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# Synthesis of bioactive nitrogen-containing heterocycles via aryne methodologies

by

Yuesi Fang

A dissertation to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:

Richard C. Larock, Co-Major Professor

George A. Kraus, Co-Major Professor

Yan Zhao

Malika Jeffries-EL

Klaus Schmidt-Rohr

Iowa State University

Ames, Iowa

2012

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To my family and everyone who supported me.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS ..... vi

CHAPTER 1. General Introduction

1.1. Dissertation Organization ..... 1

1.2. The Nature of Benzyne ..... 3

1.3. A Brief Review of Aryne Generation ..... 3

1.4. A Brief Introduction to Aryne Reactions ..... 4

1.5. Conclusions ..... 8

1.6. References ..... 8

CHAPTER 2. Nucleophilic Addition to 2,3-Pyridyne and Synthesis of Benzonaphthyridinones

2.1. Abstract ..... 13

2.2. Introduction ..... 13

2.3. Results and discussion ..... 15

2.4. Conclusions ..... 25

2.5. Experimental section ..... 25

2.6. Acknowledgment ..... 33

2.7. References ..... 33

CHAPTER 3. Formation of Acridones by Ethylene Extrusion in the Reaction of Arynes with β-Lactams and Dihydroquinolinones

3.1. Abstract ..... 37

3.2. Introduction ..... 37

3.3. Results and Discussion ..... 39

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3.4. Conclusions ..... 50

3.5. Experimental Section ..... 51

3.6. Acknowledgment ..... 64

3.7. References ..... 64

CHAPTER 4. Synthesis of 2*H*-Indazoles by the [ 3 + 2 ] Dipolar Cycloaddition of Sydnones with Arynes

4.1. Abstract ..... 68

4.2. Introduction ..... 68

4.3. Results and Discussion ..... 70

4.4. Conclusions ..... 83

4.5. Experimental Section ..... 84

4.6. Acknowledgment ..... 103

4.7. References ..... 104

CHAPTER 5. Synthesis of Isoindoles and 9,10-Dihydro-9,10-epiminoanthracenes by Aryne Dipolar Cycloaddition with Münchnones

5.1. Abstract ..... 110

5.2. Introduction ..... 110

5.3. Results and Discussion ..... 111

5.4. Conclusions ..... 118

5.5. Experimental Section ..... 118

5.6. Acknowledgement ..... 127

5.7. References ..... 127

المنارة للاستشارات

www.manaraa.com

CHAPTER 6. General Conclusions ..... 129

AKNOWLEDGEMENTS ..... 131

APPENDIX A. CHAPTER 2 $^{1}$H AND $^{13}$C NMR SPECTRA ..... 132

APPENDIX B. CHAPTER 3 $^{1}$H AND $^{13}$C NMR SPECTRA ..... 155

APPENDIX C. CHAPTER 4 COMPUTATIONAL DATA, $^{1}$H AND $^{13}$C NMR SPECTRA ..... 175

APPENDIX D. CHAPTER 5 $^{1}$H AND $^{13}$C NMR SPECTRA ..... 218

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Atm | atmospheres of pressure |
| Br | broad (spectral) |
| ºC | degrees Celsius |
| Δ | chemical shift in ppm |
| cat. | catalytic amount |
| *J* | coupling constant (spectral) |
| D | doublet (spectral) |
| Dd | doublet of doublets (spectral) |
| eq. | Equation |
| Equiv | Equivalent |
| G | Gram |
| GC | gas chromatography |
| H | Hour |
| HRMS | high resolution mass spectrometry |
| Hz | Hertz |
| IR | infrared spectrometry |
| M | multiplet (spectral) |
| *M* | Meta |
| Mg | Milligram |
| Min | Minute |

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| | |
|---|---|
| mL | Milliliter |
| Mmol | Millimole |
| Mp | melting point |
| NMR | nuclear magnetic resonance |
| *O* | Ortho |
| OTf | Triflate |
| *P* | Para |
| Ppm | parts per million |
| Q | quartet (spectral) |
| Rt | room temperature |
| TMS | Trimethylsilyl |
| TBAF | tetrabutylammonium fluoride |
| TBAT | tetrabutylammonium triphenyldifluorosilicate |
| TFAA | trifluoroacetic anhydride |
| TfOH | trifluoromethanesulfonic acid |
| Td | triplet of doublets (spectral) |
| Tq | triplet of quartets (spectral) |

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# CHAPTER 1

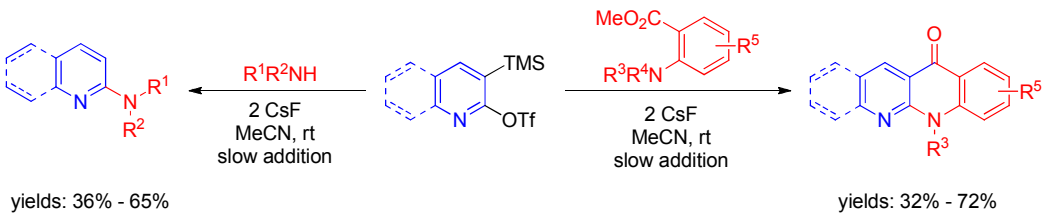
## General Introduction

### 1.1. Dissertation Organization

The six chapters of this dissertation exemplify the application of aryne chemistry in medicinally-relevant, nitrogen-containing heterocycle synthesis. The arynes discussed in this dissertation are generated from Kobayashi's aryne precursors[1] that leads to novel synthetic methodology. Chapter 1 begins by detailing the overall organization of this dissertation and follows with a brief review of arynes, which provides the reader with a general understanding of this highly reactive intermediate and its application in various organic transformations.

Chapter 2 is an article published in *Tetrahedron* in 2012 (Scheme 1).[2] This chapter describes the chemical reactivity of 2,3-pyridyne in the presence of amines. We have found that amines attack the 2-position of 2,3-pyridyne exclusively to afford the corresponding 2-aminopyridines. In addition, a series of benzonaphthyridinones have been synthesized by reacting 2,3-pyridyne with *o*-aminobenzoates.

**Scheme 1.** The pyridyne project.




Chapter 3 describes a project involving the reaction of β-lactams and arynes, which has been submitted to *The Journal of Organic Chemistry* (Scheme 2). In this process, the aryne inserts into carbon-nitrogen bond of the β-lactam to form a 2,3-dihydroquinolin-4-one, which

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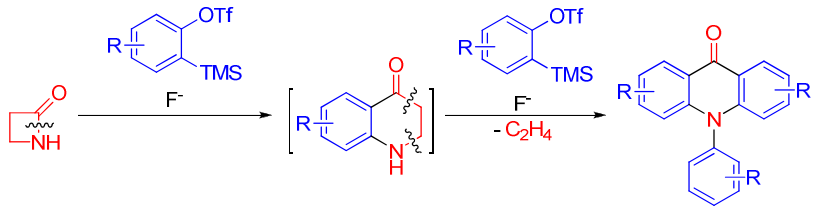
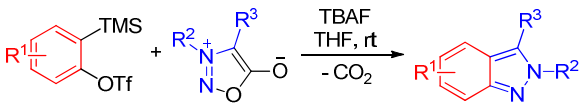
subsequently reacts with another molecule of aryne to form an acridone by extrusion of a molecule of ethylene. 2,3-Dihydroquinolin-4-ones react under the same reaction conditions to afford acridones. This is the first example of ethylene extrusion in aryne chemistry.

**Scheme 2.** The reaction of β-lactam and aryne.




Chapter 4 describes a project, which was published in *Organic Letters* in 2010[3] and in *The Journal of Organic Chemistry* in 2011 (Scheme 3).[4] This project involves a rapid and efficient synthesis of 2*H*-indazoles using a [3 + 2] dipolar cycloaddition of sydnones and arynes. A series of 2*H*-indazoles have been prepared in good to excellent yields using this protocol, and subsequent Pd-catalyzed coupling reactions can be applied to the halogenated products to generate a structurally diverse library of indazoles. This methodology has been highlighted in *Synfacts*.[5]

**Scheme 3.** The sydnone project.




Chapter 5 describes a project soon to be submitted for publication that details a methodology for synthesizing 2*H*-isoindoles and 9,10-dihydro-9,10-epiminoanthracenes from arynes and münchnones (Scheme 4). 2*H*-Isoindoles have been generated from arynes and münchnones by a [3 + 2] dipolar cycloaddition process under very mild reaction conditions. Due to the high reactivity of 2*H*-isoindoles with arynes, 9,10-dihydro-9,10-epiminoanthracenes are ultimately formed in the presence of arynes in good to excellent yields.

**Scheme 4.** The münchnone project.

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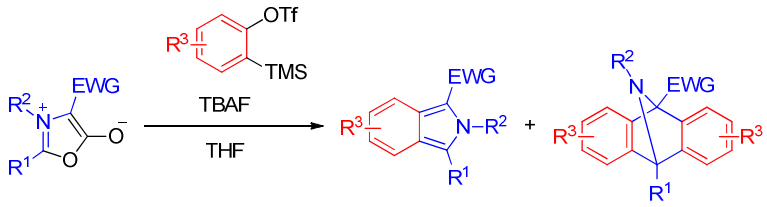


Lastly, Chapter 6 makes some general conclusions about the previous chapters.

### 1.2. The Nature of Benzyne

Benzyne or 1,2-dehydrobenzene is an extremely reactive species due to the nature of its strained triple bond (see Figure 1). This intermediate cannot be isolated under most reaction conditions; thus, it must be trapped *in situ*. The pair of p orbitals that make up the benzyne triple bond are unlike typical alkyne p orbitals, which are parallel to each other. Instead, one pair of benzyne p orbitals is parallel to each other (and part of the pi system), whereas the other pair of p orbitals is strained in order to accommodate the triple bond within the ring system.

**Figure 1.** Two pairs of benzyne triple bond p orbitals.

Generally speaking, arynes are thought to be quite electrophilic. Thus, a broad range of nucleophiles are capable of reacting with an aryne, and this reactivity has been exploited to a great extent in organic synthesis. Thus, the major types of reactions, which involve arynes, are briefly reviewed in section 1.4. Additionally, there are several excellent reviews that cover various aspects of aryne chemistry.[6]

### 1.3. A Brief Review of Aryne Generation

Benzyne was first proposed by Wittig in 1942[7] and confirmed by Roberts in 1956.[8] A numbers of methods have been developed to generate arynes since then. A major method of generating

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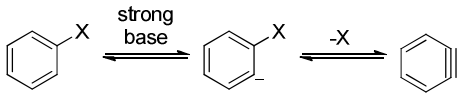
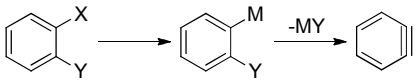
arynes involves 1,2-elimination as shown in equations 1,[9] 2,[10] and 3[11]. Another strategy that has been employed for the generation of arynes involves the retro-cycloaddition of 1-aminobenzotriazoles (eq. 4).[12]



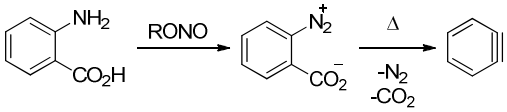

(1)

X = F, Cl, Br, I, OTf

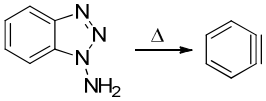



(2)

M = Metal: Li, Mg, Zn, Pd, La
X = Cl, Br, I
Y = F, Cl, OTf, OTs

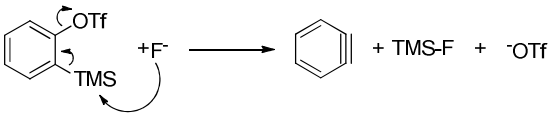



(3)




(4)

In 1983, Kobayashi first introduced a new mild method for generating benzyne by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates (eq 5).[1] Synthetic chemists have been attracted to Kobayashi's method for its convenience, efficiency, tolerance of functional groups, and mild reaction conditions. Thus, aryne chemistry has quickly developed into a hot field.




(5)

### 1.4. A Brief Introduction to Aryne Reactions

The synthetic applications of arynes are remarkably diverse, and a large number of aryne reactions found in the literature can be classified into several main categories: arylations, insertions, annulations, and transition metal-catalyzed reactions.

#### 1.4.1. Arylation Reactions

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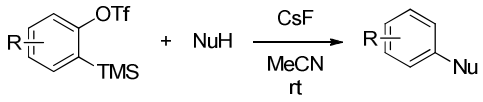
Due to the electrophilicity of the aryne triple bond, a number of nucleophiles can react with arynes leading to arylated products. Kobayashi's method for aryne formation lends itself particularly well to arylation reactions, and our group has reported a mild and efficient method to achieve this (eq. 6).[13]

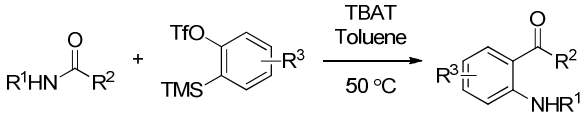



(6)

NuH = amines, sulfonamides, phenols, thiophenols, and arenecarboxylic acids

### 1.4.2. Insertion Reactions

When the nucleophile is tethered to an electrophile, the nucleophilic addition can trigger subsequent electrophilic trapping of the aryl anion, leading to a formal σ-bond cleavage. Amide functionality is one such tethered nucleophile-electrophile pair, where the nitrogen and the carbonyl group serve as the nucleophile and the electrophile, respectively.[14] One typical example reported by Greaney is shown in equation 7.[14f]




(7)

A C-H unit can act as a nucleophile when it's adjacent to one or two strong electron-withdrawing groups. Thus, C-C insertion is also possible.[9e,9f,15] The insertion of arynes into Te-Te,[16] S-S,[17] Si-Si,[18] N-Si,[19] C-Si,[20] C-Sn,[21] Sn-S,[22] Se-Se,[23] I-I,[24] C-S,[25] C-Cl,[26] and C-O[27] bonds have also been reported.

### 1.4.3. Annulation Reactions

Aryne annulation reactions involve several different reaction types. One typical reaction arises when the aryl anion generated by nucleophilic attack on an aryne is trapped by an intramolecular electrophile to form a ring structure. This type of aryne reaction can rapidly produce various heterocycles under mild reaction conditions. For example, the synthesis of

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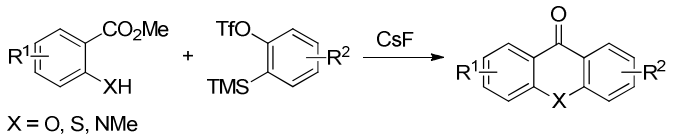
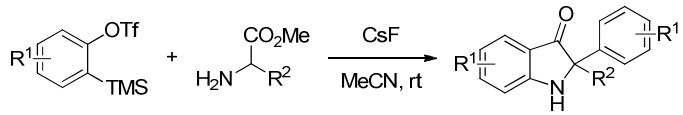
xanthones, thioxanthones, and acridones by this method has been reported by our group (eq. 8).[28] Five-membered ring heterocycles can also be achieved through a similar mechanism as shown in equation 9.[29]

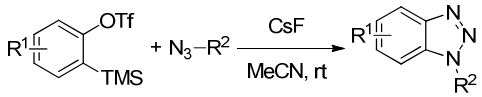



(8)

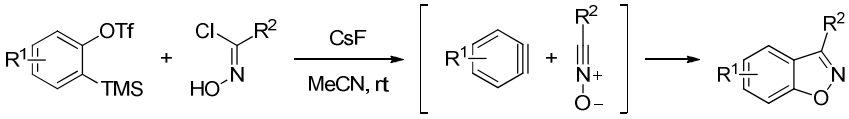



(9)

Another type of annulation, which involves 1,3-dipoles, follows a [3 + 2] cycloaddition mechanism. Many examples with 1,3-dipoles exemplify the utility and generality of arynes in cycloaddition reactions. It is common that 1,3-dipoles contain heteroatoms. Thus, this methodology appears to be a useful way to prepare various heterocycles. For example, substituted benzotriazoles have been prepared by the [3 + 2] cycloaddition of azides and arynes as shown in equation 10.[30] Our group has developed a methodology for the synthesis of benzisoxazoles using nitrile oxides (generated *in situ* from a chloroxime, eq. 11).[31]




(10)




(11)

Arynes, due to their triple bonds, can also act as a dienophile in Diels-Alder reactions. This method has proven valuable in the construction of numerous polycyclic systems. When Kobayashi first introduced his benzyne precursor, furan was used as the reacting partner to trap the benzyne generated *in situ* (eq. 12).[1] An example of an intramolecular Diels-Alder reaction can be seen in Danheiser's work in which a highly condensed polycyclic structure is formed (eq.

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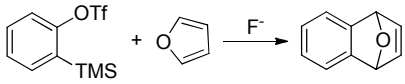
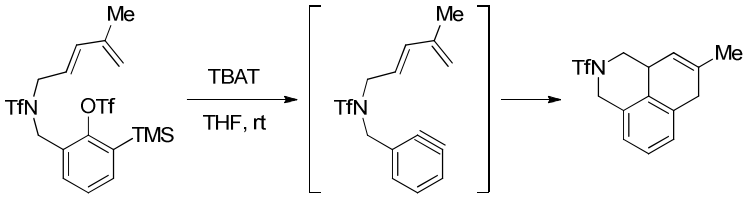
13).[32]



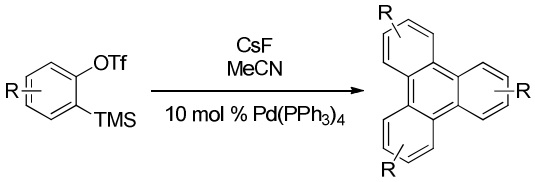

(12)



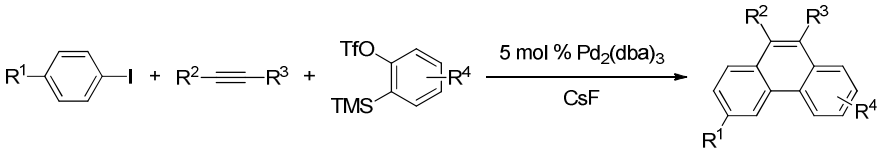

(13)

### 1.4.4. Transition Metal-Catalyzed Aryne Reactions

The triple bond of an aryne should be able to coordinate with a transition metal catalyst. Kobayashi's fluoride-induced aryne generation has allowed for the development of many useful transition metal-catalyzed aryne reactions, because of its mild reaction conditions. Palladium is one of the most widely used metals for catalyzing reactions involving arynes. As an early example reported by Peña, the use of catalytic amounts of $Pd(PPh_3)_4$ enabled the process of aryne cyclotrimerization (eq. 14).[33] Many examples of transition metal-catalyzed processes using aryl halides and catalytic palladium have been reported.[34] One example involves the three-component coupling of arynes, an alkyne, and aryl halides to afford a variety of functionally diverse phenanthrenes in good yields (eq. 15).[34e] A useful annulation for the synthesis of fluorenones is also made possible by employing catalytic amounts of palladium (eq. 16).[35]




(14)




(15)

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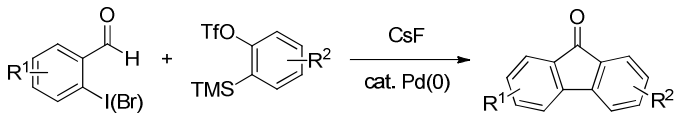


(16)

**1.5. Conclusions**

Arynes have proven very useful intermediates in a number of important organic transformations. The chemistry community has witnessed tremendous growth in the field of aryne chemistry since the discovery and utilization of Kobayashi's method for aryne generation. The potential application of arynes in organic synthesis is sure to be a very active area of research for the foreseeable future.

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# CHAPTER 2

## Nucleophilic Addition to 2,3-Pyridyne and Synthesis of Benzonaphthyridinones

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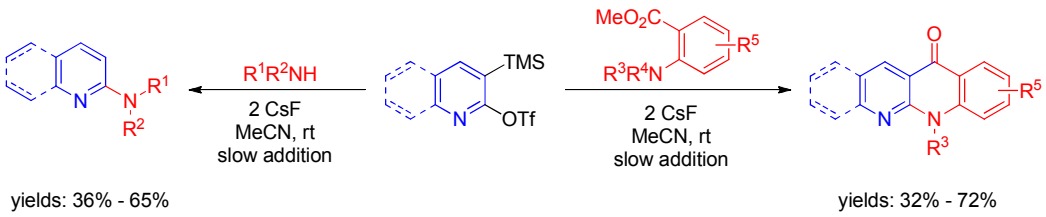
Yuesi Fang and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, IA 50011, U.S.A.

### 2.1. Abstract




A study of the nucleophilic addition of amines to 2,3-pyridyne has been carried out. 2--Aminopyridines have been generated exclusively. A series of benzonaphthyridinones have been synthesized by reacting 2,3-pyridyne and *o*-aminobenzoates.

### 2.2. Introduction

Heterocyclic compounds have attracted significant attention for decades, because of their considerable biological activity and potential medicinal applications. Among the various heterocycles, benzonaphthyridinones and dibenzonaphthyridinones (Figure 1) are known as antimicrobial alkaloids,[1] anticancer agents,[2] and compounds that can reverse multidrug resistance.[3]

**Figure 1.** A Representative Benzonaphthyridinone and a Dibenzonaphthyridinone.

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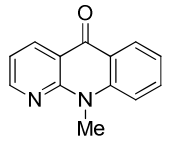
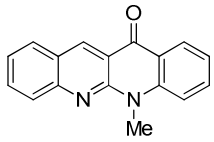


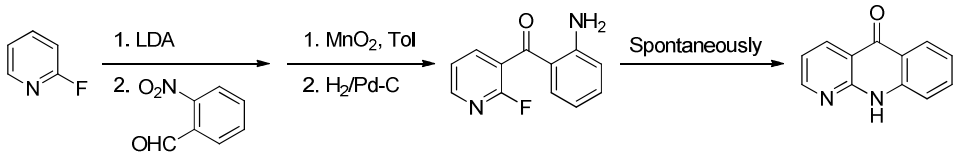
10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one



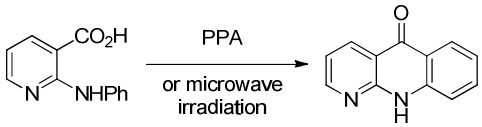
6-methyldibenzo[*b*,*g*][1,8]naphthyridin-11(6*H*)-one

However, synthetic approaches to these heterocycles remain limited. Quéguiner reported a process involving nucleophilic aromatic substitution to afford the benzonaphthyridinone core (Scheme 1).[4] This ring system can also be prepared from 2-(phenylamino)nicotinic acid using either the strong acid PPA[5] or microwave irradiation[6] (Scheme 2). Dibenzonaphthyridinones have also been synthesized using PPA and a high temperature.[7]

**Scheme 1.** Synthesis of Benzonaphthyridinone Involving Nucleophilic Aromatic Substitution.




**Scheme 2.** Synthesis of Benzonaphthyridinone under Harsh Conditions.




Benzyne, a highly reactive intermediate, was first proposed by Wittig[8] in 1942 and confirmed by Roberts[9] in 1956. Kobayashi in 1983 reported a novel way to generate arynes from silylaryl triflates in the presence of fluoride.[10] The Larock group has had an extensive ongoing research program in aryne chemistry in recent years.[11] We have reported nucleophilic addition reactions of arynes,[12] and later, a synthesis of xanthones, thioxanthones, and acridones from substituted benzoates involving nucleophilic attack on arynes, followed by ring closure.[13] The exciting possibility of extending this methodology to hetarynes[14] to generate polyheterocycles has now been examined.

2,3-Pyridyne has been the target of considerable research for decades.[15] Classic approaches to

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this interesting intermediate include oxidation of an aminotriazolopyridine[16] and a halogen-metal exchange-elimination sequence starting from 3-bromo-2-chloropyridine and employing a lithium reagent.[17] 3-(Trimethylsilyl)pyridin-2-yl triflate (**1a**) has been prepared by Effenberger and its fluoride-induced desilylation-elimination process generating 2,3-pyridyne has been reported.[18] In a classic elimination-addition reaction of 3-halopyridine using $KNH_2/NH_3$,[15a] both 2- and 3-adducts have been reported with the former predominating. Fleming reported one example of the addition of acetic acid to 2,3-pyridyne to form the 2-substituted product.[19] One example of the amination of 2,3-pyridyne has been reported in 2009, but not fully investigated.[20] Herein, we report a study of the nucleophilic addition reactions of 2,3-pyridyne and amines, and a synthesis of benzonaphthyridinones from 2,3-pyridyne and *o*-aminobenzoates.

**2.3. Results and discussion**

Our initial work began with a study of the nucleophilic addition of *N*-methylaniline to 2,3-pyridyne. The 2,3-pyridyne precursor, 3-(trimethylsilyl)pyridin-2-yl triflate, was prepared using a literature procedure[18] and the method was extended to the preparation of the 2,3-quinolyne precursor 3-(trimethylsilyl)quinolin-2-yl triflate (Scheme 3). We first allowed 3-(trimethylsilyl)pyridin-2-yl triflate to react with 2.0 equiv of CsF and 1.0 equiv of *N*-methylaniline in acetonitrile (MeCN) at room temperature for 24 h (eq 1). The tertiary amine *N*-methyl-*N*-phenylpyridin-2-amine was obtained in a 33% yield. Although two possible regioisomers could be formed in this reaction, we found that nucleophilic attack occurs exclusively at the 2-position of the 2,3-pyridyne, and the 2-pyridinylamine was the only observed product, albeit in only a relatively low yield.

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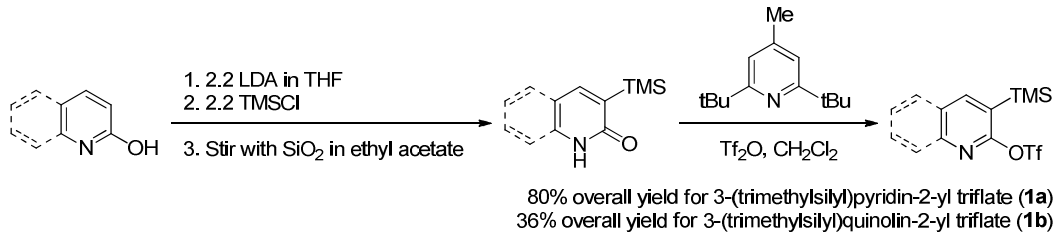
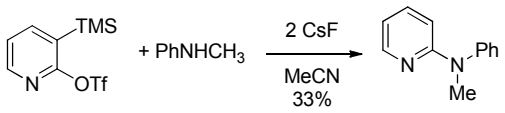
**Scheme 3.** Preparation of the 2,3-Pyridyne and 2,3-Quinolyne Precursors.

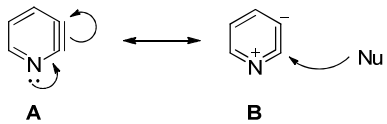



(1)

Computational chemists have reported years ago that the cumulenic structure (structure **B**, Figure 2) is favored for 2,3-pyridyne,[21] which makes the 2-position more susceptible to be attacked by nucleophiles. This cumulenic structure also makes pyridyne extraordinarily reactive, which apparently results in unexpected side reactions leading to a low yield. We have actually stirred the pyridyne precursor with the fluoride source in the absence of any other reagents to check the reactivity and relative stability of pyridyne. It appears that the precursor disappears within an hour, and the pyridyne generated immediately turns into intractable tars, which we believe are the major by-products of the pyridyne chemistry.

**Figure 2.** The Cumulenic Structure of 2,3-Pyridyne.




We have examined a number of different reaction conditions in an attempt to eliminate any undesired side reactions and improve the yield of the aminopyridine (Table 1). The yield was not improved when we changed the solvent (entries 2-6). The product was, in fact, totally different when we used tetrahydrofuran (THF) as the solvent. In THF, the THF acted as the nucleophile apparently attacking the pyridyne first to afford the final ring-opened, amine-containing product

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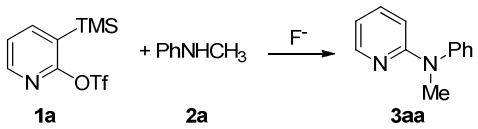
**3aa'** in up to a 58% yield (entries 7-9, Scheme 4). The yield was also not improved when we tried a different fluoride/base system (entry 10) or reaction temperature (entry 11). We did find that higher yields can be achieved when we changed the stoichiometry of the reactants **1a** and **2a**. A yield of 50% has been achieved when employing twice as much of the pyridyne precursor **1a** (entry 12). The yield also improved when we reversed the ratio of **1a** and **2a** (entry 13), although the improvement was not as large as in the previous case (44% vs 50% in entry 12). Since the pyridyne precursor is less readily available than the amine, we decided to employ an excess of the amine in all further studies. However, the yield did not increase further when we used 3 equiv and 4 equiv of **2a** (entries 14 and 15). The yield did, however, reach 49% when we diluted the reaction solution (entries 16 and 17). It appears that the pyridyne itself is so reactive that it causes side reactions. Thus, a lower concentration of pyridyne appears to reduce unwanted side reactions.

**Table 1.** Optimization of the Nucleophilic Amination of 2,3-Pyridyne.[a]




| entry | **1a** (equiv) | **2a** (equiv) | fluoride source (equiv) | solvent (mL) | *T* (°C)/time (h) | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 1 | 1 | CsF (2) | MeCN (4) | rt, 24 | 33 |
| 2 | 1 | 1 | CsF (2) | DME (4) | rt, 24 | 18 |
| 3 | 1 | 1 | CsF (2) | DMF (4) | rt, 24 | trace |
| 4 | 1 | 1 | CsF (2) | MeCN (3)/Tol (1) | rt, 24 | 32 |

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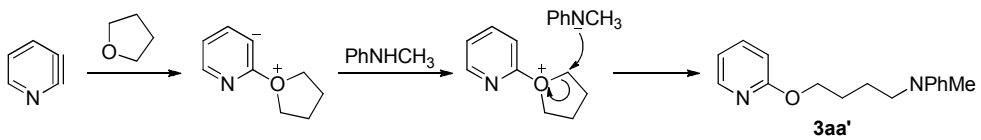
Table 1 continued

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | 1 | 1 | CsF (2) | MeCN (2)/Tol (2) | rt, 24 | 30 |
| 6 | 1 | 1 | CsF (2) | MeCN (1)/Tol (3) | rt, 24 | 29 |
| 7 | 1 | 1 | CsF (2) | THF (4) | rt, 48[c] | 36[d] |
| 8 | 1 | 1 | CsF (2) | THF (4) | 50, 24 | 58[d] |
| 9 | 1 | 1 | TBAF (2) | THF (4) | rt, 24 | trace |
| 10 | 1 | 1 | CsF (2)/$Cs_2CO_3$ (2) | MeCN (4) | rt, 24 | 35 |
| 11 | 1 | 1 | CsF (2) | MeCN (4) | 0→rt, 24 | 31 |
| 12 | 2 | 1 | CsF (4) | MeCN (4) | rt, 24 | 50 |
| 13 | 1 | 2 | CsF (2) | MeCN (4) | rt, 24 | 44 |
| 14 | 1 | 3 | CsF (2) | MeCN (4) | rt, 24 | 43 |
| 15 | 1 | 4 | CsF (2) | MeCN (4) | rt, 24 | 43 |
| 16 | 1 | 2 | CsF (2) | MeCN (8) | rt, 24 | 49 |
| 17 | 1 | 4 | CsF (2) | MeCN (8) | rt, 24 | 49 |

[a] All reactions were carried out on a 0.25 mmol scale. [b] Isolated yield. [c] The pyridyne precursor remained unreacted. [d] Product **3aa'**.

**Scheme 4.** Nucleophilic Attack of THF and the Formation of Compound **3aa'**.




A second round of optimization has been carried out based on the idea that a lower concentration of pyridyne reduces side reactions (Table 2). We prepared a solution of **1a** in 4 mL

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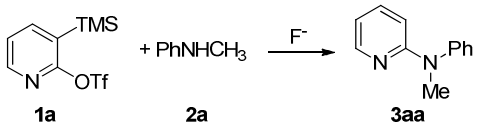
of MeCN (solution A) and a solution of **2a** and CsF in 4 mL of MeCN (solution B). Solution A was slowly added to solution B by using a syringe pump over a long period of time. We found that the yield improved significantly (compare entry 1 and entry 2), because of the slow addition. The loading of **2a** was subsequently reduced to 1 equiv, which did not affect the yield very much (entry 3). A longer addition time also did not improve the yield (entry 4). Therefore, we decided to use this optimized slow addition approach (entry 3) in all further investigations of this process.

**Table 2.** Further Optimization of the Nucleophilic Amination of 2,3-Pyridyne.[a]




| entry | **1a** (equiv) | **2a** (equiv) | solvent (mL) | time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 1 | 2 | MeCN (8) | 24 | 49 |
| 2 | 1 | 2 | MeCN (4+4)[c] | 8+16[d] | 66 |
| 3 | 1 | 1 | MeCN (4+4)[c] | 8+16[d] | 65 |
| 4 | 1 | 1 | MeCN (4+4)[c] | 12+12[d] | 65 |

[a] All reactions were carried out on a 0.25 mmol scale with 2 equiv of CsF at room temperature. [b] Isolated yield. [c] A solution of **1a** in 4 mL of MeCN (solution A) and a solution of **2a** and CsF in 4 mL of MeCN (solution B) were prepared separately. [d] Solution A was slowly added to solution B with a syringe pump over a period of time; the resulting solution was stirred for an additional period of time.

A number of 2-pyridinylamines have been synthesized by reacting 2,3-pyridyne with a number of simple amines (Table 3). As can be seen, both secondary and tertiary amines have been obtained. However, tertiary amine products have not been observed in the reaction of

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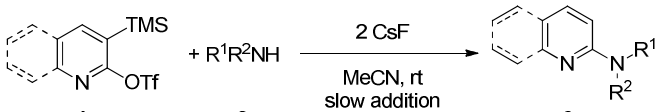
2,3-pyridyne and primary amines (entries 2-8). Halogens, such as iodine, can be tolerated under our reaction conditions to afford the corresponding halogenated products (entries 3 and 4). Both an electron-rich (entry 5) and an electron-deficient aniline (entry 6) have reacted well with pyridyne, although the electron-deficient aniline led to a lower yield. The yield was somewhat lower when the amine bears a sterically bulky group next to the amino group (entry 7). Aliphatic amines react as well under our reaction conditions to afford the corresponding products (entries 8 and 9). The quinolyne precursor **1b** reacted in the same fashion, again tolerating a halogen (entry 10). Unfortunately, we failed to achieve ethers in a satisfactory yield by reacting 2,3-pyridyne and phenols due to the lower nucleophilicity of oxygen than nitrogen.

**Table 3.** Synthesis of 2-Aminopyridines from 2,3-Pyridyne and Various Amines.[a]




**1** **2** **3**

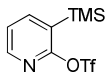
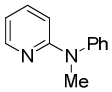
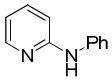
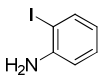
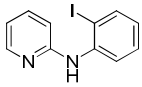
| entry | aryne precursor | amine | product | yield[b] (%) |
|---|---|---|---|---|
| 1 |  **1a** | PhMeNH **2a** |  **3aa** | 65 |
| 2 | | $PhNH_2$ **2b** |  **3ab** | 58 |
| 3 | |  **2c** |  **3ac** | 57 |

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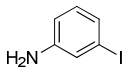
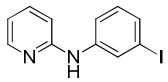
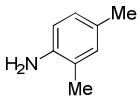
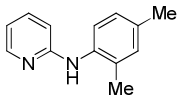
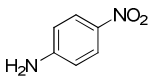
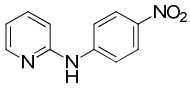
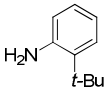
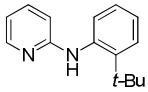
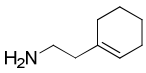
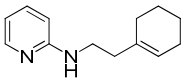
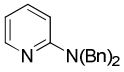
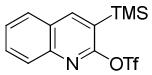
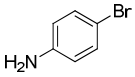
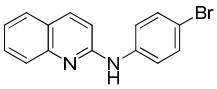
Table 3 continued

| | | | | |
|---|---|---|---|---|
| 4 | |  **2d** |  **3ad** | 64 |
| 5 | |  **2e** |  **3ae** | 61 |
| 6 | |  **2f** |  **3af** | 47 |
| 7 | |  **2g** |  **3ag** | 46 |
| 8 | |  **2h** |  **3ah** | 60 |
| 9 | | $Bn_2NH$ **2i** |  **3ai** | 57 |
| 10 |  **1b** |  **2j** |  **3bj** | 36 |

[a] All reactions were carried out on a 0.25 mmol scale with 2 equiv of CsF at room temperature. A solution of **1** in 4 mL of MeCN (solution A) and a solution of **2** and CsF in 4 mL of MeCN (solution B) were prepared separately. Solution A was slowly added to solution B with a syringe pump over 8 h, the resulting solution was stirred for an additional 16 h. [b] Isolated yield.

Next, a polycyclic system has been achieved by reacting 2,3-pyridyne and *o*-aminobenzoates.

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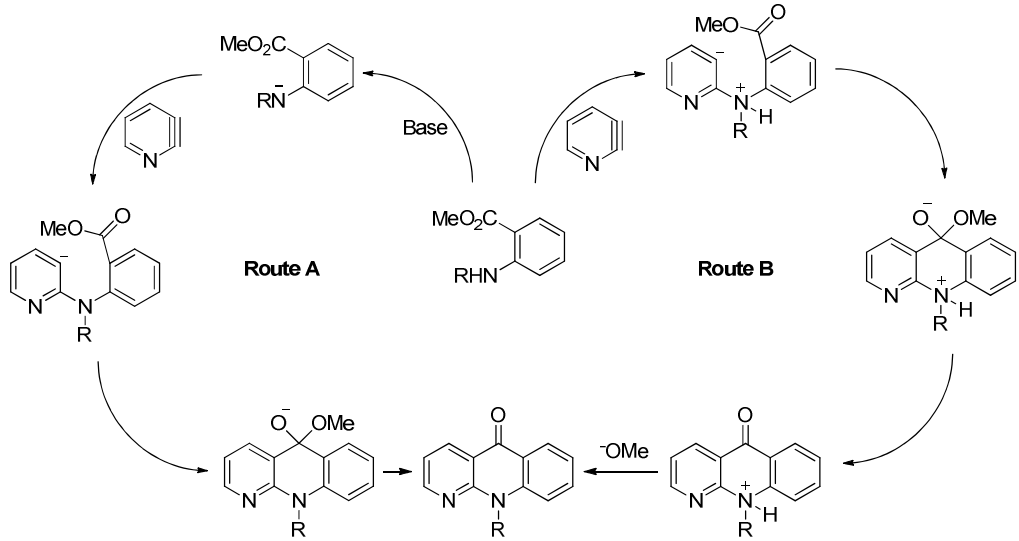
In this process, a plausible mechanism is proposed in Scheme 5. The deprotonated (Scheme 5, Route A) or neutral amino group (Scheme 5, Route B) attacks the 2-position of the pyridyne, generating a carbanion, which is then trapped intramolecularly by the ester group of the *o*-aminobenzoate to form the benzonaphthyridinone.

**Scheme 5.** Proposed Mechanism for the Formation of Benzonaphthyridinone.




Using this basic process, a variety of benzonaphthyridinones and a dibenzonaphthyridinone have been synthesized from 2,3-pyridyne and 2,3-quinolyne using our slow addition reaction conditions (Table 4). It is worth noting that primary amines led to a complex mixture in this chemistry; therefore, only secondary amines have been employed for this synthesis. *N*-Methylbenzonaphthyridinone has been synthesized in a modest 56% yield by reacting 2,3-pyridyne and methyl 2-(methylamino)benzoate (entry 1). *N*-Allylbenzonaphthyridinone has been generated from the corresponding *N*-(allylamino)benzoate in a 48% yield (entry 2). Halides from chloride to iodide are tolerated under our reaction conditions (entries 2-6). The yields are moderate in these cases. It is interesting to compare entries 3-5 and entry 6, where we observe that the yield is higher when the halogen atom is *para* to the ester group of the benzoate. This

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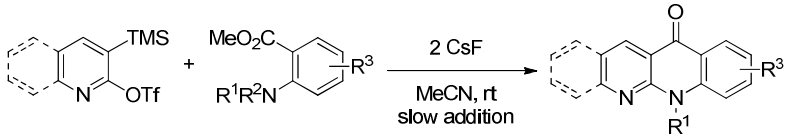
trend is more obvious in entry 7, where an electron-withdrawing group is present *para* to the ester group, which makes the ester group more electrophilic, leading to a higher yield. A tertiary amine (entry 8) reacted as well as the secondary amines, affording the same product **5aa** as in entry 1. This example shows that the neutral amine itself is nucleophilic enough for this transformation to take place (Scheme 6), suggesting that Route B in Scheme 5 is perhaps more favorable. 2,3-Quinolyne reacts the same way as 2,3-pyridyne, and the dibenzonaphthyridinone **5ba** has been formed by reacting the quinolyne with **4a** (entry 9).

**Table 4.** Synthesis of Benzonaphthyridinones and a Dibenzonaphthyridinone.[a]




**1** **4** **5**

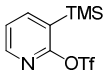
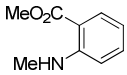
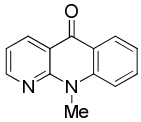
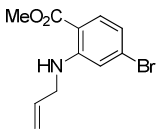
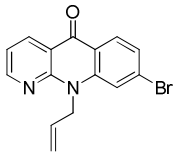
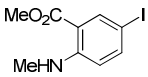
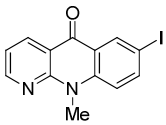
| entry | aryne precursor | amine | product | yield[b] (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **4a** |  **5aa** | 56 |
| 2 | |  **4b** |  **5ab** | 48 |
| 3 | |  **4c** |  **5ac** | 53 |

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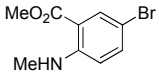
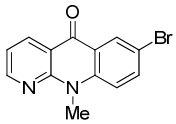
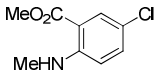
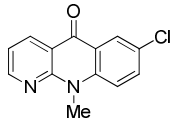
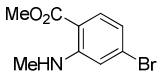
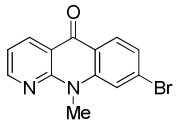
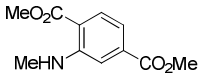
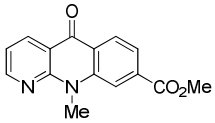
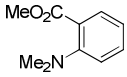
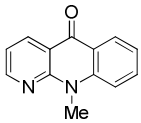
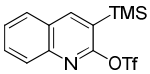
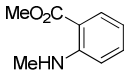
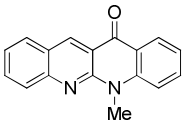
Table 4 continued

| | | | | |
|---|---|---|---|---|
| 4 | |  **4d** |  **5ad** | 52 |
| 5 | |  **4e** |  **5ae** | 48 |
| 6 | |  **4f** |  **5af** | 66 |
| 7 | |  **4g** |  **5ag** | 72 |
| 8 | |  **4h** |  **5aa** | 50 |
| 9 |  **1b** |  **4a** |  **5ba** | 32 |

[a] All reactions were carried out on a 0.25 mmol scale with 2 equiv of CsF at room temperature. A solution of **1** in 4 mL of MeCN (solution A) and a solution of **4** and CsF in 4 mL of MeCN (solution B) were prepared separately. Solution A was slowly added to solution B with a syringe pump over 8 h, the resulting solution was stirred for an additional 16 h. [b] Isolated yield.

**Scheme 6.** The Reaction of 2,3-Pyridyne and Methyl 2-(Dimethylamino)benzoate.

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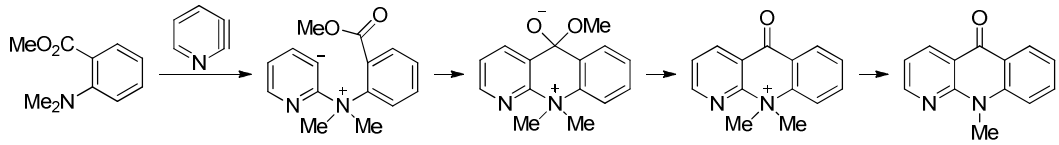
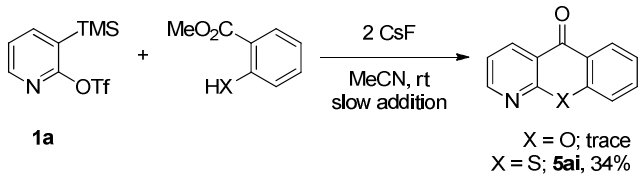



We have also tested a 2-hydroxybenzoate and a 2-mercaptobenzoate in this annulation process (Scheme 7). Again, the phenol group did not react well with the pyridyne apparently due to its lower nucleophilicity, while the sulfur-containing polyheterocycle **5ai** has been formed from the 2-mercaptobenzoate, but in only a 34% yield.

**Scheme 7.** The Reaction of 2,3-Pyridyne and 2-Hydroxy- and 2-Mercaptobenzoate.




## 2.4. Conclusions

Some nucleophilic amination reactions of 2,3-pyridyne and 2,3-quinolyne have been studied. We have found that nucleophilic attack of the amine occurs at the 2-position of 2,3-pyridyne/2,3-quinolyne exclusively, which is consistent with previous computational conclusions. 2,3-Pyridyne and 2,3-quinolyne appear to be so reactive that they cause unwanted side reactions. A slow addition procedure has thus been employed to reduce the side reactions. A variety of 2-pyridinylamines have thus been prepared using primary and secondary amines. When secondary and tertiary *o*-aminobenzoates are employed in this process, benzonaphthyridinones can be synthesized in reasonable yields.

## 2.5. Experimental section

**General information.** All reagents purchased from commercial sources were used as received.

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The solvent THF was distilled over Na/benzophenone. Anhydrous toluene and MeCN were used as received. The aryne precursors were prepared according to a literature procedure.[18] Silica gel for column chromatography was supplied as 230-400 mesh from commercial source. Powdered CsF was used as received and stored in a desiccator.

All melting points were measured and are uncorrected. The $^{1}$H and $^{13}$C NMR spectra were recorded and are referenced to the residual solvent signals (7.26 ppm for $^{1}$H in $CDCl_3$ and 77.2 ppm for $^{13}$C in $CDCl_3$).

All aryne nucleophilic addition reactions and annulations were carried out in oven-dried glassware and were magnetically stirred. A nitrogen atmosphere was not used, except that a balloon of nitrogen was attached to the reaction flask to allow for the extra volume of added solution. A syringe pump was employed for the slow addition reaction conditions.

**Preparation of pyridyne and quinolyne precursors.** These aryne precursors were prepared following the literature procedure.[18]

**3-(Trimethylsilyl)pyridin-2-yl triflate (1a).** Colorless oil: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 4.8, 2.1 Hz, 1 H), 7.92 (dd, *J* = 7.2, 2.1 Hz, 1 H), 7.31 (dd, *J* = 7.2, 5.1 Hz, 1 H), 0.37 (s, 9 H).

**3-(Trimethylsilyl)quinolin-2-yl triflate (1b).** Colorless oil: $R_f$ = 0.33 (20:1 petroleum ether/EtOAc); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.76 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.59 (t, *J* = 7.2 Hz, 1 H), 0.43 (s, 9 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 158.6, 148.8, 146.3, 131.4, 128.5, 127.7, 127.5, 127.4, 124.4, 118.8 ($CF_3$, 123.6, 120.4, 117.2, 114.1), -1.2; LRMS (EI) 349 (M); HRMS (EI) calcd for $C_{13}H_{14}F_3NO_3SSi$ (M) 349.0416, found 349.0422; IR (KBr, $cm^{-1}$) 3064 (w), 2959 (m), 2904 (w), 1590 (m).

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**General procedure for the synthesis of 2-pyridinylamines.** To an oven-dried 4 dram vial equipped with a stir bar were added 0.25 mmol of amine and 76 mg of CsF (0.5 mmol, 2.0 equiv). MeCN (4 mL) was added and the vial was sealed with a rubber septum equipped with a balloon of nitrogen. A solution of 0.25 mmol of aryne precursor in 4 mL of MeCN was prepared separately, and was added to the reaction vial slowly by using a syringe pump while stirring. After the addition was complete, the reaction mixture was allowed to stir for additional time and quenched with water, and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the 2-pyridinylamine.

***N*-Methyl-*N*-phenylpyridin-2-amine (3aa).** Following the general procedure, this product was isolated as a yellow oil: $R_f$ = 0.24 (20:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 4.8, 0.9 Hz, 1 H), 7.40 (m, 2 H), 7.30 (m, 2 H), 7.21 (m, 2 H), 6.60 (td, *J* = 6.0, 0.9 Hz, 1 H), 6.53 (d, *J* = 8.4 Hz, 1 H), 3.48 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 159.0, 148.0, 147.0, 136.7, 129.9, 126.5, 125.6, 113.3, 109.4, 38.6; LRMS (EI) 184 (M), 183 (M-H); HRMS (EI) calcd for $C_{12}H_{11}N_2$ (M-H) 183.0922, found 183.0928. The structure of this compound was assigned based on the $^1$H NMR coupling pattern and was confirmed by comparison with the reported $^1$H and $^{13}$C NMR spectral data.[22]

***N*-Phenylpyridin-2-amine (3ab).** Yellow oil: $R_f$ = 0.11 (20:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.21 (dt, *J* = 5.1, 0.9 Hz, 1 H), 7.49 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.33 (d, *J* = 4.5 Hz, 4 H), 7.05 (m, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 6.82 (s, 1 H), 6.73 (td, *J* = 3.6, 0.9 Hz, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.2, 148.6, 140.7, 137.9, 129.5, 123.0, 120.5, 115.2, 108.4; LRMS (EI) 170 (M), 169 (M-H); HRMS (EI) calcd for $C_{11}H_{10}N_2$ (M) 170.0844, found 170.0847.

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***N*-(2-Iodophenyl)pyridin-2-amine (3ac).** Yellow solid: mp 65-67 ºC; $R_f$ = 0.35 (5:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.83 (td, *J* = 7.2, 1.2 Hz, 2 H), 7.52 (td, *J* = 7.2, 1.8 Hz, 1 H), 7.31 (td, *J* = 7.8, 1.2 Hz, 1 H), 6.80 (m, 3 H), 6.65 (s, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.4, 148.6, 141.3, 139.6, 138.0, 129.2, 124.4, 120.4, 116.1, 109.7, 91.6; LRMS (EI) 296 (M); HRMS (EI) calcd for $C_{11}H_9IN_2$ (M) 295.9810, found 295.9816; IR (KBr, cm$^{-1}$) 3380 (s), 3192 (w), 3012 (m), 2954 (m), 2925 (m), 2866 (m), 1599 (s), 1573 (m), 1515 (s).

***N*-(3-Iodophenyl)pyridin-2-amine (3ad).** Yellow oil: $R_f$ = 0.33 (5:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 4.5 Hz, 1 H), 7.75 (s, 1 H), 7.52 (td, *J* = 7.8, 1.5 Hz, 1 H), 7.33 (t, *J* = 8.4 Hz, 2 H), 7.02 (m, 2 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.77 (dd, *J* = 6.9, 5.1 Hz, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.4, 148.5, 142.2, 138.0, 131.5, 130.8, 128.4, 119.0, 115.8, 109.1, 94.8; LRMS (EI) 296 (M); HRMS (EI) calcd for $C_{11}H_9IN_2$ (M) 295.9810, found 295.9816; IR (KBr, cm$^{-1}$) 3378 (s), 3190 (w), 3012 (m), 2929 (m), 2860 (m), 1595 (s), 1573 (m).

***N*-(2,4-Dimethylphenyl)pyridin-2-amine (3ae).** Yellow oil: $R_f$ = 0.22 (2:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 4.2 Hz, 1 H), 7.41 (td, *J* = 7.2, 1.8 Hz, 1 H), 7.25 (t, *J* = 3.6 Hz, 1 H), 7.08 (s, 1 H), 7.01 (d, *J* = 7.8 Hz, 1 H), 6.60 (m, 2 H), 6.31 (s, 1 H), 2.32 (s, 3 H), 2.23 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 157.5, 148.6, 137.8, 135.8, 134.7, 131.9, 131.3, 127.6, 124.2, 114.4, 107.2, 21.1, 18.1; LRMS (EI) 198 (M); HRMS (EI) calcd for $C_{13}H_{14}N_2$ (M) 198.1157, found 198.1159.

***N*-(4-Nitrophenyl)pyridin-2-amine (3af).** Yellow solid: mp 167-168 ºC (lit[23] 174-176 ºC); $R_f$ = 0.41 (1:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 4.2 Hz, 1 H), 8.20 (d, *J* = 9.3 Hz, 2 H), 7.64 (m, 3 H), 6.94 (m, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 153.9,

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148.5, 147.1, 141.4, 138.3, 125.9, 117.6, 116.9, 111.5; LRMS (EI) 215 (M), 214 (M-H); HRMS (EI) calcd for $C_{11}H_9N_3O_2$ (M) 215.0695, found 215.0699.

***N*-(2-*tert*-Butylphenyl)pyridin-2-amine (3ag).** White solid: mp 122-123 ºC; $R_f$ = 0.18 (5:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.2 Hz, 1 H), 7.46 (d, *J* = 7.5 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 7.32 (d, *J* = 7.5 Hz, 1 H), 7.20 (m, 2 H), 6.66 (t, *J* = 6.0 Hz, 1 H), 6.45 (d, *J* = 8.4 Hz, 1 H), 6.30 (s, 1 H), 1.41 (s, 9 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.3, 148.7, 145.9, 138.8, 137.8, 128.8, 127.4, 127.3, 126.1, 114.3, 107.2, 35.2, 30.8; LRMS (EI) 226 (M); HRMS (EI) calcd for $C_{15}H_{18}N_2$ (M) 226.1470, found 226.1475.

***N*-[2-(Cyclohex-1-en-1-yl)ethyl]pyridin-2-amine (3ah).** Yellow oil: $R_f$ = 0.13 (5:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 4.5, 1.2 Hz, 1 H), 7.42 (td, *J* = 7.2, 1.8 Hz, 1 H), 6.55 (t, *J* = 5.7 Hz, 1 H), 6.37 (d, *J* = 8.4 Hz, 1 H), 5.53 (s, 1 H), 4.50 (s, 1 H), 3.30 (dd, *J* = 12.3, 6.9 Hz, 2 H), 2.27 (t, *J* = 6.6 Hz, 2 H), 1.98 (m, 4 H), 1.60 (m, 4 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 159.0, 148.4, 137.6, 134.8, 124.0, 112.8, 106.6, 39.9, 37.8, 28.0, 25.4, 23.0, 22.6; LRMS (EI) 202 (M); HRMS (EI) calcd for $C_{13}H_{18}N_2$ (M) 202.1470, found 202.1474.

***N,N*-Dibenzylpyridin-2-amine (3ai).** Yellow oil: $R_f$ = 0.27 (20:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.20 (dt, *J* = 5.1, 0.9 Hz, 1 H), 7.31 (m, 11 H), 6.58 (td, *J* = 5.1, 0.9 Hz, 1 H), 6.45 (d, *J* = 8.7 Hz, 1 H), 4.79 (s, 4 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.8, 148.2, 138.6, 137.6, 128.8, 127.2, 127.1, 112.4, 106.1, 51.0; LRMS (EI) 274 (M); HRMS (EI) calcd for $C_{19}H_{18}N_2$ (M) 274.1470, found 274.1473.

***N*-(4-Bromophenyl)quinolin-2-amine (3bj).** Brown solid: mp 143-145 ºC; $R_f$ = 0.56 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.61 (m, 4 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 6.90 (d, *J* = 8.8

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Hz, 1 H), 6.75 (s, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.8, 147.6, 139.6, 138.0, 132.2, 130.1, 127.6, 127.1, 124.4, 123.7, 121.6, 115.2, 112.2; LRMS (EI) 299 (M); HRMS (EI) calcd for $C_{15}H_{11}BrN_2$ (M) 298.0106, found 298.0111.

***N*-Methyl-*N*-[4-(pyridin-2-yloxy)butyl]aniline (3aa').** Yellow oil: $R_f$ = 0.49 (20:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 4.0 Hz, 1 H), 7.54 (td, *J* = 10.0, 4.0 Hz, 1 H), 7.20 (m, 2 H), 6.84 (m, 1 H), 6.69 (m, 4 H), 4.31 (t, *J* = 6.0 Hz, 2 H), 3.38 (t, *J* = 8.0 Hz, 2 H), 2.93 (s, 3 H), 1.77 (m, 4 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.5, 147.0, 138.7, 129.3, 116.7, 116.2, 112.4, 111.3, 65.7, 52.7, 38.5, 26.9, 23.7; LRMS (ESI) 257 (M+H); HRMS (ESI) calcd for $C_{16}H_{21}N_2O$ (M+H) 257.1648, found 257.1654; IR (KBr, $cm^{-1}$) 3091 (w), 2945 (m), 2884 (m), 2867 (m), 1596 (s), 1569 (m).

**General procedure for the synthesis of benzonaphthyridinones.** The benzonaphthyridinones were prepared from the corresponding *o*-aminobenzoates and aryne precursors following the same procedure used for the synthesis of 2-pyridinylamines. The residue was purified by column chromatography (petroleum ether/EtOAc + 1% TEA) to afford the benzonaphthyridinones.

**10-Methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (5aa).** Yellow solid: mp 214-215 ºC; $R_f$ = 0.24 (3:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (300 MHz, $CDCl_3$) δ 8.79 (m, 2 H), 8.55 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.79 (td, *J* = 7.2, 1.5 Hz, 1 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 1 H), 7.25 (m, 1 H), 4.15 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 178.6, 153.5, 151.3, 142.6, 137.0, 134.6, 127.8, 122.8, 122.1, 117.6, 117.4, 115.6, 31.0; LRMS (EI) 210 (M), 209 (M-H); HRMS (EI) calcd for $C_{13}H_{10}N_2O$ (M) 210.0793, found 210.0796.

**10-Allyl-8-bromobenzo[*b*][1,8]naphthyridin-5(10*H*)-one (5ab).** Yellow solid: mp 145-146

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ºC; $R_f$ = 0.25 (5:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 6.4 Hz, 2 H), 8.38 (d, *J* = 8.4 Hz, 1 H), 7.71 (s, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.29 (m, 1 H), 6.08 (m, 1 H), 5.41 (s, 2 H), 5.26 (d, *J* = 10.0 Hz, 1 H), 5.07 (d, *J* = 17.2 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.0, 154.0, 150.9, 142.6, 137.0, 131.7, 129.7, 129.4, 125.6, 121.5, 119.1, 118.5, 117.34, 117.32, 46.0; LRMS (EI) 314 (M); HRMS (EI) calcd for $C_{15}H_{11}BrN_2O$ (M) 314.0055, found 314.0053; IR (KBr, cm$^{-1}$) 3084 (w), 2954 (m), 2924 (m), 2870 (w), 1639 (m), 1587 (s).

**7-Iodo-10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (5ac).** Yellow solid: mp 198-199 ºC; $R_f$ = 0.13 (8:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.78 (m, 3 H), 7.99 (d, *J* = 9.2 Hz, 1 H), 7.38 (d, *J* = 9.2 Hz, 1 H), 7.25 (m, 1 H), 4.11 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.2, 153.8, 151.1, 142.8, 141.9, 137.0, 136.4, 124.4, 118.0, 117.8, 117.4, 85.5, 31.1; LRMS (EI) 335 (M); HRMS (EI) calcd for $C_{13}H_9IN_2O$ (M) 335.9760, found 335.9765; IR (KBr, cm$^{-1}$) 3083 (w), 2954 (m), 2915 (m), 2869 (w), 1635 (m), 1585 (s).

**7-Bromo-10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (5ad).** Yellow solid: mp 202-203 ºC; $R_f$ = 0.18 (5:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.73 (m, 2 H), 8.55 (s, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.26 (m, 1 H), 4.09 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.3, 153.8, 151.1, 141.3, 137.2, 136.9, 130.1, 123.9, 118.0, 117.6, 117.2, 115.6, 31.1; LRMS (EI) 288 (M); HRMS (EI) calcd for $C_{13}H_9BrN_2O$ (M) 287.9898, found 287.9904.

**7-Chloro-10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (5ae).** Yellow solid: mp 210-212 ºC; $R_f$ = 0.5 (2:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.76 (m, 2 H), 8.45 (s, 1 H), 7.68 (d, *J* = 9.2 Hz, 1 H), 7.57 (d, *J* = 9.2 Hz, 1 H), 7.25 (m, 1 H),

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4.13 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.5, 153.8, 151.1, 141.0, 137.0, 134.6, 128.2, 126.9, 123.6, 118.0, 117.4, 117.2, 31.2; LRMS (EI) 244 (M); HRMS (EI) calcd for $C_{13}H_9ClN_2O$ (M) 244.0403, found 244.0408.

**8-Bromo-10-methylbenzo[*b*][1,8]naphthyridin-5(10*H*)-one (5af).** Yellow solid: mp 234-235 ºC; $R_f$ = 0.4 (3:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.77 (m, 2 H), 8.37 (d, *J* = 8.8 Hz, 1 H), 7.80 (s, 1 H), 7.44 (d, *J* = 8.4 Hz, 1 H), 7.28 (t, *J* = 6.0 Hz, 1 H), 4.12 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.0, 153.7, 151.2, 143.3, 136.9, 129.8, 129.3, 125.5, 121.4, 118.5, 118.1, 117.5, 31.1; LRMS (EI) 288 (M); HRMS (EI) calcd for $C_{13}H_9BrN_2O$ (M) 287.9898, found 287.9901; IR (KBr, cm$^{-1}$) 3084 (w), 2951 (w), 2917 (m), 2870 (m), 2849 (w), 1637 (m), 1587 (m).

**Methyl 10-methyl-5-oxo-5,10-dihydrobenzo[*b*][1,8]naphthyridine-8-carboxylate (5ag).** Yellow solid: mp 225-226 ºC; $R_f$ = 0.12 (5:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.78 (m, 2 H), 8.56 (d, *J* = 8.0 Hz, 1 H), 8.34 (s, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.27 (m, 1 H), 4.20 (s, 3 H), 4.02 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.2, 166.4, 153.9, 151.4, 142.1, 136.9, 135.0, 128.1, 125.0, 122.0, 118.0, 117.6, 117.5, 52.9, 31.2; LRMS (EI) 268 (M); HRMS (EI) calcd for $C_{15}H_{12}N_2O_3$ (M) 268.0848, found 268.0854; IR (KBr, cm$^{-1}$) 3082 (w), 2954 (m), 2923 (m), 2871 (w), 1730 (s), 1638 (s), 1614 (m), 1593 (s).

**6-Methyldibenzo[*b*,*g*][1,8]naphthyridin-11(6*H*)-one (5ba).** Yellow solid: mp 229-231 ºC; $R_f$ = 0.27 (5:1 petroleum ether/EtOAc + 1% TEA); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1 H), 8.53 (d, *J* = 7.6 Hz, 1 H), 8.00 (m, 2 H), 7.80 (m, 2 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 4.22 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 179.7, 157.1, 150.1, 143.7, 139.2, 135.2, 132.8, 129.7, 128.1, 127.8, 124.8, 122.4, 121.6, 121.5, 117.8, 115.4,

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31.0; LRMS (EI) 260 (M); HRMS (EI) calcd for $C_{17}H_{12}N_2O$ (M) 260.0950, found 260.0955; IR (KBr, $cm^{-1}$) 3064 (w), 2954 (w), 2917 (m), 2871 (m), 2850 (w), 1608 (s).

**5*H*-Thiochromeno[2,3-*b*]pyridin-5-one (5ai).** White solid: mp 236-238 ºC (lit[24] 233-234 ºC); $R_f$ = 0.24 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.83 (m, 2 H), 8.60 (d, *J* = 8.0 Hz, 1 H), 7.70 (m, 2 H), 7.53 (td, *J* = 8.0, 1.6 Hz, 1 H), 7.46 (dd, *J* = 8.0, 4.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 180.8, 158.9, 153.5, 138.0, 137.7, 133.2, 130.1, 129.0, 127.0, 126.65, 126.62, 121.8; LRMS (EI) 213 (M); HRMS (EI) calcd for $C_{12}H_7NOS$ (M) 213.0248, found 213.0253.

## 2.6. Acknowledgment

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# CHAPTER 3

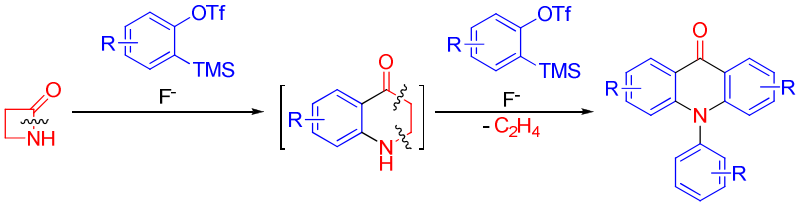
## Formation of Acridones by Ethylene Extrusion in the Reaction of Arynes with β-Lactams and Dihydroquinolinones

Yuesi Fang,[†] Donald C. Rogness,[†] Richard C. Larock,*[,†] and Feng Shi*[,‡]

[†]*Department of Chemistry, Iowa State University, Ames, IA 50011, U.S.A.*

[‡]*Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Jinming Campus, Kaifeng, Henan 475004, China PR*

### 3.1. Abstract




*N*-Unsubstituted β-lactams react with a molecule of aryne by insertion into the amide bond to form a 2,3-dihydroquinolin-4-one, which subsequently reacts with another molecule of aryne to form an acridone by extrusion of a molecule of ethylene. 2,3-Dihydroquinolin-4-ones react under the same reaction conditions to afford identical results. This is the first example of ethylene extrusion in aryne chemistry.

### 3.2. Introduction

Benzyne is a highly reactive intermediate, which was first proposed by Wittig in 1942[1] and confirmed by Roberts in 1956.[2] Since the discovery of the Kobayashi aryne precursor,[3] various nucleophiles have been shown to react with arynes by nucleophilic addition to open the strained,

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triple bond of the aryne.[4] When the nucleophile is tethered to an electrophile, the nucleophilic addition can trigger subsequent electrophilic trapping of the aryl anion, leading to a formal σ-bond cleavage.[5] Amide functionality is one such tethered nucleophile-electrophile pair, where the nitrogen and the carbonyl serve as the nucleophile and the electrophile, respectively. Although amides typically undergo simple NH arylation,[4,6] amides with more electrophilic carbonyl groups, including trifluoroacetamides, trifluoromethanesulfinamides,[7] ureas,[8] and DMF[9] have been shown to undergo carbonyl-nitrogen cleavage. Another class of substrates that could potentially exhibit such reactivity is a strained or twisted amide,[10] where the poor n-π conjugation makes the amide behave more like an independent amine and ketone. To the best of our knowledge, the reactivity of such amides towards arynes has received little attention.[11] We wish to report our initial results in this interesting area.

The substrates we have chosen to study are β-lactams. The angular strain of β-lactams renders poor conjugation of the nitrogen to the carbonyl. Thus, β-lactams have a stronger C=O double bond and a more basic nitrogen than regular amides.[12] We envisioned that the nitrogen atom of the β-lactam should exhibit greater nucleophilicity toward arynes than normal amides, thus leading to eventual C(O)-N bond cleavage to afford dihydroquinolinones (Scheme 1). While this outcome proved correct, we have observed some interesting subsequent chemistry, which we now report.

**Scheme 1.** Originally anticipated reaction of a β-lactam with an aryne

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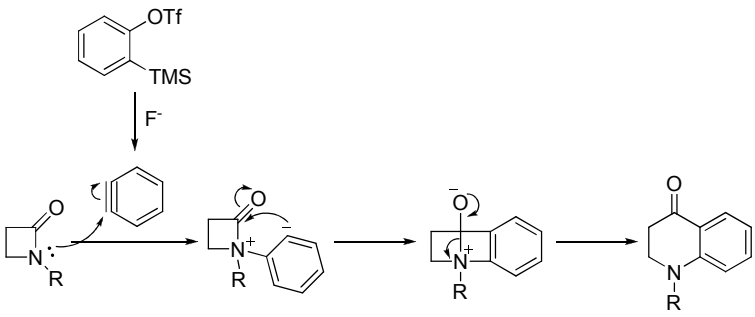
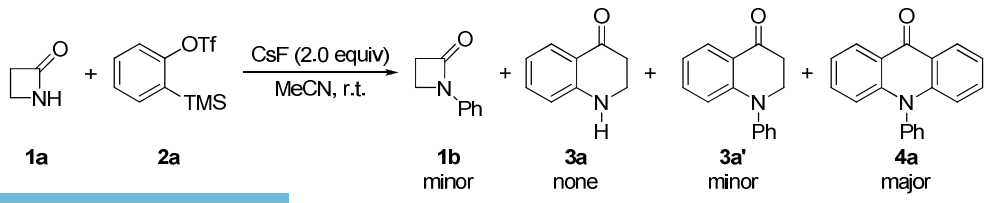



### 3.3. Results and Discussion

**Initial discovery.** We initiated our study using the *N*-unsubstituted β-lactam **1a** as the starting material (Scheme 2). Stirring lactam **1a** with 1.0 equiv of the parent aryne precursor **2a** in the presence of 2.0 equivs of CsF as the fluoride source afforded three products in addition to unreacted **1a**: the simple *N*-arylation product **1b**, product **3a'** resulting from C(O)-N bond insertion and subsequent *N*-arylation, and acridone **4a**. Much to our surprise, not only was the originally anticipated product **3a** not observed, but dihydroquinolinone **3a'** was identified as only a minor product by GC-MS analysis. The major product of this reaction was acridone **4a**. It thus appeared that the initial insertion products **3a** and/or **3a'** were also reactive toward arynes, if not even more so than lactam **1a**, and thus served merely as intermediates, eventually leading to acridone **4a**. For this to happen, however, the *C*2-*C*3 unit of the dihydroquinolinone **3a** and/or **3a'** must have been lost as a molecule of ethylene during the course of the reaction. It is very rare that aryne reactions lead to the extrusion of a neutral molecule.[13] To the best of our knowledge, this is the first example of ethylene extrusion in aryne chemistry.

**Scheme 2.** Initial Results Leading to an Acridone from a β-Lactam

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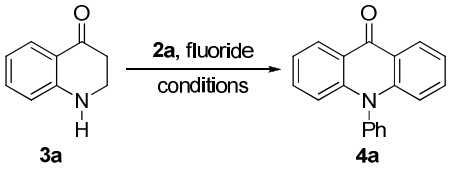
To test our hypothesis that 2,3-dihydroquinolin-4-ones **3a**/**3a'** are reactive with arynes, pure **3a** from a commercial source was subjected to our standard aryne reaction conditions. We thus found that as long as sufficient aryne was present, acridone **4a** was indeed formed under quite mild conditions, regardless of the fluoride source or the solvent used (Table 1). Thus, the intermediacy of dihydroquinolinone **3a** during the generation of acridone **4a** from β-lactam **1a** is confirmed.

**Table 1.** Formation of an Acridone from a 2,3-Dihydroquinolin-4(1*H*)-one.[a]




| entry | equiv of **2a** | fluoride source (equiv) | conditions | yield[b] (%) |
|---|---|---|---|---|
| 1 | 2 | CsF (4) | MeCN, rt, 1d | 65 |
| 2 | 2.4 | CsF (4.8) | MeCN, rt, 1d | 77 |
| 3 | 2.4 | CsF (4.8) | THF, 65 ºC, 1d | 72 |
| 4 | 2.4 | TBAF (4.8) | THF, rt, 1d | 59 |
| 5 | 2.4 | TBAT (4.8) | toluene, rt, 1d | 50 |

[a] All reactions were carried out on a 0.25 mmol scale in 4 mL of solvent. [b] Isolated yield of acridone **4a**.

To gain further evidence for the mechanism, an experiment was carried out to trap the extruded ethylene (the *C*2-*C*3 unit of the 2,3-dihydroquinolin-4-one). Thus, the reaction was repeated in a sealed vessel, and bromine was injected into the vessel after 10 h. GC-MS analysis of the crude reaction mixture revealed the presence of a large quantity of 1,2-dibromoethane, which supports the generation of ethylene in this reaction (Scheme 3).

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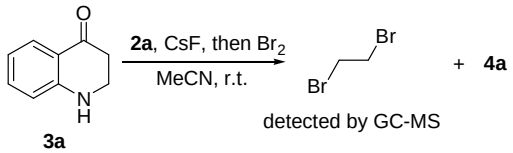
**Scheme 3.** Ethylene Trapping




**Scope of the β-lactam.** Encouraged by these findings, we first studied the scope of the reaction between various β-lactams and arynes. Although we have suggested that the reaction proceeds through the intermediacy of a dihydroquinolinone (such as **3a** and/or its *N*-arylated product **3a'**), all attempts to isolate such an intermediate have thus far been unsuccessful, even when using a 1 : 1 stoichiometry of the β-lactam and the aryne precursor. The best yields of acridone **4** have been achieved by employing 3.5 equivalents of the aryne precursor (Fig. 1) for the *N*-unsubstituted β-lactam **1a** or 2.4 equivalents for the *N*-substituted β-lactams **1b** and **1c**. As seen in Table 2, compounds **4b** and **4c** can be obtained in reasonable yields from the symmetrical aryne precursors **2b** and **2c** (entries 2 and 3), respectively. The aryne derived from **2e** is known to be attacked preferentially by nucleophiles at the *meta* position (with respect to the OMe group) for both electronic and steric reasons.[4,14] In our studies, compound **4d** was formed in a surprisingly high yield as a single regioisomer (entry 4). *N*-Substituted β-lactams have also been examined in this reaction (entries 5-7). However, the *N*-phenyl lactam **1b** proved unreactive under our standard reaction conditions, and the *N*-allyl lactam **1c** was only marginally reactive, affording no more than a trace of the desired product **4e**. The *N*-benzyl lactam **1d** was slightly more reactive, affording compound **4f** in a 13% isolated yield (entry 7). It is worth pointing out that the yields of these three reactions did not improve very much even when the reactions were performed at a higher temperature. We also examined one α,α-disubstituted β-lactam **1e** (entry 8). In this case, the anticipated chemistry would require the extrusion of an olefin much larger than ethylene.

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Gratifyingly, we were able to identify the desired product **4a** in a 30% yield, indicating that extrusion of a molecule as large as 4-methylenehepta-1,6-diene is possible.

**Figure 1.** Aryne Precursors.

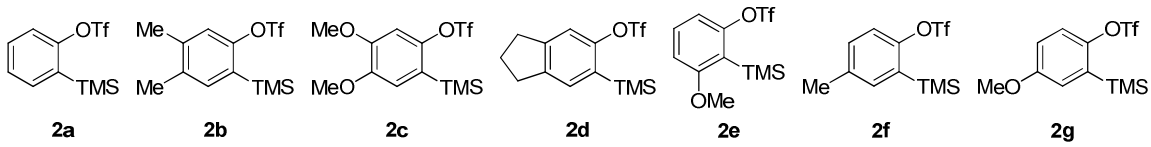
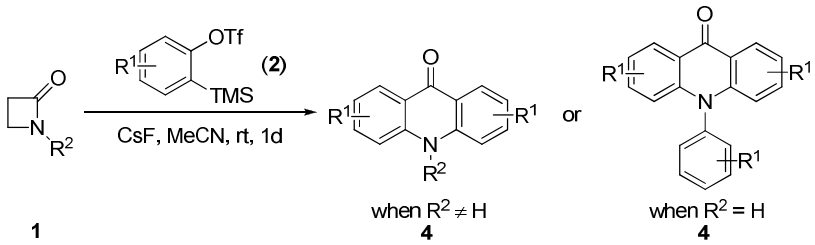
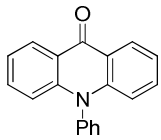
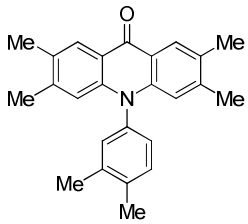
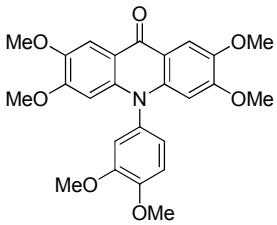



**Table 2.** Scope of the β-Lactam.[a]




| entry | β-lactam | aryne precursor | product | yield[b] (%) |
|---|---|---|---|---|
| 1 | **1a** | **2a** |  **4a** | 50 |
| 2 | **1a** | **2b** |  **4b** | 45 |
| 3 | **1a** | **2c** |  **4c** | 40 |

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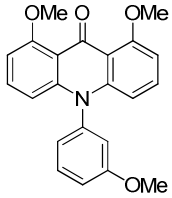
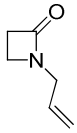
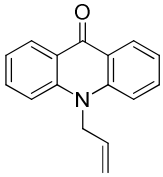
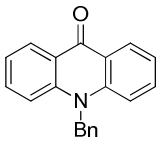
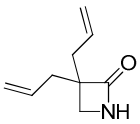
| | | | | |
|---|---|---|---|---|
| 4 | **1a** | **2e** |  <br>**4d** | 83 |

Table 2 continued

| | | | | |
|---|---|---|---|---|
| 5 | <br>**1b** | **2**[a] | **4a** | nr[c,d] |
| 6 |  <br>**1c** | **2**[a] |  <br>**4e** | trace[d,e] |
| 7 | <br>**1d** | **2a** |  <br>**4f** | 13[d] |
| 8 |  <br>**1e** | **2a** | **4a** | 30 |

[a] All reactions were carried out on a 0.25 mmol scale in 4 mL of MeCN with 3.5 equiv of the aryne precursor and 7 equiv of CsF. [b] Isolated yield. [c] All lactam starting material was recovered. [d] 2.4 Equiv of **2a** and 4.8 equiv of CsF were employed. [e] Detected by GC-MS.

**Scope of the dihydroquinolinone.** Due to the limited availability of β-lactams and the fact that incorporation of three molecules of aryne results in limited variability in the substitution pattern of the acridone product, we felt that the use of 2,3-dihydroquinolin-4-ones (series **3**) as the starting

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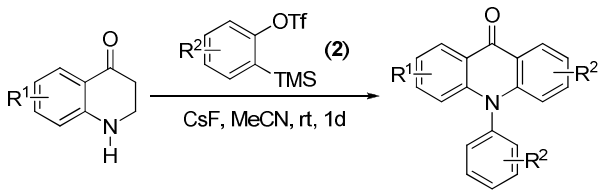
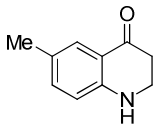
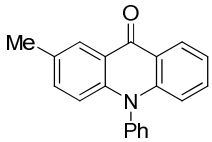
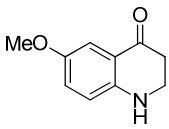
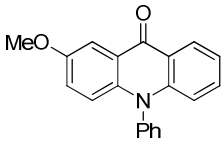
material would be more synthetically useful. Thus, we next focused our efforts on studying the reaction of dihydroquinolinones **3** with arynes.

We first examined *N*-unsubstituted substrates (Table 3). As shown previously, we have had preliminary success in the reaction of **3a** with **2a** (cf. entry 2, Table 1). Expanding the scope of the dihydroquinolinones **3** revealed that alkyl, ether, and chloride substituents are well tolerated, affording the corresponding acridones in good to excellent yields (entries 1-3). However, 6-fluorodihydroquinolinone (**3e**) proved unreactive (entry 4), presumably due to the electron-withdrawing nature of the fluoride. Different aryne precursors (cf. Fig. 1) have also been shown to react smoothly (entries 5-8), and compound **4n** has been obtained as a single regioisomer in a 90% yield (entry 8).

**Table 3.** Scope of the *N*-Unsubstituted 2,3-Dihydroquinolin-4-ones.[a]




**3** **4**

| entry | dihydroquinolinone | aryne precursor | product | yield[b] (%) |
|---|---|---|---|---|
| 1 |  **3b** | **2a** |  **4g** | 88 |
| 2 |  **3c** | **2a** |  **4h** | 75 |

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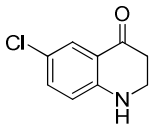
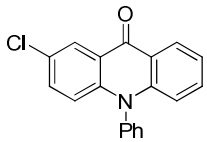
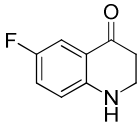
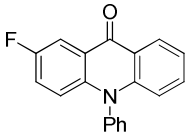
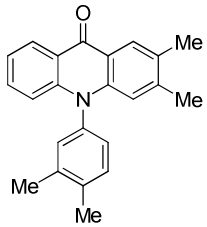
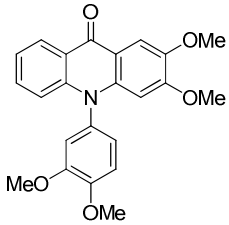
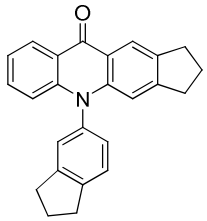
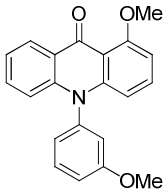
| | | | | |
|---|---|---|---|---|
| 3 |  **3d** | **2a** |  **4i** | 80 |

Table 3 continued

| | | | | |
|---|---|---|---|---|
| 4 |  **3e** | **2a** |  **4j** | trace[c] |
| 5 | **3a** | **2b** |  **4k** | 73 |
| 6 | **3a** | **2c** |  **4l** | 85 |
| 7 | **3a** | **2d** |  **4m** | 69 |
| 8 | **3a** | **2e** |  | 90 |

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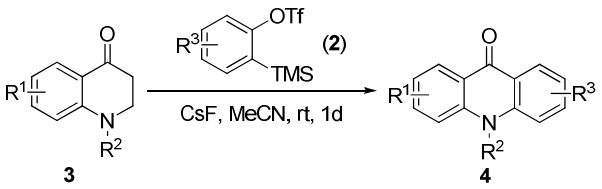
**4n**

[a] All reactions were carried out on a 0.25 mmol scale with 2.4 equiv of **2** and 4.8 equiv of CsF in 4 mL of MeCN. [b] Isolated yield. [c] Detected by GC-MS.

*N*-Substituted 2,3-dihydroquinolin-4-ones were next examined (Table 4). Compared with the results in Table 3, the yields using *N*-substituted 2,3-dihydroquinolin-4-ones are noticeably lower. Thus, the *N*-methyl dihydroquinolinone **3f** reacted with 1.2 equivs of benzyne precursor **2a** to afford acridone **4o** in a 63% yield (entry 1), a 14% drop from the corresponding *N*-unsubstituted precursor **3a** (cf. entry 2, Table 1). Similarly, substrates **3g** through **3i** were all smoothly transformed into the corresponding acridones **4p** through **4r** in moderate yields (entries 2-4). Other than a methyl group on the nitrogen, an allyl group can also be tolerated as seen in the reaction of substrate **3j**, which afforded acridone **4e** in a 48% yield (entry 5). However, placing a phenyl group on the nitrogen resulted in much lowered reactivity, as dihydroquinolinone **3a'** afforded only a trace of acridone **4a**, as detected by GC-MS (entry 6), indicating that the nucleophilicity and/or steric hindrance of the nitrogen is crucial to the reaction. This chemistry has also been extended to substituted aryne precursors. Thus, silyl triflates **2f** and **2g** reacted with dihydroquinolinone **3f** to afford the desired products in 57% and 60% yields, respectively (entries 7 and 8). Not surprisingly, since these two precursors are neither electronically nor sterically biased, mixtures of two regioisomers were obtained.

**Table 4.** Scope of the *N*-Substituted 2,3-Dihydroquinolin-4-ones.[a]

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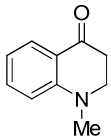
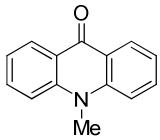
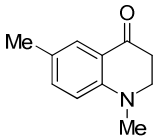
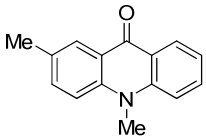
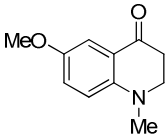
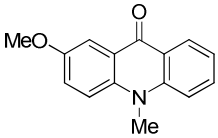
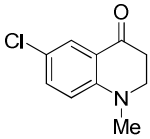
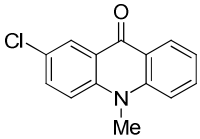
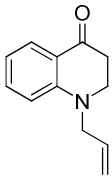
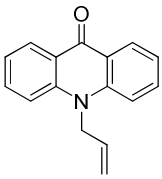
| entry | dihydroquinolinone | aryne precursor | product | yield[b] (%) |
|---|---|---|---|---|
| 1 |  **3f** | **2a** |  **4o** | 63 |
| 2 |  **3g** | **2a** |  **4p** | 62 |
| 3 |  **3h** | **2a** |  **4q** | 55 |
| 4 |  **3i** | **2a** |  **4r** | 50 |
| 5 |  **3j** | **2a** |  **4e** | 48 |

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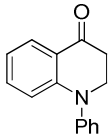
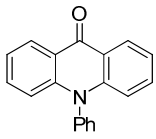
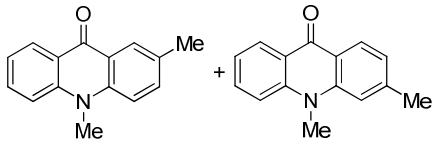
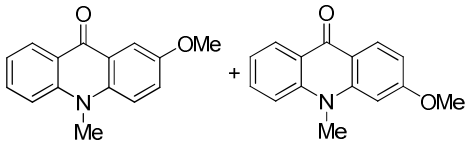
| | | | | |
|---|---|---|---|---|
| 6 |  **3a'** | **2a** |  **4a** | trace[c] |

Table 4 continued

| | | | | |
|---|---|---|---|---|
| 7 | **3f** | **2f** |  **4s + 4s'** | 57[d] (1:1) |
| 8 | **3f** | **2g** |  **4t + 4t'** | 60[d] (1:2) |

[a] All reactions were carried out on a 0.25 mmol scale with 1.2 equiv of **2** and 2.4 equiv of CsF in 4 mL of MeCN.. [b] Isolated yield. [c] Detected by GC-MS. [d] Inseparable mixtures of regioisomers. The ratios were obtained by $^{1}$H NMR spectroscopy. No attempts were made to identify the major isomer.

**Mechanistic discussion**. Based on the above results, we propose the following mechanistic picture for this overall process (Scheme 4). First, the nitrogen atom of the β-lactam (**1a**) reacts with one molecule of the aryne to form intermediate **A**. Although **A** could undergo a simple proton transfer to afford lactam **1b** (as shown in Scheme 2), this is apparently a minor route and a non-productive one with respect to the formation of acridone **4a**, since lactam **1b** does not readily react with arynes (see entry 5, Table 2). Thus, the aryl anion of intermediate **A** apparently nucleophilically adds to the carbonyl, and the resulting highly strained intermediate **B** collapses to

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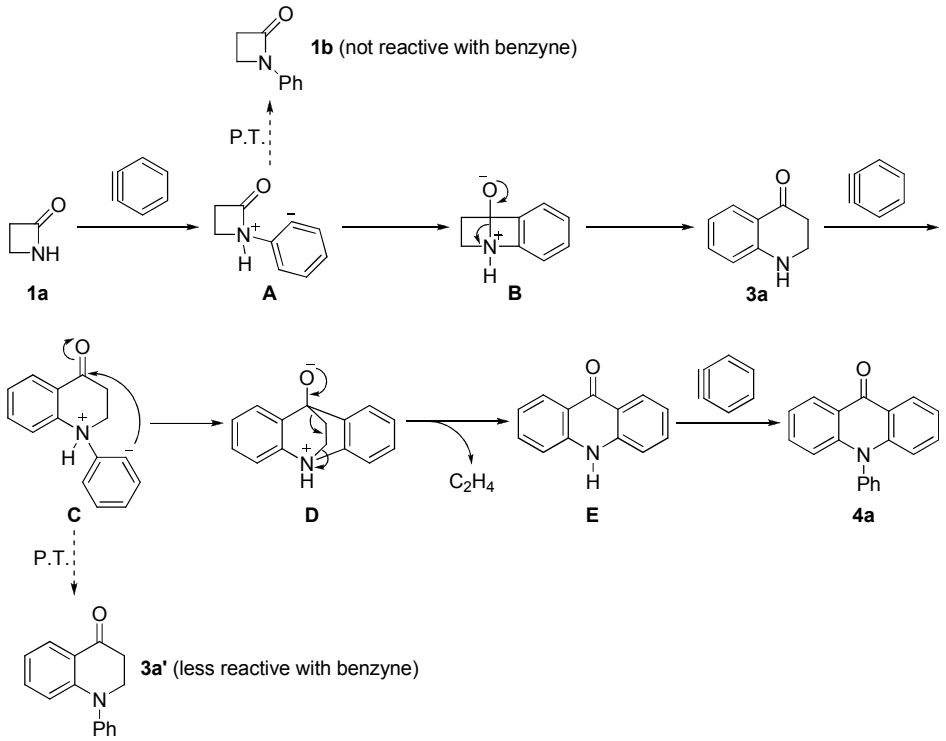
furnish dihydroquinolinone **3a** with release of the ring strain. Compound **3a** presumably then reacts with a second molecule of aryne to afford intermediate **C**. Once again proton transfer from **C** to form dihydroquinolinone **3a'** is apparently a minor and non-productive route (see entry 6, Table 4). In a fashion similar to the conversion of **A** to **B**, intermediate **C** most likely cyclizes to **D**, and subsequent extrusion of ethylene either by the arrow-pushing sequence described in Scheme 4 or by a retro-Diels-Alder process leads to the acridone **E**. Finally, acridone **E** undergoes NH arylation by a third molecule of aryne to afford the final major product acridone **4a**. In other words, the formation of acridone **4a** from lactam **1a** proceeds through the intermediacy of compounds **3a** and **E**, and compounds **1b** and **3a'** are much less important intermediates en route to acridone **4a**.

**Scheme 4.** Mechanistic pathway




**Possibilities for the extrusion of small molecules other than ethylene.** Inspired by the finding that dihydroquinolinone **3a** apparently reacts with an aryne to afford structures like intermediate **D** (Scheme 4), we were prompted to investigate other substrates that might afford a similar

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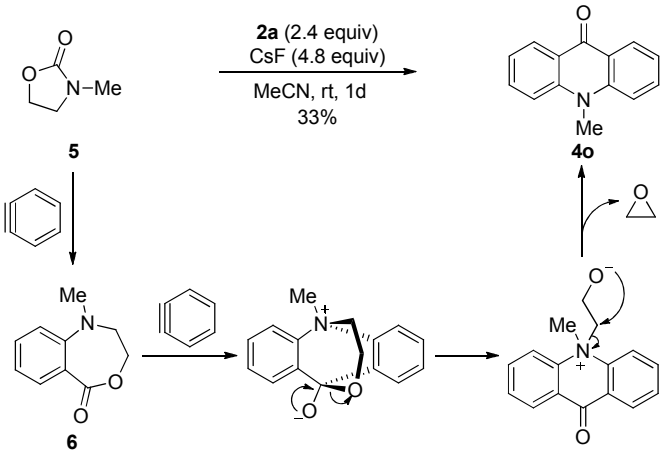
intermediate. It has been shown that a 5-membered ring urea can undergo C(O)-N cleavage upon reaction with arynes to afford products similar to compound **3**.[8] Thus, we examined the reaction of the cyclic carbamate 3-methyloxazolidin-2-one (**5**) with benzyne generated from **2a**. Gratifyingly, we were able to isolate acridone **4o** in a 33% yield (Scheme 5). This reaction is quite interesting on its own, because mechanistically, the first C(O)-N cleavage presumably results in a seven-membered ring intermediate **6**, whose subsequent reaction with benzyne must apparently extrude a molecule of ethylene oxide. Again, to the best of our knowledge, such a process is unprecedented in aryne chemistry.

