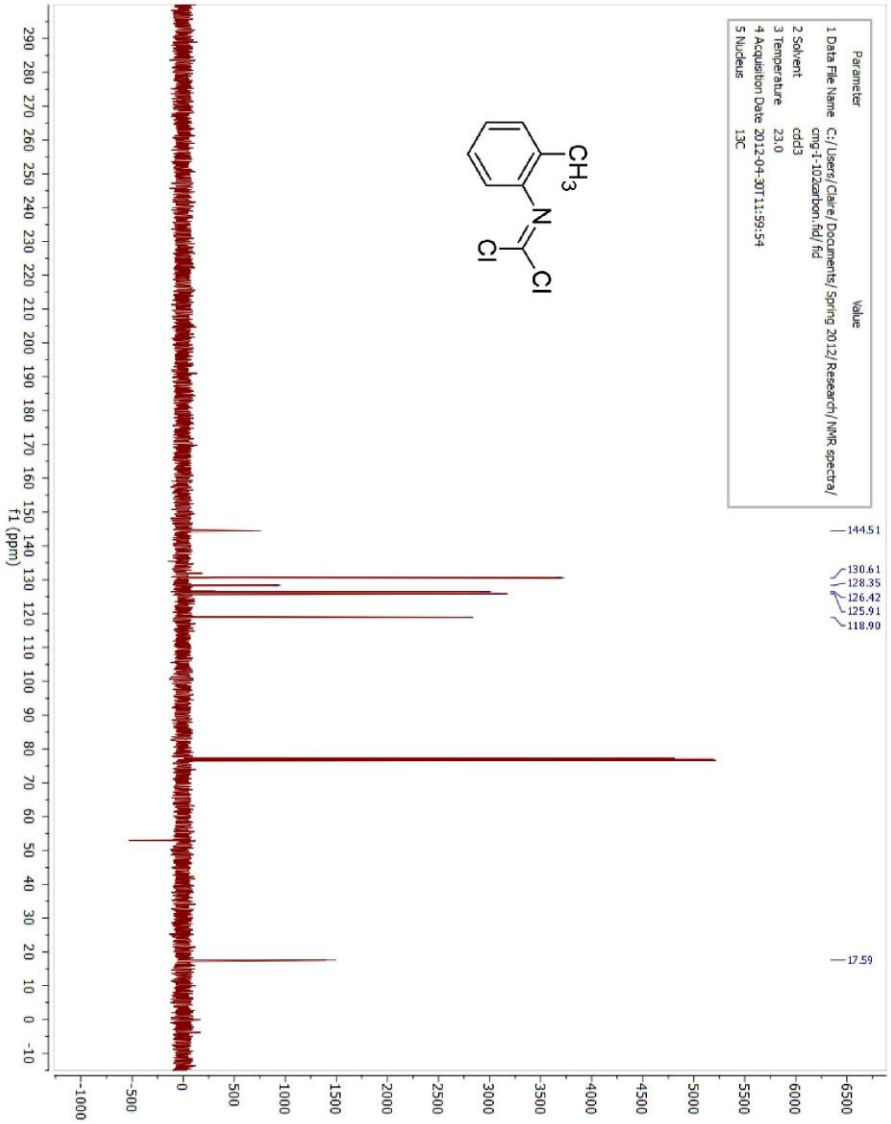


Figure 3.15 ^{13}C NMR Spectrum of (2-Methylphenyl)carbonimidic Dichloride **222d**

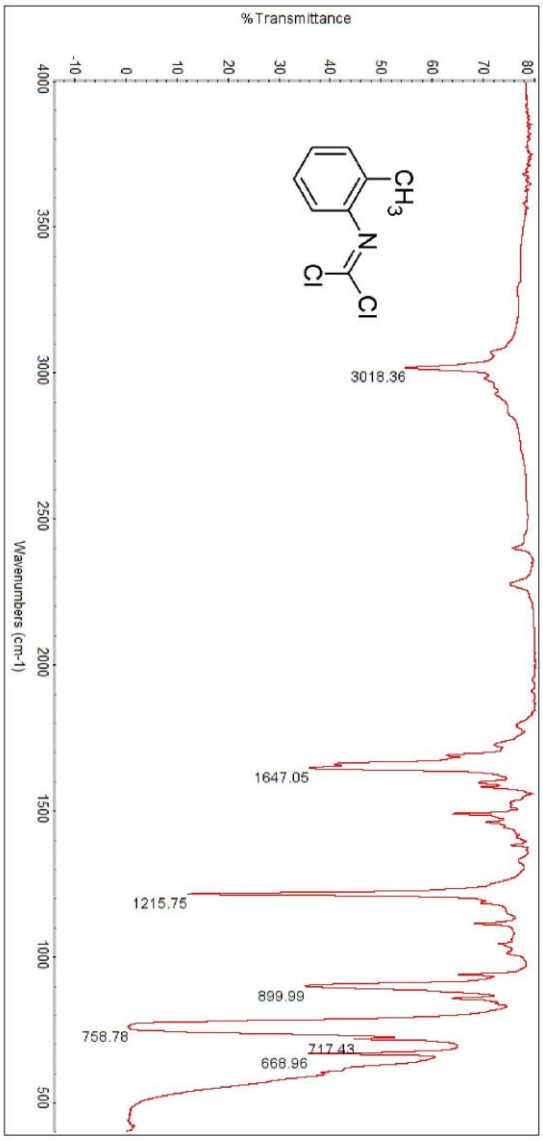


Figure 3.16 IR Spectrum of (2-Methylphenyl)carbonimidic Dichloride **222d**

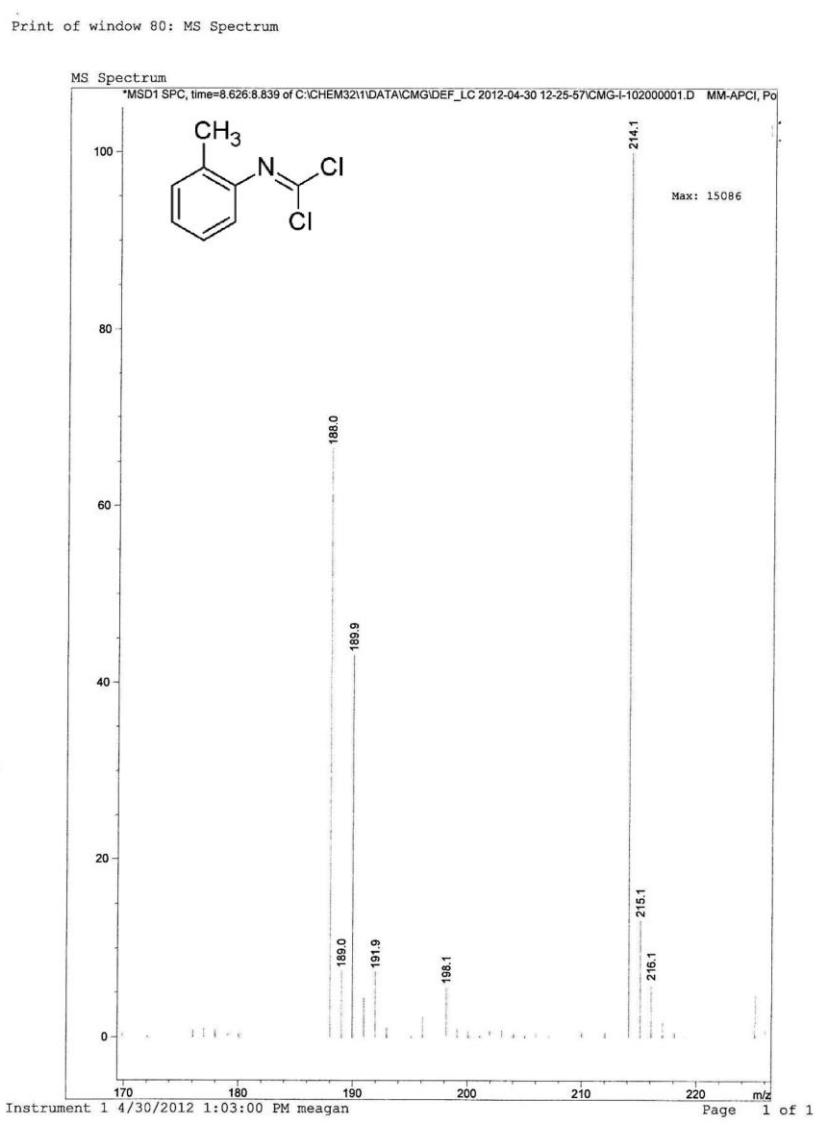


Figure 3.17 Mass Spectrum of (2-Methylphenyl)carbonimidic Dichloride **222d**

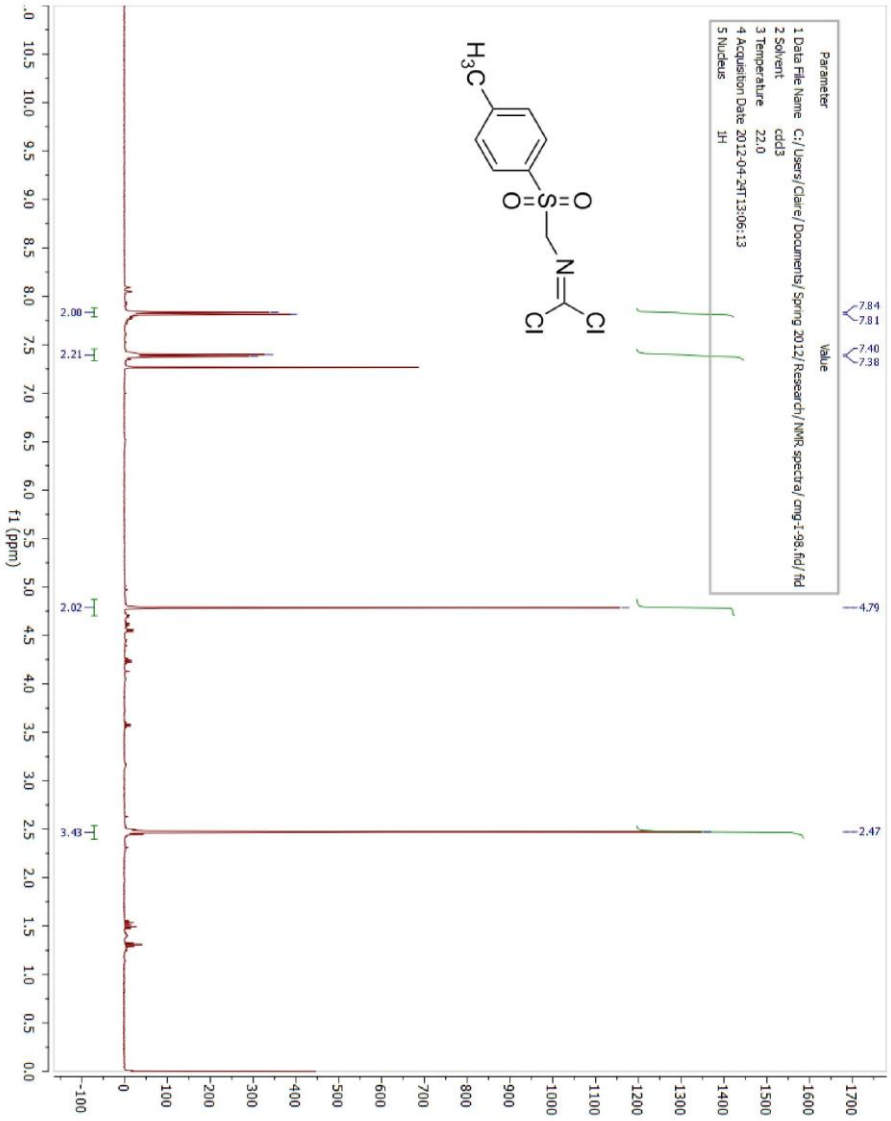


Figure 3.18 ^{1}H NMR Spectrum of {[(4-Methylphenyl)sulfonyl]methyl}carbonimidic Dichloride **222e**

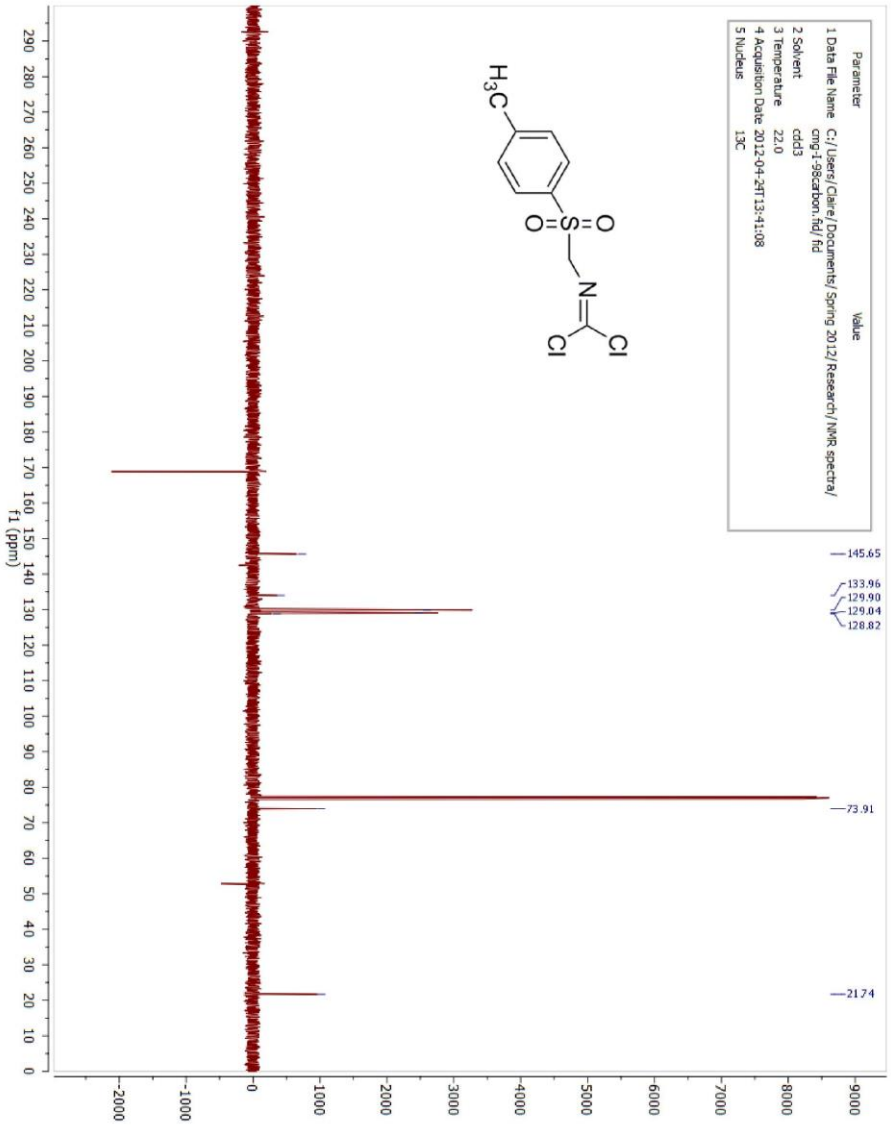


Figure 3.19 ^{13}C NMR Spectrum of {[(4-Methylphenyl)sulfonyl]methyl}carbonimidic Dichloride **222e**

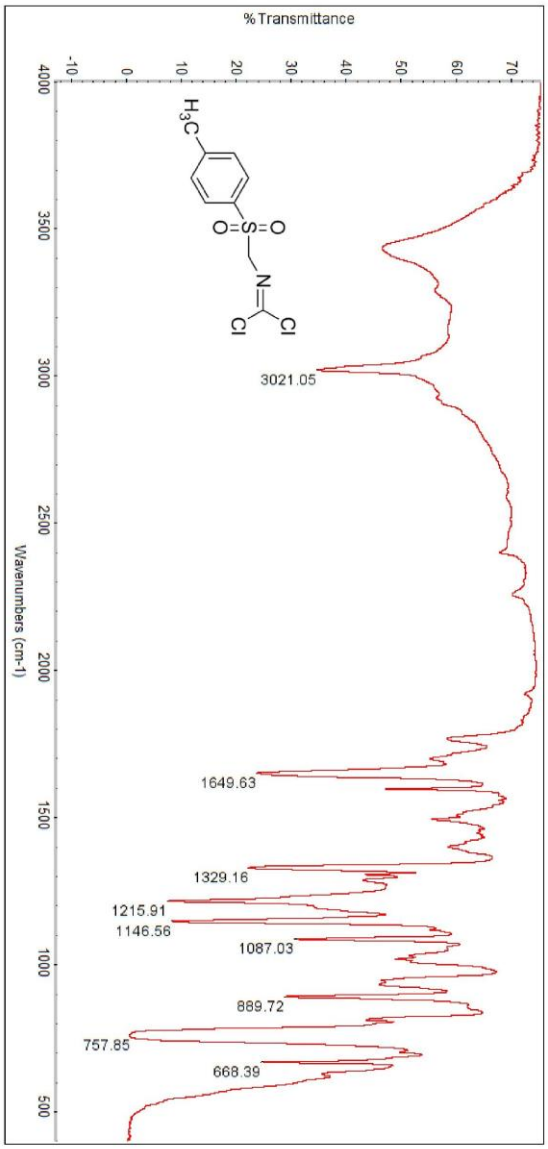


Figure 3.20 IR Spectrum of {[(4-Methylphenyl)sulfonyl]methyl}carbonimidic Dichloride **222e**

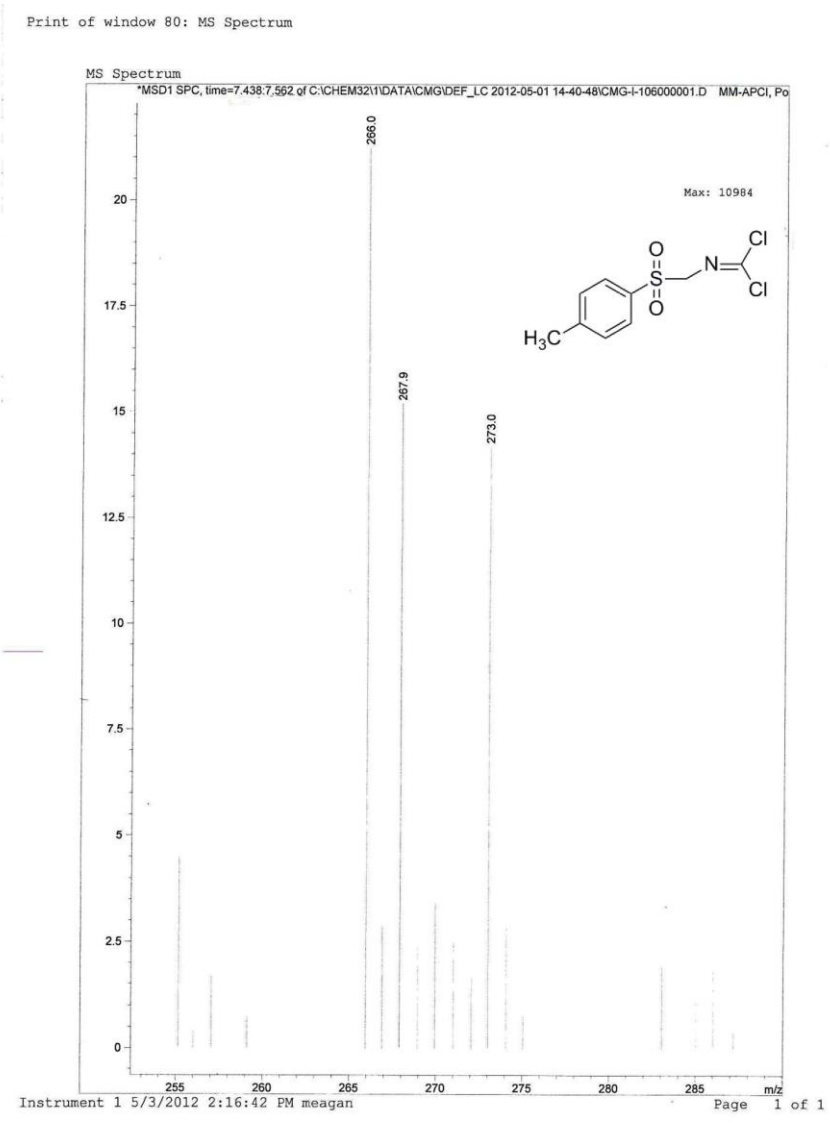


Figure 3.21 Mass Spectrum of {[(4-Methylphenyl)sulfonyl]methyl}carbonimidic Dichloride **222e**

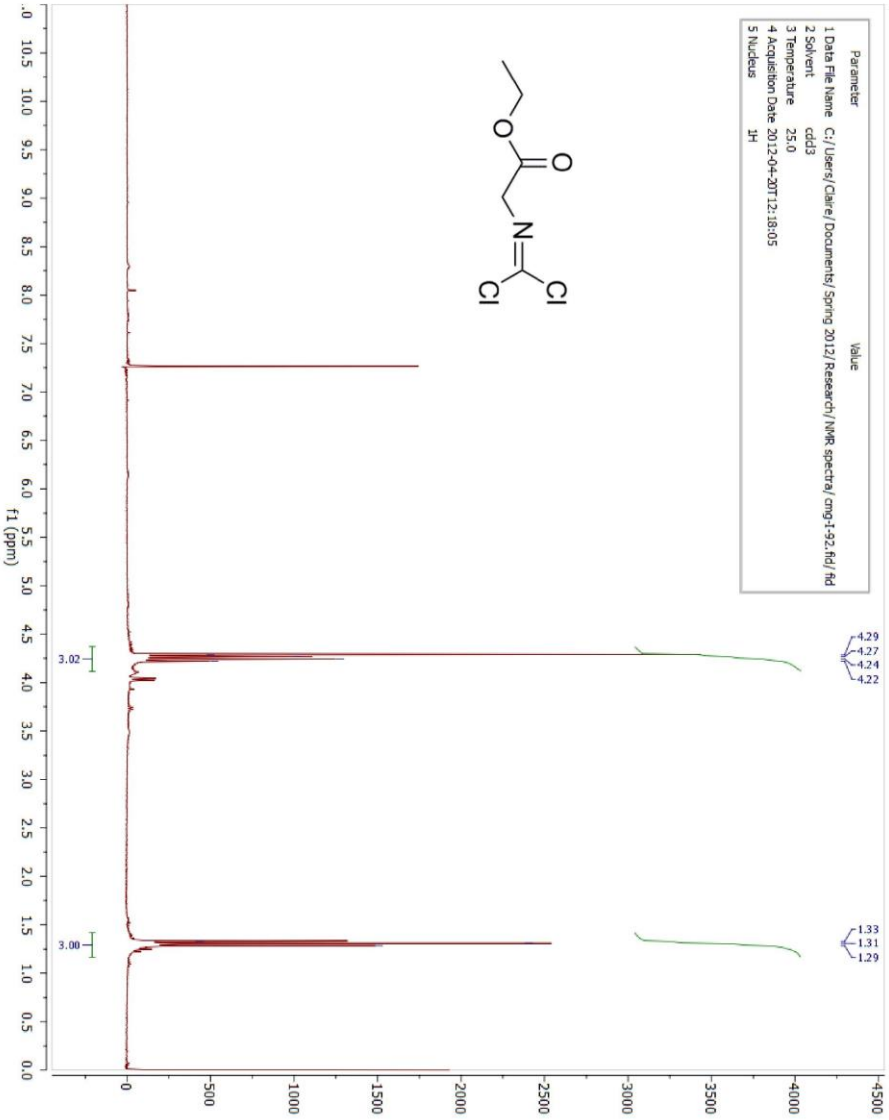


Figure 3.22 ^{1}H NMR Spectrum of Ethyl[(dichloromethylidene)amino]acetate **222f**

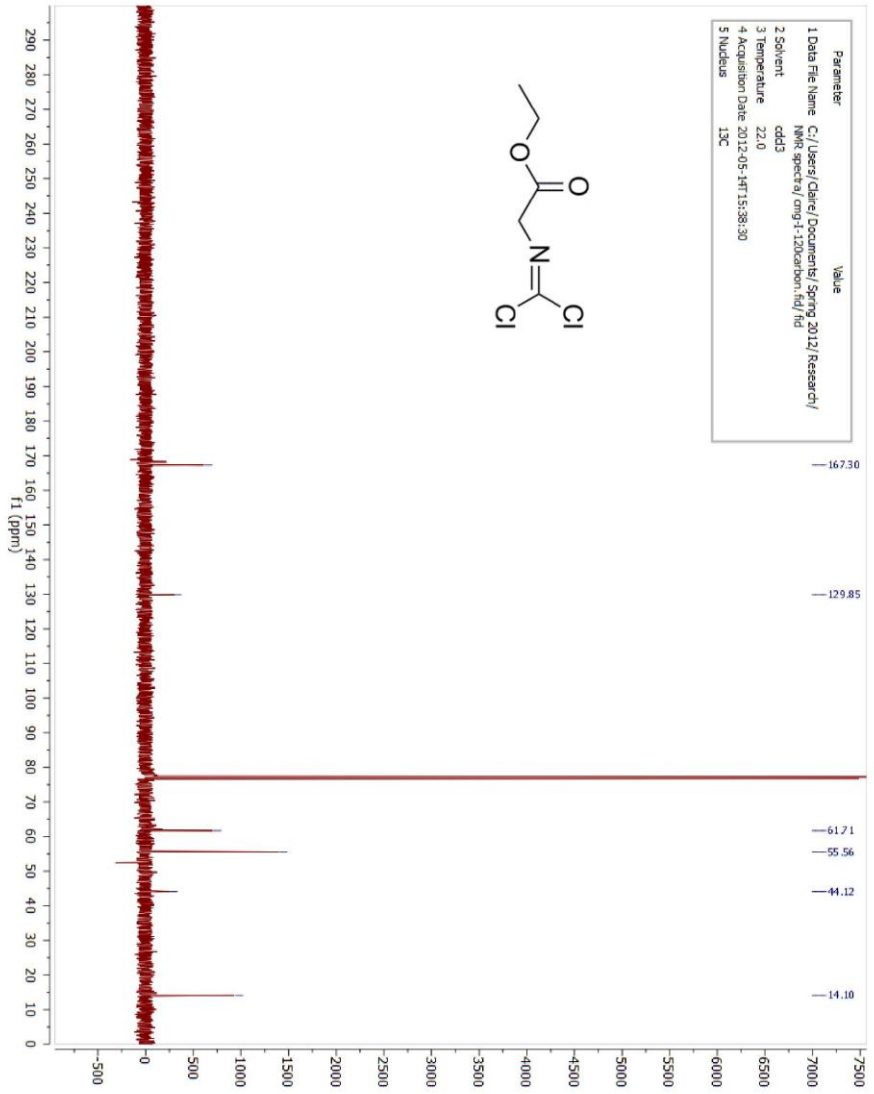


Figure 3.23 ^{13}C NMR Spectrum of Ethyl[(dichloromethylidene)amino]acetate **222f**

