2014

CARBON-NITROGEN BOND FORMATION VIA TANDEM CARBON-HYDROGEN (C-H) AND NITROGEN-HYDROGEN (N-H) BOND FUNCTIONALIZATION

Abhishek A. Kantak
University of Rhode Island, abhishek_kantak@my.uri.edu

CARBON-NITROGEN BOND FORMATION VIA TANDEM CARBON-HYDROGEN (C-H) AND NITROGEN-HYDROGEN (N-H) BOND FUNCTIONALIZATION

BY

ABHISHEK A. KANTAK

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

UNIVERSITY OF RHODE ISLAND

2014

DOCTOR OF PHILOSOPHY DISSERTATION

OF

ABHISHEK A. KANTAK

APPROVED:

Dissertation Committee:

Major Professor Brenton L. DeBoef
Brett Lucht
David Worthen

Naseer H. Zawia
DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

2014

ABSTRACT

The oxidative cross-coupling of carbon-hydrogen (C-H) and nitrogen-hydrogen (N-H) bonds to form carbon-nitrogen (C-N) bonds is an important synthetic advance, as amine and amide functional groups are ubiquitous in biologically active molecules. This technique is orthogonal to conventional amination techniques, which rely on electrophilic nitration/reduction strategies or metal catalyzed coupling of pre-functionalized arenes.

This dissertation's main focus is on the development of oxidative methods for constructing *N*-arylamines and amides via tandem C-H/N-H bond activation and increasing synthetic efficiency for total synthesis of an inhibitor of botulinum neurotoxin via direct C–H functionalization.

The first manuscript, "Metal-Free Intermolecular Oxidative C-N Bond Formation via Tandem C-H and N-H Bond Functionalization," is focused on the development of a novel intermolecular oxidative amination reaction, a synthetic transformation that involves the simultaneous functionalization of both an N-H and a C-H bond. The process, which is mediated by an I(III) oxidant and contains no metal catalysts, provides a rapid and green method for synthesizing protected anilines from simple arenes and phthalimide.

The second manuscript, "I(III)-Mediated Regioselective C-H Bond Amination of 2-Arylpyridine Derivatives," is focused on the development of a novel, useful and economical process for the direct amination of 2-phenylpyridine derivatives. This process requires cheap and commercially available copper triflate and works for a variety of different 2-phenyl- pyridine derivatives.

The third manuscript, “Increasing synthetic efficiency via direct C–H functionalization: formal synthesis of an inhibitor of botulinum neurotoxin,” is focused on designing an efficient scheme for the synthesis of one of the best known inhibitors of botulinum neurotoxin serotype A (BoNTA). The synthetic route involves two palladium catalyzed C–H functionalization reactions, formally activating three C–H bonds.

ACKNOWLEDGMENTS

My dream to obtain the highest degree in the field of science has been very challenging to achieve in the last five years. In this journey, I have shared my greatest and worst moments with many people.

First and foremost, I would like to thank my PhD Major Advisor, Dr. Brenton L. DeBoef for being a constant source of encouragement and support during these past five years. He is a fun, lively and energetic person to work with and one of the smartest people I know. He is a fantastic teacher and heads one of best research groups at URI. He has always been supportive and encouraged me to always think outside-of-the-box to figure out solutions to some of the toughest problems we have encountered. His scientific advice, insightful discussions and precious suggestions have been an important part of my PhD program. Along with graduate research, Dr. DeBoef has also supported my decision to take business courses and obtain my MBA. I will always be very grateful to him for providing me with this exciting opportunity to complete a MBA along with a PhD in Chemistry.

I would like to acknowledge my colleagues Dr. Shathaverdhan, Kyle, Paida, Ashley, Marissa, Louis, John, Sean and Joseph for the most valuable discussions and obliging suggestions with my research. I thank all of you for such a wonderful and encouraging laboratory work environment. I would also like to thank Dr. William Euler, Dr. Louis Kirshenbaum, Dr. Mike McGregor and all other faculty and staff of the chemistry department who have been helpful both directly and indirectly towards the completion of my degree.

I would like to thank my doctoral committee members, namely Dr. Brett Lucht, Dr. David Worthen, Dr. Sze Yang and Dr. Abraham Kovoor for their support, guidance and helpful suggestions.

I thank all my friends in The United States of America, India and other parts of the world. I thank you for providing me the support and friendship that I needed and being a source of joy and laughter. Special thanks go to Swapnil Dalavi, Kaushal Purohit, Vipin Jain, Anshu Jain and my football and cricket team members at URI.

I specially thank my father Ashok Kantak, mother Rashmi Kantak, brother Abhijit Kantak and sister in law Shilpa Kantak. I love them so much, and I would not have made it this far without them. My brother has been my best friend all my life and I love him dearly and thank him for all his advice and support. I also thank my beloved niece Trisha for a lot of memorable moments on Skype during the course of my studies very far from home.

Dedicated to my loving family for their constant support and unconditional love.

I love you all dearly.

PREFACE

The following research has been presented in manuscript format according to guidelines of the Graduate School of the University of Rhode Island. The entire dissertation is divided into three manuscripts.

The formation of carbon-carbon (C-C) bonds via the oxidative cross-coupling of two carbon-hydrogen (C-H) bonds has recently become a field of intense interest and has resulted in the discovery of numerous novel synthetic methods. The analogous technology for the oxidative cross-coupling of C-H and nitrogen-hydrogen (N-H) bonds to form carbon-nitrogen (C-N) bonds would also be an important synthetic advance, as amine and amide functional groups are ubiquitous in biologically active molecules. However, a relatively small amount of work has focused on the development of oxidative methods for constructing *N*-arylamines and amides via tandem C-H/N-H bond activation.

The majority of literature in this field describes the insertion of nitrenoid intermediates into C-H bonds, mediated by transition metal catalysts. Cu and Pd-catalyzed reactions, as well as metal-free conditions, have also been recently explored, but these methods are limited to the intramolecular synthesis of carbazoles, oxindoles and diazapenones. The only reported examples of intermolecular oxidative amination involve azole-type heterocycles and proceed by attack of an amine nucleophile on the substrate's imine moiety. The ability to oxidatively couple phthalimide to unfunctionalized arenes is a useful method for synthesizing anilines that is orthogonal to conventional amination techniques, which rely on electrophilic nitration/reduction strategies or metal catalyzed coupling of pre-functionalized arenes. Phthalimide, in

particular, is an ideal starting point for the development of the aforementioned oxidative amination technology. It is commercially available, inexpensive, easy to handle and, once coupled, it can be readily converted to a primary amine, which can be further derivatized. Additionally, various *N*-arylphthalimides have recently been shown to have anti-cancer activity.

The first manuscript, "Metal-Free Intermolecular Oxidative C-N Bond Formation via Tandem C-H and N-H Bond Functionalization," is focused on the development of a novel intermolecular oxidative amination reaction, a synthetic transformation that involves the simultaneous functionalization of both an N-H and a C-H bond. This process, which is mediated by an I(III) oxidant and contains no metal catalysts, provides a rapid and green method for synthesizing protected anilines from simple arenes and phthalimide. This work has been presented as a poster session at the 244th ACS National Meeting & Exposition (Philadelphia, PA, August 2012) and this paper has been published in ***J. Am. Chem. Soc.*** **2011,** *133,* 19960-19965.

The second manuscript, "I(III)-Mediated Regioselective C-H Bond Amination of 2-Arylpyridine Derivatives," is focused on the development of a novel and economical process for the direct amination of 2-phenylpyridine derivatives. This process requires cheap and commercially available copper triflate and works for a variety of different 2-phenylpyridine derivatives. This work has been presented as a poster session at the 246th ACS National Meeting & Exposition (New Orleans, LA, April 2013) and this manuscript is in preparation for publication.

The third manuscript, “Increasing synthetic efficiency via direct C–H functionalization: formal synthesis of an inhibitor of botulinum neurotoxin,” is focused on the design of an atom efficient scheme for the total synthesis of an inhibitor of botulinum neurotoxin serotype A (BoNTA). The synthetic route involves two palladium catalyzed C–H functionalization reactions and can be used to generate a library of other substrates by modifying the reactants in the scheme. This work has been published in ***Chem. Comm.*** **2011,** *47*, 4679 – 4681.

TABLE OF CONTENTS

LIST OF TABLES

TABLE **PAGE**

Manuscript 1

Manuscript 2

LIST OF FIGURES

FIGURE **PAGE**

Manuscript 1

Manuscript 3

LIST OF SCHEMES

SHCEME **PAGE**

Manuscript 1

Manuscript 2

Manuscript 3

LIST OF SPECTRUMS

SPECTRUM

PAGE

Manuscript 1

Manuscript 2

Manuscript 3

MANUSCRIPT 1

Published in ***J. Am. Chem. Soc.*** **2011,** *133,* 19960-19965.

Metal-Free Intermolecular Oxidative C-N Bond Formation via Tandem C-H and N-H Bond Functionalization

Abhishek A. Kantak, Shathaverdhan Potavathri, Rose A. Barham,

Kaitlyn M. Romano and Brenton DeBoef *

Corresponding author:

Prof. Brenton Deboef

Department of Chemistry,

University of Rhode Island,

Kingston, Rhode Island 02881.

bdeboef@chm.uri.edu

Manuscript 1

Metal-Free Intermolecular Oxidative C-N Bond Formation via Tandem C-H and N-H Bond Functionalization

Abstract

The development of a novel intermolecular oxidative amination reaction, a synthetic transformation that involves the simultaneous functionalization of both an N-H and C-H bond, is described. The process, which is mediated by an I(III) oxidant and contains no metal catalysts, provides a rapid and green method for synthesizing protected anilines from simple arenes and phthalimide. Mechanistic investigations indicate that the reaction proceeds via nucleophilic attack of the phthalimide on an aromatic radical cation, as opposed to the electrophilic aromatic amination that has been reported for other I(III) amination reactions. The application of this new reaction to the synthesis of a variety of substituted aniline derivatives is demonstrated.

Introduction

The formation of carbon-carbon (C-C) bonds via the oxidative cross-coupling of two carbon-hydrogen (C-H) bonds has recently become a field of intense interest and has resulted in the discovery of numerous novel synthetic methods.[1] The analogous technology for the oxidative cross-coupling of C-H and nitrogen-hydrogen (N-H) bonds to form carbon-nitrogen (C-N) bonds would also be an important synthetic advance, as amine and amide functional groups are ubiquitous in biologically active molecules (Figure 1). However, a relatively small amount of work has focused on the development of oxidative methods for constructing *N*-arylamines and amides via tandem C-H/N-H activation. The majority of literature in this field describes the

insertion of nitrenoid intermediates into C-H bonds, mediated by transition metal catalysts.[2] Cu and Pd-catalyzed reactions, as well as metal-free conditions, have also been recently explored, but these methods are limited to the intramolecular synthesis of carbazoles, oxindoles and diazapenones.[3-5] The only reported examples of intermolecular oxidative amination involve azole-type heterocycles and proceed by

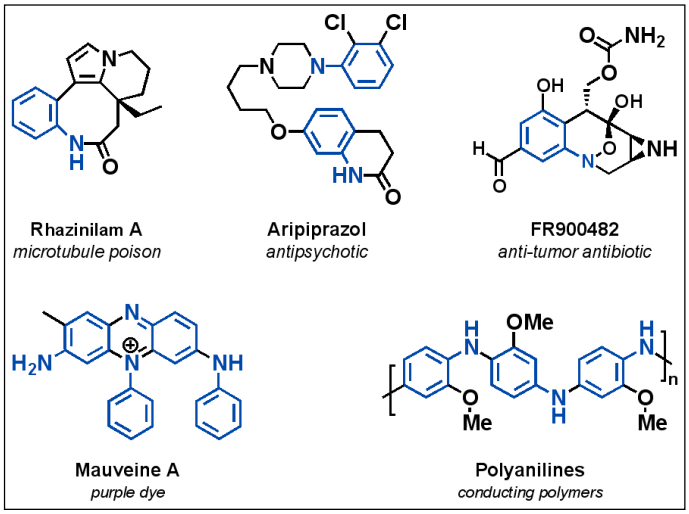


Figure 1. Examples of high-value molecules containing anilines

attack of an amine nucleophile on the substrate's imine moiety.[6,7] Herein, we disclose a novel intermolecular reaction that oxidatively constructs the C-N bond of phthalimide-protected anilines via the tandem activation of N-H and C-H bonds.

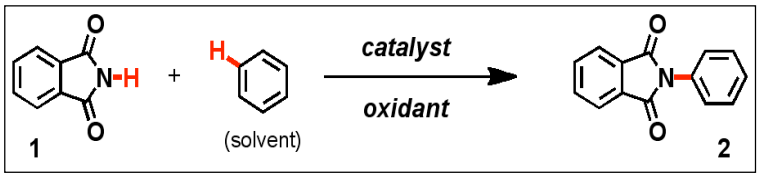
Results and Discussion

Reaction Discovery. We recently discovered that heating a solution of phthalimide (**1**) and $PhI(OAc)_2$ in benzene provides the phthalimide-protected aniline (**2**) in an 88% yield (Table 1, entry 4). We initially explored the potential of Cu(I)/(III)-catalysts to

perform this oxidative amination, but quickly realized that a metal catalyst was not necessary.[5] We are confident that trace metals are not the cause of the transformation, as reactions performed in new, acid washed flasks were similar in both yield and rate to those performed in old flasks. Furthermore, reagents from different commercial sources perform similarly.

While optimizing the process, we quickly discovered that the best conditions employed microwave heating and 2.5 equivalents of the I(III) oxidant, phenyliodine(III) diacetate (PIDA). Less than two equivalents of PIDA did not allow the reactions to proceed to completion (compare entries 2 and 3).

Importantly, we found that the arene substrate does not need to be in large excess (*i.e.* solvent) for the intermolecular oxidative amination reaction to occur. This is in stark contrast to many of the oxidative arylation reactions that have been previously studied.[8] As shown in Table 1, entry 9, acetonitrile was used as the solvent and the concentration of the arene substrate was lowered to a near-stoichiometric level (1.5 equiv). Under these conditions, the yield for the amination of benzene dropped from 88% to 51%, but we hypothesized that this was due to the volatility of the arene. This was verified by the reaction of the less volatile substrate, *p*-xylene, which provided an 80% yield (Scheme 1A).



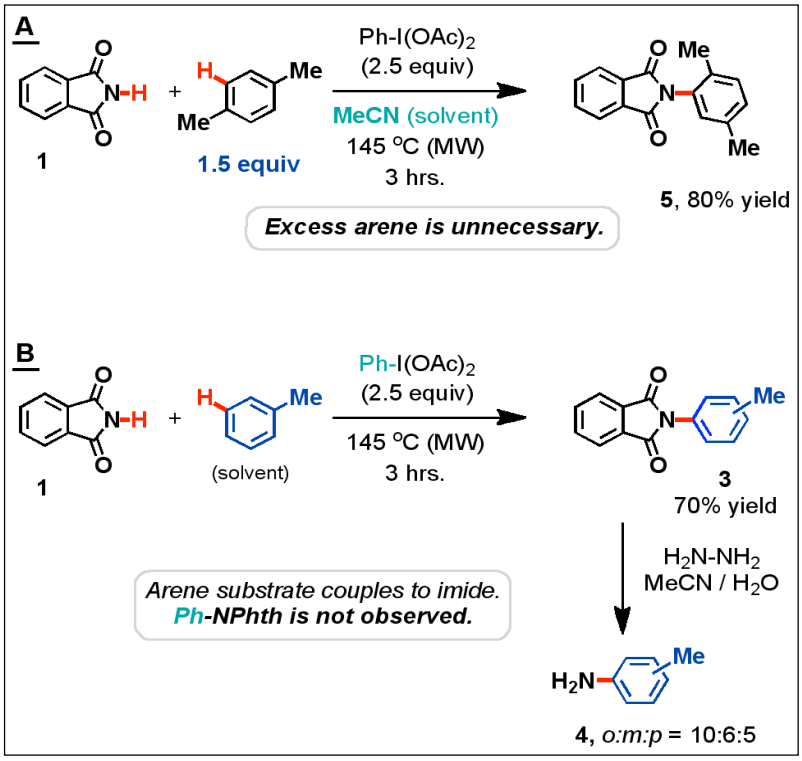
	Oxidant (equiv)	Solvent	Temp. [^{0}C]	Time [h]	Yield [%][c]
1	PIDA (1.5)	PhH	145[b]	12	26
2	PIDA (1.5)	PhH	145	3	28
3	PIDA (2.0)	PhH	145	3	45
4	**PIDA (2.5)**	**PhH**	**145**	**3**	**88**
5	PIDA (2.5)	PhH	120	3	no reaction
6	PIDA (2.5)	TFE	145	3	13
7	PIDA (2.5)	DMF	145	3	4[d]
8	PIDA (2.5)	DMSO	145	3	no reaction
9	**PIDA (2.5)**	**MeCN**	**145**	**3**	**51**
10	NCS (2.5)	MeCN	145	3	3[d]
11	Oxone (2.5)	MeCN	145	3	no reaction
12	IBX (2.5)	MeCN	145	3	no reaction
13	PIFA (1.0)	PhH	145	3	5[d]
14	PIFA (1.25)	PhH	145	3	decomposition
15	PIFA (1.0)	PhH	100	3	Trace
16	PIFA (1.0)	PhH	25[b]	3	0
17	PIFA (1.0)	TFE	145	3	3.5[d]
18	PIFA (1.0)	MeCN	145	3	3.5[d]

Table 1. Discovery of the intermolecular oxidative amination[a]

[a]General reaction conditions: **1** (0.68 mmol), oxidant (1.5 - 2.5 equiv), benzene (1.5 equiv or solvent), solvent (4 mL), microwave heating. PIDA = phenyliodine(III) diacetate, PIFA = phenyliodine(III) bis(trifluoroacetate), NCS = *N*-chloro-succinimide, IBX = 2-iodoxybenzoic acid, Oxone = potassium peroxymonosulfate, TFE = 2,2,2-trifluoro-ethanol. [b]Oil bath. [c]Yield of isolated product after column chromatography. [d]GC yield calculated using dodecane as internal standard.

Other solvent and oxidant combinations proved to be less effective. In particular, 2,2,2-trifluoroethanol (TFE), a solvent that has been shown to be particularly compatible with I(III) mediated arene substitutions provided a minimal yield (entry 6). The fluorinated derivative of PIDA, phenlyiodine(III) bis(trifluoroacetate) (PIFA), proved to be too harsh of an oxidant for these reactions. Any loading of the oxidant in excess of 1 equiv resulted in a complex mixture of products. Lowering the reaction temperature and altering the co-solvent, also failed to provide the desired anilne **2** (entries 13-18).

To determine whether the arene that participated in the oxidative amination originated from the benzene solvent or the oxidant, a crossover experiment was performed (Scheme 1B). When toluene was used as the solvent and $PhI(OAc)_2$ was the oxidant, the reaction did not produce any *N*-phenylphthalimide (**2**). Rather, an inseparable mixture of regiomers arising from the oxidative amination of the sp^2-hybridized C-H bonds of toluene was observed (**3**). This confirmed our hypothesis that the source of the aryl group that forms the new C-N bond was the solvent, not the phenyl group that resides on the oxidant.



Scheme 1. Oxidative amination of substituted arenes

Cleavage of the phthalimide protecting group allowed for the determination of the regiomeric ratios by comparison to the commercially available toluidine isomers. Interestingly, the major product of the reaction was *o*-toluidine (**4**). Amination of the sp^3-hybridized C-H bonds was not observed.

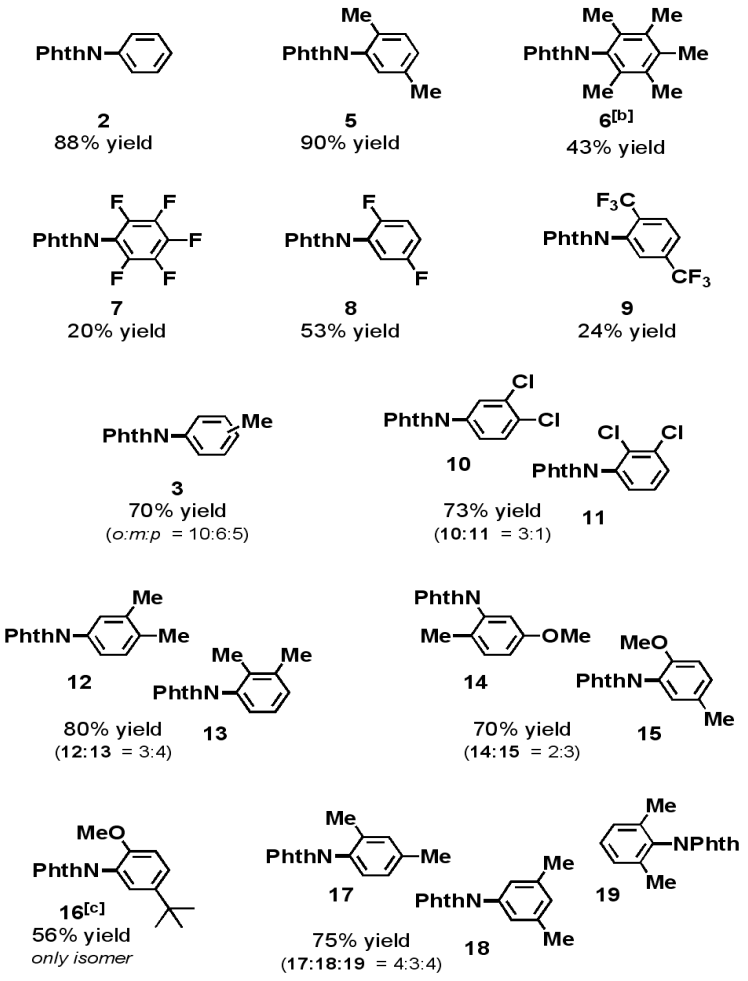
Substrate Scope. In addition to benzene, toluene and *p*-xylene, a variety of other simple arenes could be oxidatively coupled to phthalimide (Table 2). Sterically encumbered arenes (**6**) and those that contain electron-withdrawing groups (**7-11**) were oxidatively aminated, albeit at reduced yields. Like toluene, monosubstituted and asymmetrically disubstituted benzenes produced mixtures of protected aniline products (**10-19**). Electron-rich heterocycles, such as furan, decomposed under the

reaction conditions, and electron-poor heterocycles, such as benzoxazole failed to produce any aminated products.

The regioselectivity of these amination reactions appears to be slightly directed by electronic factors. For example, *p*-methylanisole was 50% more likely to be aminated at the position *ortho* to the larger, but more electron donating, methoxy group (**15**). Likewise, both the *ortho* and *para*-positions of toluene were 67% more likely to be aminated than the *meta*-position. The only exception to this rule was the amination of *p-tert*-butylanisole (**16**), where the size of the *tert*-butyl group prevented *ortho*-amination.

Other amine sources, in addition to phthalimide, were also investigated. Succinimide also provided very good yields of oxidative amination products (**20**), while pyrrolidin-2-one performed the oxidative amination reaction, but resulted in a poor yield (16%, **21**). *N*-Tosylamide and pyrrolidine failed to oxidatively aminate benzene. These data led us to conclude that the requirements for the amine coupling partner were two-fold: 1) the N-H bond must be relatively acidic (phthalimide pKa = 8.3) and 2) the amine coupling partner must be secondary, preferably a cyclic imide. In keeping with these requirements, other imides with acidic N-H bonds performed the oxidative amination reaction, albeit in lower yields (**22-24**). Surprisingly, acyclic imides, such as diacetamide, *N*-acetylanilines and hetercycles such as indole and benzimidazole produced only trace amounts of products.

Variation of Benzene-Derived Substrate[a]



Variation of Amide Substrate[c]

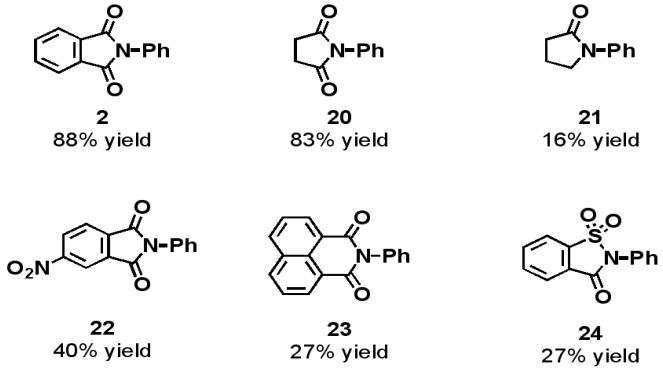
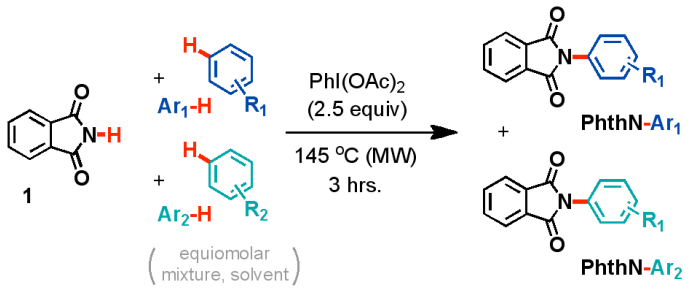


Table 2. Substrate scope of the intermolecular oxidative amination

[a] **1** (0.68 mmol), $PhI(OAc)_2$ (2.5 equiv), 4 mL of arene substrate, 145 ^oC (microwave), 3 hrs. [b] **1** (0.68 mmol), $PhI(OAc)_2$ (2.5 equiv), Arene substrate (1.5 equiv.), 4 mL of acetonitrile, 145 ^oC (microwave), 3 hrs. [c] Amide substrate (0.68 mmol), $PhI(OAc)_2$ (2.5 equiv), 4 mL of benzene, 145 ^oC (microwave), 3 hrs.

Competition and Kinetic Studies. Competition studies were performed to explore the mechanism of the novel process (Table 3). In all cases, the amination of electron-rich arenes was favored. In particular, the competition between *p*-xylene and *p*-difluorobenzene shows a dramatic preference for the amination of the electron rich *p*-xylene substrate (entry 2).

The kinetic isotope effect (KIE) of the reaction was assessed using a competition experiment between equimolar amounts of benzene and benzene-d_6. The near-unity KIE of 1.03 implies that C-H bond breaking is not involved in the rate-determining step of the reaction. This is also a stark contrast with the literature describing oxidative arylation processes for forming C-C bonds, where C-H bond breaking is often rate limiting, as indicated by large KIEs.[9] The KIE of the reaction involving equimolar amounts of phthalimide and phthalimide-*d* was observed to be 0.98, which indicates that the cleavage of the N-H bond is also not rate-limiting.



	Ar_1-H	Ar_2-H	[a] PhthN-Ar_1	[a] PhthN-Ar_2
1	*p*-xylene	benzene	71	29
2	*p*-xylene	*p*-difluoro-benzene	96	4
3	benzene	*p*-difluoro-benzene	86	14

Table 3. Competition reactions

[a] Mole fractions determined by GC/MS.

Kinetic analysis of the oxidative amination provided more mechanistic clues. The reaction rate was unaffected by changing the concentration of the arene but was dependent on the concentration of the both oxidant and phthalimide. Both reagents demonstrated first-order dependencies (Figure 2).

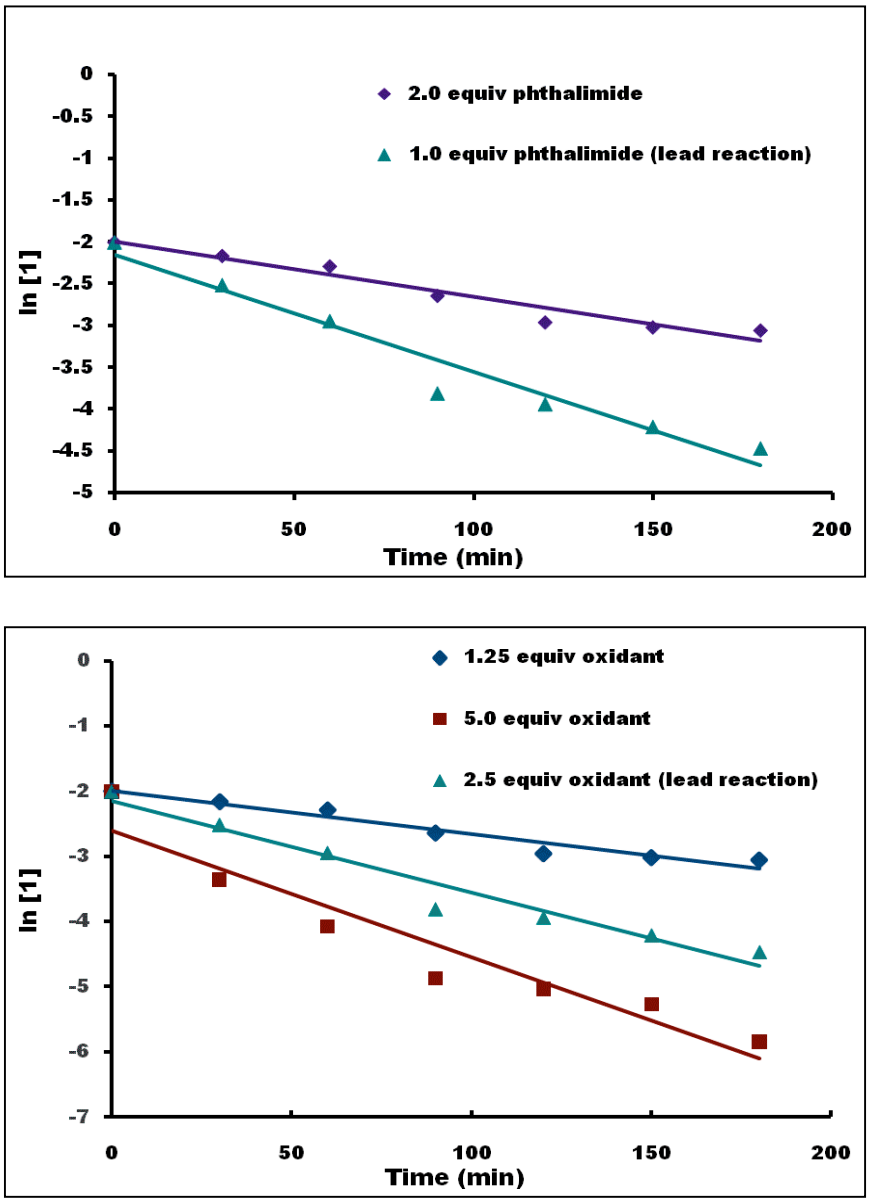
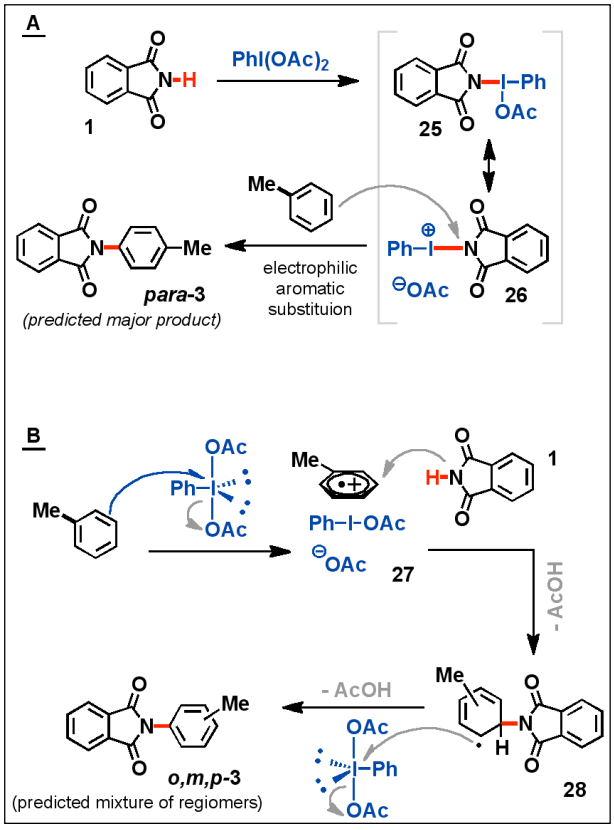


Figure 2. Kinetic analysis of oxidative amination reaction with various amounts of $PhI(OAc)_2$ (oxidant) and phthalimide.

The preference for imides and electron-rich arenes is consistent with two possible mechanisms (Scheme 2). The first involves the *in situ* formation of a $PhI(OAc)(NR_2)$ species (**25** and **26**), which is highly electrophilic, functioning essentially as an R_2N^+ equivalent.[10] Electrophilic aromatic substitution then forms the desired C-N bond (**2**)

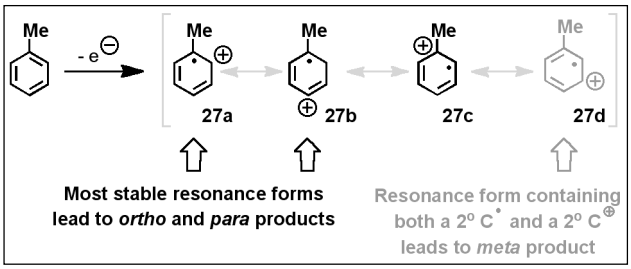
(Scheme 2A).[11] Alternatively, a single electron transfer may occur, forming an ion pair with the arene substrate and the I(III) reagent. The radical cation **27** could then undergo a nucleophilic attack by phthalimide (or its anion), giving rise to the desired product (**3**, Scheme 2B). Kita has previously described such a mechanism for oxidative reactions between arenes and soft nucleophiles such as b-diketones and TMS-N_3.[12] N-centered radicals have also been proposed in I(III) mediated C-N forming reactions,[13] but they are not likely to be involved in the reactions shown in Table 1. The weaker C-H bonds of the methyl group of toluene were not aminated, as one would expect for reactions involving N-centered radicals.



Scheme 2. Two possible mechanisms for the oxidative amination

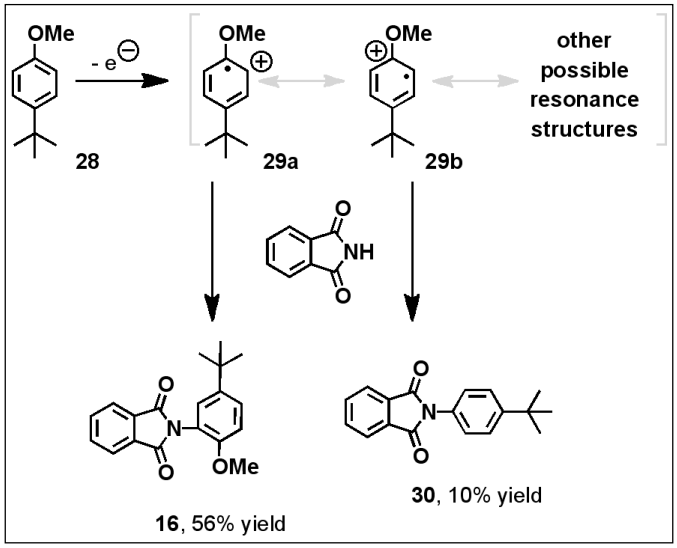
Proposed Mechanism. Based these data, a mechanism involving electrophilic aromatic substitution (EAS) seems unlikely, as the ratio of products obtained from the oxidative amination of toluene (**3**) are not indicative of the expected EAS regioselectivity (Scheme 2A). While the *ortho* and *para*- aminated products were somewhat favored in the reaction of arenes containing electron donating groups, reactions operating via S_EAr mechanisms tend to form little, if any, *meta*-substituted products. Alternatively, $PhI(OAc)_2$ could oxidize the electron-rich arene substrate to a radical cation (**27**), and nucleophilic attack on such a radical cation should be relatively non-regioselective (Scheme 2B). The consequent radical intermediate (**28**) could then be oxidized to form a Wheland-type arenium ion. These two individual oxidation steps may indicate why two equivalents of $PhI(OAc)_2$ are required to achieve complete conversion. The fates of the reduced iodine intermediates are less clear, but the two other by-products that are observed in all of these reactions are iodobenzene and phenyl acetate. Consequently, we hypothesize that a single electron transfer mechanism is operating in these oxidative amination reactions. This hypothesis is supported by the observation that the reaction was partially inhibited by BHT and completely inhibited by TEMPO, common radical inhibitors. Our hypothesis is supported by the prior work of Kita, who has extensively shown that arene radical cation intermediates such as **27** are formed by the action of I(III) oxidants and can be directly observed by EPR spectroscopy.[12] It should be noted that Cho and Chang have recently proposed an electrophilic mechanism for the same reaction described herein.[7b] This hypothesis was supported by the observation of **25** by mass spectrometry. In comparing our data with those of Kita and both Cho and Chang, it seems likely that

several I(III) species are simultaneously present in solution. However, we reason that the observed regioselectivites for aminations of monosubstituted arenes that were observed by both us and Cho and Chang are best explained by the intermediacy of a radical cation intermediate (**27**).