**Scheme 5.** Extrusion of Ethylene Oxide in the Reaction of Benzyne with 3-Methyl-2-oxazolidinone.




### 3.4. Conclusions

In summary, we have demonstrated that the reaction of β-lactams or 2,3-dihydroquinolin-4-ones with arynes could afford respectable yields of acridones through the extrusion of ethylene. This chemistry speaks for the tendency of intermediates like **A** and **C** to readily undergo intramolecular nucleophilic cyclization rather than the seemingly easier proton transfer process. Further study has suggested that the extrusion of molecules larger than ethylene, such as

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4-methylenehepta-1,6-diene and an epoxide, are also possible in aryne processes.

### 3.5. Experimental Section

**General Information.** The solvent THF was distilled over Na/benzophenone, and dichloromethane was distilled over $CaH_2$. Anhydrous MeCN, DMF, and DCE were used as received. The aryne precursors were used as received. Silica gel for column chromatography was supplied as 230-400 mesh from a commercial source. Powdered CsF and TBAF (1 *M* in THF solution) were used as received and stored in a desiccator.

All melting points are uncorrected. The $^{1}H$ and $^{13}C$ NMR spectra were recorded and are referenced to the residual solvent signals (7.26 ppm for $^{1}H$ and 77.2 ppm for $^{13}C$ in $CDCl_3$, 2.05 ppm for $^{1}H$ and 30.19 ppm for $^{13}C$ in acetone-$d_6$). A QTOF analyzer was used for all of the HRMS measurements.

**β-Lactams.** Compound **1a** was commercially available and was used as received. The rest were prepared as follows.

**1-Phenylazetidin-2-one (1b).**[15] To a suspension of 1.8 mL (20 mmol) of aniline and 3.3 g (24 mmol) of $K_2CO_3$ in 20 mL of DCM at 0 ºC was added dropwise 2.5 mL (24 mmol) of 3-bromopropanoyl chloride. The mixture was stirred at 0 ºC for minutes and allowed to warm up to room temperature for another 3 h. The reaction was quenched with water and extracted with EtOAc three times. The combined organic layers were evaporated and the residue was recrystallized in a hot solution of 1:1 petroleum ether/EtOAc to afford 3.42 g (ca. 15 mmol, ~75% as is) of 3-bromo-*N*-phenylpropanamide as white crystals. This solid was then dissolved in DMF and cooled to 0 ºC. To this solution was added 1.57 g (16.5 mmol) of sodium *tert*-butoxide in one

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portion and the mixture was allowed to warm up to room temperature gradually. The reaction was quenched with water after 3 h and extracted with EtOAc. The combined organic layers were evaporated and the residue was recrystallized from a hot solution of 1:1 petroleum ether/EtOAc to afford 1.76 g (60% overall yield) of 1-phenylazetidin-2-one as a red solid: mp 78-80 ºC (lit[16] 78-79 ºC); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53-7.32 (m, 5 H), 3.72 (t, *J* = 6.4 Hz, 1 H), 3.63 (t, *J* = 4.8 Hz, 1 H), 3.12 (t, *J* = 4.8 Hz, 1 H), 2.95 (t, *J* = 6.4 Hz, 1 H).

**1-Allylazetidin-2-one (1c).** The above procedure was applied to 1.14 g (20 mmol) of allylamine and 2.5 mL (24 mmol) of 3-bromopropanoyl chloride, followed by 1.52 g (16 mmol) of sodium *tert*-butoxide to afford 1.22 g (55% overall yield) of lactam **1c** as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.80-5.70 (m, 1 H), 5.22 (d, *J* = 5.2 Hz, 1 H), 5.19 (s, 1 H), 3.82 (d, *J* = 6.0 Hz, 2 H), 3.22 (t, *J* = 4.0 Hz, 2 H), 2.94 (t, *J* = 4.0 Hz, 2 H).

**1-Benzylazetidin-2-one (1d).** The above procedure was applied to 2.14 g (20 mmol) of benzylamine and 2.5 mL (24 mmol) of 3-bromopropanoyl chloride, followed by 1.57 g (16.5 mmol) of sodium *tert*-butoxide to afford 1.87 g (58% overall yield) of lactam **1d** as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5 H), 4.38 (s, 2 H), 3.14 (t, *J* = 3.9 Hz, 2 H), 2.95 (t, *J* = 3.9 Hz, 2 H).

**3,3-Diallylazetidin-2-one (1e).**[17] A mixture of 0.71 g (10 mmol) of azetidin-2-one (**1a**), 2.25 g (15 mmol) of *tert*-butyldimethylsilyl chloride, and 2.08 mL (15 mmol) of triethylamine in 20 mL of DCM was stirred for 12 h at room temperature. The mixture was then washed with water and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to afford a colorless oil consisting of *N-tert*-butyldimethylsilylazetidin-2-one and residual TBSCl. This mixture was dissolved in THF,

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cooled to -78 ºC under an $N_2$ atmosphere, and charged with 6.67 mL (1.8 *M* THF solution) of LDA. After being stirred for 2 h at -78 ºC, 1.04 mL (12 mmol) of allyl bromide was added and the mixture was gradually warmed up to room temperature for another 12 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by column chromatography (5:1 petroleum ether/ EtOAc) to afford 0.52 g (2.3 mmol) of 3-allyl-1-(*tert*-butyldimethylsilyl)azetidin-2-one. This intermediate was treated with the above allylation procedure again to afford 0.3 g (1.1 mmol) of 3,3-diallyl-1-(*tert*-butyldimethylsilyl)azetidin-2-one. This product was dissolved in 10 mL of methanol and 0.334 g (2.2 mmol) of CsF was added. After being stirred for 2 h, the mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated to afford 0.15 g (1.0 mmol, 10% overall yield from **1a**) of 3,3-diallylazetidin-2-one as a red oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1 H), 5.85-5.74 (m, 2 H), 5.12 (d, $J$ = 6.4 Hz, 2 H), 5.08 (s, 2 H), 3.07 (s, 2 H), 2.39 (d of ABq, $J_{AB}$ = 14.1 Hz, $J_{AX}$ = 6.7 Hz, $J_{BX}$ = 7.9 Hz, 2 H), 2.31 (d of ABq, $J_{AB}$ = 14.1 Hz, $J_{AX}$ = 6.7 Hz, $J_{BX}$ = 7.9 Hz, 2 H).

***N*-Unsubstituted 2,3-Dihydroquinolin-4-ones.** Compounds **3a** and **3e** were commercially available and used as received. The remaining dihydroquinolinones were prepared as follows.

**6-Methyl-2,3-dihydroquinolin-4(1*H*)-one (3b).**[15,18] Following the procedure described above for the synthesis of compound **1b**, 2.14 g (20 mmol) of *p*-toluidine, 2.5 mL (24 mmol) of 3-bromopropanoyl chloride, and 1.57 g (16.5 mmol) of sodium *tert*-butoxide were employed to obtain 1.92 g of *N*-(*p*-tolyl)azetidin-2-one. To a solution of 1.61 g (10 mmol) of

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1-(*p*-tolyl)azetidin-2-one in 20 mL of DCE at 0 ºC was added 2 mL (22 mmol) of TfOH. The mixture was allowed to warm up to room temperature and stirred for 2 h. The reaction was quenched with aq. $NaHCO_3$ and extracted by EtOAc three times. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by column chromatography (2:1 petroleum ether/EtOAc) to afford 1.19 g (40% overall yield from *p*-toluidine) of dihydroquinolinone **3b** as a yellow solid: mp 80-82 ºC (lit[16] 82-84 ºC); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 7.13 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 4.26 (s, 1 H), 3.55 (td, *J* = 8.0, 1.6 Hz, 2 H), 2.68 (t, *J* = 6.8 Hz, 2 H), 2.24 (s, 3 H).

**6-Methoxy-2,3-dihydroquinolin-4(1*H*)-one (3c).** Following the procedure described above for the synthesis of compound **1b**, 2.46 g (20 mmol) of *p*-anisidine, 2.5 mL (24 mmol) of 3-bromopropanoyl chloride, and 1.62 g (17 mmol) of sodium *tert*-butoxide were employed to obtain 2.3 g of *N*-(4-methoxyphenyl)azetidin-2-one. Next, 1.77 g (10 mmol) of *N*-(4-methoxyphenyl)azetidin-2-one was treated with 2 mL (22 mmol) of TfOH as described above to yield 1.28 g (47% overall yield from 4-methoxyaniline) of dihydroquinolinone **3c** as a yellow solid: mp 110-112 ºC (lit[16] 113-114 ºC); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.8 Hz, 1 H), 6.98 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.64 (d, *J* = 8.8 Hz, 1 H), 4.17 (s, 1 H), 3.77 (s, 3 H), 3.54 (t, *J* = 6.0 Hz, 2 H), 2.69 (t, *J* = 6.0 Hz, 2 H).

**6-Chloro-2,3-dihydroquinolin-4(1*H*)-one (3d).** Following the procedure described above for the synthesis of compound **1b**, 2.55 g (20 mmol) of 4-chloroaniline, 2.5 mL (24 mmol) of 3-bromopropanoyl chloride, and 1.57 g (16.5 mmol) of sodium *tert*-butoxide were employed to obtain 2.18 g of *N*-(4-chlorophenyl)azetidin-2-one. Next, 1.82 g (10 mmol) of *N*-(4-chlorophenyl)azetidin-2-one was treated with 2 mL (22 mmol) of TfOH as described above

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to yield 1.12 g (37% overall yield from 4-chloroaniline) of dihydroquinolinone **3d** as a yellow solid: mp 123-125 ºC (lit[16] 125-126 ºC); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.7 Hz, 1 H), 7.23 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 4.40 (s, 1 H), 3.58 (td, *J* = 7.8, 1.5 Hz, 2 H), 2.69 (t, *J* = 7.5 Hz, 2 H).

***N*-Substituted 2,3-Dihydroquinolin-4-ones.** Compound **3a'** was commercially available and used as received. The other *N*-substituted dihydroquinolinones were prepared as follows.

**1-Methyl-2,3-dihydroquinolin-4(1*H*)-one (3f).** To an oven-dried vial was added 0.367 g (2.5 mmol) of 2,3-dihydroquinolin-4(1*H*)-one (**3a**) and 5 mL of DMF, followed by 0.15 g (3.75 mmol, 60% dispersed in mineral oil) of NaH. The mixture was stirred under a $N_2$ atmosphere at room temperature for 2 h, and charged with 0.31 mL (5 mmol) of MeI. The vial was then capped and heated in an 80 ºC oil bath for 12 h. After being quenched with water, the mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by column chromatography (2:1 petroleum ether/EtOAc) to afford 0.173 g (1.07 mmol, 43% yield) of dihydroquinolinone **3f** as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.40 (td, *J* = 4.4, 1.6 Hz, 1 H), 6.77-6.70 (m, 2 H), 3.47 (t, *J* = 7.2 Hz, 2 H), 2.99 (s, 3 H), 2.74 (t, *J* = 7.2 Hz, 2 H).

**1,6-Dimethyl-2,3-dihydroquinolin-4(1*H*)-one (3g).** The above procedure used for the synthesis of dihydroquinolinone **3f** was applied to 0.402 g (2.5 mmol) of dihydroquinolinone **3b**, 0.15 g (3.75 mmol,) of NaH, followed by 0.31 mL (5 mmol) of MeI to afford 0.197 g (45% overall yield) of compound **3g** as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.23 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.65 (d, *J* = 7.6 Hz, 1 H), 3.42 (t, *J* = 7.2 Hz, 2 H), 2.95 (s, 3 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 2.25 (s, 3 H).

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**6-Methoxy-1-methyl-2,3-dihydroquinolin-4(1*H*)-one (3h).** The above procedure used to synthesize compound **3f** was applied to 0.442 g (2.5 mmol) of dihydroquinolinone **3c**, 0.15 g (3.75 mmol) of NaH, followed by 0.31 mL (5 mmol) of MeI to afford 0.205 g (43% overall yield) of compound **3h** as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.4 Hz, 1 H), 7.07 (dd, *J* = 8.1, 2.4 Hz, 1 H), 6.70 (d, *J* = 8.1 Hz, 1 H), 3.79 (s, 3 H), 3.39 (t, *J* = 7.5 Hz, 2 H), 2.94 (s, 3 H), 2.73 (t, *J* = 7.5 Hz, 2 H).

**6-Chloro-1-methyl-2,3-dihydroquinolin-4(1*H*)-one (3i).** The above procedure used to synthesize compound **3f** was applied to 0.454 g (2.5 mmol) of dihydroquinolinone **3d**, 0.15 g (3.75 mmol) of NaH, followed by 0.31 mL (5 mmol) of MeI to afford 0.200 g (41% overall yield) of compound **3i** as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.7 Hz, 1 H), 7.31 (dd, *J* = 9.0, 2.7 Hz, 1 H), 6.65 (d, *J* = 9.0 Hz, 1 H), 3.46 (t, *J* = 7.2 Hz, 2 H), 2.97 (s, 3 H), 2.72 (t, *J* = 7.2 Hz, 2 H).

**1-Allyl-2,3-dihydroquinolin-4(1*H*)-one (3j).** The above procedure used to synthesize compound **3f** was applied to 0.367 g (2.5 mmol) of dihydroquinolinone **3a**, 0.15 g (3.75 mmol) of NaH, followed by 0.605 g (5 mmol) of allyl bromide to afford 0.182 g (39% overall yield) of compound **3i** as a yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.36 (td, *J* = 4.4, 1.6 Hz, 1 H), 6.73-6.70 (m, 2 H), 5.90-5.82 (m, 1 H), 5.28-5.20 (m, 2 H), 3.99 (d, *J* = 5.2 Hz, 2 H), 3.52 (t, *J* = 7.2 Hz, 2 H), 2.72 (t, *J* = 7.2 Hz, 2 H).

**3-Methyloxazolidin-2-one (5).** This compound was commercially available and used as received.

**General procedures for aryne reactions affording acridones.**

Compounds **4a** through **4d** were prepared according to the following procedure (representative

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procedure for β-lactams where 3.5 equiv of arynes were used): to an oven-dried vial was added 0.875 mmol of aryne precursor, 0.25 mmol of β-lactam, 4 mL of MeCN, and 0.266 g (1.75 mmol) of CsF sequentially. A nitrogen atmosphere was not required, except that a balloon of nitrogen was attached to the reaction vial for the ventilation of ethylene. The reaction was allowed to stir for 24 h before being quenched with aq. $Na_2CO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/ EtOAc) to afford the desired products.

**10-Phenylacridin-9(10*H*)-one (4a).** The representative procedure was employed to afford 33.9 mg (0.13 mmol, 50% yield) of **4a** as a yellow solid: mp 271-273 ºC (lit[19] 276 ºC); $R_f$ = 0.38 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 8.0, 1.2 Hz, 2 H), 7.71 (t, *J* = 8.0 Hz, 2 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 7.49 (td, *J* = 8.0, 1.6 Hz, 2 H), 7.37 (d, *J* = 7.6 Hz, 2 H), 7.27 (t, *J* = 8.0 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 178.3, 143.3, 139.2, 133.4, 131.3, 130.2, 129.8, 127.5, 122.0, 121.7, 117.0; HRMS (APCI) calcd for $C_{19}H_{14}NO$ (M+H) 272.1070, found 272.1076.

**10-(3,4-Dimethylphenyl)-2,3,6,7-tetramethylacridin-9(10*H*)-one (4b).** The representative procedure was employed to afford 39.9 mg (0.11 mmol, 45% yield) of **4b** as a yellow solid: mp 306-308 ºC; $R_f$ = 0.37 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.06-7.04 (m, 2 H), 6.53 (s, 2 H), 2.45 (s, 3 H), 2.37 (s, 3 H), 2.35 (s, 6 H), 2.23 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.7, 143.2, 141.9, 140.0, 138.1, 137.0, 132.0, 130.8, 130.4, 127.3, 127.0, 120.2, 117.3, 21.0, 20.2, 19.9, 19.3; HRMS (ESI) calcd for $C_{25}H_{26}NO$ (M+H) 356.2009, found 356.2012.

**10-(3,4-Dimethoxyphenyl)-2,3,6,7-tetramethoxyacridin-9(10*H*)-one (4c).** The

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representative procedure was employed to afford 45.1 mg (0.10 mmol, 40% yield) of **4c** as a brown solid: mp 256-257 ºC; $R_f$ = 0.25 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 6.98 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.85 (d, *J* = 1.6 Hz, 1 H), 6.18 (s, 2 H), 4.04 (s, 3 H), 4.01 (s, 6 H), 3.87 (s, 3 H), 3.68 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.2, 154.0, 151.0, 149.9, 145.7, 139.2, 132.0, 122.3, 115.4, 112.4, 112.3, 106.4, 98.4, 56.51, 56.49, 56.3, 56.1; HRMS (ESI) calcd for $C_{25}H_{26}NO_7$ (M+H) 452.1704, found 452.1708.

**1,8-Dimethoxy-10-(3-methoxyphenyl)acridin-9(10*H*)-one (4d).** The representative procedure was employed to afford 74.9 mg (0.21 mmol, 83% yield) of **4d** as a brown solid: mp 250-253 ºC; $R_f$ = 0.11 (pure EtOAc); $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.65 (t, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 6.96-6.94 (m, 2 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 6.27 (d, *J* = 8.4 Hz, 2 H), 3.96 (s, 6 H), 3.87 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 179.2, 163.1, 161.6, 145.7, 142.1, 134.1, 123.7, 122.8, 120.6, 116.4, 115.0, 110.0, 104.8, 57.1, 56.3; HRMS (ESI) calcd for $C_{22}H_{20}NO_4$ (M+H) 362.1387, found 362.1389.

Compounds **4f** through **4n** were prepared according to the following procedure (representative procedure for *N*-substituted β-lactams/*N*-unsubstituted 2,3-dihydroquinolin-4-ones where 2.4 equiv of arynes were used): the general procedure used above for the synthesis of compound **4a** was applied to 0.6 mmol of aryne precursor, 0.25 mmol of *N*-substituted β-lactam/*N*-unsubstituted 2,3-dihydroquinolin-4-one starting material, 4 mL of MeCN, and 0.182 g (1.2 mmol) of CsF to afford the desired products.

**10-Benzylacridin-9(10*H*)-one (4f).** The representative procedure was employed to afford 9.3 mg (0.03 mmol, 13% yield) of **4f** as a brown solid: mp 178-180 ºC (lit[20] 176-179 ºC); $R_f$ = 0.37 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 8.0, 1.2 Hz, 2 H), 7.64 (td, *J*

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= 8.0, 1.6 Hz, 2 H), 7.38-7.15 (m, 9 H), 5.61 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.5, 142.8, 135.7, 134.3, 129.5, 128.1, 125.9, 122.8, 121.9, 115.4, 109.5, 51.1; HRMS (ESI) calcd for $C_{20}H_{16}NO$ (M+H) 286.1226, found 286.1229.

**2-Methyl-10-phenylacridin-9(10*H*)-one (4g).** The representative procedure was employed to afford 62.7 mg (0.22 mmol, 88% yield) of **4g** as a yellow solid: mp 220-221 ºC; $R_f$ = 0.38 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 7.2 Hz, 1 H), 8.36 (s, 1 H), 7.71-7.63 (m, 3 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.35-7.29 (m, 3 H), 7.23 (t, *J* = 7.6 Hz, 1 H), 6.73 (d, *J* = 8.8 Hz, 1 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 2.44 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.1, 143.1, 141.4, 139.2, 134.9, 133.2, 131.3, 131.2, 130.2, 129.6, 127.4, 126.6, 121.82, 121.77, 121.4, 116.9, 116.8, 20.9; HRMS (ESI) calcd for $C_{20}H_{16}NO$ (M+H) 286.1226, found 286.1233.

**2-Methoxy-10-phenylacridin-9(10*H*)-one (4h).** The representative procedure was employed to afford 56.4 mg (0.19 mmol, 75% yield) of **4h** as a yellow solid: mp 158-159 ºC; $R_f$ = 0.24 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 7.2 Hz, 1 H), 7.96 (d, *J* = 1.2 Hz, 1 H), 7.69-7.63 (m, 3 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.13 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 3.93 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.7, 154.8, 142.8, 139.2, 138.2, 133.1, 131.2, 130.2, 129.7, 127.3, 124.2, 122.5, 121.4, 121.2, 118.7, 116.8, 106.2, 56.0; HRMS (ESI) calcd for $C_{20}H_{16}NO_2$ (M+H) 302.1176, found 302.1182.

**2-Chloro-10-phenylacridin-9(10*H*)-one (4i).** The representative procedure was employed to afford 61.1 mg (0.20 mmol, 80% yield) of **4i** as a yellow solid: mp 228-230 ºC (lit[21] 229-230 ºC); $R_f$ = 0.45 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.4 Hz, 1 H), 8.49 (d, *J* = 2.8 Hz, 1 H), 7.73-7.67 (m, 3 H), 7.51 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.42-7.37 (m, 3 H),

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7.26 (t, $J$ = 7.6 Hz, 1 H), 6.76 (d, $J$ = 8.4 Hz, 1 H), 6.71 (d, $J$ = 8.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.1, 143.2, 141.7, 138.8, 133.7, 133.5, 131.4, 130.0, 127.6, 127.4, 126.5, 122.7, 122.1, 121.8, 118.8, 117.6, 117.1; HRMS (ESI) calcd for $C_{19}H_{13}ClNO$ (M+H) 306.0680, found 306.0688.

**10-(3,4-Dimethylphenyl)-2,3-dimethylacridin-9(10*H*)-one (4k).** The representative procedure was employed to afford 59.8 mg (0.18 mmol, 73% yield) of **4k** as a yellow solid: mp 245-247 ºC; $R_f$ = 0.37 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, $J$ = 8.0 Hz, 1 H), 8.31 (s, 1 H), 7.46-7.41 (m, 2 H), 7.21 (t, $J$ = 8.0 Hz, 1 H), 7.08-7.05 (m, 2 H), 6.77 (d, $J$ = 8.4 Hz, 1 H), 6.58 (s, 1 H), 2.43 (s, 3 H), 2.36 (s, 3 H), 2.35 (s, 3 H), 2.23 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.9, 143.7, 143.3, 142.0, 139.8, 138.2, 136.8, 132.8, 132.0, 130.8, 127.3, 127.2, 127.0, 121.9, 121.1, 120.0, 117.4, 117.3, 117.0, 20.9, 20.1, 19.9, 19.3; HRMS (ESI) calcd for $C_{23}H_{22}NO$ (M+H) 328.1696, found 328.1704.

**10-(3,4-Dimethoxyphenyl)-2,3-dimethoxyacridin-9(10*H*)-one (4l).** The representative procedure was employed to afford 83.2 mg (0.21 mmol, 85% yield) of **4l** as a yellow solid: mp 234-235 ºC; $R_f$ = 0.62 (pure EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, $J$ = 8.0, 1.2 Hz, 1 H), 7.86 (s, 1 H), 7.43 (td, $J$ = 8.0, 1.2 Hz, 1 H), 7.21 (t, $J$ = 8.0 Hz, 1 H), 7.11 (d, $J$ = 8.4 Hz, 1 H), 6.95 (dd, $J$ = 8.4, 1.6 Hz, 1 H), 6.84 (d, $J$ = 1.6 Hz, 1 H), 6.79 (d, $J$ = 8.8 Hz, 1 H), 6.18 (s, 1 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 3.86 (s, 3 H), 3.66 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 176.5, 154.5, 151.0, 149.8, 145.7, 143.0, 139.7, 132.5, 131.7, 127.0, 122.2, 121.4, 121.3, 116.8, 115.7, 112.5, 112.4, 106.4, 98.5, 56.4, 56.32, 56.28, 56.0; HRMS (ESI) calcd for $C_{23}H_{22}NO_5$ (M+H) 392.1492, found 392.1490.

**5-(2,3-Dihydro-1*H*-inden-5-yl)-2,3-dihydro-1*H*-cyclopenta[*b*]acridin-10(5*H*)-one (4m).** The representative procedure was employed to afford 60.6 mg (0.17 mmol, 69% yield) of **4m** as a

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yellow solid: mp 176-178 ºC; $R_f$ = 0.48 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.0 Hz, 1 H), 8.41 (s, 1 H), 7.51-7.43 (m, 2 H), 7.24-7.21 (m, 1 H), 7.15 (s, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.66 (s, 1 H), 3.10-2.98 (m, 6 H), 2.87 (t, *J* = 7.6 Hz, 2 H), 2.24 (t, *J* = 7.6 Hz, 2 H), 2.08 (t, *J* = 7.6 Hz, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.2, 151.5, 147.6, 145.8, 143.4, 142.9, 138.5, 137.5, 132.8, 127.7, 127.3, 126.6, 125.9, 121.9, 121.8, 121.1, 121.0, 117.1, 112.4, 33.8, 33.2, 33.0, 32.0, 26.0, 25.8; HRMS (ESI) calcd for $C_{25}H_{22}NO$ (M+H) 352.1696, found 352.1705.

**1-Methoxy-10-(3-methoxyphenyl)acridin-9(10*H*)-one (4n).** The representative procedure was employed to afford 74.6 mg (0.22 mmol, 90% yield) of **4n** as a pale white solid: mp 221-222 ºC; $R_f$ = 0.52 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.32 (t, *J* = 8.4 Hz, 1 H), 7.20 (t, *J* = 7.2 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 7.2 Hz, 1 H), 6.84 (s, 1 H), 6.66 (t, *J* = 9.6 Hz, 2 H), 6.33 (d, *J* = 8.4 Hz, 1 H), 4.01 (s, 3 H), 3.82 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.9, 161.9, 161.6, 145.7, 142.2, 140.7, 133.4, 132.8, 131.8, 127.4, 123.6, 122.0, 121.7, 116.5, 115.5, 115.3, 112.7, 109.3, 102.9, 56.4, 55.7; HRMS (ESI) calcd for $C_{21}H_{18}NO_3$ (M+H) 332.1281, found 332.1285.

Compounds **4e**, **4o** through **4r**, and the inseparable mixtures of **4s** + **4s'** and **4t** + **4t'** were prepared according to the following procedure (representative procedure for *N*-substituted 2,3-dihydroquinolin-4-ones where 1.2 equiv of arynes were used): the general procedure used above for the synthesis of acridone **4a** was applied to 0.3 mmol of aryne precursor, 0.25 mmol of *N*-substituted 2,3-dihydroquinolin-4-one, 4 mL of MeCN, and 0.091 g (0.6 mmol) of CsF to afford the desired product.

**10-Allylacridin-9(10*H*)-one (4e).** The representative procedure was employed to afford 28.2

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mg (0.12 mmol, 48% yield) of **4e** as a yellow solid: mp 131-132 ºC (lit[22] 132-134 ºC); $R_f$ = 0.36 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.6 Hz, 2 H), 7.69 (t, *J* = 7.6 Hz, 2 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.28 (t, *J* = 7.6 Hz, 2 H), 6.18-6.09 (m, 1 H), 5.31 (d, *J* = 10.8 Hz, 1 H), 5.10 (d, *J* = 17.2 Hz, 1 H), 4.96 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.4, 142.4, 134.1, 130.8, 127.6, 122.7, 121.4, 117.6, 115.2, 49.5; HRMS (ESI) calcd for $C_{16}H_{14}NO$ (M+H) 236.1070, found 236.1067.

**10-Methylacridin-9(10*H*)-one (4o).** The representative procedure was employed to afford 32.9 mg (0.16 mmol, 63% yield) of **4o** as a yellow solid: mp 201-203 ºC (lit[23] 201-203 ºC); $R_f$ = 0.22 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 7.2 Hz, 2 H), 7.68 (t, *J* = 6.4 Hz, 2 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.25 (t, *J* = 6.4 Hz, 2 H), 3.82 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.2, 142.7, 133.9, 127.9, 122.6, 121.4, 114.9, 33.8; HRMS (ESI) calcd for $C_{14}H_{12}NO$ (M+H) 210.0913, found 210.0918.

**2,10-Dimethylacridin-9(10*H*)-one (4p).** The representative procedure was employed to afford 34.6 mg (0.16 mmol, 62% yield) of **4p** as a yellow solid: mp 149-151 ºC (lit[24] 153 ºC); $R_f$ = 0.25 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.0 Hz, 1 H), 8.31 (s, 1 H), 7.66 (t, *J* = 7.2 Hz, 1 H), 7.49-7.43 (m, 2 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 1 H), 3.80 (s, 3 H), 2.44 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.1, 142.6, 140.8, 135.3, 133.7, 131.0, 127.9, 127.2, 122.6, 122.5, 121.1, 114.9, 114.8, 33.7, 20.8; HRMS (ESI) calcd for $C_{15}H_{14}NO$ (M+H) 224.1070, found 224.1075.

**2-Methoxy-10-methylacridin-9(10*H*)-one (4q).** The representative procedure was employed to afford 32.9 mg (0.14 mmol, 55% yield) of **4q** as a yellow solid: mp 139-141 ºC (lit[25] 138 ºC); $R_f$ = 0.12 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.0 Hz, 1 H), 7.92

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(d, $J$ = 2.8 Hz, 1 H), 7.66 (td, $J$ = 7.6, 1.2 Hz, 1 H), 7.46-7.42 (m, 2 H), 7.31 (dd, $J$ = 9.2, 3.2 Hz, 1 H), 7.23 (d, $J$ = 7.6 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.6, 154.5, 142.2, 137.5, 133.7, 127.9, 124.5, 123.3, 121.9, 121.0, 116.7, 114.8, 106.8, 55.9, 33.8; HRMS (ESI) calcd for $C_{15}H_{14}NO_2$ (M+H) 240.1019, found 240.1021.

**2-Chloro-10-methylacridin-9(10*H*)-one (4r).** The representative procedure was employed to afford 30.5 mg (0.13 mmol, 50% yield) of **4r** as a yellow solid: mp 171-173 ºC; $R_f$ = 0.21 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, $J$ = 7.6 Hz, 1 H), 8.39 (s, 1 H), 7.68 (t, $J$ = 8.0 Hz, 1 H), 7.53 (dd, $J$ = 9.2, 2.0 Hz, 1 H), 7.43 (d, $J$ = 8.8 Hz, 1 H), 7.36 (d, $J$ = 9.2 Hz, 1 H), 7.23 (d, $J$ = 7.2 Hz, 1 H), 3.79 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.0, 142.4, 140.9, 134.2, 133.8, 127.8, 127.3, 126.8, 123.3, 122.4, 121.7, 116.7, 115.0, 34.0; HRMS (ESI) calcd for $C_{14}H_{11}ClNO$ (M+H) 244.0524, found 244.0523.

**2,10-Dimethylacridin-9(10*H*)-one and 3,10-dimethylacridin-9(10*H*)-one (4s + 4s').** The representative procedure was employed to afford 31.8 mg (0.14 mmol, 57% total yield) of **4s** + **4s'** as a yellow solid: $R_f$ = 0.25 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.54-8.51 (m, 2 H), 8.39 (d, $J$ = 8.0 Hz, 1 H), 8.30 (s, 1 H), 7.65 (t, $J$ = 7.6 Hz, 2 H), 7.47 (dd, $J$ = 8.4, 2.0 Hz, 1 H), 7.43 (d, $J$ = 8.8 Hz, 2 H), 7.35 (d, $J$ = 8.8 Hz, 1 H), 7.22 (d, $J$ = 10.0 Hz, 3 H), 7.05 (d, $J$ = 8.0 Hz, 1 H), 3.79 (s, 3 H), 3 78 (s, 3 H), 2.48 (s, 3 H), 2.43 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.1, 177.9, 144.8, 142.8, 142.7, 142.6, 140.8, 135.3, 133.7, 131.0, 127.8, 127.4, 123.1, 123.0, 122.7, 122.6, 122.5, 121.2, 121.0, 120.7, 114.85, 114.82, 33.73, 33.71, 22.8, 20.8; HRMS (ESI) calcd for $C_{15}H_{14}NO$ (M+H) 224.1070, found 224.1072.

**2-Methoxy-10-methylacridin-9(10*H*)-one and 3-methoxy-10-methylacridin-9(10*H*)-one (4t + 4t').** The representative procedure was employed to afford 35.9 mg (0.15 mmol, 60% total

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yield) of **4t** + **4t'** as a yellow solid: $R_f$ = 0.18 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.0 Hz, 1 H), 8.49 (d, *J* = 7.6 Hz, 0.5 H), 8.43 (d, *J* = 8.8 Hz, 0.5 H), 7.91 (d, *J* = 2.8 Hz, 1 H), 7.67-7.61 (m, 1.5 H), 7.44-7.38 (m, 2.5 H), 7.30 (dd, *J* = 9.2, 3.2 Hz, 1 H), 7.25-7.21 (m, 1.5 H), 6.81 (dd, *J* = 8.8, 2.0 Hz, 0.5 H), 6.72 (s, 0.5 H), 3.91 (s, 3 H), 3.90 (s, 1.5 H), 3.81 (s, 3 H), 3.72 (s, 1.5 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.6, 177.2, 164.3, 154.5, 144.5, 142.8, 142.2, 137.5, 133.6, 133.4, 127.8, 124.5, 124.4, 123.2, 122.7, 121.8, 121.0, 117.2, 116.7, 114.7, 106.8, 98.0, 56.0, 55.7, 33.9, 33.8; HRMS (ESI) calcd for $C_{15}H_{14}NO_2$ (M+H) 240.1019, found 240.1020.

### 3.6. Acknowledgment

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# CHAPTER 4

## Synthesis of 2*H*-Indazoles by the [ 3 + 2 ] Dipolar Cycloaddition of Sydnones with Arynes

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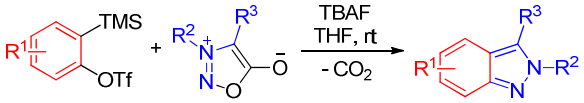
Yuesi Fang,[†] Chunrui Wu,[*,‡] Richard C. Larock,*[,†] and Feng Shi*[,‡]

[†]*Department of Chemistry, Iowa State University, Ames, IA 50011, U.S.A.*

[‡]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Jinming Campus, Kaifeng, Henan 475004, China PR

### 4.1. Abstract




A rapid and efficient synthesis of 2*H*-indazoles has been developed using a [3 + 2] dipolar cycloaddition of sydnones and arynes. A series of 2*H*-indazoles have been prepared in good to excellent yields using this protocol, and subsequent Pd-catalyzed coupling reactions can be applied to the halogenated products to generate a structurally diverse library of indazoles.

### 4.2. Introduction

The synthesis of heterocyclic compounds has attracted significant attention for decades. Among the various heterocycles, the indazole system has received significant attention due to its diverse bioactivity.[1] Although a number of methods for the preparation of indazoles are known, most methods target 1*H*-indazoles. Those focused on the selective and efficient preparation of

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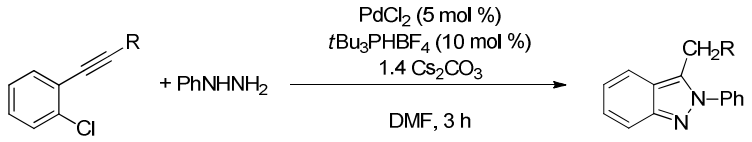
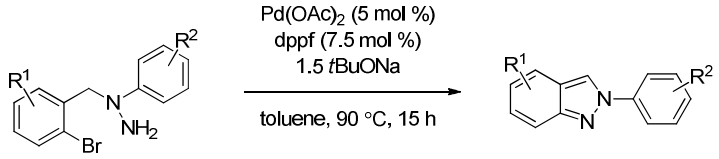
2*H*-indazoles, which also appear to have pharmaceutical promise,[2] remain limited. Recently, significant efforts have been devoted to the development of synthetic routes towards 2*H*-indazoles,[3] as highlighted by the elegant chemistry developed by Halland (eq 1)[3a] and Song (eq 2).[3b] However, it should be noted that most of these methods still have significant limitations. Thus, new routes are still desirable.




(1)




(2)

Our two groups have extensive ongoing research programs in aryne chemistry directed toward biologically important heterocycles, including approaches involving Pd-catalyzed annulation reactions,[4] electrophilic and nucleophilic reactions,[5] inter- or intramolecular annulation reactions,[6] and insertion reactions.[7] Aryne dipolar cycloadditions have provided synthetically useful methods for the synthesis of benzotriazoles,[8] indazoles,[9] and benzisoxazoles[10] by reactions with azides, diazo compounds, and nitrile oxides, respectively.

For the synthesis of 2*H*-indazoles, we have previously communicated a [3 + 2] cycloaddition approach involving arynes and readily accessible sydnones (eq 3).[11] This chemistry, which offers very mild reaction conditions, high yields, and no contamination by 1*H*-indazoles, presumably involves an initial [3 + 2] cycloaddition to afford a bicyclic adduct, followed by spontaneous extrusion of a molecule of $CO_2$ in a retro-[4 + 2] fashion. Herein, we wish to report the full details on this project, and demonstrate its potential application to the construction of a small library utilizing palladium-catalyzed cross-couplings of halogenated 2*H*-indazoles prepared by our

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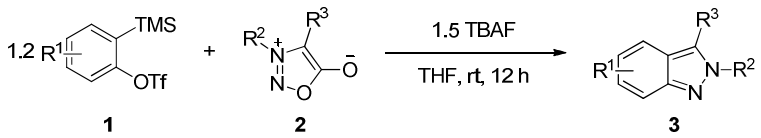
methodology.

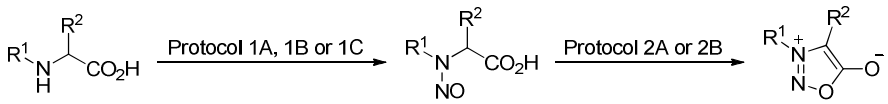



(3)

## 4.3. Results and Discussion

**Preparation of the sydnones.** Sydnones are readily prepared from the corresponding amino acids[12] by a sequence which involves *N*-nitrosation/cyclodehydration. Three different protocols, namely Protocol 1A [1.5 equiv of $NaNO_2$, 0 ºC, 1 h, then acidify], Protocol 1B [2.0 equiv of $NaNO_2$, HCl, then 0 ºC, 1 h], and Protocol 1C [1.5 equiv of *i*-amyl nitrite, DME, rt, 2 d] have been used in the nitrosation step, and two other protocols, namely 2A [$Ac_2O$ as solvent, 110 ºC, 2 h] and 2B [2 equiv of TFAA, $Et_2O$, rt, 2 h] have been used for the cyclodehydration step. A variety of sydnones have been synthesized starting from readily available amino acids (Scheme 1, see the Experimental Section for details). However, preparation of some sydnones, especially those with an alkyl group at the *C*-4 position have not been successful.

**Scheme 1.** Synthesis of Sydnones.




Sydnones not readily derived from amino acids can be accessed by further functionalization of preformed monosubstituted sydnones. Thus, arylation and vinylation at the *C*-4 position of sydnones can be achieved from monosubstituted sydnones by Pd-catalyzed cross-coupling with aryl or vinylic halides using literature procedures (eq 4).[13] Alkynylation at the *C*-4 position can be performed using the same protocol or by oxidative coupling with terminal alkynes (eq 5).[14] Monosubstituted sydnones can also be iodinated[15] or acylated[16] at the *C*-4 position by reacting

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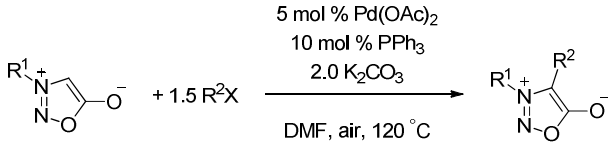
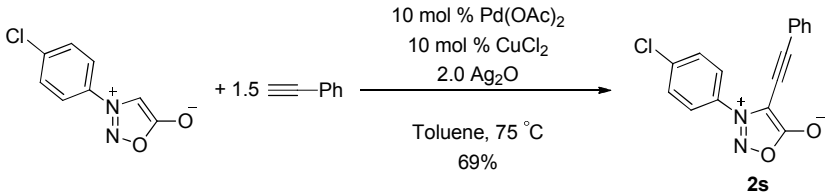
sydnones with ICl buffered with NaOAc/AcOH (eq 6) or acetic anhydride combined with NBS (eq 7) respectively.




(4)

$R^1$ = Ph, $R^2$ = vinyl, X = Br; **2l**, 40%
$R^1$ = 4-chlorophenyl, $R^2$ = 4-methoxyphenyl, X = I; **2o**, 48%
For more examples, see the Experimental Section

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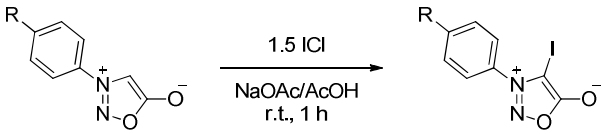
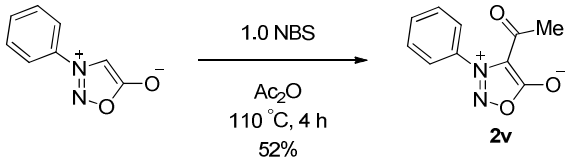



(6)

R = H; **2t**, 63%
R = Br; **2u**, 60%




(7)

**Reaction optimization.** The reaction of *o*-(trimethylsilyl)phenyl triflate (**1a**) and *N*-phenylsydnone (**2a**) was investigated as the model reaction for optimization (Table 1). In the beginning, we found that using CsF in acetonitrile only afforded a 69% yield of **3aa** with incomplete conversion of **2a**, even upon a prolonged reaction time (entry 1). Running the reaction in THF led to complete conversion with a much improved 90% yield (entry 2). We quickly found that better results and shorter reaction times could be realized by changing the fluoride source from CsF to TBAF (entries 3 and 4). With this change, THF and acetonitrile exhibited no apparent difference in yields. However, THF is slightly preferred, because it appeared to afford a pure product (white vs. yellow in acetonitrile). In addition, when using THF as the solvent, the loadings

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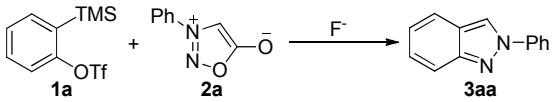
of both **1a** and fluoride could be reduced while maintaining a near quantitative yield (entries 5 and 6). The reaction provides a clean, spot-to-spot transformation with perhaps only a trace of the starting material; no other spots were observed on TLC analysis. This sydnone-aryne cycloaddition appears to represent one of the best approaches to 2*H*-indazoles in terms of efficiency and yield. The reaction conditions reported in Table 1, entries 5 and 6, which employ the same stoichiometry and concentration, but use of either solid TBAF or a THF solution of TBAF afford similar results. Thus, the procedures reported in entries 5 and 6 have been chosen as our standard reaction conditions for our study of additional substrates.

**Table 1.** Reaction Optimization[a]




| entry | **1a** (equiv) | fluoride source (equiv) | solvent | *T* (ºC) /time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 1.5 | CsF (2.5) | MeCN | rt, 36 | 69[c] |
| 2 | 1.5 | CsF (2.5) | THF | 70, 24 | 90 |
| 3[d] | 1.5 | TBAF (2.5) | MeCN | rt, 12 | 95[e] |
| 4[d] | 1.5 | TBAF (2.5) | THF | rt, 12 | 94 |
| 5[d] | 1.2 | TBAF (1.5) | THF | rt, 12 | 98 |
| 6[f] | 1.2 | TBAF (1.5) | THF | rt, 12 | 97 |

[a] All reactions were carried out on a 0.4 mmol scale at 0.1 M concentration. [b] Isolated yield. [c] Incomplete conversion of **2a** even after 2 days. [d] Solid anhydrous TBAF was used. [e] The product is significantly yellow, although no apparent impurity was detected by $^{1}$H NMR spectroscopy. [f] A

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THF solution of TBAF (1 M) was used.

**Scope and limitations.** The scope and limitations of our approach to 2*H*-indazoles have been tested, first using a range of structurally diverse sydnones (Table 2). For monosubstituted sydnones with an aryl group, the reaction smoothly afforded excellent yields of the corresponding 2*H*-indazoles (entries 1-6), with a variety of functional groups tolerated, including halogens (entries 2 and 3), and alkyl (entry 4), ether (entry 5), and acetal (entry 6) groups. However, the electron deficient *N*-(4-nitrophenyl)sydnone **2g** (entry 7) was found to be unreactive. Even with the addition of a second batch of 1.2 equiv of **1a** after the first 1.2 equiv of **1a** was consumed, **2g** remained unreacted. *N*-Alkylsydnones (entries 8 and 9) also worked well under our reaction conditions, but in somewhat lower yields.

With substitution in the *C*-4 position of the sydnone, we have observed limited success with alkyl groups. Except for the proline-derived sydnone **2j** (entry 10), which has the 3- and 4-substitution tethered into a ring, other sydnones were found unstable under our reaction conditions and afforded a fairly complex reaction mixture in the end. For example, sydnone **2k** derived from leucine (entry 11) afforded only a 23% yield with ~10% recovery of the sydnone under our standard conditions, and 1.6 equiv of **1a** and 2.4 equiv of TBAF had to be employed for the full conversion of **2k**. On the other hand, sydnones with $sp^2$- or *sp*- carbon units in the *C*-4 position, including a vinyl group (entry 12), different aryl groups varying in their electronics (entries 13-16), different heterocyclic groups (entries 17 and 18), and an alkynyl group (entry 19), were all tolerated and the desired products were obtained in good to excellent yields, although in some cases (entries 18 and 19), incomplete conversion was observed. Successful substitution at the *C*-4 position of the sydnone has been extended to halogens, as illustrated in sydnones **2t** and **2u**

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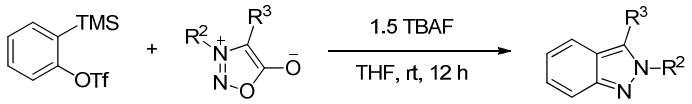
(entries 20 and 21), where 88% and 90% yields have been obtained. However, substitution of other electron-withdrawing groups at the *C*-4 position has not been tolerated. For example, 4-acetylsydnone **2v** was found to be unreactive with benzyne under our standard conditions (entry 22), leading to complete recovery of the starting sydnone. The adverse effect of electron-withdrawing groups has also been observed in entry 13, where a lower yield was obtained.

**Table 2.** Synthesis of 2*H*-Indazoles from Benzyne and Sydnones[a]



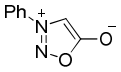
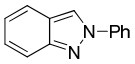
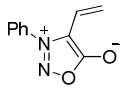
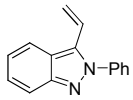
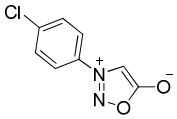
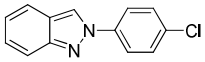
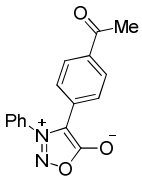
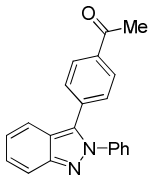
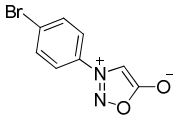
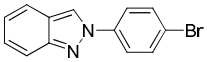
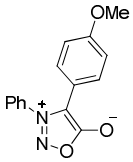
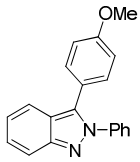
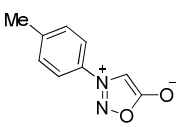
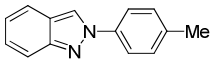
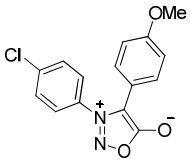
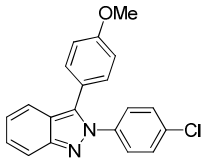

| Entry | sydnone | Product | yield[b] (%) | entry | sydnone | Product | yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **2a** |  **3aa** | 98 | 12 |  **2l** |  **3al** | 79 |
| 2 |  **2b** |  **3ab** | 95 | 13 |  **2m** |  **3am** | 71 |
| 3 |  **2c** |  **3ac** | 93 | 14 |  **2n** |  **3an** | 90 |
| 4 |  **2d** |  **3ad** | 94 | 15 |  **2o** |  **3ao** | 93 |

Table 2 continued

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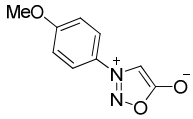
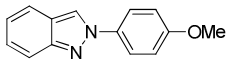
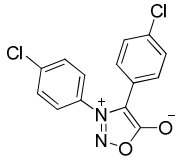
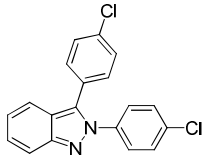
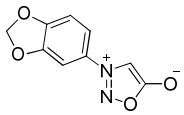
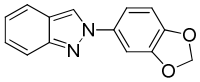
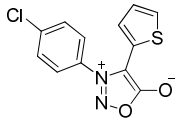
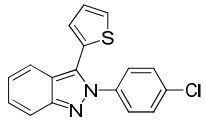
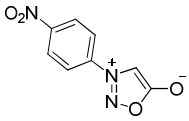
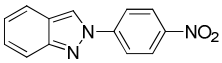
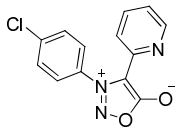
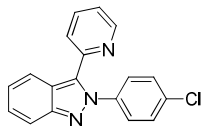
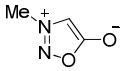
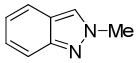
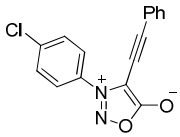
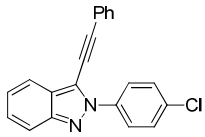
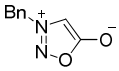
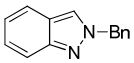
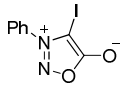
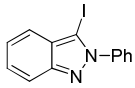
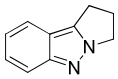
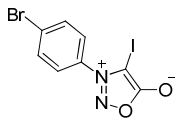
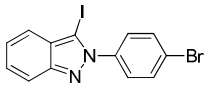
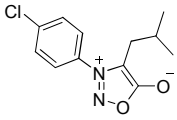
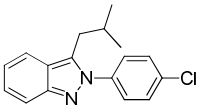
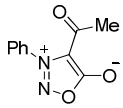
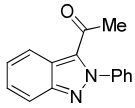
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 5 |  **2e** |  **3ae** | 92 | 16 |  **2p** |  **3ap** | 91 |
| 6 |  **2f** |  **3af** | 91 | 17 |  **2q** |  **3aq** | ~79[e] |
| 7 |  **2g** |  **3ag** | trace[c] | 18 |  **2r** |  **3ar** | 72[f] |
| 8 |  **2h** |  **3ah** | 77 | 19 |  **2s** |  **3as** | 70[g] |
| 9 |  **2i** |  **3ai** | 70 | 20 |  **2t** |  **3at** | 88 |
| 10 | **2j** |  **3aj** | 70 | 21 |  **2u** |  **3au** | 90 |
| 11 |  **2k** |  **3ak** | 63[d] | 22 |  **2v** |  **3av** | n.r.[h] |

[a] All reactions were carried out on approximately 0.4 mmol of sydnone at a concentration of 0.1 M. [b] Isolated yield. [c] A trace amount of product was detected by GC-MS. Substrate **2g** was still unreactive upon heating. [d] This reaction was performed with 1.6 equiv of **1a** and 2.4 equiv of TBAF. [e] The reaction afforded a 52% yield of pure **3aq**, together with another fraction of impure **3aq** (32% by weight, approximately 80-85% purity) that was very hard to purify. [f] With 15% recovery of **2r**. [g] With 19% recovery of **2s**. [h] With total recovery of **2v**, **1a** was consumed. Substrate

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**2v** was still unreactive upon heating.

Next, a variety of different aryne precursors have been tested under our optimized reaction conditions (Table 3). As can be seen, excellent yields can be achieved regardless of the aryne structure. Symmetrical aryne precursors **1b** and **1c** have been converted to the corresponding 2*H*-indazoles **3ba** (entry 1) and **3ca** (entry 2), respectively in almost quantitative yields. Unsymmetrical aryne precursor **1d**, which is neither electronically nor sterically biased, afforded mixtures of two possible regioisomers in nearly equal amounts (entry 3). Unsymmetrical aryne precursor **1e**, which is partially biased electronically, led to an inseparable mixture of two isomers in a 1 : 0.8 ratio (entry 4). Unsymmetrical aryne precursor **1f**, which is slightly biased by sterics, led to an inseparable mixture of two isomers in a 1 : 0.7 ratio (entry 5). An unsymmetrical naphthalyne precursor **1g** was also reactive and led to an inseparable mixture of two isomers in equal amounts (entry 6). However, 2,3-pyridyne precursor **1h**[17] proved unsuccessful using our standard reaction conditions. We observed that all sydnone starting material was recovered when compound **1h** was consumed (entry 7).

An interesting observation was made when we carried out the reaction using the unsymmetrical aryne precursor **1i**, which is both sterically and electronically biased. While we isolated two products, we were only able to assign one as the 4-MeO isomer (**3ia**) (33% yield) through extensive NMR spectroscopic analysis and comparison with literature values.[11,18] We were unable to identify the other product. While HRMS suggested the identity as the desired regioisomeric product, the presence of extra aromatic protons, as well as two aliphatic methyl groups in the $^{1}$H NMR spectrum, clearly suggested otherwise. It was not until we reacted **1i** with another sydnone **2d** that we realized what had happened. In the latter reaction, we again obtained two products. One

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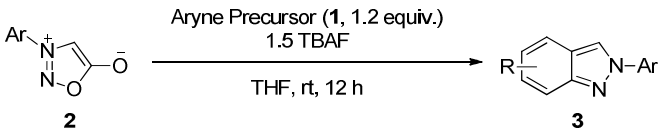
was the desired 4-MeO isomer (**3id**) in a 44% yield, and the other product was again unidentified. However, we were able to observe exactly the same extra aromatic protons and exactly the same extra methyl signals that were observed in the previously unidentified product, but here the integration no longer involved integers. That clearly suggested that these "unidentified" products were in fact mixtures of two compounds. The mixture obtained from **1i** and **2a** involved approximately a 1:1 ratio of two products. Therefore, the HRMS information was correct. The "unidentified" product from **1i** and **2a** actually contained the 7-MeO isomer **3ia'**. The other component in the mixture was later attributed to *m*-anisidine based on $^{1}$H NMR spectral analysis and comparison with literature values. The existence of *m*-anisidine was also confirmed by GC-MS. Thus, by stirring this "unidentified" product with an excess of acetic anhydride and pyridine, followed by a regular work-up and silica gel chromatography, the pure 7-MeO isomer (**3ia'**) could be obtained in a 40% yield. The $^{1}$H NMR spectral data now matched the literature values.[18] Similarly, compound **3id'**, the 7-MeO isomer from the reaction of **1i** and **2d**, could be isolated pure in about a 42% yield.

**Table 3.** Reaction with Other Aryne Precursors[a]




| Entry | sydnone | aryne precursor | product | yield[b] (%) |
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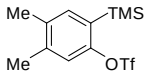
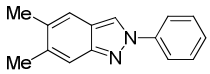
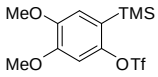
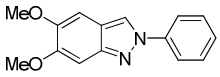
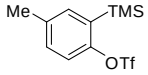
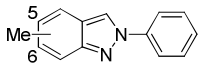
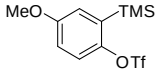
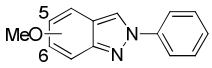
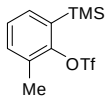
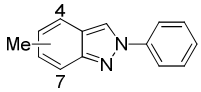
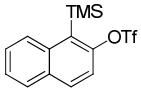
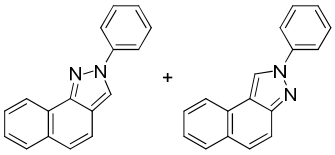
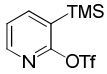
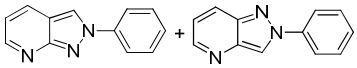
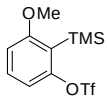
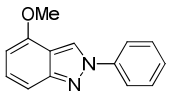
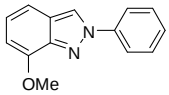
| | | | | |
|---|---|---|---|---|
| 1 | Ar = Ph<br>**2a** |  <br>**1b** |  <br>**3ba** | 97 |
| 2 | |  <br>**1c** |  <br>**3ca** | 95 |
| 3 | |  <br>**1d** |  <br>**3da + 3da'** | 93[c] |
| 4 | |  <br>**1e** |  <br>**3ea + 3ea'** | 99[d] |
| 5 | |  <br>**1f** |  <br>**3fa + 3fa'** | 98[e] |
| 6 | |  <br>**1g** |  <br>**3ga + 3ga'** | 91[f] |
| 7 | |  <br>**1h** |  <br>**3ha + 3ha'** | 0[g] |
| 8 | |  <br>**1i** |  <br>**3ia** | 33[h] |
| | | |  <br>**3ia'** | 40 |

Table 3 continued

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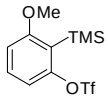
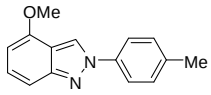
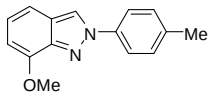
| | | | | |
|---|---|---|---|---|
| 9 | Ar = *p*-Tol **2d** |  **1i** |  **3id** | 44[i] |
| | | |  **3id'** | 42[i] |

[a] All reactions were carried out on 0.4 mmol of sydnone at a concentration of 0.1 M. [b] Isolated yield. [c] A 1:1 mixture of the 5-Me isomer and the 6-Me isomer was obtained. [d] An inseparable 0.8:1 mixture of two isomers (5-MeO and 6-MeO) was obtained. The major isomer was not identified. [e] A 0.7:1 mixture of two inseparable isomers (4-Me and 7-Me) was obtained. The major isomer was not identified. [f] A 1:1 mixture of **3ga** and **3ga'** was obtained. [g] All sydnone starting material was recovered when precursor **1h** was consumed. [h] See the Supporting Information for the structure assignment. [i] The structures were assigned based on the polarity and $^{1}$H NMR coupling pattern of the two isomers obtained from entry 6.

The regioselectivity in this cycloaddition, especially with the aryne derived from **1i**, can be explained as shown in Scheme 2. For a sydnone, there are three resonance structures (**A**, **B**, and **C**, Scheme 2), and cycloaddition with the aryne should arise from the latter two. Since the aryne derived from **1i** is known to be attacked preferentially by nucleophiles at the meta position (with respect to the OMe group) for both electronic and steric reasons,[19] resonance structure **B** should lead to formation of the 7-OMe regioisomer **3ia'**, while resonance structure **C** should lead to formation of the 4-OMe regioisomer **3ia**. While we typically draw the structure of sydnones as either **A** or **B**, computational chemists long ago realized that despite the enolate nature and the

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observed nucleophilic reactivity of *C*-4, the *N*-2 position actually carries a significant negative charge[20] and may serve as the nucleophile in the aryne reaction. Although the charge distribution of sydnones has been controversial,[21] experimental results involving the cycloaddition of sydnones with unsymmetrical alkynes have clearly suggested that both *N*-2 and *C*-4 can react as the nucleophilic site.[22] Moreover, the molecular orbital analysis of sydnones indicates that the LUMO of sydnones has very similar coefficients for *N*-2 and *C*-4,[23] rendering the *N*-2 and *C*-4 positions of a sydnone similar in reactivity. All these literature results support the formation of both isomers **3ia** and **3ia'** through cycloaddition, and the side-product, *m*-anisidine, appears to arise from a separate path during the formation of isomer **3ia**. Possibly, due to steric hindrance of the methoxy group, the [3 + 2] cycloaddition to form **3ia** is partially disrupted and therefore occurs stepwise, which stops at betaine **D**.[24] The addition of water may lead to the formation of **E**, which is attacked by hydroxide to form a ring-opened intermediate **F**. Intermediate **F** can further decompose to nitroso compound **G**, which is then reduced to *m*-anisidine.

**Scheme 2.** Regioselectivity in the Cycloaddition Reaction and Proposed Mechanism for the Formation of *m*-Anisidine.

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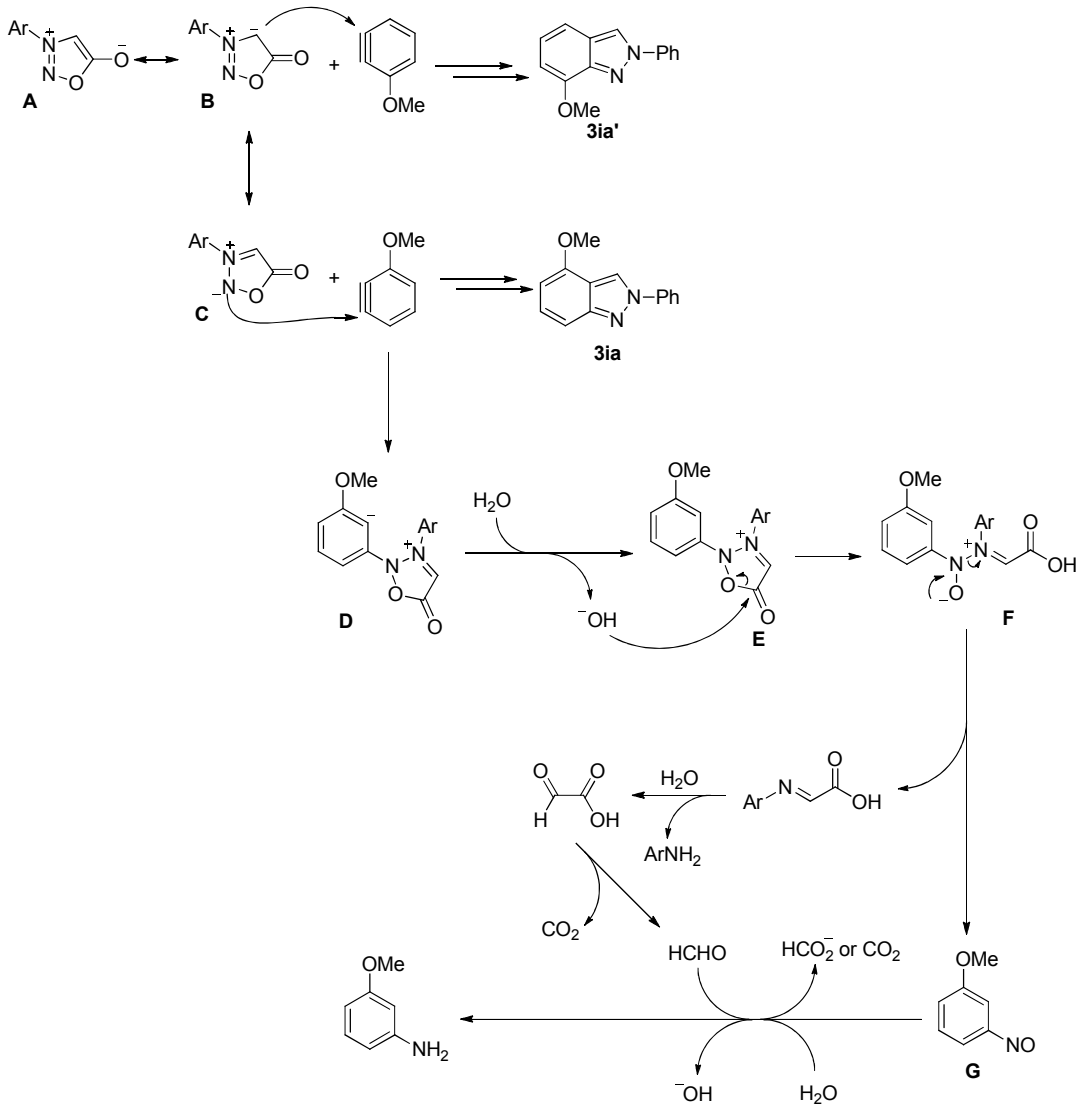


**Mechanistic investigation.** To gain further insight into this reaction, we conducted a brief Density Functional Theory and *ab initio* calculation of the reaction path using Gaussian 09. Geometry optimizations were performed with hybrid B3LYP functions in conjunction with the 6-31G(d) basis set. Higher-level relative energies were computed at the MP2/6-311+G(d,p) level based on the B3LYP/6-31G(d) optimized geometries. The schematic potential energy surface of the reaction with zero-point energy corrections is plotted in Figure 1. As can be seen, the initial [3 + 2] cycloaddition is an exothermic step. A subsequent retro-[4 + 2] reaction is again exothermic. Since we were not able to find the transition states of these cycloaddition and cycloreversion

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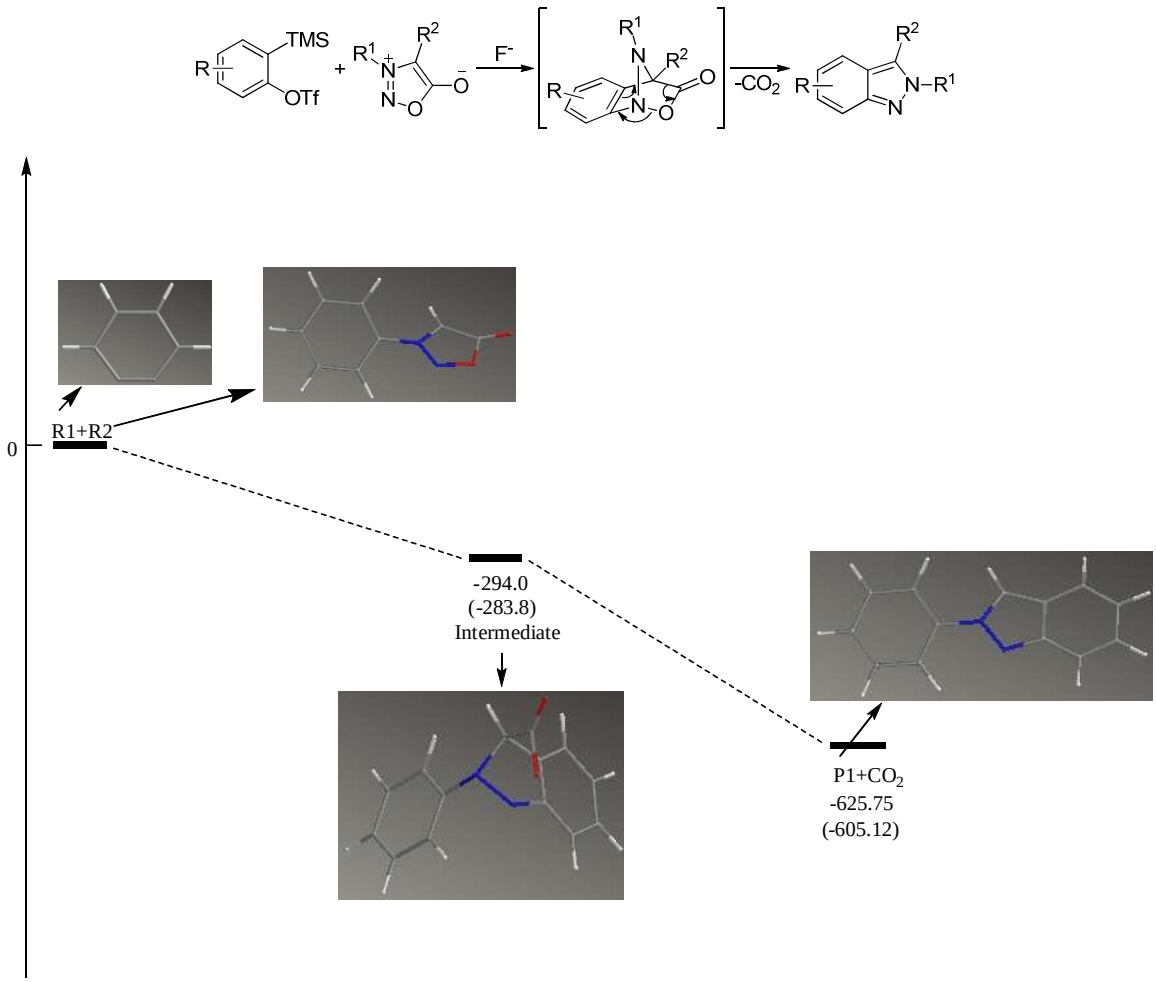
processes, a relatively smooth potential energy surface may exist.

**Figure 1.** Schematic potential energy surface with zero-point energy (ZPE) corrections at the MP2/6-311+G(d,p) level (units in kJ mol$^{-1}$). The values in parentheses are those obtained at the B3LYP/6-31G(d) level. The energy of the reactants is set to zero as a reference.




**Elaboration of 2*H*-Indazoles.** As our approach to 2*H*-indazoles tolerates halogen substituents, those halogen atoms offer an ideal site for further elaboration by subsequent Pd-catalyzed cross-couplings. Such a strategy can quickly afford a library of structurally diverse, highly functionalized 2*H*-indazoles. In this regard, we have demonstrated the feasibility of such elaborations by converting **3at** to the corresponding 3-aryl- and 3-(1-alkynyl)-2*H*-indazoles using Suzuki-Miyaura[25] and Sonogashira[26] reactions, respectively (Scheme 3).[27] By modifying the

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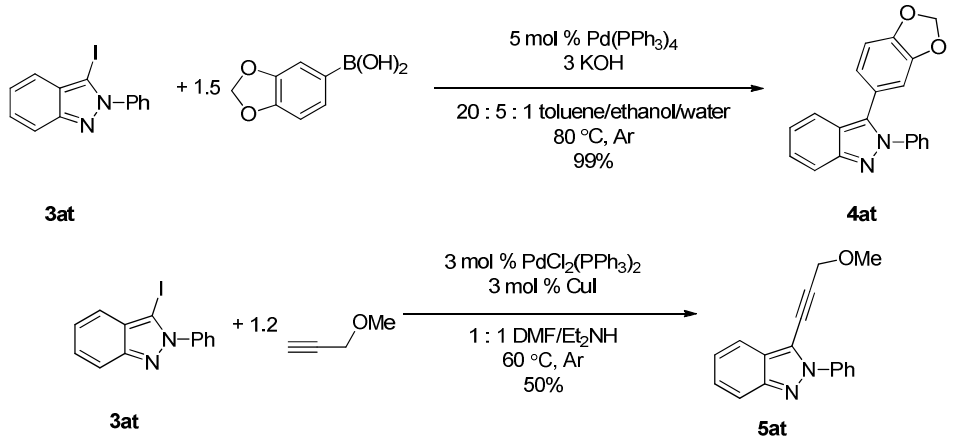
structure of the sydnones and arynes,[28] this approach can be easily exploited to provide more derivatives for potential biological activity screening. It should be noted that our direct new synthesis of alkynylsydnones[14] is unable to prepare indazoles like **5at**, and, therefore, the route described in Scheme 3 provides an effective route towards such compounds.

**Scheme 3.** Suzuki-Miyaura and Sonogashira Coupling of 2*H*-Indazoles




## 4.4. Conclusions

This work affords an efficient, new, synthetic route to 2*H*-indazoles by the [3 + 2] cycloaddition of arynes and sydnones. The reaction is applicable to a variety of sydnones and silylaryl triflates and affords the corresponding cycloadducts in moderate to excellent yields. Compared with literature protocols, our approach offers very mild reaction conditions, high yields, and no contamination by 1*H*-indazoles. The resulting halogen-substituted 2*H*-indazoles are readily elaborated to more complex products using known organopalladium chemistry. Thus, the versatility of the cycloaddition and the tolerance of halogen make this methodology ideal for pharmaceutical chemistry.

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### 4.5. Experimental Section

**General Information.** All reagents purchased from commercial sources were used as received. The solvents THF and MeCN were distilled over Na/benzophenone and $CaH_2$, respectively. The aryne precursors were used as received; those not commercially available were prepared according to literature procedures.[29,17] The sydnones were prepared as outlined below. The silica gel for column chromatography was supplied as 300-400 mesh or 230-400 mesh.[30] Powdered CsF was used as received and stored in a desiccator. TBAF (either 1 M in THF solution or anhydrous solid) was used as received. The solid TBAF was stored in a desiccator as well.

All melting points were measured and are uncorrected. The $^{1}H$ and $^{13}C$ NMR spectra were recorded and are referenced to the residual solvent signals (7.26 ppm for $^{1}H$ in $CDCl_3$ and 77.2 ppm for $^{13}C$ in $CDCl_3$).

All aryne cycloaddition reactions were carried out in oven-dried glassware and were magnetically stirred. A nitrogen atmosphere was not used, except that a balloon of nitrogen was attached to the reaction flask for the ventilation of $CO_2$.

**Computational methods.** All electronic structure calculations involved in this work utilized the Gaussian 09 program package.[31] The geometries and frequencies of all the stationary points (including reactants, intermediates, and products) were calculated by Becke's three-parameter nonlocal-exchange functional with the nonlocal correlation functional of Lee-Yang-Parr (B3LYP) using the 6-31G(d) basis set. To get more reliable reaction energies, single-point corrections were performed by restricted or unrestricted second-order Møller-Plesset perturbation theory (MP2) with the 6-311+G(d, p) basis set using the B3LYP optimized geometries.

**Preparation of the sydnones.** All the sydnones were prepared as follows. Due to long T1

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relaxation times, the acquisition of $^{13}C$ NMR spectra for many sydnones could not be achieved, even after an overnight acquisition of 8000 scans on a 400 MHz instrument.

**3-Phenylsydnone (2a).**[12a] To a suspension of 5.00 g of *N*-phenylglycine (33 mmol) in 60 mL of water at 0 ºC was added dropwise a solution of 3.50 g of $NaNO_2$ (51 mmol, 1.5 equiv) in 20 mL of water. The mixture was stirred at 0 ºC for an additional 20 min and the resultant clear red solution was filtered while cold. A scoop of activated charcoal (ca. 200-300 mg) was added and the mixture was stirred for a few minutes before being filtered again. The intermediate *N*-nitroso-*N*-phenylglycine was precipitated from the filtrate by the addition of 10 mL of concentrated HCl and was then collected by filtration. It was washed with cold water and dried overnight under a high vacuum. The resulting solid was then dissolved in 25 mL of acetic anhydride and the mixture was heated to 100 ºC for 1.5 h. After being cooled to room temperature, the resulting mixture was poured into 300 mL of ice water. A yellow solid formed, which was triturated by stirring for a few minutes in this cold water. The solid was filtered, washed thoroughly with water until no smell of acetic acid remained, and dried under a high vacuum overnight to afford 3.37 g of product (63% yield) as off-white crystals. This representative procedure for preparing sydnones from the corresponding amino acid is identified as **Protocol 1**: $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.77-7.58 (m, 5 H), 6.75 (s, 1 H).

**3-(4-Chlorophenyl)sydnone (2b).** A mixture of 5.10 g of 4-chloroaniline (40 mmol), 5.14 mL of ethyl chloroacetate (48 mmol, 1.2 equiv), and 6.53 g of $NaOAc{\bullet}3H_2O$ (48 mmol, 1.2 equiv) in 10 mL of ethanol was refluxed in a 100 ºC oil bath overnight. After being cooled to room temperature, the mixture was poured into ice water, and the precipitate was filtered and dried. The crude product, *N*-(4-chlorophenyl)glycine ethyl ester, after crystallization from ethanol (4.01 g,

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47% yield), was an off-white solid. It is strongly suggested that this intermediate be purified, either through recrystallization or column chromatography. The resulting ester (3.00 g, 14 mmol) was stirred with 1.01 g of LiOH (3.0 equiv) in 30 mL of THF/water (1:1) at 0 ºC. After 2 h at 0 ºC, the reaction mixture was gradually warmed up to room temperature, where the pH was adjusted to 3-4 with concentrated HCl. The precipitate was filtered and dried to afford 2.53 g of *N*-(4-chlorophenyl)glycine (98% yield) as an off-white solid (62% overall yield). This representative procedure for preparing an amino acid is identified as **Route 1**.[32] Sydnone **2b** was then synthesized as an off-white solid (72% overall yield) from the resulting amino acid following **Protocol 1**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74-7.67 (m, 2H), 7.64-7.56 (m, 2H), 6.79 (s, 1H).

**3-(4-Bromophenyl)sydnone (2c).** The corresponding amino acid was prepared from 4-bromoaniline following **Route 1** in a 65% overall yield. Sydnone **2c** was synthesized from this amino acid following **Protocol 1** as an off-white solid (50% overall yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 6.73 (s, 1 H).

**3-(4-Methylphenyl)sydnone (2d).** The corresponding amino acid was prepared from 4-methylaniline following **Route 1** in a 53% overall yield. Sydnone **2d** was synthesized from this amino acid following **Protocol 1** as an off-white to cream solid (60% overall yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 6.72 (s, 1 H), 2.49 (s, 3 H).

**3-(4-Methoxyphenyl)sydnone (2e).** The corresponding amino acid was prepared from 4-methoxylaniline following **Route 1** in a 50% overall yield. Sydnone **2e** was synthesized from this amino acid following **Protocol 1** as an off-white solid (78% overall yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.2 Hz, 2 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 6.64 (s, 1 H), 3.91 (s, 3 H).

**3-(3,4-Methylenedioxyphenyl)sydnone (2f).** The corresponding amino acid was prepared

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from 3,4-methylenedioxyaniline following **Route 1** in a 60% overall yield. Sydnone **2f** was synthesized from this amino acid following **Protocol 1** as a brown solid (27% overall yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, 2 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.64 (s, 1 H), 6.14 (s, 2 H).

**3-(4-Nitrophenyl)sydnone (2g).** To 0.75 g of glycine (10 mmol) was added 10 mL of tetrabutylammonium hydroxide in methanol (1 M, 10 mmol, 1.0 equiv.); the solvent was removed under vacuum, and the residue was dissolved in 20 mL of DMSO. *p*-Fluoronitrobenzene (1.55 g, 11 mmol, 1.1 equiv) and 1.51 g of $K_2CO_3$ (11 mmol, 1.1 equiv ) were added and the mixture was allowed to react under gentle warming (45 ºC) with stirring until completion (monitored by TLC). The mixture was then poured into cold water, acidified with HCl, and extracted with ethyl acetate. The combined organic layers were evaporated under vacuum and the residue was purified by column chromatography (5:1 petroleum ether/EtOAc) to afford 1.2 g (65% yield) of the desired amino acid as a yellow solid.[33] Sydnone **2g** was then synthesized from this amino acid following **Protocol 1** as an off-white solid (36% overall yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.8 Hz, 2 H), 7,98 (d, *J* = 8.8 Hz, 2 H), 6.84 (s, 1 H).

**3-Methylsydnone (2h).** To an ice-cold solution of 6.7 mL of conc. HCl and 3.56 g of sarcosine (40 mmol) in 10 mL of water, was added a saturated solution of 5.52 g of $NaNO_2$ (80 mmol) in water. The mixture was stirred at 0 ºC for 1 h and then extracted with ethyl acetate three times. The combined organic layers were concentrated under a vacuum to obtain *N*-nitroso-*N*-methylglycine as a yellow oil. The resulting oil was dissolved in 4 mL of dry ether and charged dropwise with ~500 µL of trifluoroacetic anhydride (3.6 mmol, 1.8 equiv) at 0 ºC. The reaction was stirred at 0 ºC for a few minutes and gradually warmed to room temperature and stirred for another 1 h. The

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solvents were evaporated and the residue was dissolved in EtOAc. Solid $NaHCO_3$ was added to neutralize the excess acid and was removed by filtration. The EtOAc was evaporated and the residue was purified by chromatography (2:1 petroleum ether/EtOAc) to yield 300 mg of the desired sydnone (8 % overall yield) as a yellow oil. This representative precedure for preparing sydnones from the corresponding amino acid is identified as **Protocol 2**: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1 H), 4.07 (s, 3 H).

**3-Benzylsydnone (2i).** This sydnone was synthesized from *N*-benzylglycine as a white solid (39% overall yield) following **Protocol 2**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (overlap, 3 H), 7.39 (overlap, 2 H), 6.21 (s, 1 H), 5.36 (s, 2 H).

**3,4-Cyclopenta[*c*]sydnone (2j).**This sydnone was prepared according to a literature procedure[34] as a brown oil (~11% overall yield).

**3-(4-Chlorophenyl)-4-(isobutyl)-sydnone (2k).** To a round-bottom flask equipped with a stir bar, was added 1.32 g of L-leucine (10 mmol), followed by 190 mg of CuI (1 mmol, 10 mol %), 3.04 g of anhydrous $K_2CO_3$ (22 mmol, 2.2 equiv.), 2.87 g of 4-bromochlorobenzene (15 mmol, 1.5 equiv.), and 9 mL of undistilled DMSO. The reaction system was flushed with nitrogen. The flask was sealed with a Teflon stopper and placed in a 70 ºC oil bath. The suspension was vigorously stirred. After 15 h, the stirring was found to be difficult, and another 4 mL of DMSO was added. The reaction was stopped at 40 h when the color changed from a purple-brown to blue. The reaction was poured into ice water and concentrated HCl was added until the pH reached 3-4. The precipitate was filtered, washed thoroughly with cold water (slightly acidified by HCl to pH ~4) and dried under a high vacuum to yield 2.6 g of crude *N*-(4-chlorophenyl)leucine as a slightly green solid (yield >100%).[12f,g] It should be noted that this method did not work for Met or Thr. This

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crude amino acid was used in the next step without further purification.

To a solution of 500 mg (~2 mmol considering possible impurities) of crude *N*-(4-chlorophenyl)leucine in 3 mL of undistilled DME was added dropwise ~400 μL of isoamyl nitrite (3 mmol, 1.5 equiv) at room temperature. The mixture was allowed to stir for 2 d before the solvent was removed under reduced pressure. The solid was triturated with petroleum ether and filtered. The cake was washed with petroleum ether and air dried. The solid was dissolved in 4 mL of dry ether and was charged dropwise with ~500 μL of trifluoroacetic anhydride (3.6 mmol, 1.8 equiv) at 0 ºC. The reaction was stirred at 0 ºC for a few minutes and gradually warmed to room temperature and stirred for another 1 h. The solvents were evaporated and the residue was dissolved in EtOAc. The excess acid present was neutralized by the addition of solid $NaHCO_3$, which was then removed by filtration. The EtOAc was evaporated and the residue was purified by chromatography (3:1 petroleum ether/EtOAc) to yield 130 mg of the desired sydnone (26% overall yield) as a light brown oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.6 Hz, 2 H), 7.46 (d, *J* = 8.7 Hz, 2 H), 2.37 (d, *J* = 7.4 Hz, 2 H), 1.88 (dt, *J* = 13.6, 6.8 Hz, 1 H), 0.80 (d, *J* = 6.6 Hz, 6 H).

**3-(4-Chlorophenyl)-4-(4-methoxyphenyl)sydnone (2o).**[13] To a mixture of 197 mg of *N*-(4-chlorophenyl)sydnone (1.0 mmol), 351 mg of 4-iodoanisole (1.5 mmol, 1.5 equiv), 11 mg of $Pd(OAc)_2$ (0.05 mmol, 5 mol %), 26 mg of $PPh_3$ (0.1 mmol, 10 mol %), and 276 mg of anhydrous $K_2CO_3$ in a 10 mL round-bottom flask was added 2 mL of undistilled DMF. The flask was fitted with an air condenser and placed in a 120 ºC oil bath overnight, during which time the reaction mixture was stirred open to the air. The mixture was cooled to room temperature, poured into 30 mL of water, and extracted three times with EtOAc. The combined extracts were washed once with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column

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chromatography (petroleum ether/EtOAc) to afford 145 mg of **2o** as a yellow solid (48% yield). This representative procedure for preparing functionalized sydnones is identified as **Protocol 3**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2 H), 7.47-7.40 (m, 2 H), 7.24-7.17 (m, 2 H), 6.87-6.79 (m, 2 H), 3.79 (s, 3 H).

**3-Phenyl-4-vinylsydnone (2l).** This sydnone was prepared from sydnone **2a** and vinyl bromide as a brown solid (40% yield) following **Protocol 3**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.79-7.60 (m, 3 H), 7.59-7.50 (m, 2 H), 6.40-6.16 (m, 2 H), 5.41 (d, *J* = 10.6 Hz, 1 H).

**4-(4-Acetylphenyl)-3-phenylsydnone (2m).** This sydnone was prepared from sydnone **2a** and 4-bromoacetophenone as a yellow solid (30% yield) following **Protocol 3**: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 2 H), 7.76-7.56 (m, 3 H), 7.54-7.44 (m, 2 H), 7.43-7.33 (m, 2 H), 2.54 (s, 3 H).

**4-(4-Methoxyphenyl)-3-phenylsydnone (2n).** This sydnone was prepared from sydnone **2a** and 4-iodoanisole as a yellow solid (46% yield) following **Protocol 3**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.2 Hz, 2 H), 7.48 (d, *J* = 7.6 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H).

**3,4-*Bis*(4-chlorophenyl)sydnone (2p).** This sydnone was prepared from sydnone **2b** and 4-bromochlorobenzene as a brown solid (44% yield) following **Protocol 3**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2 H), 7.47-7.42 (m, 2 H), 7.31-7.27 (m, 2 H), 7.24 7.20 (m, 2 H).

**3-(4-Chlorophenyl)-4-(2-thiophenyl)sydnone (2q).** This sydnone was prepared from sydnone **2b** and 2-iodothiophene as a brown solid (50% yield) following **Protocol 3**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 3.7 Hz, 1 H), 7.28 (d, *J* = 5.0 Hz, 1 H), 7.02 (t, *J* = 4.5 Hz, 1 H).

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**3-(4-Chlorophenyl)-4-(2-pyridyl)sydnone (2r).** This sydnone was prepared from sydnone **2b** and 2-bromopyridine as a brown solid (60% yield) following **Protocol 3**: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.6 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.7 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 7.13 (dd, *J* = 7.4, 4.9 Hz, 1 H).

**3-(4-Chlorophenyl)-4-(phenylethynyl)sydnone (2s).**[14] A solution of 79 mg of sydnone **2b** (0.4 mmol) in 2 mL of toluene was charged with 4.5 mg of $Pd(OAc)_2$ (5 mol %), 6.8 mg of $CuCl_2$•$2H_2O$ (10 mol %), and 186 mg of $Ag_2O$ (2.0 equiv), and then heated to 75 ºC in an open flask. A solution of 88 μL of phenylacetylene (0.6 mmol) in 3 mL of toluene was added over 6 h using a syringe pump while the reaction was stirred open to the air. The reaction was allowed to stir for an additional 2 h after the addition, and then EtOAc and water were added. The layers were separated and the EtOAc was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford 82 mg of **2s** as a yellow solid (69% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.67-7.61 (m, 2 H), 7.44-7.31 (m, 5 H).

**4-Iodo-3-phenylsydnone (2t).**[15] To a solution of 243 mg of sydnone **2a** (1.5 mmol) in 2.5 mL of acetic acid was added 185 mg of NaOAc (2.25 mmol, 1.5 equiv.), followed by a solution of 366 mg of ICl (2.25 mmol, 1.5 equiv.) in 1.5 mL of acetic acid. The mixture was allowed to stir for 3 h, then quenched with water and the solid was collected by filtration. The cake was washed with drops of cold ethanol and dried under vacuum to afford 272 mg of product (63%) as a brown solid. This representative procedure for preparing functionalized sydnones is identified as **Protocol 4**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 7.2 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 2 H).

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**3-(4-Bromophenyl)-4-iodosydnone (2u).** This sydnone was prepared from sydnone **2c** as a brown solid (60% yield) following **Protocol 4**: mp 160-162 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H); LRMS (ESI) 367 (M+H); HRMS (ESI) calcd for $C_8H_5BrIN_2O_2$ (M+H) 366.8574, found 366.8574.

**4-Acetyl-3-phenylsydnone (2v).**[16] To a solution of 0.81 g of sydnone **2a** (5 mmol) in 5 mL of acetic anhydride was added 0.89 g of NBS (5 mmol). The mixture was allowed to stir for 4 h, poured into 20 mL of ice water, and extracted by EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over $Na_2SO_4$, and evaporated under vacuum. The residue was purified by column chromatography (5:1 petroleum ether/EtOAc) to afford 529 mg of product (52% yield) as colorless crystals: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 7.6 Hz, 1 H).

**General procedure for the synthesis of 2*H*-indazoles.** To an oven-dried 10 mL round-bottom flask equipped with a stir bar were added 140 mg of benzyne precursor (~0.48 mmol, ~1.2 equiv) and 0.4 mmol of sydnone. THF (4 mL) was added and the mixture was stirred until all solid dissolved. To this solution was added TBAF (~160 mg of solid or ~630 µL of 1*M* THF solution, ~1.6 equiv) in one portion. The flask was sealed with a septum and a nitrogen balloon was attached. The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was poured into saturated $NaHCO_3$ and extracted three times with EtOAc. The combined extracts were washed once with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the 2*H*-indazole.

**2-Phenyl-2*H*-indazole (3aa).** Following the general procedure, this product was isolated as a white solid: mp 79-81 ºC (lit[35] 81-82 ºC); $R_f$ = 0.45 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400

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MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.92-7.89 (m, 2 H), 7.81 (dd, *J* = 8.8, 0.9 Hz, 1 H), 7.72 (d, *J* = 8.5 Hz, 1 H), 7.56-7.50 (m, 2 H), 7.43-7.38 (m, 1 H), 7.34 (ddd, *J* = 8.8, 6.6, 1.1 Hz, 1 H), 7.12 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.7, 140.5, 129.5, 127.9, 126.8, 122.7, 122.4, 120.9, 120.40, 120.37, 117.9; LRMS (ESI): 217 (M+Na), 195 (M+H); HRMS (ESI): calcd for $C_{13}H_{11}N_2$ (M+H) 195.0917, found 195.0916.

**2-(4-Chlorophenyl)-2*H*-indazole (3ab).** White solid: mp 141-143 ºC; $R_f$ = 0.50 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.89-7.84 (m, 2 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 8.5 Hz, 1 H), 7.53-7.48 (m, 2 H), 7.33 (ddd, *J* = 8.6, 6.6, 0.8 Hz, 1 H), 7.17-7.09 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.8, 138.9, 133.5, 129.7, 127.1, 122.8, 122.7, 122.0, 120.35, 122.30, 117.8; LRMS (ESI) 251 (M+Na), 229 (M+H); HRMS (ESI) calcd for $C_{13}H_{10}ClN_2$ (M+H) 229.0527, found 229.0525.