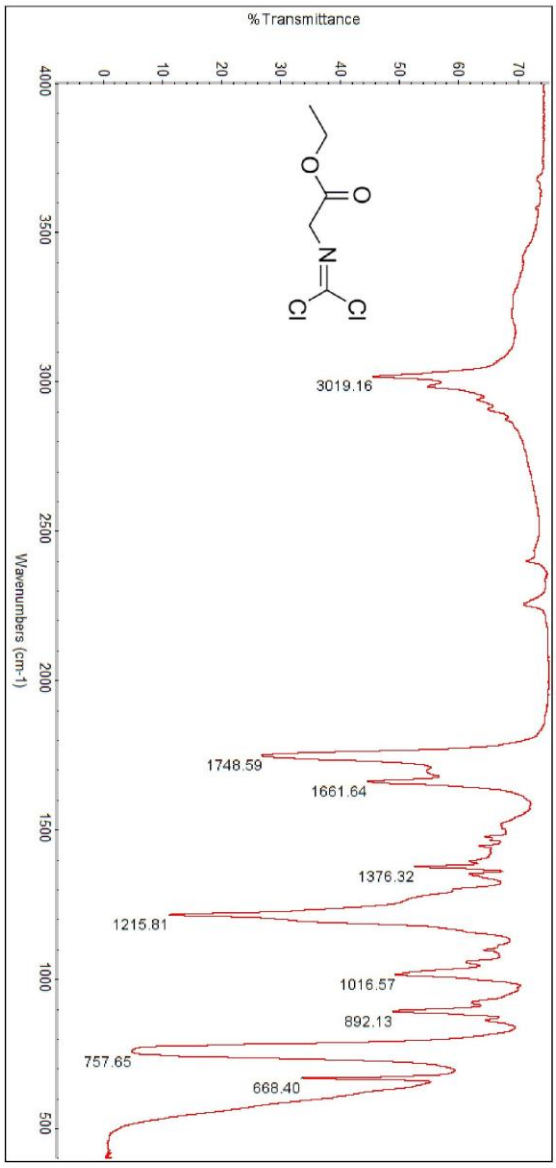


Figure 3.24 IR Spectrum of Ethyl[(dichloromethylidene)amino]acetate **222f**

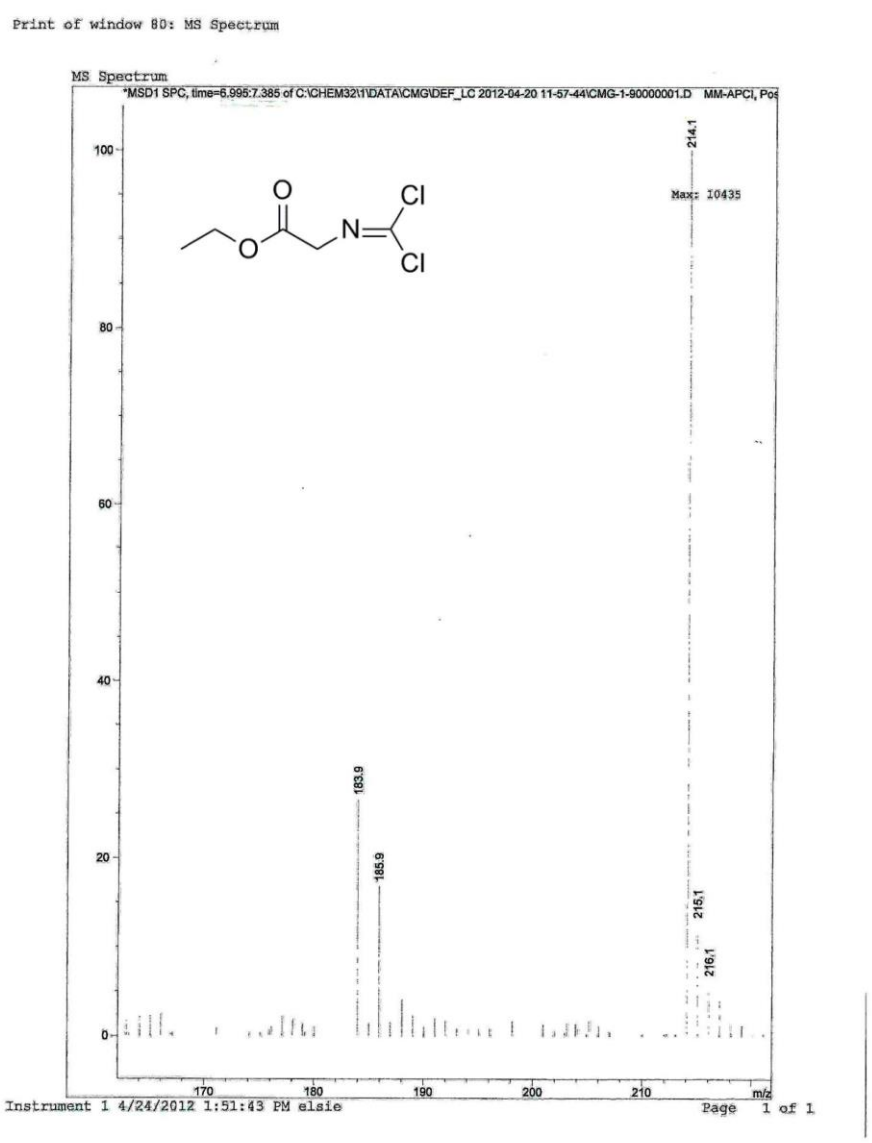


Figure 3.25 Mass Spectrum of Ethyl[(dichloromethylidene)amino]acetate **222f**

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CHAPTER 4

Studies on the Synthesis of Amidoximes from Nitroalkanes

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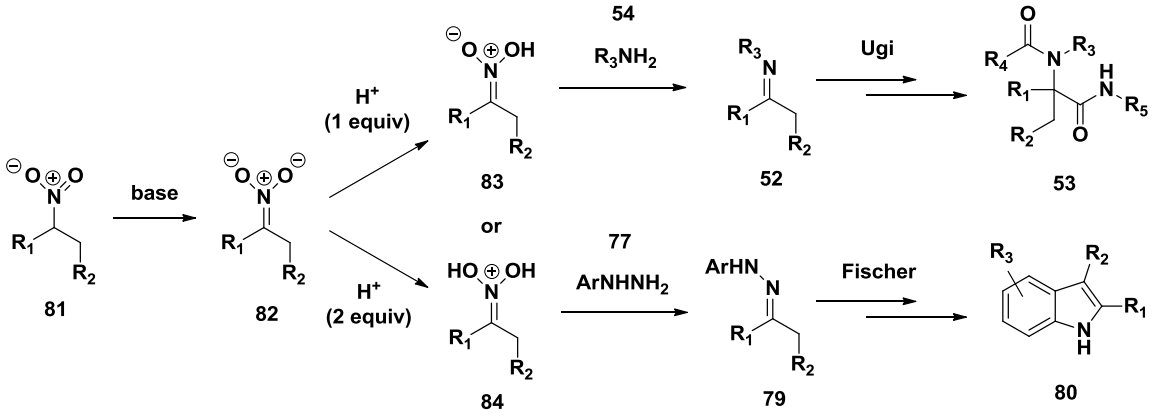
Tetrahedron **2011**, *67*, 10208–10211

4.1 Background

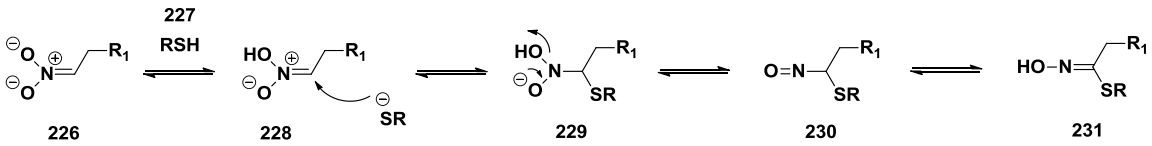
The single reactant replacement (SRR) approach to evolving new MCRs relies on identifying reactants that possess similar reactivity elements. The central role of the synthetic chemist is to recognize or elucidate such reactivity elements, which may sometimes be embodied in unusual reactants. In 2007, Simoneau *et al.* in our group realized that the intermediates in the Nef reaction of nitroalkanes, as shown in Scheme 1.13, may behave similarly to imines because they embody the C=N group.[1] If so, such inputs might be useful in the Ugi reaction or Fisher indole synthesis (Scheme 4.1). The derived nitronate anion **82** from nitroalkane **81** might be transformed to the monoprotonated aci-nitro species **83** or to the di-protonated iminium species **84**. Subsequent amine addition or hydrazine addition, followed by N/N interchange, could produce imine **52** or arylhydrazone **79**, respectively.



Scheme 4.1[1]

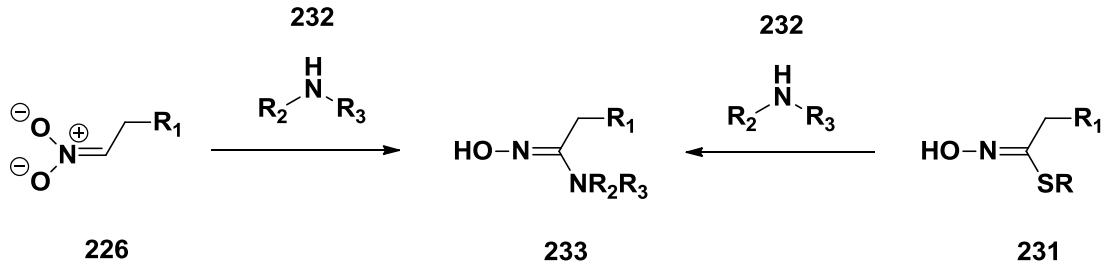
Simoneau then went on to develop a new synthesis of substituted indoles from nitroalkanes and arylhydrazines in the presence of base, as described in Chapter 1.[2] This

indole synthesis was inspired by two early patents reporting successful nucleophilic additions of thiols **227** to nitronates **226** leading to thiohydroximate esters **231** (Scheme 4.12).[3–6] Although no mechanism was proposed in the patents, one likely sequence of transformations is depicted in Scheme 4.2.[7]

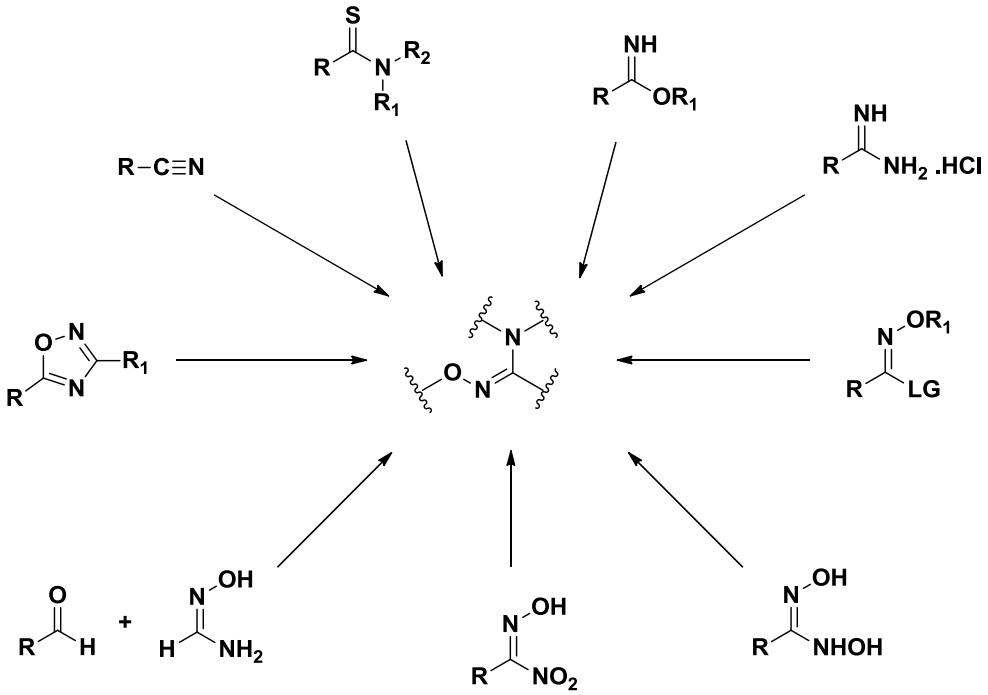


Scheme 4.2[7]

We wondered whether the direct reaction of primary or secondary amines **232** with nitronates **226** or with thiohydroximate esters **231** would afford the corresponding amidoximes **233** (Scheme 4.3). Such amidoximes are of considerable medicinal interest. Besides being involved in the biosynthesis of NO, they display potent pharmacological activity as anticoagulants, platelet inhibitors, antimicrobial agents and matrix metalloprotease inhibitors.[8,9]

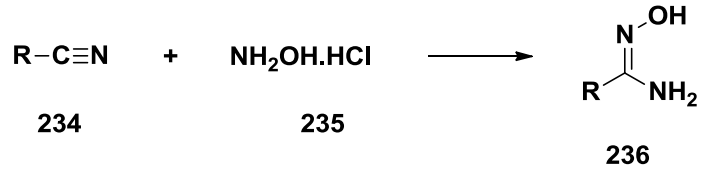


Scheme 4.3



Scheme 4.4[10]

Currently, amidoximes may be prepared by many different routes, as summarized in a recent review by Katritzky *et al.* (Scheme 4.4).[10] Of these routes, the most convenient source of amidoximes is the reaction of the corresponding nitriles **234** with hydroxyamine **235** (Scheme 4.5).[11–13] A successful synthesis of amidoximes from nitroalkanes would add a useful new route to the preparation of amidoximes.

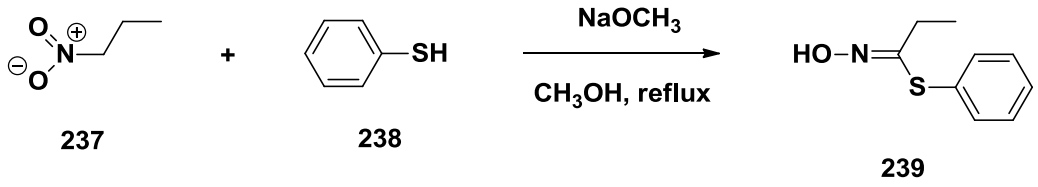


Scheme 4.5

4.2 Results and Discussion

Using 1-nitropropane as a prototype, we first explored the direct reaction of 1-nitropropane with nucleophilic amines. After numerous attempts, however, we were unable to identify conditions under which a primary or secondary amine (*n*-butylamine, aniline, pyrrolidine) would react with 1-nitropropane either neat or in a protic (methanol) or aprotic (DMSO) solvent, even at elevated temperatures, to form detectable quantities of the corresponding amidoxime.

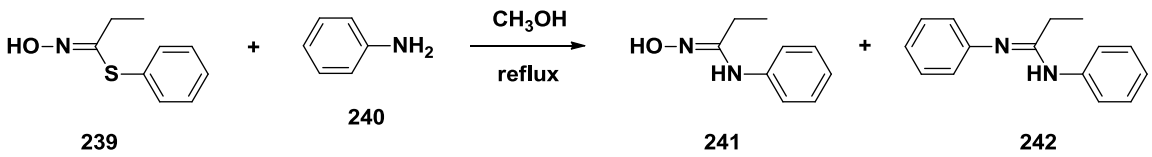
We then turned our attention to the indirect route to amidoximes from the corresponding amines and thiohydroximate esters. We successfully prepared the thiohydroximate ester **239** using 1-nitropropane **237** and thiophenol **238** according to published conditions ($NaOCH_3$ – CH_3OH, reflux) (Scheme 4.6).[3–6]



237 + **238** → **239**

Scheme 4.6

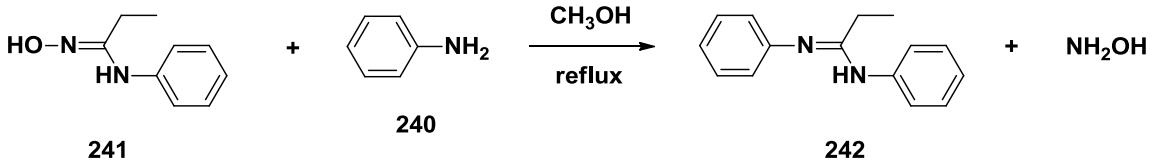
Given that **239** is an oximino analogue of a thioester, we expected it to react smoothly with an amine nucleophile to furnish the corresponding amidoxime **241**. However, the reaction of **239** with aniline **240** (CH_3OH, reflux) was extremely sluggish, and afforded a complex mixture of products (Scheme 4.7). Besides obtaining the hoped-for propionamidoxime **241**, we also identified the corresponding N,N'-diphenylpropion-amidine **242**. Both products were formed in low yield.



239 240 241 242

Scheme 4.7

Control experiments established that the amidine **242** was derived from **241** and **240** (Scheme 4.8). While amidines have been prepared by reductive deoxygenation of amidoximes,[14,15] to our knowledge the transformation of **241** into N,N'-diphenylpropion-amidine **242** appeared to be the first example of an amidoxime-to-amidine transformation by nucleophilic addition of an amine and elimination of NH_2OH.



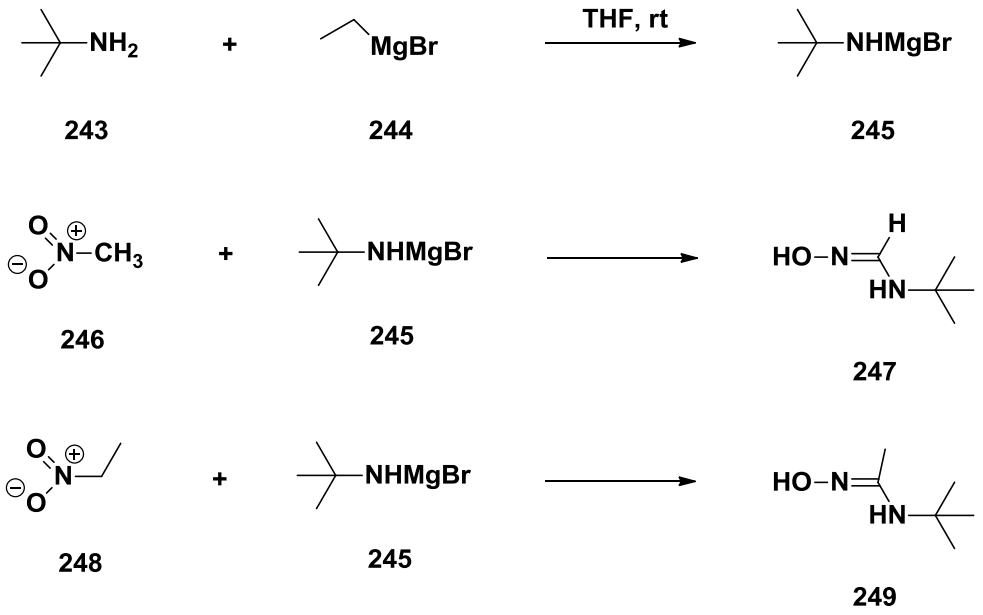
241 240 242

Scheme 4.8

Taken together, the surprisingly low reactivity of thiohydroximates and the unexpected susceptibility of amidoximes to further nucleophilic addition by amines indicated that the thiohydroximate pathway from nitroalkanes would not likely afford a viable route to amidoximes.

We decided to revisit the reaction of nitronates with amines, and considered the possibility of boosting the nucleophilicity of the amine component by metallation. A little-cited 1988 Russian report described the reaction of nitromethane **246** and

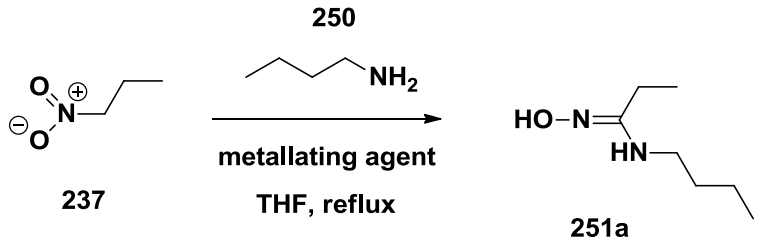
nitroethane **248** with magnesium *tert*-butylamide **245** (2.5 equiv, prepared using EtMgBr **244** and *tert*-butylamine **243** at rt in THF) to afford the corresponding N-*tert*-butyl-formamidoxime **247** and N-*tert*-butylacetamidoxime **249** in 40 and 45% yields, respectively (Scheme 4.9).[16]



Scheme 4.9[16]

In applying the published procedure to various combinations of nitroalkanes and amines, we observed that EtMgCl metallated the amine component only sluggishly at rt. Therefore, to ensure complete metallation, the amines were added to EtMgCl in THF at reflux with continued heating until gas evolution ceased. The nitroalkanes were then added to the fully metallated amines. However, the yields of the resulted amidoximes were still mediocre, ranging from 26% to 46%.

To ascertain whether the yield of amidoxime could be improved using different metallated amines, we studied the reaction of 1-nitropropane **237** and *n*-butylamine using various metallating agents (Scheme 4.10). The results are shown in Table 4.1.



Scheme 4.10

Table 4.1 Yields of *N*-(*n*-Butyl)propionamidoxime **251a** from 1-Nitropropane Using Various Metallating Agents

Base	**% Yield**
EtMgCl	28
EtMgCl / cat. CuCl	27
n-BuLi	58
NaH	27

As indicated in Table 4.1, magnesiated amides or deprotonated amines only produced mediocre yields of *N*-(*n*-Butyl)propionamidoxime **251a**. The most promising result was obtained in this pilot study using lithium amides. We therefore undertook a side-by-side comparison of magnesiated (Method A) versus lithiated (Method B) amides

in the synthesis of amidoximes derived from various primary and secondary amines. Those data are summarized in Table 4.2.

Table 4.2 Effect of Metallating Agent on the Synthesis of *N*-Alkylpropionamidoximes

Amine	**Yield w/ EtMgCl (%)**	**Yield w/ n-BuLi (%)**
	Method A	**Method B**
n-Butylamine	28	59
Cyclohexylamine	32	47
tert-Butylamine	32	19
Pyrrolidine	46	26

The amines in Table 4.2 were chosen to test the steric factors in different primary and secondary amines on the reactivity of the corresponding metallated amines. While the steric factors did not seem to affect the yields of the *N*-alkylpropionamidoximes when magnesiated amides were used, they significantly reduced the yields of the *N*-alkyl-propionamidoximes when lithiated amides were used. The yields of amidoximes from *tert*-butylamine or pyrrolidine are half of those from *n*-butylamine or cyclohexylamine when *n*-butyllithium was the reagent. These results are perhaps not surprising because lithiated agents have more nucleophilic characteristic than magnesiated agents; thus, steric factors have more effects on lithiated agents.

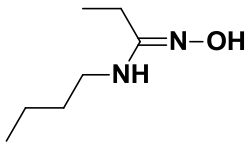
When comparing between the two methods for each entry in Table 4.2, the data suggested that *n*-butyllithium was the preferred reagent for preparing *N*-(primary alkyl)

or *N*-(secondary alkyl) amidoximes. In the cases when *n*-butyllithium gave low yields of amidoximes, such as those from *tert*-butylamine or pyrrolidine, metallation using Grignard reagents might be an alternative solution.

Having tested the effects of various metallating agents and of the amine structure, the amidoxime synthesis was further applied to several different nitroalkanes in order to expand its scope and generality. In so doing, the use of additional amine components, including unsaturated amines and anilines, was also explored. Figure 4.1 depicts the structures of various new amidoximes that were synthesized from nitromethane, nitroethane and 1-nitropropane. Each structure in the figure also indicates the optimal method of preparation, and the yield obtained.

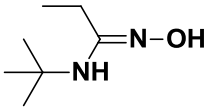
Despite the strongly basic conditions involved, the method successfully afforded amidoximes, although in moderate yields. Attempts to prepare amidoxime **251i** from allylamine were unsuccessful using Method B, probably because of polylithiation, which has been reported to be THF-catalyzed.[17,18] However, by switching to Method A, **251i** could be synthesized in low yield.

The most successful results were obtained using anilines, as indicated by the formation of amidoximes **251f** and **251j**. Besides being notable for its yield (68%), the successful preparation of **251j** establishes that the method tolerates the presence of some reactive (trifluoromethyl, nitrile) functionality in the amine component.



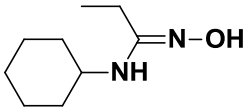
251a

(B, 59%)



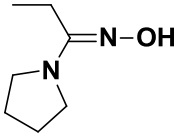
251b

(A, 32%)



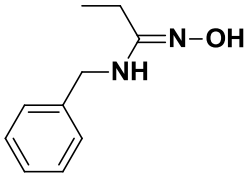
251c

(B, 47%)



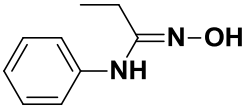
251d

(A, 46%)



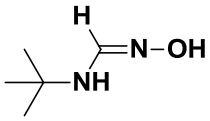
251e

(B, 44%)



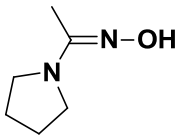
251f

(B, 56%)



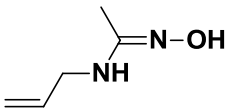
251g

(A, 41%)



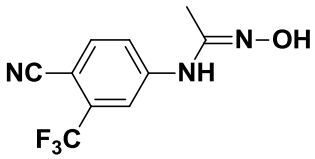
251h

(A, 40%)



251i

(A, 26%)



251j

(B, 68%)

Figure 4.1 Examples of Amidoximes Prepared from Nitroalkanes

In summary, we have investigated new routes to amidoximes from the reactions of amines with nitronates or thiohydroxymate esters. Both pathways did not afford viable access to amidoximes. During this investigation, we discovered the first example of an amidoxime-to-amidine transformation by nucleophilic addition of an amine and elimination of NH_2OH.

We have also investigated the effect of metallating agent and amine substitution pattern in the condensation of nitronate anions with amide anions to produce amidoximes, an important family of medicinally active compounds. Two generally useful sets of conditions were developed and applied to the preparation of a representative family of amidoximes. The results we reported establish a useful new dimension to the chemistry of primary nitroalkanes, which are already important building blocks in organic synthesis.

4.3 Experimental Procedures

General Procedures

^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Mercury-300 or a Varian Inova-400 spectrometer using $CDCl_3$ with 0.05% v/v TMS or DMSO-d_6 as solvents, recorded in δ (ppm), and referenced to TMS (0.00 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR) or DMSO-d_6 (2.50 ppm for ^{1}H NMR and 39.52 ppm for ^{13}C NMR). IR spectra were obtained using a Thermo Nicolet Avatar 370DTGS FT-IR spectrometer and recorded in wavenumbers (cm^{-1}). Melting points were measured using a Thomas Hoover Uni-melt capillary melting point apparatus or a Mel-Temp apparatus. Mass spectra were measured at the Life Sciences Core Laboratories Center using ABI/MDS Sciex 4000 Q

Trap. Chemicals were obtained from Aldrich, Acros, Aensar, Fisher, or Matrix Scientific, and used as received unless otherwise specified.

General Procedure for the Synthesis of Amidoximes Using Ethylmagnesium Chloride (Method A)

A solution of ethylmagnesium chloride (2 mL of 2 M solution in THF, 4 mmol) in dry THF (2 mL) in a nitrogen-flushed 2-neck 50 mL round-bottom flask fitted with a condenser and septum was brought to reflux, and the amine (4 mmol, freshly distilled over sodium hydride) was added neat dropwise. The resulting solution was stirred at reflux until the evolution of ethane gas was complete. The oil bath was lowered, and nitroalkane (1 mmol, freshly distilled over sodium hydride) was added dropwise. The septum was replaced with a glass stopper, and the resulting solution was brought to reflux for 3 h. The reaction solution was cooled to 0 ºC and acidified to pH 2 with 3 M aqueous HCl. The bulk of THF was removed in vacuo and the residual aqueous phase was washed with ethyl ether (4 x 5 mL), cooled to 0 ºC and then basified to pH 10 using 3 M NaOH. The resulting viscous suspension was saturated with sodium chloride and extracted with ethyl ether (4 x 10 mL; caution: emulsions may form). The combined ether layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the desired amidoxime.

General Procedure for the Synthesis of Amidoximes Using n-Butyllithium (Method B)

A solution of amine (4 mmol, freshly distilled over sodium hydride) in dry THF (1.5 mL) in a nitrogen-flushed 2-neck 50 mL round-bottom flask fitted with a condenser and septum was cooled to -78 ºC, then *n*-butyllithium (2.5 mL of 1.6 M solution in hexanes, 4 mmol) was added. After warming the reaction mixture to rt and then back to 0

ºC, nitroalkane (1 mmol, freshly distilled over sodium hydride) was added dropwise. The septum was replaced with a glass stopper, and the resulting suspension was brought to reflux for 3 h, (note: the stir bar was agitated to dislodge any solids sticking to the walls of the flask). The reaction suspension was cooled to 0 ºC and acidified to pH 2 with 3 M HCl. The bulk of THF was removed in vacuo and the residual aqueous phase was washed with ethyl ether (4 x 5 mL), cooled to 0 ºC and then basified to pH 10 using 3 M NaOH. The resulting mixture was saturated with sodium chloride and extracted with ethyl ether (4 x 10 mL). The combined ether layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the desired amidoxime.

