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Sulfoxides as an intramolecular sulfenylating agent for indoles and diverse applications of the sulfide-sulfoxide redox cycle in organic chemistry

Parag V. Jog
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SULFOXIDES AS AN INTRAMOLECULAR SULFENYLATING
AGENT FOR INDOLES AND DIVERSE APPLICATIONS OF THE
SULFIDE-SULFOXIDE REDOX CYCLE IN ORGANIC CHEMISTRY

By

PARAG V. JOG

A DISSERTATION

Submitted in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

(Chemistry)

MICHIGAN TECHNOLOGICAL UNIVERSITY

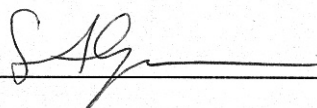
2005

This dissertation, “Sulfoxides as an Intramolecular Sulfenylating Agent for Indoles and Diverse Applications of the Sulfide-Sulfoxide Redox Cycle in Organic Chemistry”, is hereby approved in partial fulfillment of the requirements of the degree of DOCTOR OF PHILOSOPHY in the field of Chemistry.

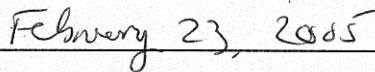
Department of Chemistry



Dissertation Advisor: Prof. Dallas K. Bates



Department Chair: Dr. Sarah A. Green



Date

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Abstract

This dissertation involves study of various aspects of sulfoxide chemistry. Specifically designed *t*-butyl and propanenitrile sulfoxides tethered to indole-2-carboxamide were used as a source of intramolecular sulfenylating agents to synthesize novel indolo[3,2-*b*]-1-5-benzothiazepinones which are structurally analogous to the other biologically active benzothiazepinones. This study reveals that the intramolecular cyclization of sulfoxide follows an electrophilic sulfenylation (Sulfoxide Electrophilic Sulfenylation, SES) reaction pathway. Evidence of the absence of sulfenic acid as a transient reactive intermediate in such intramolecular cyclization is also provided.

In another study, sulfoxide was used as a “protecting group” of thioether to synthesize 8-membered, indole substituted, thiazocine-2-acetic acid derivative via Ring Closing Metathesis (RCM). Protection (oxidation) of inert (to RCM) sulfide to sulfoxide followed by RCM produced cyclized product in good yields. Deprotection (reduction) of sulfoxide was achieved using Lawessons Reagent (L.R.). Application of the sulfide-sulfoxide redox cycle to solve the existing difficulties in using RCM methodology to thioethers is illustrated.

A new design of a “molecular brake”, based on the sulfide-sulfoxide redox cycle is described. N-Ar rotation in simple isoindolines is controlled by the oxidation state of the proximate sulfur atom. Sulfide [S(II)] shows “free” [brake OFF] N-Ar rotation whereas sulfoxide displayed hindered [brake ON] N-Ar rotation. The semi-empirical molecular orbital (PM3) calculations revealed concerted pyramidalization of amidic nitrogen with N-Ar rotation.

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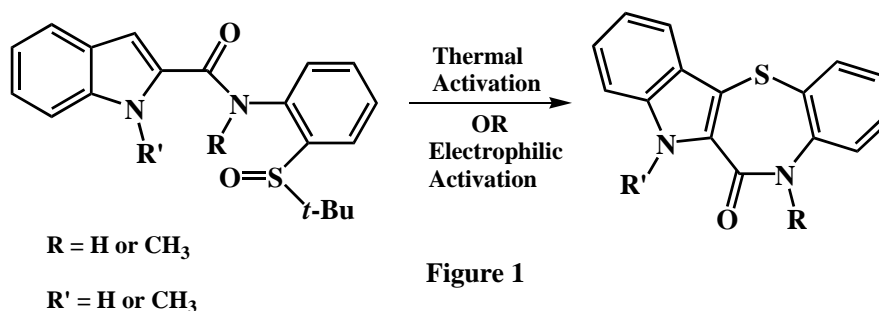
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Unifying Theme

This dissertation is a combination of efforts in understanding different aspects of sulfoxide chemistry in chemically varying substrates. The chosen sulfoxide substrates are chemically diverse in nature, however, each substrate is specifically designed to suit the requirements of the intended study. Each study is included as a separate chapter (Chapters 2, 3 and 4) and hence the chronological order of compounds and references is restricted to each chapter and is not continued from one chapter to another. Background about principles and techniques used in each study is explained in the first chapter (Chapter 1). The following brief discussion is intended to give an idea of studied aspects of sulfoxide chemistry.

Sulfoxide is an important functional group in organic chemistry. To date numerous applications of sulfoxides in organic synthesis have been disclosed and further research is in progress. Our research group has an impact in specific reaction of sulfoxides, namely Sulfoxide Electrophilic Sulfenylation (SES) reaction. In the 1980's, our research group developed SES reaction to synthesize novel *N,S*-heterocycles, which commonly exist as substructures of more complex biologically active compounds. In this reaction, sulfoxide is used as an intramolecular sulfenylating agent. Mechanistically, during this reaction, sulfoxide is activated thermally (heating in a high boiling solvent) or electrophilically (by an electrophilic species) to produce *N,S*-heterocycle. Both electrophilic and thermal activation is mechanistically different and the electrophilic activation mechanism is well-known. However, the mechanism of thermal activation is still under study mainly because it takes place in absence of any other chemical reagent. We had proposed a mechanism of thermal activation of sulfoxides involving electrophilic addition of

nucleophile at sulfur producing sulfonium salt as a reactive intermediate. As opposed to our proposed mechanism, other studies (discussed later) involving thermal activation of sulfoxides proposed existence of sulfenic acid ($R-S-OH$) as a reactive intermediate in intramolecular cyclization reactions of sulfoxides. Both sulfonium salt and sulfenic acid are extremely reactive, hence difficult to isolate species. Their presence in the reaction mixture is usually derived by the identity of by-products obtained from the reaction. However, they share one thing in common; they both originate from a sulfoxide functional group. We have shown earlier that methyl and ethyl sulfoxides follow the SES reaction pathway (sulfonium salt as reactive intermediate), for thermal activation of *t*-butyl sulfoxides, however, the sulfenic acid pathway is more common in literature. Synthesis of benzisothiazolones has been achieved by intramolecular cyclizations of *t*-butyl sulfoxides and it was argued that these proceed via sulfenic acid. However, enough evidence to prove the presence of sulfenic acid was not provided. Hence, it is unclear whether or not intramolecular cyclizations of *t*-butyl sulfoxides generate sulfenic acid under thermal activation reaction conditions. Chapter 2 of this dissertation resolves some of these mechanistic issues regarding the presence of sulfenic acid as a reactive intermediate in intramolecular cyclization of sulfoxides. We employed thermal and electrophilic activation of appropriately designed *t*-butyl sulfoxides and achieved synthesis of benzothiazepinones (Figure 1), a novel heterocyclic system which was synthesized earlier in our research laboratory from corresponding ethyl sulfoxides.



Importantly, we were able to prove that the *t*-butyl sulfoxides do not generate sulfenic acid during the intramolecular cyclization process under the employed reaction conditions.

This study emphasizes the importance of alkyl (*t*-butyl in this case) sulfoxides as intramolecular sulfenylating agents. In addition, it should be noted that if the sulfoxide is suitably substituted, it can be used to resolve some of the important mechanistic issues.

In our research laboratory, Sulfoxide Electrophilic Sulfenylation (SES) has also been applied to synthesize novel fused large ring heterocycles via ring expansion of sulfonium salt of sulfoxides. For a specific ring expansion study, we needed to synthesize an 8-membered ring sulfoxide substrate (**A**, Figure 2). We designed a new protocol to synthesize this novel 8-membered *N,S*-heterocycle via Ring Closing Metathesis (RCM) reaction in sulfide [S(II)] oxidation state, with eventual oxidation of sulfide to sulfoxide **A** in mind.

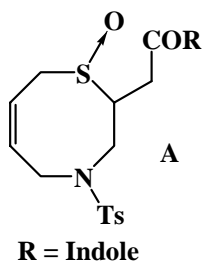


Figure 2

However, all our attempts to get successful RCM reaction with sulfide met with complete failure under varied reaction conditions. The main reason of such failure was the Ru-Sulfur coordination between sulfide substrate and the Ru-based (Grubbs 2nd generation) catalyst. To prevent such coordination,

we envisioned sulfoxide as a “protecting group” for such thioethers. Indeed sulfoxide gave good yields of a cyclized product under standard RCM reaction conditions. Protection (oxidation) of sulfide and deprotection (reduction) of sulfoxide was achieved by conventional reagents, *m*-CPBA and Lawessons Reagent (L.R.) respectively. We were able to synthesize this 8-membered ring *N,S*-heterocycle with sulfur in sulfide oxidation

This concept is novel as it is the only example of using sulfoxide as a “protecting group” for thioether, which fails to produce the cyclized product via RCM.

The sulfide-sulfoxide redox cycle is a well-known process with various procedures available to achieve both, sulfide oxidation and sulfoxide reduction. Application of this relatively simple and well studied concept to solve existing difficulties in using RCM with thioethers is the most important outcome of this research (explained in Chapter 3).

Besides change in electronic effects caused by sulfide oxidation, steric effects also play a crucial role. Due to an increase in steric hindrance with the presence of oxygen in sulfoxides, molecular motions around the sulfur center would be affected. The understanding of the steric bulk of sulfoxide oxygen and the ease with which sulfide-sulfoxide redox cycle can be achieved (reversibility, in other words) is extremely important. It is this sulfide-sulfoxide redox cycle which is the basis of our design of the “molecular brake” (Chapter 4).

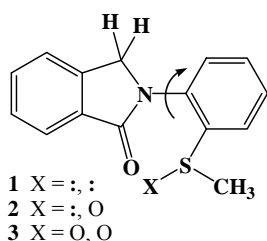


Figure 3

With the help of Dynamic NMR (DNMR) spectroscopy, we were able to show that the rate of N-Ar rotation in simple isoindolines (Figure 3) can be controlled with the oxidation state of proximate sulfur atom.

Sulfide [S(II)] shows “free” rotation [brake “OFF” mode] around the N-Ar bond, whereas sulfoxide displayed “hindered” rotation [brake “ON” mode]. Design of the molecular brake based on sulfide-sulfoxide redox cycle is one of the diverse applications of this redox chemistry. This molecular brake design can be a very useful component of the molecular machine, a molecular analog of any machine that we use in our everyday life. Further details about the design and its advantages will be discussed in Chapter 4.

This dissertation is a combination of various approaches in understanding the diverse applications of sulfoxides in organic chemistry. Although, all of the systems (Chapters) do not relate to each other directly, they all have a common thread, the presence of sulfoxide and its diverse applications.

Chapter 1

This Chapter includes a detailed introduction, along with some literature background of all the subsequent Chapters (Chapters 2, 3 and 4) that are included in this dissertation. In addition, some of the basic principles of the techniques used in following chapters (2, 3 and 4) are also covered. The Chapter is divided in three parts A, B and C and these notations are limited only to this Chapter. In addition, the compound numbers, schemes and figures are restricted to each part and are not continued from one part to another.

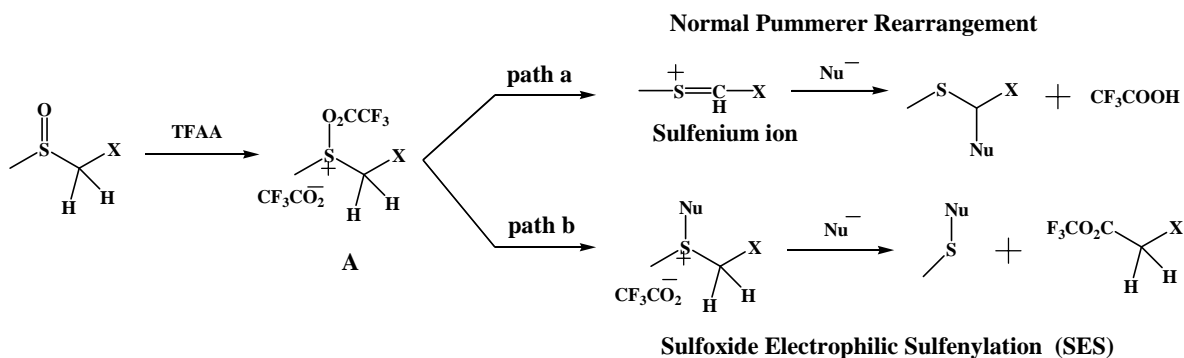
Part A: Sulfoxides as an intramolecular sulfenylating agent.

Part B: Sulfoxide as a protecting group.

Part C: Sulfoxide as a “molecular brake”.

Part A: Sulfoxides as an intramolecular sulfenylating agent

As a part of our continuing efforts to synthesize novel *N*- and *N,S*-heterocycles, we have developed an intramolecular sulfenylation reaction, Sulfoxide Electrophilic Sulfenylation (SES) reaction. In this method, sulfenylation is carried out intramolecularly by a sulfoxide moiety. This reaction takes place under the normal Pummerer reaction conditions and was initially called “Interrupted Pummerer reaction”.



Scheme 1

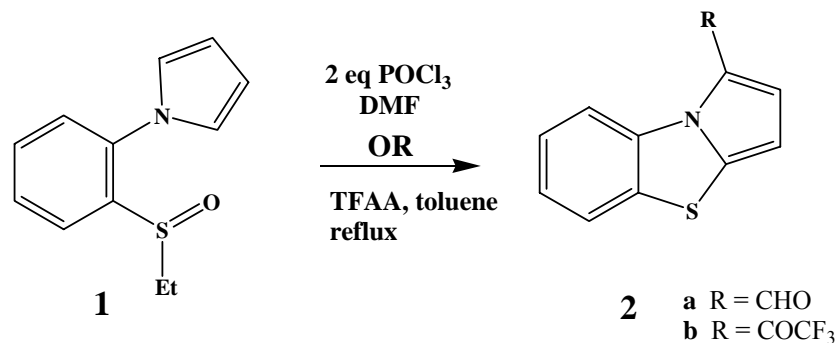
The mechanism of this reaction is shown in Scheme 1. In the Pummerer reaction, sulfoxide bearing an alpha-hydrogen is treated with anhydride, acyl halide, inorganic acids or other activating species. This converts the oxygen atom of sulfoxide into a better leaving group by forming species such as **A**. This species then loses a proton from the adjacent carbon producing sulfenium ion (path a, Scheme 1). Nucleophile then attacks the carbon producing alpha-substituted sulfide. Our research group has developed a method in which the path of the normal Pummerer reaction can be altered by varying sulfoxide substituent. Under identical reaction conditions as Pummerer reaction, sulfoxide bearing an alkyl (methyl, ethyl, etc.) group can follow path b in Scheme 1. During this path, nucleophile attacks *at sulfur* in species **A**, followed by alkyl group displacement to produce the *S*-heterocycle.

SES is a very attractive method to synthesize novel *N,S*-heterocycles. Conventional methods to carry out sulfonylation involve the use of a sulfide/positive halogen source or thiol/halogen¹, which results in polyhalogenated or polysulfonylated products when more than one unsubstituted site is available. SES products are always monosulfonylated because of the use of intramolecular sulfoxide functionality and relatively mild reaction conditions (explained later) compared to conventional methods.

History of Sulfoxide Electrophilic Sulfonylation (SES) reaction:

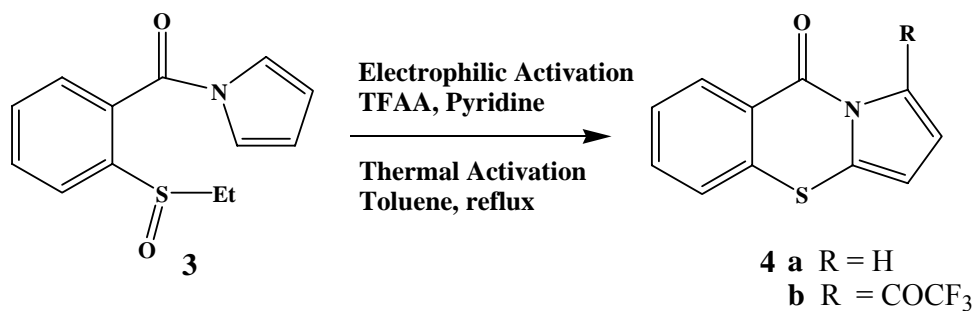
Our research group has synthesized a variety of *N,S*-heterocycles using SES methodology. One of the earliest example² of SES reaction is shown below (Scheme 2). Activation of ethyl sulfoxide using Vilsmeier-Haack reagent (POCl₃, DMF) to produce substituted pyrrolo[2,1-*b*]benzothiazole **2a** was the prominent feature of this reaction.

Compound **2b** was also synthesized from **1** later on³ by using trifluoroacetic anhydride (TFAA), in hot toluene, as an activating reagent instead of Vilsmeier-Haack reagent. The applications of this methodology were limited due to added functionality in the product in the form of aldehydic or trifluoroacetyl moiety in **2a** and **2b** respectively.



Scheme 2

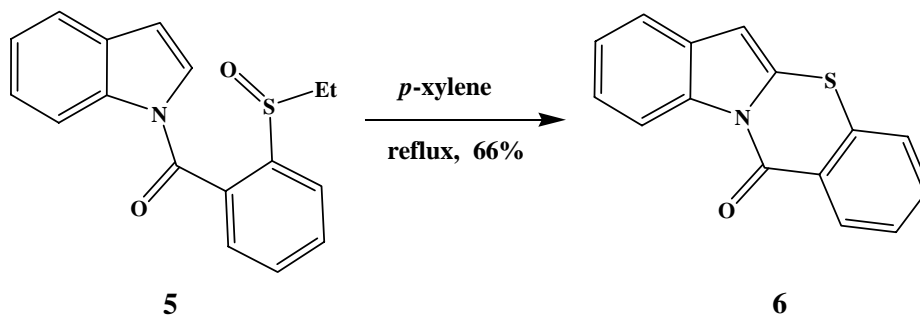
Some 6-membered *N,S*-heterocycles were also synthesized from corresponding ethyl sulfoxides using the SES method (Scheme 3).⁴ Electrophilic activation (TFAA, large excess 3.7 eq) of **3** was carried out at room temperature (several hours) with pyridine (4 eq) as an acid scavenger to prevent the formation of **4b**. Unfortunately, in spite of this, **4b** was isolated in 83% yield with the absence of **4a**. However, reducing the amount of TFAA to slight excess (1.3 eq) in presence of pyridine (1.5 eq) at 0 °C produced **4a** in 55% yield along with **4b** (10%) and unchanged starting material. In addition to electrophilic activation, thermal activation (heating sulfoxide in high boiling solvents such as benzene, toluene, *p*-xylene) of sulfoxide **3** (in *p*-xylene) produced **4a** in 88% yield as well.



Scheme 3

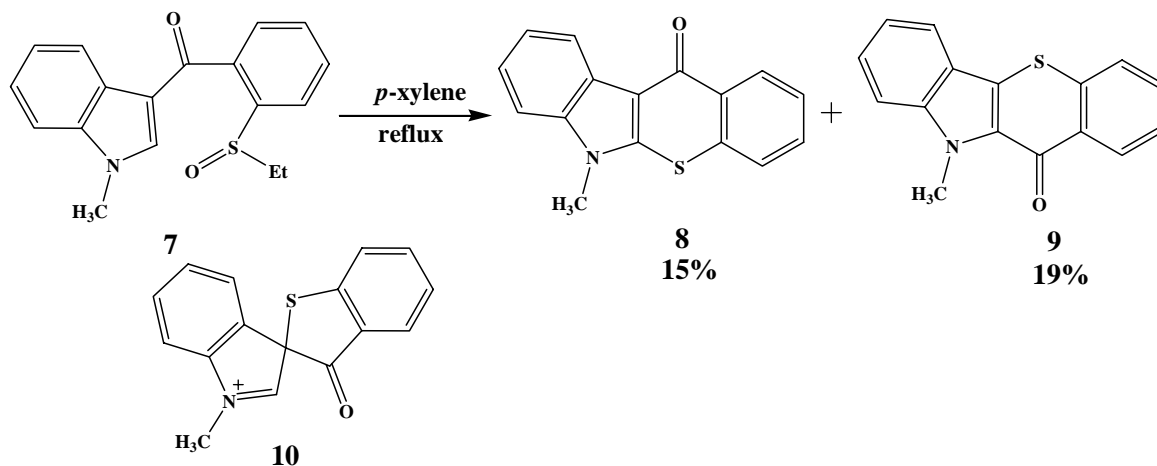
The advantage of this mode of sulfoxide activation is that no other reagent is necessary to carry out this cyclization and the product obtained is therefore unsubstituted heterocycle. Furthermore, the by-products obtained from these reactions are alkyl alcohols depending on the sulfoxide side chain. For example, in case of **3**, ethanol is produced as a by-product along with **4a**. The by-product can easily be removed from the reaction mixture during reaction (*p*-xylene, reflux, 140 °C), after reaction (during concentration of the reaction mixture under vacuo) or during work-up procedures.

As research progressed, synthesis of some indole containing heterocycles was achieved using thermal activation of **5** to produce **6** in 66% yield (Scheme 4).⁵



Scheme 4

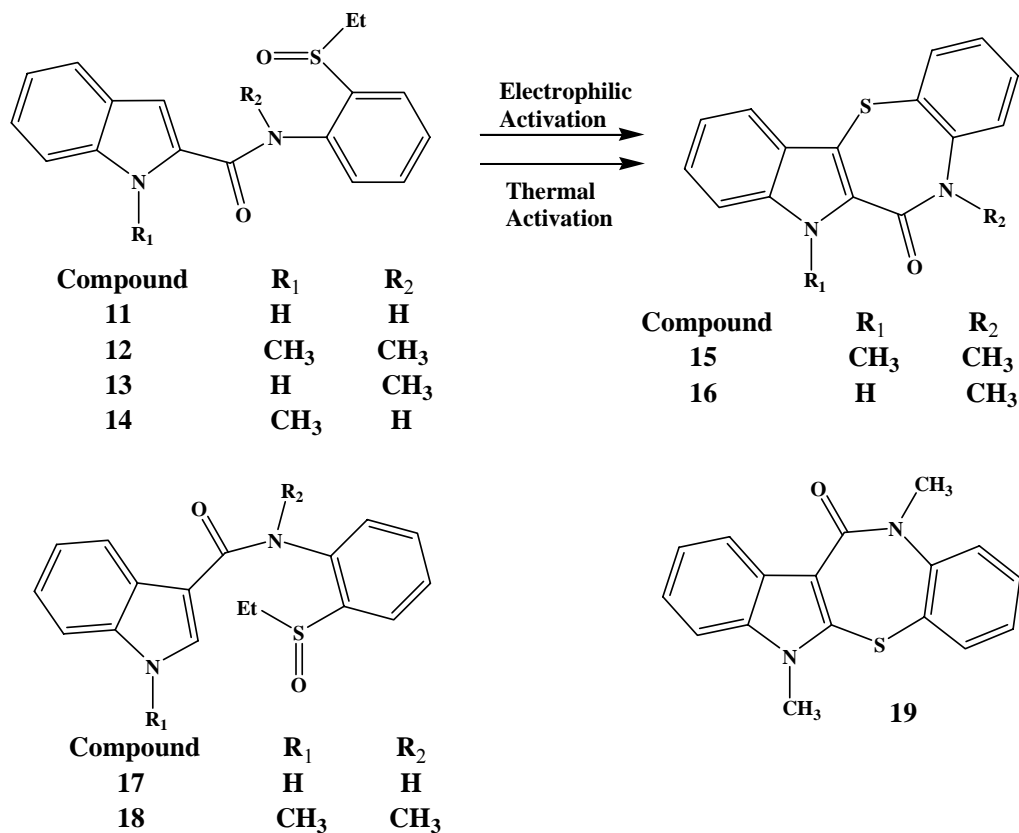
Other indole substrates produced rather unusual and mechanistically difficult to understand reaction products as shown in Scheme 5. Compound **7**, upon heating in *p*-xylene, produced **8** and **9** in 15% and 19% yields respectively.



Scheme 5

While **8** was the expected product, formation of **9** was explained on the basis of the spirocyclic intermediate such as **10**, followed by sulfur migration from the C-2 to C-3 position of the indole nucleus.

SES methodology was further extended towards synthesis of 7-membered ring thiazepinone compounds (Scheme 6). Ethyl sulfoxides tethered to indole-2-carboxamide derivatives (**11-14**) and indole-3-carboxamide derivatives (**17-18**) were synthesized and subjected to both electrophilic activation (TFAA, pyridine) and thermal activation (*p*-xylene, reflux).



Scheme 6

Amidic substitution was essential in producing successful cyclization products, hence only **12** and **13** gave cyclized products **15** and **16** respectively, and no reaction was observed with **11** and **14**. A striking result of this work was the formation of **15** instead of **19** from 3-substituted indole carboxamide **18**. All of these results (contribution of Mary Mateo, former doctoral student of our laboratory) will be discussed in detail in Chapter 2.

Methods of Sulfoxide Activation:

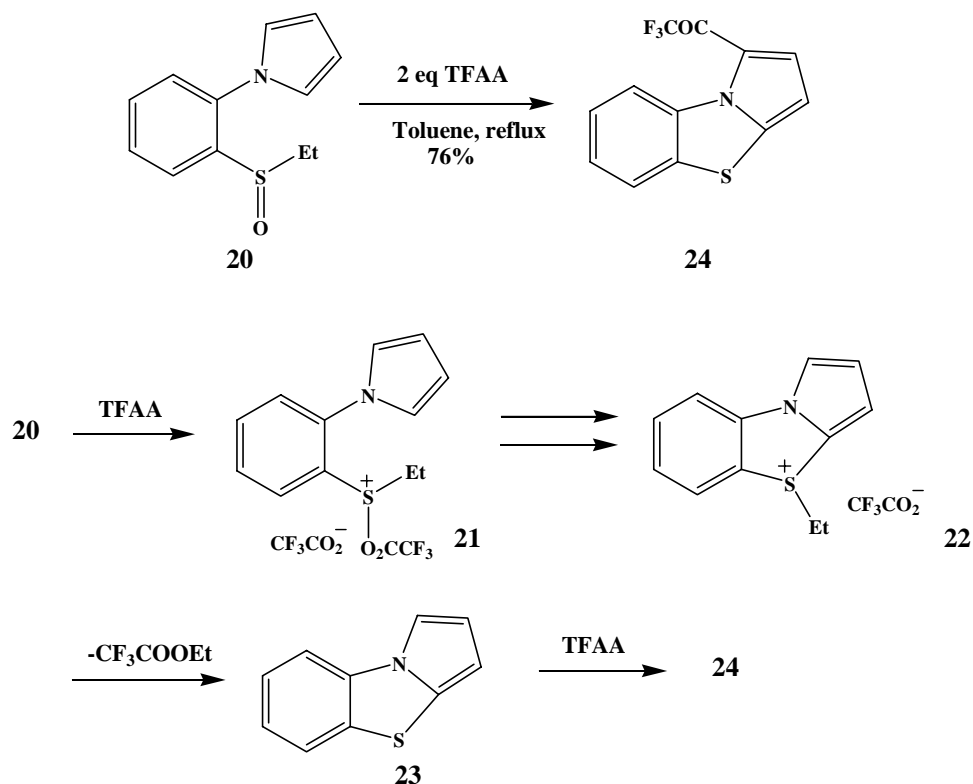
Common methods of sulfoxide activation involve electrophilic and thermal activation.

Electrophilic Activation:

As mentioned earlier, sulfoxides can be activated with the use of an electrophilic species. In all of the above-mentioned examples of SES reactions, we have used either TFAA or POCl₃/DMF as an electrophilic species. Activation of sulfoxide mainly involves conversion of oxygen of sulfoxide into a better leaving group. This also involves formation of an electron deficient sulfonium ion as an electrophilic intermediate. An electron rich heterocycle then attacks this electrophilic intermediate similar to an aromatic electrophilic substitution reaction producing, in our case, a nucleophile-sulfur bond. Displacement of the alkyl side chain then produces a parent heterocycle. However, as observed in the above-mentioned examples, any excess of an activating reagent then reacts with this parent heterocycle and incorporates added functionality in the heterocycle.

Thermal Activation:

In the past, we have performed thermal activation of alkyl (ethyl) sulfoxides by heating the sulfoxide in electron rich, high-boiling solvents such as benzene, toluene, *p*-xylene, etc. to produce novel *N,S*-heterocycles. These reactions proceed well in either the presence or the absence of TFAA. The presence of TFAA yields a trifluoroacetylated heterocycle because excess of TFAA reacts with the initially formed parent heterocycle. For example, compound **20**, upon heating in refluxing toluene in the presence of TFAA, produced **24** in 76% yield (Scheme 7).³



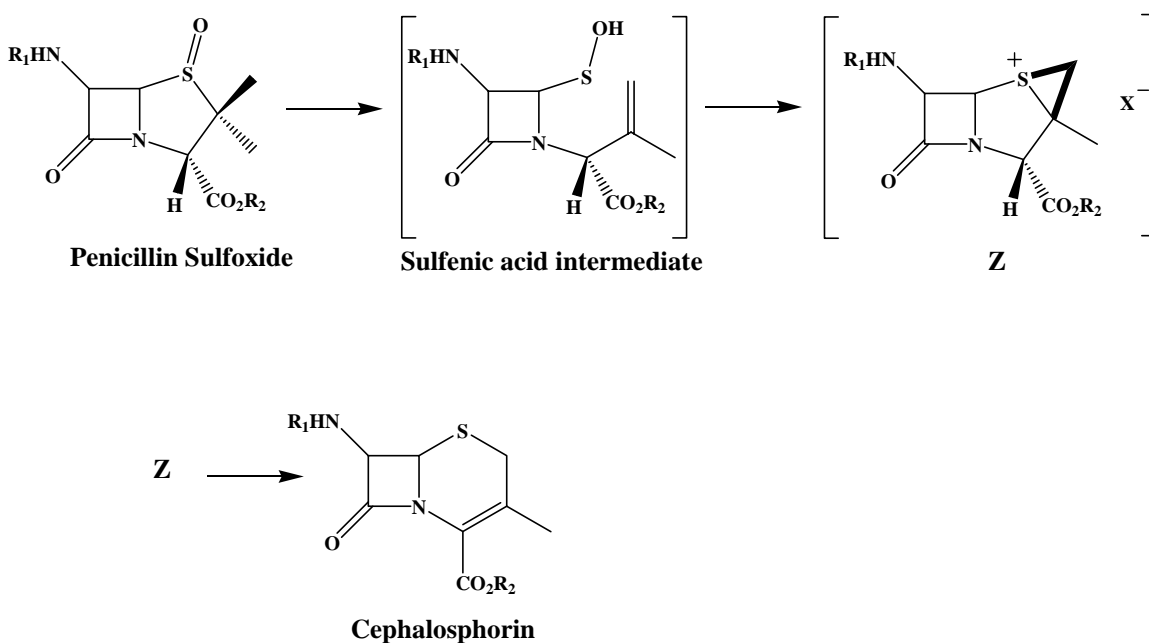
Scheme 7

We proposed that the reaction begins with the thermal activation of sulfoxide in the presence of TFAA to produce **21**, followed by a nucleophilic attack of the electron rich pyrrole ring on sulfur to produce sulfonium salt **22**. Sulfonium salt then undergoes thermal (toluene, reflux) displacement of the S-alkyl group to produce the parent heterocycle **23**, which due to the added electrophilic activating influence of sulfur, undergoes further substitution to yield **24**.

As discussed earlier, we have also carried out the thermal activation of ethyl sulfoxide in the absence of TFAA simply by heating sulfoxide in *p*-xylene. We believe, in the absence of TFAA, sulfoxide activation still takes place in a very similar fashion as described in Scheme 7. In the absence of TFAA, it is probable that acidic protons of

adjacent methylene carbons could intermolecularly protonate sulfoxide oxygen of another sulfoxide thereby activating it for the reaction.

There is literature precedence for another feasible mechanism of the thermal activation of sulfoxides in the case of penicillin to cephalosporin conversions.⁶ It was proposed that this reaction proceeds via a species called “sulfenic acid” as the reactive intermediate as shown in Scheme 8.



Scheme 8

Understanding of sulfenic acid chemistry is essential to study the mechanistic aspects of thermal activation of sulfoxides.

Introduction to the sulfenic acid chemistry:

Sulfenic acid is a highly reactive, difficult to isolate species, usually generated *in situ* by thermolysis of suitably substituted sulfoxide.⁷ Sulfoxides with one or more hydrogens on a carbon beta to a sulfur atom undergo decomposition at moderate temperatures to produce an alkene and sulfenic acid (R-S-OH). A commonly accepted mechanism of sulfenic acid formation is stereospecific cis-elimination⁸ as shown in Figure 1.

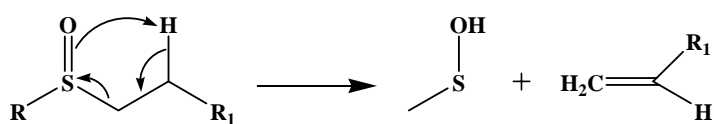
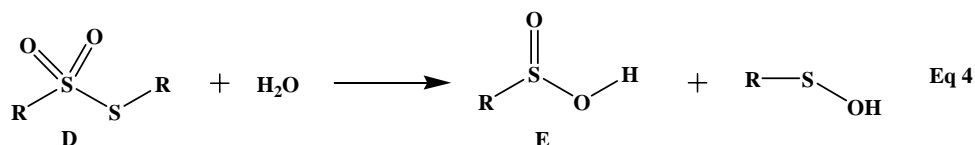
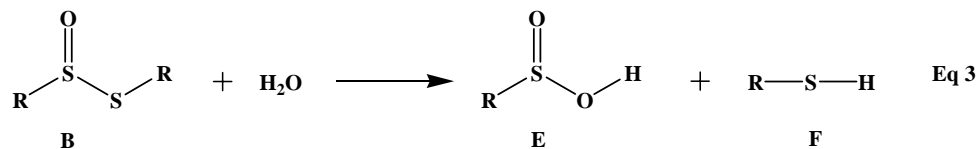
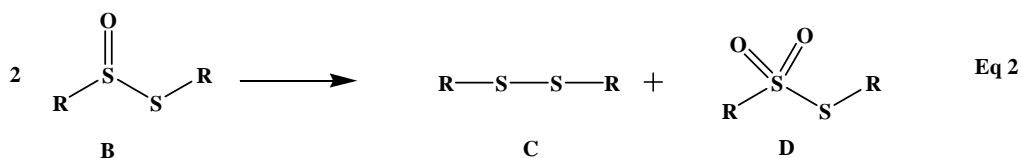
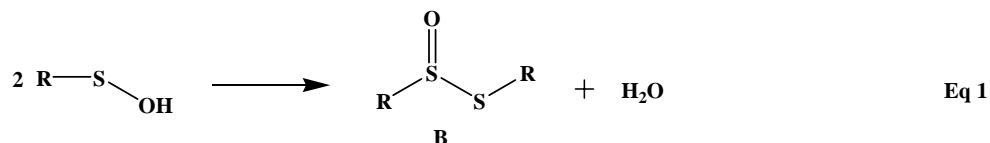


Figure 1

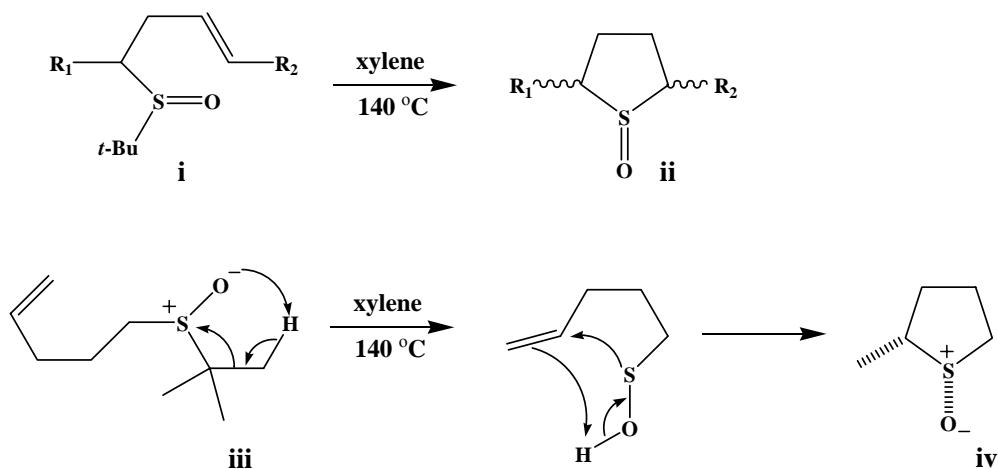
The temperature at which this thermolysis takes place varies with the R₁ group (Figure 1). The commonly studied alkyl group is the *t*-butyl group and some other examples of the functional group include the propanenitrile⁹ group. Upon heating in high boiling solvents such as toluene, xylenes, etc., *t*-butyl sulfoxides undergo thermolysis to produce sulfenic acid with the elimination of isobutene. However, due to the steric bulk and the greater number of available beta-hydrogen atoms, *t*-butyl sulfoxides are capable of forming sulfenic acids even at low temperatures.¹⁰

As mentioned earlier, sulfenic acid is a very reactive species and hence undergoes a variety of reactions. Unfortunately, due to high reactivity, the principle reactions of sulfenic acids are not observed directly and most of the evidence for the existence of sulfenic acid has to be derived from the products obtained from a specific reaction.¹¹ Some of the basic reactions of sulfenic acid involve formation of thiosulfinate **B**

(equation 1). These thiosulfinate are unstable and thermally disproportionate in disulfides **C** (R-S-S-R) and thiosulfonates **D** (R-SO₂-S-R) as shown in equation 2. Thiosulfinate **B** and thiosulfonate **D** could also react with water (formed in equation 1) to produce sulfinic acid **E**, thiol (**F**) and a molecule of sulfenic acid (equation 3, 4).

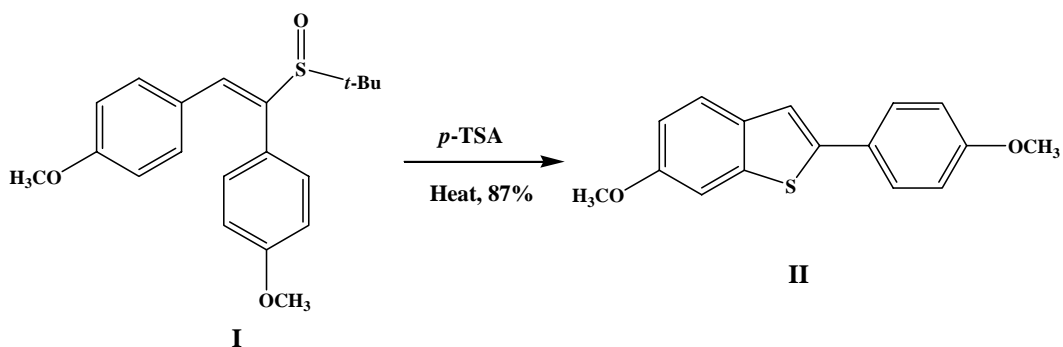


Synthetically useful reactions of sulfenic acids involve intramolecular and intermolecular additions of sulfenic acids to olefins and dienes. Examples of some of the known¹² reactions of sulfenic acids are shown in Scheme 9.



Scheme 9

Sulfenic acid mediated intramolecular cyclizations have also been reported in the synthesis of benzothiophenes by heating styrenyl sulfoxide in the presence of *p*-TSA (Scheme 10).¹³

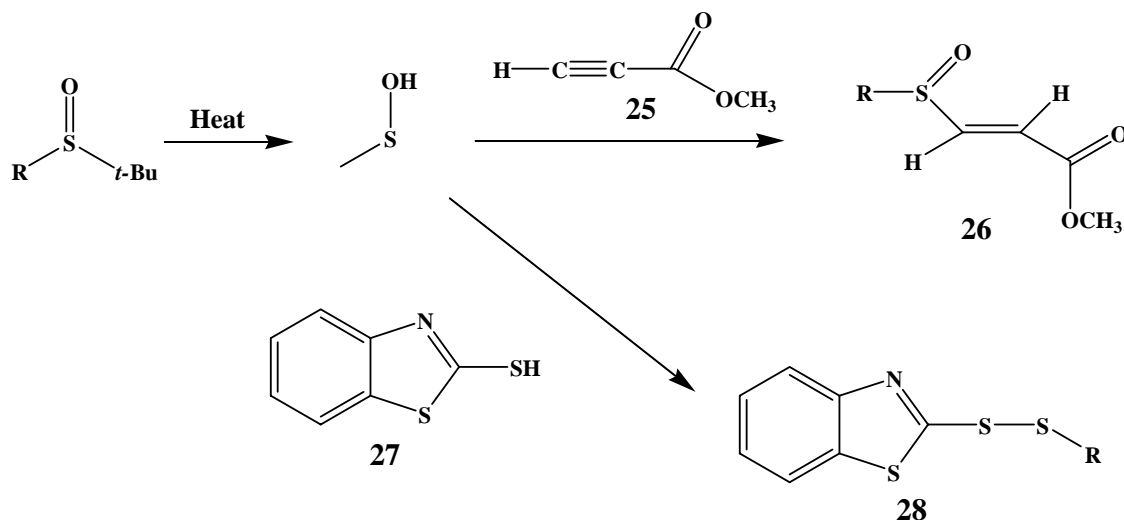


Scheme 10

The following reactions (Scheme 11) of sulfenic acids are of mechanistic importance. The presence of sulfenic acid in the reaction mixture can be confirmed by trapping it with alkyne or thiols. Methyl propiolate (**25**) is commonly used^{8,11,14} alkyne whereas 2-

mercaptobenzothiazole (**27**) is an example⁶ of thiol used as a sulfenic acid trapping agent.

Scheme 11 shows the typical products that are obtained by such trapping experiments.



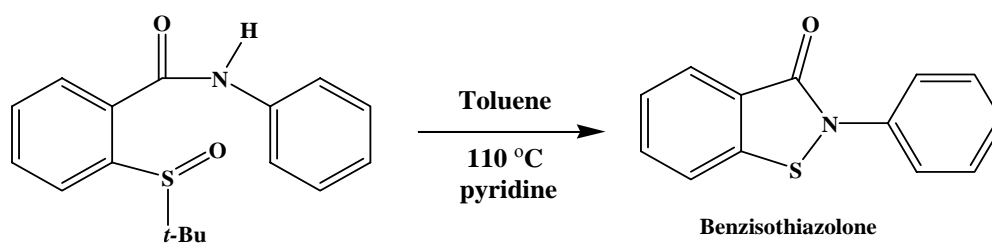
Scheme 11

Reaction of sulfenic acid with methyl propiolate can be seen as a reverse reaction of sulfenic acid formation and hence it is known¹¹ that the formation of thiosulfinates (**B**) and **26** are competitive reactions. Reactions of sulfenic acids and **27** are generally clean producing corresponding disulfide (**28**) in high yields.⁶ These results indicate that **27** is a better sulfenic acid trap than methyl propiolate and avoids any complications in results.

Objective of this study:

Because of the similarity of the sulfoxide substituent (ethyl group in our studies and *t*-butyl in sulfenic acid chemistry) and the temperature (toluene, reflux) at which we performed our thermal activation of sulfoxides, it was thought that our thermal activation process might involve sulfenic acid as a reactive intermediate.

Furthermore, Wright and co-workers¹⁵ synthesized specifically designed *t*-butyl sulfoxides and carried out thermal cyclization of these sulfoxides to produce benzisothiazolones (Scheme 12).



Scheme 12

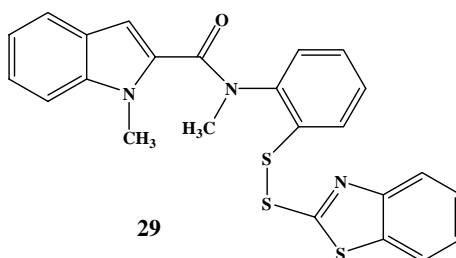
At the temperature of toluene reflux 100 °C, they postulated that, the *t*-butyl sulfoxides will undergo thermal elimination to produce sulfenic acid, which would cyclize with the loss of water, to produce the desired benzisothiazolones. However, enough evidence for the formation of sulfenic acid in the reaction mixture was not provided (for example by chemical means such as trapping experiments or any other type of experiments). In addition, unlike other reported sulfenic acid based cyclizations, this cyclization was carried out in a basic medium (pyridine).

The above example lacks enough experimental evidence to support the existence of sulfenic acid in the reaction mixture. A thorough understanding of sulfenic acid

chemistry along with experimental evidence is necessary to prove or disprove the presence of sulfenic acids as reactive intermediates in intramolecular cyclization reactions.

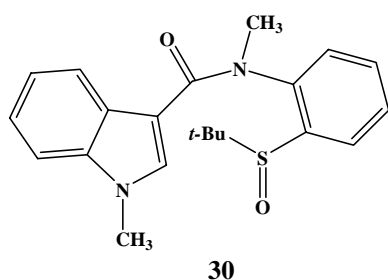
Our previous experience with intramolecular cyclizations using ethyl sulfoxides and the by-products obtained under those reaction conditions indicate that our thermal activation process follows the SES (formation of sulfonium salt) pathway. We obtained ethanol as a by-product in our cyclization reactions of ethyl sulfoxide. This is an indication of the absence of sulfenic acid (and corresponding alkene, ethene) being produced during the reaction. If sulfenic acid is to be produced in the reaction mixture, we would not have seen ethanol as a by-product of the reaction, as the ethene formed in the process of forming sulfenic acid would have been expelled (as a gas) from the reaction mixture.

Based on these observations, we pursued the following study during which, we revisited our own system (discussed earlier, Scheme 6) and used *t*-butyl sulfoxides and propanenitrile sulfoxide (in one case) as intramolecular sulfenylating agents to carry out the synthesis of benzothiazepinones. The substituent effects and reactivity patterns were identical to the ones observed before for corresponding ethyl sulfoxides. Importantly, we performed a trapping experiment with 2-mercaptobenzothiazoles and were able to isolate thiazepinone **15** without any indication (by TLC) of the formation of a corresponding disulfide product **29**.



These results indicate that the products obtained in these cyclizations are SES reactions based on the attack of an electron rich heterocycle at the sulfoxide and do not involve a sulfenic acid mechanistic pathway. It is also probable that some results, which are reported in the literature (Wright and co-workers),¹⁵ to proceed via sulfenic acid, in fact follow the SES path.

In addition to this, we also synthesized compound **30**, a *t*-butyl derivative of compound **18**, in an attempt to understand the formation of **15** from **18**. However, **30** did not



produce **18** under the reaction conditions used and we think that structural changes (by replacing the ethyl group) due to the bulky *t*-butyl group could be the reason behind this.

All of the above results of *t*-butyl, propanenitrile and ethyl sulfoxides along with experimental details and spectroscopic data are included in Chapter 2.

This research along with contribution from Mary Eggers (Mateo), former doctoral student in our research laboratory was presented at the ACS National Meeting, Jog, P. V.; Bates, D. K.; Eggers, M. E. *Book of Abstracts*, 228th ACS National Meeting, Philadelphia, PA August 22-26, 2004. ORGN-675.

This research is also submitted for publication,

Bates, D. K.; Eggers, M. E.; Jog, P. V. *J. Org. Chem.* Submitted for publication.

Part B: Sulfoxide as a protecting group

This part covers the important aspects involved in the synthesis of thiazocine-2-acetic acid derivatives via Ring Closing Metathesis (RCM).

Introduction:

Application of organometallic chemistry in organic synthesis is ever increasing. Inorganic metal complexes act as catalysts in a variety of organic reactions. Alkene metathesis is one such well-known organic reaction, catalyzed by various types of tungsten-, molybdenum-, and ruthenium-based organometallic complexes. Initially, application of this reaction was limited in polymer chemistry with a Ring-Opening Metathesis Polymerization (ROMP) reaction. Soon after, an interesting reaction, namely, Ring Closing Metathesis (RCM) was discovered and within few years, it became the most powerful synthetic tool in carbon-carbon (C-C) bond forming reactions. Application of RCM is not only limited to the synthesis of novel compounds, but it has also proved to be the better alternative approach towards previously known systems. Subsequent chapter (Chapter 3) describes the new protocol, to synthesize thiazocine-2-acetic acid derivatives via RCM.

Mechanism of RCM:

The mechanism of RCM involves a series of alternating [2+2] cycloaddition and cycloreversion reactions between substrate and catalytic species (metal alkylidene) (Figure 1).¹⁶ Also, there is some evidence of metalacyclobutanes as reactive intermediates.¹⁷ In alkene metathesis, all the individual steps of the catalytic cycle are

reversible, however, ring-closing metathesis is a forward driven reaction due to an increase in entropy in going from one substrate to two products.

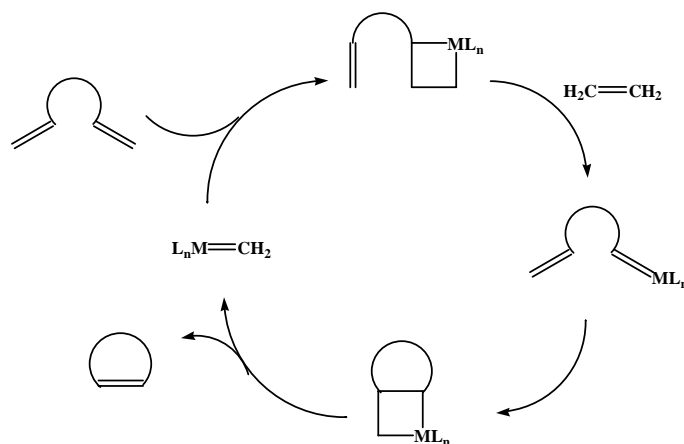


Figure 1: Mechanism of Ring Closing Metathesis.

Catalysts used in RCM:

RCM catalysts can be categorized as tungsten- (W), molybdenum- (Mo), or ruthenium- (Ru) based depending on the central transition metal atom in the complex. Tungsten-based catalysts **A** are less commonly used in RCM chemistry.¹⁶ Alkoxy imido Mo complexes **B** are the earlier developed catalysts¹⁷ followed, later on, by benzylidene Ru complexes **C** by Grubbs and co-workers¹⁸ (Figure 2). Due to their air and moisture sensitivity, short storage life and poor functional group tolerance, Mo complexes are limitedly used. However, they show pronounced metathesis activity towards a variety of substrates in varying steric and electronic environments. In contrast, Ru complexes show greater tolerance to varied functionalities from esters, ketones, acetals, ethers to even more polar alcohols, aldehydes and carboxylic acids.

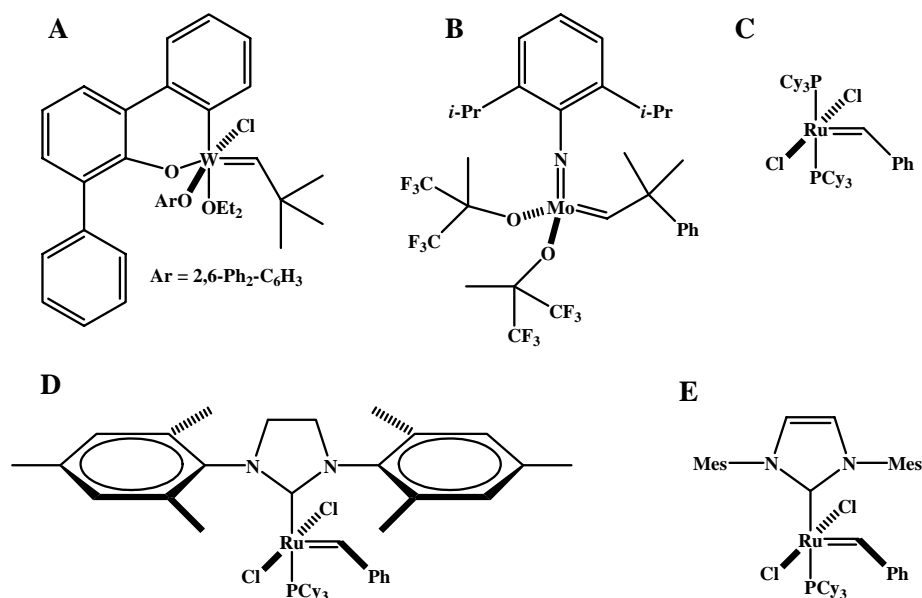


Figure 2: Various catalysts used in RCM.

This increased tolerance to functional groups, along with their ready availability and ease of handling, has made these Ru complexes commercially available over their Mo counterparts.

Later on, the focus of this research was shifted towards making more efficient, more functional group tolerant and air and moisture stable catalysts. Grubbs 2nd generation catalysts **D**¹⁹ and **E**²⁰ are the examples of such modern and efficient catalysts. The important feature of **D** and **E** is the presence of bulky electron donating imidazole and imidazoline ligand, which increases the ring-closing metathesis activity while retaining air and moisture stability. These complexes also show greater functional group and heteroatom compatibility compared to catalyst **C**.

Factors affecting RCM reaction:

Suppression of the competitive metathesis based polymerization of reactant under reaction conditions is important, in achieving successful RCM. This is achieved by performing the reaction under high dilution conditions. There is literature precedence that RCM is strongly favored over intermolecular polymerization by preexisting conformational constraints in the substrate.²¹ The choice of catalyst also plays an important role and often depends on the functional group in substrate and steric demands.²² Ring size of the expected product, steric effect, effect of certain functional groups and the presence of heteroatom are some other important aspects governing the success of RCM chemistry.²³ Discussion in this chapter is restricted to the application of RCM to sulfur containing substrates.

RCM as applied to sulfur containing substrates:

There is a lot of ongoing research towards synthesizing *S*-heterocycles using RCM methodology. This increasing interest is mainly due to well-known biologically active and synthetically useful (as intermediates) *S*-heterocycles.²³ Our interest in *S*-heterocycles is centralized on the application of Sulfoxide Electrophilic Sulfonylation (SES) reaction in synthesizing novel *N, S*-heterocycles. SES is a novel sulfonylation method developed in our research laboratory, and uses sulfoxides as intramolecular sulfonylating agents.²⁴

In order to synthesize a novel 12-membered ring *N,S*-heterocycle using SES methodology, we needed its immediate precursor, a thiazocine acetic acid derivative sulfoxide **3** (Scheme 1). Sulfoxide **3** is a novel 8-membered ring *N,S*-heterocycle. Synthesis of higher membered heterocycles, specifically, 8-membered compounds still

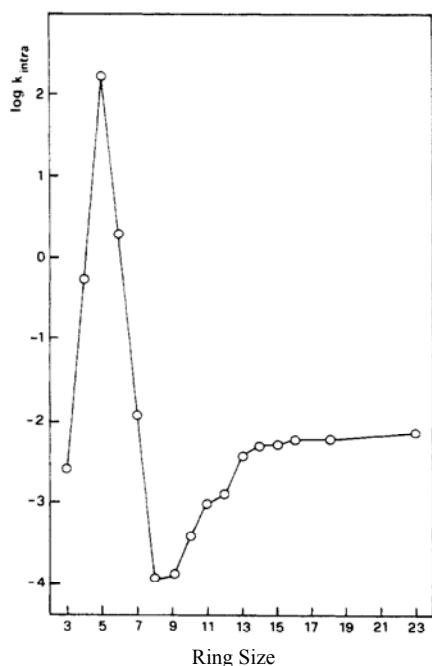


Figure 3: Adapted from Ref 25

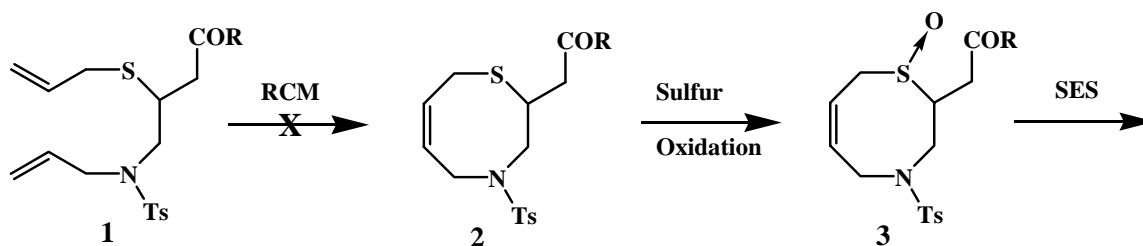
remain as a formidable task. Figure 3 is an illustrative example of the difficulties involved in the synthesis of 8-membered heterocycles.²⁵ In this graph, the rate of cyclization (lactonization from ω -bromoalkanoate) was plotted against the ring size (3 to 23) of the product obtained, which shows the decrease in the rate of lactonization for 8-membered ring heterocycles by a factor of 10^6 . In addition, the absence of examples with sulfur containing (as a nucleophile) systems displays the intensity of

the problems encountered specifically, in synthesizing 8-membered ring *S*-heterocycles.

However, there are examples in literature about 8-membered *S*-heterocycles. In one case, intramolecular cyclization of α,ω -dibromoalkanes in presence of $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ was used to make 7-15 membered ring thiacycloalkanes (48% yield of 8-membered thiacycloalkane).²⁶ The other example used [2,3] the sigmatropic rearrangement of sulfur ylides to synthesize the 8-membered *S*-heterocycle.²⁷ Additionally, examples of *S*-, *N,S*-, *N,O*- *O,O*-, *N,N*-heterocycles, which are structurally analogous to **3** are also scarce.^{25,28} The need for 8-membered *N,S*-heterocycles is increasing due to their occurrence in biologically active compounds as a substructure. This prompted us to design a suitable method for the synthesis of the 8-membered ring *N,S*-heterocycles.

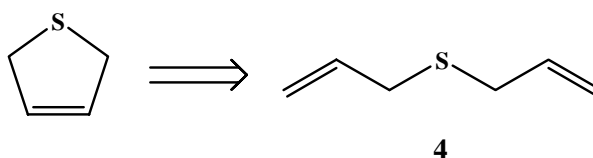
RCM has proven its wide applicability in synthesizing medium-sized *N,O*-heterocyclic systems.²⁸ We decided to apply RCM methodology to synthesize the 8-membered ring *N*-

S-heterocycle **2**, with the hope that if this, otherwise improbable to achieve synthesis of the 8-membered heterocycle is successful, then RCM can be a very important synthetic tool in making other (9,10-membered and so on..) macrocyclic systems. We decided to employ RCM to synthesize rarely studied sulfur compounds of the type **2** with subsequent oxidation of sulfur to give sulfoxide **3** (Scheme 1). Retro-synthetic analysis gave us the structure of the RCM precursor as **1**. However, our efforts to get the cyclized product **2**, met with complete failure under varied RCM reaction conditions. Although, we were disappointed, the result was not unexpected looking at the volume of literature²⁹ available about failures of sulfur containing compounds to produce successful RCM results.



Scheme 1 R = OCH₃, Indole, Indoline

Basset and co-workers³⁰ reported ring-closing metathesis on sulfur containing substrates as early as 1995. Diallyl sulfides of the type **4** gave successful cyclized products with catalyst **A**. The same substrate, with catalyst **B** gave better yields than **A**, however, catalyst **C** did not produce a cyclized product.

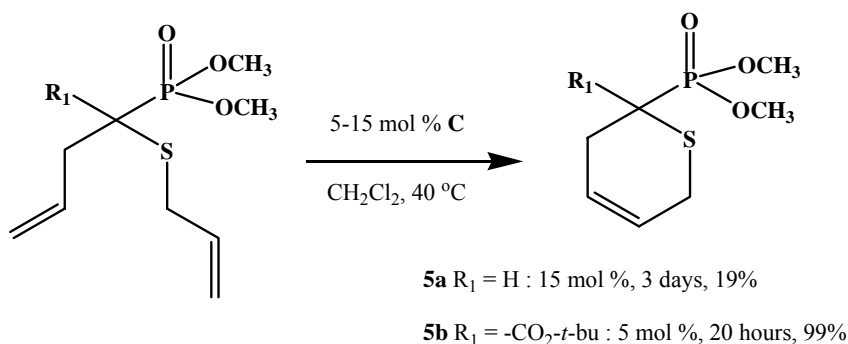


The main reason for the failure of catalyst **C** was Ru-S(II) lone pair coordination, resulting in catalyst deactivation (poisoning). It was believed that, such Mo-S (II) coordination was avoided in case of catalyst **B** due to steric bulk around the central Mo atom.¹⁶ This example demonstrates the effect of changing the catalyst in order to get improved results. Unfortunately, due to financial constraints, instrumentation requirements, timeline of research, etc., it is not always possible for chemists to do such change readily.

As mentioned earlier, research in the development of a more efficient catalyst has answered these questions to some extent. For example, Grubb's 2nd generation catalysts **D** and **E** showed improved heteroatom and functional group tolerance than generation one catalyst **C**. The added air and moisture stability along with the commercial availability of **D** and **E** has increased their wide use over air sensitive and non-commercially available Mo-based catalysts.

In spite of this, there is still no assurance of successful RCM chemistry on sulfur substrates as evident from unsuccessful cyclizations of some diallyl sulfides with catalyst **E**³¹ and our own example (Scheme 1), which uses catalyst **D**. It is extremely discouraging for a chemist to see such unsuccessful results considering the time, labor and cost of chemicals involved in the synthesis of its precursors.

In parallel to the catalyst development studies, there are some reports where substrate modifications were helpful in getting successful results to synthesize *S*-heterocycles using RCM. For example, introduction of bulky *t*-butyl ester replacing hydrogen gave an almost quantitative yield (99%) of the cyclized product **5a** compared to a mere 19% of **5b** when R₁ = H. with catalyst **C** (Scheme 2).³²



Scheme 2

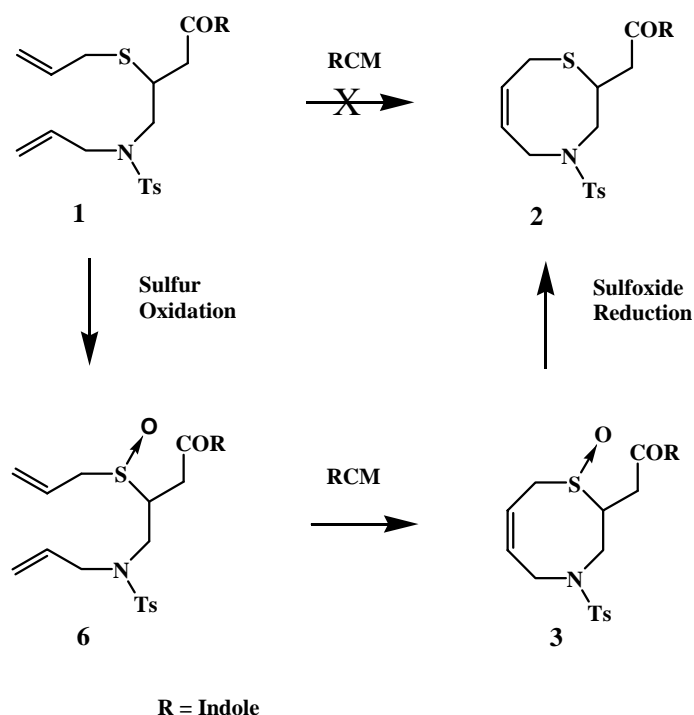
Some other substrate modifications include complete oxidation of sulfides to corresponding sulfones. Sulfones tend to give much better results compared to their sulfide analogs.³³ The success of these examples lies in avoiding the Ru-S(II) coordination by the steric bulk of *t*-butyl ester in one case (Scheme 2) and by the absence of lone pairs on sulfur, in case of sulfones.

An interesting point to note in both the above-mentioned examples is that success was achieved after making irreversible or permanent substrate modifications. This is important because, if the RCM reaction with S(II) containing substrates is to fail, then it may not always be possible for a chemist to make such irreversible substrate modifications. Furthermore, introduction of added functionality (for example, *t*-butyl ester in Scheme 2) could cause severe interference during the synthetic steps to be followed after RCM in any given reaction scheme depending on the chemical nature of functionality. Additionally, the need of sulfur (II) in the target compound is very high, as many of the biologically active *S*-heterocycles are in the form of sulfides. These issues, not only restrict the chemists ability in making their originally intended target compound but it also limits the scope of RCM as applied to sulfur chemistry.

Change in the oxidation state of sulfur, is an attractive approach, but sulfone is not the only choice, specifically because the reduction of sulfone to produced desired sulfide is difficult to pursue. Hence, we sought to carry out partial or incomplete (intermediate) oxidation of sulfide to get sulfoxide. Rather surprisingly, RCM studies on sulfoxides are rarely seen. To the best of our knowledge, prior to our work, there were only two reports of such studies with equal results of success³⁴ and failure.³⁵ It may be recalled that our earlier proposed reaction scheme involved reaction steps as RCM→ Sulfur oxidation→SES in that order (Scheme 1). After unsuccessful RCM results on sulfide **1**, we exchanged the first two steps of the proposed scheme and carried out partial sulfur oxidation first, followed by RCM on sulfoxide **6**. We were pleased to see that sulfoxide **6** successfully produced RCM cyclized sulfoxide **3** (Scheme 3). This success gave us one of our intended targets (compound **3**), however, unsuccessful RCM on **1** precluded us in getting our other intended product, sulfide **2**. The idea of incomplete or partial oxidation of sulfide plays a crucial role here because, unlike previously reported substrate modifications, this modification is reversible. Individual oxidation and reduction steps are irreversible but the concept of performing these steps in a way shown below (Scheme 3) makes this modification reversible. For example, we achieved the reduction of sulfoxide **3** using Lawesson's Reagent (L.R.) and were able to successfully synthesize the intended sulfide **2**.

The idea of using sulfoxide as an intermediate is advantageous, as there are plenty of reagents available to carry out sulfur oxidation and sulfoxide reduction.³⁶ Such redox reactions are relatively cheap (in terms of cost of chemicals), less labor intensive and easy to perform. Importantly, by this approach, the change in catalyst is not required,

which avoids the handling of the air sensitive catalyst and the need of a sophisticated instrumentation facility for such handling.



Scheme 3

In other words, sulfoxide protects sulfur, presumably by preventing Ru-S(II) coordination during the RCM reaction thereby acting as a “protecting group” of sulfide. Based on all the advantages mentioned above, it is clear that using sulfoxide as a “protecting group” is the method of choice where RCM fails to produce the cyclized product with corresponding sulfide. It extends the scope and applicability of RCM on various sulfur containing substrates. It is even worth revisiting some of the earlier unsuccessful results with sulfides and applying this methodology. Importantly, with this

powerful tool in hand, chemists will no longer have to make compromises in synthesizing their intended target compound, especially if it happens to be a sulfide [S(II)].

The demonstration of this concept with the most sensitive substrate (**3**) of this series, along with other synthetic efforts towards thiazocine-2-acetic acid derivatives was published in the following article:

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem.* **2004**, 69, 2750.

This research was also presented at the ACS National Meeting,

Bates, D. K.; Li, X.; Jog, P. V. *Book of Abstracts*, 227th ACS National Meeting, Anaheim, CA March 28-April 1, 2004. ORGN-80.

My most important contribution was developing the redox protecting scheme for the indirect sulfide RCM methodology. This involved finding a suitable reagent, reaction conditions along with preparation of sulfide **2** (Scheme 3) and thorough spectroscopic characterization. I also synthesized various diene RCM precursors for exploratory work on scope and utility of this methodology. Due to space restrictions, thorough spectroscopic characterization such as COSY, HETCOR spectra of **2** along with the detailed chemical shift and the coupling constant information is included as an appendix 3 to this dissertation and is not included in the published article.

Part C: Sulfoxide as a “molecular brake”

This part of the chapter demonstrates one of the unique applications of sulfide-sulfoxide redox chemistry.

Introduction:

Recently, there has been a lot of research interest in the area of molecular manufacturing³⁷ to develop specific molecular systems with precisely positioned atoms and functional groups to achieve a desired behavior. The ultimate, rather far away, aim of this research is to synthesize a molecular analog of what we use in our everyday life, a machine.³⁸ The idea of a molecular machine is based on the same principles as of any vehicle, appliances or even biological systems, muscles, etc. Molecular machines can achieve varied functions such as catalysis, nanoscale manipulations, information storage, and many more.³⁹ In addition, an important factor, which adds a driving force to this research, is the nanoscale dimension of the molecular systems. In short, a lot can be achieved, if we were to make a nanoscale molecular machine to perform as many varied tasks as mentioned above.

The initial research in the designing of the molecular machine was challenging, mainly because there was nothing specifically known about any design. Equally important, as applicable to any machine, was to gain control over rather continuous molecular motions. Hence, the attention was shifted towards making smaller individual components first, with the ultimate assembling of each of these, to produce a complete molecular machine. This approach is commonly called as a bottom-up approach.

The integral component of the molecular machine is a “molecular brake”. Kelley et al., were the early investigators of the molecular brake.⁴⁰ Their design of the molecular brake

involved a triptycene unit attached to a bipyridine unit. (Figure 1, adapted from reference 40).

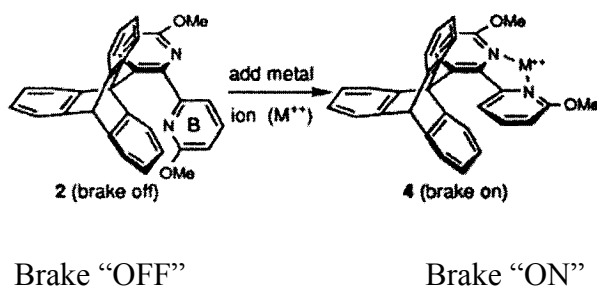


Figure 1: Example of the molecular brake

With the help of dynamic NMR spectroscopy (DNMR), they were able to show that the external addition of a metal ion solution (Hg^+ ion) was capable of restricting the free rotation of the triptycene unit (brake “ON” mode). Disengagement of the brake was achieved with the addition of an EDTA solution, which selectively complexed the added metal ion resulting in the removal of the metal ion, from the system and free rotation of the triptycene unit (brake “OFF” mode).

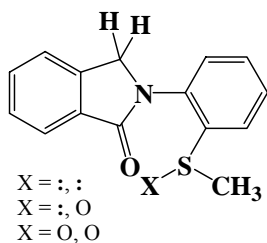


Figure 2: Isoindolines

Based on our knowledge of sulfur chemistry, we envisioned a molecular brake involving a sulfide-sulfoxide redox cycle. We designed a system Isoindoline-1-ones (Figure 2, detailed discussion about our design can be found in chapter 4), in which N-Aryl rotation was varied with the oxidation of the proximate sulfur atom. Dynamic spectroscopy studies on these compounds revealed that, sulfide [oxidation state of S(II)] shows free N-Aryl rotation while corresponding sulfoxide/sulfone resulted in hindered N-Ar rotation.

This approach is novel for many reasons, first, it will add on to the current research of molecular brakes by giving a viable alternative to the scientists in this field, where the earlier example of the molecular brake (external addition of metal ion as rotation obstructive tool) could not be used. Secondly, since sulfur oxidation or reduction can be achieved easily by both chemical and electrochemical means, this type of molecular brake can be used to engage or disengage the brake externally (redox chemical reaction) or internally (redox electrochemical reaction). Importantly, our molecular brake satisfies the basic requirements of a molecular brake. Steric hindrance of sulfoxide oxygen provides the required hindrance to the free rotational process (N-Ar rotation) a brake “ON” mode and the ease of sulfide-sulfoxide redox chemistry gives the essential reversibility to the whole process.

The synthesis and characterization of isoindolines will be explained later (Chapter 4, supporting information), but before we go further it is important to understand some basic concepts and applications of dynamic NMR (DNMR) spectroscopy as applied to the research in the field of molecular machines.

Principles and Applications of Dynamic NMR Spectroscopy⁴¹:

Dynamic NMR spectroscopy is a valuable tool for the chemists studying intramolecular motions. Intramolecular motions involve bond rotations, heteroatom inversions, ring inversions, etc. Although it is well known that the rotations about single bonds are rapid, there are examples of sterically or electronically hindered single bond rotations. Amides are probably the most widely studied example of functional groups by dynamic NMR

spectroscopy⁴² and dimethylformamide (DMF, Figure 3) is the most common compound studied among other amides.

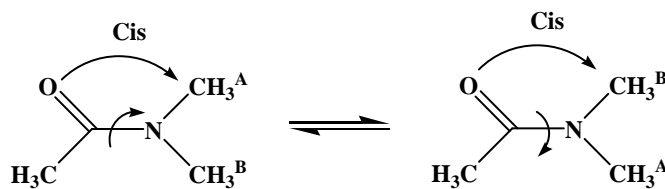


Figure 3: Dimethylformamide (DMF) with diastereotopic methyl groups.

The two methyl groups in DMF show separate signals in its ^1H NMR spectrum at room temperature. In this compound, due to amide resonance, the rotation about the amide bond is hindered. Methyl group cis to oxygen (Figure 3) is in a magnetically different environment than the methyl group trans to oxygen, which results in the two signals being separate. Chemically speaking, both methyl groups are identical. Such pairs of groups of atomic nuclei are called diastereotopic. If one of the groups is replaced by a different group then the compound forms a pair of diastereoisomers.

Another example of such class of compounds include the compound of the type **1** (Figure 4).

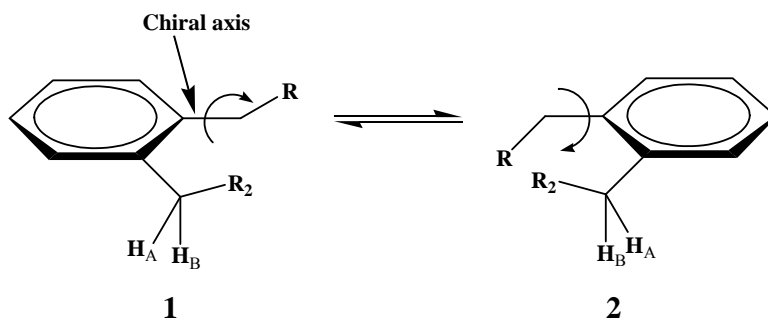


Figure 4: Schematic of enantiomeric rotational isomers.

The molecule of the type **1** and **2** are called enantiomeric rotational isomers, because of the presence of the chiral axis. If a molecule in such a case is unsymmetrically substituted and adopts non-planar conformation, then it is probable for the two groups (H_A and H_B in this case) to be magnetically nonequivalent (hence diastereotopic to each other) and give rise to two separate signals in the NMR spectra. The exact signal separation depends on the barrier to rotation about the chiral axis, a measure of ease by which these isomers interconvert. In addition, such magnetic nonequivalence is often temperature dependent (linear with temperature), in a specific range of temperatures, which is useful in quantification of the rotational barrier. This temperature dependence is non-linear for the molecules containing more than one stereogenic unit. For example, if the compounds similar to **1** contain additional stereocenter (eg. chiral center), in addition to the existing chiral axis, then such molecule shows conformational isomers when the rate of rotation is slow and configurational isomers when the rate of rotation is high (compound **3**, Figure 5). Analysis of such systems with the dynamic NMR technique could be quite problematic and the NMR spectrum often displays unusual variations with changes in temperature.

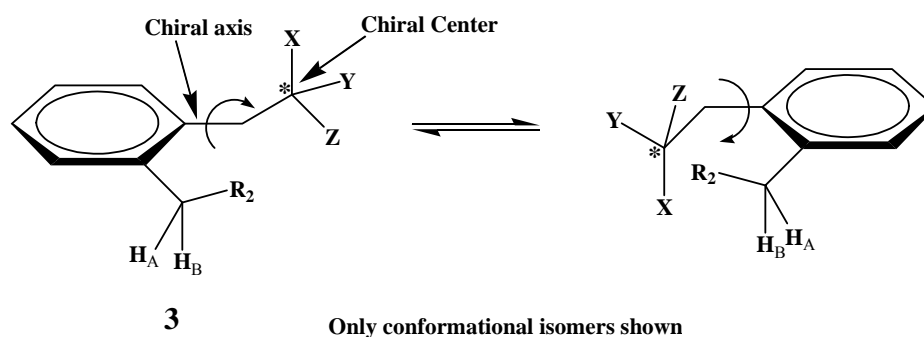


Figure 5

The direct consequence of the hindered rotation is often encountered in ^1H NMR spectrum that shows some broad peaks in addition to normal sharp peaks. If the temperature is raised, the broad signal sharpens and if it is lowered, the original signal splits into one or more signals. Such behavior is an indication of an exchange in nuclei sites taking place at the temperature at which the spectrum is recorded. As temperature is raised, the rotation becomes faster due to an external supply of heat; similarly, a slow rotation is the result of cooling. A fast exchange limit is said to be reached when there is no further sharpening of the signal with a rise in temperature. Similarly, a stage at which the exchange of nuclei is negligibly small is called a slow exchange limit. It is in between these fast and slow exchange limits where dynamic NMR spectroscopy is valuable. The spectra recorded between these limits directly reflect the rate of exchange of nuclei. The most important temperature value for a dynamic NMR chemist is coalescence temperature. It is the temperature at which two signals coalesce (merge) to give one peak and it is denoted as T_c . Coalescence temperature gives information about the rate of exchange of nuclei (Eq 1). Equation 1 can only be used for the uncoupled nuclei. However, for the coupled systems (such as H_A and H_B) equation 2 should be used to obtain the value of the rate of exchange. Using this value of the rate of exchange, the free energy of activation ΔG^\ddagger of exchange can be evaluated (Eq 3) along with other thermodynamic entities such as ΔH^\ddagger and ΔS^\ddagger .⁵

$$k_c = 2.22(\Delta\nu_{AB}) \quad (1)$$

$$k_c = 2.22\sqrt{(\nu_A - \nu_B)^2 - 6J_{AB}^2} \quad (2)$$

$$\Delta G^{\ddagger} = 4.575 \times 10^{-3} T_c \left[10.319 + \log \left(\frac{T_c}{k} \right) \right] \quad (3)$$

Free energy of activation ΔG^{\ddagger} is the most common way to express the intensity of hindered rotation. For example, the amide rotation in DMF has a free energy of activation of about 21.5 kcal/mol (89.9 kJ/mol),⁴³ a value as high as that is an indication of highly hindered rotation. This is an example of a high rotational barrier value due to a preexisting constrain in the molecule. Extrapolating the same concept, it is reasonable to say that if for a specific molecule, the rotational barrier of a given rotation increases due to structural modification in the molecule or external stimuli, then that is the result of enforced restriction of the rotation about that bond.

It is well known that dynamic NMR spectroscopy is an invaluable technique to study intramolecular motions with activation energies of 5-25 kcal/mol (21-104 kJ/mol), which corresponds to about 10^{-4} to 10^{10} sec⁻¹ rate of exchange. Isomers interconverting at such rates are impossible to isolate as separate entities at room temperature.

It is extremely important to mention here that all the things said above, about fast and slow rotations are strictly based on what is being observed at the NMR time scale. For example, a slow rotation at the NMR time scale actually means that the rate of exchange is slower than the limit detectable by the dynamic NMR spectroscopy technique. Detection of slow or fast rotation often depends on the strength of the magnetic field under which the study is performed.

Line Shape Analysis⁴¹:

As mentioned earlier, the rate of exchanging nuclei can be calculated from the coalescence temperature (T_c), however it is always desirable to analyze data further to obtain the rate of exchange at various temperatures. Total line shape analysis is the method most commonly used to get the rate of exchange in the range of coalescence temperature. Line shape analysis is often performed with specifically designed computer software.⁴⁴ The computing program requires the values of chemical shifts, coupling constant and the experimentally recorded spectrum at any given temperature. It then simulates the signal shapes (line shape) and generates a “theoretical” spectrum at that temperature. This theoretical spectrum is a good visual match of the experimental spectrum, and more importantly, it provides the value of the rate of exchange at that temperature. Similar analysis near the range of coalescence temperature (usually 10 °C below and 2-3 °C above coalescence temperature) gives reliable data of the exchange rate. Plotting a graph ($\ln k$ vs $1/T$) of such data gives a value of the free energy of activation (ΔG^\ddagger), which eventually gives the estimate of other thermodynamic parameters such as ΔH^\ddagger and ΔS^\ddagger .

Computational Methods:

A variety of computational methods such Molecular Mechanics (for example MM+), Semi-empirical (for example, PM3), *ab-initio* (for example, STO3-G), etc. have been employed in evaluating the rotational barrier about sterically hindered rotations. A major advantage of computational methods is that it gives an exact nature of steric strain caused due to the precise positioning of the atoms during the complete rotational process

(dihedral angles ranging from 0° to 360°). This information is rarely available from the experimental methods. Furthermore, computational study helps to compare the data obtained from experimental techniques.