**2-(4-Bromophenyl)-2*H*-indazole (3ac).** Yellow solid: mp 146-148 ºC; $R_f$ = 0.38 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.79-7.75 (m, 3 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 9.2 Hz, 2 H), 7.32 (dd, *J* = 7.6, 6.8 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.1, 139.7, 132.8, 127.3, 123.1, 122.9, 122.4, 121.6, 120.6, 120.4, 118.1; LRMS (ESI) 273 (M+H); HRMS (ESI) calcd for $C_{13}H_{10}BrN_2$ (M+H) 273.0022, found 273.0030.

**2-(4-Tolyl)-2*H*-indazole (3ad).** White solid: mp 101-103 ºC; $R_f$ = 0.44 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 0.9 Hz, 1 H), 7.83-7.76 (m, 3 H), 7.71 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.38-7.29 (m, 3 H), 7.11 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H), 2.43 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.6, 138.3, 137.9, 130.1, 126.6, 122.7, 122.3, 120.8, 120.30, 120.28, 117.9, 21.0; LRMS (ESI) 231 (M+Na), 209 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2$ (M+H)

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209.1073, found 209.1072.

**2-(4-Methoxyphenyl)-2*H*-indazole (3ae).** Yellow solid: mp 130-132 ºC; $R_f$ = 0.25 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 7.79 (d, *J* = 8.8 Hz, 3 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.31 (dd, *J* = 7.6, 7.2 Hz, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.4, 149.7, 134.3, 126.7, 122.8, 122.6, 122.4, 120.5, 120.4, 117.9, 114.8, 55.8; LRMS (ESI) 257 (M+Na), 225 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M+H) 225.1022, found 225.1026.

**2-(3,4-Methylenedioxyphenyl)-2*H*-indazole (3af).** Pale white solid: mp 117-118 ºC; $R_f$ = 0.31 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.77 (dd, *J* = 8.8, 0.9 Hz, 1 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 7.41 (d, *J* = 2.2 Hz, 1 H), 7.35-7.29 (m, 2 H), 7.11 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.07 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.4, 147.3, 135.2, 126.7, 125.6, 122.3, 120.5, 120.2, 117.7, 114.4, 108.4, 103.1, 101.9; LRMS (ESI) 261 (M+Na), 239 (M+H); HRMS (ESI) calcd for $C_{14}H_{11}O_2N_2$ (M+H) 239.0815, found 239.0812.

**2-Methyl-2*H*-indazole (3ah).** Yellow oil: $R_f$ = 0.21 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 4.21 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.2, 126.0, 123.7, 122.3, 121.8, 120.1, 117.4, 40.5; LRMS (APCI) 133 (M+H); HRMS (APCI) calcd for $C_8H_9N_2$ (M+H) 133.0760, found 133.0762.

**2-Benzyl-2*H*-indazole (3ai).** Yellow oil: $R_f$ = 0.31 (5:1 petroleum ether/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.73 (dd, *J* = 8.7, 0.9 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 7.34-7.30 (m, 3 H), 7.27-7.23 (m, 3 H), 7.06 (dd, *J* = 8.1, 7.5 Hz, 1 H), 5.57 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$)

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δ 149.0, 135.9, 129.1, 128.5, 128.1, 126.2, 123.0, 122.2, 121.9, 120.3, 117.7, 57.6; LRMS (APCI) 209 (M+H); HRMS (APCI) calcd for $C_{14}H_{13}N_2$ (M+H) 209.1073, found 209.1078.

**2,3-Dihydro-1*H*-pyrrolo[1,2-*b*]indazole (3aj).** Off-white solid: mp 99-100 ºC; $R_f$ = 0.31 (1:1 $CH_2Cl_2$/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.7 Hz, 1 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 4.42 (t, *J* = 7.3 Hz, 2 H), 3.18 (t, *J* = 7.2 Hz, 2 H), 2.84-2.63 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.5, 138.8, 125.5, 120.3, 119.8, 117.6, 116.1, 48.9, 25.7, 23.0; LRMS (ESI) 181 (M+Na), 159 (M+H); HRMS (ESI) calcd for $C_{10}H_{11}N_2$ (M+H) 159.0917, found 159.0915.

**2-(4-Chlorophenyl)-3-isobutyl-2*H*-indazole (3ak).** Slightly orange solid: mp 77-79 ºC; $R_f$ = 0.47 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 1 H), 7.65 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.55-7.44 (m, 4 H), 7.33 (ddd, *J* = 8.8, 6.6, 1.1 Hz, 1 H), 7.08 (ddd, *J* = 8.5, 6.6, 0.8 Hz, 1 H), 2.91 (d, *J* = 7.4 Hz, 2 H), 2.04-1.89 (m, 1 H), 0.83 (d, *J* = 6.6 Hz, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.6, 138.7, 136.3, 134.8, 129.3, 127.6, 126.8, 121.5, 121.1, 120.4, 117.5, 34.1, 29.2, 22.5; LRMS (ESI) 307 (M+Na), 285 (M+H); HRMS (ESI) calcd for $C_{17}H_{18}ClN_2$ (M+H) 285.1153, found 285.1151.

**2-Phenyl-3-vinyl-2*H*-indazole (3al).** Yellow gel: $R_f$ = 0.18 (5:1 hexanes ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 8.7 Hz, 1 H), 7.64-7.48 (m, 5 H), 7.43-7.34 (m, 2 H), 7.23-7.15 (m, 1 H), 6.81 (dd, *J* = 17.8, 11.6 Hz, 1 H), 6.04 (dd, *J* = 17.8, 0.8 Hz, 1 H), 5.53 (dd, *J* = 11.6, 0.9 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.8, 139.6, 133.2, 129.1, 128.8, 126.7, 126.2, 124.9, 122.7, 120.6, 120.3, 118.0, 117.7; LRMS (EI) 220 (M), 219 (M-H); HRMS (EI) calcd for $C_{15}H_{12}N_2$ (M) 220.1000, found 220.0990.

**3-(4-Acetylphenyl)-2-phenyl-2*H*-indazole (3am).** Yellow solid: mp 135-137 ºC (lit[18] 136-138

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ºC); $R_f$ = 0.36 (2:1 hexanes/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 2 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.72 (d, *J* = 8.5 Hz, 1 H), 7.47-7.36 (m, 8 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 2.61 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 197.3, 149.0, 139.9, 136.2, 134.4, 133.9, 129.6, 129.1, 128.6, 128.6, 127.1, 125.9, 123.2, 121.8, 120.0, 117.9, 26.6; LRMS (EI) 312 (M); HRMS (EI) calcd for $C_{21}H_{16}N_2O$ (M) 312.1263, found 312.1262.

**3-(4-Methoxyphenyl)-2-phenyl-2*H*-indazole (3an).** Yellow solid: mp 103-105 ºC; $R_f$ = 0.52 (2:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1 H); 7.69 (d, *J* = 8.4 Hz, 1 H), 7.39 (d, *J* = 2.4 Hz, 2 H), 7.38-7.33 (m, 4 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 6.91 (d, *J* = 8.8 Hz, 2 H); 3.82 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.0, 140.4, 135.5, 131.1, 129.1, 128.3, 127.1, 126.1, 122.4, 122.2, 121.7, 120.8, 117.8, 114.4, 55.4; LRMS (EI) 300 (M); HRMS (EI) calcd for $C_{20}H_{16}N_2O$ (M) 300.1263, found 300.1272.

**2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-2*H*-indazole (3ao).** Slightly brown solid: mp 122-124 ºC; $R_f$ = 0.39 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 1 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 7.42-7.33 (m, 5 H), 7.30-7.26 (m, 2 H), 7.13 (ddd, *J* = 8.4, 6.6, 0.7 Hz, 1 H), 6.99-6.91 (m, 2 H), 3.86 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.0, 138.8, 135.4, 133.9, 130.9, 129.2, 127.2, 127.1, 122.4, 121.8, 121.7, 120.6, 117.6, 114.4, 55.3; LRMS (ESI) 357 (M+Na), 335 (M+H); HRMS (ESI) calcd for $C_{20}H_{16}ClN_2O$ (M+H) 335.0946, found 335.0942.

**2,3-*Bis*(4-chlorophenyl)-2*H*-indazole (3ap).** Pale white solid: mp 126-129 ºC; $R_f$ = 0.52 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 7.43-7.35 (m, 7 H), 7.32-7.27 (m, 2 H), 7.17 (ddd, *J* = 8.5, 6.6, 0.7 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.4, 134.7, 134.3, 134.1, 130.8, 129.35, 129.29, 128.0, 127.4, 127.1,

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123.1, 121.8, 120.1, 117.8; LRMS (ESI) 361 (M+Na), 339 (M+H); HRMS (ESI) calcd for $C_{19}H_{13}Cl_2N_2$ (M+H) 339.0450, found 339.0448.

**2-(4-Chlorophenyl)-3-(2-thiophenyl)-2*H*-indazole (3aq).** Yellow solid: mp 99-101 ºC; $R_f$ = 0.49 (6:1 petroleum ether/EtOAc).[36] The product spot overlapped with a highly fluorescent spot that immediately follows the product spot. Performing column chromatography with 8:1:0.4 petroleum ether/$CH_2Cl_2$/EtOAc offers some help in separation and purification of the desired product: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 1 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.49-7.35 (m, 6 H), 7.19 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1 H), 7.03 (dd, *J* = 3.6, 1.1 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.4, 134.7, 129.9, 129.6, 129.3, 128.4, 127.69, 127.65, 127.5, 127.3, 123.0, 121.9, 120.5, 117.7; LRMS (ESI) 333 (M+Na), 311 (M+H); HRMS (ESI) calcd for $C_{17}H_{12}ClSN_2$ (M+H) 311.0404, found 311.0404. The contaminant (the fluorescent spot) shows a series of non-overlapped signals as follows: 7.87 (d, *J* = 8.5 Hz), 7.50 (apparent t, *J* = 9.0 Hz), 7.13 (d, *J* = 3.8 Hz), 6.88 (d, *J* = 3.8 Hz).

**2-(4-Chlorophenyl)-3-(2-pyridyl)-2*H*-indazole (3ar).** Slightly brown solid: mp 137-139 ºC; $R_f$ = 0.25 (6:1 petroleum ether/EtOAc);[36] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.71-8.67 (m, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.71 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.44-7.36 (m, 5 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.29-7.24 (m, 1 H), 7.21 (ddd, *J* = 8.5, 6.6, 0.7 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.2, 149.1, 139.1, 136.5, 134.3, 134.1, 129.2, 127.3, 127.1, 124.6, 123.6, 122.6, 122.3, 120.7, 117.8; LRMS (ESI) 328 (M+Na), 306 (M+H); HRMS (ESI) calcd for $C_{18}H_{13}ClN_3$ (M+H) 306.0793, found 306.0790.

**2-(4-Chlorophenyl)-3-phenylethynyl-2*H*-indazole (3as).** Yellow solid: mp 141-144 ºC; $R_f$ = 0.50 (6:1 petroleum ether/EtOAc).[36] The product spot overlapped with some spots that have a long

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wavelength UV absorption. Performing column chromatography with 8:1:0.4 petroleum ether/$CH_2Cl_2$/EtOAc offers some help in separation and purification of the desired product. The impurities do not show more than minimum contamination by $^1$H NMR spectroscopy: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (m, 2 H), 7.87-7.78 (m, 2 H), 7.58-7.49 (m, 4 H), 7.43-7.36 (m, 4 H), 7.25-7.21 (m, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.7, 138.6, 134.3, 131.3, 129.19, 129.14, 128.6, 127.6, 125.6, 125.5, 123.5, 121.9, 120.2, 118.2, 100.7, 77.7 (one overlapped signal); LRMS (ESI) 329 (M+H); HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ (M+H) 329.0840, found 329.0837.

**3-Iodo-2-phenyl-2*H*-indazole (3at).** Off-white solid: mp 104-105 ºC; $R_f$ = 0.42 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 2 H), 7.50 (m, 4 H), 7.36 (dd, *J* = 7.6, 6.8 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.1, 140.6, 129.4, 129.1, 128.4, 127.7, 126.8, 123.3, 121.2, 118.4, 76.2; LRMS (ESI) 321 (M+H); HRMS (ESI) calcd for $C_{13}H_{10}IN_2$ (M+H) 320.9883, found 320.9884.

**2-(4-Bromophenyl)-3-iodo-2*H*-indazole (3au).** Yellow solid: mp 159-161 ºC; $R_f$ = 0.38 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 1 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.4, 139.6, 132.5, 132.4, 128.7, 128.4, 128.0, 123.6, 121.3, 118.5, 76.0; LRMS (ESI) 399 (M+H); HRMS (ESI) calcd for $C_{13}H_9BrIN_2$ (M+H) 398.8988, found 398.8988.

**5,6-Dimethyl-2-phenyl-2*H*-indazole (3ba).** White solid: mp 133-135 ºC; $R_f$ = 0.24 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.87 (d, *J* = 7.8 Hz, 2 H), 7.56 (s, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.40 (s, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 2.39 (s, 3 H), 2.34 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.6, 140.5, 137.2, 132.3, 129.4, 127.3, 121.8, 120.5, 119.0, 118.6,

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116.5, 21.1, 20.5; LRMS (EI) 222 (M), 207 (M-Me); HRMS (EI) calcd for $C_{15}H_{14}N_2$ (M) 222.1157, found 222.1155.

**5,6-Dimethoxy-2-phenyl-2*H*-indazole (3ca).** White solid: mp 147-148 ºC (lit[37] 149-150 ºC); $R_f$ = 0.26 (2:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.84 (d, *J* = 7.7 Hz, 2 H), 7.49 (t, *J* = 7.9 Hz, 2 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.06 (s, 1 H), 6.89 (s, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 152.0, 148.4, 146.6, 140.5, 129.5, 127.0, 120.0, 119.1, 117.4, 96.9, 95.8, 55.9; LRMS (EI) 254 (M); HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ (M) 254.1055, found 254.1059.

**5-Methyl-2-phenyl-*2H*-indazole and 6-methyl-2-phenyl-*2H*-indazole (3da + 3da').** Slightly yellow solid: $R_f$ = 0.26 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.32 (s, 1 H), 8.27 (s, 1 H), 7.89 (s, 2 H), 7.87 (s, 2 H), 7.71 (d, *J* = 8.9 Hz, 1 H), 7.59 (d, *J* = 8.6 Hz, 1 H), 7.53-7.47 (m, 4 H), 7.55 (s, 1 H), 7.43 (s, 1 H), 7.41-7.34 (m, 2 H), 7.17 (d, *J* = 8.6 Hz, 1 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 2.48 (s, 3 H), 2.43 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 150.3, 148.7, 140.5, 136.7, 131.7, 129.8, 129.4, 127.6, 125.4, 123.0, 121.1, 120.73, 120.70, 120.1, 119.8, 119.4, 118.3, 117.5, 116.1, 22.3, 21.8 (some overlap); LRMS (EI) 208 (M); HRMS (EI) calcd for $C_{14}H_{12}N_2$ (M) 208.1000, found 208.1003.

**5-Methoxy-2-phenyl-2*H*-indazole and 6-Methoxy-2-phenyl-2*H*-indazole (3ea + 3ea').** Yellow solid: $R_f$ = 0.25 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.27 (s, 1H), 8.22 (s, 0.8 H), 7.84 (d, *J* = 8.4 Hz, 3.6 H), 7.68 (d, *J* = 9.2 Hz, 0.8 H), 7.53 (d, *J* = 9.2 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 3.6 H), 7.36-7.32 (m, 1.8 H), 7.04-7.02 (m, 1.8 H), 6.86 (d, *J* = 2.0 Hz, 0.8 H), 6.80 (dd, *J* = 8.8, 1.6 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 2.4 H); $^{13}$C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 159.5, 155.6, 151.0, 146.9, 140.7, 140.6, 129.6, 127.6,

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127.5, 122.9, 122.2, 121.4, 120.7, 120.53, 120.50, 119.46, 119.41, 118.7, 118.0, 96.4, 94.7, 55.5, 55.4 (one overlapped signal); LRMS (ESI) 225 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M+H) 225.1022, found 225.1022.

**4-Methyl-2-phenyl-*2H*-indazole and 7-methyl-2-phenyl-*2H*-indazole (3fa + 3fa').** Yellow oil: $R_f$ = 0.35 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.35 (s, 1 H), 8.32 (s, 0.7 H), 7.88(dd, *J* = 8.4, 2.0 Hz, 3.4 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.52-7.46 (m, 4.1 H), 7.37-7.34 (m, 1.7 H), 7.23-7.19 (m, 1 H), 7.07-6.98 (m, 1.4 H), 6.84 (d, *J* = 6.8 Hz, 1 H), 2.68 (s, 2.1 H), 2.54 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 150.3, 150.0, 140.8, 140.7, 130.7, 129.7, 128.2, 127.93, 127.89, 127.4, 125.8, 124.3, 122.9, 122.7, 121.7, 121.3, 121.1, 120.9, 119.7, 117.9, 115.4, 19.3, 17.3; LRMS (ESI) 209 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2$ (M+H) 209.1073, found 209.1078.

**2-Phenyl-2*H*-benzo[*g*]indazole and 2-phenyl-2*H*-benzo[*e*]indazole (3ga + 3ga').** Yellow gel: $R_f$ = 0.42 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.74 (d, *J* = 8.0 Hz, 1 H), 8.71 (s, 1 H), 8.33 (s, 1 H), 8.12 (d, *J* = 7.6 Hz, 1 H), 7.93 (t, *J* = 7.2 Hz, 4 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 9.2 Hz, 1 H), 7.62 (m, 2 H), 7.52 (m, 8 H), 7.38 (m, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 148.9, 147.7, 140.7, 140.6, 132.9, 130.6, 129.72, 129.69, 129.3, 129.1, 128.6, 127.6, 127.5, 127.4, 127.2, 127.1, 126.9, 125.8, 125.6, 124.7, 123.6, 122.8, 121.2, 120.6, 120.5, 120.2, 120.0, 118.5, 117.9, 117.5; LRMS (ESI) 245 (M+H); HRMS (ESI) calcd for $C_{17}H_{13}N_2$ (M+H) 245.1073, found 245.1064.

**4-Methoxy-2-phenyl-*2H*-indazole (3ia).** Following the general procedure, this product was isolated as a white gel by collecting the first spot: $R_f$ = 0.24 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.89 (d, *J* = 8.1 Hz, 2 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.44-7.33 (m, 2 H),

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7.31-7.18 (m, 1 H), 6.35 (d, $J$ = 7.3 Hz, 1 H), 3.96 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.2, 140.4, 129.5, 127.70, 127.65, 120.7, 119.0, 116.8, 110.3, 98.8, 55.2; LRMS (EI) 224 (M), 209 (M-Me); HRMS (EI) calcd for $C_{14}H_{12}N_2O$ (M) 224.0950, found 224.0950. The 2D NMR spectra and the analysis are included in the SI.

**7-Methoxy-2-phenyl-*2H*-indazole (3ia').** The second spot of the aforementioned column chromatography afforded a yellow gel: $R_f$ = 0.12 (5:1 hexanes/EtOAc). This material was stirred with 1 mL of $Ac_2O$ and 1 mL of pyridine at room temperature for 30 min. Then the volatiles were evaporated under a vacuum, and the product purified by column chromatography: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.93 (d, $J$ = 8.0 Hz, 2 H), 7.49 (t, $J$ = 7.8 Hz, 2 H), 7.37 (t, $J$ = 7.4 Hz, 1 H), 7.26 (d, $J$ = 8.4 Hz, 1 H), 7.02 (dd, $J$ = 8.4, 0.8 Hz, 1 H), 6.58 (d, $J$ = 7.2 Hz, 1 H), 4.04 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.6, 143.5, 140.5, 129.6, 128.0, 124.5, 123.3, 121.2, 120.8, 112.5, 103.3, 55.7; LRMS (ESI) 225 (M+H), 247 (M+Na), 471 (2M+Na); HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M+H) 225.1022, found 225.1024. This regioisomer matches the reported $^1$H and $^{13}$C NMR spectral data.[18]

**4-Methoxy-2-(4-methylphenyl)-*2H*-indazole (3id).** Following the general procedure, this product was isolated as a white gel by collecting the first spot: $R_f$ = 0.30 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1 H), 7.76 (d, $J$ = 7.6 Hz, 2 H), 7.36 (d, $J$ = 8.4 Hz, 1 H), 7.29 (d, $J$ = 7.6 Hz, 2 H), 7.24-7.20 (m, 1 H), 6.34 (d, $J$ = 7.2 Hz, 1 H), 3.94 (s, 3 H), 2.40 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.6, 151.3, 138.3, 137.9, 130.2, 127.7, 120.8, 119.1, 116.9, 110.4, 98.9, 55.4, 21.2; LRMS (ESI) 239 (M+H); HRMS (ESI) calcd for $C_{15}H_{15}N_2O$ (M+H) 239.1179, found 239.1179.

**7-Methoxy-2-(4-methylphenyl)-*2H*-indazole (3id').** The second spot of the aforementioned

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column chromatography afforded a yellow gel: $R_f$ = 0.22 (5:1 hexanes/EtOAc). This material was stirred with 1 mL of $Ac_2O$ and 1 mL of pyridine at room temperature for 30 min. Then the volatiles were evaporated under vacuum, and the product purified by column chromatography: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.26 (t, *J* = 9.2 Hz, 3 H), 7.01 (t, *J* = 7.8 Hz, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 4.03 (s, 3 H), 2.39 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.5, 143.3, 138.3, 137.9, 130.0, 124.4, 123.1, 121.0, 120.6, 112.4, 103.1, 55.6, 21.2; LRMS (ESI) 239 (M+H), 261 (M+Na); HRMS (ESI) calcd for $C_{15}H_{14}N_2ONa$ (M+Na) 261.0998, found 261.0999.

**Procedure for the Suzuki-Miyaura Coupling with Boronic Acids.** To a 4 dram vial were added the starting material **3at** (~0.4 mmol), the boronic acid (1.5 equiv.), KOH (3.0 equiv.) and $Pd(PPh_3)_4$ (5 mol %) in 20 : 5 : 1 toluene/ethanol/$H_2O$ (4 mL in total). The solution was vigorously stirred for 5 min at room temperature, flushed with argon and sealed, and then heated to 80 ºC until TLC revealed complete conversion of the starting material. Upon cooling to room temperature, the resulting reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the following product.

**3-(3,4-Methylenedioxyphenyl)-2-phenyl-2*H*-indazole (4at).** Following the general procedure, this product was isolated as a brown solid: mp 154-156 ºC; $R_f$ = 0.31 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.45 (d, *J* = 6.8 Hz, 2 H), 7.42-7.33 (m, 4 H), 7.12 (dd, *J* = 8.0, 7.2 Hz, 1 H), 6.87-6.81 (m, 2 H), 6.78 (s, 1 H), 5.98 (s, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.1, 147.9, 140.2, 135.3, 129.2, 128.4, 127.2, 126.1, 124.0, 123.5, 122.5, 121.8, 120.6, 117.8, 110.0, 108.9, 101.5; LRMS (ESI) 315 (M+H); HRMS

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(ESI) calcd for $C_{20}H_{15}N_2O_2$ (M+H) 315.1128, found 315.1125.

**Procedure for the Sonogashira Coupling with a Terminal Alkyne.** To a 4 dram vial was added the starting material **3at** (~0.4 mmol), the alkyne (1.2 equiv.), $PdCl_2(PPh_3)_2$ (3 mol %), CuI (3 mol %), DMF (1.5 mL) and $Et_2NH$ (1.5 mL). The solution was stirred at room temperature, flushed with argon and sealed, and then heated to 60 ºC until TLC analysis revealed complete conversion of the starting material. The solution was allowed to cool and diluted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the following product.

**3-(3-Methoxyprop-1-ynyl)-2-phenyl-2*H*-indazole (5at).** Yellow oil: $R_f$ = 0.25 (5:1 hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 2 H), 7.78 (dd, *J* = 15.6, 8.8 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 2 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 4.41 (s, 2 H), 3.43 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 148.7, 140.2, 129.2, 128.9, 127.5, 126.1, 124.7, 123.6, 120.2, 118.5, 117.7, 96.7, 75.4, 60.7, 58.0; LRMS (ESI) 263 (M+H); HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ (M+H) 263.1179, found 263.1180.

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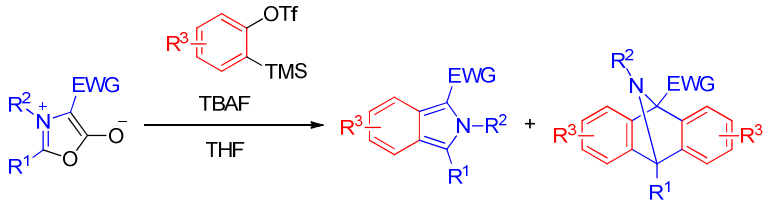
# CHAPTER 5

## Synthesis of Isoindoles and 9,10-Dihydro-9,10-epiminoanthracenes by Aryne Dipolar Cycloaddition with Münchnones

Yuesi Fang, and Richard C. Larock,*

Department of Chemistry, Iowa State University, Ames, IA 50010, U.S.A.

### 5.1. Abstract




Münchnones react with arynes under mild reaction conditions to afford 1:1 and 1:2 adducts. The 1:1 adduct, a 2*H*-isoindole, is formed by a [3 + 2] cycloaddition/[4 + 2] cycloreversion sequence, while the 1:2 adduct, a 9,10-dihydro-9,10-epiminoanthracene, is formed by a further [4 + 2] cycloaddition of the isoindole with the aryne.

### 5.2. Introduction

Recently, we have reported that the cycloaddition of arynes and sydnones affords high yields of isoindazoles.[1] As another representative cyclic 1,3-dipole,[2] münchnones have also attracted significant attention from the synthetic community.[3] With our continuing interest in aryne cycloaddition chemistry, we were encouraged to examine the aryne cycloaddition chemistry of münchnones, which might hopefully lead to the formation of 2*H*-isoindoles.[4]

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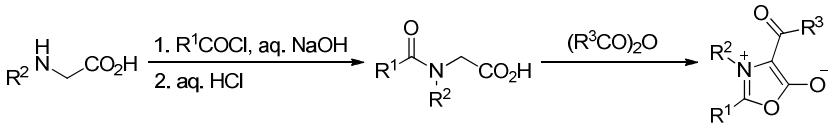
## 5.3. Results and Discussion

**Preparation of the Münchnones.** Münchnones can be prepared from amino acids as shown in Scheme 1. Münchnones with electron-withdrawing groups at the 4-position can be isolated as crystalline materials and exhibit satisfactory bench top stability. We started by preparing münchnones from sarcosine and benzoyl chloride, followed by treatment with acetic and trifluoroacetic anhydride, which lead to the münchnones **1a** ($R^1$ = Ph, $R^2$ = Me, $R^3$ = Me) and **1b** ($R^1$ = Ph, $R^2$ = Me, $R^3$ = $CF_3$).[5] Using a number of other aroyl chlorides and butyric anhydride, we were able to prepare a number of other closely related münchnones in good to excellent yields. Unfortunately, the preparation of münchnones with more diverse substitution has not been successful. Because an aqueous solution is used in the first step, the range of starting materials that can be employed is quite limited due to rapid hydrolysis of the acyl chloride.

While keeping in mind that for sydnones the presence of electron-withdrawing groups at the 4-position shuts down the aryne cycloaddition process,[1] we hoped that replacement of the nitrogen of the sydnones by a carbon (position-2) in the preparation of münchnones would allow for a slight increase in the electron density of the latter and thus provide the desired reactivity with arynes.

**Scheme 1.** Preparation of Münchnones.




$R^1$ = Ph, $R^2$ = Me, $R^3$ = Me; **1a**, 82%
$R^1$ = Ph, $R^2$ = Me, $R^3$ = $CF_3$; **1b**, 85%
$R^1$ = 4-$ClC_6H_4$, $R^2$ = Me, $R^3$ = Me; **1c**, 86%
$R^1$ = 4-$FC_6H_4$, $R^2$ = Me, $R^3$ = Me; **1d**, 78%
$R^1$ = 4-$MeC_6H_4$, $R^2$ = Me, $R^3$ = Me; **1e**, 90%
$R^1$ = 3-$MeC_6H_4$, $R^2$ = Me, $R^3$ = Me; **1f**, 92%
$R^1$ = Ph, $R^2$ = Me, $R^3$ = nPr; **1g**, 45%
$R^1$ = Thiophen-2-yl, $R^2$ = Me, $R^3$ = Me; **1h**, 79%

**Reaction and Mechanism.** Indeed, although münchnone **1b** proved unreactive towards

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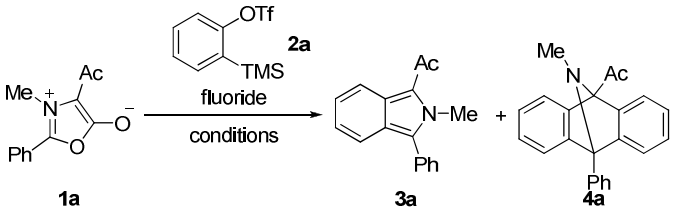
benzyne under the standard reaction conditions that were used for sydnones, münchnone **1a** reacted smoothly with benzyne to afford two products, which were identified as isoindole **3a** and a 1:2 adduct 9,10-dihydro-9,10-epiminoanthracene **4a** (Table 1, entry 1). The formation of these two products can be explained by the mechanism illustrated in Scheme 2. Thus, isoindole **3a** is first formed by a [3 + 2] cycloaddition/[4 + 2] cycloreversion sequence, while the 1:2 adduct **4a** is apparently formed by further [4 + 2] cycloaddition of the isoindole with benzyne, a process which has been observed previously.[4a,6] The ratio of the two products depends on the reaction conditions and the stoichiometry as summarized in Table 1. Using a 2-fold excess of the aryne led to the exclusive formation of **4a** in a high yield (entry 5).

**Table 1.** Survey of the Reaction Conditions.[a]




| entry | **1a** : **2a** | $F^-$/equiv | solvent, temp | **3a** (%[b]) | **4a** (%[b]) |
|---|---|---|---|---|---|
| 1 | 1 : 1 | TBAF/1.5 | THF, rt | 25 | 31 |
| 2 | 1 : 1 | CsF/1.5 | MeCN, rt | 24 | 27 |
| 3 | 1 : 1.5 | TBAF/2.2 | THF, rt | 40 | 47 |
| 4 | 1 : 2 | TBAF/3.0 | THF, rt | - | 76 |
| 5 | 1 : 3 | TBAF/4.5 | THF, rt | - | 86 |
| 6 | 1.1 : 1 | TBAF/1.6 | THF, rt | 21 | 27 |
| 7 | 1.5 : 1 | TBAF/2.2 | THF, -78 ºC to rt | 33 | 42 |

[a] All reactions were carried out on a 0.25 mmol scale in 4 mL of the solvent for 1 d. [b] Isolated yield.

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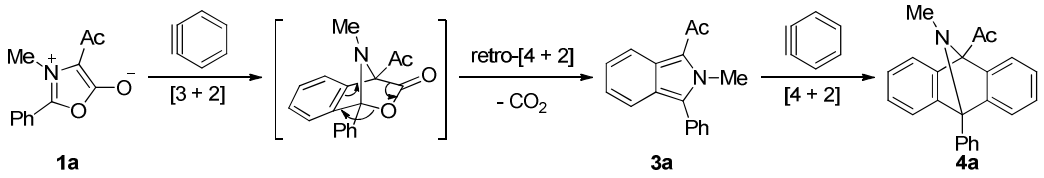
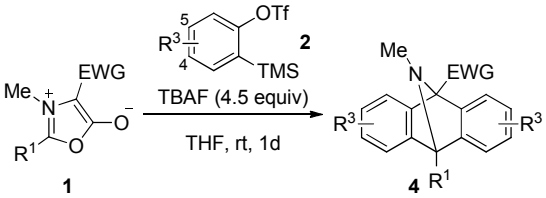
**Scheme 2.** Reaction Mechanism.




**Scope and Limitations.** The scope of the 9,10-dihydro-9,10-epiminoanthracene synthesis has been briefly examined (Table 2). While the presence of a trifluoroacetyl group in the 4 position of the münchnone gave none of the desired tricyclic product (entry 1), an electron-withdrawing acetyl group works well and the acetyl group can be replaced by a butyryl group (**4f**, entry 6). The reaction affords good yields of 9,10-dihydro-9,10-epiminoanthracenes with a variety of aryl groups present in the 2 position ($R^1$) of the münchnone, including phenyl groups with electron-withdrawing (**4b** and **4c**, entries 2 and 3) and -donating (**4d** and **4e**, entries 4 and 5) groups. A heteroaryl group (**4g**) can also be employed in this reaction (entry 7). Different arynes have been examined in this reaction and been found to afford products **4h** through **4j** in high yields (entries 8-10). Unfortunately, it is difficult to prepare münchnones with a wide variety of other substituents present in order to more fully explore the scope of this process.

**Table 2.** Synthesis of 9,10-Dihydro-9,10-epiminoanthracenes.[a]



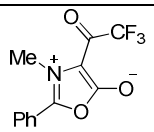

| entry | münchnone | aryne precursor | product | yield[b] (%) |
|---|---|---|---|---|
| 1 |  **1b** | **2a** | nr | -[c] |

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Table 2 continued

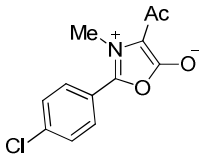
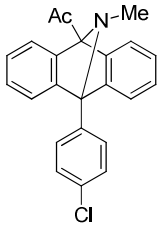
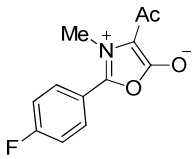
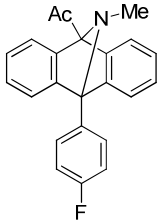
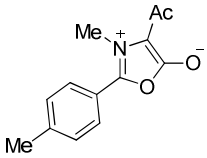
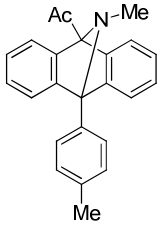
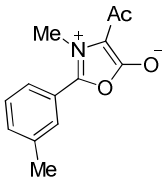
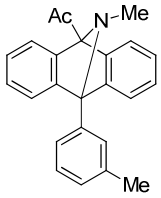
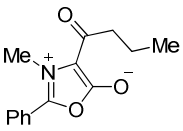
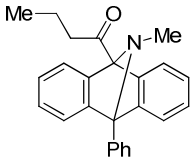
| | | | | |
|---|---|---|---|---|
| 2 |  **1c** | **2a** |  **4b** | 75 |
| 3 |  **1d** | **2a** |  **4c** | 76 |
| 4 |  **1e** | **2a** |  **4d** | 88 |
| 5 |  **1f** | **2a** |  **4e** | 89 |
| 6 |  **1g** | **2a** |  **4f** | 92 |

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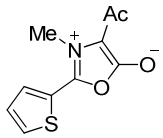
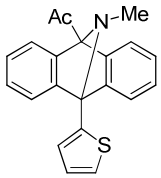
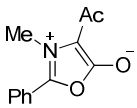
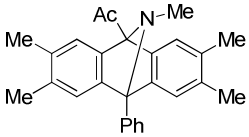
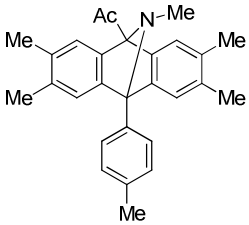
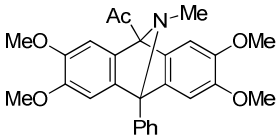
Table 2 continued

| | | | | |
|---|---|---|---|---|
| 7 |  **1h** | **2a** |  **4g** | 60 |
| 8 |  **1a** | **2b** |  **4h** | 88 |
| 9 | **1e** | **2b** |  **4i** | 85 |
| 10 | **1a** | **2c** |  **4j** | 75 |

[a] All reactions were carried out on a 0.25 mmol scale in 4 mL of THF with 3 equiv of aryne precursor and 4.5 equiv of TBAF. [b] Isolated yield. [c] All münchnone starting material was recovered.

The scope of the 2*H*-isoindole (**3**) synthesis has also been briefly examined on selected münchnones using only 1.5 equiv of two different aryne precursors (Table 3). Some reactions afford modest yields to isoindoles, which exhibit various levels of instability. Although carefully controlling the stoichiometry, we failed to obtain decent amounts of the desired 2*H*-isoindoles **3b**

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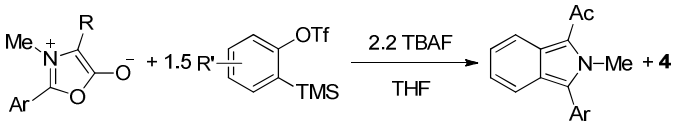
and **3c** from münchnones bearing electron-deficient aromatic groups (entries 1 and 2). Both münchnones afforded predominantly the 1:2 adducts **4b** and **4c** under our reaction conditions. Similar results have been seen when using a thiophene-containing starting material (entry 6). However, modest amounts of the 2*H*-isoindoles **3d**, **3e**, and **3f** have been obtained when using tolyl-substituted münchnones or a benzoyl-substituted substrate, although these products were accompanied by large amounts of the corresponding 9,10-dihydro-9,10-epiminoanthracenes **4** (entries 3-5). A similar pattern of reactivity has been observed when using a dimethyl-substituted aryne precursor (entries 7 and 8).

**Table 3.** Synthesis of 2*H*-Isoindoles.[a]




**1** **2** **3**

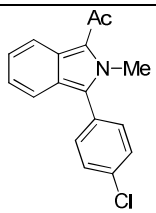
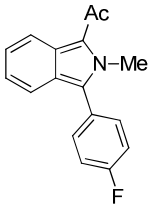
| entry | münchnone | aryne precursor | product **3** | yield[b] (%) | product **4** (% yield[c]) |
|---|---|---|---|---|---|
| 1 | **1c** | **2a** |  **3b** | 8[d] | **4b** (52%) |
| 2 | **1d** | **2a** |  **3c** | trace[d] | **4c** (55%) |

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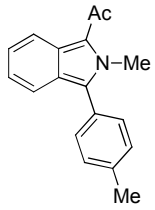
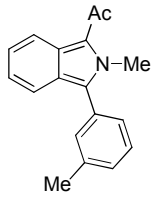
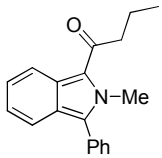
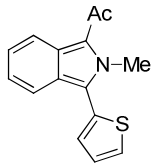
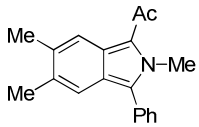
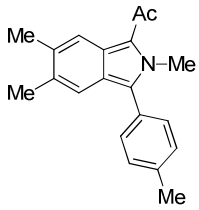
Table 3 continued

| | | | | | |
|---|---|---|---|---|---|
| 3 | **1e** | **2a** |  **3d** | 37 | **4d** (48%) |
| 4 | **1f** | **2a** |  **3e** | 41 | **4e** (46%) |
| 5 | **1g** | **2a** |  **3f** | 33 | **4f** (53%) |
| 6 | **1h** | **2a** |  **3g** | 9[d] | **4g** (42%) |
| 7 | **1a** | **2b** |  **3h** | trace[d] | **4h** (62%) |
| 8 | **1e** | **2b** |  **3i** | 15 | **4i** (57%) |

[a] All reactions were carried out on a 0.25 mmol scale in 4 mL of THF with 1.5 equiv of aryne precursor and 2.2 equiv of TBAF. [b] Isolated yield. [c] GC yield. [d] Detected by GC-MS.

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## 5.4. Conclusions

In summary, we have shown that münchnones and arynes react under mild reaction conditions to afford 2*H*-isoindoles by a [3 + 2] cycloaddition/[4 + 2] cycloreversion sequence. However, these compounds are highly reactive towards arynes under our reaction conditions and can thus only be obtained in relatively low yields. Instead, they readily react further with an excess of aryne to afford 9,10-dihydro-9,10-epiminoanthracenes in good to excellent yields by a [4 + 2] cycloaddition.

## 5.5. Experimental Section

**General Information.** The solvent THF was distilled over Na/benzophenone, and dichloromethane was distilled over $CaH_2$. Anhydrous MeCN and the aryne precursors were used as received from commercial sources. Silica gel for column chromatography was supplied as 230-400 mesh from a commercial source. Powdered CsF and TBAF (1 M in THF solution) were used as received and stored in a desiccator.

All melting points are uncorrected. The $^{1}H$ and $^{13}C$ NMR spectra were recorded and are referenced to the residual solvent signals (7.26 ppm for $^{1}H$ and 77.2 ppm for $^{13}C$ in $CDCl_3$). A QTOF analyzer was used for all of the HRMS measurements.

**Synthesis of the Münchnones.** Compounds **1a** through **1h** were prepared as follows.

**4-Acetyl-3-methyl-2-phenylmünchnone (1a).** To a solution of 1.335 g (15 mmol) of sarcosine and 1 g (25 mmol) of NaOH in 20 mL of water was added 1.4 g (10 mmol) of benzoyl chloride in one portion. The mixture was allowed to stir for 12 h before acidifying with 10% aq HCl and extracting three times with EtOAc. The combined organic layers were evaporated under high

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vacuum to obtain 1.9 g (9.8 mmol) of *N*-methylhippuric acid as a white solid. This compound was dissolved in 20 mL of acetic anhydride and allowed to stir at 100 ºC for 1 h before being poured into ice water. Solid $NaHCO_3$ was added to neutralize the mixture and 1.78 g (8.2 mmol, 82% overall yield) of münchnone **1a** was obtained as a yellow solid after filtration: mp 118-120 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.71-7.58 (m, 5 H), 4.14 (s, 3 H), 2.47 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.5, 161.8, 133.3, 129.7, 129.3, 121.5, 109.5, 99.8, 37.2, 27.7; HRMS (ESI) calcd for $C_{12}H_{12}NO_3$ (M+H) 218.0812, found 218.0810.

**3-Methyl-2-phenyl-4-(2,2,2-trifluoroacetyl)münchnone (1b).** This münchnone was prepared according to a literature procedure[5] as a pale white solid (85% overall yield).

**4-Acetyl-2-(4-chlorophenyl)-3-methylmünchnone (1c).** The above procedure was applied to 1.335 g (15 mmol) of sarcosine and 1.75 g (10 mmol) of 4-chlorobenzoyl chloride, followed by 20 mL of acetic anhydride, to afford 2.16 g (8.6 mmol, 86% overall yield) of münchnone **1c** as a yellow solid: mp 101-103 ºC; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, $J$ = 8.8 Hz, 2 H), 7.58 (d, $J$ = 8.8 Hz, 2 H), 4.14 (s, 3 H), 2.46 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.6, 161.6, 148.5, 140.0, 130.5, 130.2, 119.8, 99.8, 37.2, 27.6; HRMS (ESI) calcd for $C_{12}H_{11}ClNO_3$ (M+H) 252.0422, found 252.0415.

**4-Acetyl-2-(4-fluorophenyl)-3-methylmünchnone (1d).** The above procedure was applied to 1.335 g (15 mmol) of sarcosine and 1.59 g (10 mmol) of 4-fluorobenzoyl chloride, followed by 20 mL of acetic anhydride, to afford 1.83 g (7.8 mmol, 78% overall yield) of münchnone **1d** as a soft yellow material: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, $J$ = 5.6 Hz, 2 H), 7.29 (t, $J$ = 8.0 Hz, 2 H), 4.12 (s, 3 H), 2.45 (s, 3 H); the $^{13}$C NMR spectrum could not be obtained due to decomposition; HRMS (ESI) calcd for $C_{12}H_{11}FNO_3$ (M+H) 236.0717, found 236.0713.

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**4-Acetyl-3-methyl-2-(*p*-tolyl)münchnone (1e).** The above procedure was applied to 1.335 g (15 mmol) of sarcosine and 1.54 g (10 mmol) of 4-methylbenzoyl chloride, followed by 20 mL of acetic anhydride, to afford 2.08 g (9.0 mmol, 90% overall yield) of münchnone **1e** as a yellow solid: mp 135-137 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 4.13 (s, 3 H), 2.47 (s, 3 H), 2.46 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.4, 161.8, 149.9, 144.5, 130.4, 129.2, 118.6, 99.7, 37.2, 27.6, 22.0; HRMS (ESI) calcd for $C_{13}H_{14}NO_3$ (M+H) 232.0968, found 232.0963.

**4-Acetyl-3-methyl-2-(*m*-tolyl)münchnone (1f).** The above procedure was applied to 1.335 g (15 mmol) of sarcosine and 1.54 g (10 mmol) of 3-methylbenzoyl chloride, followed by 20 mL of acetic anhydride, to afford 2.12 g (9.2 mmol, 92% overall yield) of münchnone **1f** as a yellow solid: mp 108-109 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.0 Hz, 1 H), 7.49-7.45 (m, 3 H), 4.13 (s, 3 H), 2.47 (s, 3 H), 2.46 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.4, 161.8, 149.8, 139.9, 134.2, 129.8, 129.5, 126.4, 121.4, 99.8, 37.2, 27.6, 21.6; HRMS (ESI) calcd for $C_{13}H_{14}NO_3$ (M+H) 232.0968, found 232.0965.

**4-Butyryl-3-methyl-2-phenylmünchnone (1g).** The above procedure was applied to 1.335 g (15 mmol) of sarcosine and 1.4 g (10 mmol) of benzoyl chloride, followed by 20 mL of butyric anhydride, to afford 1.1 g (4.5 mmol, 45% overall yield) of münchnone **1g** as a soft yellow material: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.71-7.59 (m, 5 H), 4.15 (s, 3 H), 2.82 (t, *J* = 7.5 Hz, 2 H), 1.71 (tq, *J* = 7.5, 7.2 Hz, 2 H), 1.00 (t, *J* = 7.5 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.8, 161.5, 149.6, 133.2, 129.6, 129.3, 121.6, 99.7, 41.3, 37.3, 18.4, 14.1; HRMS (ESI) calcd for $C_{14}H_{16}NO_3$ (M+H) 246.1125, found 246.1118.

**4-Acetyl-3-methyl-2-(thiophen-2-yl)münchnone (1h).** The above procedure was applied to

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1.335 g (15 mmol) of sarcosine and 1.46 g (10 mmol) of thiophene-2-carbonyl chloride, followed by 20 mL of acetic anhydride, to afford 1.76 g (7.9 mmol, 79% overall yield) of münchnone **1h** as a yellow solid: mp 142-143 ºC; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.81-7.78 (m, 2 H), 7.29 (dd, *J* = 5.2, 4.0 Hz, 1 H), 4.28 (s, 3 H), 2.45 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.1, 161.1, 144.9, 133.7, 133.6, 129.1, 122.2, 99.1, 35.9, 27.7; HRMS (ESI) calcd for $C_{10}H_{10}NO_3S$ (M+H) 224.0376, found 224.0370.

**Synthesis of the 9,10-Dihydro-9,10-epiminoanthracenes.**

Compounds **4a** through **4j** were prepared according to the following representative procedure. To an oven-dried vial was added sequentially 0.75 mmol of the aryne precursor, 0.25 mmol of münchnone, 3 mL of THF, and 1.125 mL of 1M TBAF/THF solution (1.125 mmol). A nitrogen atmosphere was not required, except that a balloon of nitrogen was attached to the reaction vial for ventilation of the $CO_2$. The reaction was allowed to stir for 24 h before being quenched with aq $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/ EtOAc) to afford the desired products.

**1-(11-Methyl-10-phenyl-9,10-dihydro-9,10-epiminoanthracen-9-yl)ethanone (4a).** The representative procedure was applied to 54.3 mg (0.25 mmol) of münchnone **1a** to afford 69.9 mg (0.22 mmol, 86% yield) of compound **4a** as a yellow solid: mp 111-113 ºC; $R_f$ = 0.62 (2:1 petroleum ether/EtOAc); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 7.56 (t, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 6.8 Hz, 2 H), 7.18-7.02 (br m, 6 H), 2.55 (s, 3 H), 2.02 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 207.0, 150.7, 150.0, 146.9, 146.2, 132.7, 130.1, 128.9, 128.7, 126.05, 125.98, 125.88, 125.7, 125.6, 124.9, 122.1, 119.3, 84.3, 81.6, 32.4, 28.3; HRMS (ESI)

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calcd for $C_{23}H_{20}NO$ (M+H) 326.1539, found 326.1532.

**1-[10-(4-Chlorophenyl)-11-methyl-9,10-dihydro-9,10-epiminoanthracen-9-yl]ethanone (4b).** The representative procedure was applied to 62.9 mg (0.25 mmol) of münchnone **1c** to afford 67.5 mg (0.19 mmol, 75% yield) of compound **4b** as a yellow solid: mp 118-120 ºC; $R_f$ = 0.4 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.12-7.03 (br m, 6 H), 2.53 (s, 3 H), 1.99 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.3, 151.2, 150.0, 147.0, 146.5, 134.8, 132.2, 131.5, 129.1, 126.1, 125.83, 125.78, 124.6, 121.7, 119.4, 84.7, 81.4, 32.4, 28.1; HRMS (ESI) calcd for $C_{23}H_{19}ClNO$ (M+H) 360.1150, found 360.1143.

**1-[10-(4-Fluorophenyl)-11-methyl-9,10-dihydro-9,10-epiminoanthracen-9-yl]ethanone (4c).** The representative procedure was applied to 58.8 mg (0.25 mmol) of münchnone **1d** to afford 65.2 mg (0.19 mmol, 76% yield) of compound **4c** as a yellow gel-like material: $R_f$ = 0.3 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.85 (td, *J* = 7.2, 2.4 Hz, 2 H), 7.43 (br s, 1 H), 7.24 (t, *J* = 8.4 Hz, 2 H), 7.10-7.06 (br m, 6 H), 2.53 (s, 3 H), 1.99 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.3, 164.2, 161.7, 151.3, 150.1, 147.2, 146.6, 132.05, 131.97, 130.5, 129.7, 129.4, 129.3, 126.1, 124.7, 121.8, 119.4, 115.9, 115.7, 84.6, 81.4, 32.3, 28.1; HRMS (ESI) calcd for $C_{23}H_{19}FNO$ (M+H) 344.1445, found 344.1455.

**1-[11-Methyl-10-(*p*-tolyl)-9,10-dihydro-9,10-epiminoanthracen-9-yl]ethanone (4d).** The representative procedure was applied to 57.8 mg (0.25 mmol) of münchnone **1e** to afford 74.6 mg (0.22 mmol, 88% yield) of compound **4d** as a yellow solid: mp 87-89 ºC; $R_f$ = 0.28 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.47 (br s, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.26-7.06 (br m, 6 H), 2.55 (s, 3 H), 2.48 (s, 3 H), 2.02 (s, 3 H); $^{13}$C

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NMR (100 MHz, $CDCl_3$) δ 206.6, 151.6, 150.2, 147.6, 146.7, 138.4, 130.4, 130.0, 129.5, 126.0, 125.7, 125.6, 124.8, 122.0, 119.3, 84.7, 81.7, 32.4, 28.1, 21.4; HRMS (ESI) calcd for $C_{24}H_{22}NO$ (M+H) 340.1696, found 340.1694.

**1-[11-Methyl-10-(*m*-tolyl)-9,10-dihydro-9,10-epiminoanthracen-9-yl]ethanone (4e).** The representative procedure was applied to 57.7 mg (0.25 mmol) of münchnone **1f** to afford 75.5 mg (0.22 mmol, 89% yield) of compound **4e** as a yellow solid: mp 146-148 ºC; $R_f$ = 0.3 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 7.50 (br s, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.20-7.03 (br m, 6 H), 2.55 (s, 3 H), 2.47 (s, 3 H), 2.03 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.6, 151.6, 150.1, 147.5, 146.7, 138.5, 133.4, 130.6, 129.5, 129.4, 128.7, 127.2, 126.0, 124.9, 122.0, 119.3, 84.7, 81.9, 32.5, 28.1, 21.8; HRMS (ESI) calcd for $C_{24}H_{22}NO$ (M+H) 340.1696, found 340.1690.

**1-[11-Methyl-10-phenyl-9,10-dihydro-9,10-epiminoanthracen-9-yl]butan-1-one (4f).** The representative procedure was applied to 61.2 mg (0.25 mmol) of münchnone **1g** to afford 81.3 mg (0.23 mmol, 92% yield) of compound **4f** as a yellow solid: mp 160-161 ºC; $R_f$ = 0.41 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1 H), 7.88 (dd, *J* = 7.2, 1.6 Hz, 2 H), 7.56 (t, *J* = 7.2 Hz, 2 H), 7.49 (t, *J* = 6.8 Hz, 2 H), 7.15-6.99 (br m, 6 H), 2.99-2.85 (m, 2 H), 2.01 (s, 3 H), 1.82 (tq, *J* = 7.6, 7.2 Hz, 2 H), 1.02 (t, *J* = 7.6 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 208.6, 151.5, 150.5, 147.4, 147.0, 133.6, 130.1, 128.8, 128.6, 125.9, 124.8, 121.9, 119.4, 84.5, 81.9, 41.9, 32.5, 16.8, 14.0; HRMS (ESI) calcd for $C_{25}H_{24}NO$ (M+H) 354.1852, found 354.1862.

**1-[11-Methyl-10-(thiophen-2-yl)-9,10-dihydro-9,10-epiminoanthracen-9-yl]ethanone (4g).** The representative procedure was applied to 55.8 mg (0.25 mmol) of münchnone **1h** to afford 49.6 mg (0.15 mmol, 60% yield) of compound **4g** as a yellow gel-like material: $R_f$ = 0.5 (2:1 petroleum

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ether/EtOAc); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1 H), 7.58 (br s, 1 H), 7.53 (td, *J* = 4.8, 1.2 Hz, 2 H), 7.32 (br s, 1 H), 7.13-7.03 (br m, 5 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 2.53 (s, 3 H), 2.04 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.3, 156.0, 151.3, 149.4, 147.4, 145.7, 136.4, 129.8, 129.4, 127.4, 127.2, 126.2, 124.2, 121.7, 120.6, 119.3, 115.5, 84.4, 78.9, 32.4, 28.1; HRMS (ESI) calcd for $C_{21}H_{18}NOS$ (M+H) 332.1104, found 332.1104.

**1-(2,3,6,7,11-Pentamethyl-10-phenyl-9,10-dihydro-9,10-epiminoanthracen-9-yl)ethanone (4h).** The representative procedure was applied to 54.3 mg (0.25 mmol) of münchnone **1a** to afford 83.9 mg (0.22 mmol, 88% yield) of compound **4h** as a yellow solid: mp 226-227 ºC; $R_f$ = 0.54 (2:1 petroleum ether/EtOAc); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.6 Hz, 2 H), 7.74 (s, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.21 (s, 1 H), 6.89 (d, *J* = 4.0 Hz, 1 H), 6.85 (d, *J* = 6.8 Hz, 1 H), 2.51 (s, 3 H), 2.16-2.10 (br m, 12 H), 1.99 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 207.1, 149.3, 148.1, 145.1, 144.4, 133.9, 133.6, 133.4, 130.2, 128.7, 128.5, 128.0, 127.0, 126.2, 123.4, 120.7, 116.8, 84.6, 81.7, 32.5, 28.1, 20.04, 20.02; HRMS (ESI) calcd for $C_{27}H_{28}NO$ (M+H) 382.2165, found 382.2175.

**1-(2,3,6,7,11-Pentamethyl-10-(*p*-tolyl)-9,10-dihydro-9,10-epiminoanthracen-9-yl)ethanone (4i).** The representative procedure was applied to 57.8 mg (0.25 mmol) of münchnone **1e** to afford 84.0 mg (0.21 mmol, 85% yield) of compound **4i** as a yellow solid: mp 190-191 ºC; $R_f$ = 0.31 (5:1 petroleum ether/EtOAc); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.22 (s, 1 H), 6.94 (s, 1 H), 6.87 (s, 1 H), 6.38 (s, 1 H), 2.54 (s, 3 H), 2.48 (s, 3 H), 2.22-2.14 (br m, 12 H), 2.01 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 207.2, 154.2, 149.4, 148.1, 145.2, 144.4, 138.3, 137.8, 133.8, 133.6, 133.4, 130.8, 130.1, 129.4, 128.0, 127.0, 126.3, 84.6, 81.5, 32.4, 28.1, 21.5, 20.1, 20.0; HRMS (ESI) calcd for $C_{28}H_{30}NO$ (M+H) 396.2322, found

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396.2327.

**1-(2,3,6,7-Tetramethoxy-11-methyl-10-phenyl-9,10-dihydro-9,10-epiminoanthracen-9-yl) ethanone (4j).** The representative procedure was applied to 54.3 mg (0.25 mmol) of münchnone **1a** to afford 83.5 mg (0.19 mmol, 75% yield) of compound **4j** as a yellow gel-like material: $R_f$ = 0.2 (2:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.67 (s, 1 H), 7.57 (t, *J* = 7.6 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.04 (s, 1 H), 6.77 (s, 1 H), 6.67 (s, 1 H), 3.89-3.75 (br m, 12 H), 2.52 (s, 3 H), 1.99 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 207.4, 146.7, 146.5, 146.4, 146.2, 144.5, 143.5, 140.1, 140.0, 133.7, 130.0, 129.0, 128.7, 110.3, 109.9, 107.3, 104.6, 84.8, 82.2, 56.6, 56.5, 32.6, 28.1; HRMS (ESI) calcd for $C_{27}H_{28}NO_5$ (M+H) 446.1962, found 446.1966.

Compounds **3a**, **3d**, **3e**, **3f**, and **3i** were prepared according to the following representative procedure. To an oven-dried vial was added sequentially 0.375 mmol of the aryne precursor, 0.25 mmol of münchnone, 3.5 mL of THF, and 0.55 mL of 1M TBAF/THF solution (0.55 mmol). A nitrogen atmosphere was not required, except that a balloon of nitrogen was attached to the reaction vial for ventilation of the $CO_2$. The reaction was allowed to stir for 24 h before being quenched with aq $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/ EtOAc) to afford the desired products.

**1-(2-Methyl-3-phenyl-2*H*-isoindol-1-yl)ethanone (3a).** The representative procedure was applied to 54.3 mg (0.25 mmol) of münchnone **1a** to afford 24.9 mg (0.10 mmol, 40% yield) of compound **3a** as a yellow solid: mp 105-107 ºC; $R_f$ = 0.15 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 1 H), 7.58-7.54 (m, 3 H), 7.52-7.48 (m, 3 H), 7.35 (tq, *J* =

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7.6, 1.2 Hz, 1 H), 7.11 (tq, $J$ = 7.6, 1.2 Hz, 1 H), 4.18 (s, 3 H), 2.78 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.7, 135.9, 133.5, 130.8, 130.0, 129.2, 129.1, 126.6, 124.3, 122.2, 121.8, 121.4, 119.9, 37.4, 31.0; HRMS (ESI) calcd for $C_{17}H_{16}NO$ (M+H) 250.1226, found 150.1227.

**1-[2-Methyl-3-(*p*-tolyl)-2*H*-isoindol-1-yl]ethanone (3d).** The representative procedure was applied to 57.8 mg (0.25 mmol) of münchnone **1e** to afford 24.4 mg (0.09 mmol, 37% yield) of compound **3d** as a green solid: mp 86-88 ºC; $R_f$ = 0.14 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 ($J$ = 8.8 Hz, 1 H), 7.57 (d, $J$ = 8.4 Hz, 1 H), 7.40-7.33 (m, 5 H), 7.10 (tq, $J$ = 7.6, 0.8 Hz, 1 H), 4.17 (s, 3 H), 2.77 (s, 3 H), 2.47 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.5, 139.2, 136.3, 130.6, 129.8, 129.2, 127.0, 126.6, 124.3, 122.0, 121.6, 121.5, 119.8, 37.4, 30.9, 21.6; HRMS (ESI) calcd for $C_{18}H_{18}NO$ (M+H) 264.1383, found 264.1385.

**1-[2-Methyl-3-(*m*-tolyl)-2*H*-isoindol-1-yl]ethanone (3e).** The representative procedure was applied to 57.8 mg (0.25 mmol) of münchnone **1f** to afford 27.0 mg (0.10 mmol, 41% yield) of compound **3e** as a green solid: mp 68-70 ºC; $R_f$ = 0.19 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, $J$ = 8.8 Hz, 1 H), 7.57 (d, $J$ = 8.4 Hz, 1 H), 7.44 (t, $J$ = 7.2 Hz, 1 H), 7.37-7.26 (m, 4 H), 7.10 (t, $J$ = 7.6 Hz, 1 H), 4.18 (s, 3 H), 2.78 (s, 3 H), 2.46 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.6, 138.8, 136.3, 131.3, 130.0, 129.9, 129.2, 128.9, 127.9, 126.6, 124.4, 122.0, 121.7, 121.5, 119.8, 37.4, 30.9, 21.7; HRMS (ESI) calcd for $C_{18}H_{18}NO$ (M+H) 264.1383, found 264.1384.

**1-(2-Methyl-3-phenyl-2*H*-isoindol-1-yl)butan-1-one (3f).** The representative procedure was applied to 61.2 mg (0.25 mmol) of münchnone **1g** to afford 22.9 mg (0.08 mmol, 33% yield) of compound **3f** as a blue solid: mp 79-81 ºC; $R_f$ = 0.27 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, $J$ = 8.8 Hz, 1 H), 7.58-7.54 (m, 3 H), 7.51-7.48 (m, 3 H), 7.34 (tq, $J$ = 7.6,

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1.2 Hz, 1 H), 7.10 (tq, *J* = 7.6, 0.8 Hz, 1 H), 4.18 (s, 3 H), 3.08 (t, *J* = 7.2 Hz, 2 H), 1.89 (tq, *J* = 7.6, 7.2 Hz, 2 H), 1.11 (t, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.9, 135.8, 130.8, 130.2, 129.1, 129.0, 128.4, 126.5, 124.3, 122.1, 121.8, 121.4, 120.0, 44.3, 37.6, 18.5, 14.4; HRMS (ESI) calcd for $C_{19}H_{20}NO$ (M+H) 278.1539, found 278.1540.

**1-[2,5,6-Trimethyl-3-(*p*-tolyl)-2*H*-isoindol-1-yl]ethanone (3i).** The representative procedure was applied to 57.8 mg (0.25 mmol) of münchnone **1e** to afford 10.9 mg (0.04 mmol, 15% yield) of compound **3i** as a yellow solid: mp 110-112 ºC; $R_f$ = 0.13 (5:1 petroleum ether/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 7.38-7.34 (m, 4 H), 7.29 (s, 1 H), 4.12 (s, 3 H), 2.75 (s, 3 H), 2.47 (s, 3 H), 2.42 (s, 3 H), 2.29 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 186.1, 139.0, 136.8, 135.6, 131.8, 130.6, 129.7, 128.8, 127.3, 123.7, 121.1, 120.4, 119.4, 30.9, 21.62, 21.56, 21.50, 20.4; HRMS (ESI) calcd for $C_{20}H_{22}NO$ (M+H) 292.1696, found 292.1700.

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# CHAPTER 6

## General Conclusions

Due to their convenience, functional group tolerance, and the mild reaction conditions under which they provide the corresponding arynes, Kobayashi-type aryne precursors, namely *o*-(trimethylsilyl)aryl triflates, have been widely employed in organic synthesis. In this thesis, we have developed a number of new applications of these aryne precursors in organic synthesis.

Chapter 1 provides the reader a brief overview of arynes, including their generation, and the typical reactions they undergo.

Chapter 2 describes the development of 2,3-pyridyne, one type of hetaryne, generated from a Kobayashi-type of aryne precursor. It is remarkable that amine nucleophiles attack the 2 position of 2,3-pyridyne exclusively, affording 2-aminopyridines. Additionally, a series of benzonaphthyridinones have been synthesized by reacting 2,3-pyridyne with *o*-aminobenzoates.

Chapter 3 examines the reactions of β-lactams and arynes. Acridones are generated from β-lactams, as well as from 2,3-dihydroquinolin-4-ones. This unique process involves an unusual extrusion of a molecule of ethylene.

Chapter 4 reports a rapid and efficient synthesis of 2*H*-indazoles using a [3 + 2] dipolar cycloaddition of sydnones and arynes. It is noteworthy that 2*H*-indazoles are generated without contamination by 1*H*-indazoles. Subsequent Pd-catalyzed coupling reactions can be applied to the halogenated products to generate a library of indazoles.

Chapter 5 describes new methodology for synthesizing 2*H*-isoindoles and 9,10-dihydro-9,10-epiminoanthracenes from arynes and münchnones, which involves a [3 + 2] dipolar cycloaddition very similar to the first step of the sydnone reactions. After cycloreversion,

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the resulting 2*H*-isoindoles, being extremely reactive to arynes, immediately form 9,10-dihydro-9,10-epiminoanthracenes quite efficiently.

The success of these reactions is made possible by the versatility of the Kobayashi aryne precursors. Although elimination of the TMS and OTf groups reduces the effective atom utilization of the benzyne precursor, the mild reaction conditions under which the aryne is generated have attracted significant attention and contributed to the rapid growth in synthetic aryne chemistry. However, it is noticeable that since 1983, when Kobayashi first introduced this type of benzyne formation, little progress was made in this area until the early 2000's. Recently, aryne chemistry appears to be a particularly "hot" area in organic synthesis. So what is likely to be the next powerful synthetic methodology employing arynes to be disclosed?

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# APPENDIX A. CHAPTER 2 $^{1}$H AND $^{13}$C NMR SPECTRA

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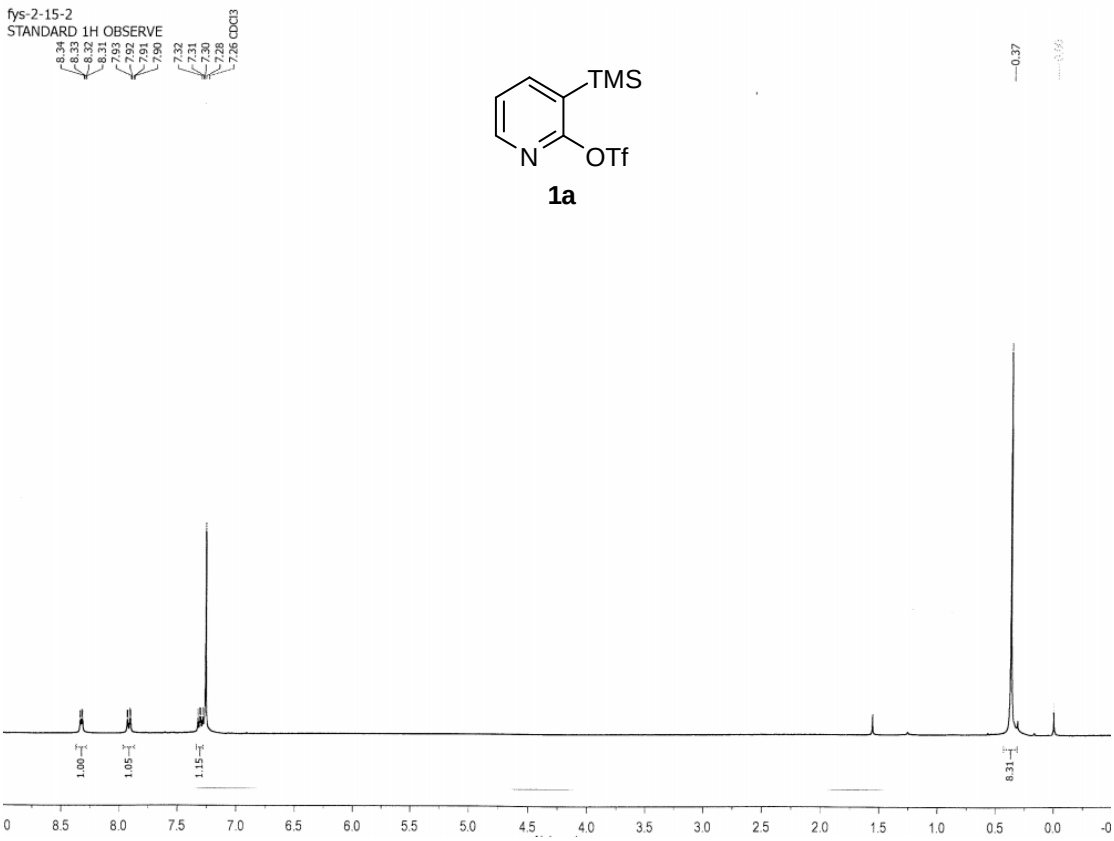


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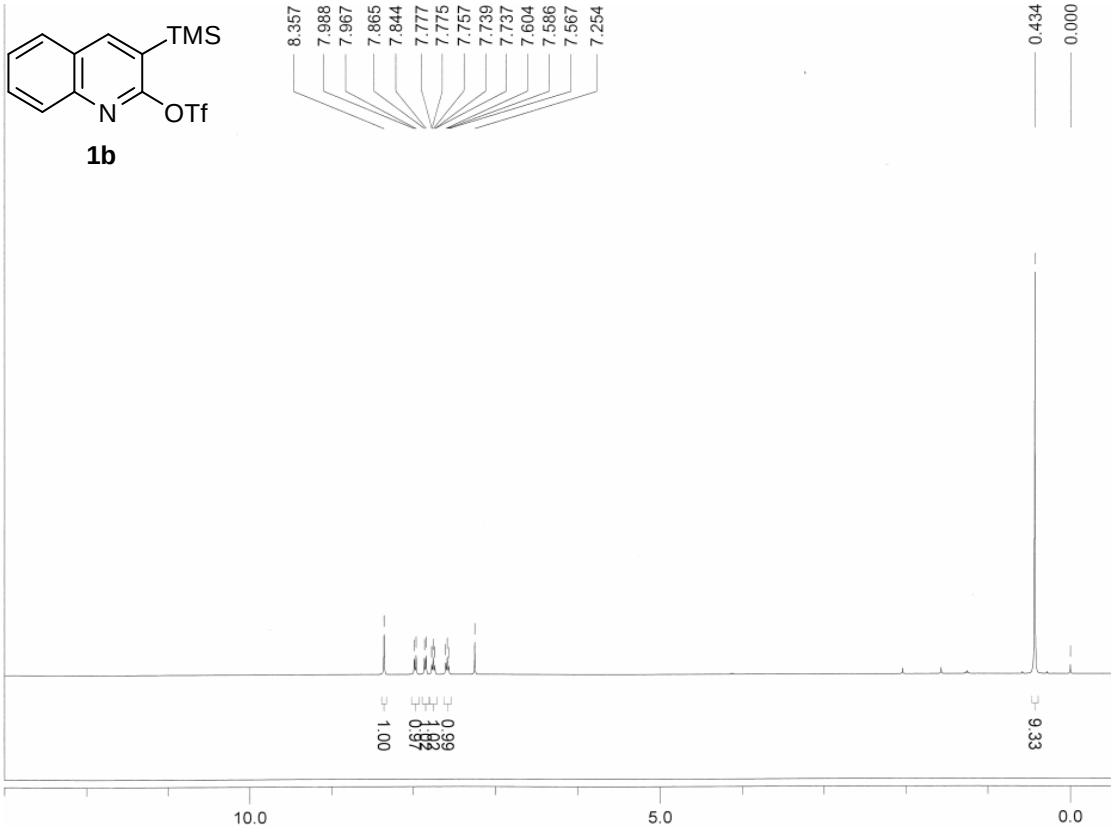


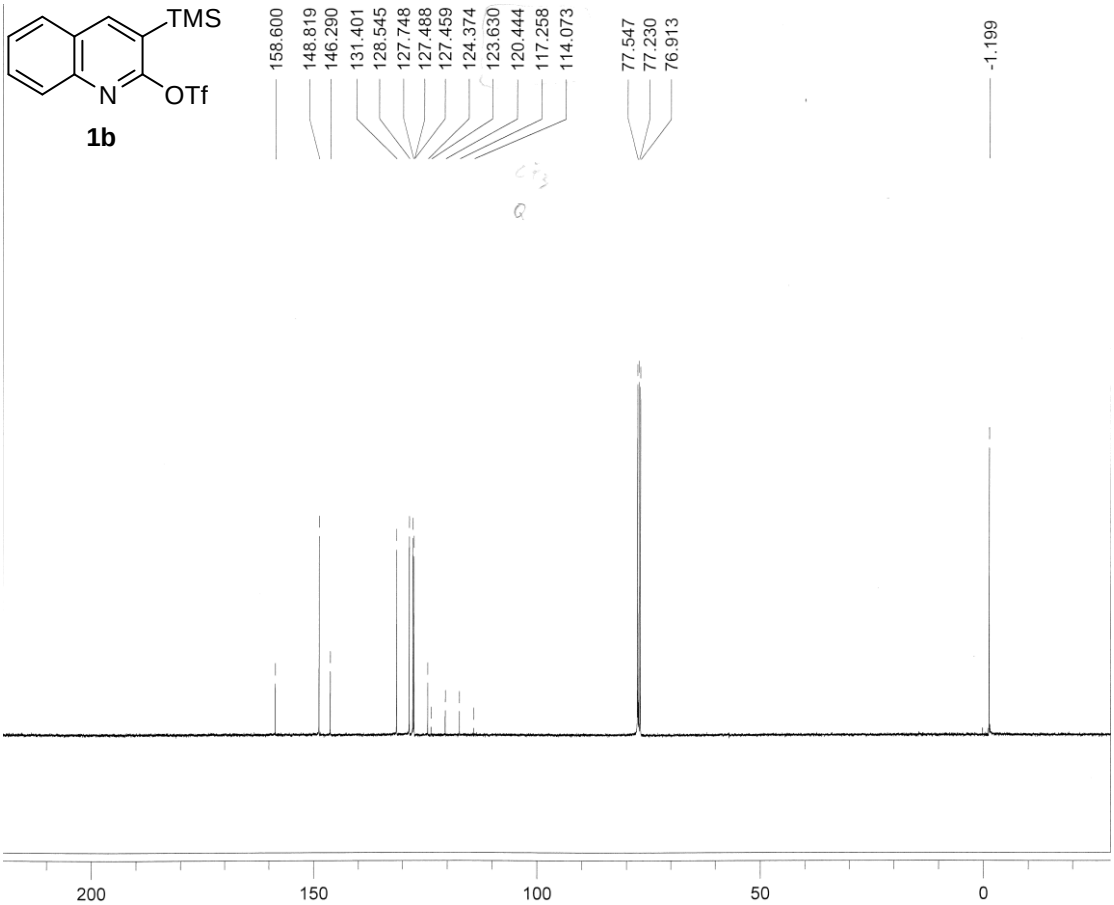


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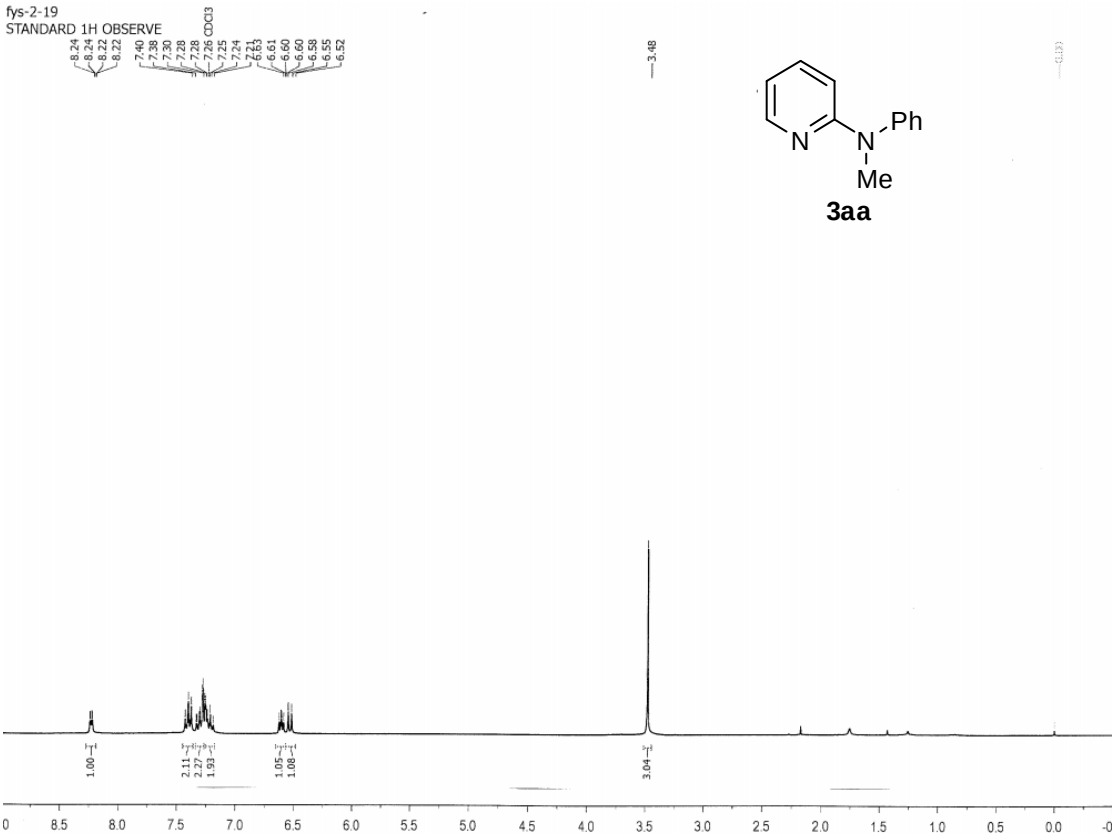


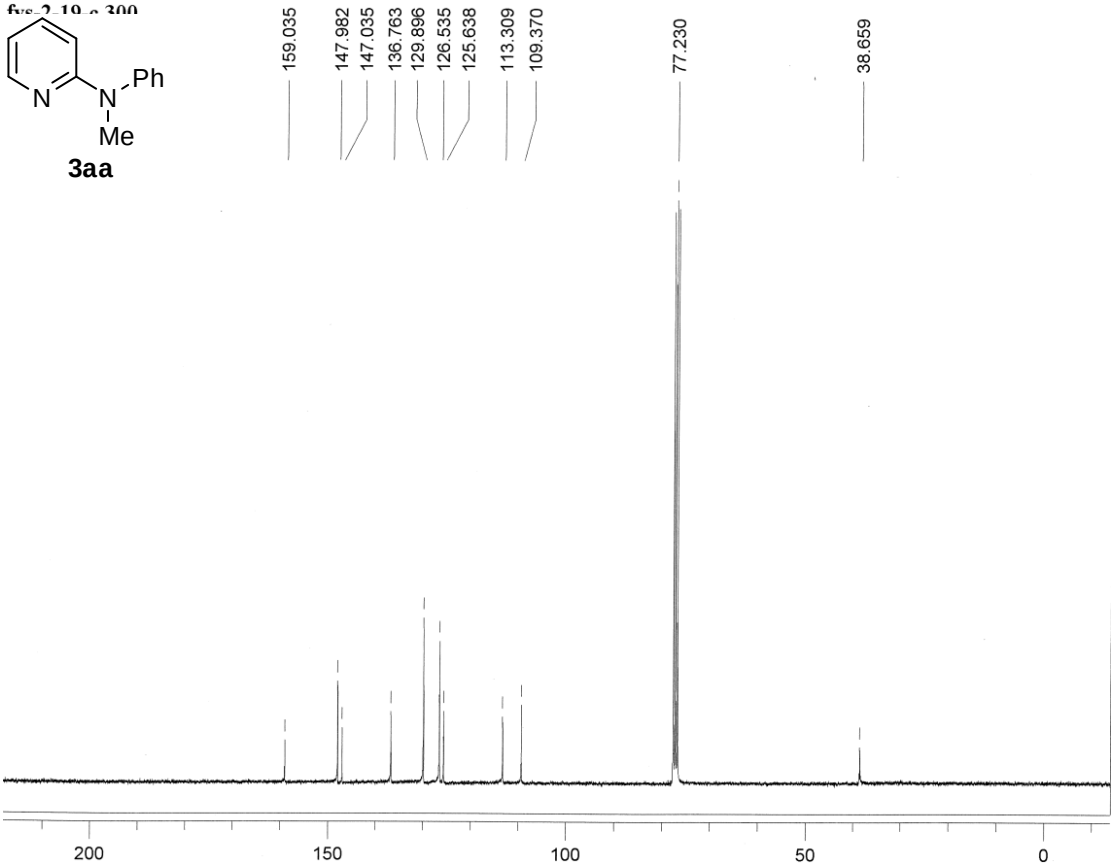


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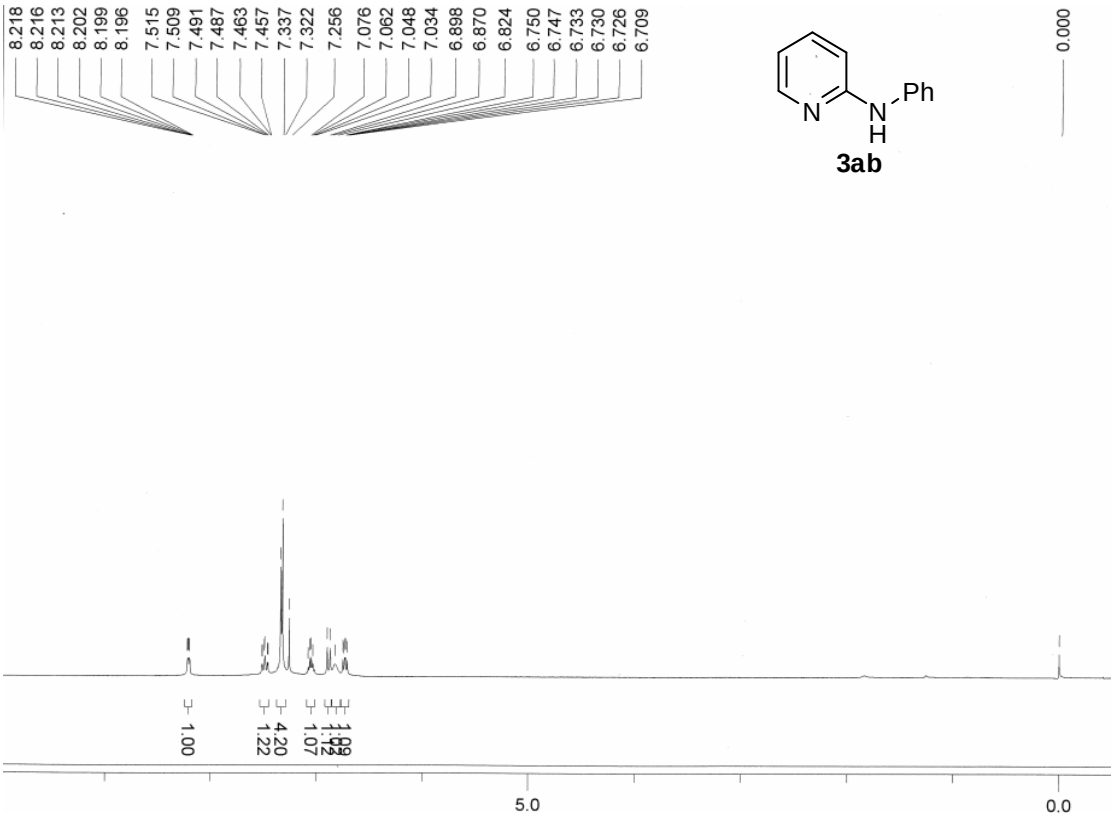


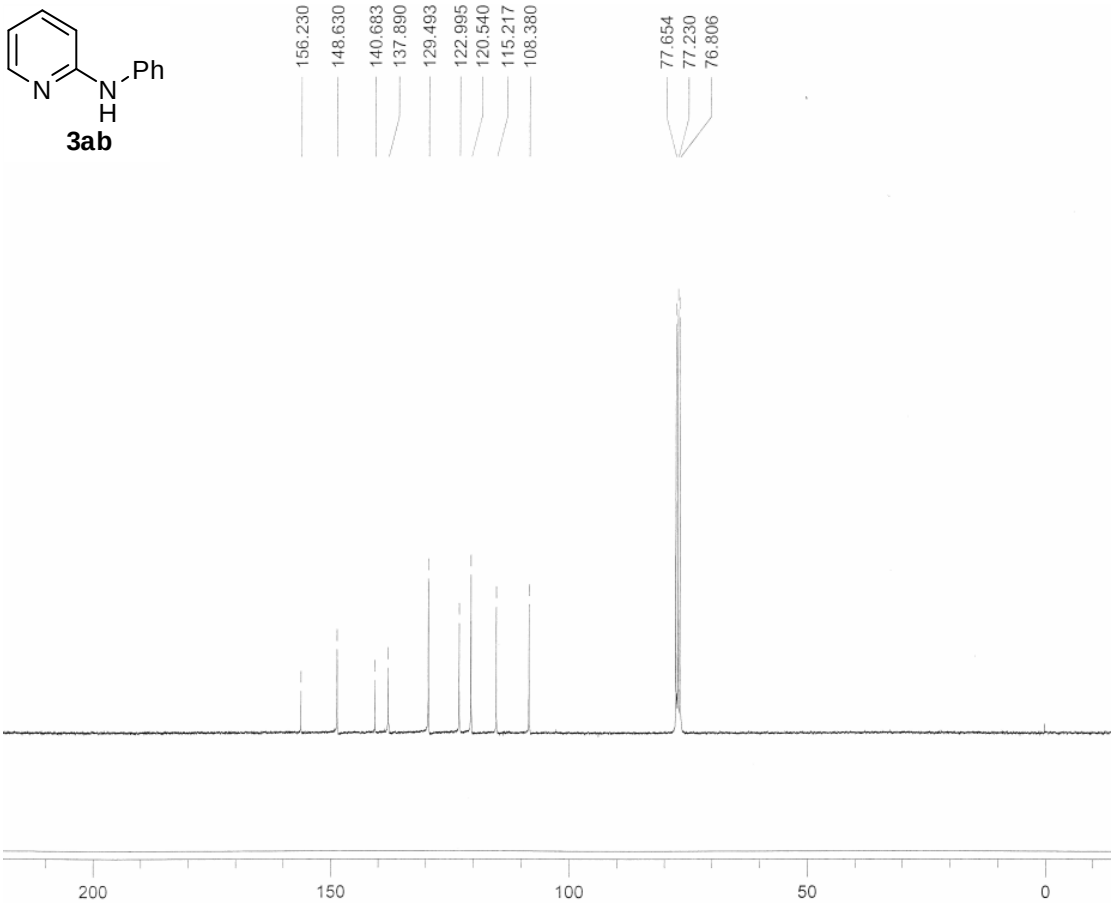


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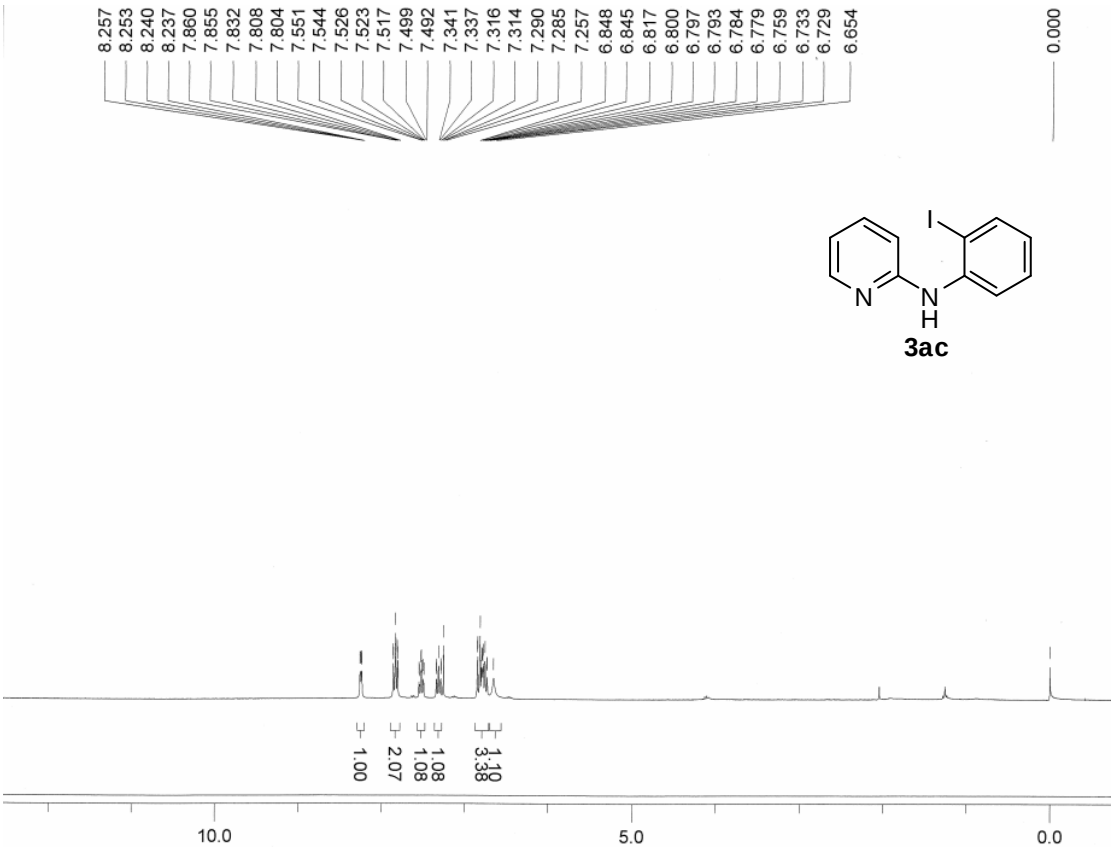