^{1}H NMR, ^{13}C NMR, IR, and MS for Amidoxime Products

*Amidoxime **251a***: The product was obtained as an orange oil (85.5 mg, 59%). ^{1}H NMR and IR matched with literature.[19] ^{1}H NMR (400 MHz, CDCl3) δ 8.52 (br, 1H), 5.14 (br s, 1H), 3.10 (m, 2H), 2.23 (q, 2H), 1.49 (m, 2H), 1.36 (m, 2H), 1.14 (t, 3H), 0.93 (t, 3H). IR (neat) 3233 (br), 2959 (s), 2933 (s), 2873 (s), 1645 (s).

*Amidoxime **251b***: The product was obtained as a yellow solid (45.9 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br, 1H), 5.30 (br s, 1H), 2.40 (q, 2H), 1.33 (s, 9H), 1.16 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.24, 50.63, 31.53, 23.65, 10.99. IR (CH_2Cl_2) 3241 (br), 2974(s), 2939 (m), 2877 (m), 1633 (s). ESI-MS (CH_3OH) 144.9 (M+H), 167.2 (M+Na), 183.2 (M+K).

*Amidoxime **251c***: The product was obtained as an orange solid (80.7 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (br, 1H), 5.13 (br d, 1H), 3.13 (m, 1H), 2.24 (q, 2H), 1.88 (m, 2H), 1.75 (m, 2H), 1.60 (m, 2H), 1.37-1.15 (m, 2H), 1.14 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.47, 50.57, 35.25, 25.43, 25.17, 22.23, 11.25. IR (CH_2Cl_2) 3207 (br),

2932(s), 2853 (s), 1641 (s). ESI-MS (CH_3OH) 171.2 (M+H), 193.2 (M+Na), 209.2 (M+K).

*Amidoxime **251d***: The product was obtained as an orange solid (64.8 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br, 1H), 3.26 (m, 4H), 2.53 (q, 2H), 1.86 (m, 4H), 1.17 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.83, 46.40, 25.02, 19.64, 10.73. IR (CH_2Cl_2) 3207 (br), 2967(s), 2874 (s), 1628 (s). ESI-MS (CH_3OH) 143.04 (M+H), 165.12 (M+Na), 181.20 (M+K).

*Amidoxime **251e***: The crude product was obtained as a yellow oil, of which a portion was purified by silica gel flash column chromatography (ethyl acetate, R_f = 0.30) to afford a yellow oil (69.4 mg, calculated total yield 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (br, 1H), 7.43-7.04 (m, 5H), 5.62 (br s, 1H), 4.31 (d, 2H), 2.21 (q, 2H), 1.11 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.13, 139.43, 128.73, 127.34, 126.78, 45.89, 22.09, 10.86. IR (neat) 3206 (br), 3085 (s), 3061 (s), 3028 (s), 2974 (s), 2935 (s), 2874 (s), 1646 (s). ESI-MS (CH_3OH) 179.1 (M+H).

*Amidoxime **251f*** : The product was purified by silica gel flash column chromatography (1:1 ethyl acetate:hexanes, R_f = 0.30) to afford a yellow solid (91.5 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (br, 1H), 7.30 (m, 2H), 7.18-6.99 (m, 3H), 2.39 (q, 2H), 1.02 (t, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.19, 139.01, 129.16, 124.64, 124.20, 22.58, 10.80. IR (CH_2Cl_2) 3187 (br), 2978 (m), 2939 (m), 2877 (m), 1641 (s), 1598 (s). ESI-MS (CH_3OH) 165.04 (M+H).

*Amidoxime **251g***: The product was obtained as a light yellow solid (47.4 mg, 41%, m.p. 73-75 ^{o}C). ^{1}H NMR and ^{13}C NMR matched with literature.[16] ^{1}H NMR (400

MHz, CDCl3) δ 9.29 (br, 1H), 6.85 (d, 1H), 5.17 (br d, 1H), 1.25 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.62, 49.98, 30.56.

*Amidoxime **251h***: The product was obtained as an orange solid (50.7 mg, 40%). ^{1}H NMR matched with literature.[20] ^{1}H NMR (400 MHz, CDCl3) δ 8.88 (br, 1H), 3.25 (m, 4H), 2.06 (s, 3H), 1.86 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.62, 46.69, 25.04, 11.90.

*Amidoxime **251i***: The product was obtained as a yellow solid (29.4 mg, 26%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (br, 1H), 5.86 (m, 1H), 5.42 (br s, 1H), 5.17 (m, 2H), 3.75 (s, 2H), 1.85 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.87, 135.77, 115.61, 44.75, 14.66. IR (CH_2Cl_2) 3241 (br), 3081(m), 2928 (m), 2859 (m), 1651 (s). ESI-MS (CH_3OH) 115.12 (M+H).

*Amidoxime **251j***: The crude product was obtained as a yellow solid, of which a portion was purified by trituration with CH_2Cl_2 (2 x 2 mL) to afford a yellow solid (142.7 mg, calculated total yield 68%, mp. 160.5-162 ^{o}C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.12 (s, 1H), 8.16 (d, 1H), 7.91 (d, 1H), 7.78 (dd, 1H), 2.02 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6) δ 151.29, 145.91, 135.99, 131.64 (q), 124.56, 120.93, 119.76, 116.52, 114.52 (q), 13.90. IR ($CHCl_3$) 3356 (s), 3320 (m), 3249 (m), 3105 (m), 2228 (s), 1612 (s), 1544 (s). ESI-MS (CH_3OH) 244.08 (M+H).