Scheme 3. Resonance structures of the aryl radical cation explain the observed regioselectivities**.**

Furthermore, the unique regioselectivities that were observed in the oxidative amination of toluene (*o:m:p* = 10:6:5) corroborate the intermediacy of an aromatic radical cation (Scheme 3). The yields of *ortho* and *para*-aminated products, which arise from the nucleophilic attack on resonance forms **27b** and **27c**, are statistically equivalent. This seems plausible as both contain a tertiary radical and a secondary carbocation. Additionally, reactions with *p*-methylanisole and *p-tert*-butylanisole (**28**) not only produced the aforementioned aminated products (**14**-**16**), but substitution products, arising from S_NAr-type attack on the tertiary cation intermediate (**29b**) followed by ejection of the methoxide leaving group (**30**), were also observed (Scheme 4).



Scheme 4. Formation of substitution products corroborates the intermediacy of arene radical cations

Conclusion

In conclusion, the ability to oxidatively couple phthalimide to unfunctionalized arenes is a useful method for synthesizing anilines that is orthogonal to conventional amination techniques, which rely on electrophilic nitration/reduction strategies or metal catalyzed coupling of pre-functionalized arenes. Phthalimide, in particular, is an ideal starting point for the development of the aforementioned oxidative amination technology. It is commercially available, inexpensive, easy to handle and, once coupled, it can be readily converted to a primary amine, which can be further derivatized. Additionally, *N*-arylphthalimides like those shown in Table 1 have recently been shown to have anti-cancer activity.[14] Future work in our laboratory will be dedicated to the mechanistic study and application of this unique method for constructing C-N bonds.

Experimental section

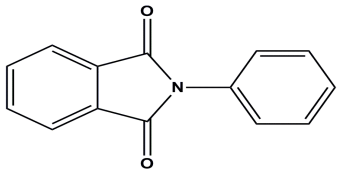
Reagents

Substrates including phthalimide, 4-nitrophthalimide, 3,4,5,6-tetrachlorophthalimide, napthalimide, saccharin, succinimde, potassium phthalimdie, 2-pyrrolidinone, benzene, *p*-xylene, *o*-xylene, *m*-xylene, toluene, 1,4-difluorobenzene, 1,2-dichlorobenzene, 4-methylanisole, pentamethylbenzene, pentalfluorobenzene were purchased from Sigma Aldrich and Fisher Scientific. Iodobenzene diacetate was purchased from Acros Chemicals. Flash chromatography was performed on Silicycle silica gel (60Å, 40-63 μm). All reagents were stored under an inert atmosphere before use.

Instrumentation

Reactions were carried out in a CEM Discover microwave. GC/MS analysis was carried out on an Agilent Technologies 6890 GC system fixed with a 5973 mass selective detector. NMR spectrum were acquired using a Bruker Avance 300MHz spectrometer.

Synthesis of 2-phenylisoindoline-1, 3-Dione (2)



2

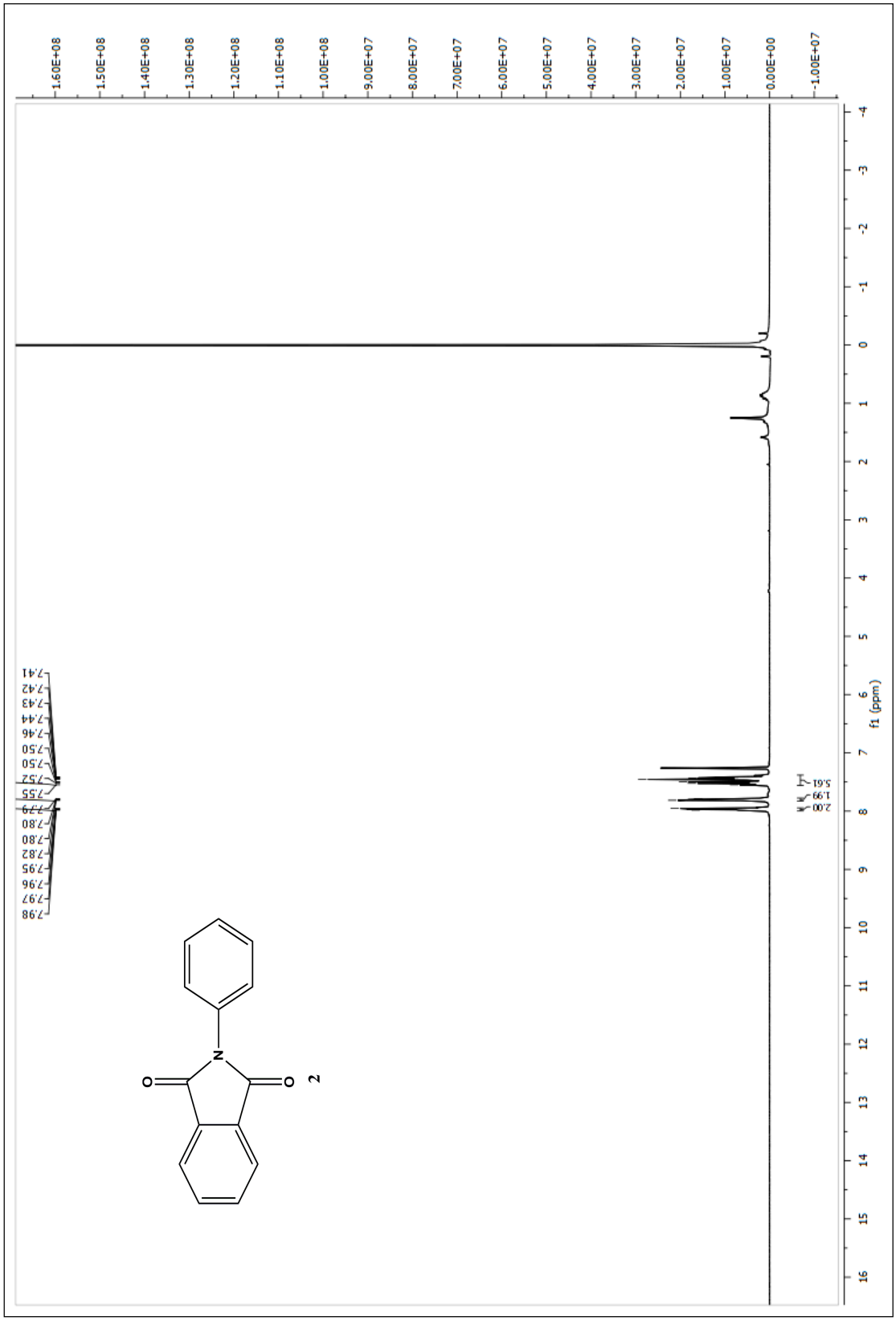
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of benzene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **2** (0.133 g, 88 %). The NMR spectrum matched with that of previously published.[15]

***R_f*-Value:** Hexane/Ethyl acetate (8:2 *v/v*) = 0.31.

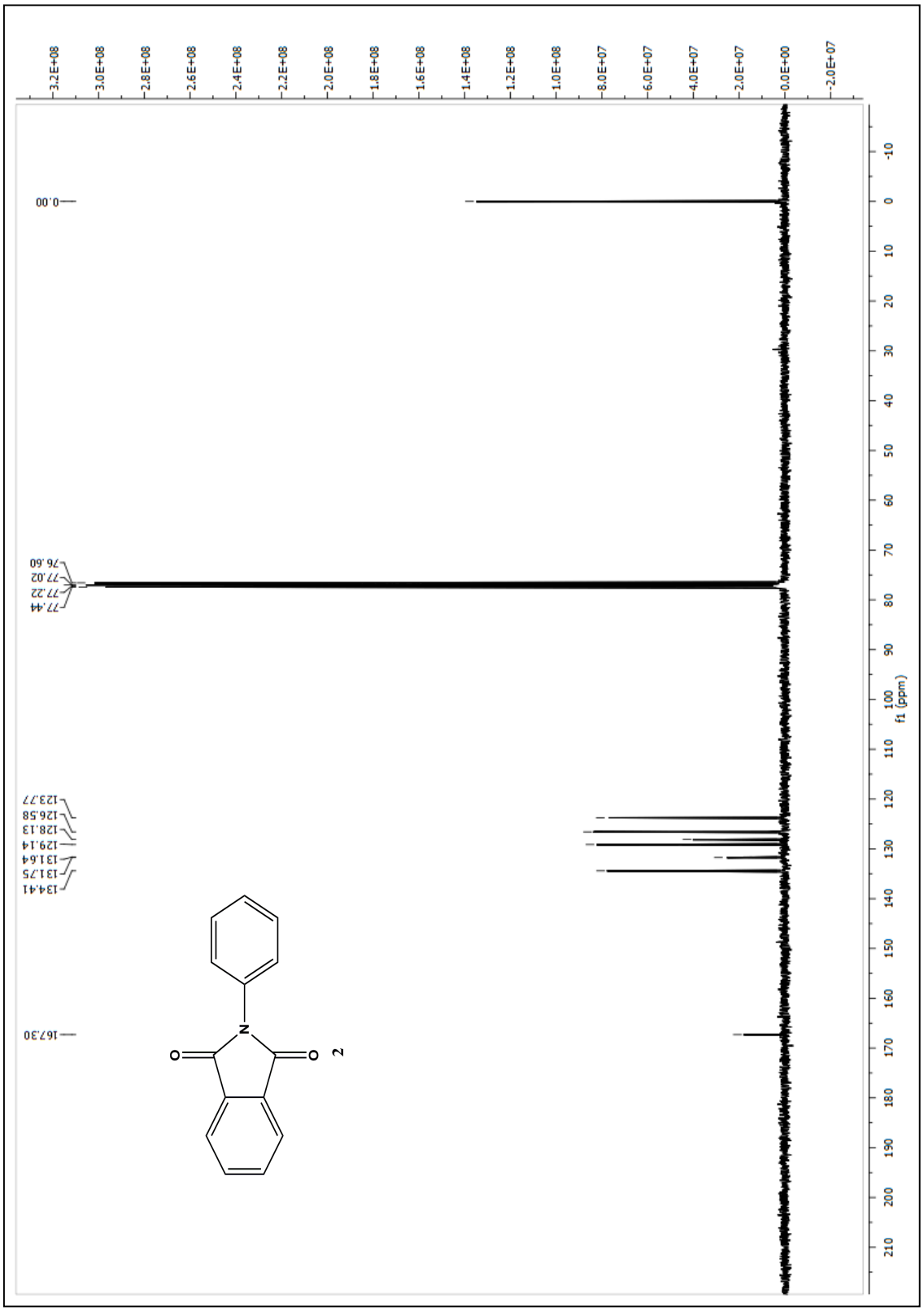
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.53 (m, 5H), 7.80 (dd, *J* = 5.4 Hz, 2.8 Hz, 2H), 7.96 (dd, *J* = 5.6 Hz, 3.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.7, 126.5, 128.1, 129.1, 131.7, 134.4, 167.30.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_9NO_2$ 223.06, observed 223.10 m/z.

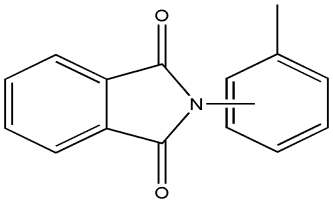


Spectrum 1. ^{1}H NMR of Compound **2**



Spectrum 2. ^{13}C NMR of Compound **2**

Synthesis of 3



3
o:m:p= 10 : 6 : 5

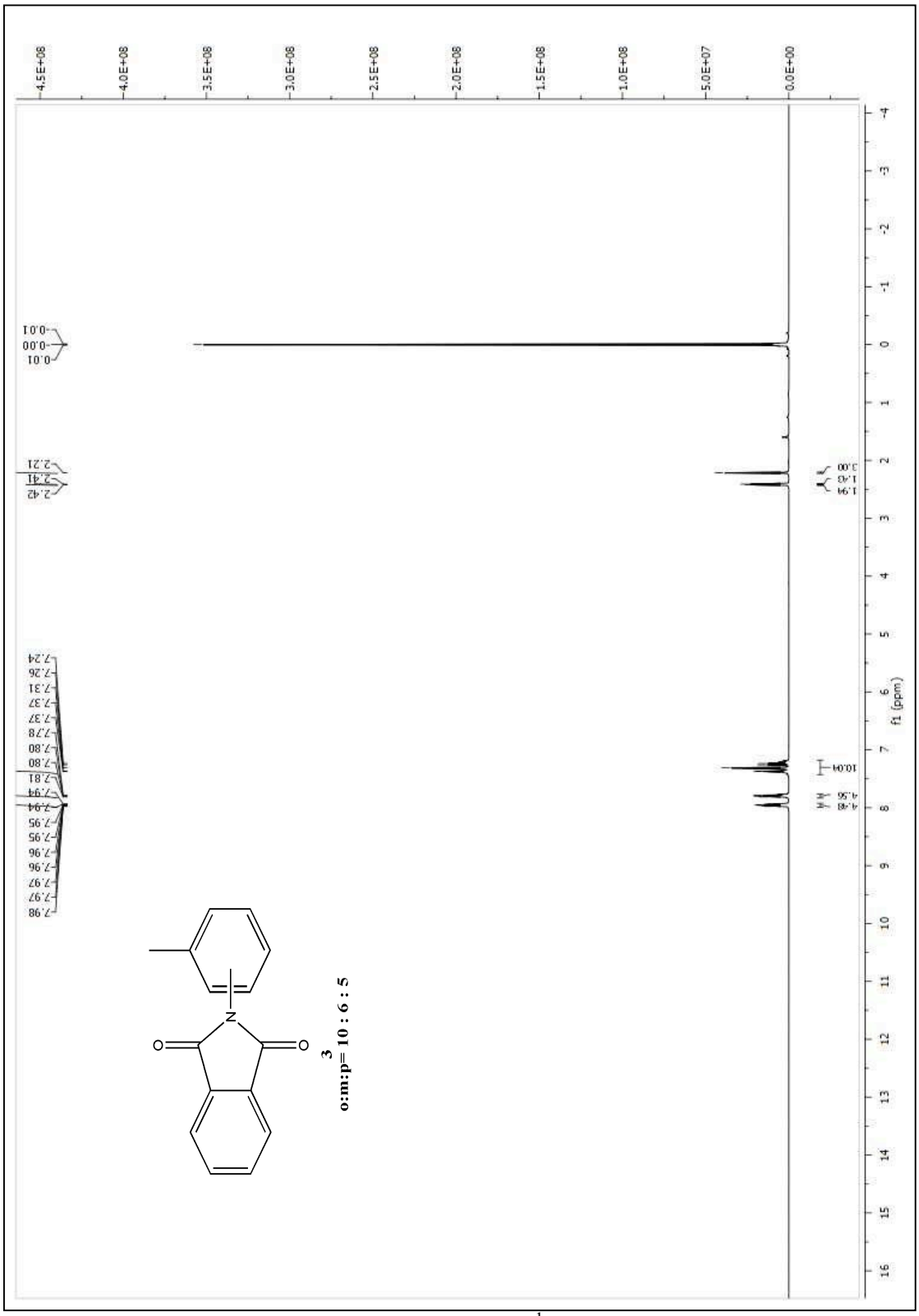
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of toluene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give pure **3** (0.1071 g, 70 %, o: m: p = **10**:**6**:**5**). The isomers were identified by comparing with known NMR spectrum.[16]

***R_f* -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.2.

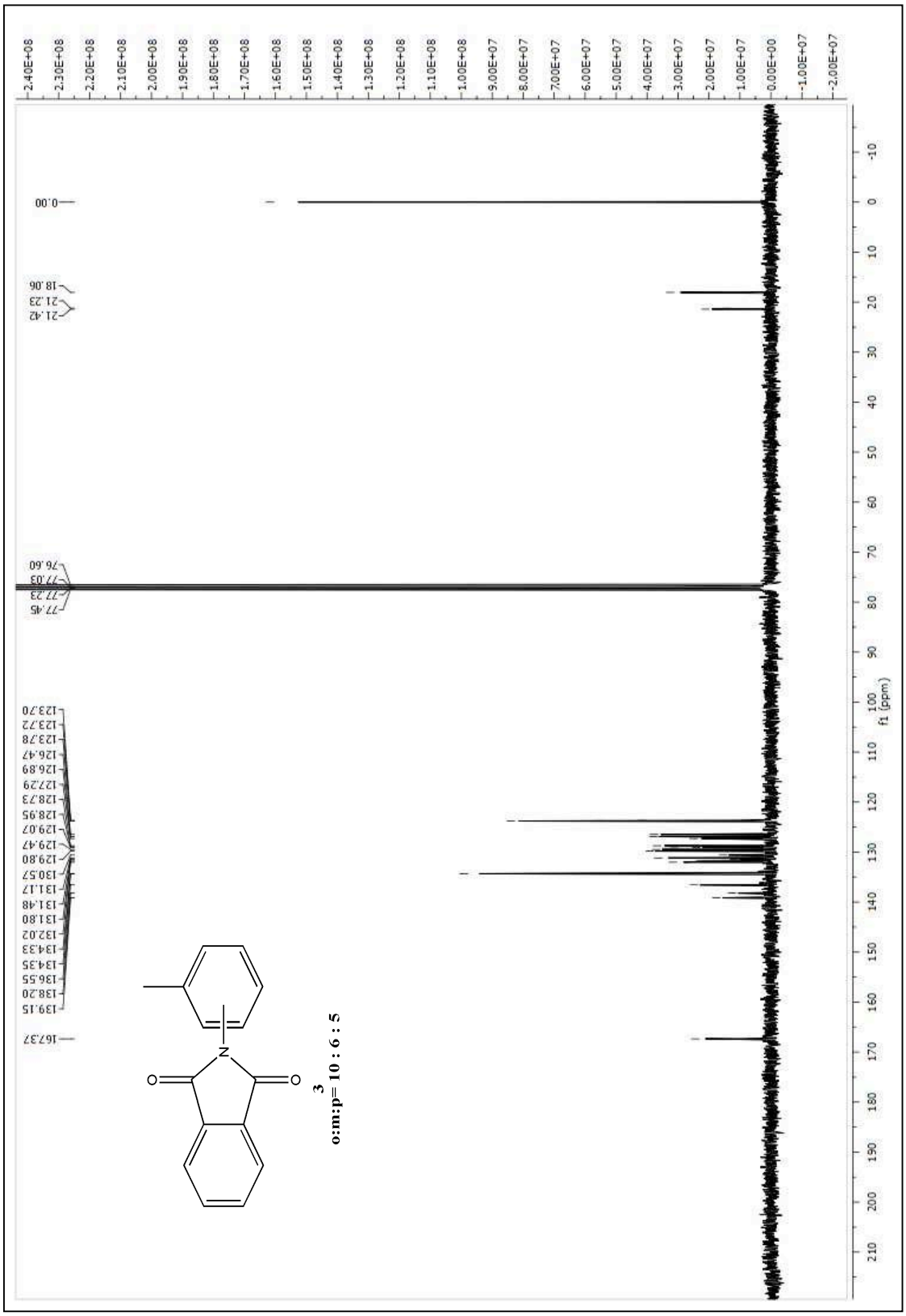
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 2.41 (s, 1H), 2.42 (s, 2H), 7.18 – 7.43 (m, 10H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 5H), 7.92 – 7.99 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.06, 21.23, 21.42, 123.70, 123.72, 123.78, 126.47, 126.89, 127.29, 128.73, 128.95, 129.07, 129.47, 129.80, 130.57, 131.17, 131.48, 131.80, 132.02, 134.33, 134.35, 136.55, 138.20, 139.15, 167.37.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_9NO_2$ 237.08, observed 237.10 m/z.

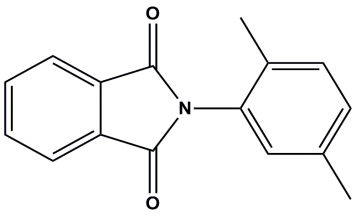


Spectrum 3. ^{1}H NMR of Compound **3**



Spectrum 4. ^{13}C NMR of Compound **3**

Synthesis of 2-(2, 5-dimethylphenyl) isoindoline-1, 3-dione (5)



5

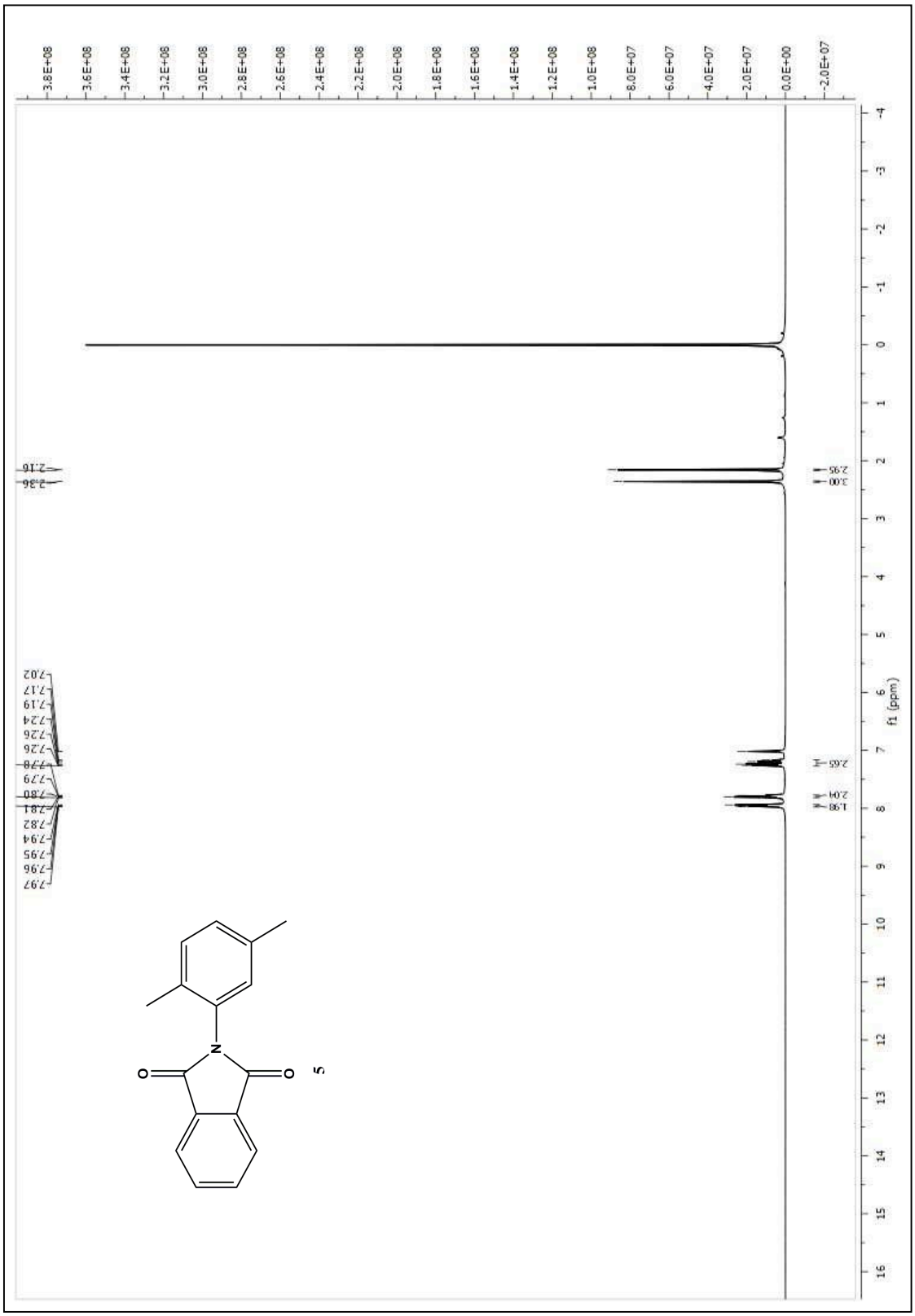
A magnetically stirred solution of Phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of *p*-xylene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **5** 0.1535g (90 %)

***R*$_f$ -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.19.

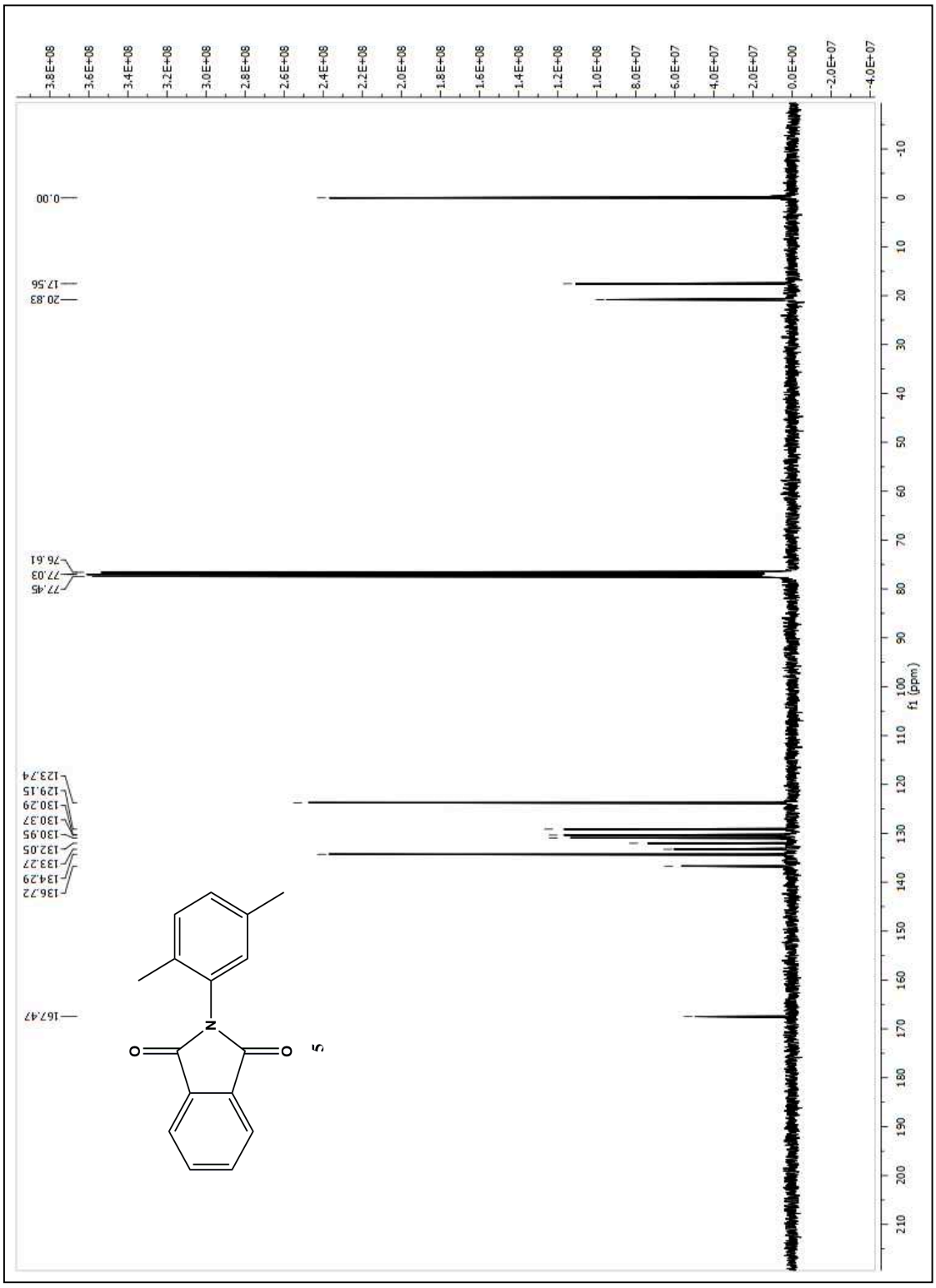
^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.16(s, 3H), 2.36 (s, 3H), 7.17-7.28 (m, 3H), 7.80 (dd, *J* = 6 Hz, *J* = 3 Hz, 2H), 7.97 (dd, *J* = 3 Hz, *J* = 3 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.56, 20.83, 123.74, 129.15, 130.29, 130.37, 130.95, 132.05, 133.27, 134.29, 136.72, 167.47.

LRMS EI (m/z): [M+] calc'd for $C_{16}H_{13}NO_2$ 251.09, observed 251.10 m/z.

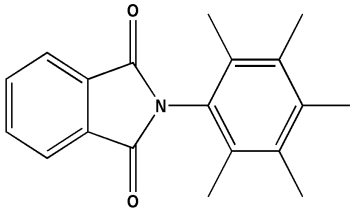


Spectrum 5. ^{1}H NMR of Compound **5**



Spectrum 6. ^{13}C NMR of Compound **5**

Synthesis of 2-(2, 3, 4, 5, 6-pentamethylphenyl) isoindoline-1, 3-dione (6)



6

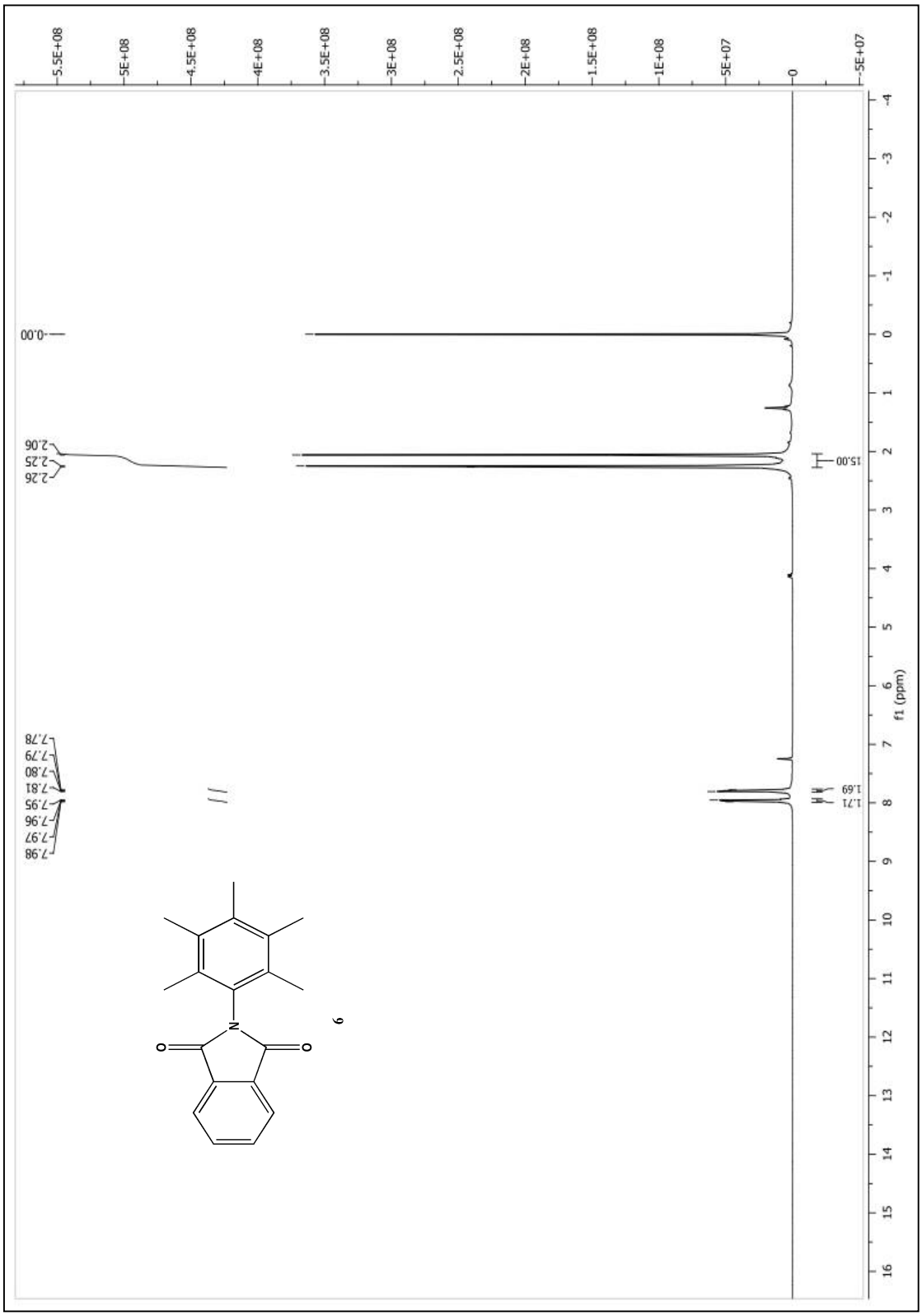
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol), pentamethyl benzene (0.3 g, 2.048 mmol) in 4 mL of acetonitrile was microwave heated at 145 ^{0}C for 3h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **6** (0.0846 g, 43 %).

***R_f* -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.23.

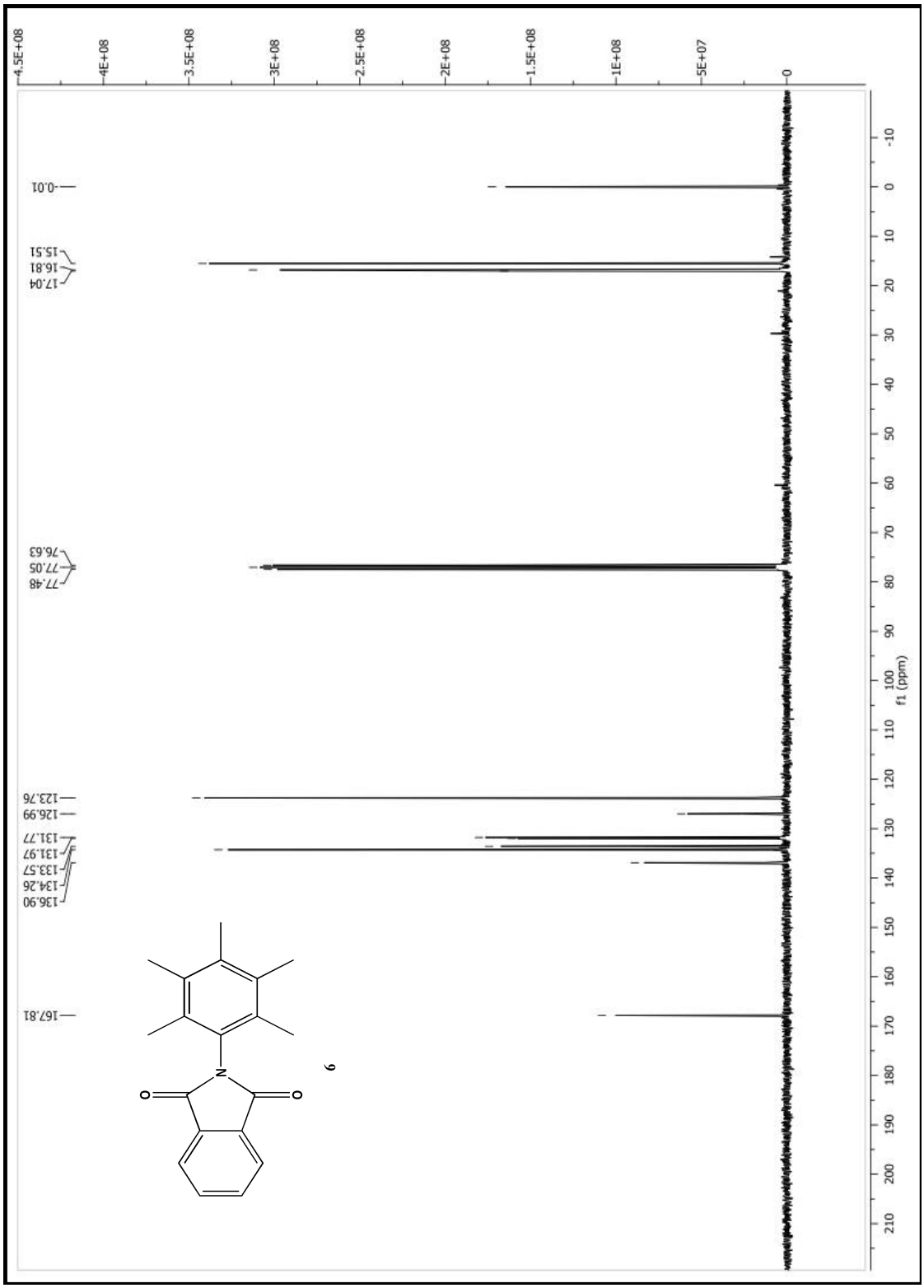
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06-2.26 (m, 15H), 7.79 (dd, *J* = 3 Hz, 3 Hz, 2H), 7.97 (dd, *J* = 3 Hz, 3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.51, 16.81, 17.04, 123.76, 126.99, 131.77, 131.97, 133.57, 134.26, 136.9, 167.81.

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{19}NO_2$ 293.14, observed 293.15 m/z.