A chemist often has to make a choice of the computational method to be used for computation, based on available computational software sophistication and the time involved in doing the calculations. Molecular mechanics (MM+) is a popular method because of its high-speed ability to do calculations, however, data obtained from this method may not compare well with the experimental techniques and hence can be intriguing. In the MM+ method, molecules are treated as mechanical parts with atoms as spheres and bonds as springs. Such treatment, sometime results in false, unrealistic energy minima (local minima). A semi-empirical method (eg. PM3) is based on the experimentally derived parameters and although it takes more time than MM+, it provides more accurate results than the MM+ method. A highly sophisticated method is an *ab-initio* method of computation, which works best for highly complex molecules. This method provides accurate, intense (sometimes unnecessary) data but suffers from serious limitations in terms of the enormous time taken to do the calculations. Based on this information, it is easy to infer that within any given time limit, the semi-empirical (PM3) method is the best suitable for moderately complex molecules.

Among others, amides are the most commonly studied functional group by computational methods. There are reports of electronic and steric effects of nitrogen substitution on hindered amide rotations.⁴⁵ There is a lot of interest in studying structure and geometries of strained amides.⁴⁶ Particularly, in understanding how the rotation about such strained amide bonds takes place and if there is any change in hybridization of

amidic nitrogen during the rotational process. While the study is still in progress, there are reports of otherwise sp^2 hybridized amidic nitrogen undergoing change in hybridization from sp^2 to sp^3 as the substituent on nitrogen rotates.⁴⁶

As noted by Streitwieser, Jr., A.; Heathcock, C. H.:

Ammonia itself and amines generally have a pyramidal structure (Section 23.1); the H—N—H bond angle in ammonia is 107.1° . The most effective conjugation of the nitrogen lone pair with the benzene ring would be obtained for a lone pair in a p -orbital parallel to the p -orbitals of the aromatic π -system. However, lone pairs are generally more stable in orbitals having some s -character. In the case of aniline, an energy compromise is reached in which the lone-pair orbital has more p -character than in ammonia but in which the orbital retains some s -character. As a result, the NH_2 group in aniline is still pyramidal but with a larger H—N—H angle (113.9°) than in ammonia. The H—N—H plane intersects the plane of the benzene ring at an angle of 39.4° .

--Streitwieser, Jr., A.; Heathcock, C. H. in *Introduction to Organic Chemistry*, (3rd ed., Macmillan Publishing Company, New York, NY **1985**.)

This effect applies, not only to anilines but also to amides. To avoid the concept of rehybridization (sp^3 in alkyl amines and sp^2 in aryl amines, etc.) the concept of “nitrogen pyramidalization” was introduced. In this terminology, a pure sp^3 hybridized nitrogen is said to have 100% pyramidalization. Any “flattening” of the nitrogen geometry decreases pyramidalization. Thus, planar nitrogen is said to have 0% of pyramidalization. Nitrogen pyramidalization is a conformational change that the molecule undergoes to minimize the steric interactions during rotation of the substituent. Nitrogen pyramidalization often results in reducing the rotational barrier of rotations. Rankin and Boyd⁴⁷ developed a method to quantify nitrogen pyramidalization by measuring the virtual dihedral angle in

case of prolyl amides. The arrows drawn (Figure 6), show how the virtual dihedral angle is defined. This value of this angle is $\pm 180^\circ$ for sp^2 hybridized nitrogen and $\pm 120^\circ$ for the sp^3 nitrogen.

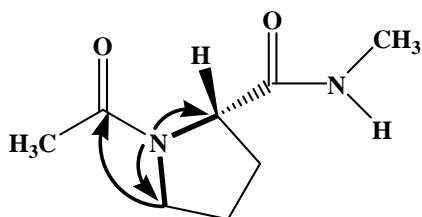


Figure 6: Definition of virtual dihedral angle as defined in prolyl amide.

The extent of nitrogen pyramidalization is a varying factor and it depends on the size of the substituent and its interaction with rest of the molecule during the rotational process. As the size of the substituent increases, its interaction with the rest of the molecule gets severe during its rotation. To reduce this sterically induced strain, nitrogen pyramidalization also increases and results in lowering the rotational barrier value of such process. However, if the steric strain is intentionally introduced in the molecule, then in that case, nitrogen pyramidalization partially nullifies the induced steric strain, giving less than the expected increase in the rotational barrier value.

It is reasonable to expect that nitrogen pyramidalization occurs only when there is a strong interaction between neighboring groups. Depending on the nature and size of the substituent, pyramidalization can occur only a few times during the complete rotational process (dihedral angles ranging from 0° to 360°). In other words, rotation and pyramidalization are concerted or correlated events. Correlated rotations are known to show less than expected rotational barrier values.^{46c}

Lunazzi and co-workers⁴⁸ developed a graphical method to show the presence of correlated rotations in molecules with the aid of computational methods. A 2D energy contour plot is plotted after driving the two dihedral angles under study (from 0° to 360°) and obtaining the energy of the molecule at each fixed pair of dihedral angle. At each fixed pair of dihedral angle, the rest of the molecule is allowed to relax to its minimum energy conformation. A schematic of the 2D energy contour plot is shown in Figure 7. For example, let's assume that the contour plot obtained after driving dihedral angles A and B during such study looks like the one shown in Figure 7a. Then, since the line joining the energy minima is parallel to one axis (axis B in figure 7a) and perpendicular to another axis (axis A in Figure 7a), it can be deduced that the two rotations are noncorrelated to each other. In case of dihedral angles C and D however, (Figure 7b) such line is diagonal to one axis (axis D in figure 7b) and hence it can be said that the two rotations are correlated or geared.

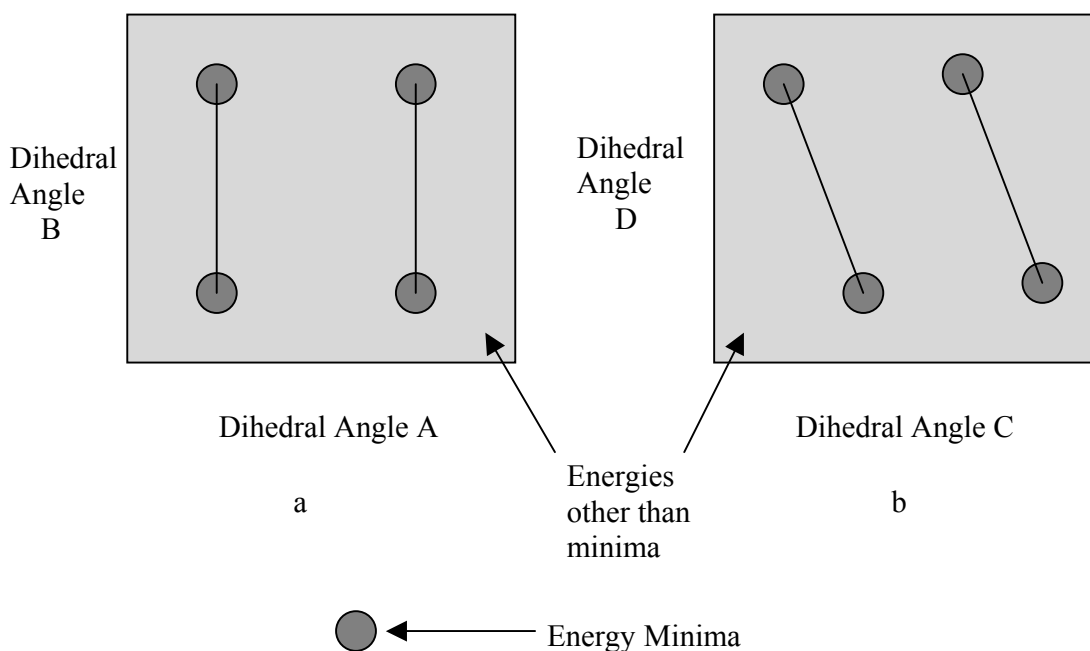


Figure 7: Schematic of 2D contour plot.

Lunazzi and co-workers used⁴⁸ this type of graphical notation to show the correlated or noncorrelated rotation between any given dihedral angles. We have designed a variant of this type of graph and plotted one dihedral angle involving complete rotation against another dihedral angle involved in nitrogen pyramidalization (virtual dihedral angle), while making sure (during the calculations) that both the dihedral angles cover the entire range of possible values. Detailed information of our results, along with the specific dihedral angles studied can be found in Chapter 4.

All of the above discussion is helpful in understanding our sulfide-sulfoxide redox mediated molecular brake design which is published in the following article:

Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem.* **2003**, 68, 8240.

This research was also presented at the ACS National Meeting, New Orleans, LA.,

Jog, P. V.; Brown, R. E.; Bates, D. K. *Book of Abstracts*, 225th ACS National Meeting, New Orleans, LA March 23-27, 2003. ORGN-541.

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Chapter 2

Sulfoxides as a sulfenylating agent

Intramolecular Sulfoxide Electrophilic Sulfenylation (SES) of 2- and 3- Indole Carbanilides: Formation of Indolo[3,2-*b*]-1,5-benzothiazepinones

Bates, D. K.; Eggers, M. E.; Jog, P. V. *J. Org. Chem.* Submitted for publication.

The contribution of Parag Jog to this work included synthesis of all compounds containing *t*-butyl and 2-cyanoethyl groups as well as studies of thermal and TFAA activated reactions of the penultimate sulfoxide derivatives. He also did all of the work related to detection of sulfenic acid intermediates.

Approved by co-author Dallas K. Bates



Intramolecular Sulfoxide Electrophilic
Sulfenylation (SES) of 2- and 3- Indole
Carbanilides: Formation of Indolo[3,2-*b*]-1,5-
benzothiazepinones

Dallas K. Bates, Mary E. Eggers, and Parag V. Jog*

Department of Chemistry, Michigan Technological University, Houghton, MI 49931

Abstract

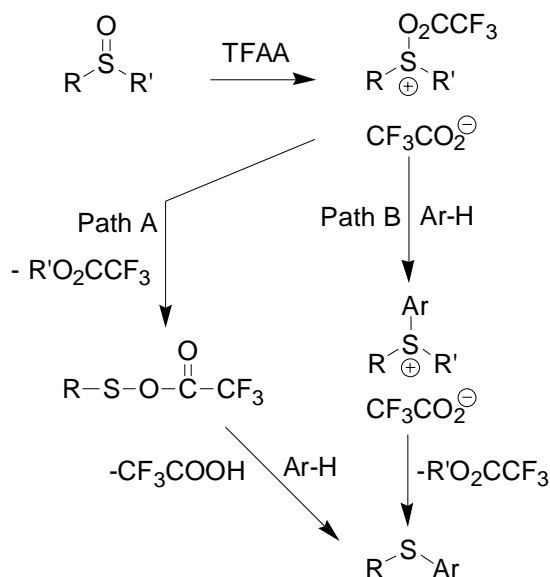
A series of *N*-[2-(alkylsulfinyl)phenyl]-1*H*-indole-2-carboxamides was prepared in which the indole and amidic nitrogens were either unsubstituted (**2ab**), partially substituted (indole N-H, amide N-Me, (**4ab**) and indole N-Me, amide N-H, (**6ab**), or fully substituted (indole N-Me, amide N-Me, (**8abc**). When these compounds were heated in an inert solvent (chloroform for *t*-butyl sulfoxides or *p*-xylene for ethyl sulfoxides) or treated with trifluoroacetic anhydride, all compounds (**4ab**, **8abc**) in which the amidic nitrogen was methylated cyclize to indolo[3,2-*b*]-1,5-benzothiazepinones (**9** or **10**, depending on indolic substitution). Successful cyclization was attributed to an ability of the N-Me amides to readily adopt a conformation conducive to cyclization, which other derivatives were unable to achieve. The same pattern of reactivity was observed with *N*-[2-(alkylsulfinyl)phenyl]-1*H*-indole-3-carboxamides (**15a**, **17ab**) under the same reaction conditions and the same product (**10**) was produced from (**17a**) upon heating in *p*-xylene. Rearrangement of a 3*H*-indolinium spirocyclic intermediate is proposed to account for this result. Accumulating evidence, including cyclization in the presence of a sulfenic acid trapping agent, suggests these reactions take place via an sulfonium salt intermediate (electrophilic sulfur of sulfoxide attacked by a nucleophile) rather than via a sulfenic acid intermediate.

Introduction

Sulfoxides are widely used as electrophilic sulfonylating agents for alkenes and aromatic (and heteroaromatic) systems. There are two general mechanistic pathways by which sulfoxides are activated to become sulfonylating agents and both occur with reagents and conditions typical for the Pummerer Reaction.¹ Many reported ‘anomalous’ reaction products from Pummerer Reactions are electrophilic sulfonylation reactions, with the ‘anomalous’ pathway favored by the presence of a proximate nucleophilic group² or a non-acidic hydrogen atom on the carbon α to the sulfoxide.³

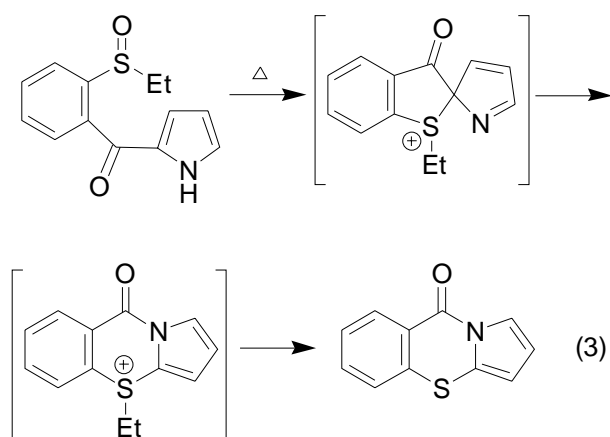
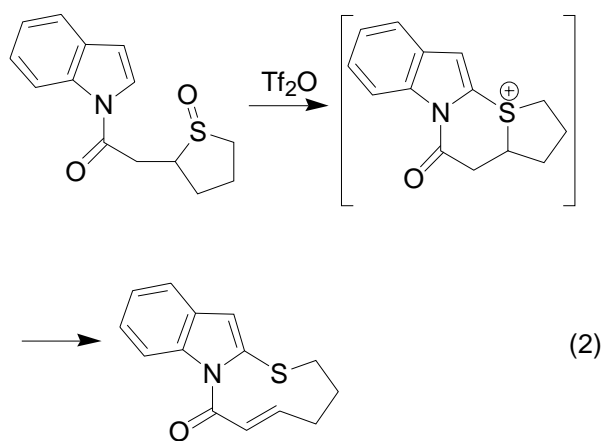
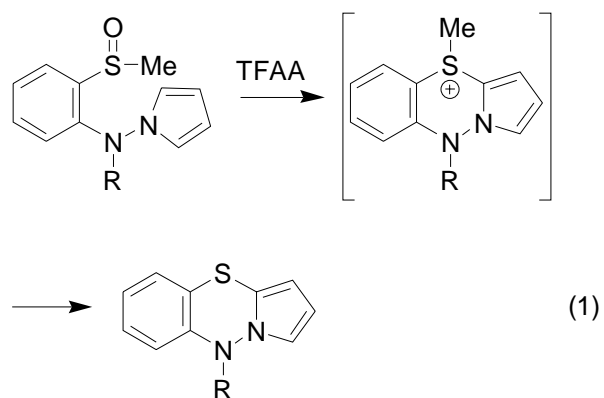
One pathway to sulfonylation involves sulfenic acid intermediates. Treatment of a sulfoxide with an anhydride or trace of acid/heat in an inert solvent may form a mixed anhydride of a sulfenic acid ($\text{RSO}(\text{COCF}_3)$, RSOAc , etc.) or a sulfenic acid (RSOH , which presumably forms, *in situ*, RSOH_2^+ as the active sulfonylating agent),⁴ which are reported to react with alkenes^{5,6} or arenes⁷ via electrophilic addition or electrophilic substitution, respectively. The other mechanistic pathway to sulfonylation with sulfoxides involves direct (nucleophilic) attack at (electrophilic) sulfur in an activated sulfoxide ($\text{R}_2\text{S}-\text{O}_2\text{CCF}_3^+$ or $\text{R}_2\text{S}-\text{OH}^+$) forming an intermediate sulfonium salt which is dealkylated, either *in situ* or as a separate step, to form the sulfonylation product. These two pathways are shown in Scheme 1. There are numerous examples of electrophilic sulfonylations of aromatics⁸ and heteroaromatics⁹ utilizing this approach.

Scheme 1. Alternative Pathways to Electrophilic Sulfenylation with Sulfoxides^{/a}



^{/a} Illustrated with trifluoroacetic anhydride as the sulfoxide activator. Other reagents may be used (see text).

We have exploited this chemistry (sulfoxide electrophilic sulfenylation-SES) followed by variations in the mode of dealkylation to prepare new *N,S*-heterocyclic systems: SES/displacement¹⁰ (eq 1) and SES/ring enlargement¹¹ (eq 2). We have also observed a third variant, SES/rearrangement¹² in a pyrrole system (eq 3). In this process, a minor product under all conditions tried was the rearranged product shown. Its formation was rationalized as resulting from rearrangement of an initially formed spirocyclic intermediate.



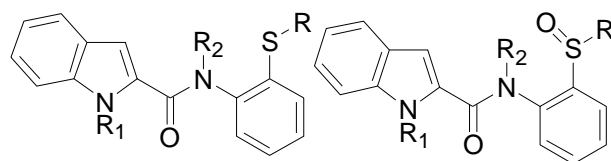
In this article we describe a study of SES/rearrangement cascade in a series of 2- and 3-substituted indole compounds. Indoles exhibit a strong preference for electrophilic attack at C-3 even when that position is already substituted. The 3-substituted target compounds

were selected to attempt to enhance rearrangement processes because 3,3-spirocyclic and other 3,3-disubstituted-3*H*-indolinium species resulting from indole/electrophile interactions are a common occurrence throughout indole chemistry.¹³ In each series, sulfoxides containing ethyl, *t*-butyl, and propanenitrile alkyl group were prepared. The latter two types of sulfoxides, having non-acidic alkyl groups, should undergo SES reactions (not Pummerer chemistry) but would be expected to dealkylate under milder conditions than ethyl substituted compounds.¹⁴ These compounds are of interest because *t*-butyl and propanenitrile sulfoxides also very easily thermally decompose to sulfenic acid derivatives¹⁵ providing a potential opportunity to study their relevance as intermediates in these reactions.

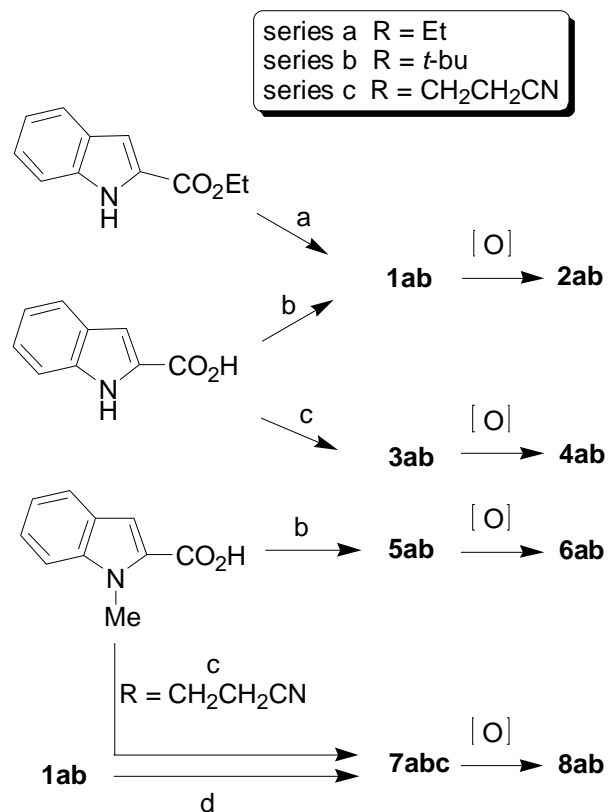
Results and Discussion

Several related (ethyl, *t*-butyl, and 2-propanenitrile) sulfoxides tethered to C-2 or C-3 of indole were prepared with indole and amidic nitrogen atoms in differing degrees of methylation. Preparation and reactions of the C-2 and C-3 substituted compounds are discussed separately below.

Scheme 2^{/a}



$R_1 = H$	$R_2 = H$	1	2
$R_1 = H$	$R_2 = Me$	3	4
$R_1 = Me$	$R_2 = H$	5	6
$R_1 = Me$	$R_2 = Me$	7	8



^{/a} conditions: (a) 2-ethylthioaniline, AlMe₃, toluene, reflux (b) SOCl₂, Et₂O, 2-(alkylthio)aniline, rt (c) SOCl₂, Et₂O, *N*-methyl-2-(alkylthio)aniline, rt (d) 50% NaOH, CH₃I, *n*-Bu₄NHSO₄, toluene.

Indoles substituted at C-2

Indole-2-carboxylic acid chloride, formed *in situ* by reaction of indole-2-carboxylic acid with thionyl chloride at room temperature¹⁶, and a 2-(alkylthio)aniline¹⁷ produced sulfides **1ac** in modest yields. Problems have been reported in reaction of indole

carboxylic acids with thionyl chloride¹⁸ and use of the unstable acid chloride (and consequent low yield of amide) could be avoided by trimethylaluminum-catalyzed condensation¹⁹ of 2-(alkylthio)anilines and ethyl indole-2-carboxylate. For example, **1a** was obtained in 92% yield by this approach. Oxidations were accomplished using standard methodologies: a slow, but selective, multi-phase reaction using NaIO₄ in CH₂Cl₂/MeOH/H₂O^{3a}; potassium peroxy monosulfate (Oxone) in THF/MeOH/H₂O²⁰; or *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane.²¹

Monoalkylated compounds bearing the methyl substituent on the amide (**4ab**) were prepared similarly replacing the aniline component with an *N*-methyl-2-(alkylthio)aniline,²² followed by sulfur oxidation.

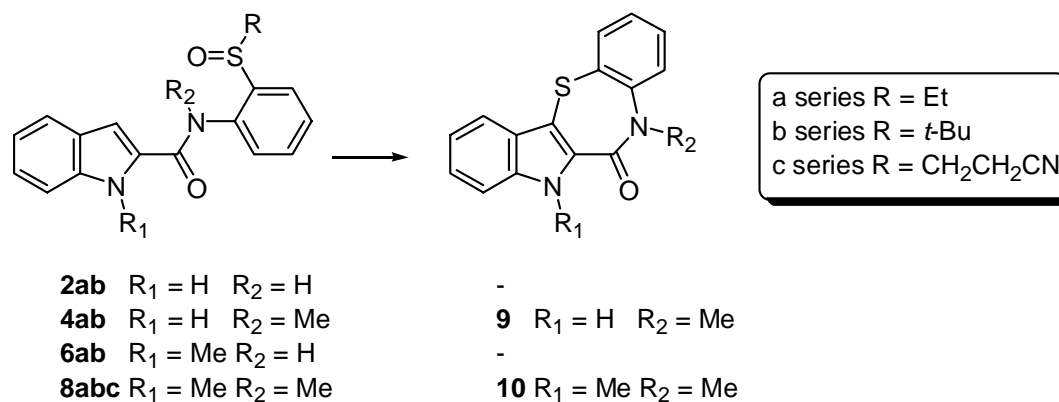
Monoalkylated compounds bearing the methyl substituent on the indole (**6ab**) were prepared similarly using alkylthioanilines and *N*-methylindole carboxylic acid, followed by oxidation.

N,N'-Dimethylated compounds (**8ab**) were prepared by dialkylation of amides (**1ab**) by catalytic phase transfer methylation, followed by oxidation. Sulfide (**1c**) decomposed under phase transfer conditions (retro-Michael) so compound **8c** was prepared in low yield by reaction of 1-methyl-1*H*-indole-2-carboxylic acid chloride with 2-propanenitrile-2-(methylaminophenyl)sulfide).

When the sulfoxides were subjected to cyclization conditions [either activation by electrophilic species (TFAA) or thermally (refluxing in chloroform or *p*-xylene)] clear patterns of reactivity emerge. For unknown reasons, thermal conditions always produced lower yield of product than with TFAA activation. As expected, in successful reactions, *t*-butyl sulfoxide derivatives cyclize thermally in refluxing chloroform whereas ethyl

sulfoxide derivatives require much higher temperatures (refluxing in *p*-xylene). In addition, as shown in Table 1, a substituent at the amidic nitrogen is essential for cyclization of all sulfoxides. Interestingly, in every case, the ^1H NMR spectrum of a sulfoxide that successfully cyclizes was very poorly resolved. This is indicative of conformational interconversion between two or more rotomers taking place on the millisecond time-scale at 25 °C. Recording ^1H NMR spectra at 100 °C showed fewer, sharper peaks as expected for an increased rate of interconversion in a dynamic process.²⁴ It seems logical that conformational flexibility could help the molecule readily obtain the geometry required for indole pi electron – sulfoxide sulfur atom interaction and it is well known that *N,N*-dialkyl amides have lower barriers to C(O)-N rotation as well as higher energy, non-planar ground states (hence the lower rotational barrier) than primary or secondary amides.²⁵

Table 1. Correlation of Cyclization and Spectral Data for Sulfoxides



Sulfoxide	Cyclization product % yield (TFAA, thermal)	1H NMR (rt)	$\nu_{S=O}$ (cm^{-1})
2a	none	sharp	1009
2b	none	sharp	985
4a	9 (75, 56)	broad	1041
4b	9 (100, 58)	broad	1040
6a	none	sharp	1003
6b	none	sharp	999
8a	10 (90, 22)	broad	1025
8b	10 (100, 66)	broad	1039
8c	10 (50, 41)	broad	1039

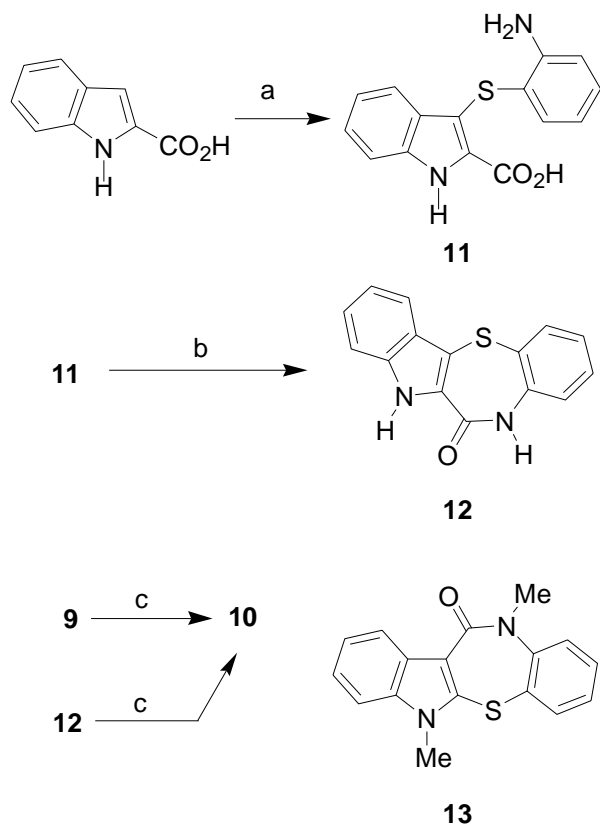
Sulfoxides which bear only a proton on the amidic nitrogen (**2ab**, **6ab**) produced either decomposition products or were recovered unchanged. This may be due to factors preventing the sulfoxide sulfur atom and the indole pi-system from assuming the correct conformation for cyclization. There is evidence of $S=O \cdots H-N$ intramolecular hydrogen-bonding in 1H NMR and IR spectra of these compounds. Sulfoxide peaks in the IR

spectra of **2ab** and **6ab** appear at a lower frequency, which is to be expected if the oxygen of the sulfoxide is involved in hydrogen bonding²⁶ (Table 1). Additionally, ¹H NMR spectra of **2ab** and **6ab** showed sharp and well-resolved peaks in contrast to ¹H NMR spectra of compounds in which the amidic nitrogen was methylated. Compounds in which the amidic site is methylated (but still contain an indole N-H) (**4ab**) cyclize both thermally and with TFAA activation to produce the same product, assigned the structure 10,11-dihydro-10-methyl-12*H*-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (**9**). The failure of compounds containing amidic N-H to cyclize is also attributable to the large energy difference in the *cis*- and *trans*- amide isomers, with the unfavorable (for cyclization) *trans*-isomer preferred. Not only are these compounds ‘locked’ into an arrangement wherein the sulfoxide oxygen is hydrogen bonded the amidic NH, but the energy barrier to interconversion of the *cis*- and *trans*- amide forms is formidable. On the other hand, the amidic N(Me) compounds not only exhibit lower rotational barriers to *cis*-/*trans*-amide isomer interconversion, but the literature^{25b} suggests that these compounds probably exist predominately in the *cis*-form (which in this case places the sulfoxide and indole entities near one another).

Compounds **8abc** gave a compound assigned the structure 10,11-dihydro-10,12-dimethylindolo[3,2-*b*]-1,5-benzothiazepin-11-one (**10**). Thermal conditions consistently produced lower yield of product than with TFAA activation with all sulfoxides. For reasons that are unclear, 2-propanenitrile compounds were inferior to both ethyl and *t*-butyl sulfoxides and were not pursued further. As with product **9**, spectral data clearly shows cyclization was effected, however, additional proof of structure was sought due to the possibilities of scrambling of the acyl and sulfur locations either during the reaction

or subsequent equilibration^{27,28} leading to compounds that would exhibit very similar spectral properties. Fortunately, the likely rearrangement product (**13**) is a known compound. The UV spectrum and melting point of our cyclization product differs considerably from that of **13** reported by Grandolini and co-workers²⁹ ruling out this alternative isomer. In addition, **10** was synthesized via an unambiguous route (Scheme 3). Using the technique described by Atkinson,³⁰ amino acid **11** was readily prepared. Refluxing **11** in toluene using SiO₂ as catalyst³¹ gave **12** which on catalytic phase transfer methylation gave a product chromatographically and spectroscopically identical to the cyclization product (**10**), clearly establishing the sites of attachment of the sulfur and carbonyl groups on the indole ring. Catalytic phase transfer methylation of **9** also produced **10** (76%) confirming the structure of that product as well.

Scheme 3^{/a}



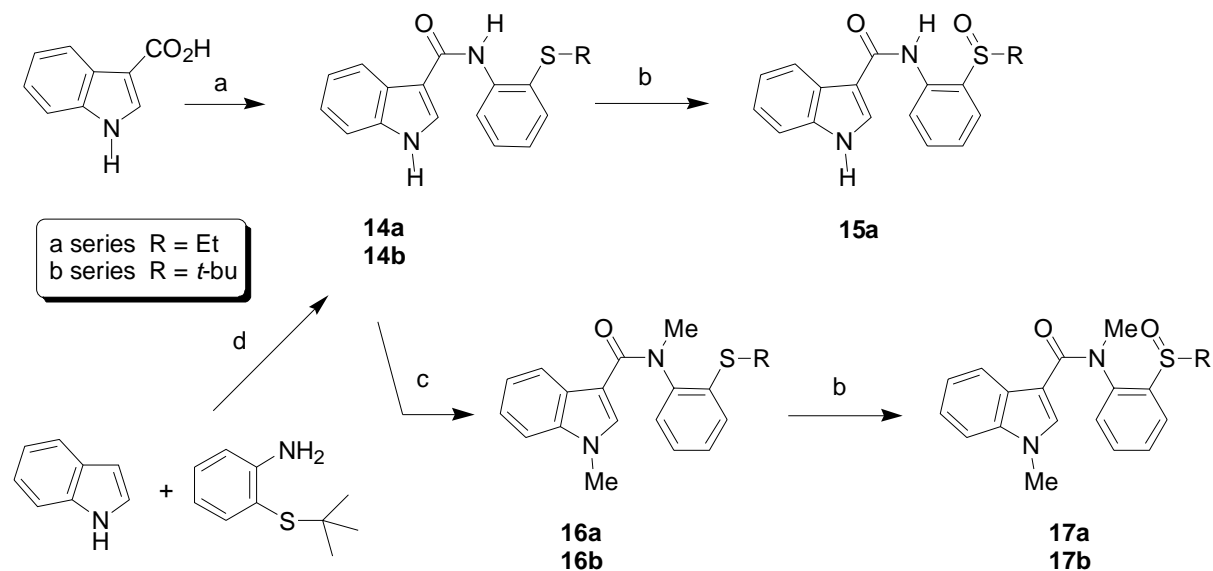
^{/a} conditions: (a) 2,2'-diaminodiphenyldisulfide, NaH, DMF (b) SiO₂, toluene, reflux (c) *n*-Bu₄NHSO₄, 50% NaOH, CH₃I, toluene, reflux.

Indoles substituted at C-3

3-Substituted indole sulfoxides were of great interest due to the propensity of indoles to react with electrophiles at C-3. The synthesis of sulfoxides (**15a**, **17ab**) is outlined in Scheme 4. Indole-3-carboxylic acid³² was converted to the acid chloride *in situ* with the use of oxalyl chloride and then reacted with 2-(ethylthio)aniline to produce sulfide **14a** which was oxidized to sulfoxides **15a**. Catalytic phase transfer methylation of **14a** to **16a** followed by oxidation gave sulfoxide **17a**. We encountered reproducibility problems with the reported preparation of 3-indole carboxylic acid so the *t*-butyl analogue was prepared by a different route. Indole and 2-(*t*-butylthio)aniline in the presence of triphosgene and

pyridine directly produced (**14b**) in 33% yield. Methylation and oxidation provided (**17b**).

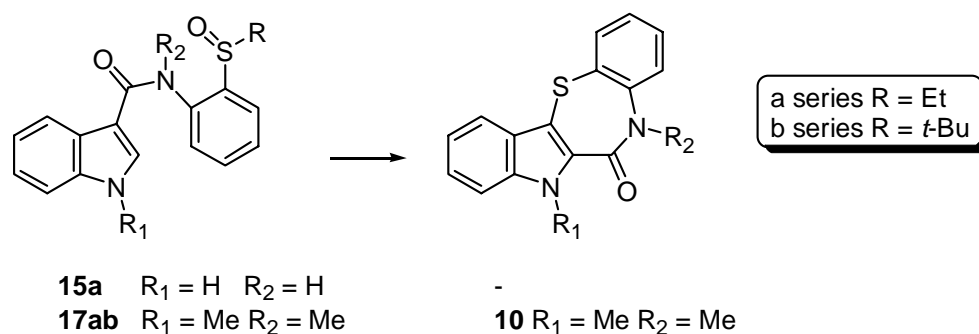
Scheme 4^{/a}



^{/a} Conditions: (a) 1. (COCl)₂, THF, 0 °C 2. ArNH₂, CH₂Cl₂ (b) Oxone or m-CPBA (c) 50% NaOH, CH₃I, *n*-Bu₄NHSO₄, toluene (d) 1. triphosgene, toluene/CH₂Cl₂/pyr 2. ArNH₂, CH₂Cl₂.

Cyclizations of sulfoxides **15a**, **17ab** was attempted under both thermal and electrophilic activation. As shown in Table 2, results in this series were mixed. Like its 2-substituted indole counterpart the compound with an amidic N-H (**15a**) did not cyclize under any conditions used. Compound **17a**, which had a broad ¹H NMR spectrum, gave a cyclized product in good yield, but decomposed under TFAA activation. The *t*-butyl sulfoxide **17b**, although it had the same ¹H NMR and IR patterns as successfully cyclized sulfoxides, decomposed under both thermal and TFAA activation.

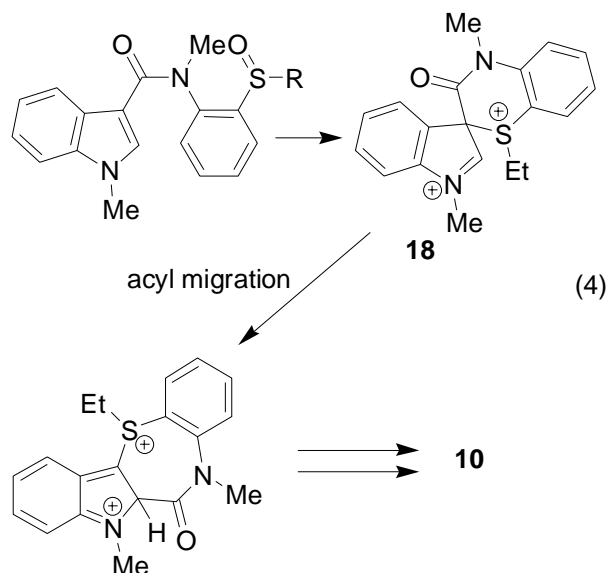
Table 2. Correlation of Cyclization and Spectral Data for Sulfoxides



Sulfoxide	Product% yield (TFAA, thermal)	^1H NMR (rt)	$\nu_{\text{S=O}}$ (cm^{-1})
15a	none	sharp	1003
17a	10 (none, 67%)	broad	1014
17b	none	broad	1030

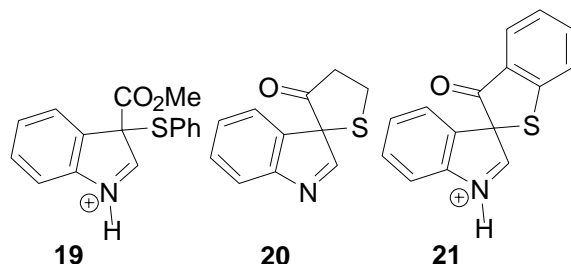
The product obtained from heating **17a** under reflux for 15 h in *p*-xylene (67% yield after chromatography) proved to be identical to **10**, the cyclization product from the 2-substituted indole sulfoxide. Mechanistically, there are several explanations for such a phenomenon. (a) migration of the acyl-amide group from C-3 to C-2 of indole prior to cyclization (**17a** \rightarrow **8a** \rightarrow **10**). However, heating the sulfide **7a** (which cannot cyclize via SES) for 12 h in *p*-xylene showed no evidence of acyl migration (95% recovery of unchanged starting material). There is literature precedence for acyl migration from C-3 to C-2 in indoles but typically much more strongly acidic conditions than used here are required.³³ (b) Initial formation of **13** by direct cyclization to C-2, followed by rearrangement to **10** upon prolonged heating in *p*-xylene, as we had observed previously in another indolic system.²⁷ However, authentic **13** (synthesized as reported by Grandolini and co-workers²⁹) showed no sign of rearrangement to **10** after 22 h in refluxing *p*-

xylene. Even after an additional 24 h at reflux in 0.1% TFA in *p*-xylene solution resulted in 92% recovery of unchanged starting material. (c) Initial formation of a 3*H*-spirocyclic intermediate (such as **18**) during SES at C-3, followed by *acyl migration* to C-2 and loss of a proton to give **10** (eq 4).



Formation of product **10** via a spirocyclic intermediate runs contrary to expectations based on the literature available. For example, formation of methyl 2-phenylthioindole-3-carboxylate from sulfenyl chloride and methyl indole-3-carboxylate is proposed to occur by way of preferential sulfur migration in the 3*H*-indolium species (**19**), although no evidence was provided to support this speculation.³⁴ Additionally, Nagarajan³⁵ proposed a spirocyclic intermediate (**20**) followed by preferential sulfur migration to C-2 to explain formation of 2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indol-4-one from 3-(3-indolylthio)propanoic acid. However, Hamel and co-workers^{36a} have shown that 3-(3-indolylthio)propanoic acid isomerizes to the 2-isomer prior to cyclization. This work also established a generalization about reaction conditions for cyclizations involving 3-indolylthioalkanoic acids: when conducted in PPA C-3 to C-2 thioalkyl migration occurs

prior to cyclization, but with PPE in CH_2Cl_2 , migration is minimal. An apparent anomaly to this behavior, for which no formal explanation could be provided, involves 2-(3-indolylthio)benzoic acid.²⁸



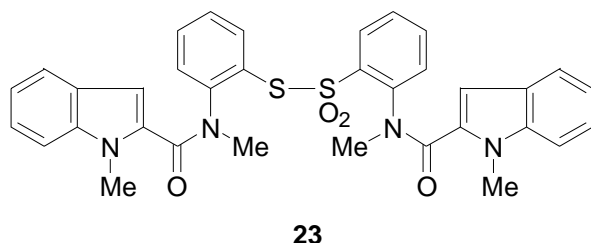
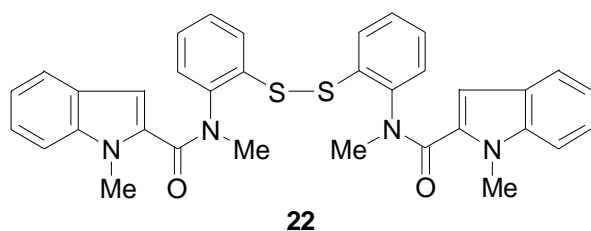
Formation of **10** via a spirocyclic intermediate requires migration of the acyl-amide group to occur in preference to an arylsulfonium group (or arylthio group).³⁷ It also seems plausible that a similar intermediate from **21** could explain the apparently anomalous behavior reported by Hamel.²⁸ Both 3-acylindoles³³ and simple 3-alkylthio- and 3-arylthioindoles³⁶ undergo acid-catalyzed conversion, respectively, to their 2-substituted counterpart in these thermodynamically-controlled processes. However, when both groups are present at indole C-2/C-3, the thermodynamically more stable product can not be determined by inspection and in both Hamel's work and this work, neither the product nor the alternative isomer is interconverted under the conditions the reaction. Thus, the product that forms predominately could be a kinetic product derived by migration in a spirocyclic intermediate of the group having the greater migratory aptitude: a resonance-stabilized acylium species [phenylacylium species (in the case of Hamel's cyclization) or of an amidic acyl (isocyanato) group in the present work in preference to a sulfur species]. Although the scant data available suggests sulfur substituents have a greater migratory aptitude than ester, aldehyde and alkyl ketone

groups, no information is available concerning the potentially more stable migrating groups amide or phenyl ketone.³⁸

Eliminating the sulfenic acid pathway for SES chemistry

Formation of sulfenic acids from sulfoxides and their sulfenylation of a nucleophilic nitrogen atom (to prepare a series of benzoisothiazolones) has been reported³⁹ to occur under nearly the same conditions reported here (trichloroacetic anhydride/pyridine or refluxing toluene/pyridine). Glucosulfinylpropanenitriles⁴⁰ as well as *t*-butyl alkyl sulfoxides,⁴¹ upon heating in an inert solvent, generate transient sulfenic acids which have been trapped using methyl propiolate or other alkynes.

To explore the possibility that **10** may also form via a transient sulfenic acid, we conducted thermal reactions of **8b** in the presence of a sulfenic acid trapping agent. When (**8b**) was refluxed in chloroform in the presence of 2-mercaptobenzothiazole as a trapping agent⁴² (1 molar equiv) cyclization product **10** was obtained in 31% yield (compared to 66% yield in the absence of the trapping agent) and no disulfide product is observed. In some cases when *t*-butyl sulfoxides were refluxed in *p*-xylene, minor amounts of **22** and **23** were isolated in addition to cyclized product. These compounds are indicative of sulfenic acid formation,⁴³ but were never detected in reactions of ethyl sulfoxides. Yields of cyclized product from *t*-butyl sulfoxides were considerably lower when they were found in the crude reaction product. We believe sulfenic acids are **not** intermediates in these sulfenylation reactions and are instead formed as an undesired side reaction; it is important to conduct reactions under conditions below the threshold for sulfenic acid formation to obtain optimal yields of cyclized products.



Conclusions

Contrary to expectations, both 2- and 3- indolecarbanilides (**8abc** and **17a**) undergo cyclization to produce the same product - indolo[3,2-*b*]-1,5-benzothiazepin-11-one (**10**). For the 3-indolecarbanilides, the possibility of indole substituent migration before or after cyclization was eliminated and a 3*H*-indolium spirocyclic intermediate, with preferential migration of the carbonyl-containing moiety from C-3 to C-2, is proposed to rationalize the results. We also discovered that successful cyclization in this series requires the *absence* of an amidic N-H in the compounds. The lack of reactivity of compounds containing an amidic N-H is attributed to N-H---O=S hydrogen bonding and a lower energy *trans*-amide conformation, both of which enforce a molecular geometry that prevents the sulfoxide sulfur atom from achieving an orientation conducive to interaction with indole pi-electrons. By extrapolation, if compounds containing an amidic N-H are required, one should consider introducing an easily removable amidic alkyl substituent (*e.g.*, benzyl) into the SES substrate.

The reaction conditions used in this study have been reported to produce sulfenic acid intermediates and some authors have suggested a sulfenic acid pathway for some

sulfenylation reactions of sulfoxides. Trapping experiments using benzothiazole and previous observations^{10b,11} suggest that both thermal and electrophile-activated sulfenylation reactions (including those with *t*-butyl sulfoxides) take place via a sulfonium salt pathway, not sulfenic acid intermediates.

Experimental Section

Melting points are uncorrected. ¹H and ¹³C NMR spectra were determined in CDCl₃ solutions unless otherwise indicated. IR spectra were recorded in KBr pellets for solid samples and neat on NaCl plates for liquid samples. Mass spectra were recorded at 70 eV (EI) unless indicated otherwise.

***N*-[2-(ethylthio)phenyl]-1*H*-indole-2-carboxamide (1a). Method A.** To a well-stirred solution of indole-2-carboxylic acid (10.0 g, 60 mmol) in Et₂O (194 mL) at 0 °C under a drying tube was added dropwise, SOCl₂ (9.6 mL, 140 moles, 2.2 eq.) neat over 5 min. The mixture was allowed to warm to room temperature. After stirring an additional 2 h, volatiles were removed in vacuo leaving a yellow solid which was redissolved in Et₂O (96 mL) and added to a well-stirred solution of 2-(ethylthio)aniline (2 eq. 18.4 g, 0.12 moles) in Et₂O (96 mL) over 8 min at 0 °C. The resulting yellow slurry was stirred for 50 min at 0 °C and at room temperature for 30 min at which time the mixture was diluted with EtOAc (100 mL). The combined organics were washed with 5% aq HCl (3 x 150 mL), 5% aq. NaHCO₃ (3 x 150 mL), H₂O (2 x 100 mL), dried (Na₂SO₄) and the solvent evaporated in vacuo to yield a wet orange solid. Column chromatography (1:1 CHCl₃:hexanes) gave a yellow solid, **1a** (5.7 g, 32%). Analytically pure material could be obtained by recrystallization from acetone: mp 153-155 °C; IR 3350, 3298, 1654 cm⁻¹; ¹H NMR (200 MHz) δ 10.09 (1H, d, *J* = 0.6 Hz), 9.51 (1H, s), 8.60 (1H, dd, *J* = 1, 6 Hz),

7.65 (1H, dd, $J = 0.6$, 8 Hz), 7.53 (1H, dd, $J = 1$, 6 Hz), 7.44 (1H, dd, $J = 0.6$, 8 Hz), 7.00-7.40 (5H, m), 2.76 (2H, q, $J = 7$ Hz), 1.18 (3H, t, $J = 7$ Hz); ^{13}C NMR δ 160.2, 140.1, 137.6, 136.3, 131.5, 131.0, 128.1, 125.4, 124.6, 123.2, 122.6, 121.3, 120.4, 112.8, 103.4, 31.3, 15.3; MS [m/z (relative intensity)] 296 (M^+ , 54), 235 (75), 153 (100); Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OS}$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.70; H, 5.55; N, 9.34.

Method B. To a N_2 -flushed flask containing toluene (123 mL) was added trimethylaluminum (2.0 M in hexane, 21 mL, 42 mmol, 1.14 eq.) via a syringe dropwise. *CAUTION: pyrophoric.* This solution was cooled to 5 °C and 2-(ethylthio)aniline (5.7 g, 37 mmol) in toluene (18 mL) was added dropwise. After stirring 20 min at 5 °C, the solution allowed to warm to room temperature over a 45-min period. To the resulting solution was added dropwise ethyl indole-2-carboxylate (7.0 g, 37 mmol) in toluene (62 mL) and CH_2Cl_2 (18 mL). When the addition was complete the reaction mixture was heated to reflux. After refluxing 16 h, the cooled solution was hydrolyzed by slow addition of 2% aq. HCl (45 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 50 mL). The combined organics were washed with saturated NaCl and then with H_2O , dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a yellow solid (9.8 g, 92%) as a single spot on TLC which was identical to the compound prepared above (^1H NMR and mixed melting point).

***N*-[2-(ethylsulfinyl)phenyl]-1*H*-indole-2-carboxamide (2a).** To a well-stirred solution of **1a** (0.5 g, 1.5 mmol) in THF/MeOH (2.5 mL/ 1 mL) at 0 °C was added all at once a solution of Oxone in H_2O (2.5 mL). The resulting mixture was stirred at 0 °C for 5 min then at room temperature for 2.5 h then extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with H_2O , dried (Na_2SO_4) and the solvent removed in

vacuo to yield a light yellow solid which was recrystallized in MeOH to yield a very faint yellow solid, **2a** (0.3 g, 58%): mp 156-157 °C; IR 3289, 3168, 1662, 1009 cm⁻¹; ¹H NMR (200 MHz) δ 11.84 (1H, s, br), 10.29 (1H, s, br), 8.80 (1H, dd, J = 1, 8 Hz), 7.10-7.72 (8H, m, containing 1H at δ 7.45, dd, J = 1, 8 Hz), 3.07-3.19 (2H, dm), 1.26 (3H, t, J = 7 Hz); ¹³C NMR δ 160.4, 141.6, 133.0, 131.2, 128.2, 127.7, 127.2, 127.1, 125.4, 125.1, 123.5, 122.9, 121.1, 112.4, 104.8, 48.9, 7.8; MS [m/z (relative intensity)] 312 (M⁺, 63), 283 (20), 144 (100). Anal Calcd for C₁₇H₁₆N₂O₂S: C, 65.36, H, 5.16, N, 8.97. Found: C, 65.35, H, 5.33, N, 8.86.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (4b).** To an ice-cooled solution of **3b** (5.0 g, 14.8 mmol) in CH₂Cl₂ (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 21.1 mmol, 3.6 g) in CH₂Cl₂ (50 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (-8 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution (150 mL) and extracted with CH₂Cl₂ (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc-hexane, 9:1) gave yellowish white solid which was recrystallized (hexane) to give a white solid (3.68 g, 70%): mp 114-116 °C; IR 3453, 1624 cm⁻¹; ¹H NMR and ¹³C NMR was not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 144 (6), 56 (58), 41 (100).

***N*-[2-(ethylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7a).** To a well-stirred suspension of **1a** (5.2 g; 17 mmol) and tetra-*n*-butylammonium sulfate (0.6 g; 2 mmol; 0.1 eq.) in toluene (22 mL) was added 50% aq. NaOH solution (22 mL) in one portion. The resulting two-layer mixture was heated to reflux and a solution of CH₃I (5.4 g; 38 mmol; 2.2 eq) in toluene (5 mL) added dropwise over 5 min. This mixture was

refluxed for 24 h, cooled to room temperature and the layers separated. The organic layer was washed with H₂O several times (until washings were neutral to litmus), dried (Na₂SO₄) and the solvent evaporated in vacuo to yield a brown solid which was filtered through a silica gel column (1:1 CHCl₃:hexanes as eluent) to give **7a** (4.7 g, 82%) as a white solid. Recrystallization (acetone) gave pure **7a**: mp 127-128 °C; IR 1635 cm⁻¹; ¹H NMR (200 MHz) δ 6.95-7.38 (8H, m), 6.07 (1H, s), 3.97 (3H, s), 3.41 (3H, s), 2.80 (2H, apparent qd, J = 7.2, 4.9, 2.3 Hz,), 1.20 (2H, t, J = 7.3 Hz); ¹³C NMR δ 164.6, 143.1, 138.4, 136.5, 132.3, 129.0, 128.8, 128.6, 127.9, 126.5, 123.7 122.2, 120.1, 110.1, 107.1, 37.2, 32.0, 26.4, 14.2; MS [m/z (relative intensity)] 324 (M⁺, 2), 158 (100); Anal. Calcd for C₁₉H₂₀N₂OS: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.27; H, 6.34; N, 8.58.

10,11-Dihydro-10-methyl-12*H*-indolo[3,2-*b*][1,5]benzothiazepin-11-one (9) from 4a.

Method A (Thermal Cyclization). A solution of **4a** (1.7 g, 5 mmol) in *p*-xylenes (66 mL) was heated under reflux for 12 h. Upon cooling to room temperature, the solution was filtered to give a green solid, **9** (0.8 g, 56%): mp 290 °C (dec); IR 3228, 1618 cm⁻¹; ¹H NMR (200 MHz, DMSO-*d*₆) δ 12.13 (1H, s, br), 7.15-7.67 (8H, m), 3.51 (3H, s); MS [m/z (relative intensity)] 280 (M⁺, 100). Anal Calcd. for C₁₆H₁₂N₂OS: C, 68.55, H, 4.31, N, 9.51. Found: C, 68.63, H, 4.65, N, 9.91.

Method B (excess of TFAA). The reaction was carried out as for **8** from TFAA (0.2 mL, 1.2 mmol, 3.75 eq) in CH₂Cl₂ (2 mL), pyridine (0.1 mL, 1.2 mmol, 4 eq.), **4a** (0.10 g, 0.3 mmol) in CH₂Cl₂ (1 mL). Stirring at 0 °C for 15 min, then at room temperature for 0.5 h, to yielded **9** as a yellow solid (0.3 g, 75%).

10,11-dihydro-10-methyl-12*H*-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (9) from 4b.

Method A (Thermal Cyclization): A solution of **4b** (0.73 g, 2.1 mmol) in chloroform (75 mL) was heated under reflux for 64 hours. The solution was allowed to cool to room temperature and the solid formed was filtered and air dried to give white solid **9** (0.33 g, 58%): mp 295 °C (dec); IR 1619 cm⁻¹; ¹H NMR δ 10.61 (broad, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.28 Hz, 1H), 7.17-7.19 (m, 2H), 7.11 (dt, *J* = 6.99, 1.07 Hz, 1H), 6.95-7.03 (m, 2H), 3.44 (s, 3H); ¹³C NMR could not be taken due to insolubility of **9** in common solvents. MS [*m/z* (rel. intensity)] 280 [*M*⁺, 100], 248(27).

Method B (Electrophilic Activation). To a well-stirred solution of TFAA (0.45 g, 2.1 mmol, 3.75 eq.) in CH₂Cl₂ (20 mL) at 0 °C was added pyridine (0.18 g, 2.3 mmol, 4 eq.), neat via syringe. The reaction vessel was kept under a drying tube throughout the reaction. To the resulting yellow solution was added, a solution of **4b** (0.20 g, 0.57 mmol) in CH₂Cl₂ (15 mL) which was previously cooled to 0 °C. This was stirred at 0 °C for 15 min then at room temperature for 30 min. The solution was poured onto 10% Na₂CO₃ (30 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH₂Cl₂ (30 mL). The combined organics were washed with 5% aqueous solution of HCl (3 X 40 mL), 10% aqueous solution of Na₂CO₃ (1 X 40 mL), H₂O and dried over sodium sulfate. The solvent was removed in vacuo to yield pure yellow solid, **9** (0.16 g, 100%).

10,11-Dihydro-10,12-dimethylindolo[3,2-*b*][1,5]benzothiazepin-11-one (10) from 8a.

Method A (Thermal Cyclization). A solution of **8a** (1.0 g, 3 mmol) in *p*-xylenes (35 mL) was heated under reflux for 30 h. After solvent evaporation in vacuo, the brown

solid was passed thru a silica gel column (CHCl₃) to give **10** (0.2 g, 22%): mp 198-200 °C; IR 1627 cm⁻¹; ¹H NMR (200 MHz) δ 7.77 (1H, d, J = 0.9 Hz), 7.73 (1H, d, J = 0.9 Hz), 7.08 - 7.58 (6H, m), 3.91 (3H, s), 3.62 (3H, s); ¹³C NMR δ 163.5, 146.0, 138.2, 137.4, 132.3, 131.0, 128.9, 126.2, 125.8, 125.5, 125.0, 120.6, 120.3, 117.5, 110.1, 38.6, 31.6; MS [m/z (relative intensity)] 294 (M⁺, 100). Anal. Calcd for C₁₇H₁₄N₂OS: C, 69.36; H, 4.79; N 9.52. Found: C, 69.35; H, 4.89; N, 9.28.

Method B (excess of TFAA). To a well-stirred solution of TFAA (1.4 mL, 11 mmol, 3.75 eq) in CH₂Cl₂ (17 mL) at 0 °C was added pyridine (1 mL, 12 mmol, 4 eq.), neat via a syringe. To this solution was added, **8a** (1 g, 3 mmol) in CH₂Cl₂ (9 mL) which had been previously cooled to 0 °C. After stirring at 0 °C for 15 min then at room temperature for 3 h., the solution was poured onto a 10% aqueous Na₂CO₃ (30 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH₂Cl₂ (1 x 30 mL). The combined organics were washed with 5% HCl (3 x 40 mL), 10% Na₂CO₃ (1 x 40 mL), H₂O and dried (Na₂SO₄). The solvent was removed in vacuo to yield a relatively pure yellow solid **10** (0.8 g, 90%). mp 196-198 °C.

Trapping experiment. To a solution of **8b** (0.1 g, 0.27 mmol) in chloroform (50 mL) was added 2-mercaptobenzothiazole (1.0 eq., 0.27 mmol, 45.0 mg) and the resulting mixture was heated under reflux for 72 h (until no starting material on TLC). The solution was allowed to cool to room temperature and the solvent evaporated in vacuo to yield a brown solid. Column chromatography (CH₂Cl₂) gave white solid **10** (0.025 g, 32%).

3-[(2-aminophenyl)thio]-1*H*-indole-2-carboxylic acid (11**).** To a well-stirred suspension of NaH (1.1 g, 45 mmol, 3.0 eq) in DMF (30 mL) under N₂ at room

temperature was added dropwise a solution of indole-2-carboxylic acid (2.4 g, 15 mmol) in DMF (10 mL). After the evolution of H₂ had ceased, a solution of 2,2'-diaminodiphenyldisulfide (15 mmol) in DMF (5 mL) was added dropwise and the dark colored solution was heated at 50 °C for 24 h, then poured to H₂O (75 mL) and extracted with Et₂O (3 x 50 mL). The aqueous layer was acidified to pH ~5-6 precipitating a light brown solid (**11**, 4.1 g, 93%). The solid was used in the next step without purification.

10,11-Dihydro-10,12H-indolo[3,2-*b*][1,5]benzothiazepin-11-one (12). A suspension of **11** (5g, 17.6 mmol) and SiO₂ (column chromatographic grade, 20 g) in toluene (250 mL) was heated under reflux for 13 h under a Dean-Stark trap. The partially cooled reaction mixture was filtered through a sintered glass funnel (10-15 μ) and the SiO₂ washed with 1:1 CH₂Cl₂: MeOH (50 mL) and then with MeOH (2 x 30 mL). The combined organics were evaporated *in vacuo* and the light brown solid recrystallized to produce **12** (2.95 g, 63%) as an off-white solid: mp 237-239 °C (50% EtOH); IR 3414, 3197, 1654 cm⁻¹; ¹H NMR (200 MHz) δ 12.14 (1H, s, br), 10.46 (1H, s, br), 7.12-7.70 (8H, m); ¹³C NMR δ 164.7, 142.3, 137.6, 133.0, 131.5, 130.6, 130.3, 127.0, 126.9, 126.8, 126.3, 125.2, 121.8, 120.8, 114.0; MS [m/z (relative intensity)] 266 (M⁺, 100). Anal. calcd for C₁₅H₁₀N₂OS: C, 67.65, H, 3.78, N, 10.52. Found: C, 67.48, H, 4.12, N, 10.42.

N-[2-(ethylthio)phenyl]-1H-indole-3-carboxamide (14a). To a magnetically stirred solution of indole-3-carboxylic acid (1.5 g, 9 mmol) in THF (20 mL) at 0 °C was added dropwise neat oxalyl chloride (2.3 g, 18 mmol, 2 eq.). After 12 h at room temperature, the solvent was evaporated *in vacuo* and the yellow residue (in dichloroethane (40 mL)) was added to a mechanically stirred solution of 2-(ethylthio)aniline (2.8 g, 18 mmol, 2 eq) in dichloroethane (30 mL). After 5 h at room temperature, the mixture was washed with 5%

HCl (3 x 50 mL), 5% NaHCO₃ (3 x 50 mL), H₂O and dried (Na₂SO₄). The solvent was evaporated *in vacuo* to leave a dark brown oil. Column chromatography (CHCl₃) produced **14a** as a faint brown solid, (0.9 g, 35%): mp 103-105 °C; IR 3352, 3216, 1638 cm⁻¹; ¹H NMR (200 MHz) δ 9.31 (1H, s), 8.66 (1h, dd, J = 1.3, 7 Hz), 8.31-8.36 (1H, m), 7.88 (1h, d, J = 3 Hz), 7.58, (1H, dd, J = 1.4, 6.2 Hz), 7.25-7.48 (4H, m), 7.07 (1H, td, J = 1.4, 6.2 Hz), 2.78 (2H, q, J = 7 Hz), 1.20 (3H, t, J = 7 Hz); ¹³C NMR δ 165.4, 141.5, 138.2, 136.8, 131.0, 130.8, 125.8, 125.1, 124.4, 124.3, 123.3, 121.8, 121.2, 113.9, 113.5, 31.7, 16.1; MS [m/z (relative intensity)] 296 (M⁺, 12), 153 (100). Anal. Calcd. for C₁₇H₁₆N₂OS: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.49; H, 5.62; N, 9.44.

N-[2-(*tert*-butylthio)phenyl]-1H-indole-3-carboxamide (14b). Triphosgene (1.1 g, 3.66 mmol) was dissolved in toluene (5 mL). This was added to a well-stirred solution of indole (1.3 g, 11.0 mmol) and pyridine (0.88 g, 11.0 mmol) in CH₂Cl₂ (40 mL) dropwise over 30 min at 25 °C. The resulting dark red mixture was stirred for 3.5 h at 25 °C under drying tube. At this point, the solvent was evaporated *in vacuo* to half of its volume and an additional CH₂Cl₂ (10 mL) was added. To this, was added a solution of 2-(*tert*-butylthio)aniline (4.0 g, 22.1 mmol) in CH₂Cl₂ (25 mL) dropwise. The resulting dark green mixture was stirred at room temperature under a drying tube for 4 h. The reaction mixture was washed with 5% HCl (3 x 50 mL), 5% Na₂CO₃ (3 x 50 mL), H₂O (1 x 50 mL) and dried over sodium sulfate. The solvent was removed *in vacuo* to get a dark solid, which was purified by column chromatography (CH₂Cl₂) to give white solid (1.20 g, 33%): mp 185-187 °C; IR 3335, 1637 cm⁻¹; ¹H NMR δ 9.88 (broad, 1H), 9.64 (broad, 1H), 8.76 (d, J = 7.88 Hz, 1H), 8.46 (d, J = 7.88 Hz, 1H), 7.89 (d, J = 2.64 Hz, 1H), 7.58 (d, J = 7.74 Hz, 1H), 7.46 (t, J = 7.03 Hz, 2H), 7.32 (t, J = 7.03 Hz, 1H), 7.25 (t, J = 7.74

Hz, 1H), 7.08 (t, $J = 7.74$ Hz, 1H), 1.27 (s, 9H); ^{13}C NMR δ 163.6, 142.1, 138.7, 136.8, 130.8, 129.5, 124.3, 123.0, 121.8, 120.3, 120.2, 120.0, 112.6, 112.4, 48.5, 31.0, 30.8; MS [m/z (rel. intensity)] 324 [M^+ , 13], 268 (6), 144 (100), 125 (24), 57 (5).

***N*-[2-(ethylsulfinyl)phenyl]-1*H*-indole-3-carboxamide (15a).** (96%): mp 60-61 °C; IR 3217, 3168, 1652, 1003 cm^{-1} ; ^1H NMR (200 MHz) δ 11.15 (1H, s); 9.72 (1H, s), 8.71 (1H, d, $J = 8$ Hz), 8.40-8.45 (1H, m, cont. $J = 3$ Hz), 7.90 (1H, d, $J = 3$ Hz), 7.06-7.60 (6H, m, cont. $J = 1, 8$ Hz), 3.02-3.24 (2H, dm), 1.18 (3H, t, $J = 7$ Hz); ^{13}C NMR δ 164.9, 142.8, 137.8, 134.1, 128.8, 128.2, 127.3, 125.6, 124.4, 124.0, 123.8, 123.1, 122.7, 113.1, 113.0, 49.3, 8.8; MS [m/z (relative intensity)] 312 (M^+ , 15), 144 (100). Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.48; H, 5.23; N, 8.99.

***N*-[2-(ethylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (16a).** To a stirred suspension of **14a** (1.8 g, 6.1 mmol) and tetra-*n*-butylammonium sulfate in toluene (10 mL) was added 50% aqueous NaOH (7 mL) in one portion. After reflux for 2 h, a solution of CH_3I (1.9 g, 13.3 mmol, 2.2 eq.) in toluene (2 mL) was added and the mixture heated under reflux for an additional 17 h. The organics were collected, washed with H_2O until neutral to litmus, dried (Na_2SO_4), the volatiles removed *in vacuo*, and the brown solid chromatographed (CHCl_3) to produce **16a** (1.8 g, 90%) as an off-white solid: mp 172-173 °C (acetone); IR 1621 cm^{-1} ; ^1H NMR (200 MHz) δ 8.41-8.46 (1H, m), 7.12-7.34 (7H, m), 6.06 (1H, d, $J = 0.6$ Hz), 3.49 (3H, s), 3.38 (3H, s), 2.90 (2H, apparent qd, $J = 7.1, 0.2$ Hz), 1.27 (3H, t, $J = 7.0$ Hz); ^{13}C NMR δ 166.7, 143.6, 138.4, 136.8, 132.6, 130.3, 124.4, 124.2, 127.5, 126.7, 123.5, 123.2, 122.0, 110.0 109.8 37.3, 33.8, 26.2, 14.5; MS [m/z (relative intensity)] 324 (M^+ , 3), 158 (100). Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{OS}$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.28; H, 6.41; N, 8.69.

***N*-[2-(*tert*-butylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (16b).** To a well-stirred suspension of **14b** (1.1 g, 3.4 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.3 eq, 1 mmol, 0.35 g) in toluene (100 mL) was added all at once 50% NaOH (aq) solution (100 mL). The resulting two layer mixture was heated under reflux at which a solution of iodomethane (2.5 eq, 8.5 mmol, 1.20 g) in toluene (10 mL) was added dropwise over 5 min. The resulting two phase mixture was maintained at reflux for 87 h. It was cooled to room temperature and the layers separated. The organic layer was washed with water several times (until washings were neutral to litmus), dried over sodium sulfate and evaporated in vacuo to yield an off-white solid. Purification by column chromatography (chloroform:ether, 9:1) gave white compound (0.87 g, 73%): mp 156-158 °C; IR 1630 cm⁻¹; ¹H NMR δ 8.34-8.41 (m, 1H), 7.59 (d, *J* = 7.72 Hz, 1H), 7.31-7.39 (m, 2H), 7.28 (ddd, *J* = 7.71, 2.12 Hz, 1H), 7.17-7.22 (m, 2H), 7.10-7.16 (m, 1H), 5.81 (s, 1H), 3.43 (s, 6H), 1.29 (s, 9H); ¹³C NMR δ 166.1, 147.6, 136.5, 136.0, 131.6, 129.0, 128.9, 128.2, 127.3, 122.6, 122.3, 121.0, 109.8, 108.9, 46.7, 32.8, 31.6; MS [*m/z* (rel. intensity)] 295 (12), 263 (21), 158 (100).

***N*-[2-(ethylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (17a).** (72%). mp 188-189 °C (acetone); IR 1627, 1014 cm⁻¹; ¹H NMR (200 MHz, taken at 100 °C in DMSO-*d*₆) δ 8.25-8.31 (1H, m), 7.96-8.01 (1H, m), 7.19-7.60 (7H, m), 6.25 (1H, s), 3.54 (3H, s), 3.46 (3H, s), 2.56-2.80 (2H, m, cont. *J* = 6.6 Hz), 1.12 (3H, t, *J* = 6.6 Hz); ¹³C NMR δ 167.0, 143.3, 143.1, 137.4, 133.5, 133.2, 133.0, 130.3, 121.9, 124.3, 123.7, 123.1, 123.0, 110.6, 110.5, 50.8, 49.5, 34.5, 7.3; MS [*m/z* (relative intensity)] 340 (M⁺, 0.2), 158 (100). Anal. Calcd for C₁₉H₂₀N₂O₂S: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.25; H, 6.10; N, 8.27.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (17b).** To an ice-cooled solution of **16b** (0.82 g, 2.30 mmol) in CH₂Cl₂ (50 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 3.32 mmol, 0.57 g) in CH₂Cl₂ (10 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (-8 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution (50 mL) and extracted with CH₂Cl₂ (50 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (acetone:CH₂Cl₂, 1:1) gave white solid (0.42 g, 49%): mp 159-160 °C; IR 1631, 1030 cm⁻¹; ¹H NMR and ¹³C NMR was not well-resolved due to presence of rotational isomers; MS [*m/z* (rel. intensity)] 294 (35), 158 (100).

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Supporting Information Available: Experimental procedures for 2-(ethylthio)-*N*-methylaniline, 2-(*tert*-butylthio)-*N*-methylaniline, ethyl *N*-methylindole-2-carboxylate,

1b, 2b, 3ab, 4a, 5ab, 6ab, 7bc, 8abc, and the thermal and TFAA-promoted cyclization of **8b**; ^1H NMR and ^{13}C NMR spectra for **1b-3b, 5b-8b, 7c, 10, 14b**, and **16b**; ^1H NMR for **4b** and **9**. This material is available free of charge via the internet at <http://pubs.acs.org>.

Chapter 3

Sulfoxide as a “protecting group”

Simple Thiazocine-2-acetic acid Derivatives via Ring Closing Metathesis

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem.* **2004**, *69*, 2750.

The contribution of Parag Jog to this work mainly involved design and execution of the use of sulfoxides as protecting groups in RCM chemistry. To my knowledge use of the sulfide \leftrightarrow sulfoxide redox cycle has never been applied as a protecting group strategy. His work is very significant in this respect as the full potential of this approach to other areas where the S(II) oxidation state poses problems remains to be determined. He also conducted extensive NMR studies to assign all chemical shifts and coupling constants to the sulfide thiazocine derivative.

Approved by co-author Dallas K. Bates



Simple Thiazocine-2-acetic Acid Derivatives via Ring-Closing Metathesis

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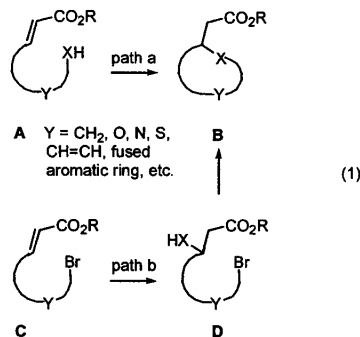
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A new protocol for synthesis of 2-heterocytylacetic acid derivatives involving conjugate addition of allyl mercaptan to an acrylate containing a tethered olefinic site followed by RCM (ring-closing metathesis) is described. In this series, sulfanyl derivatives were unreactive, while sulfoxide and sulfone analogues provided the corresponding thiazocines in fair to excellent yields. Use of the sulfoxide oxidation state as a protecting group for sulfides inert to RCM is demonstrated also. Thus, oxidation of sulfide **9** [*N*-allyl-*N*-[2-(allylthio)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide] followed by cyclization yielded the corresponding thiazocine sulfoxide **12**. Deprotection (deoxygenation) of **12** was accomplished using Lawesson's reagent, producing 1-[[4-(4-methylphenyl)sulfonyl]-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (**21**) in 67% unoptimized yield.

Introduction

Heterocytylacetic acid derivatives are a diverse and important group of compounds. In addition to examples of NSAIDs (Myalex/fenclozic acid)¹ (including COX-2 specific inhibitors)² and nonbenzodiazepine hypnotics (Ambien/zolpidem),³ compounds acting as blood platelet aggregation inhibitors,⁴ aldose reductase inhibitors,⁵ antimicrobial agents,⁶ TACE inhibitors,⁷ and medicinal chelating agents⁸ and many others exhibiting useful biological activity have been reported. Many synthetic efforts have concentrated on five-, six-, seven-, and eight-membered ring examples of **B** ($Y = (\text{CH}_2)_n$, $X = \text{O}$) because of their prominence as building blocks for

synthesis of fused polyether marine toxins (e.g., ciguatoxin)⁹ and other natural products.¹⁰ Compounds **B** ($X = \text{S}$) have also been prepared, but examples are scarce. Of the synthetic approaches developed, most target a specific member and are not general. Common general protocols (typically applicable only to five-, six-, and seven-membered ring compounds) involve conjugate addition to an α,β -unsaturated ester. Specifically, Michael addition of *N*-, *O*-, or *S*-centered nucleophiles to tethered acrylates¹¹ (**A**, eq 1, path a) or Michael addition of a protected nucleophile to an acrylate (for example, **C**) followed by deprotection and cyclization¹² (eq 1, path b)¹³ have been used extensively.



Here we describe a new protocol for assembling compounds of type **B** making use of conjugate addition followed by ring-closing metathesis (RCM) (eq 2). This approach is illustrated by preparation of 2-thiazocinyl-

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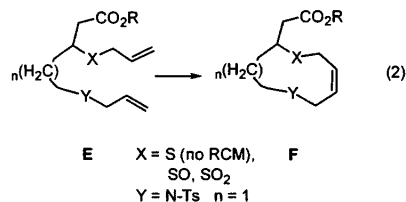
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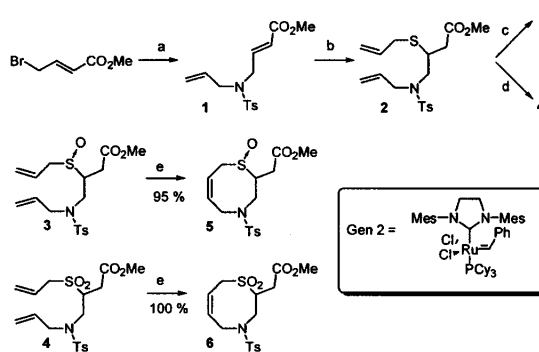
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acetic acid derivatives and should be readily adaptable to other analogues as well. The specific target compounds were chosen because RCM has been shown to be an excellent methodology for N- and O-containing medium-sized ring synthesis¹⁴ and eight-membered rings are the smallest simple *S*- and *N,S*-cycloalkanes for which conventional synthetic approaches fail.¹⁵



Although olefin metathesis has experienced explosive growth, reports of applications of RCM to sulfur-containing compounds are comparatively rare. Initial work found

SCHEME 1^a

^a Reagents: (a) *N*-tosylallylamine, NaOH, TBAH, DCM, rt, 100%; (b) allyl mercaptan, NaOMe, MeOH, reflux, 68%; (c) NaIO₄, acetone/water, 22 h, rt, 35%; (d) Oxone (3 equiv), MeOH/water, 3 d, rt, 58%; (e) 5 mol % Gen 2, DCM, reflux (6 h for 5, 8 h for 6).

the Grubbs first generation catalyst inferior to Mo- and W-based catalysts with respect to sulfur(II) tolerance.^{16,17} Although Mo-based catalysts are quite tolerant of sulfur(II) sites in the substrate, the highly active N-heterocyclic carbene catalysts such as Grubbs' second generation catalyst (Gen 2; see Scheme 1) are more widely used as a result of their improved tolerance for sulfur(II) and their air and moisture stability. Numerous examples of additional successful RCM reactions of sulfides, disulfides, and dithioacetals using Ru/carbene complexes have been reported.¹⁸ The literature suggests the sulfonyl oxidation state (sulfones,¹⁹ sulfonamides,²⁰ etc.²¹) is better tolerated in RCM substrates than lower oxidation states of sulfur. Deactivation via Ru-sulfonyl oxygen coordination does not occur (even though Ru-sulfonyl ligation to assist ring closure has been suggested).²² In contrast to the body of work available for sulfides and sulfones,

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sulfoxides have been studied very little. DMSO treatment has been proposed²³ as a means of removing Ru-containing contaminants from RCM reaction mixtures, presumably due to coordination Ru. Only two reports of RCM chemistry applied to sulfoxides have been reported. One was successful²⁴ and the other was not.^{19a} Therefore, sulfur-containing substrates for this study were prepared not only in the sulfanyl and sulfonyl oxidation states but also in the sulfinyl state as well.

Results and Discussion

Reaction of methyl 4-bromocrotonate with *N*-tosylallylamine²⁵ under phase transfer conditions followed by conjugate addition of allyl mercaptan provided the key intermediate **2** in 68% overall yield (Scheme 1). Oxidation of **2** to sulfoxide **3** (obtained as a 1:1 mixture of diastereomers) and sulfone **4** was readily accomplished by conventional means. Although **2** failed to undergo RCM²⁶ (Gen 2 catalyst),²⁷ both sulfone **4** and sulfoxide **3** cyclized [to thiazocines **6** and **5** (obtained as a 2:3 mixture of diastereomers), respectively] in excellent yield.

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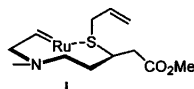
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(26) Starting material (**2**) was recovered unchanged quantitatively. The lack of reactivity is probably not due to Ru coordination with the ester [no reaction was observed when Ti(O*i*Pr)₄ was added to the RCM reaction according to Fuerstner's protocol (Fuerstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, 119, 9130–9136) and both S-oxidized counterparts to the sulfide (**3** and **4**) readily undergo RCM]. The problem is more likely due to inactivation of the catalyst by coordination of the Ru to S(II). Coordination/inactivation could occur intermolecularly prior to interaction of the Ru with the olefinic sites or intramolecularly, perhaps as shown in structure **i**.

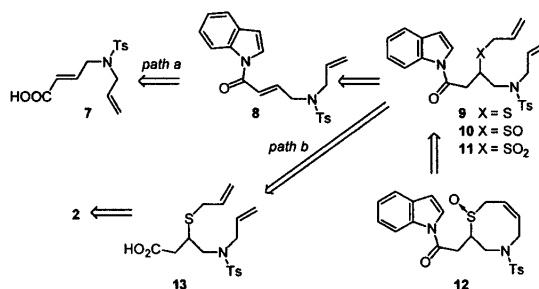


The latter process (involving coordination of ruthenium to hydroxyl oxygen via a six-membered ring rather than the eight-membered ring as in **i**) has been suggested previously (for example, Washburn, D. G.; Heidebrecht, R. W.; Martin, S. F. *Org. Lett.* **2003**, 5, 3523–3525) to explain Grubbs' catalyst inactivation. This process seems less likely in the present context because of the size of the ring involved and the necessity to invoke selective reaction of the *N*-allylic olefinic site, even though the *S*-allylic olefinic site is sterically and electronically similar.

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SCHEME 2. Alternative Pathways to Thiazocine 12



With this success in hand we applied the methodology to preparation of acyl indole **12** (Scheme 2), a system useful for SES/ring opening studies.²⁸ Preparation of this target demonstrates some of the potential obstacles in syntheses of RCM substrates of the type shown in eq 2. Thus, sulfide **9** was prepared in three steps from **1** in 19% overall yield, realizing path a in Scheme 2. The low yield is due to poor conversion of the acid chloride of **7** to the acylindole. The problem stems from the lability of the initially formed acylindole to nucleophilic attack; no acylation procedure attempted involving a strong nucleophile (OH[−]) or nucleophilic solvent (H₂O) gave satisfactory yields of **8**. Alternative acylation conditions were not thoroughly explored because an alternative process forming the labile acylindole later in the sequence was developed. Reversing the order of the reactions leading to **9** (forward synthesis version of path b, Scheme 2) did not improve overall yield because ester hydrolysis of **2** to **13** proceeded in poor yield as a result of unavoidable (in our hands) retro-Michael addition of allyl mercaptan.