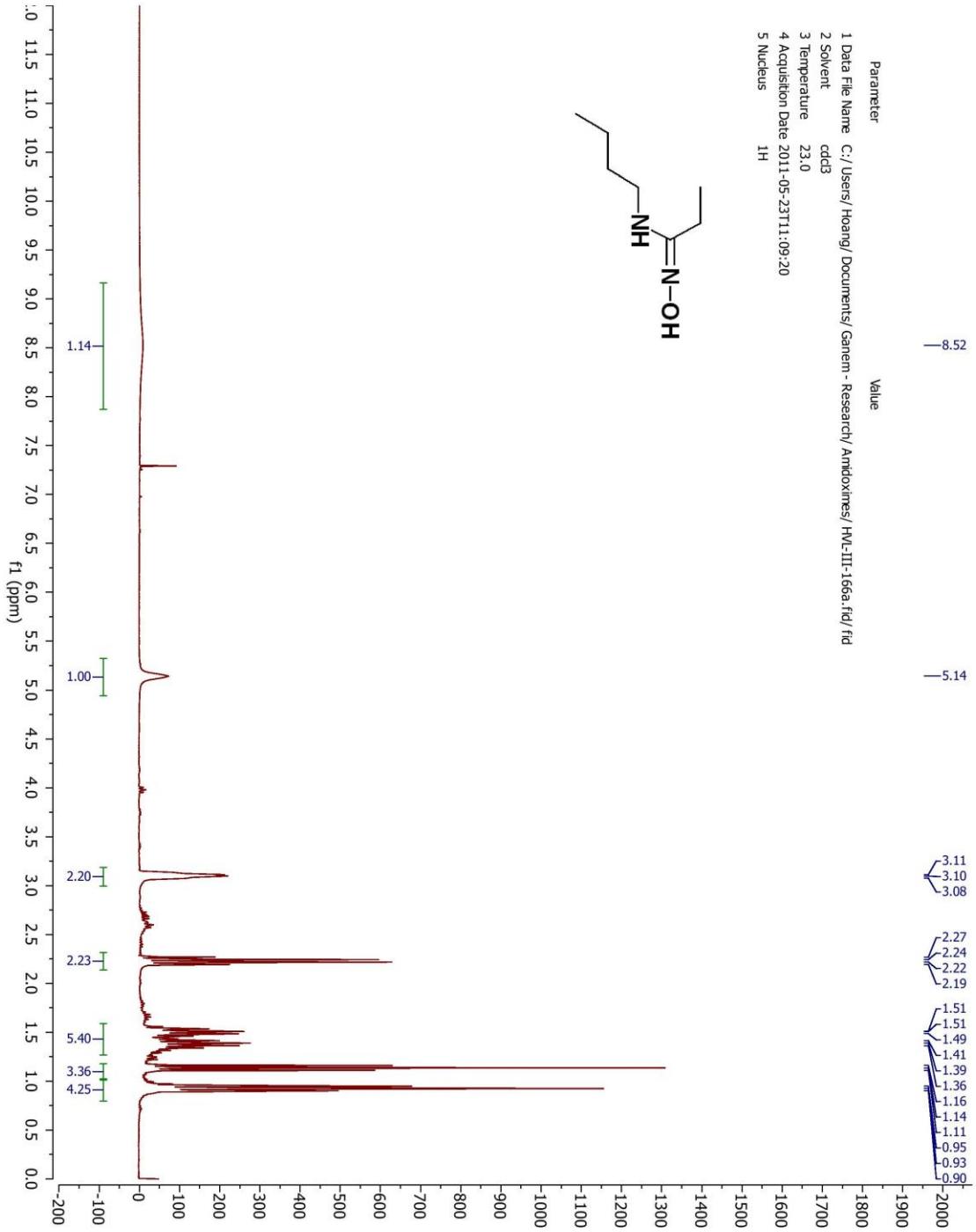


Figure 4.2 ^{1}H NMR Spectrum of Amidoxime **251a**

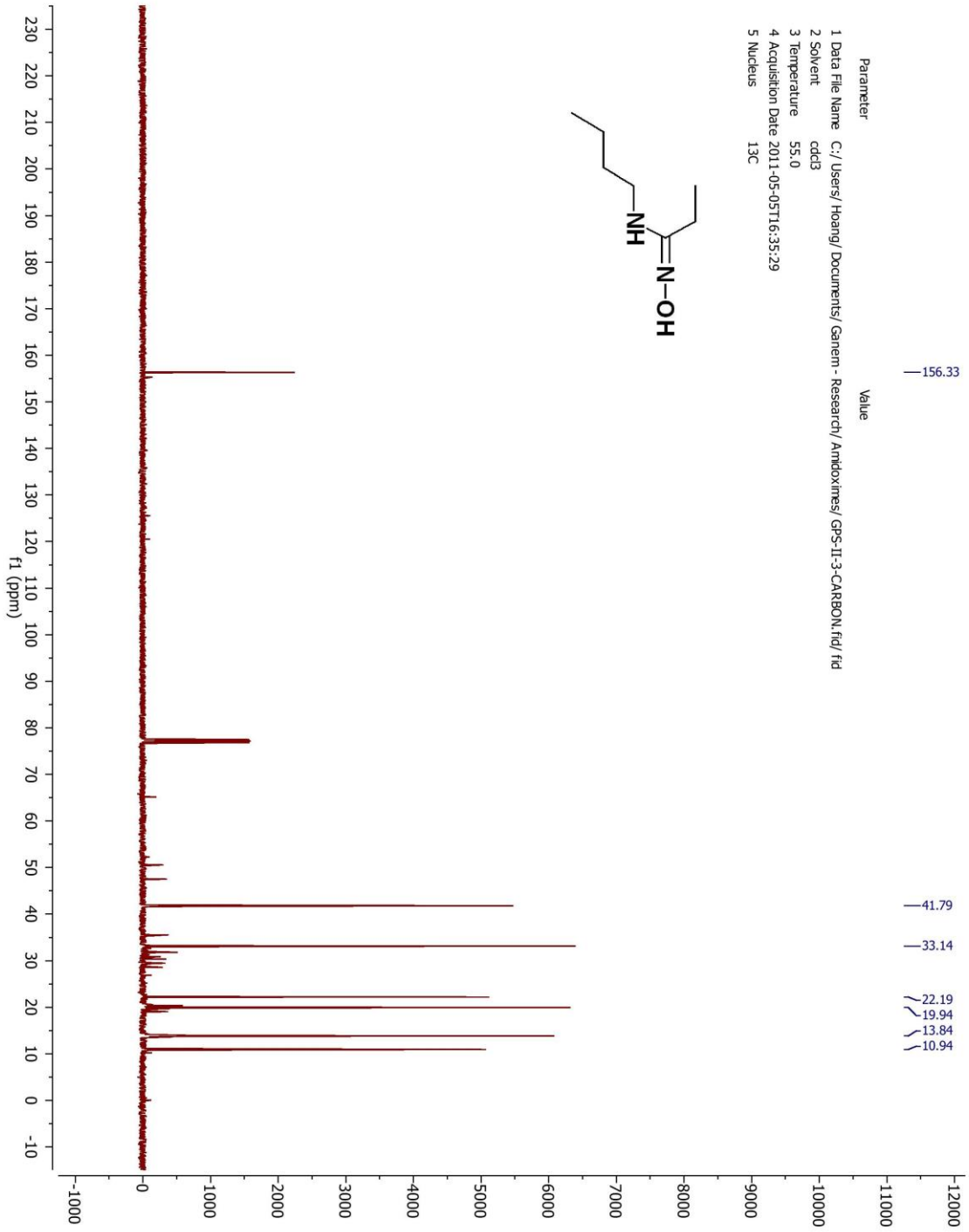


Figure 4.3 ^{13}C NMR Spectrum of Amidoxime **251a**

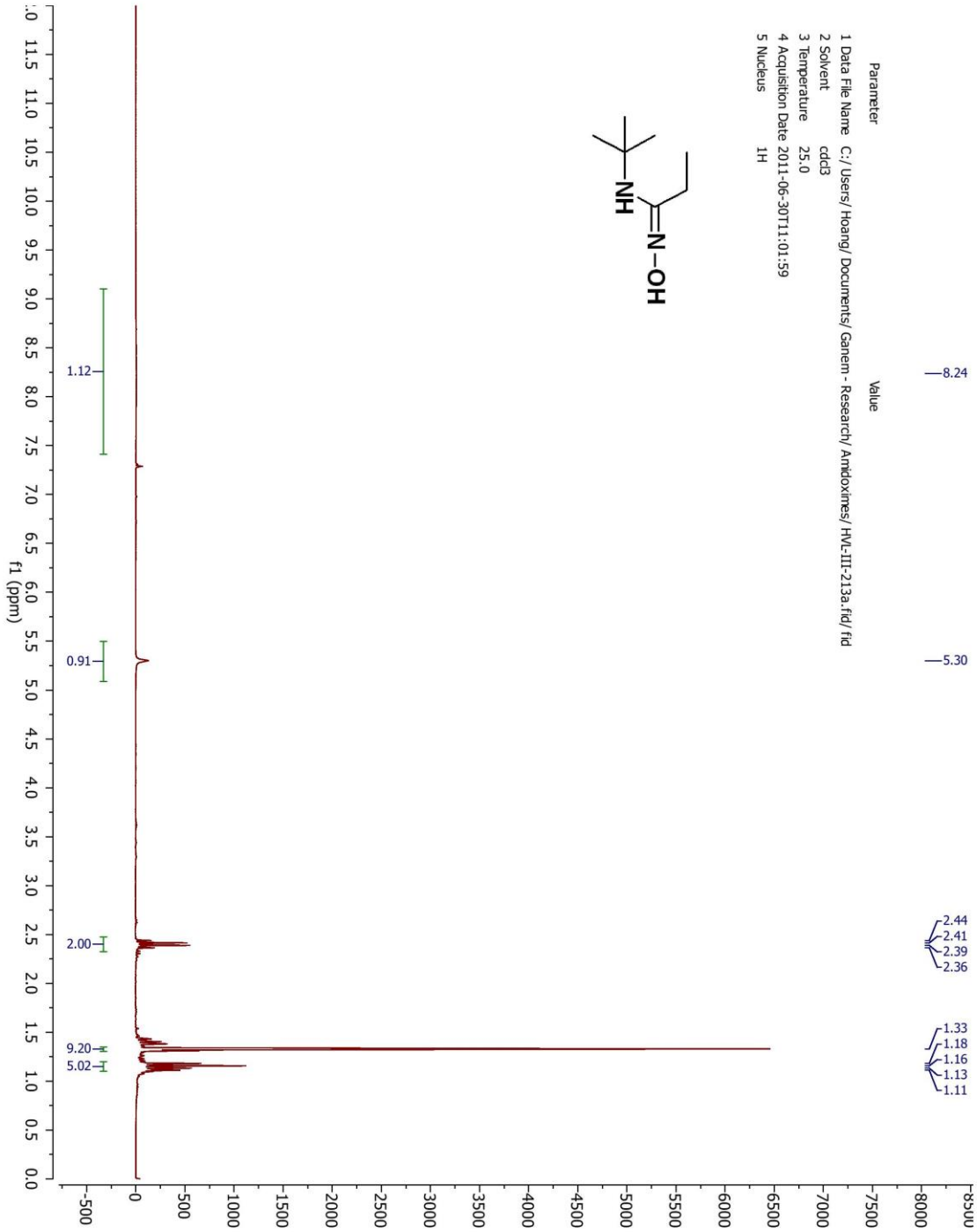


Figure 4.4 ^{1}H NMR Spectrum of Amidoxime **251b**

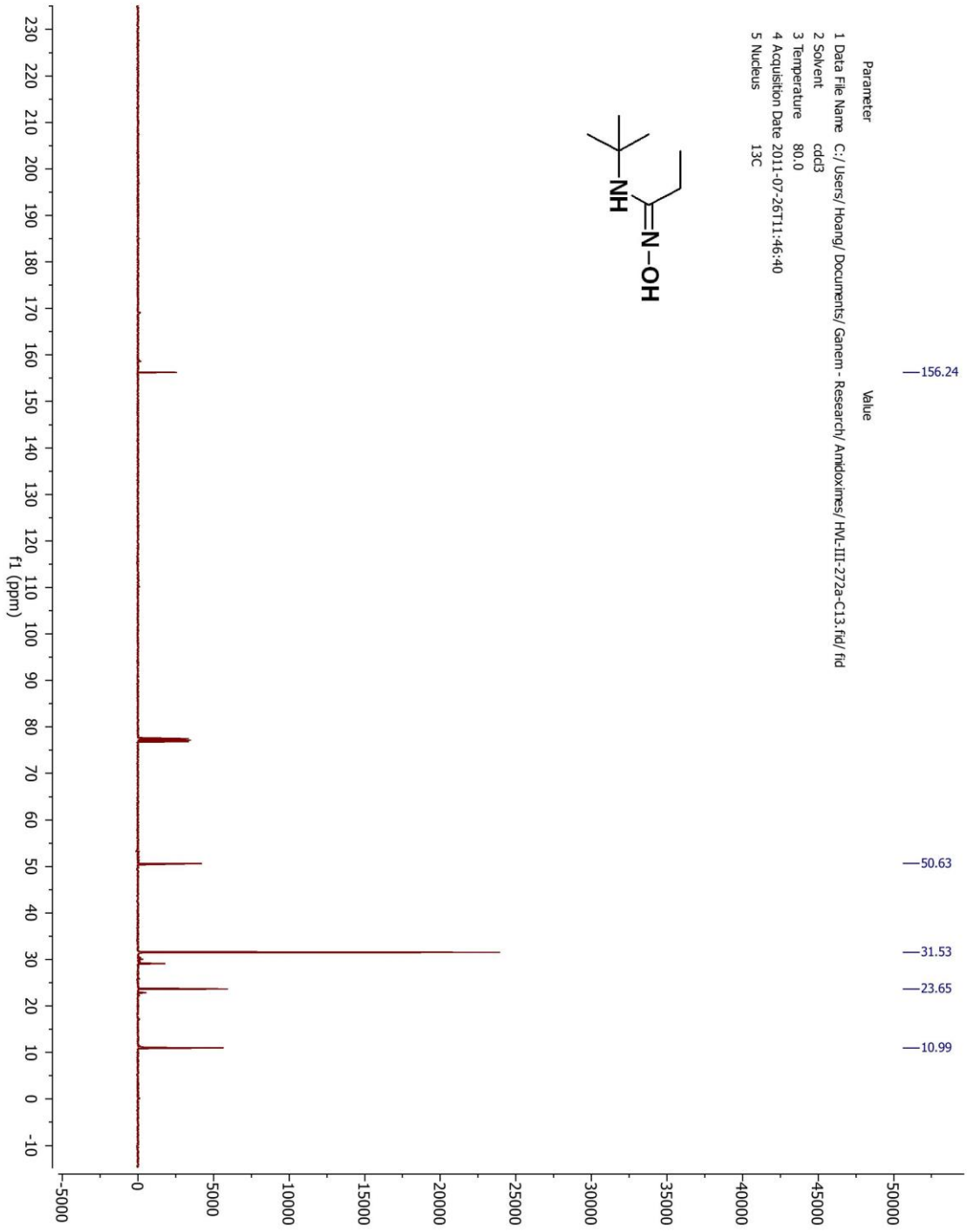


Figure 4.5 ^{13}C NMR Spectrum of Amidoxime **251b**

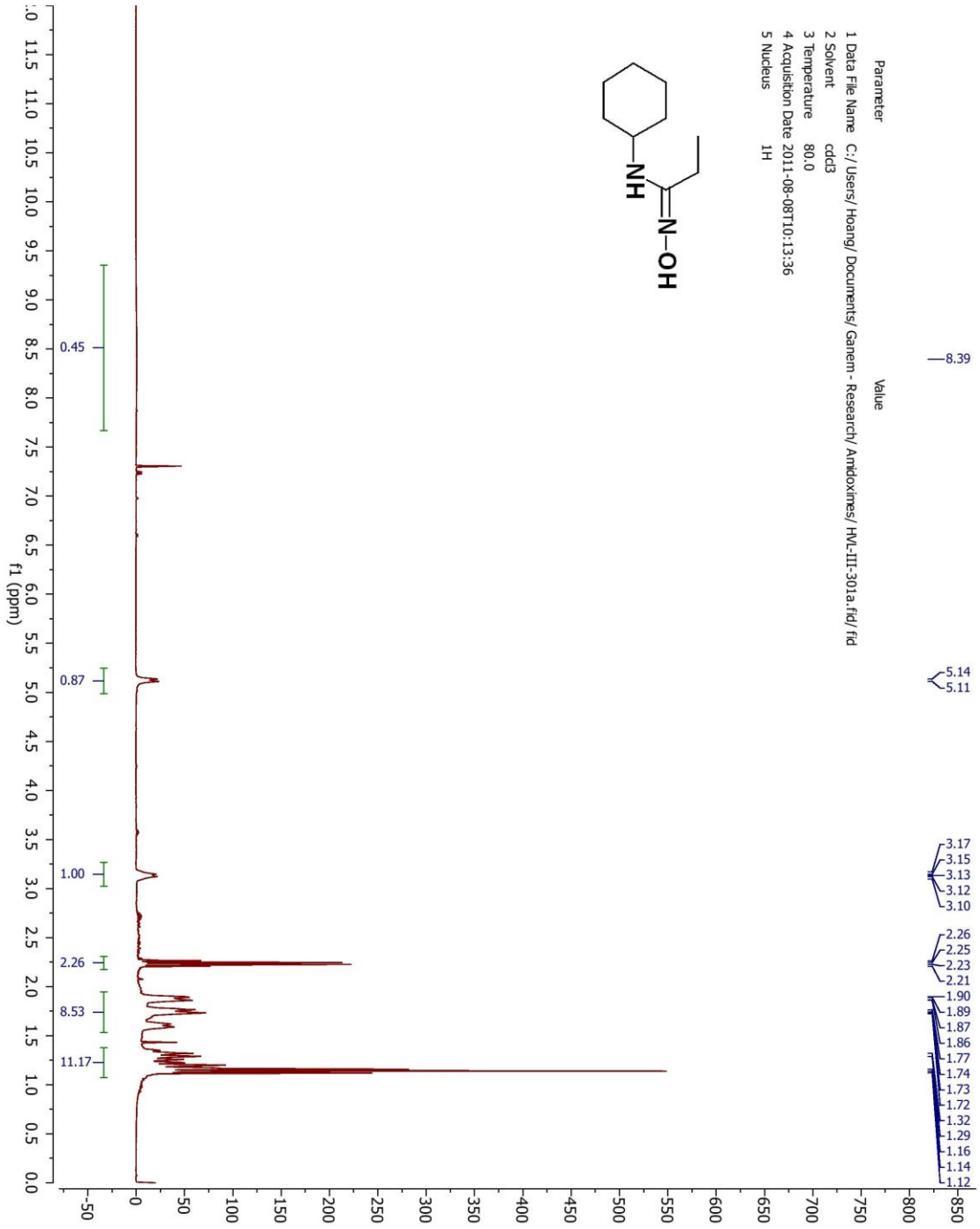


Figure 4.6 ^{1}H NMR Spectrum of Amidoxime **251c**

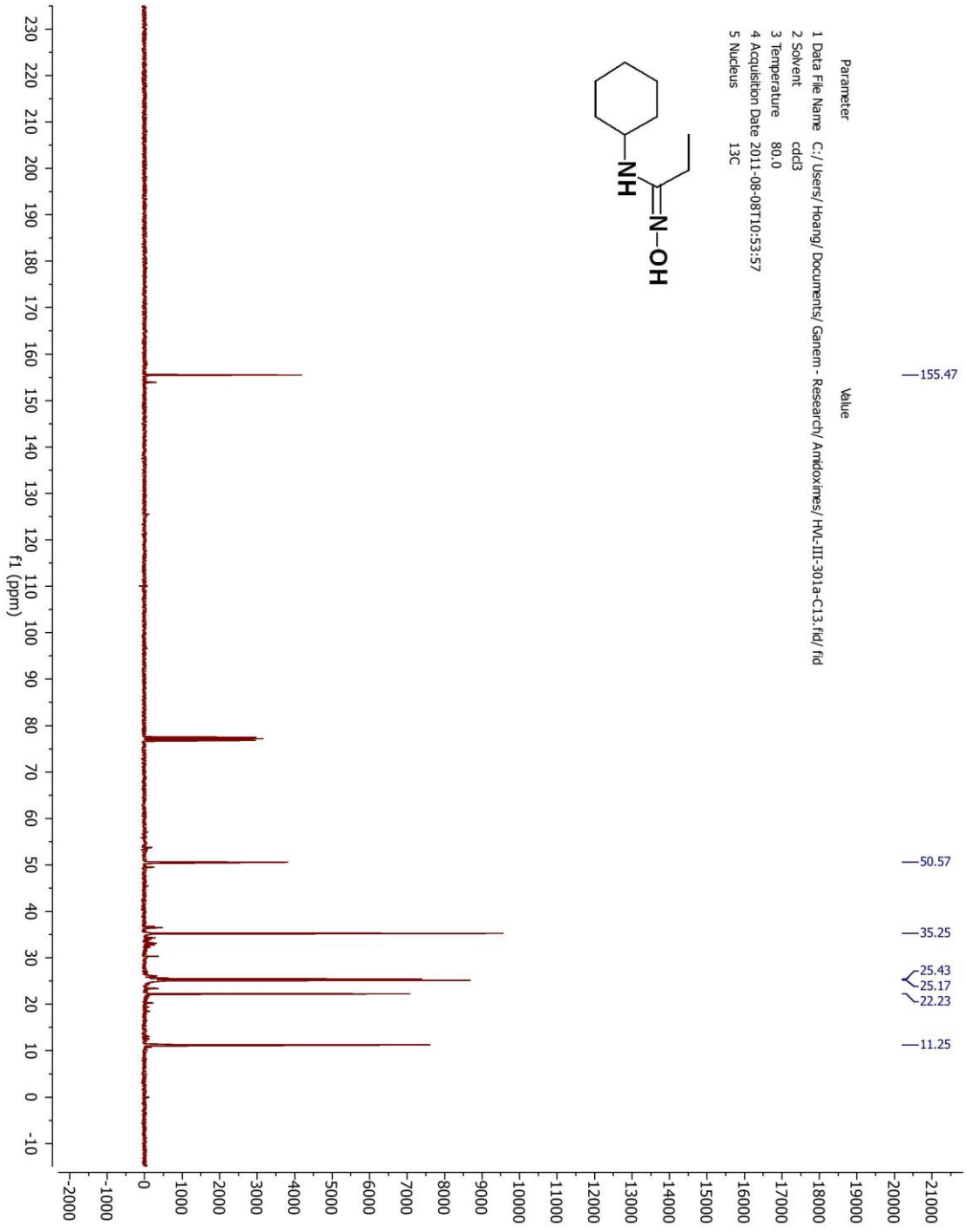


Figure 4.7 ^{13}C NMR Spectrum of Amidoxime **251c**

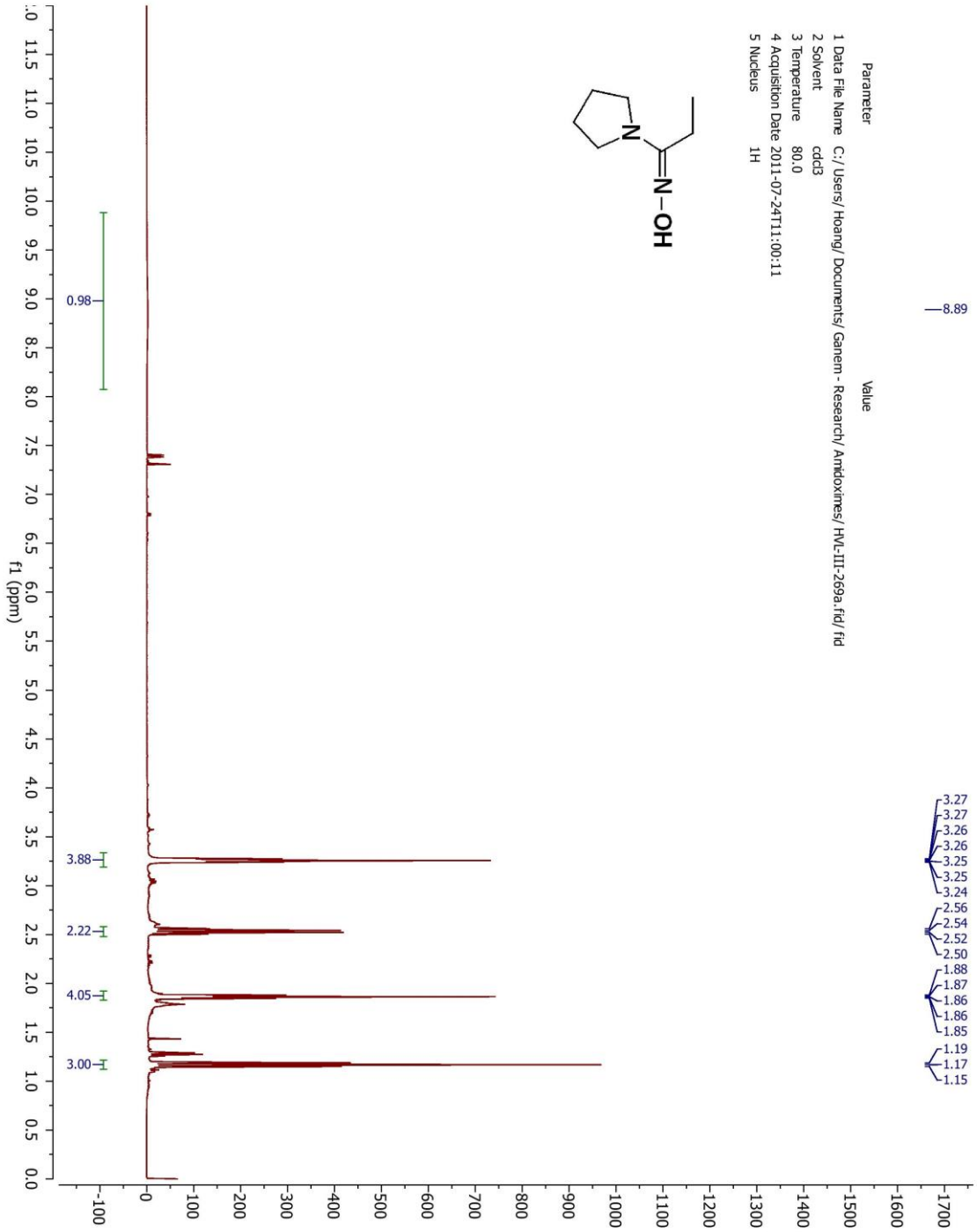


Figure 4.8 ^{1}H NMR Spectrum of Amidoxime **251d**

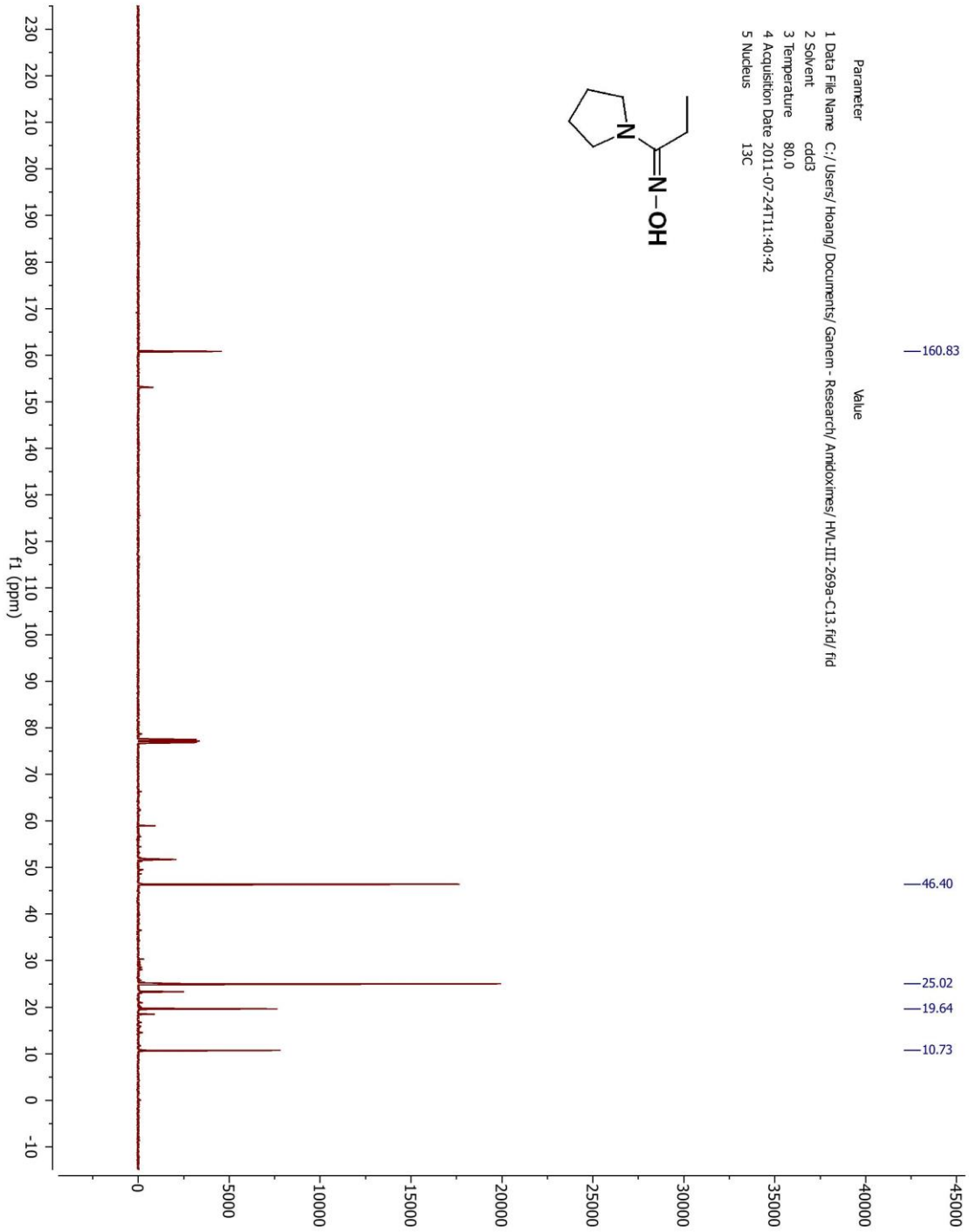


Figure 4.9 ^{13}C NMR Spectrum of Amidoxime **251d**

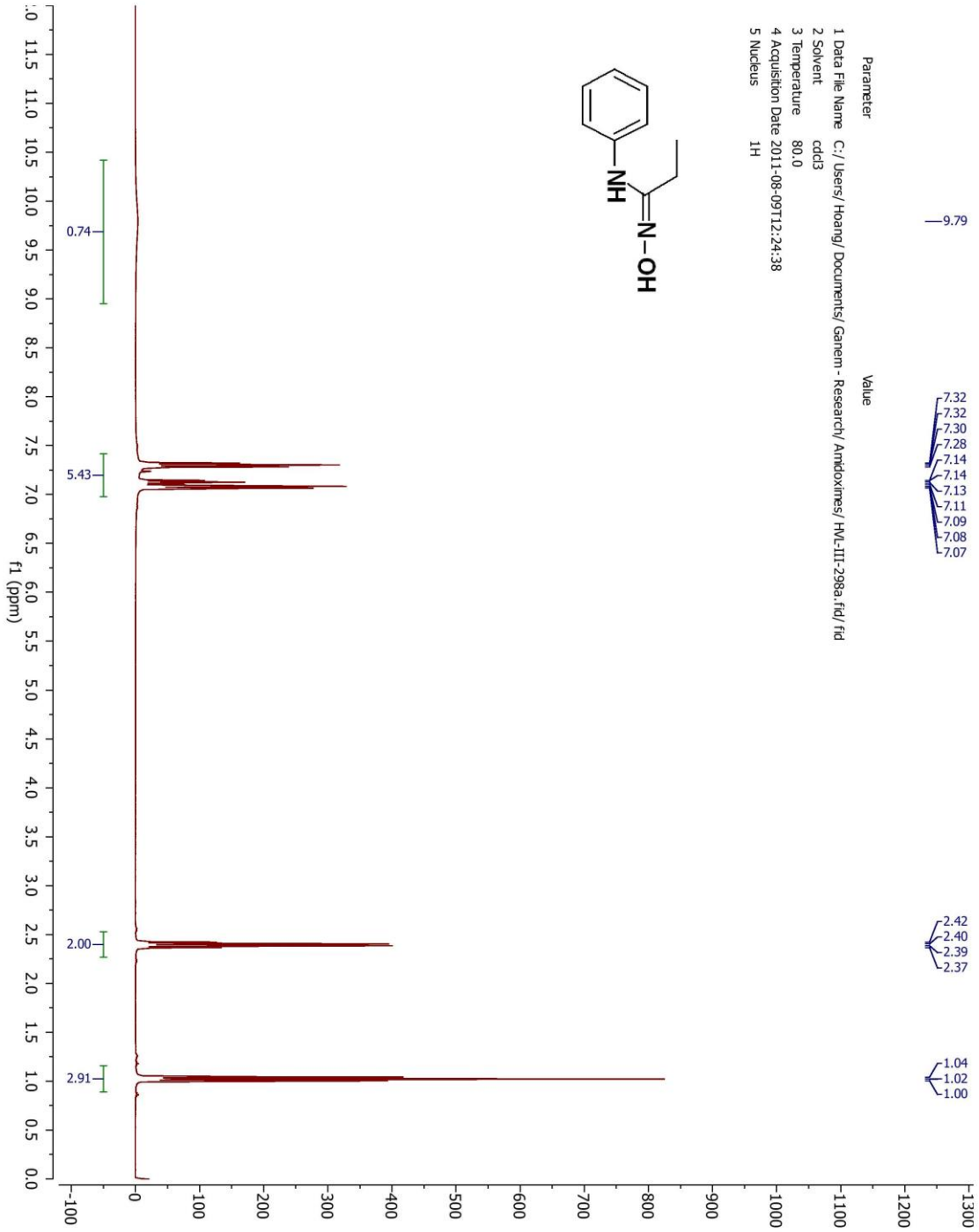


Figure 4.10 ^{1}H NMR Spectrum of Amidoxime **251f**

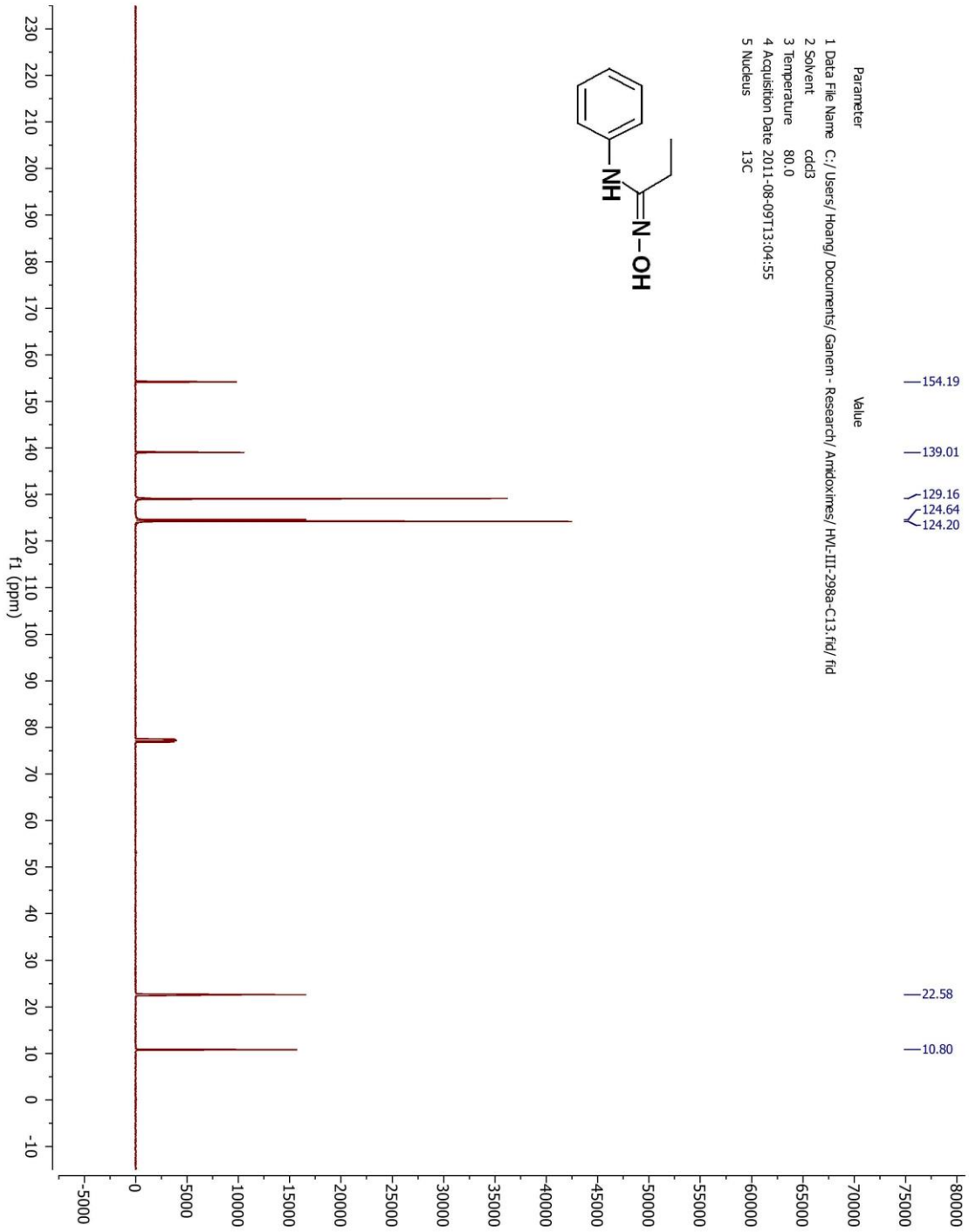


Figure 4.11 ^{13}C NMR Spectrum of Amidoxime **251f**

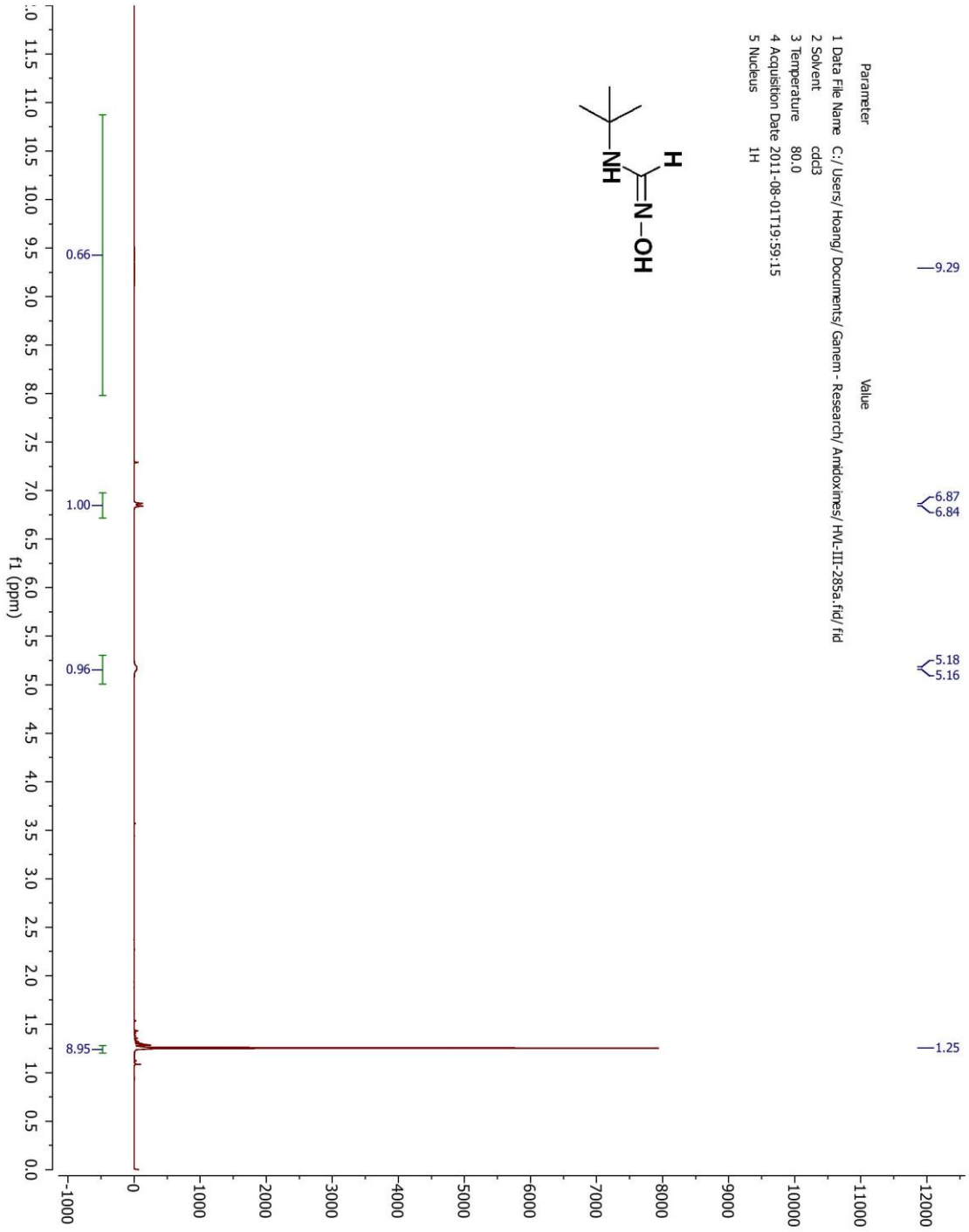


Figure 4.12 [1]H NMR Spectrum of Amidoxime **251g**

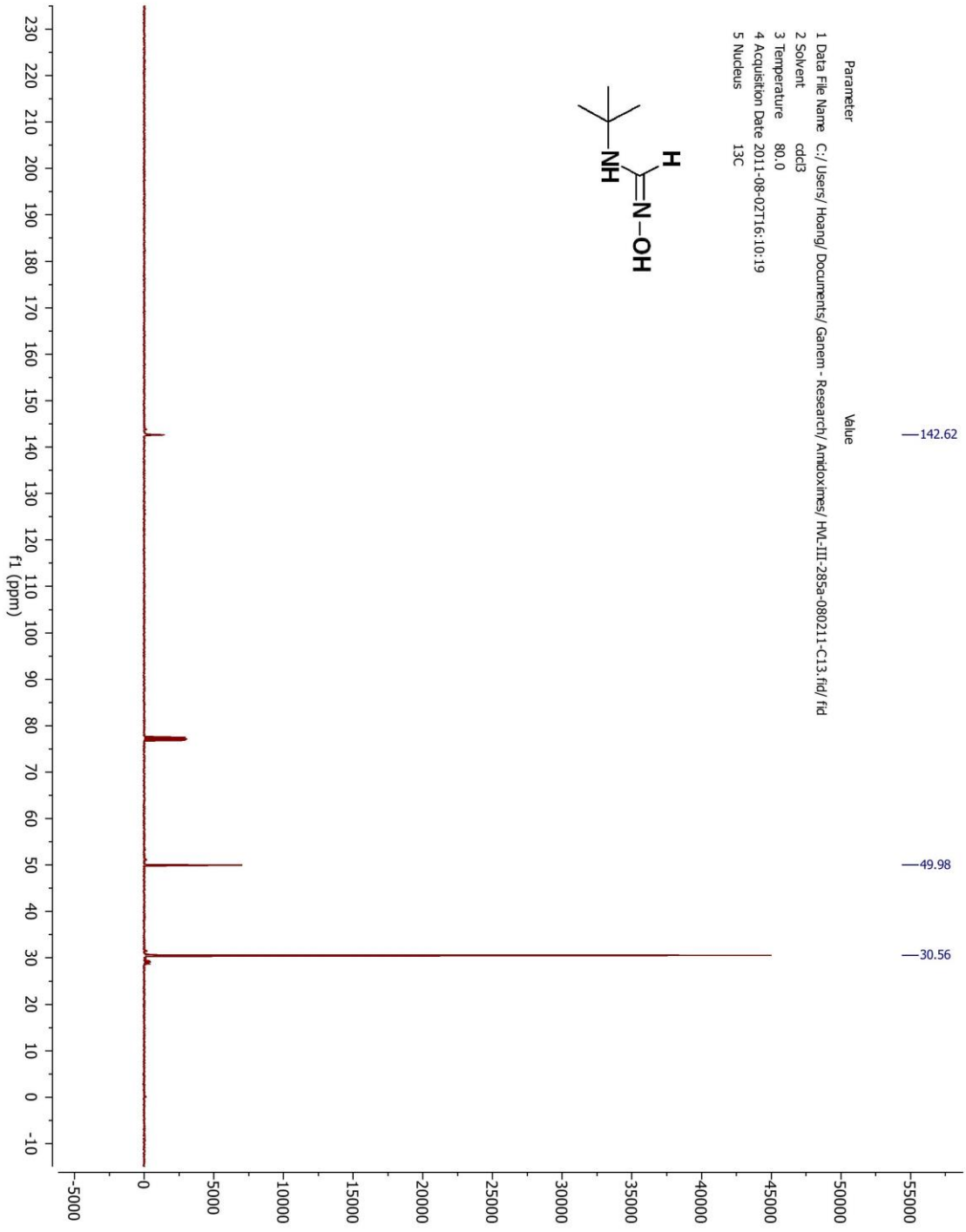


Figure 4.13 ^{13}C NMR Spectrum of Amidoxime **251g**

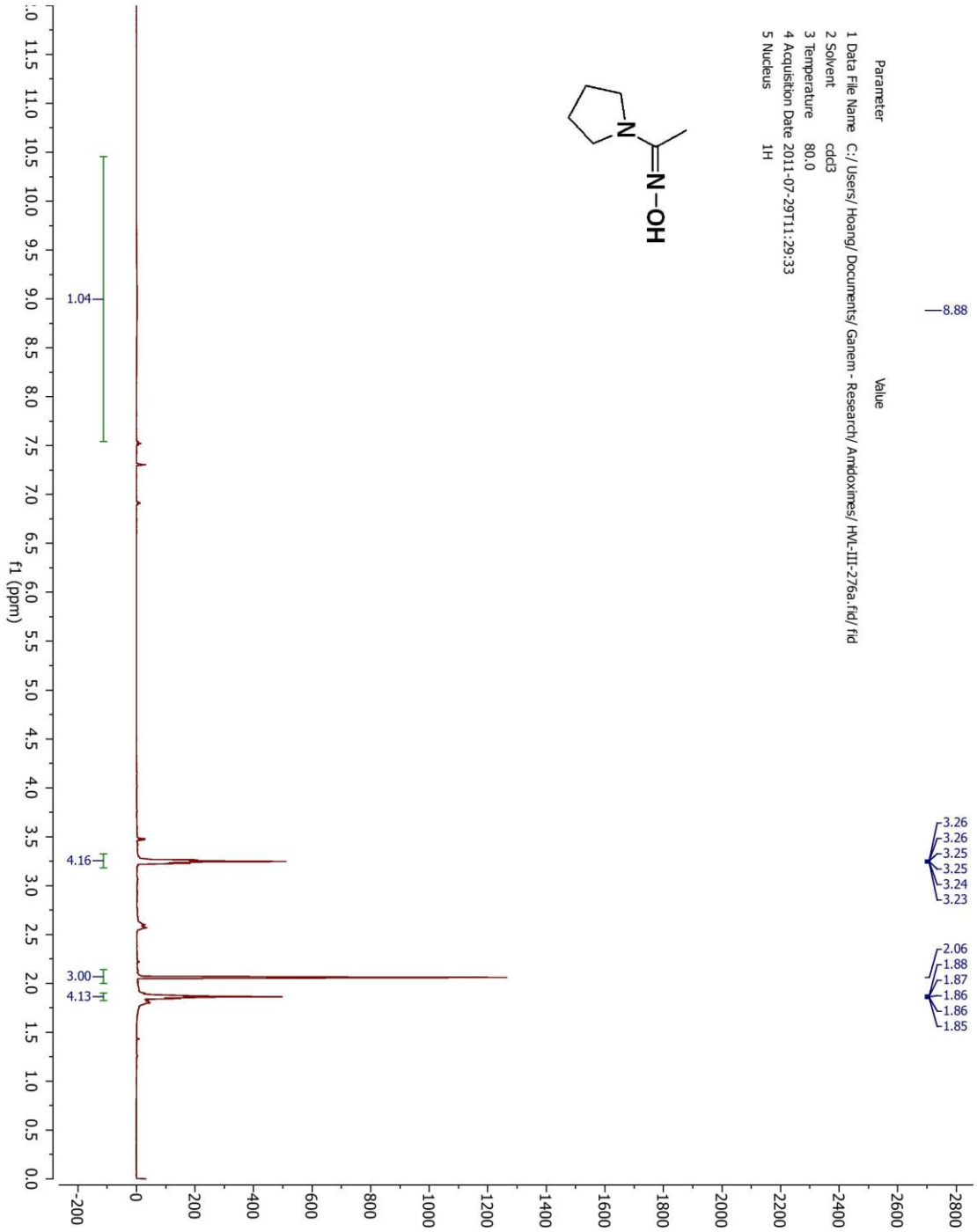


Figure 4.14 ^{1}H NMR Spectrum of Amidoxime **251h**

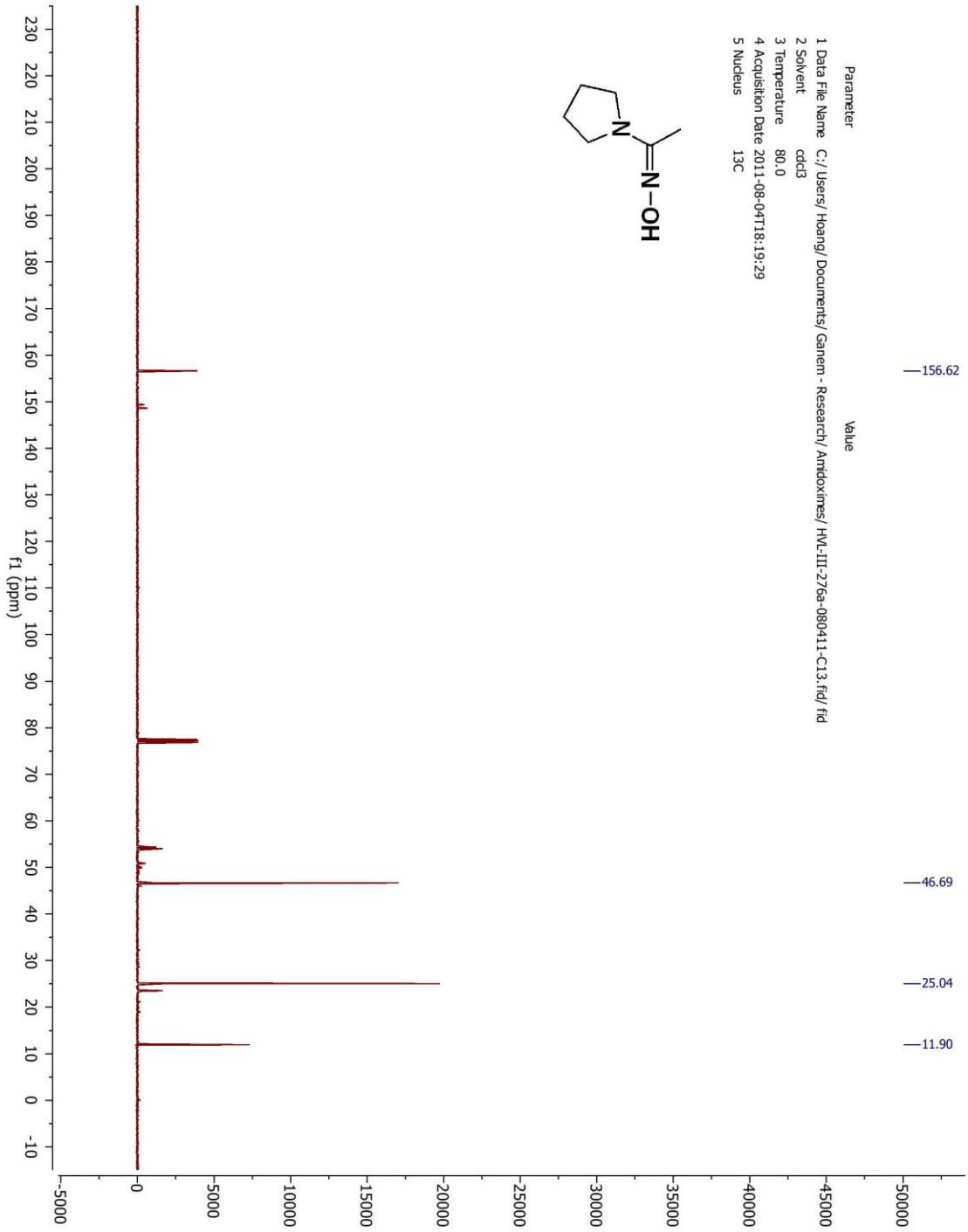


Figure 4.15 ^{13}C NMR Spectrum of Amidoxime **251h**

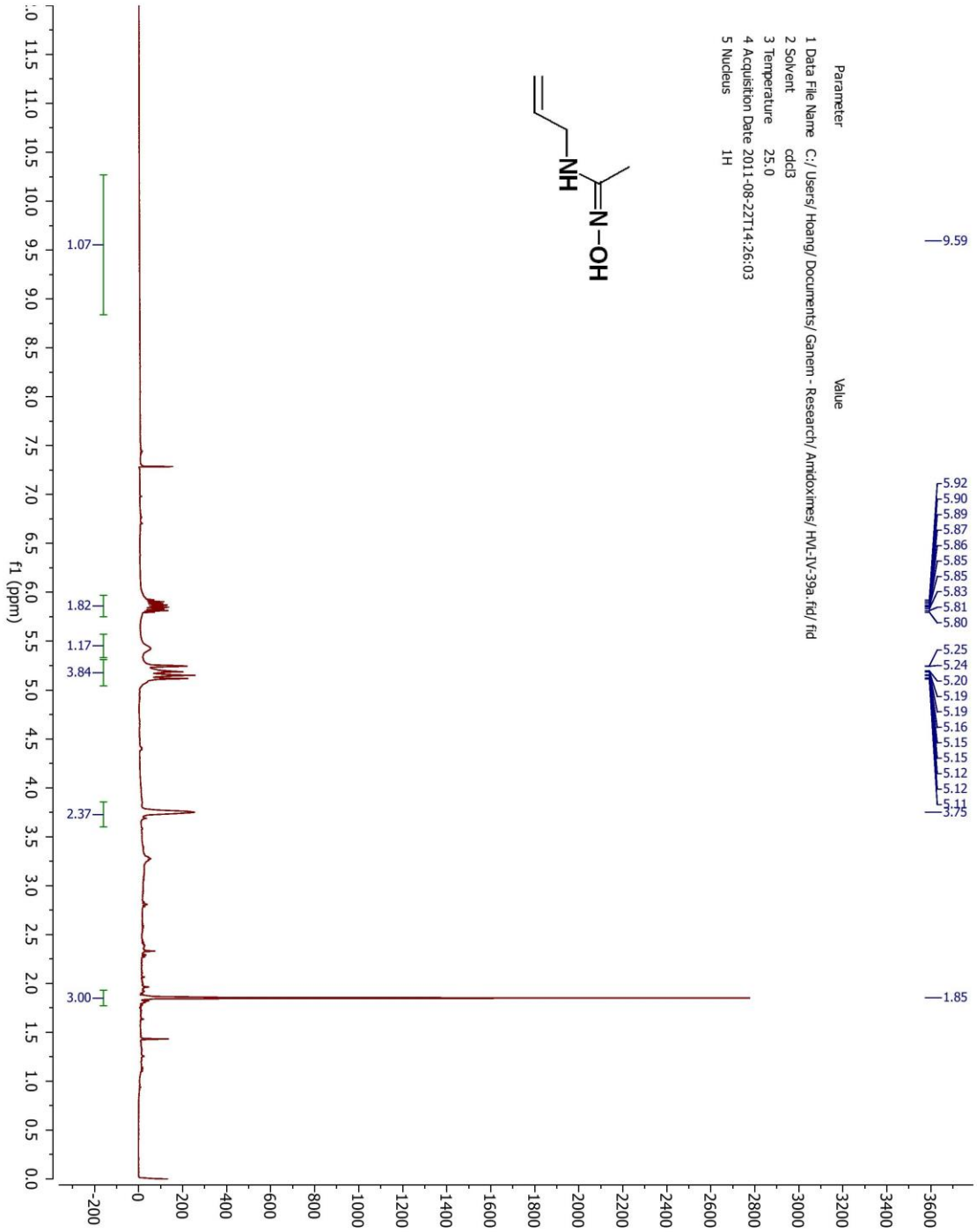


Figure 4.16 ^{1}H NMR Spectrum of Amidoxime **251i**

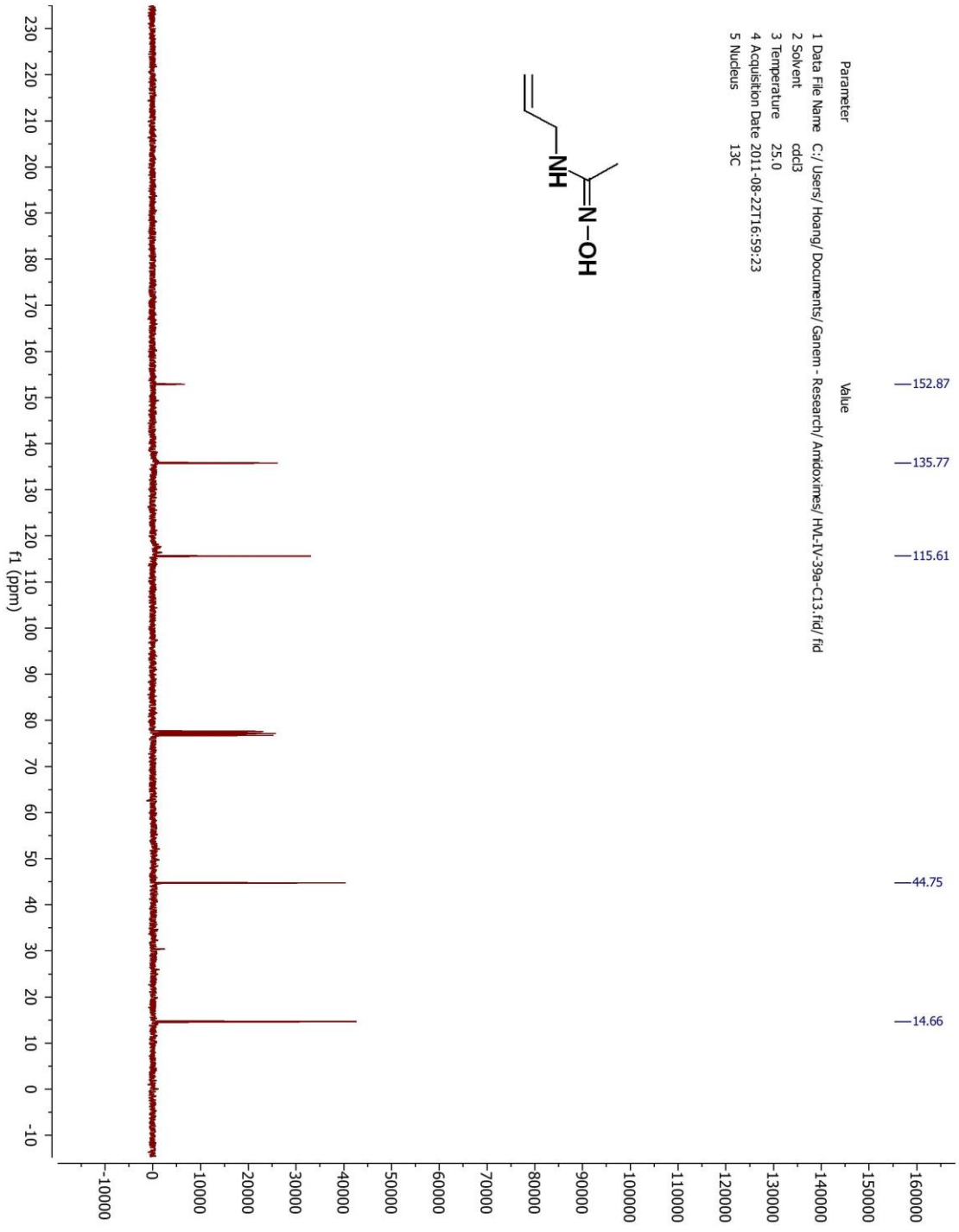


Figure 4.17 ^{13}C NMR Spectrum of Amidoxime **251i**

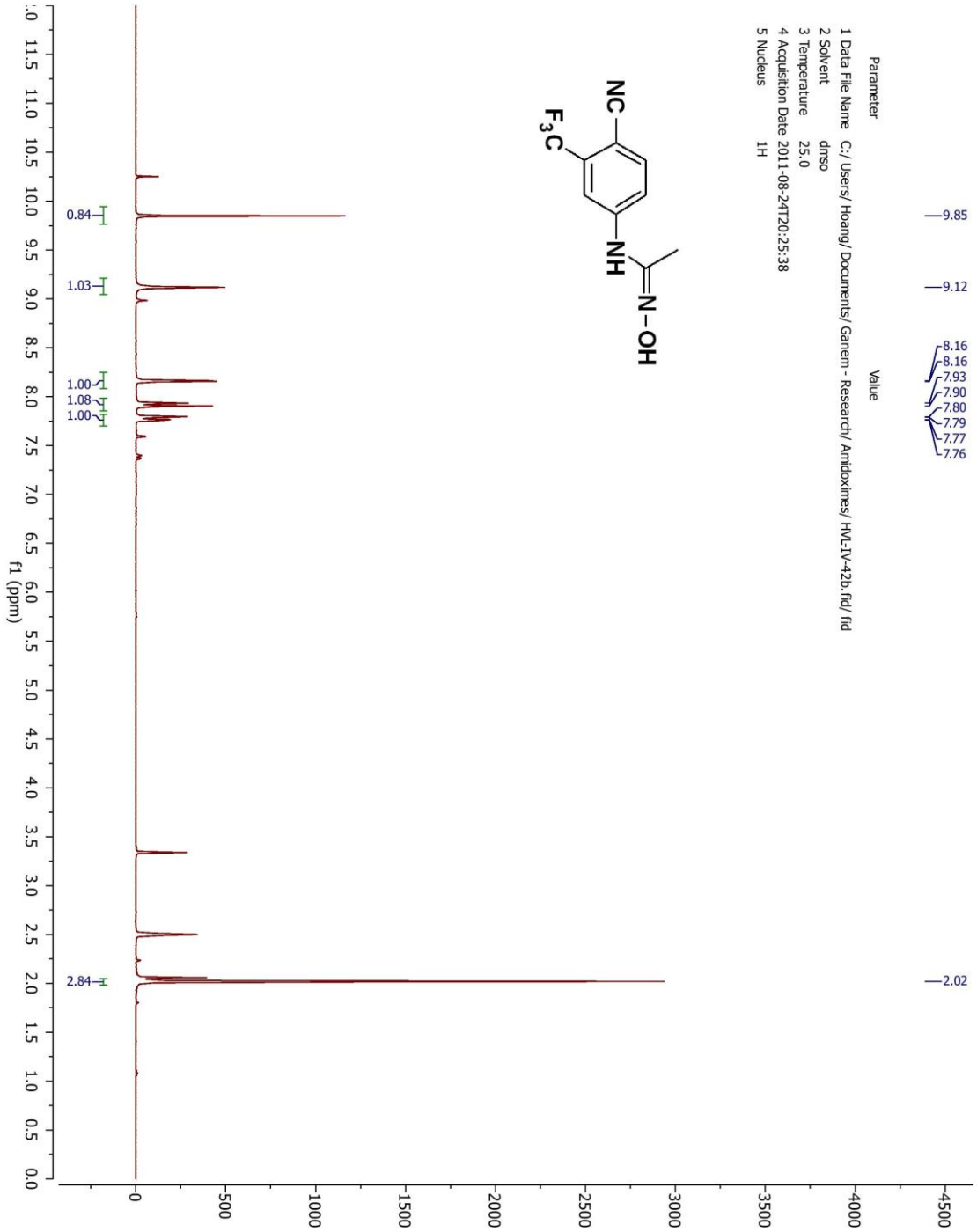


Figure 4.18 ^{1}H NMR Spectrum of Amidoxime **251j**

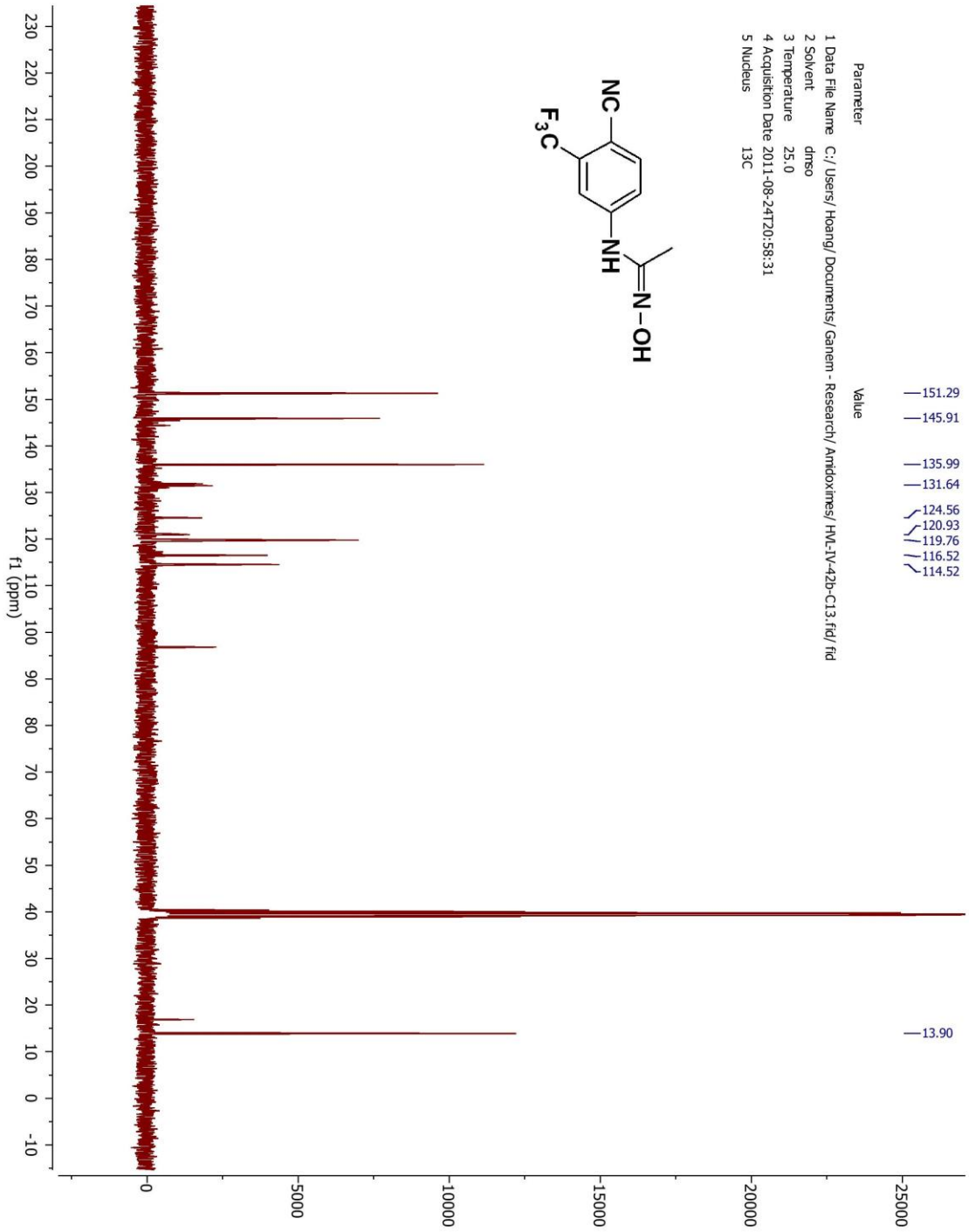


Figure 4.19 ^{13}C NMR Spectrum of Amidoxime **251j**

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CHAPTER 5

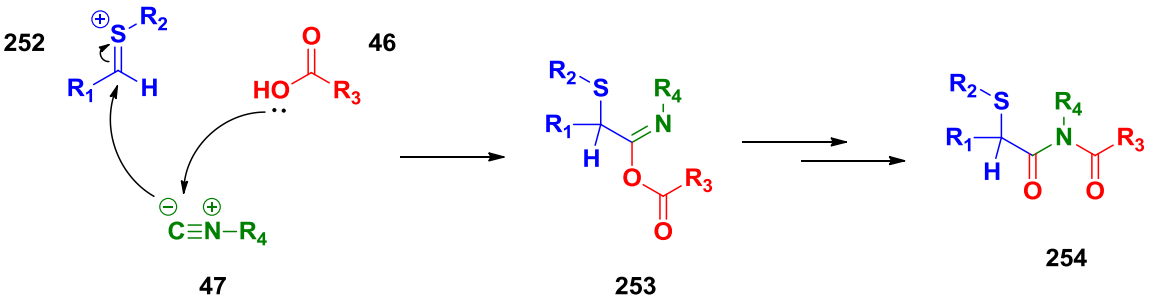
Studies on a thia-Ugi Reaction: A Catalytic Oxidation of Isonitriles to Isocyanates

5.1 Background

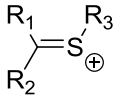