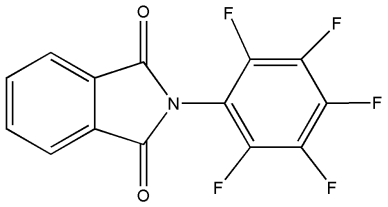


Spectrum 7. ^{1}H NMR of Compound **6**



Spectrum 8. ^{13}C NMR of Compound **6**

Synthesis of 2-(perfluorophenyl)isoindoline-1,3-dione (7)



7

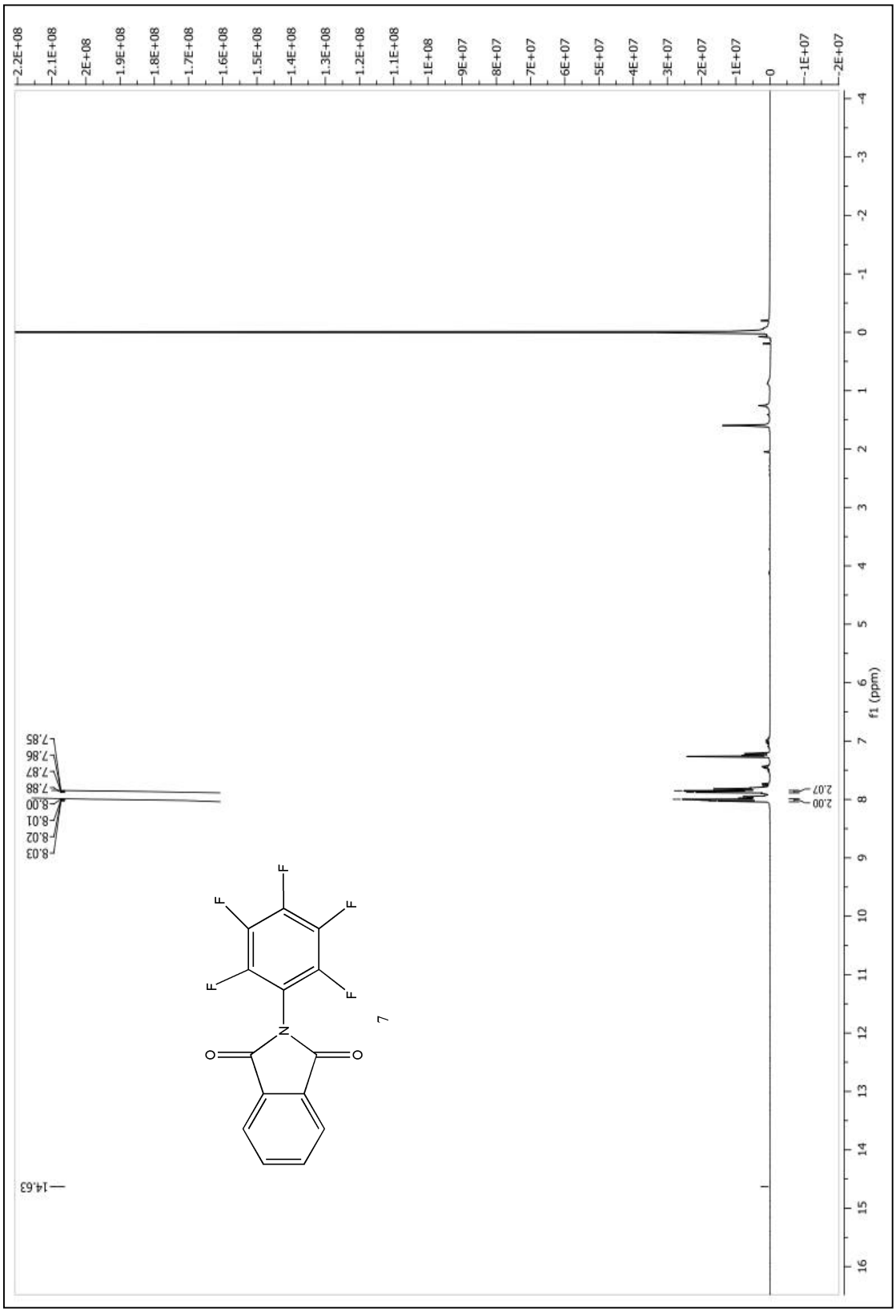
A magnetically stirred solution of Phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol), in 4 mL of pentafluorobenzene was microwave heated at 145 ^{0}C for 3h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **7** (0.04 g, 20 %).

***R_f*-Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.18.

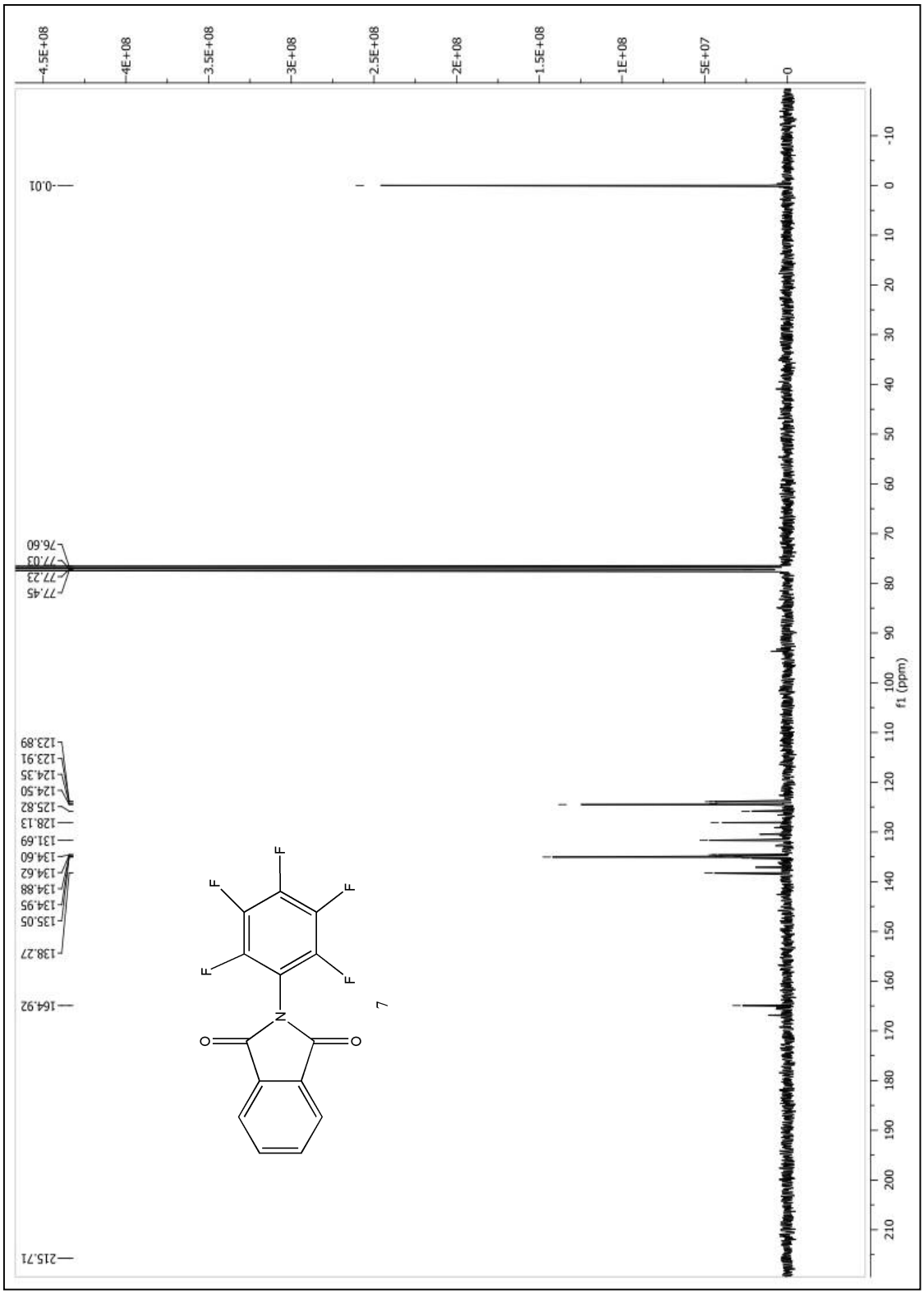
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 3 Hz, *J* = 3 Hz, 2H), 8.01 (dd, *J* = 3 Hz, *J* = 3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 123.89, 123.91, 124.35, 124.5, 125.82, 128.13, 131.69, 134.62, 134.88, 134.95, 135.05, 138.27.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_4F_5NO_2$ 313.02, observed 313.0 m/z.

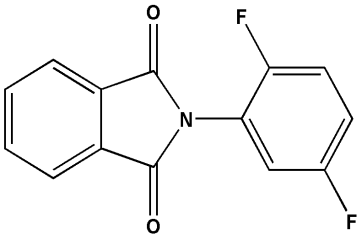


Spectrum 9. ^{1}H NMR of Compound **7**



Spectrum 10. ^{13}C NMR of Compound **7**

Synthesis of 2-(2,5-difluorophenyl)isoindoline-1,3-dione (8)



8

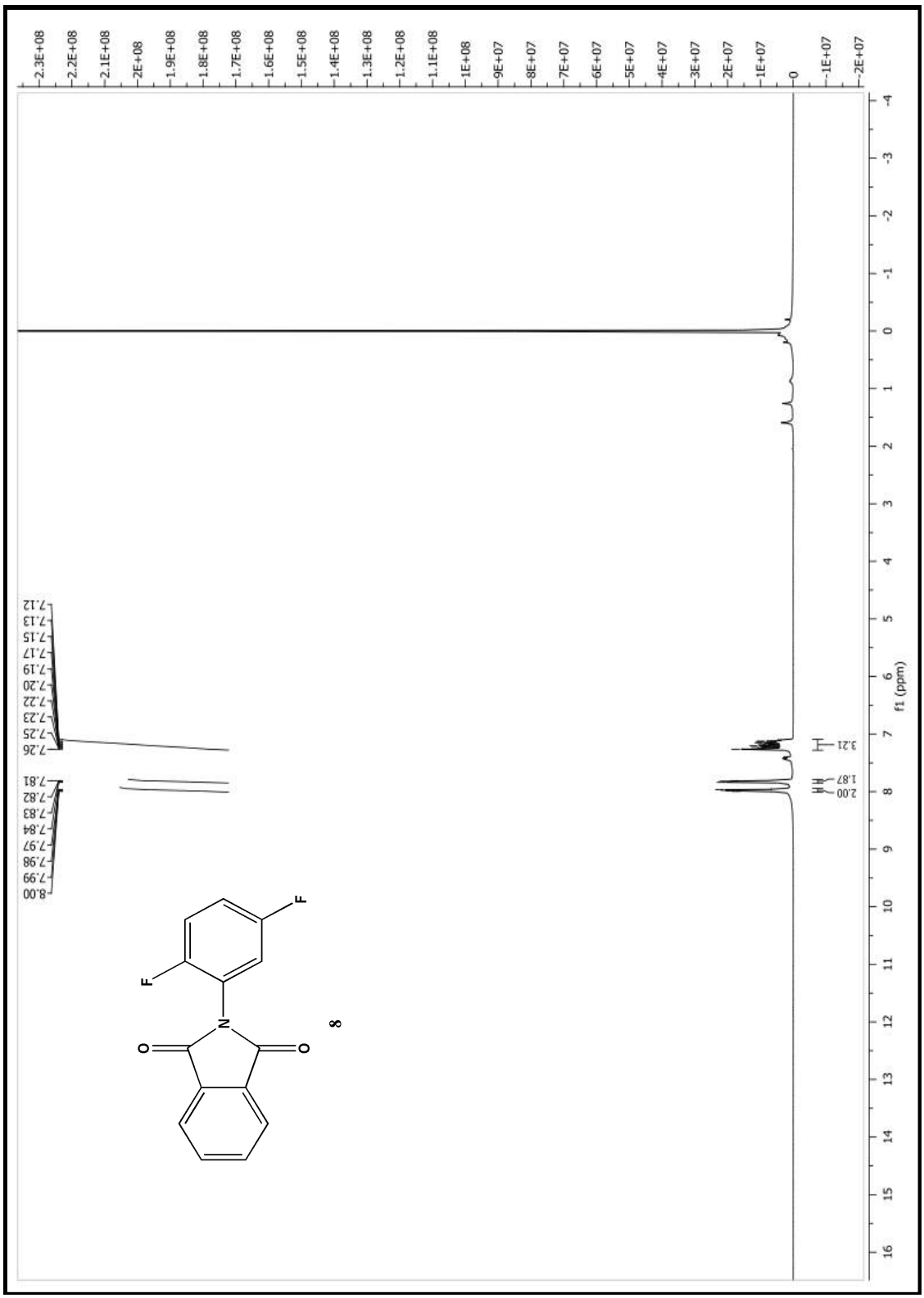
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of 1, 4-difluorobenzene was microwave heated at 145 ^{0}C for 3h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give pure **8** (0.0917 g, 53 %).

***R_f* -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.19.

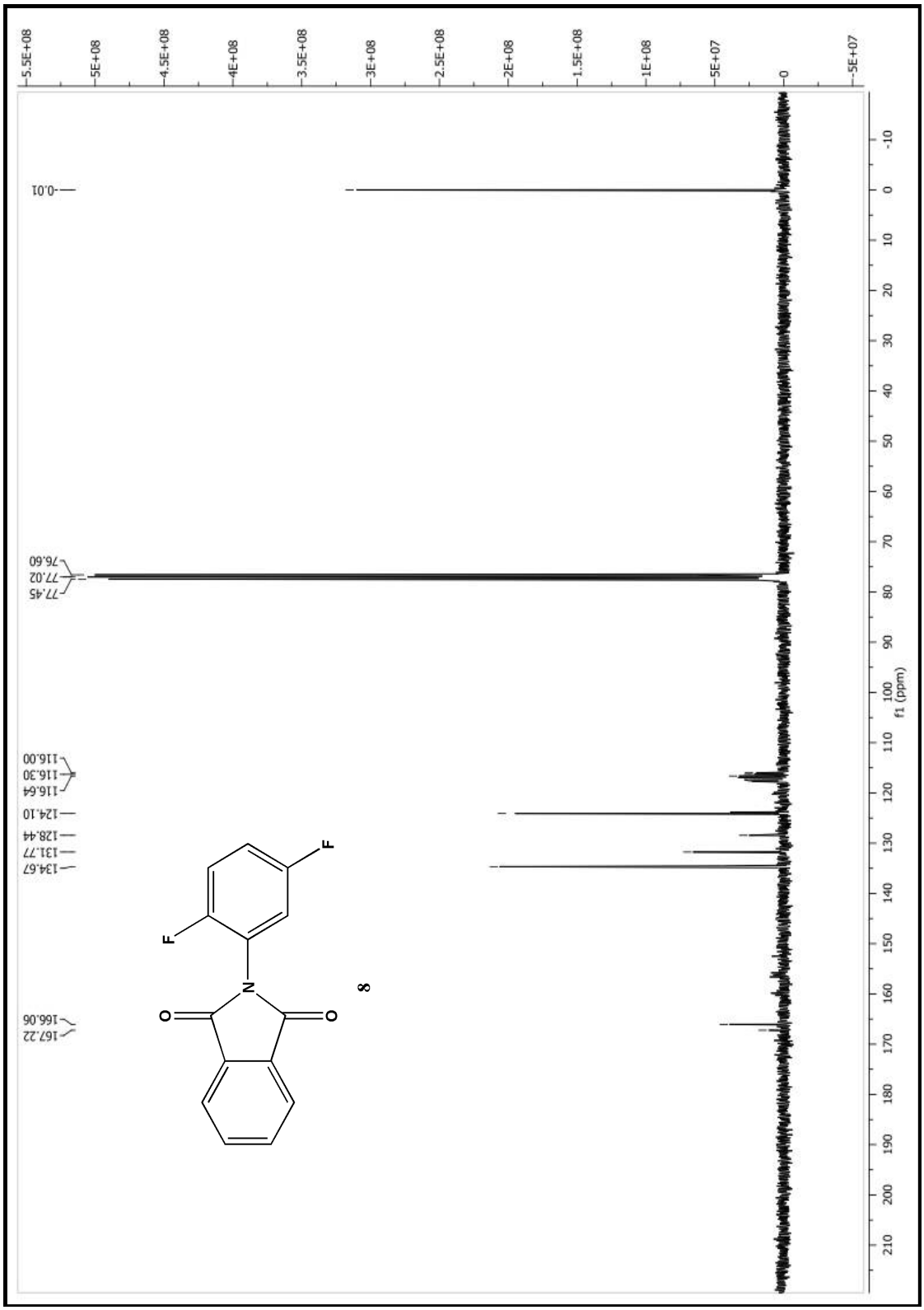
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12-7.26 (m, 3H), 7.82 (dd, *J* = 3 Hz, *J* = 3 Hz, 2H), 7.98 (dd, *J* = 3 Hz, *J* = 3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 116.00, 116.30, 116.64, 124.10, 128.44, 131.77, 134.67, 166.06, 167.22.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_7F_2NO_2$ 259.04, observed 259.1 m/z.

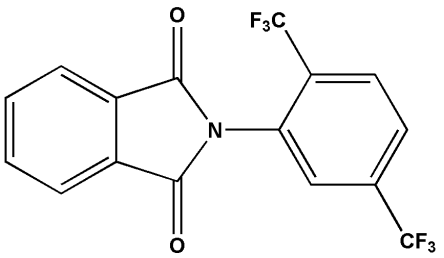


Spectrum 11. ^{1}H NMR of Compound **8**



Spectrum 12. ^{13}C NMR of Compound **8**

Synthesis of 2-(2, 5-bis (trifluoromethyl) phenyl) isoindoline-1, 3-dione (9)



9

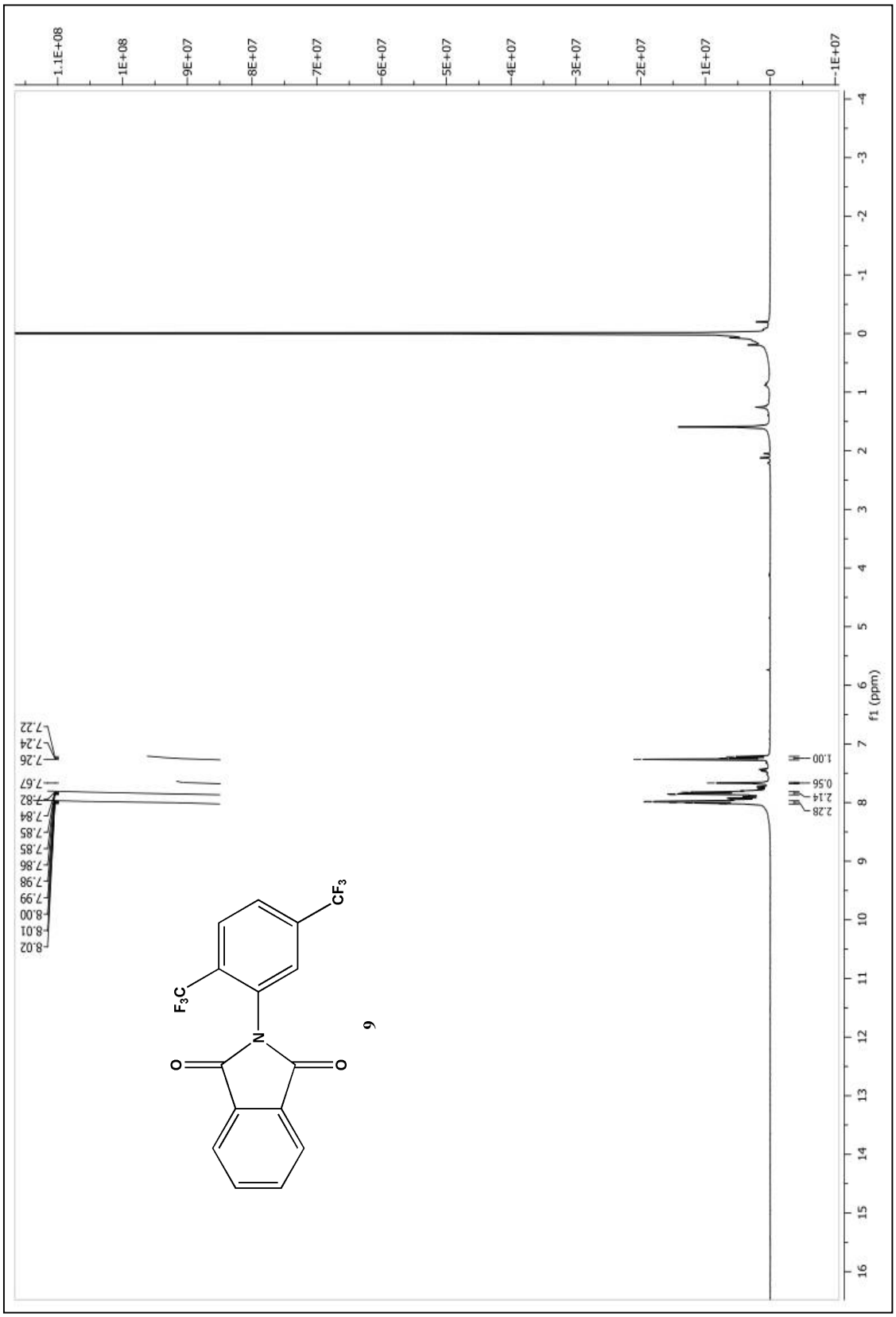
A magnetically stirred solution of Phthalimide (0.1g, 0.68mmol), (Diacetoxyiodo) benzene (0.55 g, 1.7mmol), in 4 mL of 1,4-bistrifluoromethylbenzene was microwave heated at 145 ^{0}C for 3h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give pure **9** (0.2441 g, 24 %).

***R_f*-Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.2187.

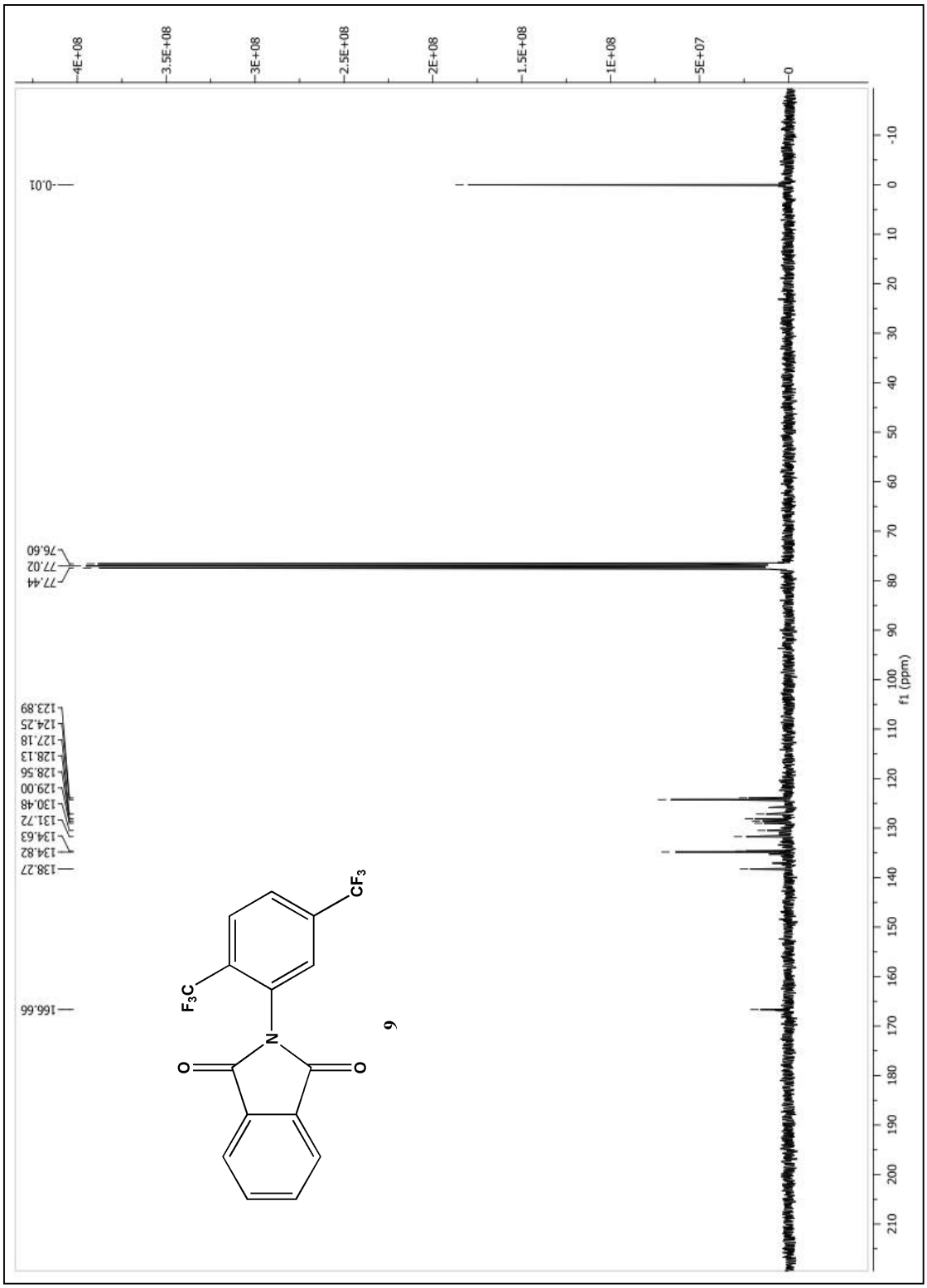
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22-7.26 (m, 1H), 7.67 (s, 1H), 7.82-8.02 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ= 123.89, 124.25, 127.18, 128.13, 129.00, 130.48, 131.72, 134.63, 134.82, 138.27, 166.66.

LRMS EI (m/z): [M+] calc'd for $C_{16}H_7F_6NO_2$ 359.0, observed 359.0 m/z.

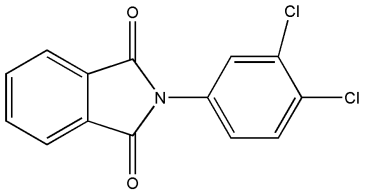


Spectrum 13. ^{1}H NMR of Compound **9**



Spectrum 14. ^{13}C NMR of Compound **9**

Synthesis of 2-(3, 4-dichlorophenyl) isoindoline-1,3-dione (10)



10

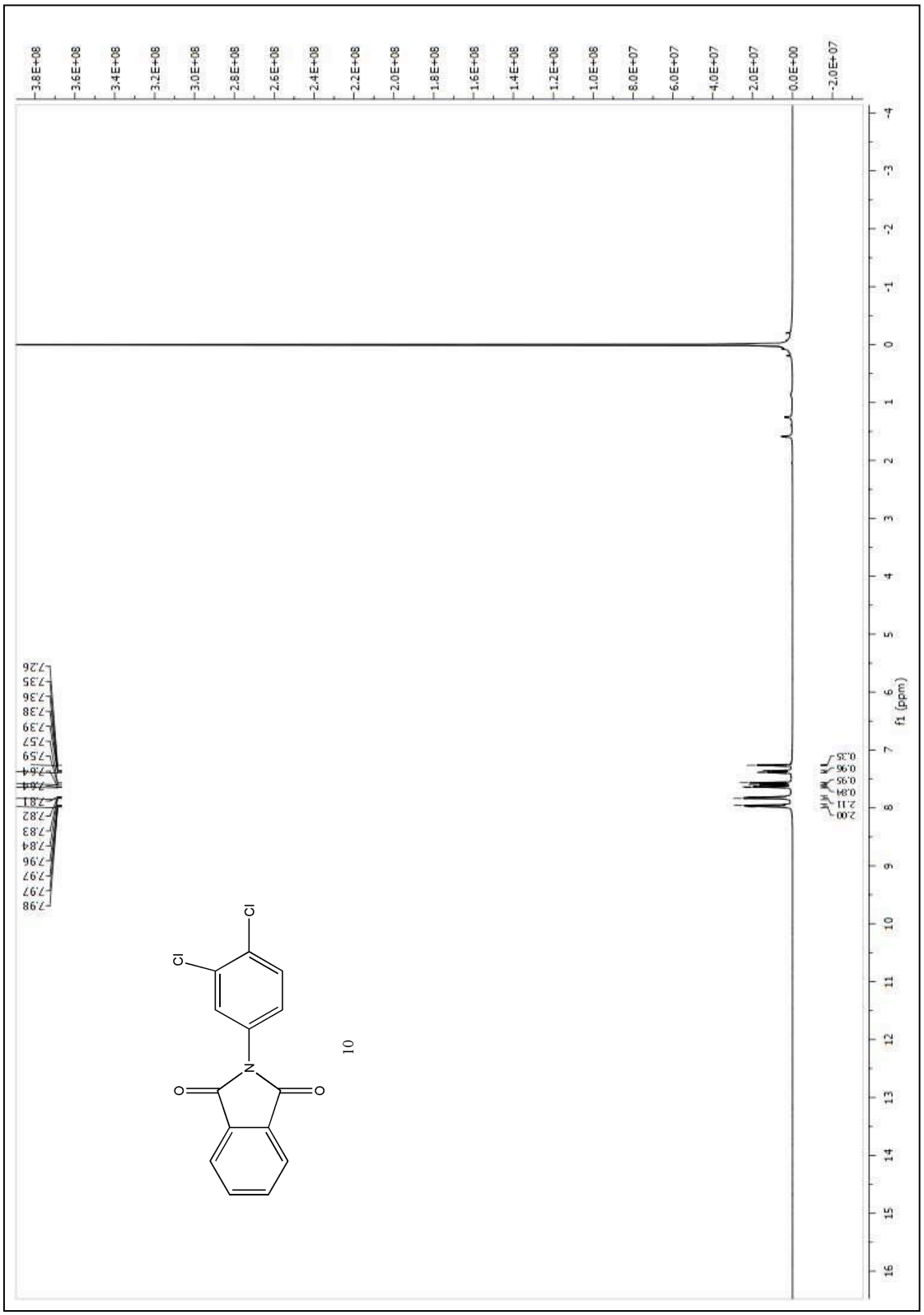
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of 1,2-dichlorobenzene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give pure **10** (0.1118 g, 56 %).

***R*$_f$ -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.19.

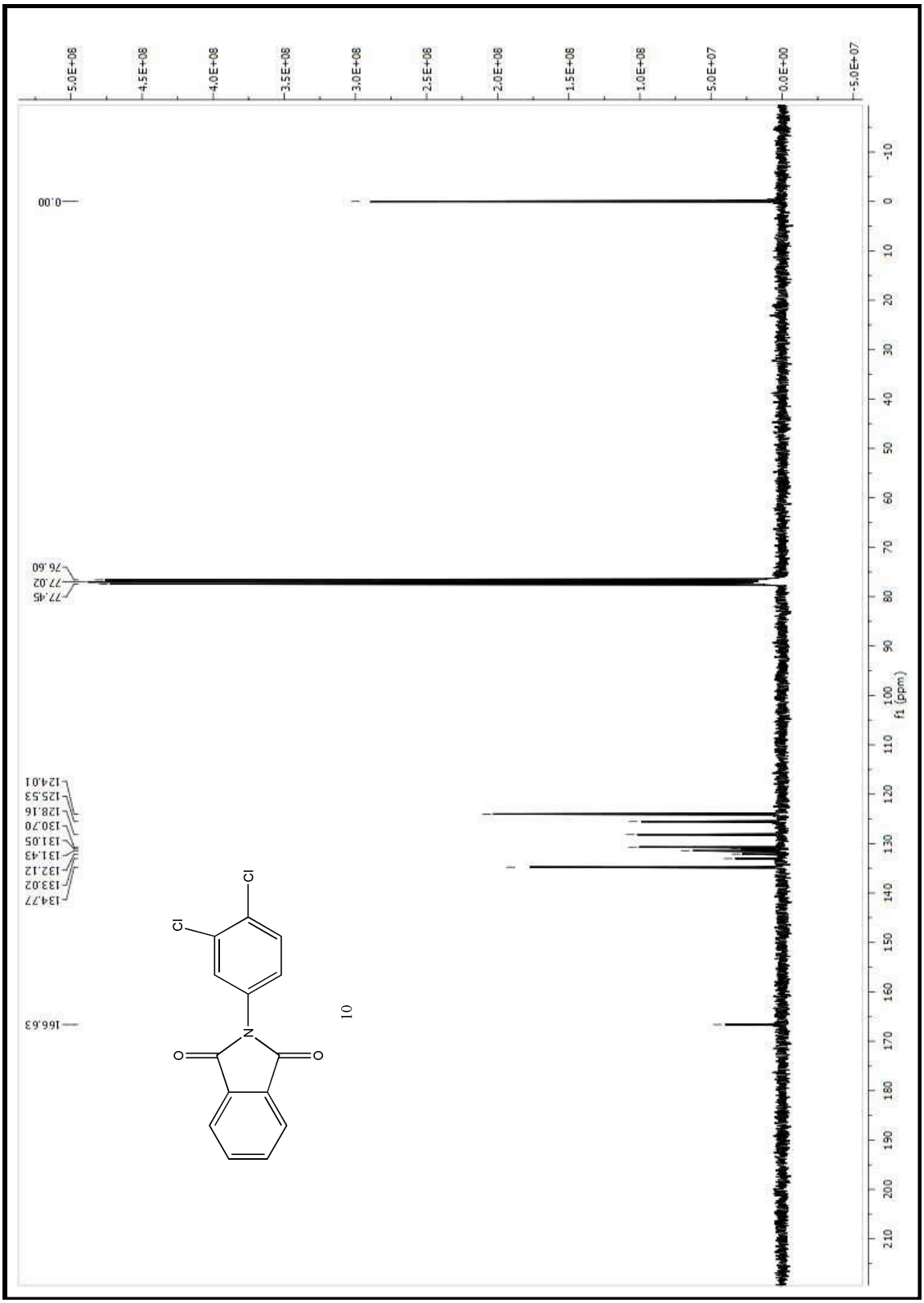
^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.37 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.98 – 7.94 (m, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 124.01, 125.53, 128.16, 130.70, 131.05, 131.43, 132.12, 133.02, 134.77, 166.63.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_7F_2NO_2$ 291.0, observed 291.0 m/z.

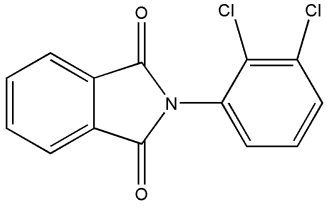


Spectrum 15. ^{1}H NMR of Compound **10**


0.00
76.60
77.02
77.45
124.01
125.53
128.16
130.70
131.05
131.43
132.12
133.02
134.77
166.63
Cl
Cl
N
O
O
10
f1 (ppm)

Spectrum 16. ^{13}C NMR of Compound **10**

Synthesis of 2-(2,3-dichlorophenyl)isoindoline-1,3-dione (11)



11

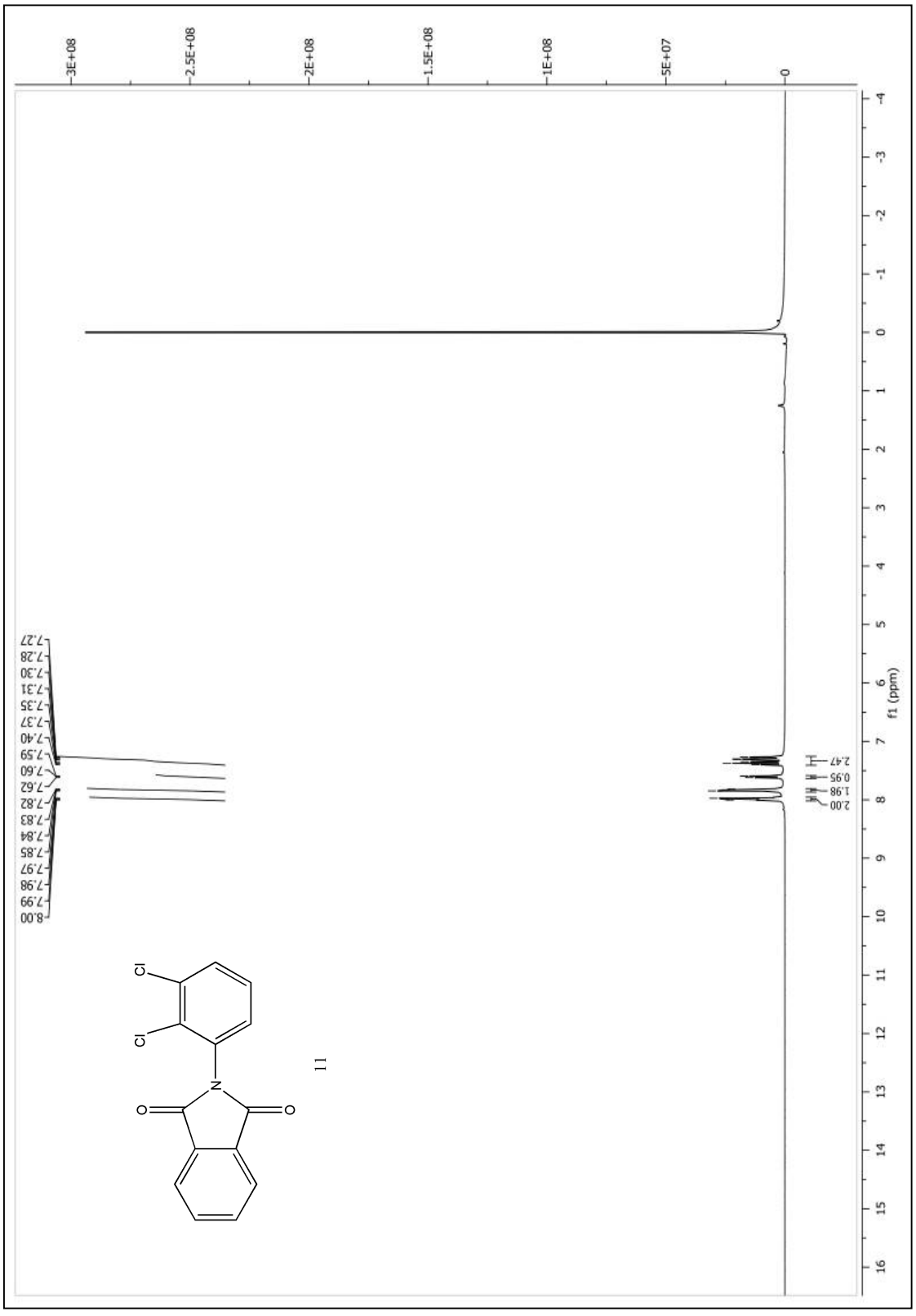
A magnetically stirred solution of Phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of 1,2-dichlorobenzene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give pure **11** (0.034 g, 17 %).