These difficulties were overcome using the well-known²⁹ stability of indoline amides relative to their indole amide counterpart and the ease of conversion of the former to the latter.³⁰ Execution of this strategy led to **9** in 44% yield (from **1**, path a in Scheme 3). Reversing the sequence of Michael addition and indoline oxidation (path b, Scheme 3) was not effective. Although Michael addition of allyl mercaptan to **14** proceeded very cleanly, subsequent reaction of **15** with DDQ gave not only oxidation of the indoline but also retro-Michael addition providing mainly compound **8**.

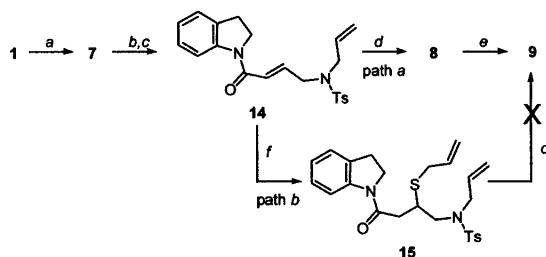
Oxidation³¹ of indole **9** with 1 or 2 equiv of *m*-CPBA gave the corresponding sulfoxide (**10**, 72%, 2:3 inseparable mixture of diastereomers) or sulfone (**11**, 99%). Treatment of these compounds with Gen 2 (10 mol % for the sulfoxide and 5 mol % for the sulfone) produced the corresponding thiazocinyl acetamide derivatives **12** and **16** in 48% and 89%, respectively (Scheme 4). Compound **12** was isolated as a 2:3 mixture of diastereomers.

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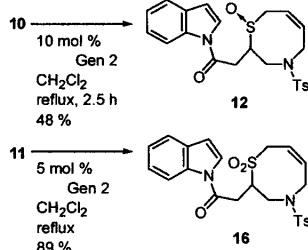
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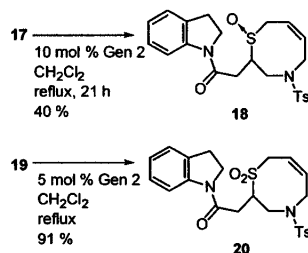
SCHEME 3. Acylindole 9 via Oxidation of Indoline Amide 8^a

^a Reagents: (a) LiOH, THF/H₂O, 0 °C, 95%; (b) oxalyl chloride, THF, 24 h, 0 °C; (c) indoline, pyridine, DMAP, 64%; (d) DDQ, dioxane, 70 °C, 3 d, 89%; (e) allyl mercaptan, Et₃N, CH₂Cl₂, 80%; (f) allyl mercaptan, NaOMe, MeOH/THF, 15 min, 0 °C, 95%.

SCHEME 4. RCM of Acylindoles 10 and 11



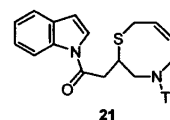
SCHEME 5. RCM of Indoline Amides 17 and 19



This pattern of reactivity was duplicated in the corresponding indoline analogues. Thus, treatment of **15** with either 1 or 2 equiv of *m*-CPBA gave the corresponding sulfoxide **17** (as an inseparable 2:3 ratio of diastereomers) or sulfone (**19**). Treatment of these compounds with Gen 2 (10 mol % for the sulfoxide and 5 mol % for the sulfone) produced the corresponding thiazocines **18** and **20** in 40% and 91%, respectively (Scheme 5). Compound **18** was isolated as a 3:4 mixture of diastereomers.

In view of the mixed history of success with S(II) substrates in RCM processes, our current results on successful RCM on sulfoxides where the corresponding sulfides fail, the abundance of simple oxidation procedures for the sulfide to sulfoxide transformation,³² and the ease of the reverse deoxygenation process³² suggest sulfoxides may be useful protecting groups for thioethers undergoing RCM.³³ As a demonstration of the concept, the most labile sulfoxide in the series (compound **12**) was

treated with Lawesson's reagent³⁴ to produce sulfide **21** in 67% yield.



In conclusion, sulfone and sulfoxide derivatives of compound **E** (Y = *N*-Ts, eq 2) undergo RCM in good to excellent yield with Grubbs' second generation catalyst, providing a new route to (1,4-thiazocinyl)-2-acetic acid derivatives. Sulfide derivatives in the series do not undergo RCM with Grubbs' second generation catalyst, but such compounds are available through a protection/deprotection sequence involving the corresponding sulfoxide. Application of the methodology to other 2-heterocyclyl acetic acid derivatives is underway.

Experimental Section

Methyl (2*E*)-4-[Allyl]-(4-methylphenyl)sulfonylamino]-but-2-enoate (1). To a well-stirred mixture of *N*-allyl-4-methylbenzenesulfonamide (0.42 g, 2 mmol), powdered NaOH (2.0 equiv, 0.16 g, 4 mmol), and tetrabutylammonium hydrogen sulfate (0.06 equiv, 0.04 g) in CH₂Cl₂ (15 mL) was added dropwise a solution of methyl γ -bromocrotonate (1.5 eq, 0.537 g, 3 mmol) in CH₂Cl₂ (5 mL) in an ice-water bath. The resulting mixture was stirred at 0 °C for 5 min and at room temperature for 2 h. After filtering, the filtrate was washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.62 g (100%) of **1** as a white solid: mp 58–60 °C; IR 1724 cm⁻¹; ¹H NMR δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 6.68 (dt, 1H, *J* = 15.6, 6.0 Hz), 5.87 (d, 1H, *J* = 15.6 Hz), 5.55 (m, 1H), 5.13–5.07 (m, 2H), 3.87 (d, 2H, *J* = 6.0 Hz), 3.75 (d, 2H, *J* = 6.4 Hz), 3.68 (s, 3H), 2.38 (s, 3H); ¹³C NMR δ 166.0, 143.6, 142.6, 136.7, 132.1, 129.8, 127.1, 123.4, 119.7, 51.6, 50.4, 47.2, 21.4; MS [*m/z*] 278 (M⁺). Anal. Calcd for C₁₅H₁₉O₄NS: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.36; H, 6.32; N, 4.53.

Methyl 4-[Allyl]-(4-methylphenyl)sulfonylamino]-3-(allylthio)butanoate (2). To a well-stirred solution of allyl mercaptan (5.0 equiv, 0.20 mL, 2.5 mmol) and MeONa (1.1 equiv, 0.03 g, 0.6 mmol) in methanol (7 mL) was added a solution of **1** (0.16 g, 0.5 mmol) in MeOH (4 mL) at room temperature. The resulting mixture was refluxed for 3 h, cooled, poured into ice water, and extracted with EtOAc. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.13 g (68%) of **2** as an oily liquid: IR 1739 cm⁻¹; ¹H NMR δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 5.74 (m, 1H), 5.48 (m, 1H), 5.16–5.03 (m, 4H), 3.80–3.76 (m, 2H), 3.67 (s, 3H), 3.37 (dd, 1H, *J* = 14.0, 10.0 Hz), 3.22 (m, 1H), 3.14 (d, 2H, *J* = 6.8 Hz), 3.09 (dd, 1H, *J* = 14.0, 4.8 Hz), 2.87 (dd, 1H, *J* = 16.4, 4.8 Hz), 2.49 (dd, 1H, *J* = 16.4, 8.4 Hz), 2.39 (s, 3H); ¹³C NMR δ 171.9, 143.5, 136.4, 134.4, 132.4, 129.7, 127.2, 119.7, 117.4, 51.7, 51.6, 51.5, 39.1, 37.4, 34.8, 21.4; MS [*m/z*] (rel intensity) 228 (78), 224 (79), 155 (100).

Methyl 4-[Allyl]-(4-methylphenyl)sulfonylamino]-3-(allylsulfinyl)butanoate (3). To an ice-cooled solution of **2**

(33) Gladysz and co-workers have reported use of a cationic rhenium compound that serves both as a protecting group for S(II) and RCM catalyst for thioethers: Martin-Alvarez, J. M.; Hampel, F.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1999**, *18*, 955–957.

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(0.81 g, 2.12 mmol) in acetone (12 mL) was added a solution of sodium periodate (1.05 equiv, 0.48 g, 2.23 mmol) in H₂O (6 mL) at 0 °C. The resulting mixture was stirred at room temperature for 22 h and concentrated in vacuo. The residue was diluted with H₂O (40 mL) and extracted with CHCl₃. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated in vacuo. Column chromatography on silica gel (EtOAc) gave 0.30 g (35%) of **3** as a colorless sticky liquid (mixture of two diastereomers in a 1:1 ratio): IR 1725 cm⁻¹; ¹H NMR δ 7.66 (d, 2H, *J* = 7.6 Hz), 7.29 (d, 2H, *J* = 7.6 Hz), 5.85 (m, 1H), 5.55–5.39 (m, 3H), 5.19–5.11 (m, 2H), 3.82–3.75 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.60 (dd, 1H, *J* = 12.0, 6.8 Hz), 3.51 (m, 1H), 3.41 (dd, 2H, *J* = 13.6, 7.6 Hz), 3.27 (dd, 1H, *J* = 14.8, 7.6 Hz), 2.96 (dd, 1H, *J* = 18.0, 5.2 Hz), 2.89 (dd, 1H, *J* = 18.0, 5.6 Hz), 2.79 (dd, 1H, *J* = 18.0, 8.0 Hz), 2.52 (dd, 1H, *J* = 18.0, 6.4 Hz), 2.40 (s, 3H); ¹³C NMR δ 171.9, 171.4, 143.9, 135.6, 135.5, 132.1, 132.0, 129.9, 129.8, 127.4, 127.3, 125.9, 125.8, 123.9, 123.8, 120.5, 120.4, 54.6, 53.9, 53.4, 52.4, 52.3, 52.2, 52.1, 52.0, 47.4, 44.6, 32.0, 28.3, 21.5; MS [*m/z* (rel intensity)] 224 (47), 155 (66).

Methyl 4-[Allyl[(4-methylphenyl)sulfonyl]amino]-3-(allylsulfonyl)butanoate (4). To an ice-cooled solution of **2** (0.73 g, 1.91 mmol) in MeOH (15 mL) was added a solution of Oxone (3.0 equiv, 3.52 g, 5.73 mmol) in H₂O (15 mL) at 0 °C. The resulting cloudy slurry was stirred at room temperature for 3 d. After filtering, the filtrate was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexane, 2:3) gave 0.46 g (58%) of **4** as a colorless sticky liquid: IR 1739 cm⁻¹; ¹H NMR δ 7.67 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 5.89 (m, 1H), 5.54–5.40 (m, 3H), 5.19–5.12 (m, 2H), 4.07 (m, 1H), 3.85–3.76 (m, 4H), 3.73 (s, 3H), 3.45–3.42 (m, 2H), 2.99 (dd, 1H, *J* = 18.0, 6.4 Hz), 2.84 (dd, 1H, *J* = 18.0, 5.6 Hz), 2.42 (s, 3H); ¹³C NMR δ 171.0, 144.2, 135.3, 131.7, 131.0, 127.5, 125.5, 123.9, 120.8, 58.3, 56.1, 52.5, 52.4, 46.1, 30.9, 21.5; MS [*m/z* (rel intensity)] 260 (5), 224 (1), 155 (8).

Methyl 4-(4-Methylphenylsulfonyl)-1-oxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetate (5). To a solution of **3** (0.26 g, 0.65 mmol) in CH₂Cl₂ (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.028 g) in CH₂Cl₂ (4 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 6 h. The mixture was cooled to room temperature and concentrated in vacuo. Column chromatography of the residue on silica gel (EtOAc) gave 0.23 g (95%) of **5** separable mixture of two diastereomers in a 2:3 ratio both of which were viscous, tacky semiliquids. Minor diastereomer (higher *R*_f): IR 1733 cm⁻¹; ¹H NMR δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 5.84 (dd, 1H, *J* = 11.2, 4.0 Hz), 5.57 (m, 1H), 4.14 (d, 2H, *J* = 8.8 Hz), 4.00–3.76 (m, 3H), 3.70 (s, 3H), 3.48 (m, 1H), 3.04 (d, 1H, *J* = 14.8 Hz), 2.83 (dd, 1H, *J* = 16.4, 6.4 Hz), 2.44 (dd, 1H, *J* = 16.4, 8.0 Hz), 2.40 (s, 3H); ¹³C NMR δ 170.6, 144.2, 133.5, 133.1, 130.0, 127.4, 119.0, 53.1, 52.2, 49.2, 45.5, 44.2, 33.3, 21.5; MS [*m/z* (rel intensity)] 371 (M⁺, 9), 216 (8), 155 (68). Major diastereomer (lower *R*_f): IR 1736 cm⁻¹; ¹H NMR δ 7.59 (d, 2H, *J* = 8.4 Hz), 7.30 (d, 2H, *J* = 7.6 Hz), 5.87–5.74 (m, 2H), 4.30 (dd, 1H, *J* = 14.0, 8.0 Hz), 4.21 (d, 1H, *J* = 18.0 Hz), 3.92 (dd, 1H, *J* = 14.0, 8.0 Hz), 3.65 (s, 3H), 3.60–3.50 (m, 3H), 3.14–3.07 (m, 2H), 2.60 (dd, 1H, *J* = 17.2, 9.2 Hz),

2.40 (s, 3H); ¹³C NMR δ 171.0, 144.2, 134.1, 132.2, 130.0, 127.1, 118.8, 55.6, 52.2, 49.7, 48.6, 47.9, 31.8, 21.5; MS [*m/z* (rel intensity)] 371 (M⁺, 15), 216 (11), 155 (56).

Methyl 4-(4-Methylphenylsulfonyl)-1,1-dioxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetate (6). To a solution of **4** (0.40 g, 0.96 mmol) in CH₂Cl₂ (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.041 g) in CH₂Cl₂ (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 8 h. The mixture was cooled to room temperature and concentrated in vacuo. Column chromatography of the residue on silica gel (EtOAc/hexane, 2:3) gave 0.38 g (100%) of **6** as a white solid: mp 155–7 °C; IR 1740 cm⁻¹; ¹H NMR δ 7.63 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 5.77–5.66 (m, 2H), 4.39 (m, 1H), 4.12–3.94 (m, 3H), 3.77–3.69 (m, 2H), 3.66 (s, 3H), 3.22 (dd, 1H, *J* = 14.4, 2.8 Hz), 3.03 (dd, 1H, *J* = 16.8, 3.6 Hz), 2.41–2.35 (m, 4H); ¹³C NMR δ 170.2, 144.3, 134.4, 132.7, 130.0, 127.3, 118.7, 55.6, 52.8, 52.1, 49.4, 49.0, 29.0, 21.3; MS [*m/z* (rel intensity)] 232 (14), 155 (32). Anal. Calcd for C₁₆H₂₁O₆NS₂: C, 49.60; H, 5.46; N, 3.62. Found: C, 49.54; H, 5.56; N, 3.64.

1-[[4-[4-(Methylphenyl)sulfonyl]-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetyl]-1H-indole (21). To a solution of **12** (see Supporting Information for preparation; 30.8 mg, 0.0675 mmol) in CH₂Cl₂ (5 mL) was added portionwise a freshly solution of Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, 27.3 mg, 0.0654 mmol] in CH₂Cl₂ (3 mL). The mixture was stirred at room temperature until TLC indicated the reaction was complete (15 min), at which time solvent was evaporated in vacuo. One milliliter of methanol was added, and the mixture was stirred (1 min) during which time the product was obtained as a white solid (20.0 mg, 67%): mp 177–178.5 °C; ¹H NMR δ 8.39 (d, 1H, *J* = 7.9 Hz), 7.61 (d, 2H, *J* = 8.2 Hz), 7.55 (d, 1H, *J* = 7.3 Hz), 7.40 (d, 1H, *J* = 3.6 Hz), 7.34–7.26 (m, 4H), 6.65 (d, 1H, *J* = 3.6 Hz), 5.79 (ddd, 1H, *J* = 11.3, 7.6, 2.7 Hz), 5.66 (ddd, 11.3, 4.0, 3.7 Hz), 4.37 (dd, 1H, *J* = 13.1, 8.6 Hz), 4.25 (dd, 1H, *J* = 17.7, 3.7 Hz), 3.99–3.94 (m, 1H), 3.77 (dd, 1H, *J* = 13.1, 9.2 Hz), 3.55 (dd, 1H, *J* = 17.7, 4.0 Hz), 3.36 (dd, 1H, *J* = 13.1, 2.7 Hz), 3.23–3.17 (m, 2H), 3.04 (dd, 1H, *J* = 16.4, 8.2 Hz), 2.38 (s, 3H); ¹³C NMR δ 168.3, 143.9, 135.8, 135.0, 130.6, 130.1, 128.1, 127.3, 125.6, 125.5, 124.5, 124.2, 121.2, 116.7, 110.1, 58.1, 49.4, 38.3, 37.0, 27.2, 21.7; MS [*m/z*, rel int]: 440 (6), 117 (100).

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Supporting Information Available: Full experimental details for preparation of compounds **7–12** and **14–20** and selective spectroscopic and analytical data for these compounds and copies of ¹H and ¹³C NMR spectra for compounds **1–12** and **14–21**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Chapter 4

Sulfoxide as a “molecular brake”

A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and *S*-Oxidized Counterparts

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**A Redox-Mediated Molecular Brake:
Dynamic NMR Study of
2-[2-(Methylthio)phenyl]isoindolin-1-one
and S-Oxidized Counterparts**

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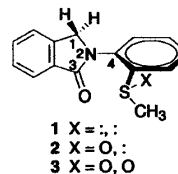
Received May 9, 2003

Abstract: A redox-mediated molecular brake based on the sulfide–sulfoxide redox cycle is illustrated by modulation of the rotation rate of an N–Ar “shaft” by varying the oxidation state of sulfur in 2-[2-(sulfur-substituted)phenyl]isoindolin-1-ones. N–Ar rotational barriers in methylsulfinyl (2) and methylsulfonyl (3) derivatives (13.6 kcal mol^{−1}) are ~5 kcal mol^{−1} higher than sulfide 1. Rate reduction for N–Ar rotation is ~10⁴ s^{−1} (280 K) upon oxidation. Correlated *N*-pyramidalization/N–Ar rotation reduces the effectiveness of the brake by decreasing the energy barrier to N–Ar bond rotation.

Rotational motion is an integral behavior of molecules. Controlling these motions in a reproducible fashion is a key design element for molecular machines. For a molecular brake,¹ an integral component of a molecular machine, reversibility and hindrance to motion are the two most important aspects. Recently, organic molecules designed specifically to achieve certain desired motions leading to a molecular motor have been reported.² For example, a ratcheted “drive shaft” containing intramolecular features which allow rotation of the shaft in only one direction has been reported,³ and approaches to intramolecular brakes based upon changes of pH,⁴ metal ion concentration,^{1,5} or coordination number (or oxidation state of the metal)⁶ have been disclosed.

We now wish to introduce the concept of an organic-based redox-mediated molecular brake. The system is based on the sulfide–sulfoxide redox cycle and is illustrated in a minimalist system by modulation of the

rate of rotation of an N–Ar “shaft” by varying the oxidation state of a proximate sulfur atom in 2-[2-(sulfur-substituted)phenyl]isoindolin-1-ones 1–3. Oxidized sulfur acts as the braking mode (rotation hindered) while the reduced [S(II)] counterpart shows “free” rotation. This approach is attractive because there are numerous high-yield chemical and electrochemical processes for both sulfur oxidation to sulfoxide^{7,8} and sulfoxide deoxygenation to sulfide.^{9,10} Thus, the processes of applying and removing the brake are readily reversible, easily controllable actions.



Simple isoindolin-1-ones exist as enantiomeric rotational isomers with slow rotation about the aryl C–N bond giving rise to diastereotopic methylene protons.¹¹ Ortho-substitution of the aryl group of 2-phenylisoindolin-1-one with sulfur-containing groups (compounds 1–3) had a pronounced line broadening effect on methylene proton signals in the ¹H NMR spectra (25 °C) (Figure 1) indicating the sulfur oxidation level dramatically affects the rate of rotation about the N–Ar bond in these compounds.

On cooling below −20 °C, the methylene “bump” in sulfone (3) splits into an AB quartet ($\Delta\nu$ = 191.5 Hz and J_{AB} = 16.8 Hz at 400 MHz in the absence of exchange)

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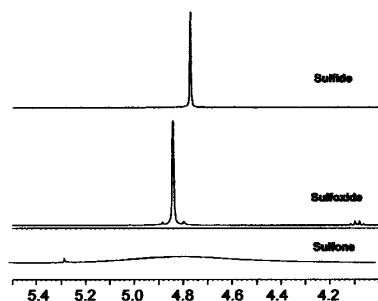


FIGURE 1. ^1H NMR spectra of isoindolin-1-one sulfide (1), sulfoxide (2), and sulfone (3) (400 MHz, CDCl_3 , 25 $^\circ\text{C}$).

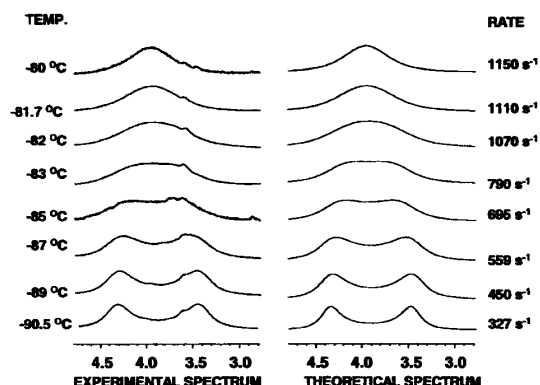


FIGURE 2. Line-shape analysis of 1.

TABLE 1. NMR Parameters and Thermodynamic Data for Isoindolin-1-ones (1–3)

compd	T_c (K)	ΔH^\ddagger (kcal mol $^{-1}$)	ΔS^\ddagger (cal mol $^{-1}$)	ΔG^\ddagger ^c (kcal mol $^{-1}$)	ΔG^\ddagger ^d (kcal mol $^{-1}$)
1 ^a	<188	8.10	−1.5	8.4 (8.6)	9.2, 9.0
2 ^b	280			(13.6)	10.4, 11.9
3 ^b	295	12.2	4.9	13.6 (13.7)	17.2, 13.5

^a NMR in toluene- d_6 . ^b NMR in CDCl_3 . ^c Experimental value from line-shape analysis or (coalescence measurement). ^d Calculated from minima on either side of the transition state.

with a coalescence temperature (T_c) of 22 $^\circ\text{C}$. These data provide a value of 13.7 kcal/mol (57.2 kJ/mol) for the free energy of activation (ΔG^\ddagger) of 3. Line-shape analysis of spectra obtained at various temperatures confirms this value ($\Delta G^\ddagger = 13.6$, 56.9 kJ/mol) and allows calculation of ΔH^\ddagger and ΔS^\ddagger (Table 1). Similarly, sulfide (1) gives $T_c = -85$ $^\circ\text{C}$ (188 K) and $\Delta G^\ddagger = 8.56$ kcal/mol (35.8 kJ/mol) [$\Delta G^\ddagger = 8.40$ kcal/mol (35.1 kJ/mol) by line-shape analysis]. The rate data obtained from line-shape analysis of ^1H NMR spectra of 1 are shown in Figure 2.

Analyses of the variable-temperature (VT) ^1H NMR spectra of sulfoxide 2 were problematic. The methylene signals appeared as an AB quartet in the absence of exchange ($H_a = 4.95$, $H_b = 4.85$, $J = 16.78$ Hz, CDCl_3 , -60 $^\circ\text{C}$). As the sample was warmed these peaks gradually collapsed to a single broad peak and, upon further heating, decoalesced into another AB quartet ($H_a = 4.86$, $H_b = 4.80$, $J = 16.78$ Hz, CDCl_3 , 50 $^\circ\text{C}$). Throughout this

process, the centerline of the absorptions migrated linearly upfield, becoming constant in appearance and chemical shift at about 120 $^\circ\text{C}$ (CDBr_3). This behavior is unique to the sulfoxide; both the sulfide and the sulfone showed classical decoalescence upon warming from the absence of exchange regime to give a singlet having a chemical shift equal to the average values for H_a and H_b in the low-temperature AB quartet. In analogy with sulfide (1) and sulfone (3), coalescence of the low-temperature AB quartet in sulfoxide (2) is a physical manifestation of increased N–Ar rotation. However, in 2, even as H_a and H_b rapidly exchange, they are diastereotopic due to the presence of the chiral sulfoxide moiety, hence the reappearance of separate signals for H_a and H_b at higher temperatures. In other words, as noted by Lunazzi,¹² sulfoxides which contain a chiral center and also a stereogenic axis (in our case the N–Ar bond) will display a set of conformational enantiomers (or atropisomers) at low temperature (under conditions of slow exchange) and a pair of configurational enantiomers when exchange is rapid.

For sulfoxide 2, ΔG^\ddagger and k were determined at the coalescence temperature (280 K, 13.6 kcal mol $^{-1}$ and 1.3×10^2 s $^{-1}$, respectively). By comparison, k_{280} for 1 and 3 are 1.6×10^6 and 1.4×10^2 s $^{-1}$, respectively. As expected from the scant literature available,¹³ the sulfoxide and sulfone barriers to rotation are very similar. Thus, at 280 K, oxidation of sulfide 1 to either the sulfoxide 2 or sulfone 3 slows this rate of rotation by about 10^4 s $^{-1}$.¹⁴

Based on a "rigid shaft" model, we had expected an increase in rotational barrier of more than 5 kcal/mol upon sulfur oxidation. Examination in models of the N–Ar rotation reveals a severe steric interaction during

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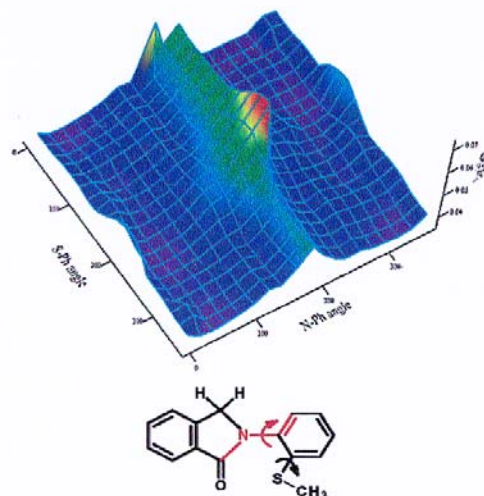


FIGURE 3. Potential energy surface plot for **1** (Gaussian 98).

the passage of the ortho substituents over the carbonyl group during rotational interconversion of enantiomers. Transition-state nitrogen pyramidalization to avoid steric interactions during rotational motion has been reported.¹⁵ To get a better picture of rotational processes and to determine theoretical rotational barriers, semiempirical molecular orbital calculations were performed on compounds **1–3**.¹⁶ Figure 3 shows the potential energy surface diagram for sulfide **1** for concurrent N–Ar and S–Ar rotations, with central maxima and minima on either side indicating noncorrelated N–Ar and S–Ar rotations.¹⁷ The calculated barrier is ~9 kcal/mol for passage of *o*-SMeAr over the carbonyl group, which matches well with the values obtained from experimental

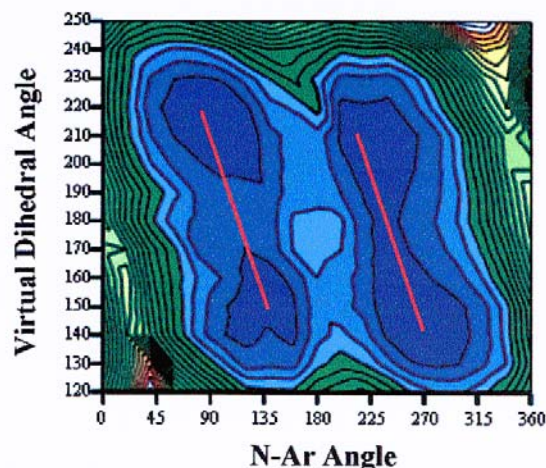


FIGURE 4. Surface plot of N–Ar angle and virtual dihedral angle for **1**.

work (~8.5 kcal mol⁻¹). Similar calculations were performed on **2** and **3** (Table 1). These values also agree quite well with experimental results but are not as close as for **1**. Theoretical values may deviate slightly from the experimental values due to chirality considerations or parametrizations in the PM3 program. The barrier to passage of *o*-SMeAr over the methylene portion of the isoindolinone is calculated to be much lower than for passage over the carbonyl (3.3 kcal mol⁻¹).

A major finding of the calculations is that pyramidalization of the amidic nitrogen is predicted in all three 2-(*o*-substituted phenyl)isoindolinone derivatives. This process cannot be observed by NMR in our model systems. Calculations show the degree of nitrogen pyramidalization¹⁸ in the highest energy conformations greatly increases with the initial oxidation from –S– to S=O (9.6° to 13.3°), but changes little upon further oxidation (13.3° to 13.9° in the sulfone). One can visualize nitrogen pyramidalization during N–Ar bond rotation in our model system as a “wobbling” rotating shaft rather than a rigid rotating shaft. At torsion angles where steric repulsion of the indolinone ring and *o*-Ar substituent is minimal, N-pyramidalization is also minimal. However as the steric interaction increases so does N-pyramidalization.

The calculations suggest (and it is reasonable to expect) N–Ar rotation and N-pyramidalization to be coupled or correlated motions. The coordinated movement of two proximate groups in order to minimize steric interactions during rotation of these groups is termed correlated or cogwheel rotation and is a well-studied phenomenon.^{17,19–21} Motions in which rotation is coupled to nitrogen inversion

(14) As a practical matter, oxidation to the sulfone state offers little or no increase in the barrier to rotation, while methods for converting sulfones to sulfides are not nearly as diverse nor simply executed as for sulfoxide deoxygenation. This is why our focus is on the S ↔ S=O redox cycle even though DNMR studies are, in general, easier to conduct on sulfone derivatives.

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(18) Different measures have been used to describe nitrogen pyramidalization: (a) Degree of pyramidalization equals 360 – Σ bond angles to the nitrogen atom (Canguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103). (b) Measurement of a virtual dihedral angle (Rankin, K. N.; Boyd, R. J. *J. Phys. Chem. A* **2002**, *106*, 11168) and (c) measurement of the distance from the nitrogen atom to the plane containing by the three atoms bonded to nitrogen (Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783).

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have been studied extensively by both experimental and computational methods²² and correlated rotation–nitrogen pyramidalization has been studied computationally.²³ Lunazzi¹⁷ has developed a graphical method to demonstrate correlated bond rotations by generating a contour map of the potential energy surface described by incremental rotations of the dihedral angles about the bonds suspected of correlated rotation. Correlated rotation is present when the rotation pathways (indicated by lines joining energy minima) run diagonal to the x – y axes and parallel to each other. To demonstrate computationally the correlated nature of N–Ar rotation and N-pyramidalization in **1**–**3**, we have developed a variant of the Lunazzi graphical approach: a “virtual dihedral angle” is plotted against the N–Ar torsion angle. Rankin and Boyd^{18b} introduced the virtual dihedral angle as a means of quantitating nitrogen pyramidalization. The virtual dihedral angle given by C1–N2–C3–C4 (see structure **1**) in compounds **1**–**3** having a value of 180° corresponds to planar nitrogen (flat, sp², degree of pyramidalization^{18a} = 0°) and a value of 120° corresponds to tetrahedral nitrogen (sp³, degree of pyramidalization = 31.5°). In the calculations (PM3), the virtual dihedral angle and the N–Ar torsion angle were locked, and then the other angles and bond distances were allowed to relax to their minima for each of the locked values. The N–Ar torsion angle values were fixed in 20° increments from 0 to 360° and virtual dihedral angle values were fixed in 10° increments from –90° to +90°. The resulting plot (Figure 4) has the appearance of a Lunazzi diagram, but relates N–Ar rotation to N-pyramidalization. Thus, diagonal lines joining the energy minima in Figure 4 are indicative of correlated motions.

Redox disengagement/engagement of the molecular brake can be observed in situ in an NMR tube. Addition of a solution of Lawesson's reagent^{9k} (in CDCl₃) to an NMR sample of compound **2** equilibrated to –40 °C in the NMR probe leads to a rapid replacement of the AB quartet (δ 4.95) observed for the methylene hydrogen atoms in the “stopped” sulfoxide with a broad singlet (δ 4.78) corresponding to the methylene hydrogen atoms in sulfide **1** as rotation about the N–Ar bond takes place.

Conversely engagement of the brake may be observed by addition of a solution of *m*-CPBA (in CDCl₃) to an NMR sample of compound **1** equilibrated to –40 °C in the NMR probe. This leads to a rapid replacement of the broad singlet (δ 4.78) corresponding to the methylene hydrogen atoms in the slowly rotating sulfide with an AB quartet (δ 4.95) corresponding to the methylene hydrogen atoms in the absence of N–Ar rotation in sulfoxide **2**. These reagents are nearly ideal for these experiments because the reactions are rapid (even at –40 °C), quantitative, and exhibit no interfering peaks in the region δ 4–5. A sample spectrum from titration of **1** with *m*-CPBA to approximately 80% conversion at –40 °C in an NMR tube is shown in Figure 5 (Supporting Information). The redox conversions may also be monitored by changes in intensity of the methyl signals in **1** (δ 2.41) and **2** (δ 3.05).

In conclusion, we have shown that the rate of N–Ar rotation in isoindolin-1-ones **1**–**3** is controlled by the oxidation state of sulfur in a proximate ortho substituent. The rate difference between sulfane and the sulfinyl/sulfonyl forms is $\sim 10^4$ s^{–1}. The model compounds are shown computationally to undergo correlated N-pyramidalization and C–N bond rotation. As the *o*-Ar substituent passes the plane of the isoindolinone, N-pyramidalization reaches maximum, but the nitrogen becomes planar when the isoindolinone and Ar groups are nearly orthogonal. Pyramidalization of nitrogen causes the redox brake to be less effective than expected. Design of a system in which shaft element flexing (in the form of atom pyramidalization) is avoided should provide more dramatic rate reductions using this molecular brake concept.

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Supporting Information Available: Experimental details for preparation and characterization of compounds **1**–**3**, ¹H and ¹³C NMR spectra for compounds **1**–**3**, 3D potential energy surface plots for **2** and **3**, PM3-computed *Z*-matrices for the lowest energy conformation of compounds **1**–**3** (when N–Ar and S–Ar torsion angles are locked and incremented), 2D surface plots of N–Ar torsion angle vs virtual dihedral angle for **2** and **3**, rate data for **3** from line-shape analysis, and PM3-computed *Z*-matrices for the lowest energy conformation of compounds **1**–**3** (when N–Ar and the virtual dihedral angle torsion angle are locked and incremented). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Future Directions

The use of sulfoxide as a source of intramolecular sulfonylating agents was well-known. Different modes (electrophilic and thermal) of sulfoxide activation were also well documented. However, the following observation warrants further study in understanding the actual process of sulfoxide activation. Mass spectrometric analysis of *t*-butyl, propane nitrile, and ethyl sulfoxides, which successfully produced a cyclized product in reaction conditions, was eventful. These sulfoxides, which are proven to have several rotameric isomers in solution, ambiguously yet cleanly produce the intended cyclized product (based on M^+ values) directly from solid samples during the mass spectrometric data collection. Further work is necessary to understand this phenomenon, especially because this phenomenon was observed for only those sulfoxides, which successfully produced the cyclized product under both electrophilic and thermal reaction conditions in the laboratory.

In chapter 3, sulfoxide was introduced as a “protecting group” for thioether which was unreactive under RCM reaction conditions. A well-known Ru-S(II) coordination was presumably avoided in the sulfoxide oxidation state. The next step in this research is to define the scope and utility of this approach. It is important to note that in an example described in chapter 3, one of the unsaturated components in the RCM diene precursor was directly attached to a sulfur atom. It would be interesting to apply this methodology of using sulfoxide as a protecting group to a sulfur containing system in which either of the alkene components is not directly attached to the sulfur atom. The results obtained from such an experiment would provide more insight in understanding the exact nature of

the interaction between the Ru-based catalyst and the sulfur containing substrate. Precisely, the validity of using sulfoxide as a protecting group of thioether needs to be tested with respect to the precise positioning of both the alkenes undergoing RCM reaction and the sulfur atom in substrate.

As discussed in chapter 4, nitrogen pyramidalization lowers the rotational barrier in sulfoxide, which results in a lower than expected increase in the rotational barrier. A system where nitrogen pyramidalization can be avoided should provide a more effective molecular brake based on the sulfide-sulfoxide redox cycle. If nitrogen pyramidalization is unavoidable, then the sulfide [S(II)] oxidation state of such system should have even lower barrier than Isoindoline **1** in chapter 4 to be a more efficient molecular brake than the one described in chapter 4 based on this redox cycle.

Appendix 1

Intramolecular Sulfoxide Electrophilic Sulfenylation (SES) of 2- and 3- Indole Carbanilides: Formation of Indolo[3,2-*b*]-1,5-benzothiazepinones

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Supplemental Information

(Compound numbers correspond to the numbers in the article:

Bates, D. K.; Eggers, M. E.; Jog, P. V. *J. Org. Chem.* Submitted for publication)

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2-(ethylthio)-*N*-methylaniline. Sodium metal (29.9 g, 260 mmol) was added to MeOH (390 mL) over 30 min with vigorous stirring. After H₂ evolution was complete (10 min), neat 2-(ethylthio)aniline (40.3 g, 260 mmol) was added dropwise then this solution was added dropwise to a well-stirred suspension of paraformaldehyde (10.9 g, 360 mmol) in MeOH (260 mL). After stirring 7 h at room temperature, neat NaBH₄ (9.1 g, 0.26 mol) was added to the reddish brown mixture. After refluxing 45 min, 1 M KOH (400 mL) was added to the cooled orange solution, which was then stirred for 30 min. This mixture was reduced to ½ its original volume in vacuo and poured into a saturated NaCl solution (200 mL). Extraction with CH₂Cl₂ (3 x 200 mL) followed by washing the combined organic layers with saturated aqueous NaCl, drying (Na₂SO₄) and solvent evaporation in vacuo produced a brown liquid. Flash chromatography (1:1 CHCl₃:hexanes) gave pure 2-(ethylthio)-*N*-methylaniline (18.2 g, 42%): IR 3390 cm⁻¹; ¹H NMR (200 MHz) δ 7.18-7.41 (2H, m), 6.57- 6.67 (2H, m), 5.10 (1H, s, br), 2.86 (3H, s), 2.70 (2H, q, J = 7.3 Hz), 1.20 (3H, t, J = 7.3 Hz); ¹³C NMR δ 150.8, 136.6, 130.6, 117.9, 117.1, 110.1, 31.2, 29.5, 15.5; MS [m/z (relative intensity)] 167 (M⁺, 100).

2-(*tert*-butylthio)-*N*-methylaniline. A mixture of 2-(*tert*-butylthio)aniline (3.5 g, 19 mmol) and 100 mL of glacial acetic acid was heated under reflux for 14 h. The reaction mixture was cooled to room temperature and poured onto an ice-water mixture. The organic layer was extracted with chloroform (2 x 250 mL), washed with water (2 x 250 mL) and dried over sodium sulfate. Evaporation of solvent in vacuo gave *N*-[2-(*tert*-butylthio)phenyl]acetamide as a brown liquid. (4.2 g, 97%): IR 3343, 1693 cm⁻¹; ¹H NMR δ 8.79 (broad, 1H), 8.44 (d, J = 8.16, 1H), 7.46 (ddd, J = 7.72, 1.67, 0.40 Hz, 1H),

7.34 (dt, $J = 7.52, 1.64$ Hz, 1H), 6.99 (dt, $J = 7.61, 1.33$ Hz, 1H), 2.16 (s, 3H), 1.25 (d, $J = 0.67$ Hz, 9H); ^{13}C NMR δ 167.9, 141.4, 138.5, 130.7, 123.1, 119.7, 119.5, 48.2, 30.9, 30.8, 24.8; MS [m/z (rel. intensity)] 223 [M^+ , 16], 125 (100), 57 (36).

To a well-stirred suspension of *N*-[2-(*tert*-butylthio)phenyl]acetamide (12.8 g, 57 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.2 eq, 11.5 mmol, 3.89 g) in toluene (250 mL) was added all at once 50% NaOH aqueous solution (500 mL). The resulting two layer mixture was heated under reflux at which a solution of iodomethane (excess, (2.0 eq), 114 mmol, 16.3 g) in toluene (40 mL) was added dropwise over 15 min. The resulting two phase mixture was maintained at reflux for 24 h. It was cooled to room temperature and the layers separated. The organic layer was washed with water several times (until washings were neutral to litmus), dried over sodium sulfate and evaporated in vacuo to yield ***N*-[2-(*tert*-butylthio)phenyl]-*N*-methylacetamide** as an off-white solid (8.5 g, 63%): mp 56-58 °C; IR 1651 cm^{-1} ; ^1H NMR δ 7.63 (dd, $J = 7.23, 1.37$ Hz, 1H), 7.31 (ddd, $J = 7.45, 1.85$ Hz, 1.18 Hz, 1H), 7.27 (ddd, $J = 7.45, 1.89, 1.18$ Hz, 1H), 7.18 (ddd, $J = 6.86, 1.81, 0.94$ Hz, 1H), 3.18 (dd, $J = 1.37, 0.3$ Hz, 3H), 1.75 (dd, $J = 1.45, 0.35$ Hz, 3H), 1.34 (d, $J = 1.35$ Hz, 9H); ^{13}C NMR δ 170.8, 146.6, 136.6, 133.5, 129.0, 128.5, 127.8, 47.2, 37.1, 31.7, 31.6, 22.7; MS [m/z (rel. intensity)] 181 (34), 57 (17).

To a solution of *N*-[2-(*tert*-butylthio)phenyl]-*N*-methylacetamide (8.3 g, 35 mmol) in 95% ethanol (400 mL) was added a solution of 30% aqueous HCl (70 mL). The resulting reaction mixture was refluxed for 6 d. The cooled reaction mixture was neutralized with 30% aqueous NaOH solution until pH=8. Organic layer was extracted with chloroform (2 x 250 mL), washed with water (2 x 400 mL) and dried over sodium sulfate.

Evaporation of solvent in vacuo gave 2-(*tert*-butylthio)-*N*-methylaniline as brown liquid

(5.7 g, 83%): IR 3400 cm^{-1} ; ^1H NMR δ 7.41 (dd, $J = 7.44, 1.63$ Hz, 1H), 7.29 (dt, $J = 7.38, 1.67$ Hz, 1H), 6.60-6.67 (m, 2H), 5.37 (broad, 1H), 2.87 (s, 3H), 1.33 (s, 9H); ^{13}C NMR δ 151.9, 139.1, 130.7, 115.7, 115.2, 109.3, 47.3, 30.8, 30.2; MS [m/z (rel. intensity)] 195 (16), 139 (100), 57 (13).

Ethyl *N*-methylindole-2-carboxylate. To a well-stirred solution of ethyl indole-2-carboxylate (5.0 g, 26 mmol), CH_3I (11.2 g, 79 mmol, 3 eq) and tetra-*n*-butylammonium sulfate (9.0 g, 26 mmol, 1 eq) in toluene (50 mL) at 0 $^\circ\text{C}$ was added 50% aqueous NaOH (25 mL) in one portion. The resulting two-phase mixture was heated to reflux for 1 h and, after cooling, the layers separated. The organic layer was washed with 5% HCl (2 x 50 mL), H_2O (1 x 50 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a wet yellow solid. Column chromatography (CHCl_3) and collection of the higher R_f component gave ethyl *N*-methylindole-2-carboxylate (4.2 g, 80%) as an off-white solid: mp 59-60 $^\circ\text{C}$; IR 1704 cm^{-1} ; ^1H NMR δ 7.70 (1H, dd, $J = 0.8, 7$ Hz), 7.17-7.39 (4H, m), 4.40 (2H, q, $J = 7$ Hz), 4.08 (3H, s), 1.43 (3H, t, $J = 7$ Hz); MS [m/z (relative intensity)] 203 (M^+ , 46), 89 (100). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.82; H, 6.45; N, 6.89. Found: C, 70.76; H, 6.47; N, 6.98.

***N*-[2-(*tert*-butylthio)phenyl]-1*H*-indole-2-carboxamide (1b).** To a well-stirred solution of indole-2-carboxylic acid (4.25 g, 26.4 mmol) in ether (100 mL) at 0 $^\circ\text{C}$ under a drying tube was added dropwise thionyl chloride neat (3 x 3.66 g portionwise over 12 h, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (4.50 g,

95%). This solid was redissolved in ether (100 mL) and added to a well-stirred solution of 2-(*tert*-butylthio)aniline (1.2 eq, 5.64 g, 31 mmol) in dioxane-water-ether (40-5-50 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL), 5% NaHCO₃ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to yield a off-white solid. Recrystallization with hexane gave white compound (6.1 g, 71%): mp 191-193 °C; IR 3453, 1660 cm⁻¹; ¹H NMR δ 10.4 (broad, 1H), 9.9 (broad, 1H), 8.80 (d, J = 8.16 Hz, 1H), 7.76 (d, J = 7.91 Hz, 1H), 7.61 (d, J = 7.91 Hz, 1H), 7.54 (d, J = 7.91 Hz, 1H), 7.49 (d, J = 7.91 Hz, 1H), 7.32 (t, J = 7.35 Hz, 1H), 7.09-7.22 (m, 3H), 1.36 (s, 9H); ¹³C NMR δ 159.5, 141.2, 138.7, 137.0, 131.1, 130.9, 127.7, 124.8, 123.5, 122.1, 120.8, 120.5, 119.6, 112.2, 102.9, 48.5, 30.9; MS [m/z (rel. intensity)] 324 [M⁺, 9], 144 (100), 89 (20), 57 (14). Anal. Calc. for C₁₉H₂₀N₂OS: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.21; H, 6.43; N, 8.56.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-1*H*-indole-2-carboxamide (2b).** To an ice-cooled solution of **1b** (5.10 g, 15.7 mmol) in CH₂Cl₂ (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 22.4 mmol, 3.9 g) in CH₂Cl₂ (50 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (-8 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution (150 mL) and extracted with CH₂Cl₂ (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc-hexane, 3:7) gave yellowish white solid which was recrystallized (hexane) to give a white solid (3.51 g, 66%): mp

228-230 °C (dec); IR 1664 cm⁻¹; ¹H NMR δ 12.1 (broad, 1H), 9.46 (broad, 1H), 8.74 (dd, J = 8.34, 0.62 Hz, 1H), 7.72 (d, J = 8.15 Hz, 1H), 7.53 (dt, J = 8.49, 1.70 Hz, 1H), 7.44 (d, J = 8.25, 0.83 Hz, 1H), 7.26-7.31 (m, 2H), 7.09-7.19 (m, 3H), 1.28 (s, 9H); ¹³C NMR δ 159.6, 142.5, 136.7, 132.4, 131.1, 128.8, 127.9, 124.8, 122.6, 122.4, 122.3, 120.8, 120.7, 111.8, 104.2, 59.1, 23.4; MS [m/z (rel. intensity)] 340 [M⁺, 1], 144 (100), 89 (26), 57 (18). Anal. Calc. for C₁₉H₂₀N₂O₂S: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.04; H, 6.07; N, 8.18.

***N*-[2-(ethylthio)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (3a).** This compound was prepared analogously to compound **1a**. The crude orange solid was chromatographed (CHCl₃) to give **3a** as a yellow solid (38%): mp 188-190 °C (acetone); IR 3316, 1611 cm⁻¹; ¹H NMR (200 MHz) δ 9.73 (s, 1H, br), 6.95-7.49 (8H, m), 5.25 (1H, s), 3.45 (3H, s), 2.88 (2H, apparent qd, J=7.3, 0.1 Hz), 1.24 (3H, t, J = 7 Hz); ¹³C NMR δ 163.3, 142.3, 138.7, 136.5, 130.5, 130.3, 130.2, 128.8, 128.3, 127.2, 125.2, 123.0, 120.9, 112.6, 107.2, 38.1, 26.7, 14.7; MS [m/z (relative intensity)] 310 (M⁺, 15), 249 (100). Anal. Calcd for C₁₈H₁₈N₂OS: C, 69.65, H, 5.84, N, 9.02. Found: C, 69.53, H, 5.95, N, 8.86.

***N*-[2-(*tert*-butylthio)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (3b).** To a well-stirred solution of indole-2-carboxylic acid (3.75 g, 23 mmol) in ether (100 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 3.23 g portionwise over 12 h, 82 mmol, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (4.0 g, 96%). This solid was redissolved in ether (100 mL) and

added to a well-stirred solution of *N*-[2-(tert-butylthio)phenyl]-*N*-methylamine (1.1 eq, 5.0 g, 26 mmol) in dioxane-water-ether (40-5-50 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL), 5% NaHCO₃ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to give yellowish white solid, which was recrystallized (EtOAc) to give a white solid (5.94 g, 79%): mp 213-214 °C; IR 3454, 1622 cm⁻¹; ¹H NMR δ 9.37 (broad, 1H), 7.69 (dd, *J* = 7.24, 1.79 Hz, 1H), 7.37-7.47 (m, 3H), 7.35 (d, *J* = 8.35 Hz, 1H), 7.30 (d, *J* = 8.35 Hz, 1H), 7.17 (t, *J* = 7.43 Hz, 1H), 6.96 (t, *J* = 7.40 Hz, 1H), 5.11 (s, 1H), 3.45 (s, 3H), 1.29 (s, 9H); ¹³C NMR δ 162.6, 146.3, 137.2, 135.2, 134.4, 129.9, 129.4, 128.9, 128.4, 127.7, 124.3, 122.1, 120.0, 111.5, 106.3, 47.1, 38.7, 31.8; MS [*m/z* (rel. intensity)] 338 [*M*⁺, 6], 249 (41), 144 (100), 89 (25). Anal. Calc. for C₂₀H₂₂N₂OS: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.82; H, 6.54; N, 8.17.

***N*-[2-(ethylsulfinyl)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (4a).** (59%): mp 177-179 °C (acetone); IR 3282, 1628, 1041 cm⁻¹; ¹H NMR (200 MHz taken at 100 °C in DMSO-*d*₆) δ 9.53 (1H, s, br), 8.04-8.09 (1H, m), 6.95- 7.73 (7H, m), 5.39 (1H, s), 3.48 (3H, s), 2.5 -2.8 (2H, m, cont. *J* = 6.5 Hz), 1.13 (3H, t, *J* = 6.4 Hz); ¹³C NMR δ 164.2, 143.4, 142.3, 137.7, 134.4, 132.0, 131.7, 130.5 129.2, 129.1, 126.9, 124.1, 122.4, 113.8, 108.8, 50.1, 40.6, 7.6; MS [*m/z* (relative intensity)] 326 (*M*⁺, 8), 249 (100). Anal. Calcd for C₁₈H₁₈N₂O₂S: C, 66.23, H, 5.56, N, 8.58. Found: C, 65.98, H, 5.70, N, 8.26.

***N*-[2-(ethylthio)phenyl]-1-methyl-1*H*-indole-2-carboxamide (5a).** This compound was prepared analogously to compound **9** from toluene (15 mL), trimethylaluminum (2.0 M in hexane, 2.5 mL, 4.96 mmol, 1.14 eq.), 2-(ethylthio)aniline (0.7 g, 4.4 mmol) in toluene (2 mL), ethyl *N*-methylindole-2-carboxylate (0.9 g, 4.4 mmol) in toluene (7 mL) and CH₂Cl₂ (5 drops). The orange oil **5a** (1.1 g, 84%) solidified on standing: mp 86-87.5 °C (light yellow solid, acetone/hexane); IR 3321, 1660 cm⁻¹; ¹H NMR (200 MHz) δ 9.49 (1H, d, J = 1 Hz), 8.56 (1H, dd, J = 1, 7 Hz), 7.72 (1H, dd, J = 1, 7 Hz), 7.59 (1H, dd, J = 2, 6 Hz), 7.05-7.42 (8H, m, containing 1H, d, dd, J = 2, 6 Hz), 4.14 (3H, s), 2.83 (2H, q, J = 7 Hz), 1.25 (3H, t, J = 7 Hz); ¹³C NMR δ 161.5, 141.2, 140.3, 136.8, 133.2, 131.1, 127.3, 125.2, 123.3, 123.0, 120.9, 111.5, 105.9, 33.0, 31.9, 16.2; MS [m/z (relative intensity)] 310 (M⁺, 7), 158 (100). Anal. Calcd for C₁₈H₁₈N₂OS: C, 69.57; H, 5.84; N, 9.02. Found: C, 69.23; H, 5.95; N, 9.06.

***N*-[2-(*tert*-butylthio)phenyl]-1-methyl-1*H*-indole-2-carboxamide (5b).** To a well-stirred solution of 1-methyl-1*H*-indole-2-carboxylic acid (3.25 g, 18.6 mmol) in ether (100 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 2.6 g portionwise over 12 h, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (3.0 g, 84%). This solid was redissolved in ether (100 mL) and added to a well-stirred solution of 2-(*tert*-butylthio)aniline (1.1 eq, 3.69 g, 20.4 mmol) in dioxane-water-ether (40-5-50 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL),

5% NaHCO₃ (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to yield a greenish solid which was purified by column chromatography (chloroform: hexane, 8:2) to give pale yellow solid (3.71 g, 59%): mp 86-88 °C; IR 3326, 1670 cm⁻¹; ¹H NMR δ 9.78 (broad, 1H), 8.65 (dd, J = 8.34, 1.19 Hz, 1H), 7.74 (dt, J = 8.07, 0.88 Hz, 1H), 7.58 (dd, J = 7.74, 1.58 Hz, 1H), 7.42-7.49 (m, 2H), 7.37 (ddd, J = 6.79, 1.12 Hz, 1H), 7.20 (ddd, J = 6.88, 1.15 Hz, 1H), 7.13 (s, 1H), 7.10 (dt, J = 7.53, 1.40 Hz, 1H), 4.14 (s, 3H), 1.34 (s, 9H); ¹³C NMR δ 160.0, 141.6, 139.4, 138.6, 131.9, 130.8, 126.0, 124.5, 123.3, 122.1, 120.7, 120.4, 119.4, 110.2, 104.6, 48.4, 31.7, 30.9; MS [m/z (rel. intensity)] 338 [M⁺, 7], 158 (100), 89 (29), 57 (12). Anal. Calc. for C₂₀H₂₂N₂OS: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.88; H, 6.79; N, 8.22.

***N*-[2-(ethylsulfinyl)phenyl]-1-methyl-1*H*-indole-2-carboxamide (6a).** (73%): mp 96-99 °C (acetone); IR (KBr) 3219, 1667, 1003 cm⁻¹; ¹H NMR (200 MHz) δ 11.60 (1H, s, br), 8.67 (1H, d, J = 8 Hz), 7.08-7.71 (8H, m), 4.15 (3H, s), 3.02-3.22 (2H, dm, cont. J = 7 Hz), 1.24 (3H, t, J = 7 Hz); ¹³C NMR δ 162.0, 142.4, 140.9, 133.8, 132.3, 128.0, 127.3, 126.2, 125.9, 124.2, 123.8, 123.7, 121.7, 111.4, 107.0, 49.6, 33.1, 8.7; MS [m/z/(relative intensity) 326 (M⁺, 10), 158 (100). Anal. Calcd for C₁₈H₁₈N₂O₂S: C, 66.23; H, 5.56; N 8.58. Found: C, 65.88, H, 5.63, N, 8.77.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-1-methyl-1*H*-indole-2-carboxamide (6b).** To an ice-cooled solution of **5b** (4.0 g, 11.8 mmol) in CH₂Cl₂ (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 16.8 mmol, 2.90 g) in CH₂Cl₂ (50 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (-8 °C) overnight. The

reaction mixture was then poured into 5% NaHCO₃ solution (150 mL) and extracted with CH₂Cl₂ (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (chloroform-ether, 9:1) gave white solid (2.6 g, 62%): mp 135-137 °C; IR 1669 cm⁻¹; ¹H NMR δ 11.87 (broad, 1H), 8.69 (dd, J = 8.49, 0.99 Hz, 1H), 7.71 (dt, J = 8.05, 0.96 Hz, 1H), 7.51 (dt, J = 7.21, 1.74 Hz, 1H), 7.35-7.41 (m, 2H), 7.33 (dt, J = 6.80, 1.07 Hz, 1H), 7.12-7.18 (m, 2H), 7.10 (dt, J = 7.26, 1.03 Hz, 1H), 4.14 (s, 3H), 1.28 (s, 9H); ¹³C NMR δ 160.1, 142.5, 139.6, 132.3, 131.3, 128.7, 126.1, 124.5, 122.6, 122.4, 122.1, 120.9, 120.5, 110.1, 106.0, 59.1, 31.9, 23.4; MS [m/z (rel. intensity)] 354 [M⁺, 2], 158 (100), 89 (16). Anal. Calc. for C₂₀H₂₂N₂O₂S: C, 67.77; H, 6.26; N, 7.90. Found: C, 68.09; H, 6.22; N, 7.88.

***N*-[2-(*tert*-butylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7b).** To a well-stirred suspension of **1b** (6.5 g, 20 mmol) and tetra-*n*-butylammonium hydrogen sulfate (0.3 eq, 6 mmol, 2.0 g) in toluene (250 mL) was added all at once 50% NaOH (aq) solution (200 mL). The resulting two layer mixture was heated under reflux at which a solution of iodomethane (2.5 eq, 50 mmol, 7.11 g) in toluene (10 mL) was added dropwise over 5 min. The resulting two phase mixture was maintained at reflux for 24 h. It was cooled to room temperature and the layers separated. The organic layer was washed with water several times (until washings were neutral to litmus), dried over sodium sulfate and evaporated in vacuo to yield an off-white solid. Recrystallization with hexane gave white compound (5.6 g, 79%): mp 105-106 °C; IR 3007, 1636 cm⁻¹; ¹H NMR δ 7.48 (d, J = 7.99 Hz, 1H), 7.42 (dt, J = 7.33, 1.42 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.24 Hz, 2H), 7.17 (q, J = 7.72 Hz, 2H), 6.95 (t, J = 7.43 Hz, 1H), 5.72

(s, 1H), 4.02 (s, 3H), 3.49 (s, 3H), 1.24 (s, 9H); ^{13}C NMR δ 164.4, 148.4, 138.3, 137.9, 132.4, 131.5, 129.6, 126.9, 126.8, 126.0, 123.3, 121.7, 119.5, 109.7, 106.8, 46.5, 38.4, 31.6, 31.4; MS [m/z (rel. intensity)] 263 (100), 158 (80), 89 (33). Anal. Calc. for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{OS}$: C, 71.55; H, 6.86; N, 7.95. Found: C 71.79; H 7.06; N 7.91.

***N*-{2-[(2-cyanoethyl)thio]phenyl}-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7c).** To a well-stirred solution of 1-methyl-1*H*-indole-2-carboxylic acid (0.65 g, 3.71 mmol) in ether (50 mL) at 0 °C under a drying tube was added dropwise thionyl chloride neat (3 x 0.5 g portionwise over 12 h, 3.5 eq.). The reaction mixture was allowed to stir at room temperature during 12 h. The resulting clear yellow solution was evaporated in vacuo to produce yellow solid (0.6 g, 84%). This solid was redissolved in ether (50 mL) and added to a well-stirred solution of 2-propanenitrile-2-(methylaminophenyl)sulfide (1.1 eq, 0.65 g, 3.38 mmol) in dioxane-water-ether (20-3-25 mL) mixture over 10 min at room temperature. The reaction mixture was stirred at room temperature for 3 h and then diluted with ethyl acetate (150 mL). The combined organics were washed with 5% HCl (aq, 3 x 150 mL), 5% NaHCO_3 (aq, 3 x 150 mL), water (2 x 150 mL) dried over sodium sulfate and solvent evaporated in vacuo to yield a sticky solid which was purified by column chromatography (chloroform: Ether, 9:1) to give white solid (0.35 g, 27%): mp 124-125 °C; IR 2240, 1635 cm^{-1} ; ^1H NMR δ 6.92-7.80 (m, 8H), 5.95 (s, 1H), 3.98 (s, 3H), 3.44 (s, 3H), 2.41 (s, 2H), 2.30 (s, 2H); ^{13}C NMR was not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 349 [M^+ , 3], 263 (72), 158 (100), 89 (24). Anal. Calc. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{OS}$: C, 68.74; H, 5.48; N, 12.02. Found: C 68.80; H 5.58; N 11.87.

***N*-[2-(ethylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (8a).** (95%); mp 165-167 °C (acetone); IR 1633, 1052, 1025 cm⁻¹; ¹H NMR (200 MHz, taken at 100 °C) δ 7.87-7.91 (1H, m), 7.50-7.56 (2H, m), 7.24-7.43 (4H, m), 7.03 - 7.08 (1H, m), 6.14 (1H, s), 3.97 (3H, s), 3.40 (3H, s), 2.65 (2H, m, containing J = 7 Hz), 1.19 (3H, t, J = 7 Hz); ¹³C NMR δ 163.0, 141.8, 138.8, 133.1, 132.0, 129.5, 129.3, 129.0, 126.9, 126.8, 124.9, 122.6, 121.0, 110.6, 108.8, 49.2, 39.0, 32.3, 7.0; MS [m/z (relative intensity)] 340 (M⁺, 1), 158 (100). Anal. Calcd for C₁₉H₂₀N₂O₂S: C, 67.02; H, 6.11; N, 8.00. Found: C, 67.03; H, 5.92; N, 8.23.

***N*-[2-(*tert*-butylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (8b).** To an ice-cooled solution of **7b** (5.38 g, 15.2 mmol) in CH₂Cl₂ (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 eq, 21.7 mmol, 3.74 g) in CH₂Cl₂ (50 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (-8 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution (150 mL) and extracted with CH₂Cl₂ (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc-hexane, 6:4) gave yellowish white solid which was recrystallized (hexane) to give a white solid (3.42 g, 61%): mp 125-127 °C; IR 3003, 1639 cm⁻¹; ¹H NMR and ¹³C NMR were not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 158 (100), 89 (26). Anal. Calc. for C₂₁H₂₄N₂O₂S: C, 68.45; H, 6.56; N, 7.60. Found: C 68.30; H 6.64; N 7.51.

***N*-{2-[(2-cyanoethyl)sulfinyl]phenyl}-*N*,1-dimethyl-1*H*-indole-2-carboxamide (8c).**

To an ice-cooled solution of **7c** (0.2 g, 0.57 mmol) in CH₂Cl₂ (50 mL) was added slowly

a solution of *m*-CPBA (77%, 1.1 eq, 0.81 mmol, 0.141 g) in CH₂Cl₂ (50 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (-8 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution (50 mL) and extracted with CH₂Cl₂ (75 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc:hexane, 9:1) gave sticky liquid (0.15 g, 72%): IR 1637, 1039 cm⁻¹; ¹H NMR and ¹³C NMR were not well-resolved due to presence of rotational isomers; MS [m/z (rel. intensity)] 312 (15), 294 (38), 158 (100), 53 (99).

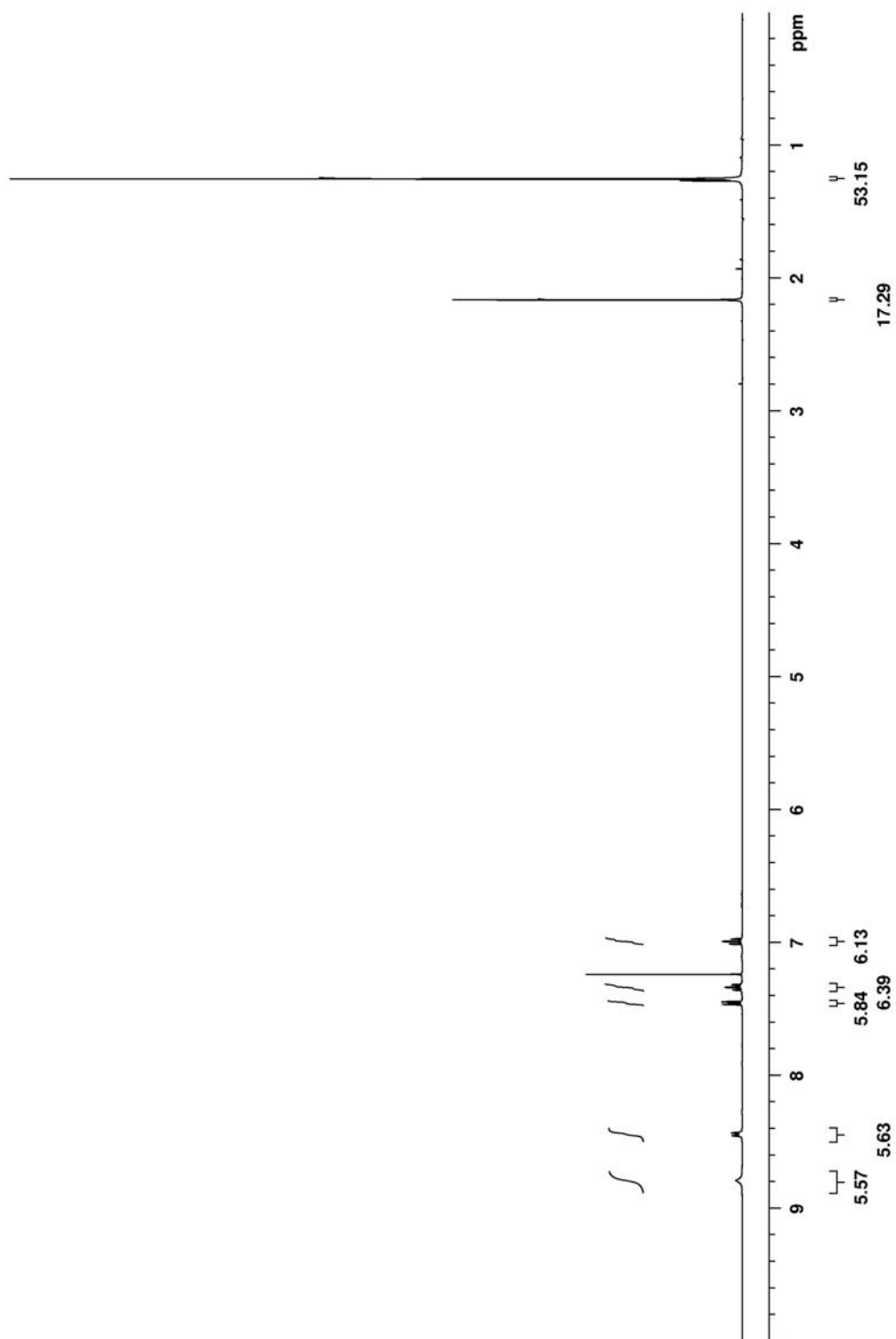
10,11-dihydro-10,12-dimethylindolo[3,2-*b*]-1,5-benzothiazepin-11-one (10) from 8b.

Method A (Thermal Cyclization): A solution of **8b** (0.3 g, 0.82 mmol) in chloroform (50 mL) was heated under reflux for 6 d. The solution was allowed to cool to room temperature and the solvent evaporated in vacuo to yield a brown solid. Column chromatography (CHCl₃: ether, 9:1) gave white solid (0.16 g, 67%): mp 196-198 °C; IR 1624 cm⁻¹; ¹H NMR δ 7.73 (dt, *J* = 8.06, 0.93 Hz, 1H), 7.54 (dd, *J* = 7.75, 0.8 Hz), 7.26-7.34 (m, 4H), 7.17 (ddd, *J* = 8.11, 4.54, 1.12 Hz, 2H), 3.91 (s, 3H), 3.61 (s, 3H); ¹³C NMR δ 163.4, 146.0, 138.2, 137.4, 132.3, 131.0, 128.9, 126.2, 125.8, 125.5, 125.0, 120.6, 120.2, 117.5, 110.1, 38.6, 31.6; MS [m/z (rel. intensity)] 294 [M⁺, 100].

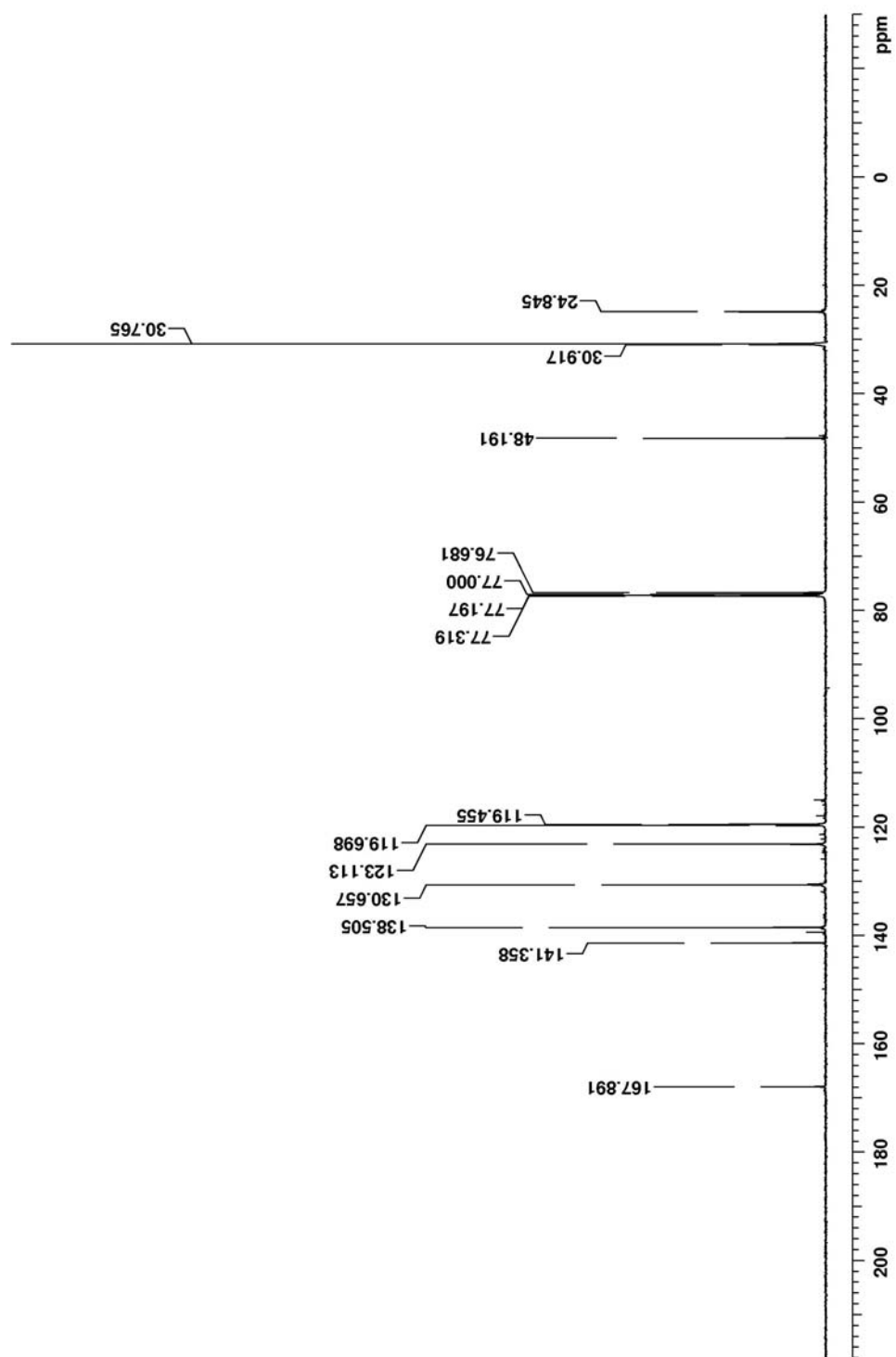
Method B (Electrophilic Activation): To a well-stirred solution of TFAA (0.64 g, 3.1 mmol, 3.75 eq.) in CH₂Cl₂ (20 mL) at 0 °C was added pyridine (0.25 g, 3.2 mmol, 4 eq.), neat via syringe. The reaction vessel was kept under a drying tube throughout the reaction. To the resulting yellow solution was added, a solution of **8b** (0.3 g, 0.82 mmol) in CH₂Cl₂ (15 mL) which was previously cooled to 0 °C. This was stirred at 0 °C for 15

min then at room temperature for 3 h. The solution was poured onto 10% Na₂CO₃ (25 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH₂Cl₂ (30 mL). The combined organics were washed with 5% aqueous solution of HCl (3 X 40 mL), 10% aqueous solution of Na₂CO₃ (1 X 40 mL), H₂O and dried over sodium sulfate. The solvent was removed in vacuo to yield pure yellow solid, **10** (0.23 g, 100%).