Since its discovery in 1959, the Ugi reaction has arguably been one of the most important multicomponent reactions (MCRs).[1,2] By producing the biologically relevant α-aminoacyl amide or dipeptide motif, the Ugi reaction is widely used in the synthesis of many drugs and bioactive compounds.[3,4]

As discussed earlier in Chapter 1, our laboratory has recently developed a variant of the Ugi reaction resulting in a 5-component condensation (Scheme 1.11).[5] The process was based on an alternative synthetic approach to imine, from the condensation of organometallic reagents with nitriles and primary amines.

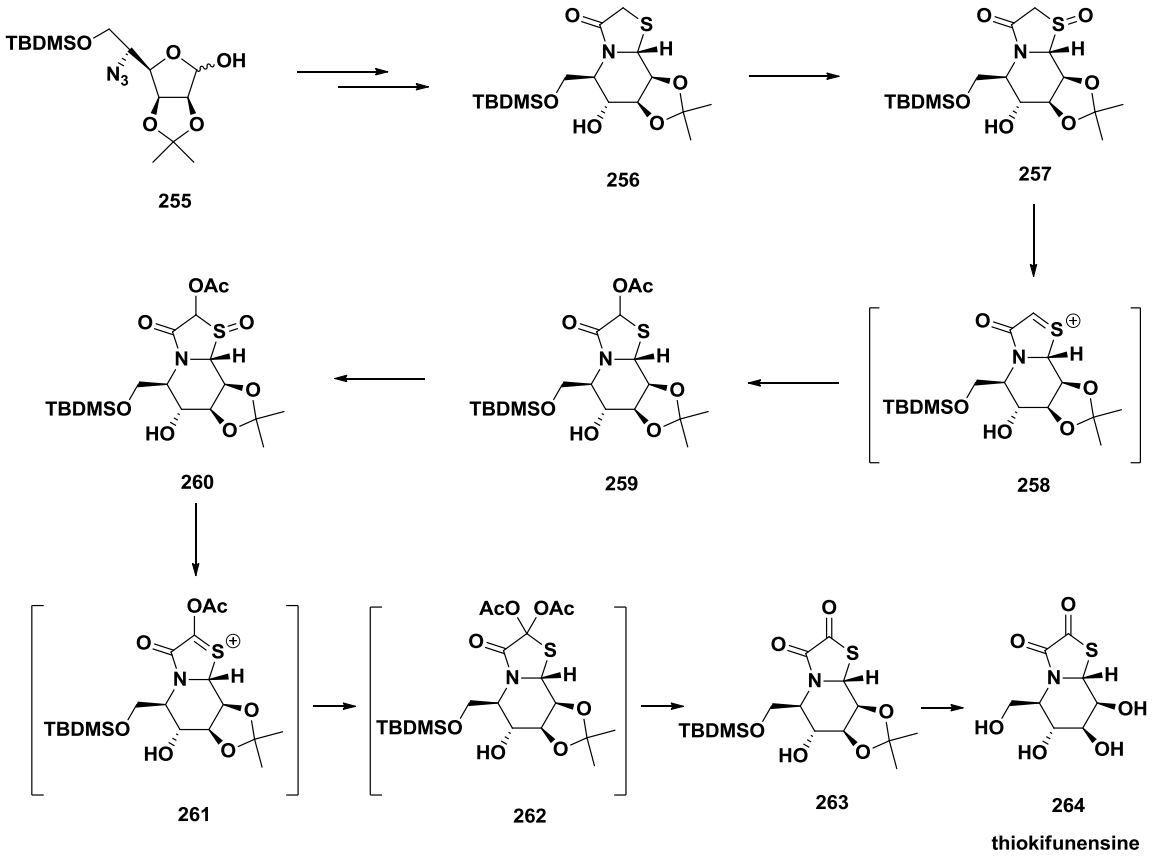
Guided by the single reactant replacement (SRR) approach, we wondered whether the imine species in the Ugi reaction could be replaced with a comparable electrophilic thionium ion species. Such replacement might lead to products involving new motifs like **253** and **254** (Scheme 5.1).



Scheme 5.1

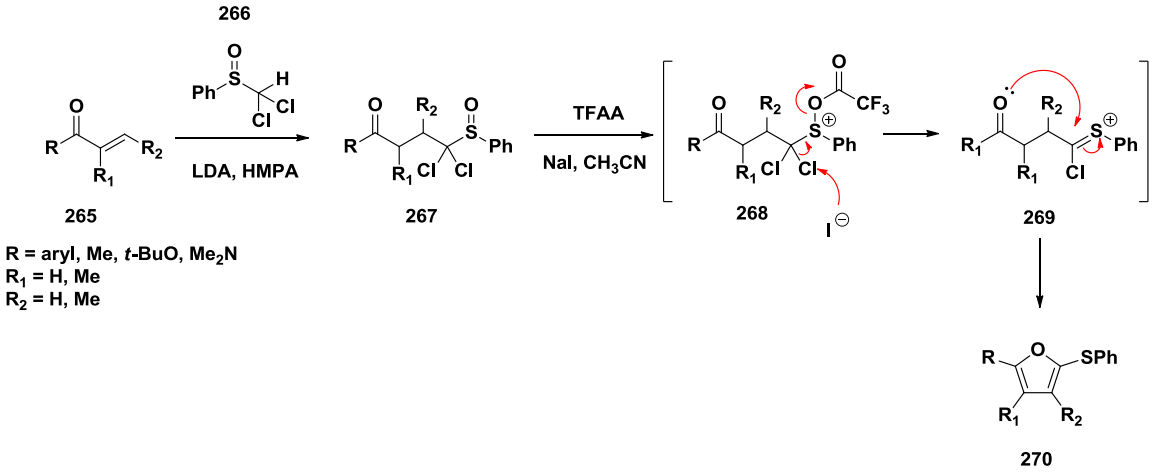
Thionium ions, which have the general structure  , are synthetically useful species and have been widely used in the preparation of α-substituted sulfides.[6,7] For example, Li *et al.* recently used thionium ions **258** and **261** as intermediates in their

synthesis of thiokifunensine **264** (Scheme 5.2), which is a thioanalog of the naturally-occurring anti-HIV, anti-cancer, and immunomodulating agent kifunensine.[8] A preliminary biological evaluation showed that **264** also exhibited good anti-HIV inhibitory activity. The thionium species **258** was generated by a Pummerer reaction between sulfoxide **257** and acetic acid or acetic anhydride at 100 °C, affording α-substituted sulfide **259**. A second Pummerer reaction was performed on sulfoxide **260** to form the corresponding unstable ketal **262**, which converted to the protected thiokifunensine **263**. Subsequent hydrolysis of **263** led to the formation of thiokifunensine **264**.