***R_f* -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.09.

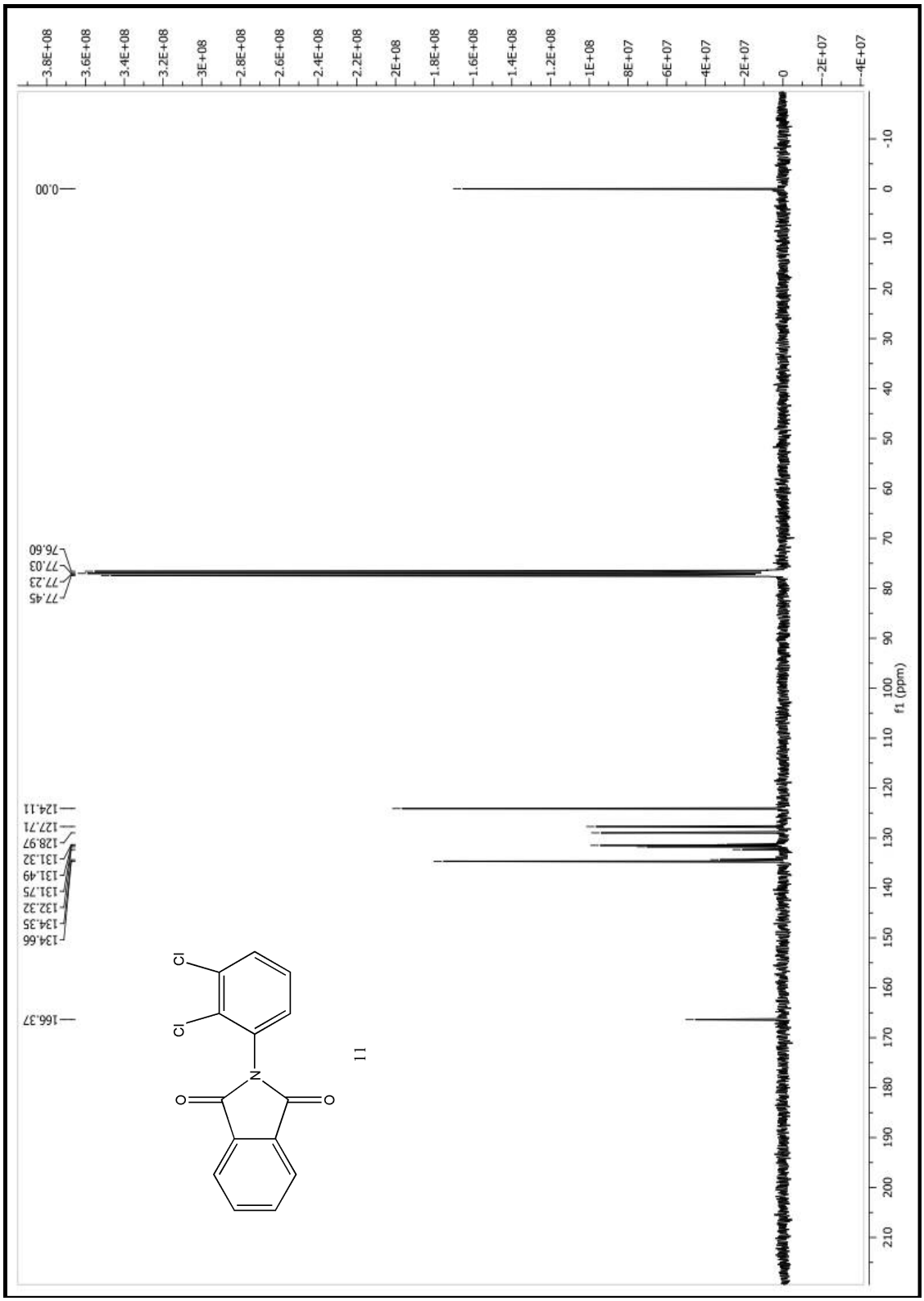
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.4 (m, 2H), 7.59-7.62 (m, 1H), 7.83 (dd, *J* = 3, 3 Hz, 2H), 7.99 (dd, *J* = 3 Hz, 3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.11, 127.71, 128.97, 131.32, 131.49, 131.75, 132.32, 134.35, 134.66, 166.37.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_7F_2NO_2$ 291.0, observed 291.0 m/z.

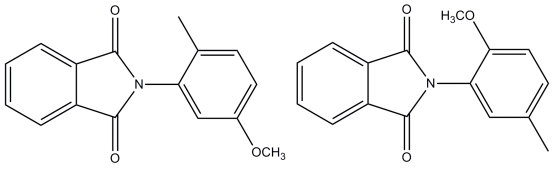


Spectrum 17. ^{1}H NMR of Compound **11**



Spectrum 18. ^{13}C NMR of Compound **11**

Synthesis of 14 and 15



14 15

14:15 = 2:3

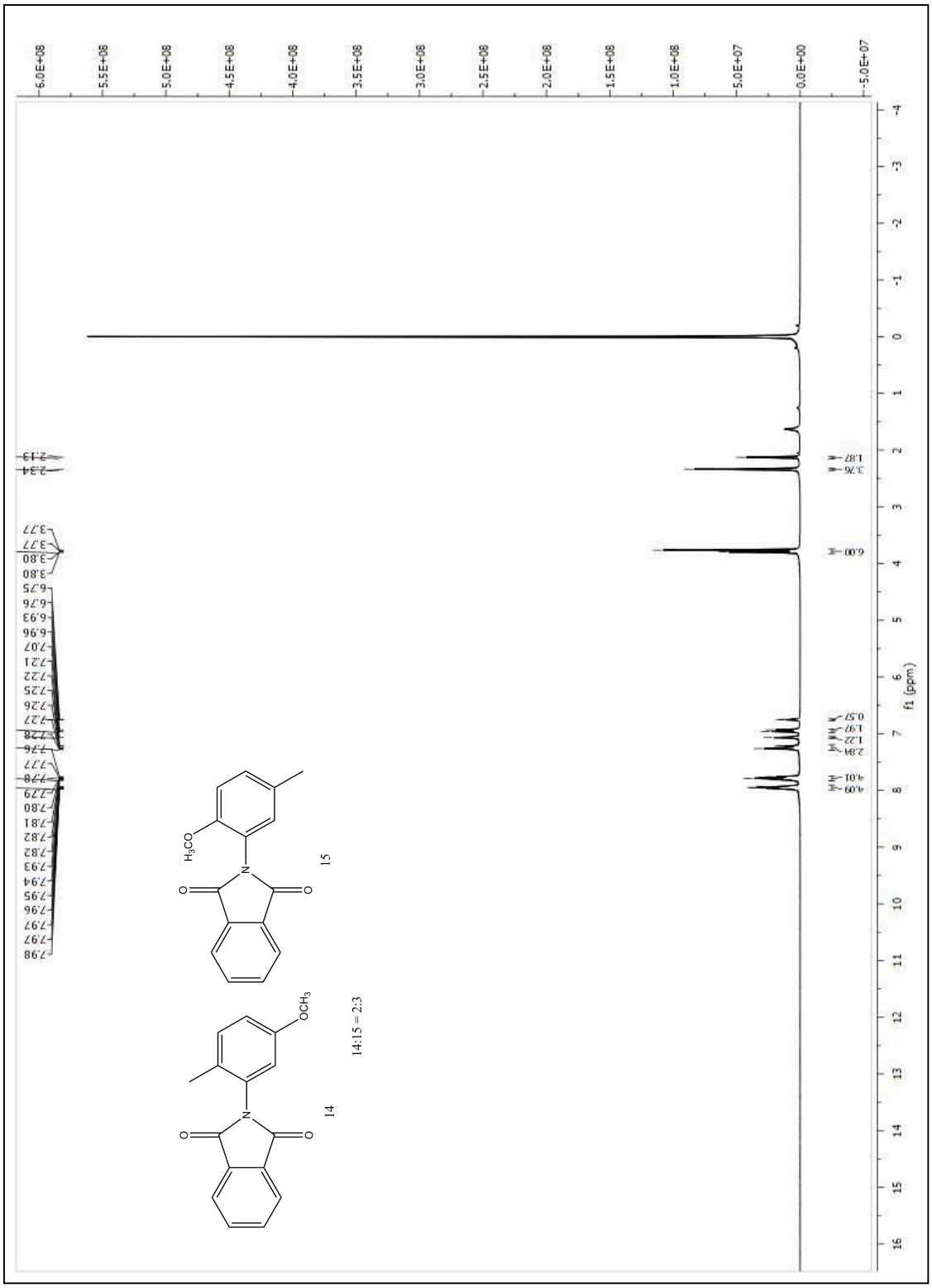
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of 4-methylanisole was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give a mixture of **14** and **15** (0.1287 g, 70 %, **14**:**15** = 2:3).

***R_f*-Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.1714.

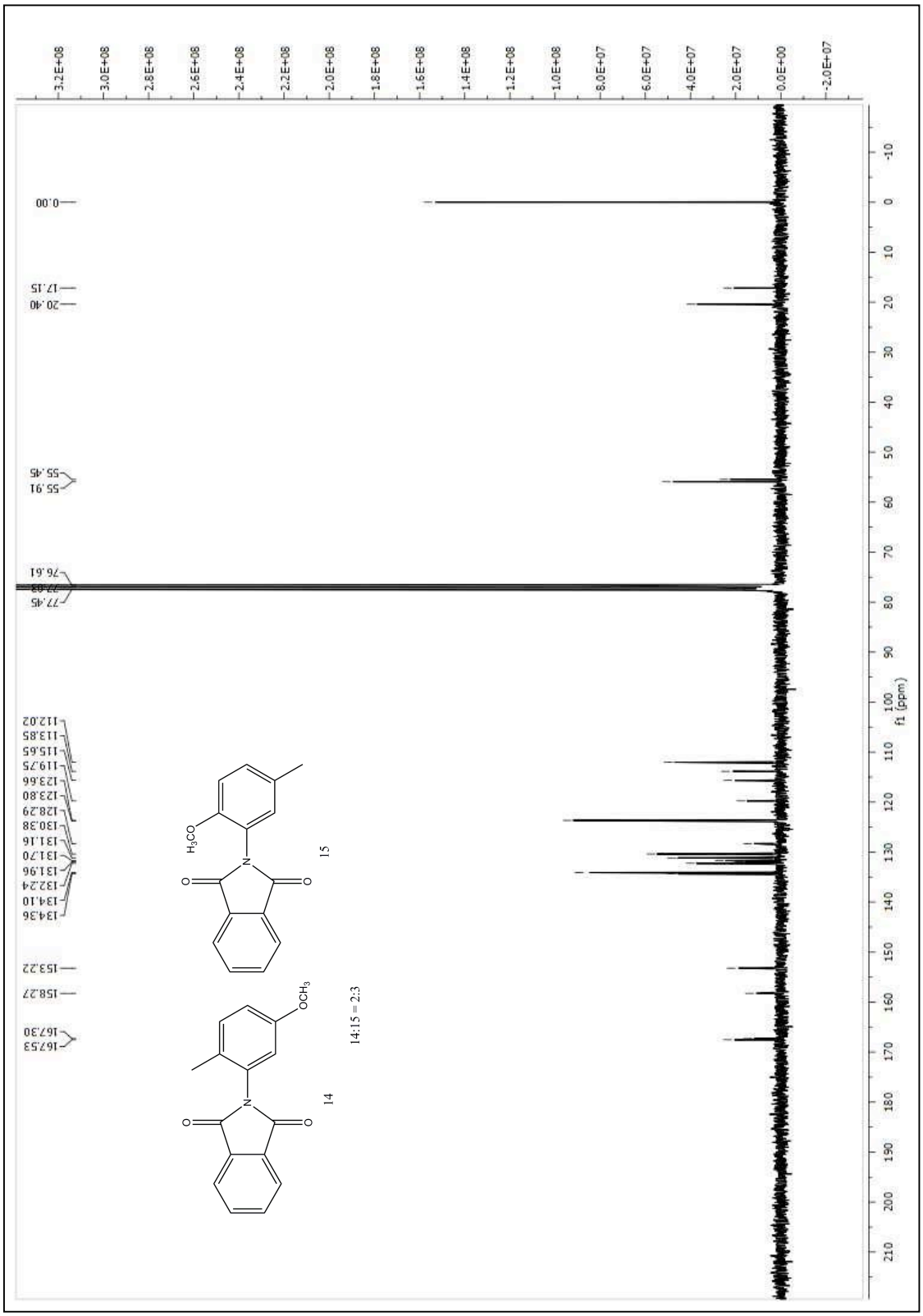
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 2H), 2.34 (s, 3H), 3.78 (dd, *J* = 9.6, 2.1 Hz, 6H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.07 (s, 1H), 7.20 – 7.30 (m, 3H), 7.76-7.82 (m, 4H), 7.91 – 7.99 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.15, 20.40, 55.45, 55.91, 112.02, 113.85, 115.65, 119.75, 123.66, 123.80, 128.29, 130.38, 131.16, 131.70, 131.96, 132.24, 134.10, 134.36, 153.22, 158.27, 167.30, 167.53.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_9NO_2$ 267.09, observed 267.10 m/z.

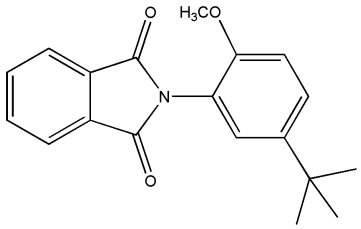


Spectrum 19. ^{1}H NMR of Compound **14** and **15**



Spectrum 20. ^{13}C NMR of Compound **14** and **15**

Synthesis of 2-(5-tert-butyl-2-methoxyphenyl) isoindoline-1,3-dione (16)



16

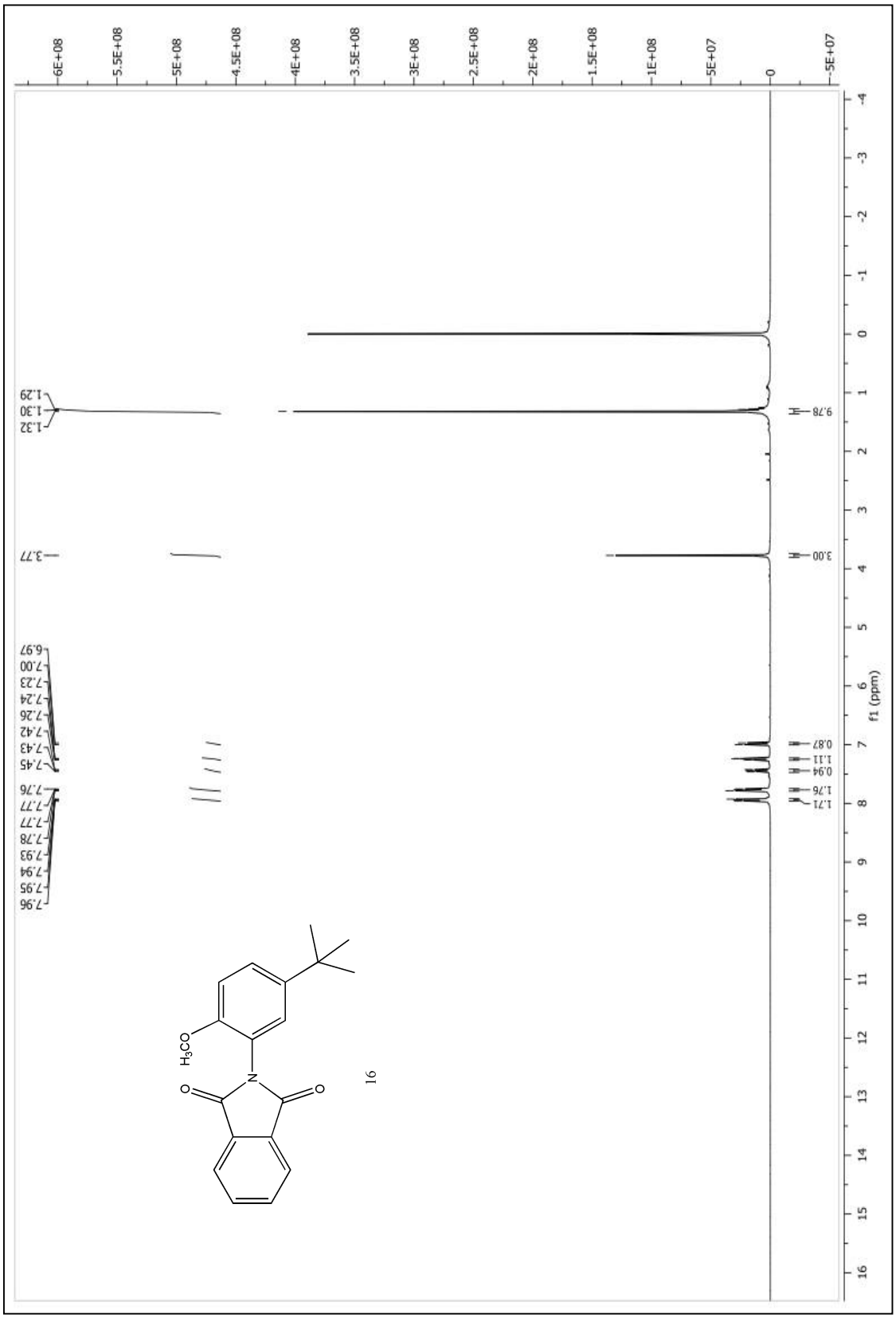
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol), 1-*tert*-butyl-4-methoxybenzene (0.22 g, 1.359 mmol) in 4 mL of acetonitrile was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give pure **16** (0.117 g, 56 %).

***R*$_f$ -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.11.

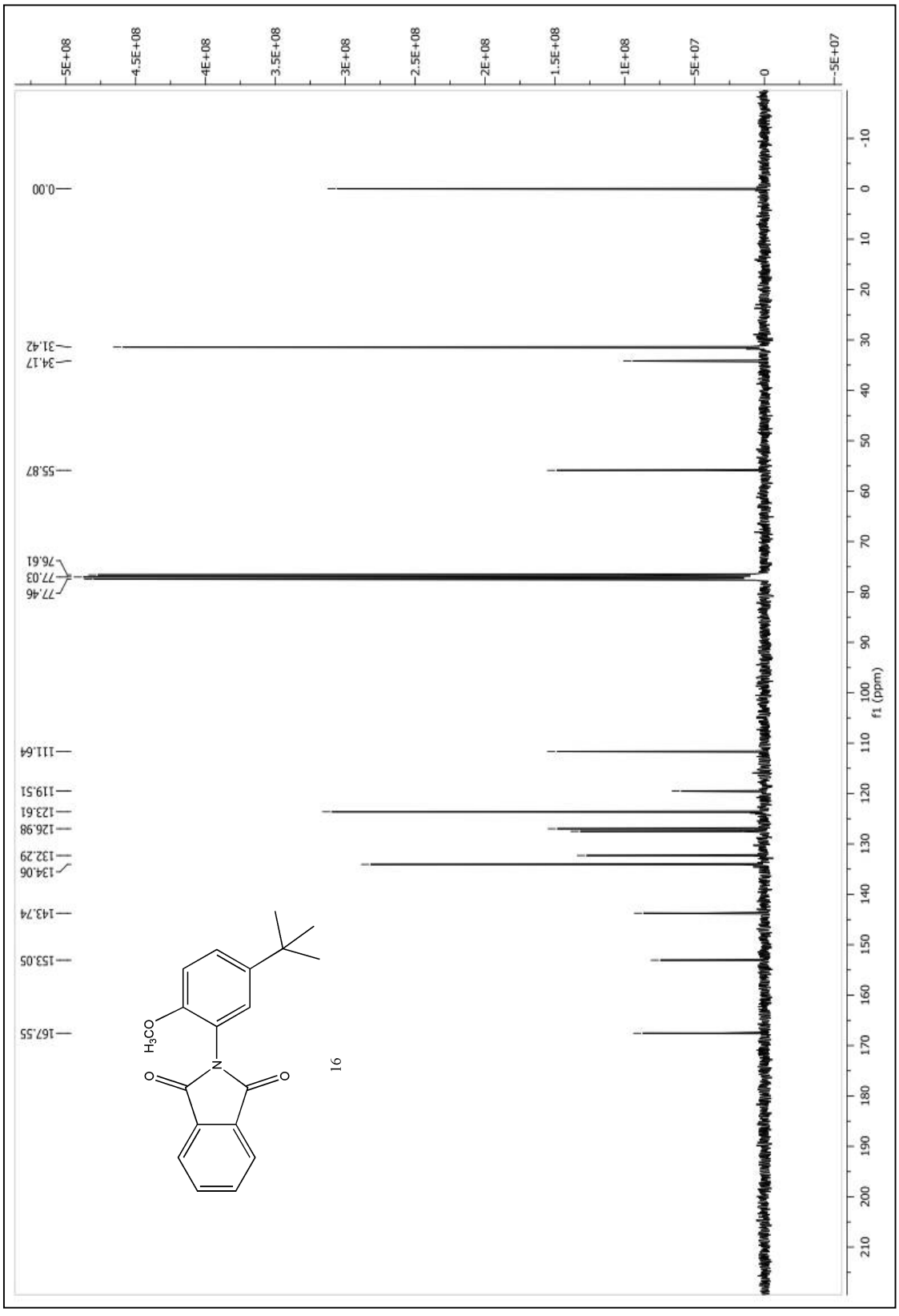
^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.29-1.32 (m, 9H), 3.77 (s, 3H), 6.98 (d, *J* = 9 Hz, 1H), 7.25 (m, 1H) 7.44 (dd, *J* = 3 Hz, 3 Hz, 1 H) 7.77 (dd, *J* = 3 Hz, 3 Hz, 2H), 7.94 (dd, *J* = 3 Hz, 3 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 31.42, 34.17, 55.87, 111.64, 119.51, 123.61, 126.98, 132.29, 134.06, 143.74, 153.05, 167.55.

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{19}NO_3$ 309.14, observed 309.12 m/z.

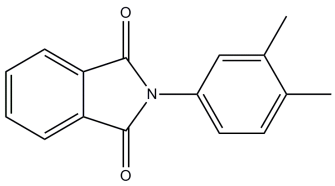


Spectrum 21. ^{1}H NMR of Compound **16**

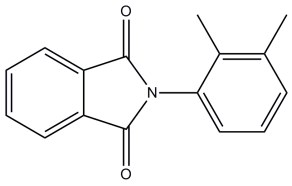


Spectrum 22. ^{13}C NMR of Compound **16**

Synthesis of 12 and 13



12



13

12:13 = 3:4

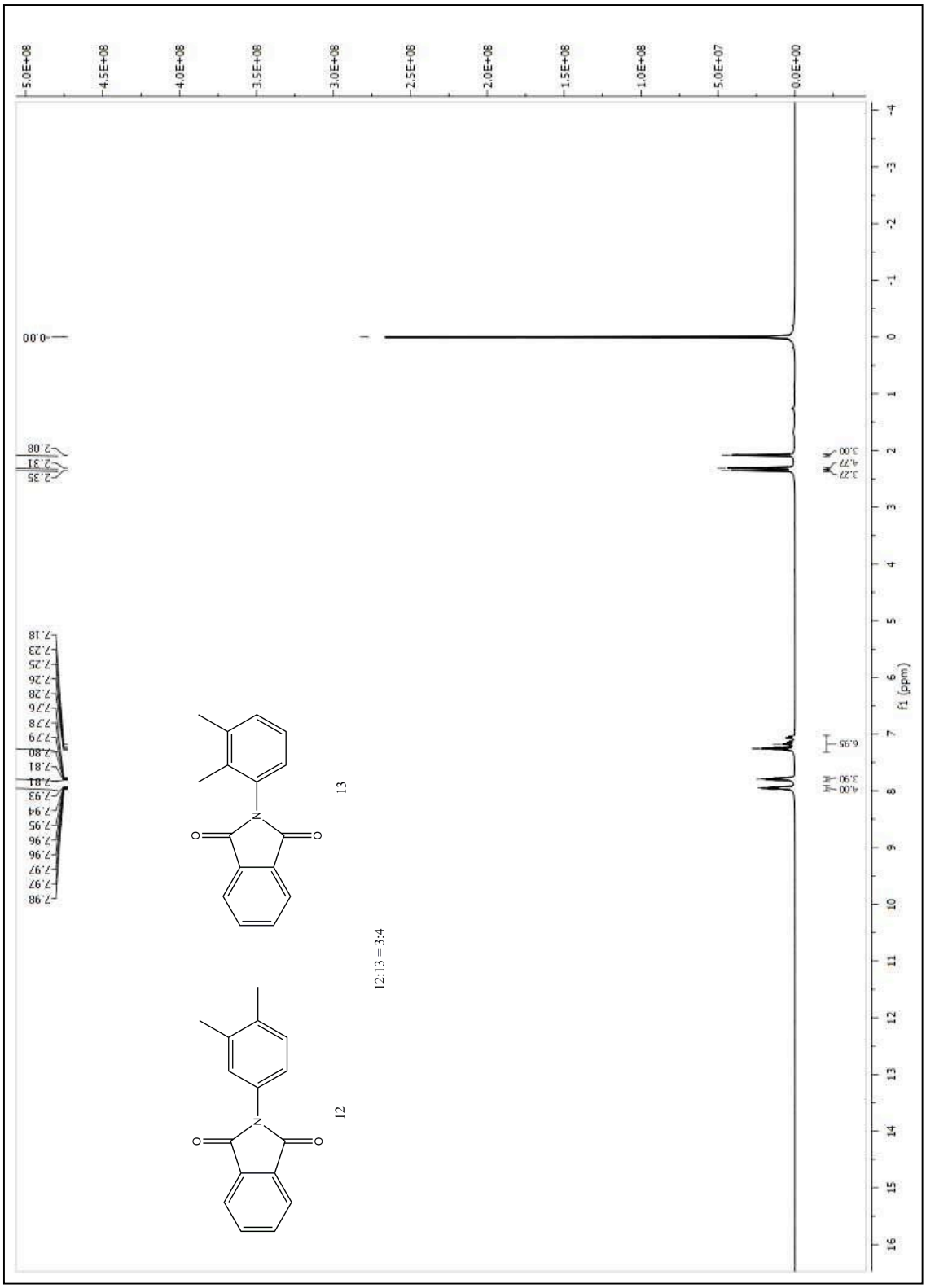
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of *o*-xylene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give a mixture of **12** and **13** (0.1333 g, 80 %, **12**:**13** = 3:4).

***R*$_f$ -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.22.

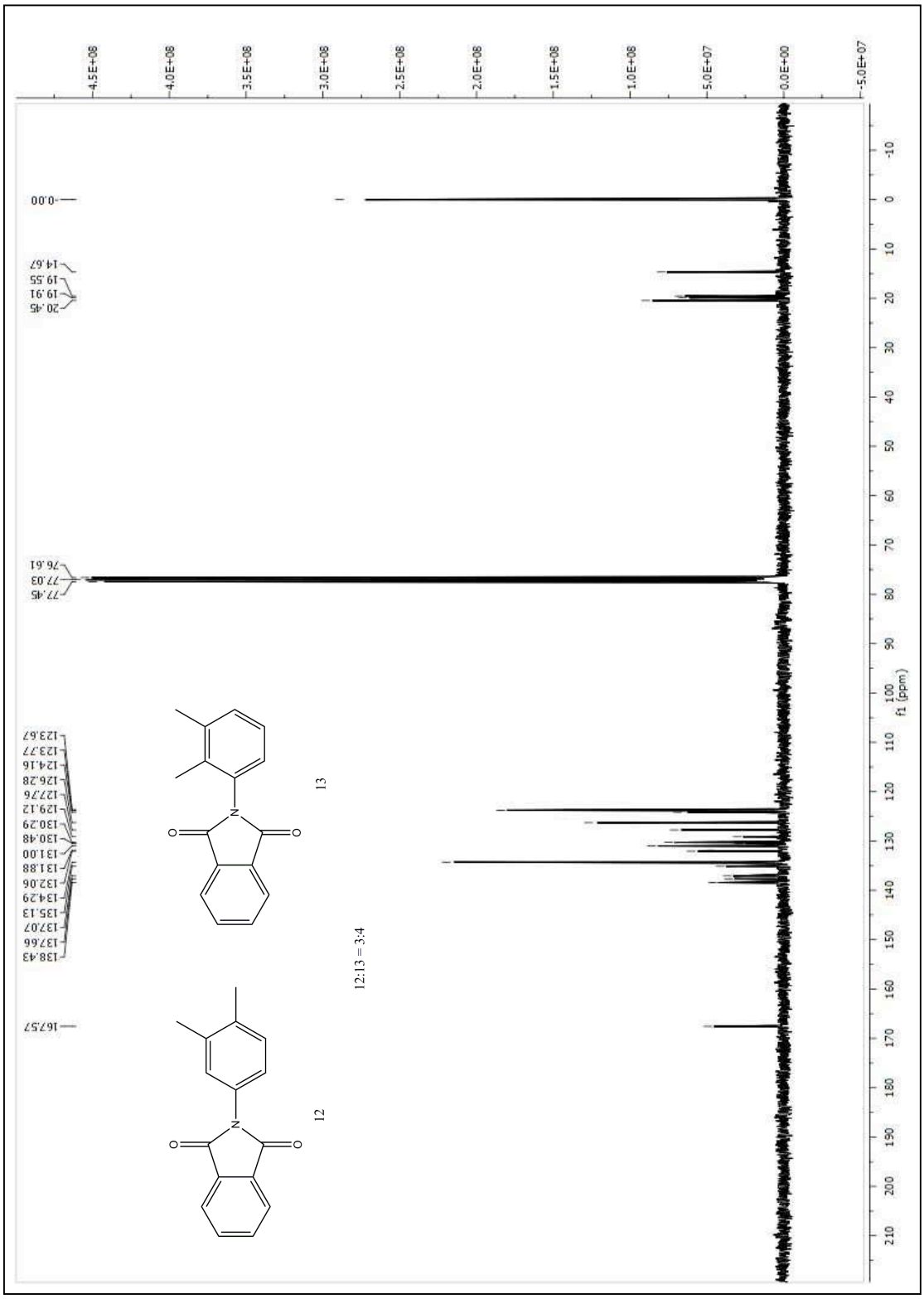
^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.08 (s, 3H), 2.31 (s, 5H), 2.35 (s, 3H), 7.23 – 7.28 (m, 7H), 7.76 – 7.81 (m, 4H), 7.93-7.98 (m, 4H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.67, 19.55, 19.91, 20.45, 123.67, 123.77, 124.16, 126.28, 127.76, 129.12, 130.29, 130.48, 131.00, 131.88, 132.06, 134.29, 135.13, 137.07, 137.66, 138.43, 167.57.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_9NO_2$ 251.09, observed 251.10 m/z.

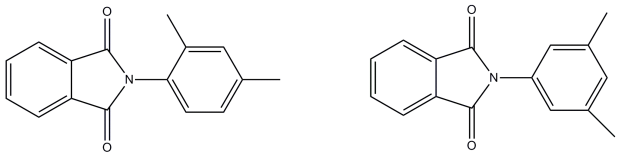


Spectrum 23. [1]H NMR of Compound **12** and **13**



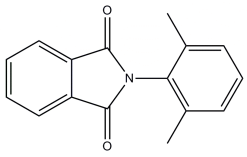
Spectrum 24. ^{13}C NMR of Compound **12** and **13**

Synthesis of 17, 18, 19



17

18



19

17:18:19 = 4:3:4

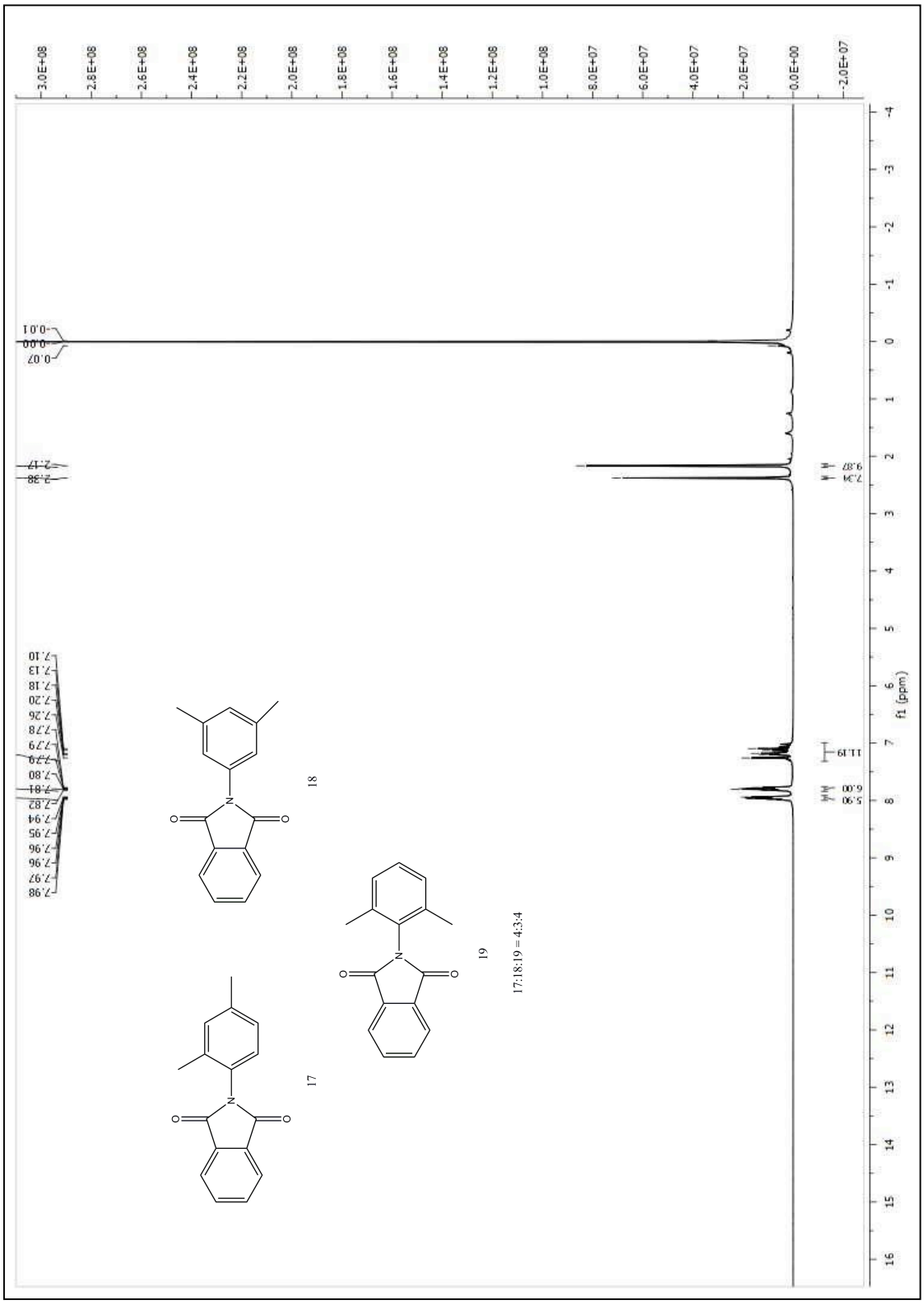
A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) in 4 mL of *m*-xylene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and crude product was purified by column chromatography to give a mixture of **17**, **18** and **19** (0.128 g, 75%, **17**:**18**:**19** = 4:3:4).