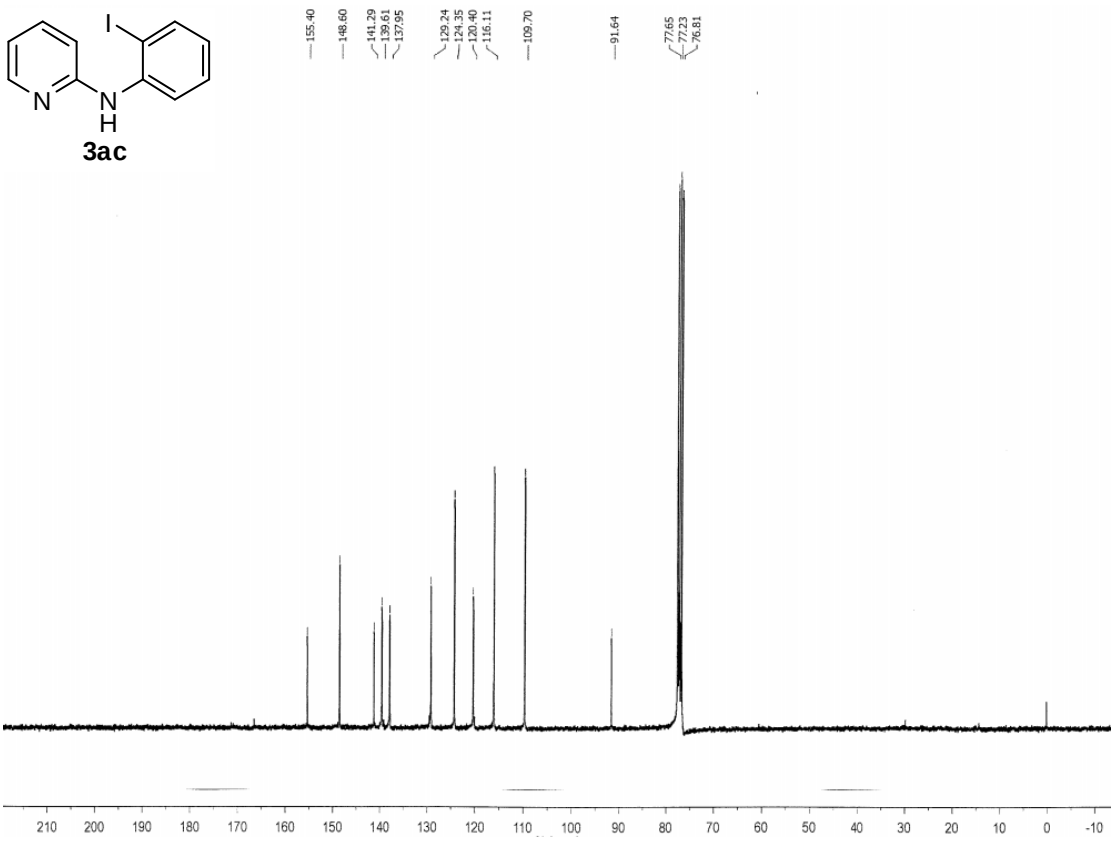


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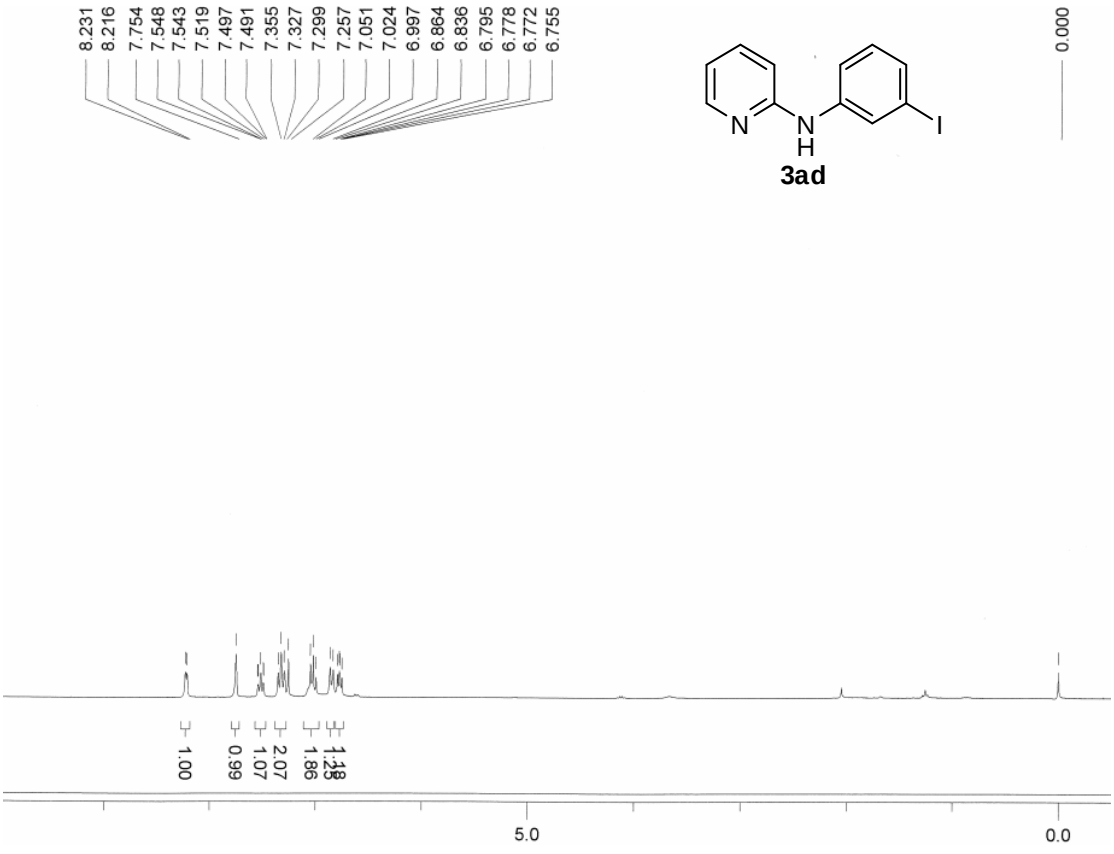


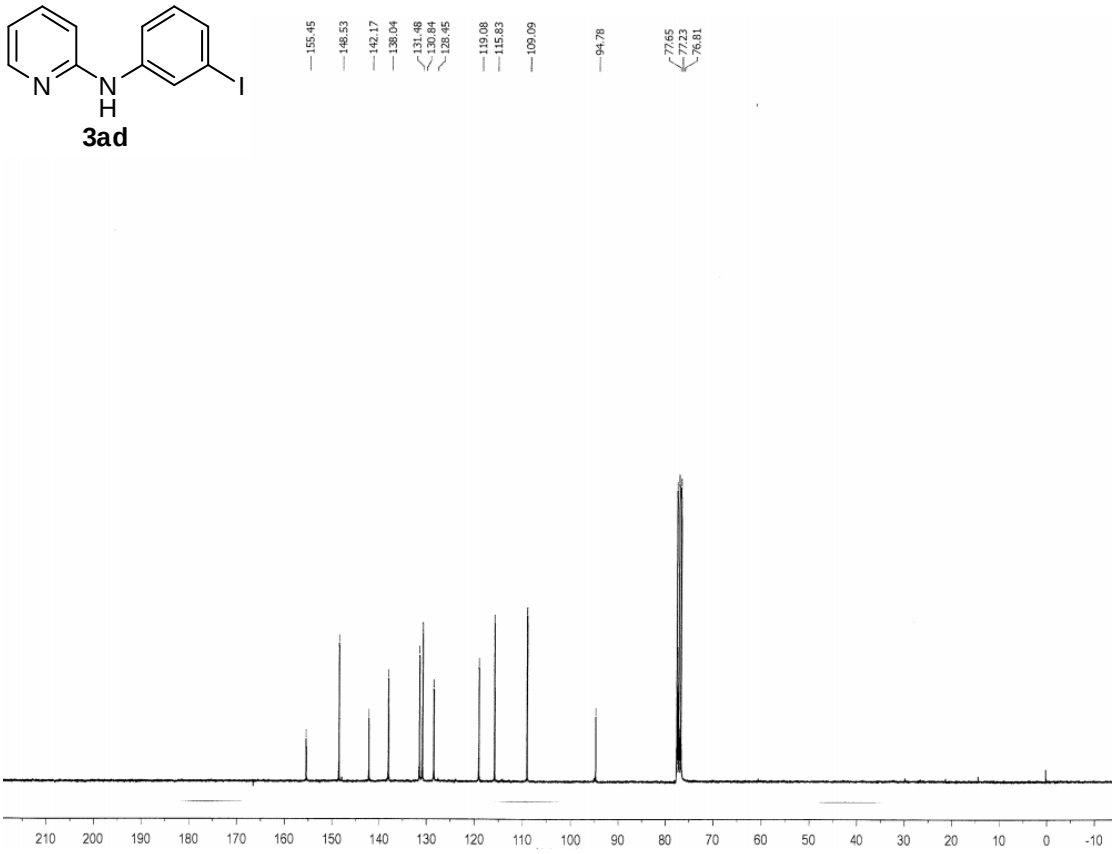


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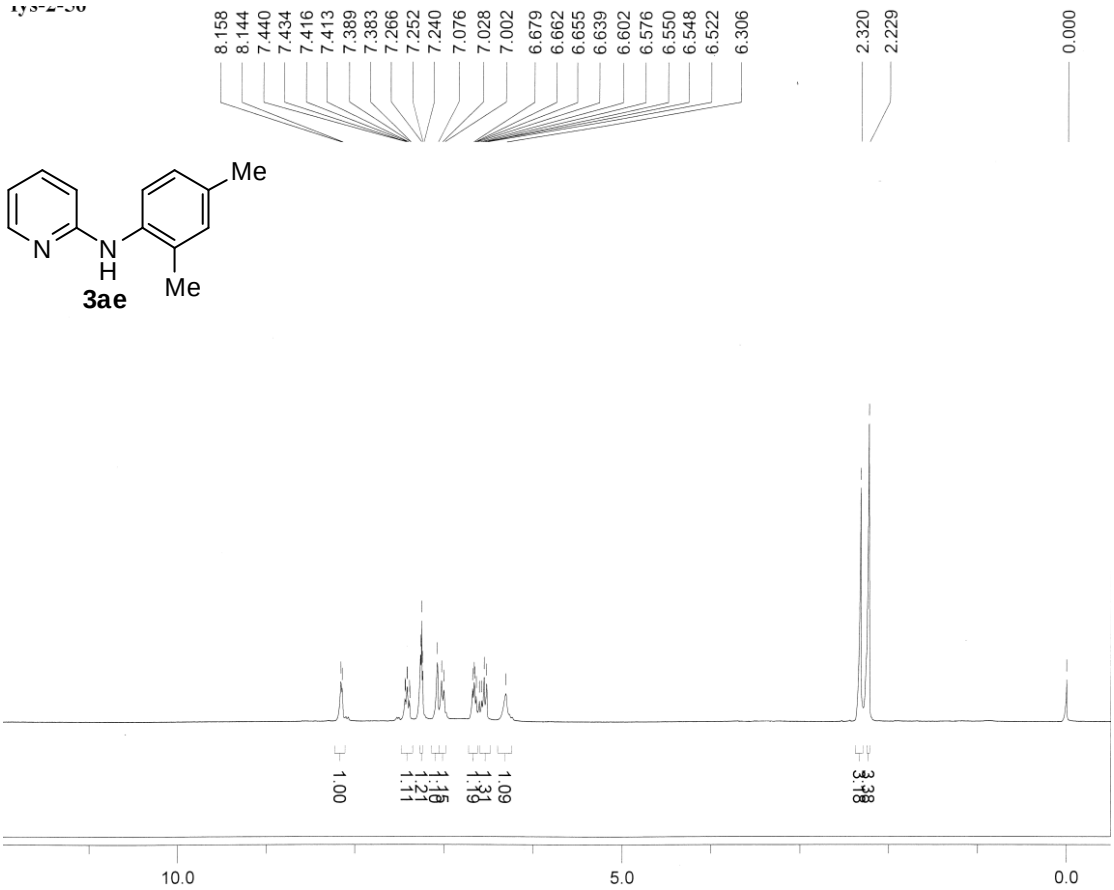


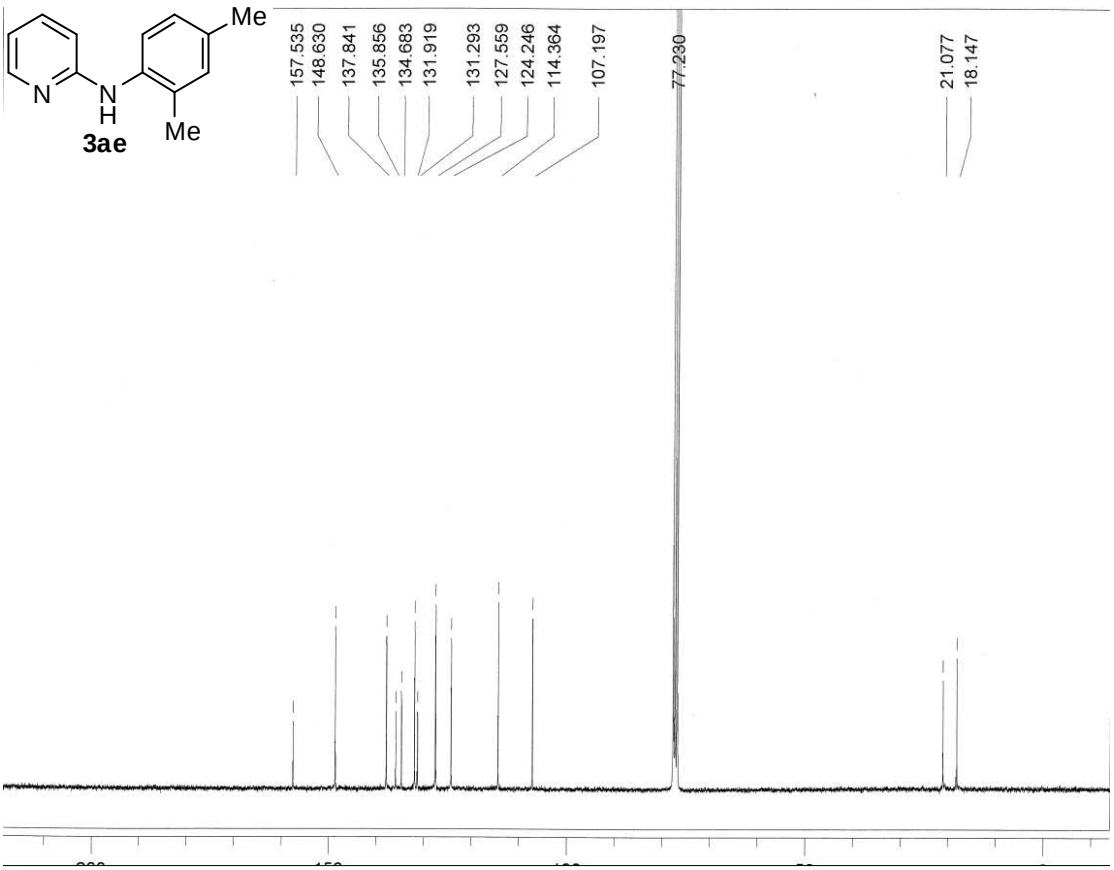


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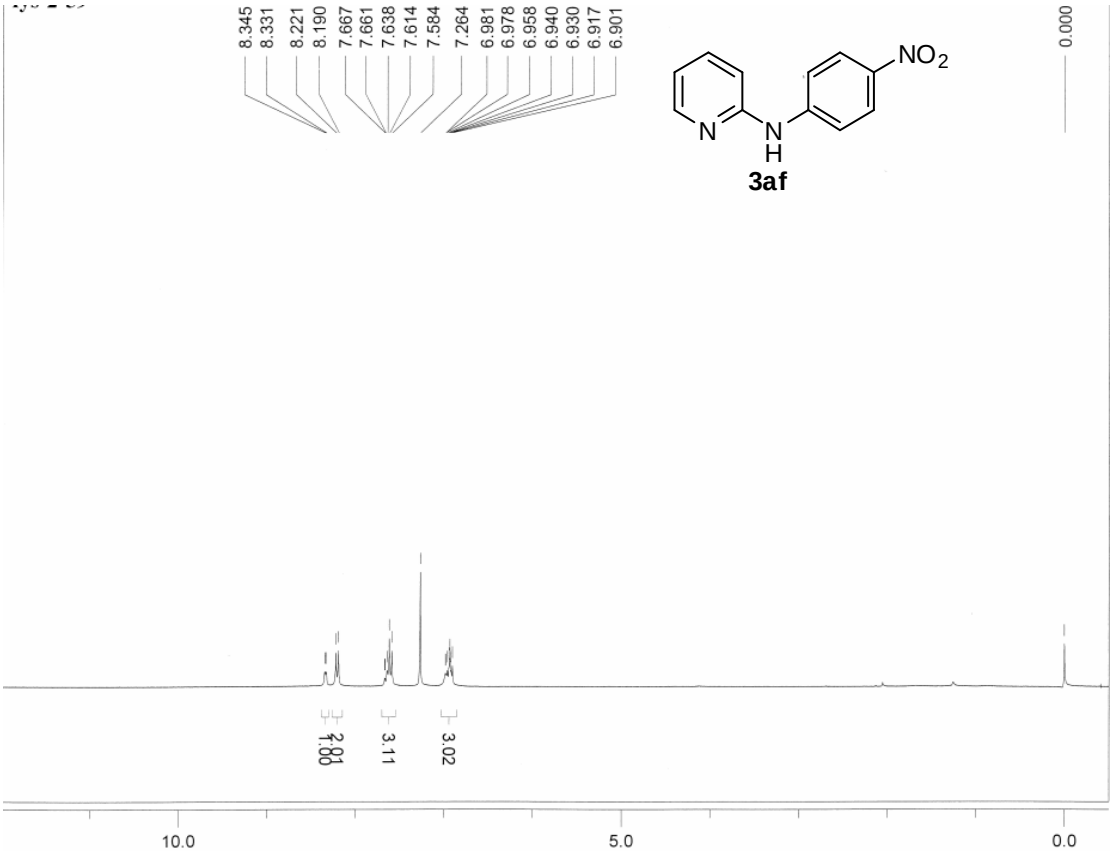


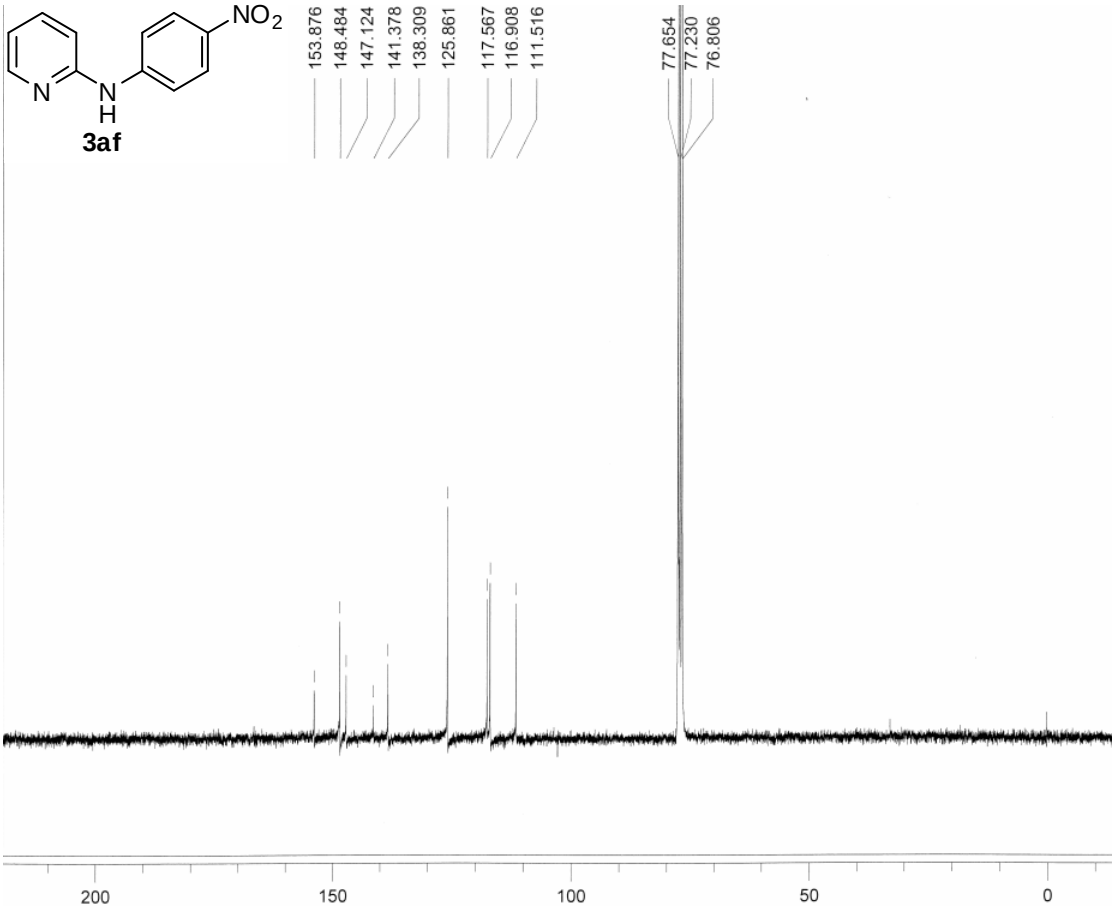


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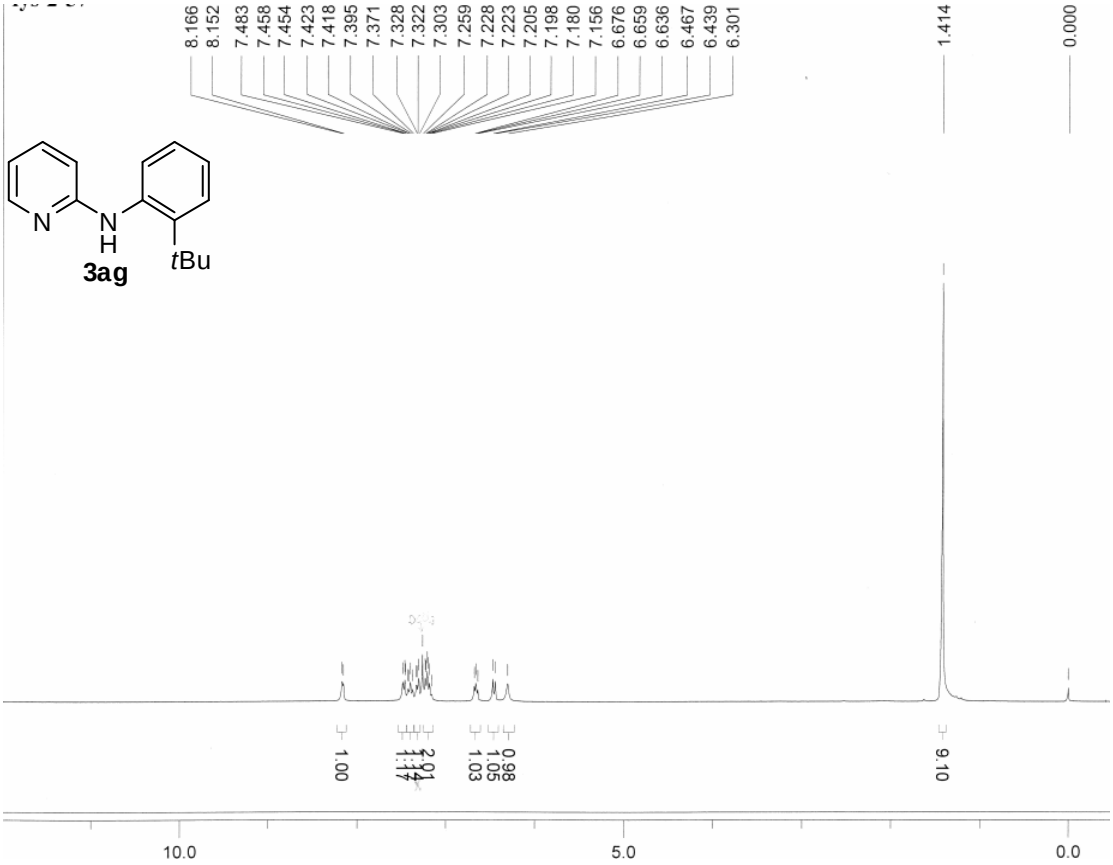


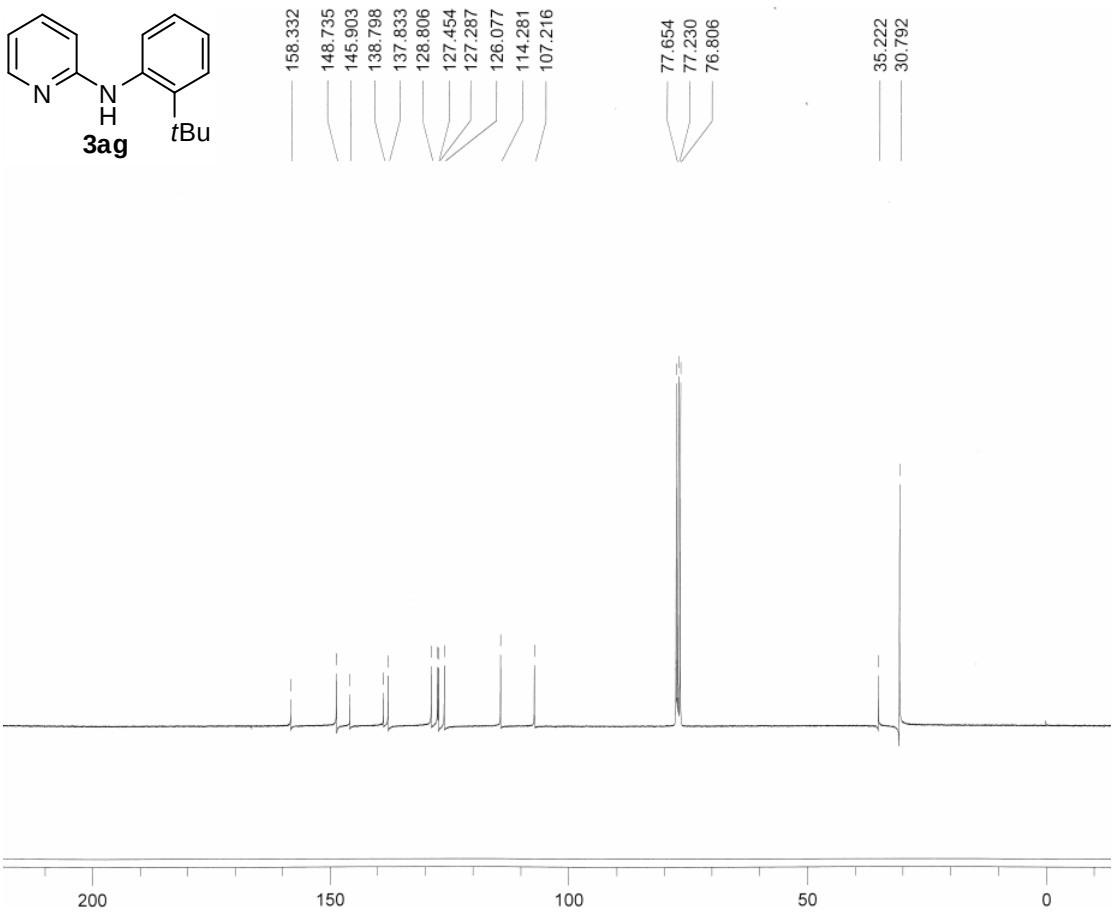


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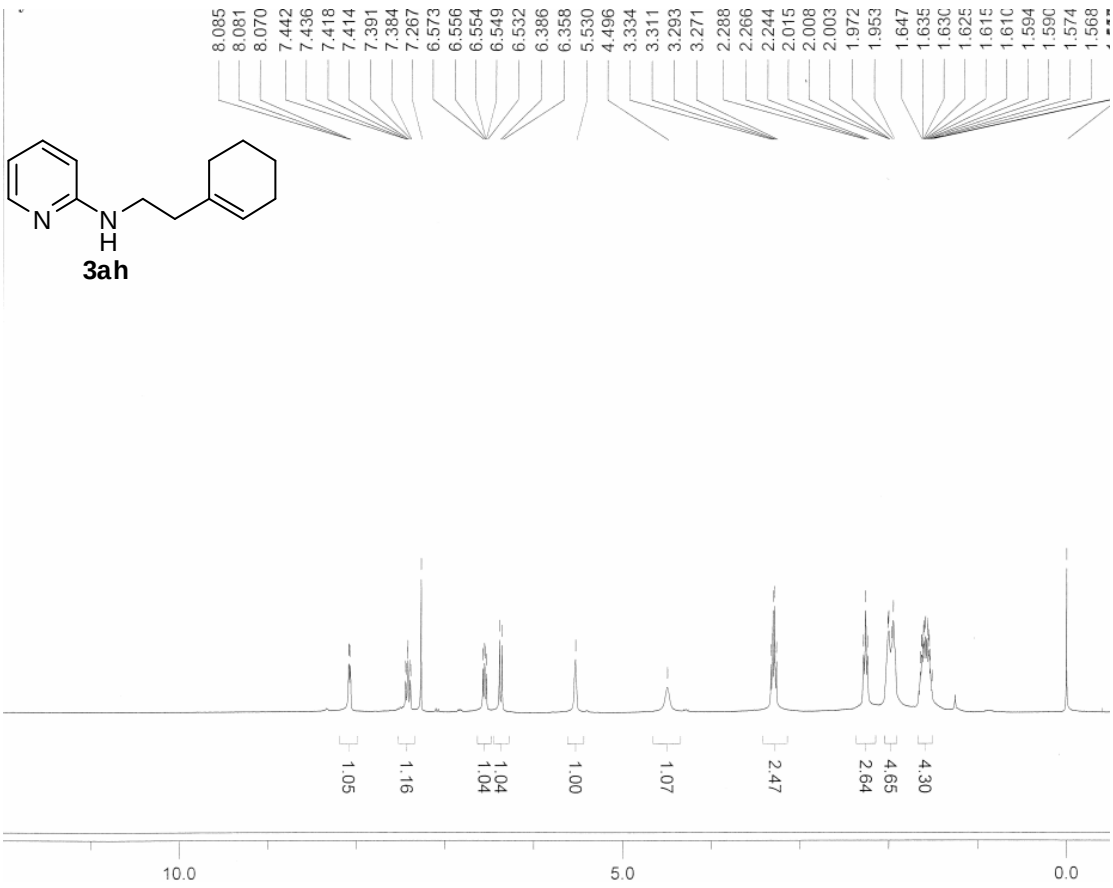


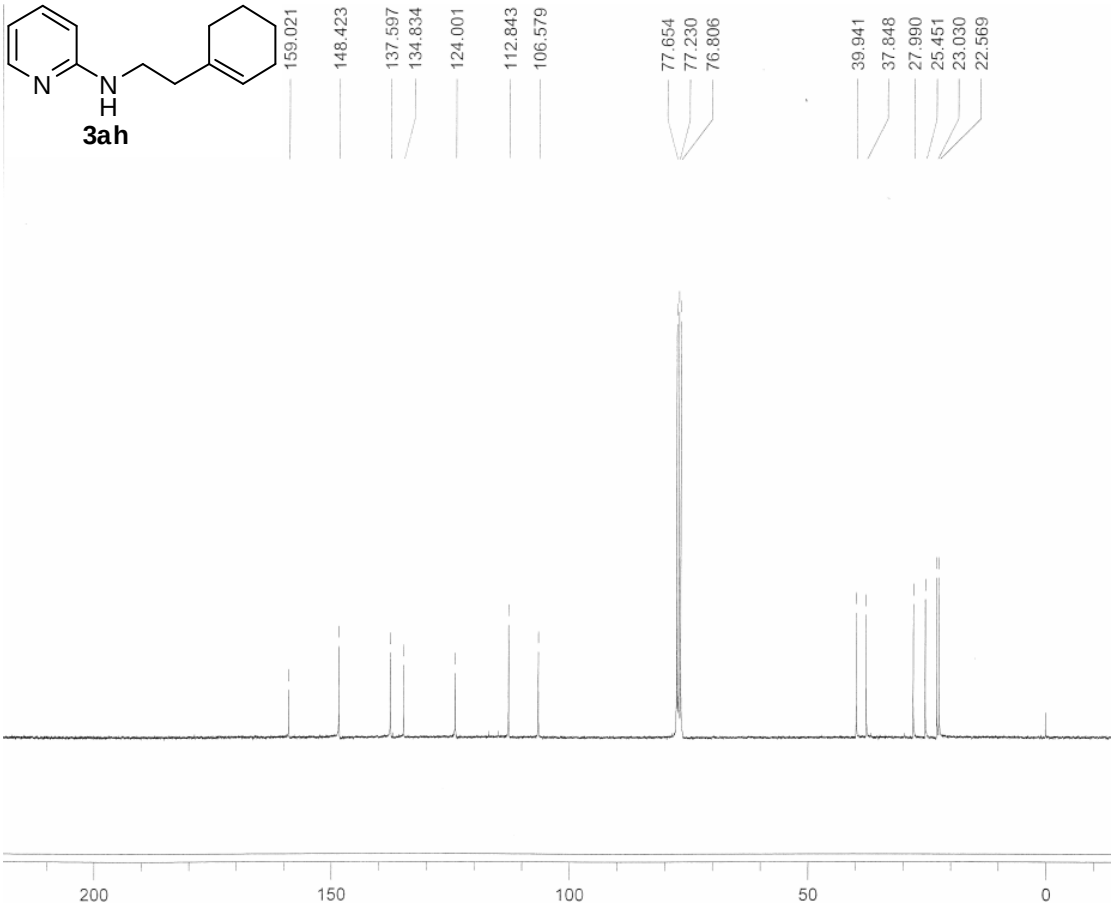


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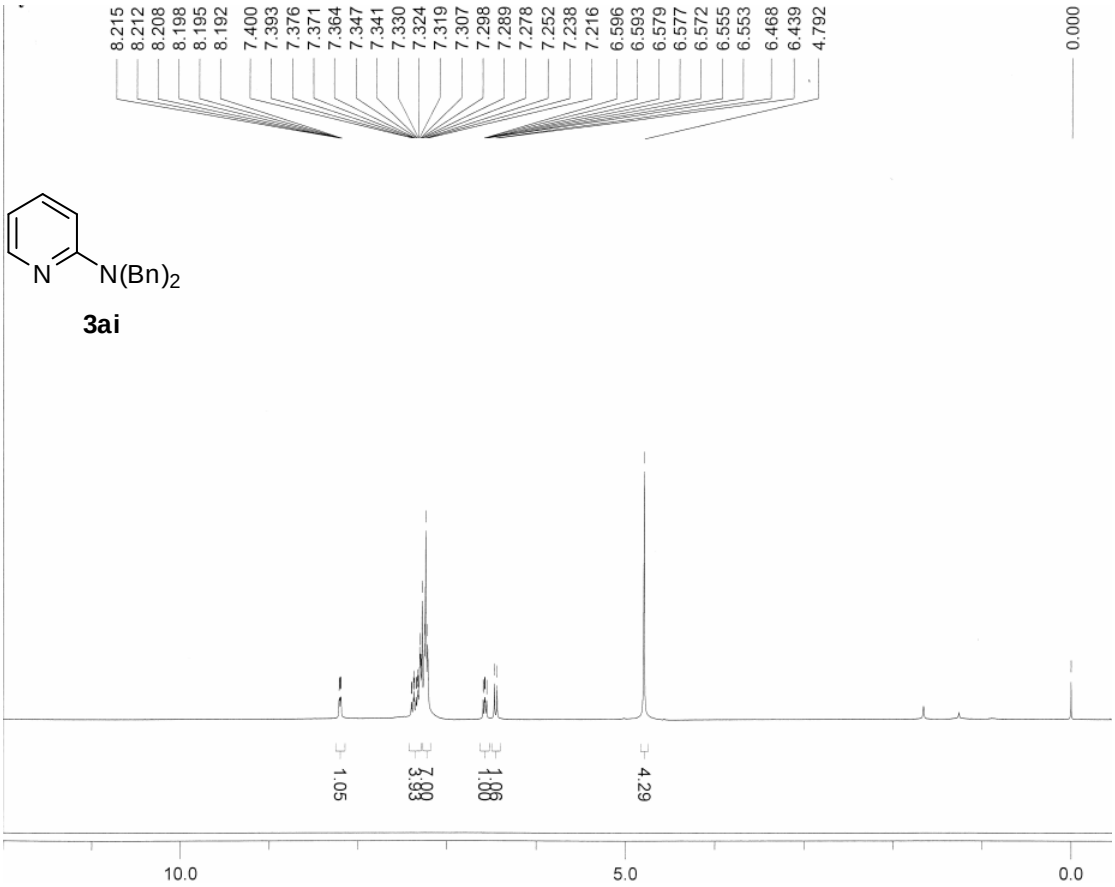


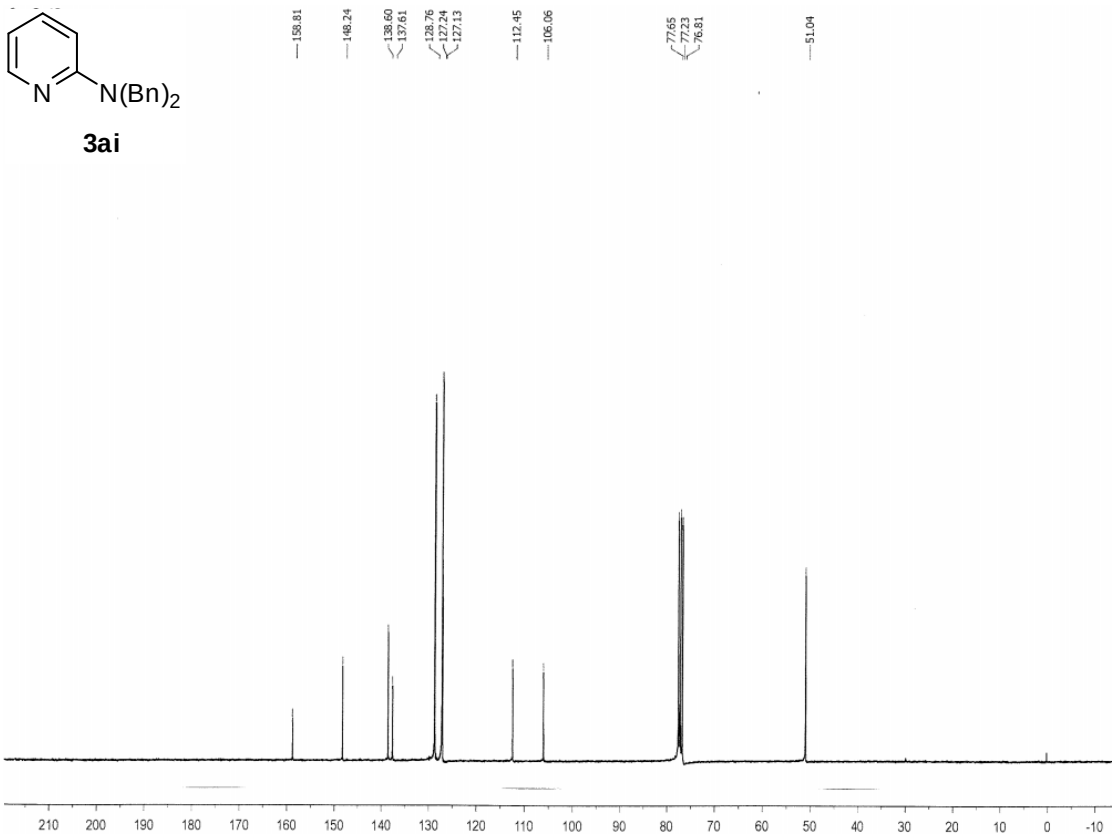


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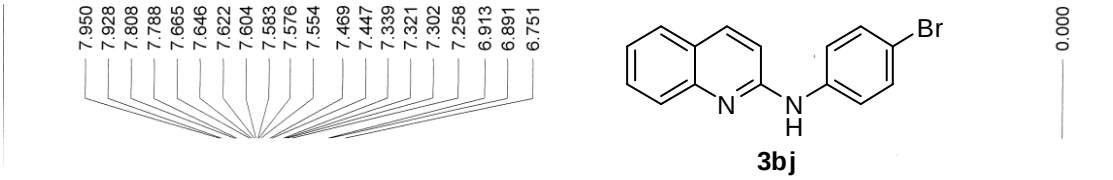


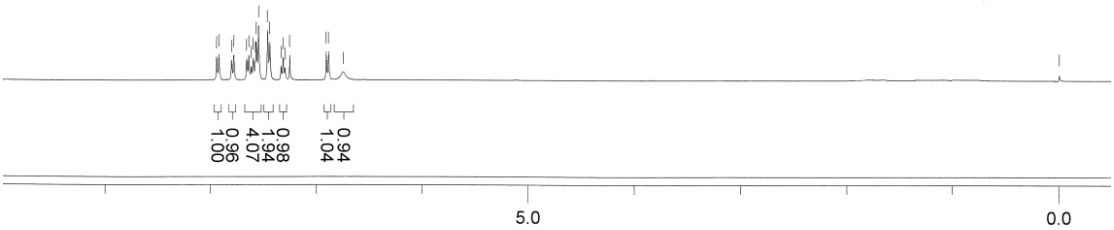


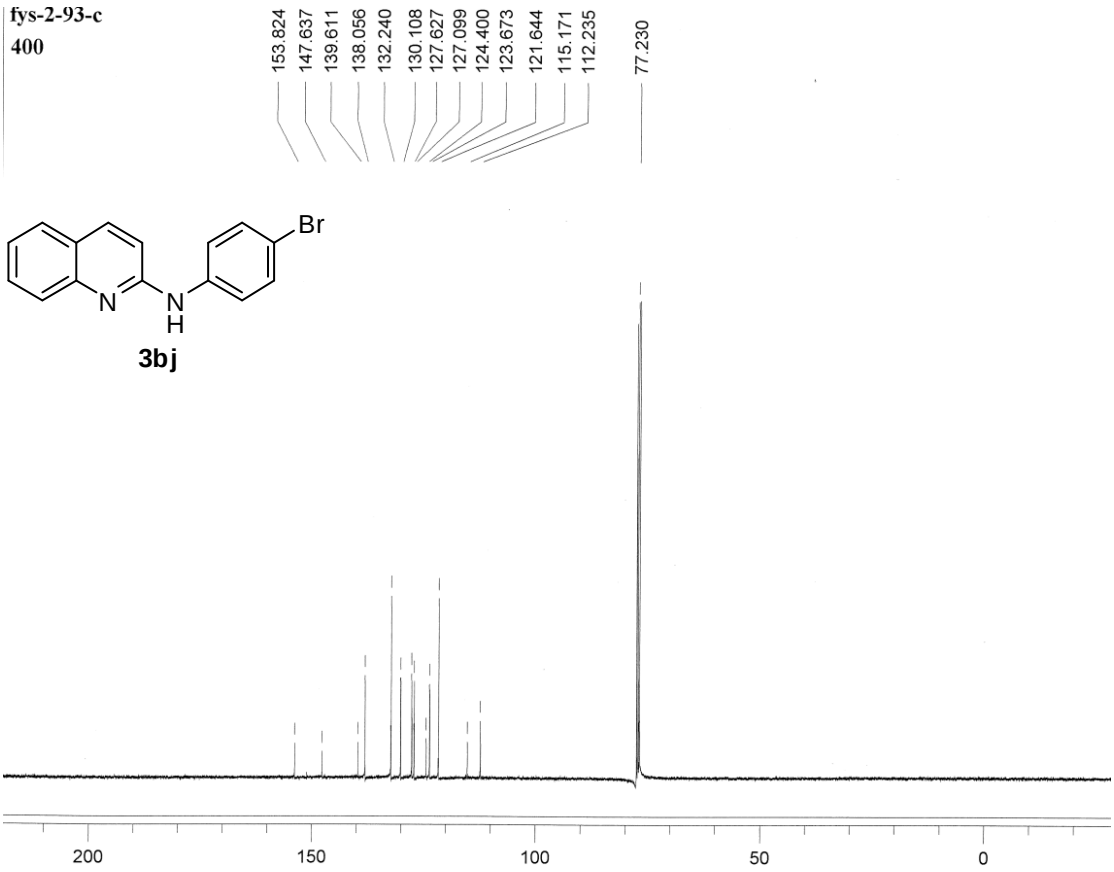


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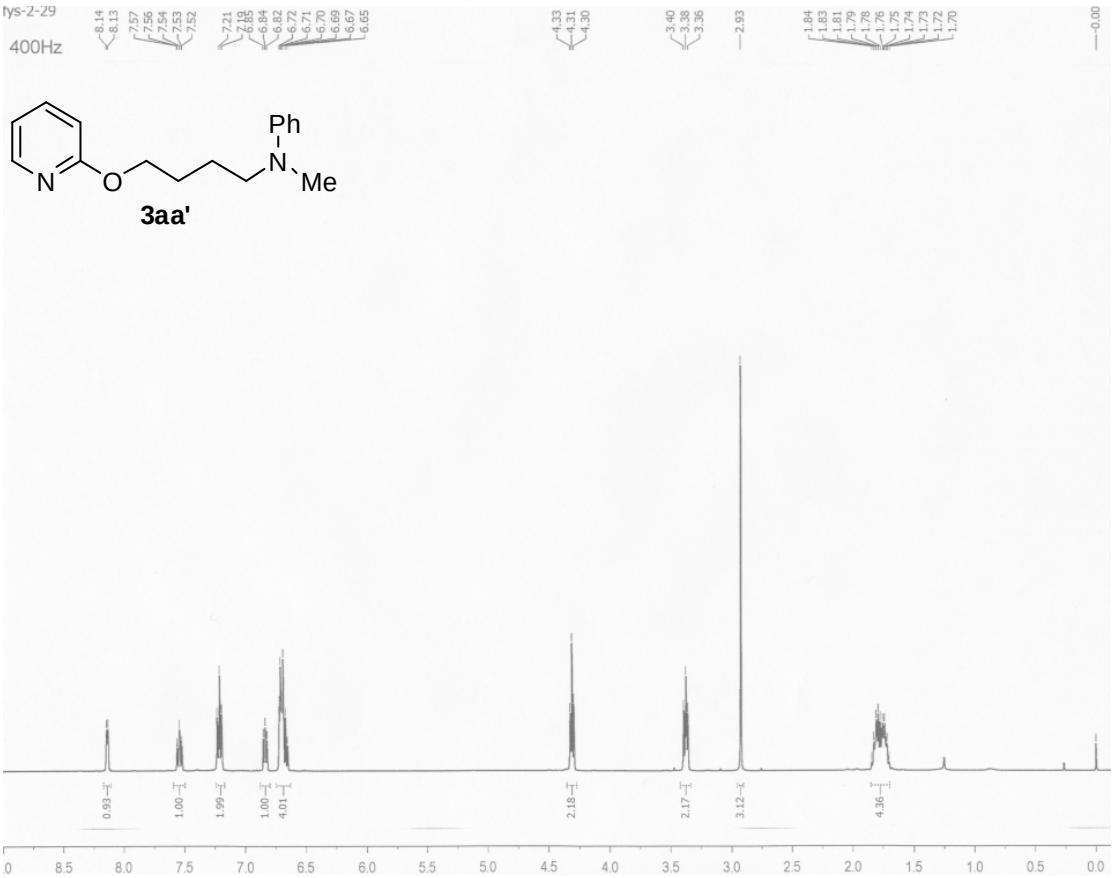


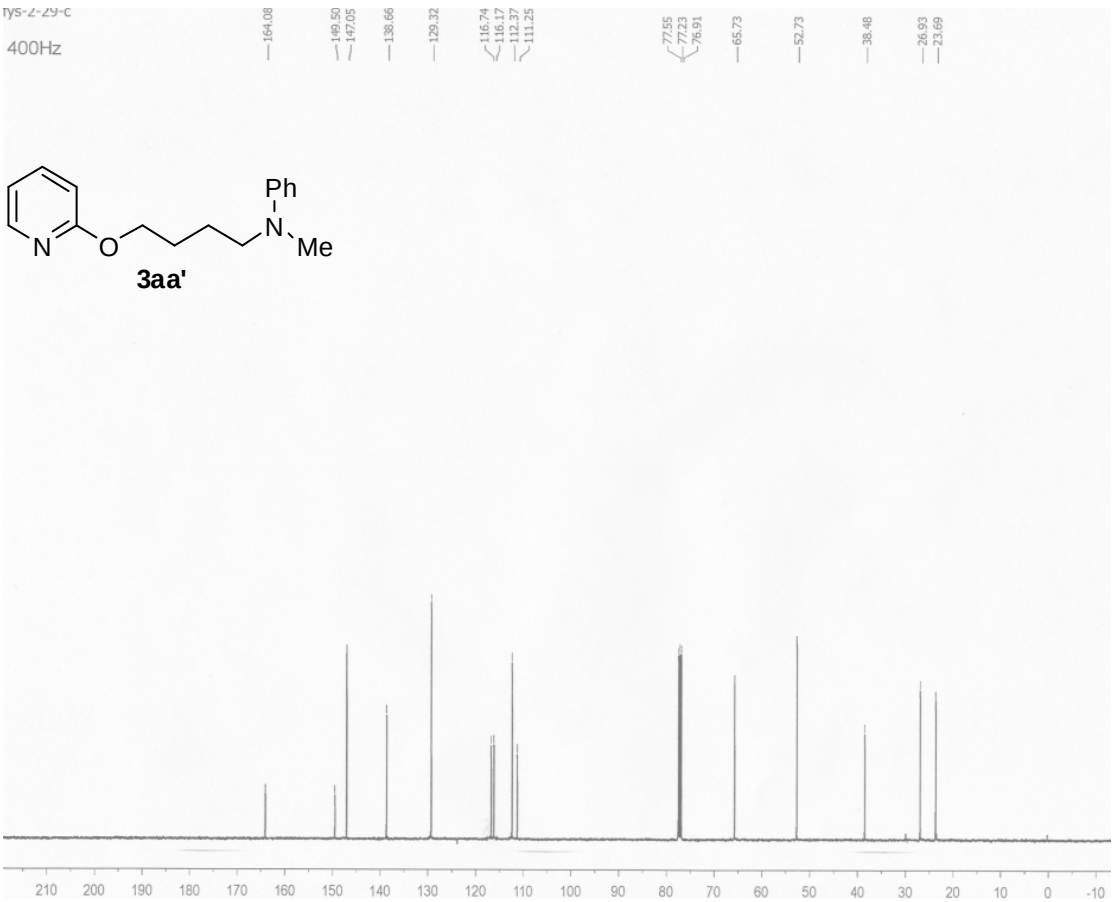


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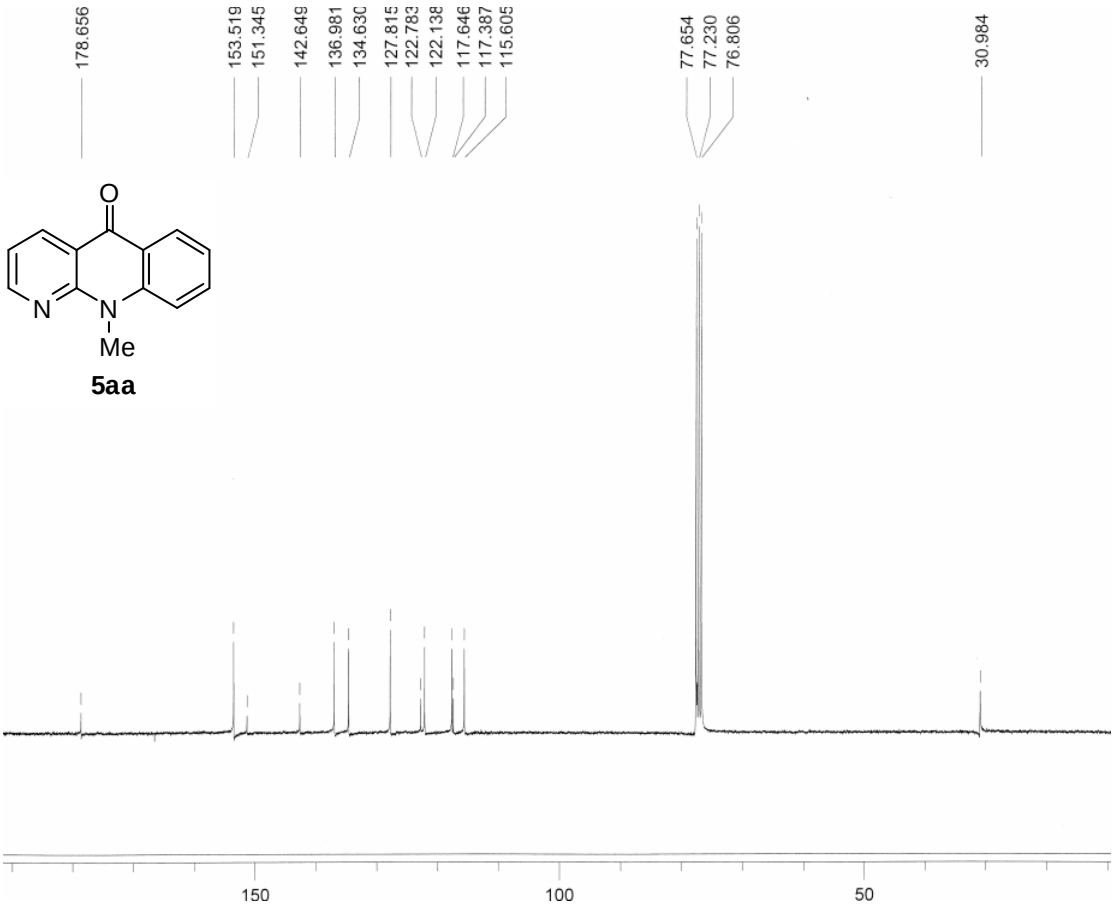


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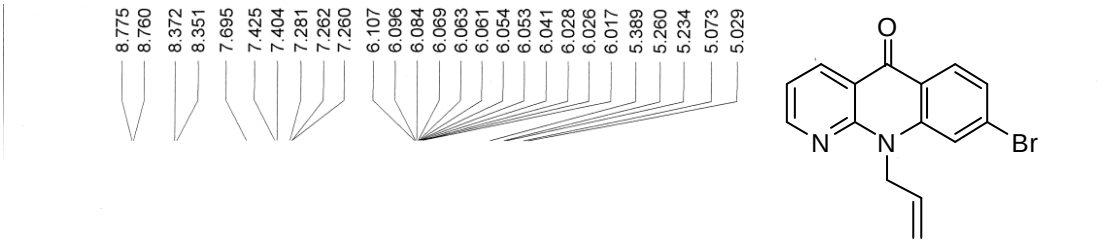


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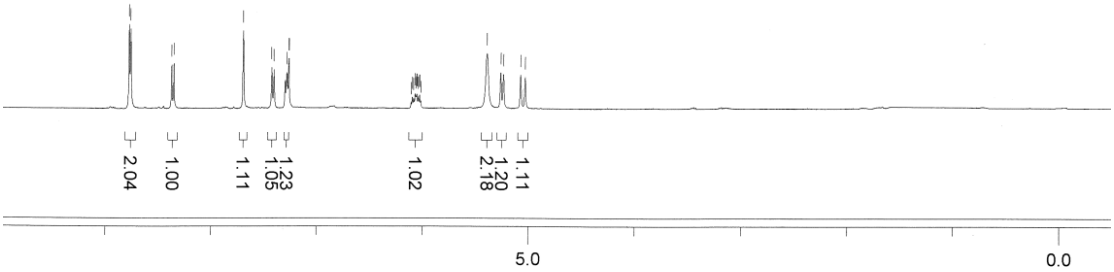


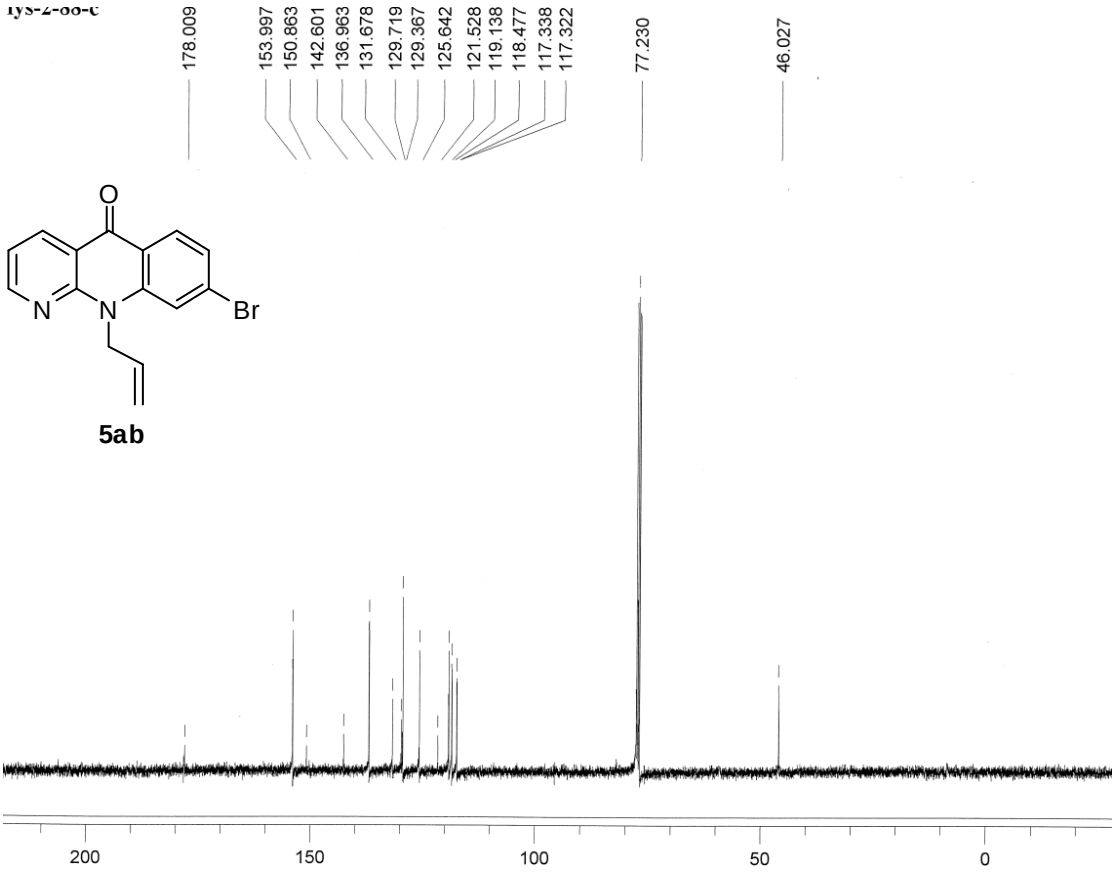


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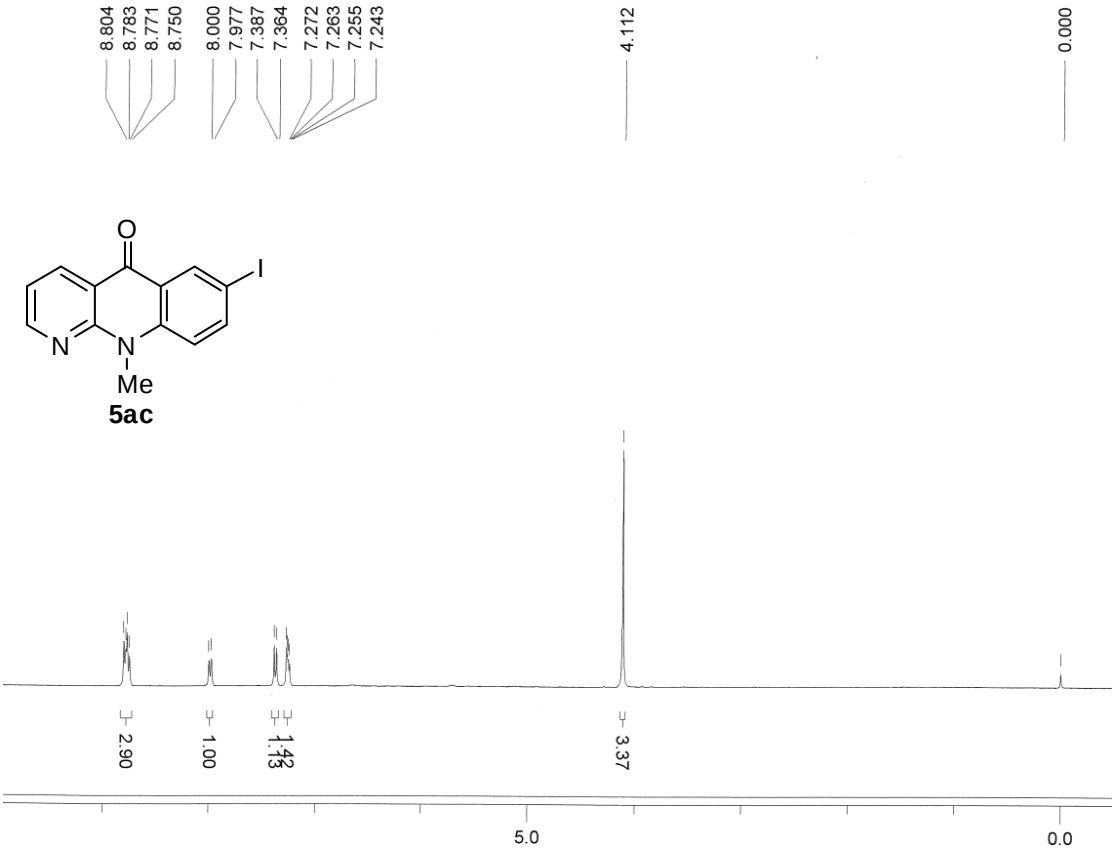


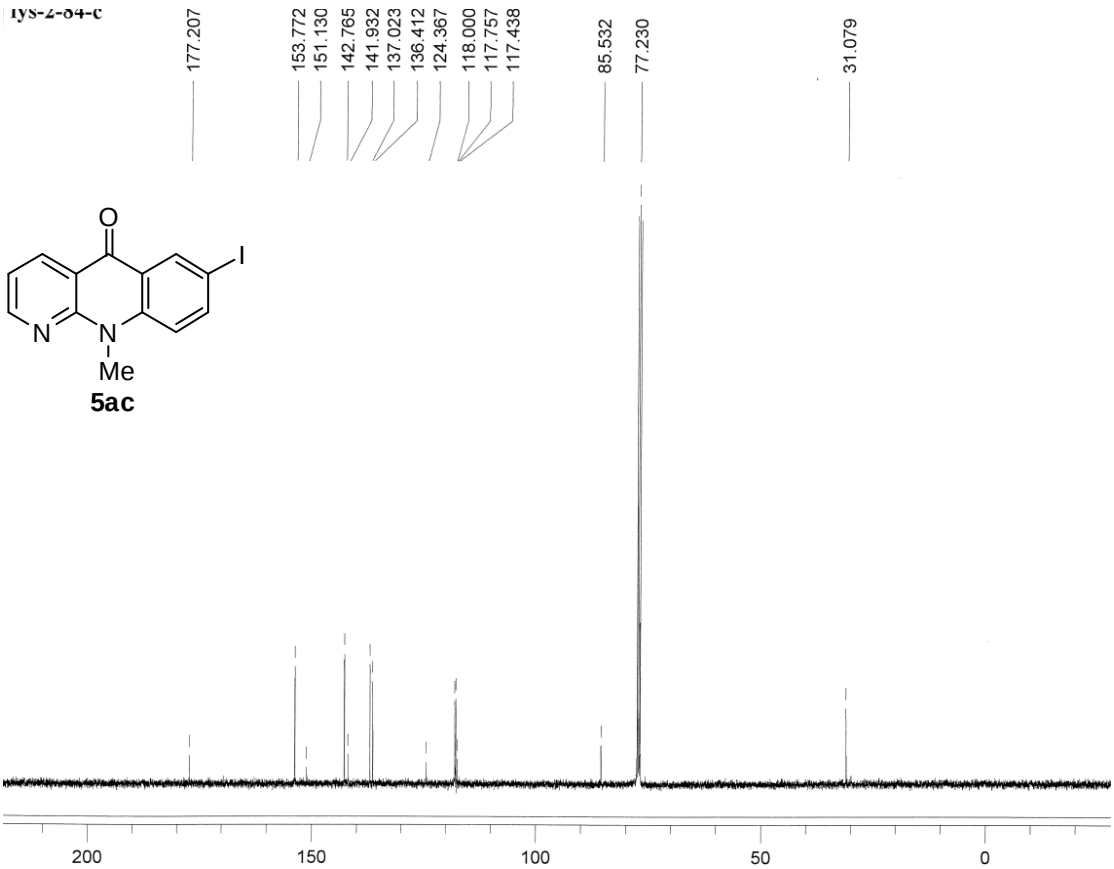


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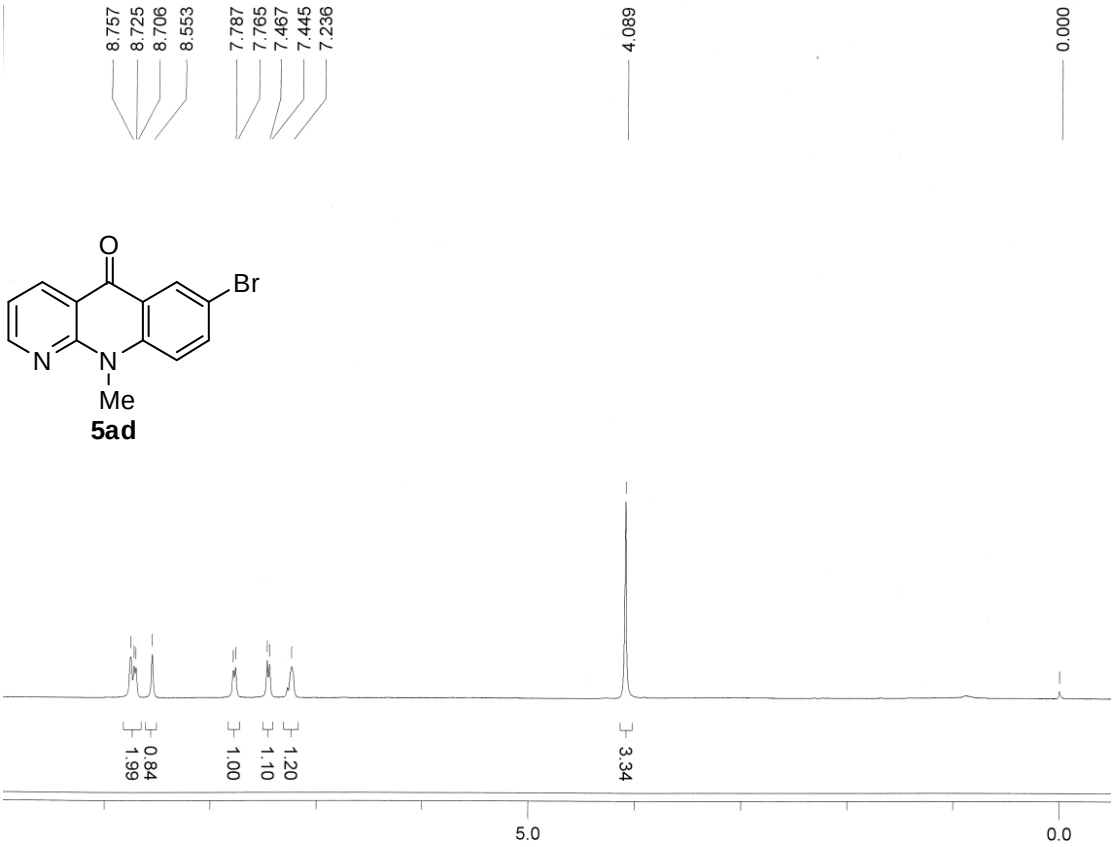


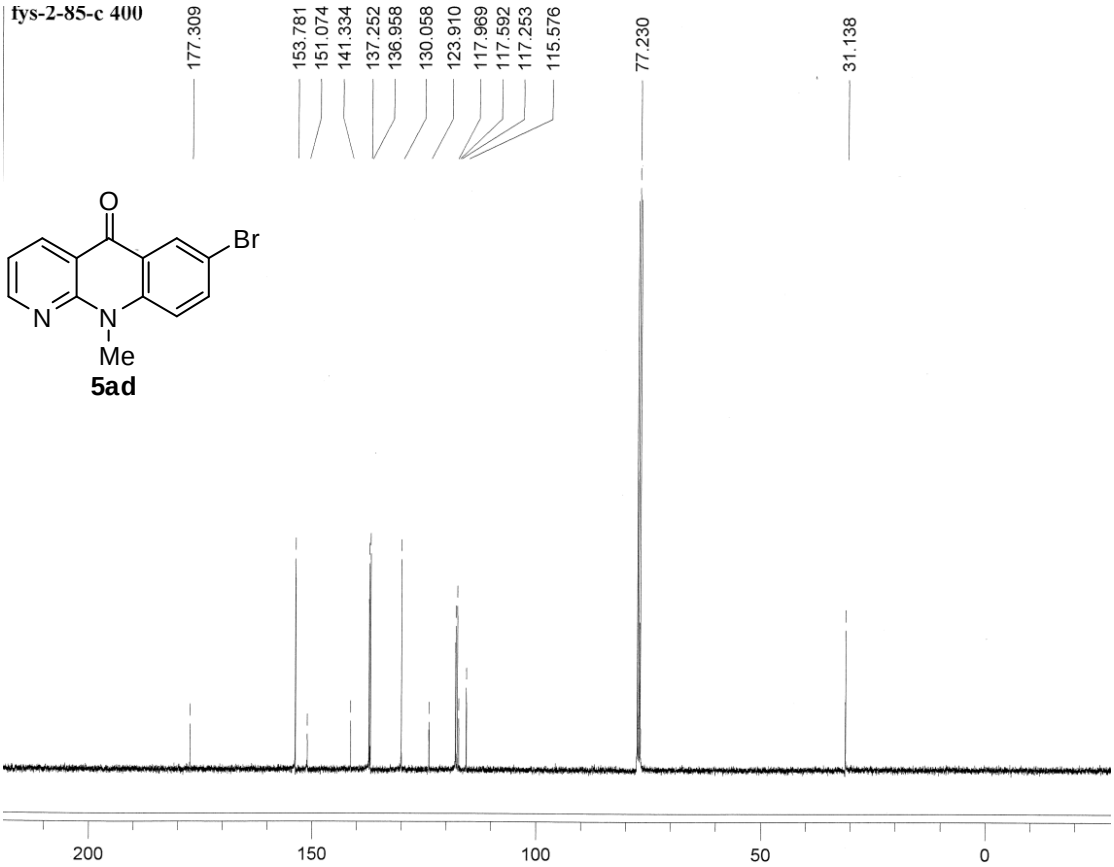


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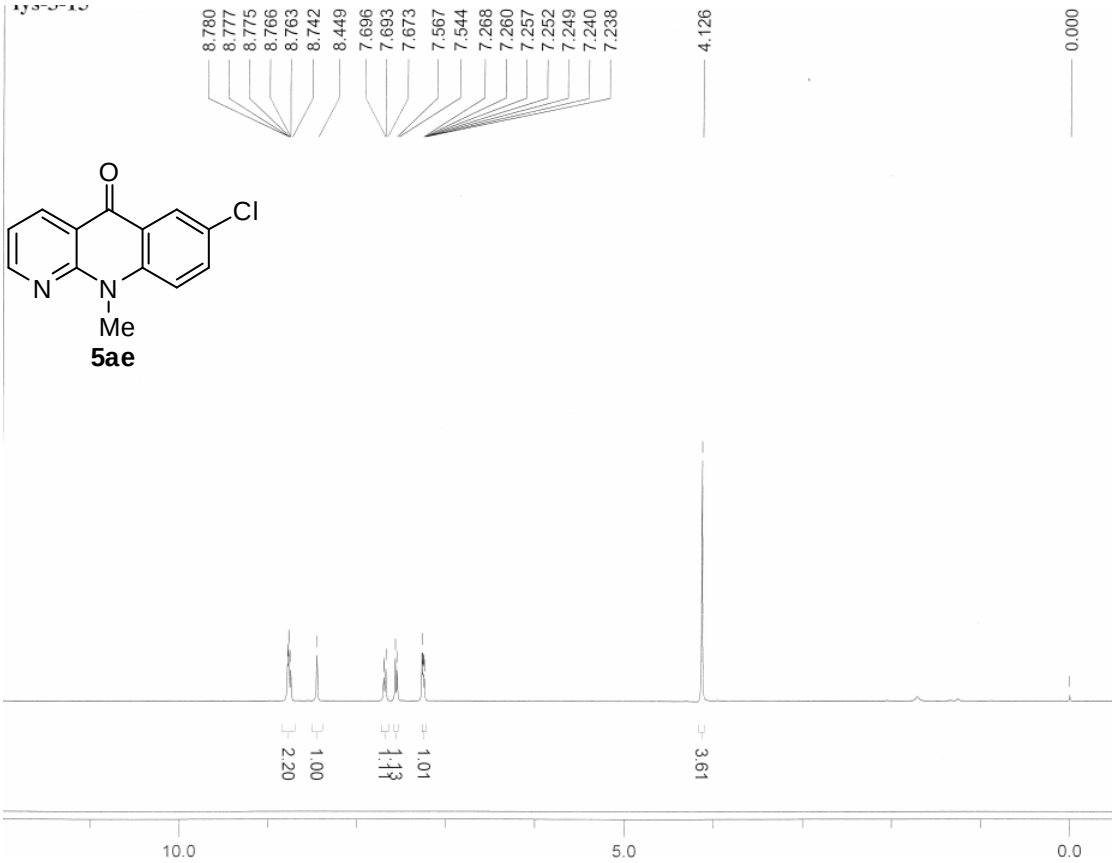


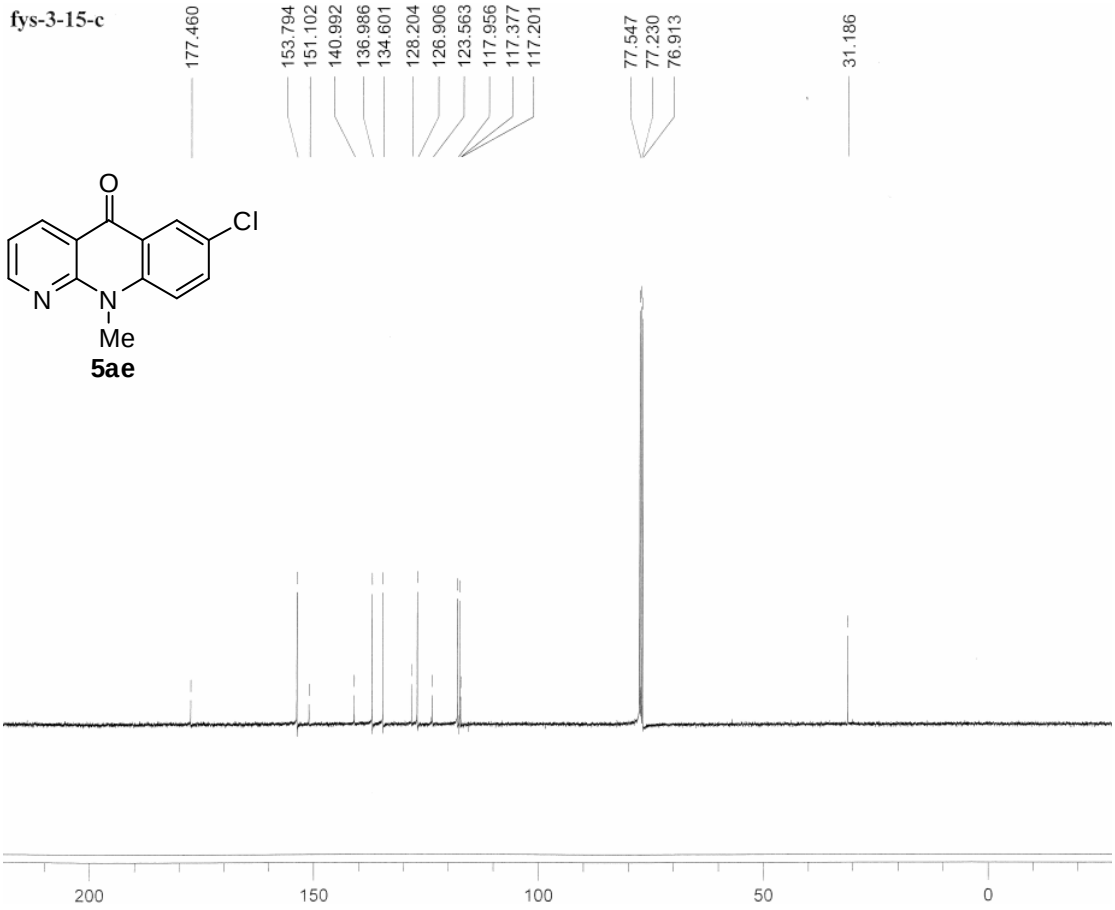


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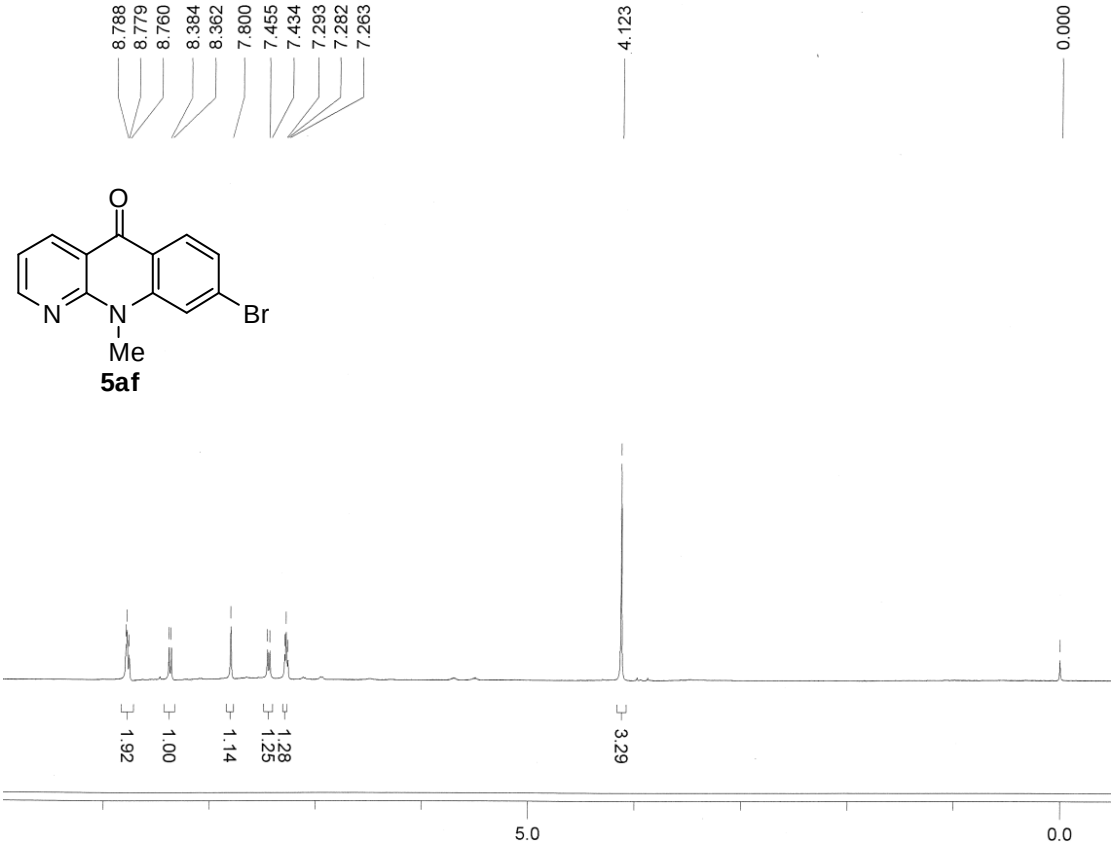


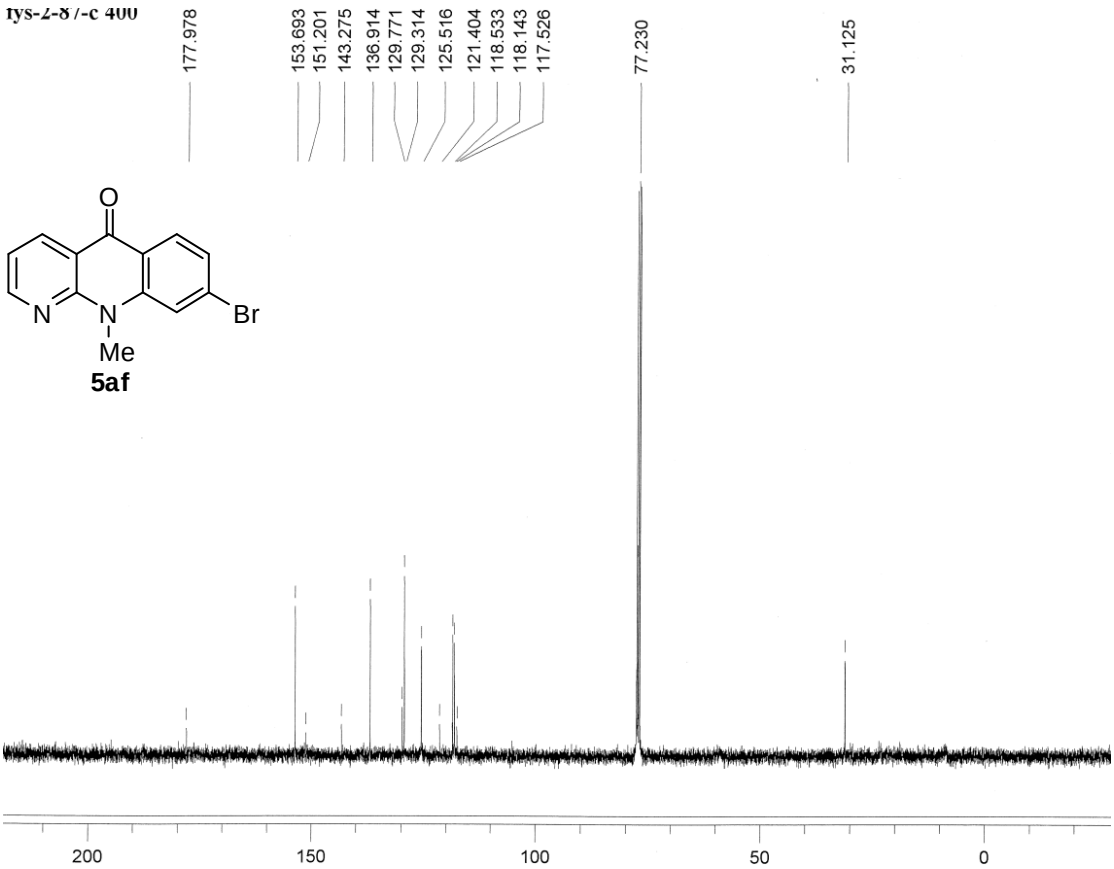


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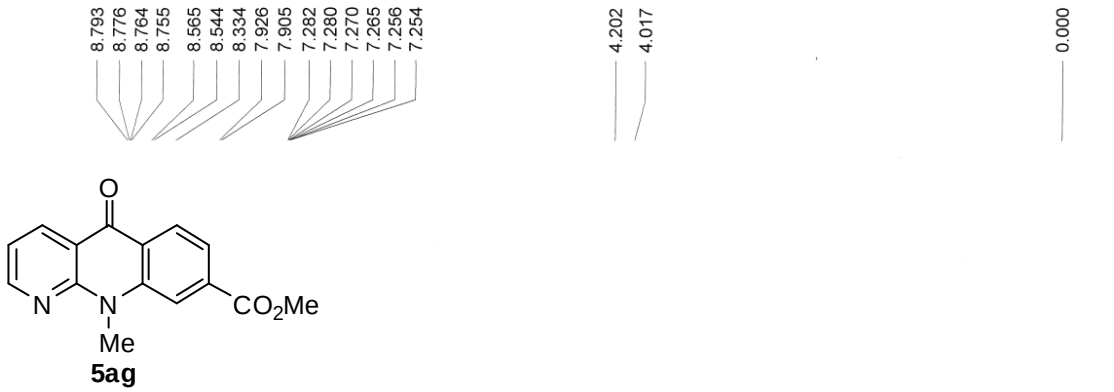


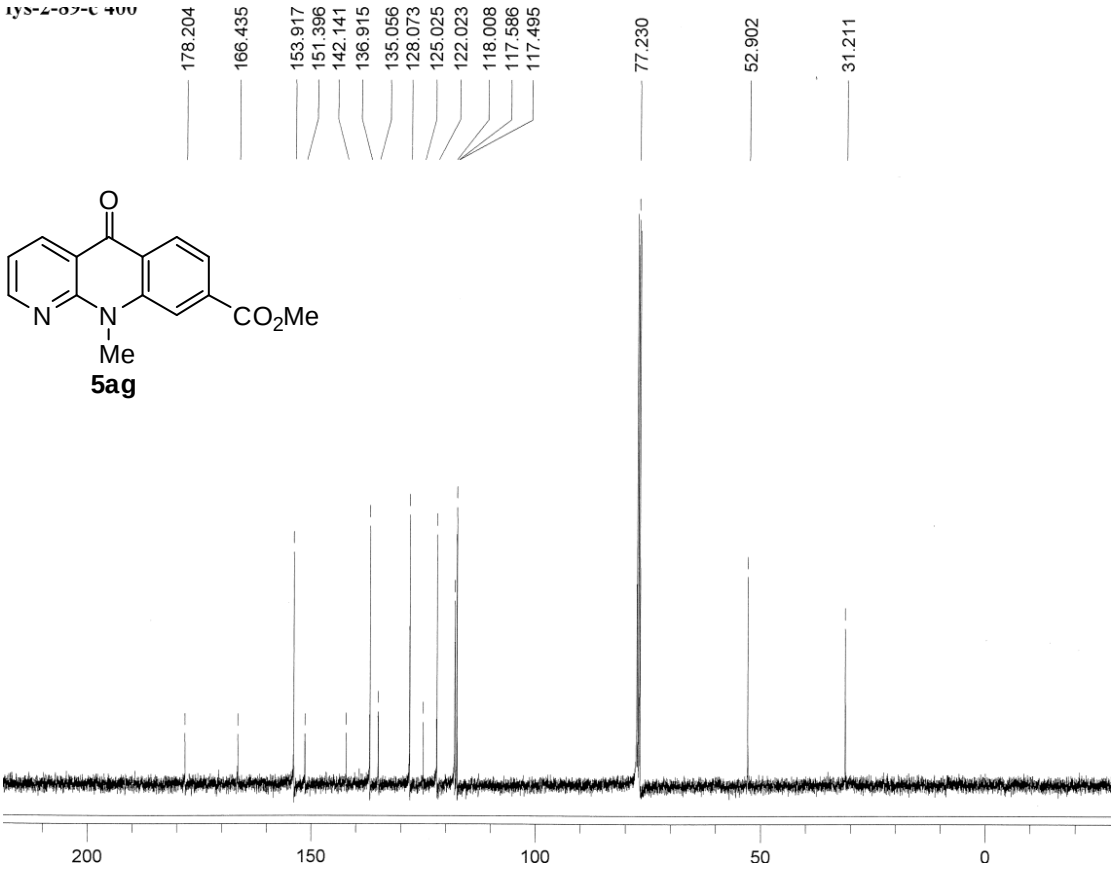


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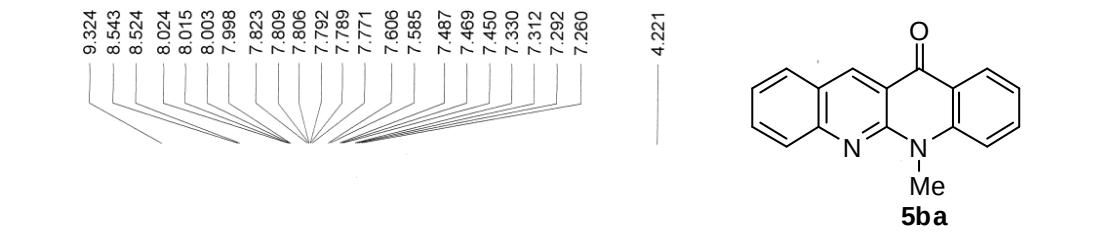


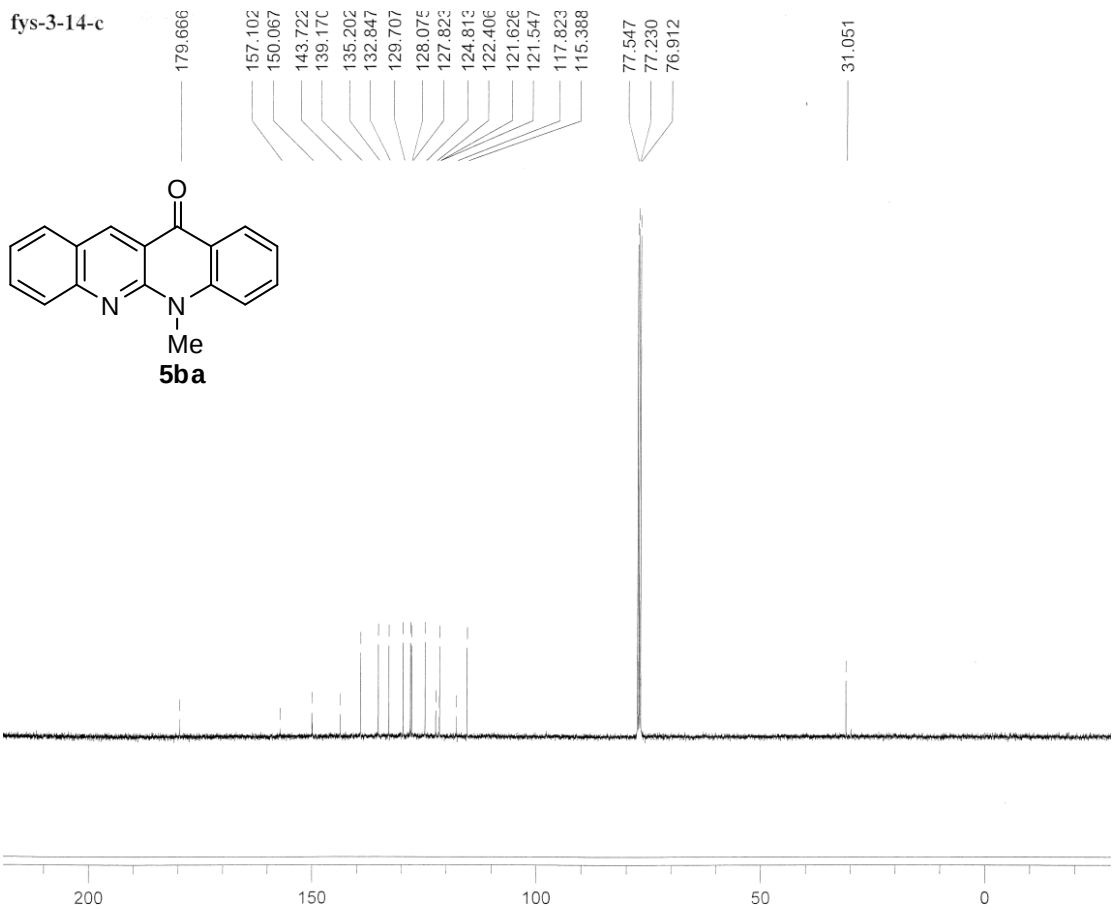


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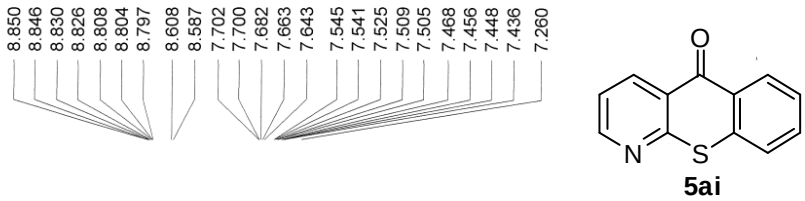