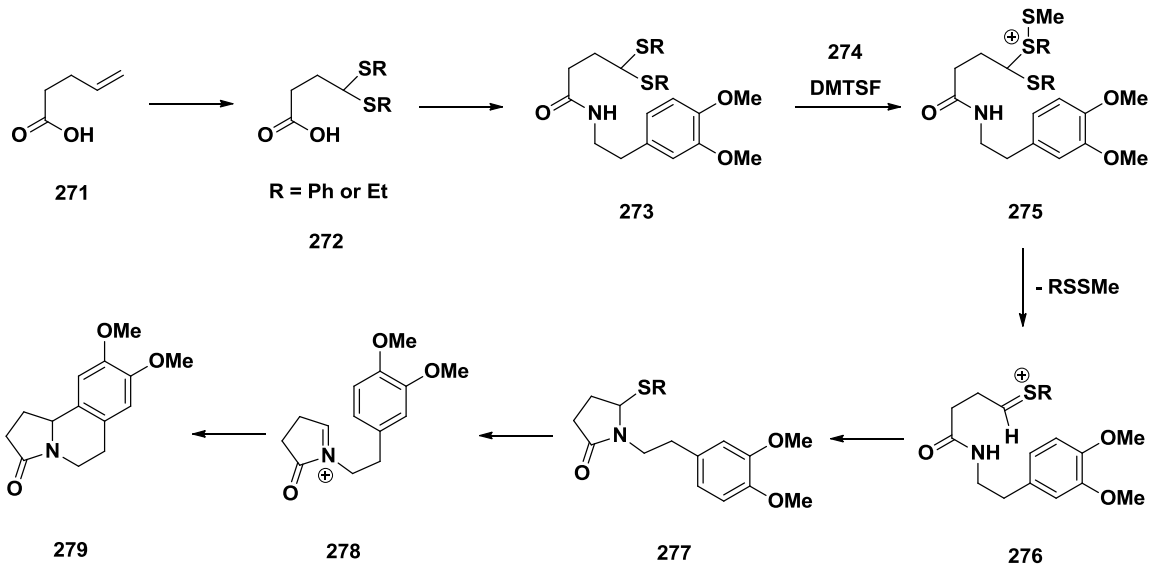
Scheme 5.2[8]

Thionium ions can also be used as intermediates to make heteroaromatic rings. For example, Satoh and Miyagawa cleverly used thionium species **269** as an electrophilic intermediate for the attack of an internal ketone nucleophile to form the substituted furan **270** in a two-step procedure (Scheme 5.3).[9] Intermediate **269** was formed by the Pummerer reaction of the sulfoxide **267** with trifluoroacetic anhydride (TFAA).

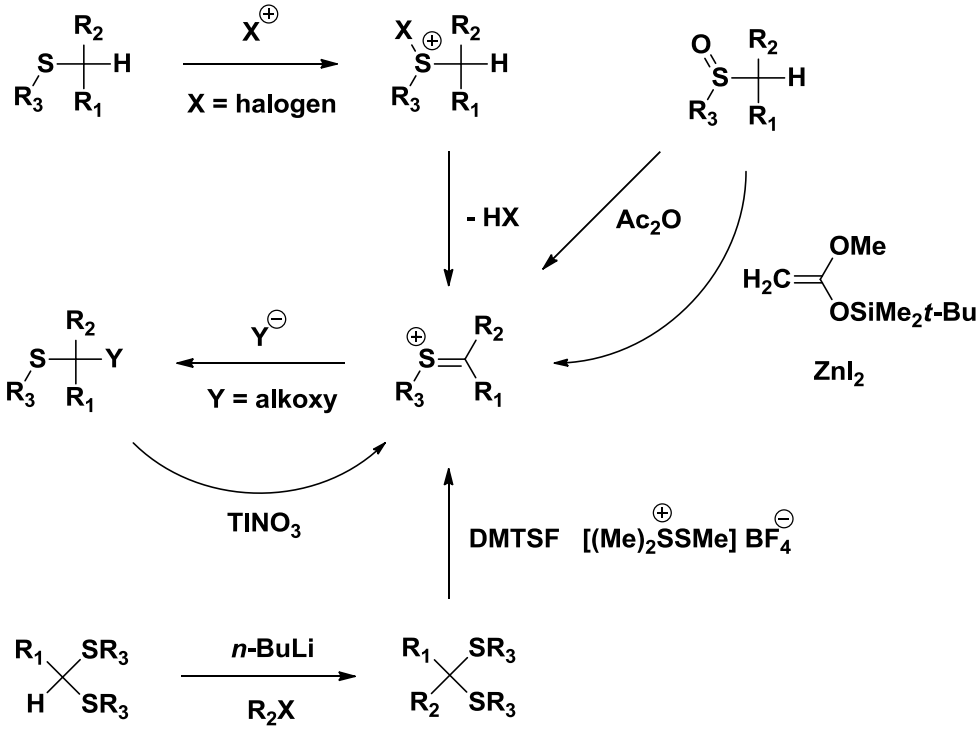


Scheme 5.3[9]

Recently, Padwa *et al.* used thionium ions to promote Mannich cyclization reactions.[10,11] For example, the isoquinolinone ring system **279** was formed from a thionium ion cyclization cascade (Scheme 5.4). The thionium ion **276** was generated from the reaction between thioacetal **273** and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) **274**. This reaction provided an alternative method for thionium ions and was first discovered by Trost and Murayama in 1981.[12,13] The electrophilic thionium ion in **276** was then attacked by the amido nitrogen atom to produce the phenylthio-substituted lactam **277**, which then underwent elimination of thiophenol to afford N-acyliminium ion **278**.[10,11] Subsequent cyclization with the aromatic ring led to the isoquinolinone ring system **279**.

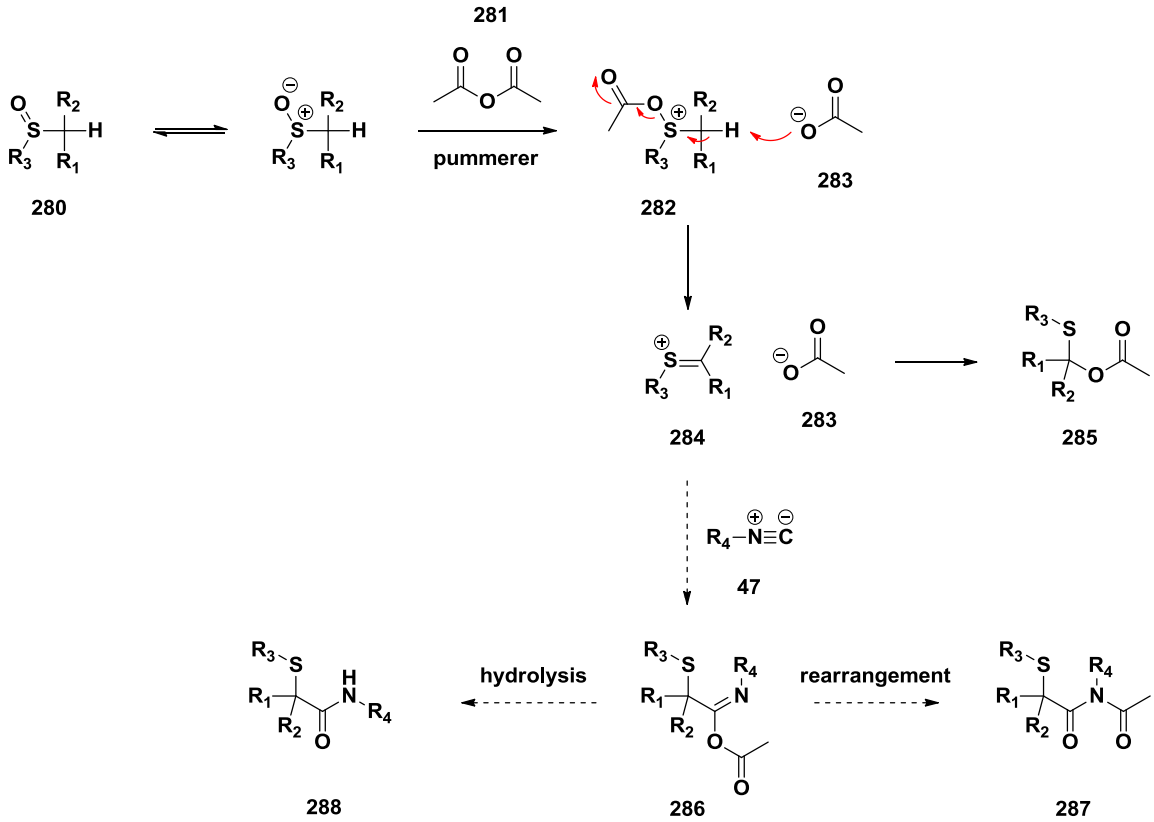


Scheme 5.4[10,11]



Scheme 5.5[11]

Currently, thionium ions may be prepared from several different precursors, as summarized in a recent report by Padwa and Waterson (Scheme 5.5).[11] Of these routes, the most convenient source of a thionium ion comes from the Pummerer reaction, in which the corresponding sulfoxide **280** reacts with acetic anhydride **281** (Scheme 5.6). The normal product of the Pummerer reaction is the α-acyloxy-thioether **285**. We hoped that by adding an isonitrile to the Pummerer reaction mixture, it would compete with the carboxylate ion **283** in attacking the electrophilic thionium ion intermediate **284**, which would lead to the formation of the intermediate **286**. Subsequent rearrangement of **286** would lead to a structure like **287**. However, if **286** instead underwent hydrolysis, a structure like **288** would arise.

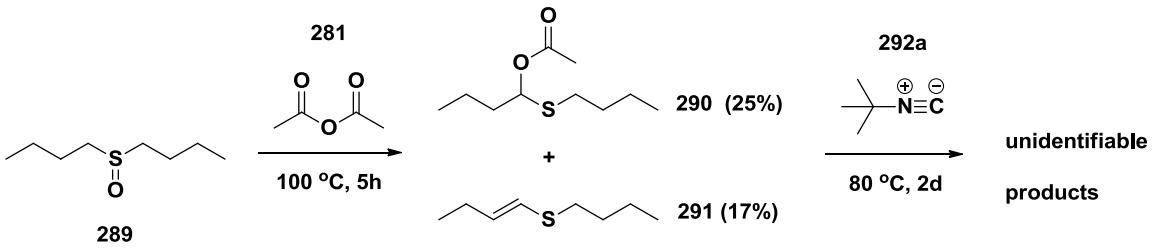


Scheme 5.6

5.2 Results and Discussion

To begin this study, we chose di-*n*-butyl sulfoxide as a prototype and conducted the Pummerer reaction using acetic anhydride under typical conditions (neat Ac_2O, 100 °C, 5 h). Initially, the product after extractive workup was lost under high vacuum drying (0.3 mm Hg) overnight. Subsequently, the product after extractive workup was carefully concentrated under high vacuum (0.3 mm Hg, 30 min) to a constant weight. ^{1}H NMR showed that the resulting orange oil was mixture of the expected Pummerer product **290** (60%) and the elimination product butyl 1-butenyl sulfide **291** (40%) (Scheme 5.7). This result agreed with a previous report by Horner and Kaiser.[14]

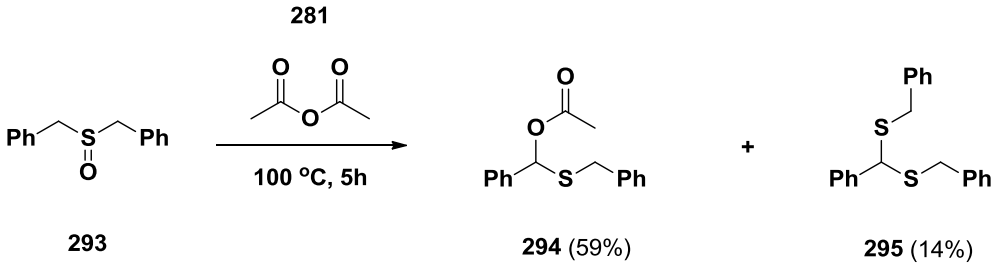
An aliquot of that mixture was then subjected to a reaction with excess neat *tert*-butylisonitrile **292a** at 80 °C for 2 days in an attempt to regenerate and intercept the desired thionium ion. However, a mixture of unidentifiable products was obtained after rotary evaporation (25 °C, 20 mm Hg). TLC of the resulting yellow oil showed multiple spots. ^{1}H NMR spectrum showed broad and unresolved peaks. IR spectrum showed a weak amide carbonyl absorption.



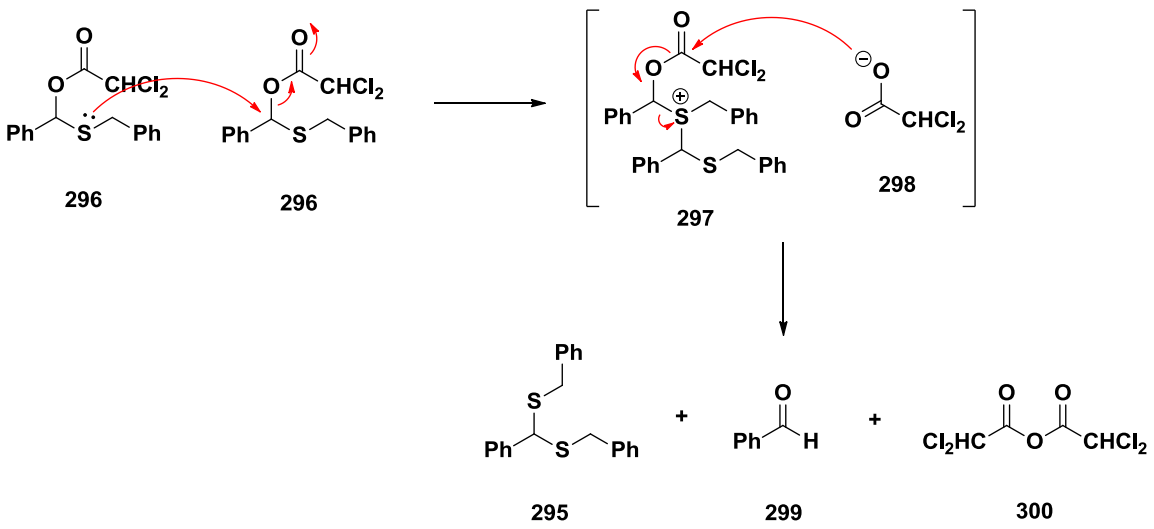
Scheme 5.7

We next turned our attention to dibenzyl sulfoxide as an alternative test of the approach, for two reasons. First, the higher MW sulfoxide would form less volatile products, thus reducing the loss upon workup. Second, the Pummerer reaction of dibenzyl sulfoxide would not form elimination products like **291**.

After dibenzyl sulfoxide **293** was stirred in neat acetic anhydride **281** at 100 °C for 5 hours, the reaction mixture was subjected to extractive workup. The expected product **294** (59%) and benzaldehyde dibenzyldithioacetal **295** (14%) were isolated after flash column chromatography (Scheme 5.8). Control experiments established that **295** was derived from **294**. In fact, the formation of thioacetals from sulfoxides under Pummerer-type conditions had been observed previously by Harris and Boekelheide, who proposed the mechanism of the self-condensation of α-dichloroacyloxy sulfide **296** shown in Scheme 5.9.[15]



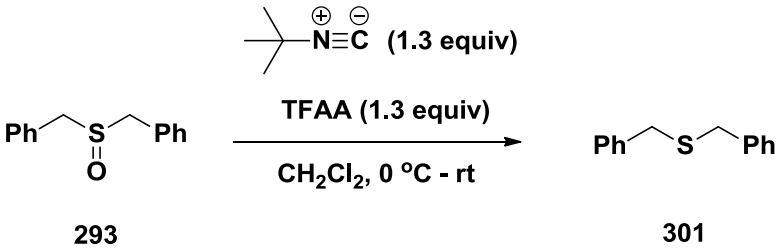
Scheme 5.8



Scheme 5.9[15]

Interestingly, no reactions occurred when a purified sample of the normal Pummerer product **294** was subjected to a reaction with 1 equiv of *tert*-butylisonitrile at rt for 20 hours, and pure **294** was recovered in near-quantitative yield. A small amount of **295** was also observed. An attempt to intercept the Pummerer reaction between dibenzyl sulfoxide **293** and acetic anhydride by including 3 equiv of *tert*-butylisonitrile in the reaction mixture was also unsuccessful, and led to unidentifiable products.

We reasoned that since the Pummerer reaction between sulfoxides and acetic anhydride required prolonged heating at high temperature, such conditions might favor by-product formation. The Pummerer reaction may be conducted at lower temperature using trifluoroacetic anhydride (TFAA). To our surprise, when dibenzyl sulfoxide was reacted with TFAA (1.3 equiv) and *tert*-butylisonitrile (1.3 equiv) in CH_2Cl_2 (0 °C → rt), dibenzyl sulfide **301** was obtained in near-quantitative yield (Scheme 5.10). This unexpected and efficient reduction of the sulfoxide was not observed in the comparable reaction of **293** with *tert*-butylisonitrile using acetic anhydride.

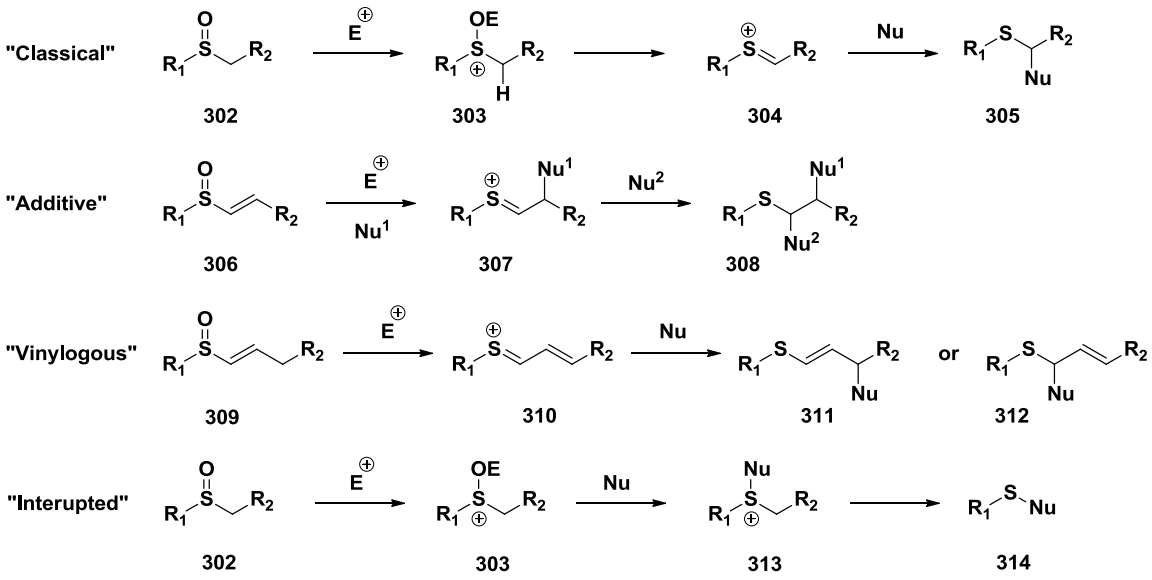


Scheme 5.10

From the mechanistic point of view, the reduction of sulfoxide **293** must be accompanied by an oxidation, most likely of *tert*-butylisonitrile. Real-time monitoring of the reaction mixture by IR unambiguously established the formation of isocyanate (strong band at 2257 cm^{-1}).

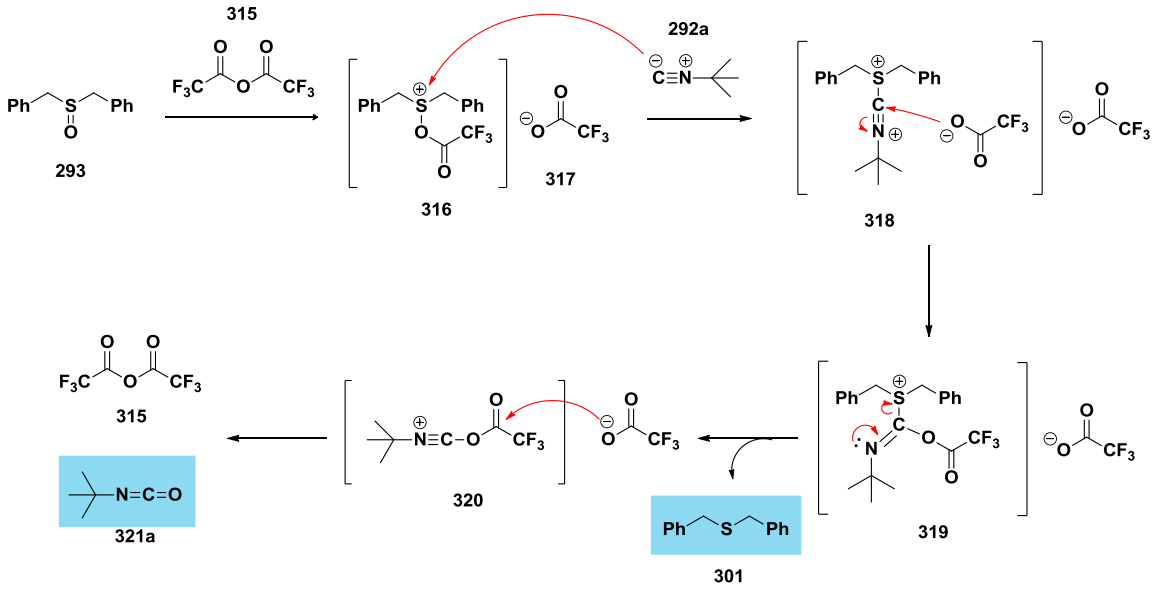
A literature search revealed that the Pummerer process could be intercepted using nucleophiles in different fashions as summarized in a recent report by Procter *et al* (Scheme 5.11).[7] In the "classical" Pummerer reaction, sulfoxide **302** undergoes elimination upon O activation, leading to the formation of thionium ion **304**. Nucleophiles such as acetate, arenes, alkenes, and phenols attack **304** to afford α-substituted sulfide **305**. Electrophiles used to activate sulfoxide **302** include acetic anhydride, TFAA, trifluoromethanesulfonic anhydride (Tf_2O), or a silyl chloride. Nucleophiles used in the "classical" Pummerer reaction are usually unreactive towards these activators. Aromatic and vinyl sulfoxides would participate in "additive" and "vinylogous" reactions, respectively, to afford compounds such as **308**, **311**, and **312**. Various nitrogen-containing nucleophiles, such as aromatic amines, carboxylic acid amides, and sulfonamides,[16] would interrupt the Pummerer process at an earlier stage by

attacking the tricoordinate sulfur intermediate **303** at the sulfur atom, affording unexpected products like **313** and **314**.



Scheme 5.11[7]

Based on those findings, a plausible mechanism for the formation of isocyanate is depicted in Scheme 5.12. Nucleophilic attack of the oxy-sulfonium species **316** by *tert*-butylisonitrile **292a** afforded the nitrium species **318** which then fragmented, leading to the isocyanate **321a**.



Scheme 5.12

Isocyanates, which embody the N=C=O functional group, undergo several synthetically useful reactions, including nucleophilic addition of alcohols and amines to produce urethanes and ureas, respectively.[17] Isocyanates are also intermediates in several well-known organic reactions, including the Hofmann rearrangement of primary amides,[18] the Curtius rearrangement of acyl azides,[19,20] the Schmidt reaction of carboxylic acids with hydrazoic acid,[21] and the Lossen rearrangement of hydroxamic acids.[22,23] Diisocyanates are widely used in chemical industry to produce polyurethanes and other polymers.[24,25]

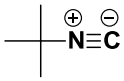
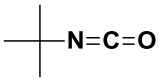
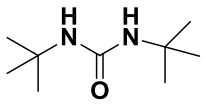
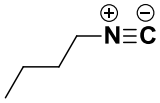
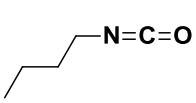
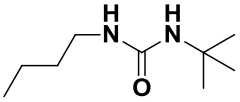
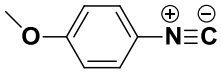
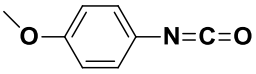
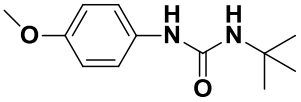
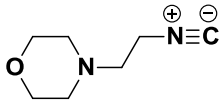
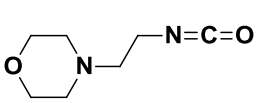
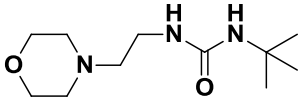
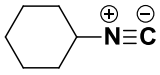
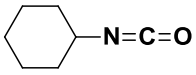
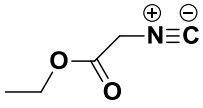
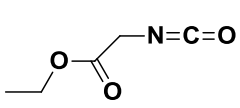
Given the broad synthetic utility of isocyanates, dozens of procedures have been described for preparing them, including several routes from isonitriles. Isonitrile-to-isocyanate oxidations have been reported with the use of mercuric oxide,[26] lead tetraacetate,[27] and ozone,[28] as well as halogen- or acid-catalyzed oxidations by

DMSO[29,30] and pyridine N-oxide.[31] However, recent interest in highly functionalized isocyanates drives the continuing demand for new synthetic methodology.[32,33]

The proposed mechanism suggested that dimethyl sulfoxide (DMSO) might replace dibenzyl sulfoxide as a more convenient oxidizing agent. The mechanism also suggested that only a catalytic quantity of TFAA might be needed for the oxidation. To test these predictions, a sample of *tert*-butylisonitrile was treated with DMSO (1.1 equiv) and TFAA(0.05 equiv) at low temperature (CH_2Cl_2, - 78 °C to rt, 10 min), whereupon a strong isocyanate band was observed in the IR and trapping with *tert*-butylamine afforded di(*tert*-butyl)urea in 96% yield.

TFAA-catalyzed oxidations of representative isonitriles **292a – f** by DMSO are summarized in Table 5.1, and illustrate the broad scope and efficiency of the method. The data indicated that alkyl, cycloalkyl, and aryl isonitriles were smoothly transformed into isocyanates by using catalytic amounts of TFAA, with one exception. Oxidations of morpholinoethylisonitrile **292d** with 5 – 20 % TFAA returned substantial amounts of the starting isonitrile. To test whether the morpholinyl group interfered with the catalysis, the oxidation of morpholinoethylisonitrile **292d** was conducted with 1.1 equiv of TFAA. While the isonitrile was completely consumed, no characteristic stretching frequency for the isocyanate group in **321d** was detected. Nevertheless, addition of *tert*-butylamine to the crude product afforded the expected urea **322d**. This suggested that there were some other species that suppressed the signal of the isocyanate in the IR measurement. We were not sure about the structure of this new compound; it could be the adduct of the morpholinyl group and isocyanate. However, this new compound behaved just like an isocyanate because it reacted with *tert*-butylamine to afford the expected urea **322d**.

Table 5.1 Oxidation of Isonitriles to Isocyanates

Isonitrile	Isocyanate (% Yield)	Derivative (% Yield) [a]
 **292a**	 **321a**	 (96) **322a**
 **292b**	 **321b**	 (95) **322b**
 **292c**	 **321c**	 (61) **322c**
 **292d**	 **321d**	 (67) [b] **322d**
 **292e**	 (94) **321e**	
 **292f**	 (95) **321f**	

[a] Spectroscopic data for all derivatives matched literature values.

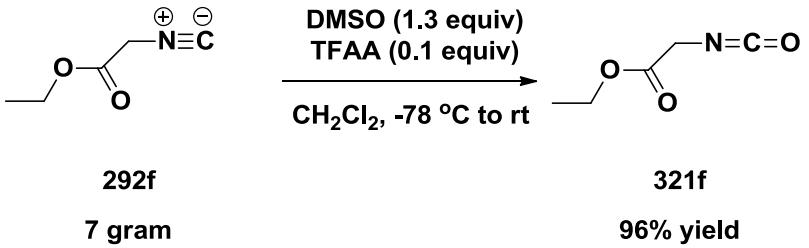
[b] 1.1 equiv of TFAA was used in this experiment.

Since the only byproducts accompanying isocyanate formation, dimethyl sulfide and residual TFAA, are volatile, it was of interest to determine whether some isocyanates might be isolated directly in nearly pure form by careful evaporative workup. Entries 5 and 6 in Table 5.1 showed that cyclohexyl isocyanate **321e** and ethyl isocyanatoacetate **321f** could be isolated in excellent yield by rotary evaporation of solvent and concentrated *in vacuo* to a constant weight. In each case, the only byproduct detectable by NMR was a few percent of residual DMSO.