***R*$_f$ -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.1666.

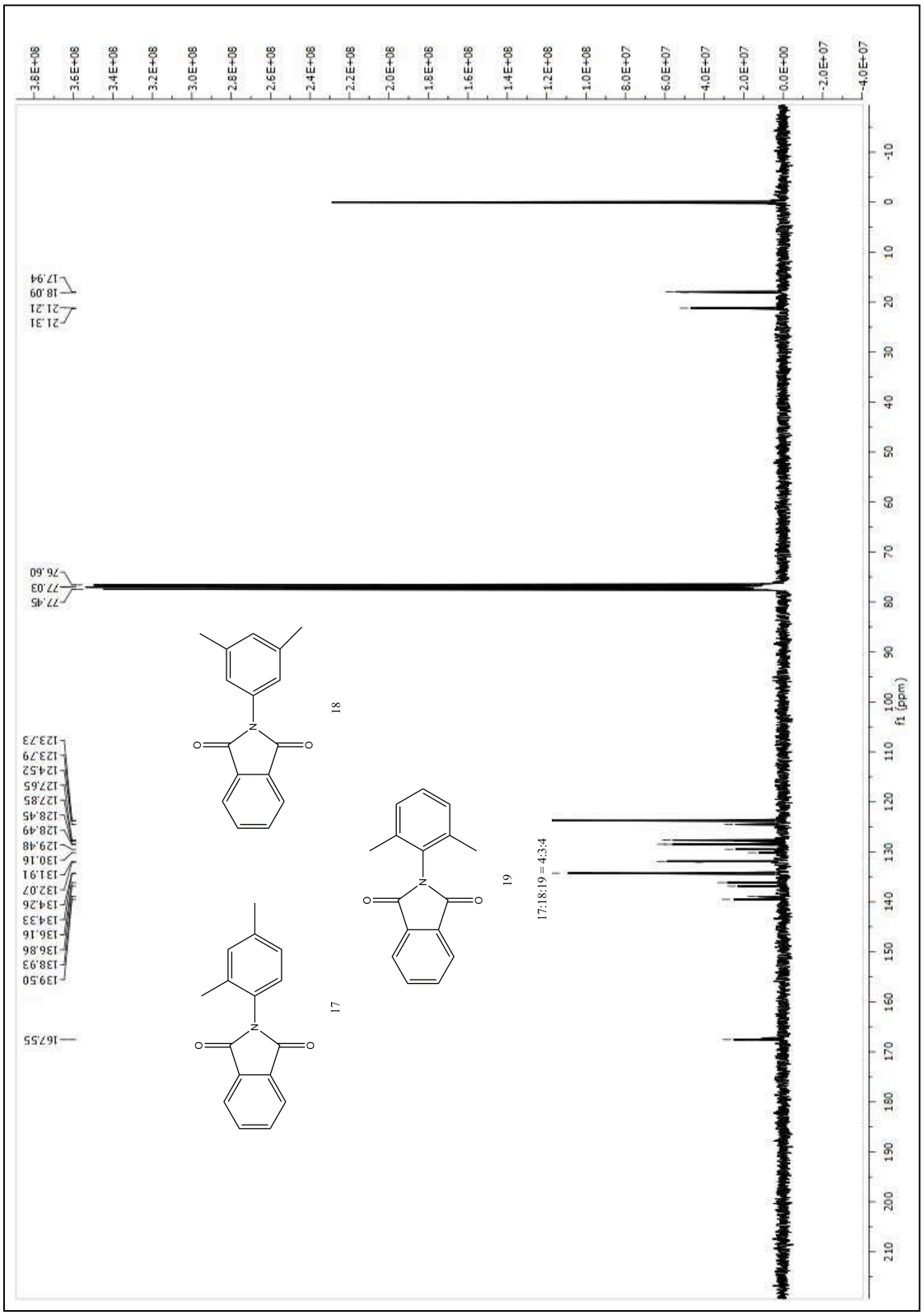
^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.17 (s, 9H), 2.38 (s, 7H), 7.32 – 6.99 (m, 11H), 7.76 – 7.84 (m, 6H), 7.92 – 8.00 (m, 6H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.94, 18.09, 21.21, 21.31, 123.73, 123.79, 124.52, 127.65, 127.85, 128.45, 128.49, 129.48, 130.16, 131.91, 132.07, 134.26, 134.33, 136.16, 136.86, 138.93, 139.50, 167.55.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_9NO_2$ 251.09, observed 251.10 m/z.

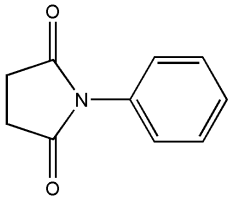


Spectrum 25. ^{1}H NMR of Compound **17**, **18**, **19**



Spectrum 26. ^{13}C NMR of Compound **17**, **18**, **19**

Synthesis of 1-phenylpyrrolidine-2,5-dione (20)



20

A magnetically stirred solution of succinimide (0.10 g, 1.009 mmol), iodobenzene diacetate (0.81 g, 2.522 mmol), in 4 mL of benzene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **20** (0.0982 g, 83 %). The NMR spectrum matched with that of previously published.[15]

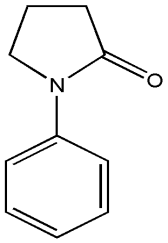
***R_f* -Value:** Hexane/Ethyl acetate (1:1 *v/v*) = 0.44.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.9 (s, 4H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.39-7.4 (m,1H), 7.49-7.5 (m,2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4, 126.4, 128.6, 129.2, 131.8, 176.2.

LRMS EI (m/z): [M+] calc'd for $C_{10}H_9NO_2$ 175.06, observed 175.10 m/z.

Synthesis of 1-phenylpyrrolidin-2-one (21)



21

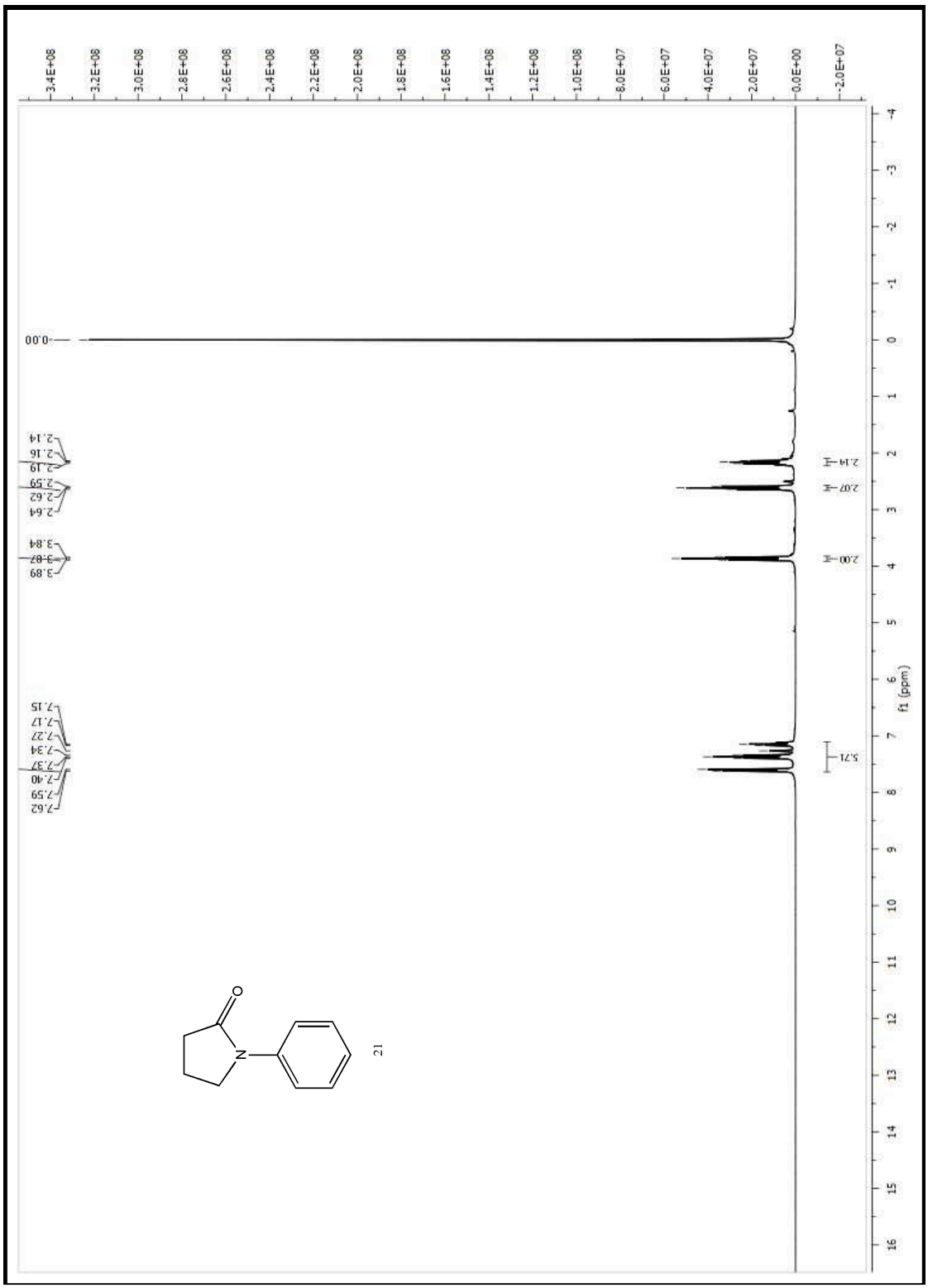
A magnetically stirred solution of 2-pyrolidinone (0.10 g, 1.1749 mmol), (Diacetoxyiodo) benzene (0.95 g, 2.937 mmol), in 4 mL of benzene was microwave heated at 145 ^{0}C for 3h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **21** 0.0303 g (16 %)

***R_f*-Value:** Hexane/Ethyl acetate (1:1 *v/v*) = 0.45.

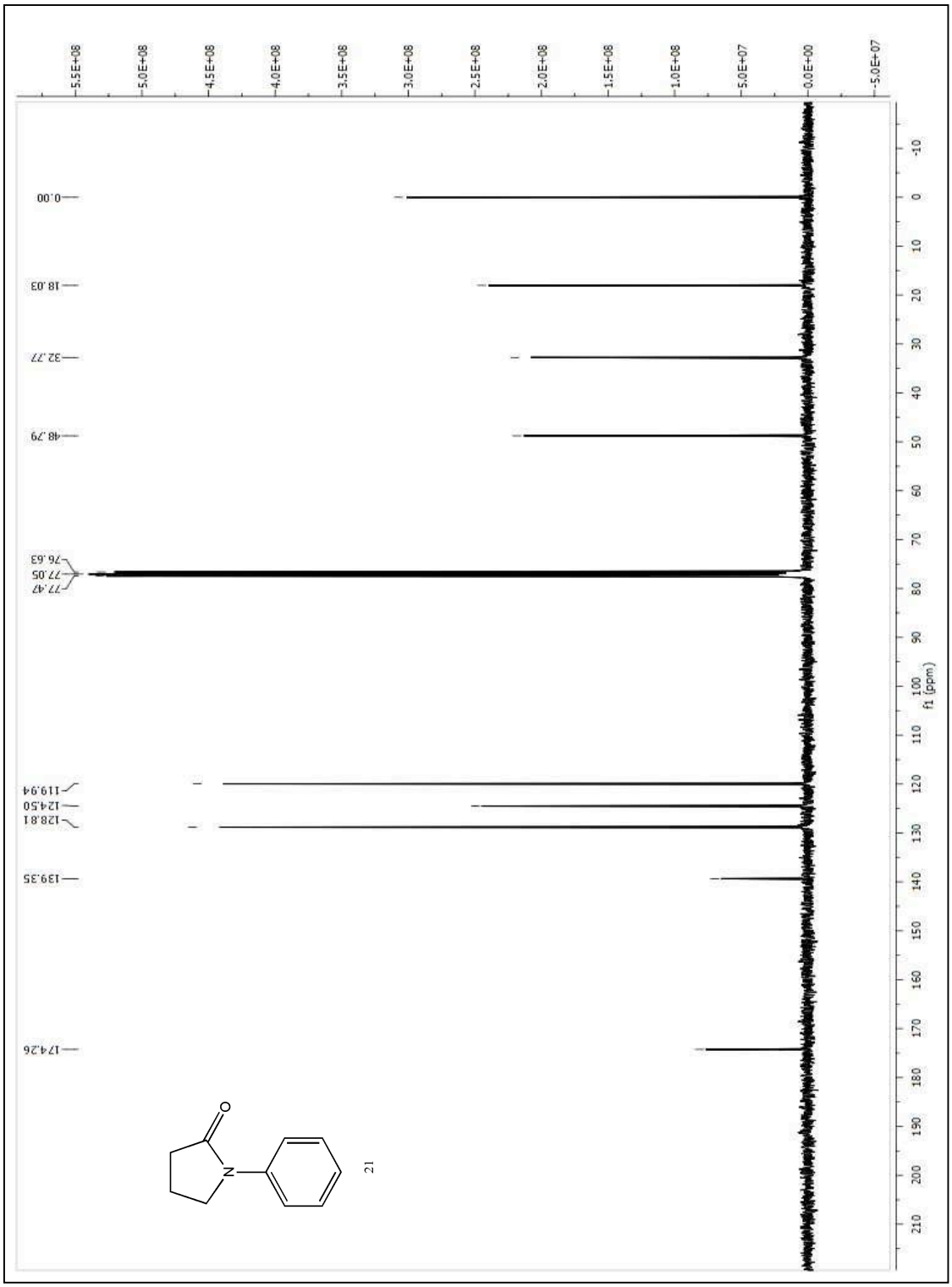
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16 (m, 2H), 2.61 (t, *J* = 15 Hz, 2H), 3.87 (t, *J* = 15 Hz, 2H), 7.15-7.62 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.03, 32.77, 48.79, 119.94, 124.50, 128.81, 139.35, 174.26.

LRMS EI (m/z): [M+] calc'd for $C_{10}H_{11}NO_2$, 161.08, observed 161.10 m/z.

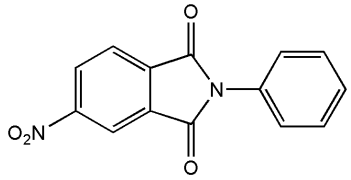


Spectrum 27. ^{1}H NMR of Compound **21**



Spectrum 28. ^{13}C NMR of Compound **21**

Synthesis of 5-nitro-2-phenylisoindoline-1, 3-dione (22)



22

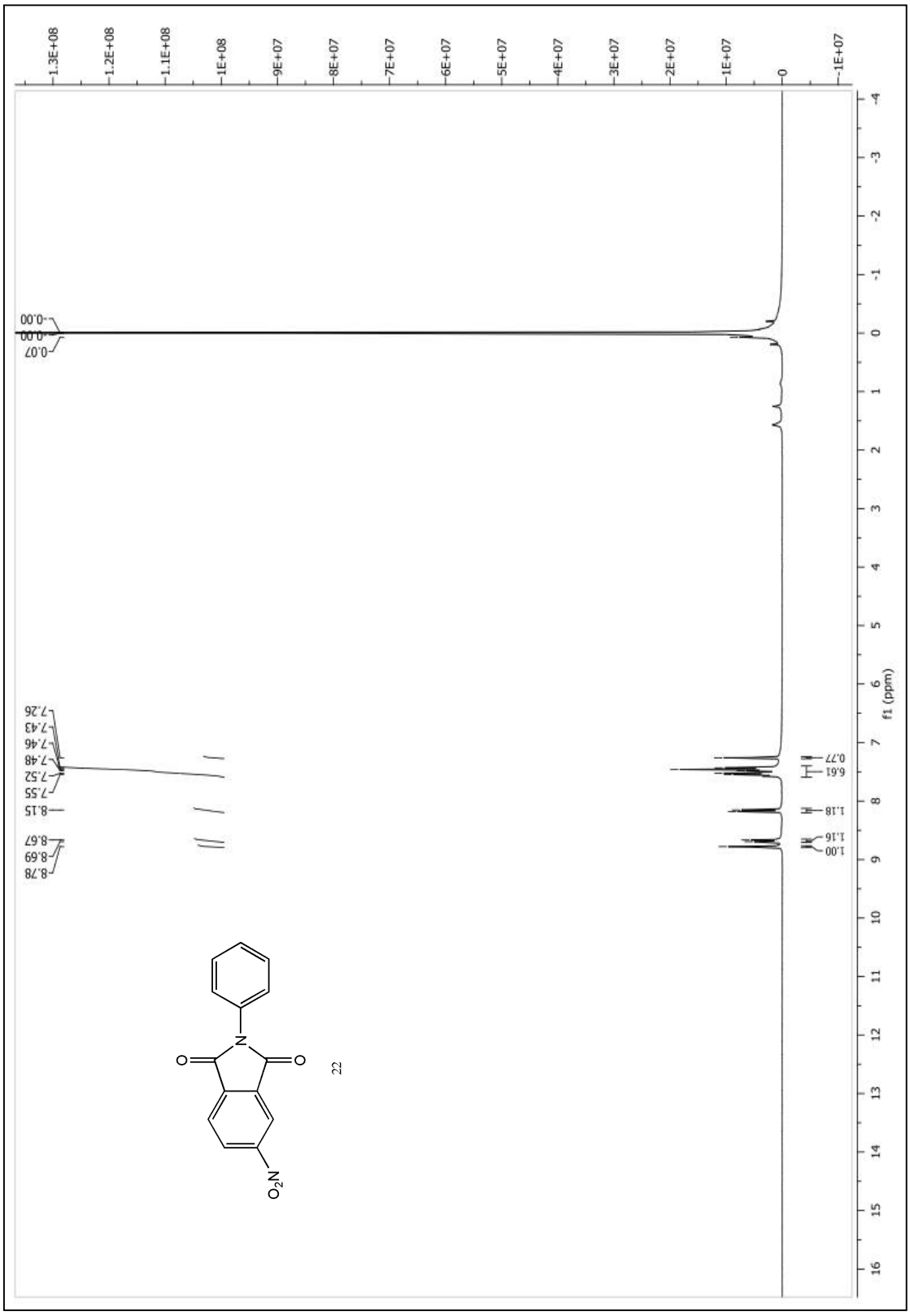
A magnetically stirred solution of 5-nitroisoindoline-1,3-dione (0.10 g, 0..5220 mmol), iodobenzene diacetate (0.42 g, 1.30 mmol), in 4 mL of benzene was microwave heated at 145 ^{0}C for 3h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **22** (0.0557 g, 40 %).

***R_f* -Value:** Hexane/Ethyl acetate (8:2 *v/v*) = 0.33.

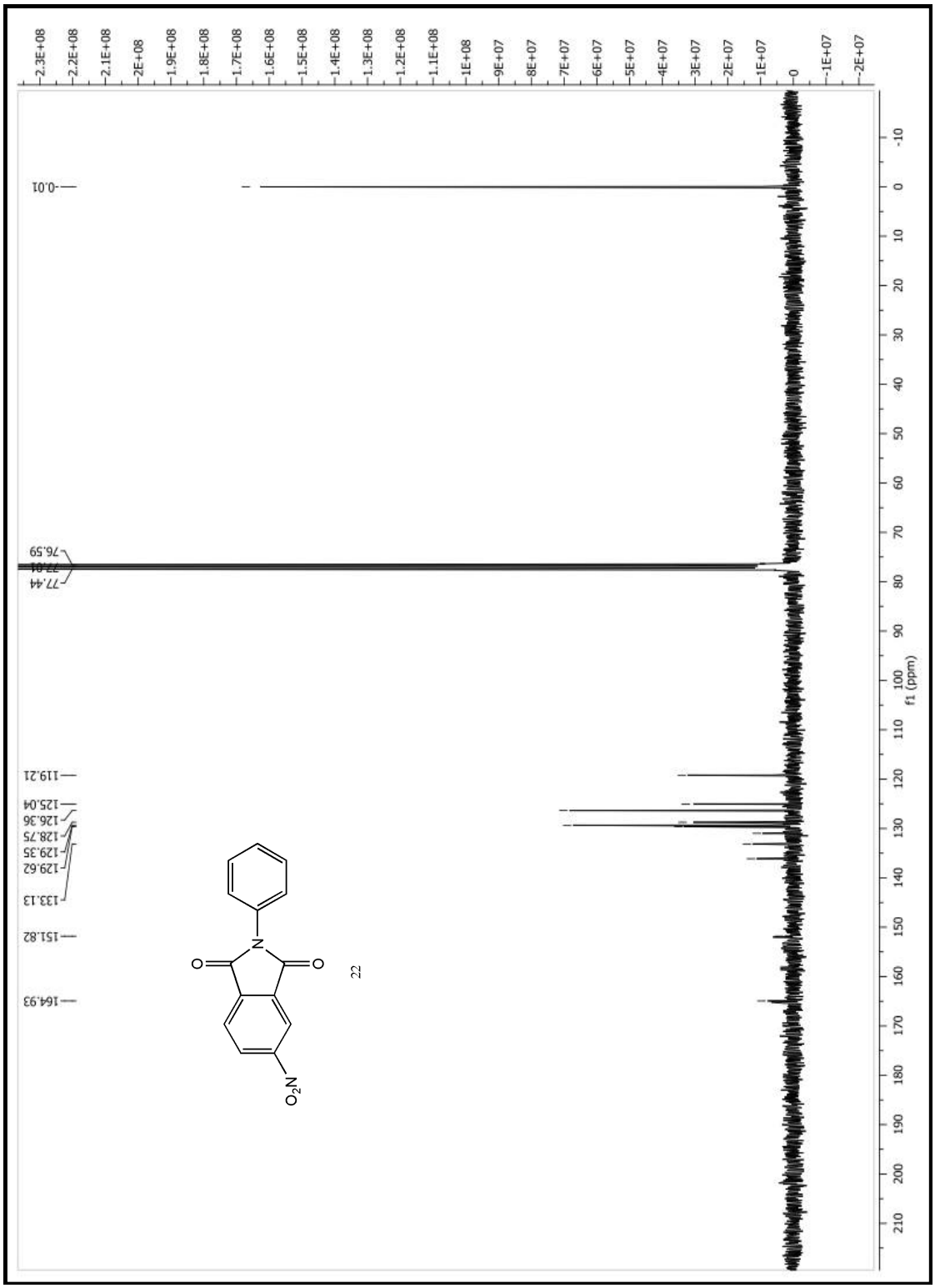
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26-7.55 (m, 5H), 8.17 (d, *J* = 9Hz, 1H), 8.68 (d, *J* = 6Hz, 1H), 8.78 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ= 119.21, 125.04, 126.36, 128.75, 129.35, 129.62, 133.13, 151.82, 164.93.

LRMS EI (m/z): [M+] calc'd for $C_{14}H_8N_2O_4$ 268.05, observed 268.0 m/z.

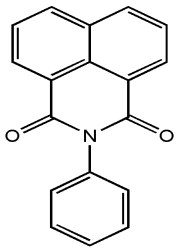


Spectrum 29. ^{1}H NMR of Compound **22**



Spectrum 30. ^{13}C NMR of Compound **22**

Synthesis of N-phenyl-1,8-naphthalimide (23)



23

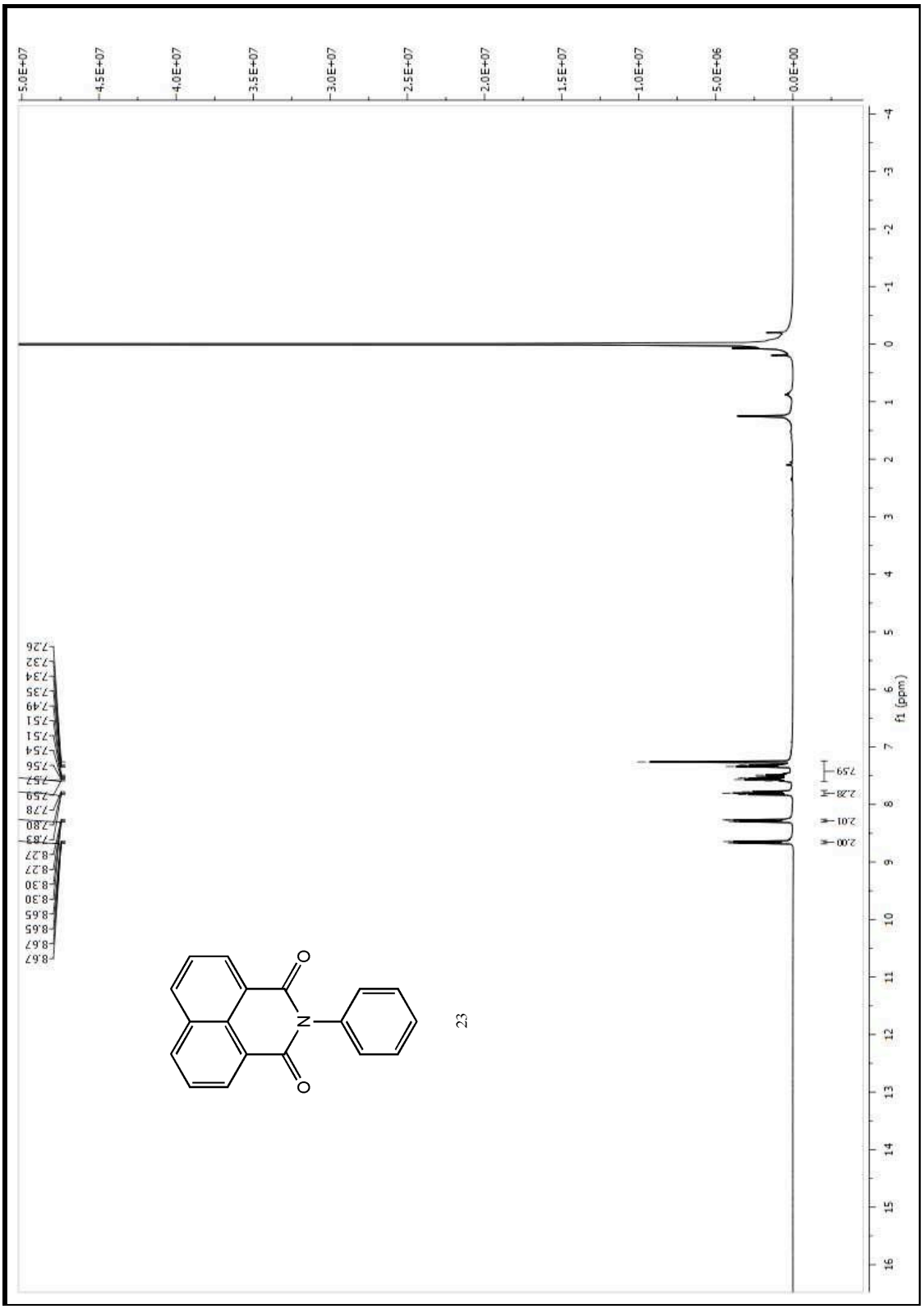
A magnetically stirred solution of 1,8- naphthalimide (0.10 g, 0.507 mmol), iodobenzene diacetate (0.41 g, 1.267 mmol), in 4 mL of benzene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **23** (0.0356 g, 27 %).

***R_f* -Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.34.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32-7.59 (m, 5H), 7.78-7.83 (m, 2H), 8.28 (d, *J* = 9 Hz, 2H), 8.66 (d, *J* = 6 Hz, 2H).

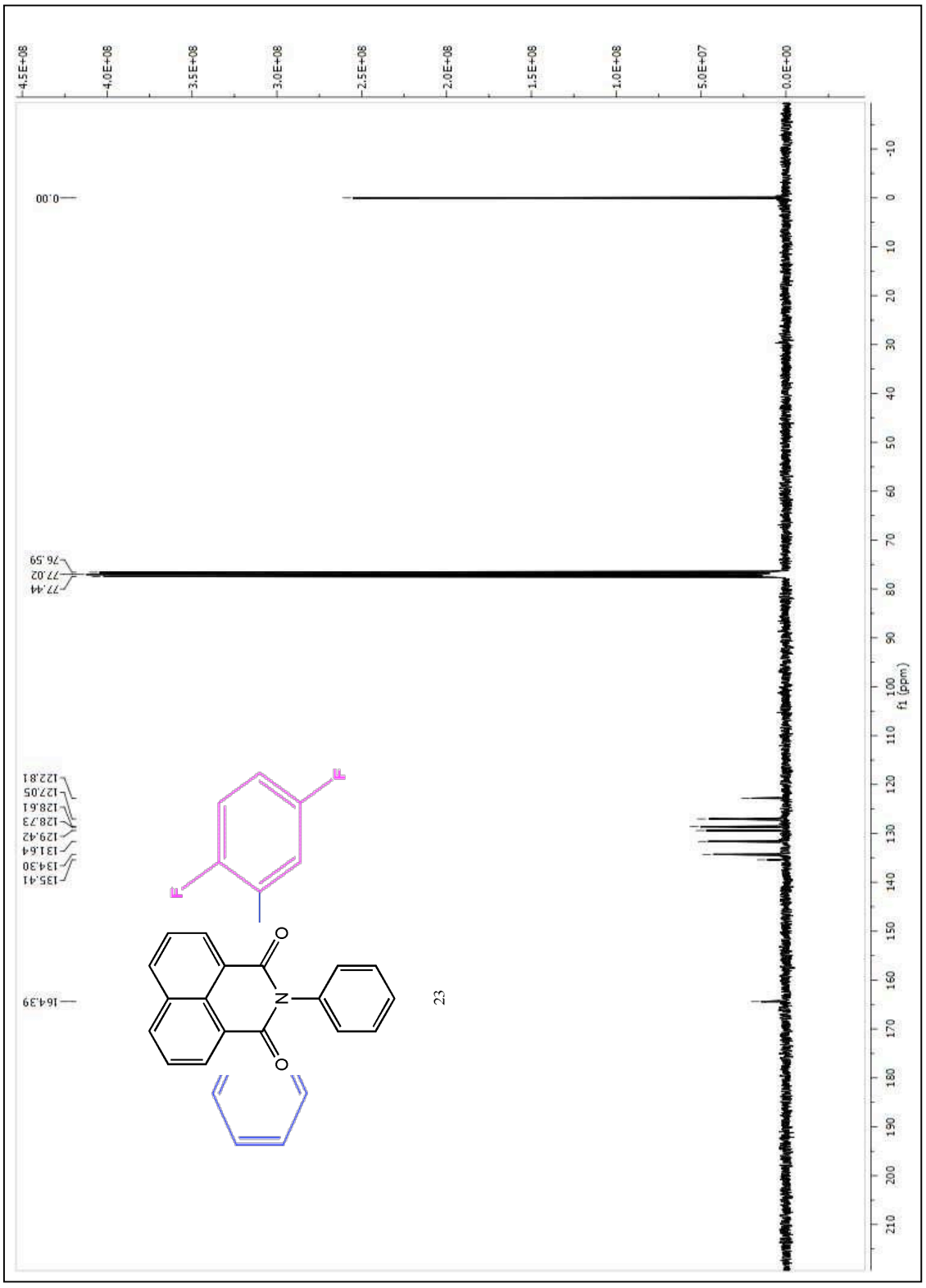
^{13}C NMR (75 MHz, $CDCl_3$): δ = 122.81, 127.05, 128.61, 128.73, 129.42, 131.64, 134.30, 135.41, 164.39.

LRMS EI (m/z): [M+] calc'd for $C_{18}H_{11}NO_2$, 273.08, observed 273.10 m/z.


5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
f1 (ppm)
2.00
2.01
2.28
7.59
8.67
8.67
8.65
8.65
8.30
8.30
8.27
8.27
7.83
7.80
7.78
7.59
7.57
7.56
7.54
7.51
7.51
7.49
7.35
7.34
7.32
7.26
O
N
O

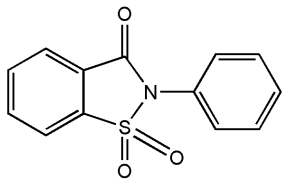
23

Spectrum 31. ^{1}H NMR of Compound **23**



Spectrum 32. ^{13}C NMR of Compound **23**

Synthesis of N-phenyl-1, 1-Dioxo-1, 2-benzothiazol-3-one (24)



24

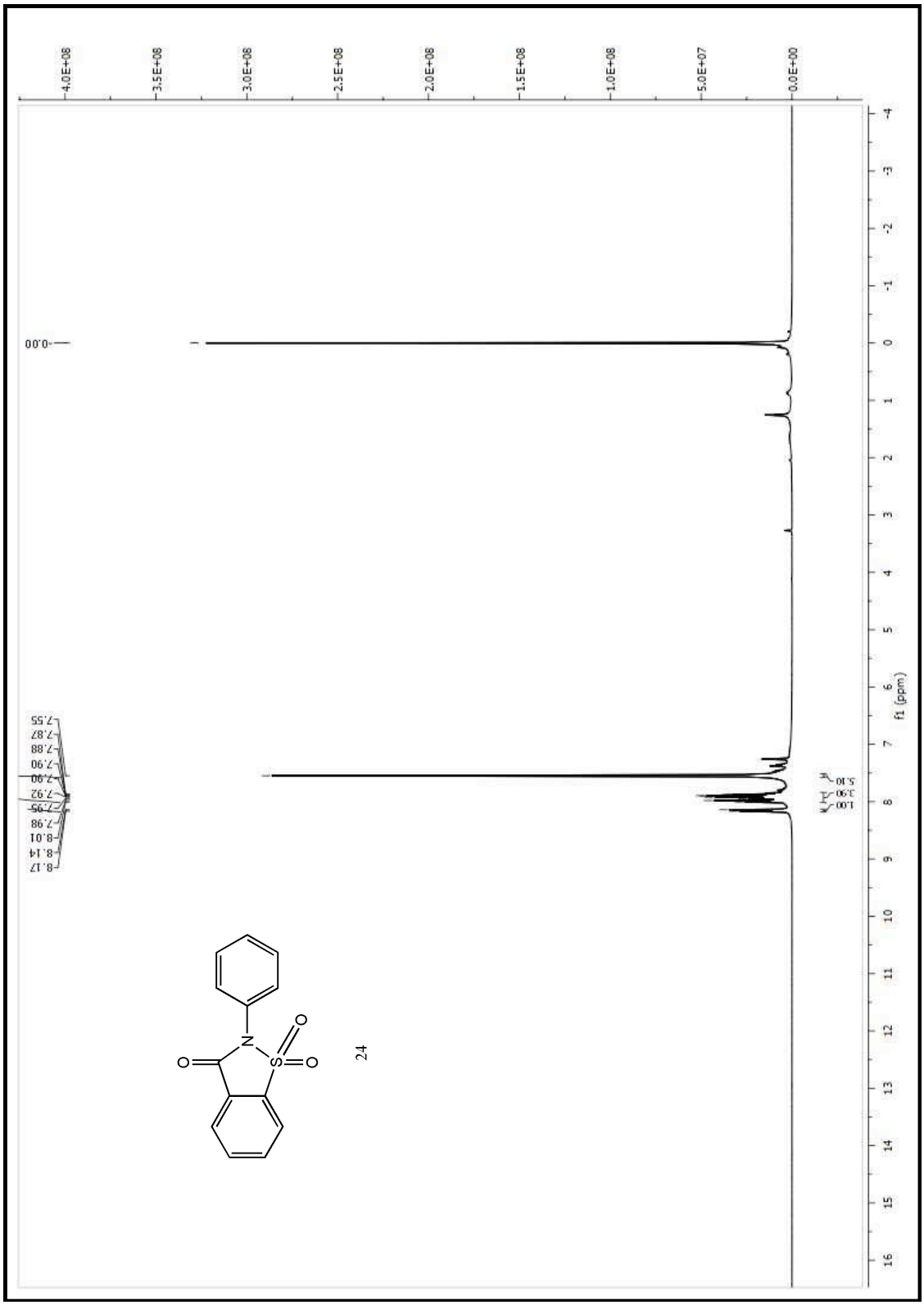
A magnetically stirred solution of 1,1-dioxo-1,2-benzothiazol-3-one (0.10 g, 0.546 mmol), iodobenzene diacetate (0.44 g, 1.365 mmol), in 4 mL of benzene was microwave heated at 145 ^{0}C for 3 h. The excess solvent from the mixture is removed at reduced pressure and the crude product was purified by column chromatography to give pure **24 (**0.037 g, 26 %).

***R_f* -Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.26.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 5H), 7.87-8.01(m, 3H), 8.15 (d, J = 9 Hz, 1H).