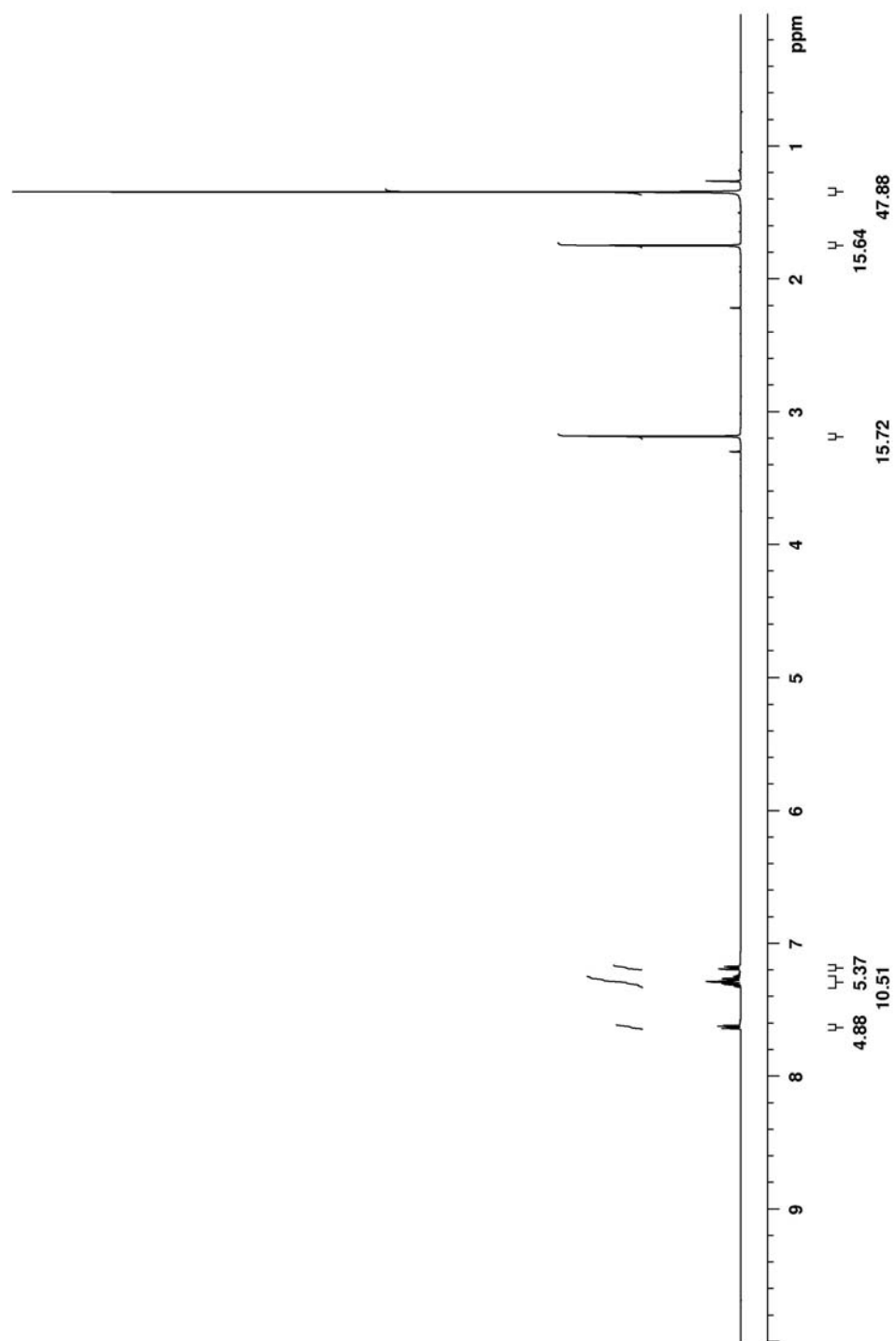
¹H NMR Spectrum of *N*-[2-(*tert*-butylthio)phenyl]acetamide



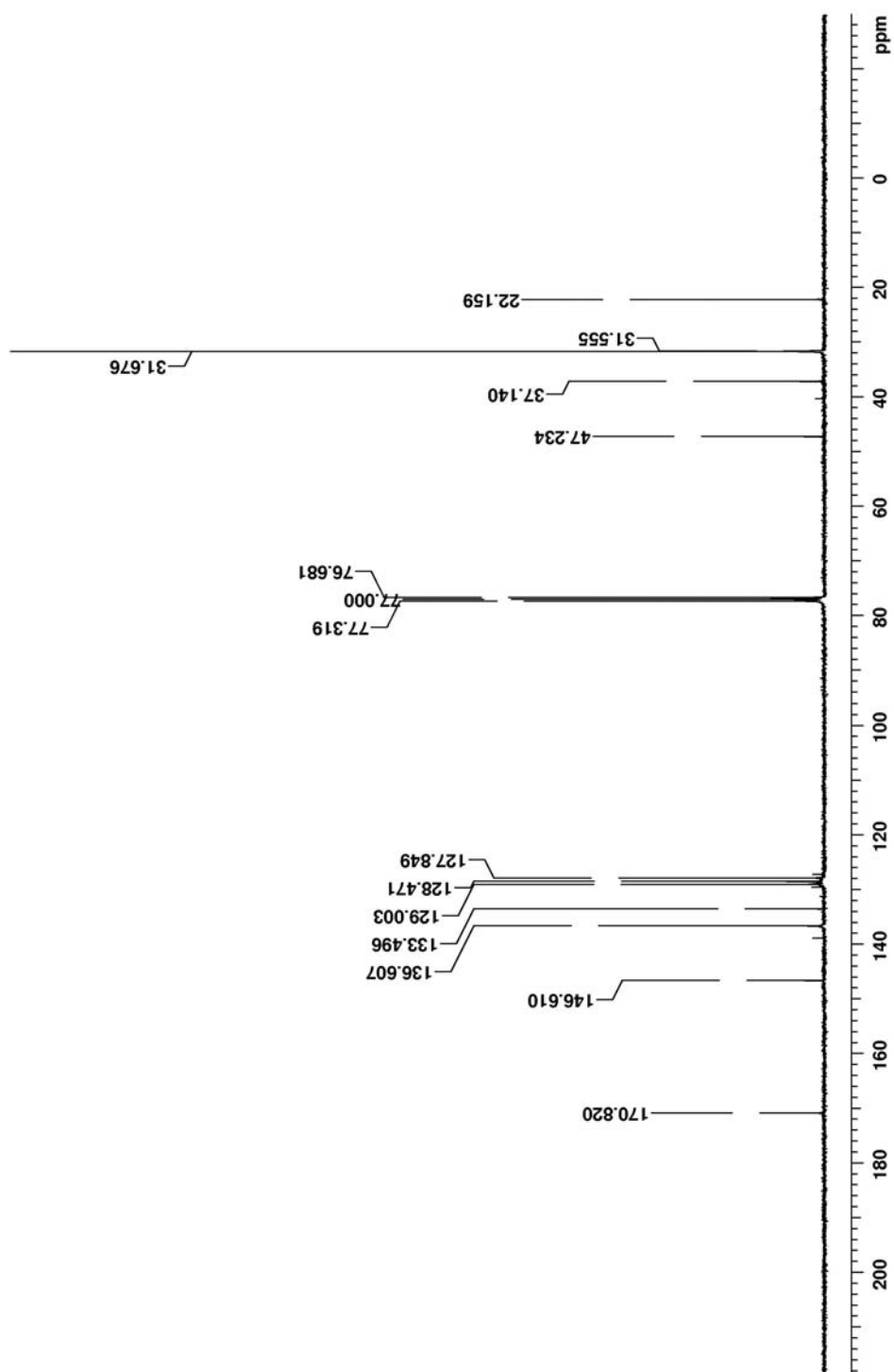
^{13}C NMR Spectrum of *N*-[2-(*tert*-butylthio)phenyl]acetamide



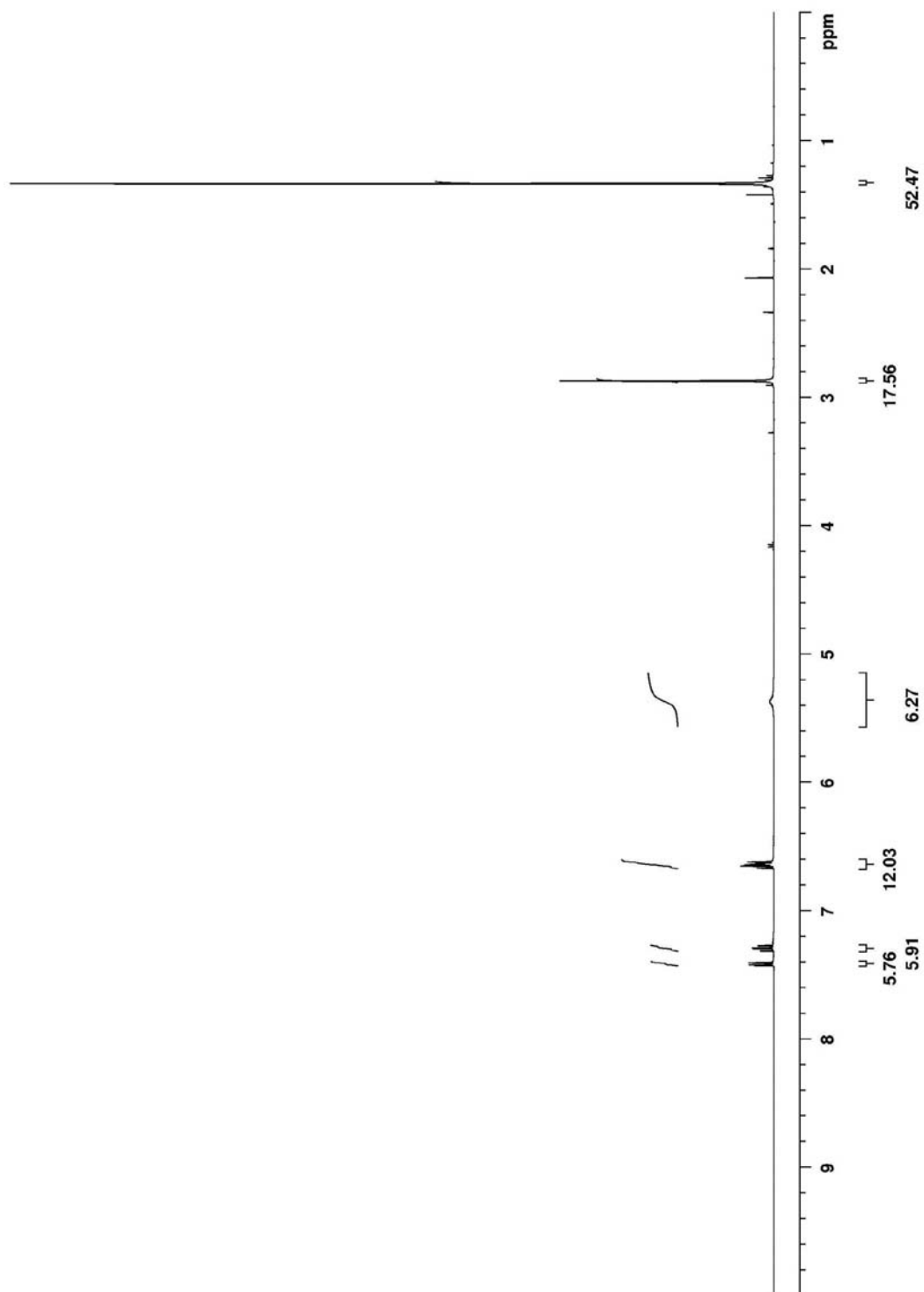
¹H NMR Spectrum of *N*-[2-(*tert*-butylthio)phenyl]-*N*-methanamide



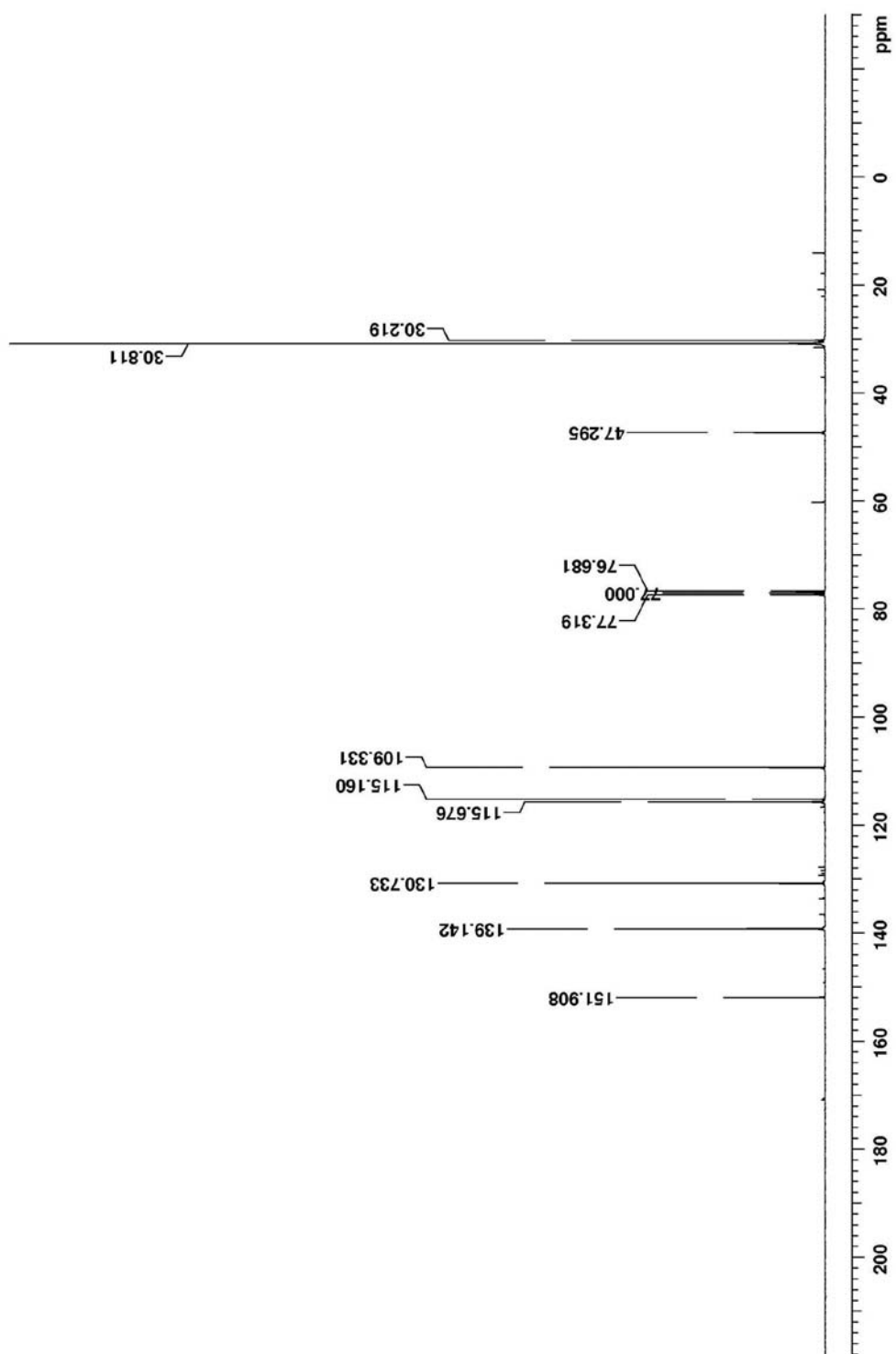
^{13}C NMR Spectrum of *N*-[2-(*tert*-butylthio)phenyl]-*N*-methanamide



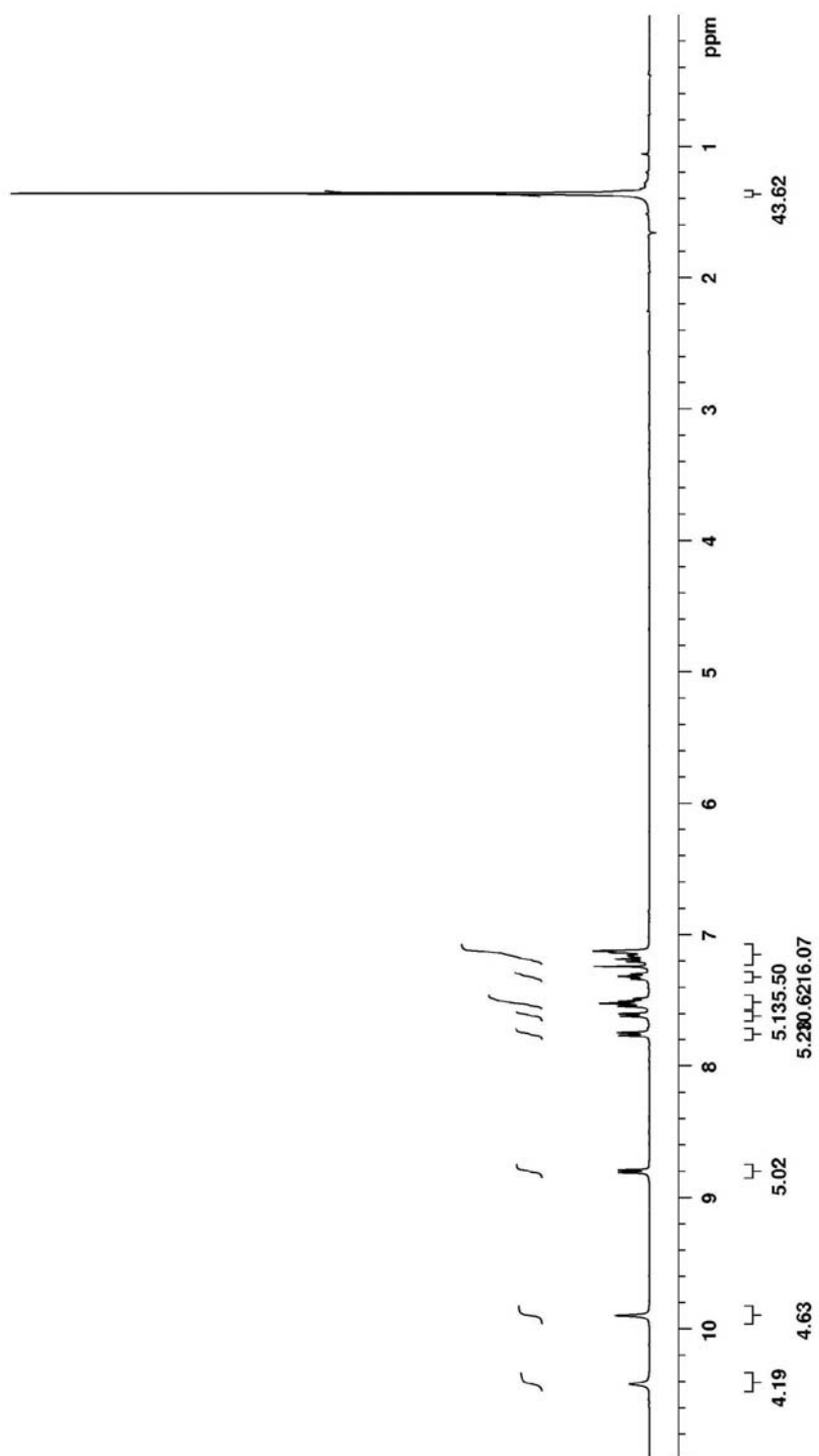
¹H NMR Spectrum of *N*-[2-(*tert*-butylthio)phenyl]-*N*-methylamine



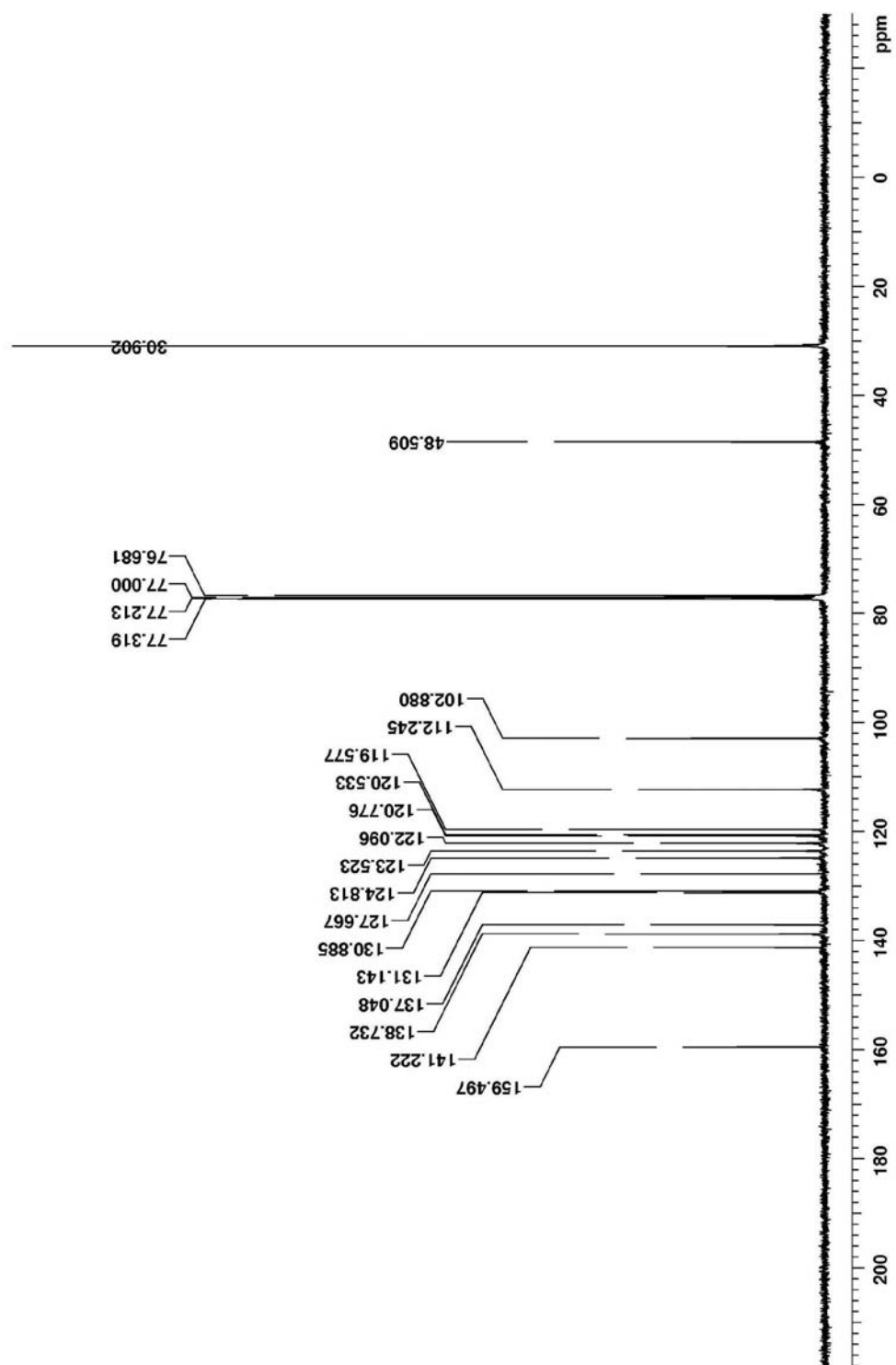
¹³C NMR Spectrum of *N*-[2-(*tert*-butylthio)phenyl]-*N*-methylamine