The method reported here for catalytic oxidation of isonitriles to isocyanates is rapid and mild, and promises to be of utility to synthetic chemists. Besides using inexpensive, readily available reagents, the method generates volatile and innocuous byproducts, often making possible direct isolation of the desired isocyanates without extractive workup.

Unlike the halogen-catalyzed DMSO oxidations reported earlier,[29] which require prolonged heating at reflux and have been proposed to involve isonitrile – halogen adducts, the TFAA-catalyzed oxidations that we developed occur rapidly at low temperature by a different mechanism. Our method is simple and easy to use, and represents a very mild, rapid, and environmentally acceptable procedure for preparing isocyanates from isonitriles. Not to be overlooked is the concomitant and equally useful synthetic conversion of sulfoxides to sulfides.

As a demonstration on the simplicity and usefulness of the method, ethyl 2-isocyanatoacetate **321f** was successfully synthesized from ethyl 2-isocyanoacetate **292f** on a 7g scale in 96% yield (Scheme 5.13).

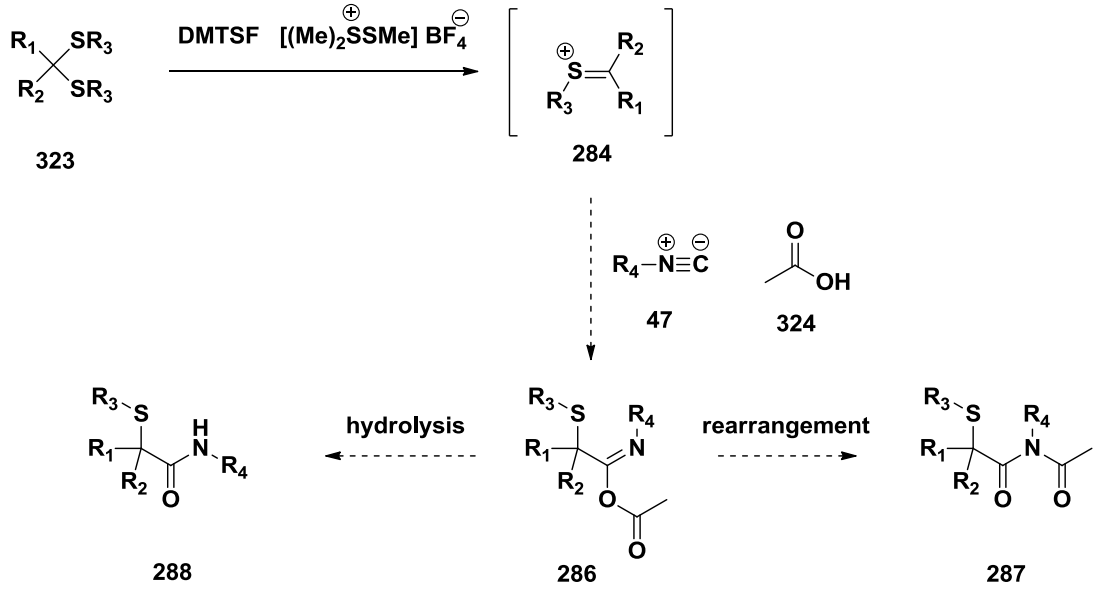


Scheme 5.13

Ethyl 2-isocyanatoacetate **321f** has previously been prepared by the reaction of ethanol with 2-isocyanatoacetyl chloride.[34] It has also been synthesized by the reaction of ethyl hydrogen malonate using diphenylphosphoryl azide *via* a Curtius rearrangement.[35] Ethyl 2-isocyanatoacetate can also be prepared from various glycine derivatives, including the reaction of N-tosylglycine ethyl ester[36] or N-trimethylsilylglycine ethyl ester[37] with phosgene, or the reaction of glycine ethyl ester hydrochloride with bis(trichloromethyl)carbonate.[38]

5.3 Future Directions

Guided by the SRR approach, an attempt to replace the imine species in the Ugi reaction with a comparable electrophilic thionium ion species instead uncovered a fast and gentle catalytic oxidation of isonitriles to isocyanates. The formation of isocyanates instead of the desired "thia-Ugi" process may be understood if the tricoordinate sulfur intermediate **303** is intercepted by the isonitrile before it is converted into thionium ion **304**. Thus, Pummerer reaction was not a fruitful source of thionium ions in our study. To solve this problem, we need to access thionium ions from an alternative route.



Scheme 5.14

Of all the routes to thionium ions from different precursors shown in Scheme 5.5, the approach from thioketals and DMTSF does not go through a tricoordinate sulfur intermediate, thus it might prevent the problem observed in the Pummerer reaction of sulfoxides (Scheme 5.14).

5.4 Experimental Procedures

General Procedures

^{1}H NMR spectra were taken on a Varian Inova-400 spectrometer using $CDCl_3$ with 0.05% v/v TMS or DMSO-d6 as solvents, recorded in δ (ppm), and referenced to TMS (0.00 ppm) or DMSO-d6 (2.50 ppm). ^{13}C NMR spectra were taken on a Varian Inova-400 spectrometer using $CDCl_3$ with 0.05% v/v TMS as solvent, recorded in δ (ppm), and referenced to $CDCl_3$ (77.16 ppm for ^{13}C NMR). IR spectra were obtained using a Thermo Nicolet Avatar 370DTGS FT-IR spectrometer and recorded in

wavenumbers (cm^{-1}). Melting points were measured using a Thomas Hoover Uni-melt capillary melting point apparatus. Mass spectra were measured at the Life Sciences Core Laboratories Center using ABI/MDS Sciex 4000 Q Trap. Chemicals were obtained from Aldrich, Acros, Aensar, or Fluka and used as received unless specified.

Reduction of Dibenzyl Sulfoxide 293 to Dibenzyl Sulfide 301

Dibenzyl sulfoxide (115 mg, 0.5 mmol, recrystallized from ethanol) was dissolved in dry CH_2Cl_2 (0.5 mL) under N_2 in a 25 mL round-bottom flask. *tert*-Butyl isonitrile (74 µL, 0.65 mmol) was added *via* syringe. After cooling the solution to 0 °C, TFAA (91µL, 0.65 mmol) was added dropwise. The resulting solution was stirred vigorously at 0 ^oC for 5 min, then warmed to rt and stirred for 5 min. The solution was then concentrated *in vacuo* to afford a white paste, which was then purified by flash column chromatography (1:15 ethyl acetate:hexane, R_f=0.35) to afford the desired sulfide **301** as a white solid (94 mg). Yield: 88%.

Representative Procedure for the Catalytic Oxidation of Isonitriles to Isocyanates: Oxidation of tert-Butyl Isonitrile 292a and Trapping with tert-Butylamine to Afford di(tert-Butyl)urea 322a

A solution of *tert*-butylisonitrile (113 µL, 1 mmol) in dry CH_2Cl_2 (1 mL) and dry DMSO (78 µL, 1.1 mmol) under N_2 in a 25 mL round-bottom flask was cooled to -60 ^oC, then TFAA (7 µL, 0.05 mmol) was added. The resulting solution was stirred vigorously at -60 ^oC for 5 min, then warmed to rt and stirred for 5 min. After cooling the solution again to -60 ^oC, *t*-butylamine (315 µL, 3 mmol) was added dropwise. The resulting solution was stirred at rt for 2 hr, then concentrated *in vacuo* to afford a white solid. Water (3 mL) was added and the aqueous phase was extracted with ethyl acetate (4 x 5

mL). The combined organic extracts were washed with brine (2 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford di(*tert*-butyl)urea **322a** as a white solid (165 mg). Yield: 96%, m.p. 252 – 254 ^oC (sealed capillary tube) (lit.[39] 240 ^oC).

N-n-butyl-N'-tert-butylurea ***322b***: Yield: 95%, m.p. 73–76 ^oC (lit.[40] 71–72 ^oC).

N-tert-butyl-N'-4-methoxyphenylurea ***322c***: Yield: 61%, m.p. = 129 – 130. 5 ^oC (lit.[41] 128 – 130 ^oC).

N-tert-butyl-N'-2-morpholinoethylurea ***322d***: Yield: 67%. IR (neat) 3350(s), 2961(s), 2926(m), 2856(m), 2811(m), 1638(s), 1558(s). ESI-MS (CH_3OH) 230 (M+H).

Representative Procedure for the Catalytic Oxidation of Isonitriles with Direct Isolation of the Isocyanate: Ethyl 2-Isocyanatoacetate 321f

A solution of ethyl 2-isocyanoacetate (115 µL, 1 mmol) in dry CH_2Cl_2 (1 mL) and dry DMSO (78 µL, 1.1 mmol) under N_2 in a 25 mL round-bottom flask was cooled to -60 ^oC, then TFAA (7 µL, 0.05 mmol) was added. The resulting solution was stirred vigorously at -60 ^oC for 5 min, then warmed to rt and stirred for 5 min. The solution was then concentrated using a rotary evaporator and then *in vacuo* (0.2 Torr) for 1 min to afford the desired isocyanate **321f** as brown oil (122 mg). Yield: 95%. IR and ^1H NMR matched with those in the Aldrich Spectral Library. IR (neat) 3349(m), 2986(m), 2254(s), 1747(s).

Cyclohexyl isocyanate ***321e***: Yield: 94%. IR and ^1H NMR matched those in the Aldrich Spectral Library. IR (neat) 2937(s), 2858(m), 2263(s).

Procedure for the Synthesis of Ethyl 2-Isocyanatoacetate 321f on a 7g Scale

Caution: Dimethyl sulfide, a by-product of this reaction, is a highly flammable liquid and an irritant with an extremely unpleasant odor. The experimentalist should

wear gloves, and the reaction and its workup should always be performed in a well-ventilated hood.

A 250-mL round-bottomed flask with a 24/40 joint equipped a Teflon-coated oval-shaped magnetic stir bar (3.2 cm x 1.5 cm) and topped with a rubber septum is flushed with nitrogen (Note 1). Dichloromethane (60 mL) is added *via* syringe (Note 2). Ethyl 2-isocyanoacetate (7.0 mL, 60.8 mmol) is added *via* syringe to afford a brown solution (Note 3). Dimethyl sulfoxide (5.4 mL, 76 mmol) is added *via* syringe (Note 4). The resulting solution is cooled to –78 °C in a dry ice/acetone bath, then trifluoroacetic anhydride (0.86 mL, 6.2 mmol) is added dropwise *via* syringe over 5 min (Note 5). The resulting solution is stirred for 5 min at –78 °C, then the dry ice/acetone bath is removed, and the dark brown solution is allowed to warm to rt over 1 h and stirred for an additional 5 min (Note 6). The magnetic stir bar is removed using a Teflon-coated magnet retriever and rinsed with dichloromethane (0.5 mL). The reaction mixture is concentrated in the hood by rotary evaporation at 20 mm Hg. The resulting brown concentrate is dissolved in ice-cold dichloromethane (20 mL) and washed with three 10 mL portions of ice-cold deionized water. The organic layer is dried over anhydrous magnesium sulfate powder (1g) and filtered through a 30 mL sintered glass funnel using 3 x 5 mL portions of fresh solvent for rinsing (Note 7). The filtrate is concentrated by rotary evaporation (25 °C, 20 mm Hg) (Note 8) and then under high vacuum (0.3 mm Hg) for 30 min to afford 7.58–7.66 g (96–97%) of ***321f*** as a dark brown oil (Notes 9 and 10).

Note:

1. The round-bottomed flask and the magnetic stir bar were dried in an oven, cooled to room temperature under high vacuum, and subsequently maintained under a positive pressure of nitrogen.

2. Dichloromethane (Optima® grade) was purchased from Fisher Scientific and dried over activated alumina solvent purification system (Innovative Technology Inc. Pure Solv™).

3. Ethyl 2-isocyanoacetate (95%) was purchased from Aldrich Chemical Company Inc. and the dark brown oil was used without further purification.

4. Dimethyl sulfoxide (DMSO, anhydrous, ≥99.9%) was purchased from Sigma-Aldrich and used without further purification.

5. Trifluoroacetic anhydride (≥99%) was purchased from Sigma-Aldrich and used without further purification.

6. After stirring at room temperature for 5 min, a few drops of the reaction solution were removed *via* Pasteur pipet and submitted to IR analysis to confirm that the reaction was complete (complete disappearance of isonitrile stretch at 2164 cm^{-1}; appearance of isocyanate stretch at 2255 cm^{-1}).

7. Magnesium sulfate anhydrous powder was purchased from Fisher Scientific and used without further purification.

8. Removing the bulk of the solvent by rotary evaporation was judged complete when the flask no longer felt cold to the touch after the water bath was lowered from the evaporator.

9. The product was a dark brown oil which appeared pure by ^{1}H and ^{13}C NMR spectroscopy. When stored at room temperature, the neat product decomposed with a half-life of ca. 12 h into unidentifiable solid. However, decomposition could be suppressed by wrapping the sample in aluminum foil and storing it neat at –10 °C. After 4 days, only traces of solid decomposition product were observed.

10. The product isocyanate displayed the following spectroscopic characteristics, which matched published spectra:[37,42] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (t, 3 H, J = 7.2 Hz), 3.94 (s, 2 H), 4.29 (q, 2 H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 44.4, 62.4, 127.3 (weak), 169.2; IR (neat, cm^{-1}): 3363 (m), 2987 (m), 2943 (m), 2255 (s), 1749 (s).