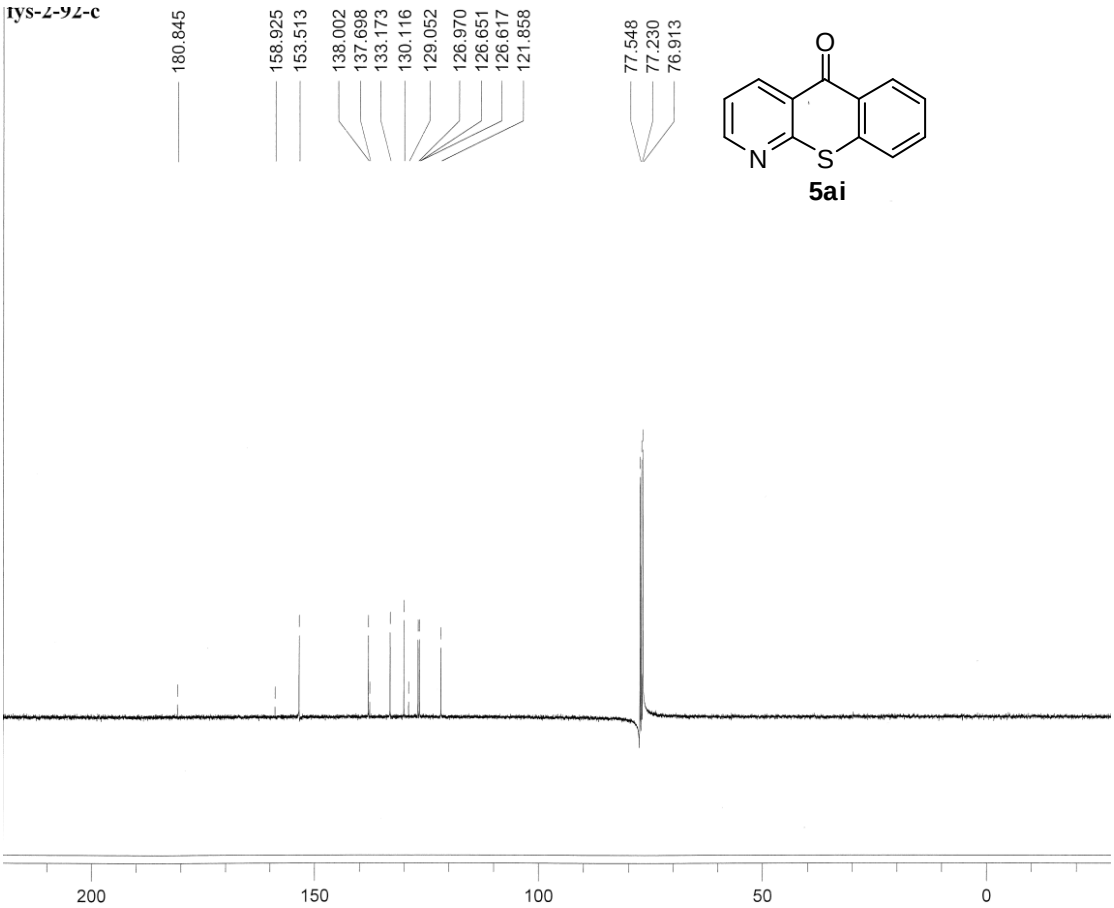


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# APPENDIX B. CHAPTER 3 $^{1}$H AND $^{13}$C NMR SPECTRA

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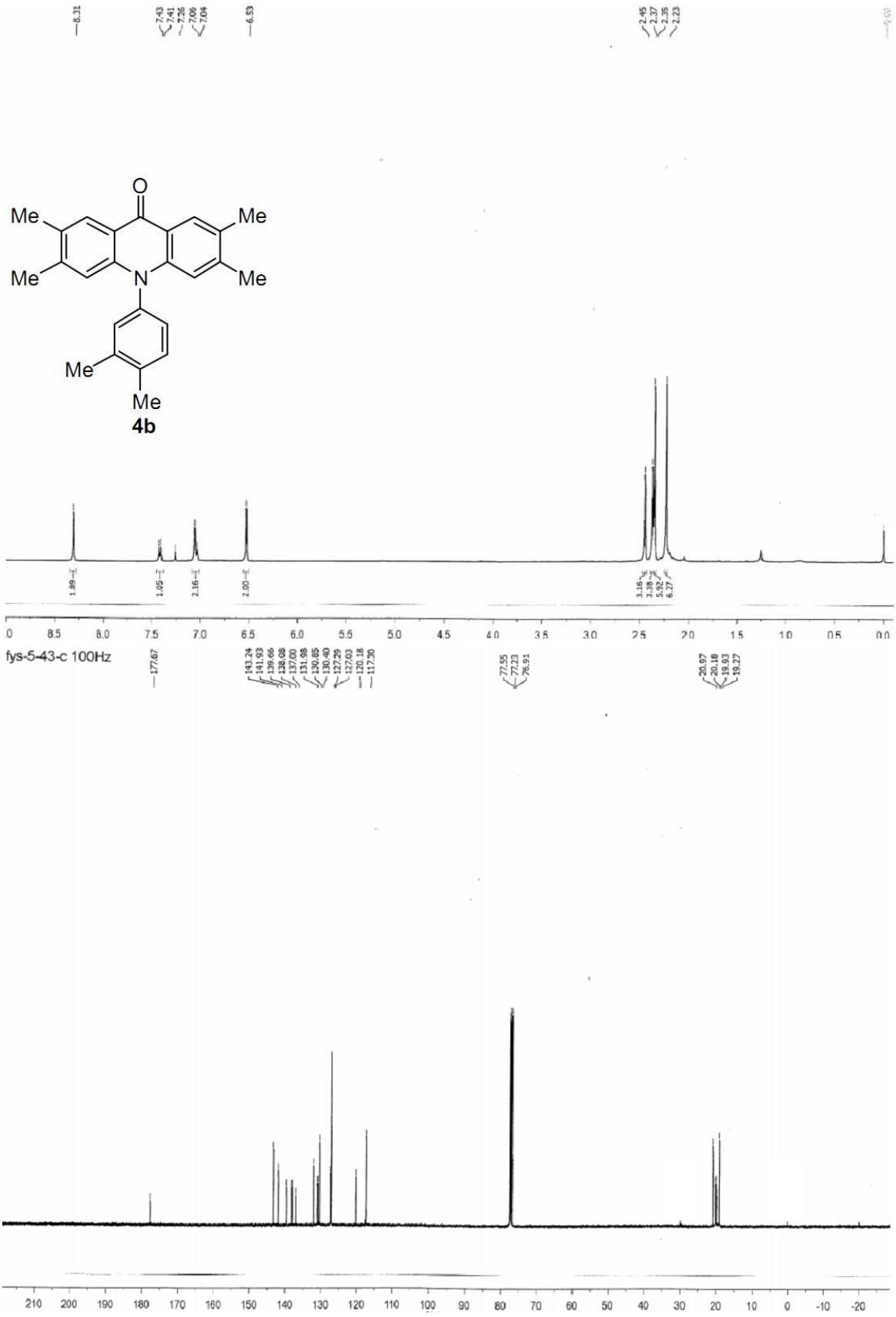


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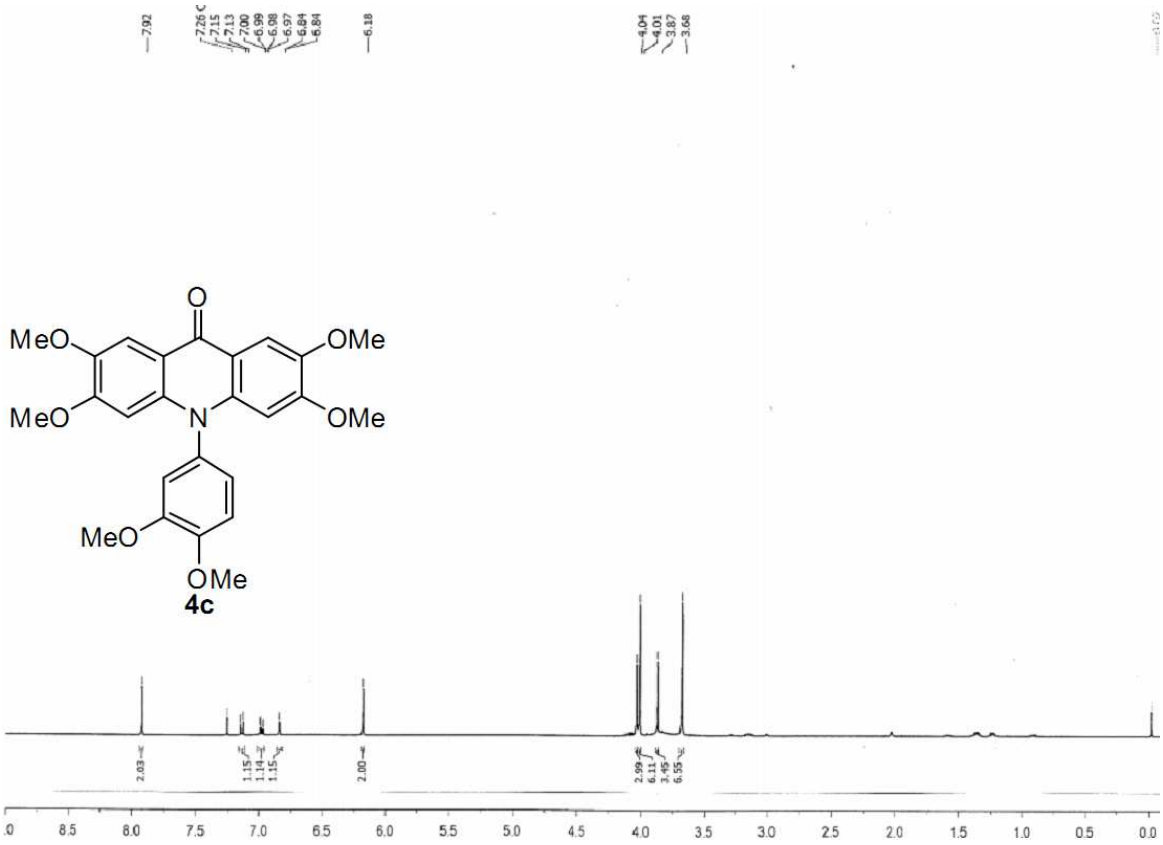


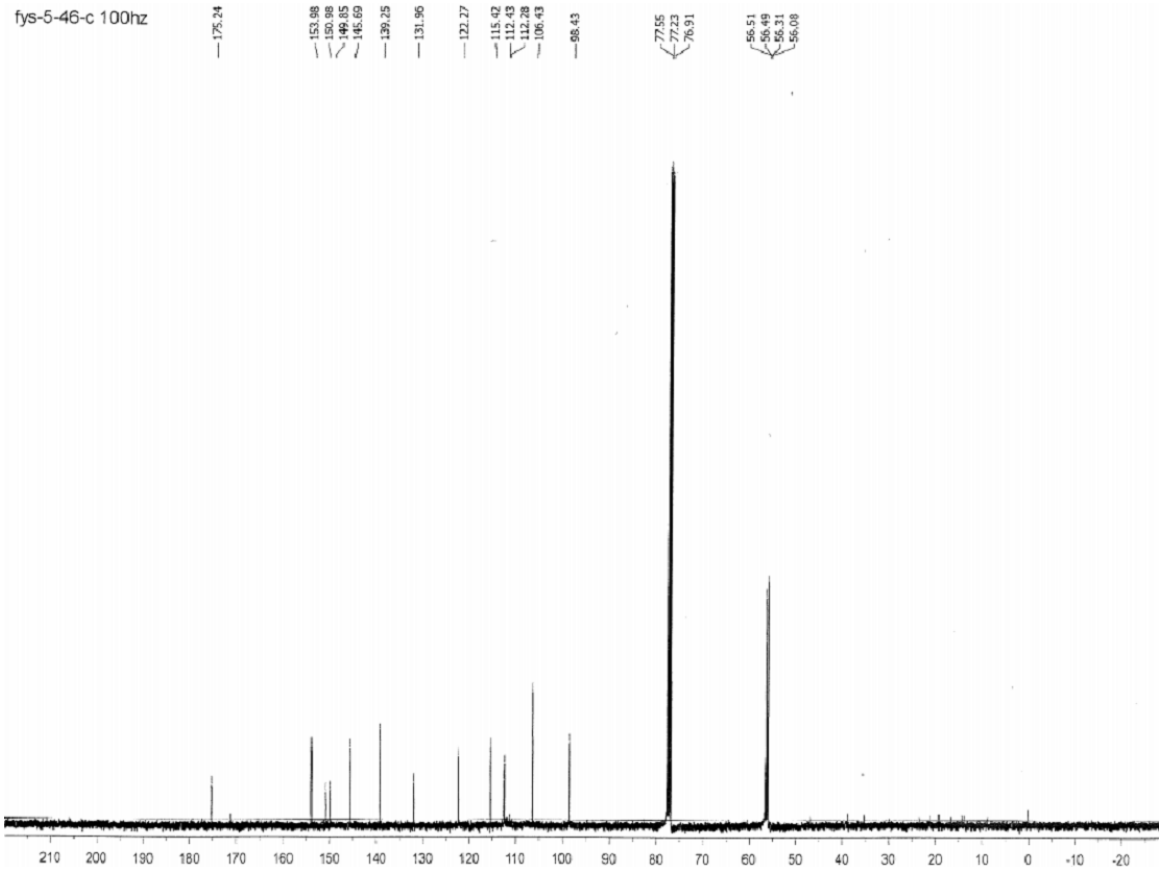


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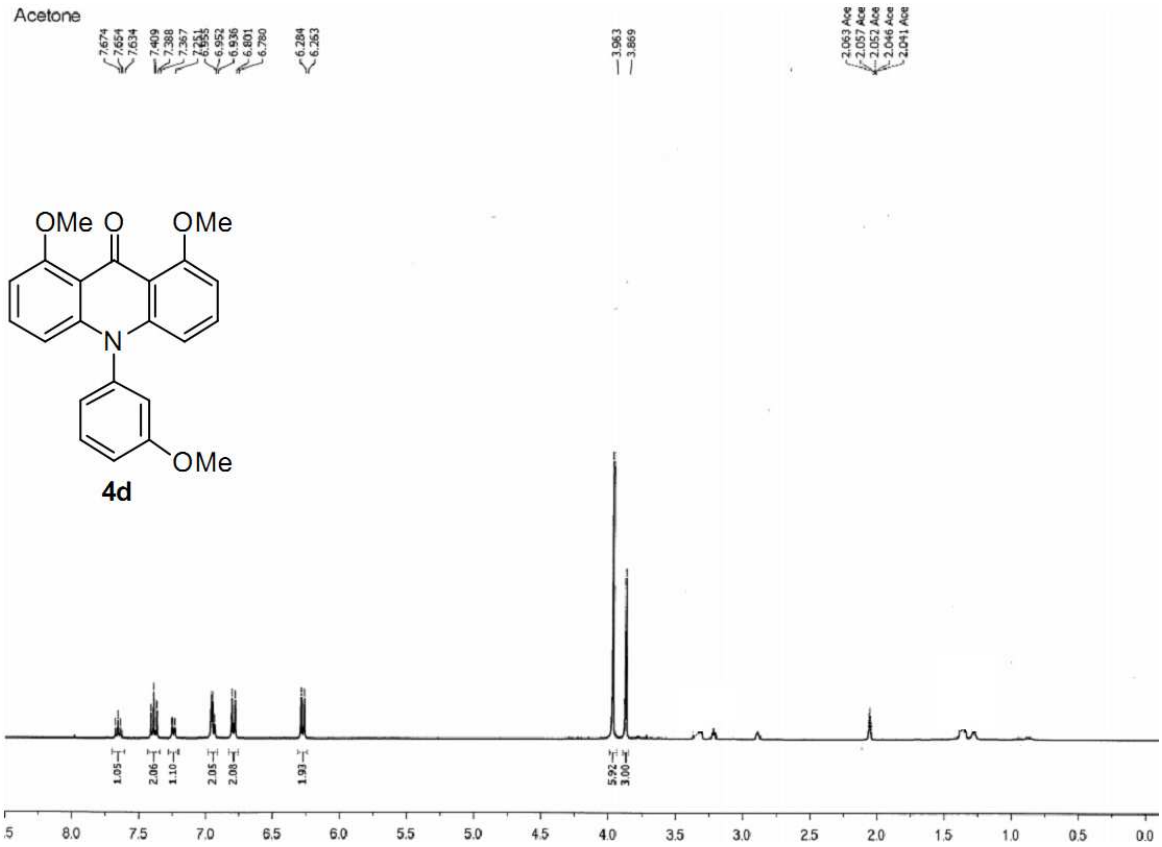


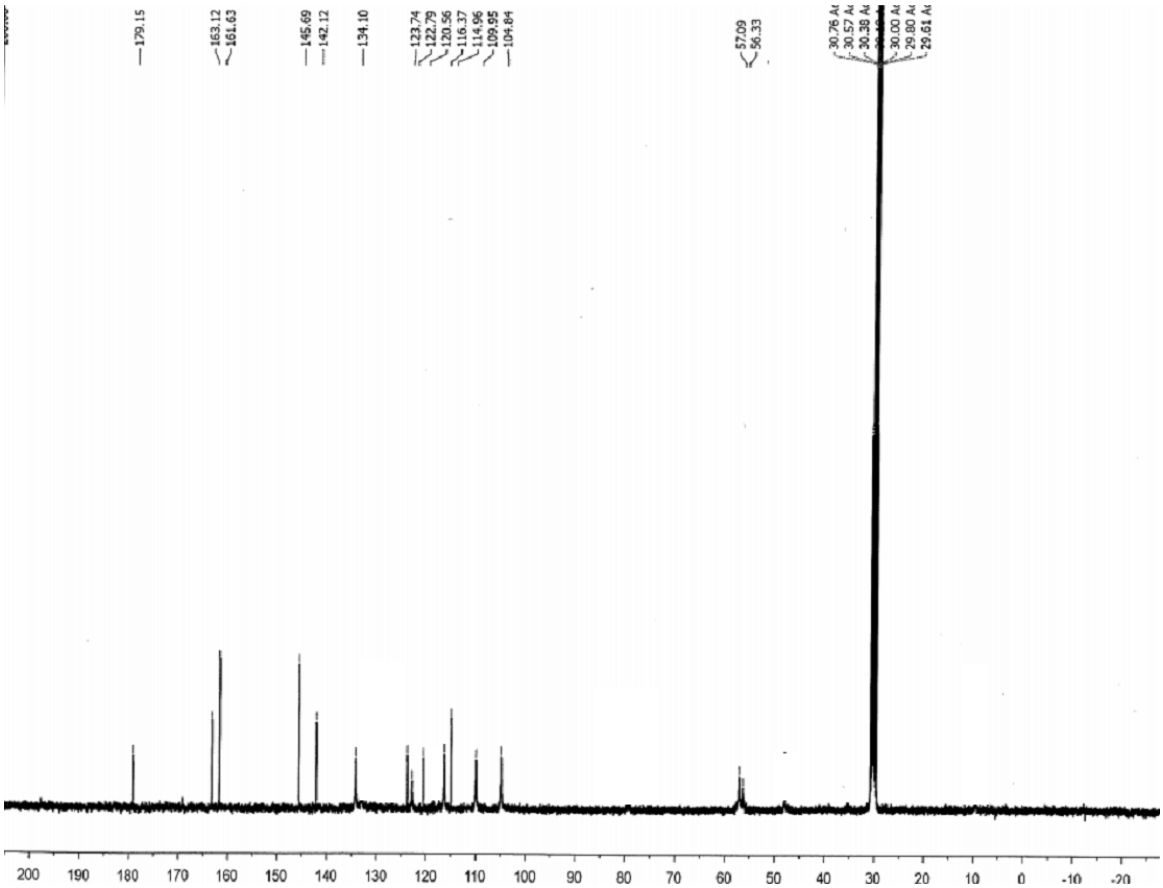

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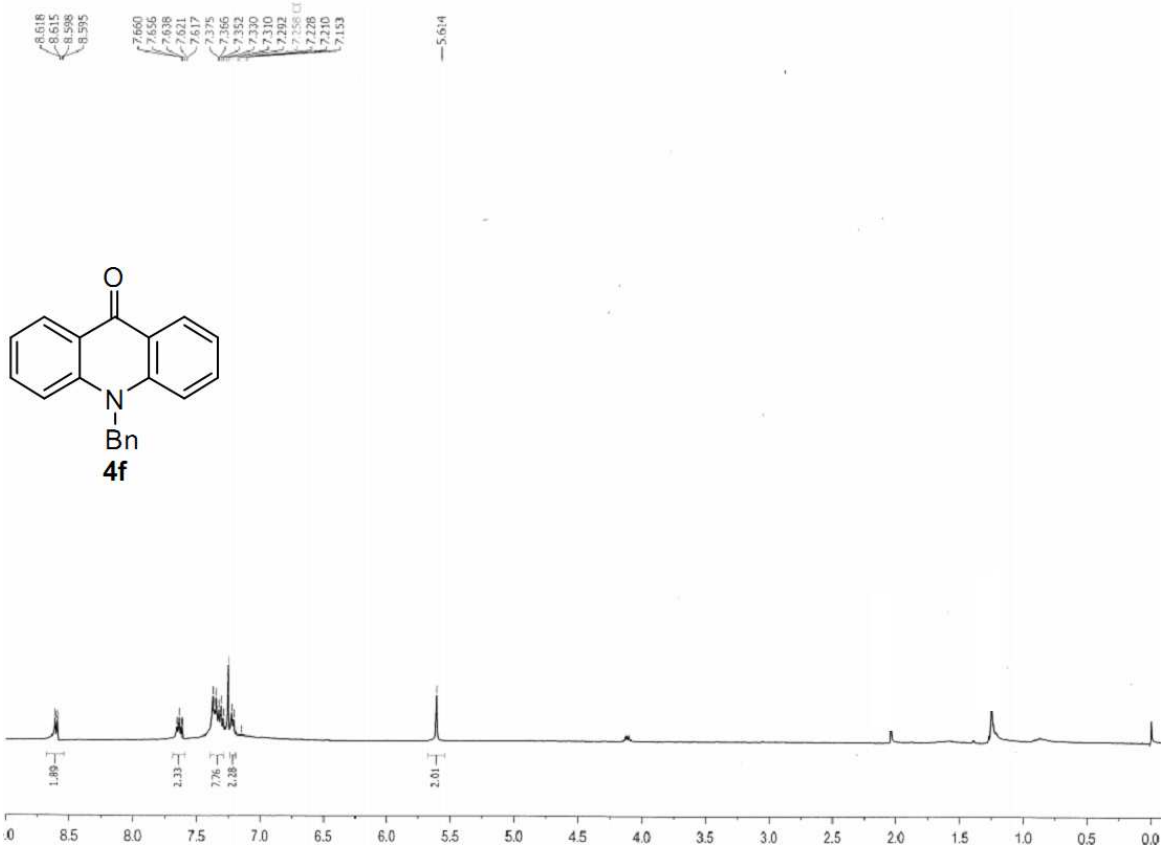


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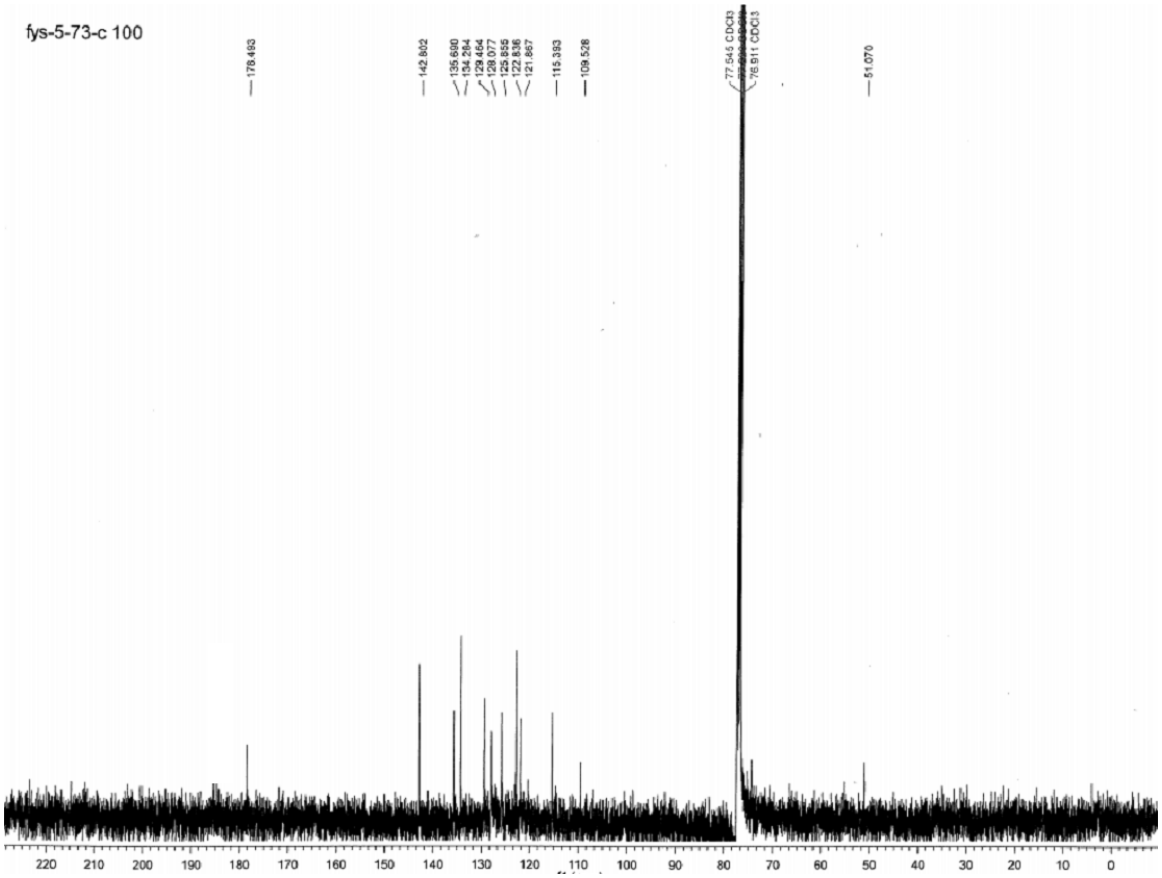


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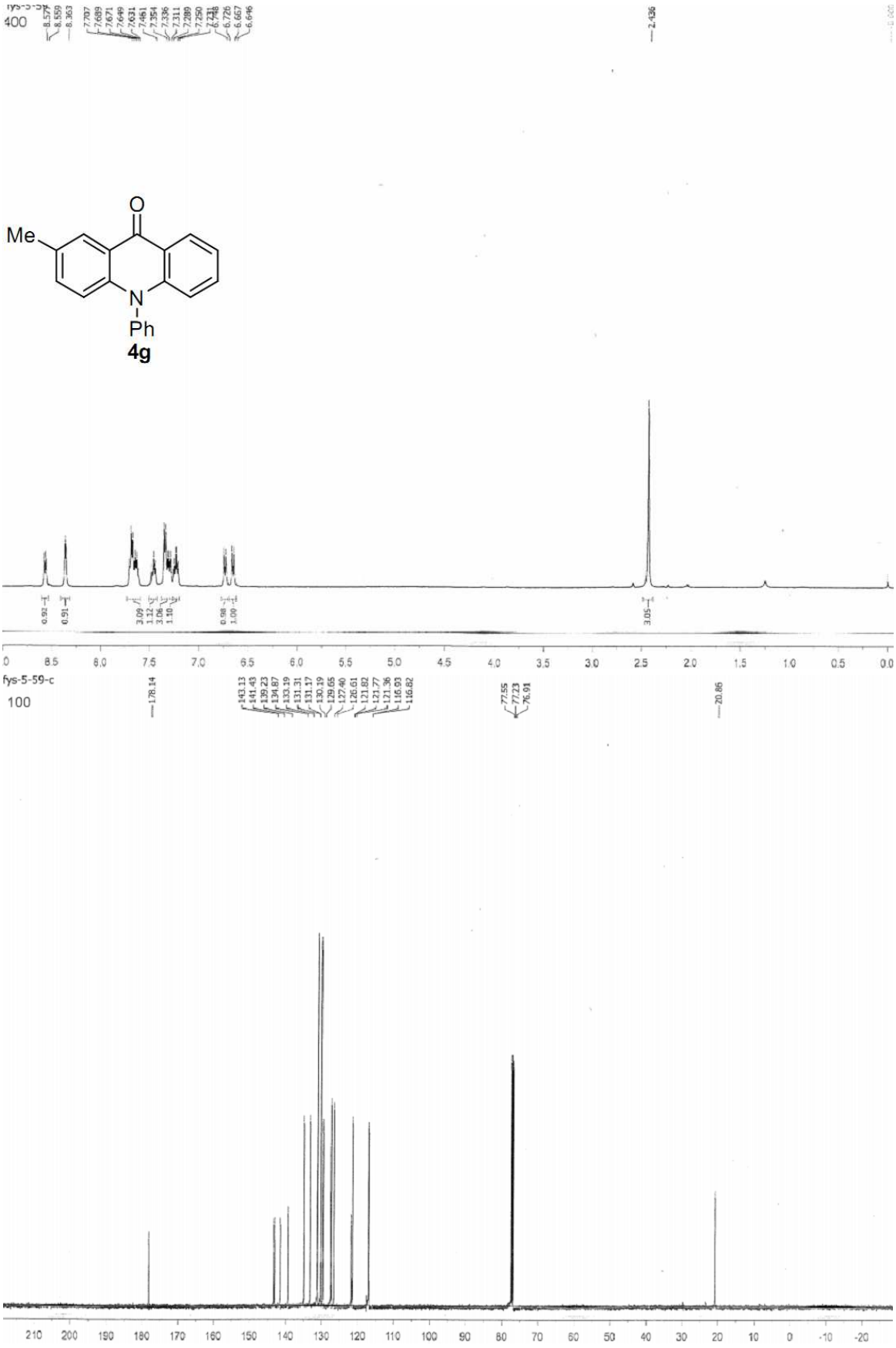


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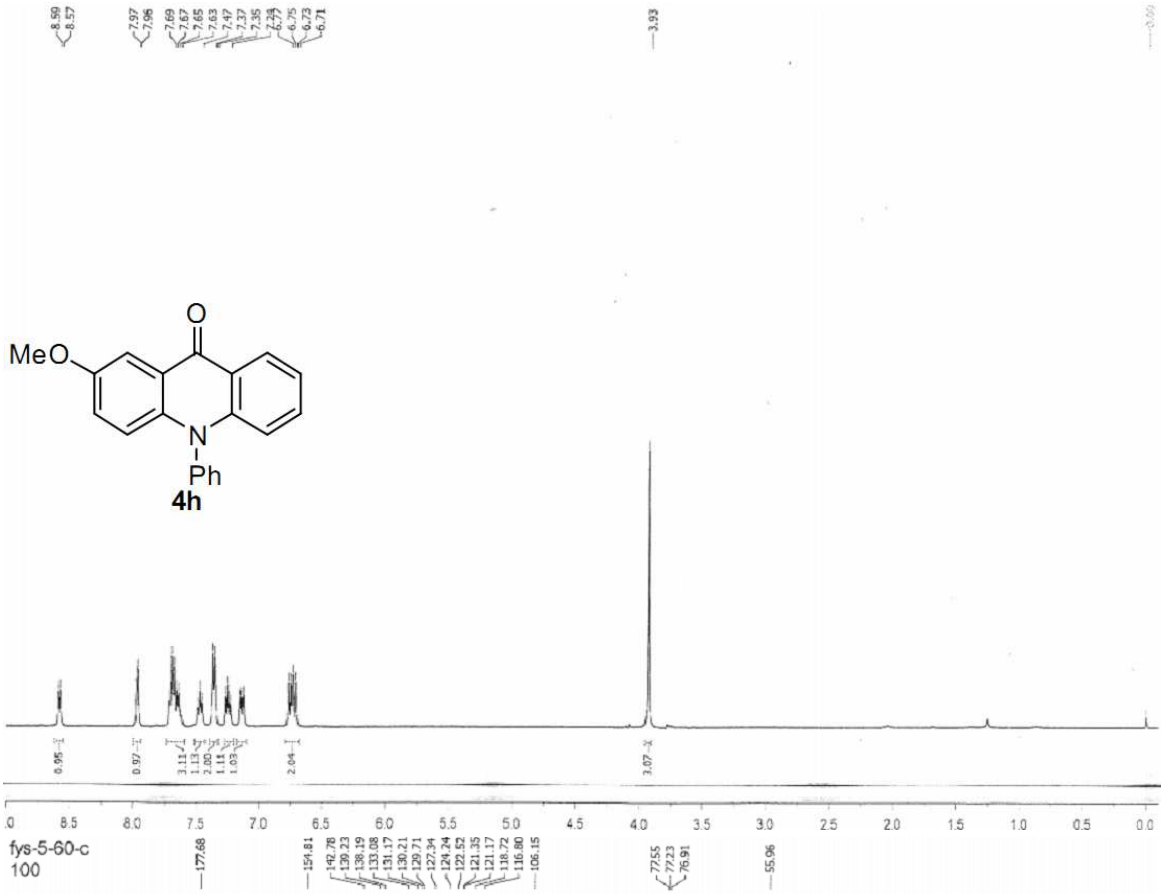


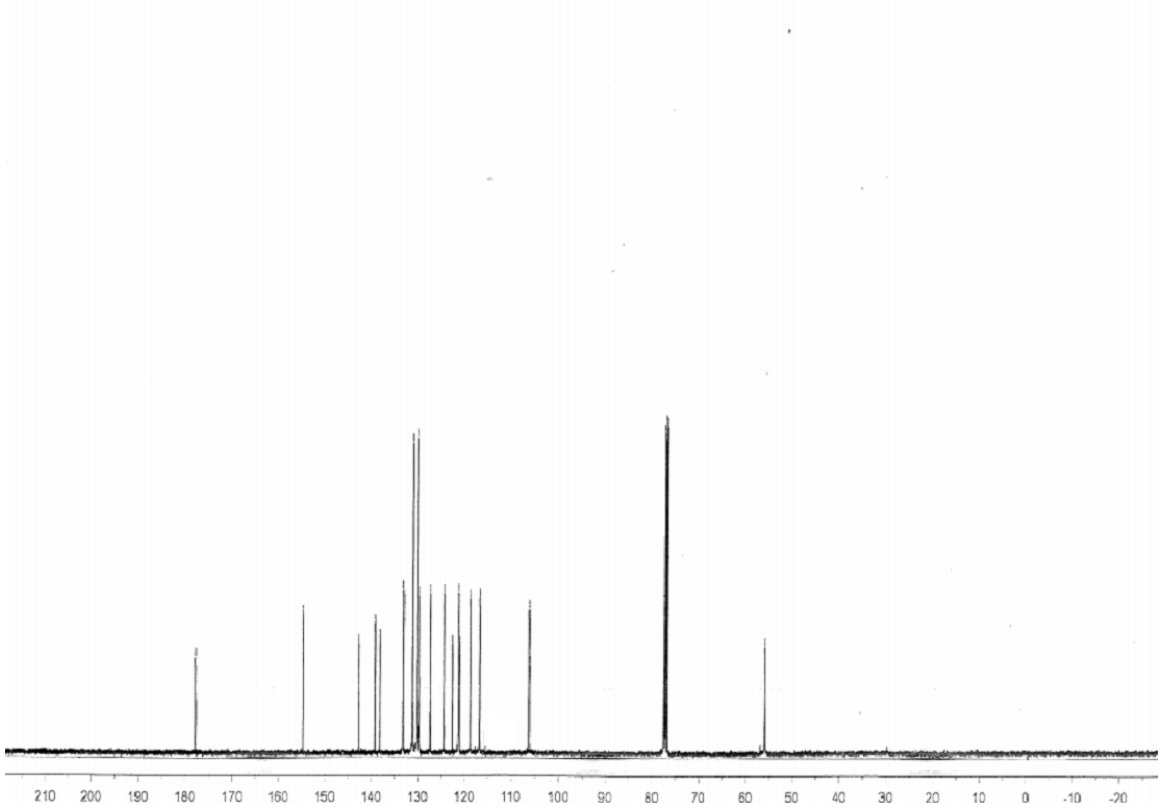

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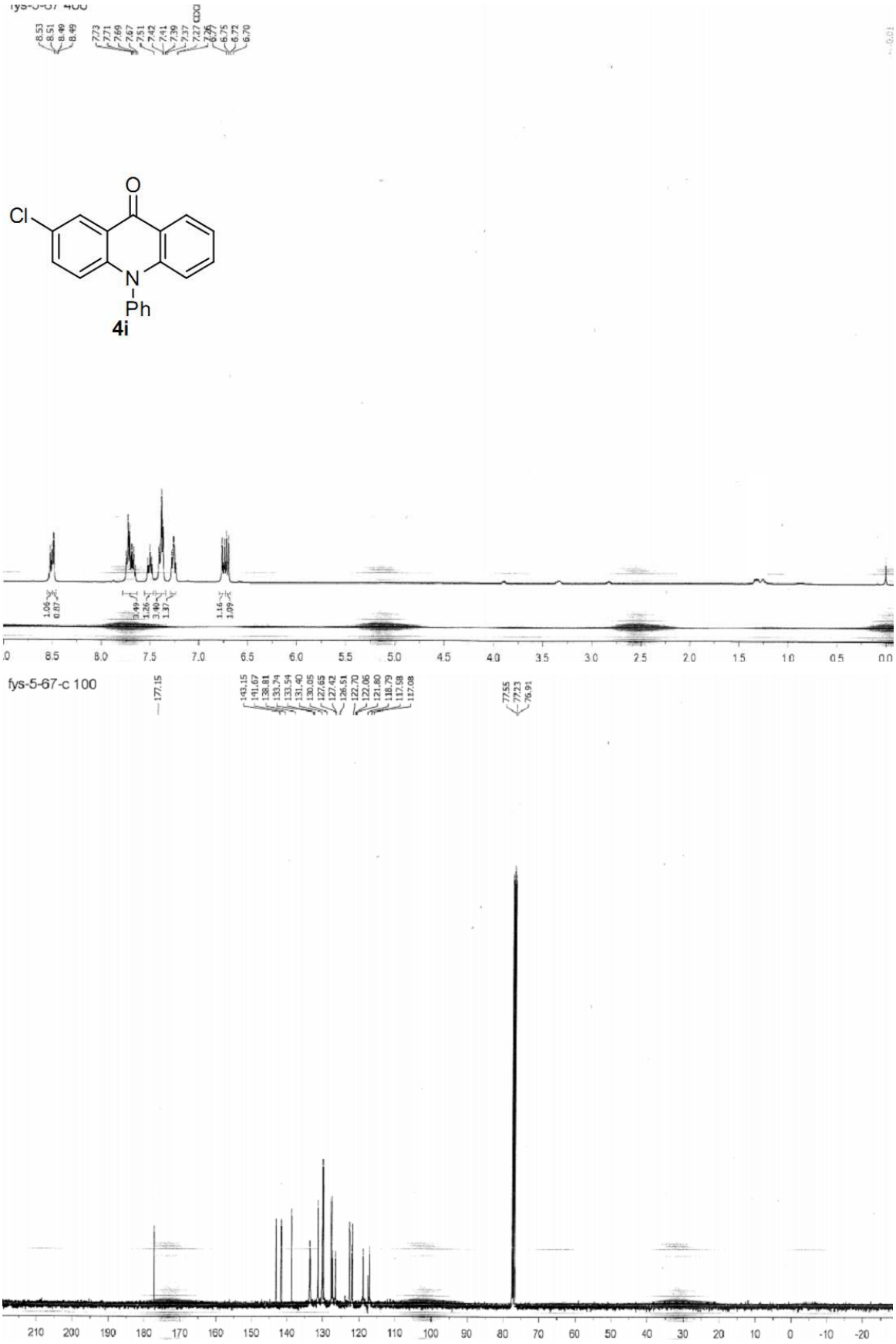


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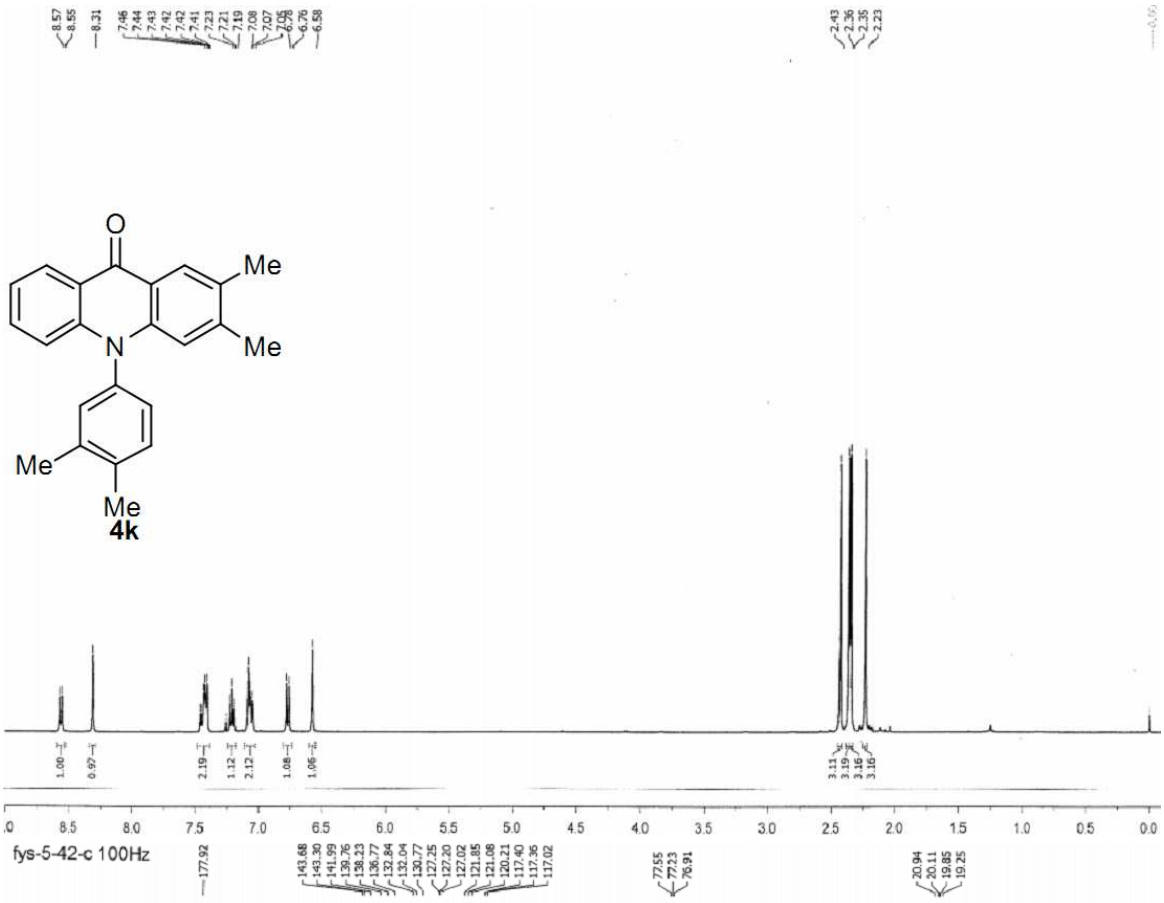


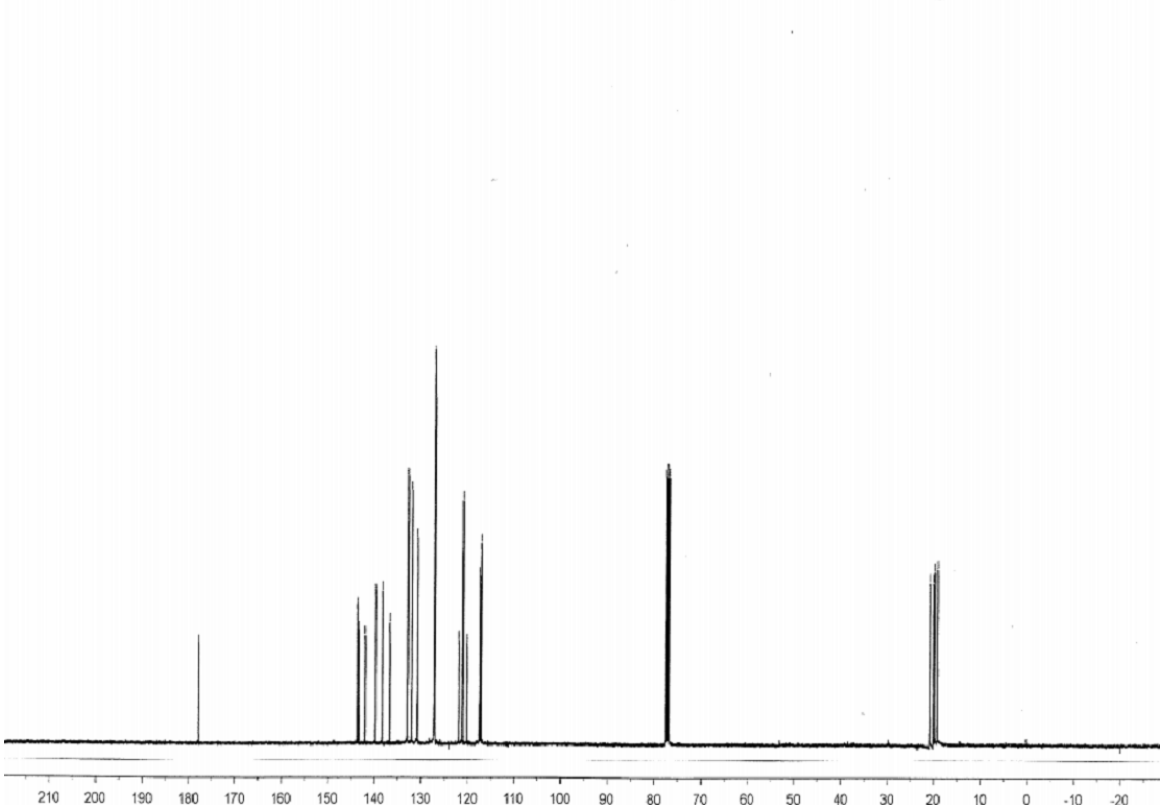


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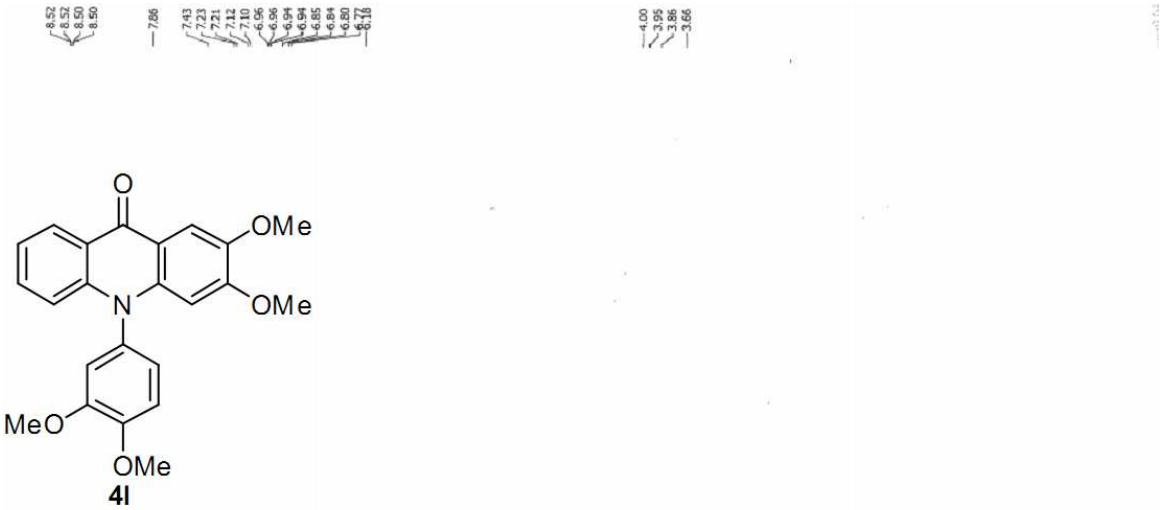


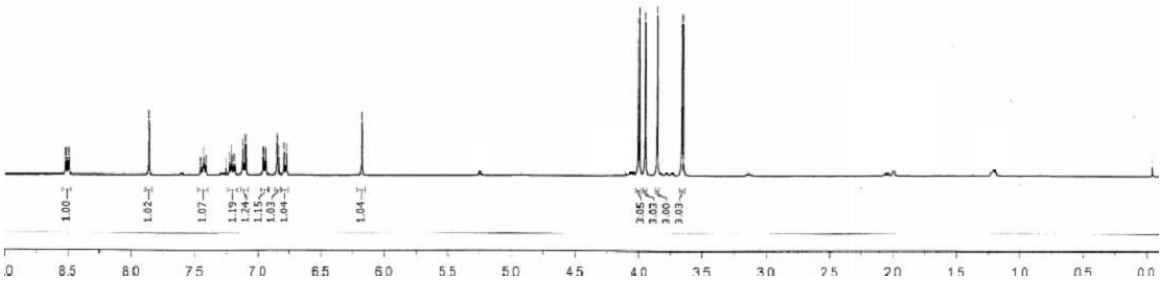

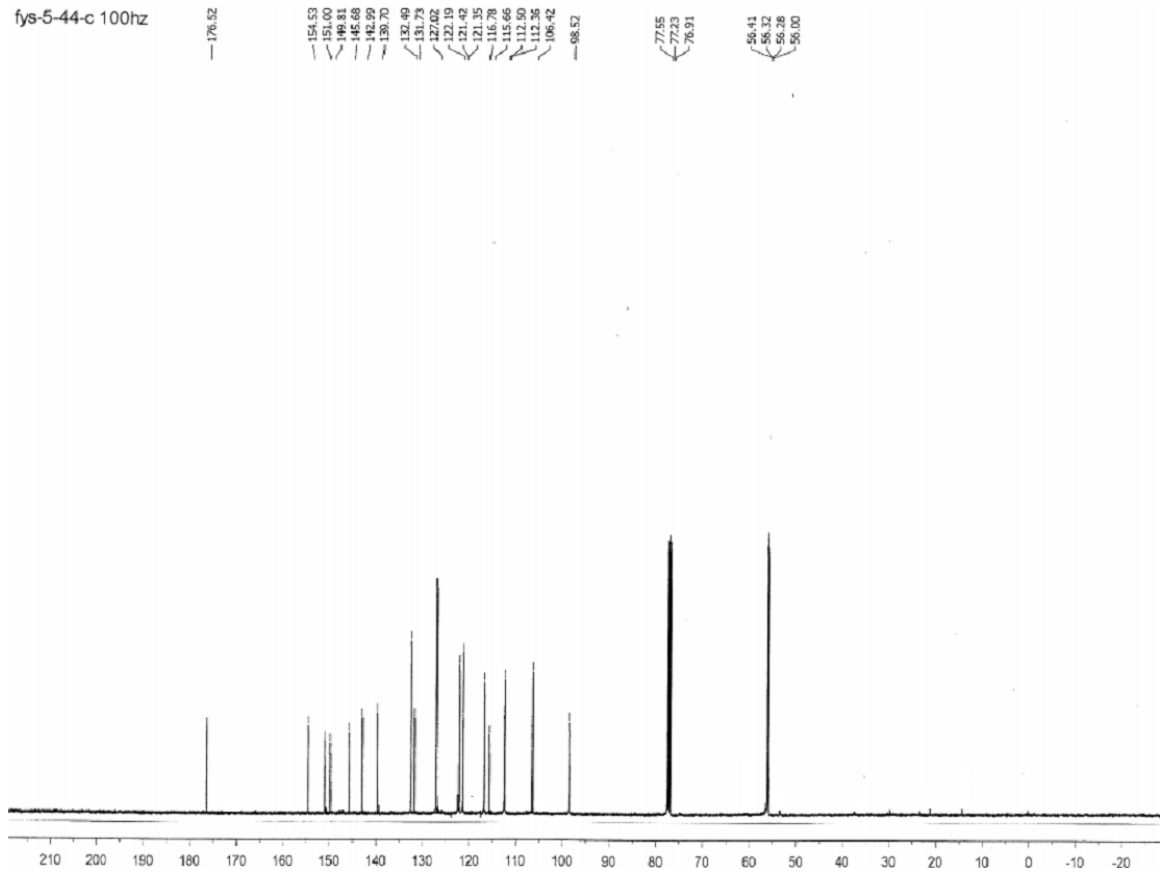


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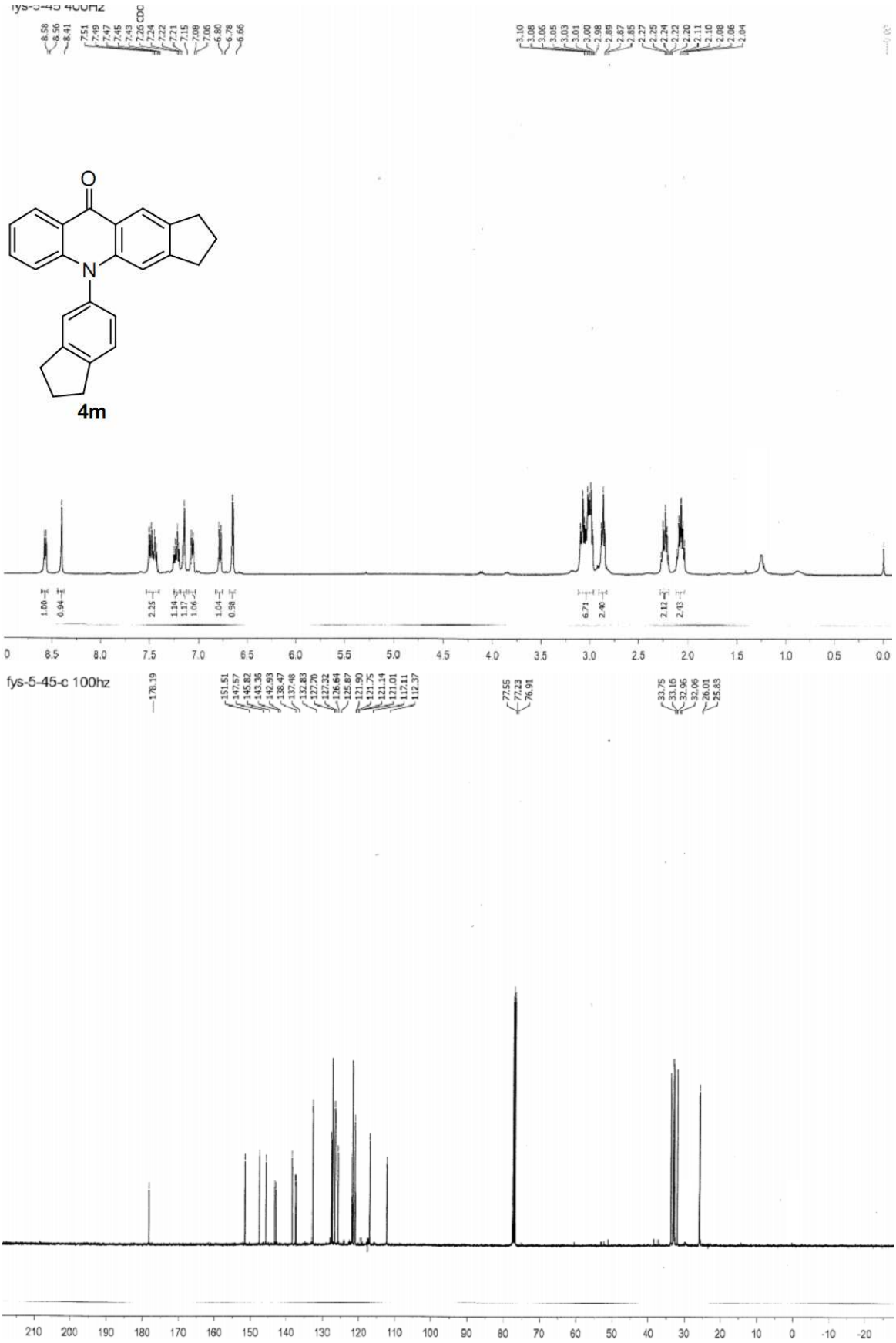


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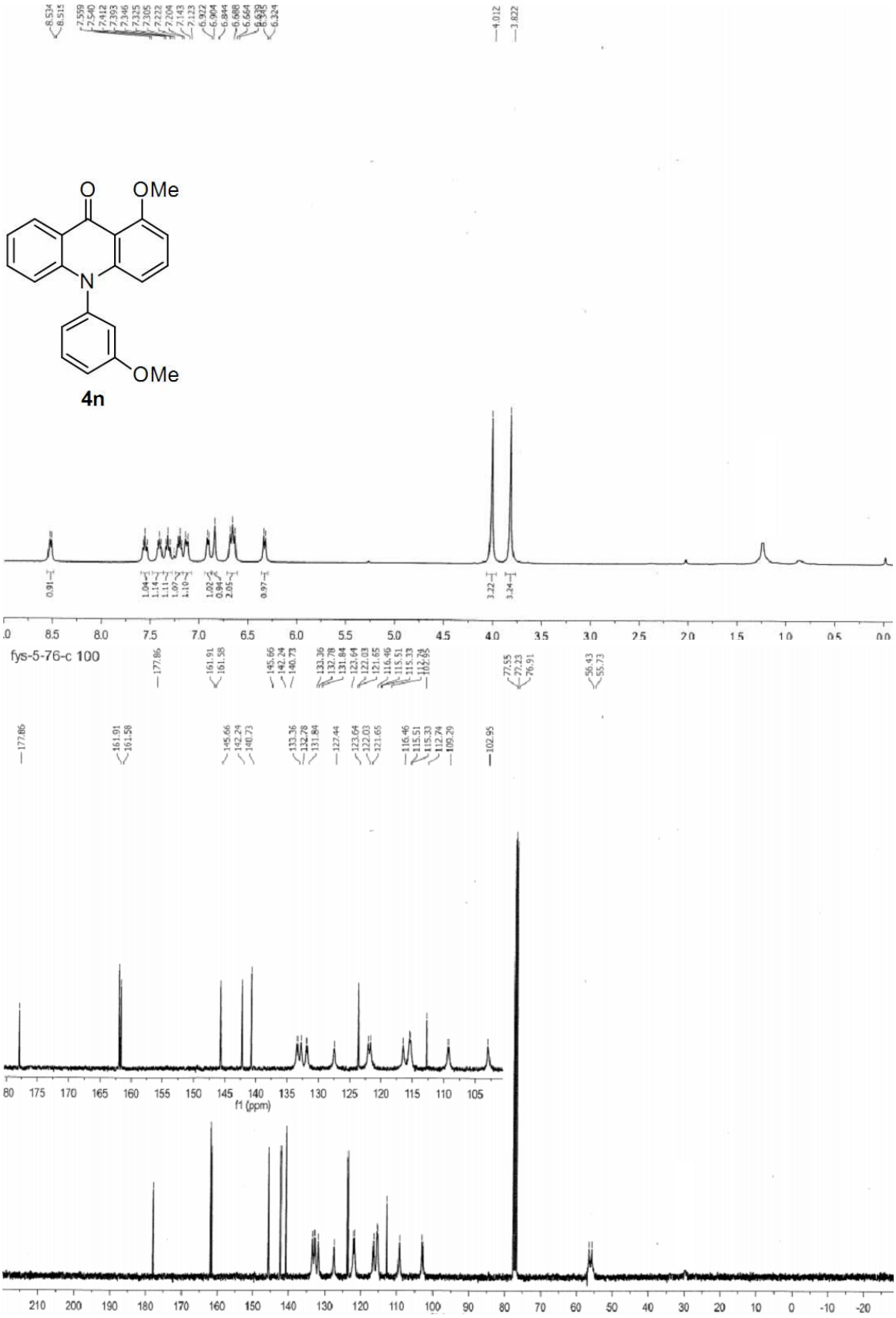


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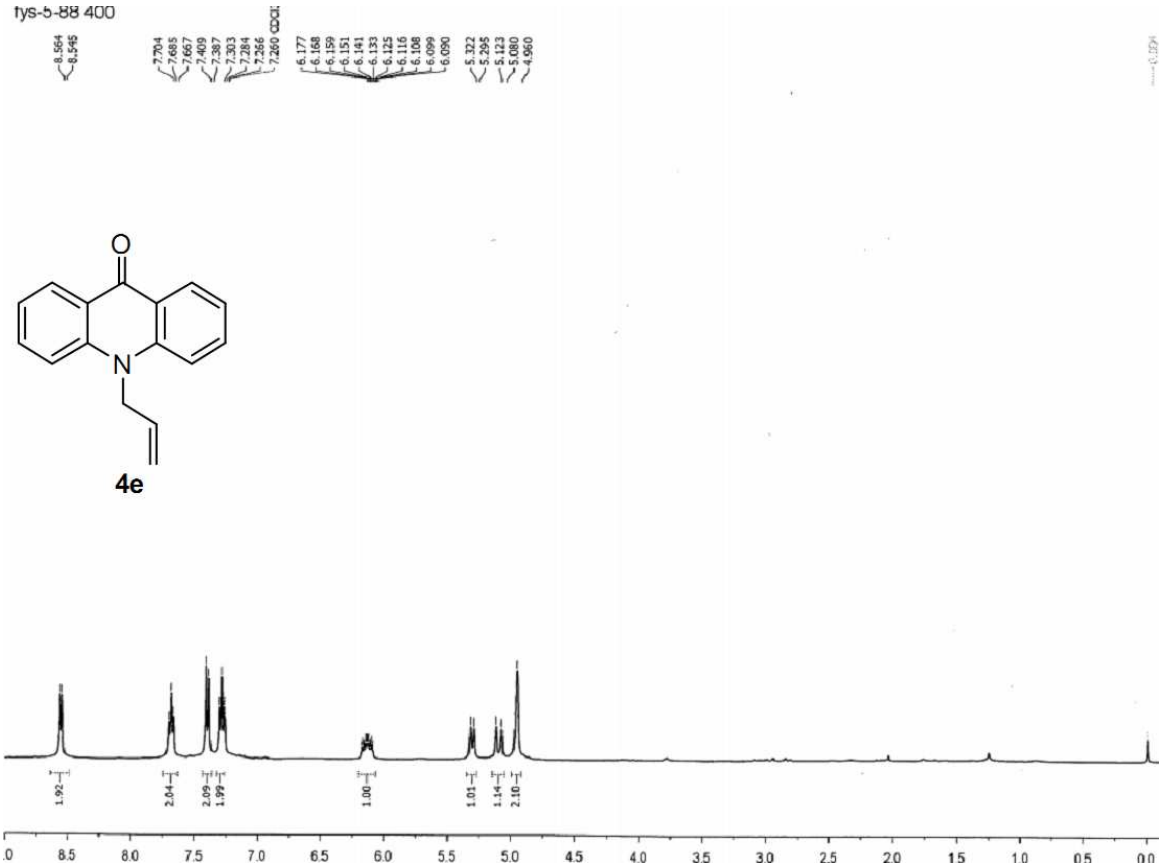


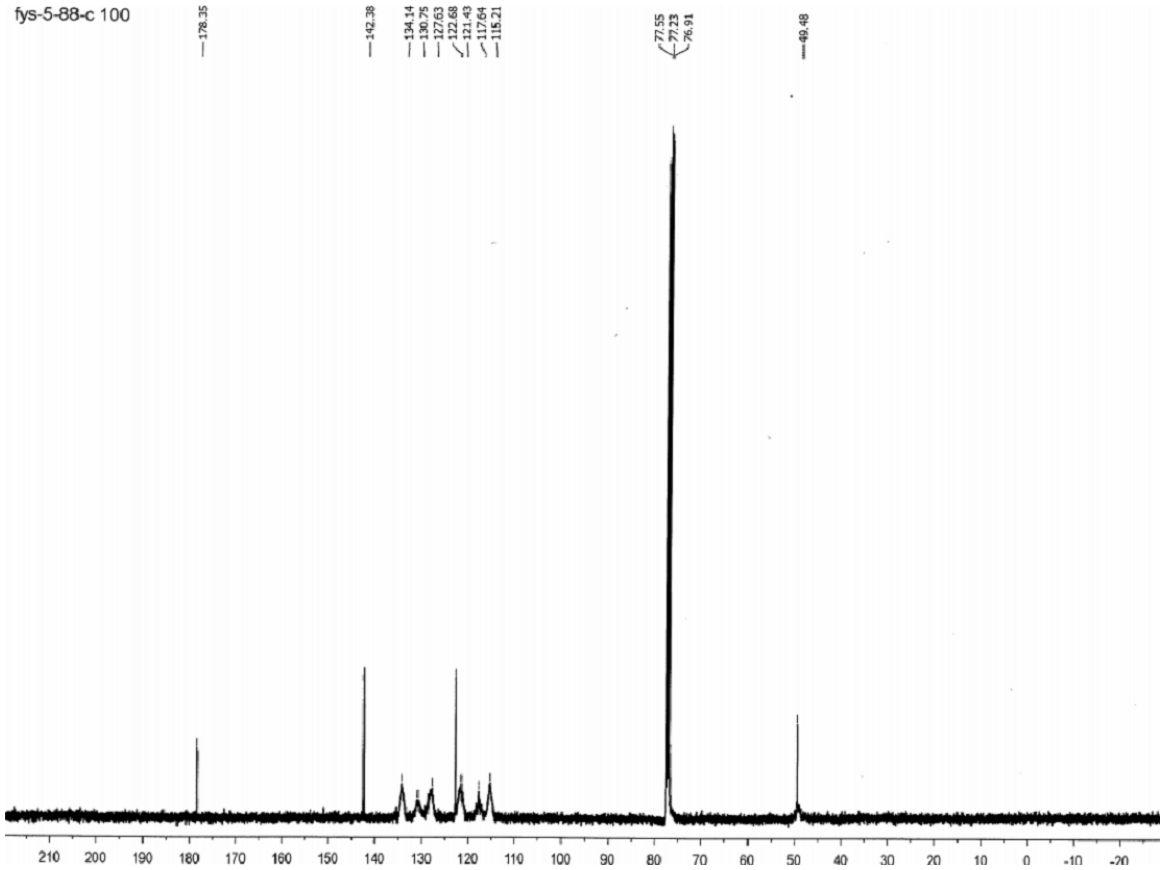


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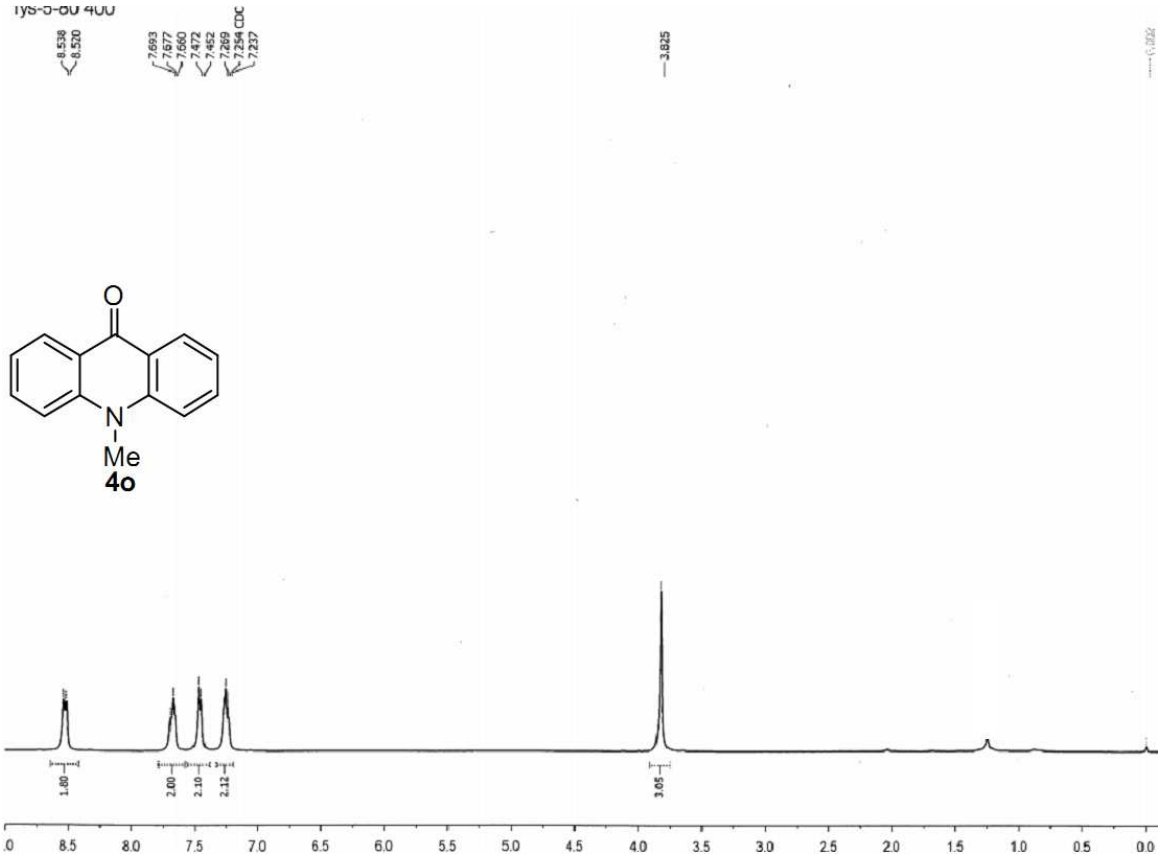


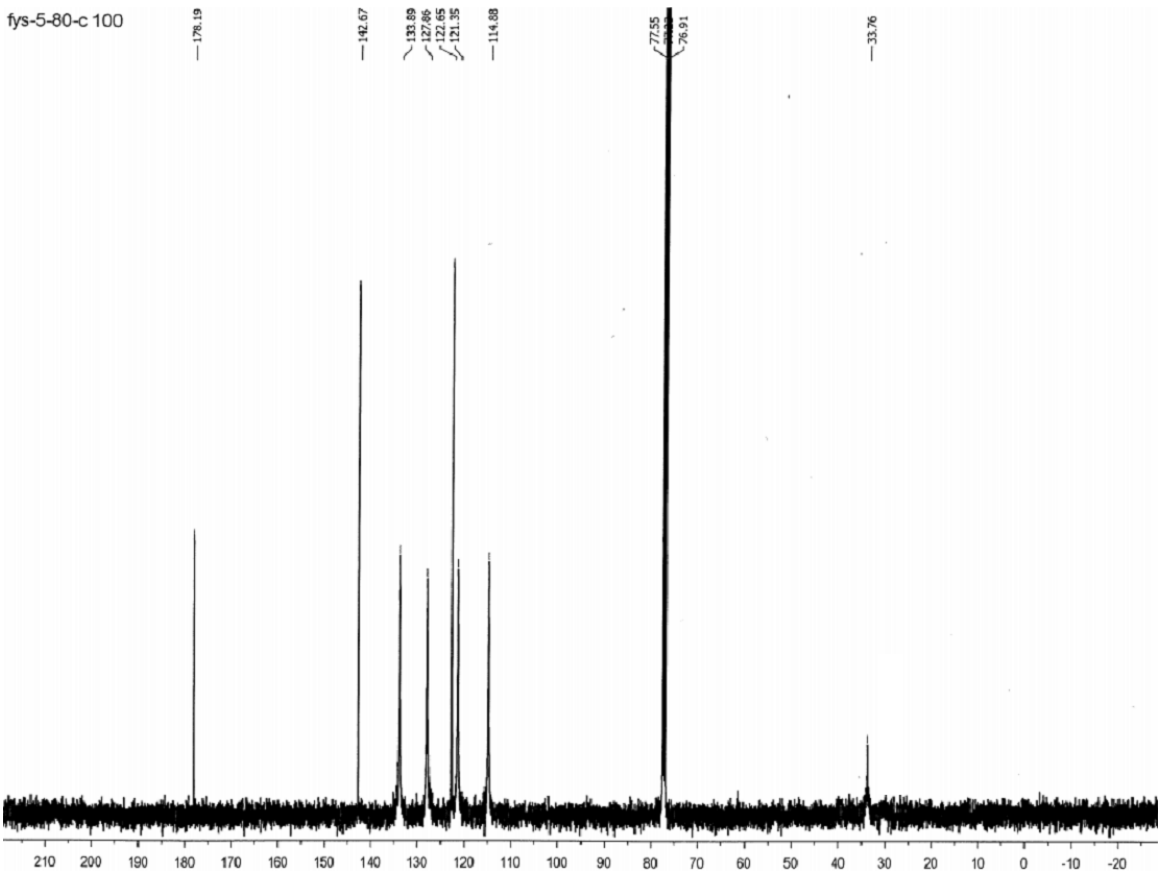


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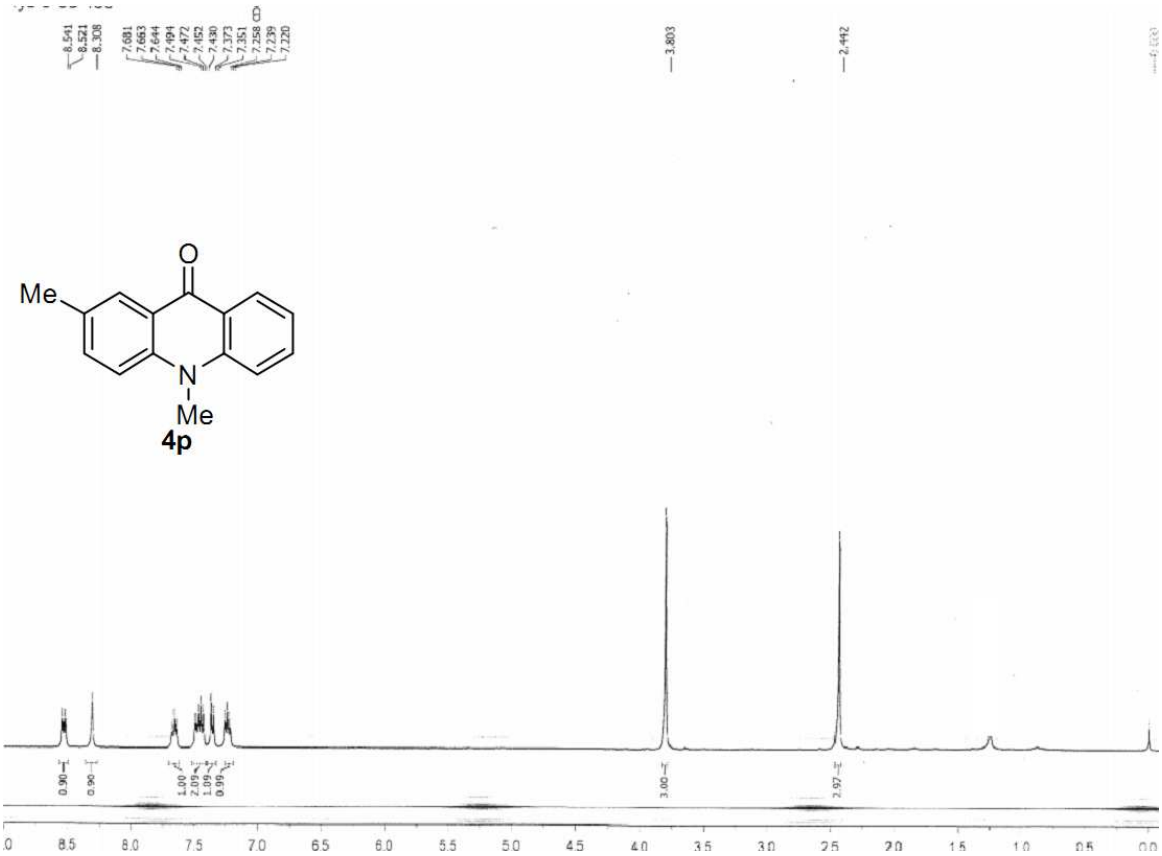


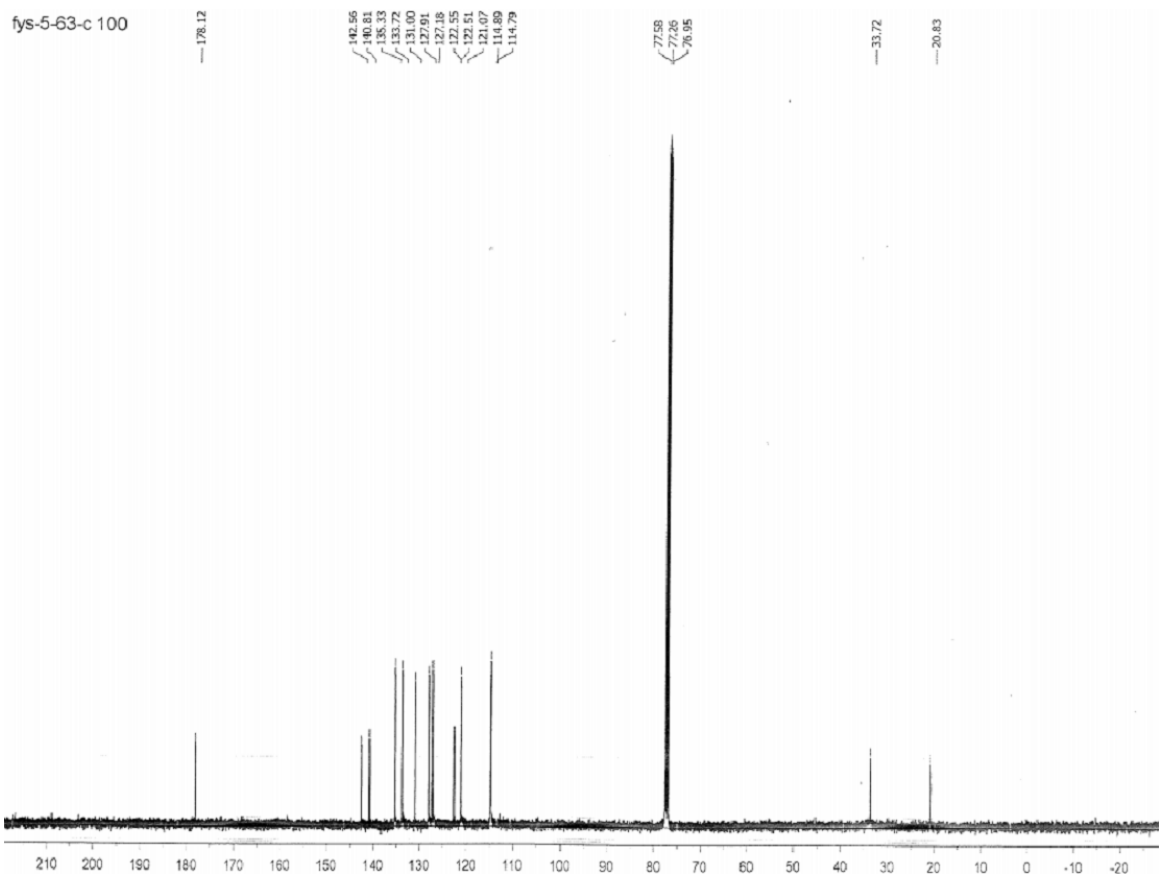


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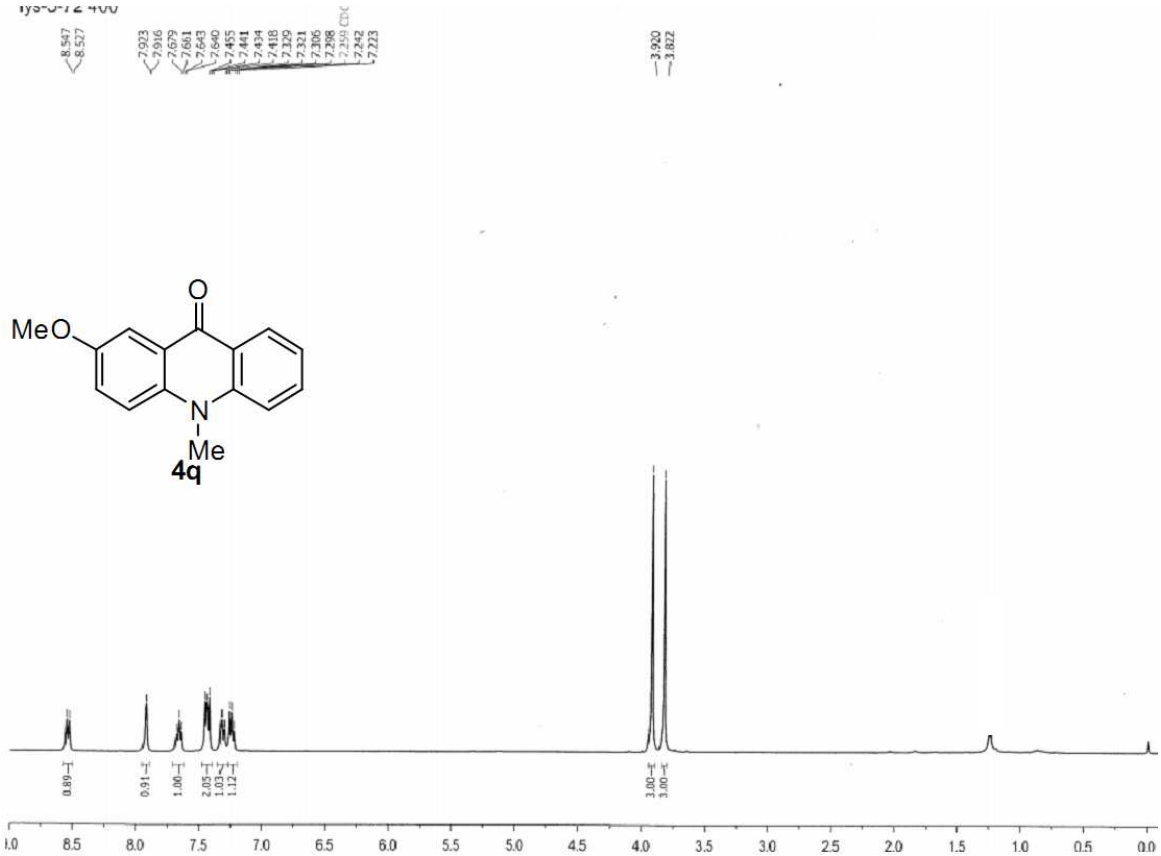


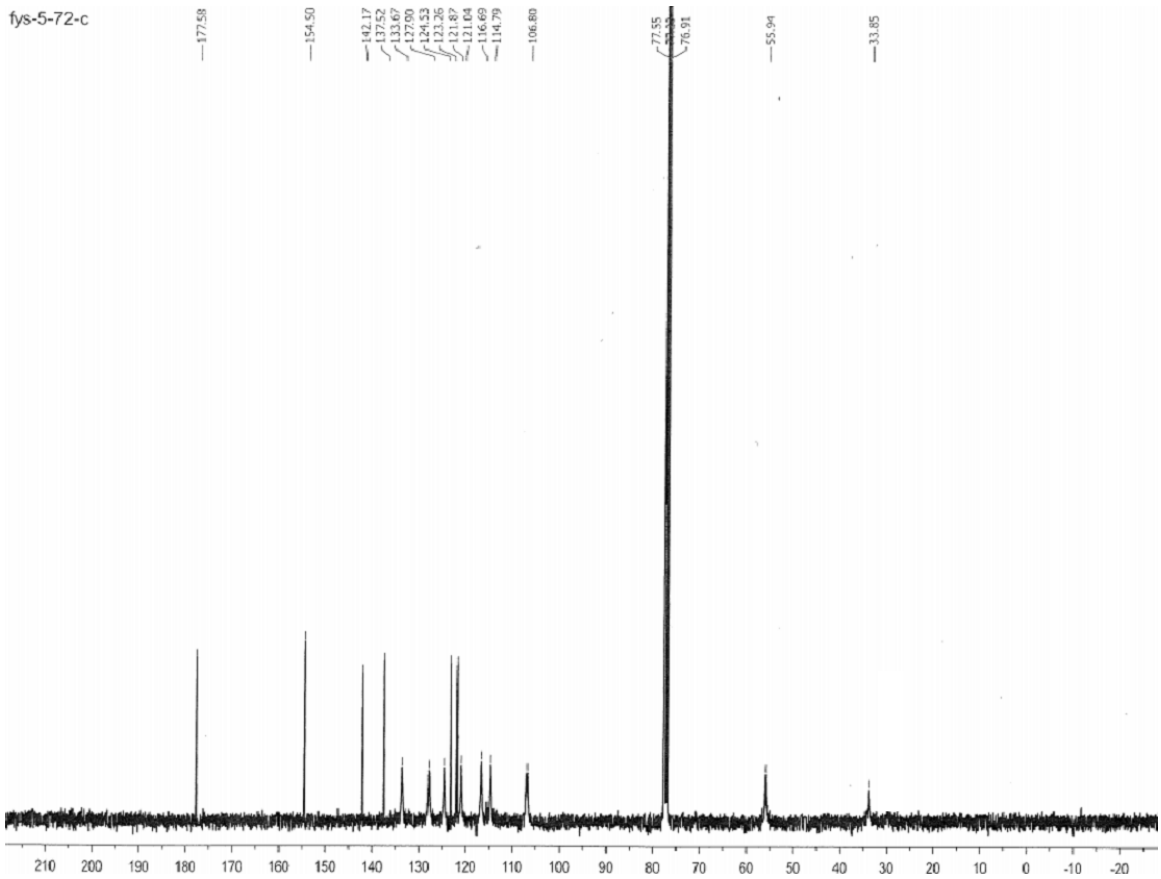


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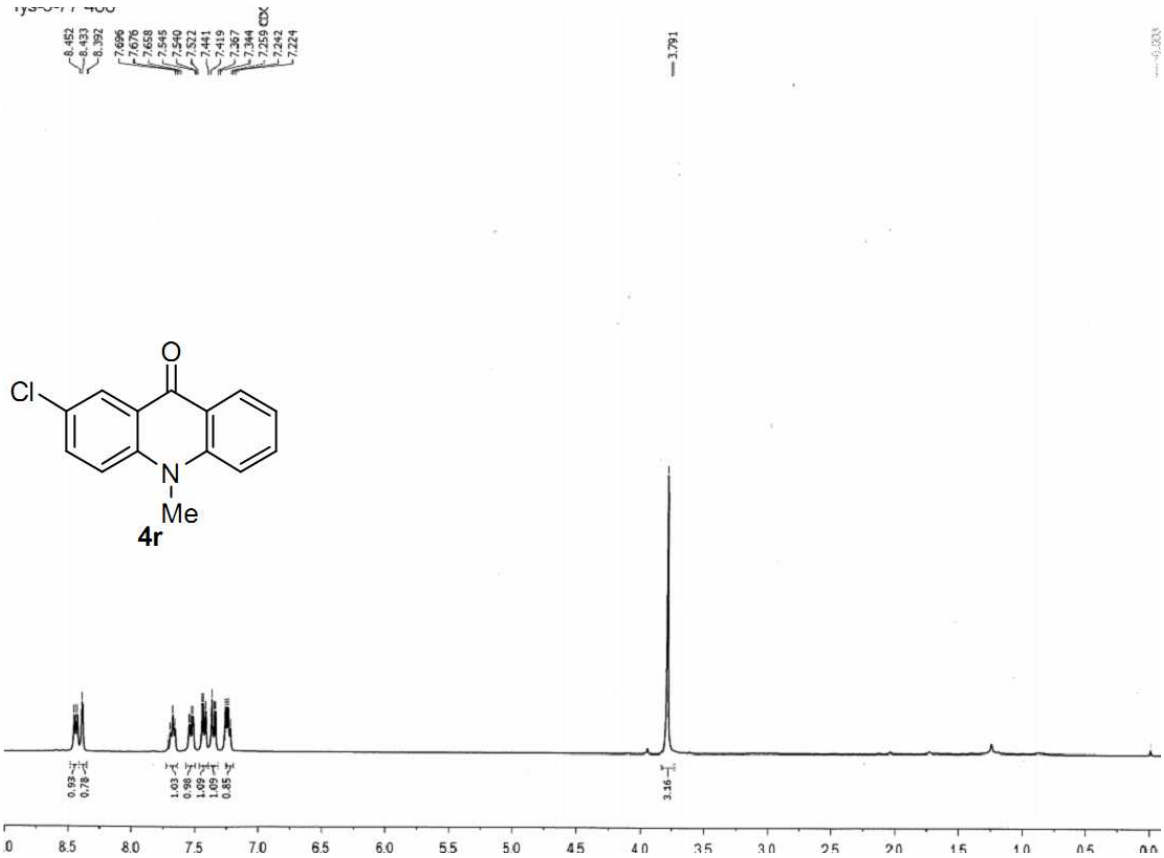