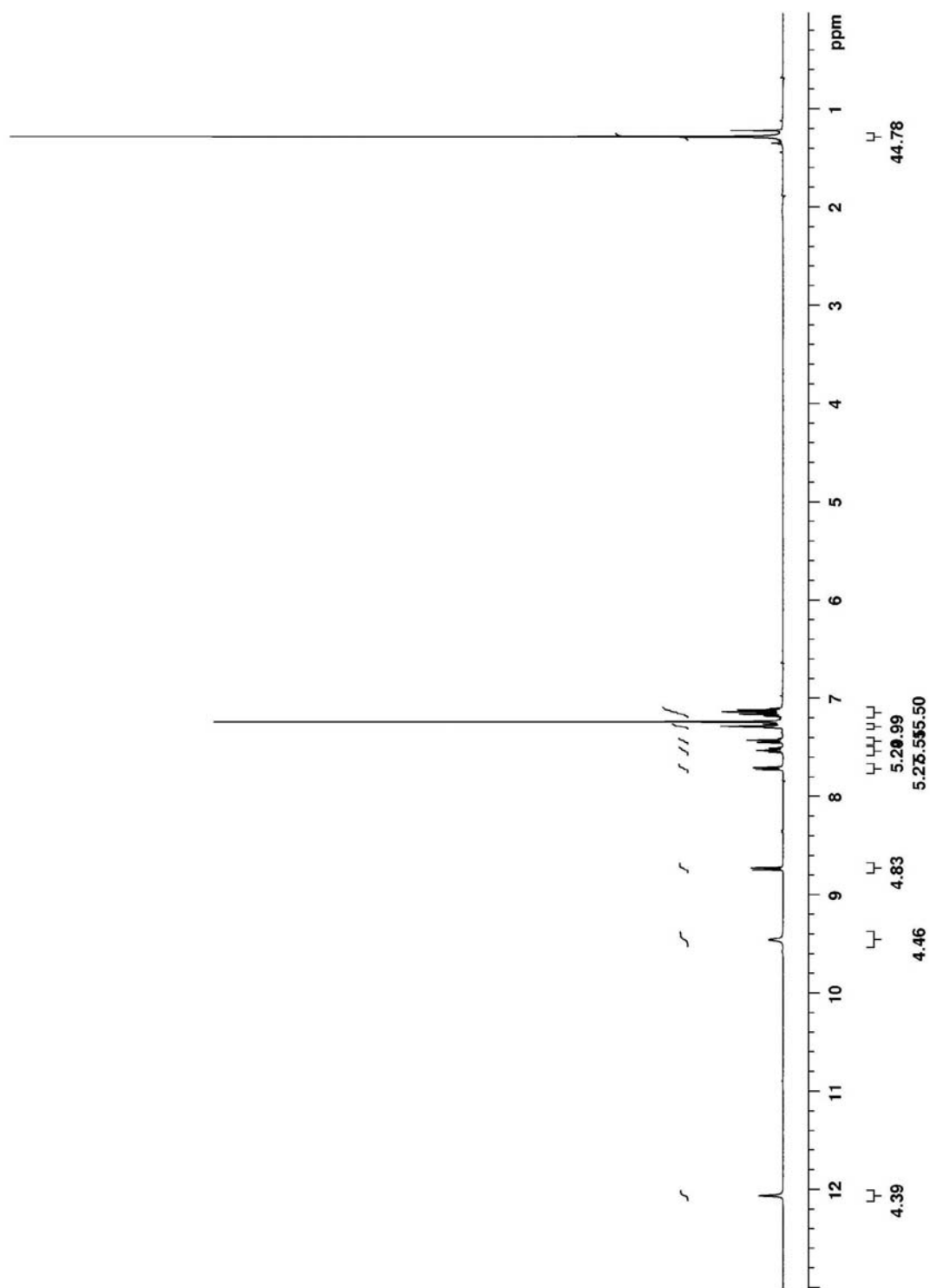
^1H NMR Spectrum of **1b**



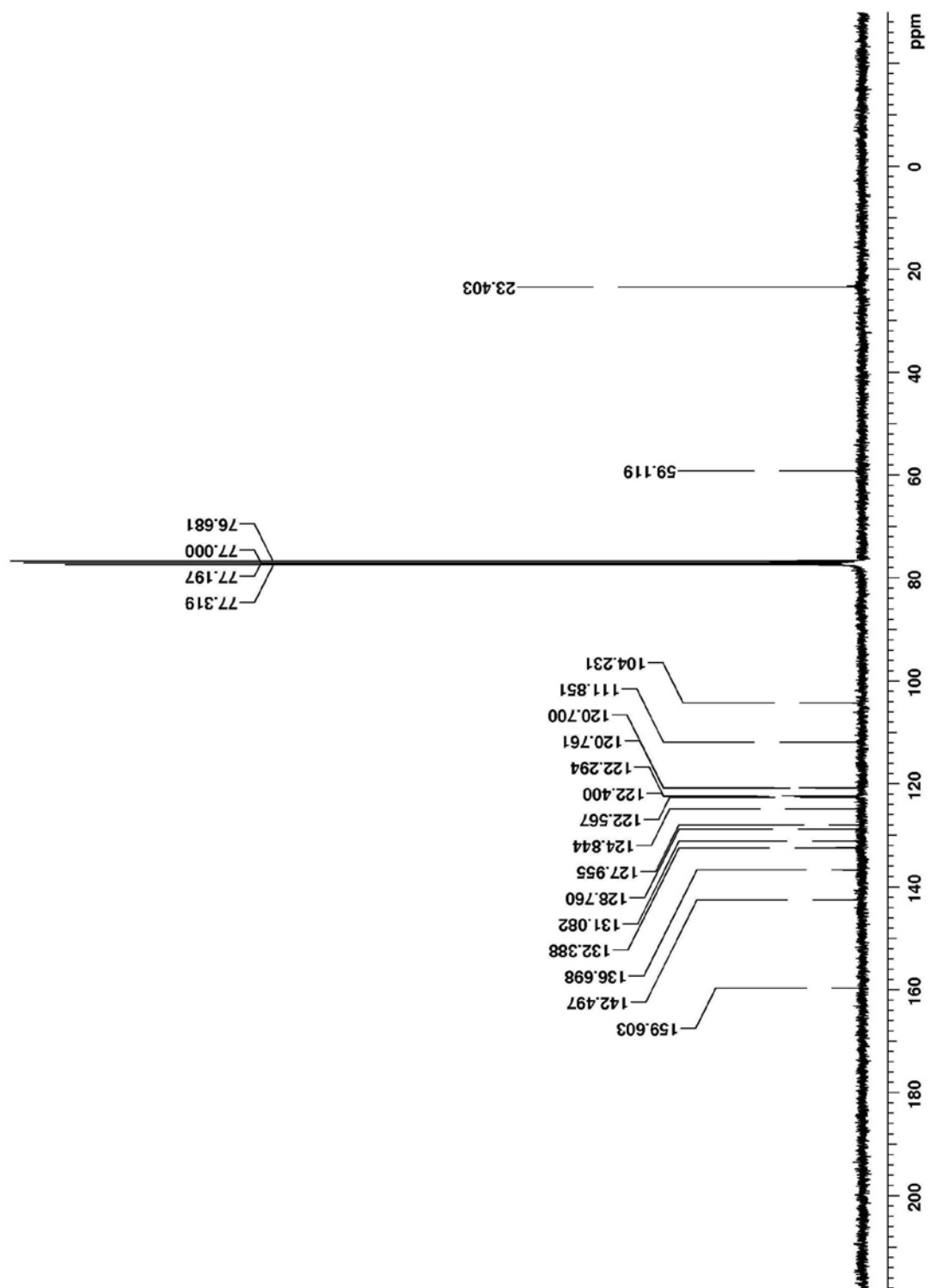
^{13}C NMR Spectrum of **1b**



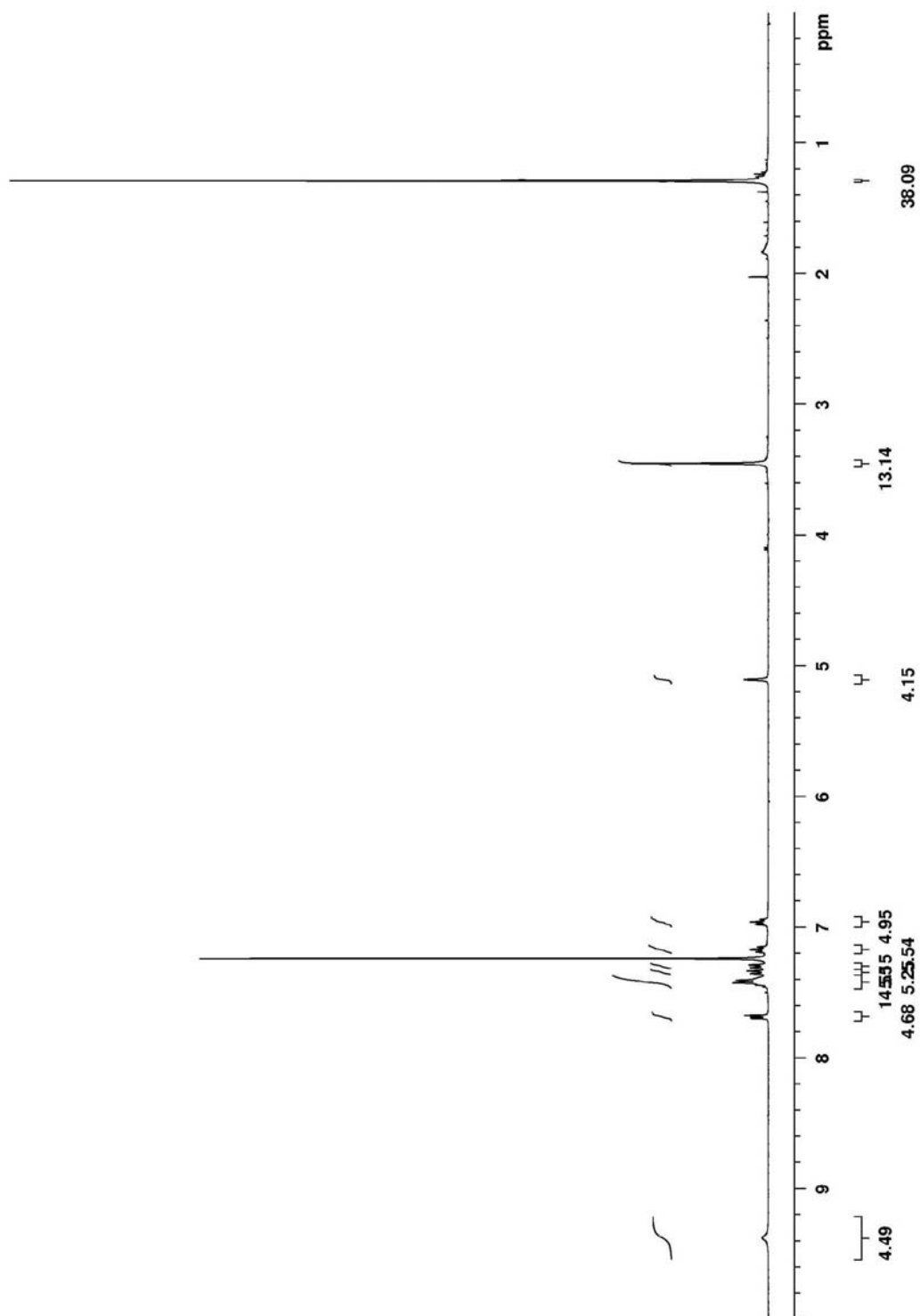
^1H NMR Spectrum of **2b**



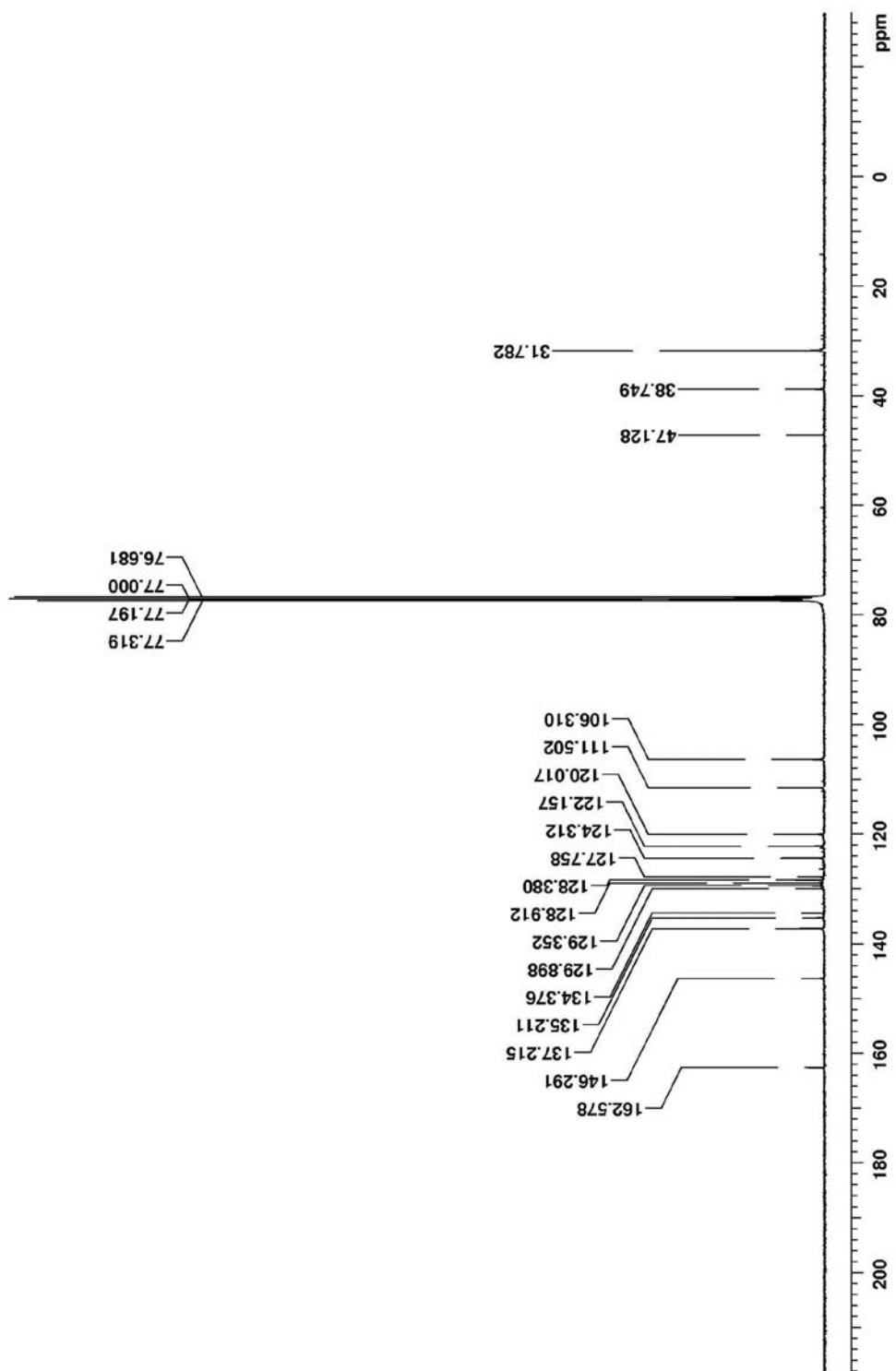
^{13}C NMR Spectrum of **2b**



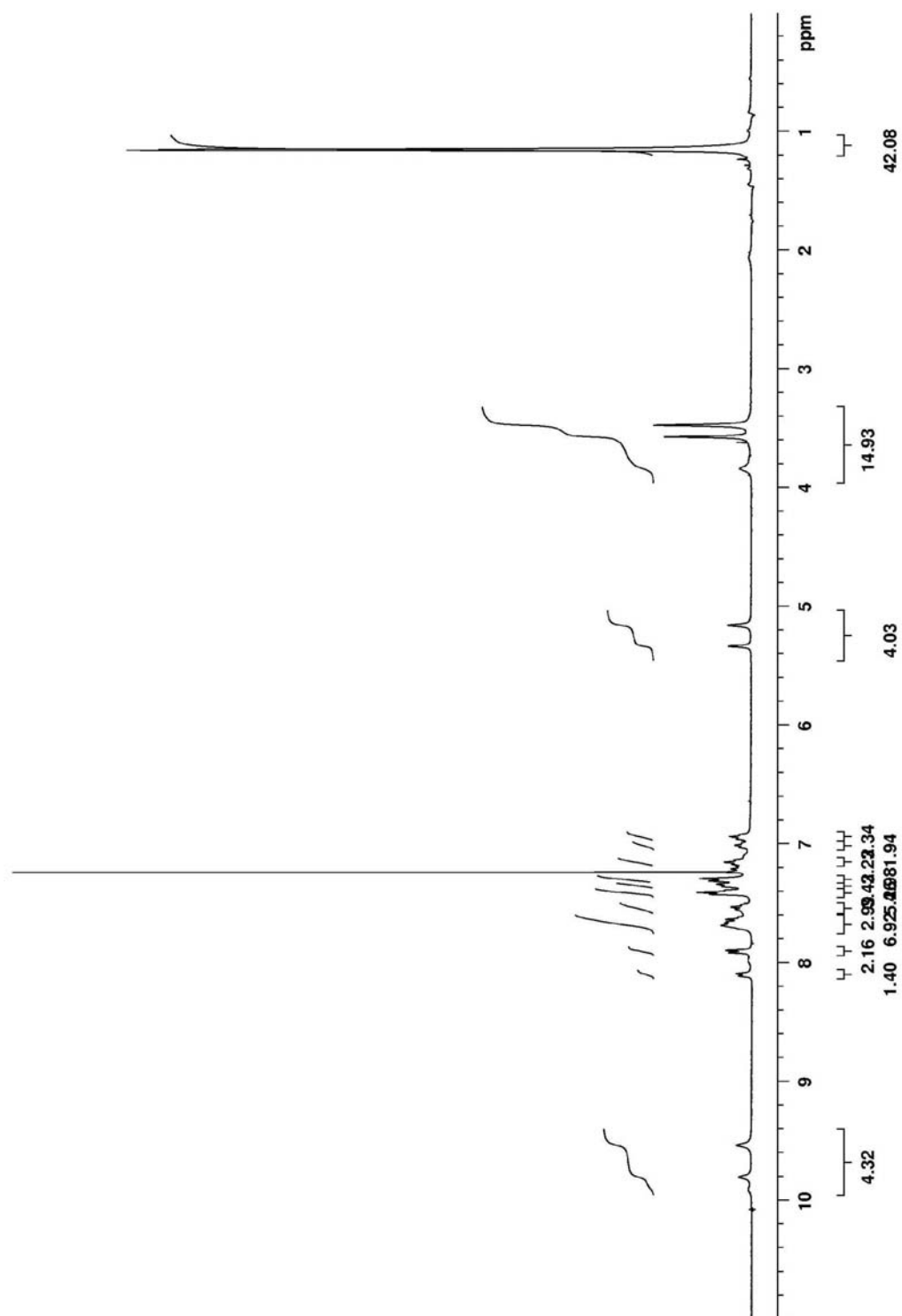
^1H NMR Spectrum of **3b**



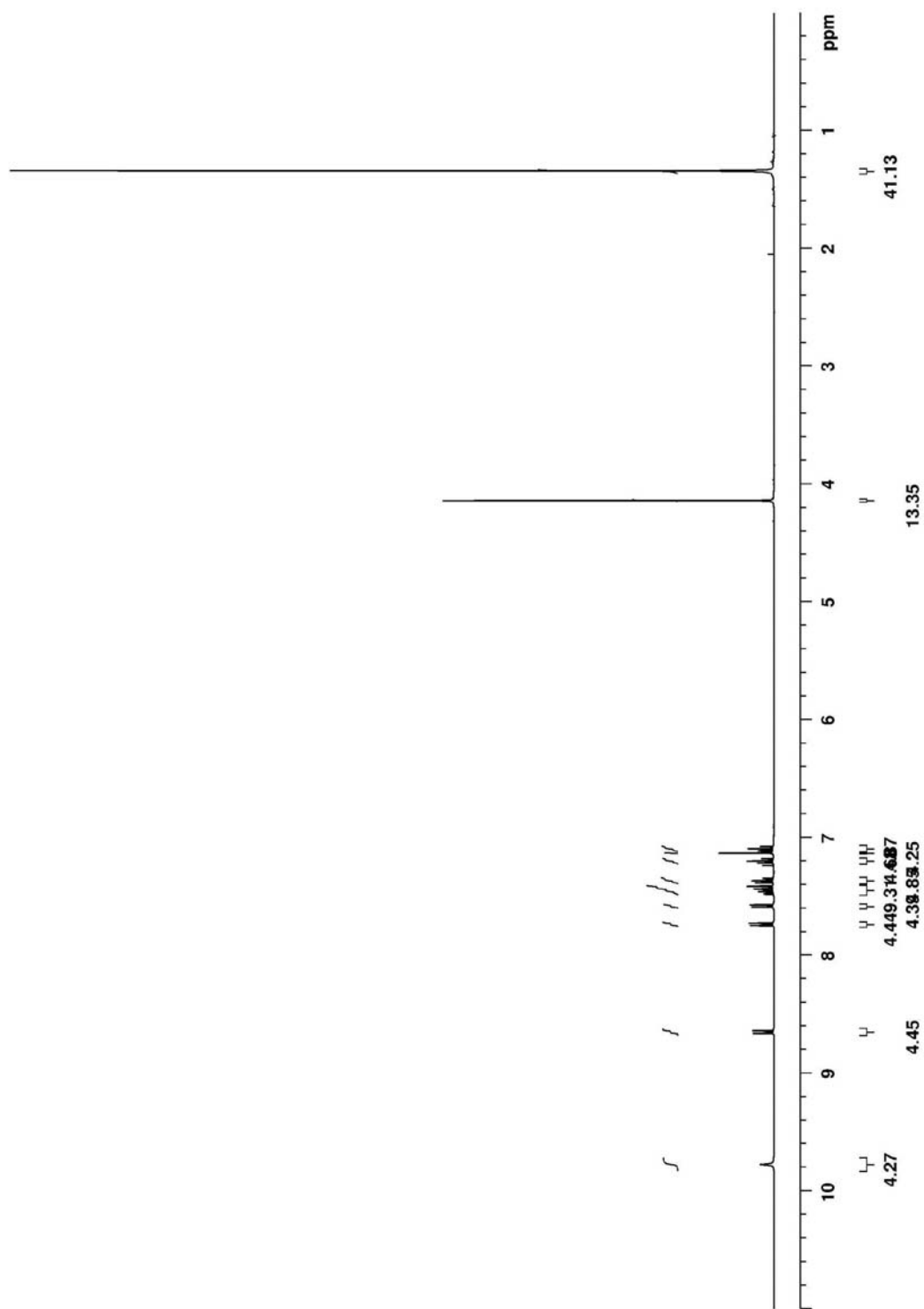
^{13}C NMR Spectrum of **3b**



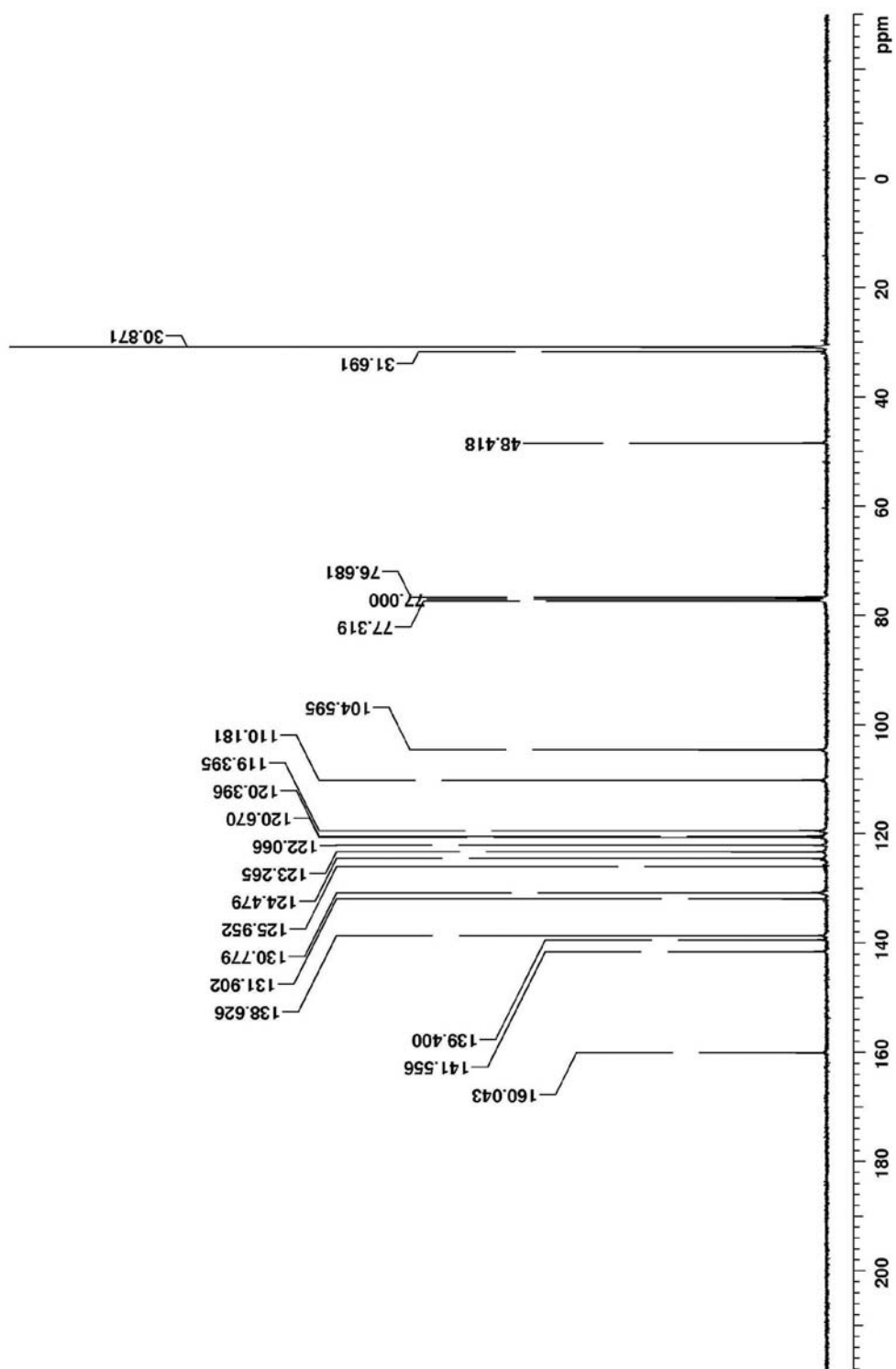
^1H NMR Spectrum of **4b**



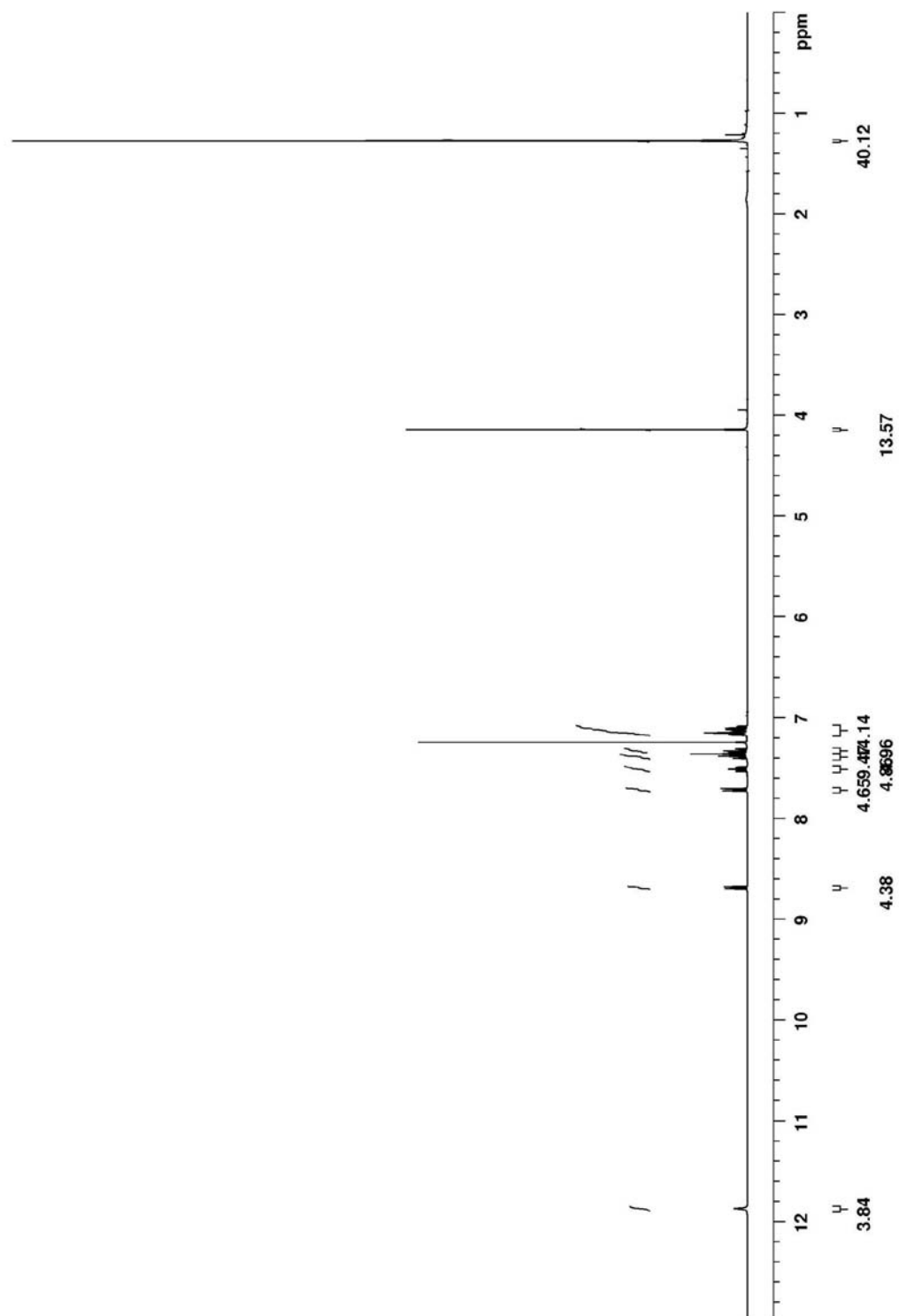
^1H NMR Spectrum of **5b**



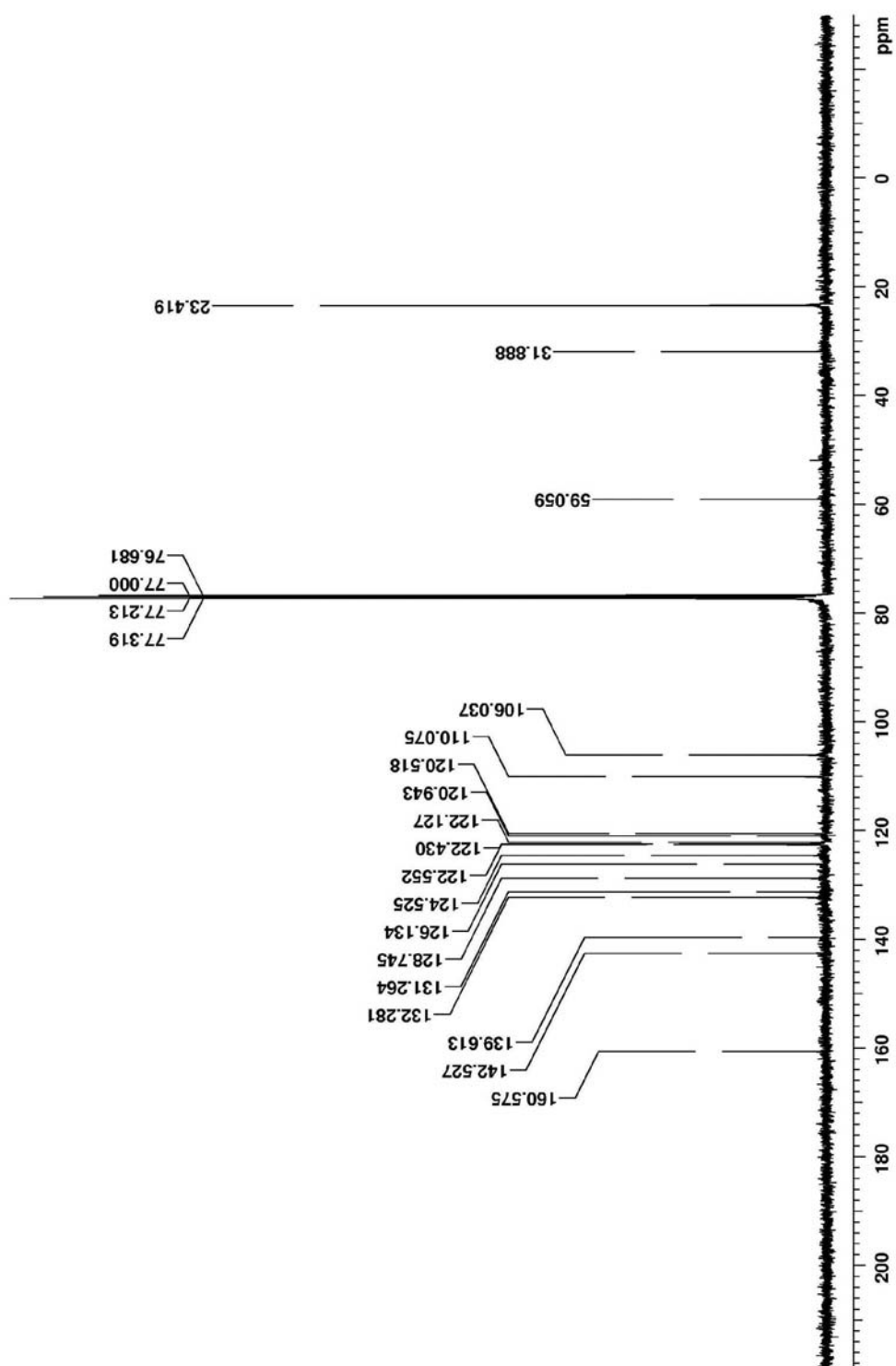
^{13}C NMR Spectrum of **5b**



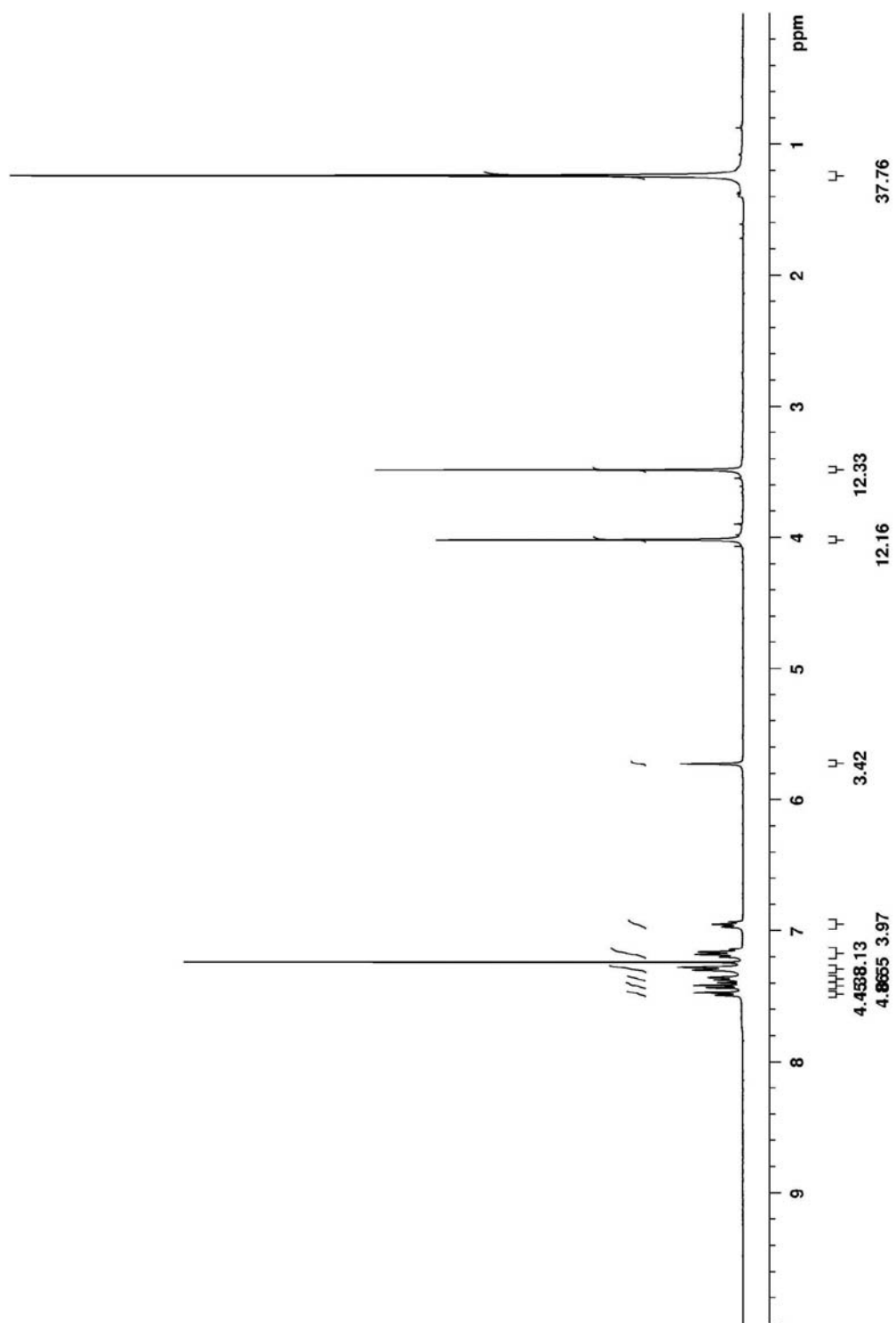
^1H NMR Spectrum of **6b**



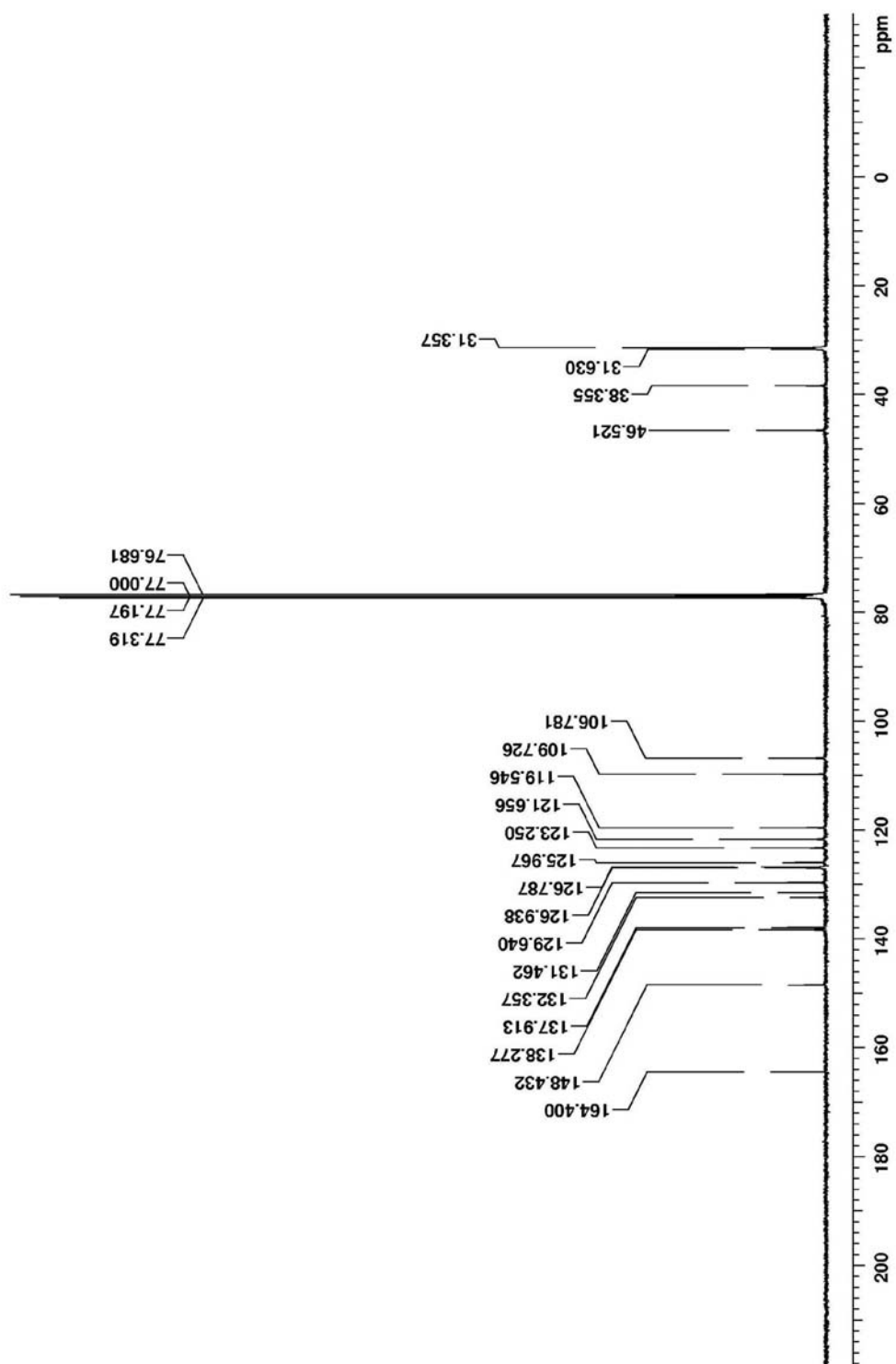
^{13}C NMR Spectrum of **6b**



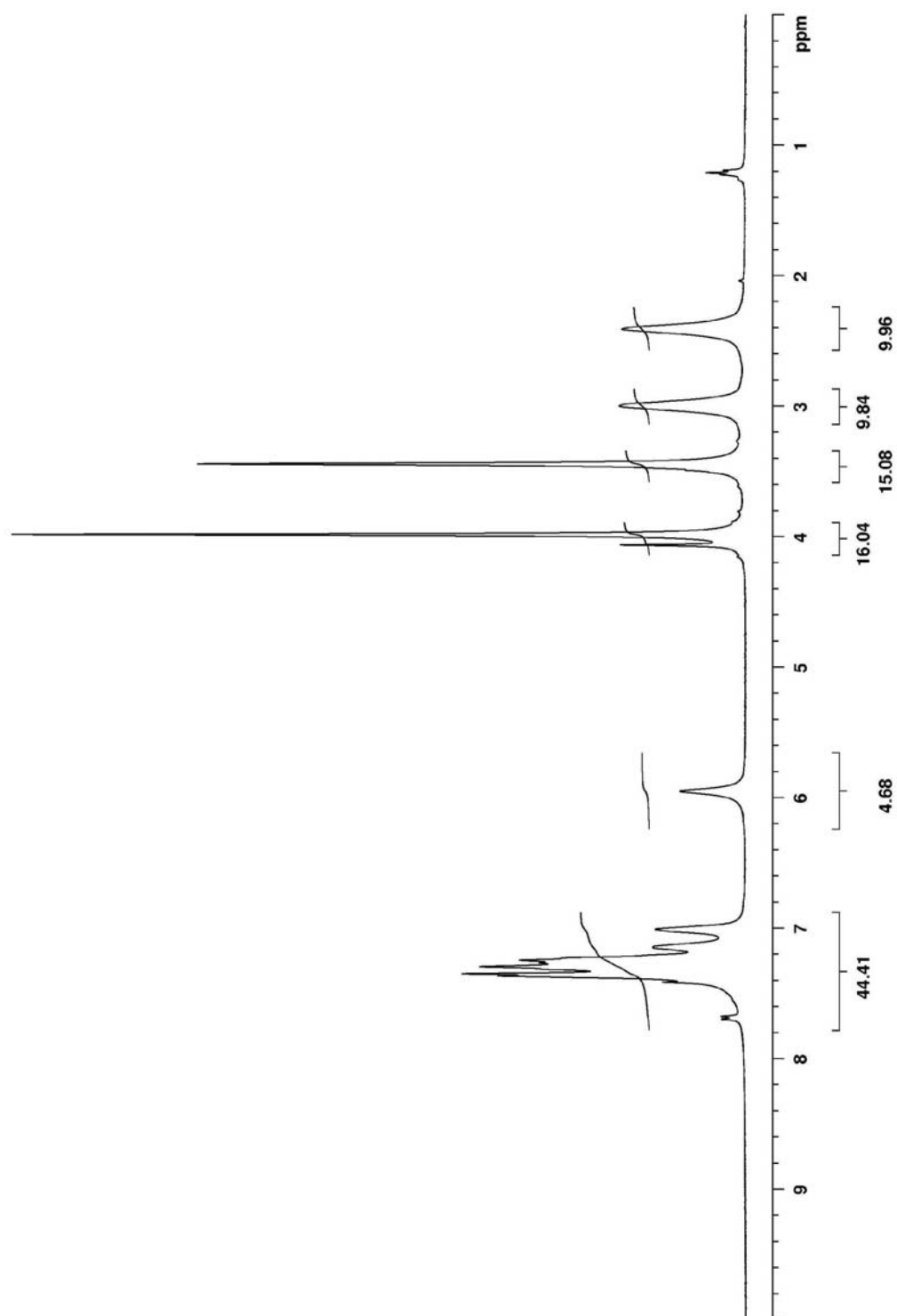
^1H NMR Spectrum of **7b**



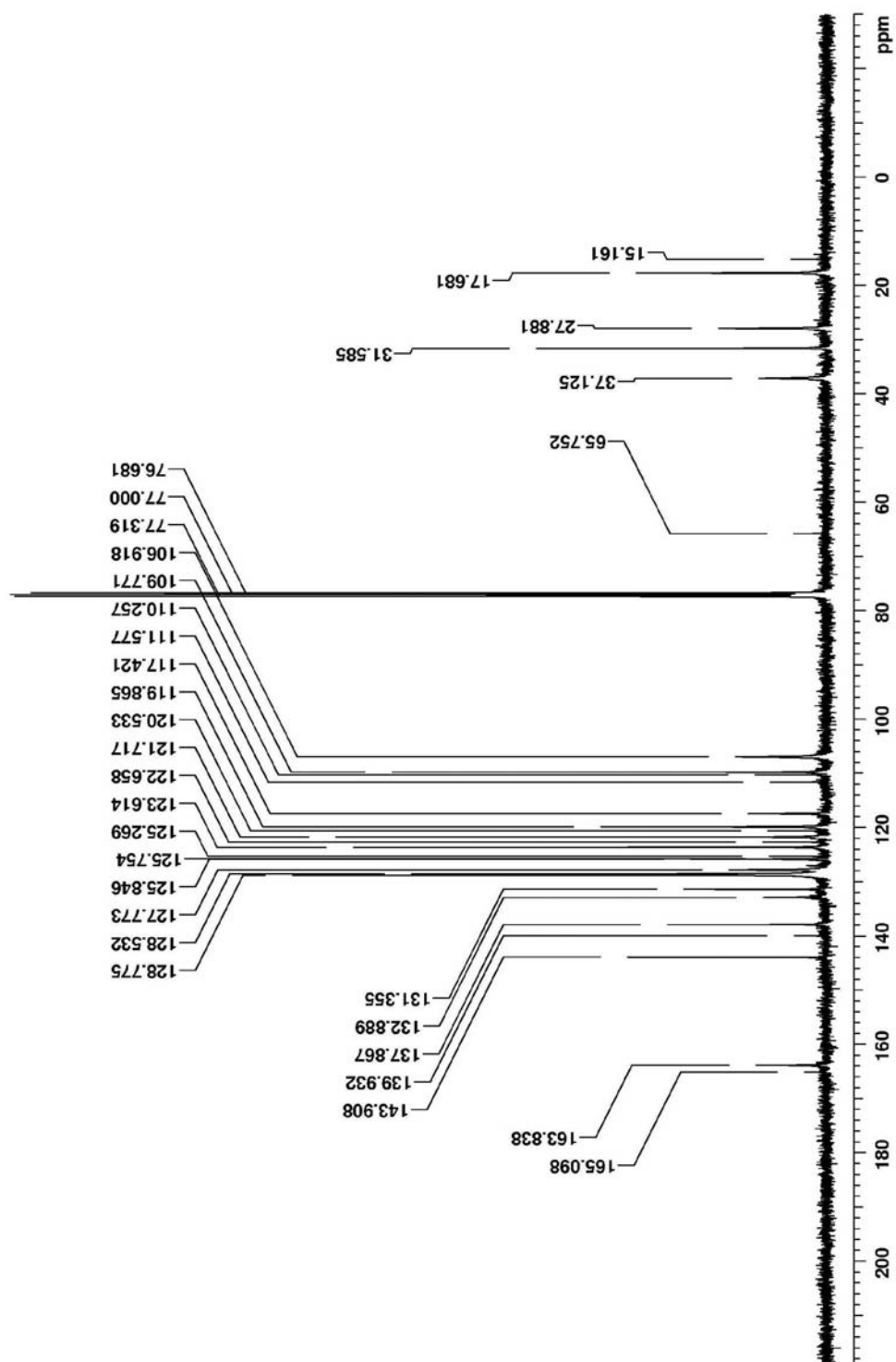
^{13}C NMR Spectrum of **7b**



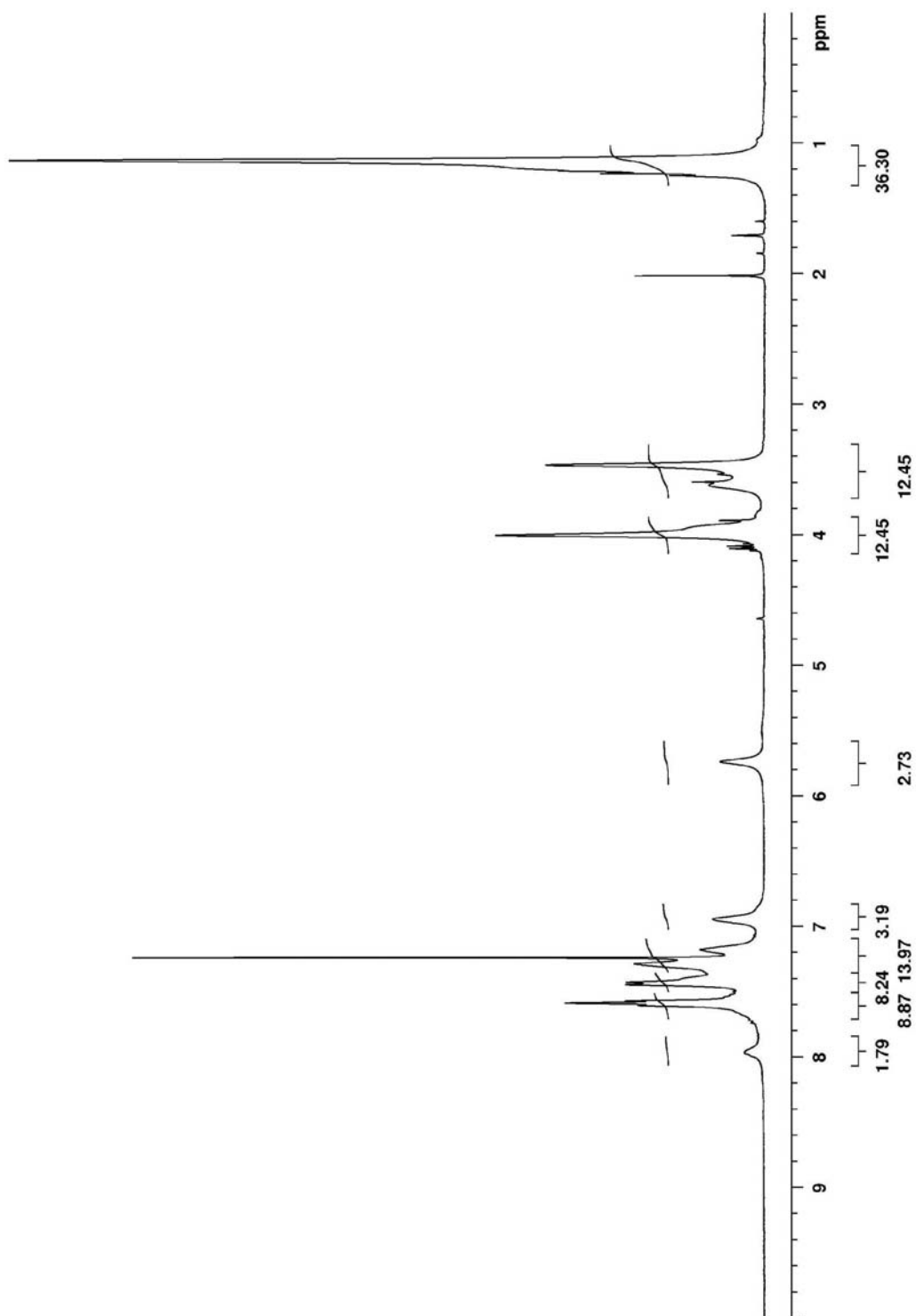
^1H NMR Spectrum of **7c**



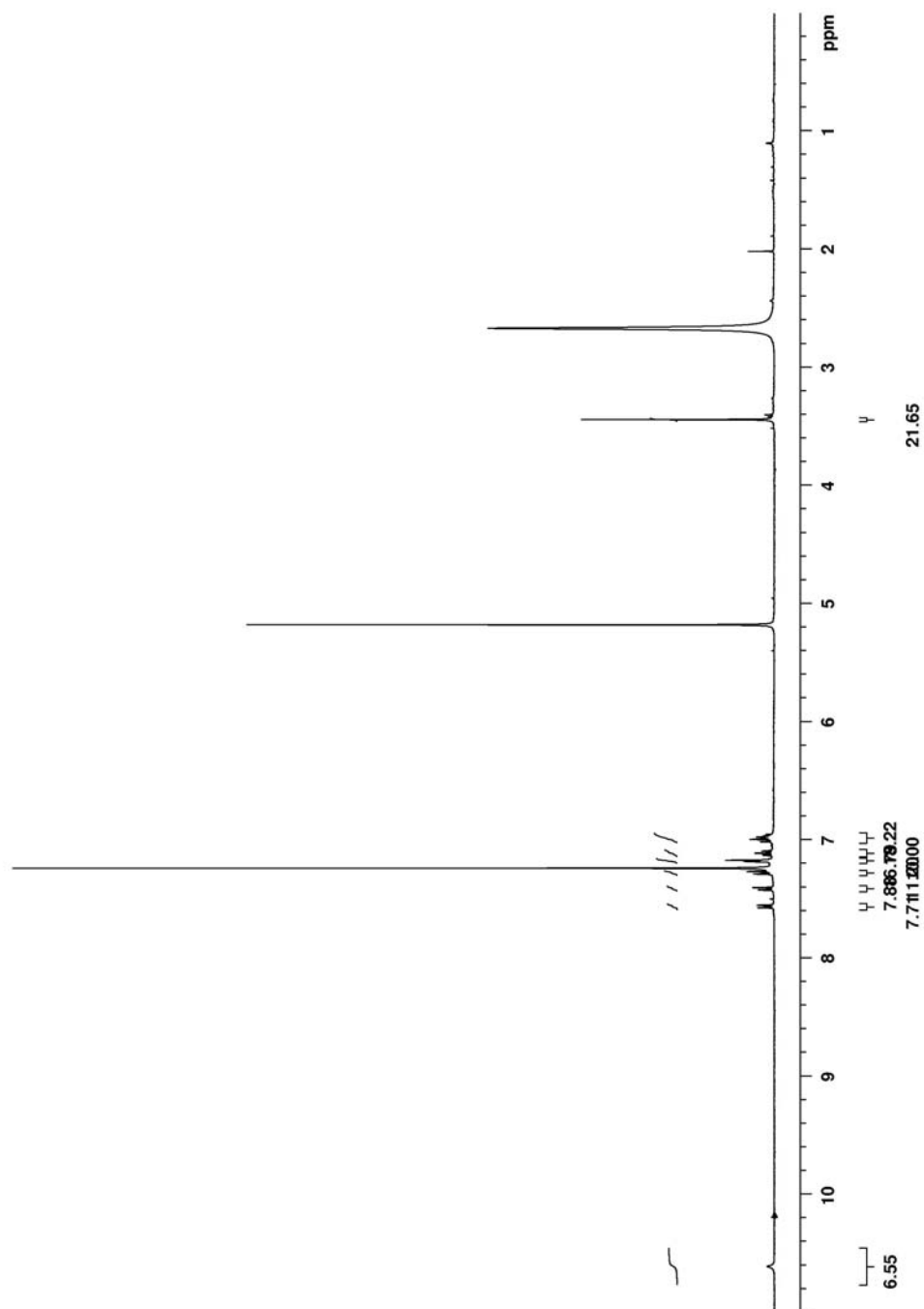
^{13}C NMR Spectrum of **7c**



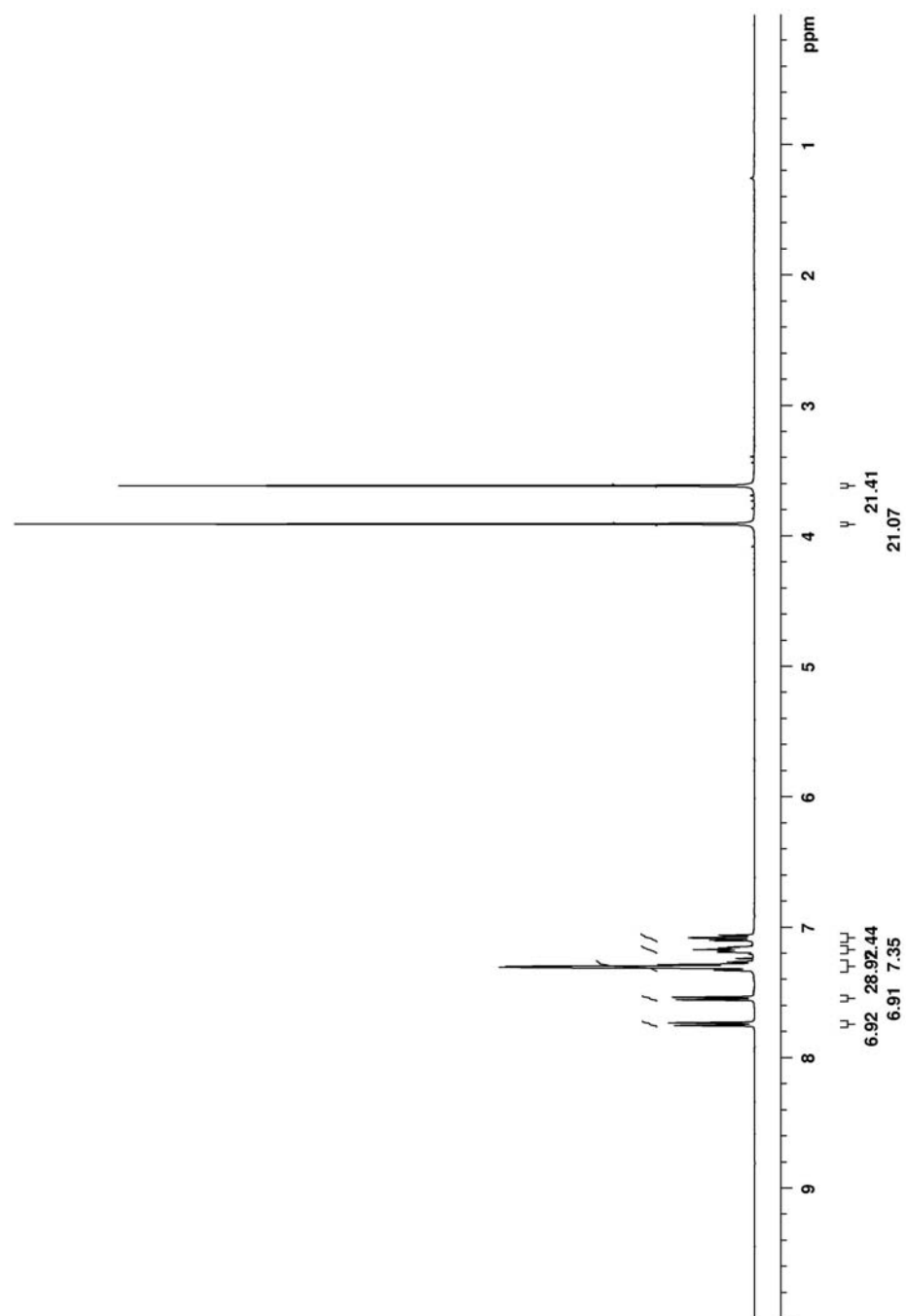
^1H NMR Spectrum of **8b**



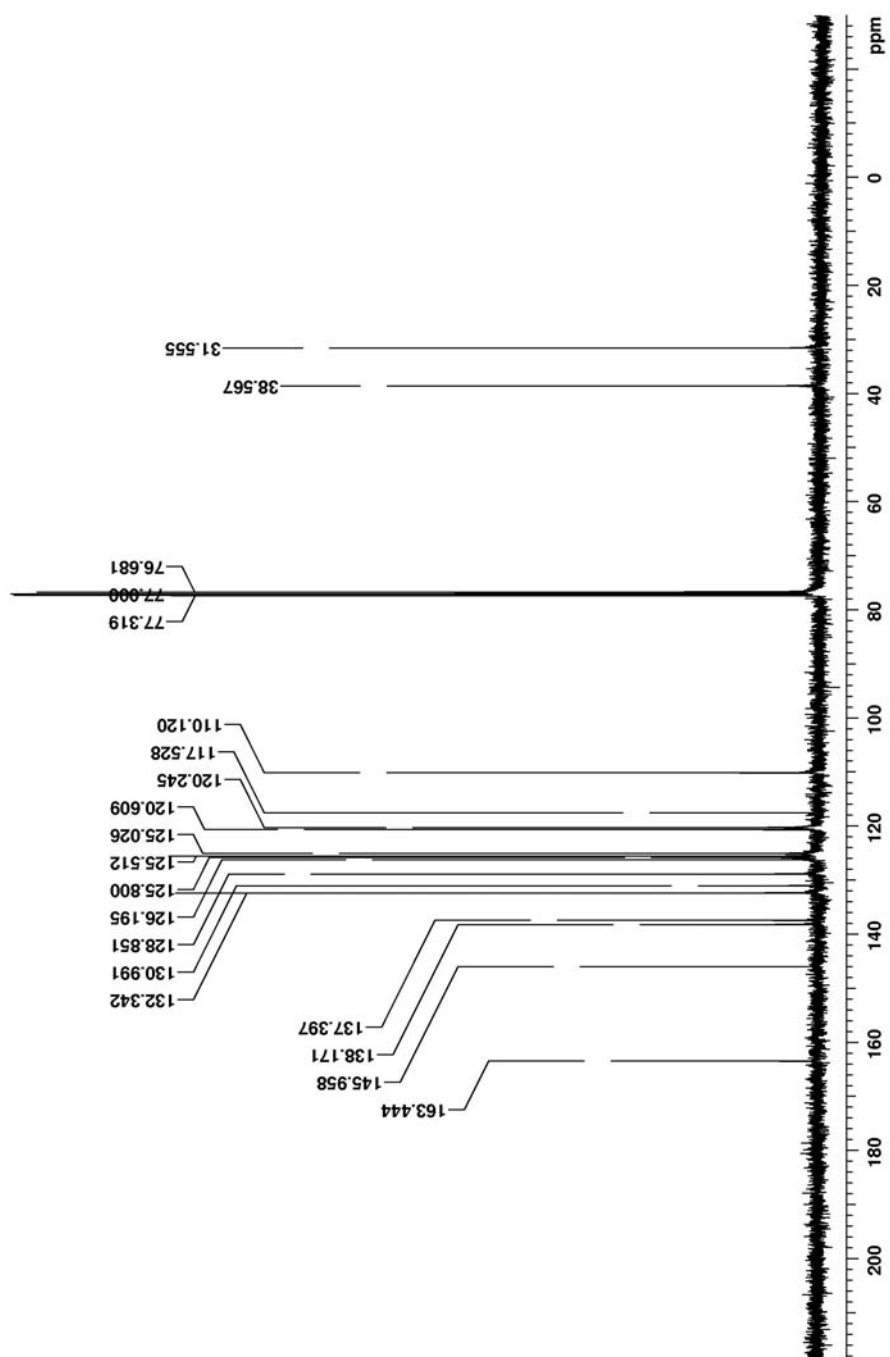
^1H NMR Spectrum of **9**



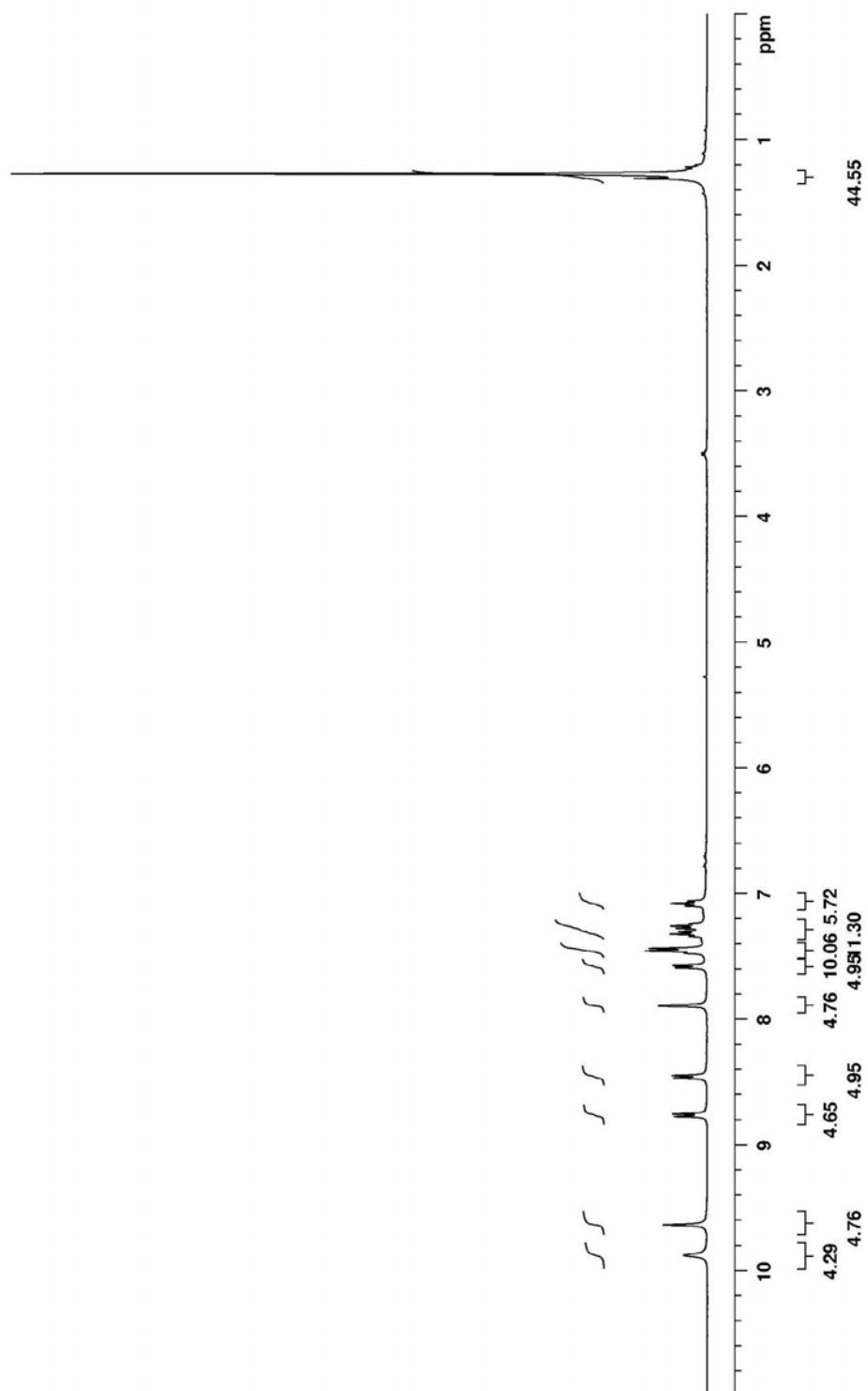
^1H NMR Spectrum of **10**



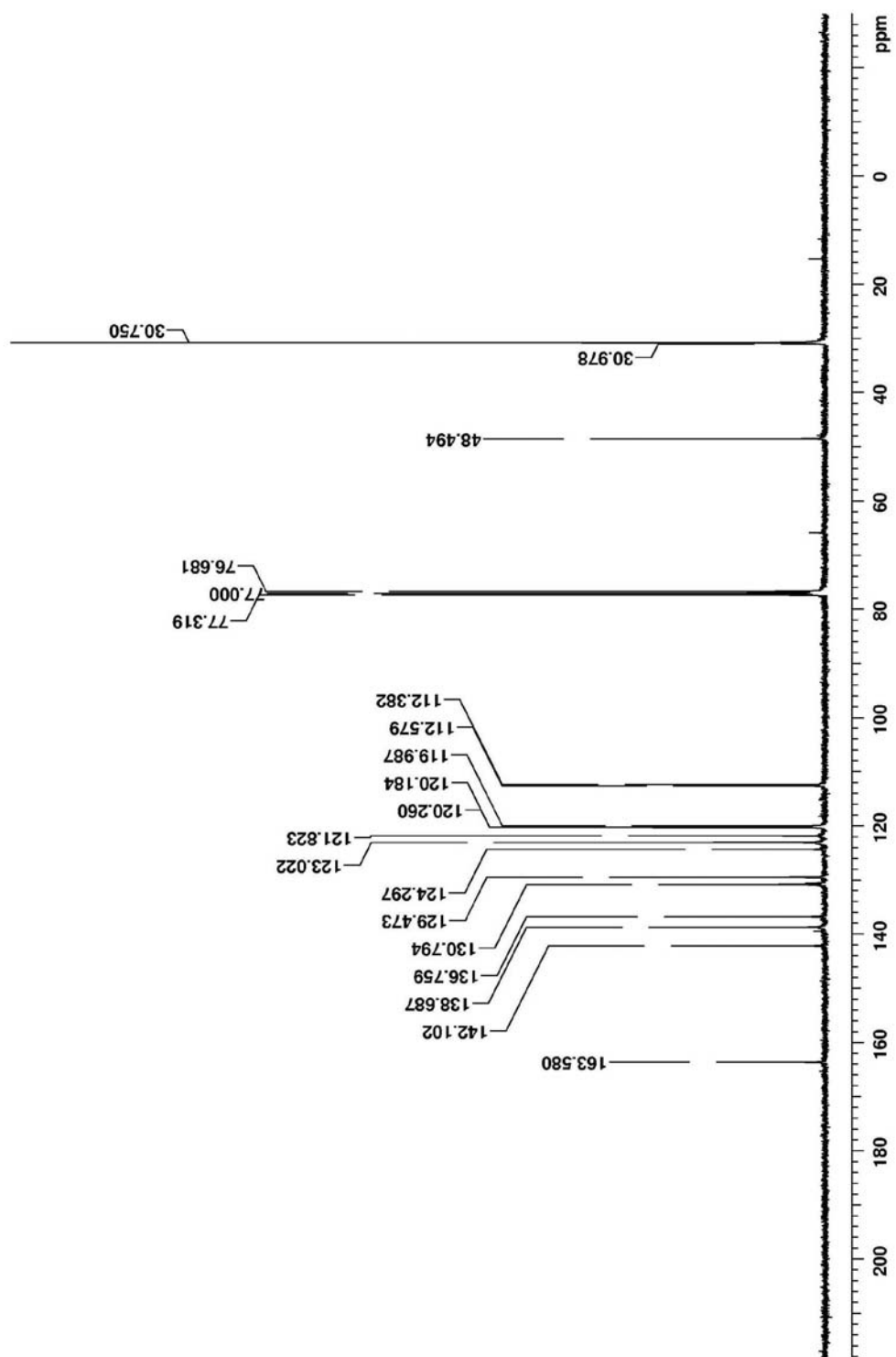
^{13}C NMR Spectrum of **10**



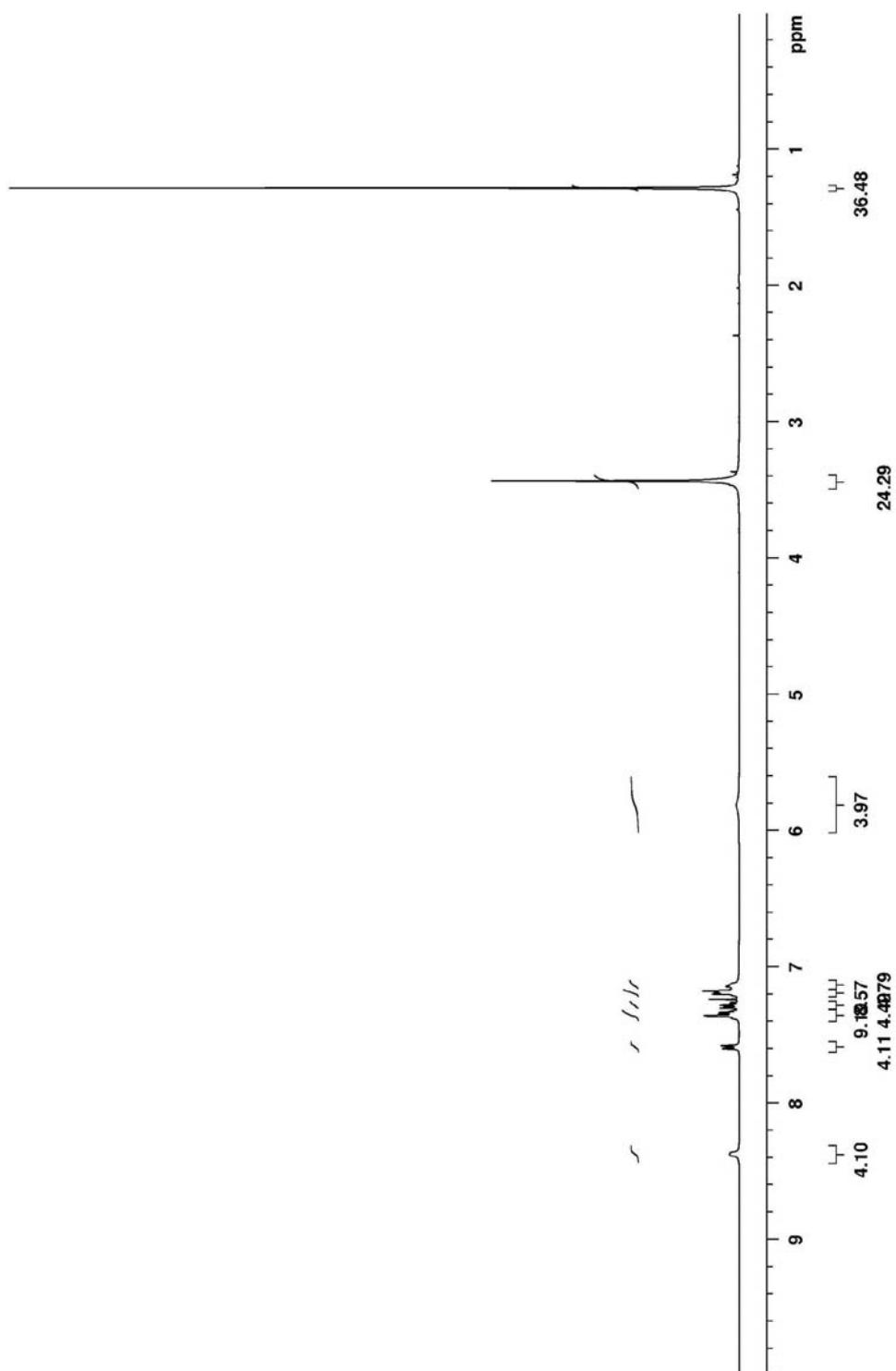
^1H NMR Spectrum of **14b**



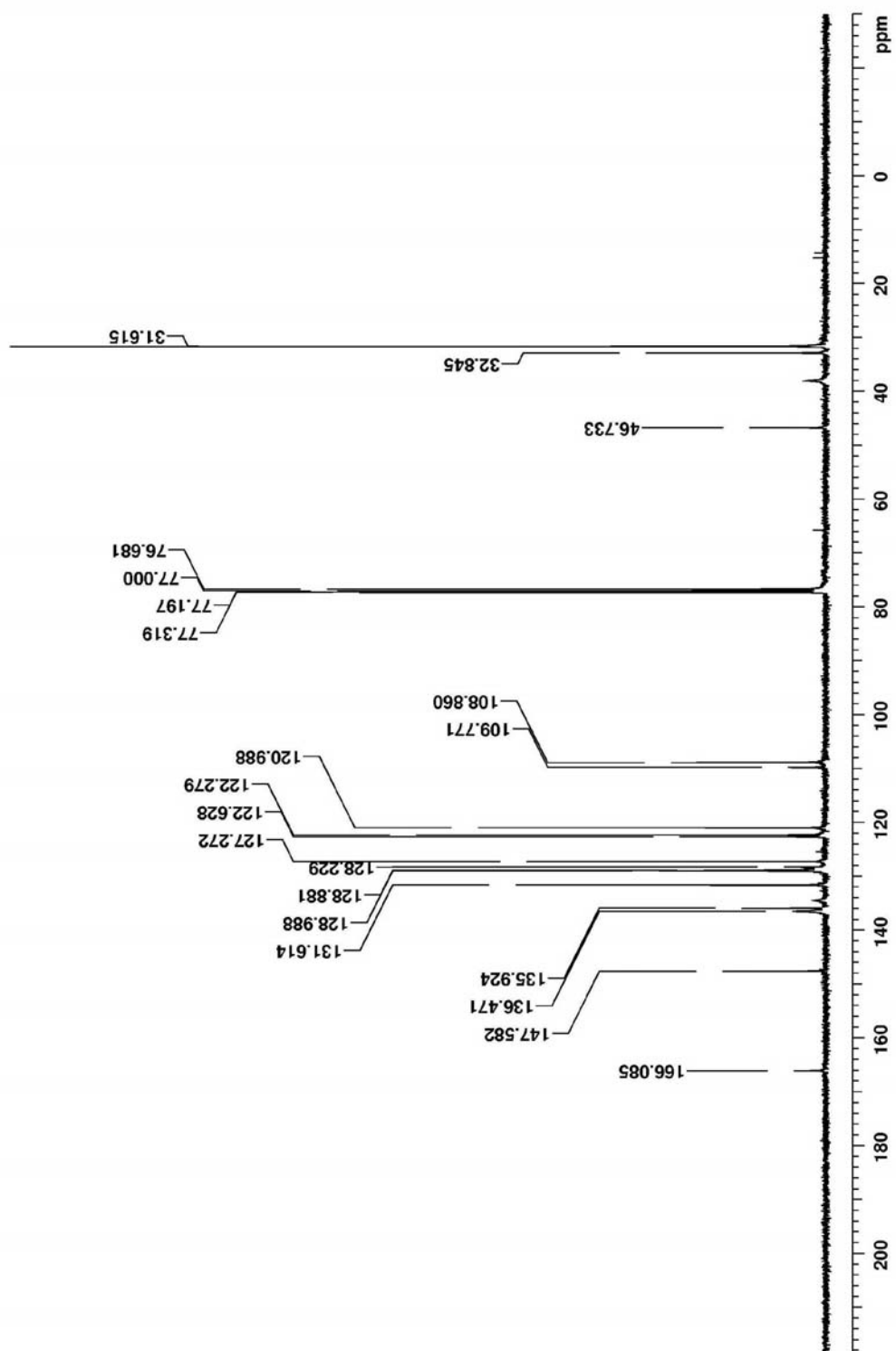
^{13}C NMR Spectrum of **14b**



^1H NMR Spectrum of **16b**



^{13}C NMR Spectrum of **16b**



Appendix 2

Simple Thiazocine-2-acetic Acid Derivatives via Ring Closing Metathesis

Dallas K. Bates,* Xiaofen Li and Parag V. Jog

Supplemental Information

(Compound numbers correspond to the numbers in the article:

Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem.* **2004**, 69, 2750)

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Experimental Section (Introduction and compounds 7-12 and 13-20)

All reagents were used without purification unless otherwise noted. Silica gel (70-230 mesh, 60 Å) was used for column chromatography. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded in chloroform solution. NMR spectra were recorded in CDCl₃ solution unless otherwise noted (¹H NMR at 400 MHz and ¹³C NMR at 100 MHz). Mass spectra were obtained under electron impact at 70 eV. Gen2 refers to Grubbs' second Generation catalyst [CAS registry number 246047-72-3, 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium].

Methyl γ -bromocrotonate was prepared according to the literature:³⁵ ¹H NMR δ 6.95 (m, 1H), 5.99 (dt, 1H, J = 15.6, 1.2 Hz), 3.97 (dd, 2H, J = 7.6, 1.2 Hz), 3.71 (s, 3H); ¹³C NMR δ 165.9, 141.9, 124.1, 51.8, 29.0. *N*-Allyl-4-methylbenzensulfonamide was prepared according to the literature: mp 62-63 °C (lit.³⁶ 63-65 °C); ¹H NMR δ 7.73 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 5.70 (m, 1H), 5.14 (dd, 1H, J = 17.2, 1.2 Hz), 5.08 (dd, 1H, J = 9.2, 1.2 Hz), 4.50 (br s, 1H), 3.56 (t, 2H, J = 6.0 Hz), 2.41 (s, 3H); ¹³C NMR δ 143.5, 137.0, 133.0, 129.7, 127.1, 117.7, 45.8, 21.5.

(2*E*)-4-[allyl[(4-methylphenyl)sulfonyl]amino]but-2-enoic acid (7). To an ice-cooled solution of LiOH·H₂O (1.5 eq, 0.95 g, 22.5 mmol) in H₂O (40 mL) and THF (40 mL) was added at 0 °C a solution of **1** (4.64 g, 15 mmol) in THF (40 mL). This mixture was stirred at 0 °C for 3 h under a nitrogen atmosphere, then extracted with EtOAc. The aqueous layer was acidified with 5% HCl solution followed by extraction with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to

give 4.22 g (95%) of **7** as a white solid, which was used directly for preparation of **8** or **14**. ^1H NMR δ 7.68 (d, 2H, J = 8.0 Hz), 7.30 (d, 2H, J = 8.0 Hz), 6.81 (dt, 1H, J = 15.6, 5.6 Hz), 5.85 (dt, 1H, J = 15.6, 1.6 Hz), 5.59 (m, 1H), 5.17-5.10 (m, 2H), 3.93 (dd, 2H, J = 5.6, 1.6 Hz), 3.79 (d, 2H, J = 6.4 Hz), 2.42 (s, 3H); ^{13}C NMR δ 174.6, 145.3, 143.8, 136.7, 132.2, 129.8, 127.2, 119.9, 117.6, 50.6, 47.3, 21.6.

***N*-allyl-*N*-[(2*E*)-4-(1*H*-indol-1-yl)-4-oxobut-2-enyl]-4-methylbenzenesulfonamide**

(8). Method 1: To an ice-cooled solution of **7** (0.71 g, 2.4 mmol) in THF (25 mL) was added dropwise oxalyl chloride (12.0 eq, 2.52 mL, 28.9 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 24 h and concentrated *in vacuo*. The residue was used directly for the following reaction. To a well-stirred mixture of indole (1.1 eq, 0.31 g, 2.7 mmol), powdered NaOH (1.5 eq, 0.14 g, 3.6 mmol) and tetrabutylammonium hydrogen sulfate (0.01 eq, 0.01 g) in CH_2Cl_2 (15 mL) was added dropwise a solution of above residue in CH_2Cl_2 (10 mL) in an ice-water bath. The resulting mixture was stirred at 0 °C for 15 min and at room temperature for 3 h, poured into ice-water, and extracted with CH_2Cl_2 . The combined organic layers were washed with distilled water, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 1:9) gave 0.24 g (25%) of **8** as a sticky liquid.

Method 2: To a solution of **14** (1.10 g, 2.78 mmol) in dioxane (50 mL) was added a solution of DDQ (6.0 eq, 3.78 g, 16.68 mmol) in dioxane (30 mL) at 55 °C through a syringe. The resulting mixture was then heated to 70 °C and stirred for 3 days. The mixture was vacuum filtered and the filtrate was concentrated *in vacuo*. The residue was then stirred in MeOH (60 mL) at room temperature for 1 h. After the evaporation of

MeOH, the residue was diluted with CH₂Cl₂ (100 mL), washed with 5% NaHCO₃ solution followed by distilled water and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.98 g (89%) of **8** as a sticky liquid: IR 1690 cm⁻¹; ¹H NMR δ 8.45 (d, 1H, *J* = 7.6 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.39 (d, 1H, *J* = 4.0 Hz), 7.36-7.25 (m, 4H), 6.98 (dt, 1H, *J* = 15.2, 5.2 Hz), 6.76 (dt, 1H, *J* = 15.2, 1.6 Hz), 6.64 (dd, 1H, *J* = 4.0, 0.8 Hz), 5.64 (m, 1H), 5.19-5.14 (m, 2H), 4.05 (dd, 2H, *J* = 5.2, 1.6 Hz), 3.85 (d, 2H, *J* = 6.4 Hz), 2.39 (s, 3H); ¹³C NMR δ 163.3, 144.1, 143.8, 136.7, 135.7, 132.3, 130.6, 130.0, 127.2, 125.1, 124.6, 123.9, 123.0, 120.9, 119.9, 116.7, 109.4, 50.9, 47.7, 21.5; MS [*m/z* (rel intensity)] 394 (M⁺, 27), 278 (8), 239 (13), 155 (69), 123 (6), 117 (60).

***N*-allyl-*N*-[2-(allylthio)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (**9**).** To an ice-cooled solution of allyl mercaptan (1.2 eq, 0.07 mL, 0.9 mmol) and Et₃N (1.2 eq, 0.125 mL, 0.9 mmol) in CH₂Cl₂ (10 mL) was added a solution of **8** (0.30 g, 0.75 mmol) in CH₂Cl₂ (6 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and at room temperature for 6 h, then diluted with CH₂Cl₂, washed with 5% HCl solution followed by distilled water. The organic layer was dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 1:4) gave 0.28 g (80%) of **9** as a sticky liquid: IR 1705 cm⁻¹; ¹H NMR δ 8.47 (d, 1H, *J* = 8.0 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.47 (d, 1H, *J* = 4.0 Hz), 7.36-7.26 (m, 4H), 6.64 (d, 1H, *J* = 3.6 Hz), 5.76 (m, 1H), 5.56 (m, 1H), 5.23-5.02 (m, 4H), 3.89-3.78 (m, 2H), 3.57-3.46 (m, 3H), 3.29-3.06 (m, 4H), 2.40 (s, 3H); ¹³C NMR δ 169.3, 143.7, 136.3, 135.7, 134.5, 132.5, 130.4, 129.8, 127.3,

125.0, 124.7, 123.7, 120.8, 120.0, 117.6, 116.7, 109.3, 52.0, 51.8, 39.1, 38.6, 35.5, 21.5;
MS [m/z (rel intensity)] 313 (65), 224 (72), 155 (89), 117 (68).

***N*-allyl-*N*-[2-(allylsulfinyl)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (10).** To an ice-cooled solution of **9** (1.5 g, 3.21 mmol) in CH₂Cl₂ (25 mL) was added slowly a solution of *m*-CPBA (1.0 eq) in CH₂Cl₂ (20 mL). The resulting mixture was stirred at 0 °C for 15 min and put in a freezer (-20 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution. After separating and saving the organic layer, the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:2) gave 1.12 g (72%) of **10** as a sticky liquid (as a mixture of two diastereomers in a 2:3 ratio): IR 1698 cm⁻¹, ¹H NMR δ 8.38 (d, 1H, *J* = 7.6 Hz), 7.69 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.47 (d, 1H, *J* = 3.6 Hz), 7.36-7.25 (m, 4H), 6.67 (d, 1H, *J* = 4.0 Hz), 5.97 (m, 1H), 5.59 (m, 1H), 5.48-5.43 (m, 2H), 5.22 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.16 (dd, 1H, *J* = 10.0, 1.2 Hz), 3.86 (d, 2H, *J* = 6.4 Hz), 3.79 (m, 1H), 3.69 (m, 1H), 3.64-3.59 (m, 2H), 3.57 (m, 1H), 3.48 (m, 1H), 3.43 (dd, 1H, *J* = 7.2, 2.0 Hz), 2.39 (s, 3H); ¹³C NMR δ 168.6, 144.0, 135.6, 132.4, 130.4, 130.0, 127.4, 127.2, 126.0, 125.3, 124.4, 124.0, 123.9, 121.1, 120.5, 116.5, 110.2, 54.2, 52.5, 51.0, 44.7, 34.1, 21.5.

***N*-allyl-*N*-[2-(allylsulfonyl)-4-(1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (11).** To an ice-cooled solution of **9** (0.28 g, 0.60 mmol) in CH₂Cl₂ (8 mL) was added a solution of *m*-CPBA (2.0 eq) in CH₂Cl₂ (6 mL). The

resulting mixture was stirred at room temperature for 12 h and poured into 5% NaHCO₃ solution. After separating and saving the organic layer, the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:7) gave 0.17 g (57%) of **11** as a sticky liquid: IR 1703 cm⁻¹; ¹H NMR δ 8.42 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 7.6 Hz), 7.48 (d, 1H, *J* = 4.0 Hz), 7.35-7.33 (m, 1H), 7.30-7.26 (m, 3H), 6.67 (dd, 1H, *J* = 4.0, 0.4 Hz), 5.93 (m, 1H), 5.59-5.48 (m, 3H), 5.23 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.16 (dd, 1H, *J* = 10.0, 1.2 Hz), 4.37 (m, 1H), 3.99-3.78 (m, 4H), 3.70-3.59 (m, 2H), 3.53-3.46 (m, 2H), 2.39 (s, 3H); ¹³C NMR δ 168.0, 144.2, 135.6, 135.2, 131.8, 130.5, 130.0, 127.5, 125.7, 125.3, 124.4, 124.1, 124.0, 121.1, 121.0, 116.5, 110.2, 58.8, 54.9, 52.4, 46.2, 32.6, 21.5.

1-[[4-[4-(methylphenyl)sulfonyl]-1-oxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]-1*H*-indole (12). To a solution of **10** (0.79 g, 1.63 mmol, 1:1 ratio) in CH₂Cl₂ (10 mL) was added a solution of Gen 2 catalyst (10% mol, 0.14 g) in CH₂Cl₂ (8 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 2.5 h, cooled to room temperature and concentrated *in vacuo*, Column chromatography of the residue on silica gel (EtOAc) gave 0.36 g (48%) of **12** as a white solid (a mixture of two diastereomers in a 2:3 ratio): mp 149-51 °C.

minor diastereomer: ¹H NMR δ 8.39 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 2H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 7.6 Hz), 7.41 (d, 1H, *J* = 4.0 Hz), 7.35-7.25 (m, 4H), 6.64 (d, 1H, *J* = 4.0 Hz), 5.90 (m, 1H), 5.64 (m, 1H), 4.42 (m, 1H), 4.17-3.79 (m, 5H), 3.47 (dd, 1H, *J* = 17.2, 6.0 Hz), 3.09-3.03 (m, 2H), 2.36 (s, 3H).

major diastereomer: IR 1702 cm⁻¹; ¹H NMR δ 8.32 (d, 1H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 7.2 Hz), 7.47 (d, 1H, *J* = 4.0 Hz), 7.34-7.26 (m, 4H), 6.66 (d, 1H, *J* = 4.0 Hz), 5.95 (dt, 1H, *J* = 11.6, 3.2 Hz), 5.84 (m, 1H), 4.44 (m, 1H), 4.30 (d, 1H, *J* = 18.4 Hz), 3.99 (dd, 1H, *J* = 14.0, 8.8 Hz), 3.91 (m, 1H), 3.83 (dd, 1H, *J* = 17.2, 2.4 Hz), 3.74-3.64 (m, 2H), 3.26 (dd, 1H, *J* = 14.0, 2.4 Hz), 3.16 (dd, 1H, *J* = 17.2, 10.0 Hz), 2.39 (s, 3H); ¹³C NMR δ 168.0, 167.5, 144.2, 144.1, 135.6, 135.5, 134.0, 133.7, 132.7, 130.4, 130.1, 130.0, 127.4, 127.1, 125.4, 125.3, 124.3, 124.1, 124.0, 121.1, 118.8, 116.4, 116.3, 110.3, 110.2, 55.4, 51.2, 49.9, 49.2, 48.8, 48.1, 46.2, 44.6, 34.7, 33.6, 21.46. Anal. Calcd for C₂₃H₂₄O₅N₂S₂: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.18; H, 5.43; N, 6.00 (on diastereomer mixture).