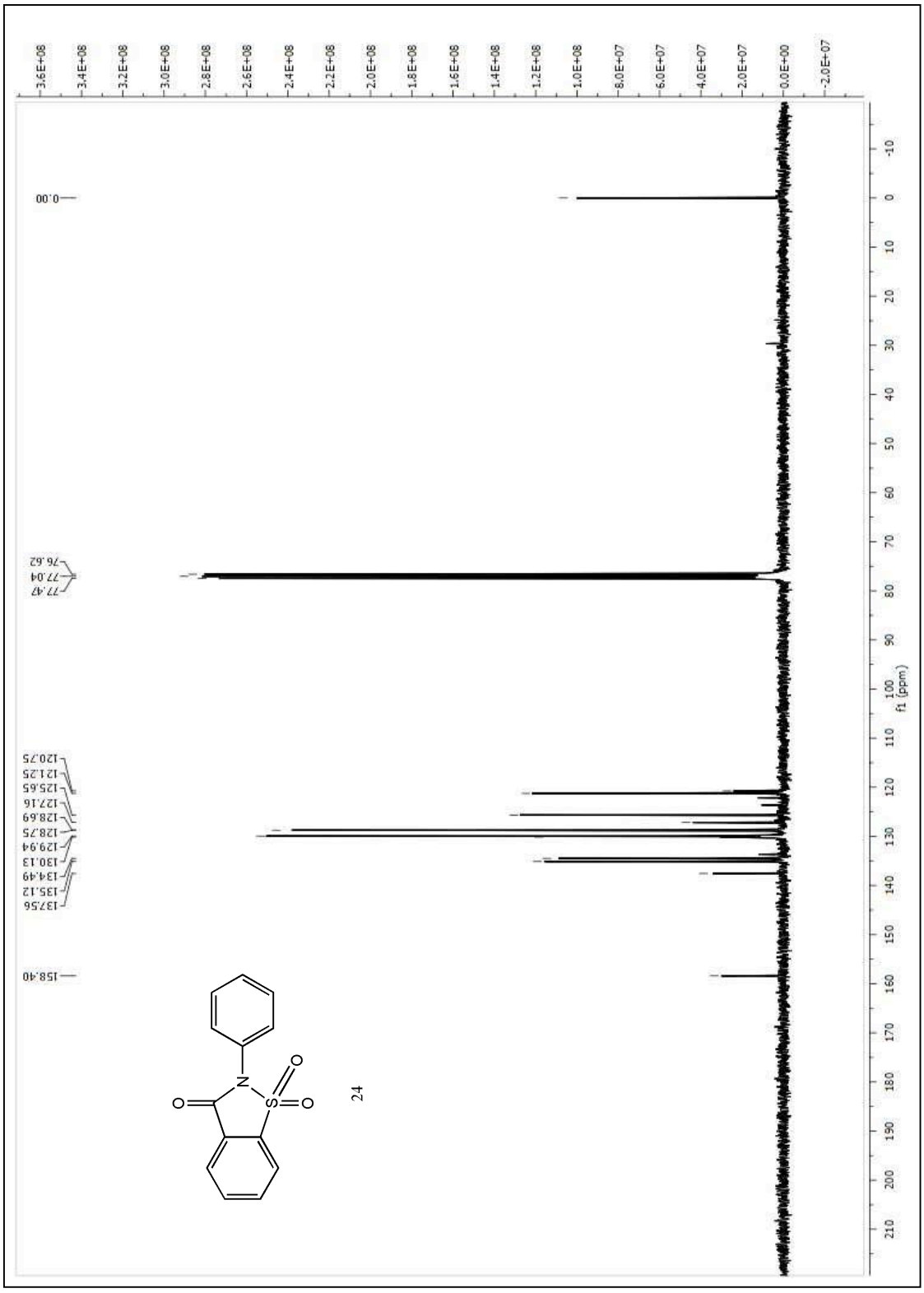
^{13}C NMR (75 MHz, $CDCl_3$): δ = 120.75, 121.25, 125.65, 127.16, 128.69, 128.75, 129.94, 130.13, 134.49, 135.12, 137.56, 158.40.

LRMS EI (m/z): [M+] calc'd for $C_{13}H_9NO_3S$, 259.03, observed 259.0 m/z.


4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
0.00
8.17
8.14
8.01
7.98
7.95
7.92
7.90
7.90
7.88
7.87
7.55
1.00
3.90
5.10
f1 (ppm)
O
N
S
O
O

24

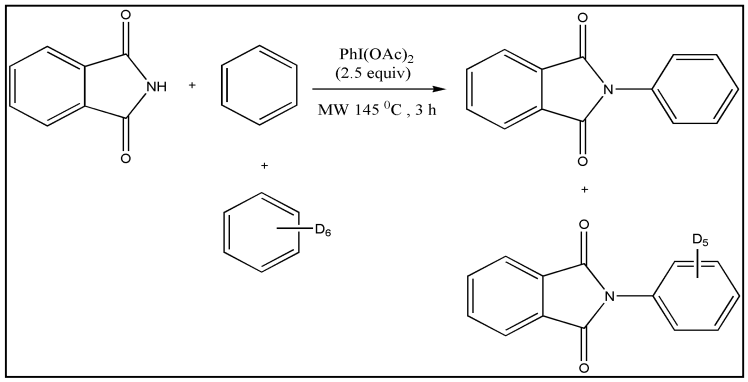
Spectrum 33. ^{1}H NMR of Compound **24**



Spectrum 34. ^{13}C NMR of Compound **24**

KIE experiments

1) Benzene and benzene-*d_6*

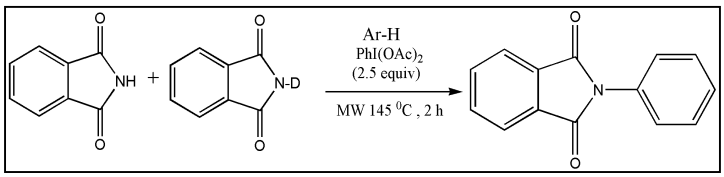


A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7mmol) with equimolar amounts of benzene (2 mL, 22.5 mmol) and benzene-*d_6* (2 mL, 22.5 mmol) was microwave heated at 145 ^{0}C for 3 h. The reaction was then cooled, and an aliquot was removed and analyzed by GC/MS.

GC/MS Conditions: J & W Scientific DB-1, capillary 25.0m x 200µm x 0.33µm, 1.3 mL/min, 40 ^{o}C, hold 0.50min, 12 ^{o}C/min to 320 ^{o}C, hold 6.0min.

$\mathbf{k_H/k_D}$ = 1.03

2) Phthalimide and phthalimide-*d*



A magnetically stirred equimolar mixture of phthalimide (0.05 g, 0.339 mmol) and phthalimide -*d* (0.05 g, 0.339 mmol), iodobenzene diacetate (0.27 g, 0.849 mmol) with

4 mL of benzene was microwave heated at 145 ^{0}C for 2 h. The reaction was then cooled, and an aliquot was removed and analyzed by GC/MS.

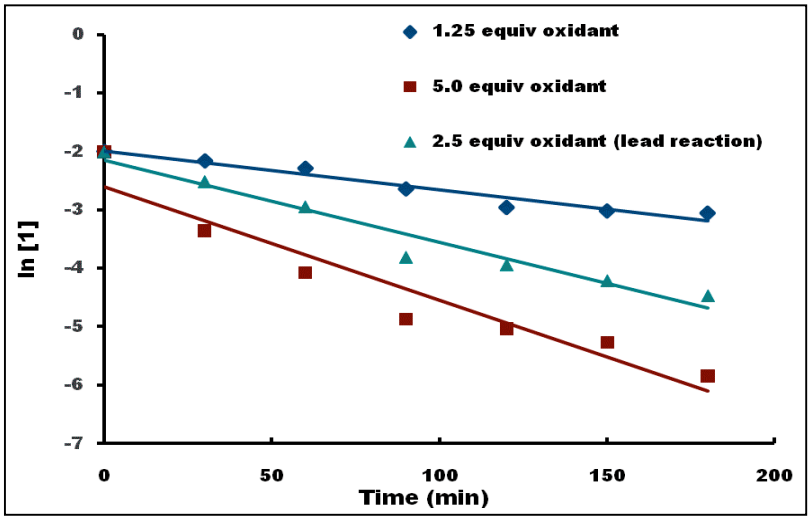
GC/MS Conditions: J & W Scientific DB-1, capillary 25.0 m x 200 µm x 0.33 µm, 1.3 mL/min, 40 ^{o}C, hold 0.50 min, 12 ^{o}C/min to 320 ^{o}C, hold 6.0 min.

$\mathbf{k_H/k_D}$ = 0.98

Kinetic experiments

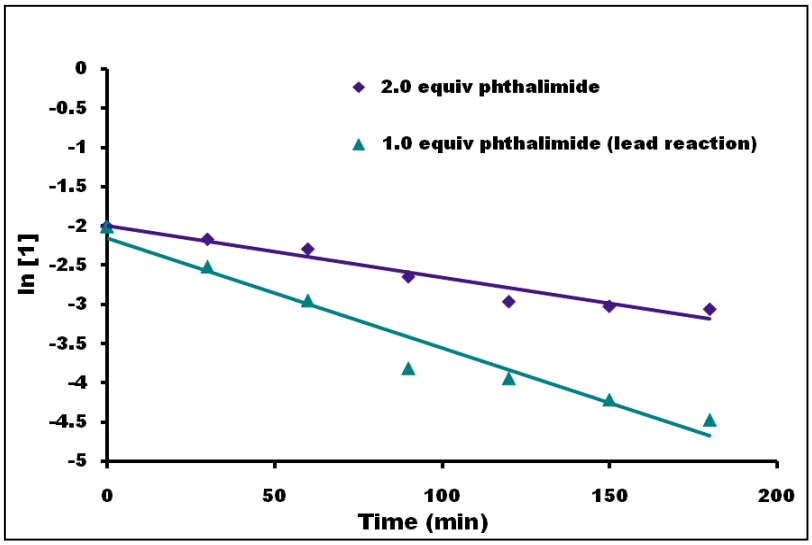
1) Order in oxidant

The order in the oxidant iodobenzene diacetate was determined by studying the conversion of starting material (**1**) with three different iodobenzene diacetate concentrations. A magnetically stirred solution of phathimide (0.10 g, 0.68 mmol), iodobenzene diacetate (0.85 mmol, 1.7 mmol or 3.4 mmol) in 4 mL of benzene was microwave heated at 145 ^{0}C for 3 h. The reaction was monitored over a time interval of 30 min. The conversion of starting material (**1**) from time t = 0 min to time t =180 min was calculated by GC-MS using dodecane as an internal standard. A log plot of concentration of (**1**) versus time gave a straight line indicating the first order dependence on oxidant.

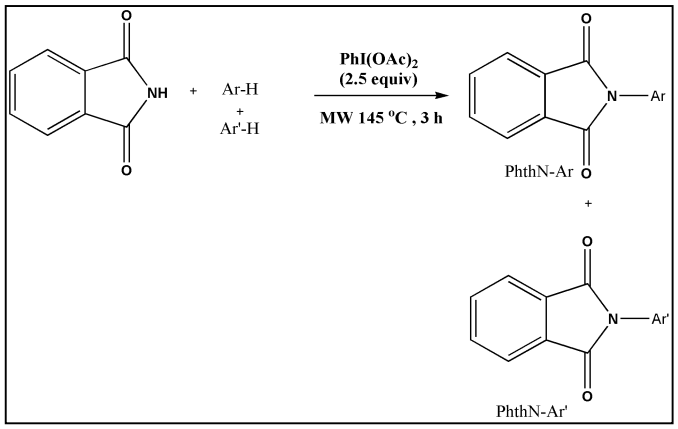


2) Order in Substrate

The order in the substrate (**1**) was determined by studying the conversion of starting material (**1**) with varying amounts of (diacetoxyiodo)benzene. A magnetically stirred solution of phthalimide (0.68 mmol or 1.4 mmol), (diacetoxyiodo)dbenzene (1.7mmol) in 4 mL of benzene was microwave heated at 145 ^{0}C for 3 h. The reaction was monitored over a time interval of 30 min. The conversion of starting material (**1**) from time t = 0 min to time t =180 min was calculated by GC/MS using dodecane as an internal standard. A log plot of concentration of **1** versus time gave a straight line indicating the first order dependence on substrate **1**.



Competition experiment

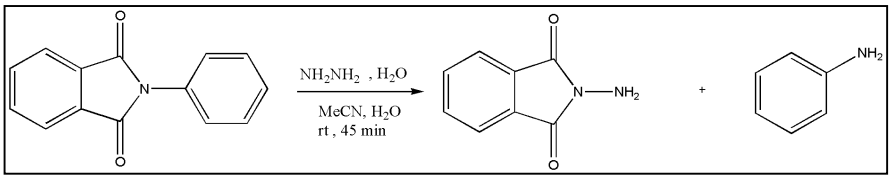


A magnetically stirred solution of phthalimide (0.10 g, 0.68mmol), iodobenzene diacetate (0.55 g, 1.7 mmol) with equimolar amounts of Ar-H (2.0 mL) and Ar'-H (2.0 mL,) was microwave heated at 145 ^{0}C for 3 h. The reaction was then cooled, and an aliquot was removed and analyzed by GC/MS.

Entry	Ar-H	Ar'-H	PhthN-Ar	PhthN-Ar'
1	*p*-xylene	benzene	71%	29%
2	*p*-xylene	*p*-difluoro-benzene	96%	4%
3	benzene	*p*-difluoro-benzene	86%	14%

The ratios of the products were determined by GC/MS.

Phthalimide Deprotection



N-Hydrazine hydrate (0.15 g, 4.5 mmol) and 3 mL of water was added to a solution of *N*-phenyl phthalimide (0.10 g, 0.45 mmol) in 5 mL acetonitrile. The mixture was stirred for 45 min at room temperature until TLC shows the complete conversion of *N*-phenylphthalimide. An aliquot was removed from the reaction mixture and analyzed by GC/MS.[17]

References

[1] For recent reviews describing oxidative C-C formation, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068-5083; (b)Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215; (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.

[2] For recent reviews describing C-N formation via nitreneoid intermediates, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417; (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

[3] For a partial review, see: ref. 1a, pp. 12-16.

[4] For recent examples of Cu and Pd-catalyzed aminations, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* 2005, *127*, 14560; (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.M. *J. Am. Chem. Soc.* **2006**, *128*, 9048; (c) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* 2008, *73*, 7603; (d) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew. Chem. Int. Ed.* 2008, *47*, 1115; (e) Jordan-Hore, J. A.; Johansson, C. C. C.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* 2008, *130*, 16184; (f) Miura, T.; Murakami, M. *Chem. Lett.* 2009, *38*, 328; (g) John, A.; Nicholas, K. M. *J. Org. Chem.* 2011, *76*, 4158; (h) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466; (i) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhan, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694; (j) Yoo, E.J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652.

[5] For a recent examples of a metal-free amination, see: (a) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5696; (b) Lamani, M.; Prabhu, K. R. Iodine-Catalyzed Amination of Benzoxazoles: A Metal-Free Route to 2-Aminobenzoxazoles under Mild Conditions. *J. Org. Chem.* **2011**, [Online early access]. DOI: 10.1021/jo201402a. PublishedOnline: Aug 25, 2011.

[6] (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607; (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178; (c) Cho, S. H. ; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127; (d) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899; (e) Wang, J.; Hou, J.-T.; Wen, J.; Zhang, J; Yu, X.-Q. *Chem. Commun.* **2011**, *47*, 3652.

[7] While preparing this manuscript, two communications were published that describe metal-free intermolecular C-H amination: (a) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 8605; (b) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382.

[8] For examples, see: (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172; (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137; (c) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331; (d) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676.

[9] (a) Campeau, L.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581; (b) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727.

[10] Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Hadjipavlou-Litina, D. *J. Org. Chem.* **2009**, *74*, 7315.

[11] (a) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919; (b) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417.

[12] Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

[13] Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627.

[14] Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 327.

[15] Xie, Y.-T.; Hou, R.-S.; Wang, H.-M.; Kang, I.-J.; Chen, L-C. *J. Chin. Chem. Soc.* **2009**, *56*, 839-842.

[16] Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Biorg. Med. Chem.*, **2004**, *12*, 327-336.

[17] Arifn, A.; Khan, M. N.; Lan, L. C.; May, F. Y.; Yun, C. S. *Synthetic Commun.* **2004**, *34*, 4439-4445.

MANUSCRIPT 2

Manuscript is in preparation

I(III)-Mediated Regioselective C-H Bond Amination of 2-Arylpyridine Derivatives

Abhishek A. Kantak, Louis Marchetti and Brenton DeBoef*

Corresponding author:

Prof. Brenton Deboef

Department of Chemistry,

University of Rhode Island,

Kingston, Rhode Island 02881.

bdeboef@chm.uri.edu

Manuscript 2

I(III)-Mediated Regioselective C-H Bond Amination of 2-Arylpyridine Derivatives

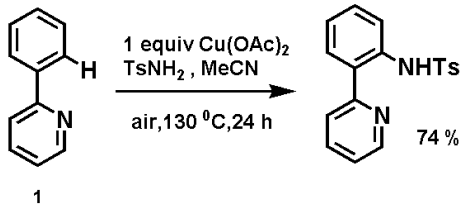
Abstract

A new approach for the direct amination of 2-pheynlpyridine derivatives using bis phthalimide hypervalent iodane and copper triflate was developed. A series of different 2-pheynlpyridine derivatives are shown to undergo amination with up to 88 % yield. Mechanistic investigations indicate that the reaction proceeds via an intramolecular phthalimide anion transfer from a Cu(I) co-ordinated intermediate on an aromatic cation radical generated by a single electron transfer from the aryl ring of 2-aryl pyridine substrate.

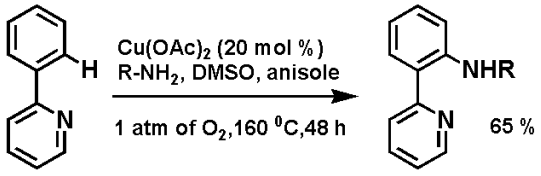
Introduction

Over the past decade new advances in transition metal catalyzed C-H functionalization have provided efficient strategies for the construction of C-C and C-heteroatom bonds.[1] Contemporary research in the field of C-H activation has devoted an extensive amount of work to the development of novel methodologies for the construction of C-N bonds.C-N bonds are ubiquitous in pharmaceuticals and other high value, biologically active molecules. Being a new and relatively unexplored field, synthetic routes for direct amination of arenes are rare, and researchers are only now beginning to scratch the surface.[2] Recent literature examples in the field involve the addition of nitrene intermediates into allylic and benzylic C-H bonds.[3] Moreover, most of the examples of intermolecular directed aminations involve some form of palladium

catalysis.[4] Recently, quests to discover highly efficient, economical, and environmentally benign methods for C-N bond formation have led to advances in copper mediated and copper catalyzed C-H amination.[5] Yu and coworkers reported a C-N bond formation process using stoichiometric copper acetate (Eq 1). [2b]Similarly, Nicholas and associates reported a copper catalyzed C-N bond formation process; however this required the incorporation of additives and extremely harsh conditions (Eq 2).[6] Likewise, Li reported a copper catalyzed direct amidation of 2-phenylpyridine **(1)** with acetanilide through a cross dehydrogenative coupling (CDC) process.[7]

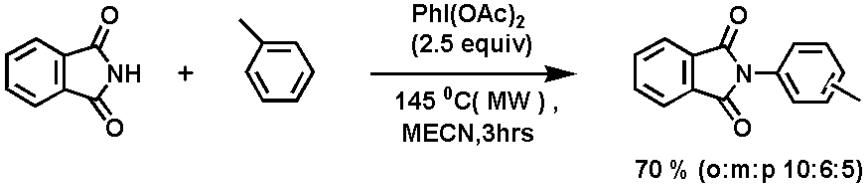


1 (1)



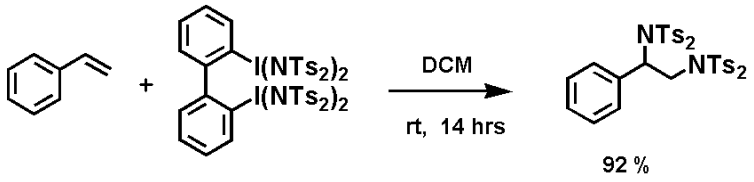
1 (2)

Recently, we and others have reported metal free intermolecular oxidative C-N bond formation processes. Though these reactions provide high yield of amination products, the regioselevtivity appears to be directed by electronic factors (Eq 3).[2d, 2e, 8] In addition , Hartwig, reported a palladium catalyzed amination reaction to sterically control the regioselectivity.[9]



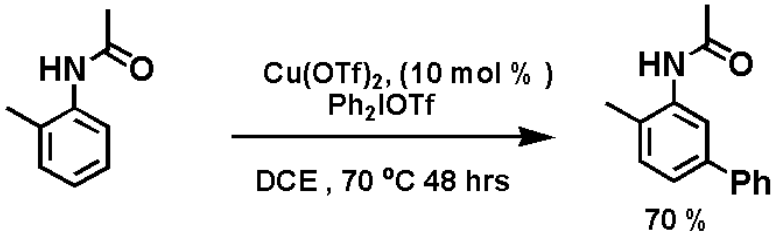
(3)

Our initial approach to aminate 2-phenylpyridine substrates using our reported I(III) mediated metal free oxidative amination process were not successful.[2d] Recently, Muniz has reported a variety of novel hypervalent iodine (III) reagent for metal free intermolecular allyic amination and di-aminiation of alkenes (Eq 4).[10]



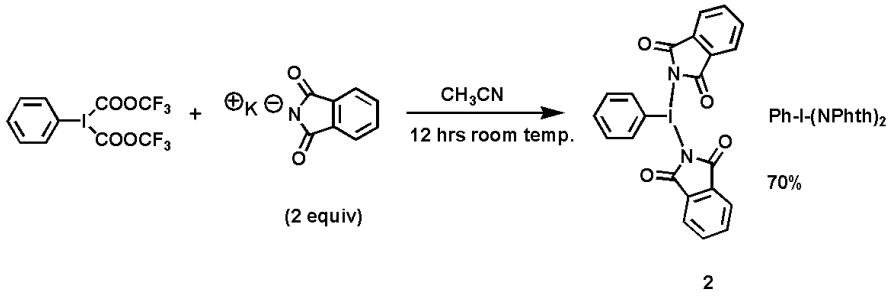
(4)

Furthermore, diaryl iodonium salts have been used by the Sanford group to acetoxylate C-H bonds in presence of catalytic palladium;[11] and by the Gaunt group to arylate C-H bonds in the presence of catalytic copper (Eq 5).[12]



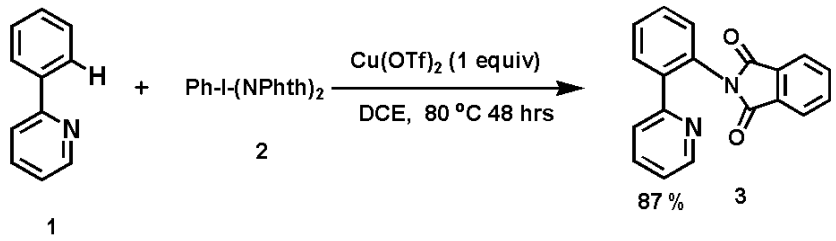
(5)

As a result, we synthesized a phenyliodine (III)bis[phthalimidate] containing iodine-nitrogen (I-N) bond (Eq 6).[13]



(6)

This new Iodane **(2)** was subjected to both metal-free and catalytic palladium/copper conditions with 2-arylpyridine substrates. We hypothesized that 1) Iodane could be used to generate electrophilic amine moieties which could react non-selectively with arenes and 2) regioselectivity can be achieved by using selective metalation of specific C_{aryl}-H bonds using a transition metal catalyst. Our results proved fruitful, and lead us to conclude that a metal was necessary to facilitate C-N bond formation. Herein, we report a novel method to selectively aminate 2-phenyl pyridine substrate using the Iodane and copper triflate (Eq 7).

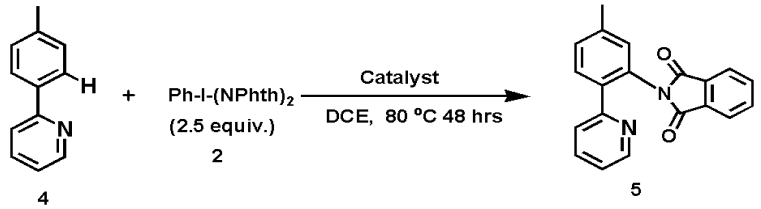


(7)

Results and Discussion

Our initial investigation began by heating a solution of phthalimide, 2-phenylpyridine **(1)**, and iodobenzene diacetate (PIDA) in acetonitrile at elevated temperatures in a microwave. However, we determined that PIDA was not able to assist the amination of pyridine derivative. As a result, the incorporation of catalytic palladium, along with PIDA or iodobenzene bis(trifluoroacetate) (PIFA), was also explored. While progress was made and amination was observed, this methodology still did not facilitate amination with acceptable yields (See SI, Table 4).

Thus, we concluded that either a different catalyst or different hypervalent iodine reagents, which are serving as our oxidant, were required. These theories lead to the construction of the bis-phthalimide iodane **(2)**, to replace our original nitrogen source, phthalimide. A control experiment was conducted where this iodane, along with with 2-phenyl pyridine **(1)**, was heated without any catalyst or oxidant. This experiment did not yield the desired aminated product **(3)**. The next step was to use either an oxidant or metal catalyst to achieve the required amination. Initial experiments had shown that oxidants like PIDA and PIFA had no effect on the amination reaction.



4 5

Entry	Catalyst (equiv.)	Yield (%)[c]
1	No catalyst	0
2	copper(II)triflate (0.25)	47[b]
3	copper(II)triflate (1)	71[b]
4	copper(II)triflate (1)	88[b]
5	copper(II)fluoride (1)	5
6	copper(II)acetate (1)	12
7	copper(I)chloride (1)	6
8	copper(II)chloride (1)	5
9	copper(I)bromide (1)	9
10	copper(II)bromide (1)	5
11	copper(I)sulfate (1)	5
12	Copper(II)nitrate (1)	5
13	copper(I)cyanide (1)	5

Table 1. Discovery of the Regioselective Amination of 2-arylpyridine derivatives.[a]

[a] General reaction conditions: **4** (0.146 mmol), **2** (0.365 mmol), catalyst (0.25-1 equiv), DCE = dichloroethane (4ml), heated in a vial in an oil bath for 48 hrs. [b] Yield of isolated products after column chromatography. [c] GC yield calculated using calibration curve method..

As a result, we elected to screen metal additives and discovered that copper (II) triflate showed higher amounts of amination products when compared to the previously successful experiment with palladium acetate. It is worth noting that freshly prepared iodane exhibited higher yields in comparison to salts left exposed to atmospheric conditions. We theorize this is a result of atmospheric moisture hydrolyzing the iodane **(2)**. Low equivalents of copper triflate, reduced reaction time, and decreasing the temperature also showed a reduction in reaction yield. (See SI, Table 4).

Encouraged by our initial screening with various amounts of copper triflate, we further explored the potential of Cu(I)/(II) catalysts to determine if higher conversions of arene substrates could be obtained. Dichloroethane was determined to be the preferred solvent, and copper acetate and copper chloride provided the aminated product along with acetylated and chlorinated byproducts of 2-arylpyridine substrate **(4)** (Table 1, entries 6,7). This was observed by GC/MS. When determining the stoichiometric necessity for the iodane an interesting pattern was observed. Since the salt acts as both our nitrogen source as well as oxidant, it has to be used in excess as reactions ran with equimolar quantities showed lower yields (See SI, Table 1). Optimized conditions required heating the iodane **(2)**, 2-arylpyridine substrate **(4)** and 1 eq. (relative to the **4**) of copper triflate in dicholoethane at 80 ^{0}C for 48 hrs on a hotplate. Amination was exclusively observed at the ortho position, relative to the pyridine substituent to yield **(5)** and was confirmed via COSY NMR.

Substrate scope

Table 2 shows a variety of 2-phenyl pyridine substrates that could be aminated using our novel reaction conditions. Substrates with electron withdrawing functional groups **(9-11)** exhibited diminished yields in amination when compared to substrates with electron rich groups. First, substrates containing different phenyl-substituted groups were screened. 2–toylpyridine **(5)** showed the highest yield as compared to the methoxy derivative **(7)**.

A chlorinated derivative **(10)** showed a substantially lower yield as compared to its competitive halogen counterpart, fluorine **(9)**. The aminated product was also observed when the aldehyde derivate **(11)** was subjected to our reaction conditions; albeit at reduced yields. This is a promising result as aldehydes can be easily converted into a carboxylic acid and can be used to obtain the carboxy aminated product. Substitution on the pyridine side of the substrate also provided the required products in moderate to high yields **(12-14)**. Additionally, the process also works with a bis-saccharin iodane, to yield the expected aminated product **(15)**.

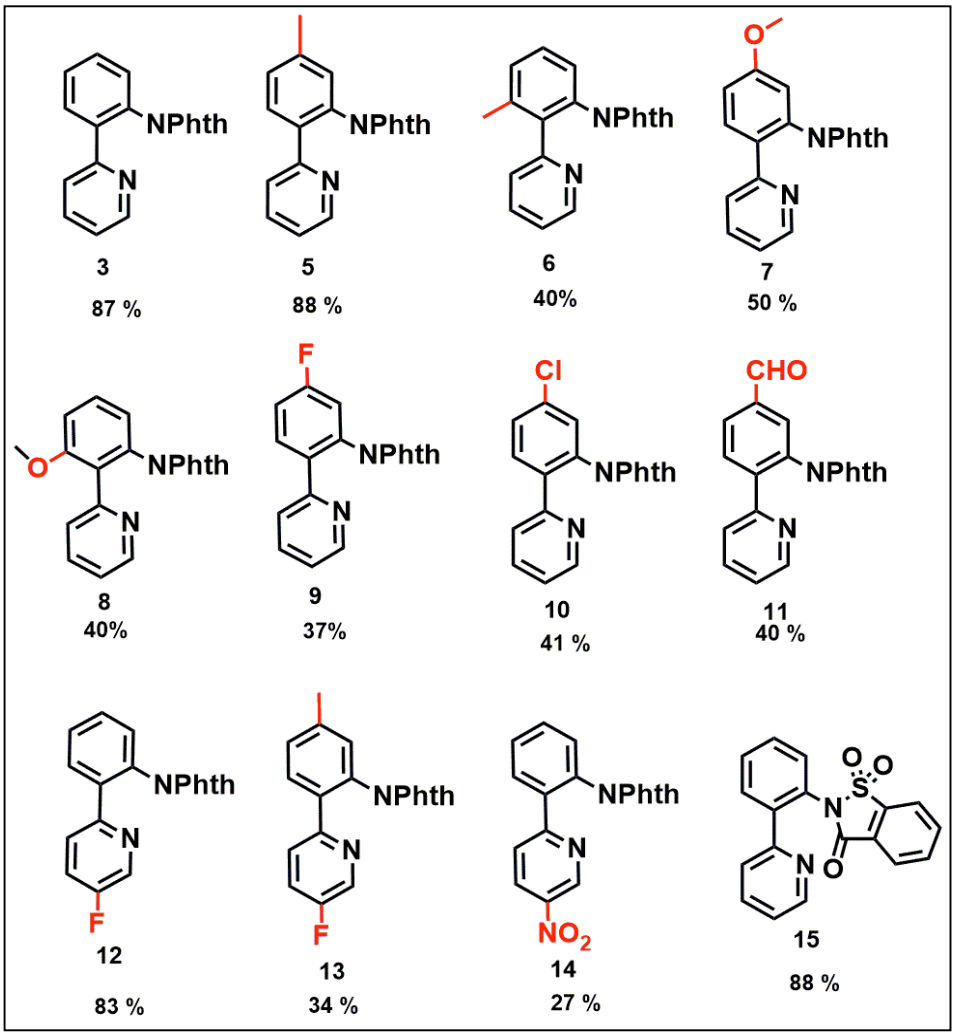
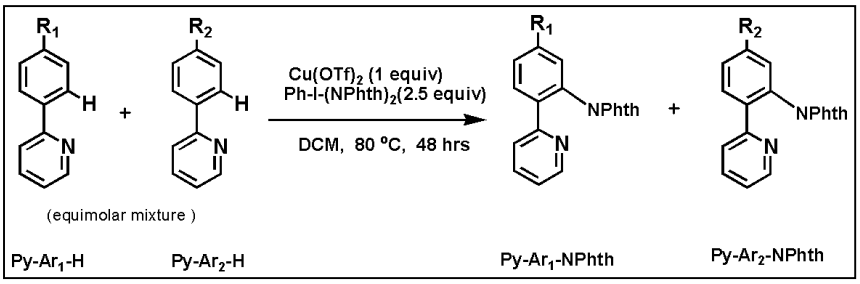


Table 2. Substrate scope of the Regioselective Amination of 2-arylpyridine derivatives.[a]

[a] General reaction conditions: 2-arylpyridine substrate (0.146 mmol), **2** (0.365 mmol), $Cu(OTf)_2$ (0.146 mmol), DCE = dichloroethane (4ml), heated in a vial in an oil bath for 48 hrs.

Competition and kinetic studies

To elucidate the mechanism of this novel reaction, competition studies were conducted using a mixture of equimolar amounts of two different pyridine substrates in the lead reaction. In most of the cases, amination of electron rich pyridine substrates was more favored over electron poor pyridine substrates.

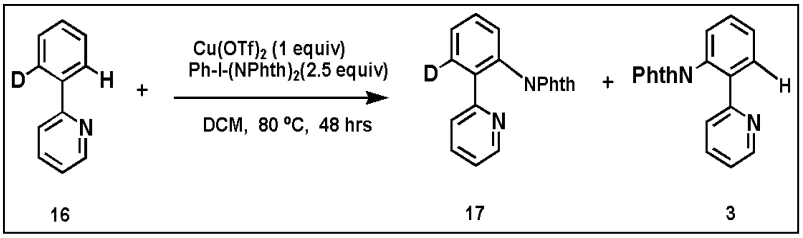


	Py-Ar$_1$-H **R$_1$**	**Py-Ar$_2$-H** **R$_2$**	**Py-Ar$_1$-NPhth (%)[a]**	**Py-Ar$_2$-NPhth (%)[a]**
1	H	Me	42	58
2	H	F	92	8
3	Me	F	94	6

Table 3. Competition Reactions.

[a] Mole fractions determined by GC/MS

Kinetic Isotope Effect

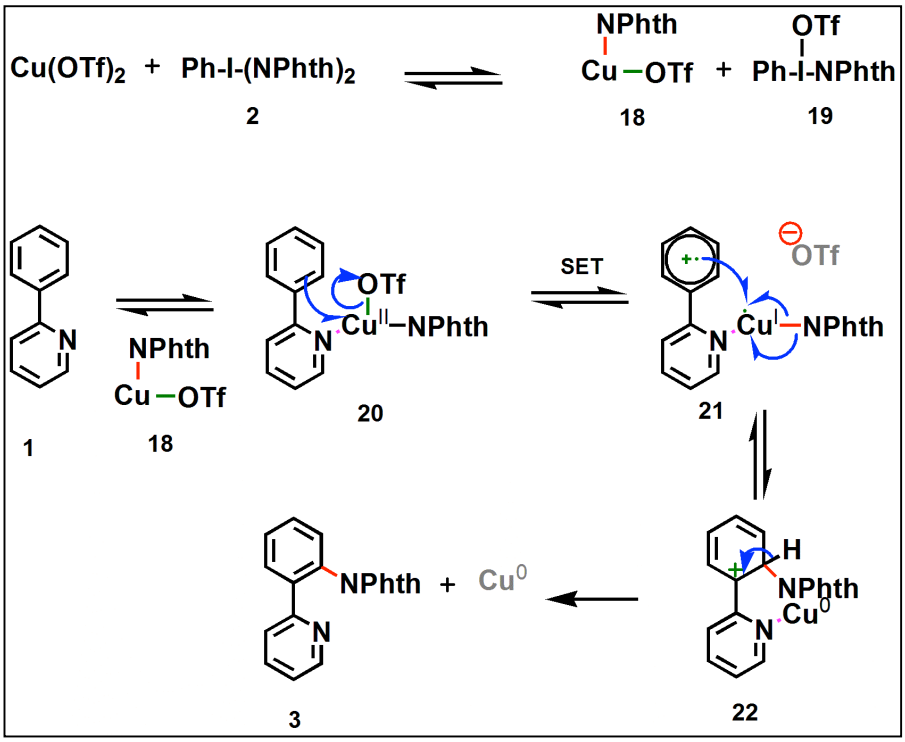


Scheme 1. Kinetic Isotope Effect.

The kinetic isotope effect was also studied using an intramolecular competition between a C-H bond and C-D bond in 2-phenyl pyridine. An observed KIE of 1.15 shows that C-H bond cleavage is not involved in the rate determining step of the reaction.

Proposed mechanism

A number of insights were obtained from the experiments carried out for determination of the reaction mechanism. The deuterated substrate **(16)** did not show any isotope effect. This rules out the possibility of copper catalyzed fuctionalization reactions, wherein significant isotope effects are usually observed. Thus we propose a radical cation pathway (Scheme 2) to explain the data obtained from our mechanistic studies.



Scheme 2. Proposed Mechanism for the Regioselective Amination.

Copper triflate reacts with the iodane **(2)** to generate **(18)** and **(19)**. We have been successful to isolate and confirm **(19)** by NMR and GC/MS (see SI). Thus, we propose that **(18)** reacts with 2-pheynlpyridine **(1)** to generate the Cu(II) co-ordinated to pyridine intermediate **(20)**. A single electron transfer (SET) from the aryl ring to the co-ordinated Cu(II) generates the radical cation intermediate **(21)**. Homolytic Cleavage of Cu-N bond and subsequent intramolecular anion transfer from the Cu (I) intermediate generates the ortho-aminated product **(3)**. Competition studies show that the reaction is much favored by an electron donating group on the aryl ring as compared to an electron withdrawing group on the aryl ring. Thus a SET from the aryl

ring with electron donating group will be much faster than that from an aryl ring with electron withdrawing group. Thus SET step has to be the rate limiting step in this reaction.