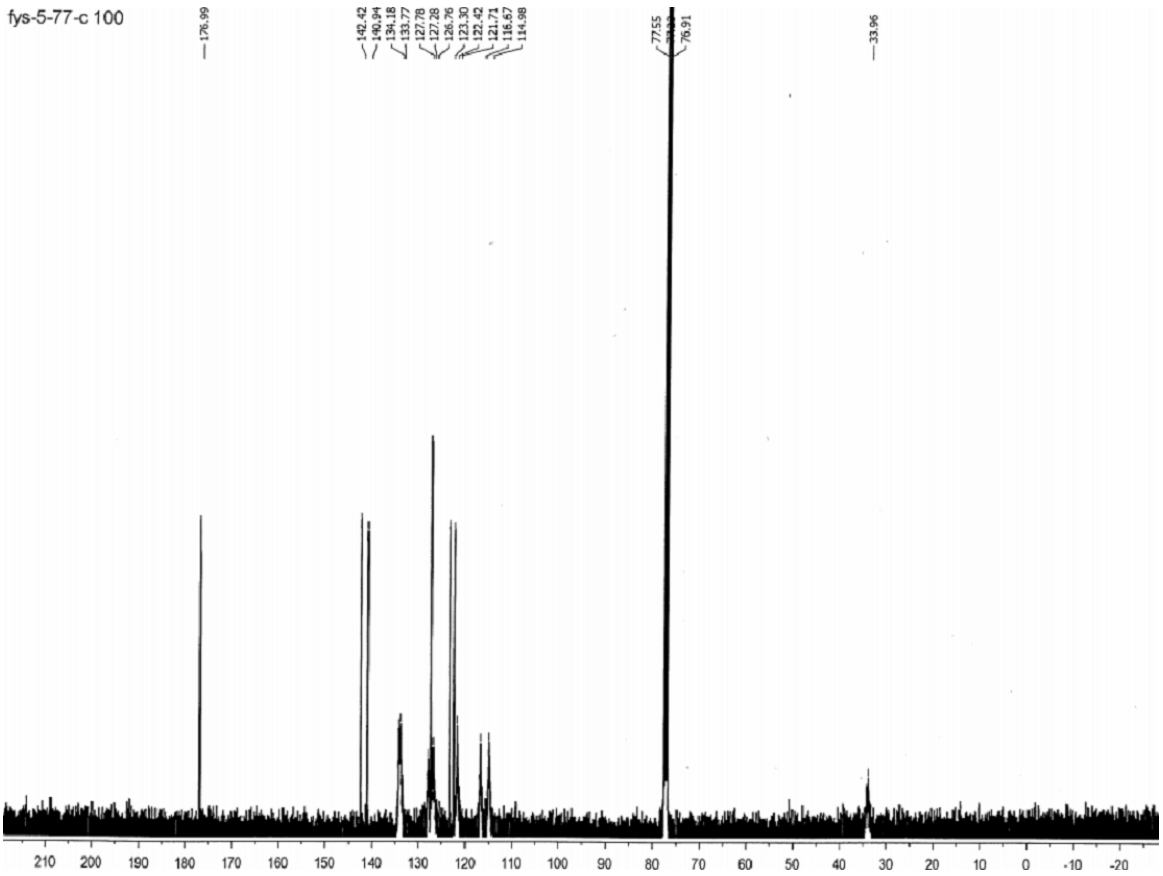


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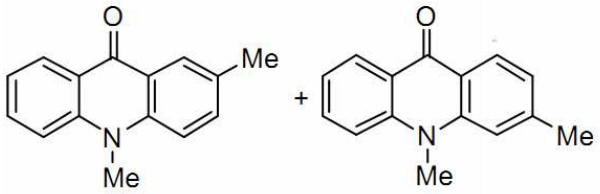
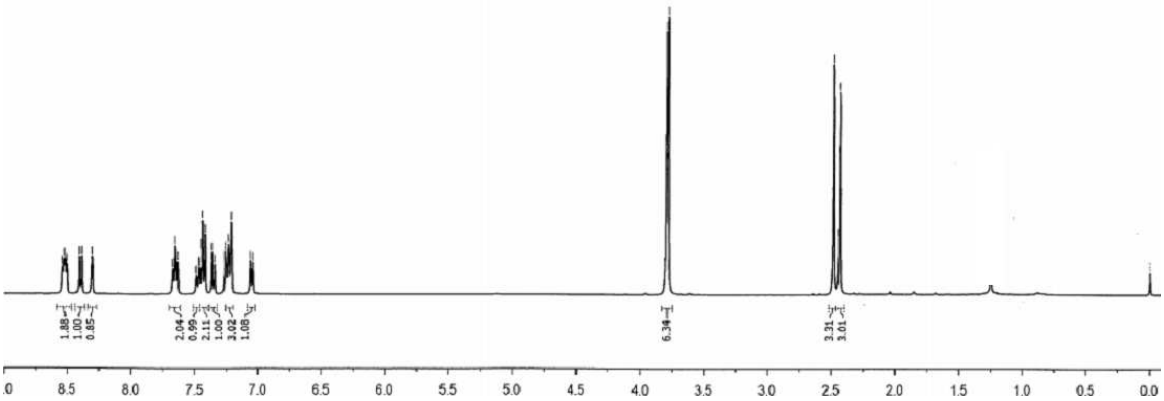
fys-5-81 400




**4s + 4s'**



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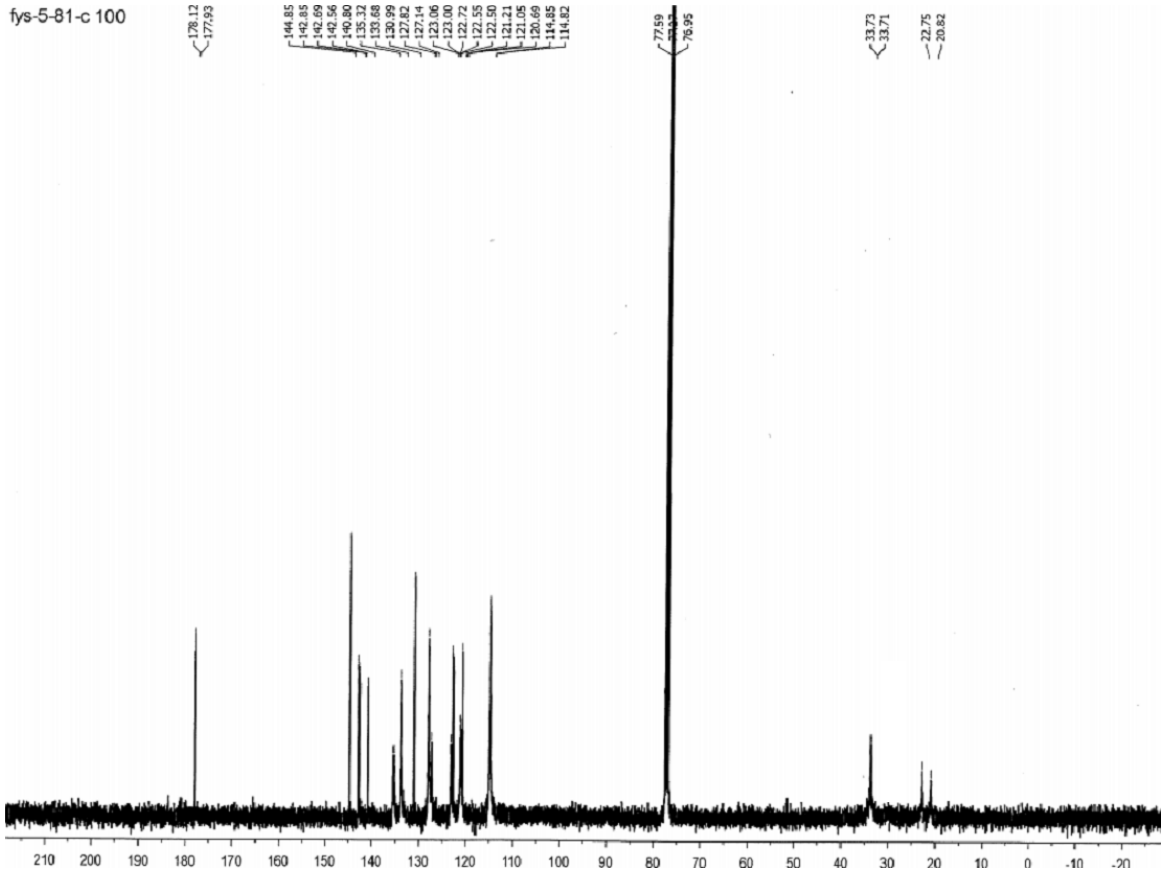

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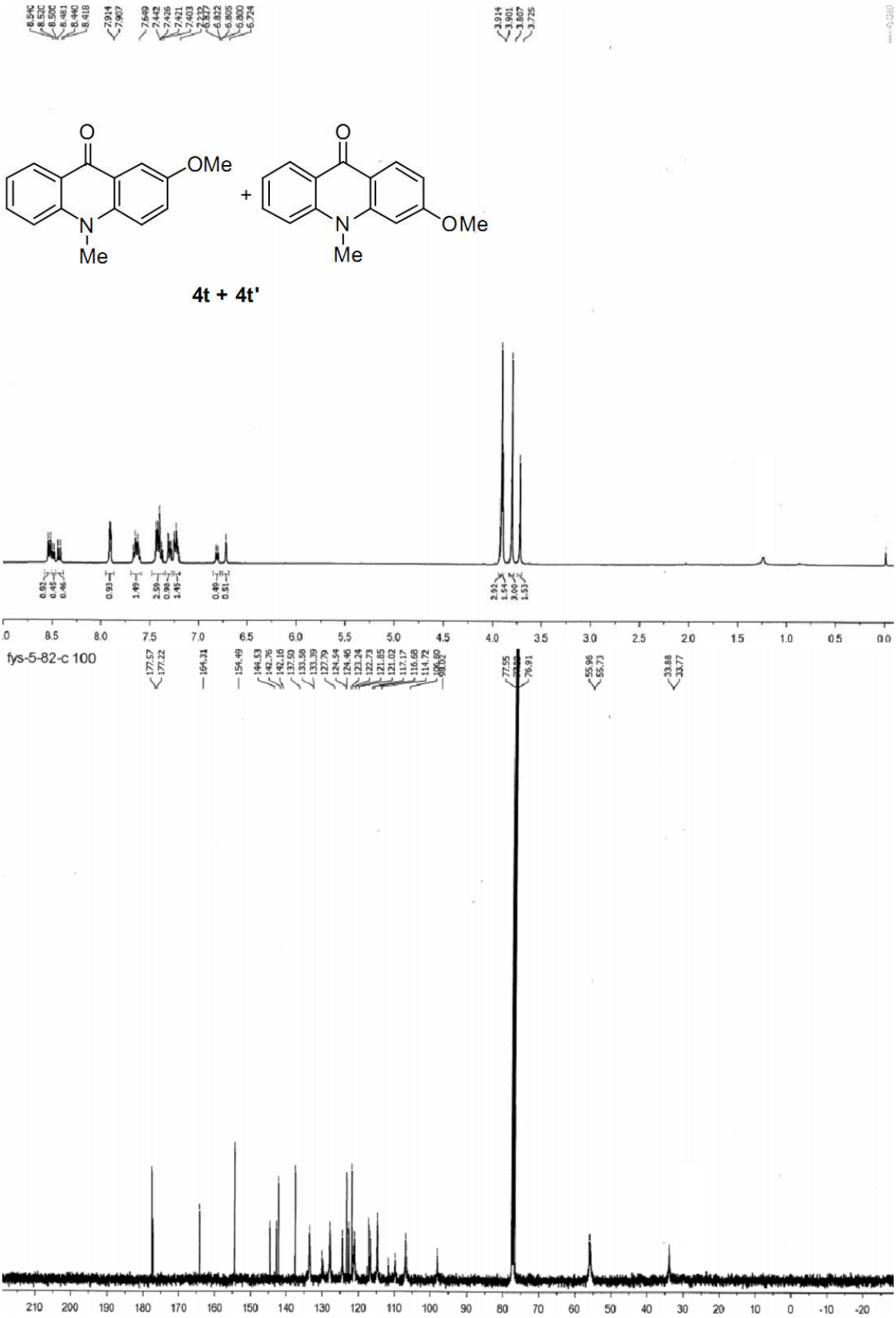


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# APPENDIX C. CHAPTER 4 COMPUTATIONAL DATA, $^{1}$H AND $^{13}$C NMR SPECTRA

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Coordinates obtained from computational results:

R1 benzyne

| | | | |
|---|---|---|---|
| C | 0.70365 | 1.05843 | 0.00003 |
| C | -0.70358 | 1.05847 | 0.00003 |
| C | -1.46151 | -0.13352 | -0.00013 |
| C | -0.62556 | -1.23765 | 0.00009 |
| C | 0.62546 | -1.23764 | 0.00008 |
| C | 1.46151 | -0.1336 | -0.00013 |
| H | 1.22878 | 2.01132 | 0.00016 |
| H | -1.22865 | 2.01139 | 0.00016 |
| H | -2.54672 | -0.13475 | -0.00006 |
| H | 2.54673 | -0.13491 | -0.00005 |

R2, sydnone **2a**

| | | | |
|---|---|---|---|
| C | 2.81574 | 0.31815 | -0.13556 |
| C | 1.514 | 0.85201 | -0.334 |
| O | 2.5172 | -1.0016 | 0.38566 |
| H | 1.2161 | 1.78972 | -0.76772 |
| C | -0.79846 | -0.01409 | 0.0136 |
| C | -1.41618 | 1.20673 | 0.2868 |

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| | | | |
|---|---|---|---|
| C | -1.53894 | -1.1576 | -0.28968 |
| C | -2.80777 | 1.28152 | 0.24544 |
| H | -0.82136 | 2.07531 | 0.54927 |
| C | -2.92934 | -1.06831 | -0.31762 |
| H | -1.0267 | -2.08914 | -0.50068 |
| C | -3.56477 | 0.14763 | -0.05559 |
| H | -3.29834 | 2.22631 | 0.45905 |
| H | -3.51557 | -1.95122 | -0.55386 |
| H | -4.64855 | 0.21113 | -0.08462 |
| N | 0.6343 | -0.0989 | 0.0442 |
| N | 1.1799 | -1.21021 | 0.48699 |
| O | 3.95146 | 0.68979 | -0.29818 |

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Intermediate

| | | | |
|---|---|---|---|
| C | 1.11713 | 0.5297 | -0.71018 |
| C | 0.74732 | -1.03278 | 0.91162 |
| C | 1.2765 | 0.37694 | 0.67049 |
| H | 0.48957 | -1.36369 | 1.91332 |
| C | 1.8655 | 1.37634 | 1.42447 |
| C | 1.50332 | 1.66386 | -1.39216 |
| C | 2.24975 | 2.55188 | 0.75445 |
| C | 2.07237 | 2.69401 | -0.62317 |
| H | 2.02175 | 1.2718 | 2.49425 |
| H | 1.37175 | 1.75505 | -2.46535 |
| N | -0.30571 | -1.15909 | -0.121 |
| C | -1.56801 | -0.51804 | -0.00222 |
| C | -2.09659 | -0.18532 | 1.25088 |
| C | -2.33141 | -0.29362 | -1.15847 |
| C | -3.37941 | 0.35769 | 1.34366 |
| H | -1.51996 | -0.35153 | 2.1549 |
| C | -3.6032 | 0.26138 | -1.05157 |
| H | -1.91821 | -0.5562 | -2.12588 |
| C | -4.13808 | 0.58848 | 0.19754 |
| H | -3.77863 | 0.60741 | 2.32302 |

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| | | | |
|---|---|---|---|
| H | -4.18322 | 0.43412 | -1.95421 |
| H | -5.13306 | 1.01697 | 0.27432 |
| C | 1.76602 | -1.94649 | 0.19669 |
| O | 2.56639 | -2.72158 | 0.63655 |
| O | 1.60086 | -1.69834 | -1.14845 |
| N | 0.49924 | -0.69524 | -1.25091 |
| H | 2.69132 | 3.36619 | 1.32183 |
| H | 2.37863 | 3.61547 | -1.1097 |

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P1, 2*H*-indazole **3aa**

| | | | |
|---|---|---|---|
| C | 1.73401 | -0.64588 | 0.11918 |
| C | 0.51588 | 1.19706 | -0.19819 |
| C | 1.83934 | 0.76712 | -0.12743 |
| C | 3.11394 | 1.37977 | -0.2464 |
| C | 2.901 | -1.44218 | 0.25601 |
| C | 4.22816 | 0.58506 | -0.11286 |
| C | 4.12033 | -0.81824 | 0.1383 |
| H | 3.20516 | 2.44582 | -0.43608 |
| H | 2.81554 | -2.50741 | 0.44688 |
| H | 5.21762 | 1.02599 | -0.19778 |
| H | 5.03264 | -1.40051 | 0.23718 |
| N | 0.45094 | -1.04425 | 0.19444 |
| N | -0.25882 | 0.09431 | 0.00156 |
| C | -1.68101 | 0.03849 | 0.00631 |
| C | -2.31749 | -1.17069 | -0.29223 |
| C | -2.43253 | 1.17894 | 0.30815 |
| C | -3.70921 | -1.22773 | -0.29847 |
| H | -1.71211 | -2.04201 | -0.5101 |
| C | -3.825 | 1.11002 | 0.28763 |
| H | -1.93872 | 2.10554 | 0.58175 |

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| | | | |
|---|---|---|---|
| C | -4.46907 | -0.09029 | -0.01562 |
| H | -4.20155 | -2.16772 | -0.53162 |
| H | -4.40517 | 1.99754 | 0.52413 |
| H | -5.55408 | -0.14048 | -0.02527 |
| H | 0.08578 | 2.16405 | -0.40735 |

P2, $CO_2$

| | | | |
|---|---|---|---|
| C | 0 | 0 | 0 |
| O | 0 | 0 | 1.16917 |
| O | 0 | 0 | -1.16917 |

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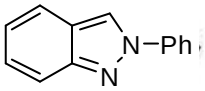
Copies of $^{1}H$ and $^{13}C$ NMR Spectra

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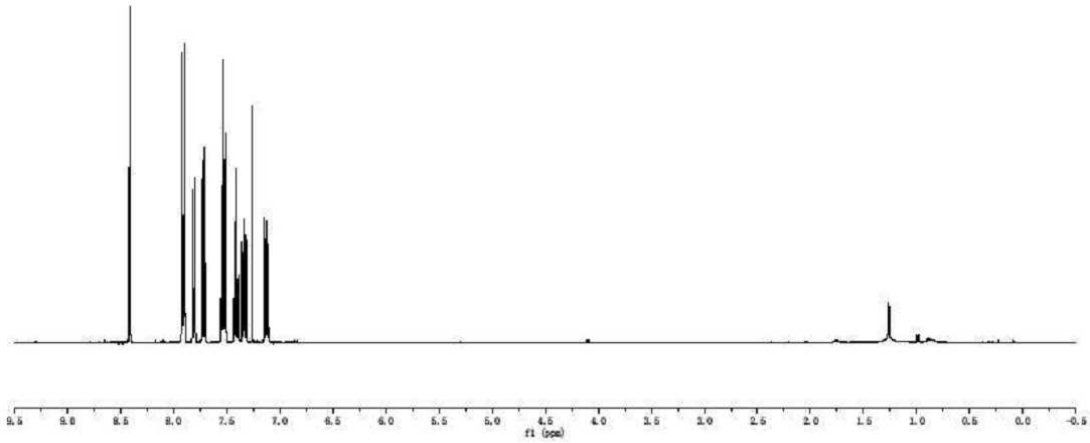


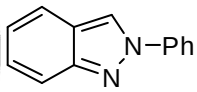


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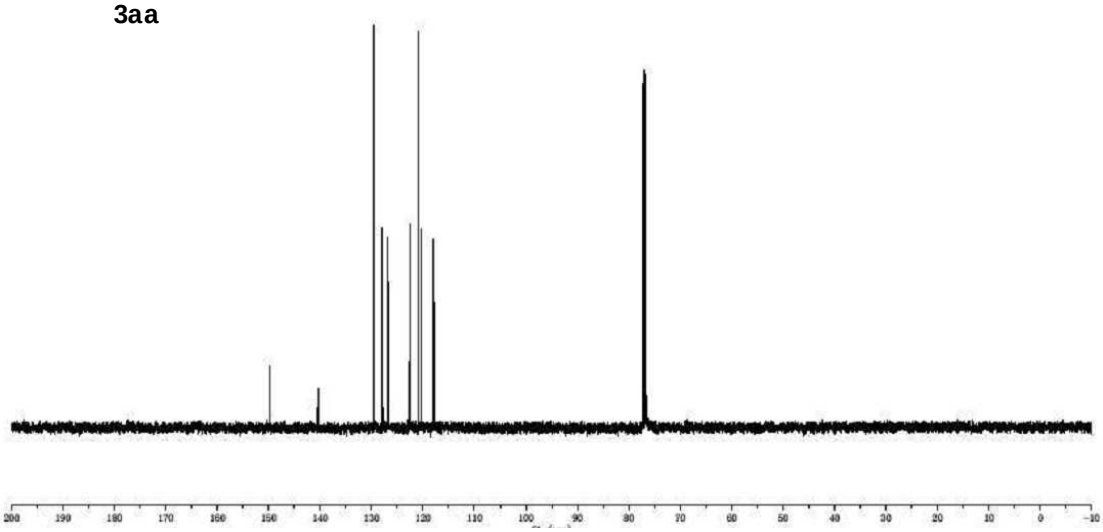

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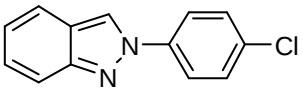


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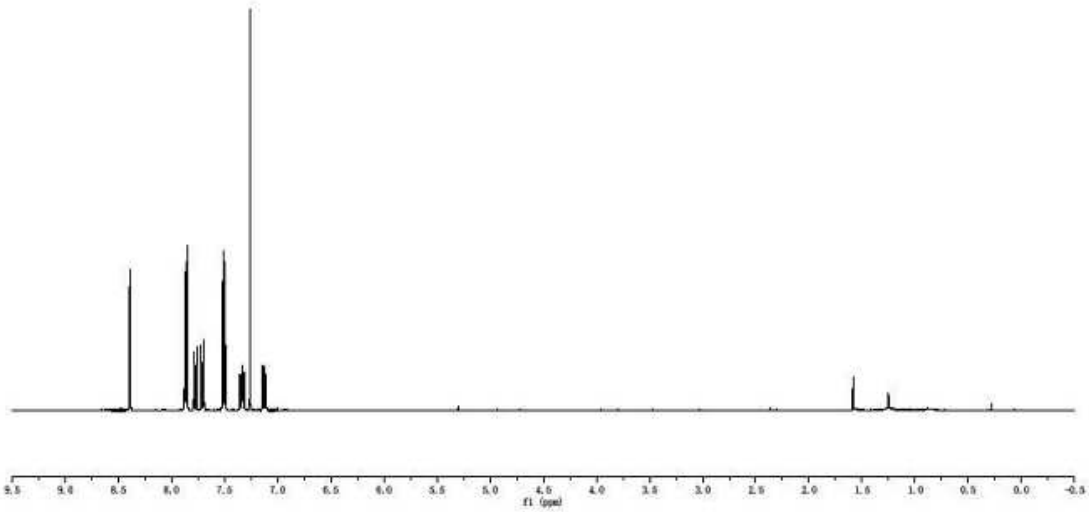


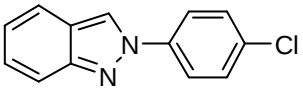


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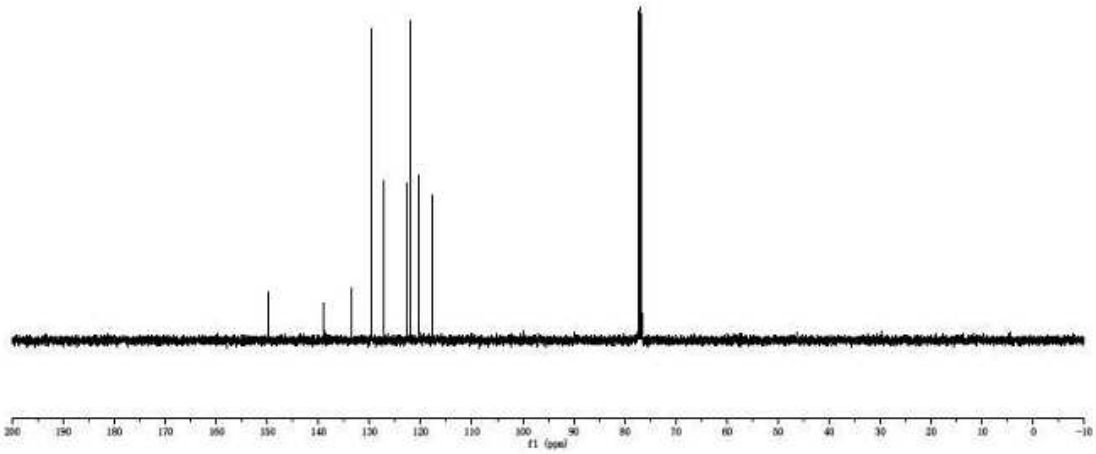


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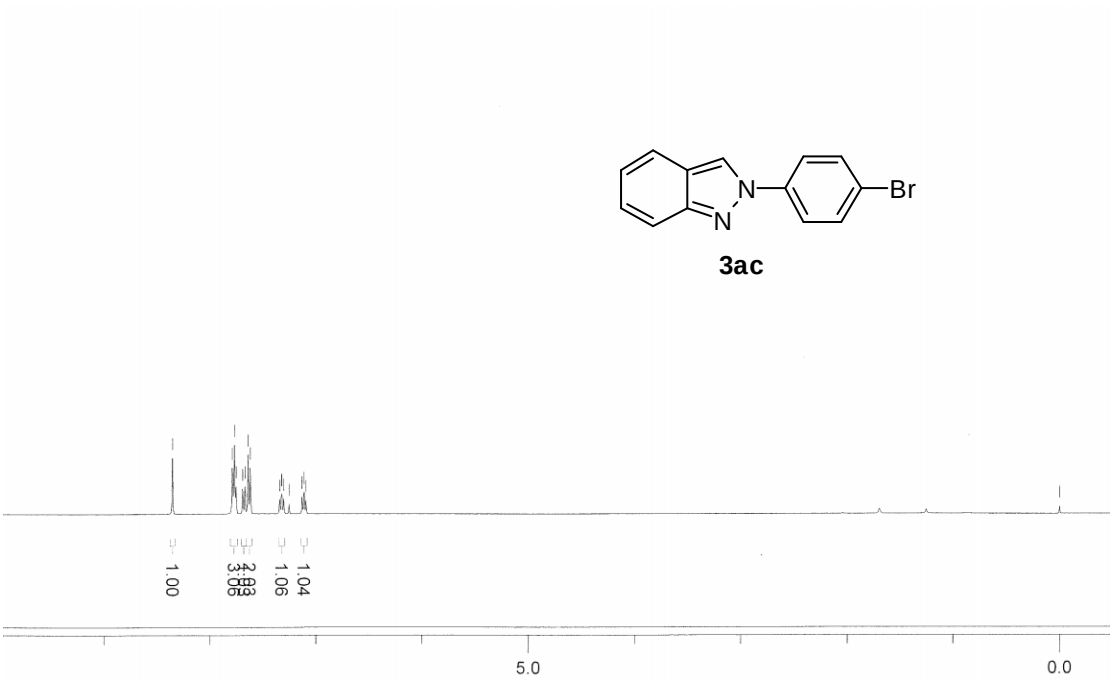


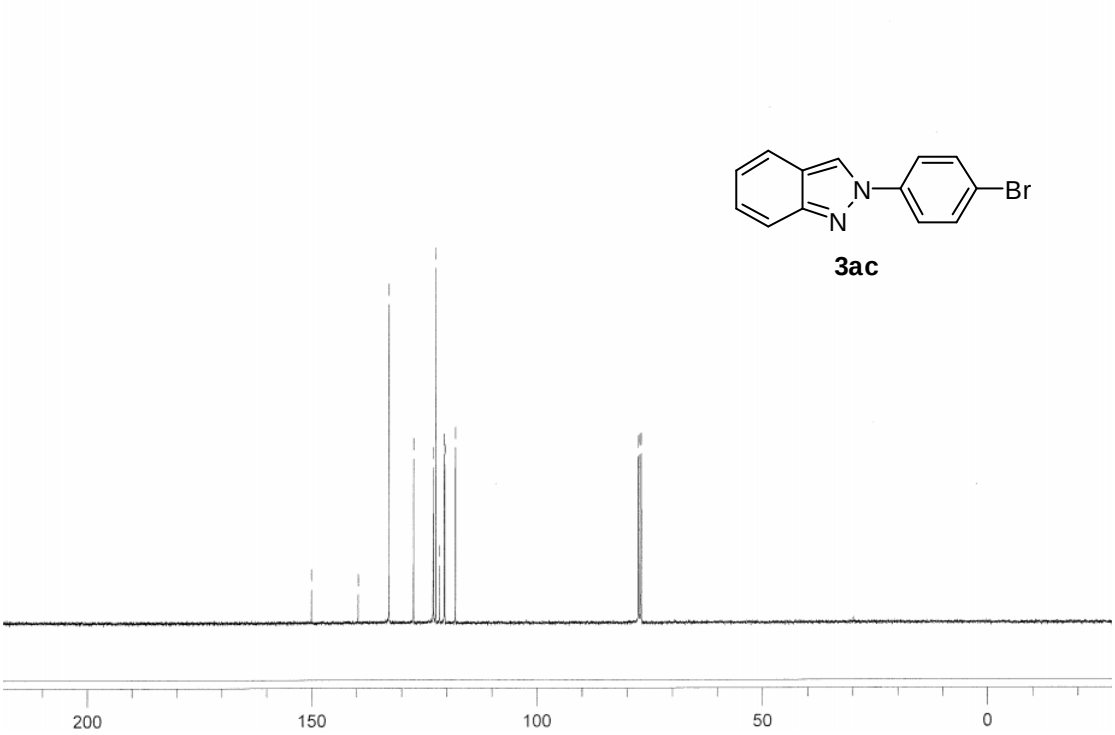


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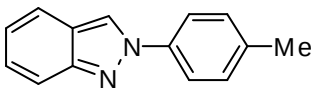


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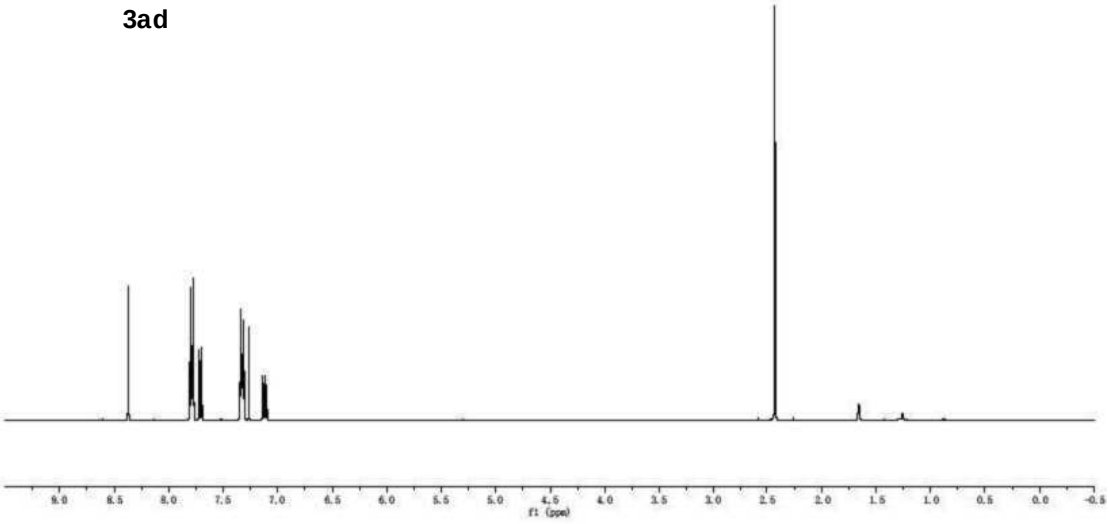


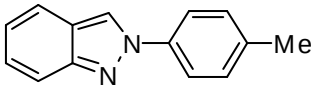


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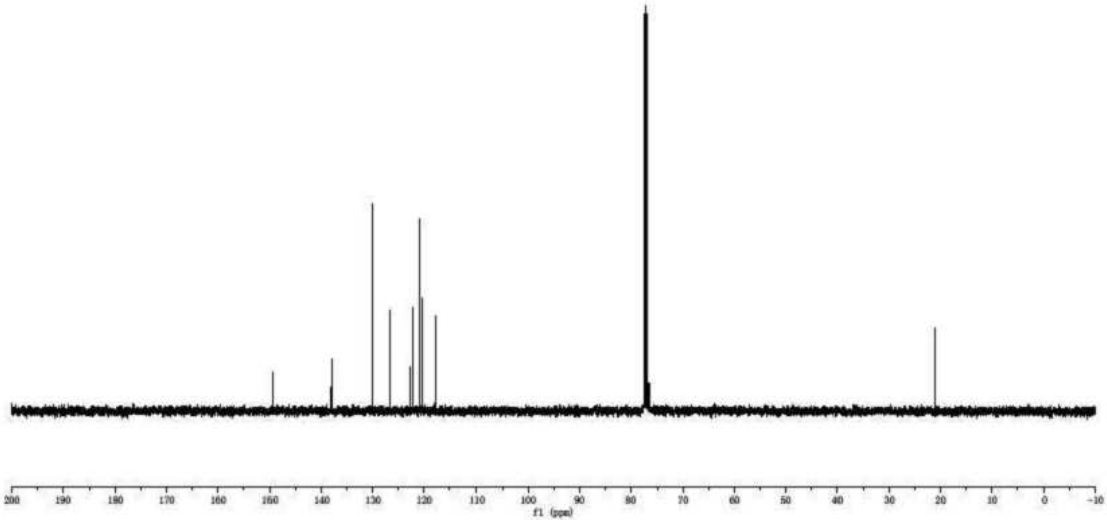


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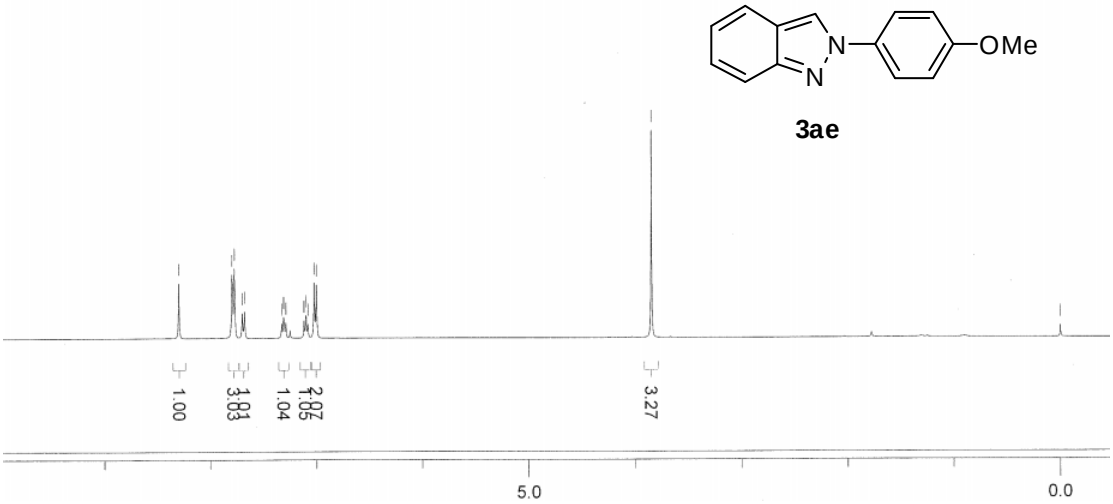


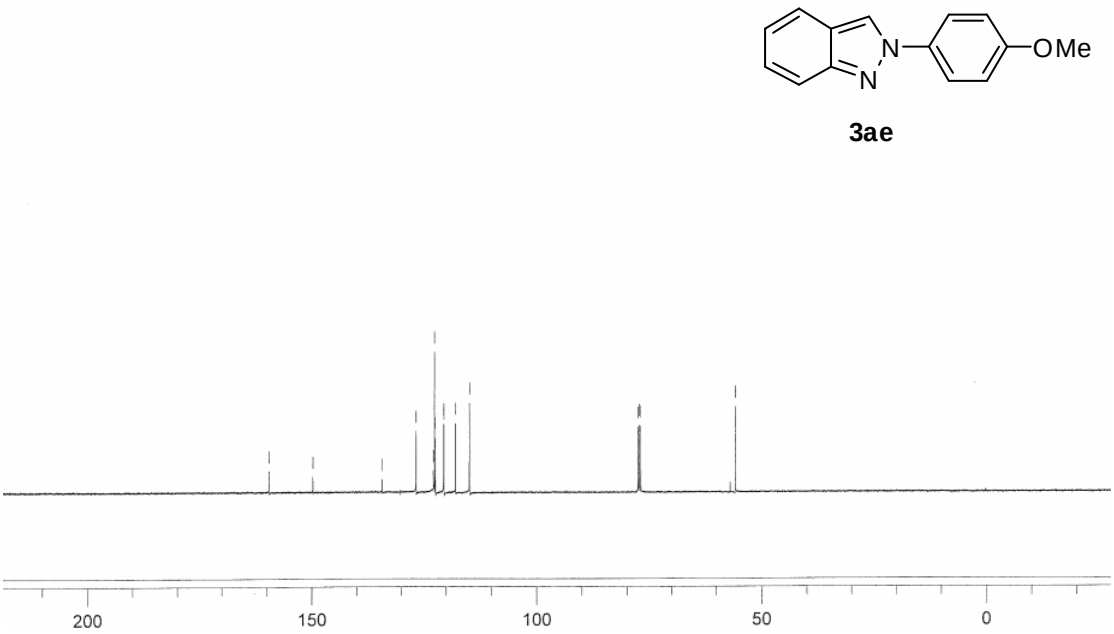


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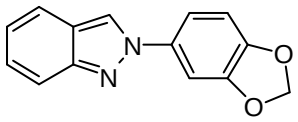

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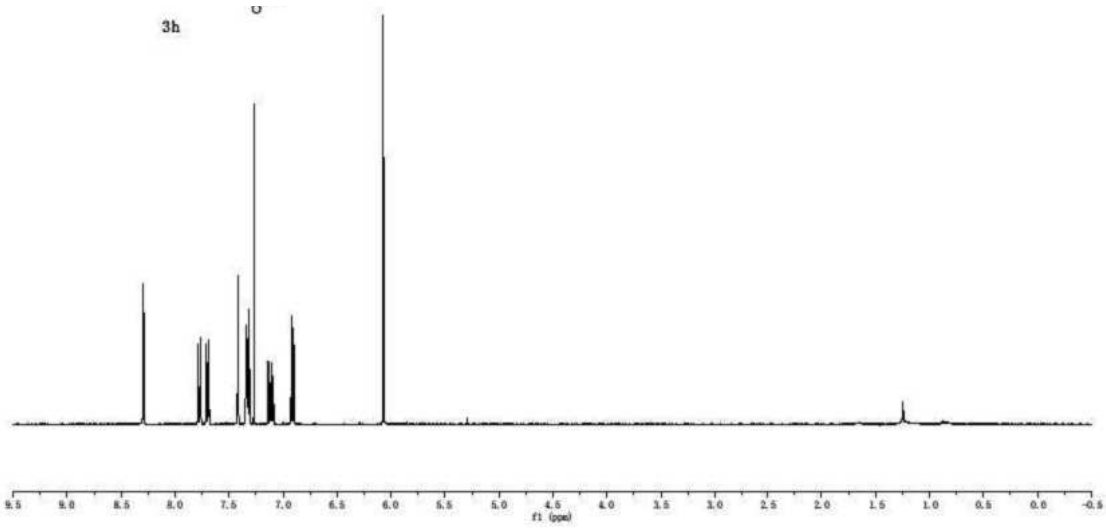


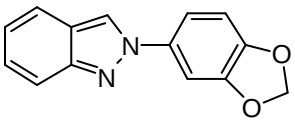

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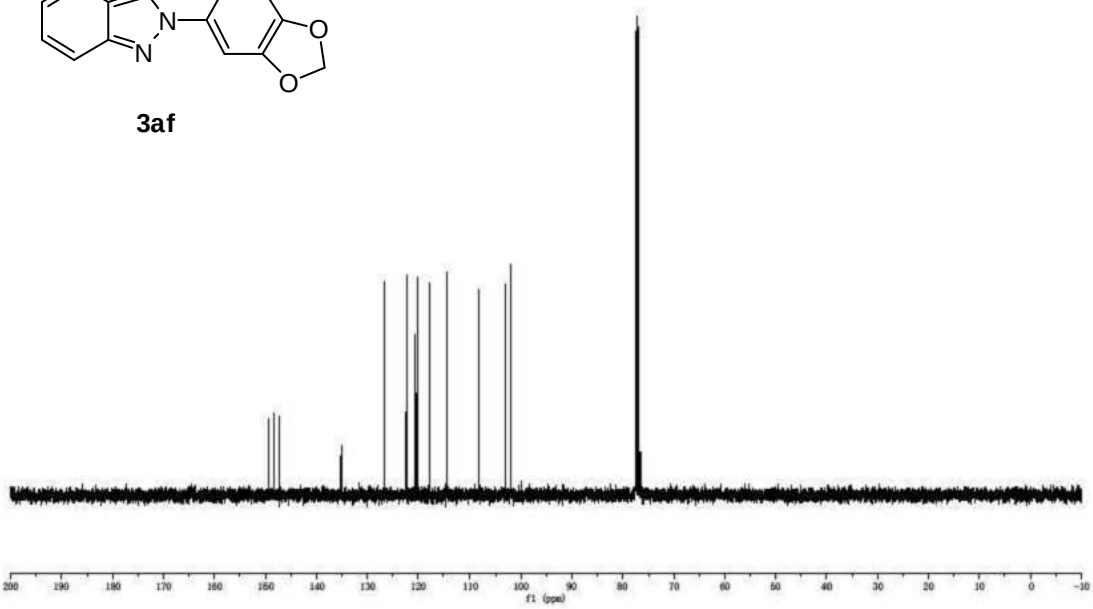


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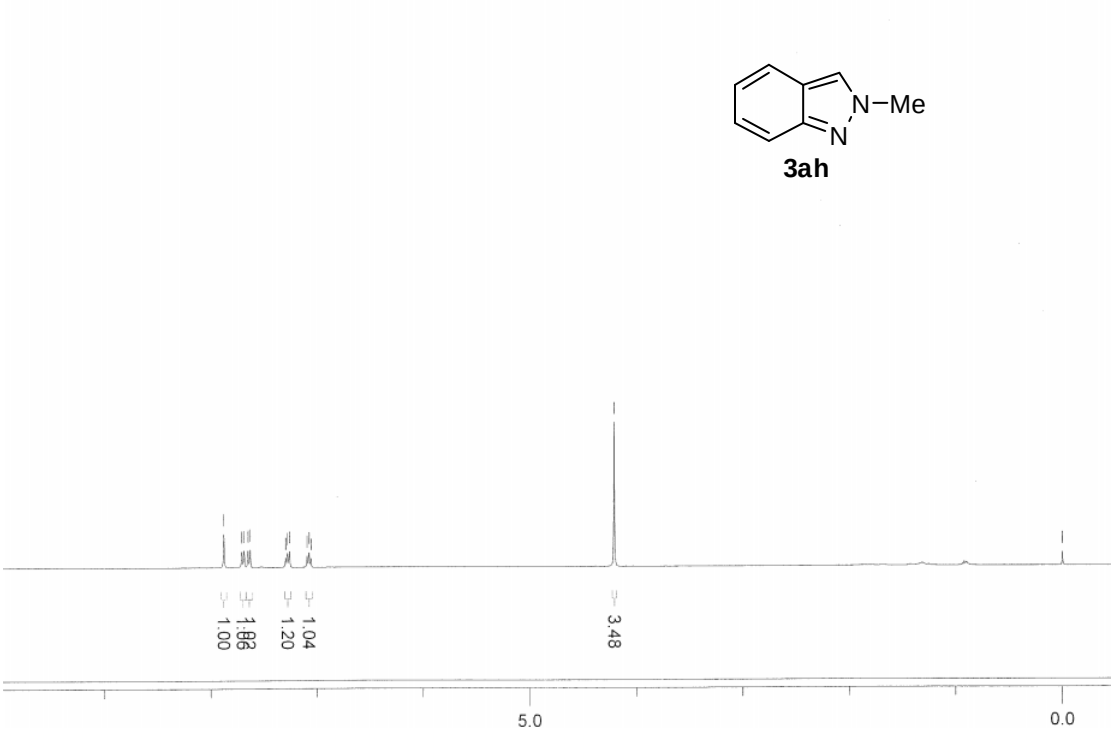


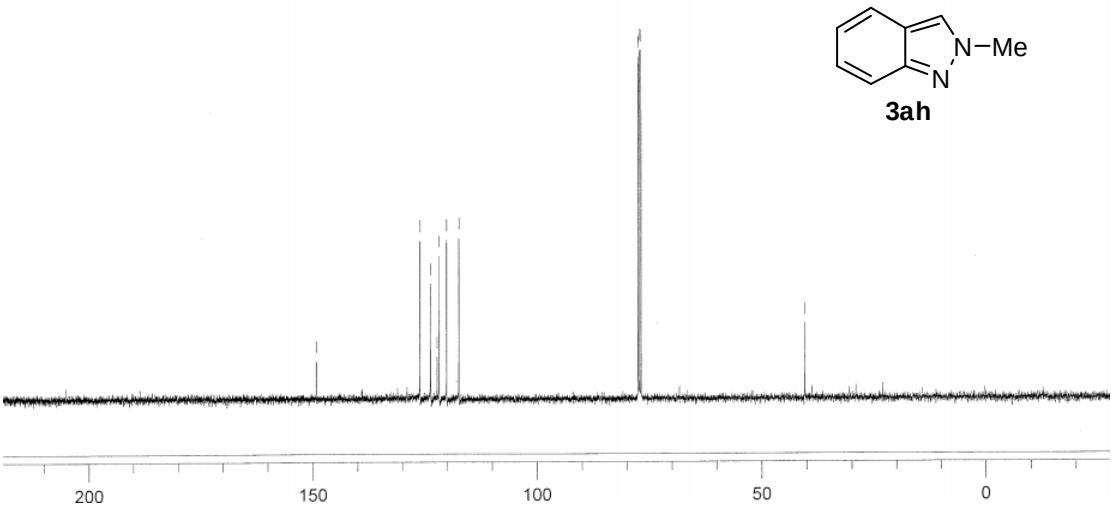


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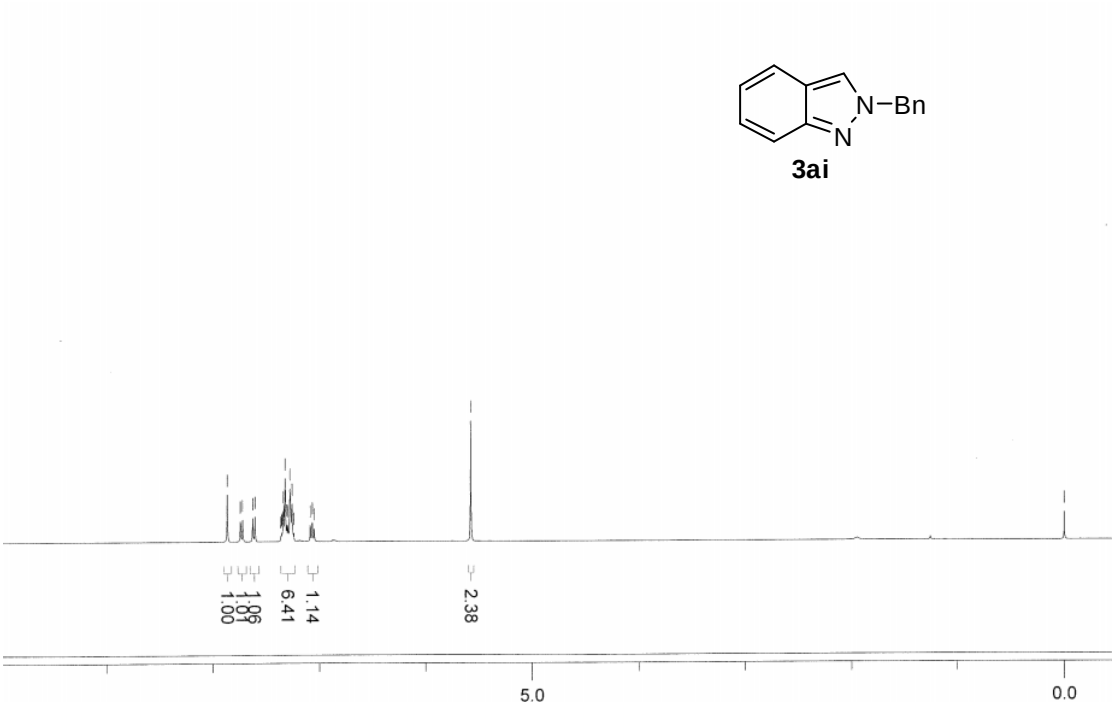


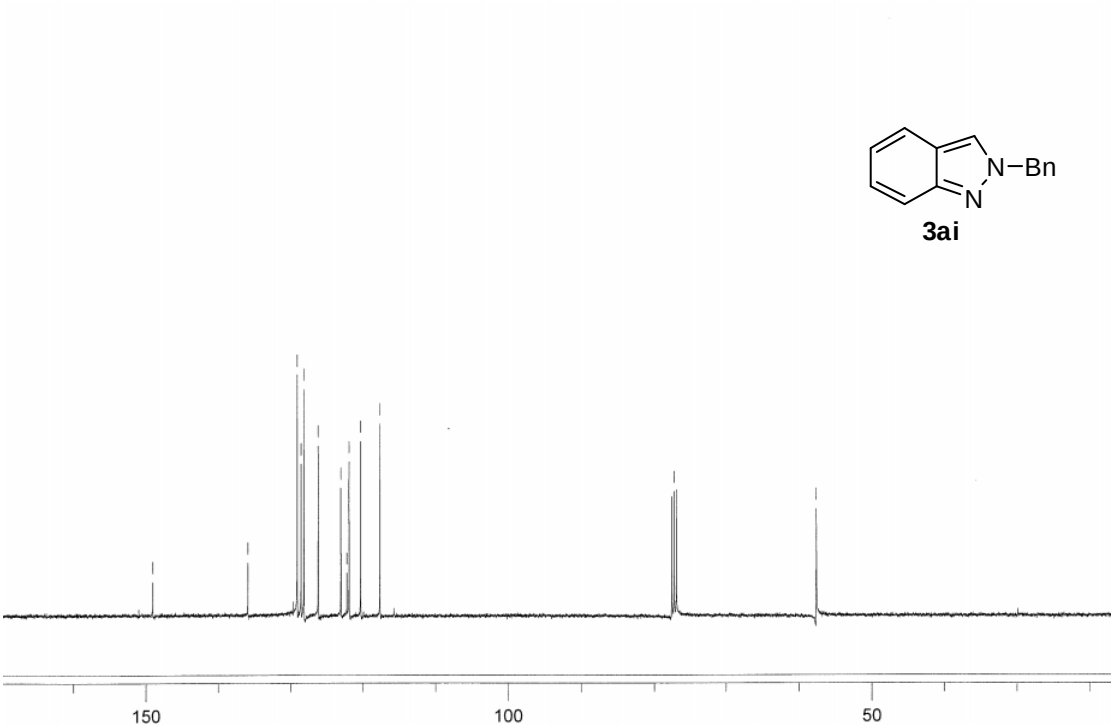


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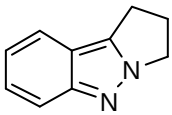

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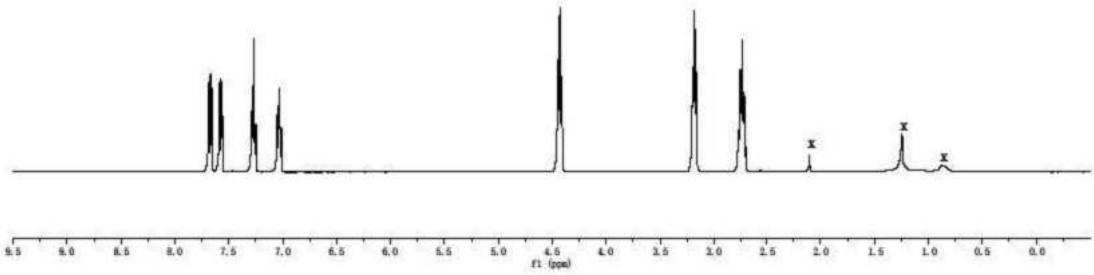


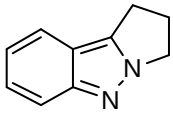

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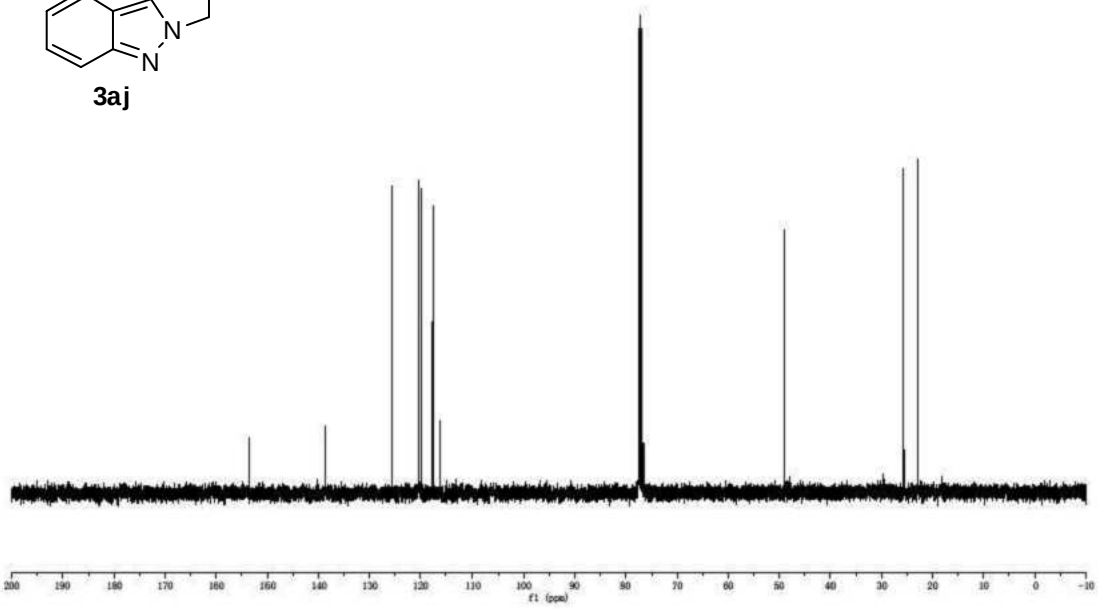


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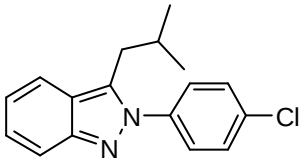


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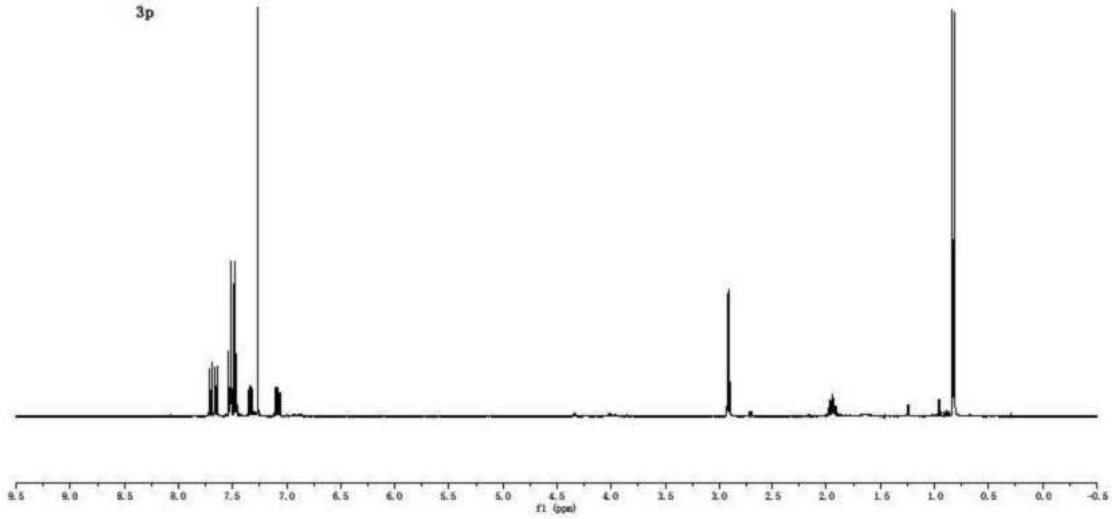


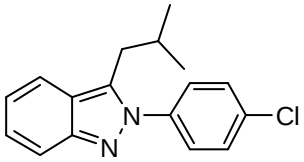


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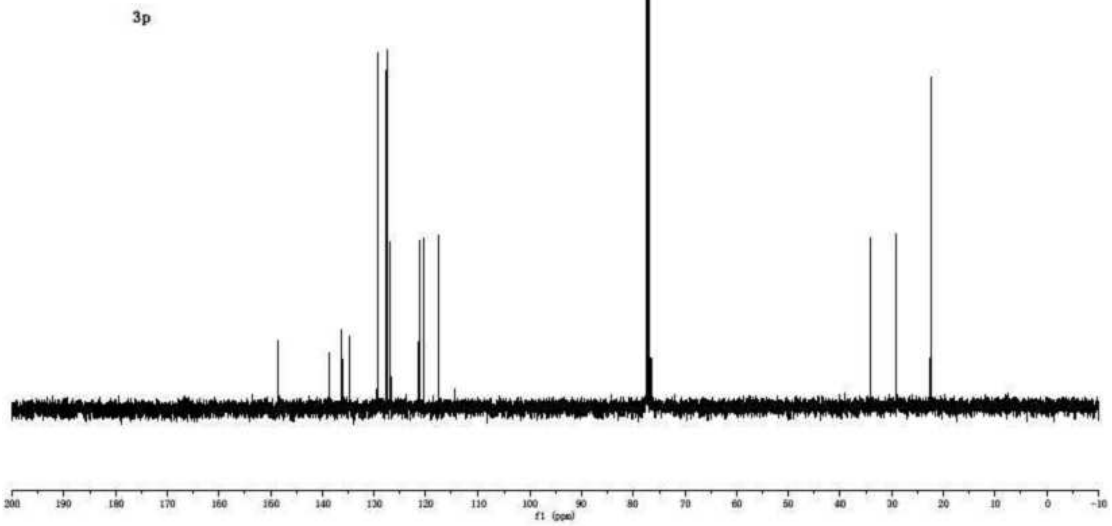


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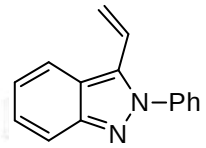


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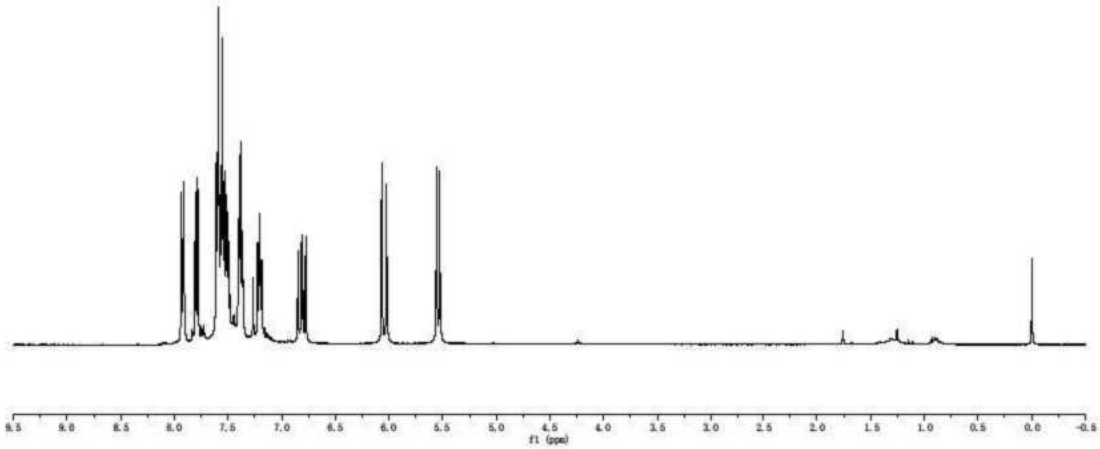


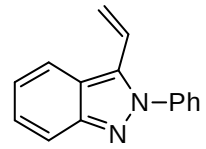


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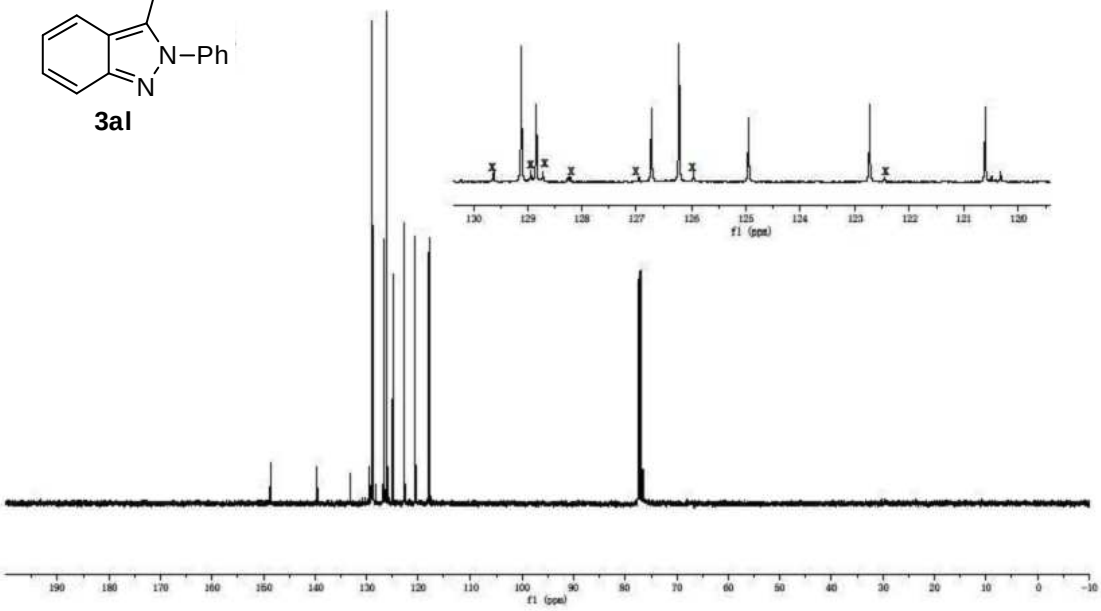


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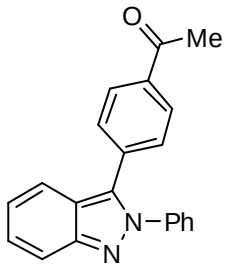


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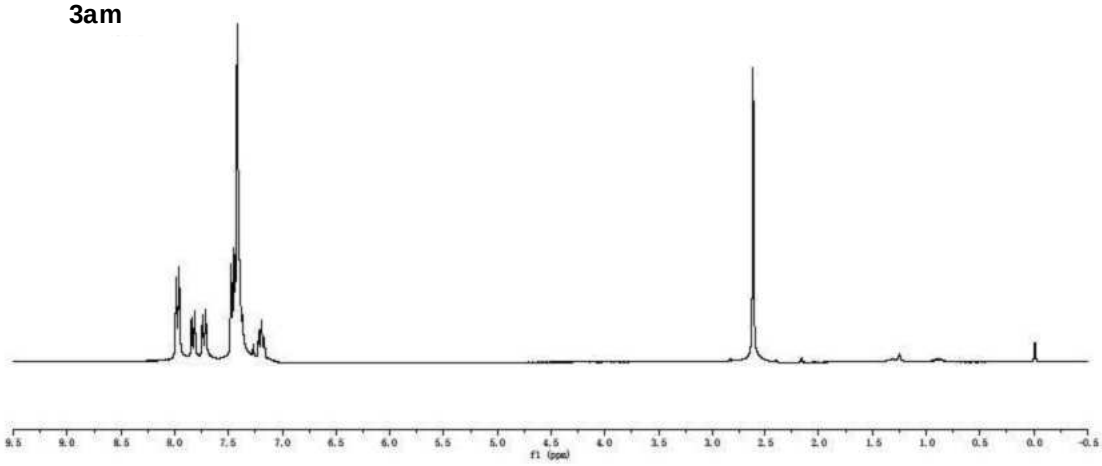


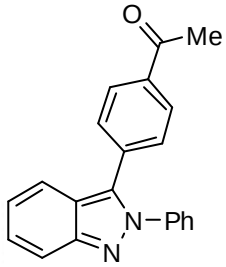


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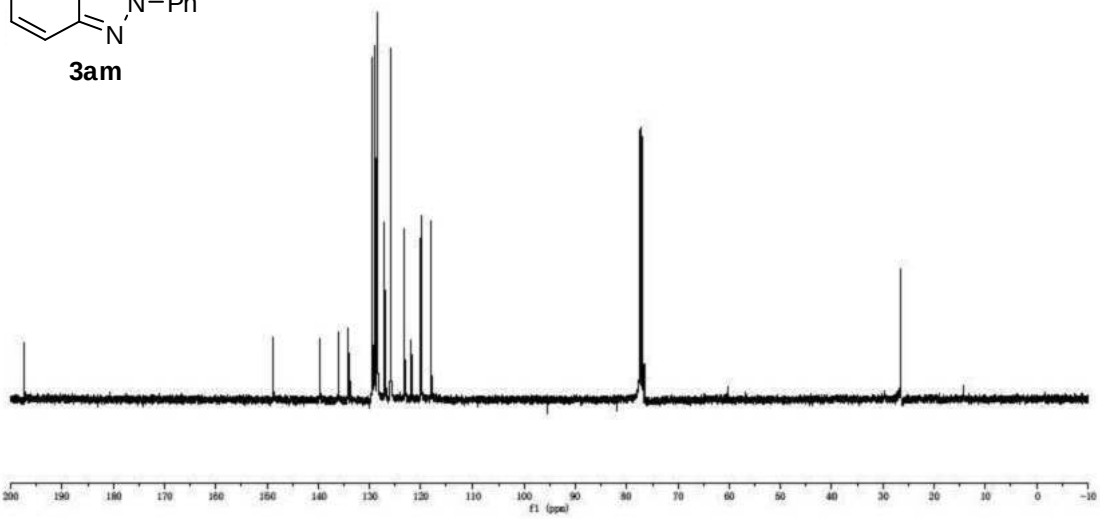


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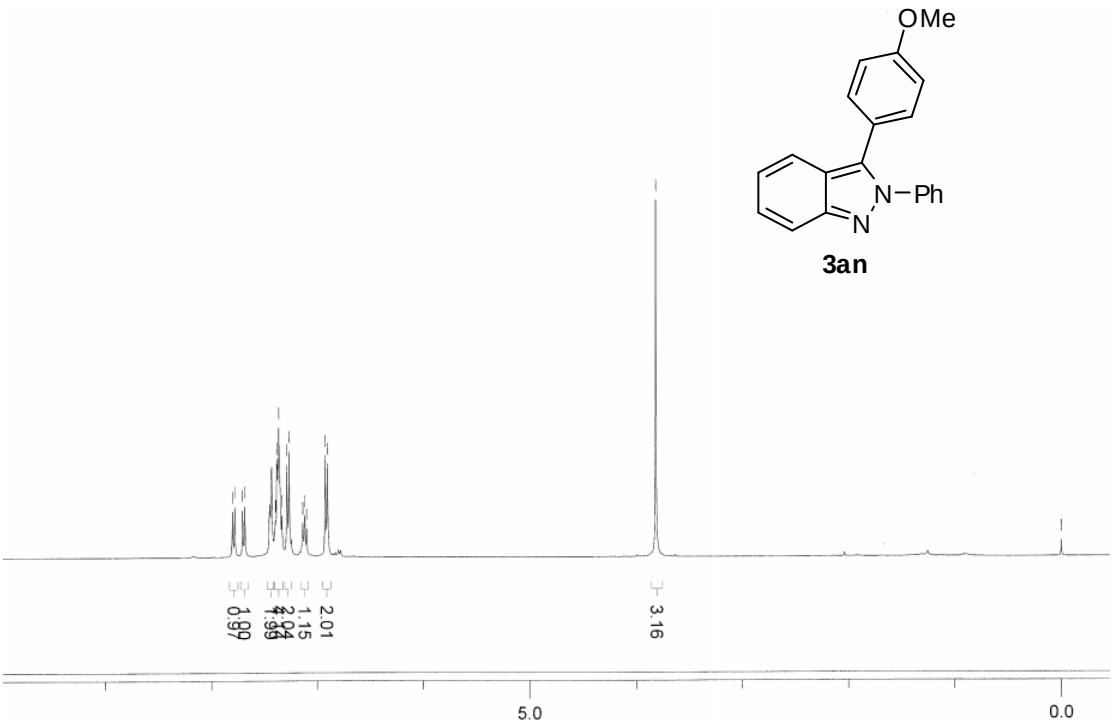


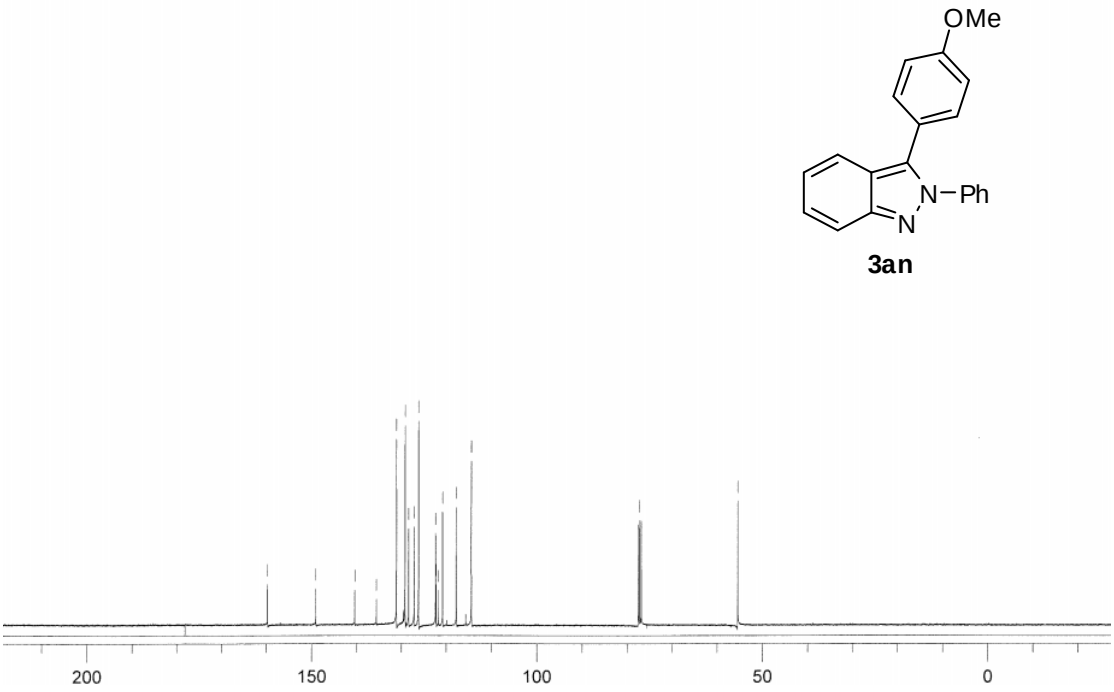


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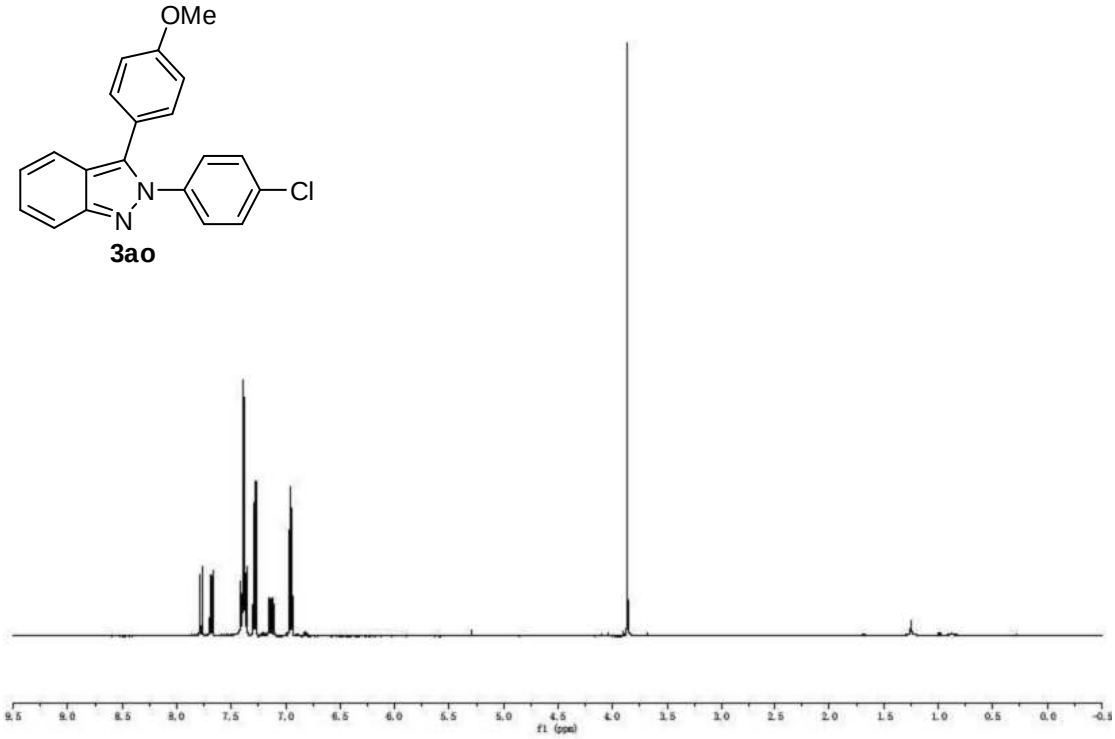


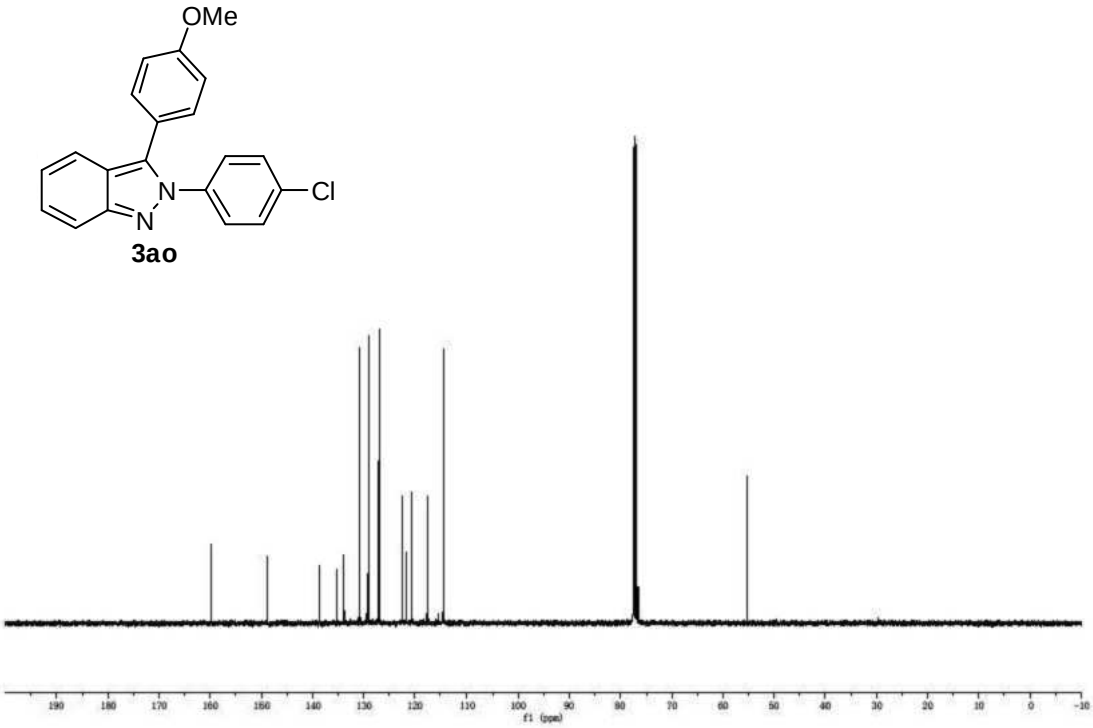


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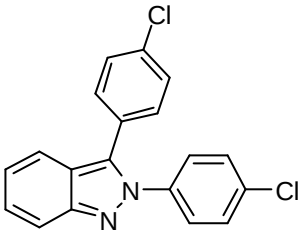


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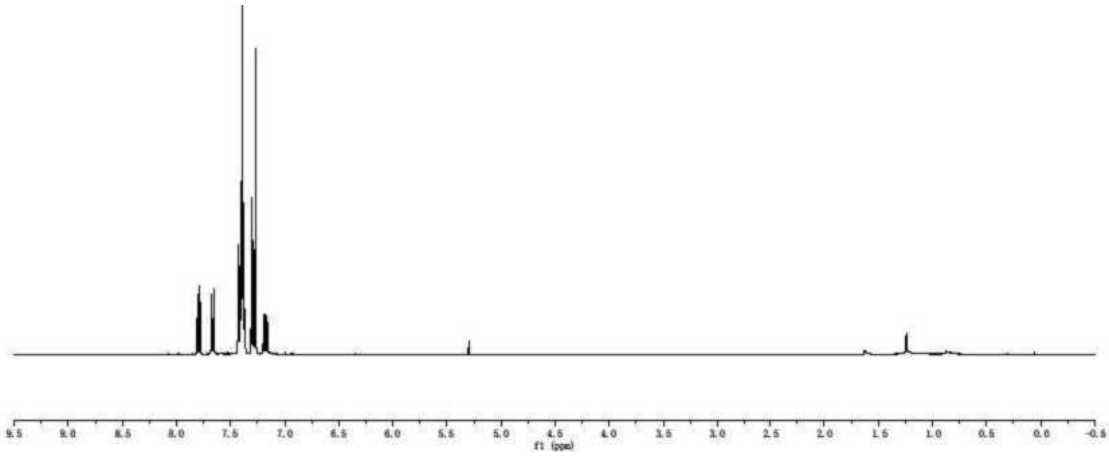





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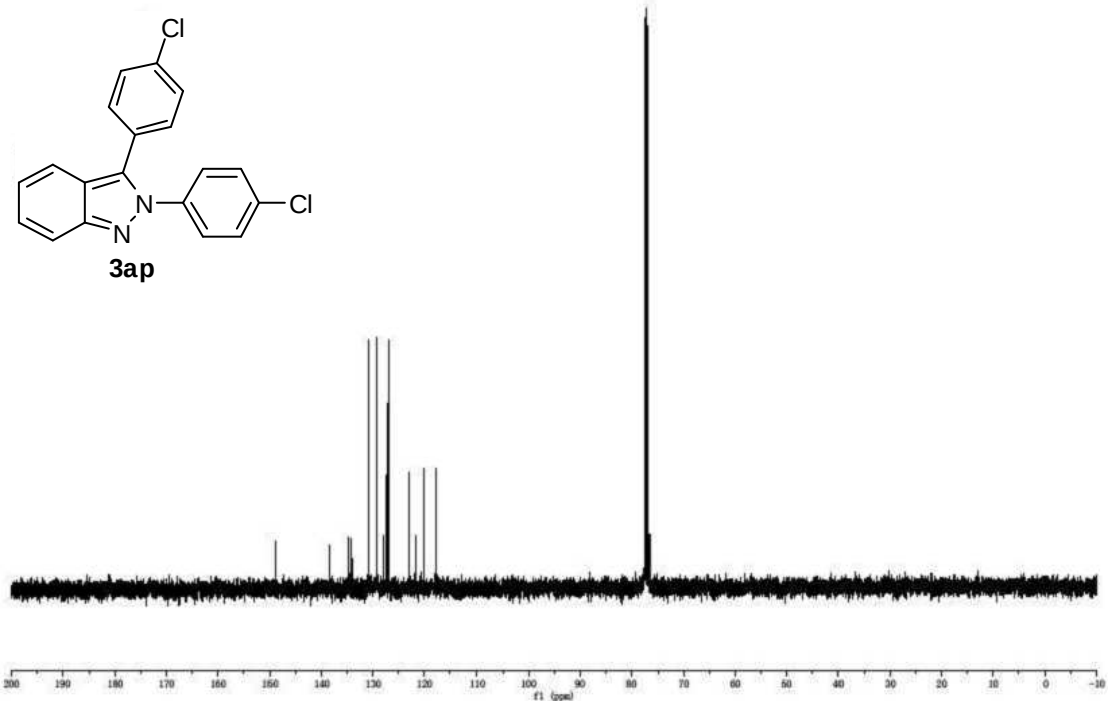


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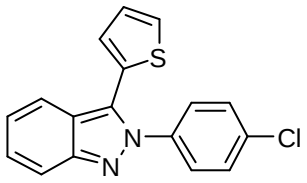


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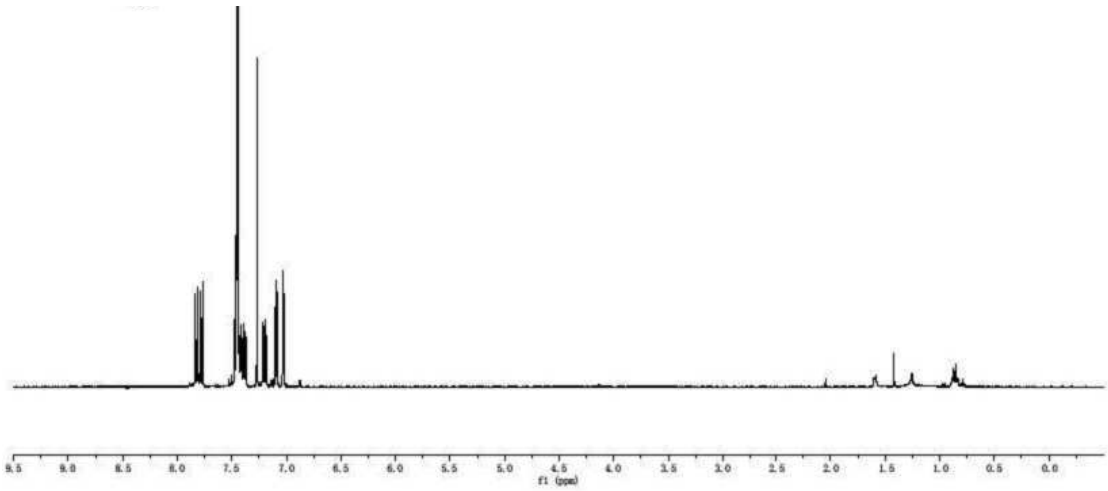





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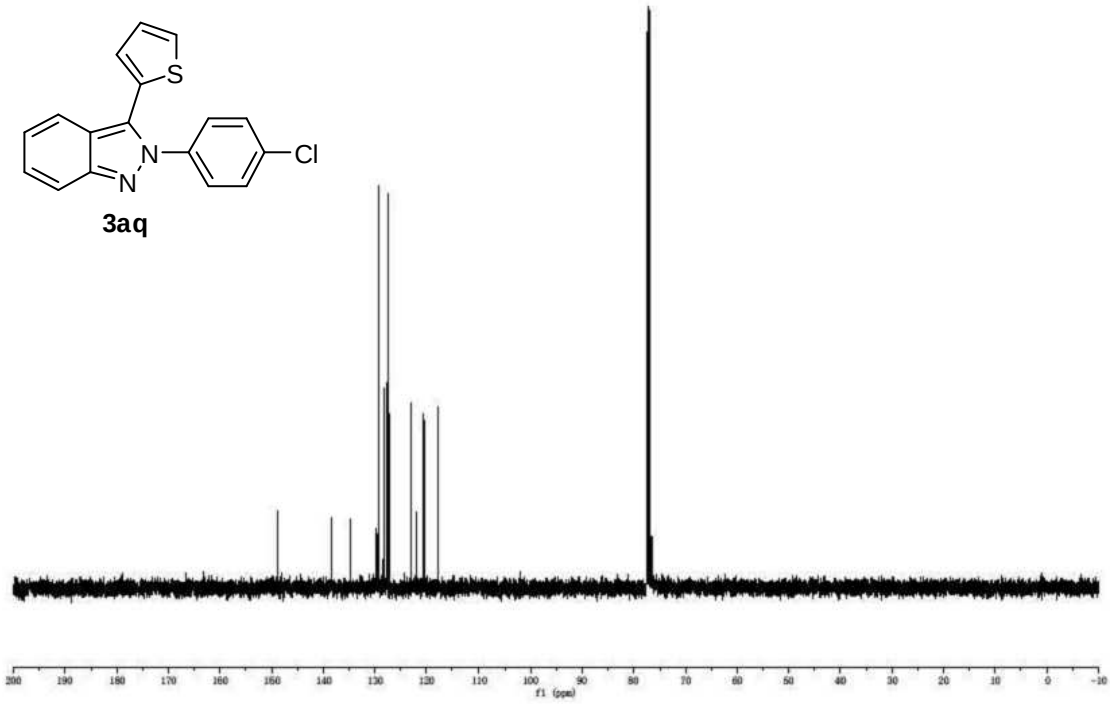


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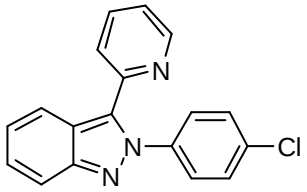


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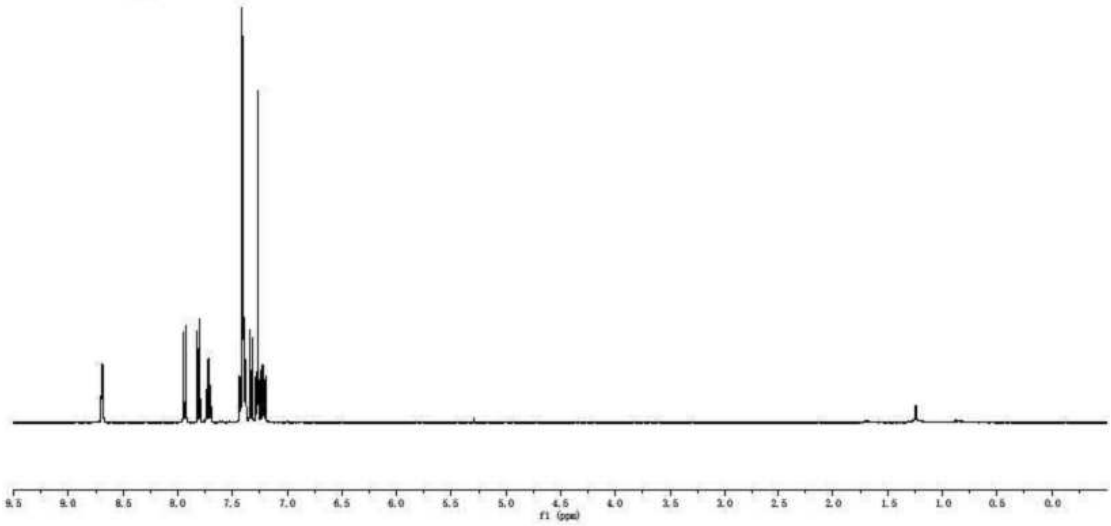


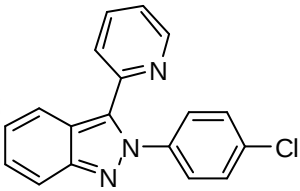


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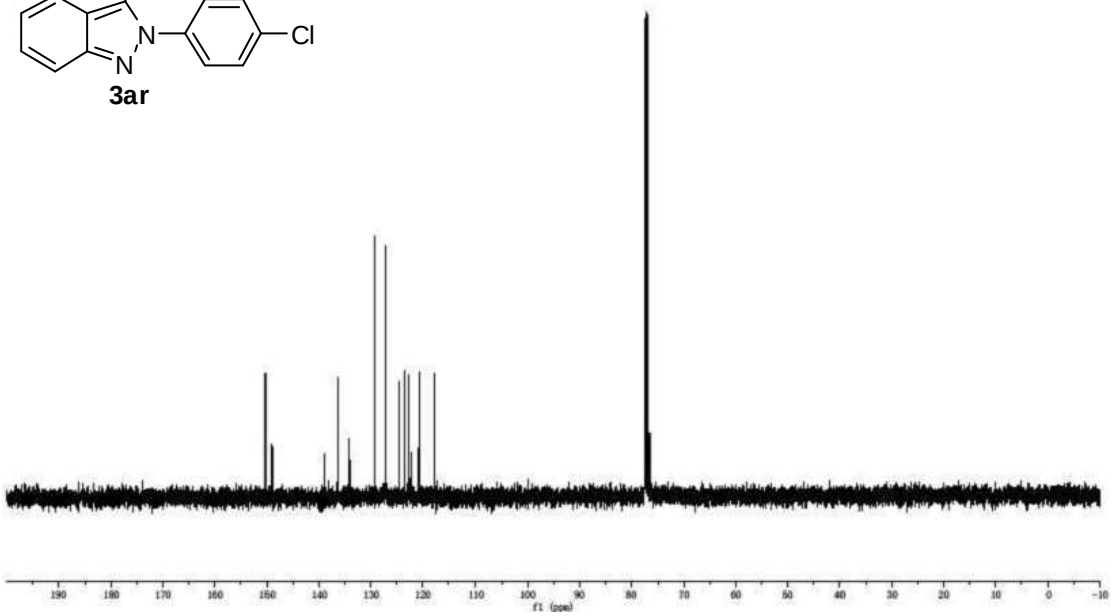


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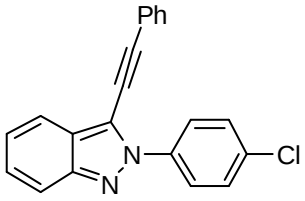


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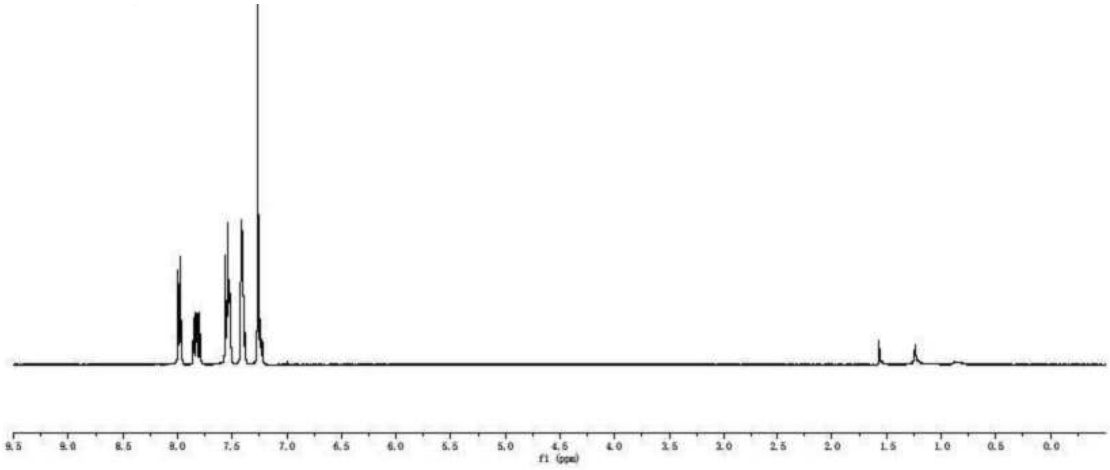