***N*-Allyl-*N*-[(2*E*)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobut-2-enyl]-4-methylbenzenesulfonamide (14).** To an ice-cooled solution of **7** (0.68 g, 2.3 mmol) in THF (25 mL) was added dropwise oxalyl chloride (12.0 eq, 2.41 mL, 27.66 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 24 h then concentrated *in vacuo* and the residue was used directly in the following reaction. To an ice-cooled solution of indoline (1.2 eq, 0.33 g, 2.8 mmol), pyridine (10.0 eq, 1.88 mL, 23.1 mmol) and DMAP (0.05 g) in CH₂Cl₂ (15 mL) was added slowly a solution of the above residue in CH₂Cl₂ (15 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and at room temperature overnight. The solution was poured into 5% aqueous HCl and extracted with CH₂Cl₂. The combined organic layers were washed with 5% HCl solution followed by distilled water, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 2:3) gave 0.59 g (64%) of **14** as a

white solid: mp 123-5 °C; IR 1666 cm⁻¹; ¹H NMR δ 8.22 (d, 1H, *J* = 7.2 Hz), 7.69 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.17 (t, 2H, *J* = 7.6 Hz), 7.00 (t, 1H, *J* = 7.6 Hz), 6.77 (dt, 1H, *J* = 14.8, 5.2 Hz), 6.37 (d, 1H, *J* = 14.8 Hz), 5.61 (m, 1H), 5.15-5.11 (m, 2H), 4.10-4.05 (m, 2H), 3.98 (d, 2H, *J* = 4.8 Hz), 3.81 (d, 2H, *J* = 6.4 Hz), 3.16 (t, 2H, *J* = 7.6 Hz), 2.39 (s, 3H); ¹³C NMR δ 163.2, 143.6, 142.7, 140.2, 136.9, 132.3, 131.5, 129.8, 127.5, 127.1, 124.5, 123.9, 119.6, 117.4, 50.4, 48.0, 47.6, 27.9, 21.4; MS [*m/z* (rel intensity)] 396 (M⁺, 10), 241 (4), 155 (29), 119 (83). Anal. Calcd for C₂₂H₂₄O₃N₂S: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.56; H, 6.16; N, 7.07.

***N*-allyl-*N*-[2-(allylthio)-4-(2,3-dihydro-1*H*-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (**15**).** To an ice-cooled solution of allyl mercaptan (3.0 eq, 0.36 mL, 4.5 mmol) and sodium methoxide (1.12 eq, 0.09 g, 1.7 mmol) in MeOH (15 mL) and THF (5 mL) was added a solution of **14** (0.59 g, 1.5 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. The solution was then poured into ice water and extracted with CH₂Cl₂. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:7) gave 0.67 g (95%) of **15** as a sticky liquid: IR 1659 cm⁻¹; ¹H NMR δ 8.22 (d, 1H, *J* = 8.8 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.27 (d, 2H, *J* = 8.4 Hz), 7.16 (t, 2H, *J* = 7.2 Hz), 6.98 (t, 1H, *J* = 7.2 Hz), 5.78 (m, 1H), 5.49 (m, 1H), 5.19-5.04 (m, 4H), 4.11-4.05 (m, 2H), 3.84 (d, 2H, *J* = 6.4 Hz), 3.55-3.42 (m, 2H), 3.28-3.13 (m, 5H), 3.00 (dd, 1H, *J* = 16.8, 4.4 Hz), 2.65 (dd, 1H, *J* = 16.8, 7.6 Hz), 2.39 (s, 3H); ¹³C NMR δ 168.7, 143.4, 143.0, 136.7, 134.6, 132.3, 131.3, 129.7, 127.4,

127.2, 124.5, 123.6, 119.8, 117.4, 117.0, 51.5, 51.4, 48.1, 39.0, 38.7, 35.4, 27.9, 21.5; MS [m/z (rel intensity)] 315 (25), 224 (21), 155 (52), 119 (65).

1-[[4-[4-(methylphenyl)sulfonyl]-1,1-dioxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetyl]-1H-indole (16). To a solution of **11** (0.07 g, 0.14 mmol) in CH₂Cl₂ (4 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.006 g) in CH₂Cl₂ (3 mL) under a nitrogen atmosphere. The mixture was refluxed until TLC showed the reaction to be complete, cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc/hexane, 3:2) gave 0.06 g (91%) of **16** as a white solid: mp 237-9 °C; IR 1711 cm⁻¹; ¹H NMR δ 8.32 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.55 (d, 1H, *J* = 7.2 Hz), 7.45 (d, 1H, *J* = 4.0 Hz), 7.34-7.25 (m, 4H), 6.67 (d, 1H, *J* = 4.0 Hz), 5.88 (d, 1H, *J* = 12.4 Hz), 5.79 (m, 1H), 4.80 (m, 1H), 4.42-4.35 (m, 2H), 4.02-3.92 (m, 2H), 3.79-3.73 (m, 2H), 3.22 (dd, 1H, *J* = 13.2, 3.2 Hz), 3.03 (dd, 1H, *J* = 17.6, 10.8 Hz), 2.39 (s, 3H); ¹³C NMR δ 167.1, 144.4, 135.5, 133.8, 130.4, 130.2, 127.3, 125.4, 124.3, 124.1, 121.2, 117.7, 116.3, 110.6, 60.4, 53.1, 49.8, 49.1, 30.2, 21.5. Anal. Calcd for C₂₃H₂₄O₅N₂S₂: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.18; H, 5.28; N, 5.76.

N-allyl-N-[2-(allylsulfinyl)-4-(2,3-dihydro-1H-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (17). To an ice-cooled solution of **15** (0.85 g, 1.81 mmol) in CH₂Cl₂ (20 mL) was added slowly a solution of *m*-CPBA (1.0 eq) in CH₂Cl₂ (10 mL). The resulting mixture was stirred at 0 °C for 15 min and put in a freezer (-20 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution. After

separating and saving the organic layer, the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc) gave 0.87 g (99%) of **17** as a sticky liquid (a mixture of two diastereomers present in a ratio of 2:3).

minor diastereomer: IR 1656 cm⁻¹; ¹H NMR δ 8.14 (d, 1H, *J* = 7.6 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.18-7.15 (m, 2H), 7.00 (m, 1H), 5.95 (m, 1H), 5.53 (m, 1H), 5.44-5.40 (m, 2H), 5.21 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.14 (dd, 1H, *J* = 10.0, 0.8 Hz), 4.12-4.06 (m, 2H), 3.84 (d, 2H, *J* = 6.8 Hz), 3.70-3.54 (m, 4H), 3.38 (dd, 1H, *J* = 13.2, 3.6 Hz), 3.20 (t, 2H, *J* = 8.4 Hz), 3.12 (dd, 1H, *J* = 17.6, 4.4 Hz), 2.91 (dd, 1H, *J* = 17.6, 8.0 Hz), 2.39 (s, 3H); ¹³C NMR δ 167.8, 143.8, 142.6, 135.9, 132.3, 131.2, 129.9, 127.4, 127.3, 126.3, 124.7, 124.0, 123.6, 120.3, 116.9, 54.3, 52.1, 51.3, 48.0, 44.7, 34.2, 27.9, 21.5.

major diastereomer: IR 1656 cm⁻¹; ¹H NMR δ 8.17 (d, 1H, *J* = 8.8 Hz), 7.68 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.17 (m, 2H), 7.01 (td, 1H, *J* = 7.2, 1.6 Hz), 5.87 (m, 1H), 5.53-5.39 (m, 3H), 5.22-5.11 (m, 2H), 4.17-4.06 (m, 2H), 3.87-3.84 (m, 3H), 3.59 (dd, 1H, *J* = 14.4, 9.2 Hz), 3.54 (dd, 1H, *J* = 13.6, 8.0 Hz), 3.40 (dd, 1H, *J* = 12.8, 7.2 Hz), 3.30 (dd, 1H, *J* = 14.4, 6.4 Hz), 3.22-3.13 (m, 3H), 2.68 (dd, 1H, *J* = 18.0, 4.8 Hz), 2.39 (s, 3H); ¹³C NMR δ 168.1, 143.8, 142.8, 135.9, 132.4, 132.0, 131.3, 129.9, 127.3, 127.2, 126.0, 124.7, 123.9, 120.4, 116.9, 54.9, 52.1, 51.7, 48.0, 29.0, 28.0, 21.5; MS [*m/z* (rel intensity)] 396 (9), 241 (9), 155 (35), 119 (100) for diastereomer mixture.

1-[[4-[4-(methylphenyl)sulfonyl]-1-oxido-3,4,5,8-tetrahydro-2H-1,4-thiazocin-2-yl]acetyl]indoline (18). To a solution of **17** (0.58 g, 1.193 mmol) in CH₂Cl₂ (12 mL) was added a solution of commercial Gen 2 catalyst (10% mol, 0.10 g) in CH₂Cl₂ (10 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 21 h, cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc) gave 0.22 g (40%) of **18** as a mixture of two diastereomers in a 3:4 ratio).

minor diastereomer: ¹H NMR δ 8.14 (d, 1H, *J* = 7.6 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 7.19-7.15 (m, 2H), 7.02 (m, 1H), 5.89 (dt, 1H, *J* = 11.6, 3.2 Hz), 5.64 (m, 1H), 4.47 (m, 1H), 4.21-3.71 (m, 7H), 3.19 (t, 2H, *J* = 8.4 Hz), 3.04-2.95 (m, 2H), 2.57 (dd, 1H, *J* = 17.2, 4.0 Hz), 2.39 (s, 3H); ¹³C NMR δ 166.7, 144.0, 142.5, 134.2, 134.0, 131.2, 130.0, 127.5, 127.4, 124.7, 124.2, 118.9, 116.9, 49.1, 48.0, 46.6, 44.6, 37.5, 34.9, 28.0, 21.5.

major diastereomer: IR 1655 cm⁻¹; ¹H NMR δ 8.06 (d, 1H, *J* = 8.0 Hz), 7.59 (d, 2H, *J* = 8.8 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 7.17-7.11 (m, 2H), 7.00 (m, 1H), 5.88 (dt, 1H, *J* = 11.6, 4.0 Hz), 5.80 (m, 1H), 4.39 (m, 1H), 4.28-3.61 (m, 7H), 3.30 (td, 2H, *J* = 14.0, 2.8 Hz), 3.18 (t, 2H, *J* = 8.4 Hz), 2.66 (dd, 1H, *J* = 16.8, 10.0 Hz), 2.38 (s, 3H); ¹³C NMR δ 167.3, 144.1, 142.4, 134.2, 134.0, 132.7, 130.0, 127.4, 127.1, 124.7, 124.1, 118.5, 116.7, 55.6, 49.8, 48.6, 48.3, 48.0, 33.5, 28.0, 21.5; MS [*m/z* (rel intensity)] 155 (26), 119 (88) for diastereomer mixture.

N-allyl-N-[2-(allylsulfonyl)-4-(2,3-dihydro-1H-indol-1-yl)-4-oxobutyl]-4-methylbenzenesulfonamide (19). To an ice-cooled solution of **15** (0.62 g, 1.32 mmol) in CH₂Cl₂ (20 mL) was added a solution of *m*-CPBA (2.0 eq) in CH₂Cl₂ (10 mL). The

resulting mixture was stirred at room temperature for 16 h, poured into 5% NaHCO₃ solution. After separating and saving the organic layer, the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with distilled water, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Column chromatography on silica gel (EtOAc/hexane, 3:7) gave 0.62 g (94%) of **19** as a sticky liquid: IR 1658 cm⁻¹; ¹H NMR δ 8.17 (d, 1H, *J* = 8.0 Hz), 7.68 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), 7.19-7.16 (m, 2H), 7.01 (td, 1H, *J* = 7.6, 0.8 Hz), 5.91 (m, 1H), 5.56-5.43 (m, 3H), 5.21 (dd, 1H, *J* = 17.2, 1.2 Hz), 5.14 (dd, 1H, *J* = 10.0, 1.2 Hz), 4.28 (m, 1H), 4.18-4.06 (m, 2H), 3.96-3.77 (m, 4H), 3.64 (dd, 1H, *J* = 14.4, 9.6 Hz), 3.45 (dd, 1H, *J* = 14.4, 5.2 Hz), 3.20 (t, 2H, *J* = 8.4 Hz), 3.13 (dd, 1H, *J* = 18.0, 6.4 Hz), 3.05 (dd, 1H, *J* = 18.0, 5.6 Hz), 2.40 (s, 3H); ¹³C NMR δ 167.1, 144.0, 142.6, 135.6, 131.7, 131.3, 129.9, 127.4, 125.4, 124.7, 124.1, 124.0, 120.6, 116.8, 58.5, 54.9, 51.8, 47.9, 45.7, 32.6, 27.9, 21.5; MS [*m/z* (rel intensity)] 347 (16), 155 (43), 119 (100).

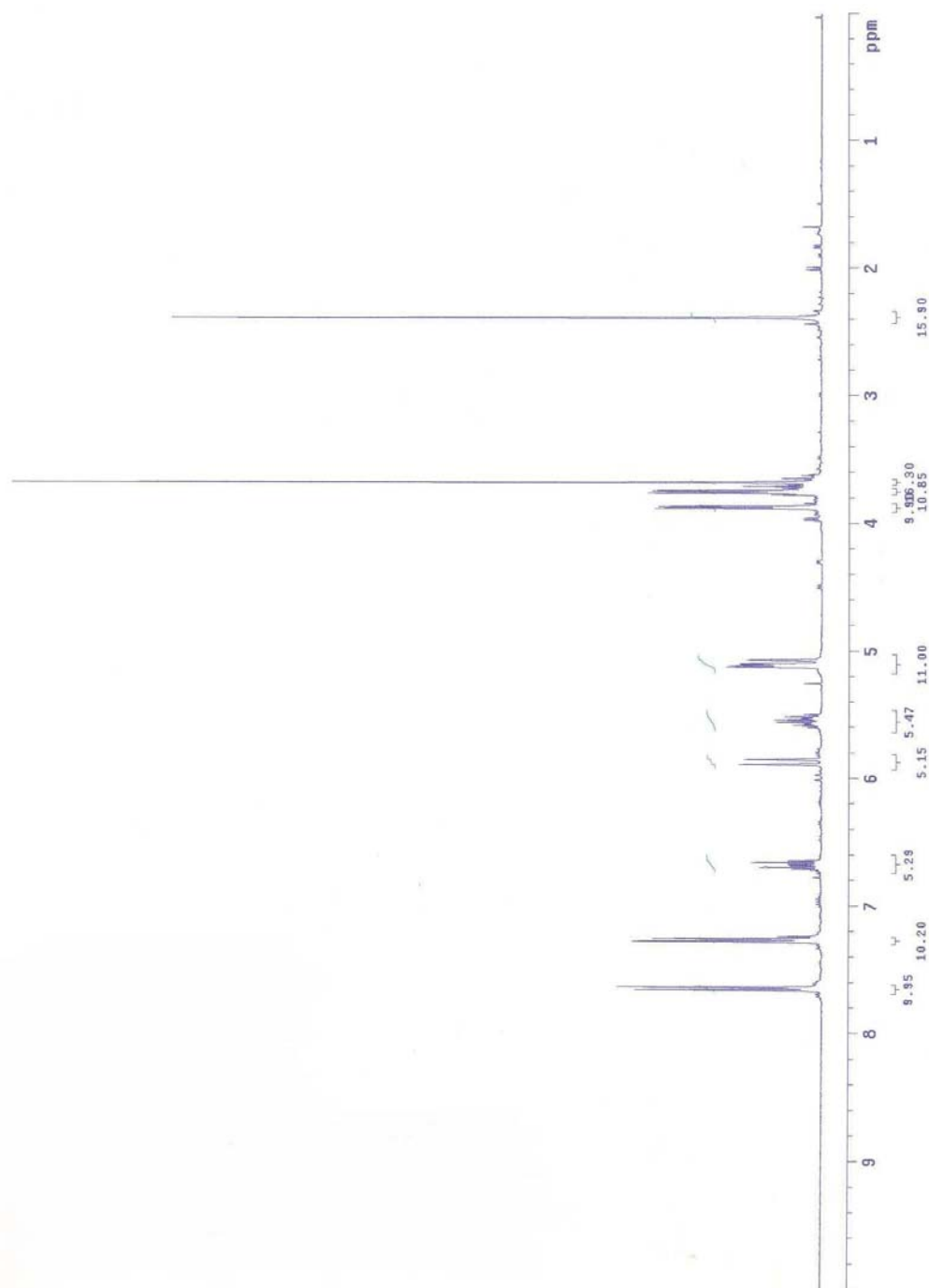
1-[[4-[4-(methylphenyl)sulfonyl]-1,1-dioxido-3,4,5,8-tetrahydro-2*H*-1,4-thiazocin-2-yl]acetyl]indoline (20). To a solution of **19** (0.31 g, 0.62 mmol) in CH₂Cl₂ (10 mL) was added a solution of commercial Gen 2 catalyst (5% mol, 0.026 g) in CH₂Cl₂ (5 mL) under a nitrogen atmosphere. The mixture was refluxed until TLC showed the reaction to be complete, then cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue on silica gel (EtOAc) gave 0.26 g (89%) of **20** as a white solid: mp 267-9 °C; IR 1651 cm⁻¹; ¹H NMR δ 8.05 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.15 (dd, 2H, *J* = 15.6, 7.6 Hz), 7.01 (td, 1H, *J* = 7.6, 1.2 Hz), 5.86 (d, 1H, *J* = 11.6 Hz), 5.75 (m, 1H), 4.85 (dd, 1H, *J* = 13.6, 7.2 Hz), 4.41 (d,

1H, $J = 19.6$ Hz), 4.06-4.02 (m, 2H), 3.97-3.85 (m, 2H), 3.69 (d, 2H, $J = 19.2$ Hz), 3.26-3.17 (m, 4H), 2.51 (dd, 1H, $J = 17.2, 10.4$ Hz), 2.39 (s, 3H); ^{13}C NMR δ 166.2, 144.3, 142.4, 134.0, 131.3, 130.1, 127.4, 127.2, 124.8, 124.3, 117.4, 116.7, 53.1, 52.9, 49.7, 49.2, 47.9, 29.9, 27.9, 21.5; MS [m/z (rel intensity)] 474 (M^+ , 1), 155 (26), 119 (100). Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{O}_5\text{N}_2\text{S}_2$: C, 58.21; H, 5.52; N, 5.90. Found: C, 57.98; H, 5.69; N, 5.85.

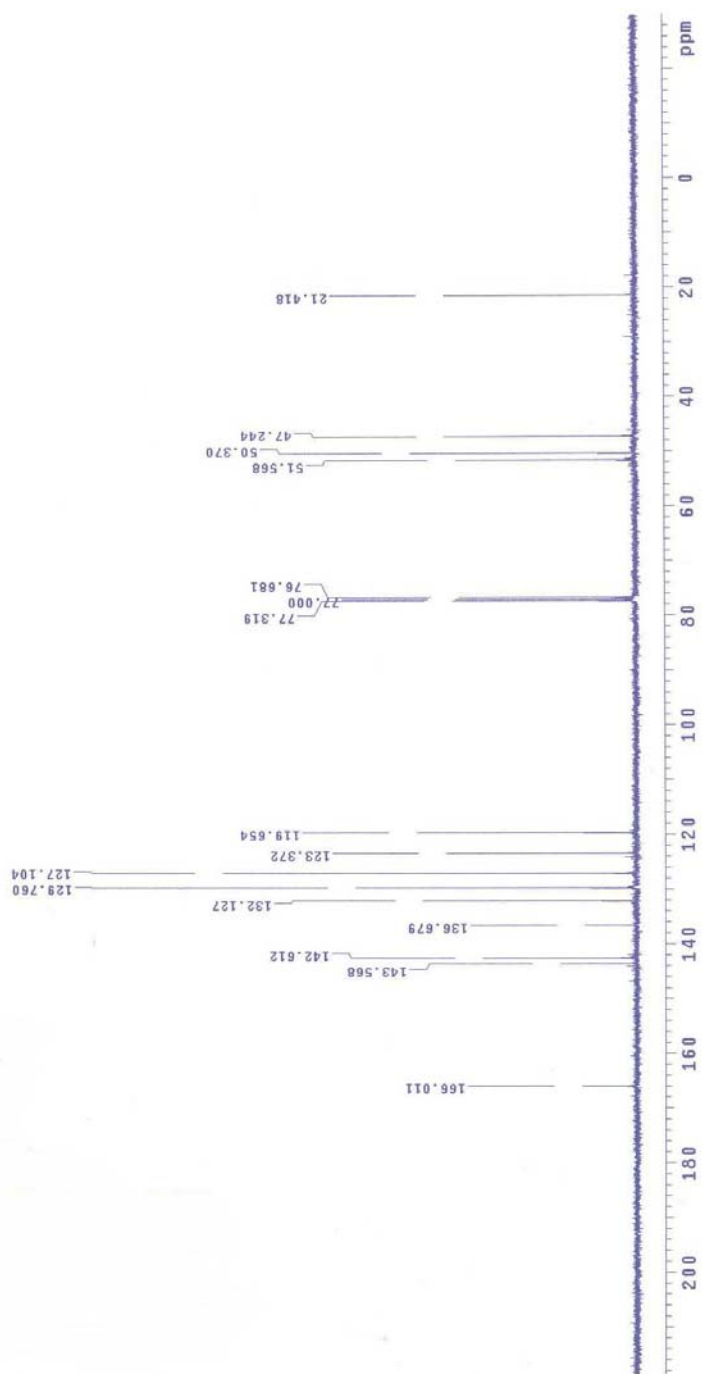
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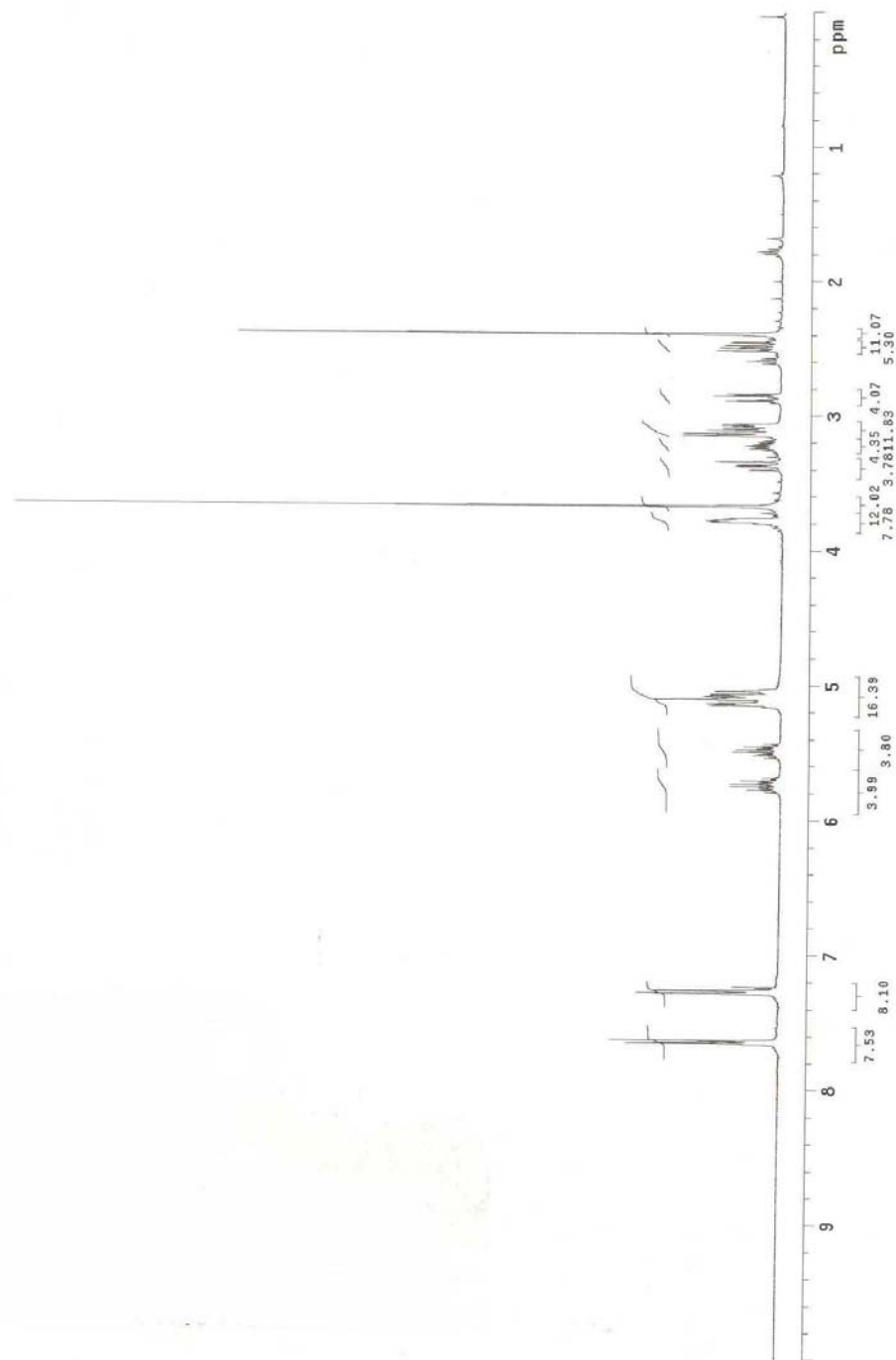
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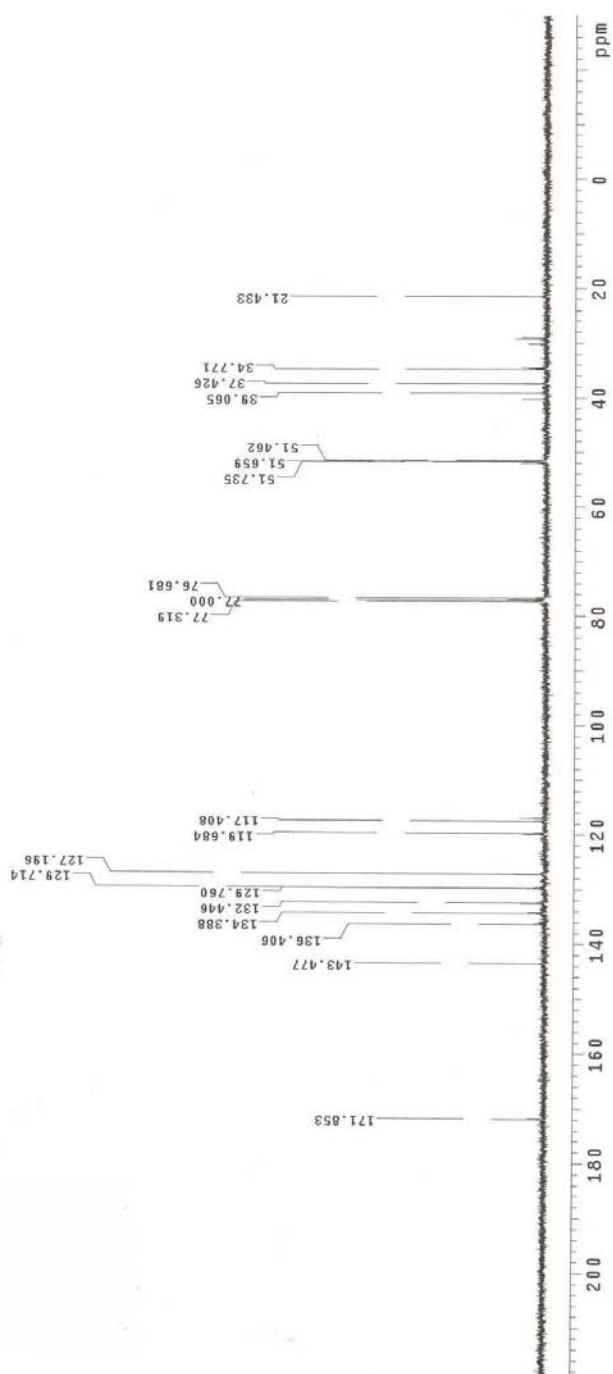
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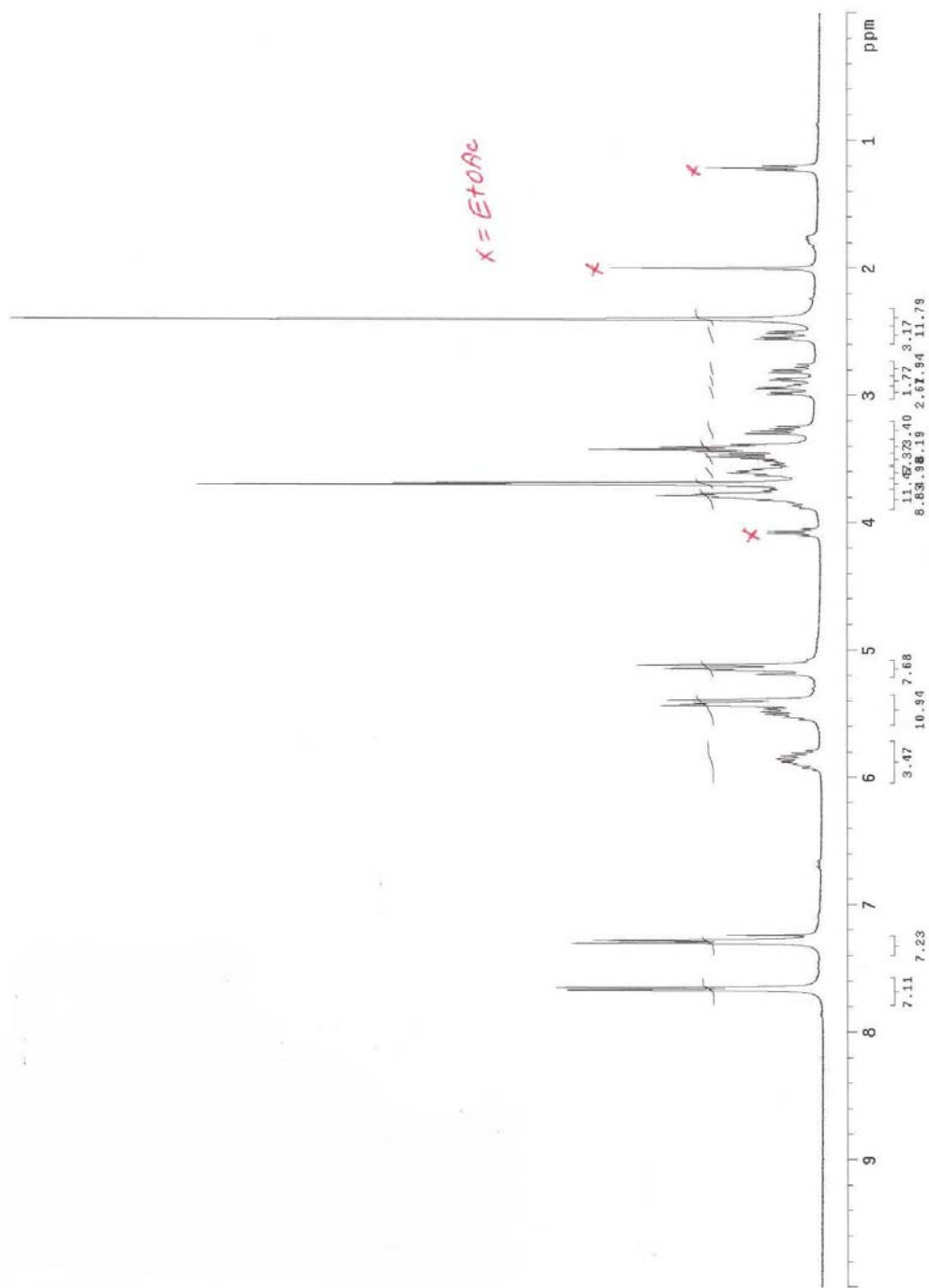
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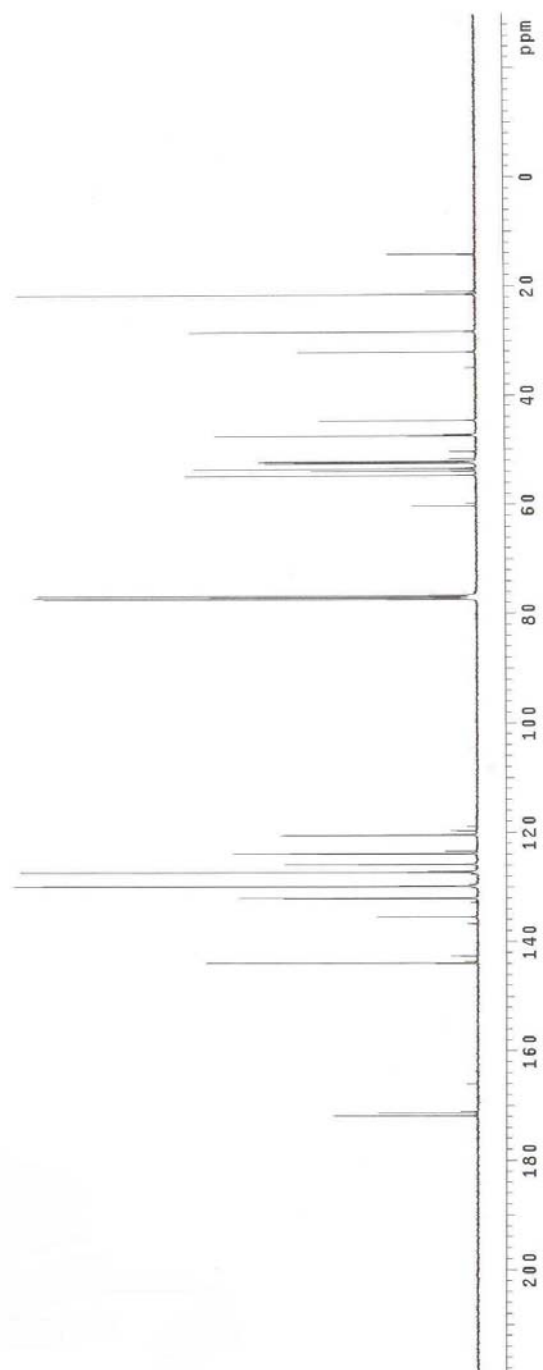
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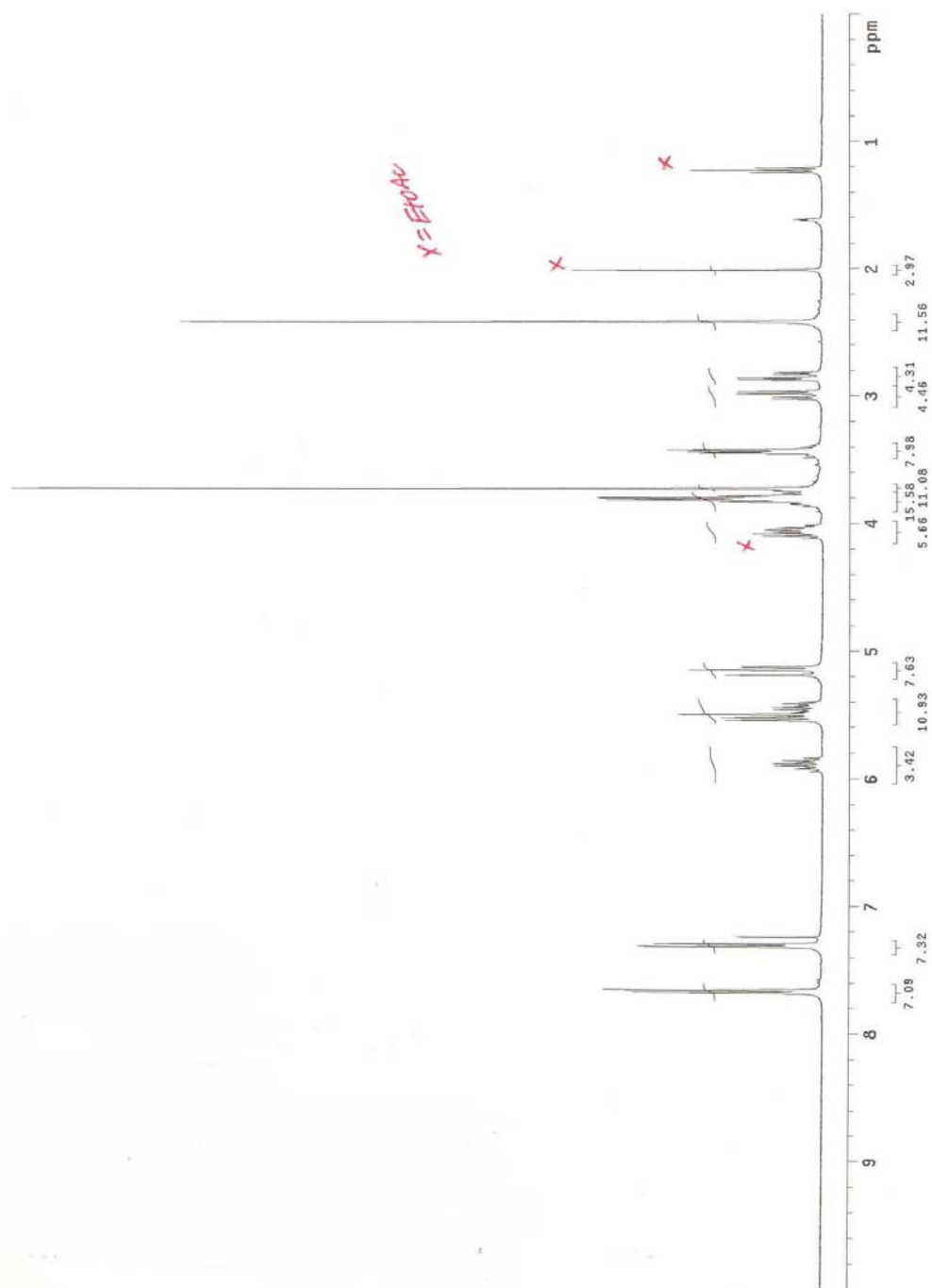
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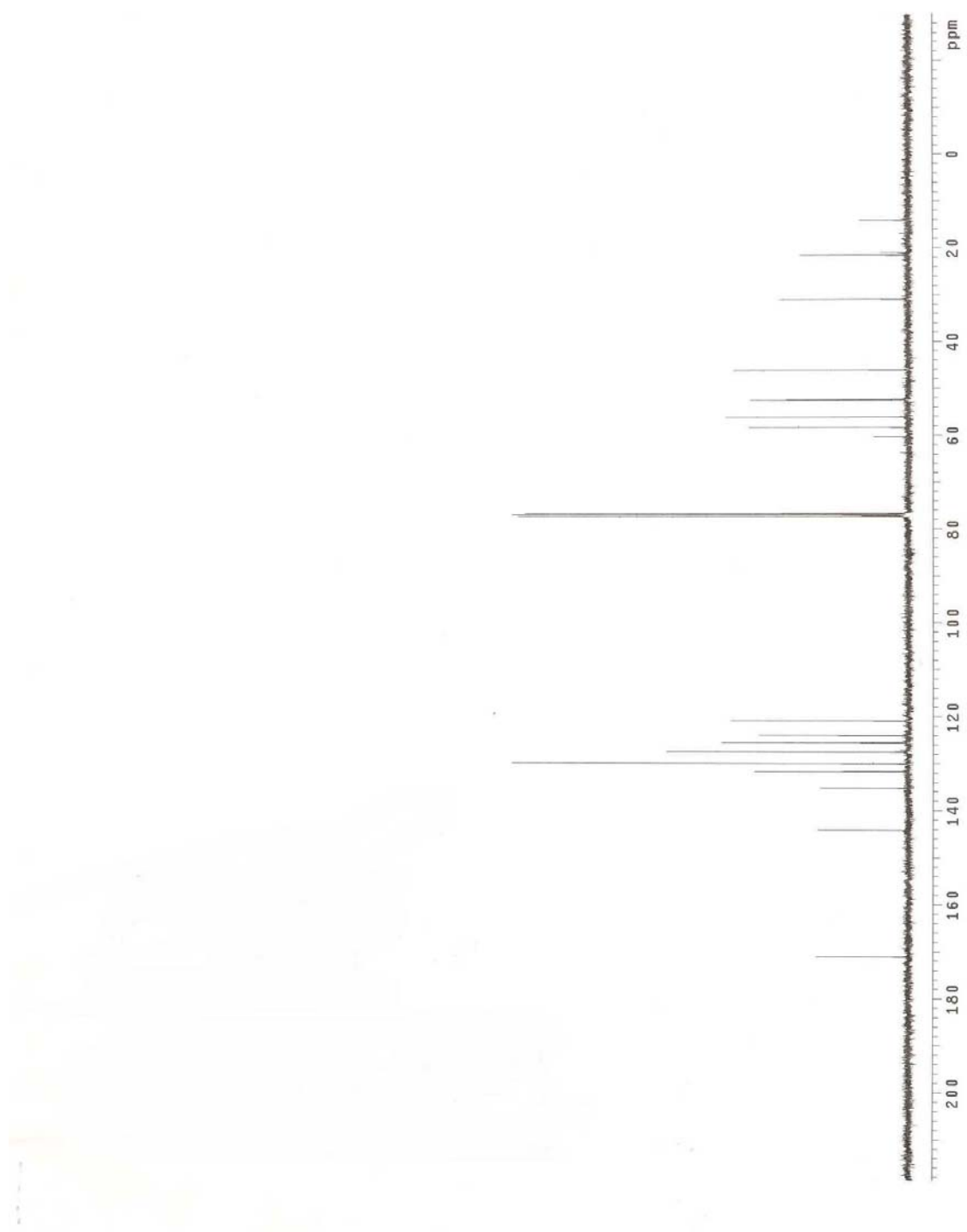
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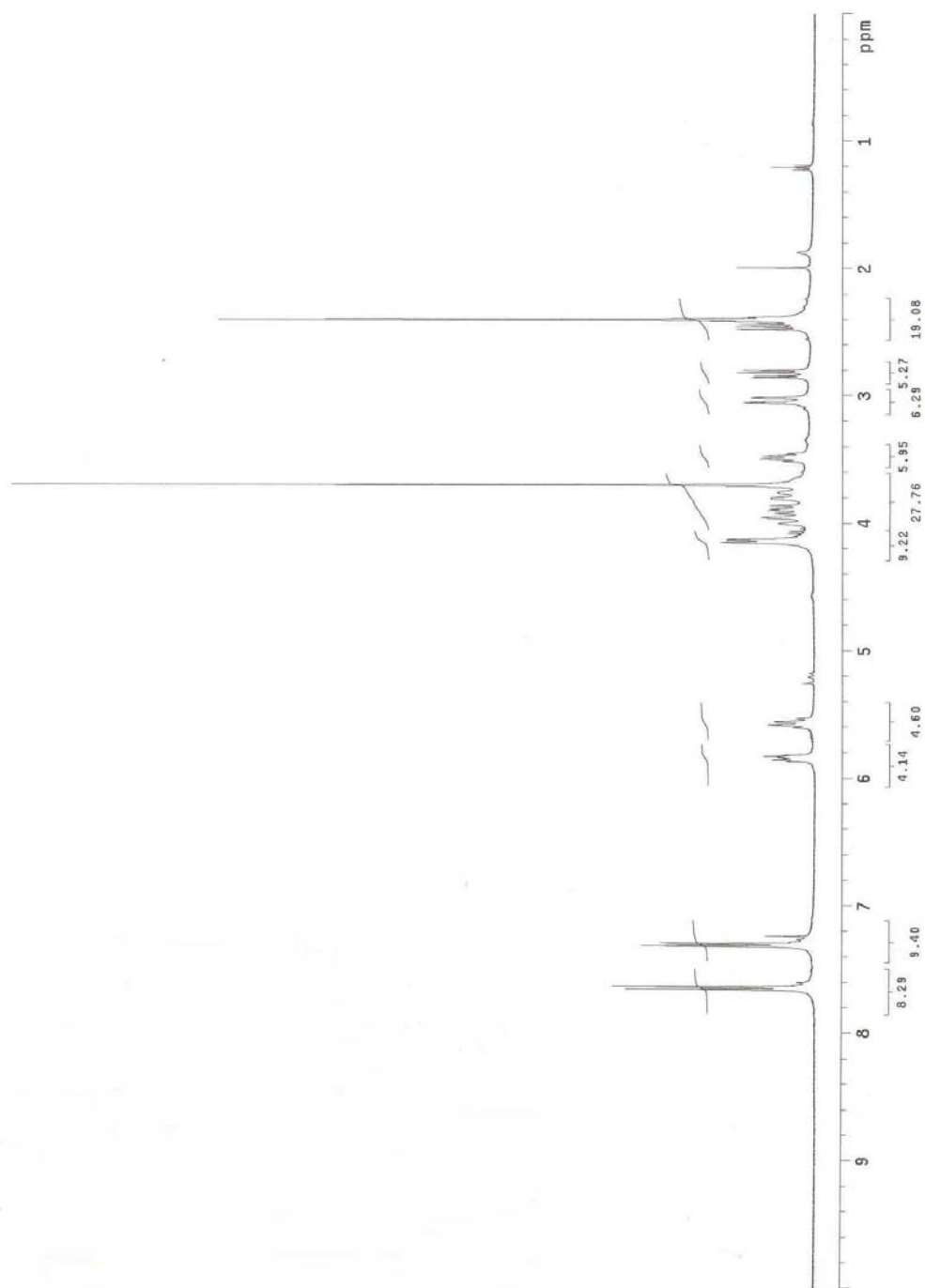
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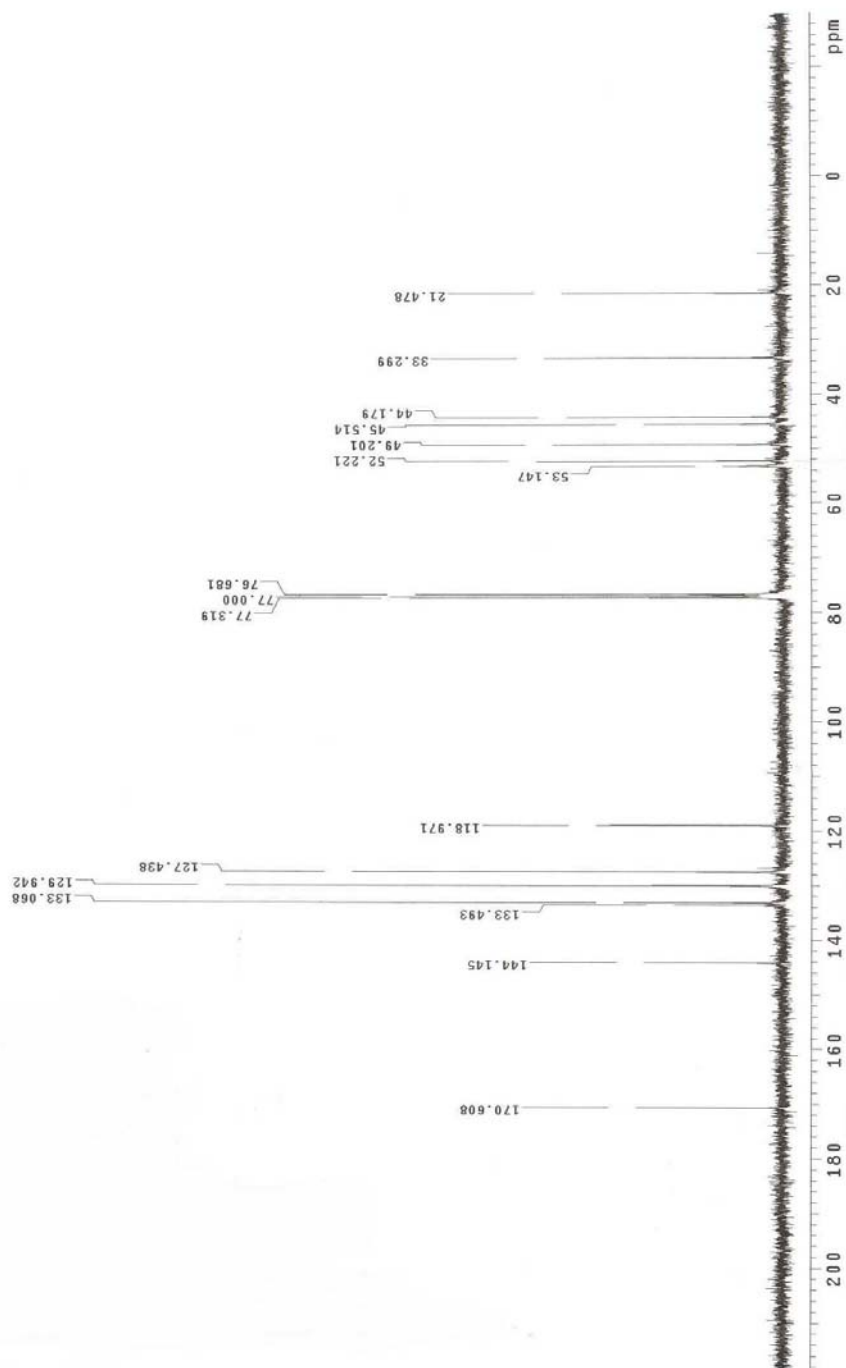
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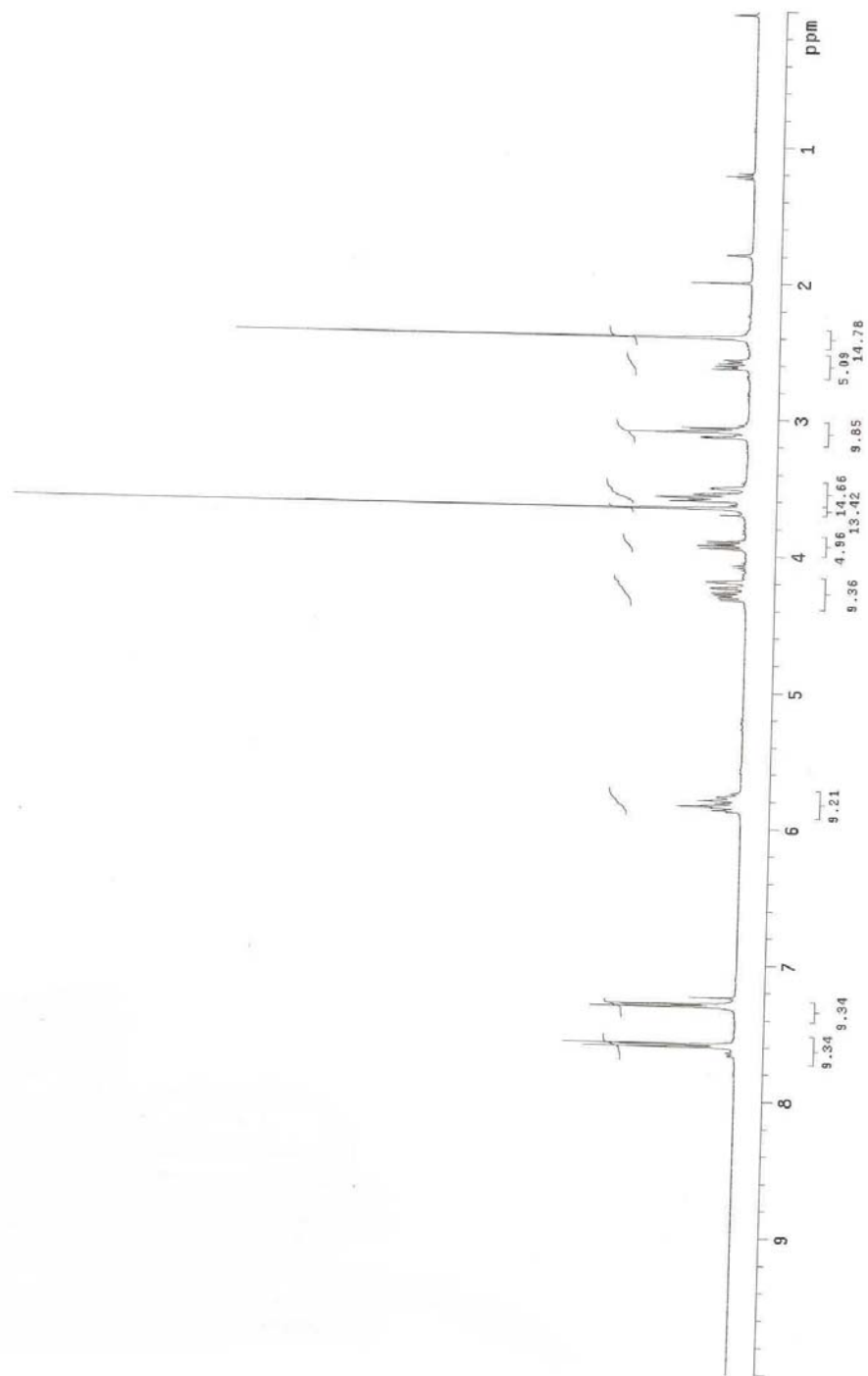
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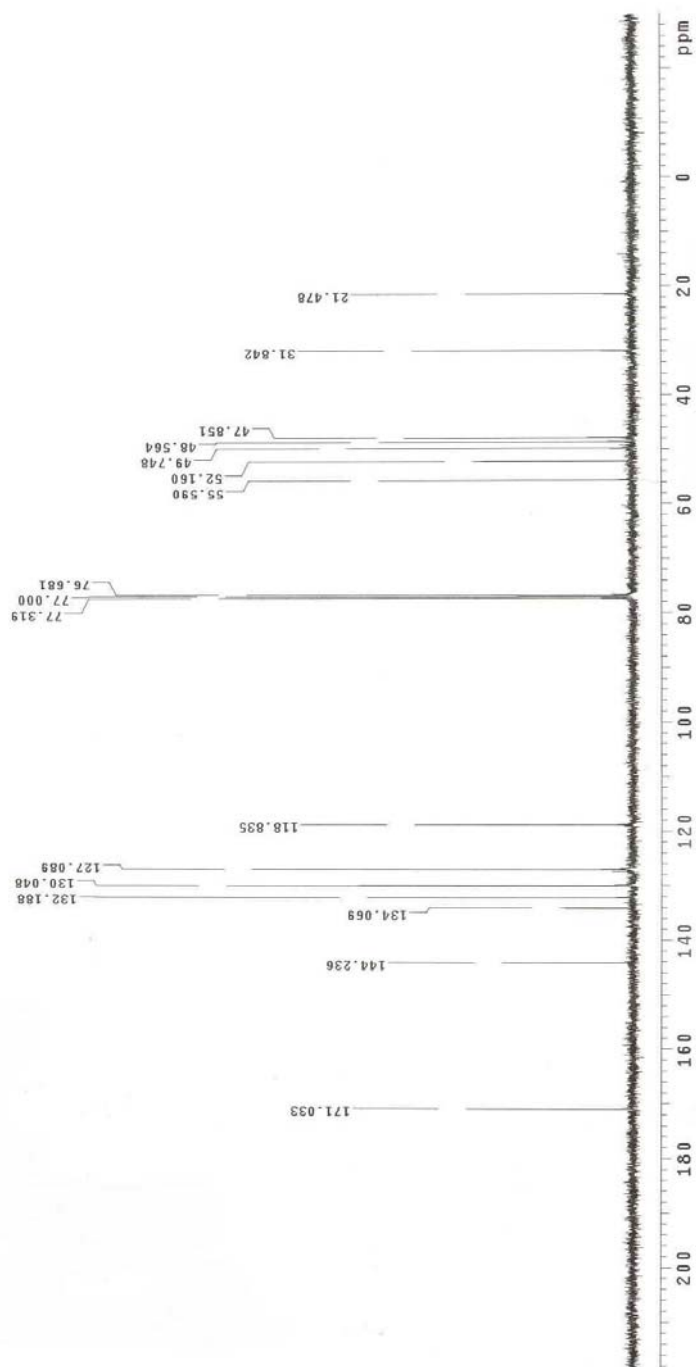
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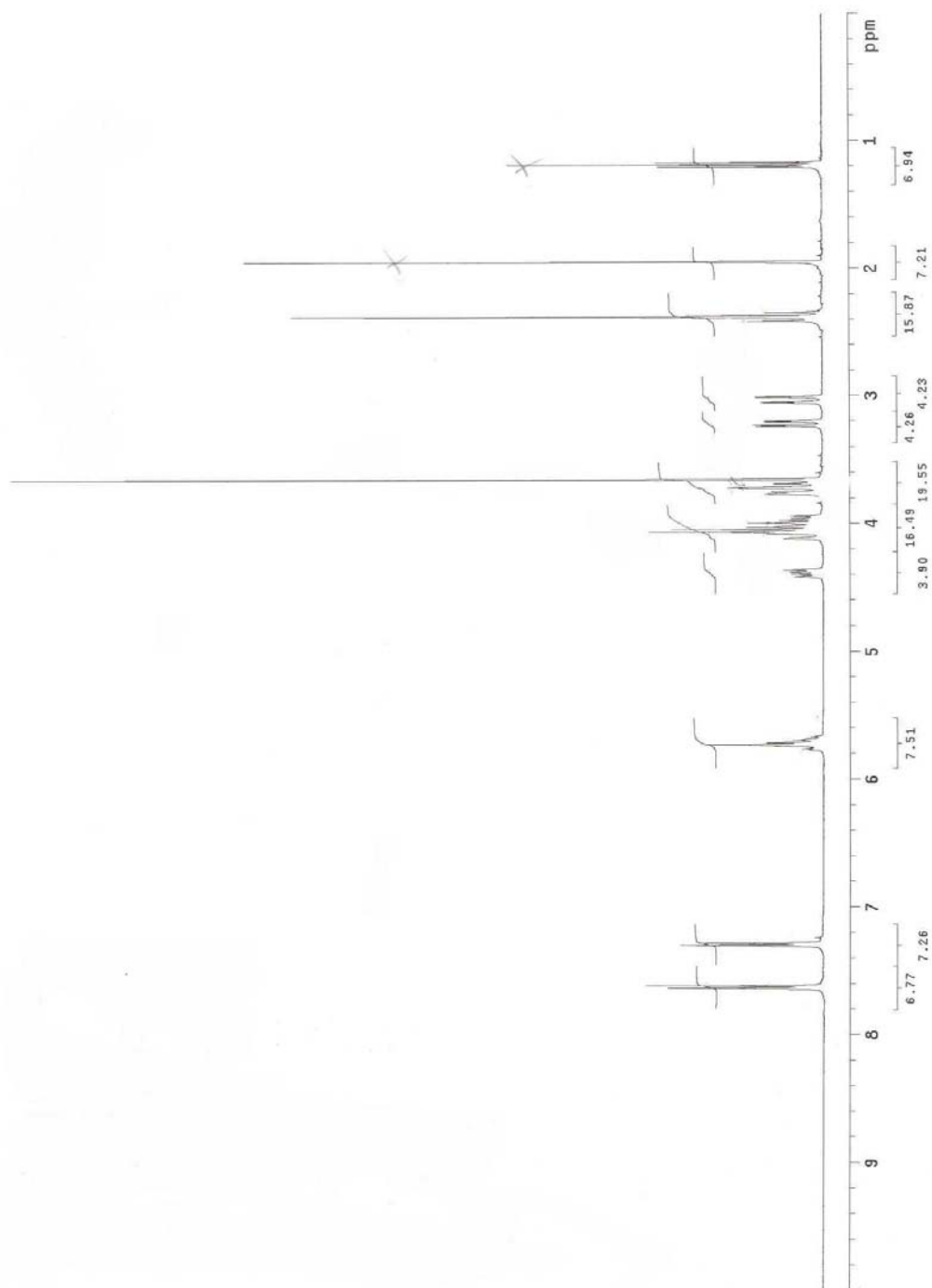
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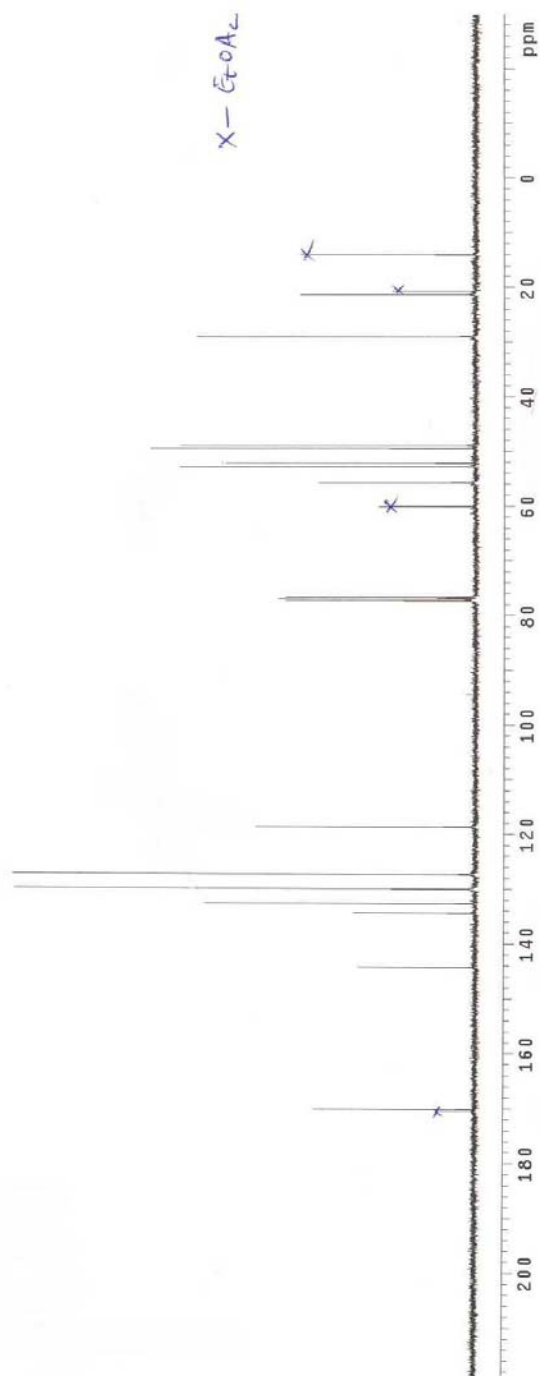
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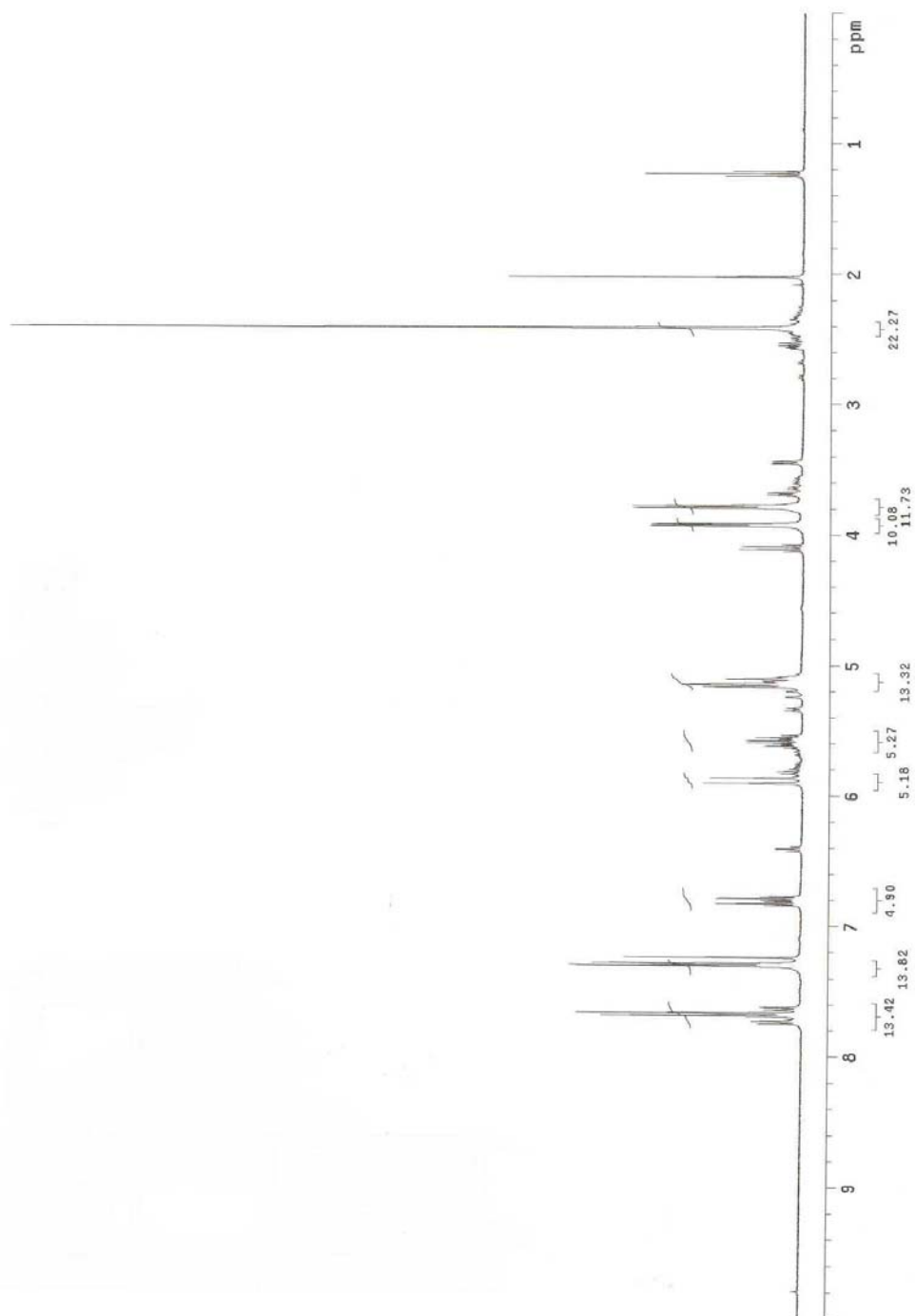
^1H NMR Spectrum of 6