Conclusion

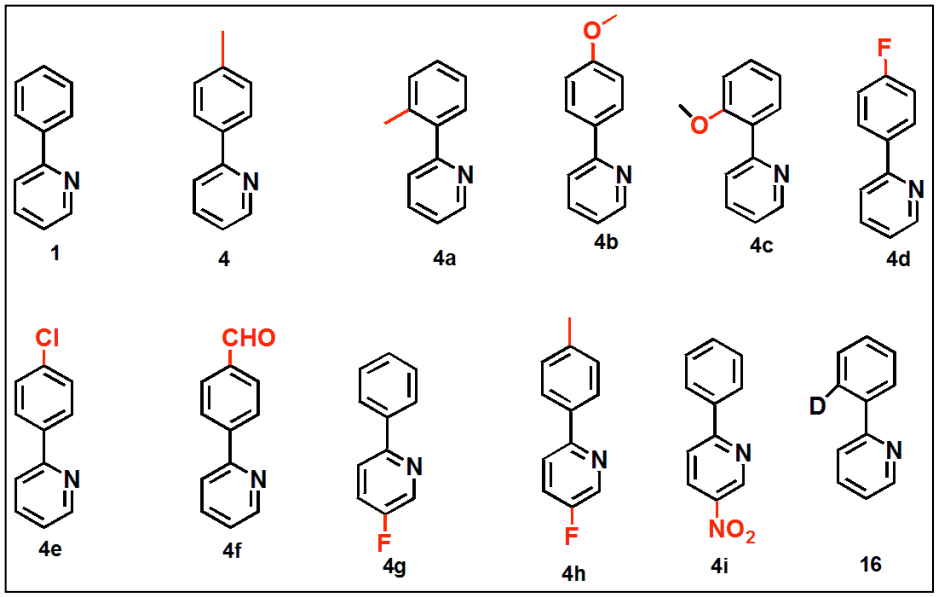
In conclusion, we have developed a novel, useful and economical process for the direct amination of 2-phenylpyridine derivatives. This process requires cheap and commercially available copper triflate and works for a variety of different 2-phenyl-pyridine derivatives. Additionally, the process also works with a bis-sachhrain iodane and thus future endeavors aim to synthesize such novel iodanes with various other amine sources in order to further extend this process. Future work in our laboratory will focus on studying the mechanistic insights and application of this method to heterocyclic intermediates.

Experimental Section

Substrates , Reagents and Catalysts.

Potassium phthalimide, saccharin, sodium methoxide, **(PIFA)** Phenyliodine bis(trifluoroacetate), **(PIDA)** Iodobenzene diacetate, methanol, **(ACN)** acetonitrile, **(DCM)** dichloromethane, **(DCE)** dichloroethane, copper triflate, palladium acetate and other copper catalysts were purchased from Sigma Aldrich and Fisher Scientific. Flash chromatography was performed on Silicycle silica gel (60Å, 40-63 μm). All reagents were stored under an inert atmosphere before use.

Preparation of different 2- aryl pyridine derivatives from literature procedures.



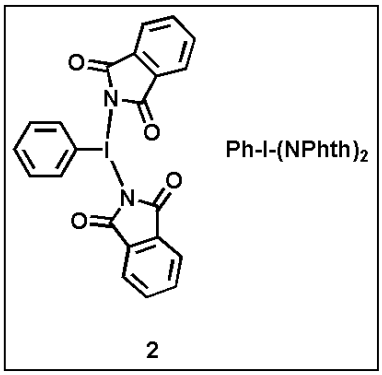
Substrates 1, 4, 4f were purchased from Sigma Aldrich. Other remaining substrates 4a,4b, 4c, 4f,4g,4h were prepared via Suzuki coupling using a literature procedure.[14] Substrate 4e was prepared by literature procedure.[15] 4i was prepared via Suzuki

coupling using a literature procedure.[16] Substrate 16 was prepared by literature procedure.[17]

Instrumentation

Microwave reactions were carried out in a CEM Discover microwave. Flash chromatography was performed using CombiFlash®Rf 200. GC/MS analysis was carried out on an Agilent Technologies 6890 GC system fixed with a 5973 mass selective detector. NMR spectrum were acquired using a Bruker Avance 300MHz spectrometer.

Synthesis of phenyliodine(III) bis(phthalimidate) Iodane (2)

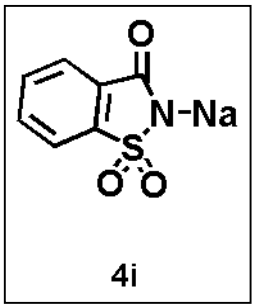


A mixture of (4.5 g, 1.04 mmol) phenyliodine(III) bis(trifluoroacetate) and potassium phthalimide (3.7 g, 2.0 mmol) in 100 mL of acetonitrile is stirred at 40 ^{0}C in an oil bath for 12 h. The off white precipitate is collected, washed with acetonitrile and dried under vaccum to obtain (3.6 g, 70 %) of the phenyliodine (III) bis(phthalimidate) **Iodane (2).** The NMR matched with the one published in literature.[18]

^{1}H NMR (300 MHz, $(CD_3)_2SO$): 7.84 (s, 5H), 7.76 (s, 3H), 7.69 – 7.64 (m, 1H), 7.53 – 7.32 (m, 3H), 7.21 (d, J = 7.8 Hz, 1H).

HRMS EI (m/z): [M+] calc'd for $C_{14}H_9INO_2$ [M–Phthalimidate] $^{+}$ 349.9672, 349.1 observed m/z

Synthesis of sodium-saccharin (4i)

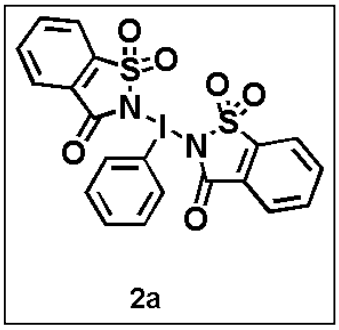


4i

In a dry round bottom flask, a mixture of saccharin (0.25 g, 1.36 mmol) and sodium methoxide (0.073 g, 1.36 mmol) in 10 mL of methanol under nitrogen atmosphere is refluxed for 25 minutes in an oil bath. After the reflux is finished the flask is cooled and then the excess solvent is removed under pressure to get a white solid **4i** (0.26 g, 92.83 %)

LRMS EI (m/z): [M+] calc'd for $C_7H_4NNa_3O_3S$ 205.1663, observed 206.0 m/z.

Synthesis of phenyliodine(III) bis(saccharin)Iodane (2a)



2a

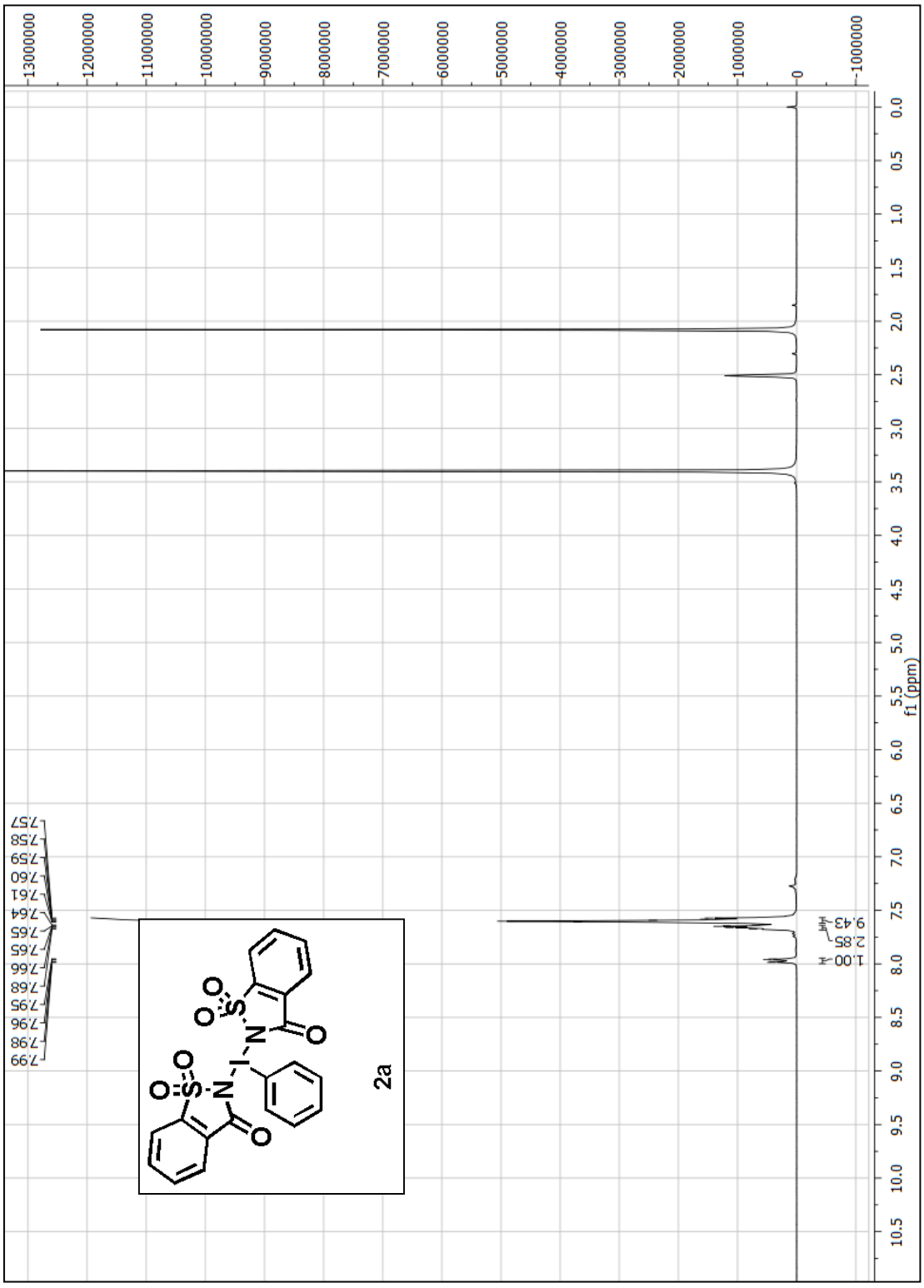
A mixture of (0.27 g, 0.633 mmol) phenyliodine(III) bis(trifluoroacetate) and sodium saccharin (0.26 g, 1.267 mmol in 100 mL of acetonitrile is stirred at 40 ^{0}C in an oil bath for 12 h. The white precipitate is collected, washed with acetonitrile and

dried under vaccum to obtain (0.234 g, 65%) of the phenyliodine(III) bis(saccharin) Iodane **(2a).**

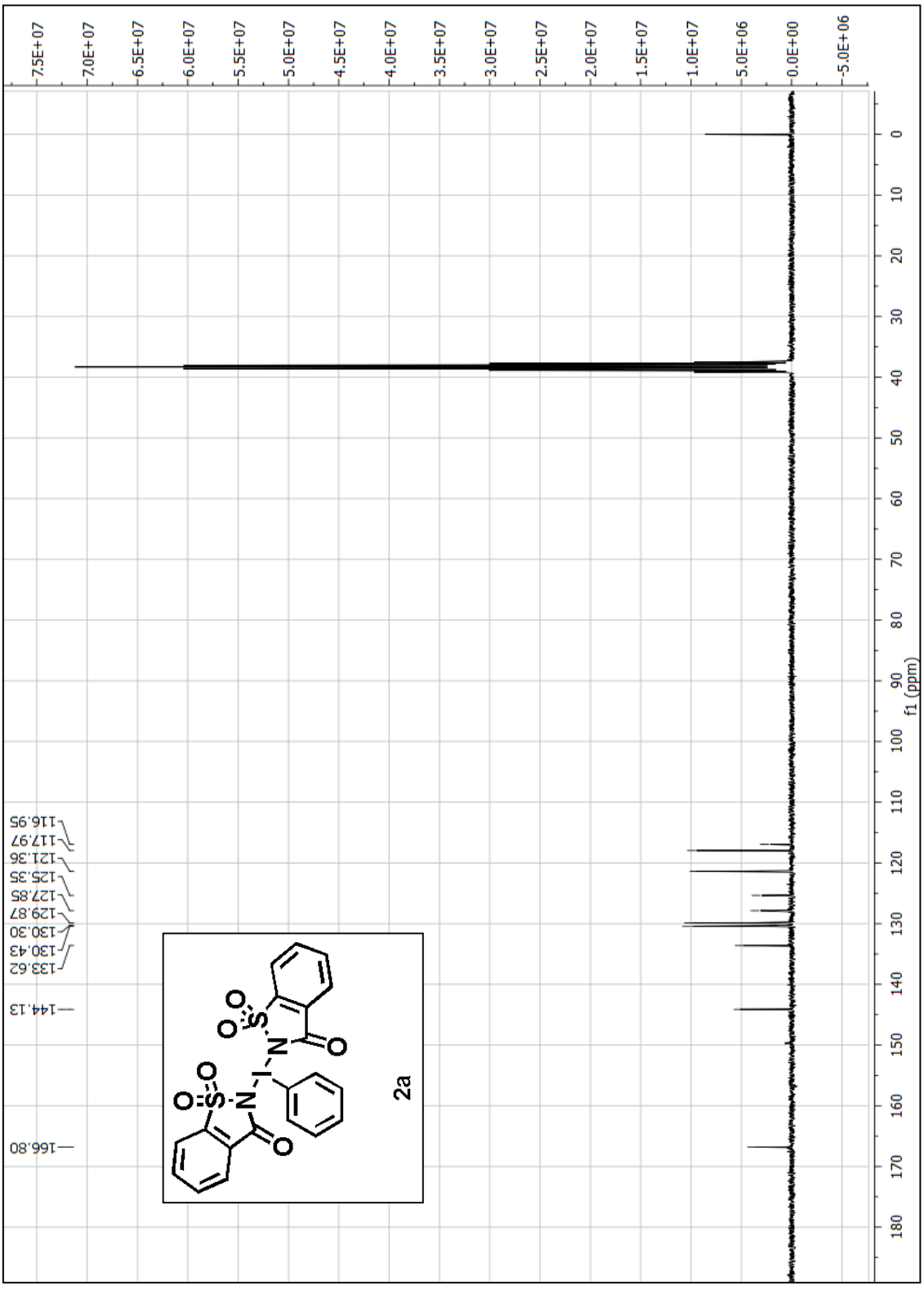
^{1}H NMR (300 MHz, $(CD_3)_2SO$): δ 8.00 – 7.95 (m, 1H), 7.68 – 7.64 (m, 3H), 7.62 – 7.57 (m, 9H).

^{13}C NMR (75 MHz, $(CD_3)_2SO$): δ 166.80, 144.13, 133.62, 130.43, 130.30, 129.87, 127.85, 125.35, 121.36, 117.97, 116.95.

LRMS EI (m/z): [M-succinimide^{+}] calc'd for and $C_{13}H_9INO_3S$ 386.9342, observed 387.91 m/z.

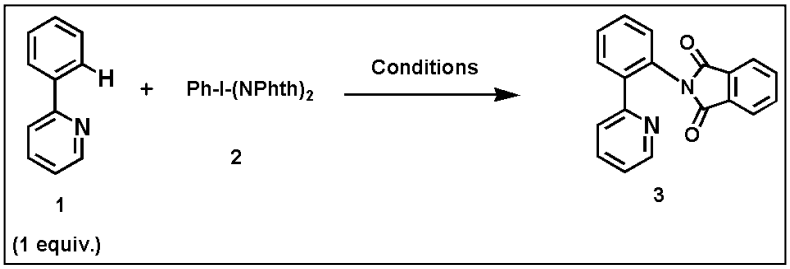


Spectrum 1. ^{1}H NMR of Compound **2a**



Spectrum 2. ^{13}C NMR of Compound **2a**

Initial Optimization Studies



Entry	Conditions	Yield 3 (%)
1	2 (1 eq.) , PIDA (2.5 eq.) , ACN, 145 ^{0}C (MW) , 3h	-
2	2 (1 eq.) , PIFA (2.5 eq.) , ACN , 145 ^{0}C (MW) , 3h	-
3	2 (1 eq.) , $Pd(OAc)_2$ (25 mol %) , ACN , 145 ^{0}C (MW) , 3h	13
4	2 (1 eq.) , $Cu(OTf)_2$ (25 mol %) , DCM, 70 ^{0}C , 48 h	47
5	2 (2.5 eq.) , $Cu(OTf)_2$ (25 mol %) , DCM, 70 ^{0}C , 48 h	63
6	Fresh salt 2 (1 eq.) , $Cu(OTf)_2$ (25 mol %) , DCM, 70 ^{0}C , 48 h	80
7	2 (2.5 eq.) , $Cu(OTf)_2$ (100 mol %) , DCE, 70 ^{0}C , 48 h	87

Table 4. Initial Optimization Studies

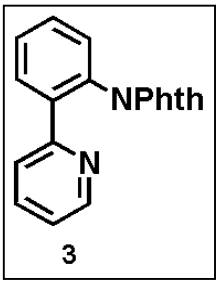
General procedure for Regioselective C-H Bond Amination of 2-Arylpyridine Derivatives

To a solution of the appropriate 2-arylpyridine (1 eq.) in 1,2-dichloroethane (4 mL) was added the appropriate iodane (2.5 eq.) and $Cu(OTf)_2$ (1 eq). The reaction was stirred for the 48 h at 80 ^{o}C in an oil bath before dilution with DCM (30 mL) and washing with saturated sodium bicarbonate solution (30 mL). The aqueous phase was extracted further with DCM (25 mL) and the combined organic layers were dried over

sodium sulphate and the excess solvent was removed under pressure. The crude residue was purified by flash column chromatography to obtain the pure aminated product.

This general procedure was followed for synthesis of **3,5,6,7,8,9,10,11,12,13,14,15.**

Synthesis of 2-(2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (3)



3

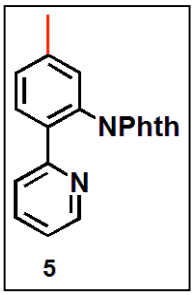
Substrate 1 was subjected to the general procedure. After purification by column chromatography, **3** was obtained (91 mg, 87%). The NMR matched with the one published in literature.[19]

***R_f*-Value:** Hexane/Ethyl acetate (3:2 *v/v*) = 0.29.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 – 7.71 (m, 3H), 7.65 (td, *J* = 7.9, 2.1 Hz, 1H), 7.59-7.54 (m, 2H), 7.47 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.44-7.40 (m, 1H), 7.07 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H).

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{12}N_2O_2$ 300.0899, 300.11 observed m/z.

Synthesis of 2-(5-methyl-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (5)



5

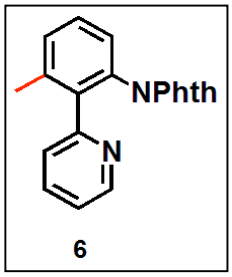
Substrate 4 was subjected to the general procedure. After purification by column chromatography, **5** was obtained (40.2 mg, 88 %). The NMR matched with the one published in literature.[19]

***R*$_f$-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.29.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (ddd, *J* = 4.8, 1.9, 1.0 Hz, 1H), 7.84 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.62 (td, *J* = 7.8, 1.7 Hz, 2H), 7.48 – 7.35 (m, 2H), 7.22 (d, *J* = 1.1 Hz, 1H), 7.03 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 2.46 (s, 3H).

LRMS EI (m/z): [M+] calc'd for $C_{20}H_{14}N_2O_2$ 314.1055, 314.19 observed m/z

Synthesis of 2-(3-methyl-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (6)



6

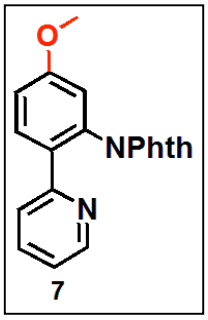
Substrate 4a was subjected to the general procedure. After purification by column chromatography, **6** was obtained (13.1 mg, 40 %). The NMR matched with the one published in literature.[19]

***R*$_f$-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.3.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (ddd, J = 4.8, 1.7, 1.0 Hz, 1H), 7.83-7.75 (m, 4H), 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.5 -7.45 (m, 2H), 7.37-7.33 (m, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.14 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 2.06 (s, 3H)

LRMS EI (m/z): [M+] calc'd for $C_{20}H_{14}N_2O_2$ 314.1055, 314.19 observed m/z

Synthesis of 2-(5-methoxy-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (7)



7

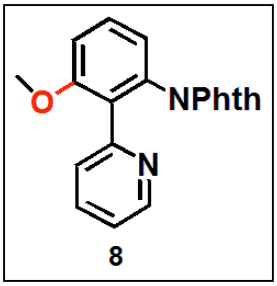
4b was subjected to the general procedure. After purification by column chromatography, **7** was obtained (22.1 mg, 50%). The NMR matched with the one published in literature.[19]

***R*$_f$-Value:** Hexane/Ethyl acetate (7:3*v/v*) = 0.24.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, *J* = 4.9 Hz, 1H), 8.33 – 8.29 (m, 1H), 8.04 – 7.67 (m, 4H), 7.60 – 7.48 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.05 – 6.99 (m, 2H), 3.82 (s, 3H).

LRMS EI (m/z): [M+] calc'd for $C_{20}H_{14}N_2O_3$ 330.1005, observed 330 m/z

Synthesis of 2-(3-methoxy-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (8)



8

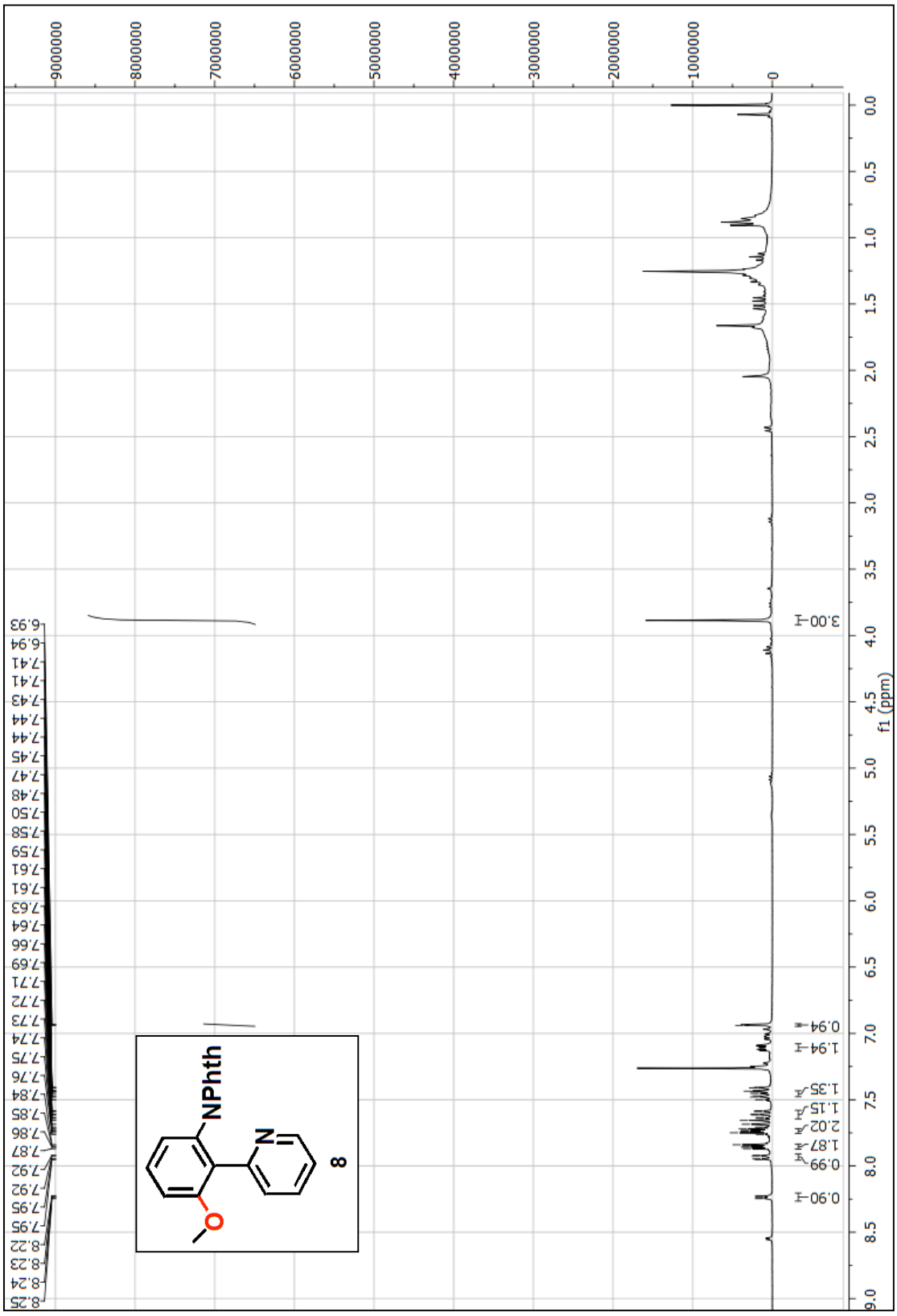
Substrate 4c was subjected to the general procedure. After purification by column chromatography, **8** was obtained (59.2 mg, 45 %).

***R_f*-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.26.

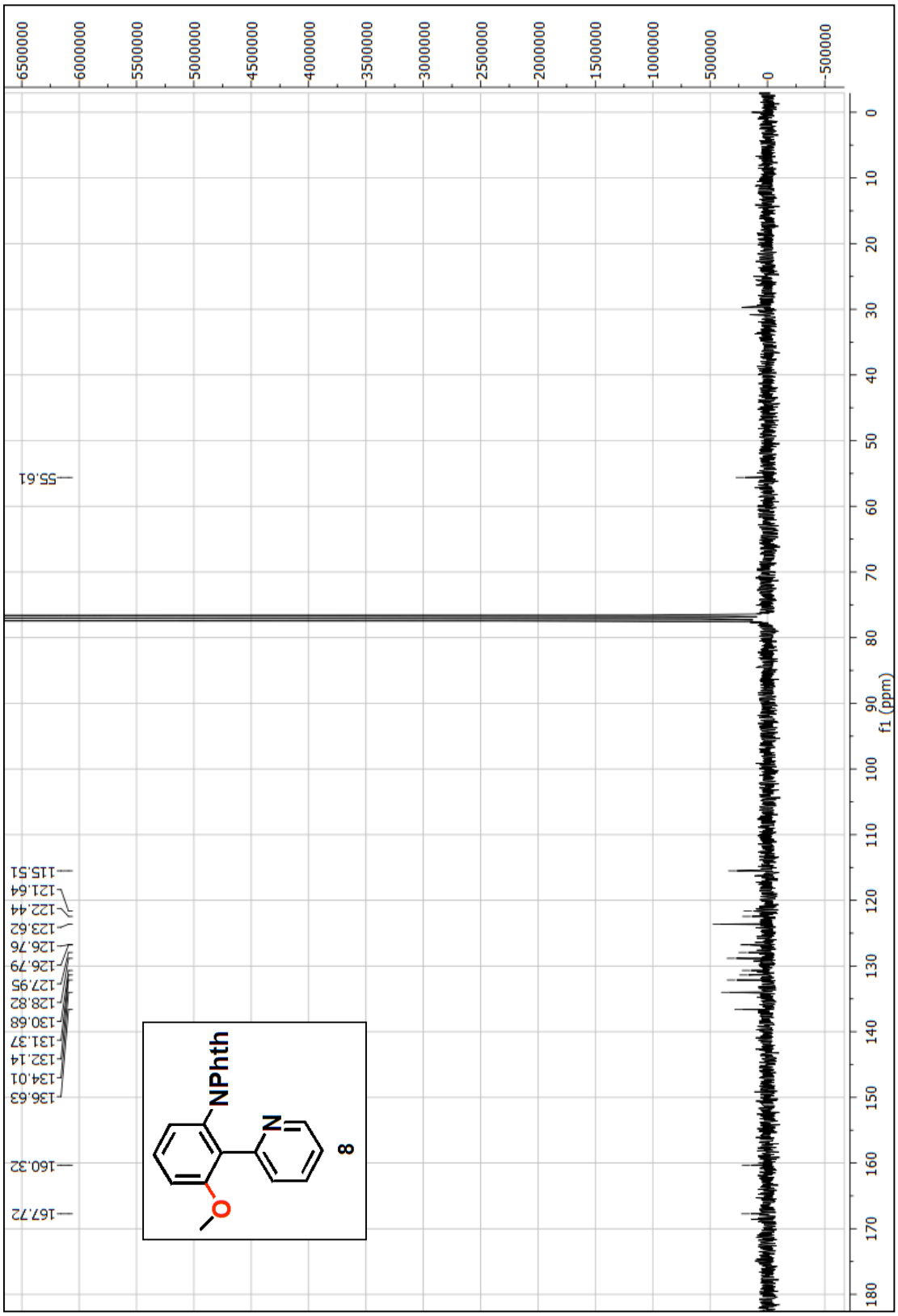
^{1}H NMR (300 MHz, $CDCl_3$):, 8.23 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.96 – 7.91 (m, 1H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.61 (td, *J* = 7.7, 1.9 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.13 – 7.08 (m, 2H), 6.94 (d, *J* = 2.7 Hz, 1H), 3.89 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.72, 160.32, 136.63, 134.01, 132.14, 131.37, 130.68, 128.82, 127.95, 126.79, 126.76, 123.62, 122.44, 121.64, 115.51, 55.61.

LRMS EI (m/z): [M+] calc'd for $C_{20}H_{14}N_2O_3$ 330.1005, 330 observed m/z

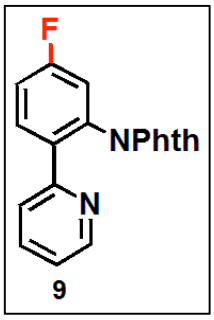


Spectrum 3. ^{1}H NMR of Compound **8**



Spectrum 4. ^{13}C NMR of Compound **8**

Synthesis of 2-(5-fluoro-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (9)



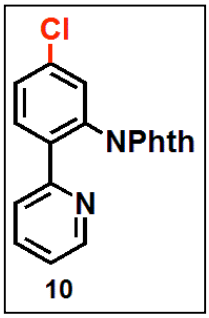
Substrate 4d was subjected to the general procedure. After purification by column chromatography, **9** was obtained (16 mg, 37 %). The NMR matched with the one published in literature.[19]

***R_f*-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.23

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.78 – 7.61 (m, 4 H), 7.44 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.31 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.17 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H).

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{11}F\,N_2O_2$ 318.0805, 318.01 observed m/z

Synthesis of 2-(5-chloro-2-(pyridin-2-yl)phenyl)isoindoline-1,3-dione (10)



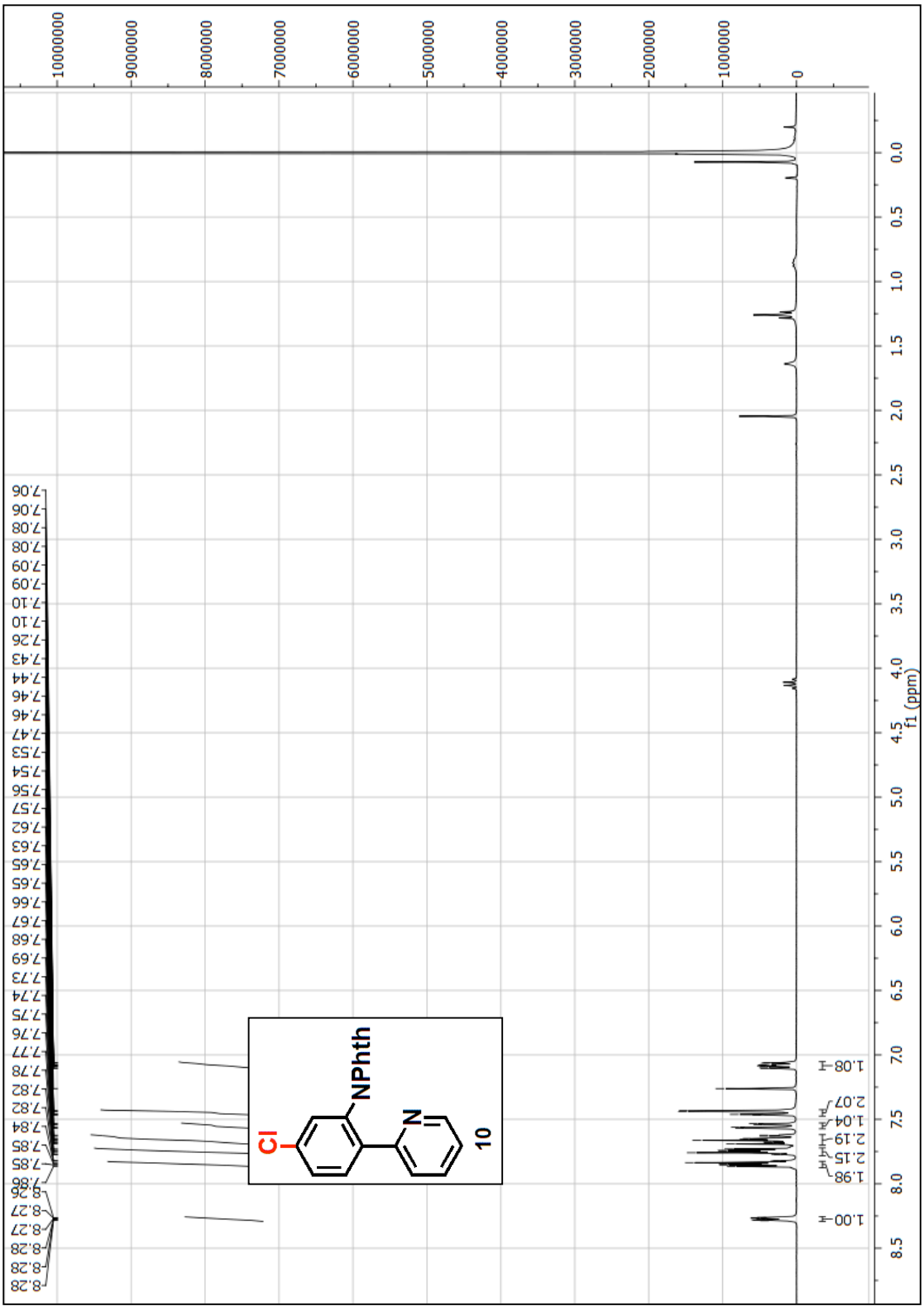
Substrate 4e was subjected to the general procedure. After purification by column chromatography, **10** was obtained (106.5 mg, 41 %).

***R*$_f$-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.26

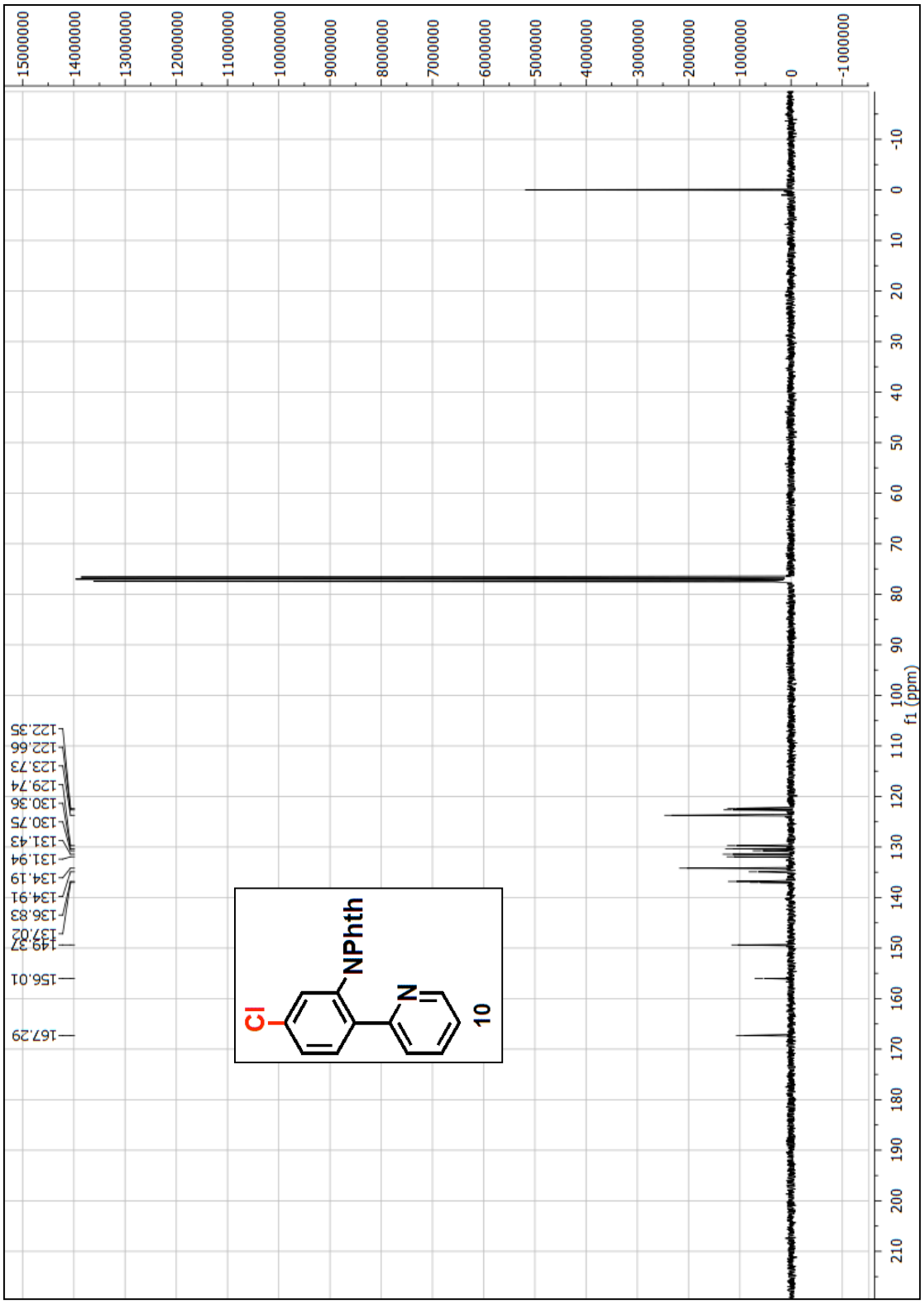
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 – 7.72 (m, 2H), 7.70 – 7.62 (m, 2H), 7.55 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.45 (dd, *J* = 7.3, 1.5 Hz, 2H), 7.08 (ddd, *J* = 7.7, 4.9, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.29, 156.01, 149.37, 137.02, 136.83, 134.91, 134.19, 131.94, 131.43, 130.75, 130.36, 129.74, 123.73, 122.66, 122.35.