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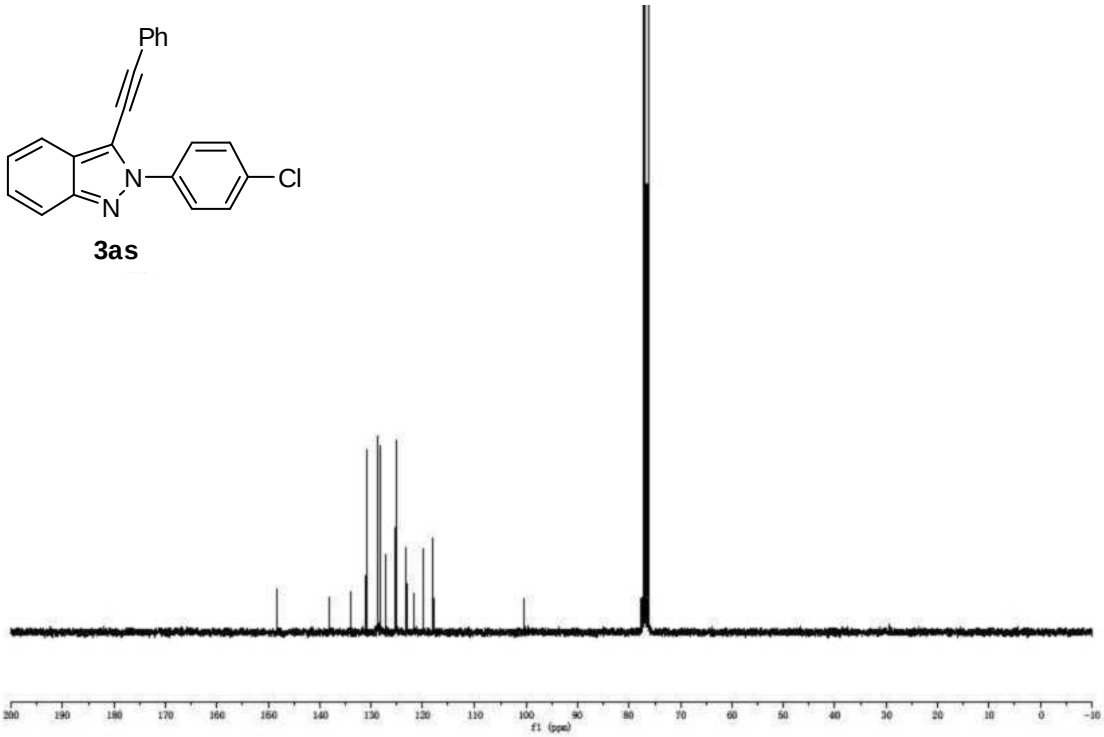


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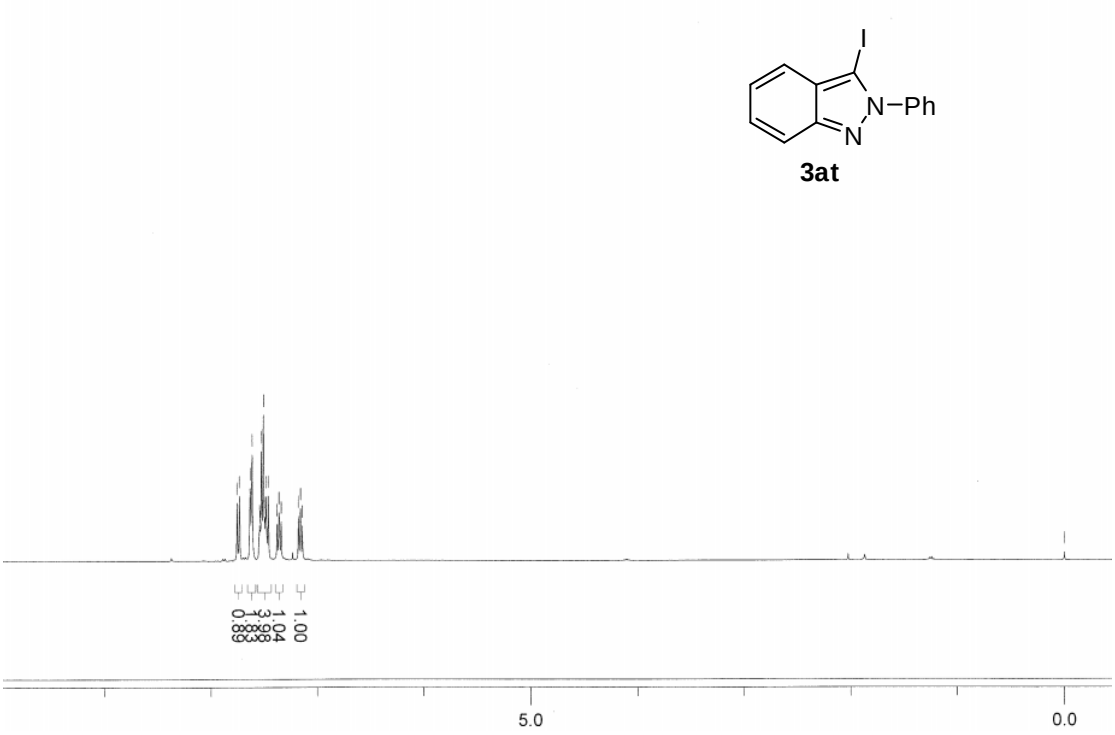


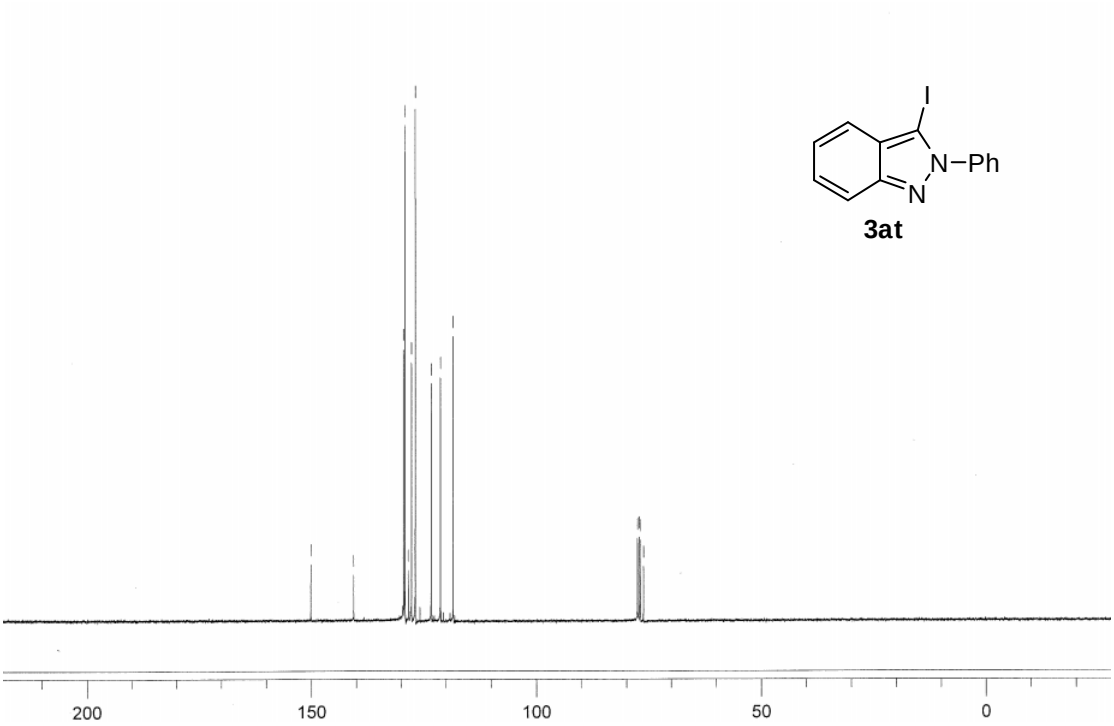


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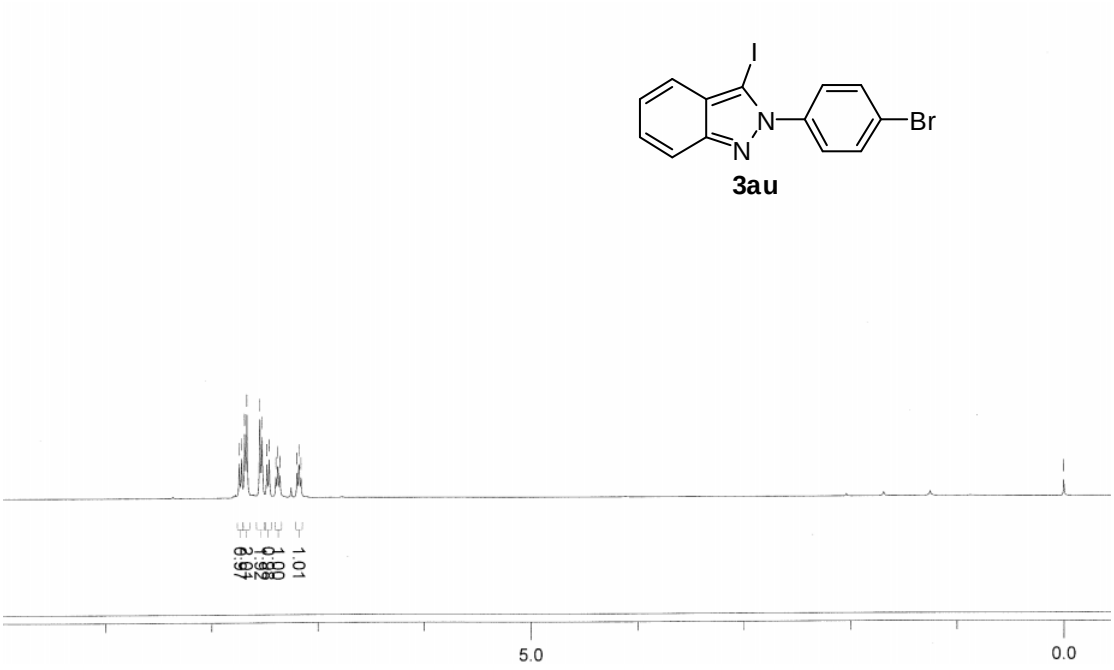


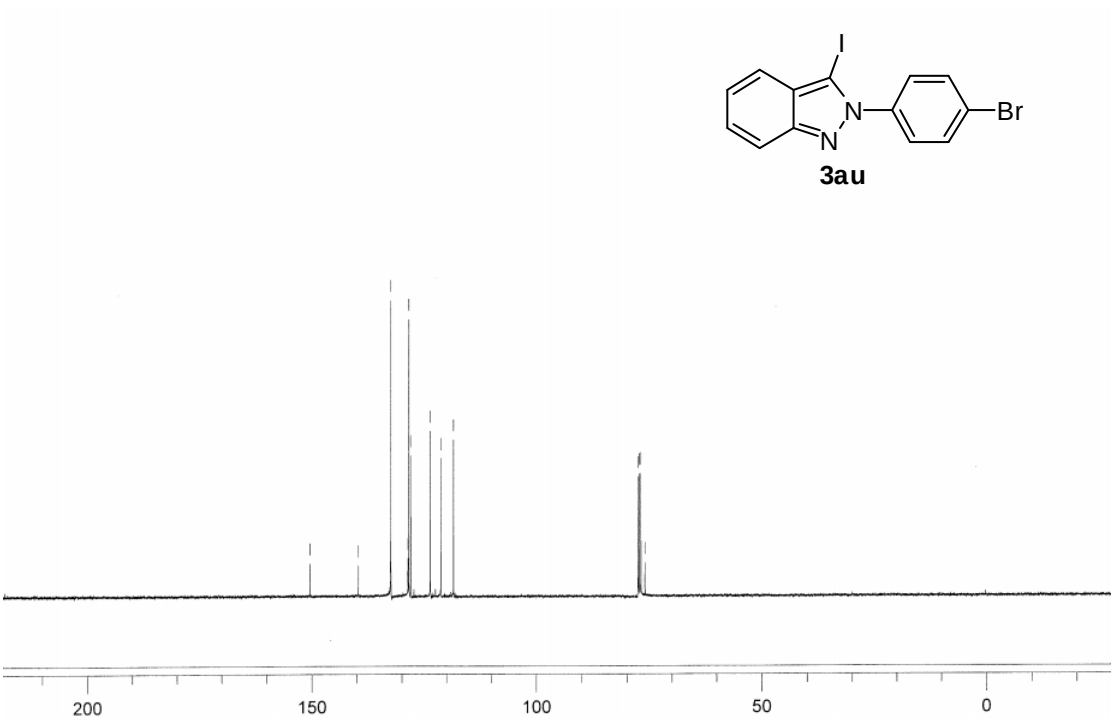


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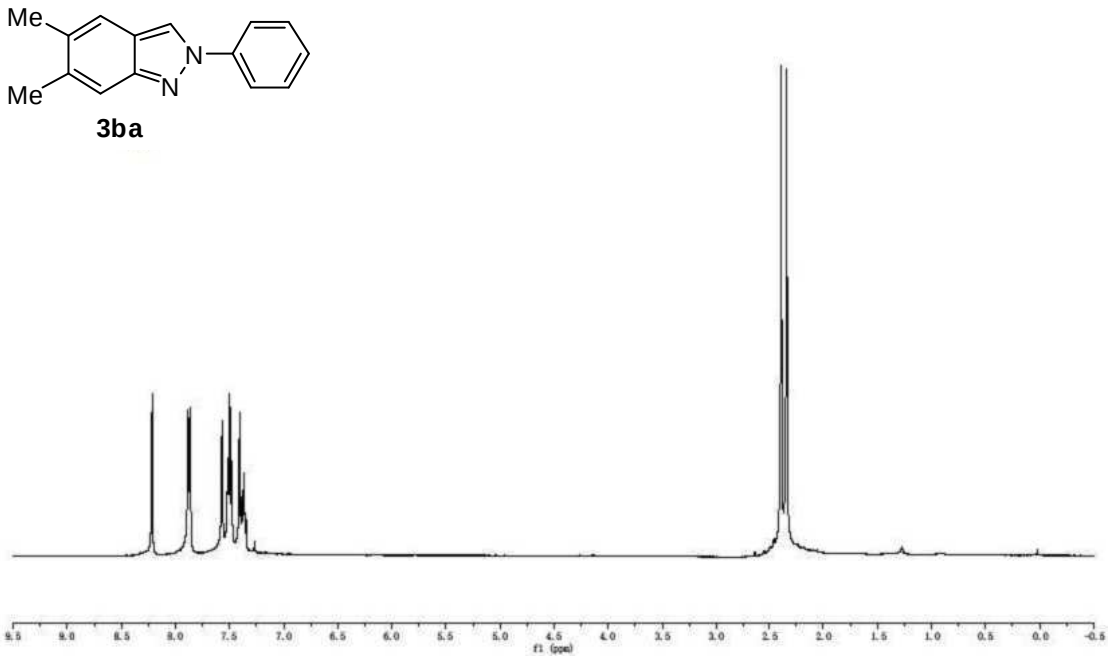


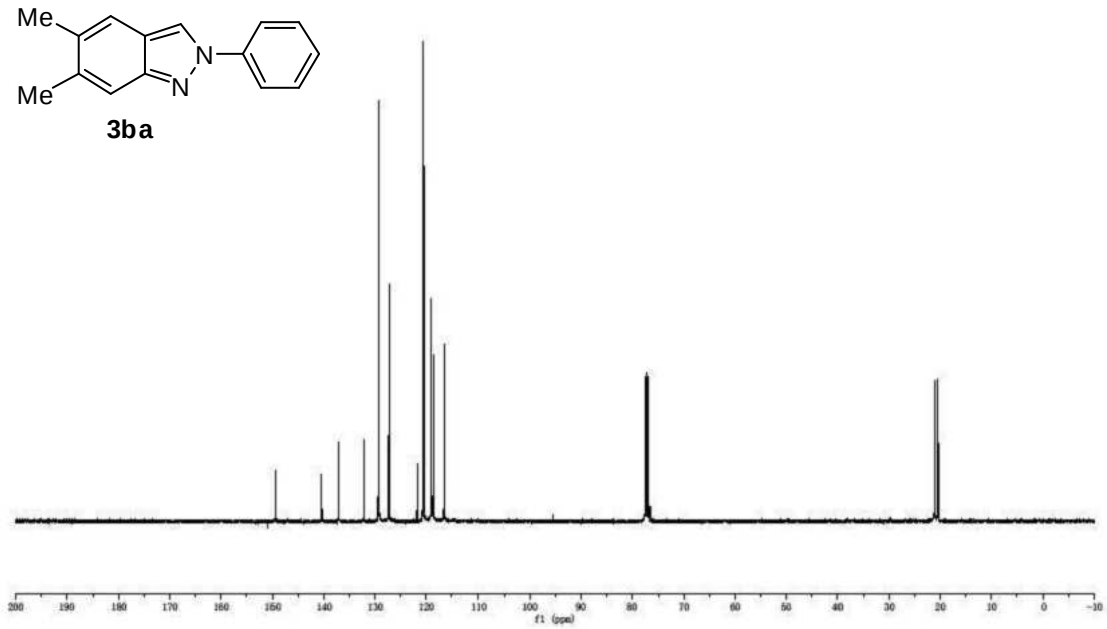


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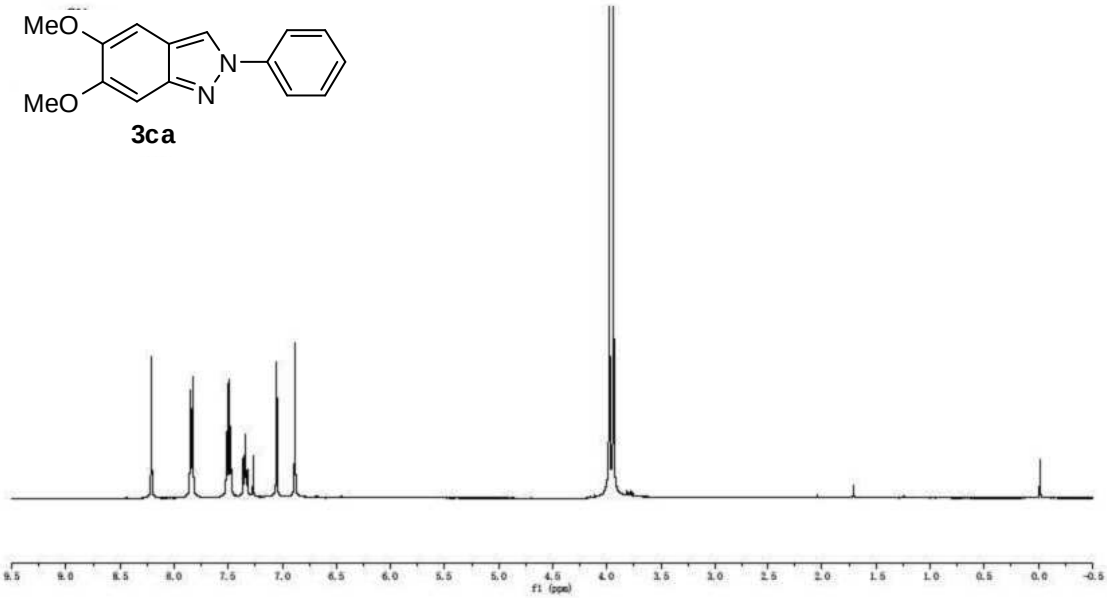


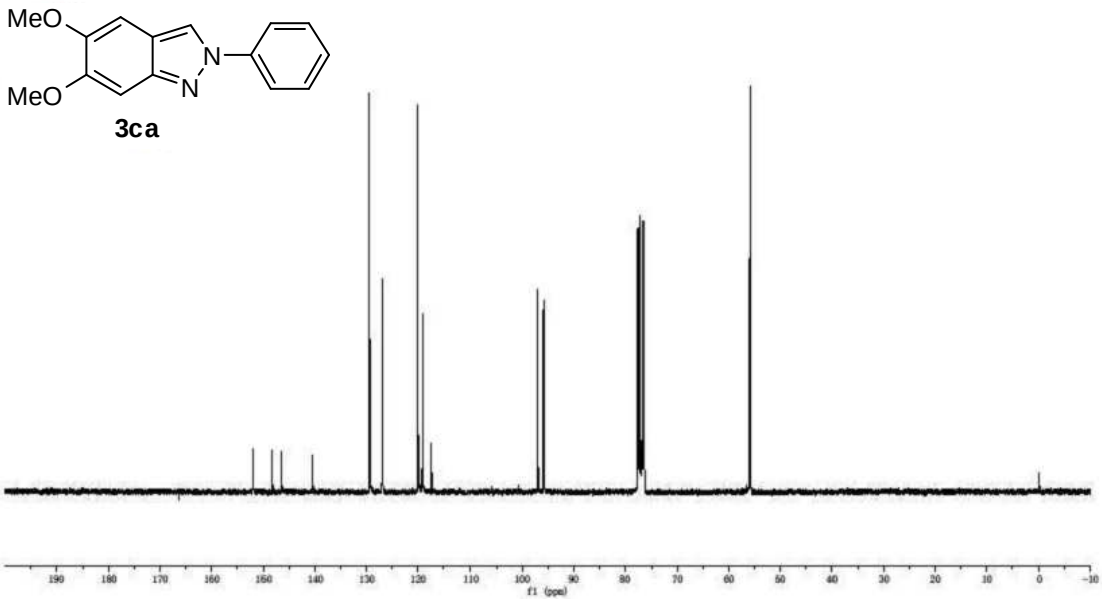


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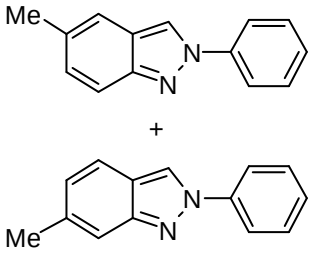


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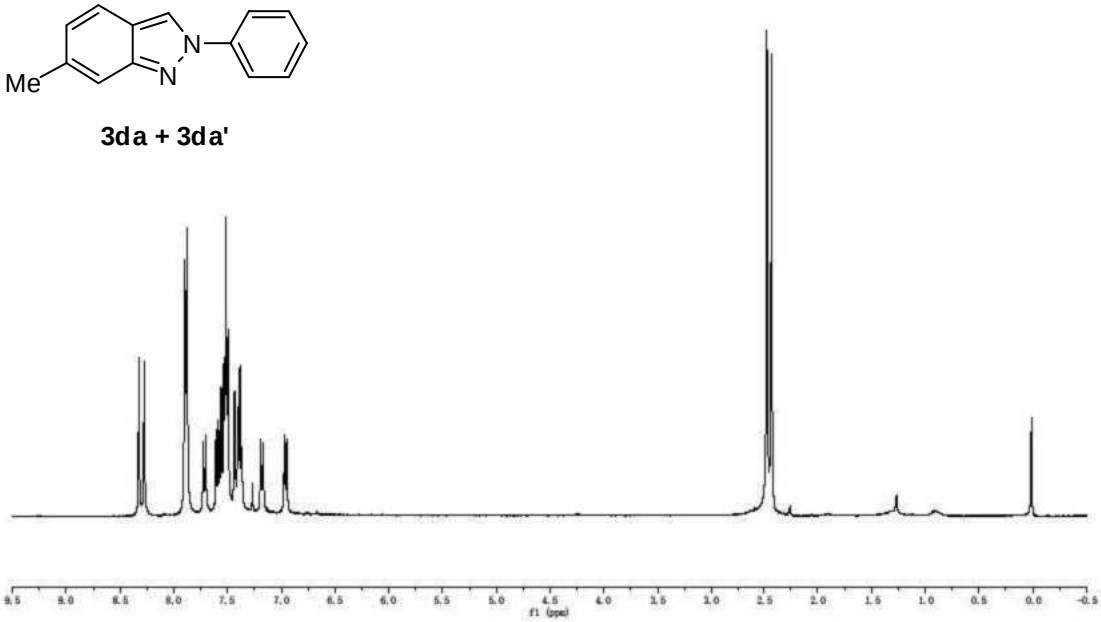


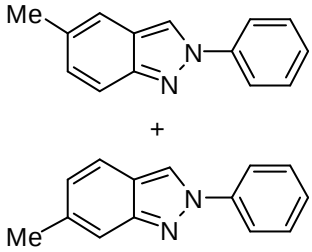


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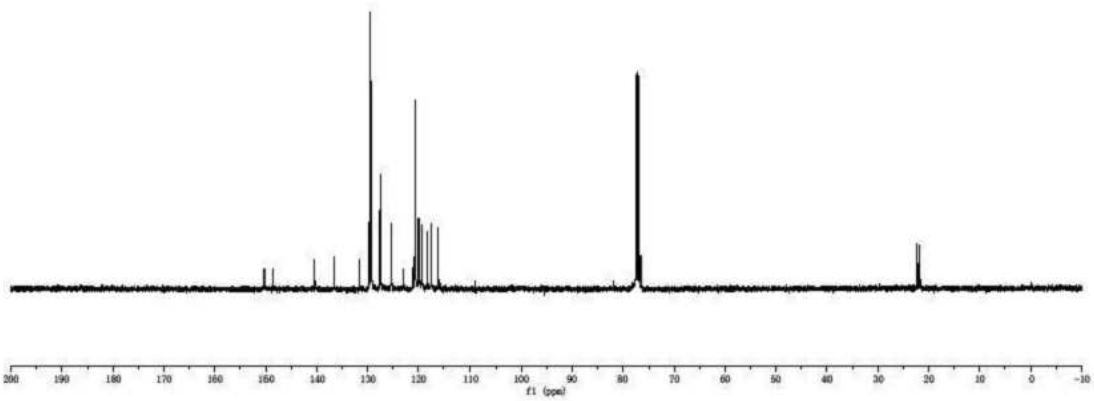


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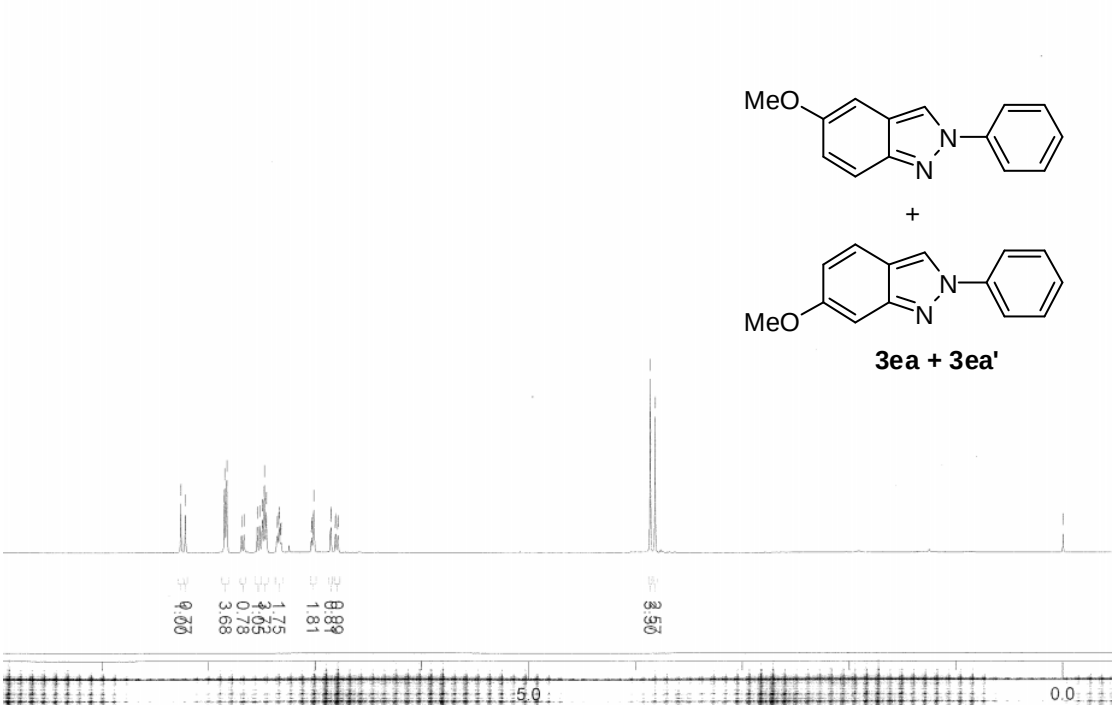


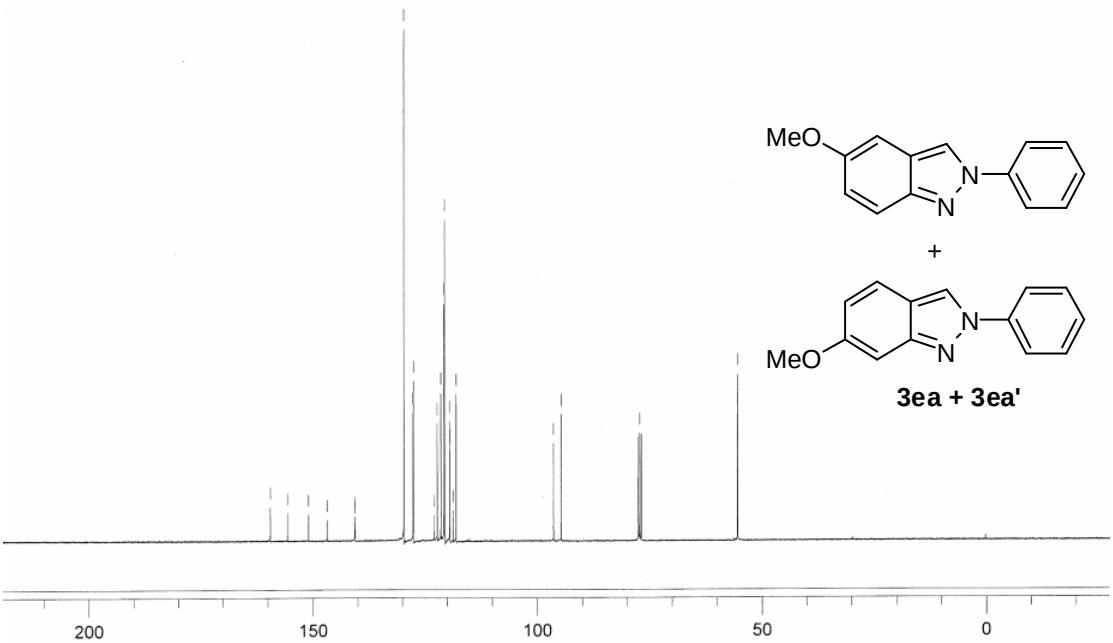


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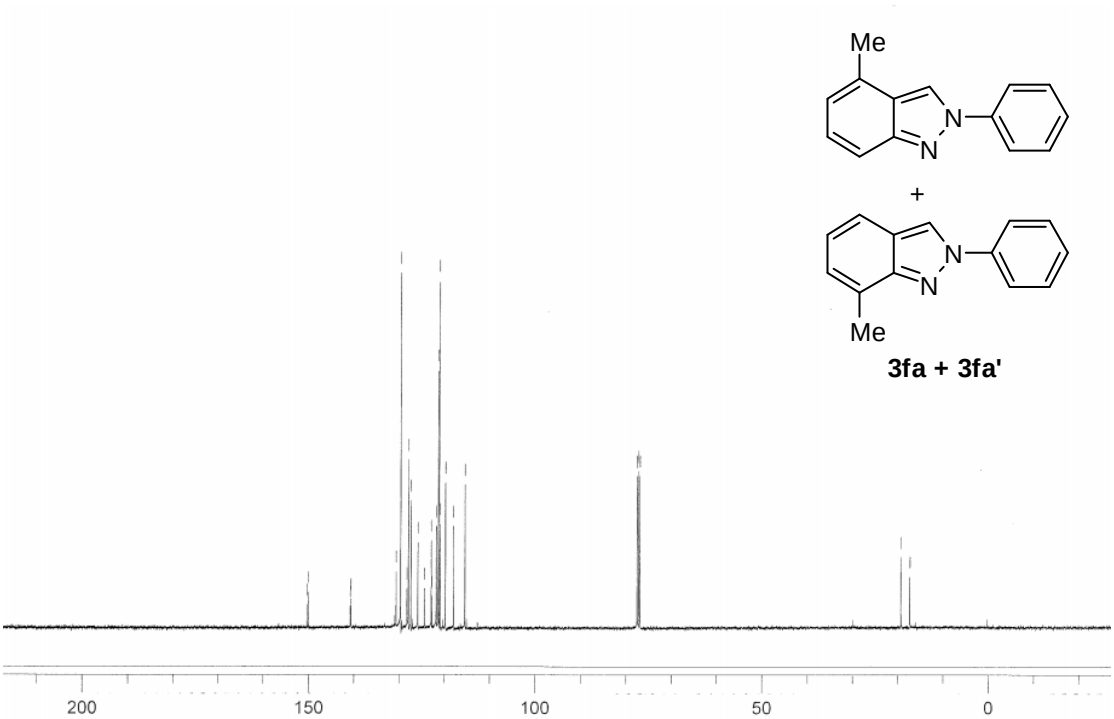


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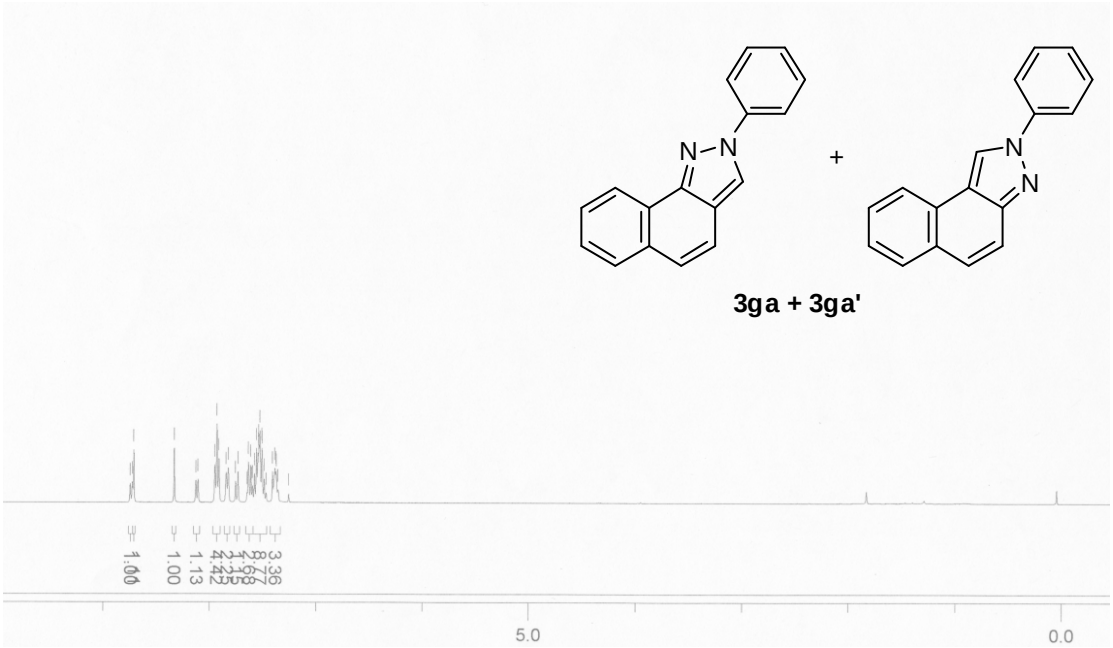


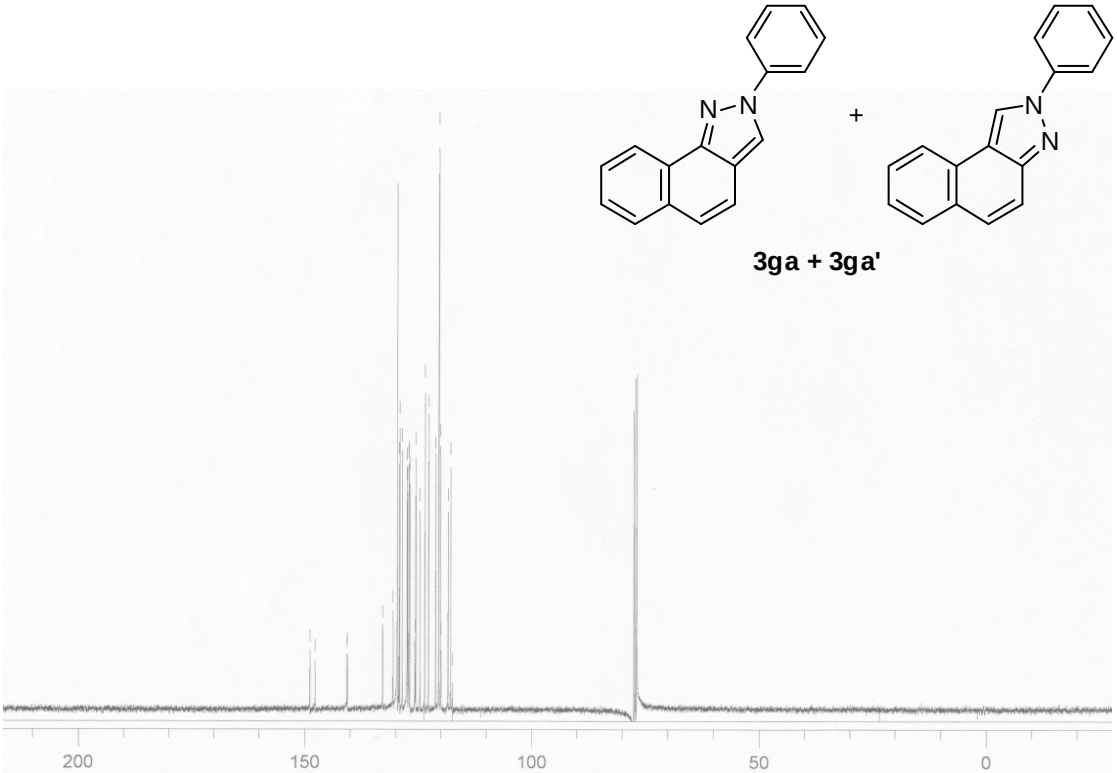


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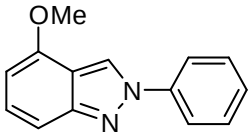


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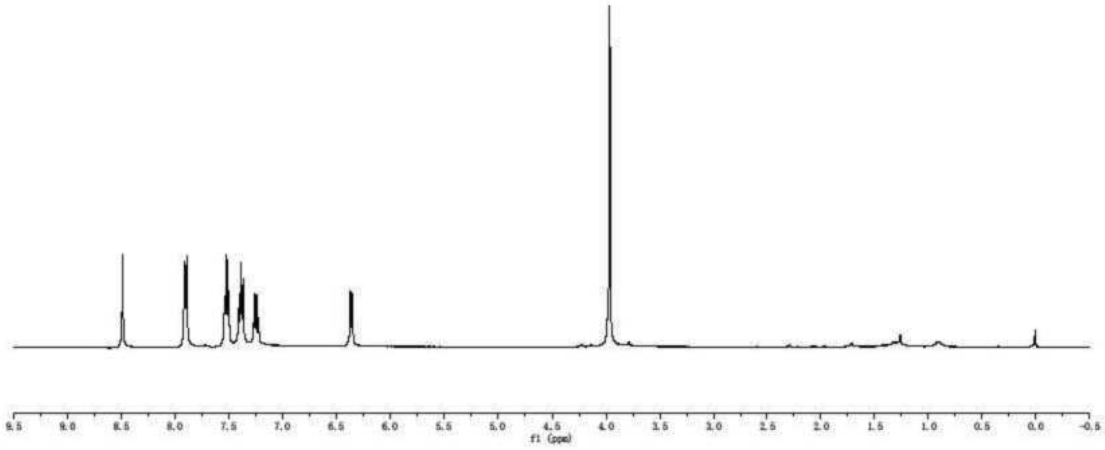
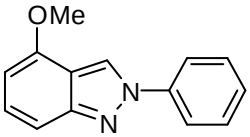
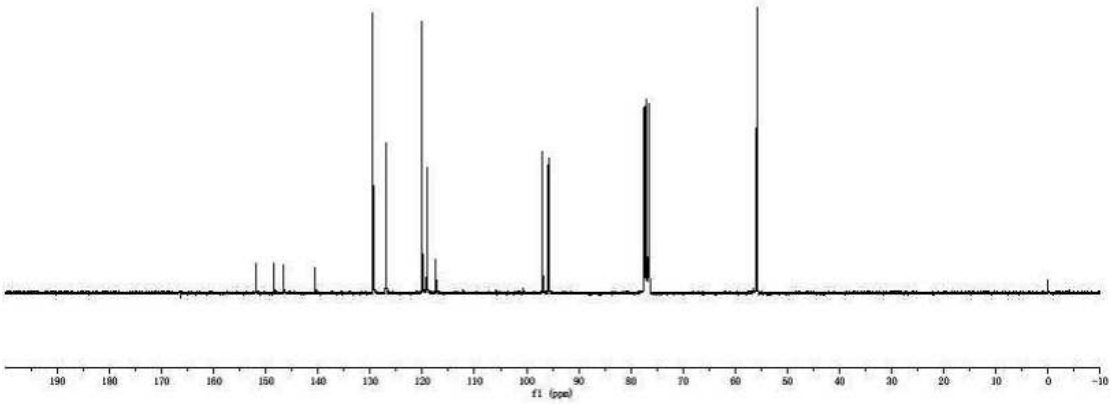



**3ia**

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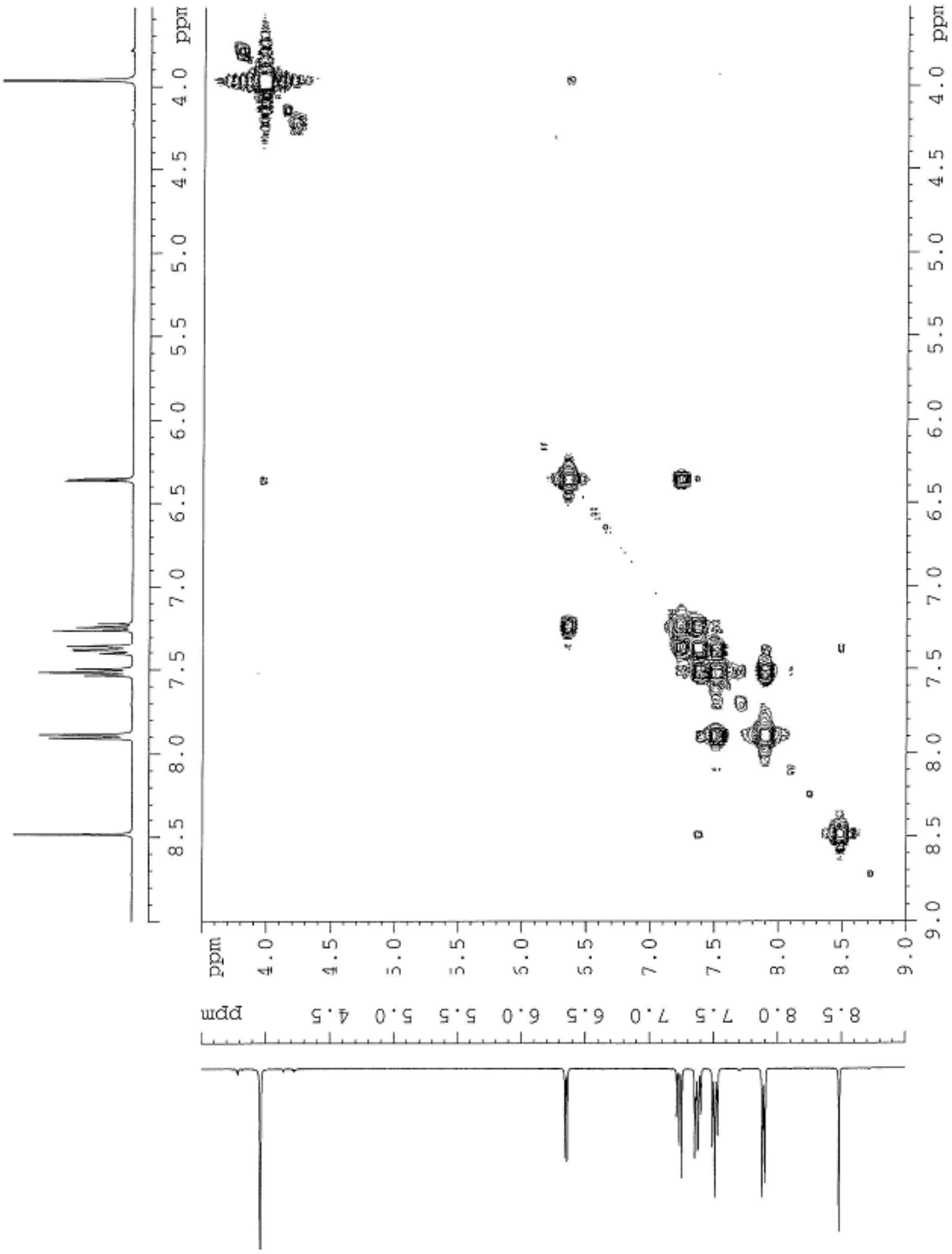
2D NMR Spectra for **3ia**.

NOESY, showing OMe group close to the H at 6.35 ppm

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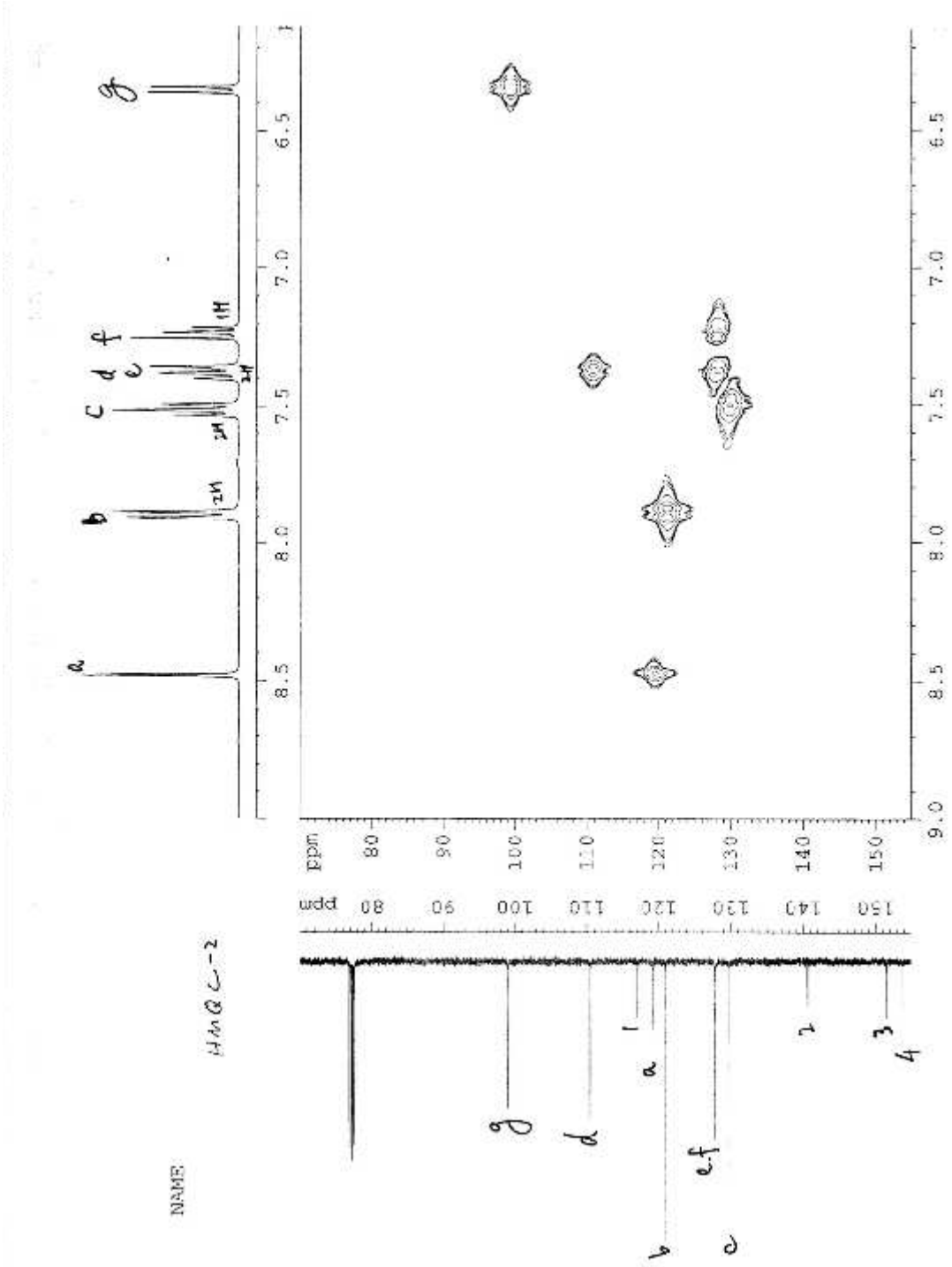
HMQC

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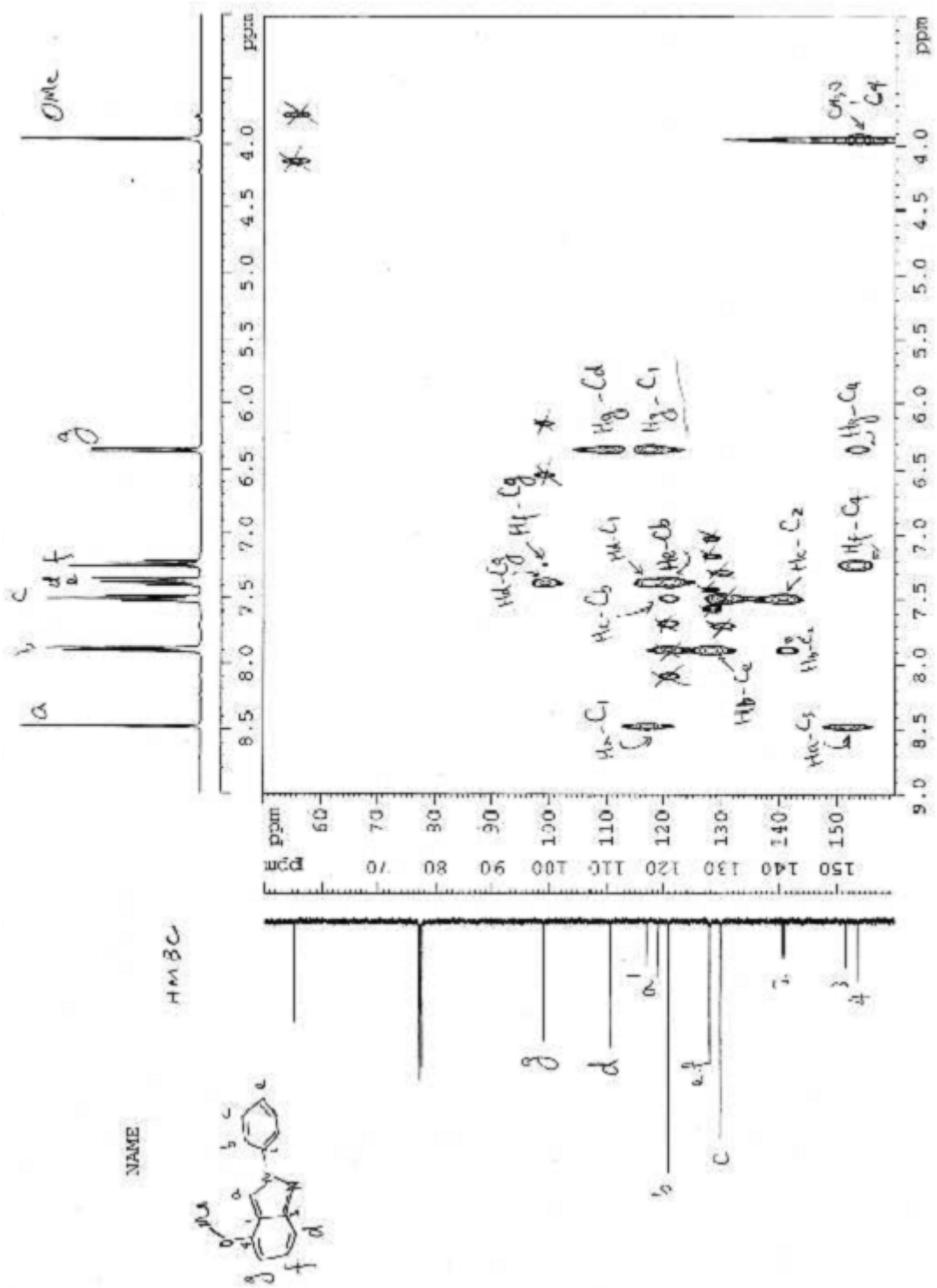
HMBC. The cross-peak of $H_g$-$C_1$ supports this regioisomer. However, an equally important cross-peak of $H_a$-$C_4$ is not ovserved.

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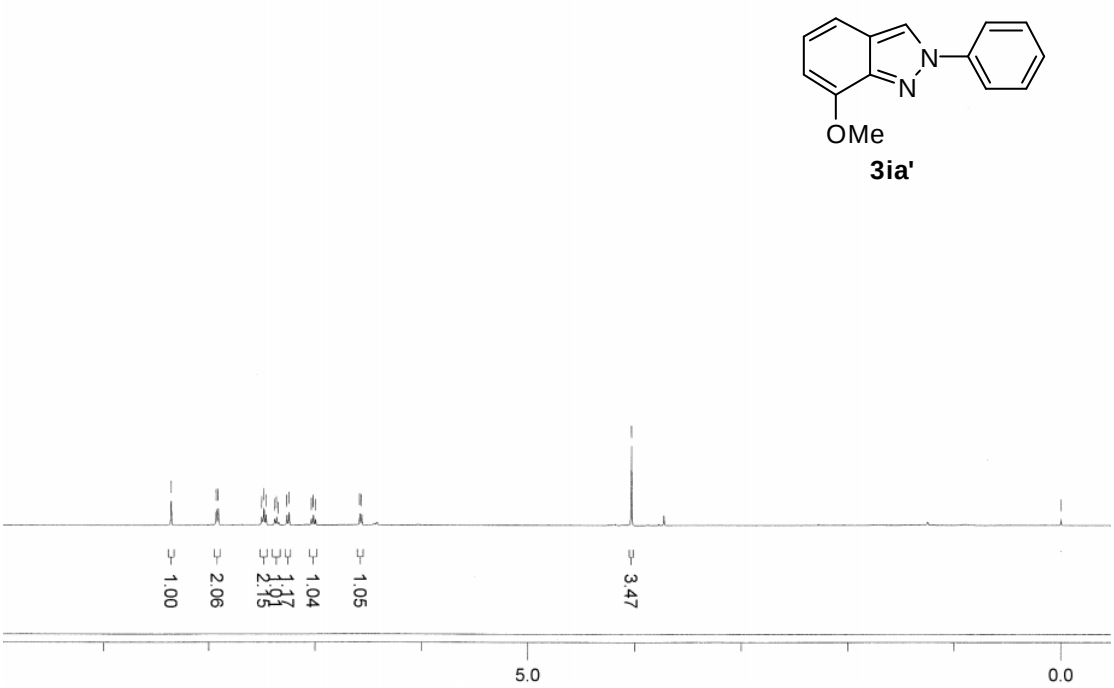


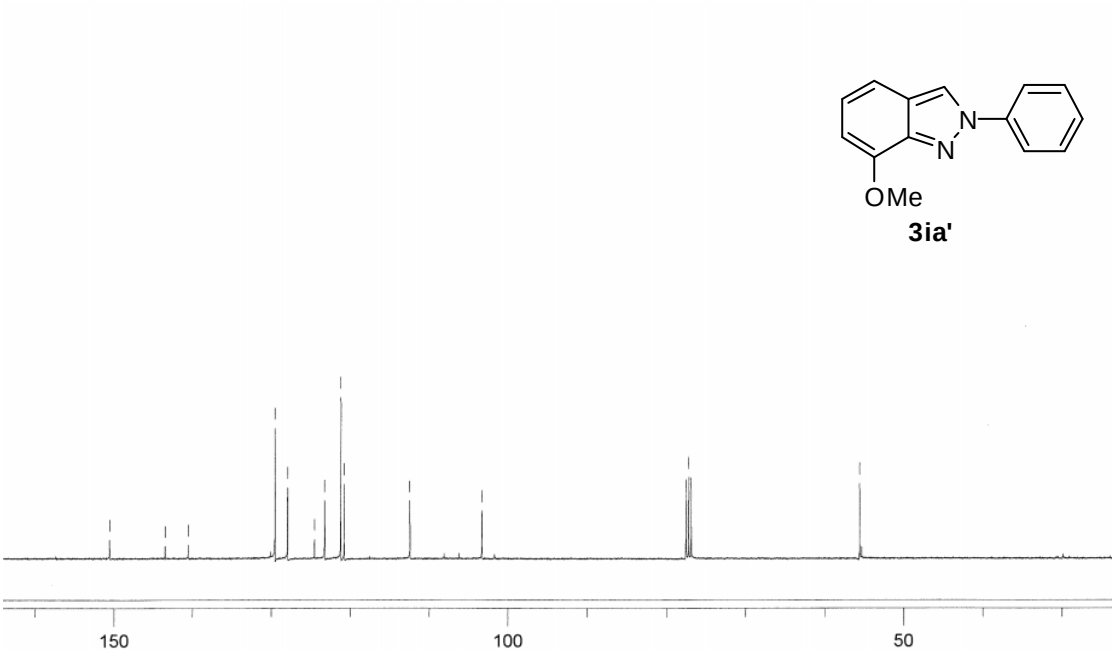


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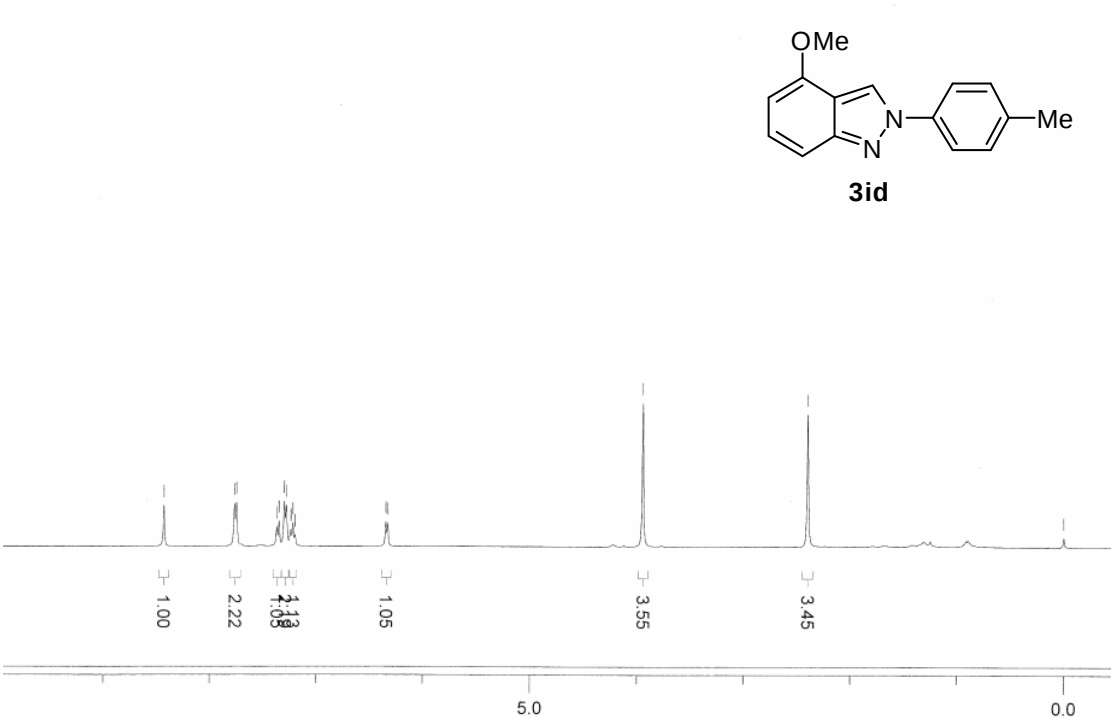


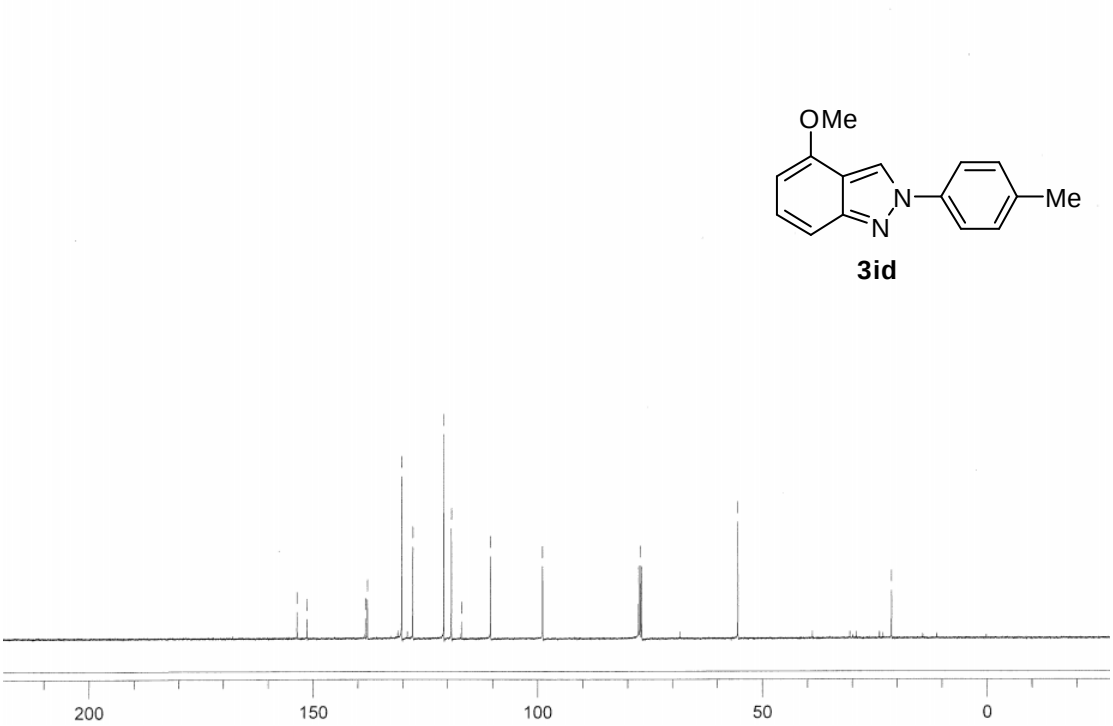


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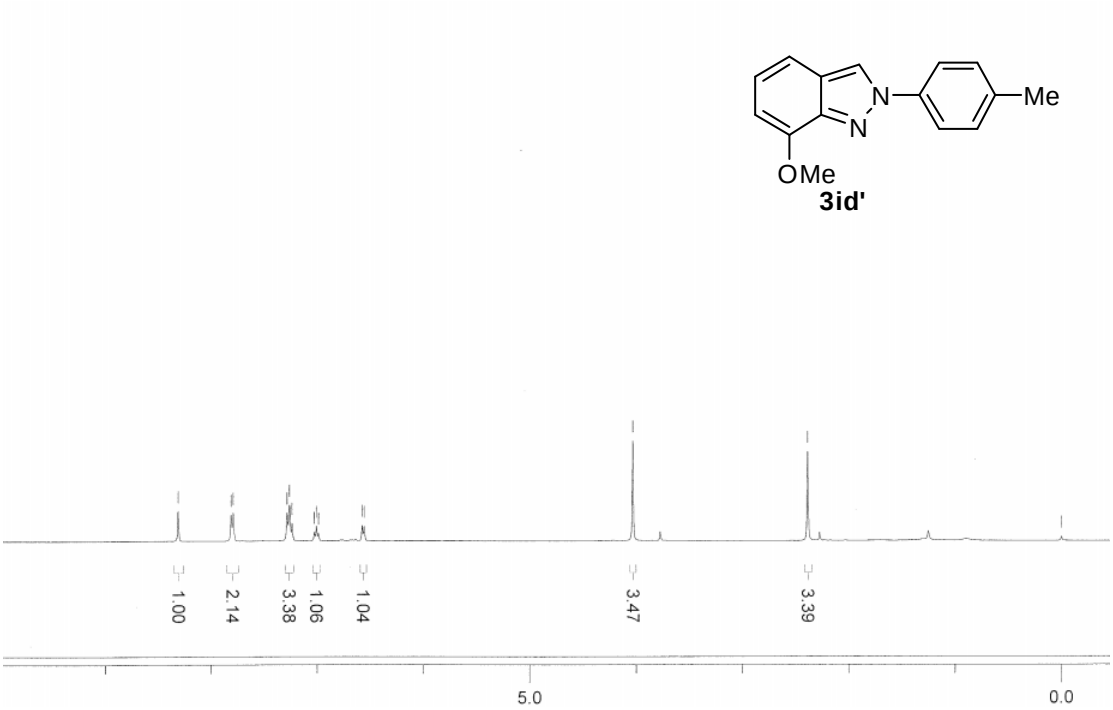


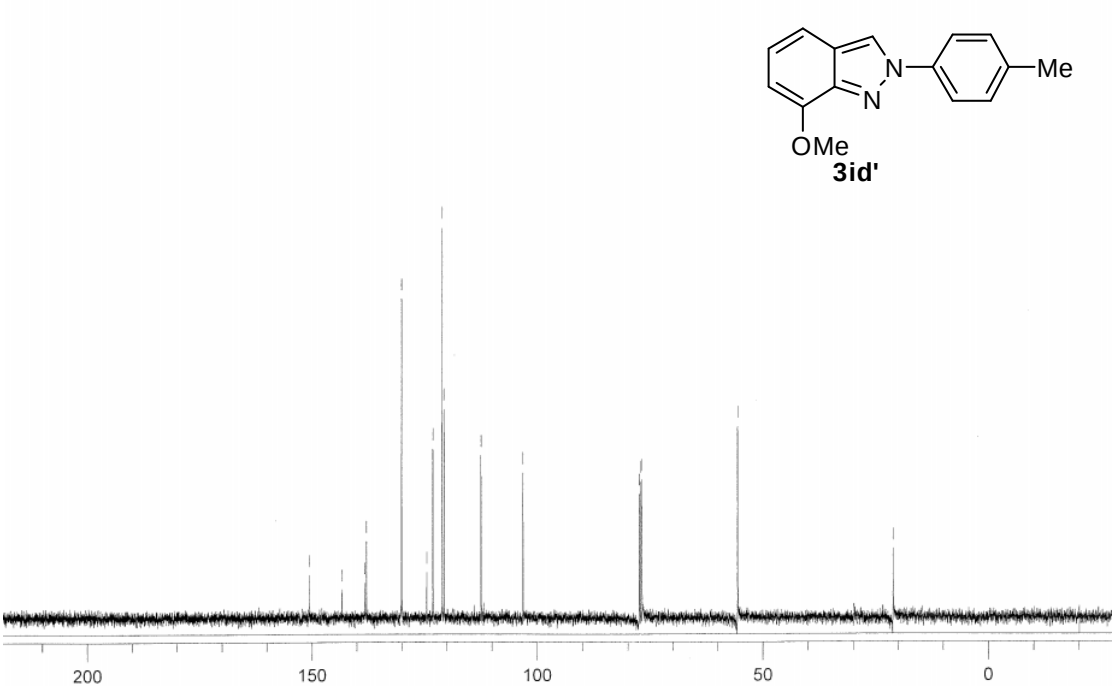


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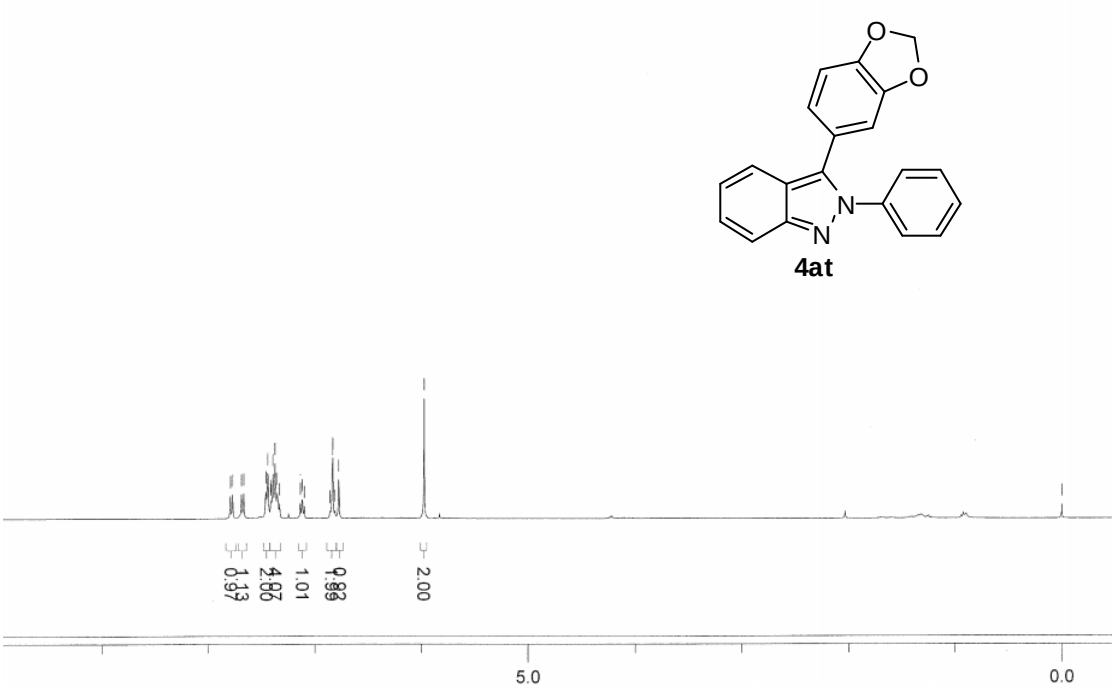


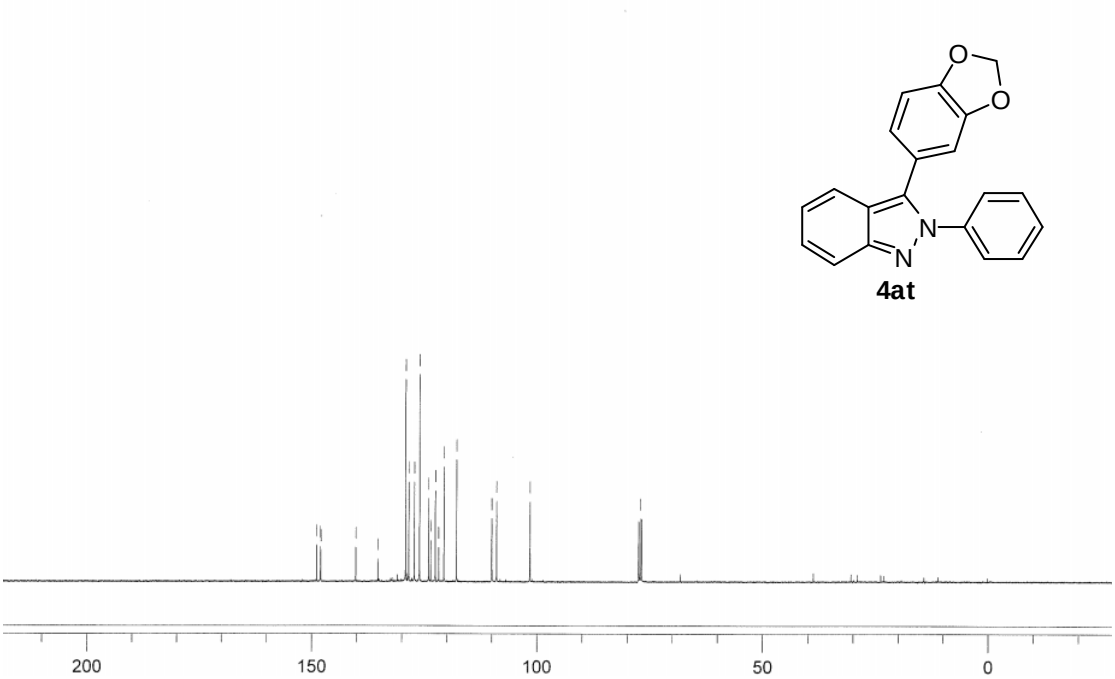


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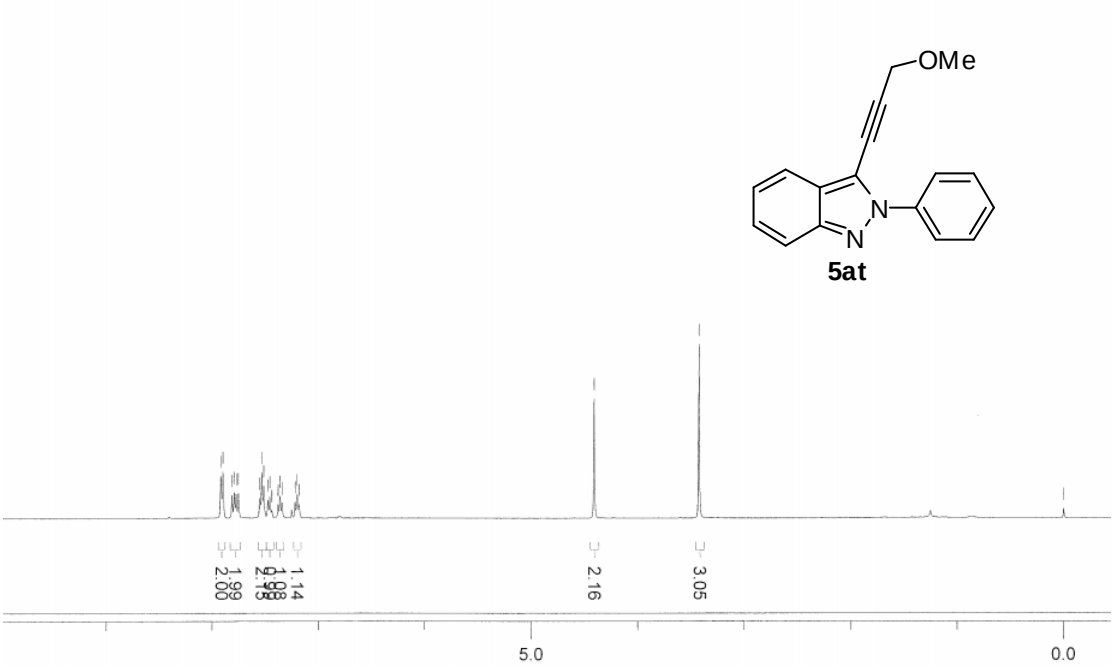


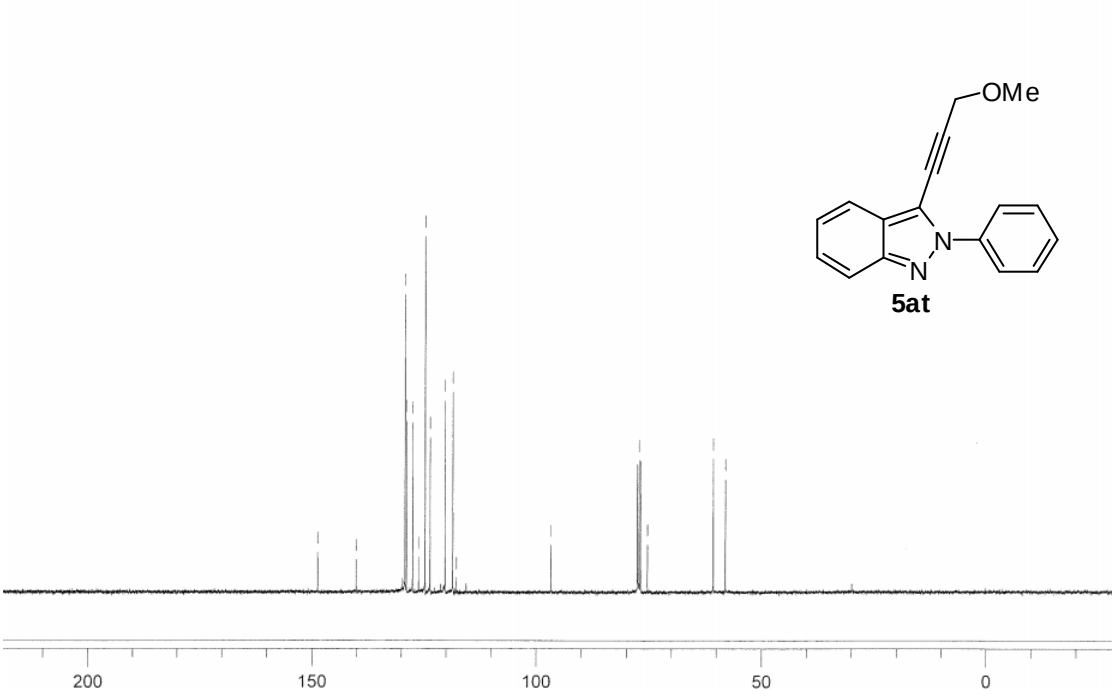


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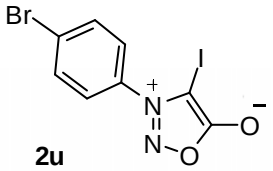


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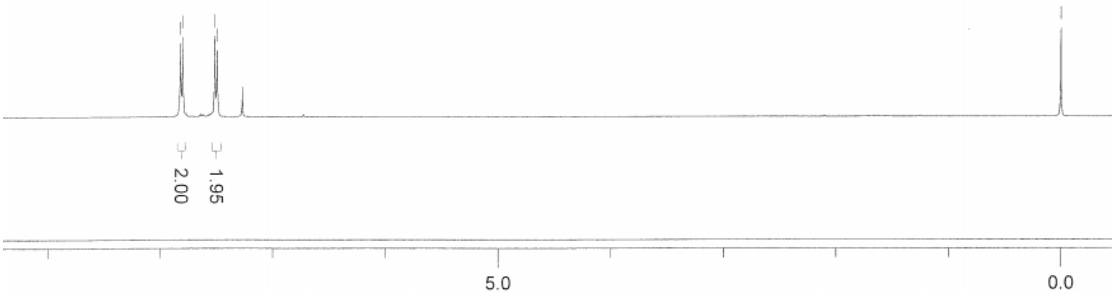


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# APPENDIX D. CHAPTER 5 $^{1}$H AND $^{13}$C NMR SPECTRA

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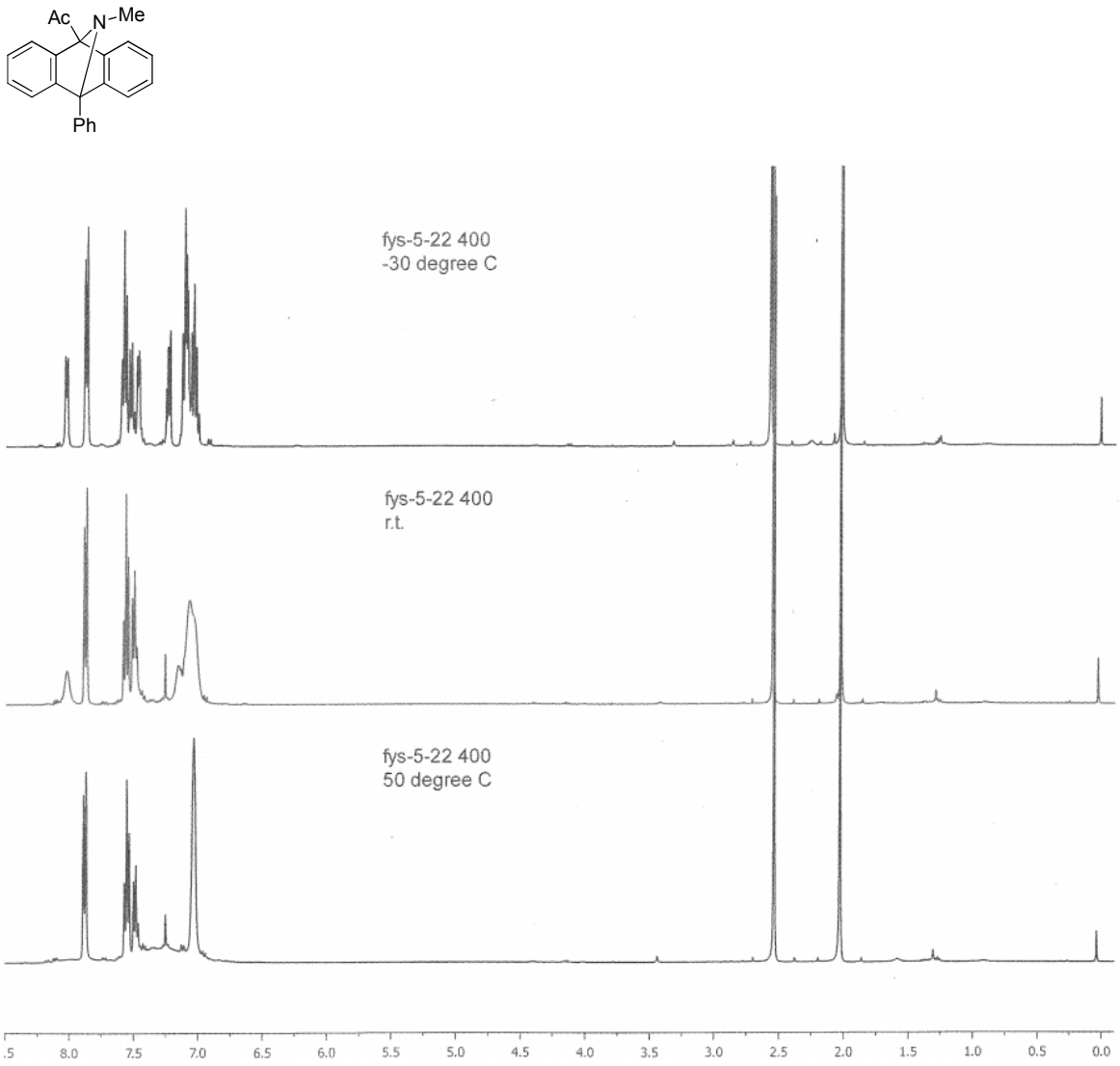
Temperature effect on $^{1}H$ NMR of 9,10-Dihydro-9,10-epiminoanthracene.

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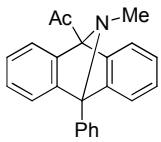
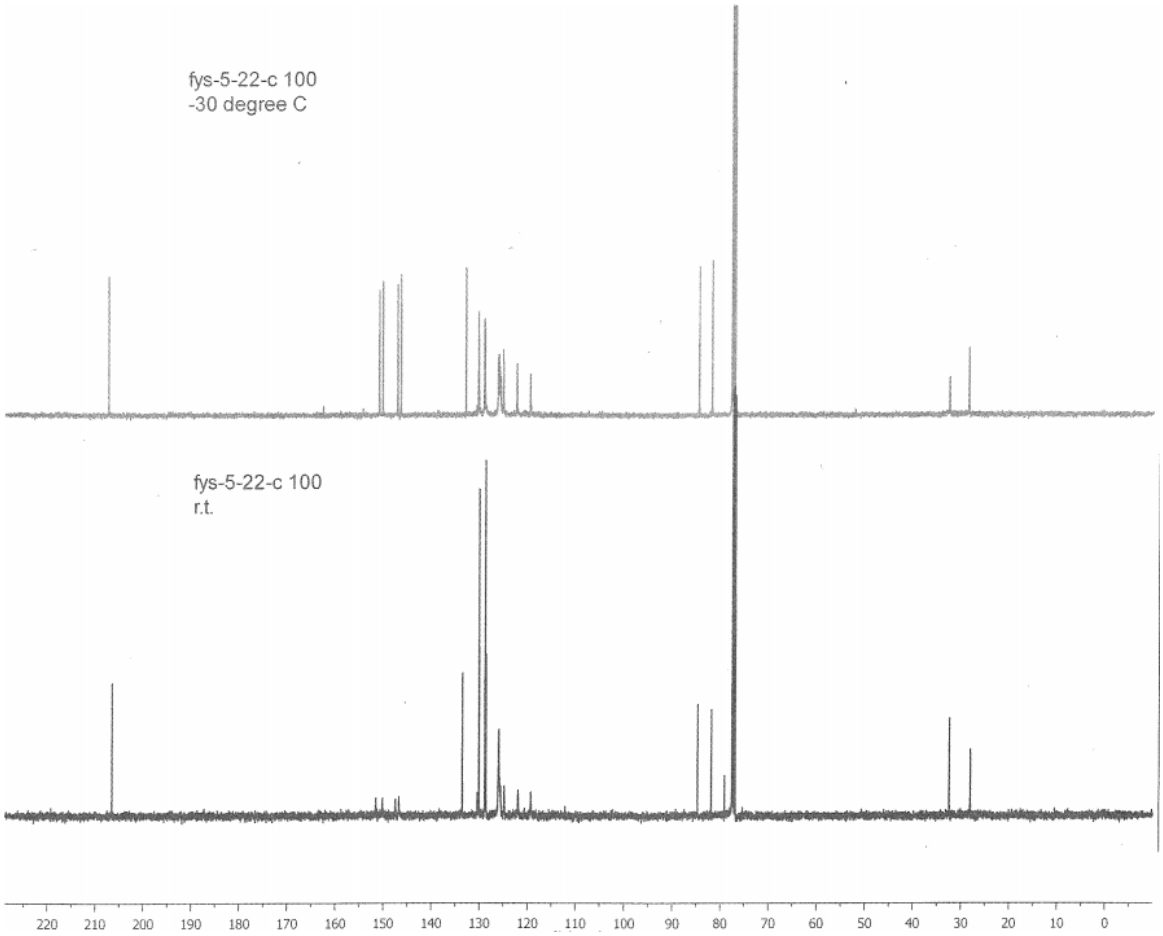
Temperature effect on $^{13}C$ NMR of 9,10-Dihydro-9,10-epiminoanthracene.