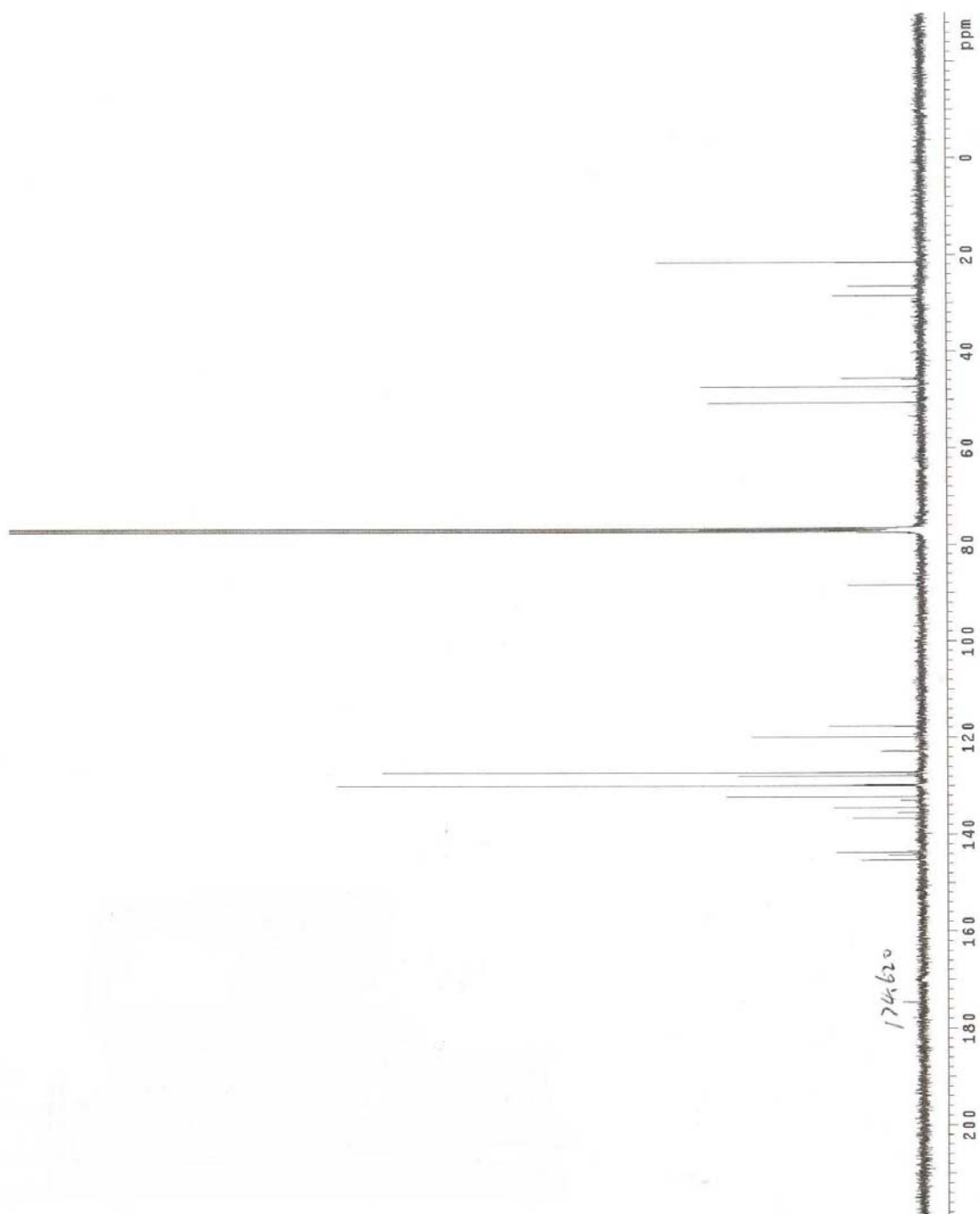
¹³C NMR Spectrum of 6



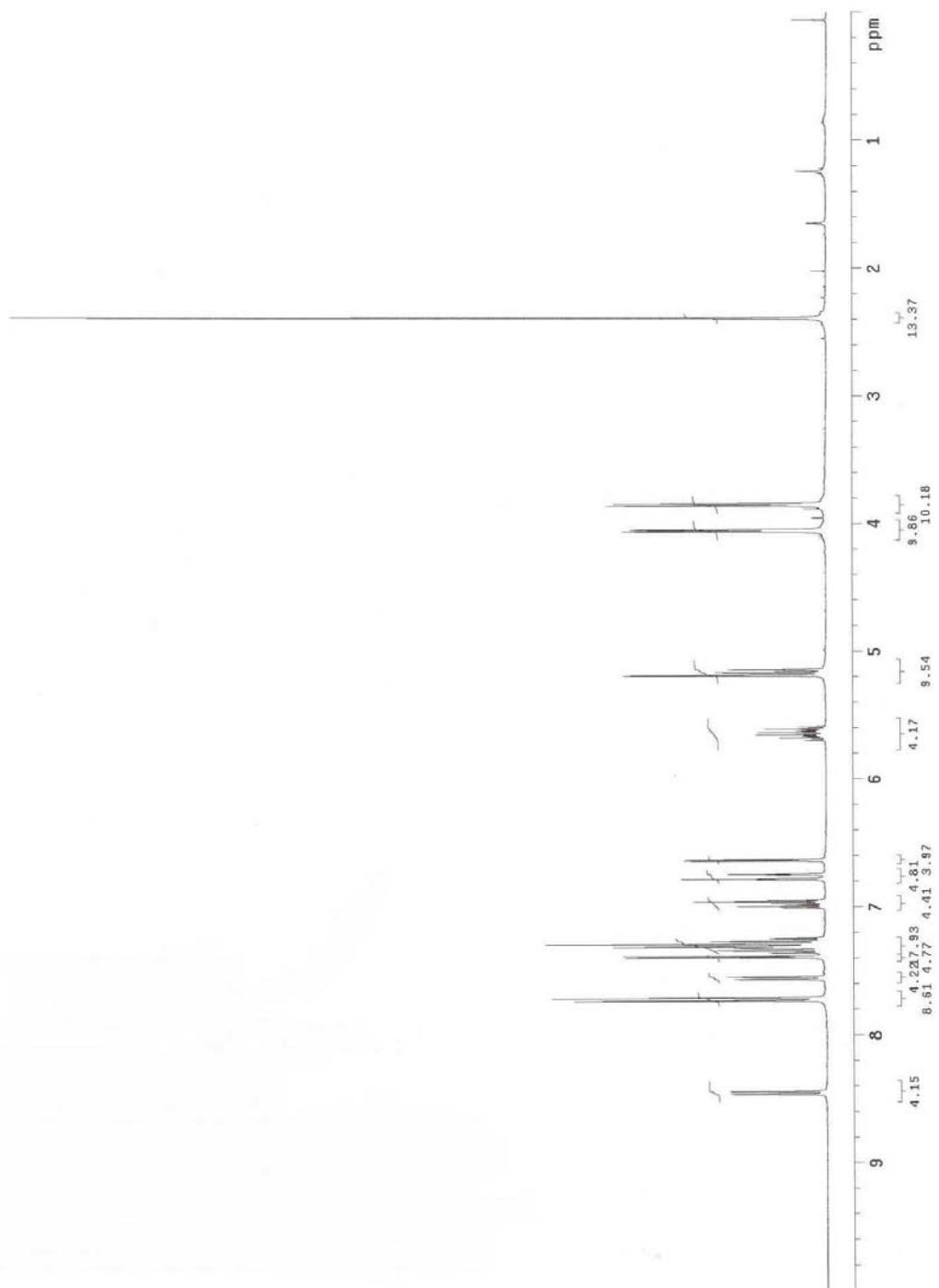
^1H NMR Spectrum of 7



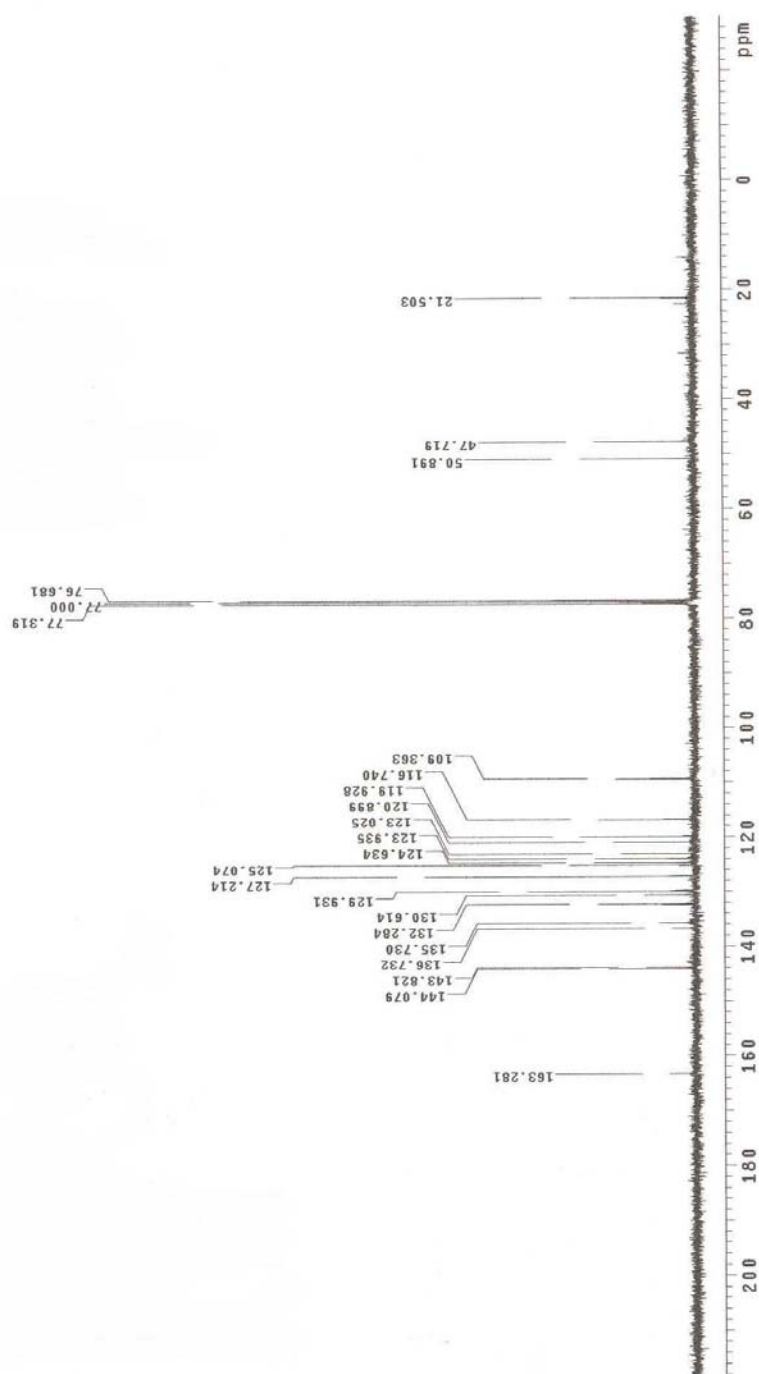
^{13}C NMR Spectrum of 7



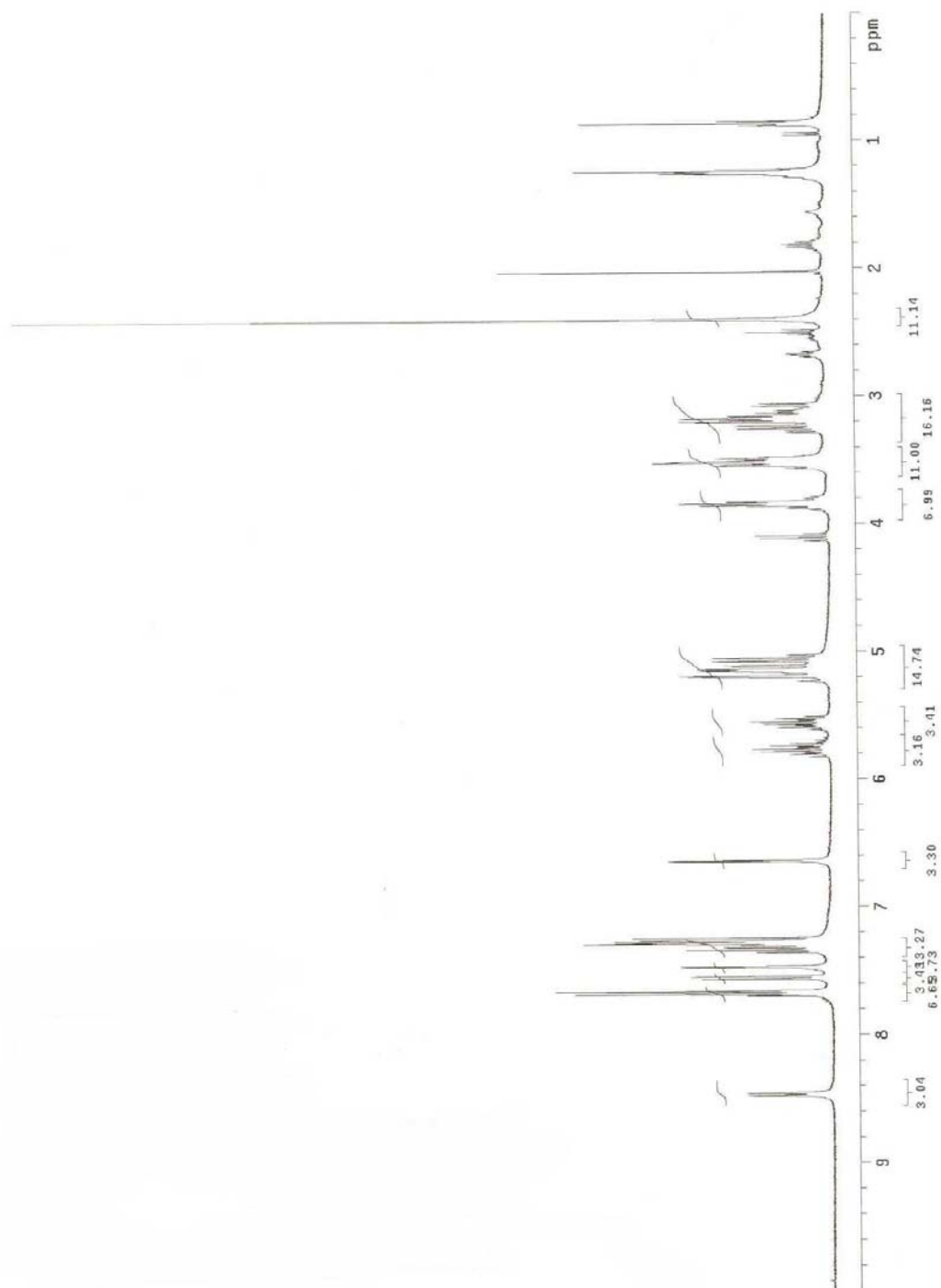
^1H NMR Spectrum of 8



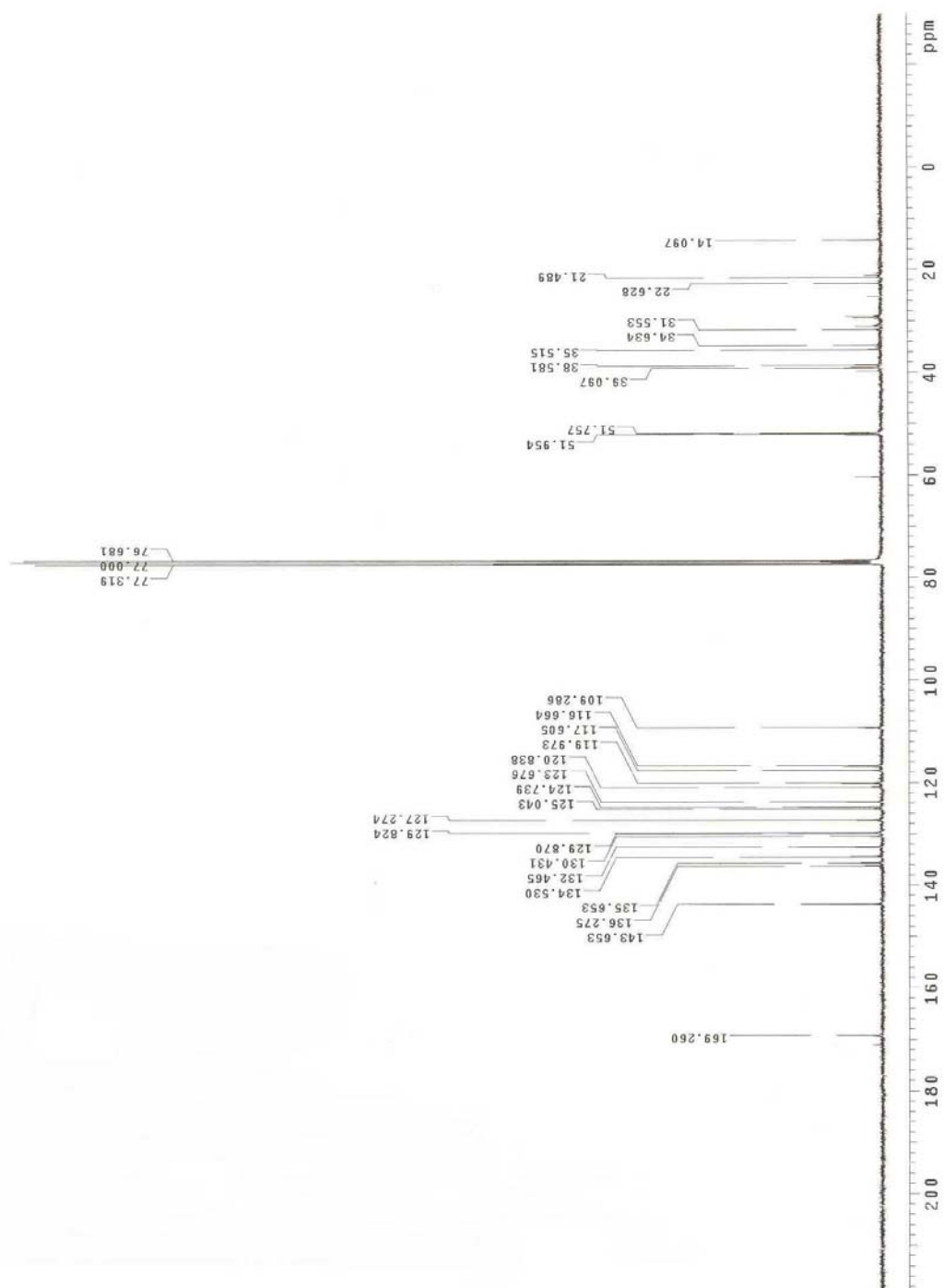
¹³C NMR Spectrum of 8



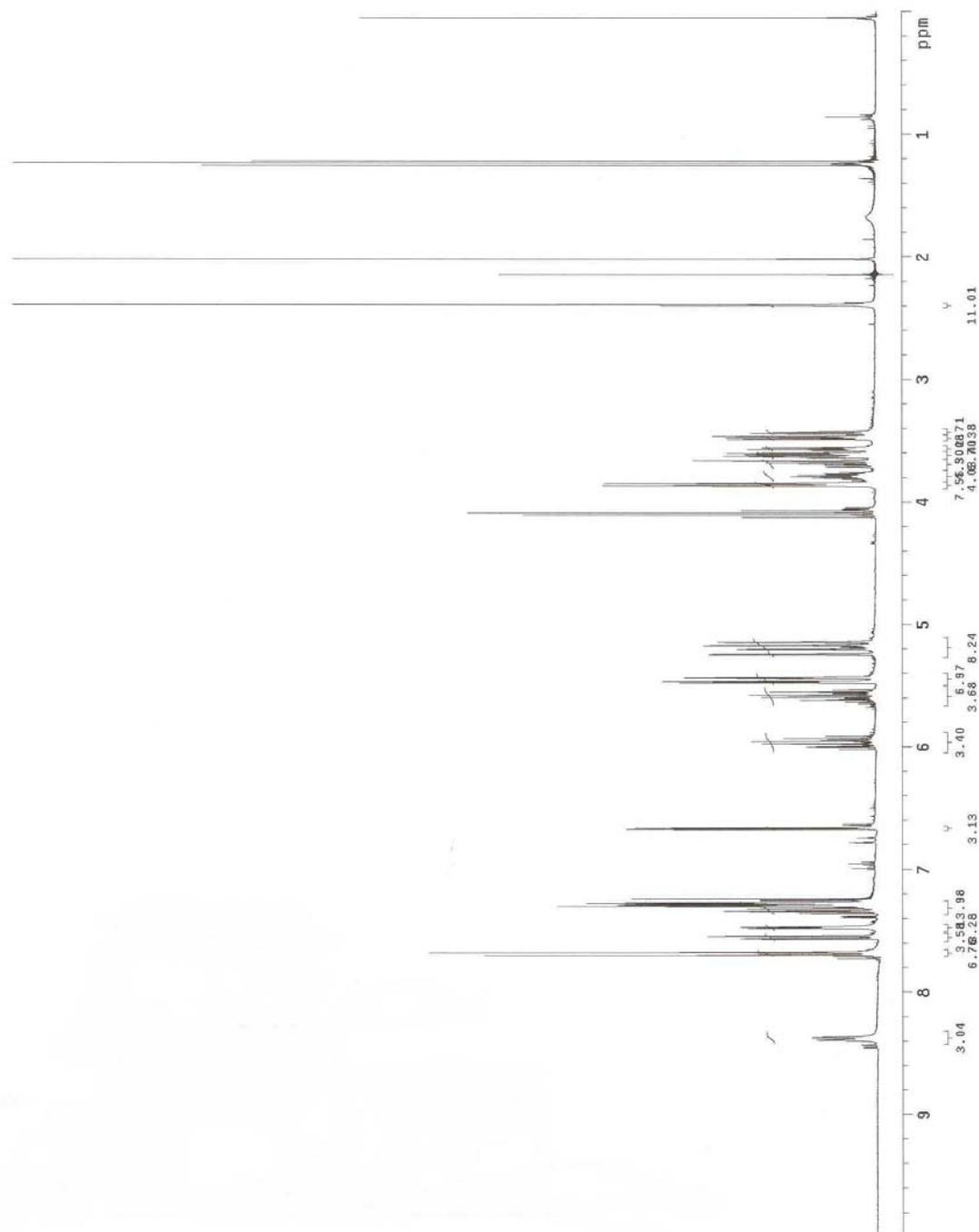
^1H NMR Spectrum of 9



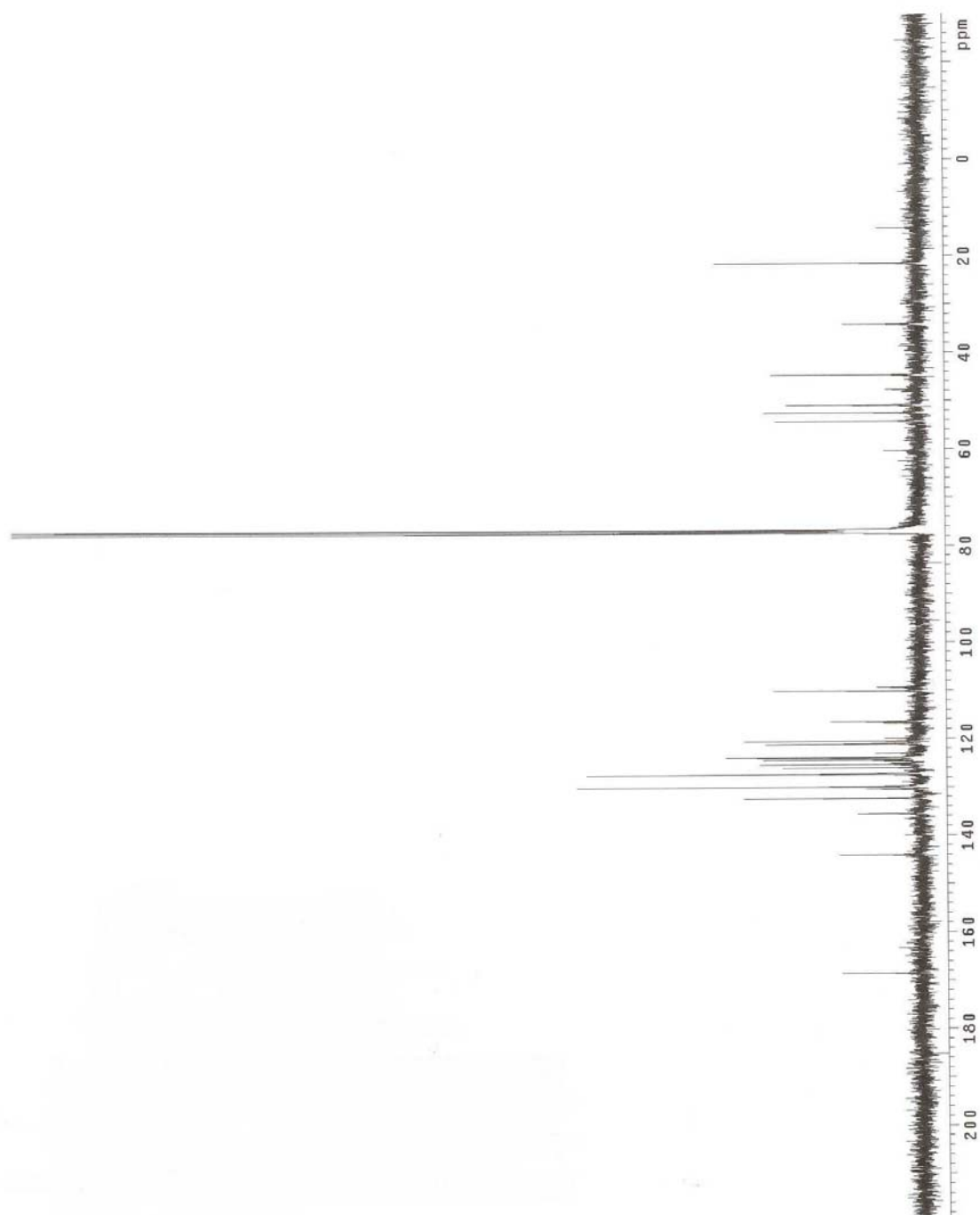
¹³C NMR Spectrum of 9



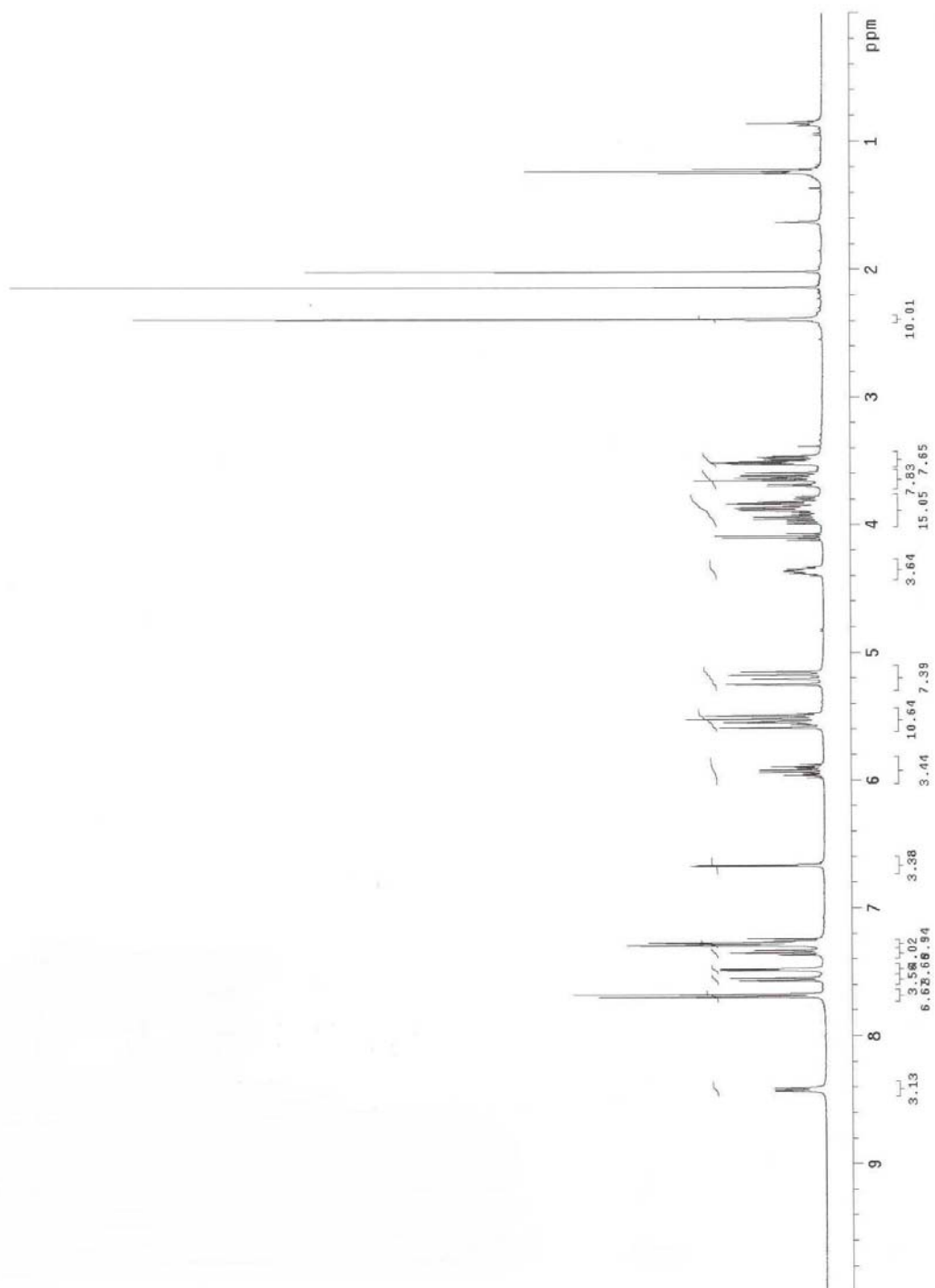
¹H NMR Spectrum of 10



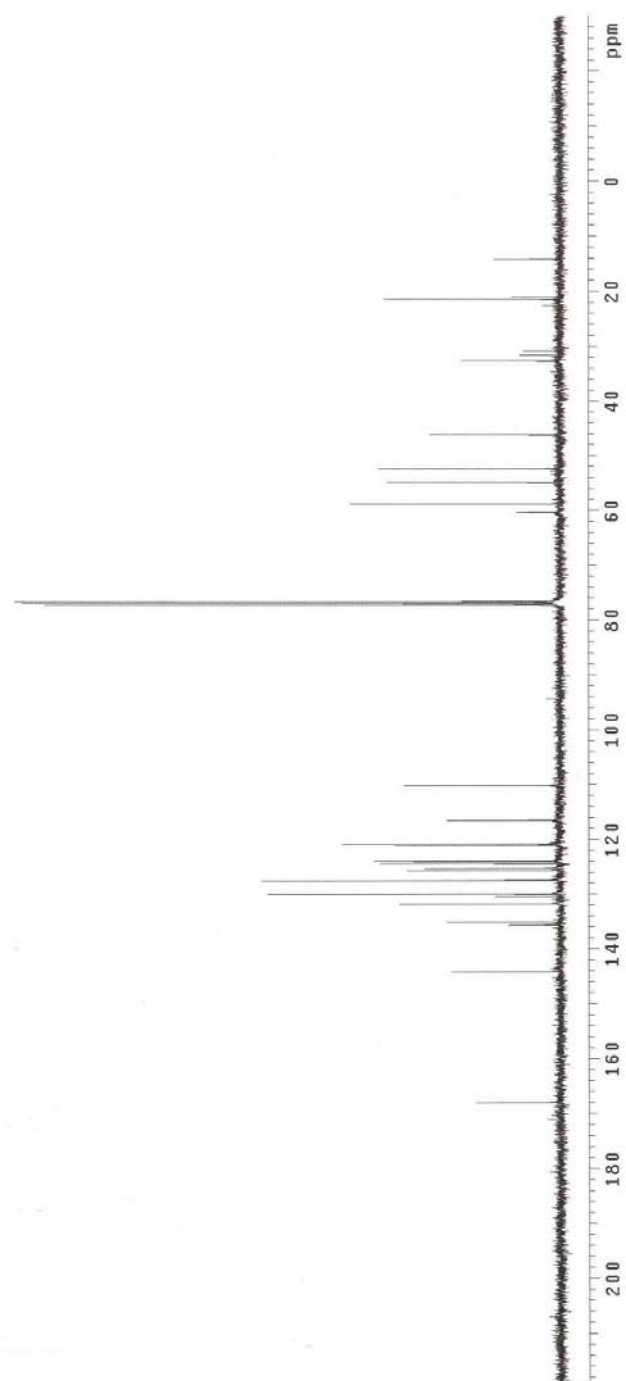
^{13}C NMR Spectrum of 10



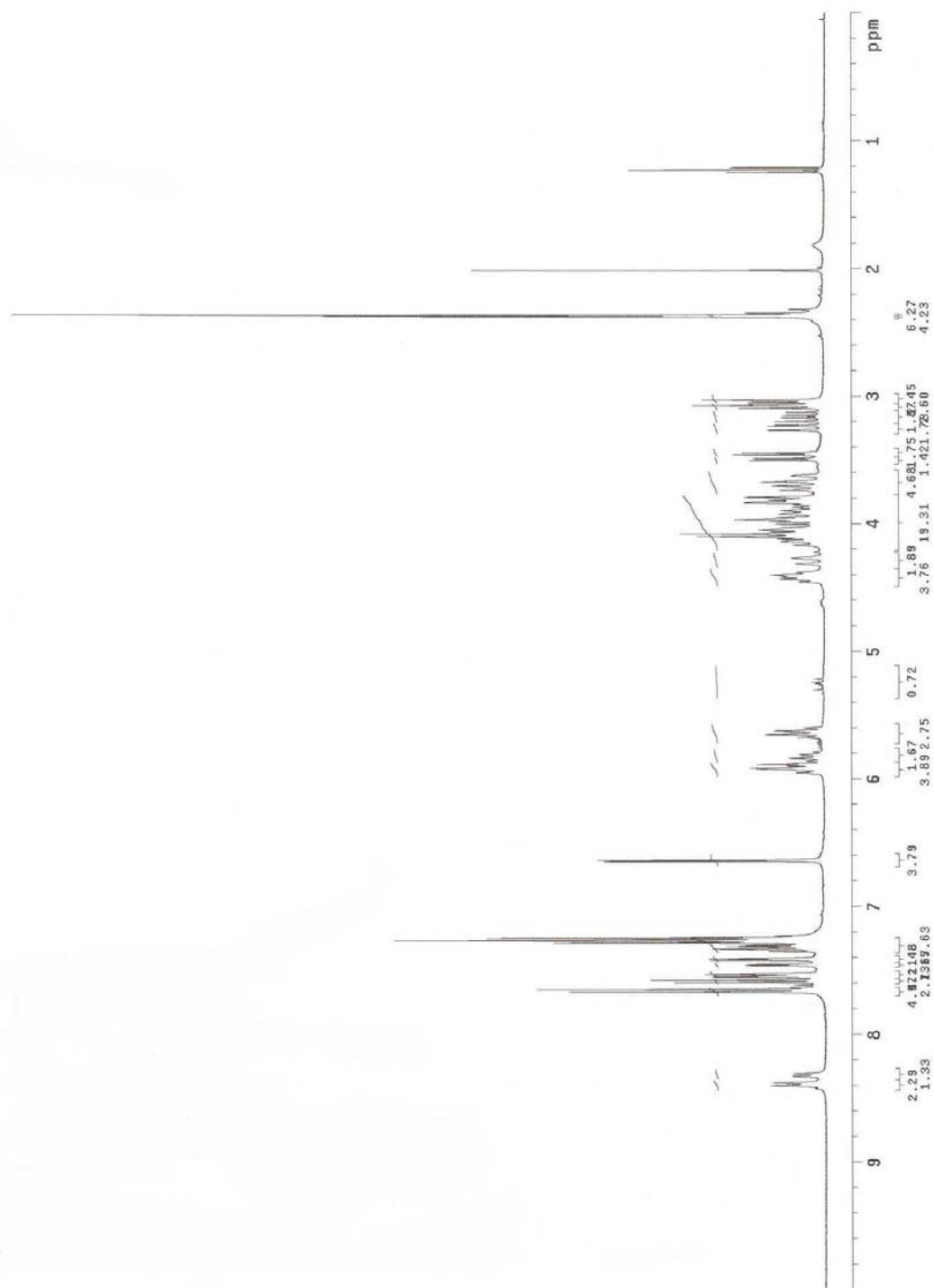
¹H NMR Spectrum of 11



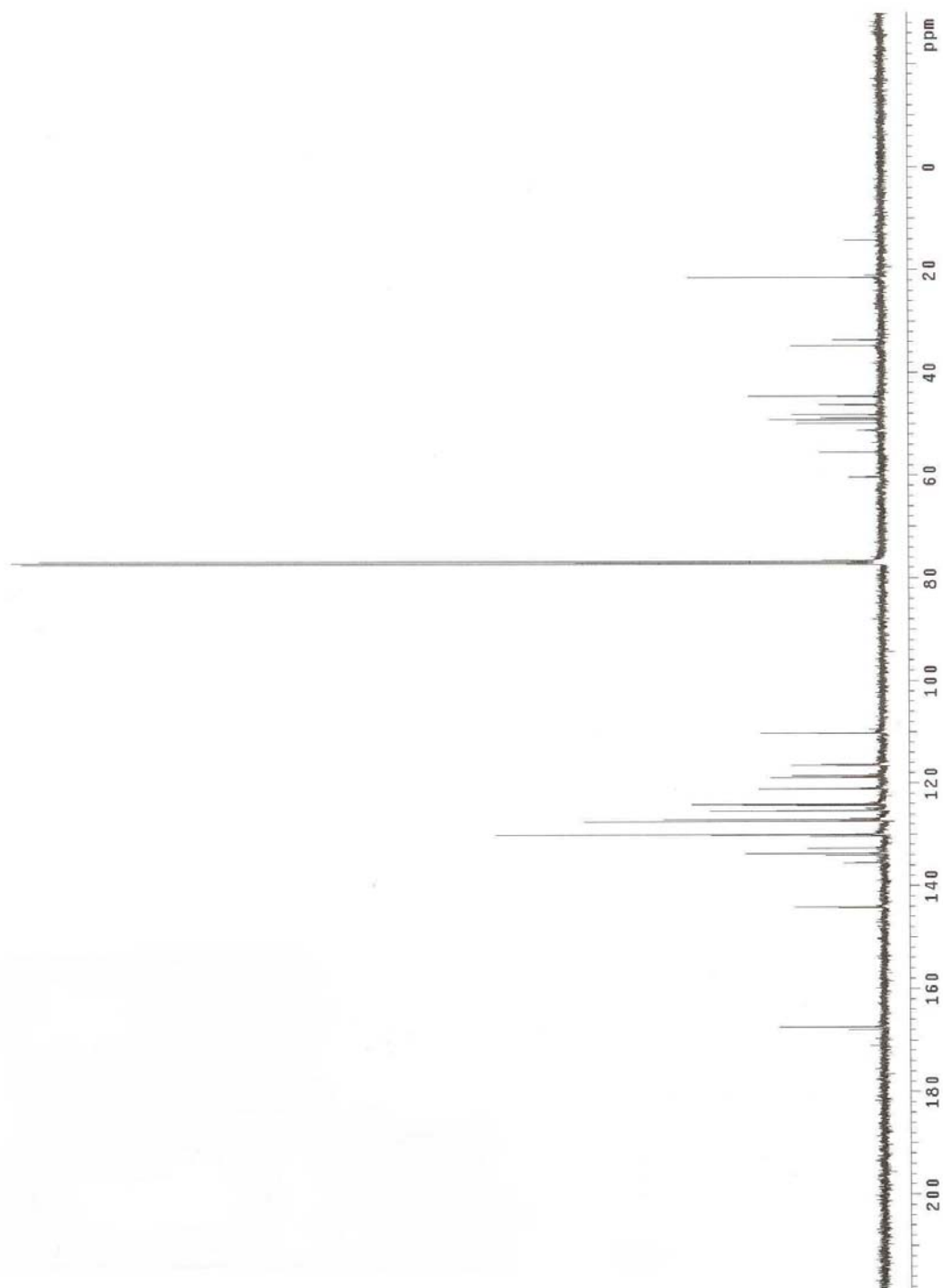
^{13}C NMR Spectrum of 11



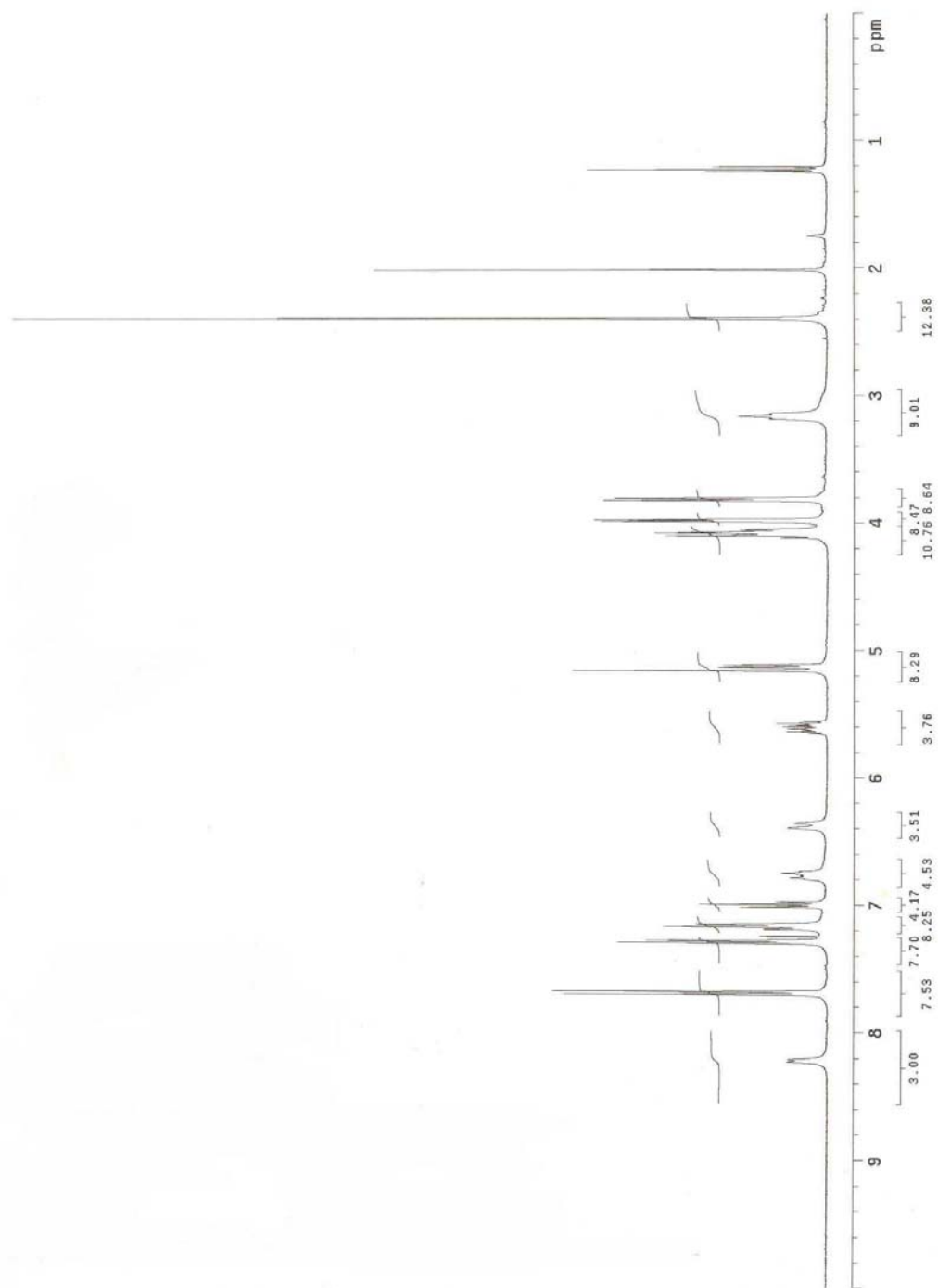
¹H NMR Spectrum of 12



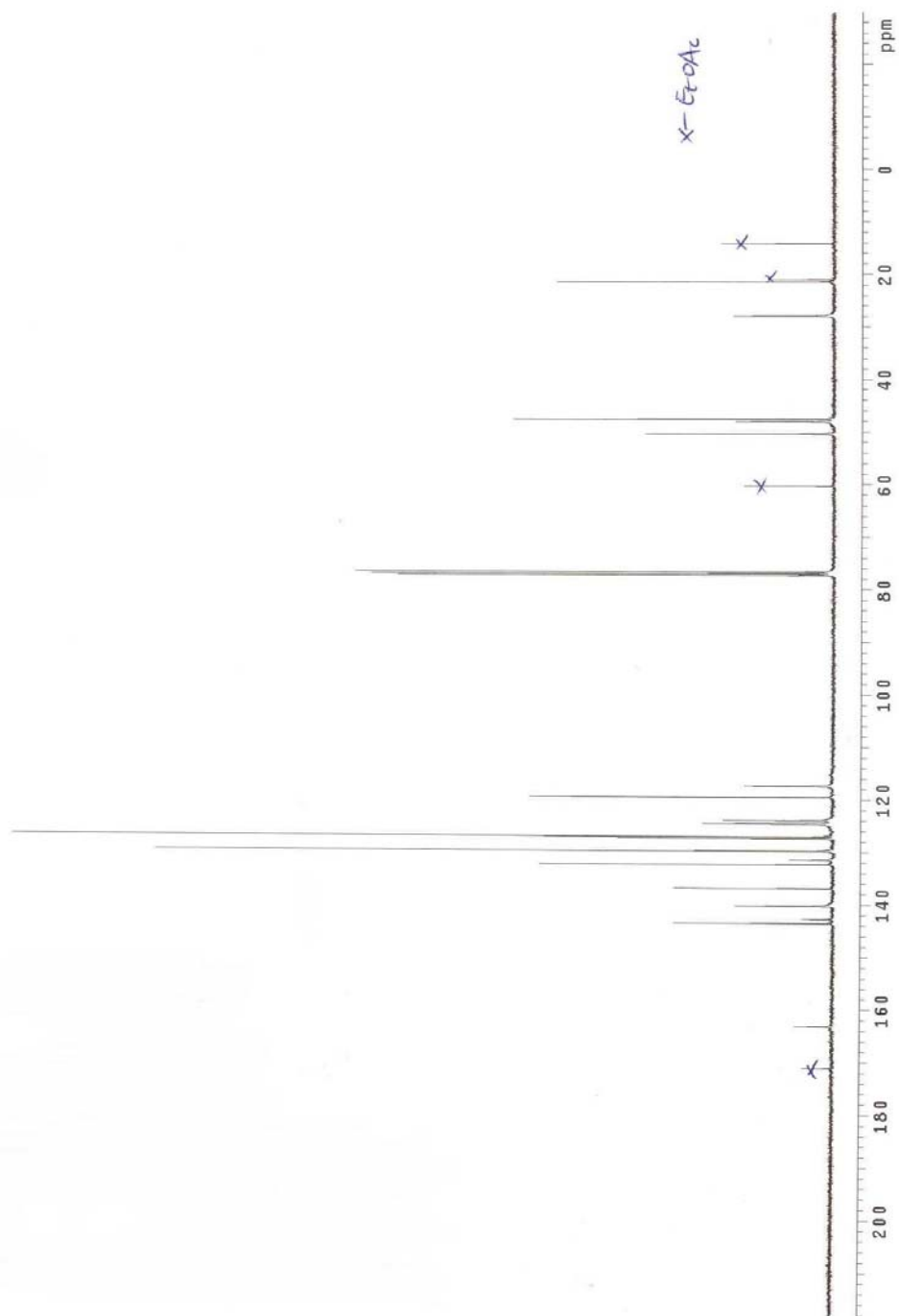
^{13}C NMR Spectrum of 12



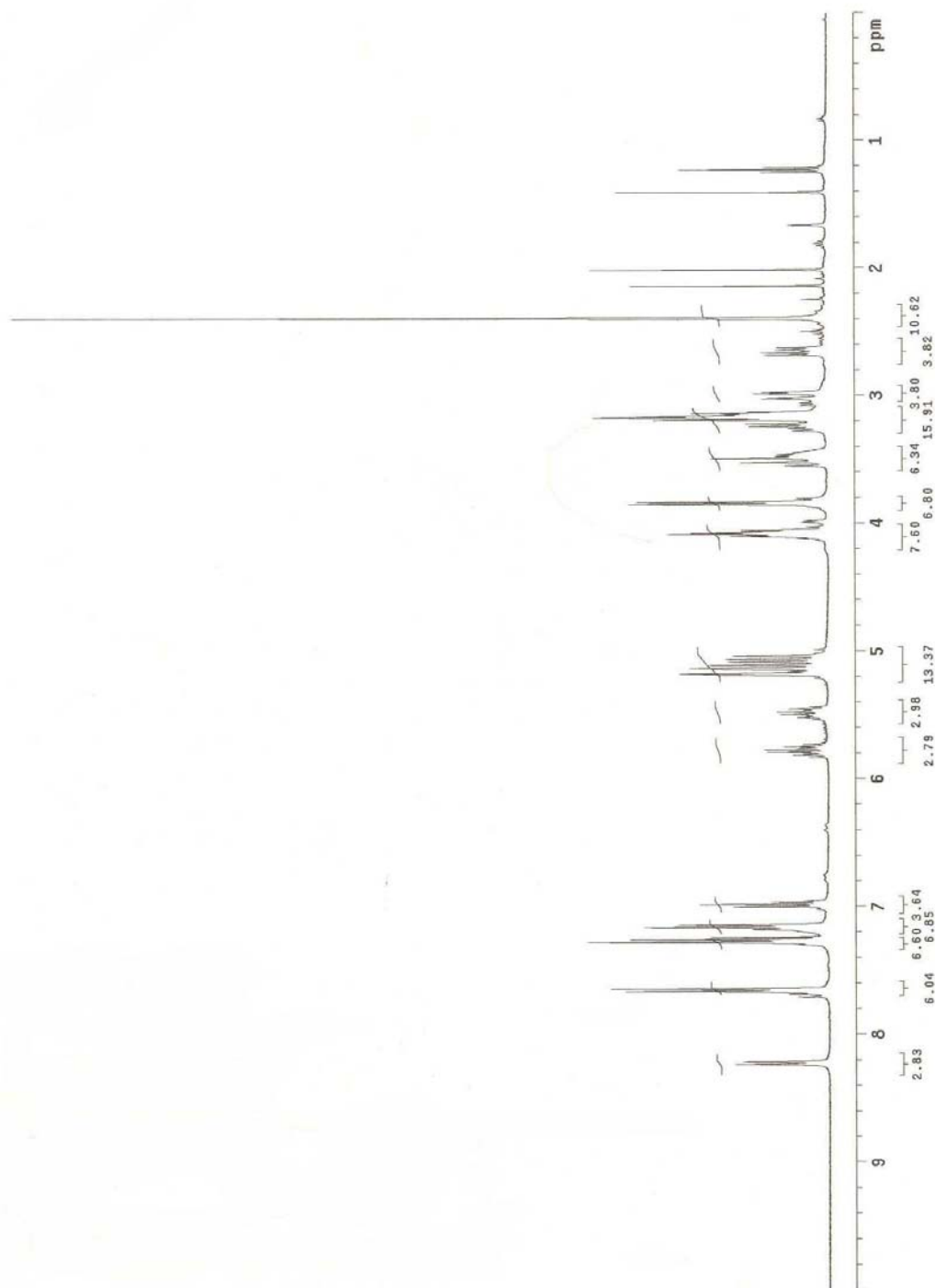
^1H NMR Spectrum of 14



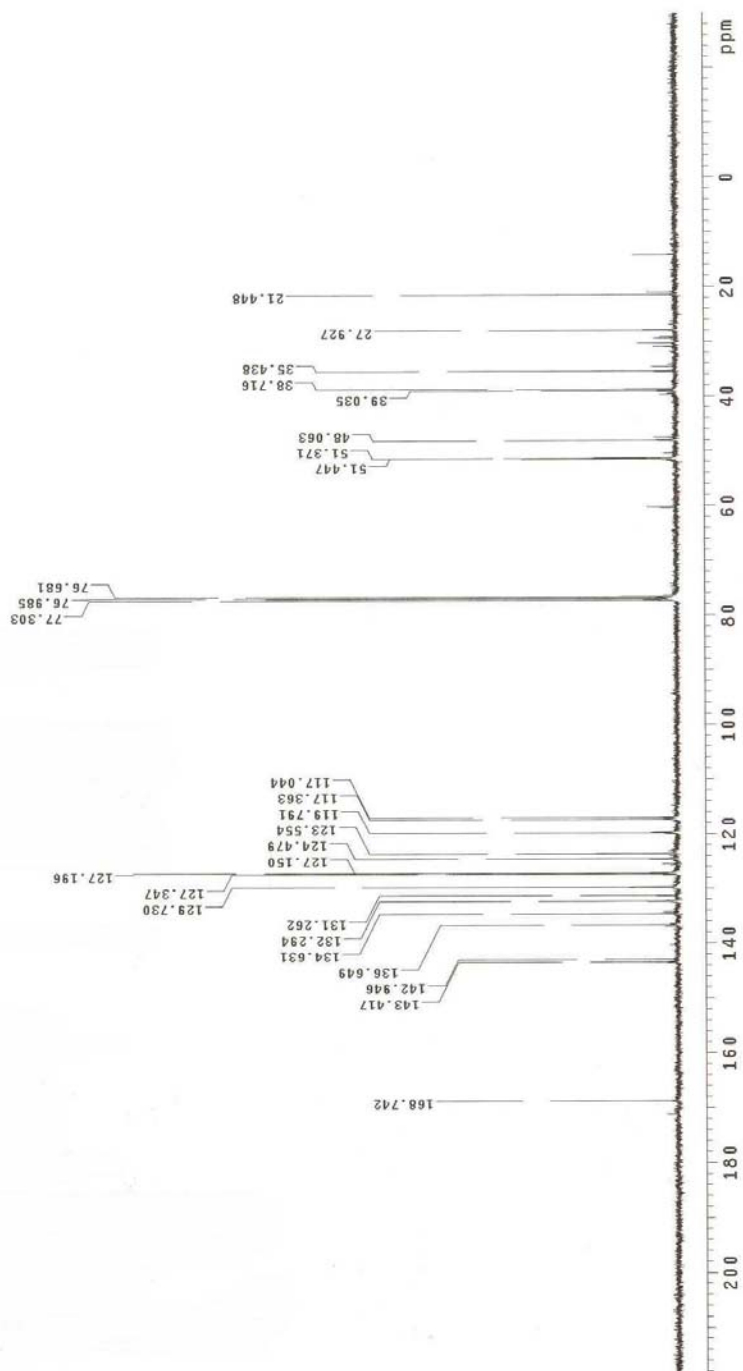
¹³C NMR Spectrum of 14



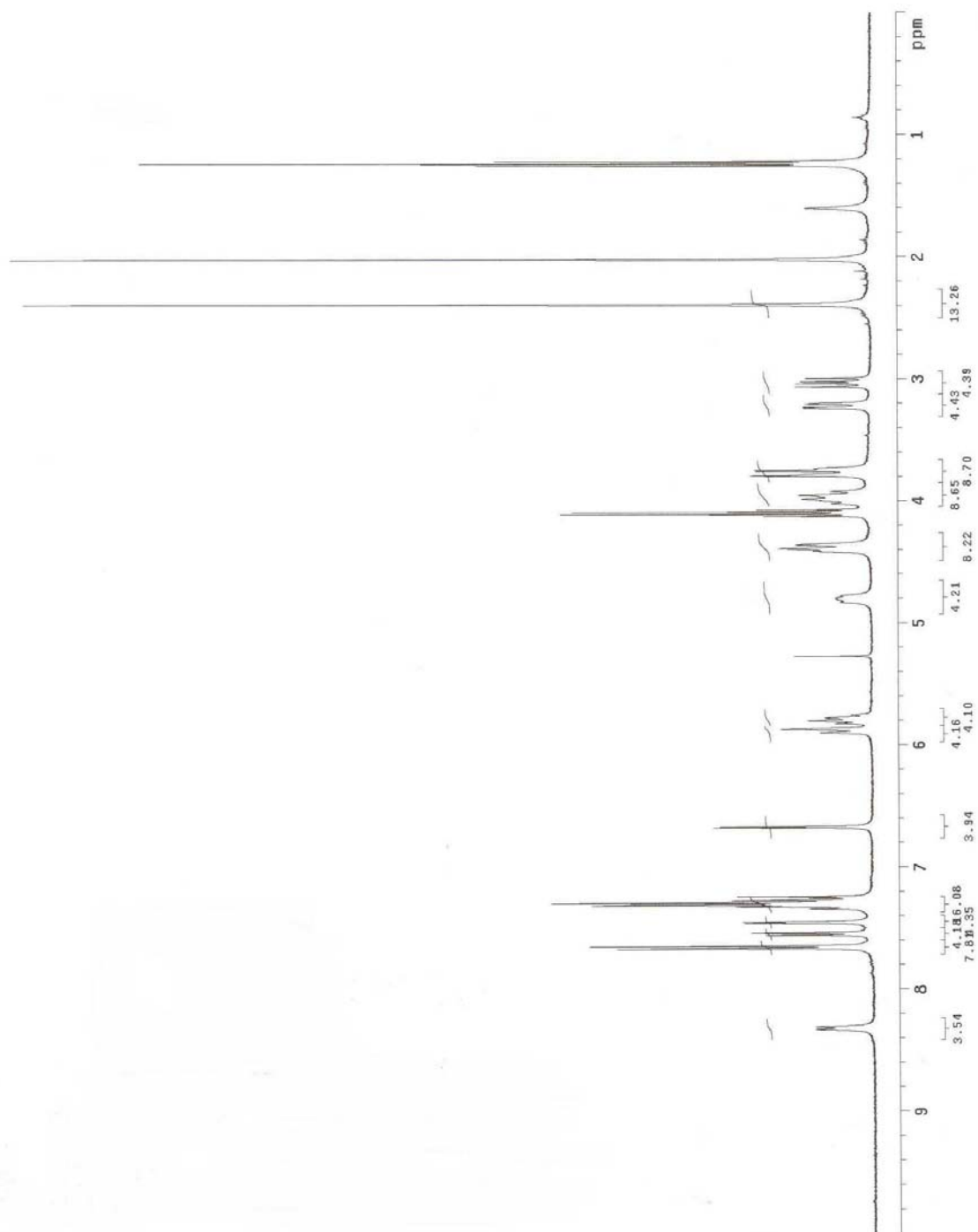
^1H NMR Spectrum of 15



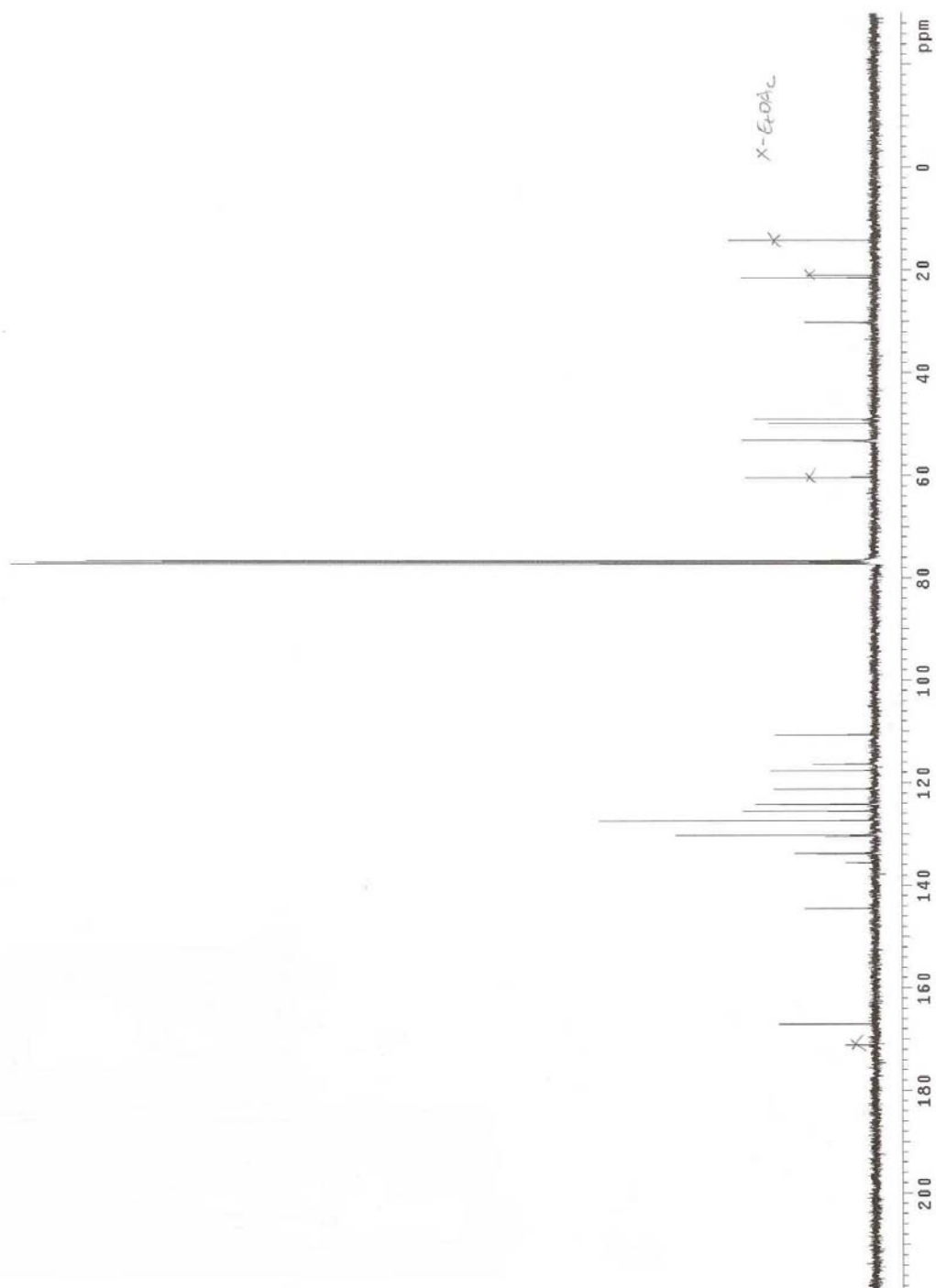
¹³C NMR Spectrum of 15



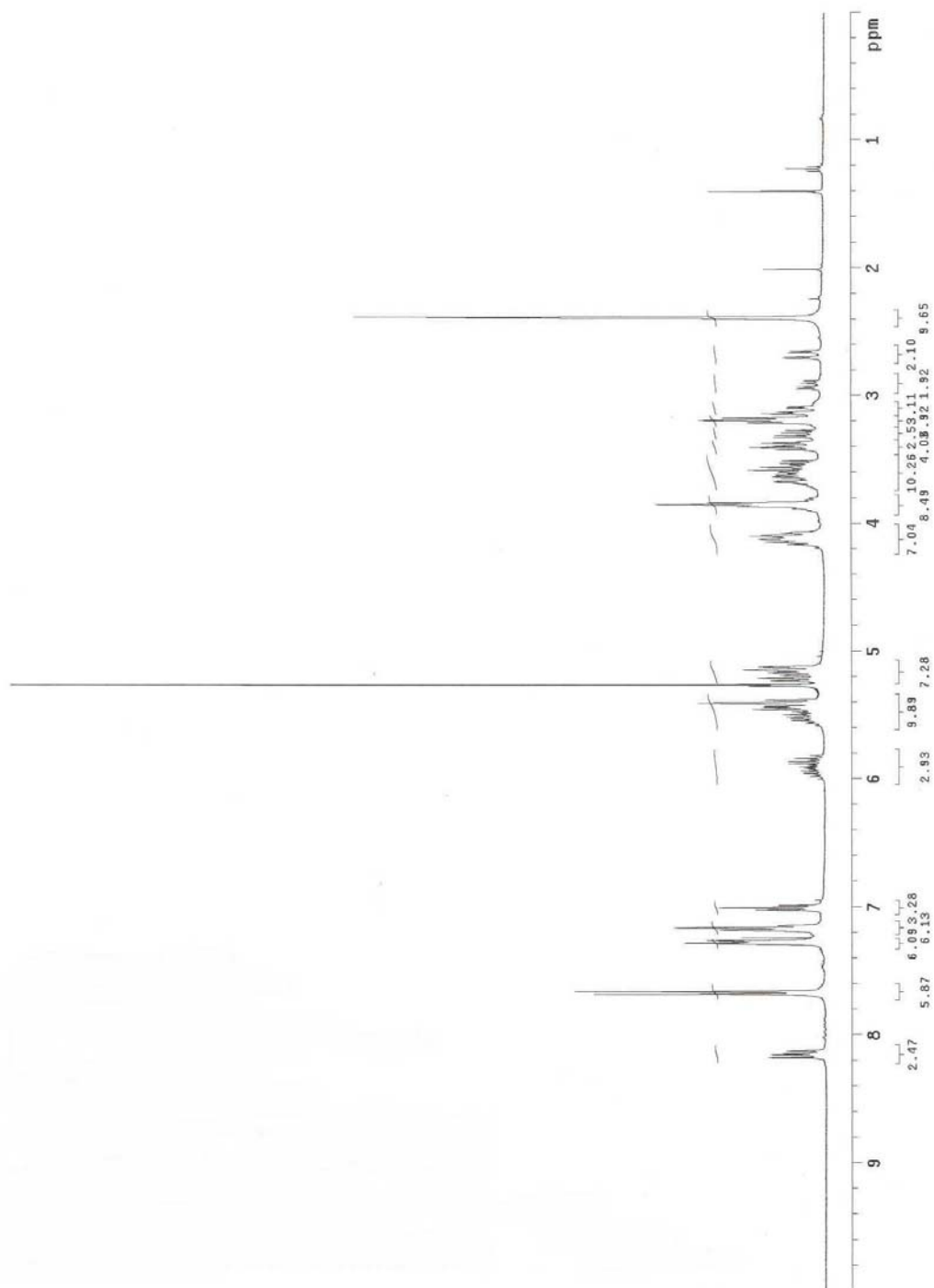
¹H NMR Spectrum of 16



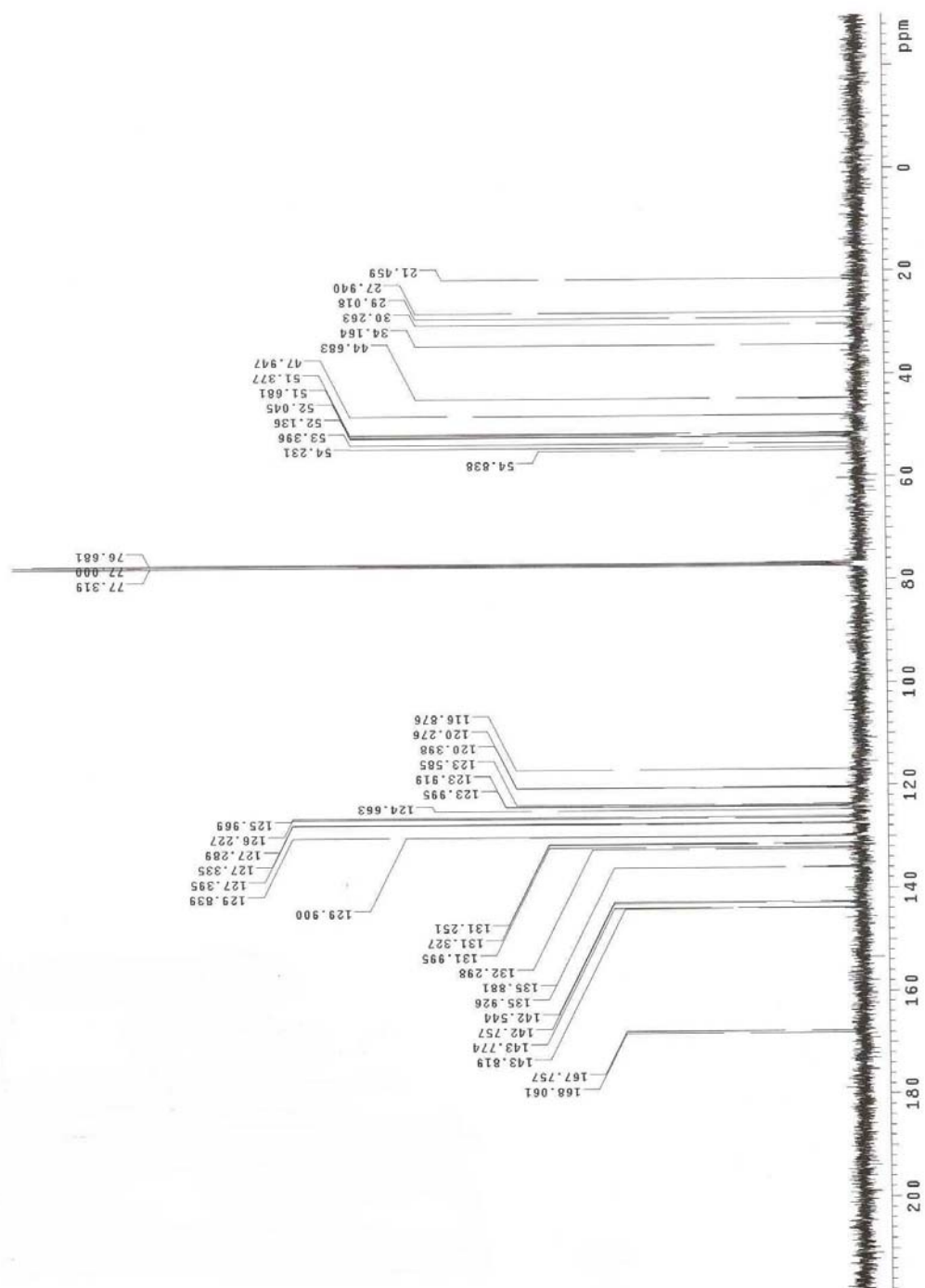
¹³C NMR Spectrum of 16



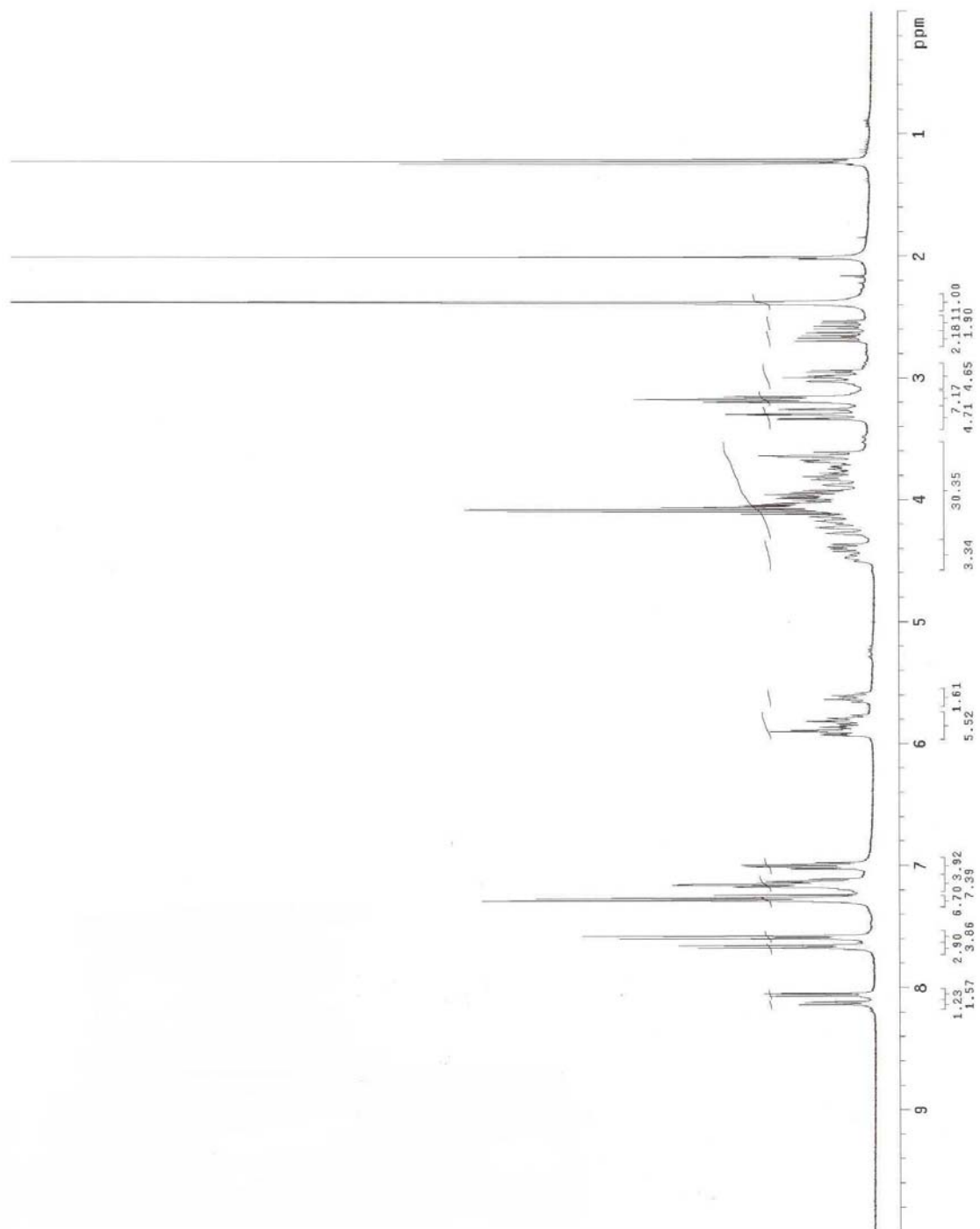
¹H NMR Spectrum of 17



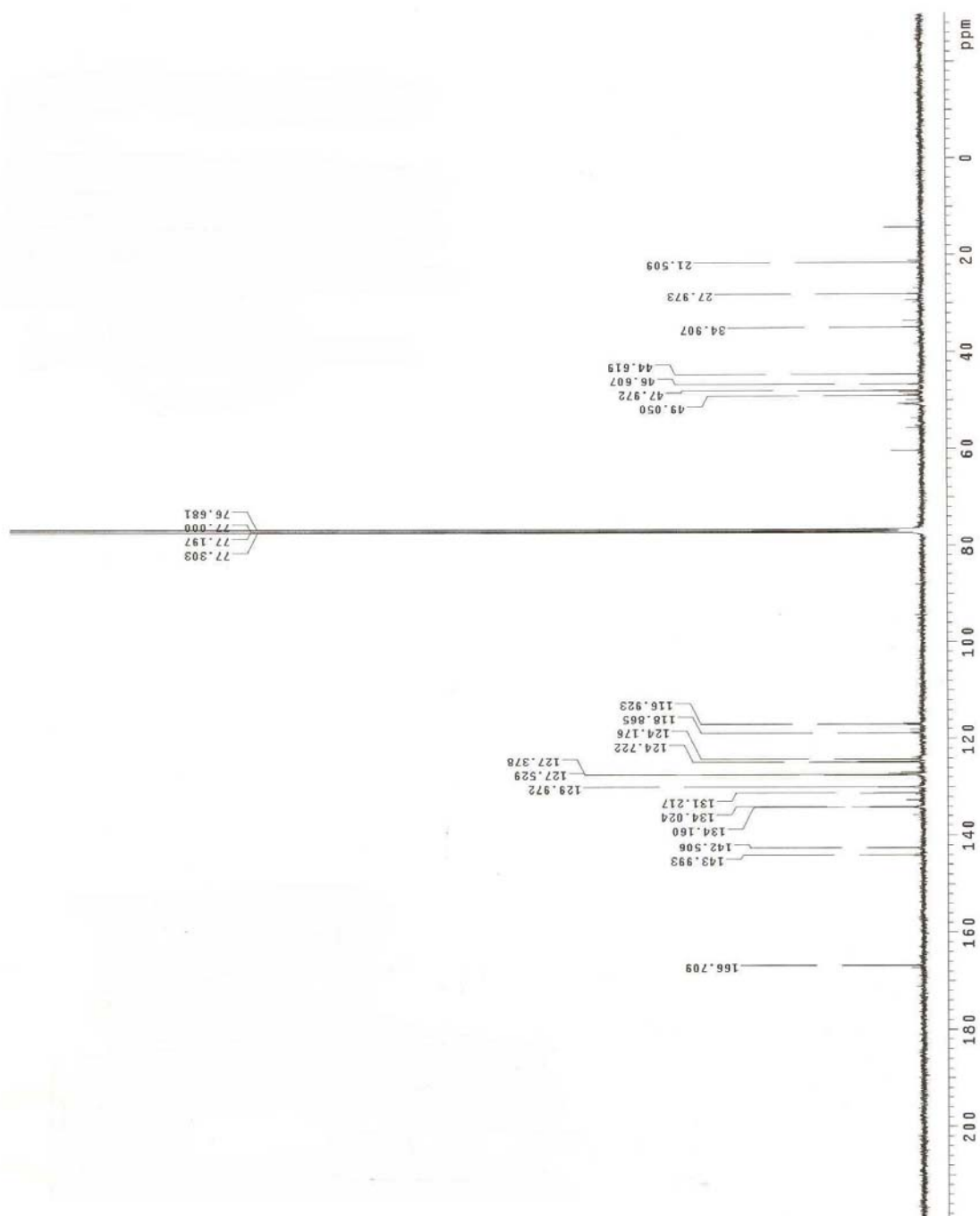
¹³C NMR Spectrum of 17



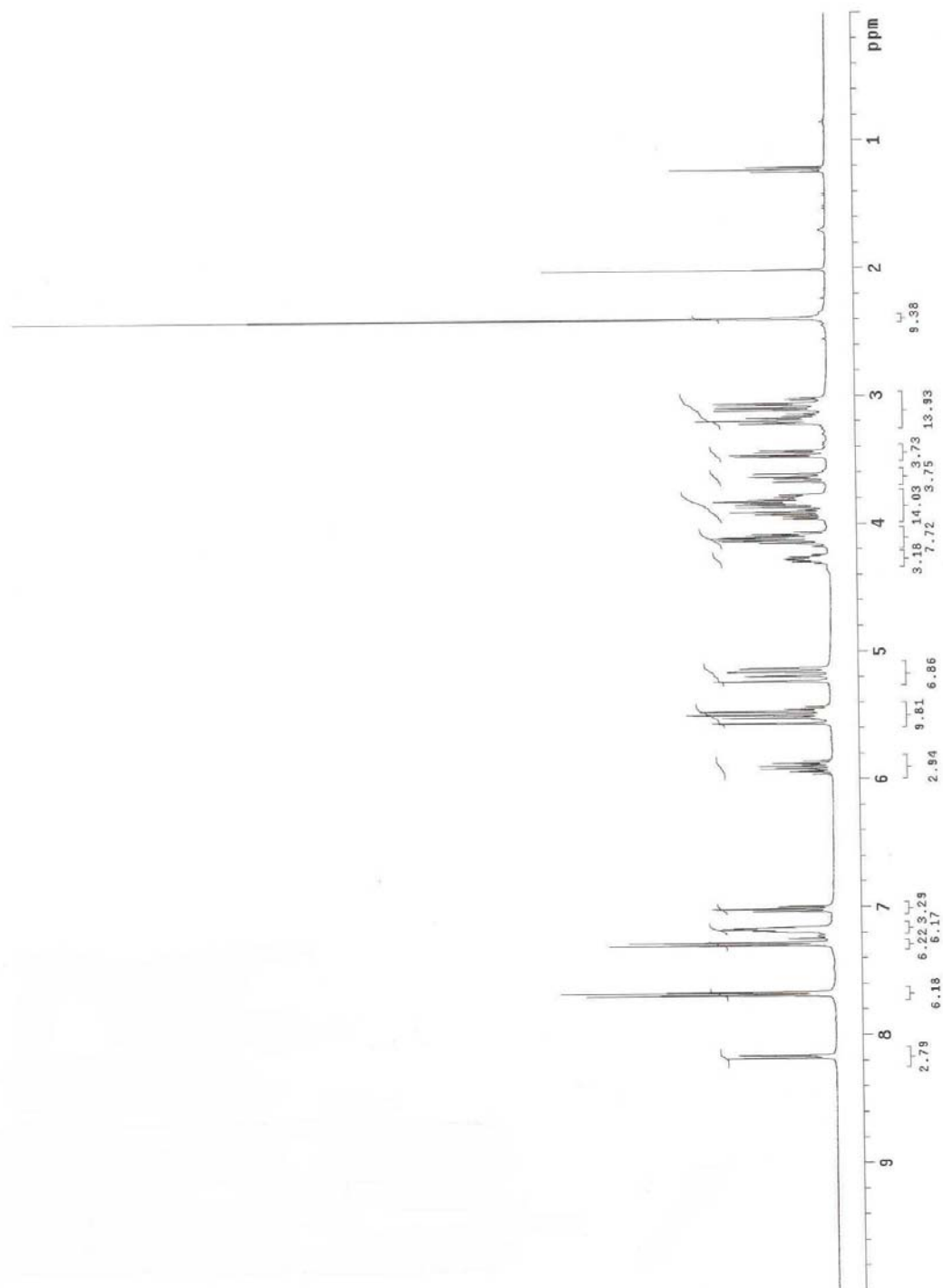
¹H NMR Spectrum of 18



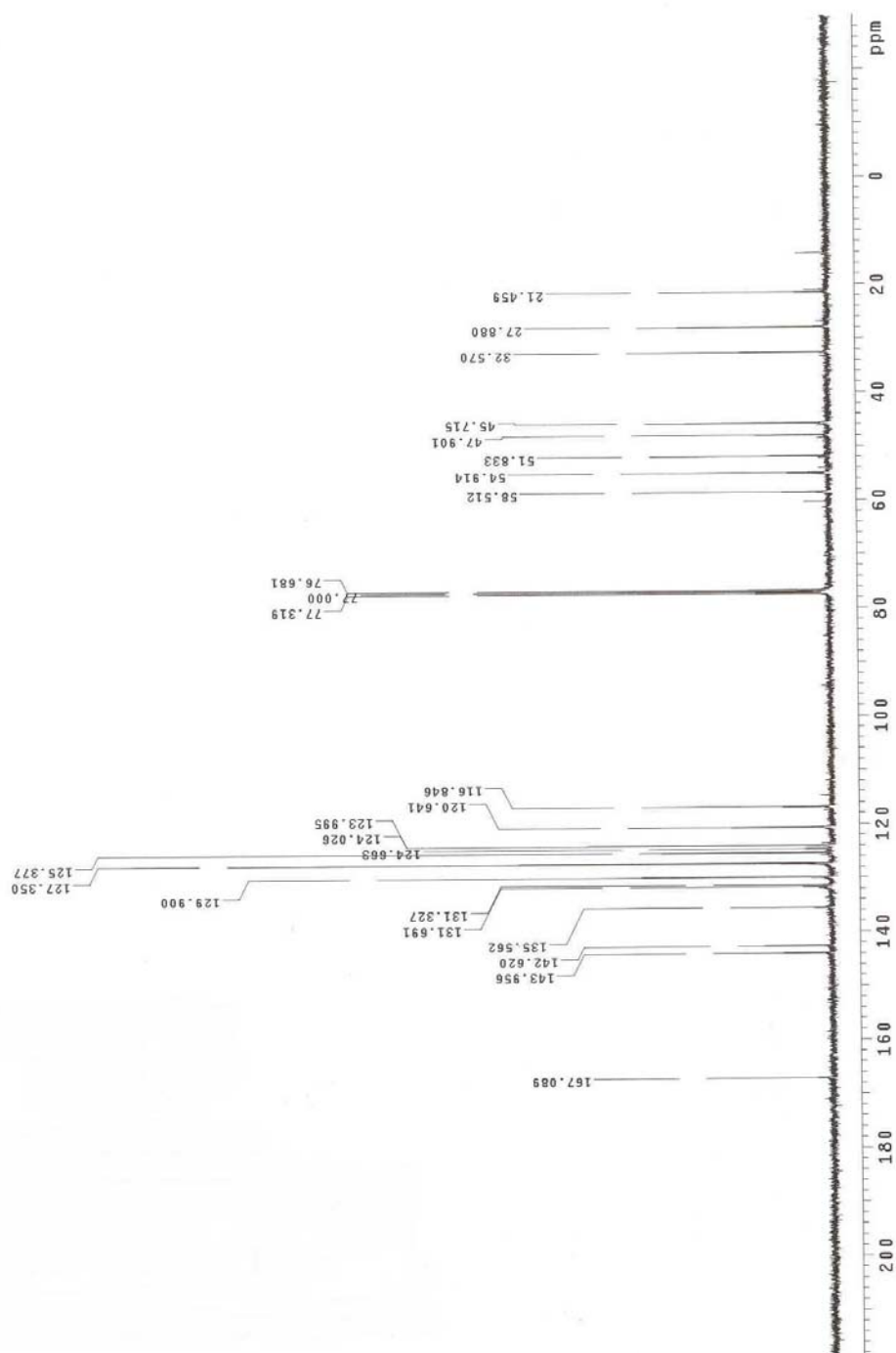
^{13}C NMR Spectrum of 18



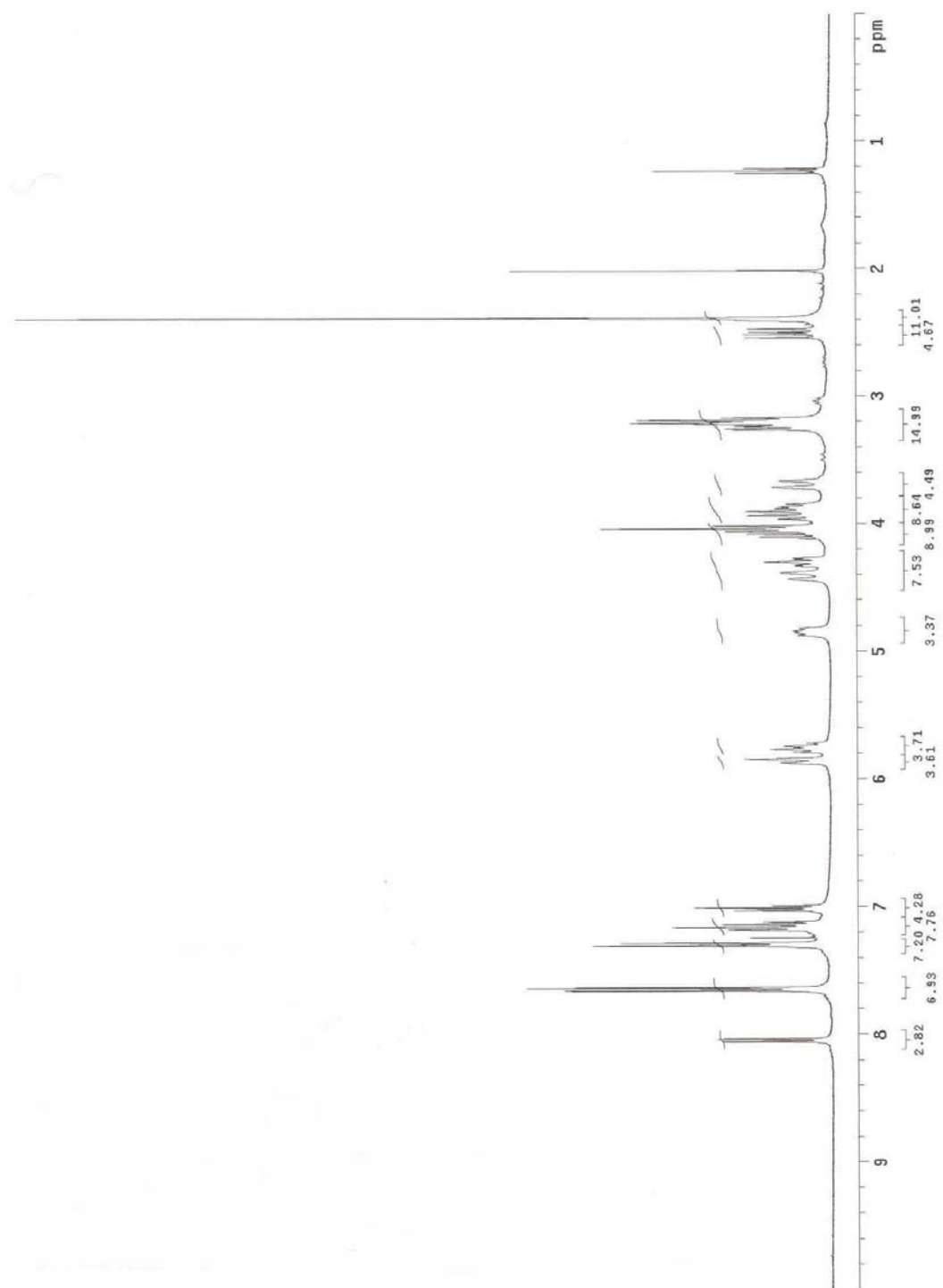
^1H NMR Spectrum of 19



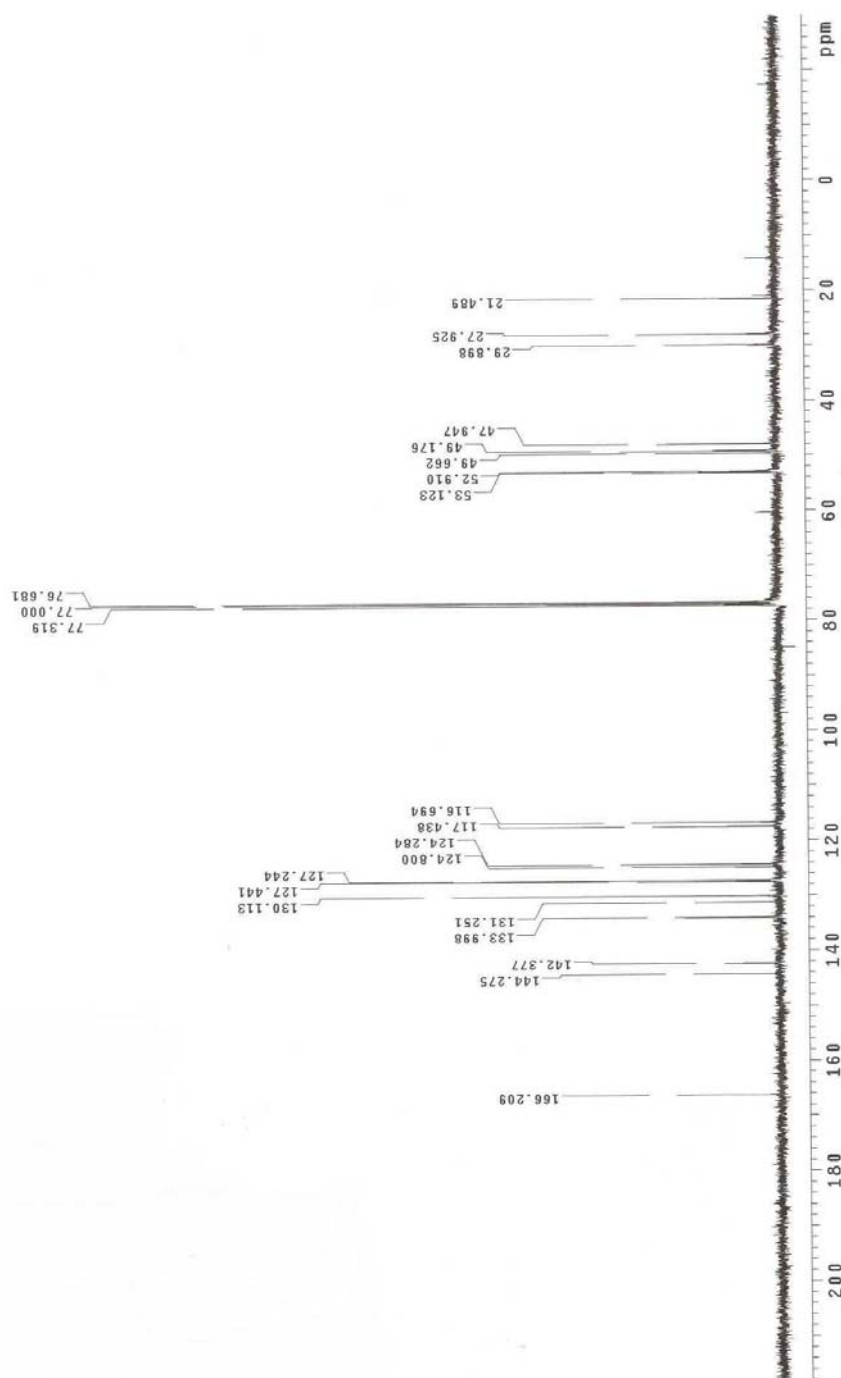
¹³C NMR Spectrum of 19



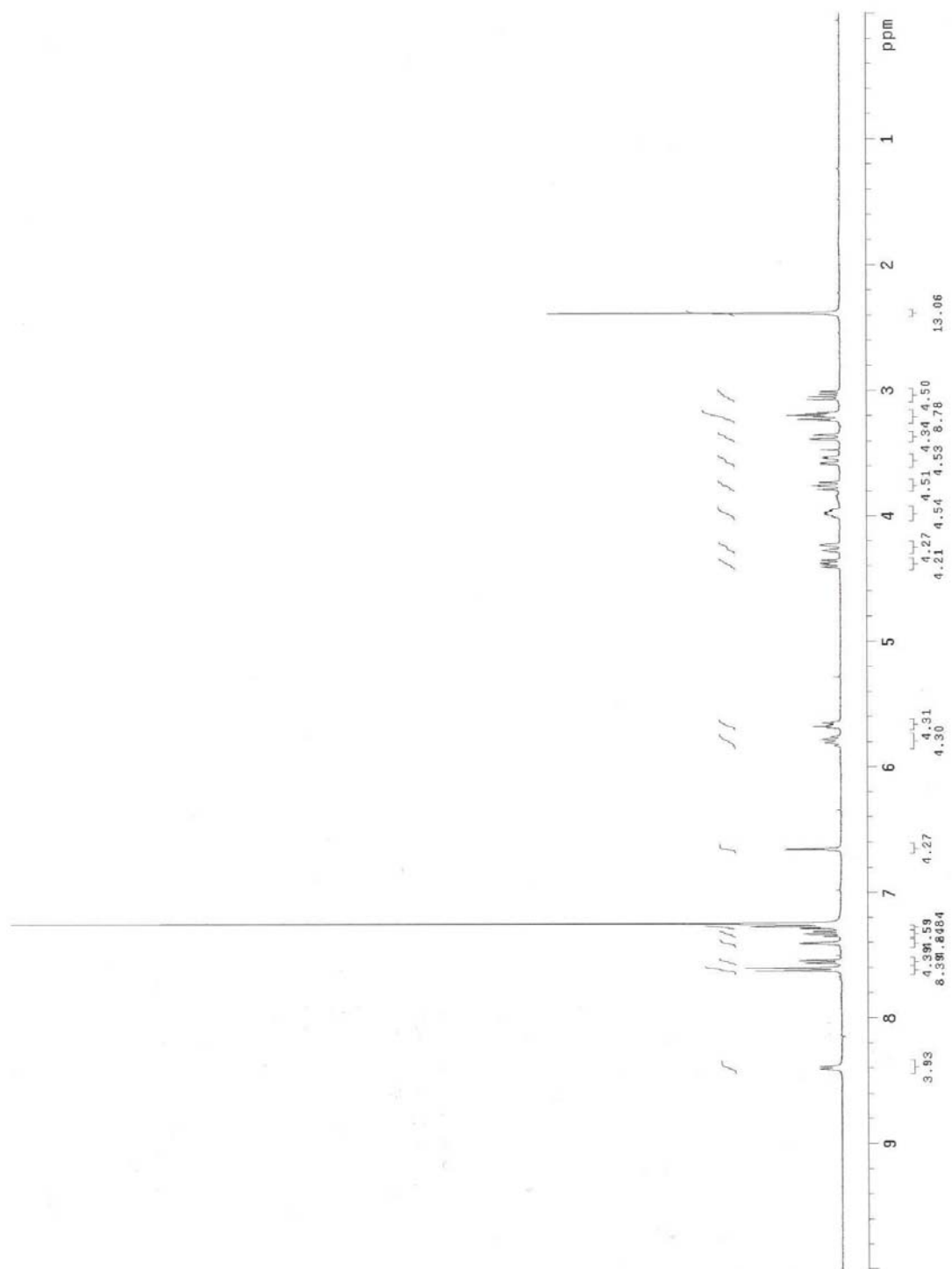
^1H NMR Spectrum of 20



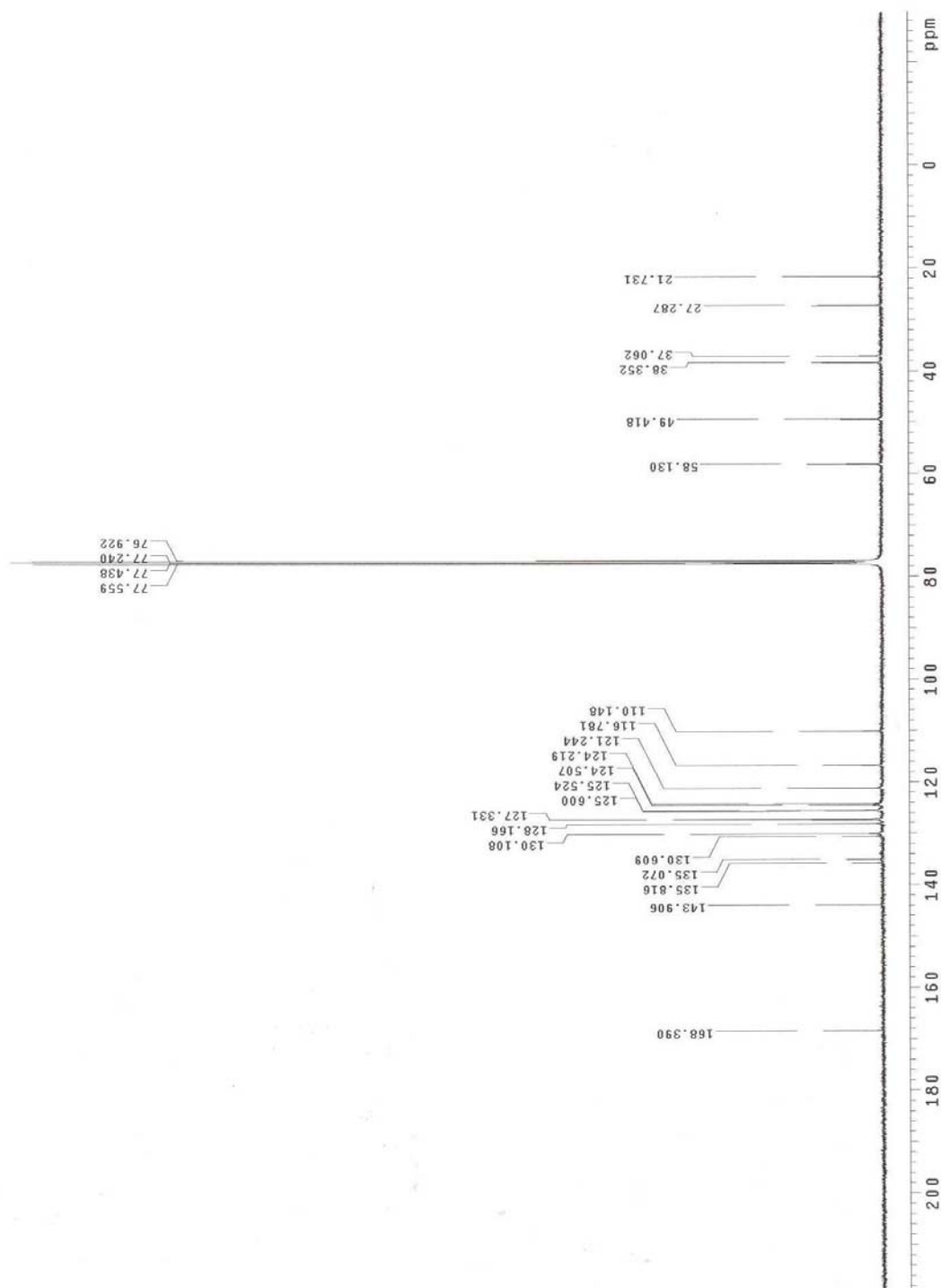
^{13}C NMR Spectrum of 20



^1H NMR Spectrum of 21



¹³C NMR Spectrum of 21



Appendix 3

Simple Thiazocine-2-acetic Acid Derivatives via Ring Closing Metathesis

Dallas K. Bates,* Xiaofen Li and Parag V. Jog

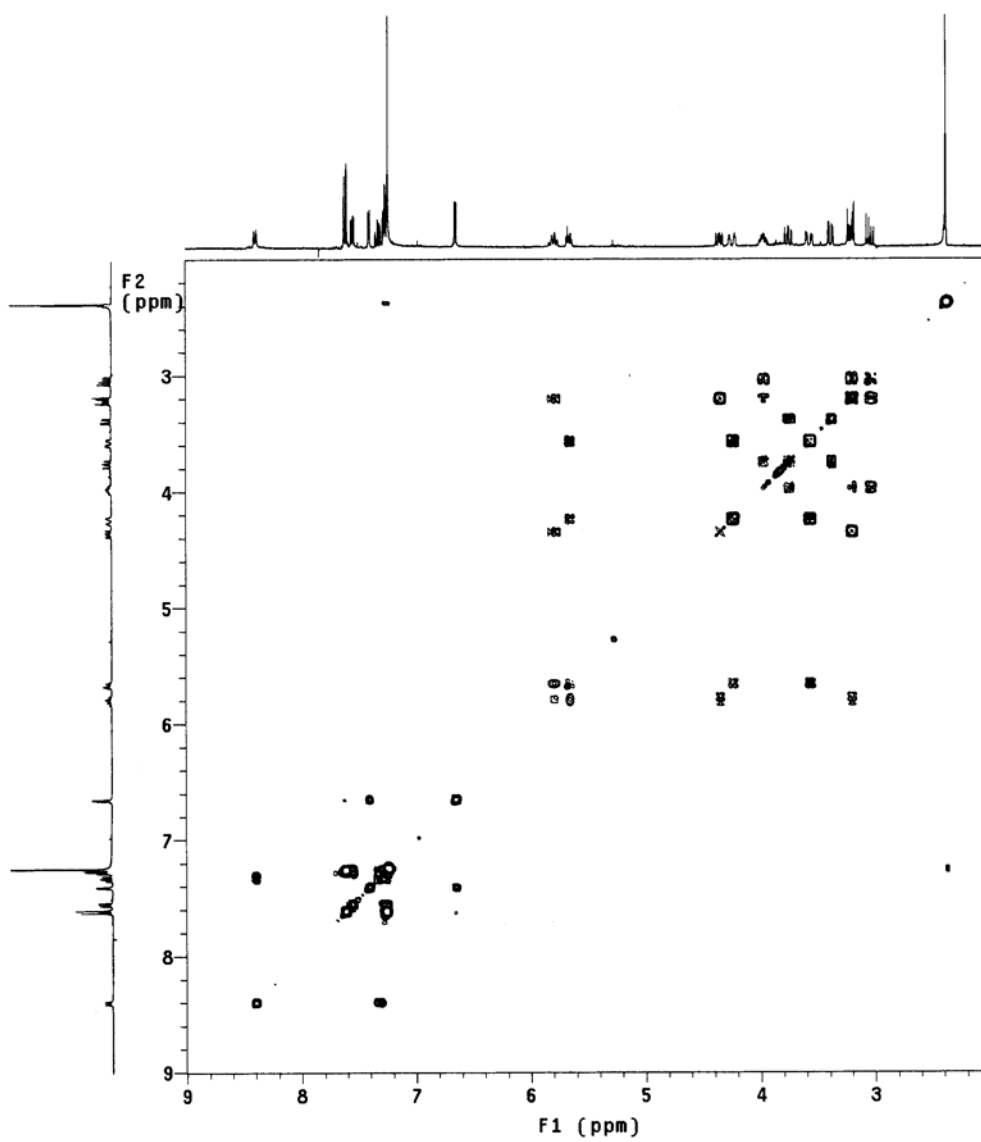
Additional Supplemental Information

(Compound numbers correspond to the numbers in the article:

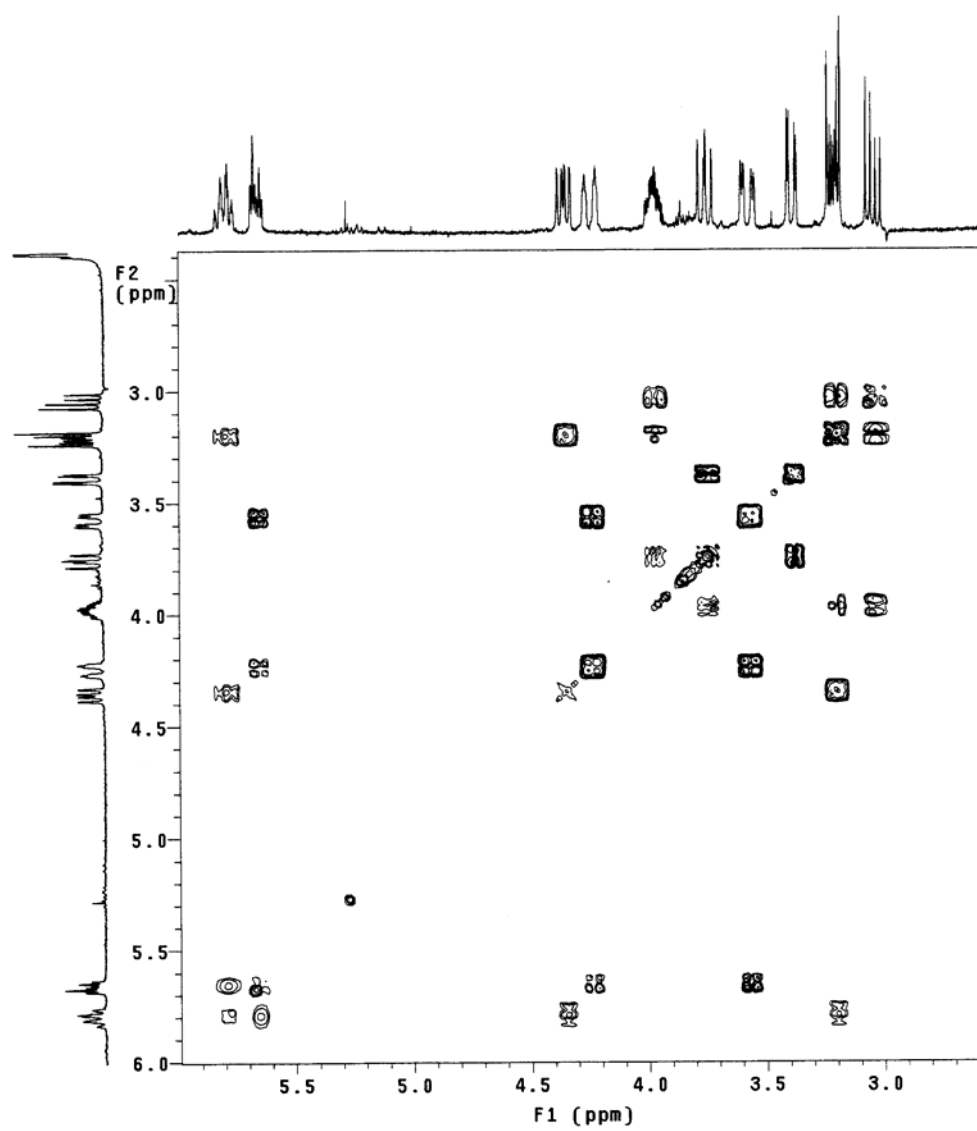
Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem.* **2004**, 69, 2750)

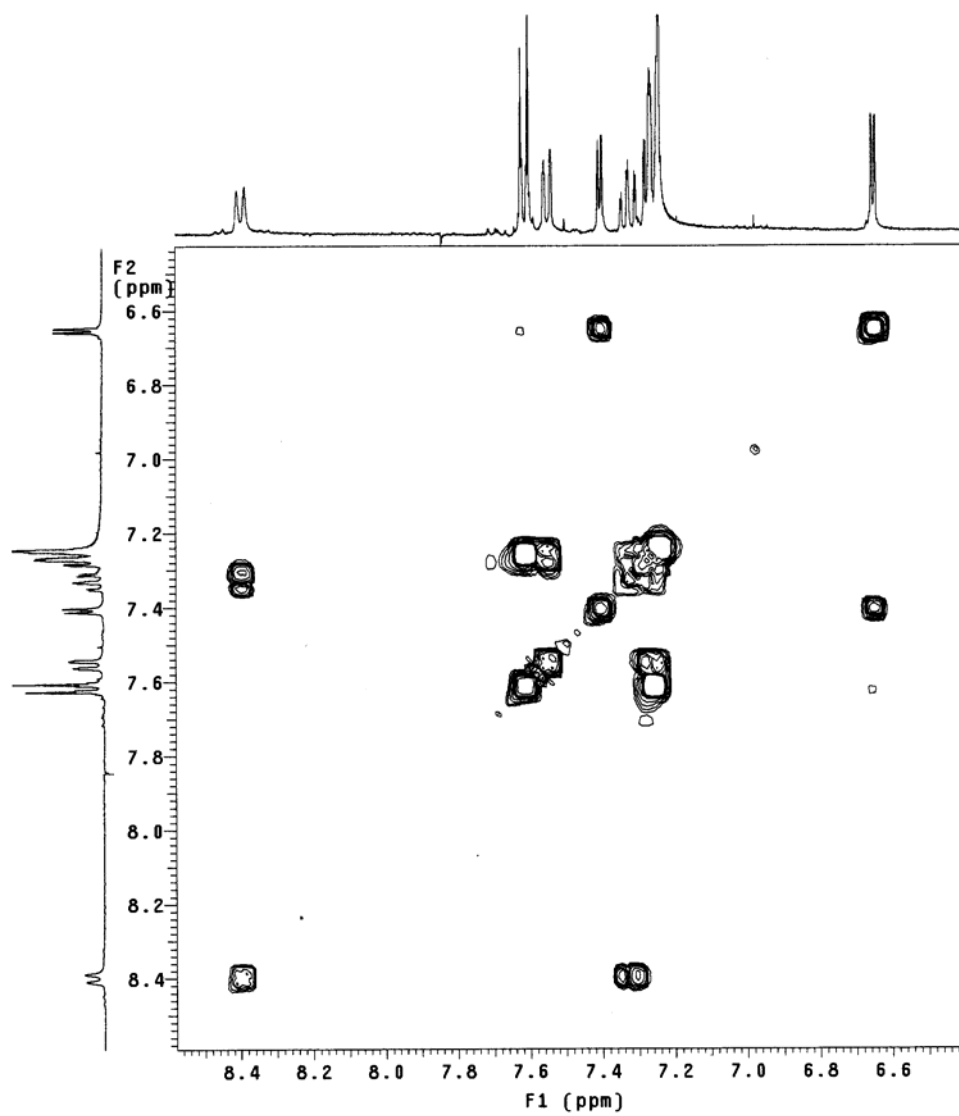
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^1H - ^1H COSY NMR Spectrum of **21**

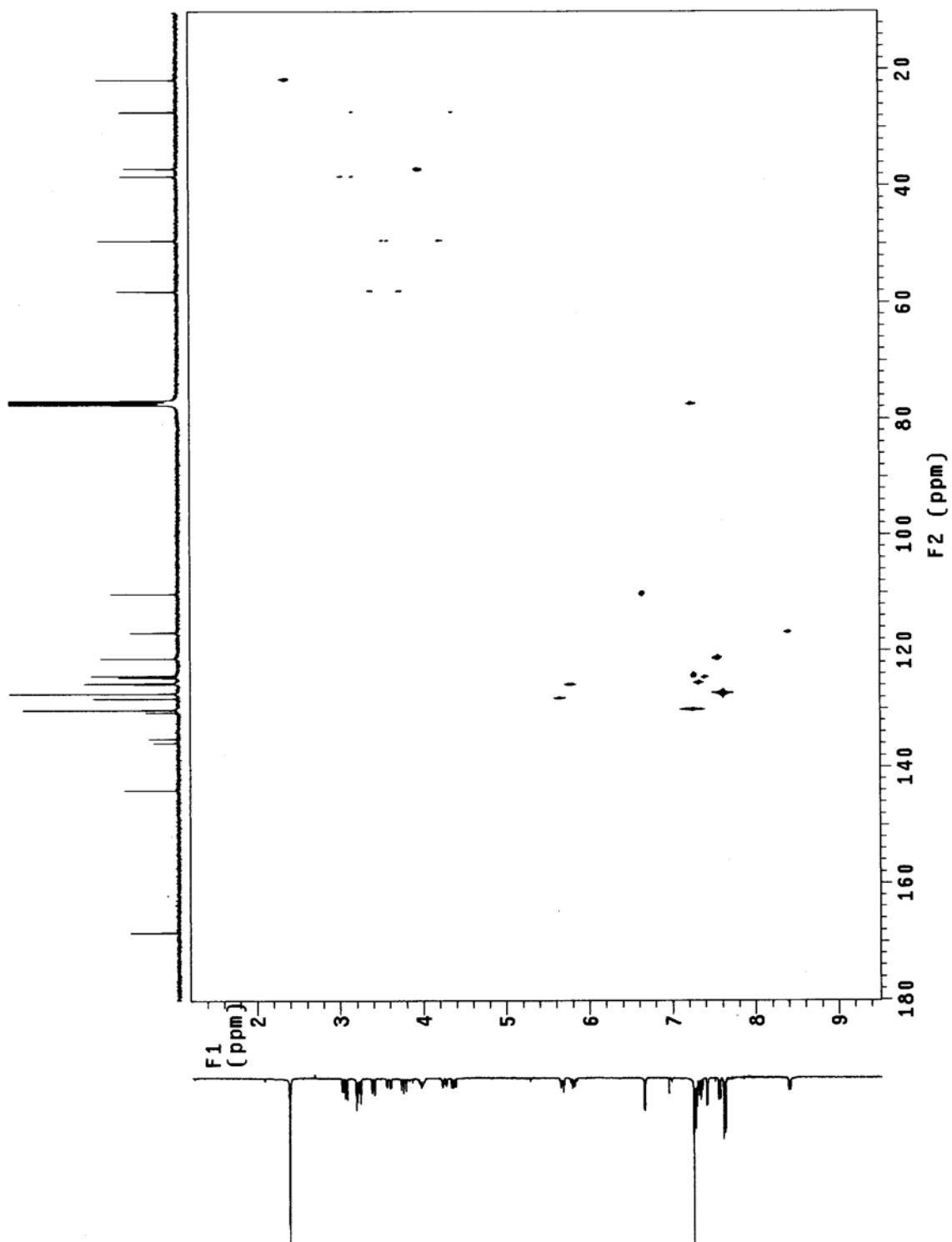


^1H - ^1H COSY NMR Spectrum of **21** (Expansion 1)

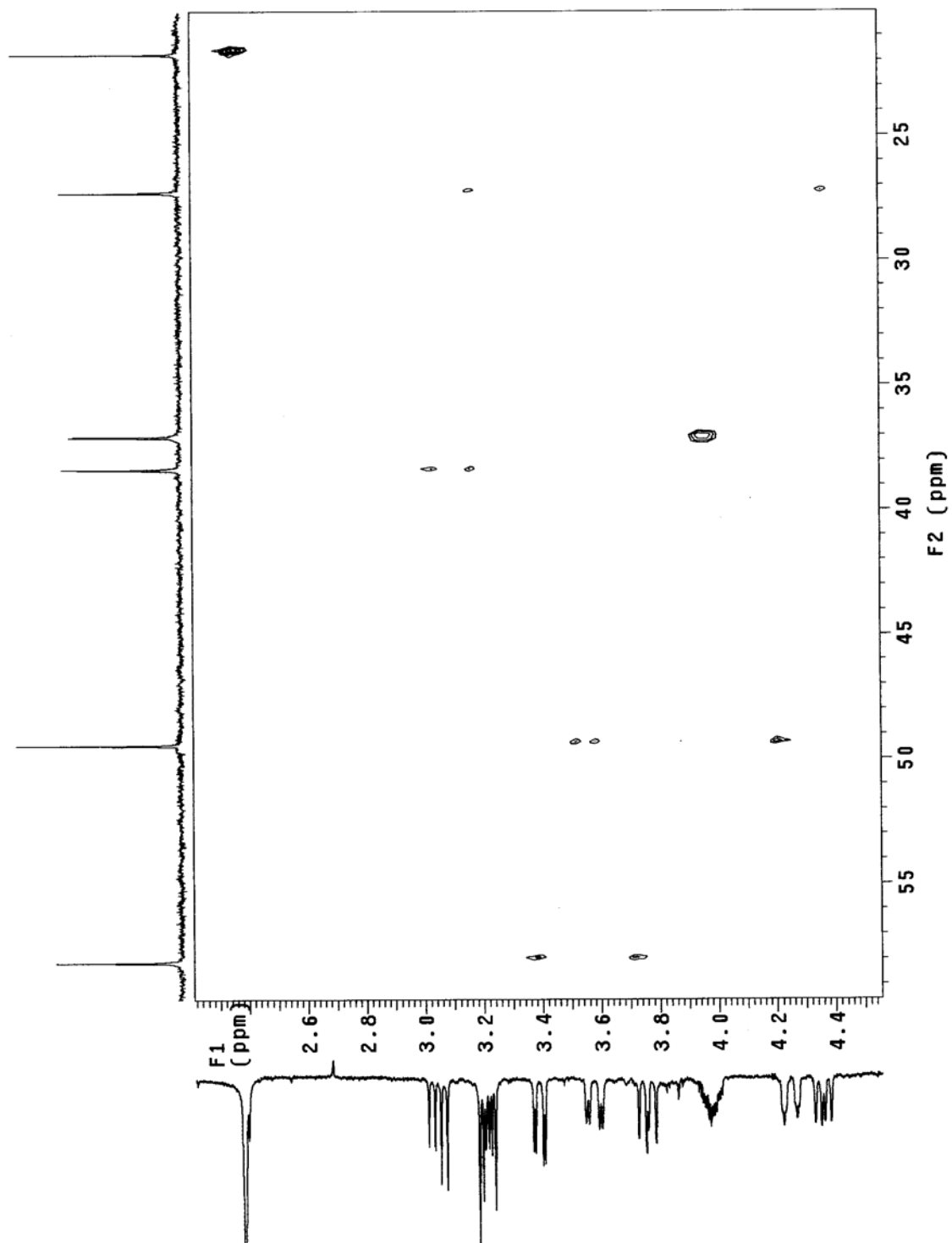


^1H - ^1H COSY NMR Spectrum of **21** (Expansion 2)

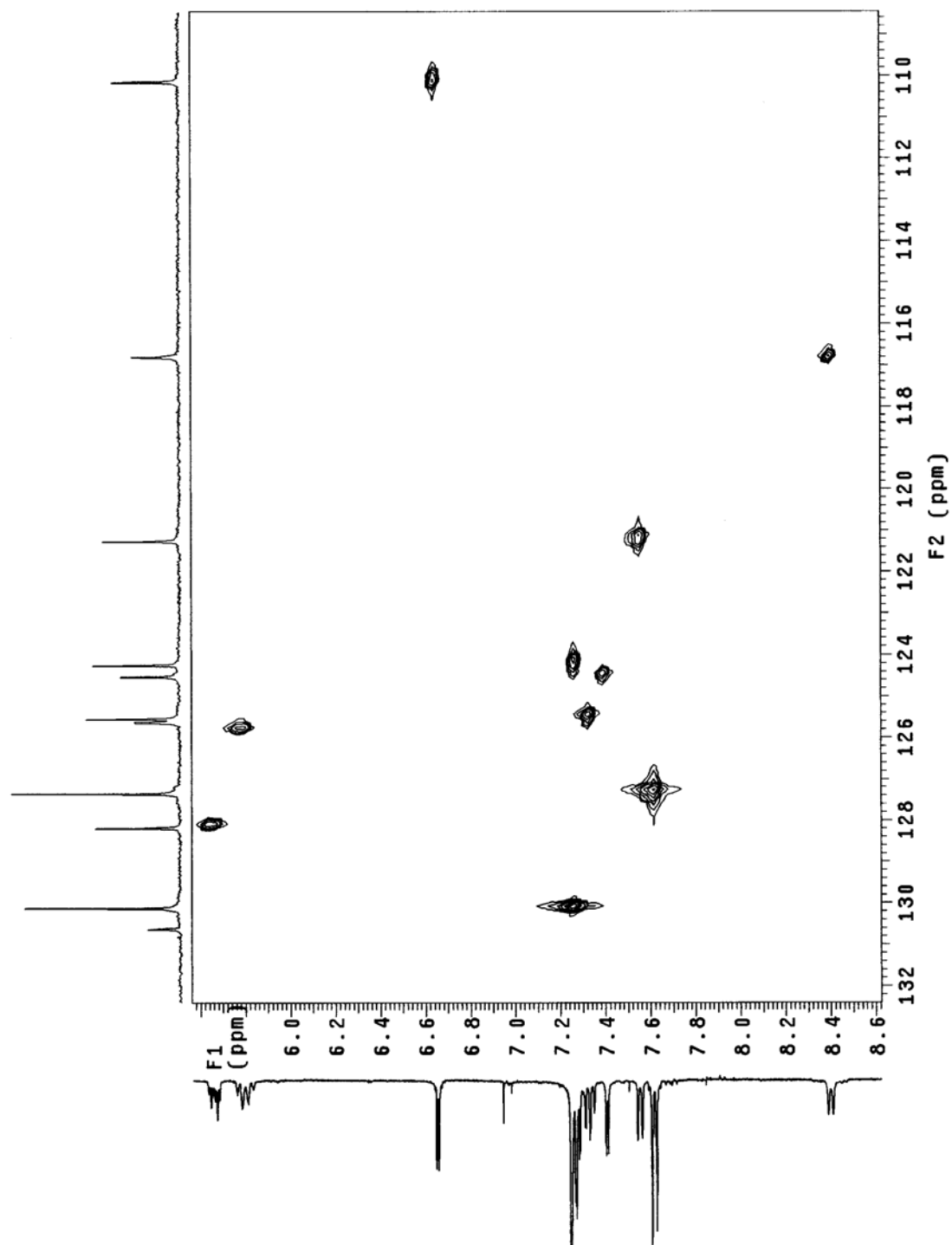
^1H - ^{13}C HETCOR NMR Spectrum of **21**



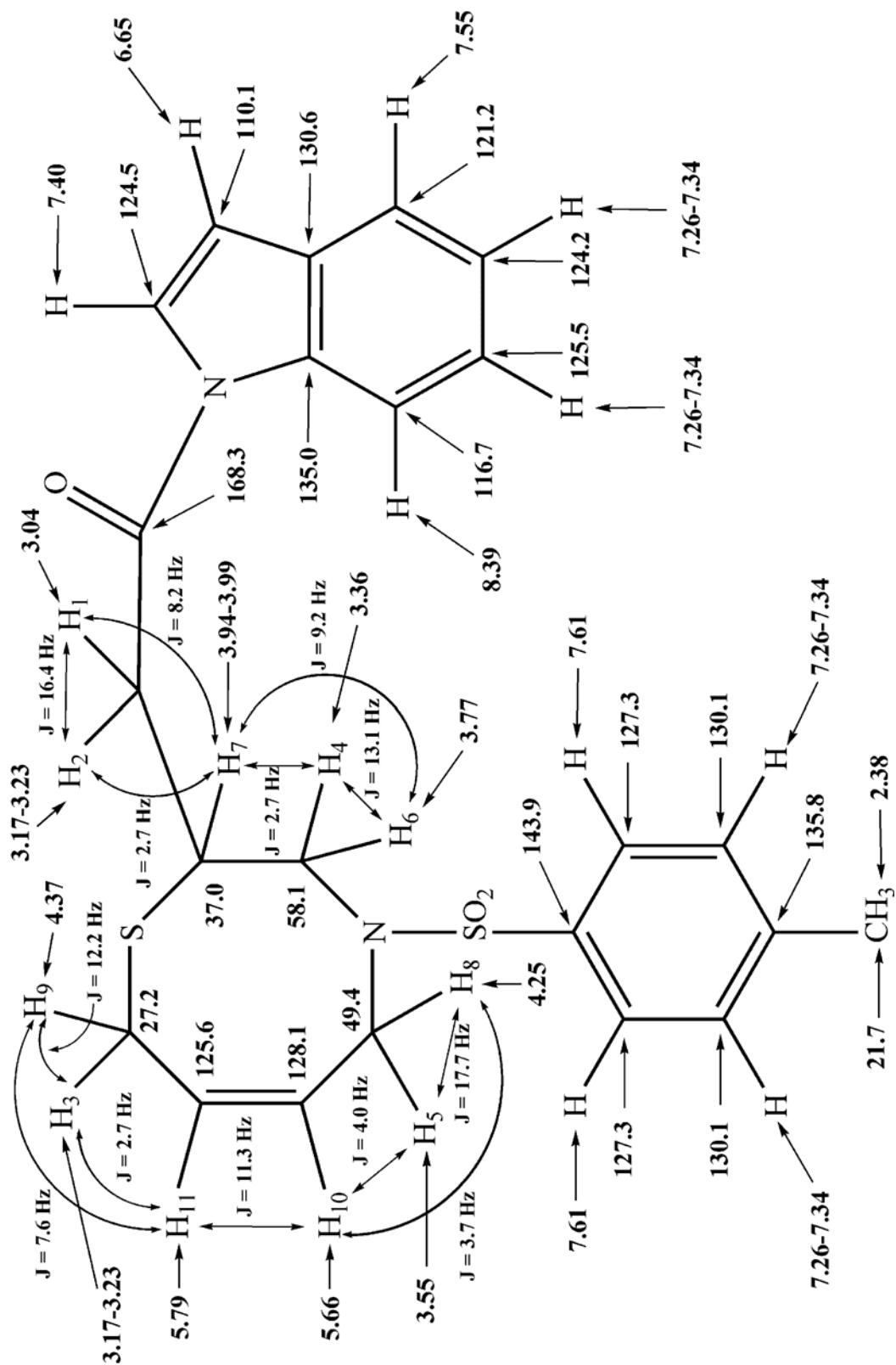
^1H - ^{13}C HETCOR NMR Spectrum of **21** (Expansion 1)



^1H - ^{13}C HETCOR NMR Spectrum of **21** (Expansion 2)



Peak Assignments in Compound 21



Appendix 4

A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and S-Oxidized Counterparts

Parag V. Jog, Richard E. Brown and Dallas K. Bates*

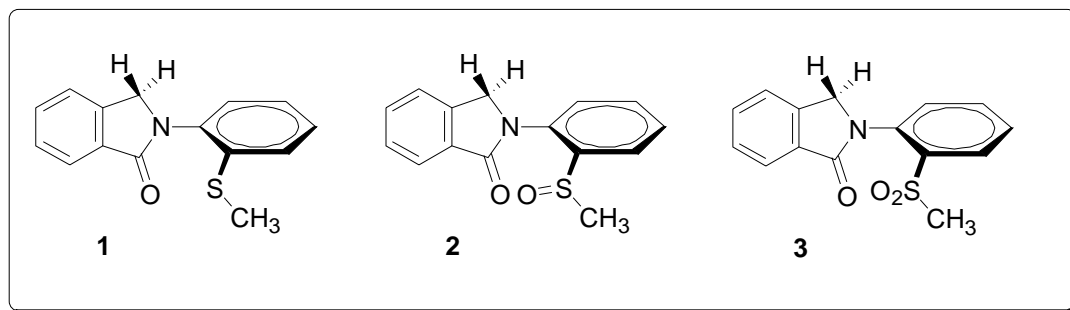
(Compound numbers correspond to the numbers in the article:

Jog, P. V.; Brown, R. E.; Bates, D. K. *J. Org. Chem.* **2003**, 68, 8240)

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Experimental Section

^1H and ^{13}C NMR spectra were recorded in CDCl_3 (unless otherwise noted) and were recorded at 400 MHz or 100 MHz, respectively. Mass spectra were obtained by electron impact (70 eV), relative intensities are given in parenthesis. IR spectra were recorded in chloroform solution. Column chromatography was carried out on silica gel (0.06-0.20 mm, pore diameter ~ 6 nm). Organic phases were dried over anhydrous Na_2SO_4 . Phthalaldehyde, 2-aminothiophenol, *m*-chloroperbenzoic acid were commercial samples and used without further purification.

2-[2-(methylthio)phenyl]isoindolin-1-one (1). *o*-Phthalaldehyde (4 mmol, 0.5 g) in AcOH (20 mL) was heated to reflux. To this was added dropwise 2-(methylthio)aniline (1.4 g, 10 mmol) in 2 mL of AcOH. After 20 min at reflux the mixture was poured into water and extracted with EtOAc. The organic layer was washed sequentially with 2*N* HCl, saturated NaHCO_3 and brine and then dried. Solvent was evaporated and the crude orange-red solid was purified by column chromatography (benzene/EtOAc, 80/20) and recrystallization (EtOAc) to give a white solid (0.32 g, 30 %): mp 153-154 °C; IR ν 1692 cm^{-1} ; ^1H NMR δ 2.40 (s, 3H), 4.77 (s, 2H), 7.21-7.38 (m, 4H), 7.49 (t, $J = 7.94$ Hz, 2H), 7.58 (dt, $J = 7.62, 0.89$ Hz, 1H), 7.94 (d, $J = 7.56$ Hz, 1H); ^{13}C NMR δ 15.5, 52.2, 123.0, 124.6, 126.1, 126.9, 128.3, 129.1, 129.1, 132.0, 132.3, 136.1, 138.3, 142.0, 168.3; MS (EI) [m/z (rel. intensity)] 255 [M^+ , 43], 208 (100), 180 (25). Anal. Calc. for $\text{C}_{15}\text{H}_{13}\text{NOS}$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.80; H, 5.32; N, 5.59.

2-[2-(methylsulfinyl)phenyl]isoindolin-1-one (2). To an ice-cooled solution of **1** (0.1 g, 0.39 mmol) in CH_2Cl_2 (20 mL) was added slowly a solution of *m*-CPBA (1.1eq, 0.43 mmol, 0.074 g) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at 0 °C for 15 min

and then put it in a freezer (-8 °C) overnight. The reaction mixture was then poured into 5% NaHCO₃ solution (40 mL) and extracted with CH₂Cl₂ (40 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc) gave yellowish white solid (0.082 g, 77 %), which was recrystallized (EtOAc-hexane, 8:2) to give a white solid: mp 161-162 °C; IR ν 1698 cm⁻¹; ¹H NMR δ 2.88 (s, 3H), 4.84 (s, 2H), 7.29 (dd, J = 7.67, 1.44 Hz, 1H), 7.50–7.64 (m, 5H), 7.89 (d, J = 7.46 Hz, 1H), 8.11 (dd, J = 7.64, 1.67 Hz, 1H); ¹³C NMR δ 43.3, 53.4, 123.2, 124.6, 125.5, 127.4, 128.8, 129.8, 131.3, 132.5, 132.7, 135.2, 141.7, 144.9, 169.1; MS (EI) [m/z (rel. intensity)] 271 [M⁺, 23], 254 (100), 238 (77), 208 (53). Anal. Calc. for C₁₅H₁₃ NO₂S: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.18; H, 4.94; N, 4.97.

2-[2-(methylsulfonyl)phenyl]isoindolin-1-one (3). To an ice-cooled solution of **1** (0.10 g, 0.39 mmol) in CH₂Cl₂ (20 mL) was added a solution of *m*-CPBA (2.2 eq, 0.86 mmol, 0.15 g) in CH₂Cl₂ (10 mL). The resulting mixture was stirred at room temperature for 18 h, then poured into 5% NaHCO₃ (40 mL) solution. The aqueous layer was extracted with CH₂Cl₂ (30 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc: hexane, 6:4) gave yellowish white solid (0.091 g, 82%), which was recrystallized (EtOAc-hexane, 7:3) to give a white solid: mp 186-187 °C; IR ν 1694 cm⁻¹; ¹H NMR δ 3.15 (s, 3H), 4.84 (br, 2H), 7.39 (dd, J = 7.83, 1.2 Hz, 1H), 7.48-7.53 (m, 2H), 7.59-7.64 (m, 2H), 7.74 (dt, J = 7.65, 4.6 Hz, 1H), 7.89 (d, J = 7.59 Hz, 1H), 8.17 (d, J = 7.94, 1.48 Hz, 1H); ¹³C NMR δ 44.2, 55.5, 123.2, 124.4, 128.5, 129.8, 131.1, 131.5, 131.7, 132.5, 135.3, 137.8, 140.0, 142.6, 169.8; MS (EI) [m/z (rel. intensity)] 287 [M⁺, 34], 208 (100), 179 (17), 105 (50). Anal. Calc. for C₁₅H₁₃ NO₃S: C, 62.70; H, 4.56; N, 4.87. Found: C 62.69; H 4.59; N 4.76.

Computational procedures. Rate constants at the coalescence temperature (k_c) were calculated using the standard equation for an AB coupled system (eq 1). ΔG^\ddagger (in Kcal mol⁻¹) was calculated from rate constants obtained by line shape analysis of the methylene protons in ¹H NMR spectra taken at various temperatures using eq 2. Probe temperatures were measured using a neat methanol sample and automated calibration procedures. Plotting $\log \frac{k}{T}$ vs $\frac{1}{1000T}$ gives ΔH^\ddagger (in Kcal mol⁻¹) as -4.576 times the slope and ΔS^\ddagger (in cal mol⁻¹) was calculated according to eq 3. For a detailed discussion of these procedures see: (a) Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982, pp. 84-100. (b) Nelson, J. H. *Nuclear Magnetic Resonance Spectroscopy*; Prentice Hall: Upper Saddle River, NJ, 2003, Chapter 11.

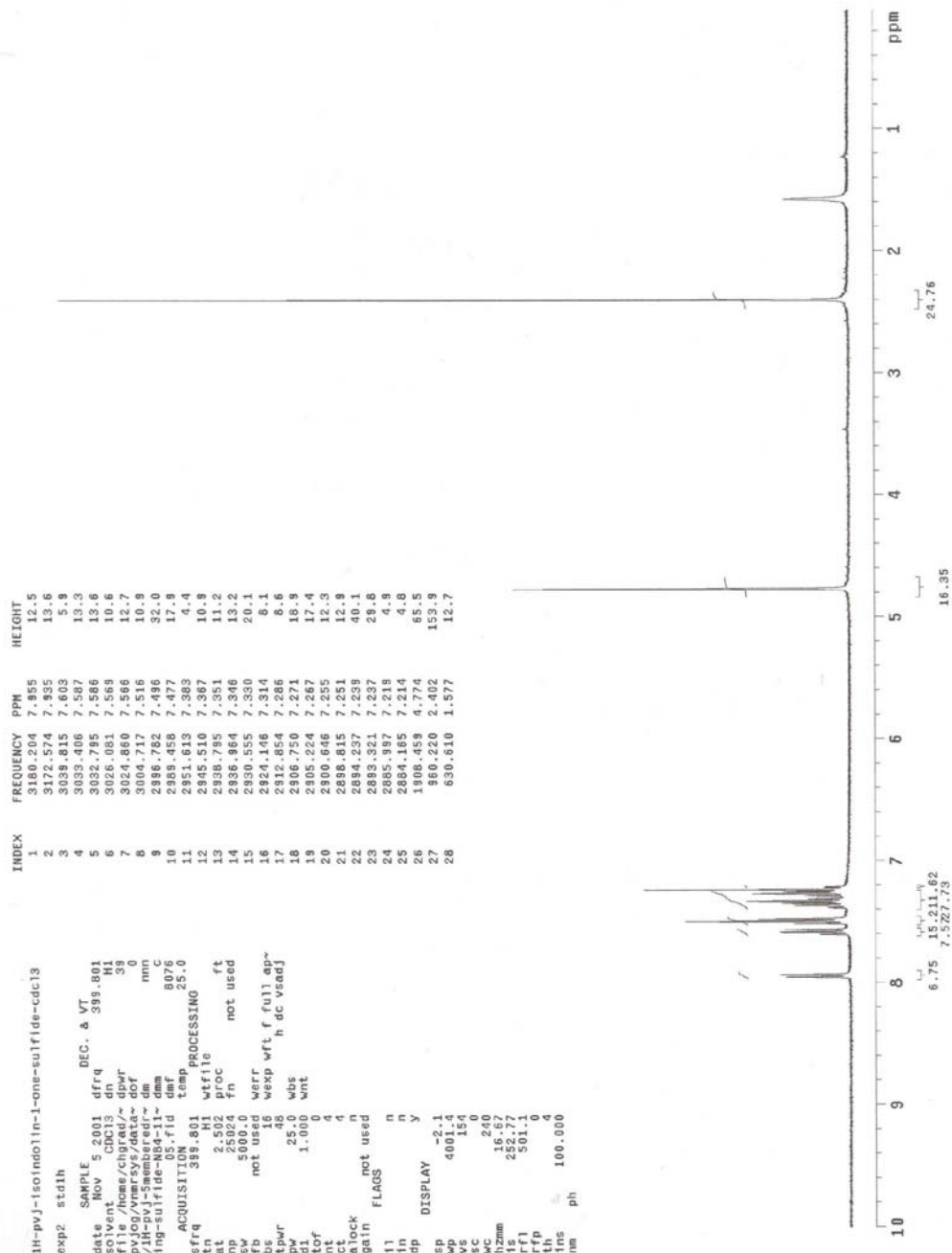
$$k_c = 2.22\sqrt{(\nu_A - \nu_B)^2 - 6J_{AB}^2} \quad (1)$$

$$\Delta G^\ddagger = 4.575 \times 10^{-3} T \left[10.319 + \log \left(\frac{T}{k} \right) \right] \quad (2)$$

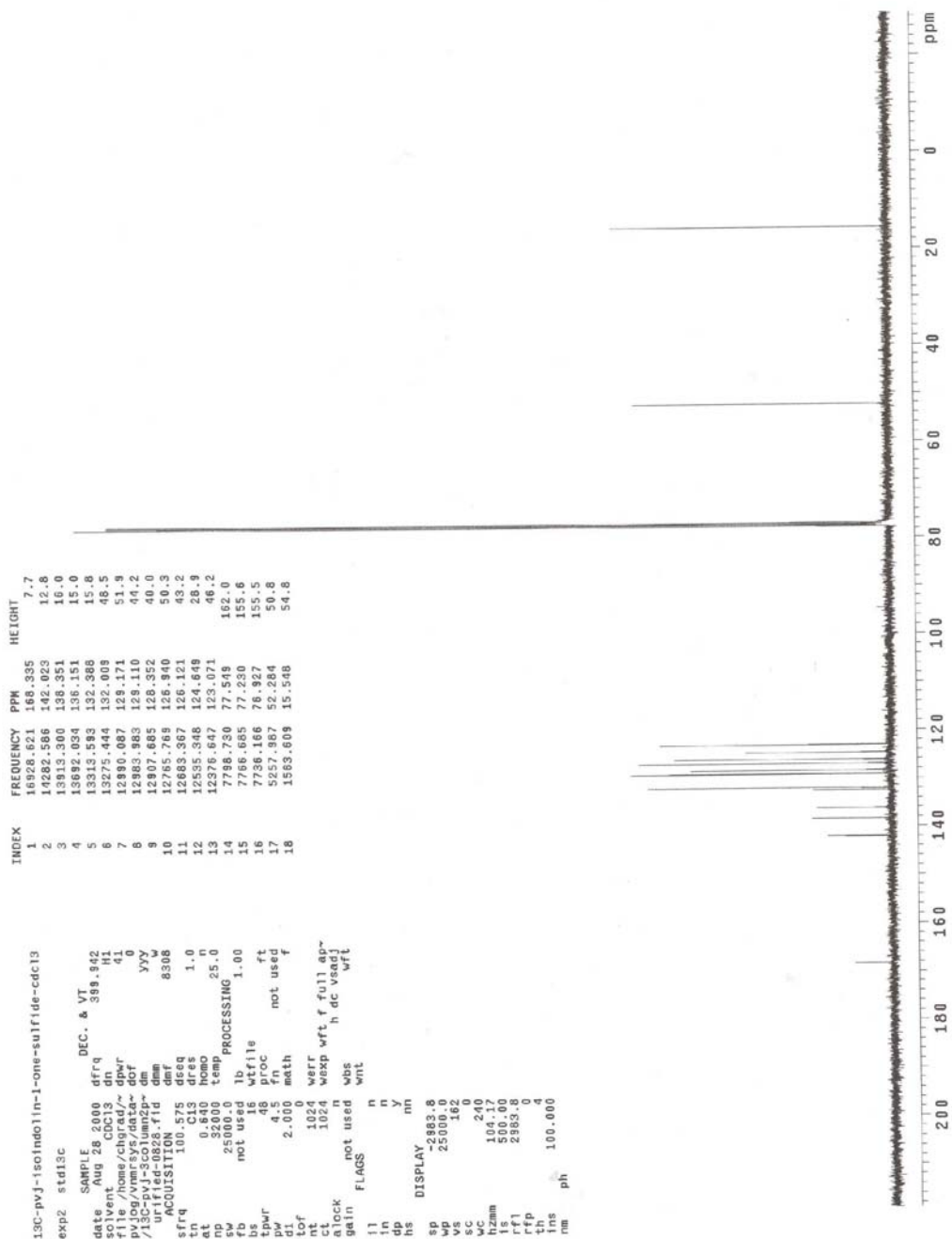
$$\Delta S^\ddagger = 4.576 \log \frac{k}{T} + \frac{\Delta H^\ddagger}{T} - 47.218 \quad (3)$$

Structures **1**, **2** and **3** were optimized in PM3 by driving the N-Ar and S-Ar torsion angles in 20 ° steps from 0 ° to 360 ° and allowing the other angles and bond distances to relax to their minima for each fixed value of the torsion angles. The barriers (ΔG^\ddagger) were computed by locating the transition state (saddle point) by the QST3 method followed by frequency calculations of the minima on either side of the transition state and at the transition state (TS). Z-matrices for minima on both sides of the TS and for the TS are provided in the Supplemental Information (pp 224-232).