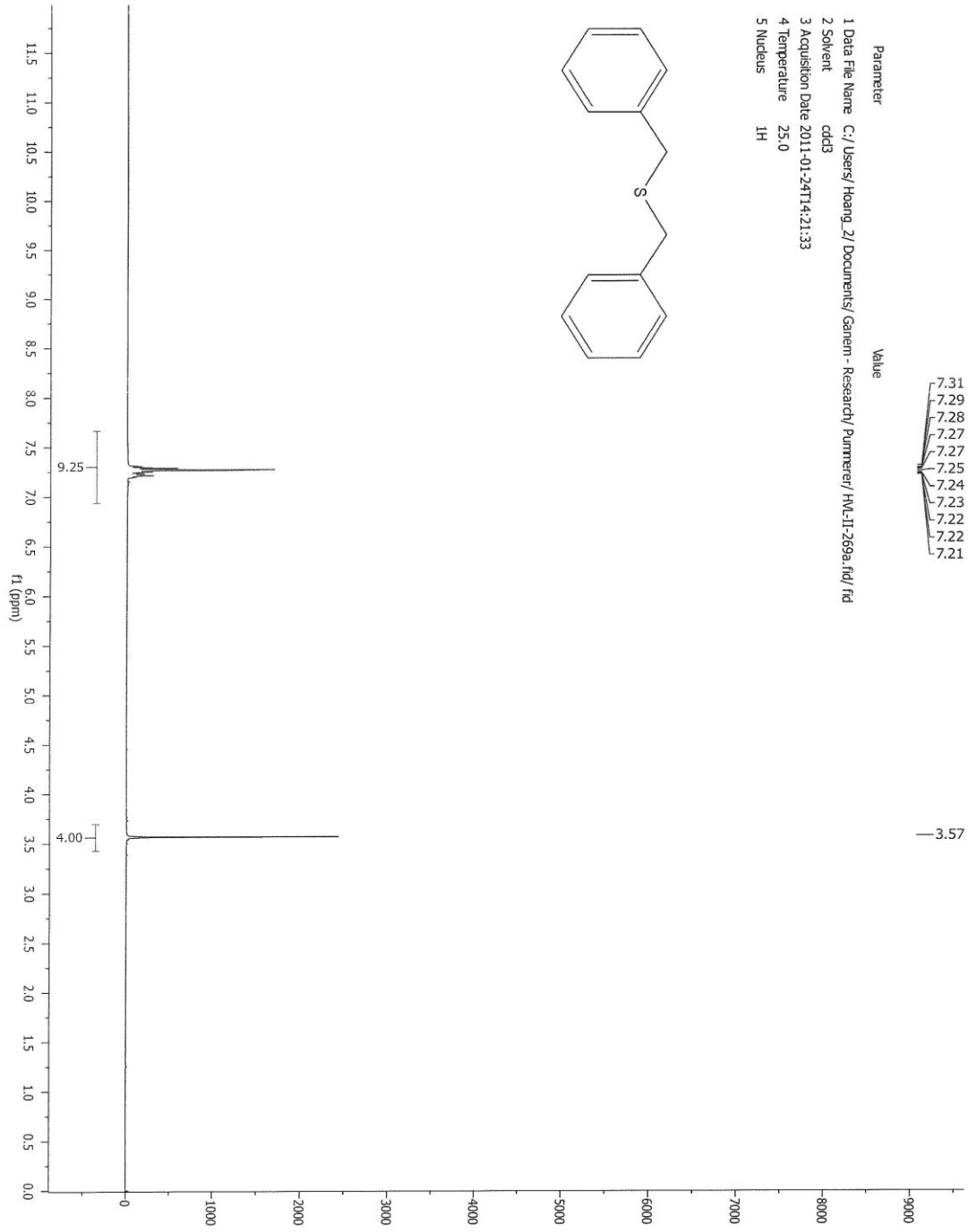


Figure 5.1 ^{1}H NMR Spectrum of Dibenzyl Sulfide **301**

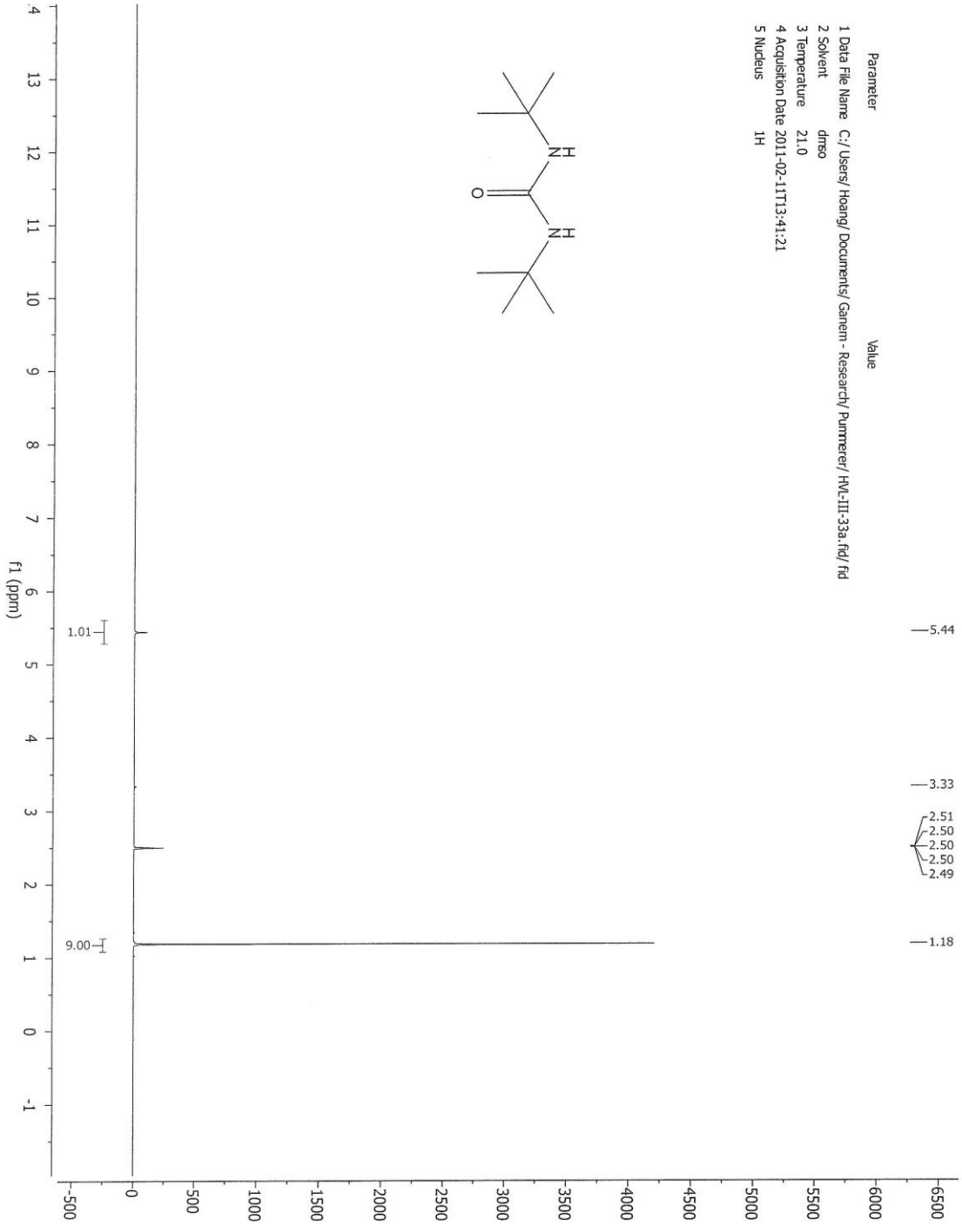


Figure 5.2 ^{1}H NMR Spectrum of di(*tert*-Butyl)urea **322a**

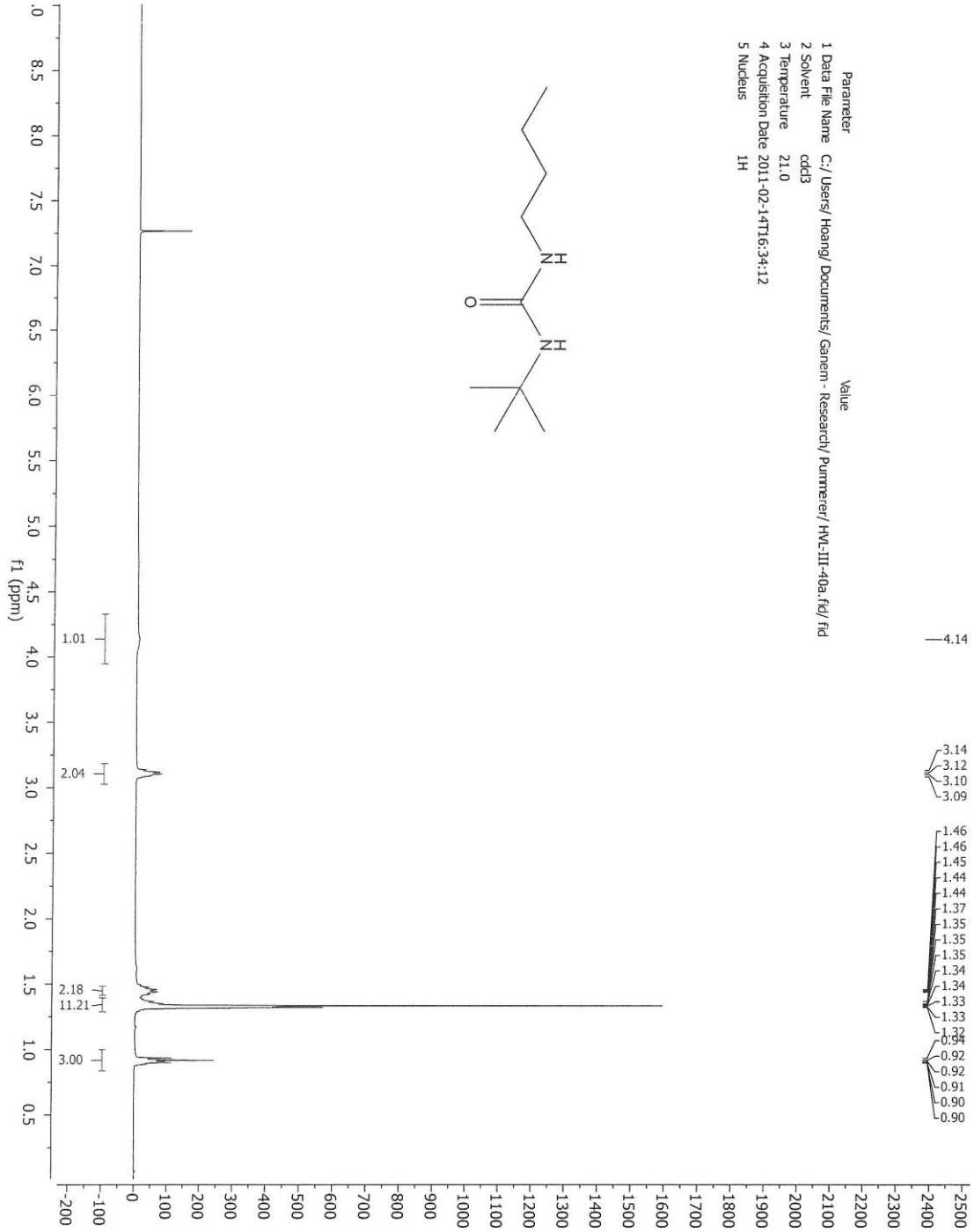


Figure 5.3 ^{1}H NMR Spectrum of N-*n*-Butyl-N'-*tert*-Butylurea **322b**

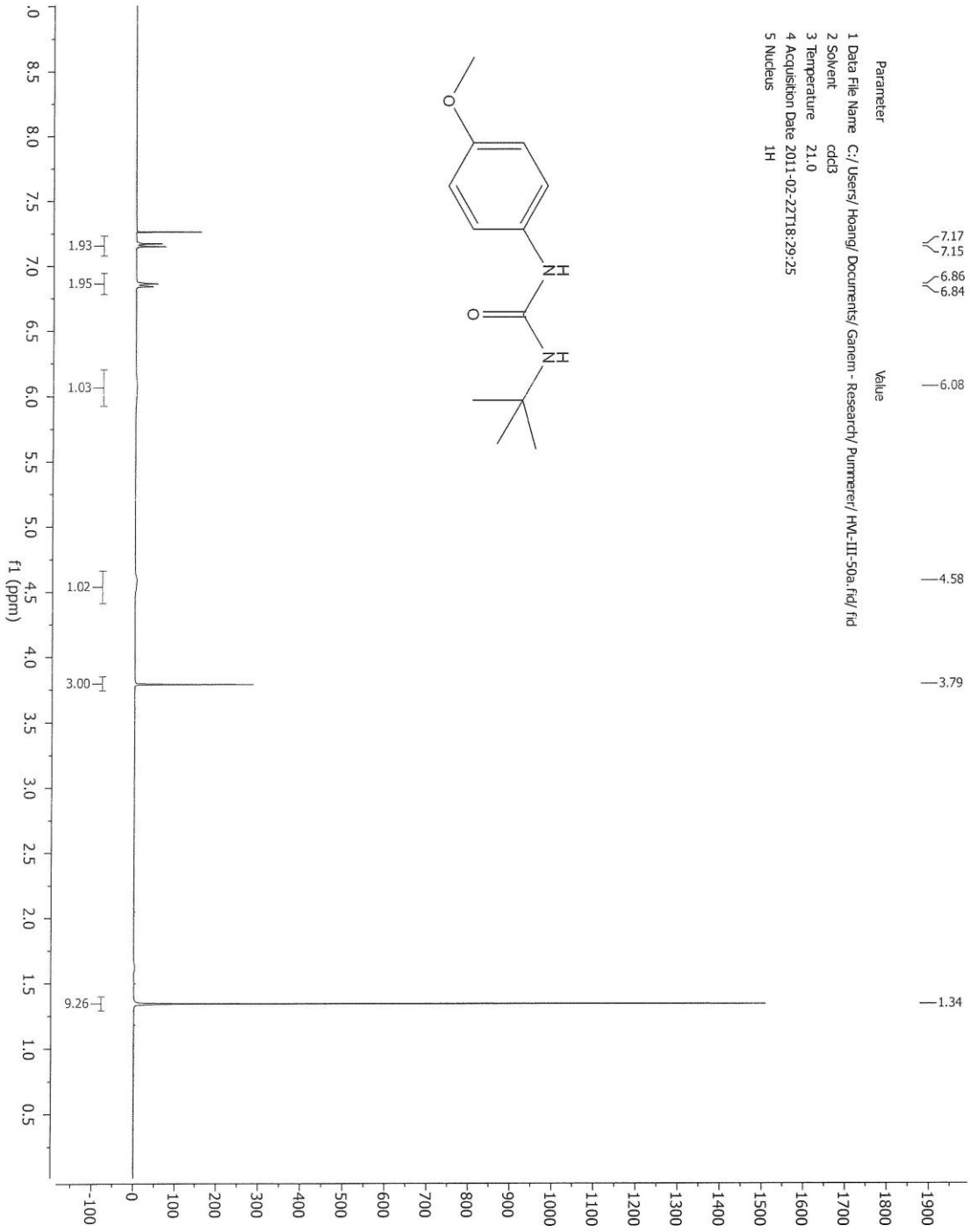


Figure 5.4 ^{1}H NMR Spectrum of N-*tert*-Butyl-N'-4-Methoxyphenylurea **322c**

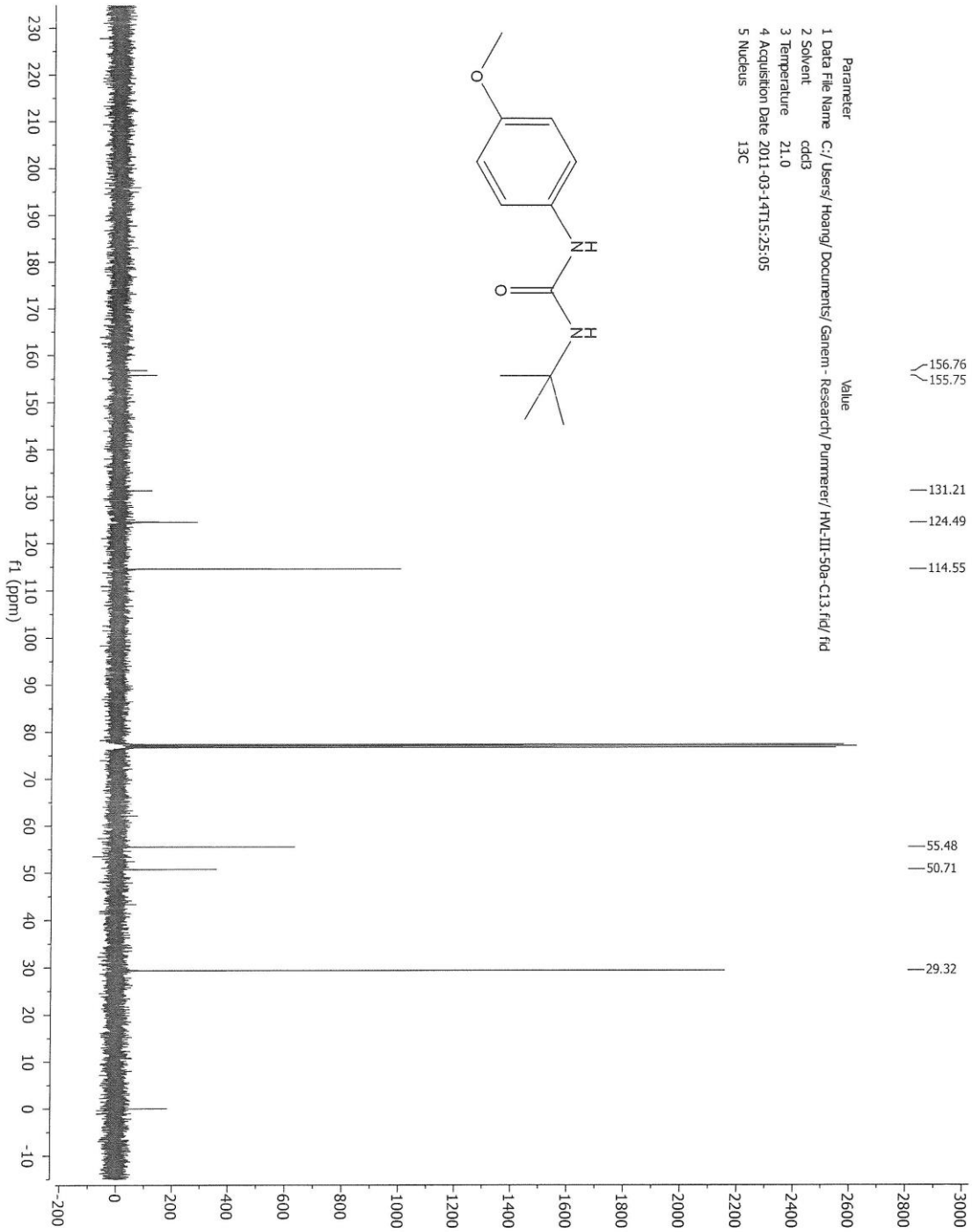


Figure 5.5 ^{13}C NMR Spectrum of N-*tert*-Butyl-N'-4-Methoxyphenylurea **322c**

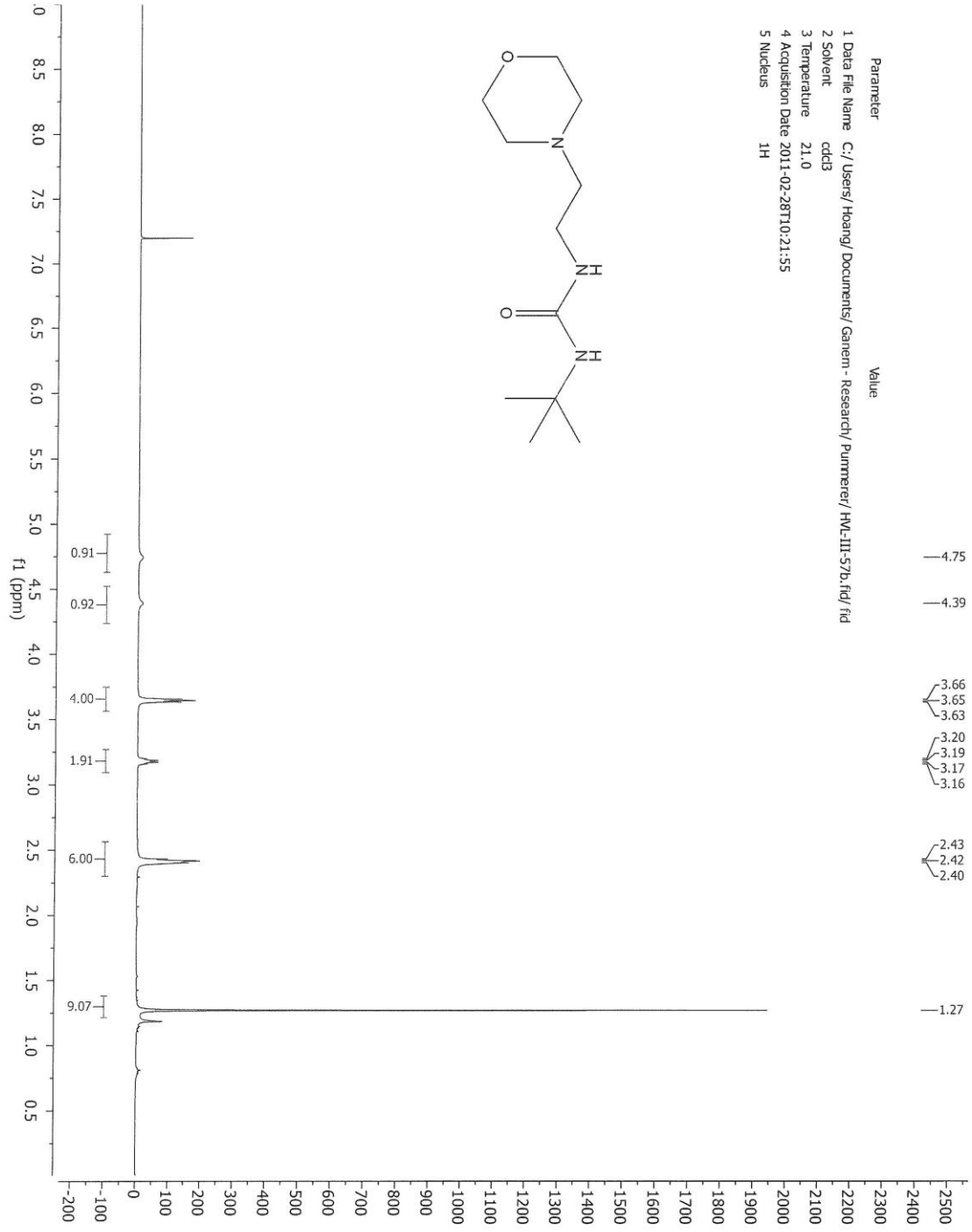


Figure 5.6 ^{1}H NMR Spectrum of N-*tert*-Butyl-N'-2-Morpholinoethylurea **322d**

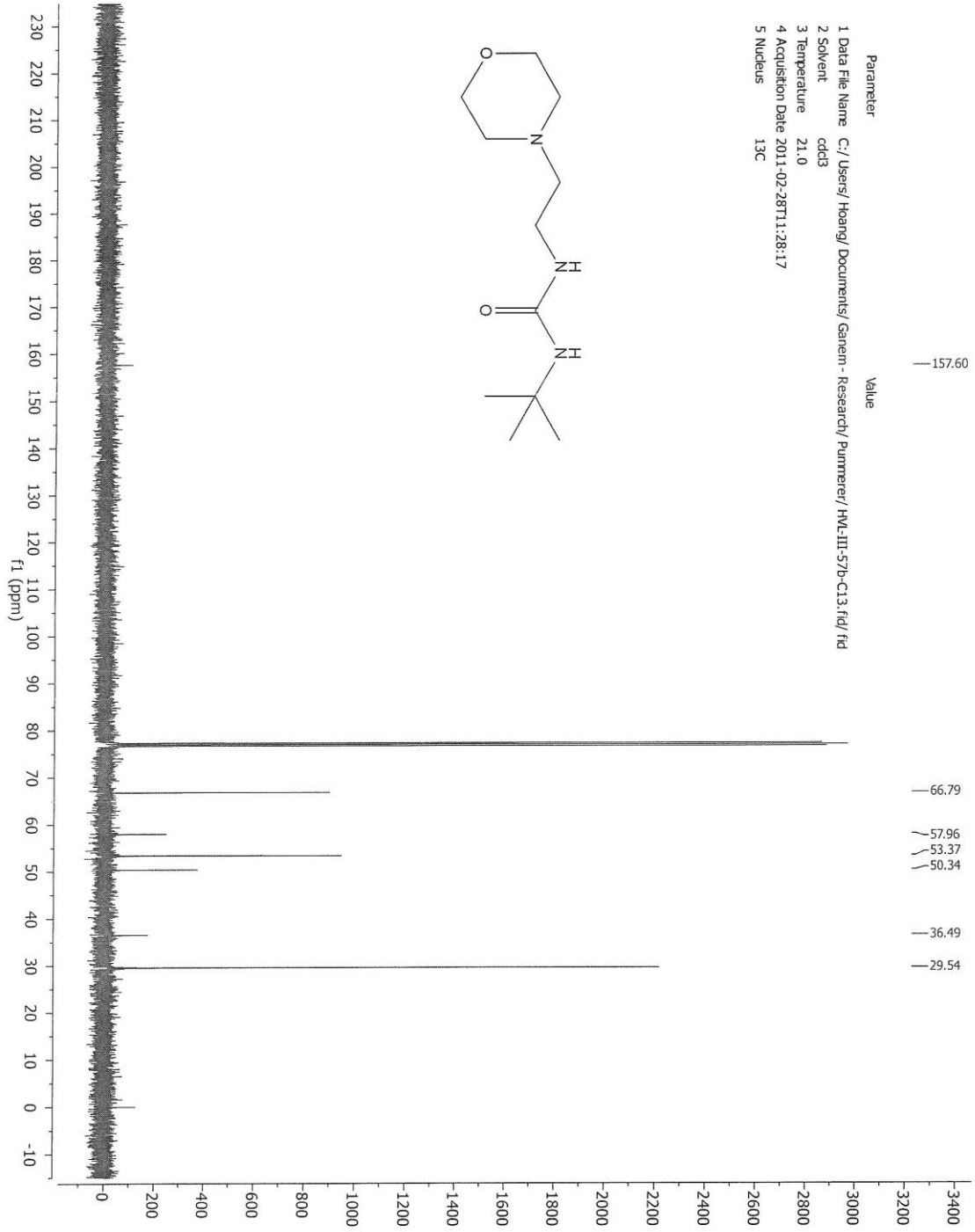


Figure 5.7 ^{13}C NMR Spectrum of N-*tert*-Butyl-N'-2-Morpholinoethylurea **322d**

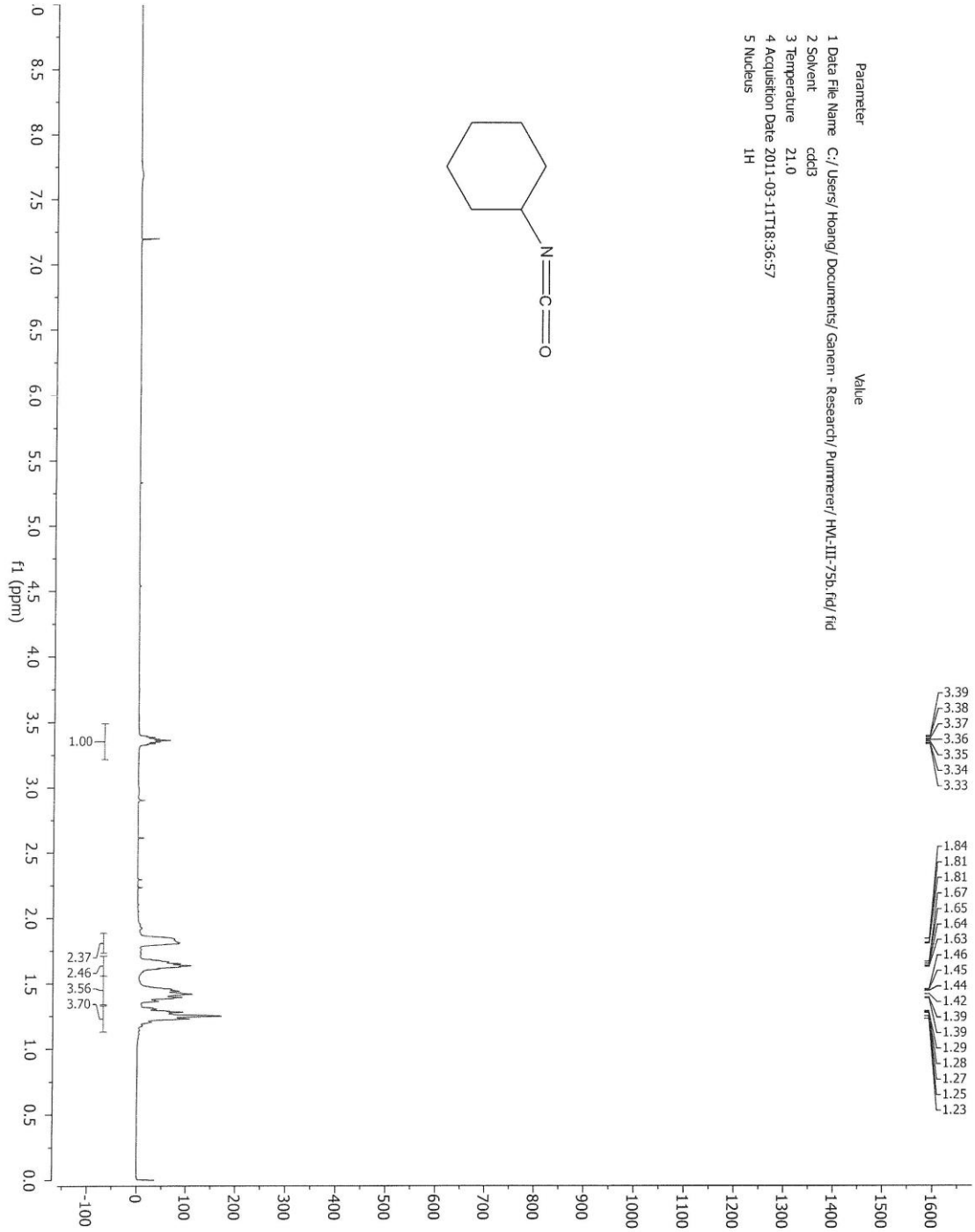


Figure 5.8 ^{1}H NMR Spectrum of Cyclohexyl Isocyanate **321e**

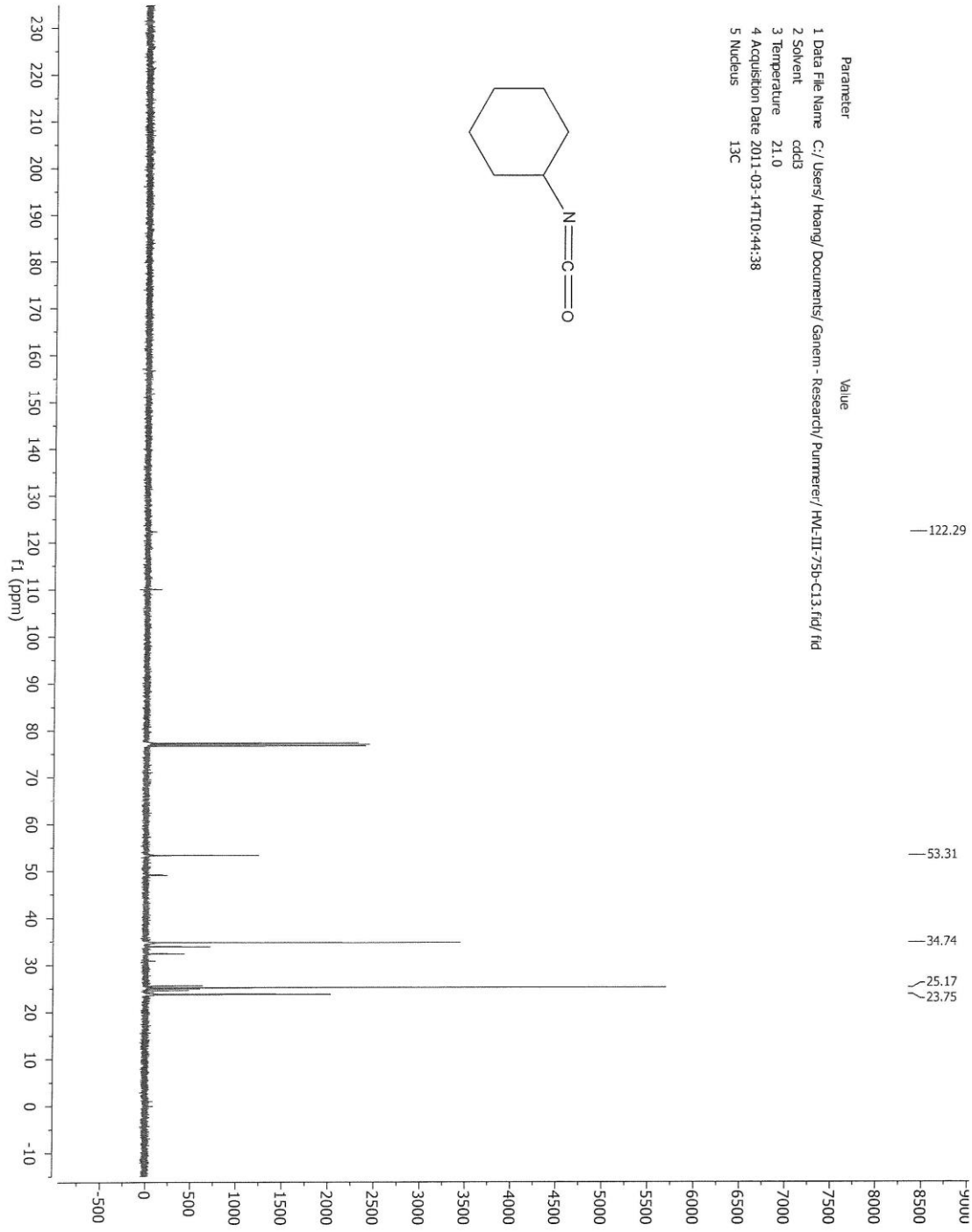


Figure 5.9 ^{13}C NMR Spectrum of Cyclohexyl Isocyanate **321e**

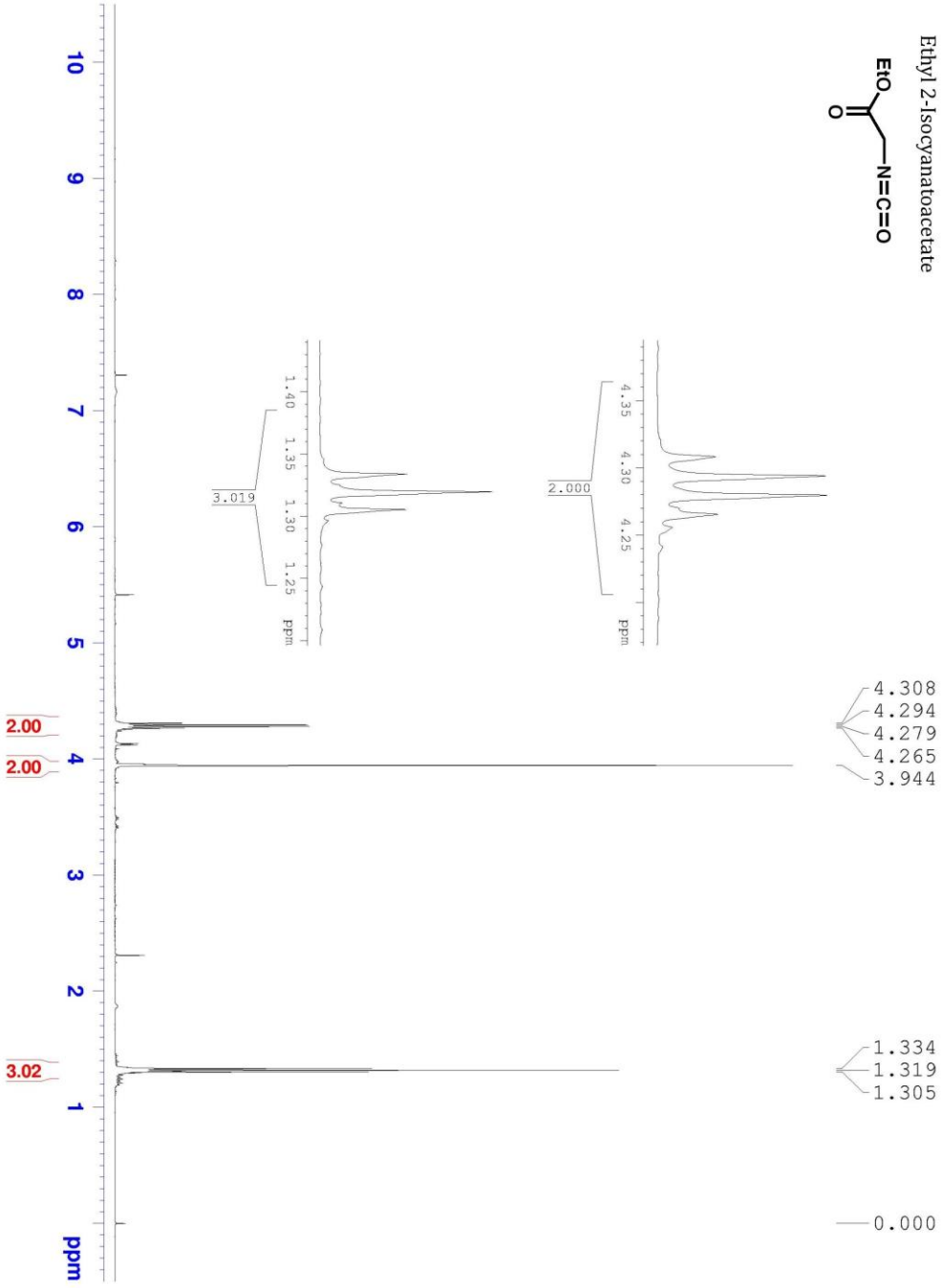


Figure 5.10 ^{1}H NMR Spectrum of Ethyl 2-Isocyanatoacetate **321f**

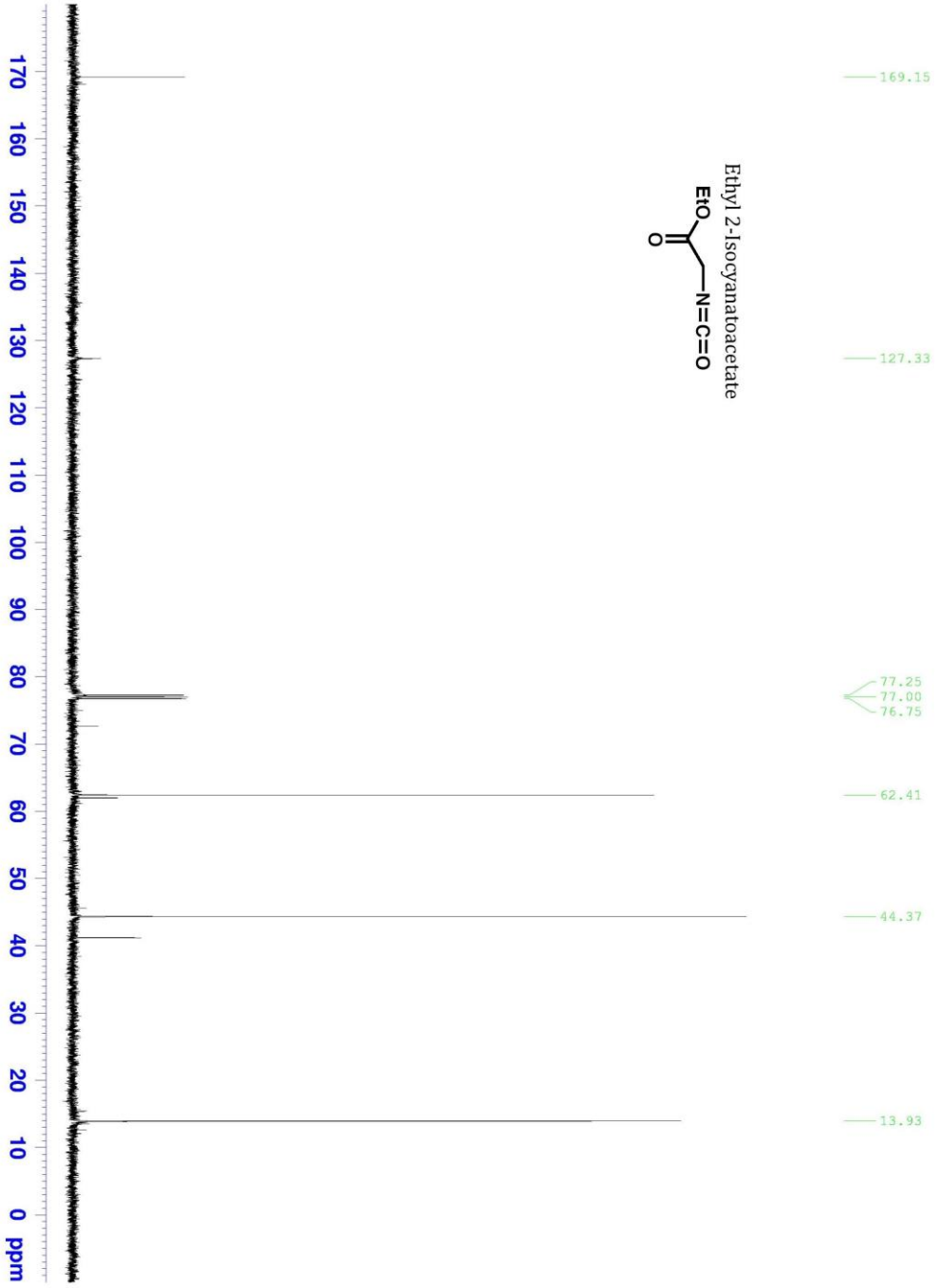


Figure 5.11 ^{13}C NMR Spectrum of Ethyl 2-Isocyanatoacetate **321f**

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