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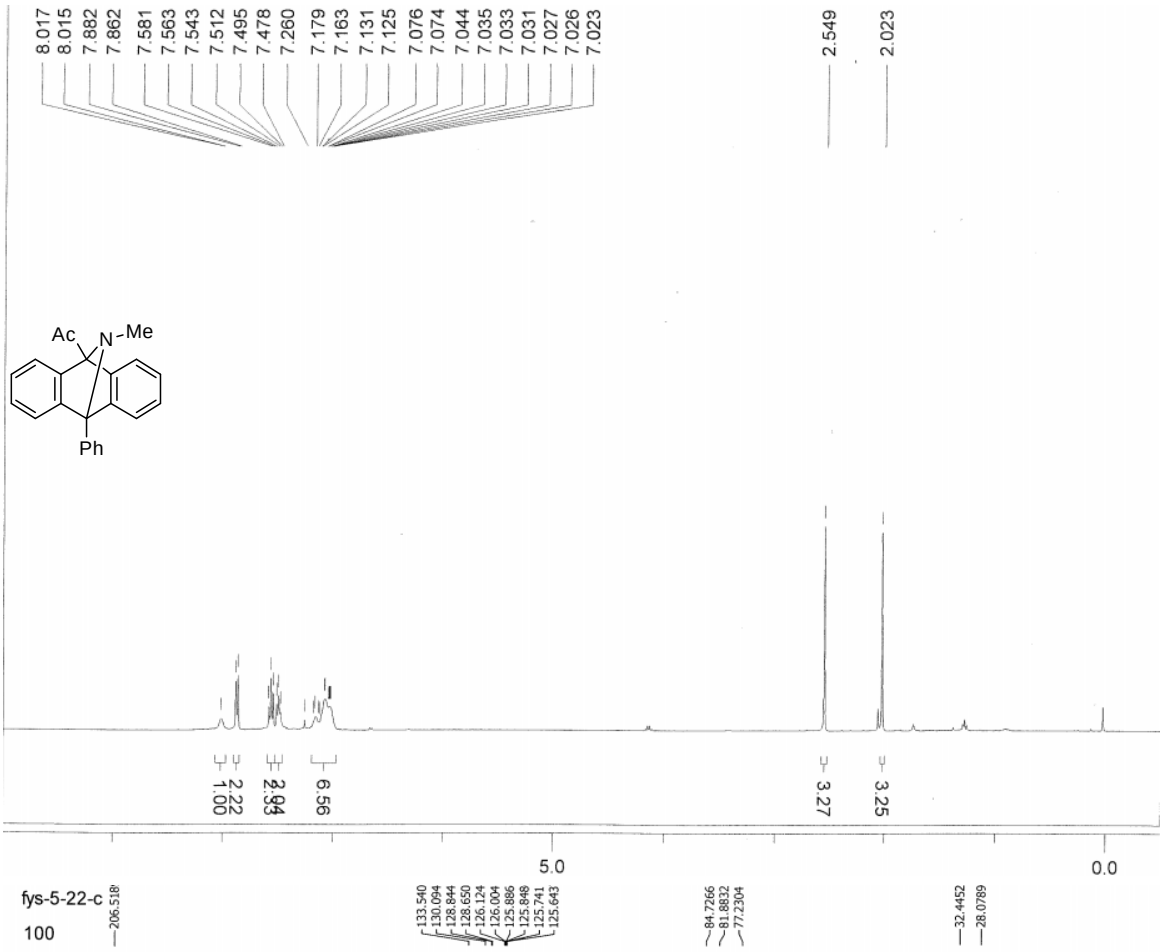


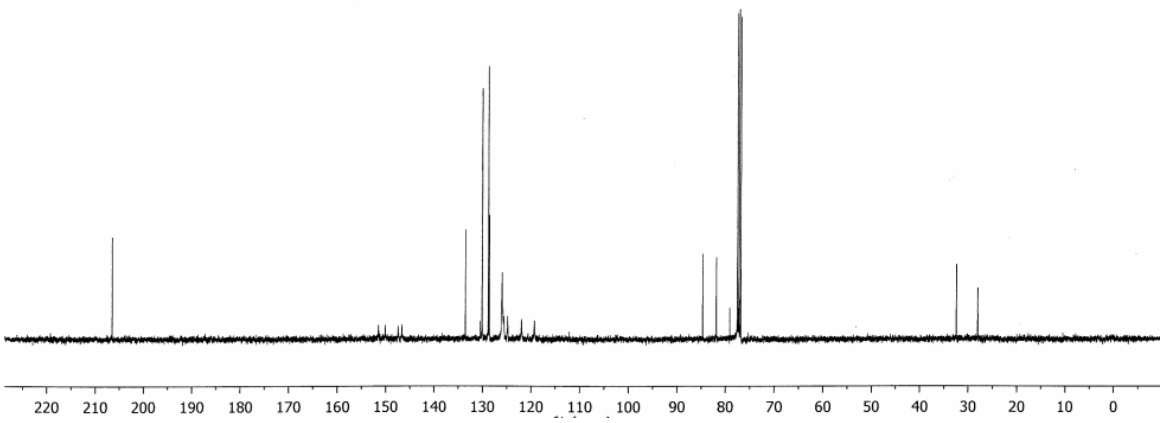


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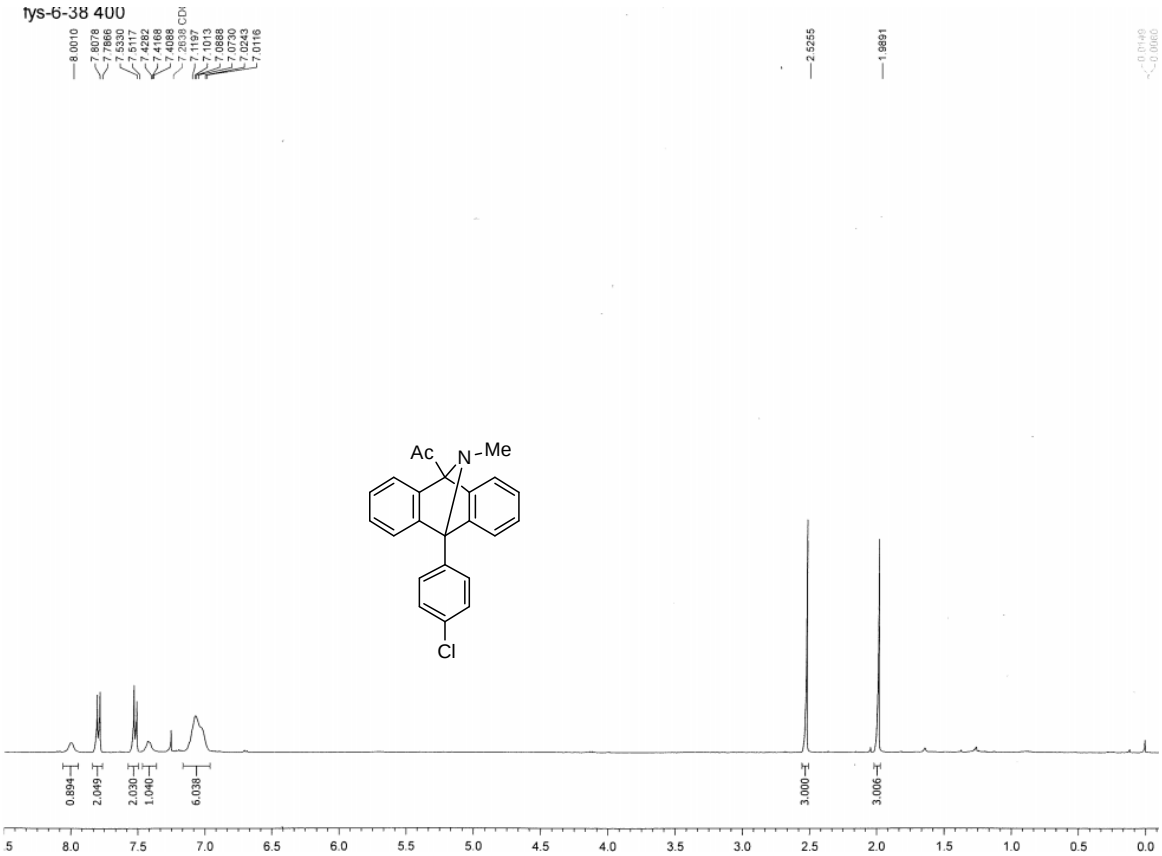


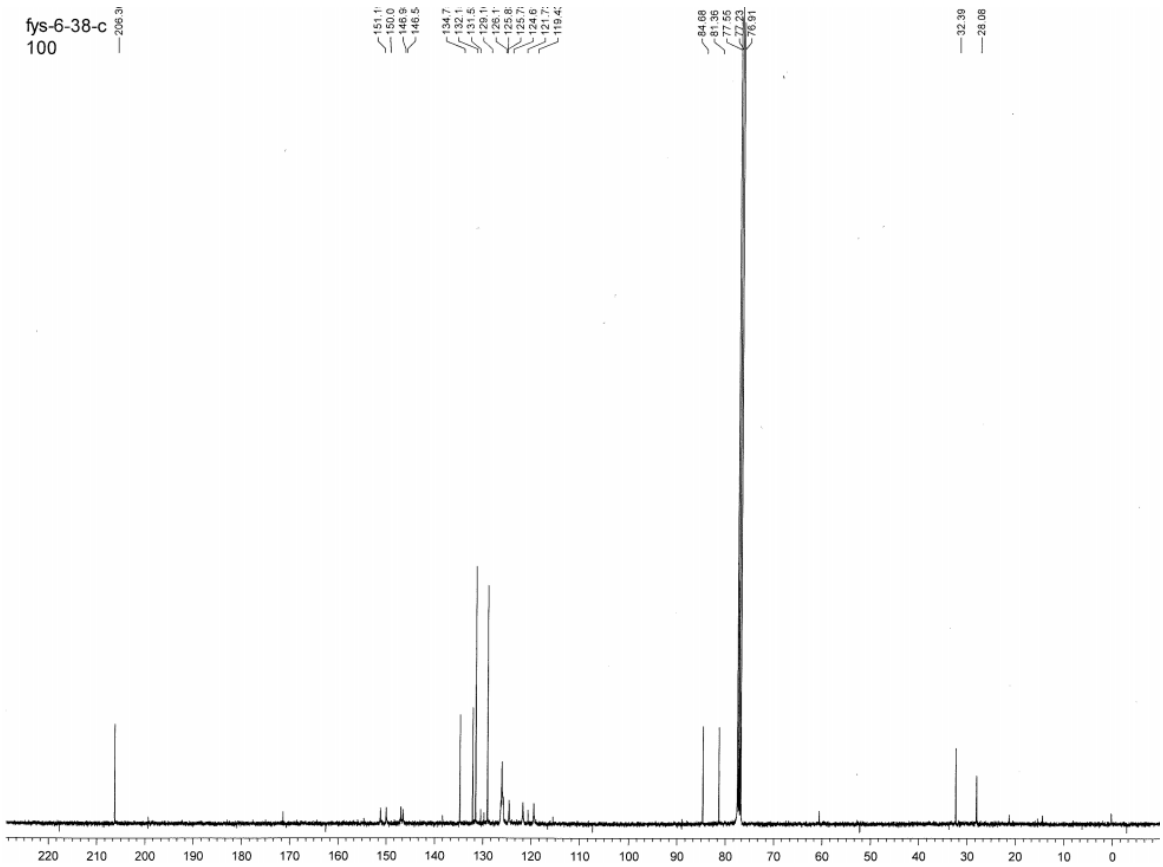


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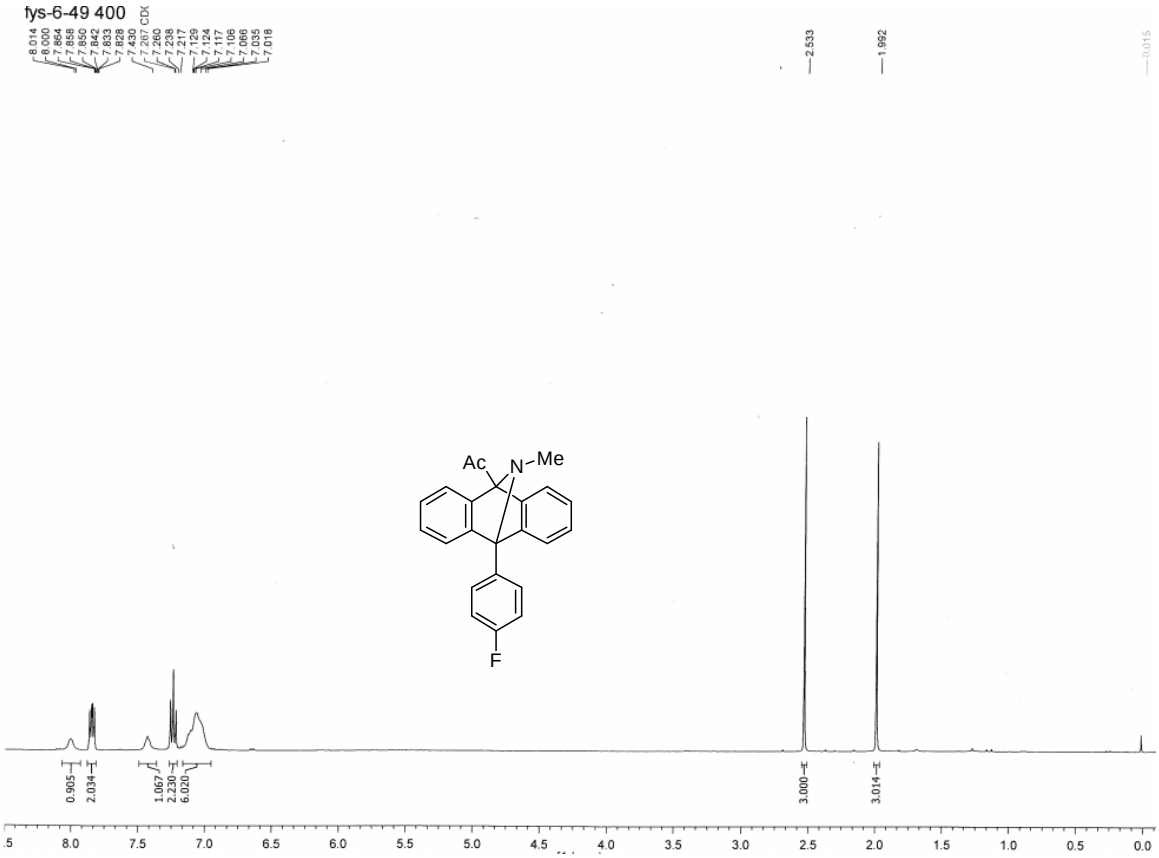


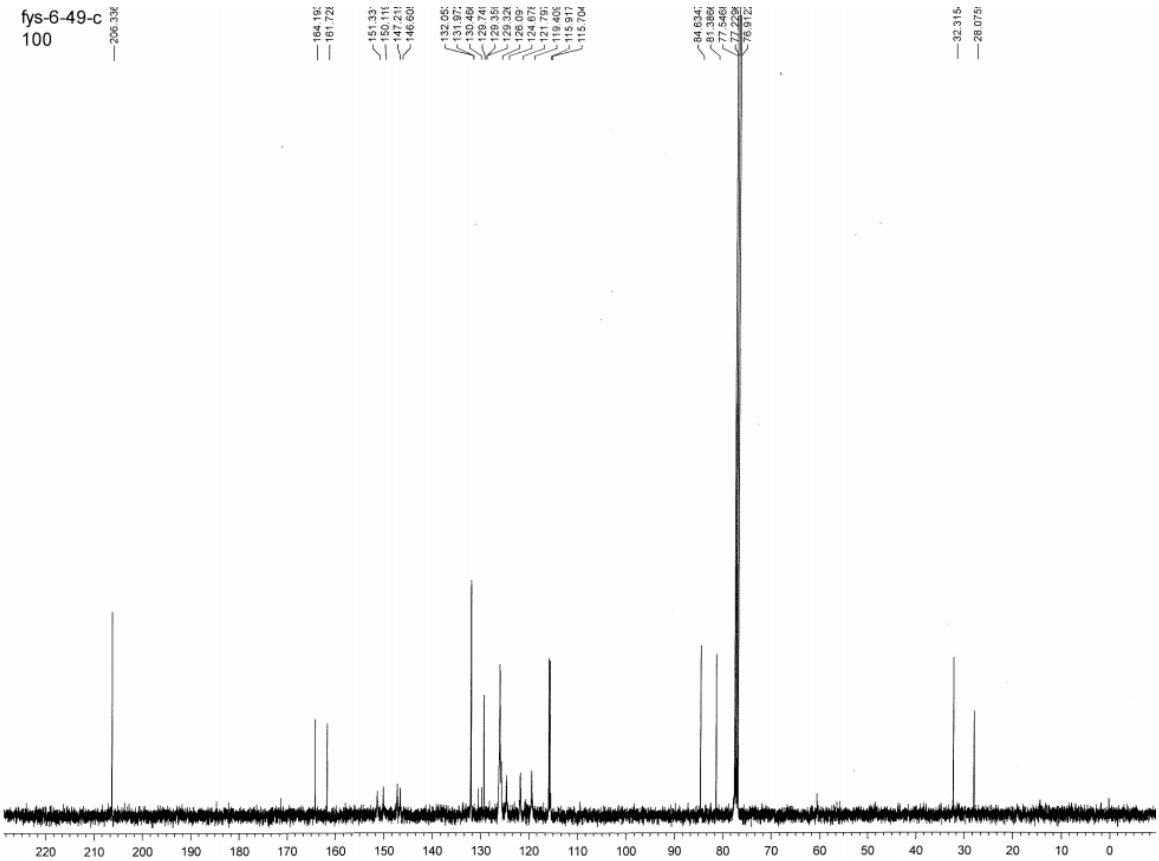


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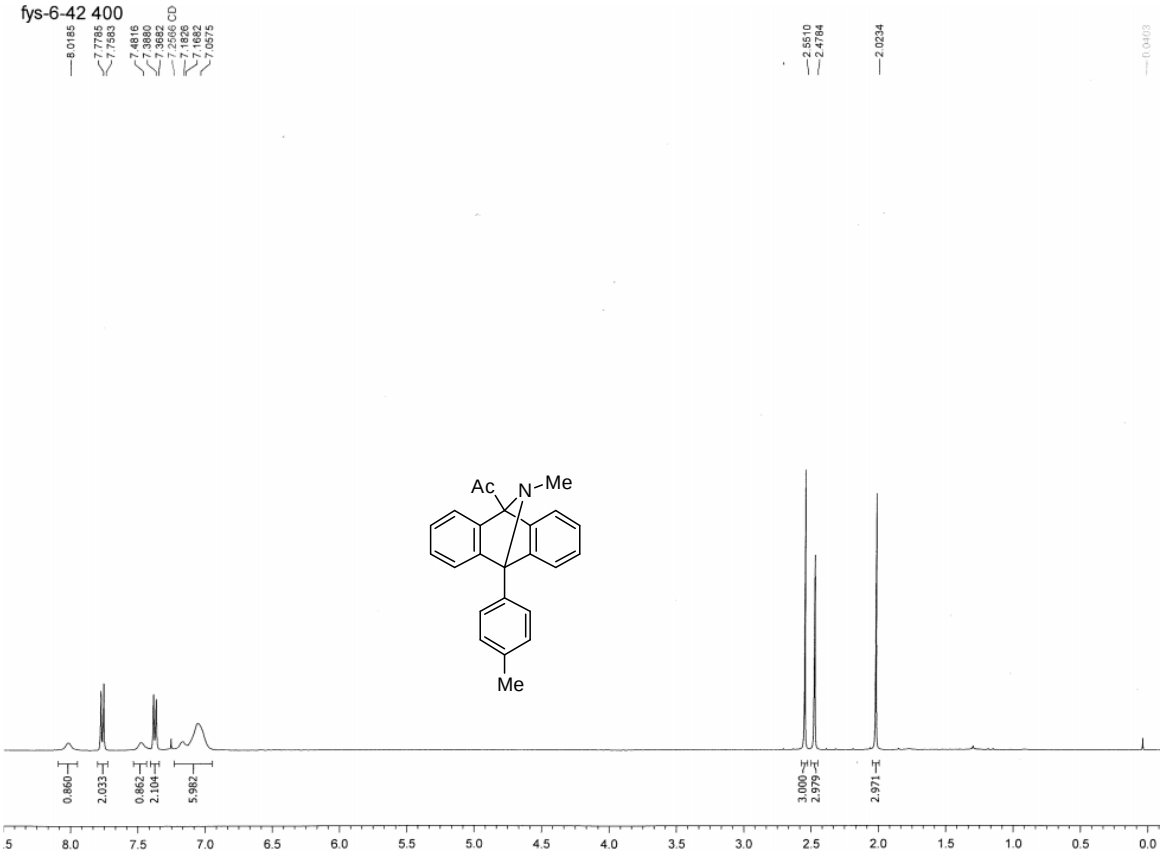


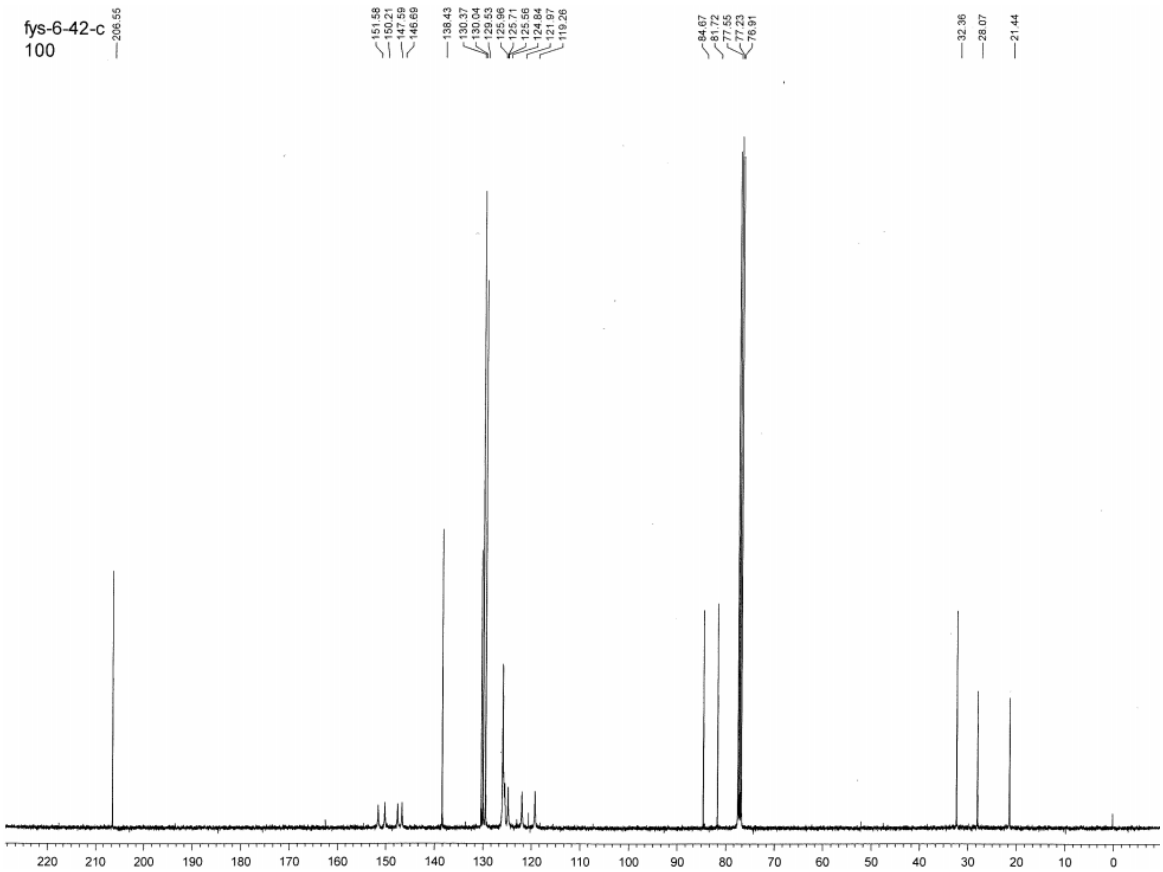


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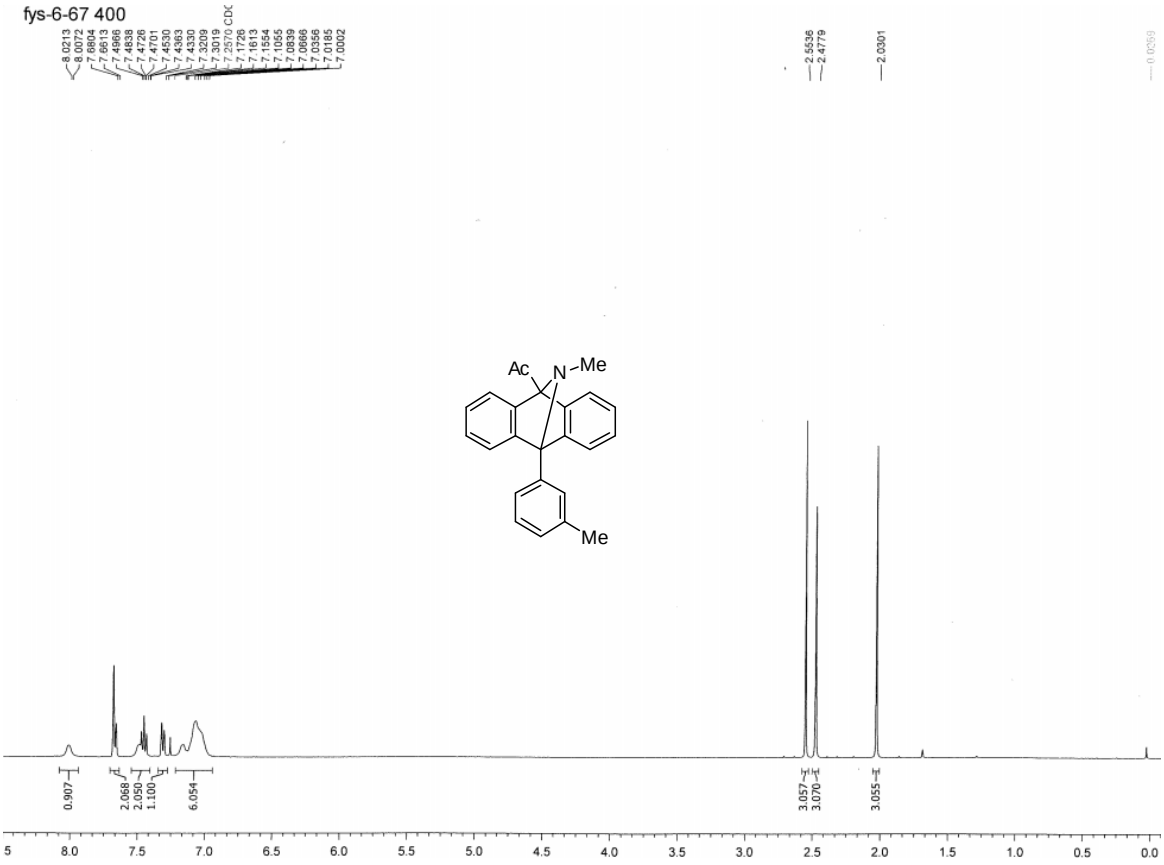


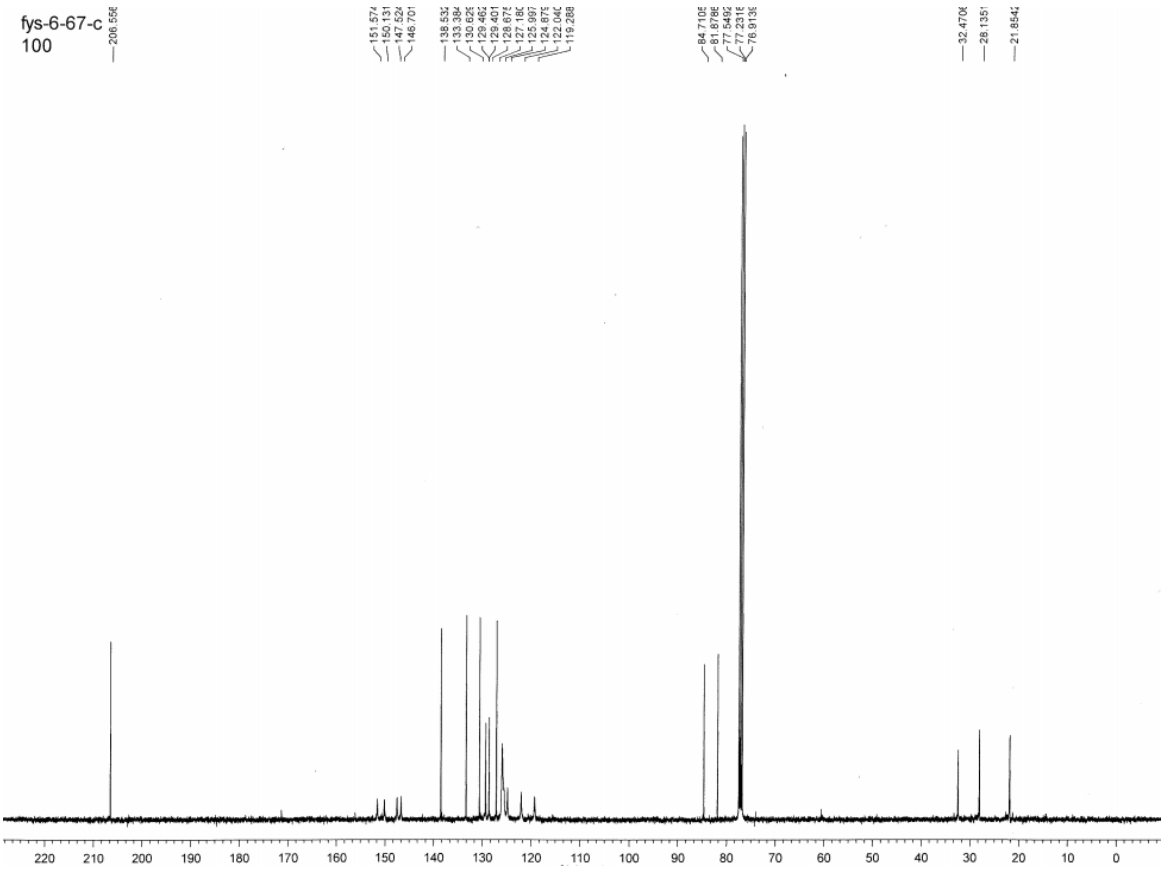


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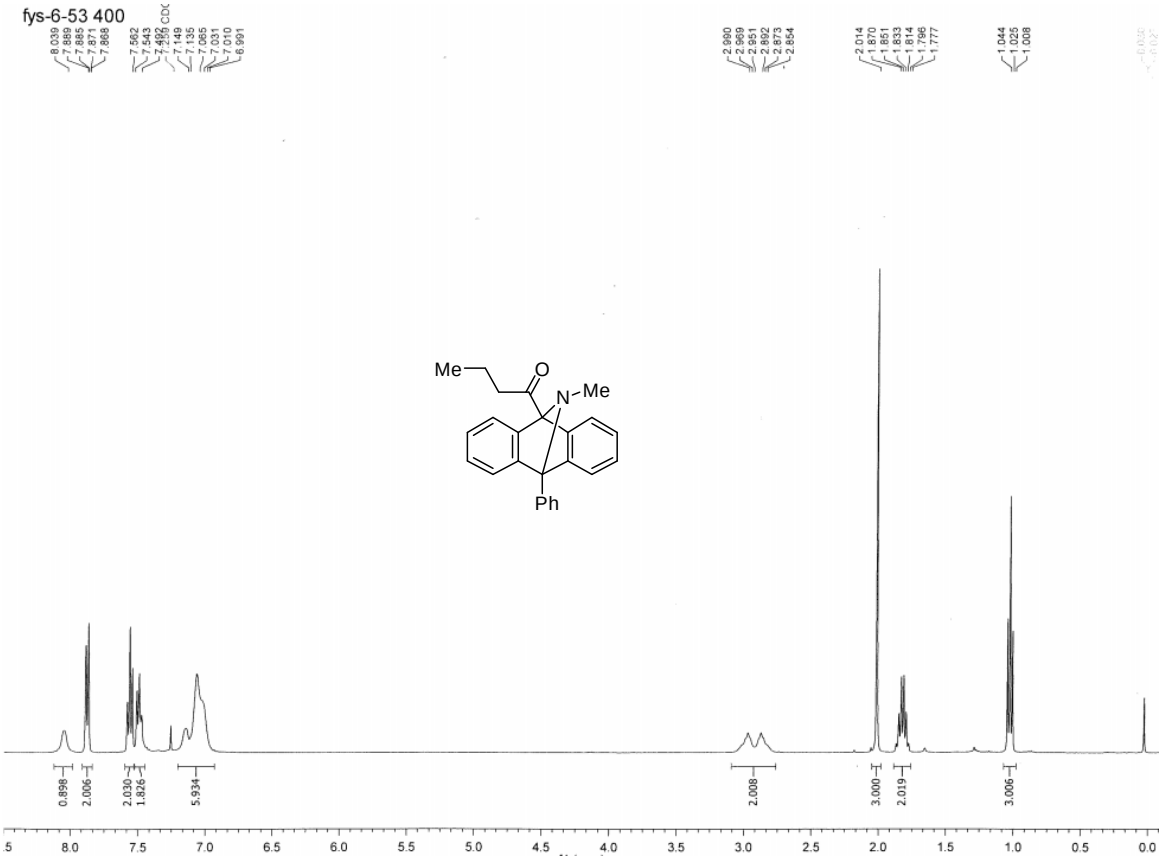


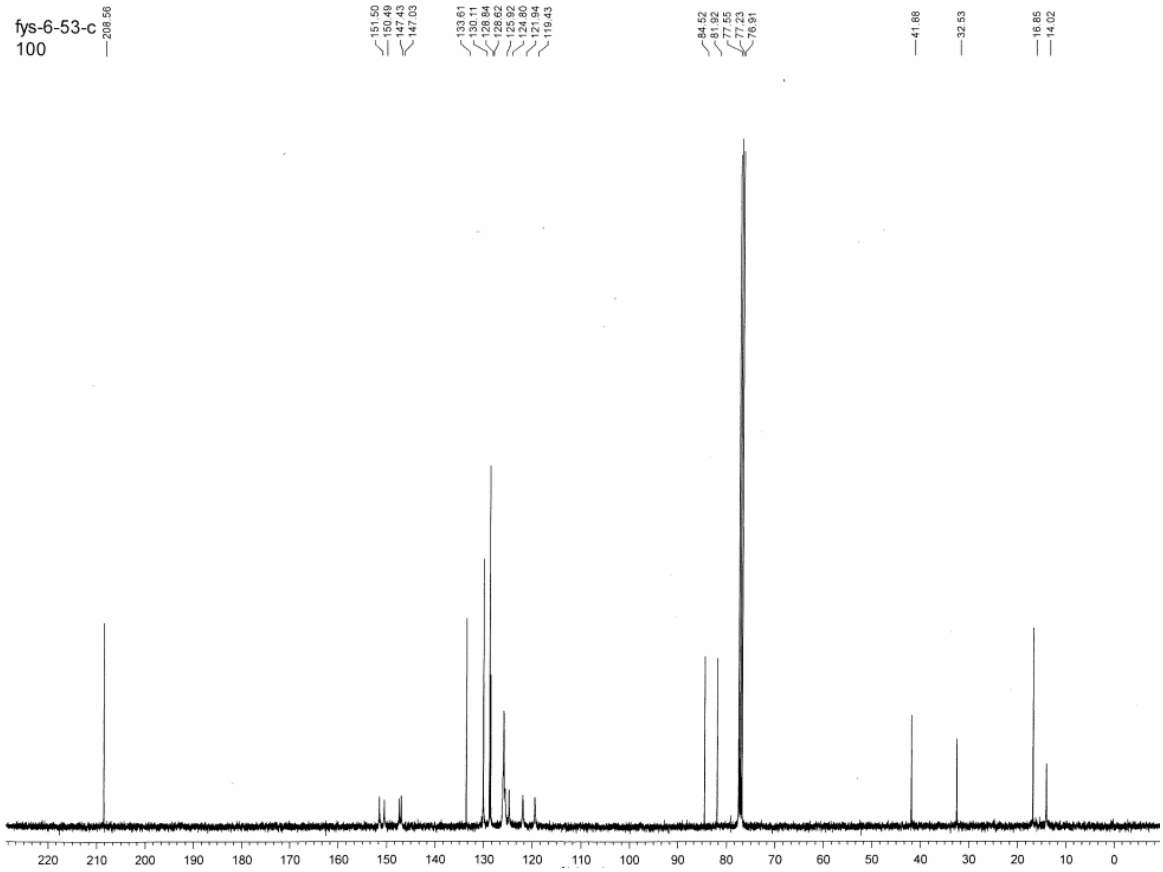


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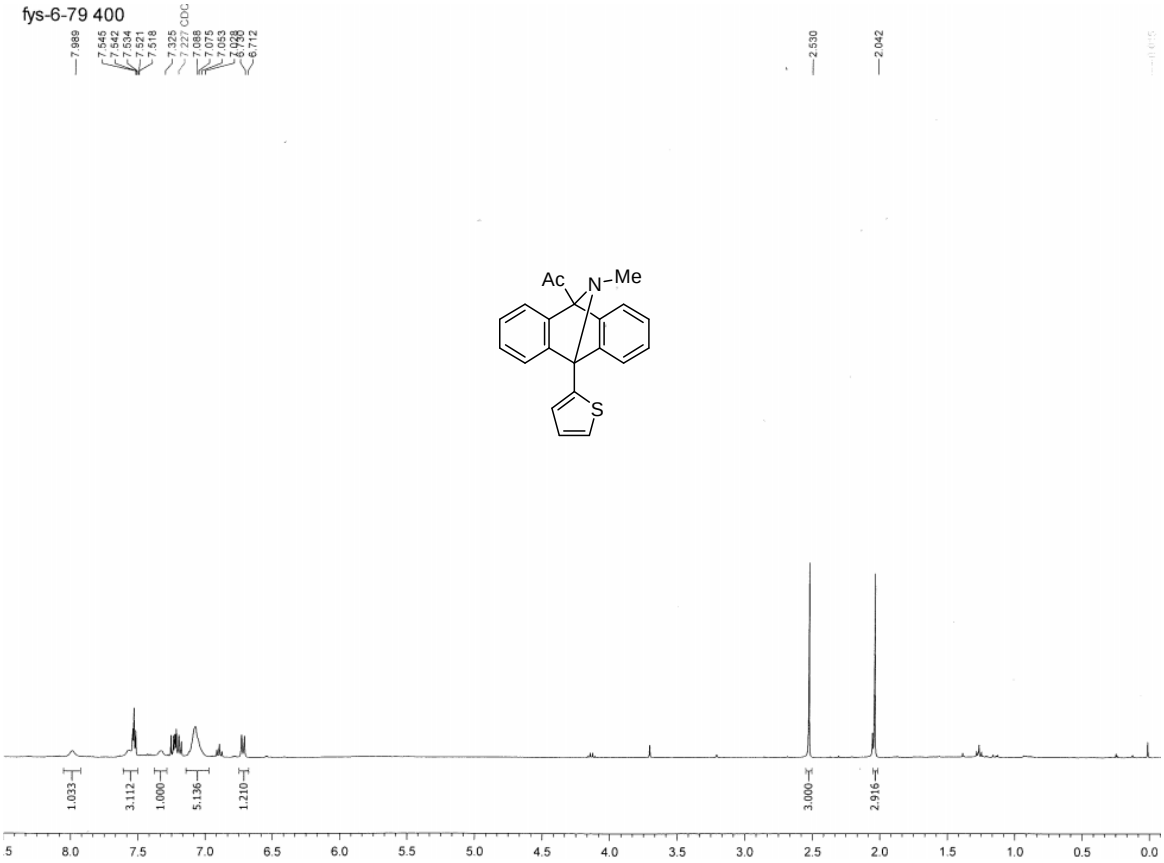


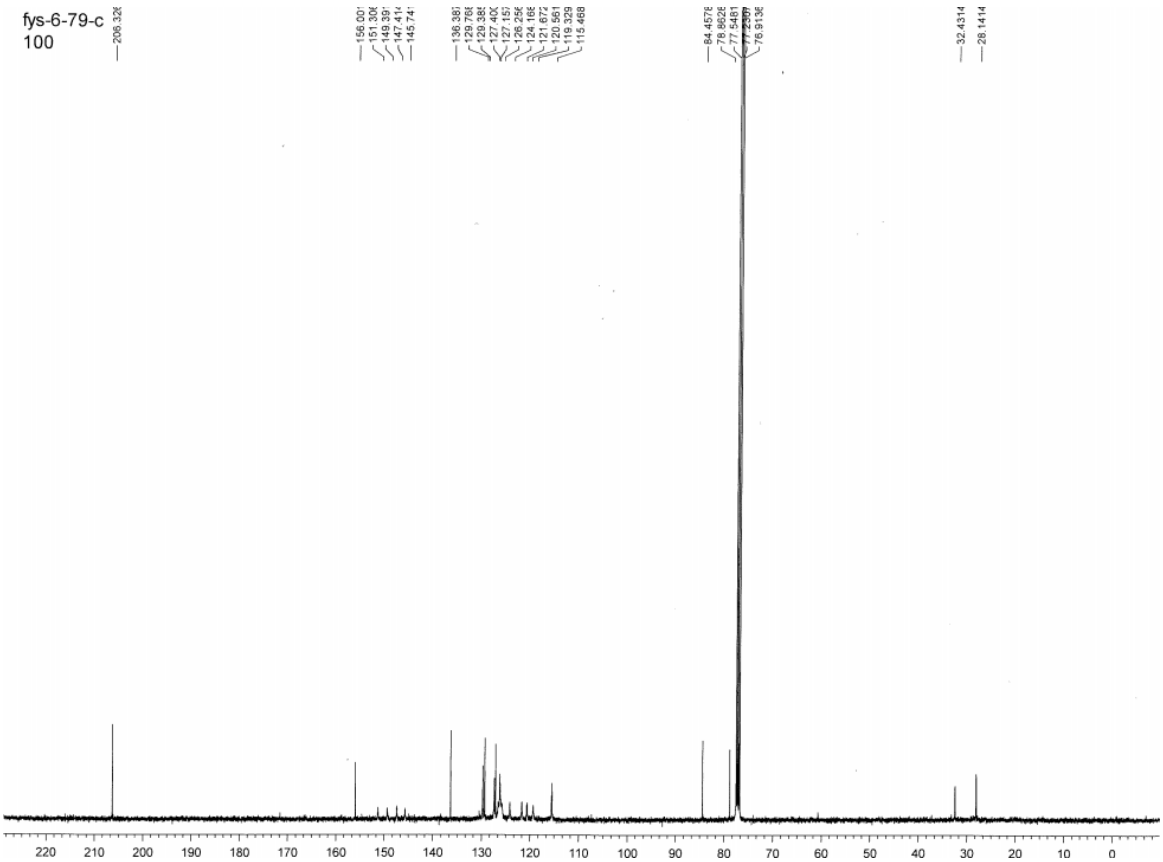


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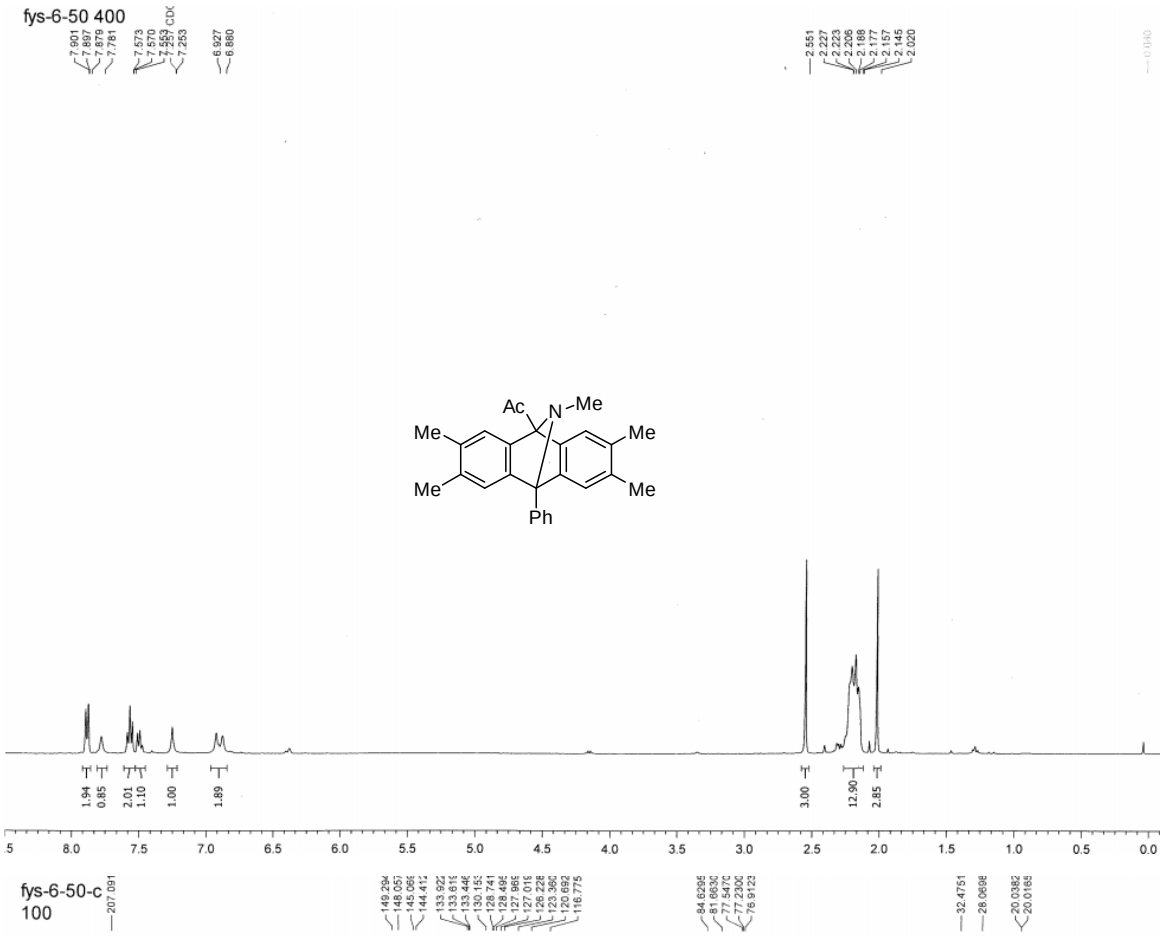


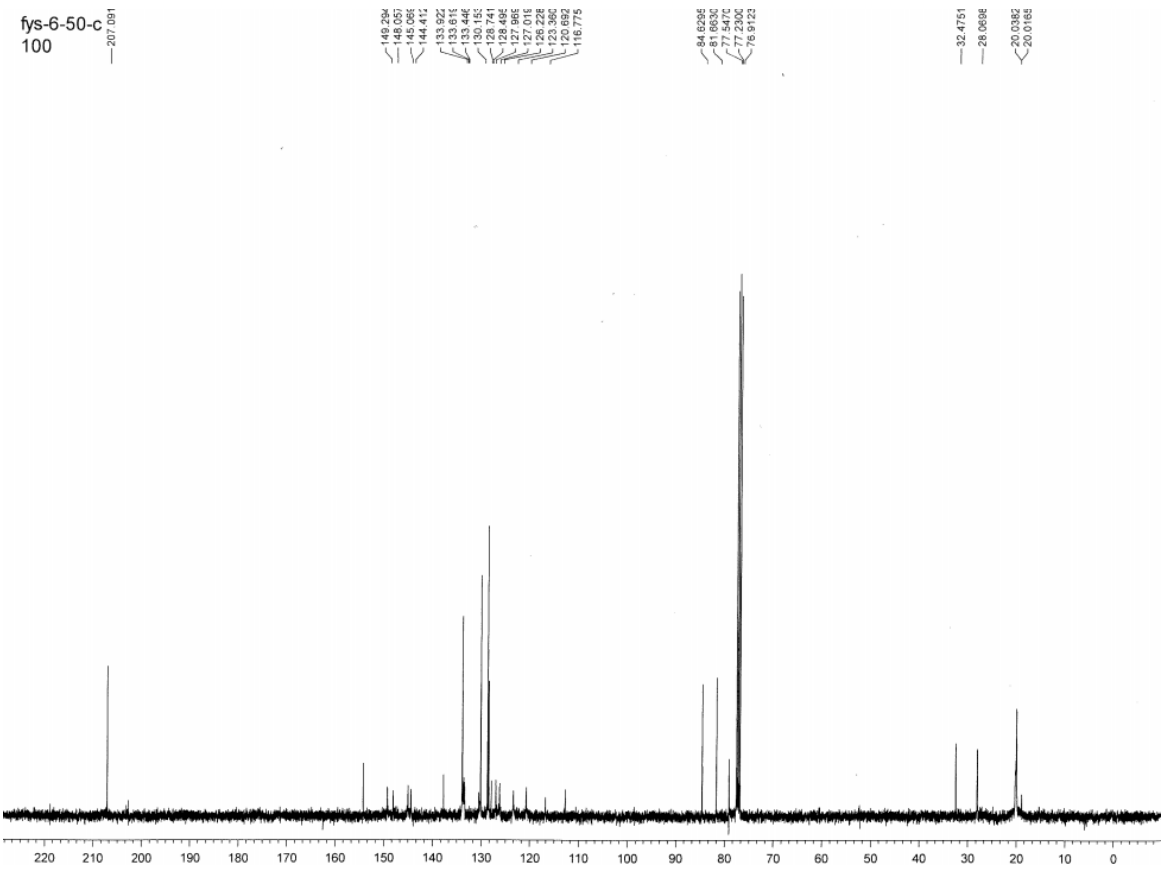


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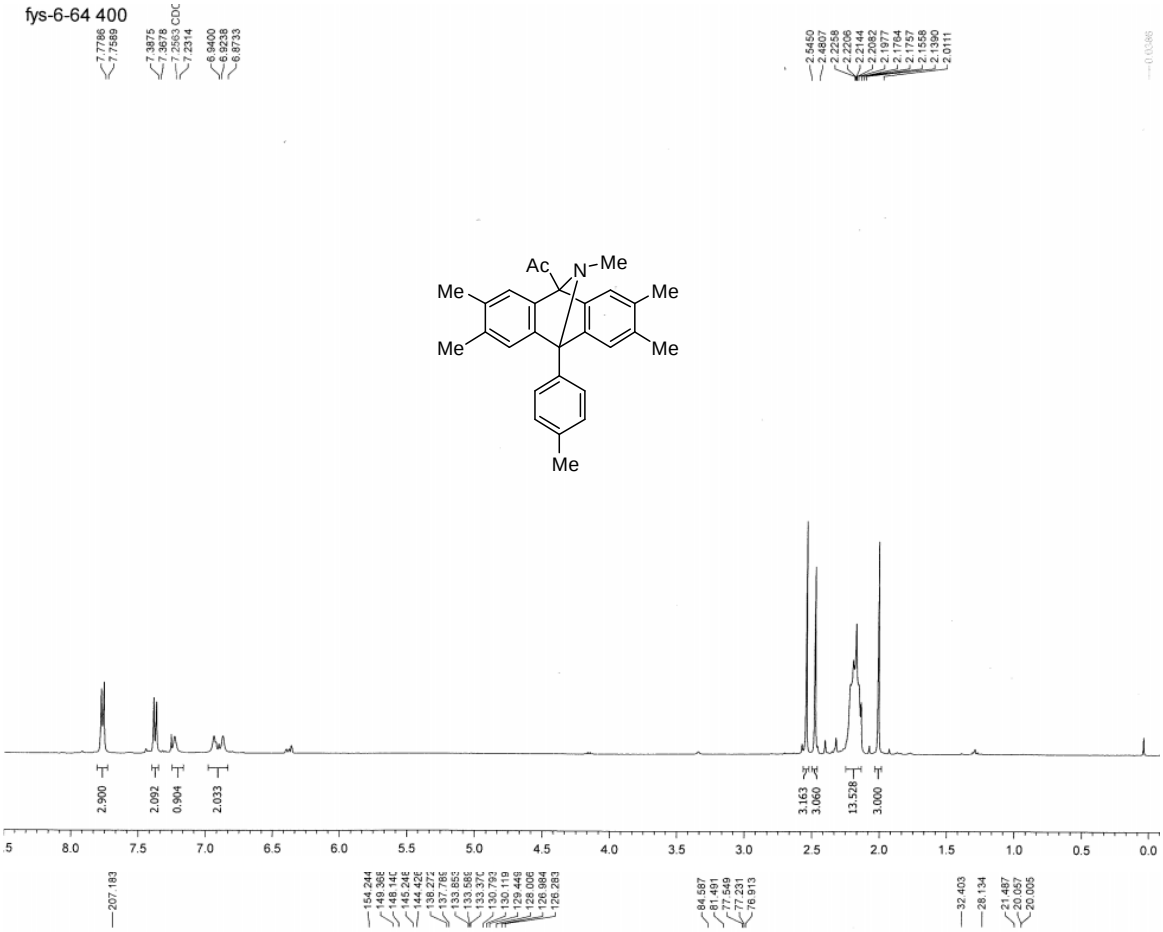


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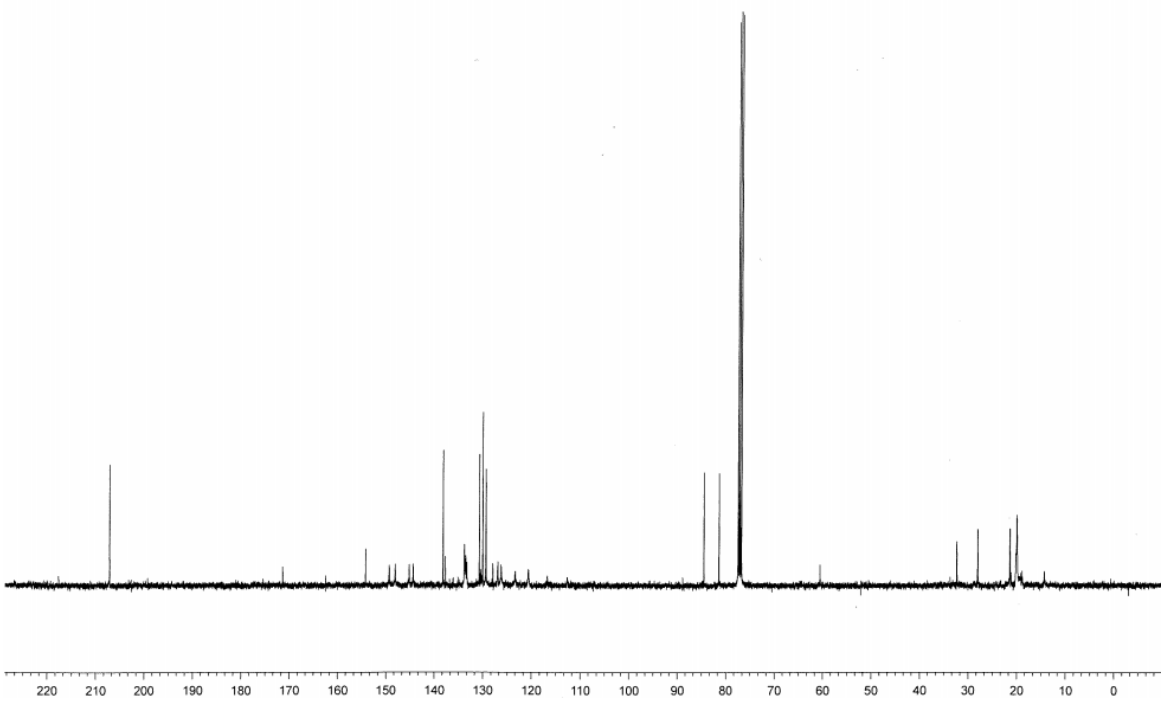

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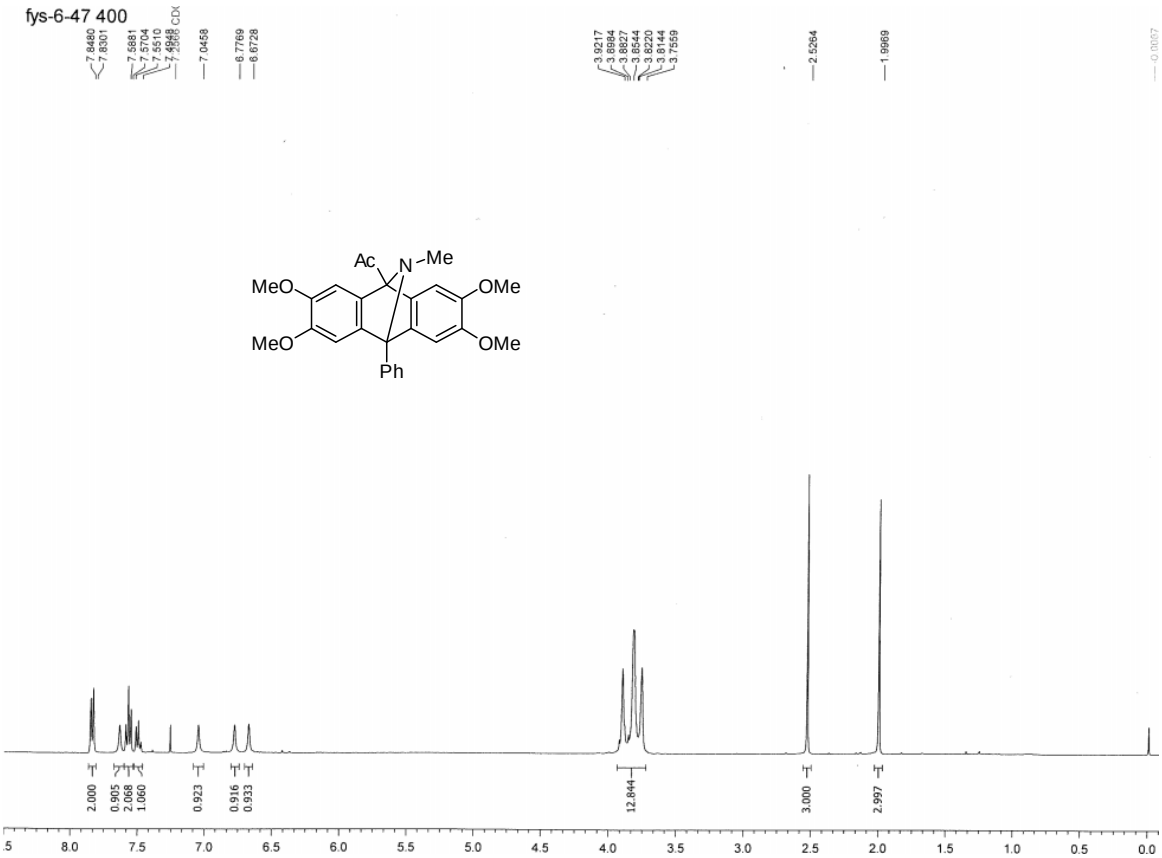


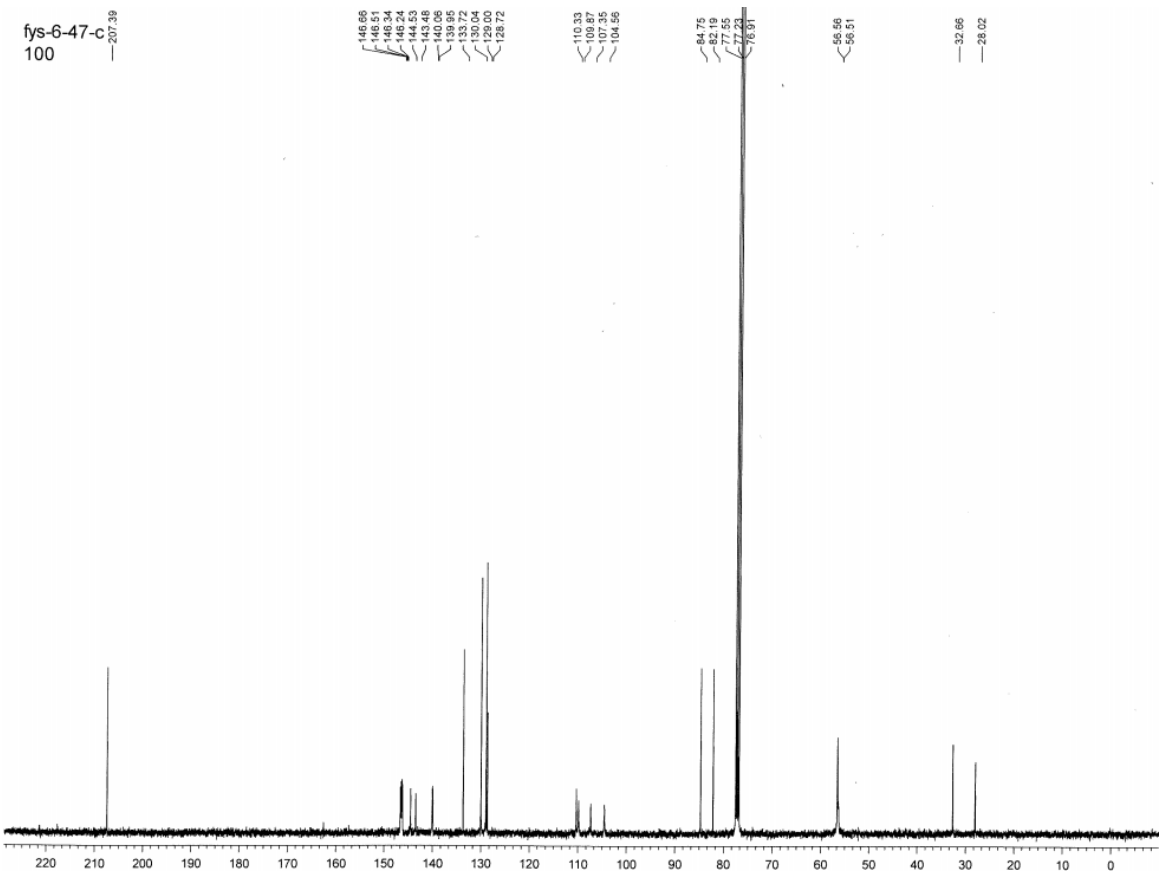


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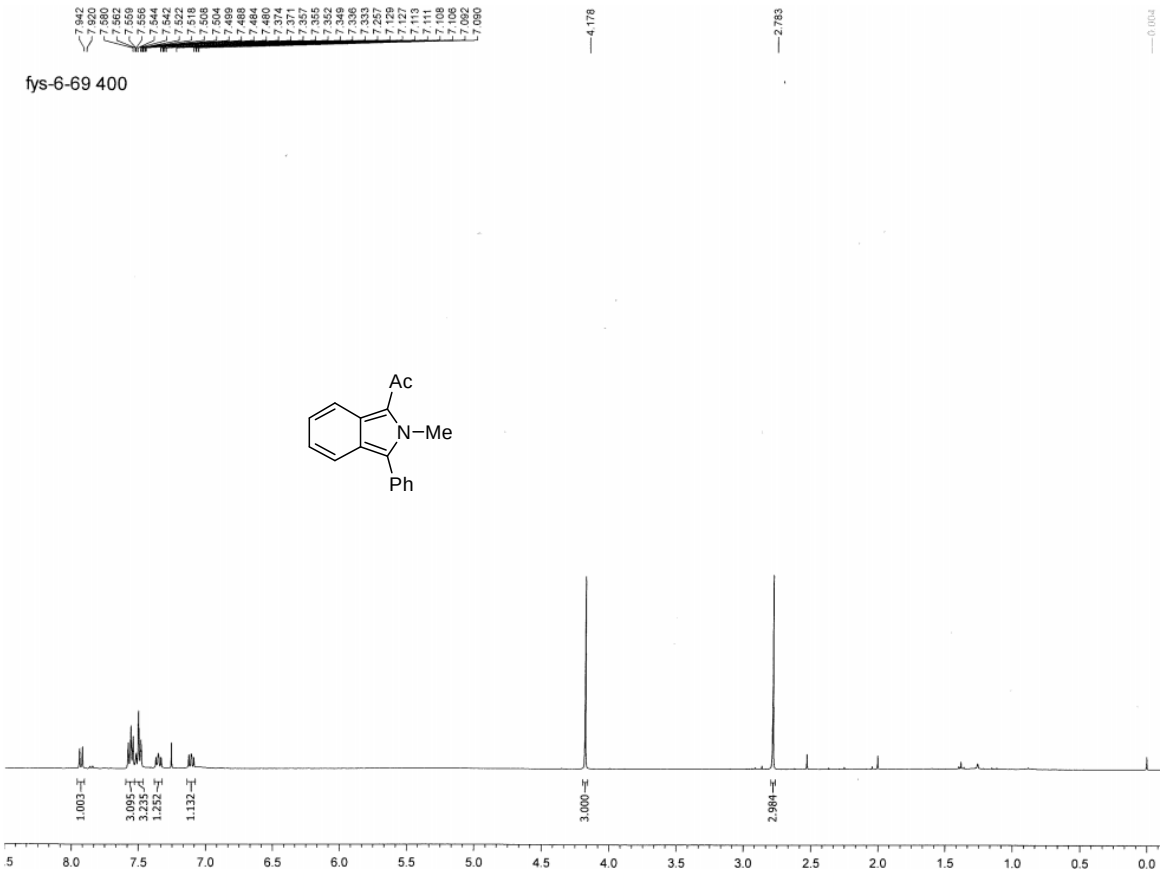


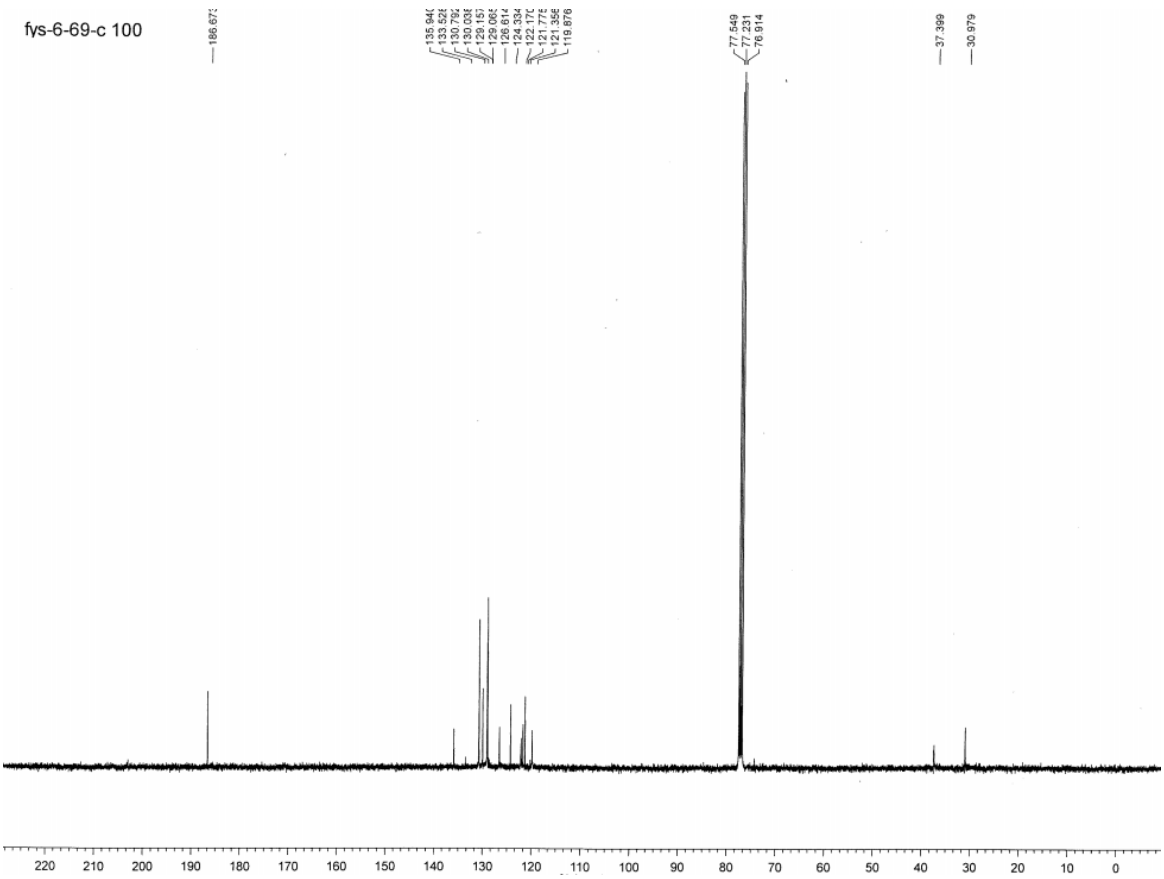


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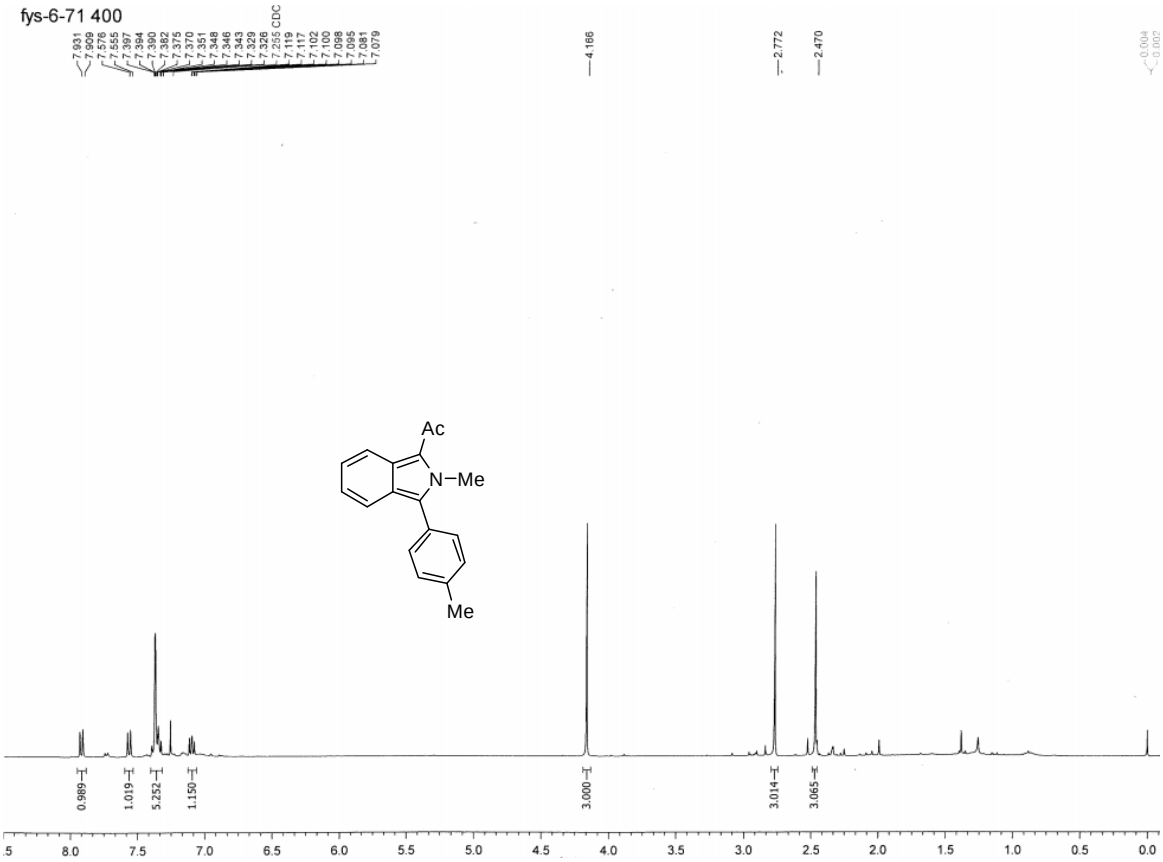


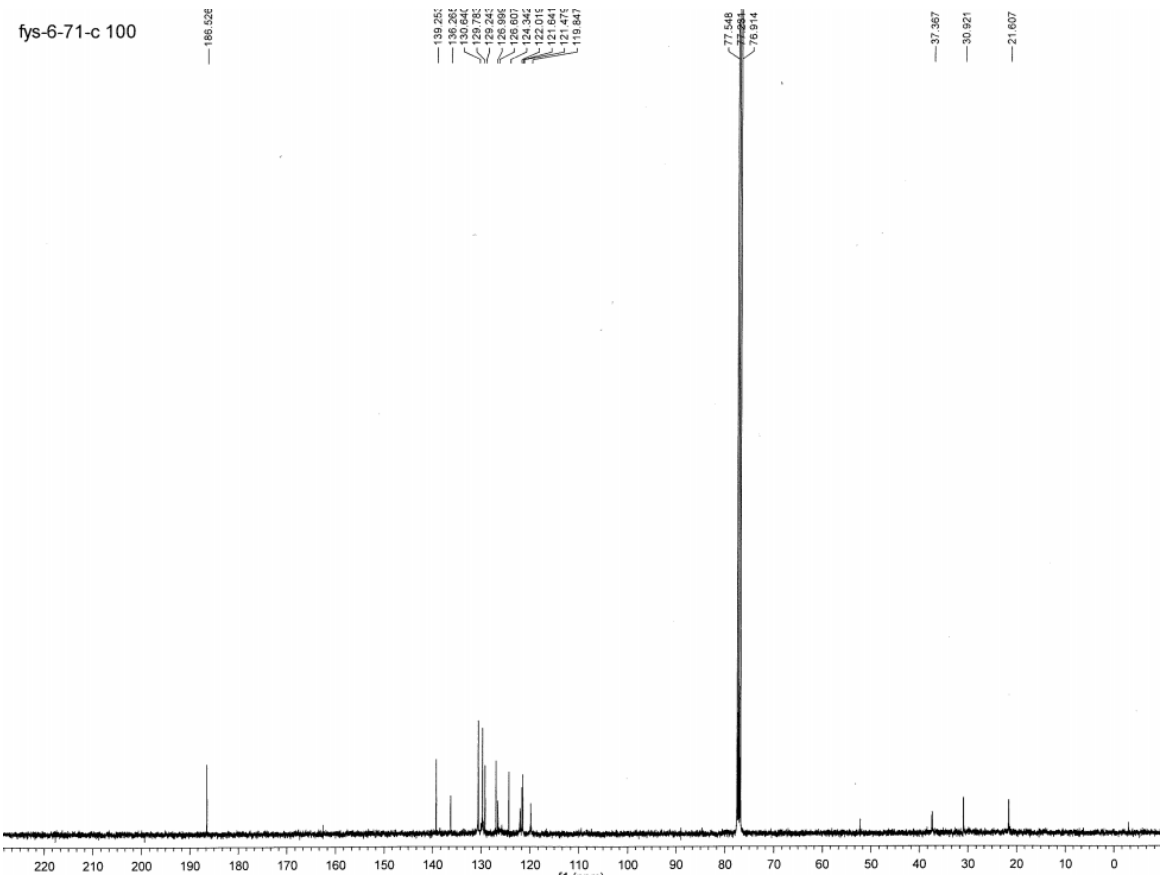


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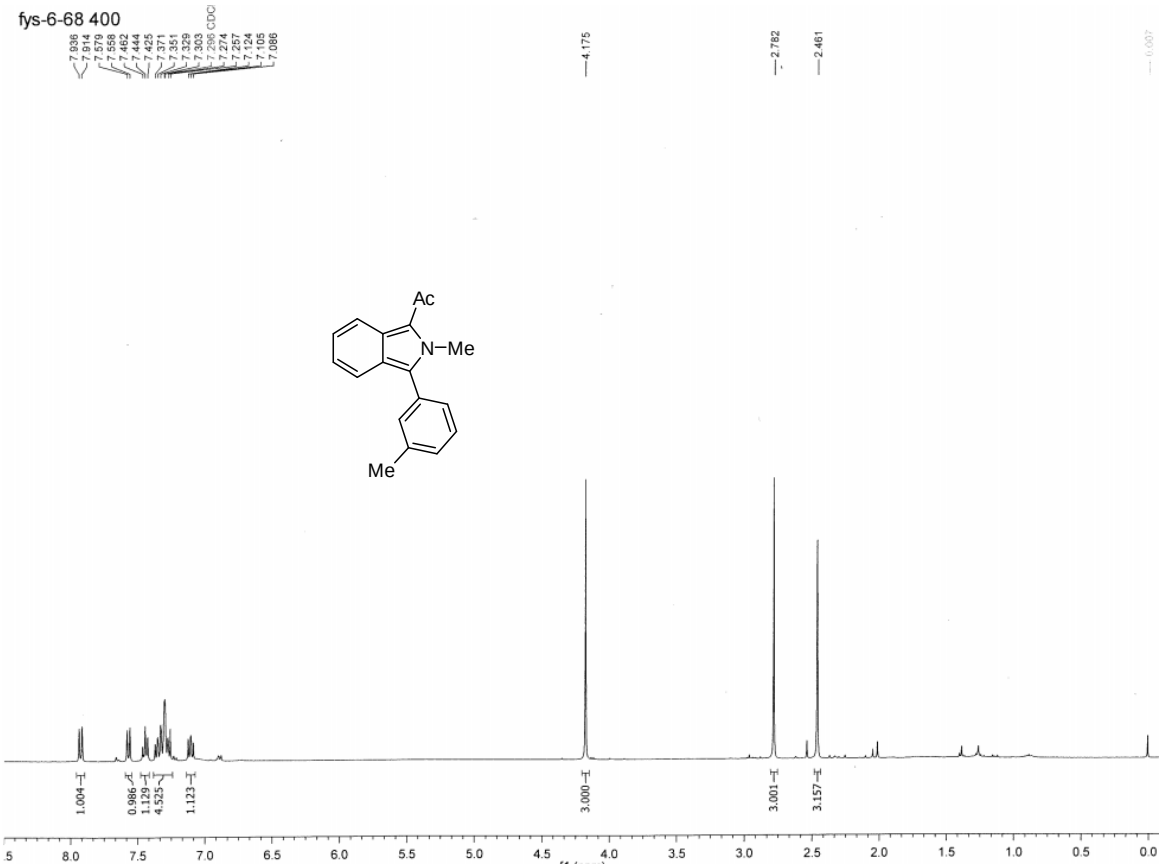


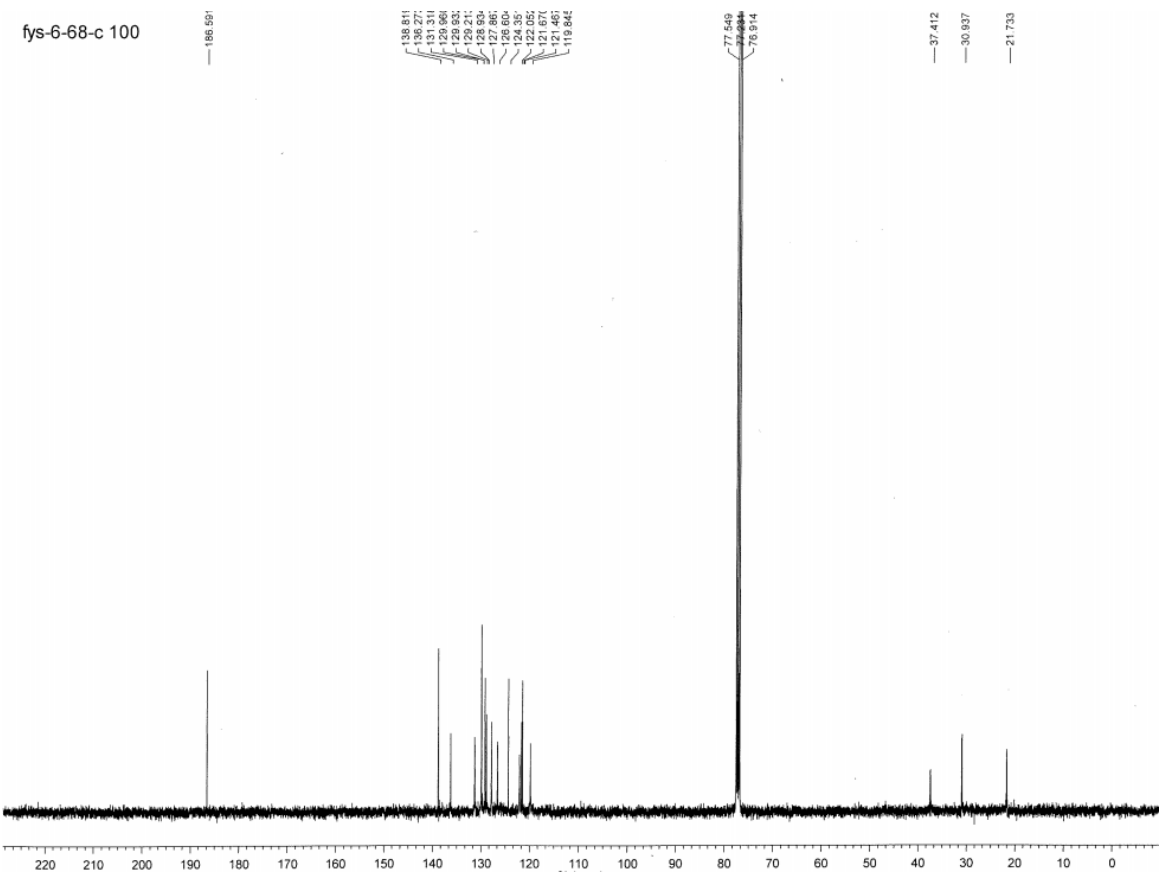


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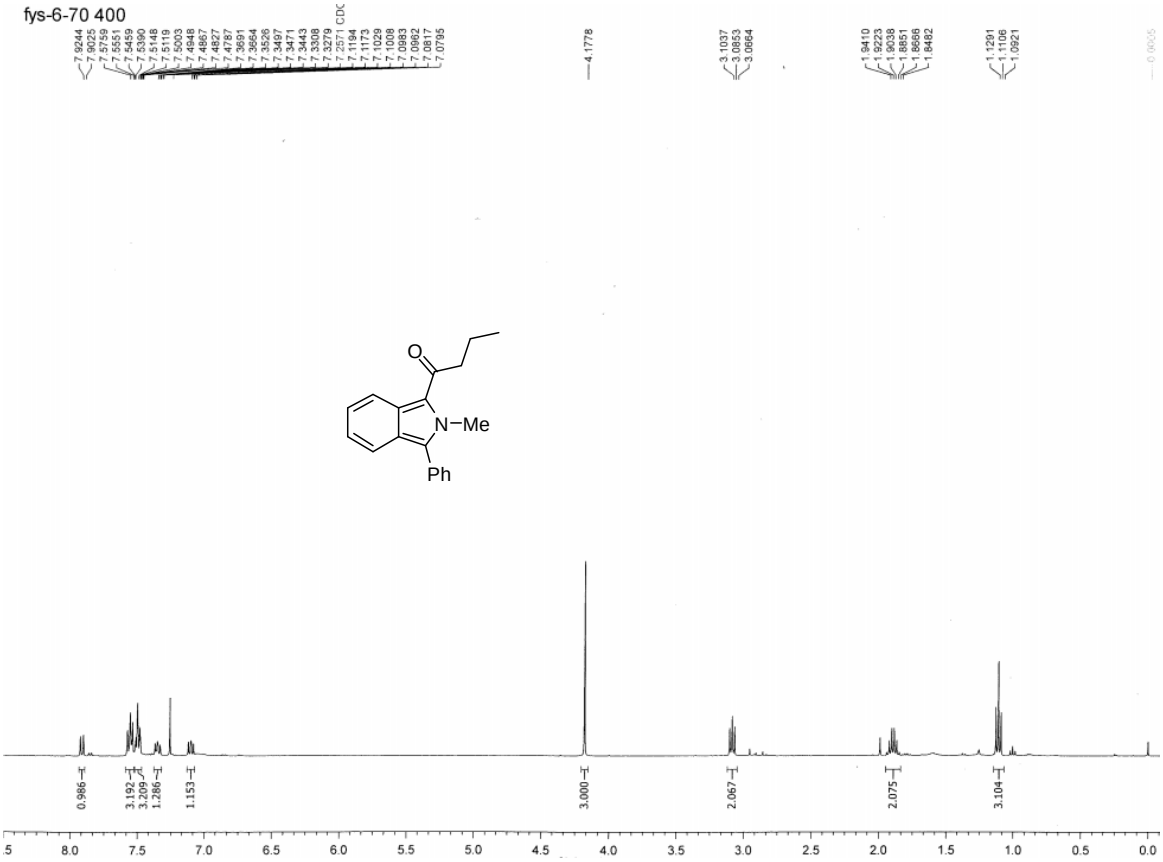


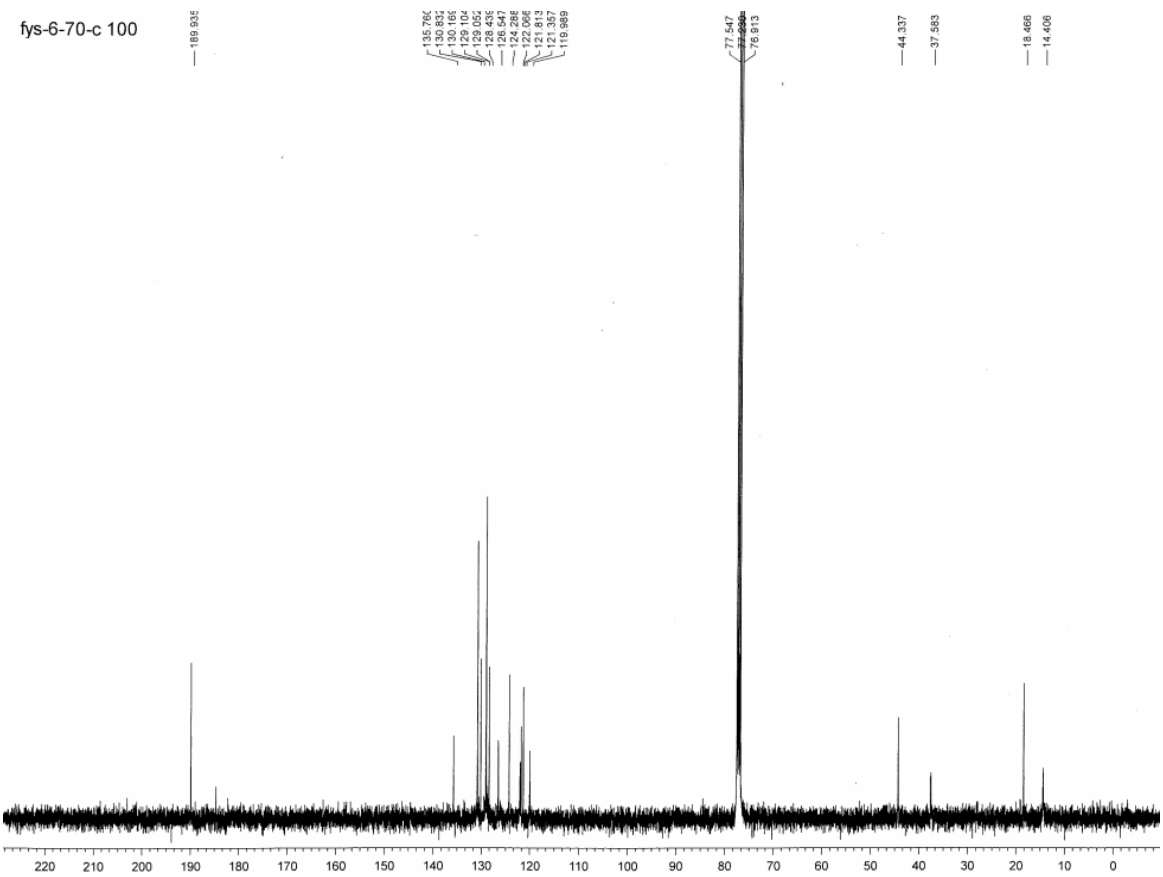


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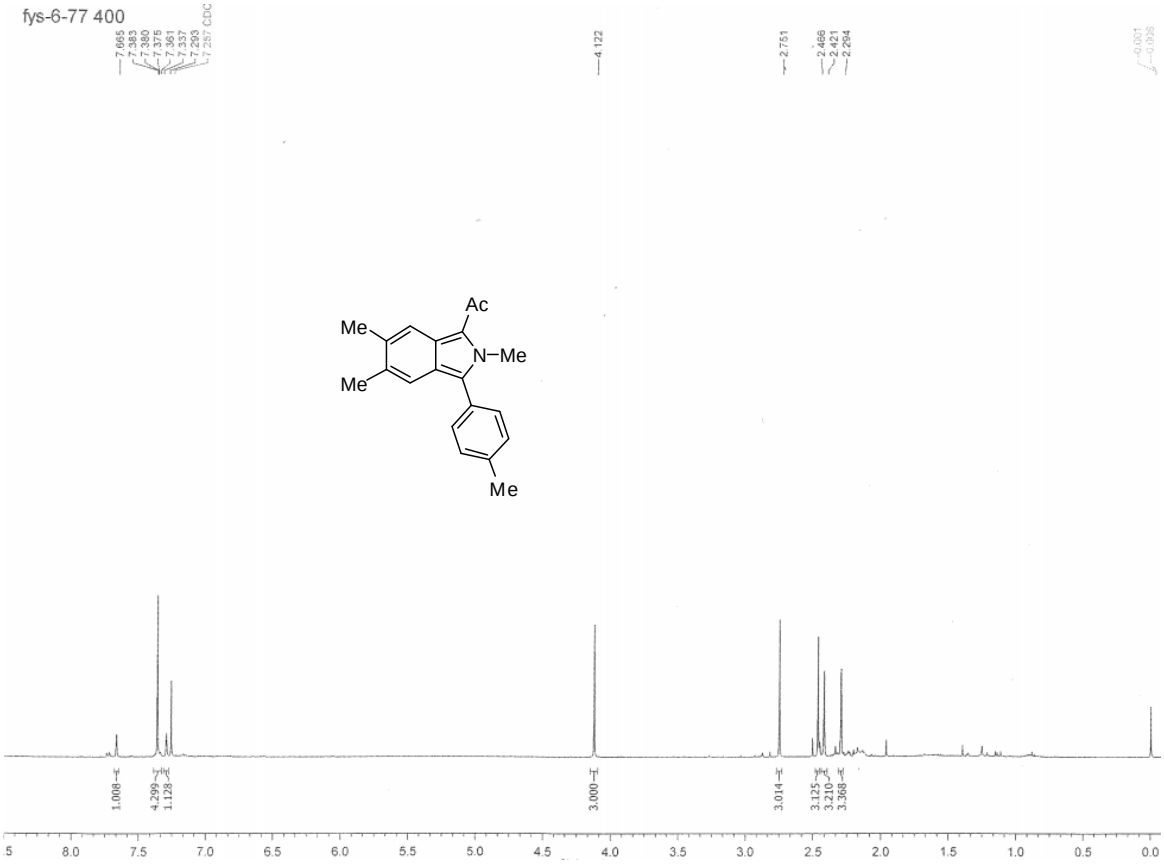


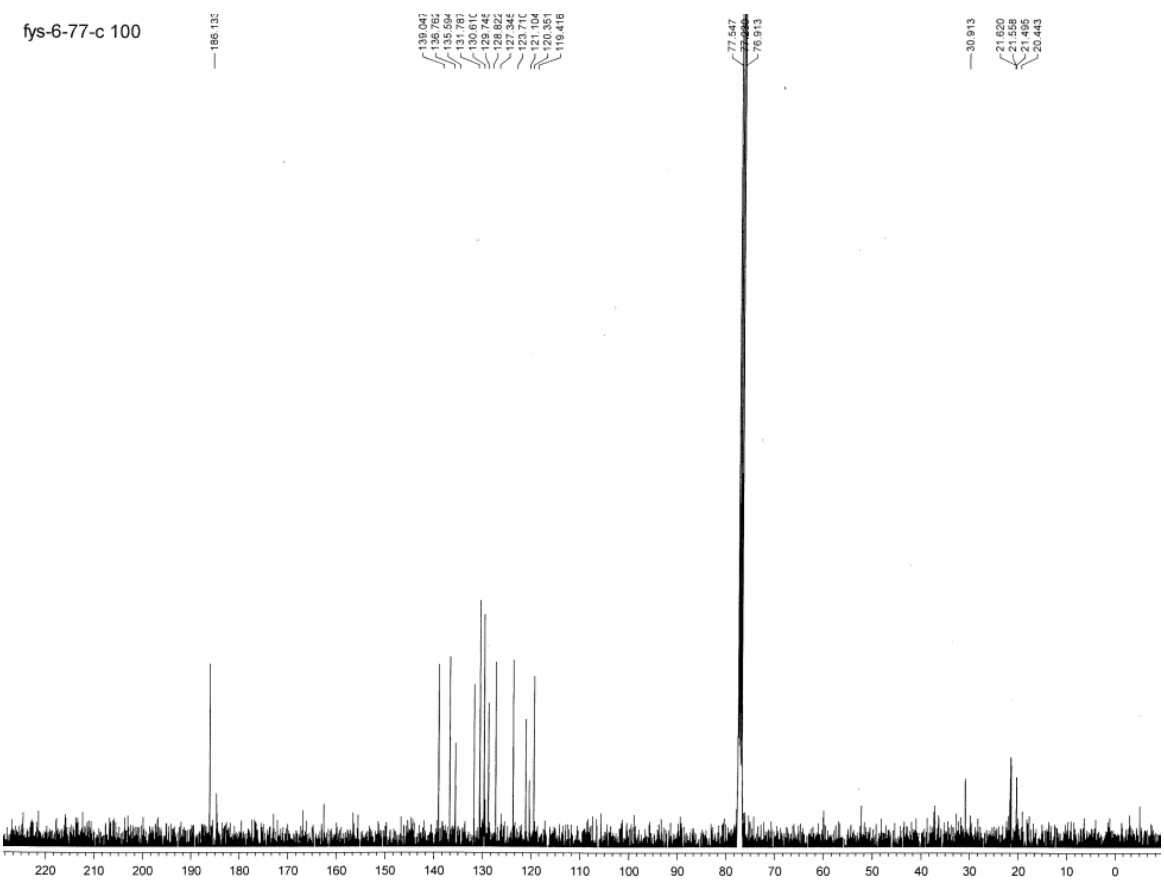


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