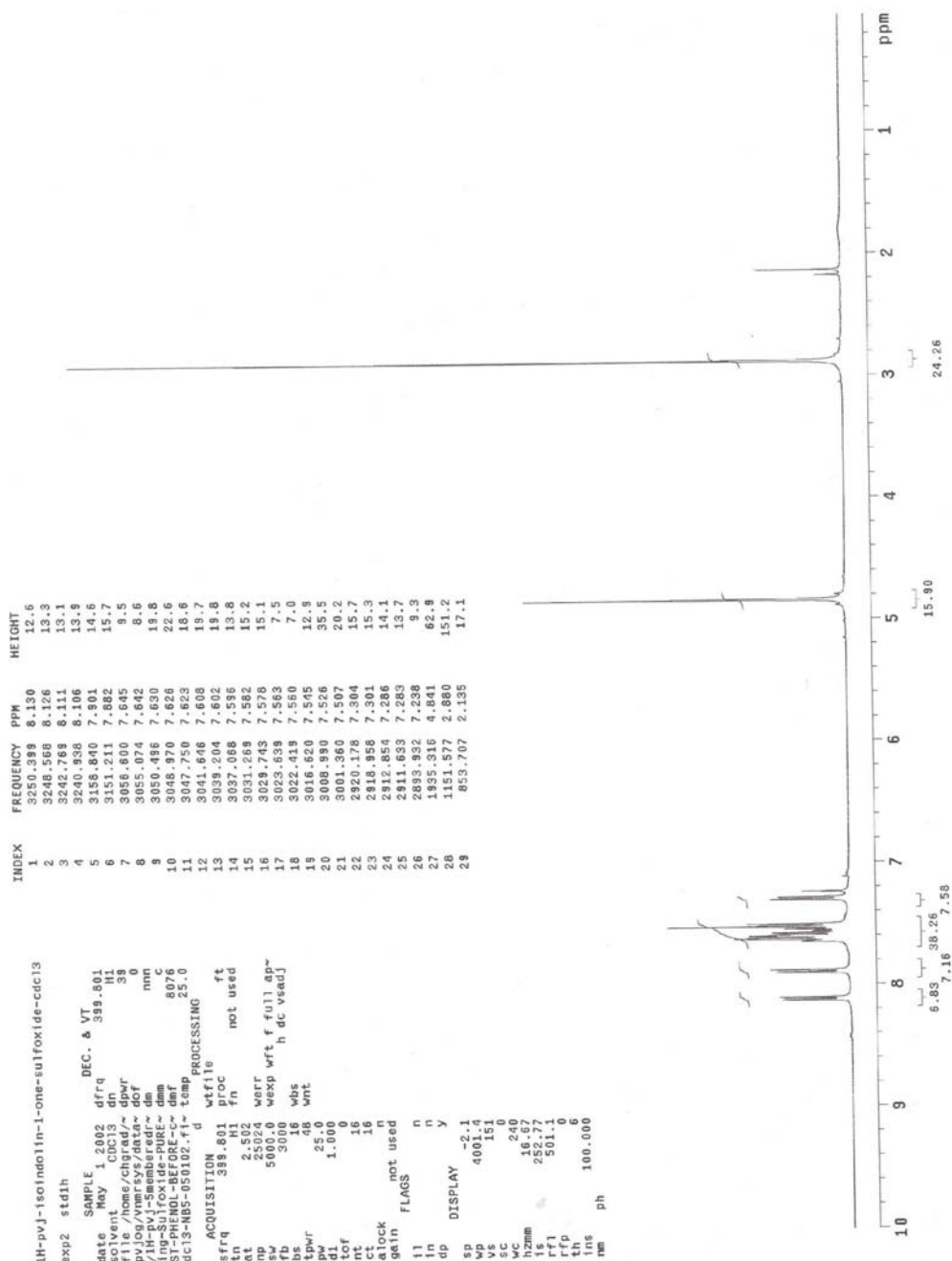
¹H NMR Spectrum of **1**



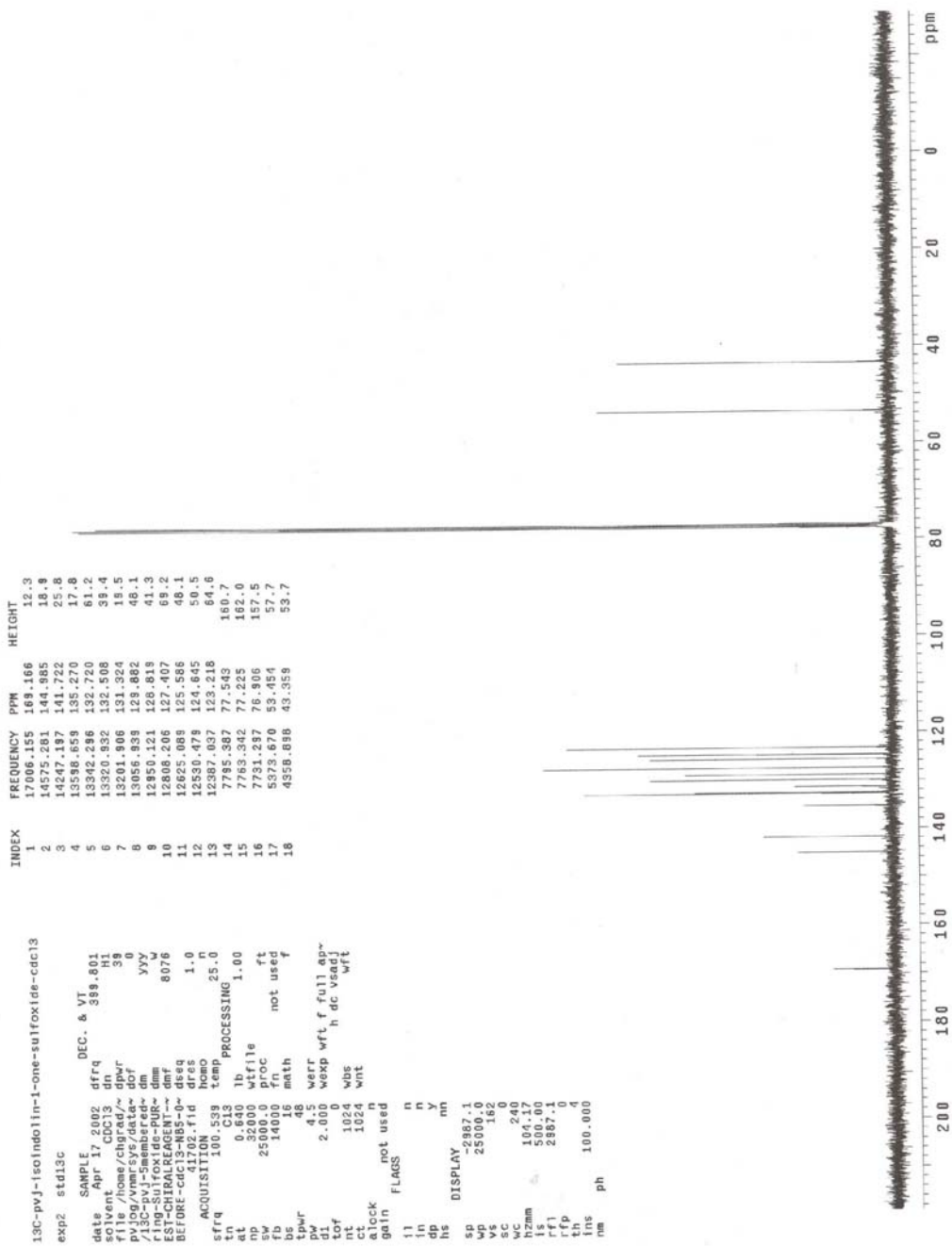
¹³C NMR Spectrum of 1



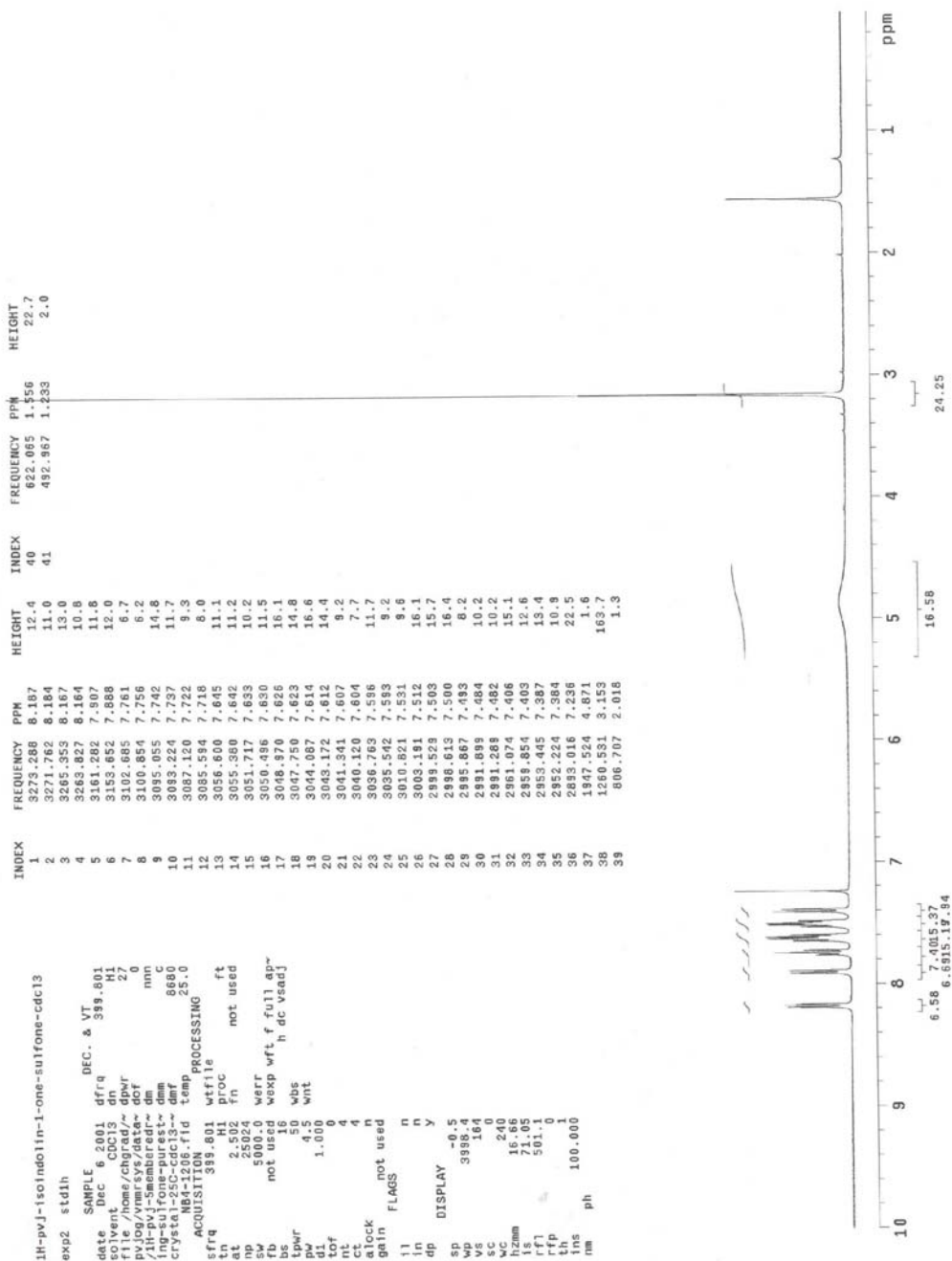
¹H NMR Spectrum of 2



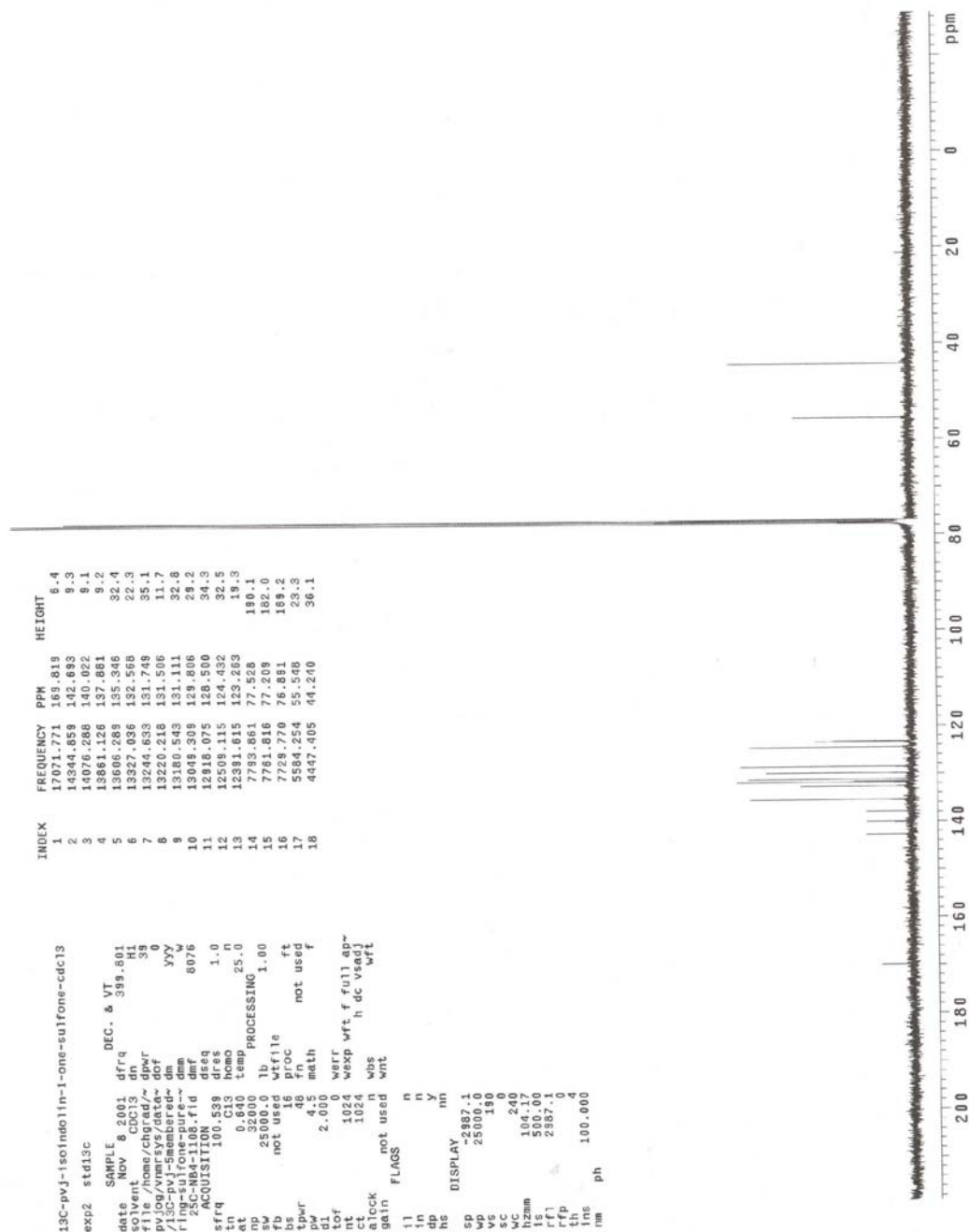
¹³C NMR Spectrum of **2**



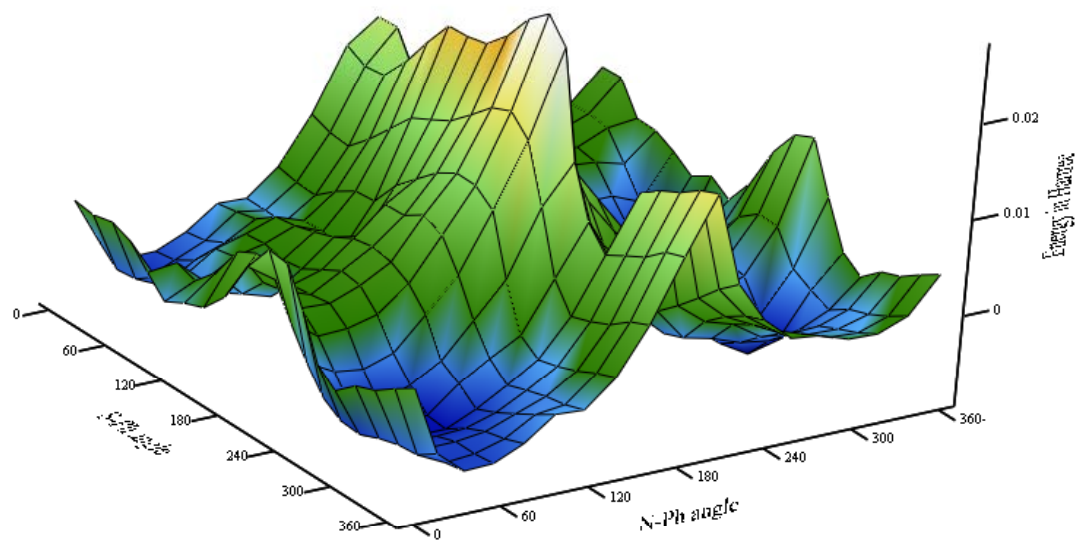
¹H NMR Spectrum of **3**



¹³C NMR Spectrum of 3

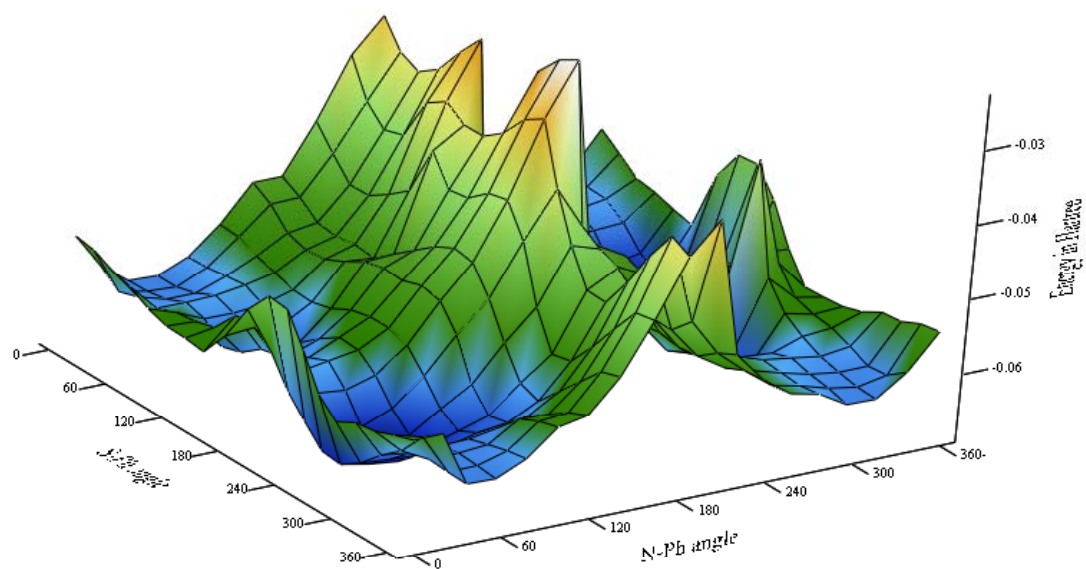


Potential Energy Surface Plot for Sulfoxide 2



(z,s,q)

Potential Energy Surface Plot for Sulfone **3**



(z, v, w)

Z-matrix for **1** [N-Ar & S-Ar locked] (Lowest Energy Conformation)

0 1			sch5	107.46093	dih18	0.04480
h			dih5	-122.80381	cc19	1.38323
c 1 ch2			cs6	1.77180	ccc19	118.18847
h 2 hc3	1 hch3		csc6	104.68279	dih19	0.10850
h 2 hc4	3 hch4	1 dih4	dih6	273.94890	cc20	1.49561
s 2 sc5	3 sch5	1 dih5	cc7	1.39784	ccc20	128.80482
c 5 cs6	2 csc6	4 dih6	ccs7	121.14130	dih20	-179.71856
c 6 cc7	5 ccs7	2 dih7	dih7	340.00000	hc21	1.09441
c 7 cc8	6 ccc8	5 dih8	cc8	1.38719	hcc21	120.89667
c 8 cc9	7 ccc9	6 dih9	ccc8	121.44158	dih21	-179.79813
c 9 cc10	8 ccc10	7 dih10	dih8	-178.14156	hc22	1.10957
c 10 cc11	9 ccc11	8 dih11	cc9	1.39036	hcc22	112.67464
n 11 nc12	10 ncc12	9 dih12	ccc9	119.92977	dih22	57.76910
c 12 cn13	11 cnc13	10 dih13	dih9	0.47929	hc23	1.10793
c 13 cc14	12 ccn14	11 dih14	cc10	1.38814	hcc23	111.99601
c 14 cc15	13 ccc15	12 dih15	ccc10	119.82708	dih23	-63.50499
c 15 cc16	14 ccc16	13 dih16	dih10	-0.01575	hc24	1.09540
c 16 cc17	15 ccc17	14 dih17	cc11	1.40013	hcc24	119.32075
c 17 cc18	16 ccc18	15 dih18	ccc11	120.43985	dih24	-179.96237
c 18 cc19	17 ccc19	16 dih19	dih11	-0.57748	hc25	1.09523
c 19 cc20	18 ccc20	17 dih20	nc12	1.44748	hcc25	119.69272
h 18 hc21	17 hcc21	16 dih21	ncc12	119.98005	dih25	179.91169
h 20 hc22	19 hcc22	18 dih22	dih12	-178.86414	hc26	1.09533
h 20 hc23	19 hcc23	18 dih23	cn13	1.44925	hcc26	120.72678
h 17 hc24	18 hcc24	19 dih24	cnc13	123.18632	dih26	-179.87909
h 16 hc25	17 hcc25	18 dih25	dih13	40.00000	oc27	1.21465
h 15 hc26	14 hcc26	19 dih26	cc14	1.48613	occ27	129.64647
o 13 oc27	14 occ27	19 dih27	ccn14	106.28642	dih27	-177.22970
h 10 hc28	11 hcc28	12 dih28	dih14	-153.21541	hc28	1.09724
h 9 hc29	10 hcc29	11 dih29	cc15	1.38357	hcc28	120.23132
h 8 hc30	9 hcc30	10 dih30	ccc15	129.70692	dih28	-0.25801
h 7 hc31	8 hcc31	9 dih31	dih15	-174.86795	hc29	1.09497
			cc16	1.39713	hcc29	119.97327
ch2	1.10030		ccc16	118.05980	dih29	179.33372
hc3	1.09627		dih16	-179.83891	hc30	1.09494
hch3	108.22882		cc17	1.39069	hcc30	120.17359
hc4	1.09548		ccc17	120.86810	dih30	-179.97353
hch4	107.98874		dih17	-0.10851	hc31	1.10200
dih4	116.05034		cc18	1.39723	hcc31	119.28782
sc5	1.80450		ccc18	121.05078	dih31	-179.60645

Z-matrix for **1** [N-Ar & S-Ar locked]-Lowest Energy Conformation
(other side of the Transition State)

0 1					
h			sch5	113.36711	
c 1 ch2			dih5	-124.71193	dih18 -0.02993
h 2 hc3	1 hch3		cs6	1.77176	cc19 1.38326
h 2 hc4	3 hch4	1 dih4	csc6	104.47674	ccc19 118.19311
s 2 sc5	3 sch5	1 dih5	dih6	156.37300	dih19 -0.09453
c 5 cs6	2 csc6	4 dih6	cc7	1.39795	cc20 1.49557
c 6 cc7	5 ccs7	2 dih7	ccs7	121.13414	ccc20 128.80335
c 7 cc8	6 ccc8	5 dih8	dih7	340.00000	dih20 -180.33293
c 8 cc9	7 ccc9	6 dih9	cc8	1.38714	hc21 1.09438
c 9 cc10	8 ccc10	7 dih10	ccc8	121.48684	hcc21 120.89301
c 10 cc11	9 ccc11	8 dih11	dih8	-178.59292	dih21 -180.21847
n 11 nc12	10 ncc12	9 dih12	cc9	1.39027	hc22 1.10780
c 12 cn13	11 cnc13	10 dih13	ccc9	119.91684	hcc22 112.00740
c 13 cc14	12 ccn14	11 dih14	dih9	0.30620	dih22 63.47436
c 14 cc15	13 ccc15	12 dih15	cc10	1.38809	hc23 1.10916
c 15 cc16	14 ccc16	13 dih16	ccc10	119.80609	hcc23 112.70075
c 16 cc17	15 ccc17	14 dih17	dih10	-0.07069	dih23 -57.88287
c 17 cc18	16 ccc18	15 dih18	cc11	1.40019	hc24 1.09539
c 18 cc19	17 ccc19	16 dih19	ccc11	120.47830	hcc24 119.32389
c 19 cc20	18 ccc20	17 dih20	dih11	0.09825	dih24 -180.02871
h 18 hc21	17 hcc21	16 dih21	nc12	1.44817	hc25 1.09522
h 20 hc22	19 hcc22	18 dih22	ncc12	119.89669	hcc25 119.69281
h 20 hc23	19 hcc23	18 dih23	dih12	-180.84774	dih25 180.09458
h 17 hc24	18 hcc24	19 dih24	cn13	1.45040	hc26 1.09534
h 16 hc25	17 hcc25	18 dih25	cnc13	122.92543	hcc26 120.72589
h 15 hc26	14 hcc26	19 dih26	dih13	320.00000	dih26 -180.16468
o 13 oc27	14 occ27	19 dih27	cc14	1.48601	oc27 1.21447
h 10 hc28	11 hcc28	12 dih28	ccn14	106.32454	occ27 129.63091
h 9 hc29	10 hcc29	11 dih29	dih14	-207.53316	dih27 -182.74933
h 8 hc30	9 hcc30	10 dih30	cc15	1.38359	hc28 1.09727
h 7 hc31	8 hcc31	9 dih31	ccc15	129.71296	hcc28 120.22351
			dih15	-185.19813	dih28 0.46814
	ch2	1.09521	cc16	1.39712	hc29 1.09497
	hc3	1.10046	ccc16	118.05721	hcc29 119.98013
	hch3	107.43616	dih16	-180.15880	dih29 180.38169
	hc4	1.09643	cc17	1.39070	hc30 1.09494
	hch4	108.13139	ccc17	120.86550	hcc30 120.18186
	dih4	116.30416	dih17	0.09091	dih30 -179.70674
	sc5	1.80446	cc18	1.39721	hc31 1.10206
			ccc18	121.05022	hcc31 119.27032
					dih31 -179.33

Z-matrix for **1** [N-Ar & S-Ar locked] (Transition State)

0 1			ccs7	113.860	dih22	106.849
h			dih7	-80.000	hc23	1.108970
c 1 ch2			cc8	1.383890	hcn23	113.030
h 2 hc3	1 hch3		ccc8	121.945	dih23	-11.940
h 2 hc4	1 hch4	3 dih4	dih8	-167.543	hc24	1.095420
s 2 sc5	1 sch5	3 dih5	cc9	1.391820	hcc24	119.626
c 5 cs6	2 csc6	4 dih6	ccc9	119.114	dih24	179.891
c 6 cc7	5 ccs7	2 dih7	dih9	1.229	hc25	1.095259
c 7 cc8	6 ccc8	5 dih8	cc10	1.383731	hcc25	119.441
c 8 cc9	7 ccc9	6 dih9	ccc10	119.935	dih25	-179.847
c 9 cc10	8 ccc10	7 dih10	dih10	-3.221	hc26	1.095240
c 6 cc11	5 ccs11	2 dih11	cc11	1.406218	hcc26	120.801
n 11 nc12	6 ncc12	5 dih12	ccs11	126.822	dih26	1.136
c 12 cn13	11 enc13	6 dih13	dih11	108.433	oc27	1.210421
c 13 cc14	12 ccn14	11 dih14	nc12	1.448799	ocn27	122.107
c 14 cc15	13 ccc15	12 dih15	ncc12	127.185	dih27	-64.649
c 15 cc16	14 ccc16	13 dih16	dih12	-13.679	hc28	1.098219
c 16 cc17	15 ccc17	14 dih17	cn13	1.478770	hcc28	117.944
c 17 cc18	16 ccc18	15 dih18	cnc13	125.317	dih28	-177.593
c 14 cc19	13 ccc19	12 dih19	dih13	-3.546	hc29	1.095250
c 12 cn20	11 enc20	6 dih20	cc14	1.483710	hcc29	120.096
h 18 hc21	17 hcc21	16 dih21	ccn14	108.296	dih29	177.200
h 20 hc22	12 hcn22	11 dih22	dih14	126.389	hc30	1.094580
h 20 hc23	12 hcn23	11 dih23	cc15	1.383850	hcc30	120.432
h 17 hc24	16 hcc24	15 dih24	ccc15	129.947	dih30	179.880
h 16 hc25	15 hcc25	14 dih25	dih15	-175.077	hc31	1.098531
h 15 hc26	14 hcc26	13 dih26	cc16	1.397120	hcc31	118.543
o 13 oc27	12 ocn27	11 dih27	ccc16	117.940	dih31	10.603
h 10 hc28	9 hcc28	8 dih28	dih16	-178.826		
h 9 hc29	8 hcc29	7 dih29	cc17	1.390980		
h 8 hc30	7 hcc30	6 dih30	ccc17	120.875		
h 7 hc31	6 hcc31	5 dih31	dih17	0.237		
			cc18	1.397160		
ch2	1.096500		ccc18	121.050		
hc3	1.095300		dih18	-0.203		
hch3	108.279		cc19	1.402776		
hc4	1.095800		ccc19	108.787		
hch4	108.038		dih19	5.953		
dih4	116.613		cn20	1.523247		
sc5	1.806980		cnc20	112.780		
sch5	106.835		dih20	128.384		
dih5	-121.419		hc21	1.094360		
cs6	1.774350		hcc21	120.923		
csc6	103.566		dih21	-179.905		
dih6	-65.629		hc22	1.107700		
cc7	1.402980		hcn22	108.251		

Z-matrix for 2 [N-Ar & S-Ar locked] (Lowest Energy Conformation)

0 1			dih5	-124.12739	dih19	-0.02548
h			os6	1.55430	cc20	1.38282
c 1 ch2			osc6	103.54371	ccc20	118.17325
h 2 hc3	1 hch3		dih6	-170.36889	dih20	-0.13061
h 2 hc4	3 hch4	1 dih4	cs7	1.81353	cc21	1.49554
s 2 sc5	4 sch5	3 dih5	csc7	99.20021	ccc21	128.81170
o 5 os6	2 osc6	1 dih6	dih7	-62.34639	dih21	180.11303
c 5 cs7	2 csc7	1 dih7	cc8	1.39511	hc22	1.10096
c 7 cc8	5 ccs8	2 dih8	ccs8	119.82700	hcc22	119.41420
c 8 cc9	7 ccc9	5 dih9	dih8	260.00000	dih22	180.50051
c 9 cc10	8 ccc10	7 dih10	cc9	1.39024	hc23	1.09533
c 10 cc11	9 ccc11	8 dih11	ccc9	121.18599	hcc23	120.13650
c 11 cc12	10 ccc12	9 dih12	dih9	182.70993	dih23	179.81577
n 12 nc13	11 ncc13	10 dih13	cc10	1.38955	hc24	1.09529
c 13 cn14	12 cnc14	11 dih14	ccc10	120.02758	hcc24	119.90238
c 14 cc15	13 ccn15	12 dih15	dih10	-0.37211	dih24	-179.45886
c 15 cc16	14 ccc16	13 dih16	cc11	1.38963	hc25	1.09667
c 16 cc17	15 ccc17	14 dih17	ccc11	119.87169	hcc25	120.48748
c 17 cc18	16 ccc18	15 dih18	dih11	-0.40344	dih25	2.17593
c 18 cc19	17 ccc19	16 dih19	cc12	1.39855	hc26	1.11309
c 19 cc20	18 ccc20	17 dih20	ccc12	120.02754	hcc26	113.13319
c 20 cc21	19 ccc21	18 dih21	dih12	0.56045	dih26	-56.53884
h 8 hc22	9 hcc22	10 dih22	nc13	1.45486	hc27	1.10853
h 9 hc23	10 hcc23	11 dih23	ncc13	120.03917	hcc27	111.87746
h 10 hc24	11 hcc24	12 dih24	dih13	-178.40211	dih27	64.76130
h 11 hc25	12 hcc25	13 dih25	cn14	1.45796	hc28	1.09444
h 21 hc26	20 hcc26	19 dih26	cnc14	121.62636	hcc28	120.84958
h 21 hc27	20 hcc27	19 dih27	dih14	300.00000	dih28	179.87908
h 19 hc28	18 hcc28	17 dih28	cc15	1.48572	hc29	1.09554
h 18 hc29	19 hcc29	20 dih29	ccn15	106.24593	hcc29	119.30489
h 17 hc30	18 hcc30	19 dih30	dih15	-210.52975	dih29	-180.09249
h 16 hc31	15 hcc31	20 dih31	cc16	1.38343	hc30	1.09541
o 14 oc32	15 occ32	20 dih32	ccc16	129.69823	hcc30	119.69885
			dih16	-186.31504	dih30	-179.92354
	ch2	1.10134	cc17	1.39752	hc31	1.09550
	hc3	1.09530	ccc17	118.04530	hcc31	120.76047
	hch3	107.87237	dih17	179.98928	dih31	179.98403
	hc4	1.09661	cc18	1.39043	oc32	1.21189
	hch4	106.98438	ccc18	120.88130	occ32	130.05433
	dih4	115.61616	dih18	0.05553	dih32	-184.01239
	sc5	1.82361	cc19	1.39767		
	sch5	109.12847	ccc19	121.04680		

Z-matrix for **2** [N-Ar & S-Ar locked]-Lowest Energy Conformation
(other side of the Transition State)

0 1				dih5	-124.04437		
h				os6	1.55766	dih19	0.07119
c 1 ch2				osc6	104.05640	cc20	1.38313
h 2 hc3	1 hch3			dih6	85.50938	ccc20	118.18491
h 2 hc4	3 hch4	1 dih4		cs7	1.81315	dih20	0.11656
s 2 sc5	4 sch5	3 dih5		csc7	99.63681	cc21	1.49611
o 5 os6	2 osc6	1 dih6		dih7	193.80876	ccc21	128.76282
c 5 cs7	2 csc7	1 dih7		cc8	1.39509	dih21	180.20338
c 7 cc8	5 ccs8	2 dih8		ccs8	119.82092	hc22	1.10103
c 8 cc9	7 ccc9	5 dih9		dih8	260.00000	hcc22	119.43878
c 9 cc10	8 ccc10	7 dih10		cc9	1.39015	dih22	180.01546
c 10 cc11	9 ccc11	8 dih11		ccc9	121.21552	hc23	1.09531
c 11 cc12	10 ccc12	9 dih12		dih9	181.63503	hcc23	120.16159
n 12 nc13	11 ncc13	10 dih13		cc10	1.38946	dih23	180.32260
c 13 cn14	12 cnc14	11 dih14		ccc10	119.99494	hc24	1.09527
c 14 cc15	13 ccn15	12 dih15		dih10	-0.15081	hcc24	119.89841
c 15 cc16	14 ccc16	13 dih16		cc11	1.38944	dih24	-180.25913
c 16 cc17	15 ccc17	14 dih17		ccc11	119.85499	hc25	1.09674
c 17 cc18	16 ccc18	15 dih18		dih11	0.57367	hcc25	120.48839
c 18 cc19	17 ccc19	16 dih19		cc12	1.39890	dih25	-1.06252
c 19 cc20	18 ccc20	17 dih20		ccc12	120.08958	hc26	1.10853
c 20 cc21	19 ccc21	18 dih21		dih12	-0.25717	hcc26	111.93514
h 8 hc22	9 hcc22	10 dih22		nc13	1.45738	dih26	-63.35717
h 9 hc23	10 hcc23	11 dih23		ncc13	119.90203	hc27	1.10678
h 10 hc24	11 hcc24	12 dih24		dih13	-180.74428	hcc27	112.26433
h 11 hc25	12 hcc25	13 dih25		cn14	1.46098	dih27	57.60945
h 21 hc26	20 hcc26	19 dih26		cnc14	119.92638	hc28	1.09456
h 21 hc27	20 hcc27	19 dih27		dih14	60.00000	hcc28	120.88112
h 19 hc28	18 hcc28	17 dih28		cc15	1.48358	dih28	180.15011
h 18 hc29	19 hcc29	20 dih29		ccn15	106.80321	hc29	1.09557
h 17 hc30	18 hcc30	19 dih30		dih15	-144.08230	hcc29	119.31253
h 16 hc31	15 hcc31	20 dih31		cc16	1.38379	dih29	-179.91646
o 14 oc32	15 occ32	20 dih32		ccc16	129.78477	hc30	1.09539
				dih16	-175.00663	hcc30	119.69713
	ch2	1.09664		cc17	1.39715	dih30	-180.04044
	hc3	1.09649		ccc17	118.02809	hc31	1.09542
	hch3	107.79691		dih17	180.04681	hcc31	120.77150
	hc4	1.09613		cc18	1.39075	dih31	179.97922
	hch4	107.67140		ccc18	120.86742	oc32	1.21322
	dih4	115.26090		dih18	-0.08525	occ32	130.00511
	sc5	1.82015		cc19	1.39744	dih32	-178.09089
	sch5	113.79521		ccc19	121.05986		

Z-matrix for 2 [N-Ar & S-Ar locked] (Transition State)

0 1			cc9	1.381290	hcn26	108.555
h			ccc9	122.665	dih26	-115.341
c 1 ch2			dih9	-177.428	hc27	1.109179
h 2 hc3	1 hch3		cc10	1.391639	hcn27	112.762
h 2 hc4	3 hch4	1 dih4	ccc10	118.609	dih27	125.726
s 2 sc5	3 sch5	4 dih5	dih10	0.332	hc28	1.094490
o 5 os6	2 osc6	1 dih6	cc11	1.384120	hcc28	120.981
c 5 cs7	2 csc7	1 dih7	ccc11	119.891	dih28	-0.089
c 7 cc8	5 ccs8	6 dih8	dih11	1.584	hc29	1.095581
c 8 cc9	7 ccc9	5 dih9	cc12	1.402553	hcc29	119.325
c 9 cc10	8 ccc10	7 dih10	ccc12	118.881	dih29	179.808
c 10 cc11	9 ccc11	8 dih11	dih12	-2.477	hc30	1.095410
c 7 cc12	8 ccc12	9 dih12	nc13	1.452680	hcc30	119.675
n 12 nc13	7 ncc13	8 dih13	ncc13	128.169	dih30	-179.992
c 13 cn14	12 cnc14	7 dih14	dih13	-173.352	hc31	1.095360
c 14 cc15	13 ccn15	12 dih15	cn14	1.466101	hcc31	120.827
c 15 cc16	14 ccc16	13 dih16	cnc14	127.376	dih31	0.677
c 16 cc17	15 ccc17	14 dih17	dih14	-3.881	oc32	1.212820
c 17 cc18	16 ccc18	15 dih18	cc15	1.482800	ocn32	122.994
c 18 cc19	17 ccc19	16 dih19	ccn15	108.405	dih32	166.499
c 15 cc20	14 ccc20	13 dih20	dih15	133.065		
c 13 cn21	14 cnc21	15 dih21	cc16	1.384400		
h 8 hc22	7 hcc22	12 dih22	ccc16	129.834		
h 9 hc23	8 hcc23	7 dih23	dih16	-177.514		
h 10 hc24	9 hcc24	8 dih24	cc17	1.396809		
h 11 hc25	12 hcc25	13 dih25	ccc17	117.925		
h 21 hc26	13 hcn26	14 dih26	dih17	-179.190		
h 21 hc27	13 hcn27	14 dih27	cc18	1.391310		
h 19 hc28	20 hcc28	21 dih28	ccc18	120.883		
h 18 hc29	19 hcc29	20 dih29	dih18	0.226		
h 17 hc30	18 hcc30	19 dih30	cc19	1.397120		
h 16 hc31	15 hcc31	14 dih31	ccc19	121.064		
o 14 oc32	13 ocn32	21 dih32	dih19	-0.096		
			cc20	1.402509		
ch2	1.096780		ccc20	108.913		
hc3	1.096430		dih20	3.313		
hch3	107.641		cn21	1.523925		
hc4	1.095801		cnc21	106.686		
hch4	107.807		dih21	-4.485		
dih4	-115.637		hc22	1.120990		
sc5	1.821640		hcc22	114.589		
sch5	113.034		dih22	175.797		
dih5	-124.649		hc23	1.094440		
os6	1.571731		hcc23	120.510		
osc6	103.173		dih23	-179.835		
dih6	104.233		hc24	1.095301		
cs7	1.818280		hcc24	120.204		
csc7	100.900		dih24	-179.060		
dih7	-151.203		hc25	1.098290		
cc8	1.400960		hcc25	120.549		
ccs8	110.337		dih25	-6.119		
dih8	5.992		hc26	1.108090		

Z-matrix for **3** [N-Ar & S-Ar locked] (Lowest Energy Conformation)

0 1			dih5	-124.63797	cc20	1.39722
h			os6	1.47390	ccc20	121.07655
c 1 ch2			osc6	108.64523	dih20	0.07727
h 2 hc3	1 hch3		dih6	131.88368	cc21	1.38338
h 2 hc4	1 hch4	3 dih4	os7	1.47044	ccc21	118.20547
s 2 sc5	1 sch5	4 dih5	osc7	110.11663	dih21	0.14110
o 5 os6	2 osc6	3 dih6	dih7	3.20854	cc22	1.49586
o 5 os7	2 osc7	3 dih7	cs8	1.80548	ccc22	128.68415
c 5 cs8	2 csc8	3 dih8	csc8	102.43726	dih22	-179.68976
c 8 cc9	5 ccs9	2 dih9	dih8	-113.17858	hc23	1.10086
c 9 cc10	8 ccc10	5 dih10	cc9	1.39880	hcc23	118.78132
c 10 cc11	9 ccc11	8 dih11	ccs9	117.65770	dih23	180.46665
c 11 cc12	10 ccc12	9 dih12	dih9	240.00000	hc24	1.09548
c 12 cc13	11 ccc13	10 dih13	cc10	1.38930	hcc24	120.14084
n 13 nc14	12 ncc14	11 dih14	ccc10	121.73317	dih24	180.06867
c 14 cn15	13 cnc15	12 dih15	dih10	182.60748	hc25	1.09543
c 15 cc16	14 ccn16	13 dih16	cc11	1.38945	hcc25	120.02478
c 16 cc17	15 ccc17	14 dih17	ccc11	120.00626	dih25	179.58515
c 17 cc18	16 ccc18	15 dih18	dih11	0.46026	hc26	1.09695
c 18 cc19	17 ccc19	16 dih19	cc12	1.38878	hcc26	120.44742
c 19 cc20	18 ccc20	17 dih20	ccc12	119.66164	dih26	-0.88799
c 20 cc21	19 ccc21	18 dih21	dih12	-0.10997	hc27	1.10810
c 21 cc22	20 ccc22	19 dih22	cc13	1.39911	hcc27	112.02833
h 9 hc23	10 hcc23	11 dih23	ccc13	120.10613	dih27	-63.47290
h 10 hc24	11 hcc24	12 dih24	dih13	-0.47293	hc28	1.10898
h 11 hc25	12 hcc25	13 dih25	nc14	1.45603	hcc28	112.63312
h 12 hc26	13 hcc26	14 dih26	ncc14	119.47104	dih28	58.05908
h 22 hc27	21 hcc27	20 dih27	dih14	-180.31466	hc29	1.09467
h 22 hc28	21 hcc28	20 dih28	cn15	1.45872	hcc29	120.91787
h 20 hc29	19 hcc29	18 dih29	cnc15	120.43549	dih29	-179.68163
h 19 hc30	20 hcc30	21 dih30	dih15	60.00000	hc30	1.09557
h 18 hc31	19 hcc31	20 dih31	cc16	1.48247	hcc30	119.31294
h 17 hc32	16 hcc32	21 dih32	ccn16	106.60514	dih30	-179.95191
o 15 oc33	16 occ33	21 dih33	dih16	-146.45113	hc31	1.09533
			cc17	1.38404	hcc31	119.69677
	ch2	1.09971	ccc17	129.73281	dih31	179.91773
	hc3	1.09952	dih17	-175.14111	hc32	1.09532
	hch3	106.21738	cc18	1.39682	hcc32	120.77368
	hc4	1.09959	ccc18	118.03437	dih32	-179.96664
	hch4	105.97175	dih18	-179.96996	oc33	1.21398
	dih4	-112.40045	cc19	1.39096	occ33	130.36602
	sc5	1.78959	ccc19	120.85873	dih33	-178.22304
	sch5	111.98676	dih19	-0.11570		

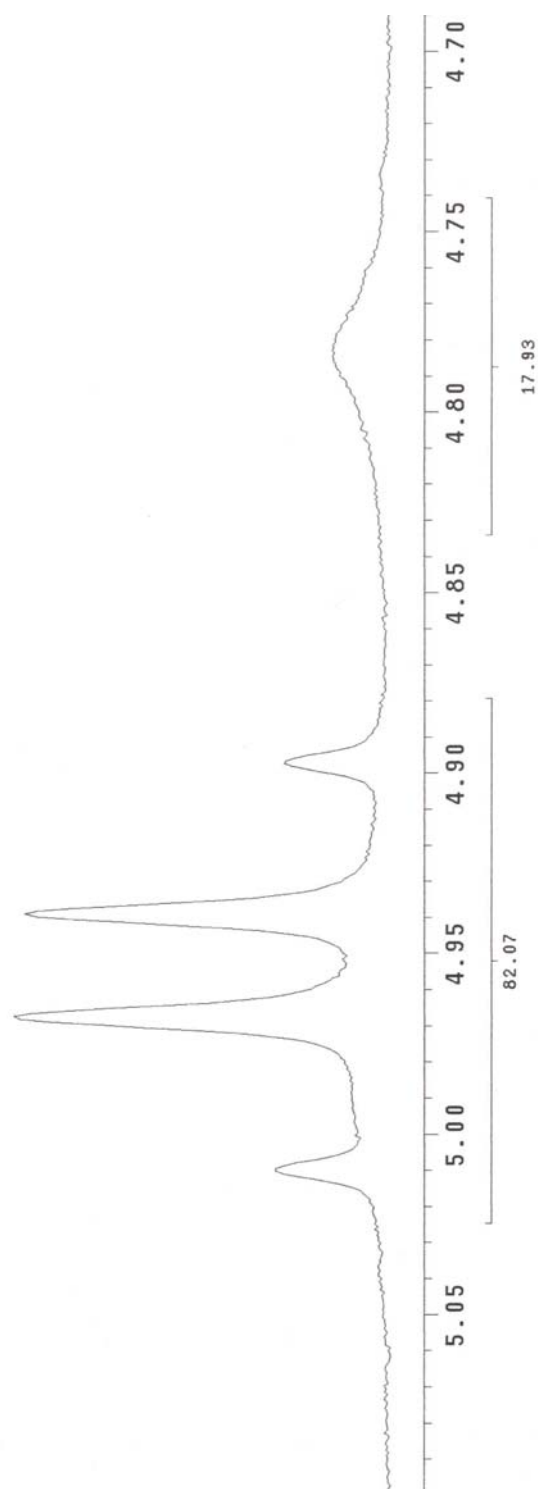
Z-matrix for **3** [N-Ar & S-Ar locked]-Lowest Energy Conformation
(other side of the Transition State)

0 1							
h				sch5	111.21516		
c 1 ch2				dih5	-122.87967	dih19	0.06610
h 2 hc3	1 hch3			os6	1.47375	cc20	1.39770
h 2 hc4	1 hch4	3 dih4		osc6	107.64784	ccc20	121.04128
s 2 sc5	1 sch5	4 dih5		dih6	185.40933	dih20	0.02836
o 5 os6	2 osc6	3 dih6		os7	1.45920	cc21	1.38284
o 5 os7	2 osc7	3 dih7		osc7	109.80237	ccc21	118.15817
c 5 cs8	2 csc8	3 dih8		dih7	57.35084	dih21	-0.11619
c 8 cc9	5 ccs9	2 dih9		cs8	1.80967	cc22	1.49550
c 9 cc10	8 ccc10	5 dih10		csc8	101.71621	ccc22	128.75587
c 10 cc11	9 ccc11	8 dih11		dih8	-60.86019	dih22	-180.46183
c 11 cc12	10 ccc12	9 dih12		cc9	1.39996	hc23	1.10117
c 12 cc13	11 ccc13	10 dih13		ccs9	116.74231	hcc23	118.50807
n 13 nc14	12 ncc14	11 dih14		dih9	240.00000	dih23	180.27528
c 14 cn15	13 cnc15	12 dih15		cc10	1.38894	hc24	1.09549
c 15 cc16	14 ccn16	13 dih16		ccc10	121.96251	hcc24	120.15787
c 16 cc17	15 ccc17	14 dih17		dih10	181.94320	dih24	180.86882
c 17 cc18	16 ccc18	15 dih18		cc11	1.38929	hc25	1.09538
c 18 cc19	17 ccc19	16 dih19		ccc11	119.97856	hcc25	120.08803
c 19 cc20	18 ccc20	17 dih20		dih11	0.39892	dih25	180.43433
c 20 cc21	19 ccc21	18 dih21		cc12	1.38823	hc26	1.09709
c 21 cc22	20 ccc22	19 dih22		ccc12	119.53758	hcc26	120.38783
h 9 hc23	10 hcc23	11 dih23		dih12	0.48979	dih26	-1.02120
h 10 hc24	11 hcc24	12 dih24		cc13	1.39977	hc27	1.11203
h 11 hc25	12 hcc25	13 dih25		ccc13	120.24649	hcc27	112.37338
h 12 hc26	13 hcc26	14 dih26		dih13	-0.14237	dih27	-56.47234
h 22 hc27	21 hcc27	20 dih27		nc14	1.45672	hc28	1.10830
h 22 hc28	21 hcc28	20 dih28		ncc14	19.11798	hcc28	112.04060
h 20 hc29	19 hcc29	18 dih29		dih14	-182.08878	dih28	64.74615
h 19 hc30	20 hcc30	21 dih30		cn15	1.46750	hc29	1.09439
h 18 hc31	19 hcc31	20 dih31		cnc15	19.84711	hcc29	120.84516
h 17 hc32	16 hcc32	21 dih32		dih15	300.00000	dih29	-180.22042
o 15 oc33	16 occ33	21 dih33		cc16	1.48528	hc30	1.09551
				ccn16	06.28676	hcc30	119.30561
				dih16	-212.02691	dih30	-180.00989
				cc17	1.38346	hc31	1.09541
ch2	1.09970			ccc17	129.66633	hcc31	119.69926
hc3	1.10231			dih17	-187.26582	dih31	180.18099
hch3	105.74564			cc18	1.39762	hc32	1.09556
hc4	1.09789			ccc18	118.02603	hcc32	120.76542
hch4	105.95278			dih18	-180.32705	dih32	-180.24083
dih4	-112.75818			cc19	1.39040	oc33	1.20973
sc5	1.79502			ccc19	120.88550	occ33	130.02882
						dih33	-186.76067

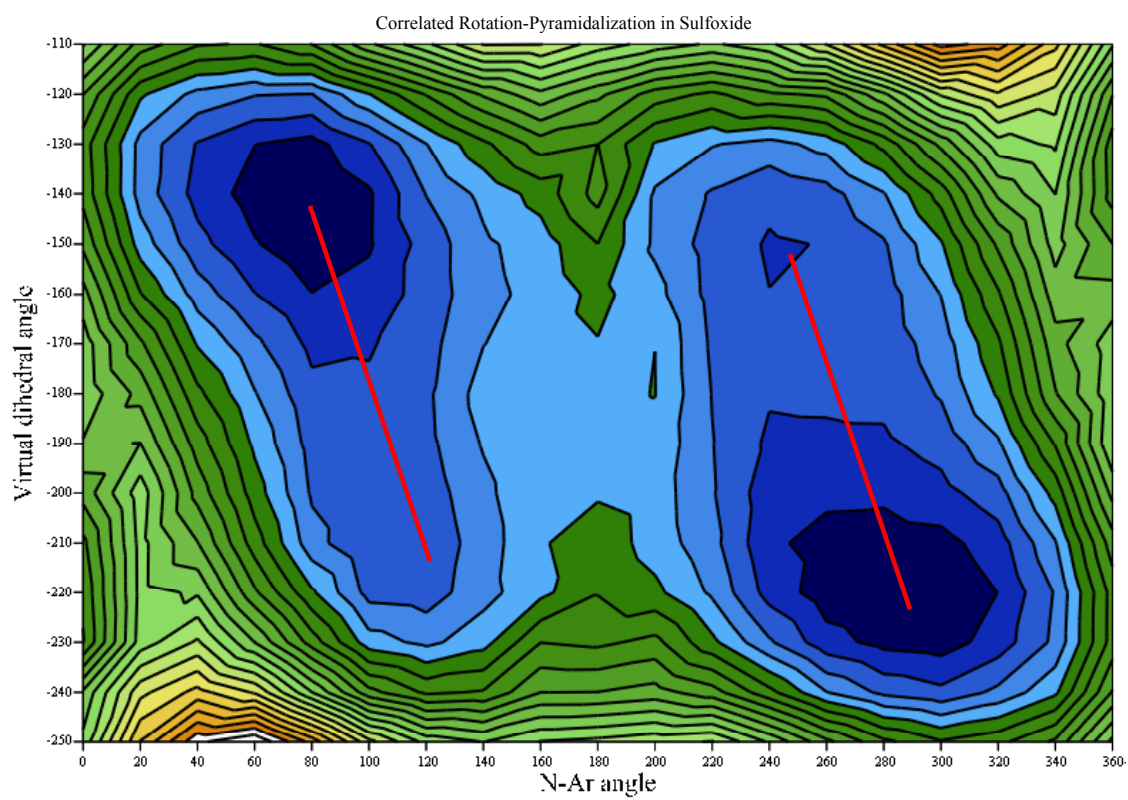
Z-matrix for 3 [N-Ar & S-Ar locked] (Transition State)

0 1			dih5	-124.023	cc20	1.397420
h			os6	1.470110	ccc20	121.080
c 1 ch2			osc6	110.626	dih20	-0.262
h 2 hc3	1 hch3		dih6	-134.467	cc21	1.402138
h 2 hc4	3 hch4	1 dih4	os7	1.477129	ccc21	108.789
s 2 sc5	3 sch5	1 dih5	osc7	108.060	dih21	5.973
o 5 os6	2 osc6	4 dih6	dih7	-6.084	cn22	1.529506
o 5 os7	2 osc7	4 dih7	cs8	1.812850	cnc22	105.710
c 5 cs8	2 csc8	4 dih8	csc8	103.415	dih22	-8.079
c 8 cc9	5 ccs9	6 dih9	dih8	109.750	hc23	1.103960
c 9 cc10	8 ccc10	5 dih10	cc9	1.408819	hcc23	119.015
c 10 cc11	9 ccc11	8 dih11	ccs9	111.067	dih23	175.163
c 11 cc12	10 ccc12	9 dih12	dih9	122.586	hc24	1.094950
c 8 cc13	9 ccc13	10 dih13	cc10	1.381291	hcc24	120.472
n 13 nc14	8 ncc14	9 dih14	ccc10	123.568	dih24	-179.613
c 14 cn15	13 cnc15	8 dih15	dih10	-178.699	hc25	1.095320
c 15 cc16	14 ccn16	13 dih16	cc11	1.390710	hcc25	120.493
c 16 cc17	15 ccc17	14 dih17	ccc11	118.887	dih25	-177.180
c 17 cc18	16 ccc18	15 dih18	dih11	-0.068	hc26	1.099151
c 18 cc19	17 ccc19	16 dih19	cc12	1.380629	hcc26	120.428
c 19 cc20	18 ccc20	17 dih20	ccc12	119.163	dih26	-10.627
c 16 cc21	15 ccc21	14 dih21	dih12	3.842	hc27	1.109131
c 14 cn22	15 cnc22	16 dih22	cc13	1.409000	hen27	112.960
h 9 hc23	8 hcc23	13 dih23	ccc13	116.943	dih27	128.767
h 10 hc24	9 hcc24	8 dih24	dih13	-6.076	hc28	1.108030
h 11 hc25	10 hcc25	9 dih25	nc14	1.454090	hcn28	108.372
h 12 hc26	13 hcc26	14 dih26	ncc14	129.566	dih28	-112.168
h 22 hc27	14 hcn27	15 dih27	dih14	-166.547	hc29	1.094310
h 22 hc28	14 hcn28	15 dih28	cn15	1.474890	hcc29	121.022
h 20 hc29	21 hcc29	22 dih29	cnc15	128.925	dih29	0.413
h 19 hc30	20 hcc30	21 dih30	dih15	-4.888	hc30	1.095461
h 18 hc31	19 hcc31	20 dih31	cc16	1.480160	hcc30	119.297
h 17 hc32	16 hcc32	15 dih32	ccn16	108.764	dih30	179.726
o 15 oc33	14 ocn33	22 dih33	dih16	128.314	hc31	1.095340
			cc17	1.384155	hcc31	119.673
ch2	1.100849		ccc17	129.875	dih31	179.591
hc3	1.098890		dih17	-174.318	hc32	1.095350
hch3	106.006		cc18	1.397320	hcc32	120.843
hc4	1.100061		ccc18	117.828	dih32	1.106
hch4	105.962		dih18	-179.263	oc33	1.210931
dih4	112.294		cc19	1.390990	ocn33	121.728
sc5	1.786330		ccc19	120.914	dih33	161.262
sch5	114.114		dih19	0.060		

Figure 6. Partial ^1H NMR of **1** (and **2**) [$-40\text{ }^\circ\text{C}$, CDCl_3] with *m*-CPBA as a limiting reagent (0.85 equiv) after ~ 5 min.

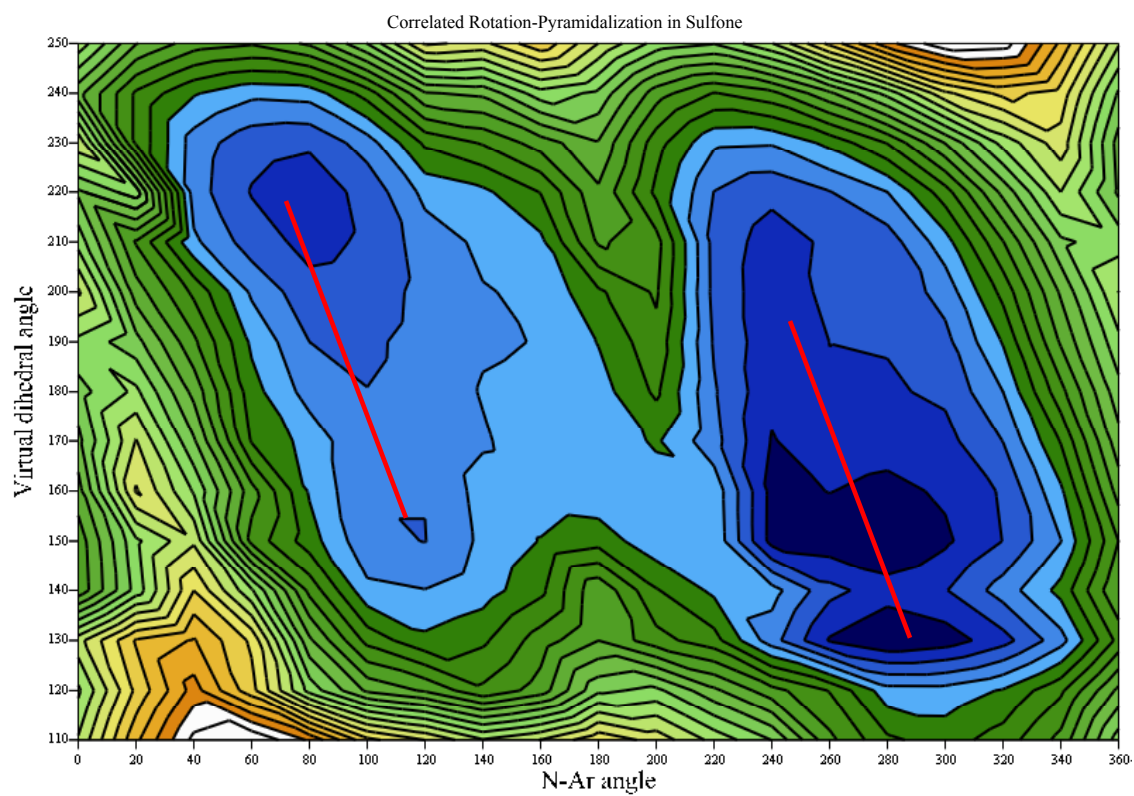


N-Ar torsion angle vs virtual dihedral angle for **2**



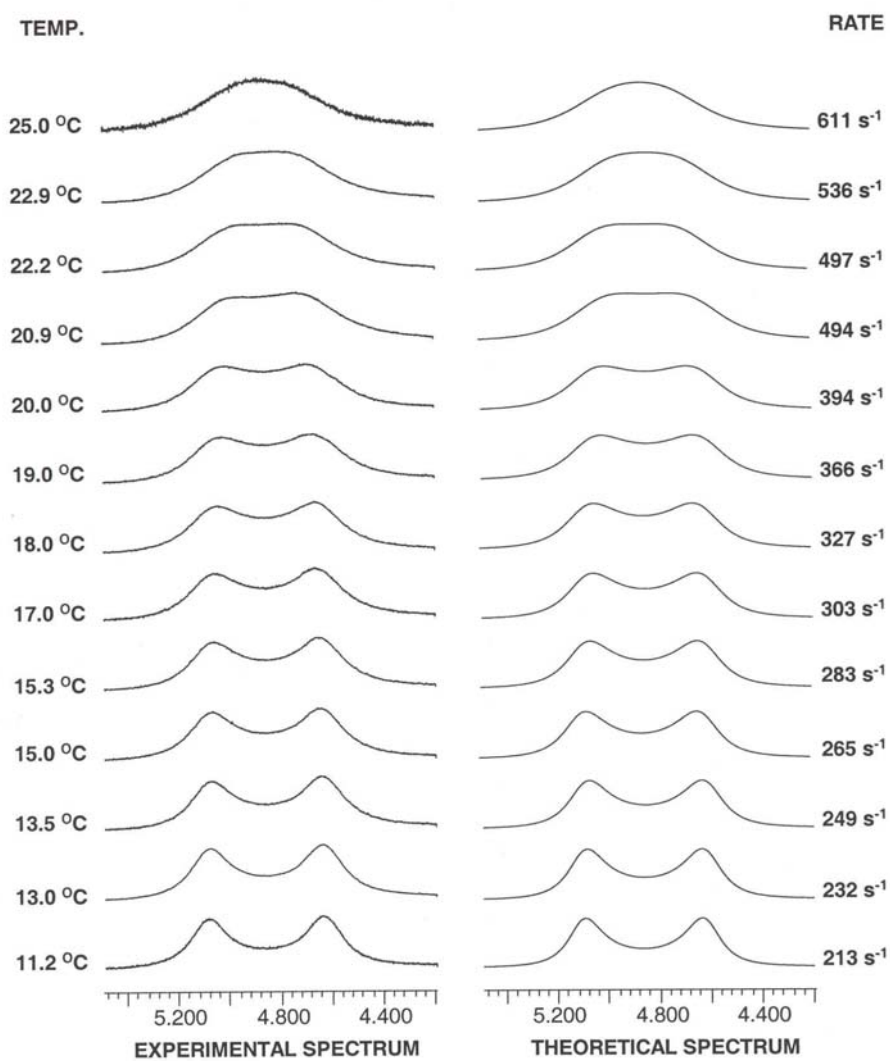
(q, w, z)

N-Ar torsion angle vs virtual dihedral angle for **3**



(q, w, z)

Line-shape analysis for **3**



Z-matrix for **1** (N-Ar & Virtual Dihedral Angle locked)-Lowest Energy Conformation

0 1			cc6	1.38813	cc20	1.49509
c			ccc6	120.32517	ccn20	104.07437
n 1 nc2			dih6	180.30749	dih20	-7.77877
c 2 cn3	1 cnc3		cc7	1.39057	hc21	1.09453
c 2 cn4	1 cnc4	3 dih4	ccc7	119.99521	hcc21	120.91192
c 4 cc5	2 ccn5	1 dih5	dih7	0.13847	dih21	179.85103
c 5 cc6	4 ccc6	2 dih6	cc8	1.38826	hc22	1.09548
c 6 cc7	5 ccc7	4 dih7	ccc8	119.88847	hcc22	119.62039
c 7 cc8	6 ccc8	5 dih8	dih8	-0.83974	dih22	179.92606
c 8 cc9	7 ccc9	6 dih9	cc9	1.39864	hc23	1.09528
s 9 sc10	8 scc10	7 dih10	ccc9	121.15526	hcc23	119.44568
c 10 cs11	9 csc11	8 dih11	dih9	0.65545	dih23	-180.02428
h 11 hc12	10 hcs12	9 dih12	sc10	1.77391	hc24	1.09535
h 11 hc13	10 hcs13	9 dih13	scc10	115.13803	hcc24	120.74788
h 11 hc14	10 hcs14	9 dih14	dih10	-182.92343	dih24	-0.14571
c 3 cc15	2 ccn15	1 dih15	cs11	1.80565	oc25	1.21366
c 15 cc16	3 ccc16	2 dih16	csc11	104.79719	ocn25	123.56947
c 16 cc17	15 ccc17	3 dih17	dih11	121.01170	dih25	184.69508
c 17 cc18	16 ccc18	15 dih18	hc12	1.09502	hc26	1.09723
c 18 cc19	17 ccc19	16 dih19	hes12	112.92958	hcc26	120.38630
c 1 cc20	2 ccn20	3 dih20	dih12	-53.82583	dih26	1.02506
h 19 hc21	18 hcc21	17 dih21	hc13	1.09690	hc27	1.09520
h 18 hc22	17 hcc22	16 dih22	hes13	106.58306	hcc27	119.85616
h 17 hc23	16 hcc23	15 dih23	dih13	187.62173	dih27	-179.86280
h 16 hc24	15 hcc24	3 dih24	hc14	1.09534	hc28	1.09501
o 3 oc25	2 ocn25	1 dih25	hes14	113.32572	hcc28	120.15262
h 5 hc26	4 hcc26	2 dih26	dih14	68.90601	dih28	-180.29603
h 6 hc27	5 hcc27	4 dih27	cc15	1.48438	hc29	1.09809
h 7 hc28	6 hcc28	5 dih28	ccn15	106.75227	hcc29	119.88264
h 8 hc29	7 hcc29	6 dih29	dih15	8.05609	dih29	-179.21689
h 1 hc30	2 hcn30	3 dih30	cc16	1.38385	hc30	1.10803
h 1 hc31	2 hcn31	3 dih31	ccc16	129.75096	hcn30	112.44261
			dih16	-185.05184	dih30	113.49984
	nc2	1.50975	cc17	1.39697	hc31	1.10844
	cn3	1.45978	ccc17	118.04217	hcn31	108.42942
	cnc3	108.89349	dih17	-180.06020	dih31	-127.97887
	cn4	1.45190	cc18	1.39085		
	cnc4	115.49531	ccc18	120.85820		
	dih4	220.00000	dih18	0.07523		
	cc5	1.40060	cc19	1.39719		
	ccn5	120.34846	ccc19	121.05840		
	dih5	100.00000	dih19	-0.03954		

Z-matrix for **2** (N-Ar & Virtual Dihedral Angle locked)-Lowest Energy Conformation

0 1			dih5	80.00000	dih19	0.05810
c			cc6	1.38930	cc20	1.39760
n 1 nc2			ccc6	120.14908	ccc20	121.04756
c 2 cn3	1 cnc3		dih6	-179.95374	dih20	-0.02686
c 2 cn4	1 cnc4	3 dih4	cc7	1.38938	cc21	1.49548
c 4 cc5	2 ccn5	1 dih5	ccc7	119.81206	ccn21	103.94507
c 5 cc6	4 ccc6	2 dih6	dih7	0.21161	dih21	-9.72510
c 6 cc7	5 ccc7	4 dih7	cc8	1.38996	hc22	1.09445
c 7 cc8	6 ccc8	5 dih8	ccc8	119.99130	hcc22	120.85500
c 8 cc9	7 ccc9	6 dih9	dih8	-0.53188	dih22	179.88917
s 9 sc10	8 scc10	7 dih10	cc9	1.39567	hc23	1.09554
o 10 os11	9 osc11	8 dih11	ccc9	121.31522	hcc23	119.64446
c 10 cs12	9 csc12	8 dih12	dih9	0.13450	dih23	179.93527
h 12 hc13	10 hcs13	11 dih13	sc10	1.81380	hc24	1.09541
h 12 hc14	10 hcs14	11 dih14	scc10	119.27278	hcc24	119.42383
h 12 hc15	10 hcs15	11 dih15	dih10	-174.97989	dih24	179.95733
c 3 cc16	2 ccn16	1 dih16	os11	1.55492	hc25	1.09550
c 16 cc17	3 ccc17	2 dih17	osc11	105.05411	hcc25	120.76097
c 17 cc18	16 ccc18	3 dih18	dih11	2.37140	dih25	-0.16359
c 18 cc19	17 ccc19	16 dih19	cs12	1.82252	oc26	1.21180
c 19 cc20	18 ccc20	17 dih20	csc12	100.13442	ocn26	123.57681
c 1 cc21	2 ccn21	3 dih21	dih12	-104.63445	dih26	-172.35769
h 20 hc22	19 hcc22	18 dih22	hc13	1.10017	hc27	1.09677
h 19 hc23	18 hcc23	17 dih23	hcs13	111.02151	hcc27	120.44826
h 18 hc24	17 hcc24	16 dih24	dih13	190.15458	dih27	0.75426
h 17 hc25	16 hcc25	3 dih25	hc14	1.09546	hc28	1.09527
o 3 oc26	2 ocn26	1 dih26	hcs14	114.24206	hcc28	119.92624
h 5 hc27	4 hcc27	2 dih27	dih14	-47.66955	dih28	-179.59390
h 6 hc28	5 hcc28	4 dih28	hc15	1.09687	hc29	1.09532
h 7 hc29	6 hcc29	5 dih29	hcs15	108.92310	hcc29	120.15927
h 8 hc30	7 hcc30	6 dih30	dih15	71.80602	dih29	179.89879
h 1 hc31	2 hcn31	3 dih31	cc16	1.48530	hc30	1.10120
h 1 hc32	2 hcn32	3 dih32	ccn16	106.43772	hcc30	119.28023
			dih16	9.98057	dih30	-179.14006
	nc2	1.50780	cc17	1.38353	hc31	1.11234
	cn3	1.46060	ccc17	129.72086	hcn31	108.53149
	cnc3	108.99248	dih17	173.83040	dih31	-129.97678
	cn4	1.45591	cc18	1.39744	hc32	1.10843
	cnc4	115.57518	ccc18	118.03958	hcn32	112.51186
	dih4	-140.00000	dih18	179.92783	dih32	111.49100
	cc5	1.39903	cc19	1.39052		
	ccn5	119.73399	ccc19	120.87865		

Z-matrix for **3** (N-Ar & Virtual Dihedral Angle locked)-Lowest Energy Conformation

0 1			dih5	280.00000	cc20	1.39094
c			cc6	1.38865	ccc20	120.86398
n 1 nc2			ccc6	120.17543	dih20	-0.12616
c 2 cn3	1 cnc3		dih6	180.43492	cc21	1.39717
c 2 cn4	1 cnc4	3 dih4	cc7	1.38943	ccc21	121.07761
c 4 cc5	2 ccn5	1 dih5	ccc7	119.62737	dih21	0.06926
c 5 cc6	4 ccc6	2 dih6	dih7	-0.22696	cc22	1.49620
c 6 cc7	5 ccc7	4 dih7	cc8	1.38907	ccn22	103.28453
c 7 cc8	6 ccc8	5 dih8	ccc8	119.98758	dih22	5.60369
c 8 cc9	7 ccc9	6 dih9	dih8	-0.24592	hc23	1.09462
s 9 sc10	8 scc10	7 dih10	cc9	1.39914	hcc23	120.91318
o 10 os11	9 osc11	8 dih11	ccc9	121.81343	dih23	-179.63482
o 10 os12	9 osc12	8 dih12	dih9	0.23831	hc24	1.09553
c 10 cs13	9 csc13	8 dih13	sc10	1.80502	hcc24	119.60882
h 13 hc14	10 hcs14	12 dih14	scc10	117.45896	dih24	-179.81812
h 13 hc15	10 hcs15	12 dih15	dih10	-178.51055	hc25	1.09530
h 13 hc16	10 hcs16	12 dih16	os11	1.46922	hcc25	119.44171
c 3 cc17	2 ccn17	1 dih17	osc11	110.10983	dih25	-179.96762
c 17 cc18	3 ccc18	2 dih18	dih11	130.58371	hc26	1.09530
c 18 cc19	17 ccc19	3 dih19	os12	1.47372	hcc26	120.76568
c 19 cc20	18 ccc20	17 dih20	osc12	108.75719	dih26	0.19854
c 20 cc21	19 ccc21	18 dih21	dih12	2.07529	oc27	1.21568
c 1 cc22	2 ccn22	3 dih22	cs13	1.78958	ocn27	123.06084
h 21 hc23	20 hcc23	19 dih23	csc13	101.70444	dih27	176.48206
h 20 hc24	19 hcc24	18 dih24	dih13	-112.38465	hc28	1.09697
h 19 hc25	18 hcc25	17 dih25	hc14	1.09965	hcc28	120.41018
h 18 hc26	17 hcc26	3 dih26	hcs14	112.14765	dih28	-0.19398
o 3 oc27	2 ocn27	1 dih27	dih14	115.81963	hc29	1.09543
h 5 hc28	4 hcc28	2 dih28	hc15	1.09956	hcc29	120.05234
h 6 hc29	5 hcc29	4 dih29	hcs15	112.17576	dih29	179.69153
h 7 hc30	6 hcc30	5 dih30	dih15	-3.55484	hc30	1.09548
h 8 hc31	7 hcc31	6 dih31	hc16	1.10000	hcc30	120.15398
h 1 hc32	2 hcn32	3 dih32	hcs16	113.90818	dih30	-180.12789
h 1 hc33	2 hcn33	3 dih33	dih16	-124.00706	hc31	1.10091
			cc17	1.48301	hcc31	118.70130
	nc2	1.50527	ccn17	106.29511	dih31	-179.46263
	cn3	1.44679	dih17	-6.02150	hc32	1.10926
	cnc3	110.25045	cc18	1.38395	hcn32	109.08437
	cn4	1.45191	ccc18	129.66198	dih32	125.42292
	cnc4	118.26006	dih18	-176.11360	hc33	1.10783
	dih4	150.00000	cc19	1.39682	hcn33	112.04193
	cc5	1.39955	ccc19	118.03828	dih33	-115.34331
	ccn5	118.76147	dih19	-179.87980		

Appendix 5

Step by step guide to convert and analyze NMR spectra from VNMR to gNMR

There are 3 different programs, which you have to use,

1. gCVT: This program is used to import spectrum from VNMR (which is our NMR processing software).
2. gSPG: This is the program in which imported spectra from gCVT opens up. In this program you can process your spectrum. For example, you can adjust your spectra for Line width, Phasing and other things. Be sure to SAVE your spectrum after you think it's perfect for processing in gNMR.
3. gNMR: This is the program which gives your theoretical and experimental spectrum

Now, following are the instructions for using gCVT program:

(Before doing this you might want to make a NEW sub-folder (as gSPG) in your main folder where you have your all VNMR spectrums for that particular compound. But you can do this later.)

1. Open gCVT program.
2. Along with gCVT program a window opens up which says Convert File. There are 4 different options in this window.
 - i) VNMR Parameter file: propar file
 - ii) VNMR spectrum file: NONE
 - iii) VNMR FID file: fid file

iv) VNMR text file: text file

Now, next to each of those there is a browse option. Click on that and go to your own spectrum file from VNMR.

When you open your file you may not see all your spectrum files. Therefore click on 'all files' then you will be able to see all your files.

For each of the above type select particular file from your spectrum EXCEPT FOR SPECTRUM file.

After you fill in all the file names click on GO. Then you will see some series of messages in gCVT window, which shows you the progress of your processing. (It's very fast..) Then it will give you a message

“ generating spectrum by unweighted FFT

Phasing will probably be incorrect.” Click OK.

This will open up your gSPG program and you will see your spectrum but with phasing totally wrong. You will have to phase this spectrum.

Now we are in gSPG program:

1. Try clicking on Spectrum menu and then Auto phase. This might be helpful but not for sure.
2. If the spectrum doesn't look good then Click on Spectrum Menu and then Phase. One window will open up. In this window it's usually good idea to Select – Quick phasing option. Then by clicking on

- i) Left Phase
- ii) Right phase
- iii) Pivot phase

Adjust your spectrum till it looks as good as a normal NMR spectrum in VNMR.

When you are satisfied Click on Done.

Now if you are planning to simulate Whole Spectrum then at this stage you will have to SAVE this spectrum. Be sure to SAVE your spectrum after you think it's perfect for processing in gNMR.

As I am more interested in only methylene protons (i.e. 4.2-5.5 ppm) I will do the following:

- i) Put the cursor on 4.2 ppm
- ii) Drag the cursor till 5.5 ppm
- iii) Click anywhere in the middle, this will show now only 4.2-5.5 ppm of the spectrum
- iv) Click on Spectrum Menu, Reduce followed by Sub spectrum, this will now kind of enlarge your spectrum
- v) If you want your spectrum in this enlarged form for the processing in gNMR then you will have to save this spectrum. I usually save this as same name which I used to save spectra in gSPG with added name as
*-sub

Now you are ready to process this spectrum in gNMR to get,

- i) theoretical and experimental spectrum comparison
- ii) rate of exchange process.

Repeat all of the above procedure for all your spectra at each temperature.

All these things are usually done as follows:

Open gNMR program now.

1. gNMR program opens up with a small window with title Welcome to gNMR inside the main big window.
2. Click on “start with an empty molecule”.
3. GO to gSPG program where you have your experimental spectrum and note down the ppm values for the two peaks.(note: you can put the cursor on the peak and it's ppm value will appear in the left corner of the spectrum window)
4. In gNMR in document1-molecule1 window.
5. Enter approximate ppm value for 1st peak in column for δ (The one, which you noted down in step 3 above). Press Enter. **Also remember to keep this ppm value as variable. To do this, type any alphabetical letter in the window exactly below your ppm value window.**
6. Enter the approximate ppm value for 2nd peak in column for δ (the one which you noted down in step 3 above). Press Enter. **Also remember to keep this ppm value as variable. To do this, type any (must be different from the letter which you used in step 5) alphabetical letter in the window which exactly below your ppm value window.**

7. Click on Spectrum. Spectrum with 2 peaks (sharp) will appear.
8. Click on Settings – Spectrum, a small window will appear inside which you will see all the spectrum parameters like,
 - i) Line width
 - ii) Scale
 - iii) From ppm
 - iv) To ppm
 - v) Verticle size
9. In from-ppm put 4.2 ppm (this comes from the spectrum which you saved in your gSPG program) **REFER to page 2 above.**
10. In to –ppm put 5.5 ppm (this comes from the spectrum which you saved in your gSPG program) **REFER to page 2 above.**
11. Click on OK
12. New spectrum window appears in which you have to scroll horizontally to see your 2nd peak. Therefore close this spectrum window by clicking on **X**

Again in document 1-molecule1 window click on spectrum. Now you will see your spectrum with 2 peaks in one window without doing scroll. (The height of the 2 peaks might be different but don't worry!)
13. Now go to Settings—Spectrum—Iteration your Left hand side you will see that Iteration is in blue.
14. In right hand side it shows Spectrum: None

15. Click on File. Go and find out your corresponding gSPG spectrum which you saved as *-sub file above.
16. Click OK. A message will appear saying “Spectrometer frequency mismatch. Adjust automatically?” say OK to this.
17. You will now see that your experimental spectrum is now on TOP and theoretical Spectrum is now on BOTTOM in your spectrum 1 window.
18. In Spectrum –Settings window in Display choose option as Overlapping. Click on Apply Check “full line shape iteration” and click OK. You will see in Spectrum window that one spectrum is in Red color.
19. Next to your UNDO—REDO icons there is one icon, which is for exchange click on that icon and one exchange window opens up.

Rate: type any number (I usually type 100)

Iter? : incompl

1-2 : 2-1

2-1 : 1-2

After you type all these things the 2nd option Iter? Will change from Incoml to Fixed. Change that option by scrolling down to variable. Then, Click on Recalculate.
20. Now you will see that spectrum window has changed and you will see 2 sets of peaks not overlapping exactly.
21. **IMPORTANT:** In your left hand corner you will see a minimized window which is a LOG window open that window and adjust it’s size so that you can clearly see your spectrum iteration.
22. **IMPORTANT:** you will see that in the spectrum window

RED color spectrum: theoretical Spectrum has a base line UP certain height from your experimental BLACK Spectrum there for to fix that problem go to Settings—Spectrum—Baseline and you will see 3 options:

Phase(0):

Phase (1):

Height :

In any height window 1st type very small number say 0.01 and click Apply.

Now you will see that in spectrum window both the peaks RED and BLACK have nearly same Baseline Height. If you still see a very large difference in base line height then try typing very small number in Phase(0) and then in Phase (1) in same order. Try one at a time. Sometimes you have to type number in all of the above 3 windows. IMPORTANT: also be sure to check Iterate on Baseline in Settings—Spectrum—Iteration option. This is below “full line shape iteration”, which you checked earlier. Click on APPLY—OK

23. Now you are all set to do iteration. Click on **Iterate—GO** you will see movement in two spectrums to match exactly with each other. At the same time you will see something is going on in LOG window and also in Exchange window. At the end of the matching you will now see that two spectrums match exactly and in exchange window you will see the exchange rate of this process. Take down this value and remember this value is for particular spectrum, which was recorded at particular temperature.

SAVE your Results in gNMR.

Sometimes if you see in gNMR Log window you will see that Error in Rate measurement is very high. To minimize the error you can do one thing. Go to your Molecule window where you put your ppm value initially and remove the alphabetical

letters which have put in there at the beginning and then again click on Iterate—GO. Again same calculations will be performed but this time you will see that the error in K measurement is very less. Till today I haven't been able to find out the reasoning behind this but this is just my observation.

24. Repeat ALL these steps (1-23) for all of your recorded spectrums in VNMR to get exchange rate at all that temperature.

25. Plot graph of $\ln k$ vs $1/T$ in excel and calculate ΔG value from slope.

Step by step guide to perform PM3 Semi-empirical calculations using Gaussian™

The following steps were followed to do the semi-empirical PM3 molecular orbital calculations on all of the isoindolines (**1-3**, Chapter 4).

1. Draw the structure in HyperChem™ v 6.02.
2. Import the structure in Gaussian™ 1998.
3. Optimize the structure using PM3 semi-empirical molecular orbital calculation method.
4. Define the z-matrix of the structure using z-mat editor in molden (program used to see the structure of the molecule).
5. Identify the two dihedral angles which you would like to study.
6. In gaussian, do the geometry optimization calculations by holding each of the dihedral angle at its fixed value and allowing rest of the molecule to relax to its minimum energy conformation. For example, rotate one dihedral angle from 0 to 360° while holding the other dihedral angle at any particular fixed value between 0 to 360°. Energies in the form of eigenvalues (in atomic units) would be provided during these calculations in the “.log” file of each of these calculations.
7. Plot a 3D surface plot (preferably in MathCad™) of the energy values obtained at each of the data point versus two dihedral angle values at the same data point.
8. Locate the minimum (on either side of the maxima) and maximum energy conformation on the surface plot (using the obtained energy values) and further

- single point frequency calculations on each of these points were performed. This is necessary as the calculations performed in PM3 are the gas phase calculations.
9. From the energy values obtained from the frequency calculations rotational barrier was evaluated, after converting atomic units into kcal/mol.
 10. Identical calculations were performed in a study, which showed correlated nitrogen pyramidalization and N-Ar rotation by making the only change in one dihedral angle. Instead of using S-Ar angle as one dihedral angle and N-Ar as the other in **1-3**, virtual dihedral angle was used along with N-Ar as the second dihedral angle.