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{11}Cl\,N_2O_2$ 334.0509, 334.15 observed m/z

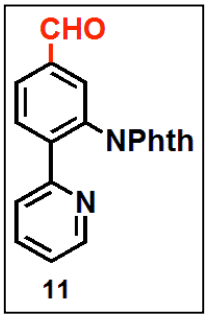


Spectrum 5. ^{1}H NMR of Compound **10**



Spectrum 6. ^{13}C NMR of Compound **10**

Synthesis of 3-(1,3-dioxoisoindolin-2-yl)-4-(pyridin-2-yl)benzaldehyde (11)



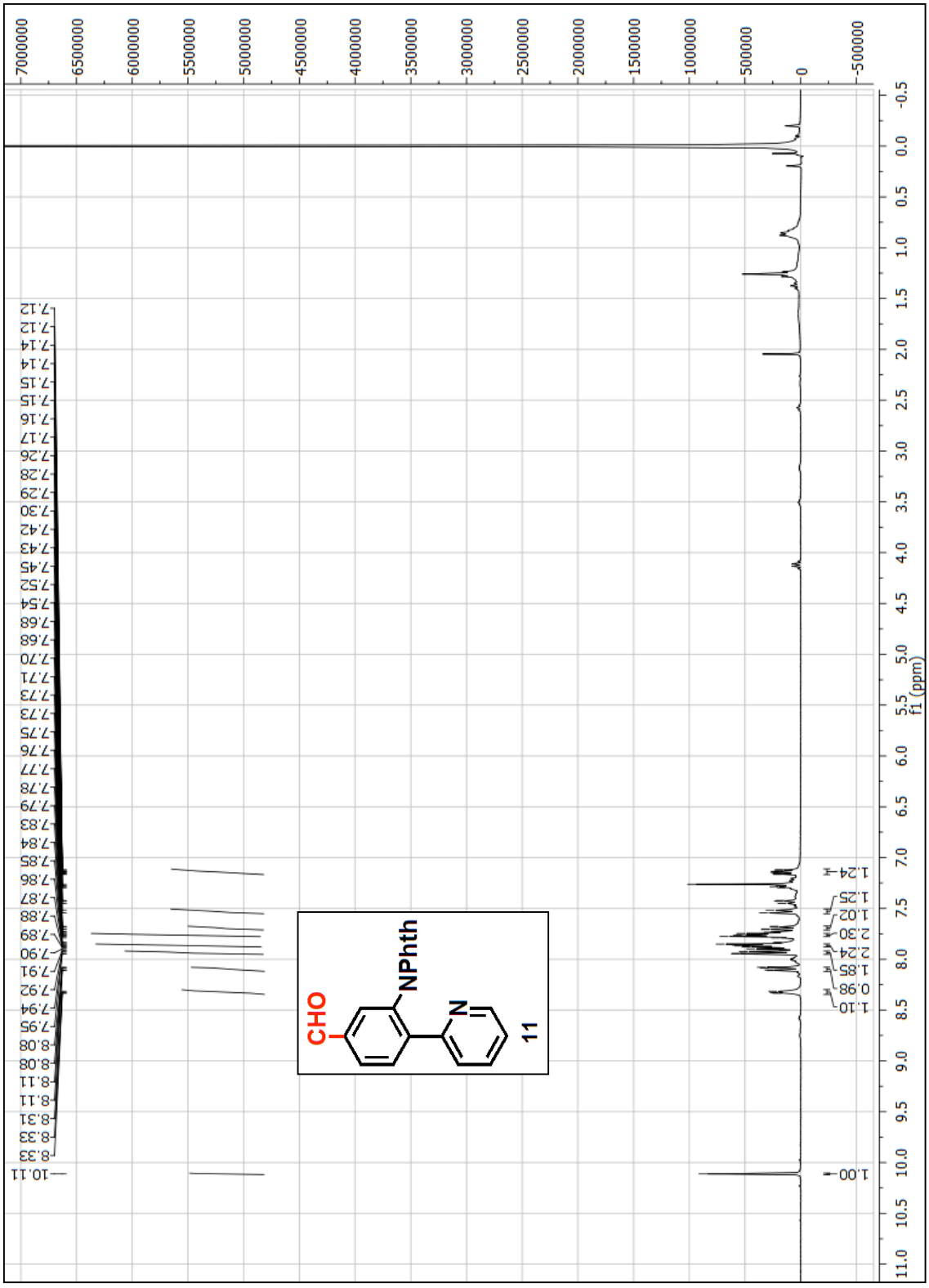
Substrate 4f was subjected to the general procedure. After purification by column chromatography, **11** was obtained (69.3 mg, 40 %).

***R_f*-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.2

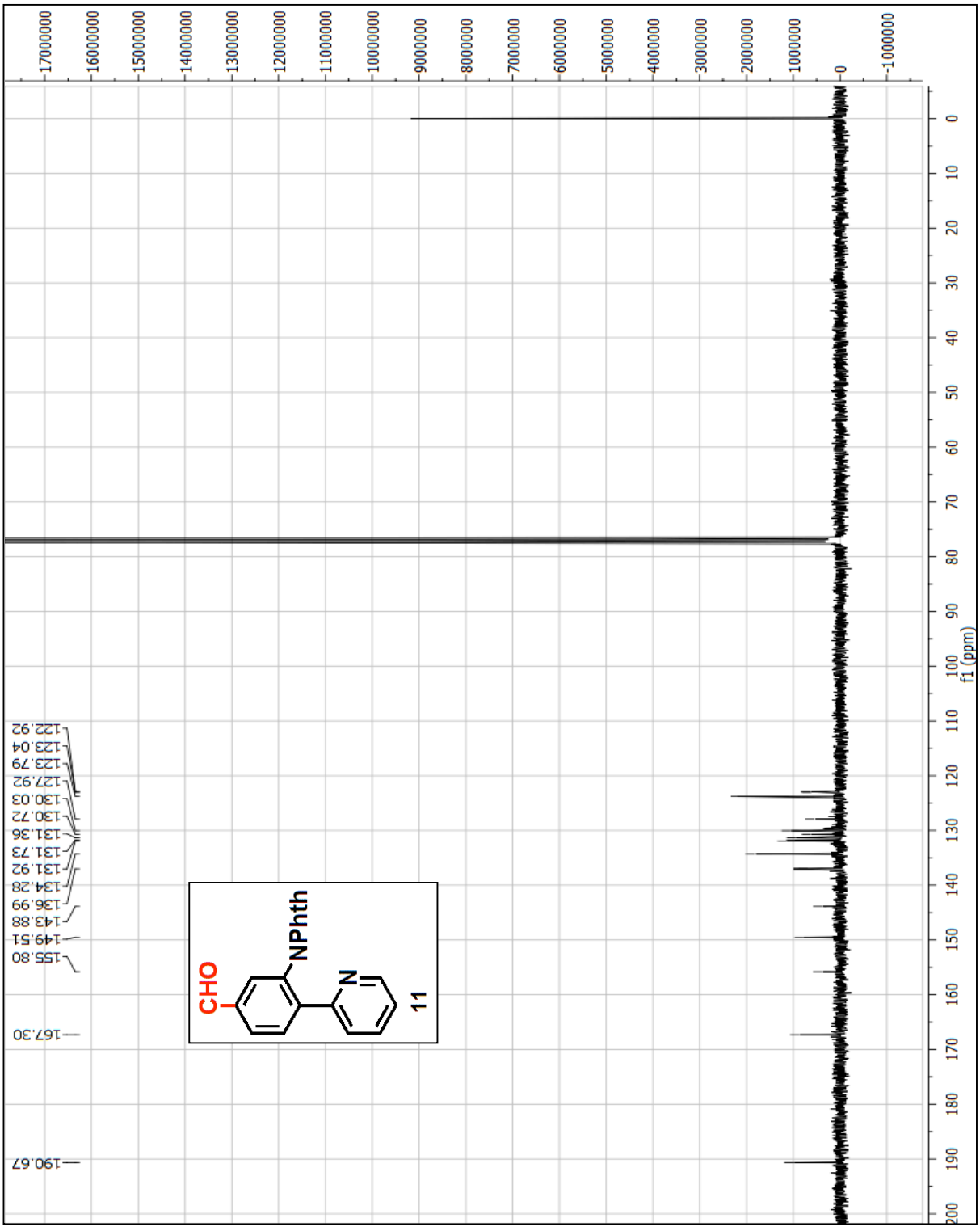
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.35 – 8.30 (m, 1H), 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.95 – 7.92 (m, 2H), 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.14 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 190.67, 167.30, 155.80, 149.51, 143.88, 136.99, 134.28, 131.92, 131.73, 131.36, 130.72, 130.03, 127.92, 123.79, 123.04, 122.92.

LRMS EI (m/z): [M+] calc'd for $C_{20}H_{12}N_2O_3$ 328.0848, 328.04 observed m/z

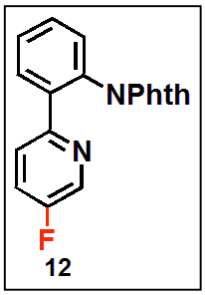


Spectrum 7. ^{1}H NMR of Compound **11**



Spectrum 8. ^{13}C NMR of Compound **11**

Synthesis of 2-(2-(5-fluoropyridin-2-yl)phenyl)isoindoline-1,3-dione (12)



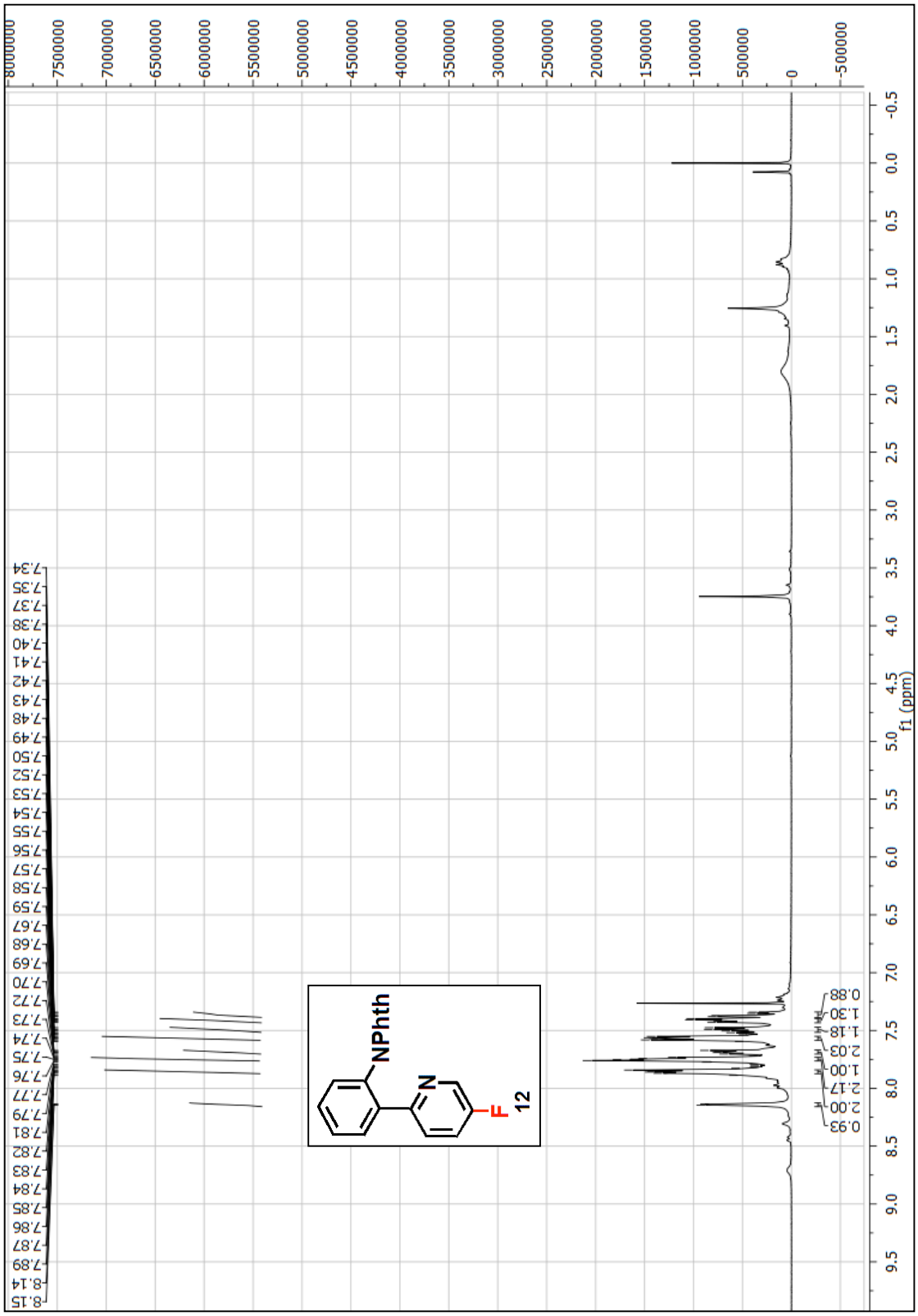
Substrate 4g was subjected to the general procedure. After purification by column chromatography, **12** was obtained (152.1 mg, 83 %).

***R_f*-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.2.

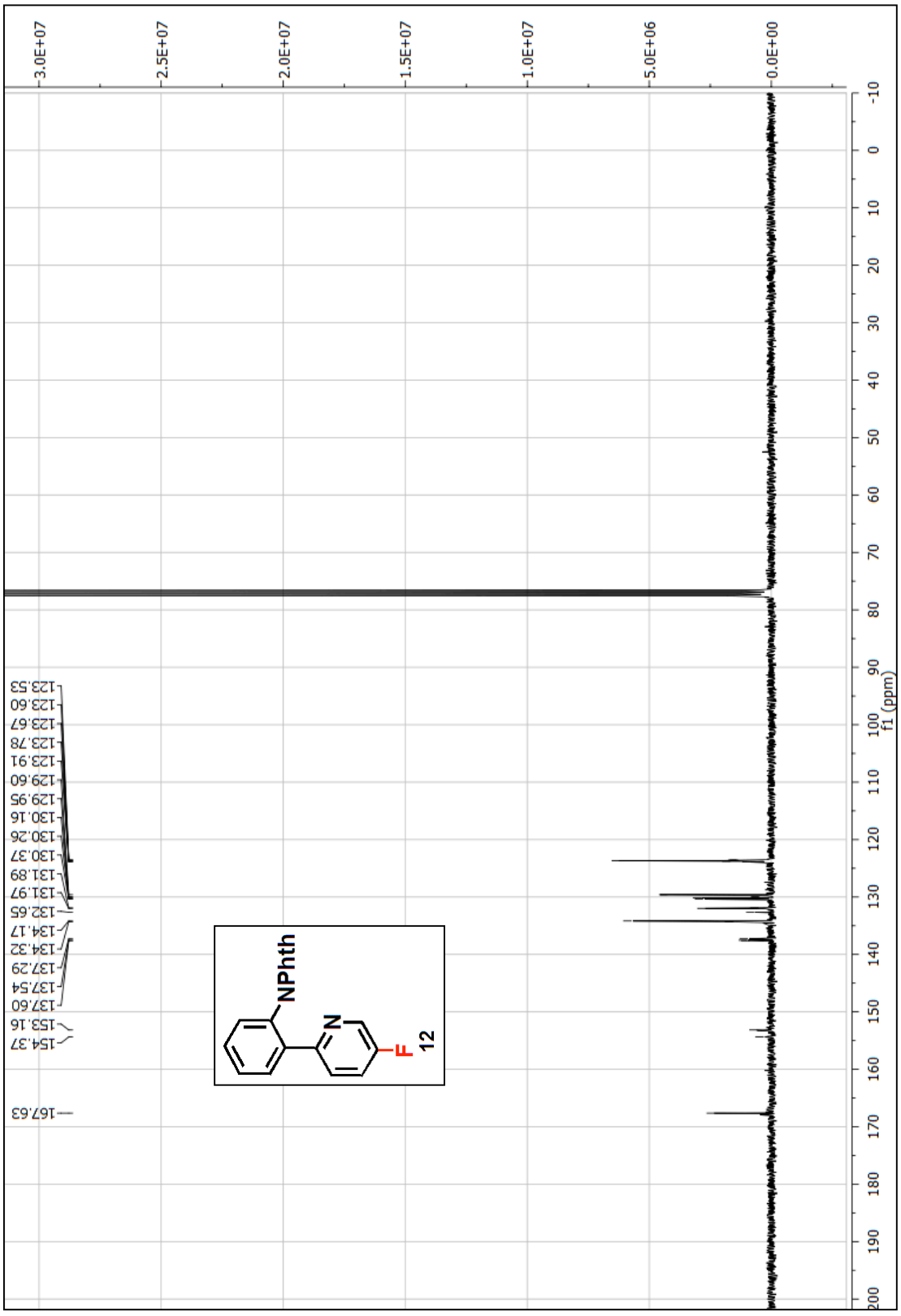
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 2.8 Hz, 1H), 7.87 – 7.84 (m, 2H), 7.76 – 7.73 (m, 2H), 7.69 (dd, *J* = 5.7, 3.4 Hz, 1H), 7.57 (dd, *J* = 5.7, 3.4 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.41 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.63, 153.21, 137.59, 137.29, 134.32, 134.17, 132.65, 131.97, 130.37, 130.16, 129.59, 123.78, 123.67, 123.60, 123.53.

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{11}FN_2O_2$ 318.0805, 318.11 observed m/z

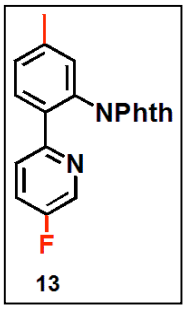


Spectrum 9. [1]H NMR of Compound **12**



Spectrum 10. ^{13}C NMR of Compound **12**

Synthesis of 2-(2-(5-fluoropyridin-2-yl)-5-methylphenyl)isoindoline-1,3-dione (13)



13

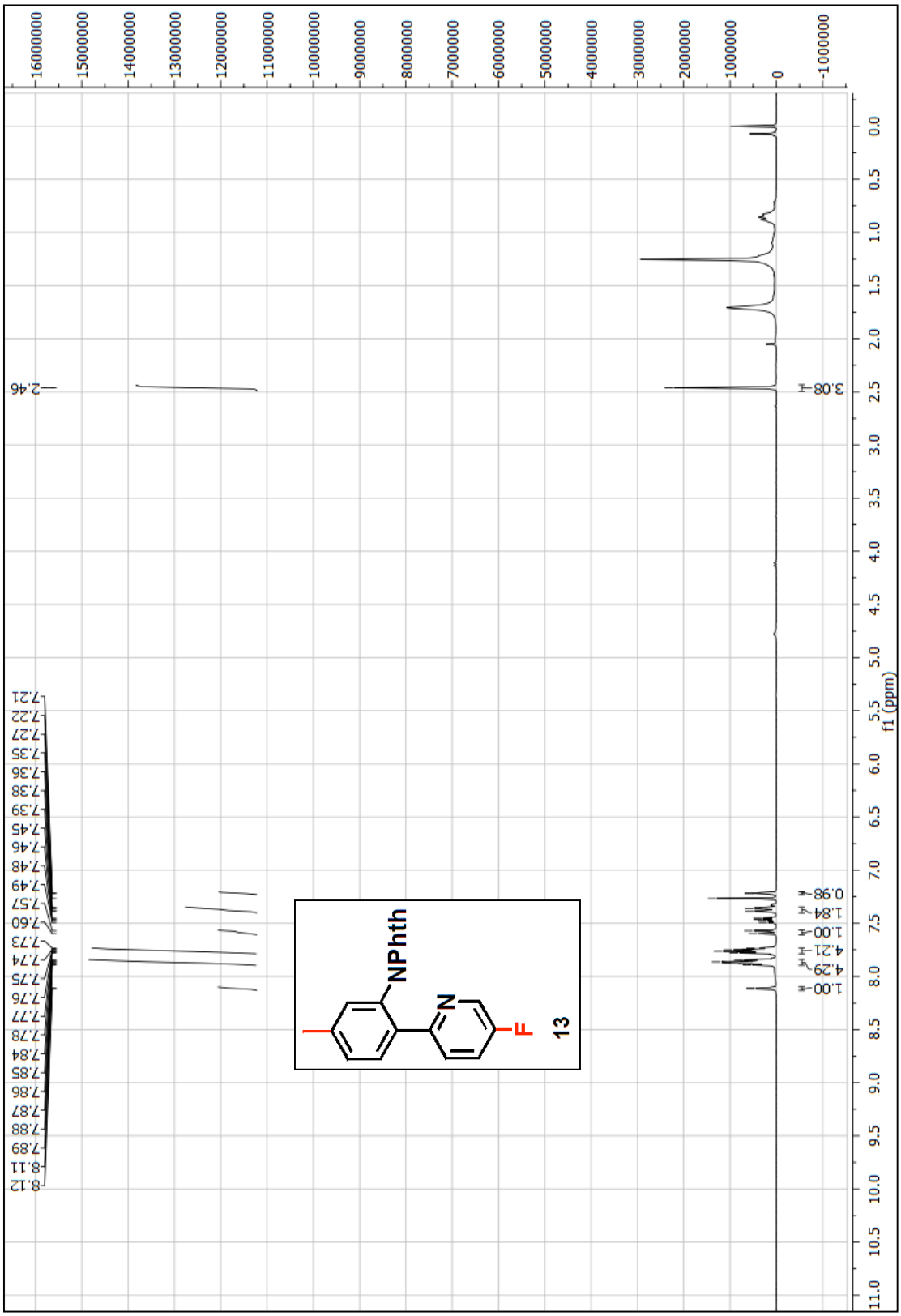
4h was subjected to the general procedure as described above. After purification by column chromatography, **13** was obtained (66.6 mg, 34 %).

***R*$_f$-Value:** Dichloromethane = 0.81.

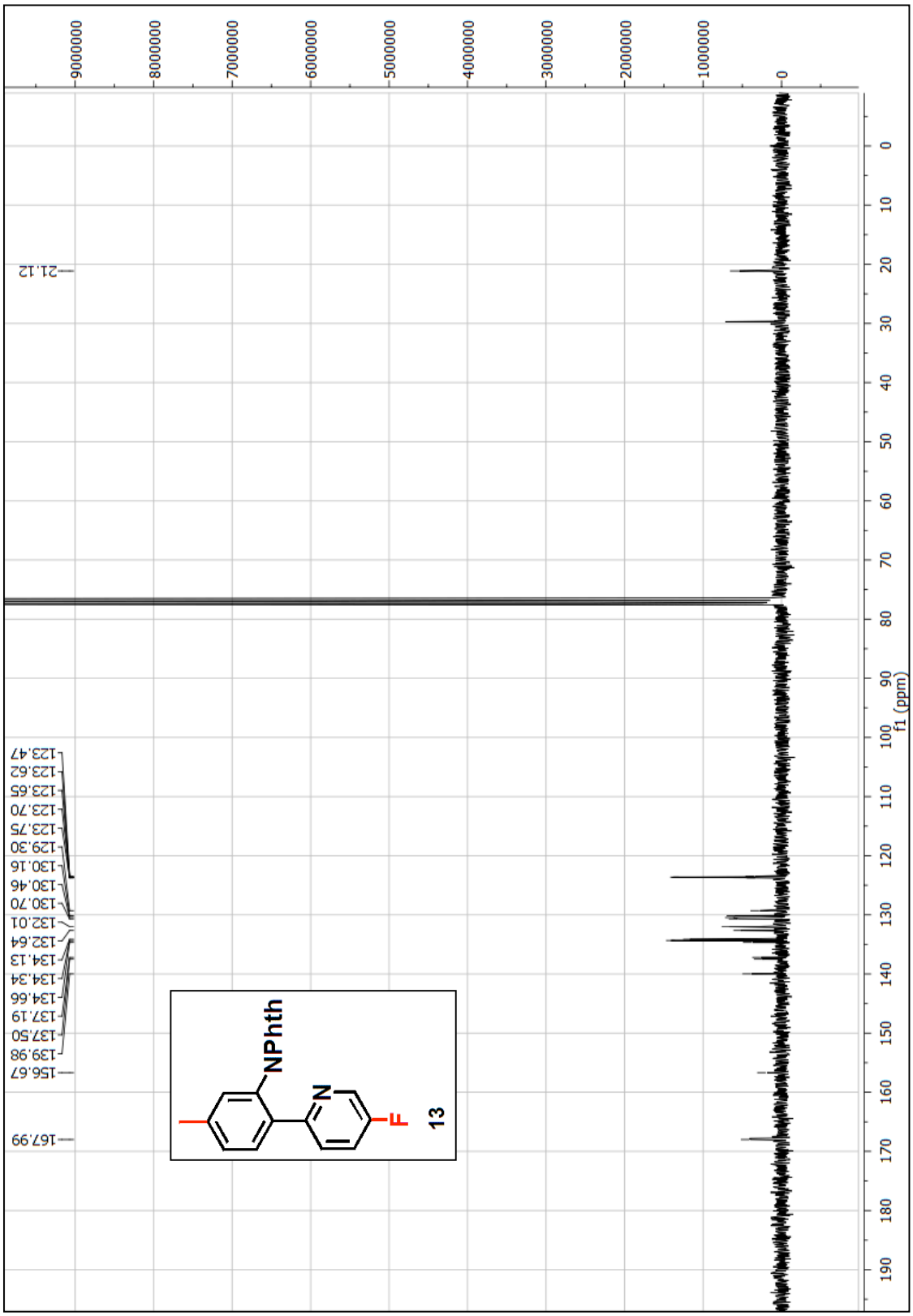
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 2.9 Hz, 1H), 7.87 (td, *J* = 5.6, 3.0 Hz, 4H), 7.76 (td, *J* = 5.3, 3.0 Hz, 4H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.37 (dd, *J* = 8.7, 2.6 Hz, 2H), 7.22 (d, *J* = 1.8 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.99, 156.67, 139.98, 137.50, 137.19, 134.66, 134.34, 134.13, 132.64, 132.01, 130.70, 130.46, 130.16, 129.30, 123.65, 123.62, 21.12

LRMS EI (m/z): [M+] calc'd for $C_{20}H_{13}FN_2O_2$ 332.0961, 332 observed m/z

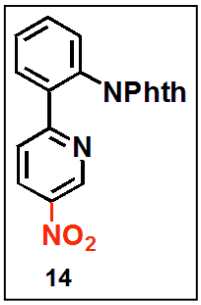


Spectrum 11. ^{1}H NMR of Compound **13**



Spectrum 12. ^{13}C NMR of Compound **13**

Synthesis of 2-(2-(5-nitropyridin-2-yl)phenyl)isoindoline-1,3-dione (14)



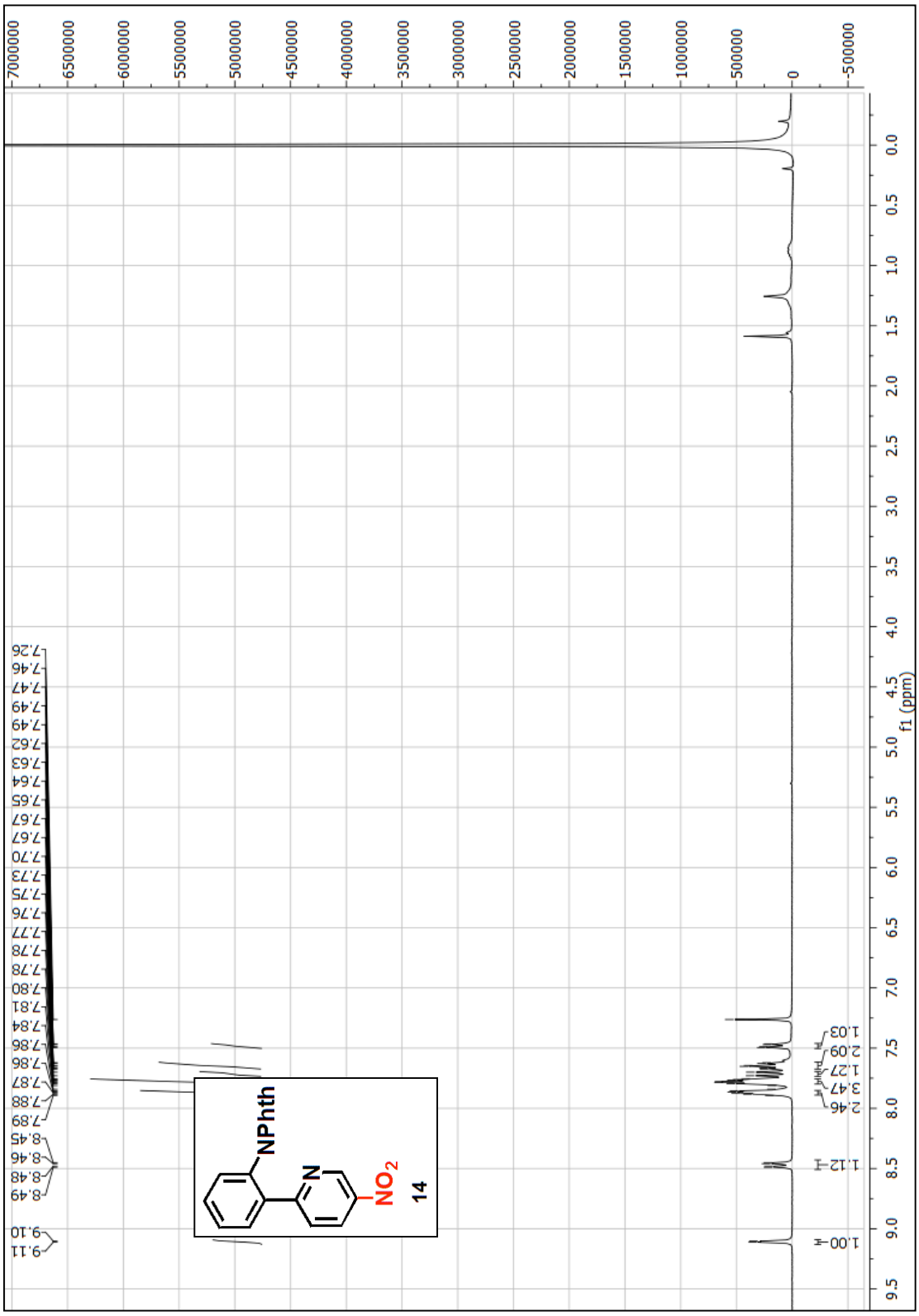
4i was subjected to the general procedure as described above. After purification by column chromatography, **14** was obtained (36.3 mg, 27%).

***R*$_f$-Value:** Dichloromethane = 0.69

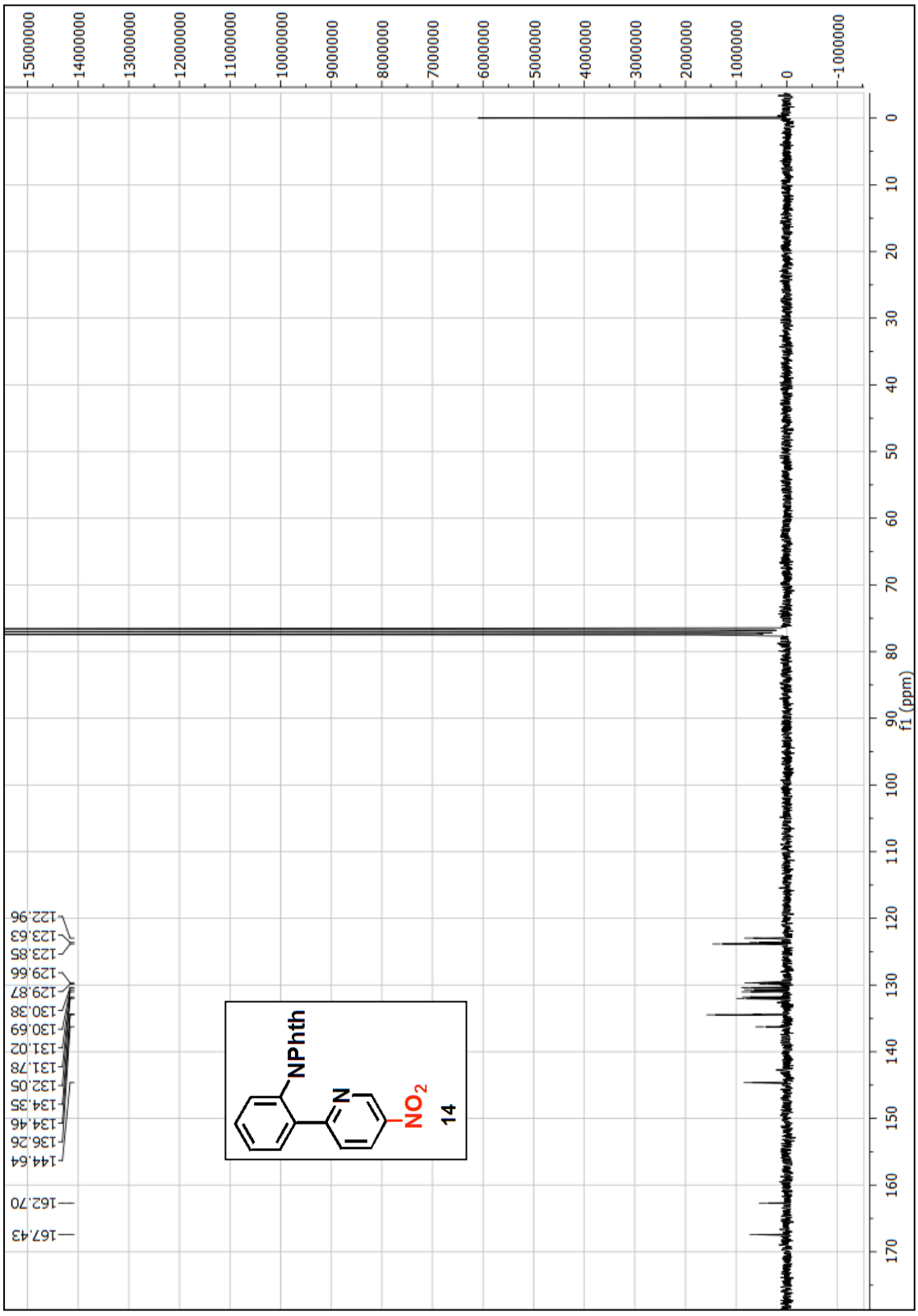
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.11 (d, *J* = 2.7 Hz, 1H), 8.47 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.87 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.80 – 7.76 (m, 3H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.65 (td, *J* = 6.7, 1.9 Hz, 2H), 7.48 (dd, *J* = 7.3, 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.43, 162.70, 144.64, 136.26, 134.46, 134.35, 132.05, 131.78, 131.02, 130.69, 130.38, 129.87, 129.66, 123.85, 123.63, 122.96.

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{11}N_3O_4$ 345.075, 345.02 bserved m/z

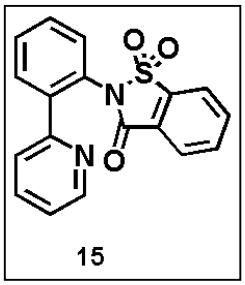


Spectrum 13. ^{1}H NMR of Compound **14**



Spectrum 14. ^{13}C NMR of Compound **14**

Synthesis of 2-(2-(5-nitropyridin-2-yl)phenyl)isoindoline-1,3-dione (15)



15

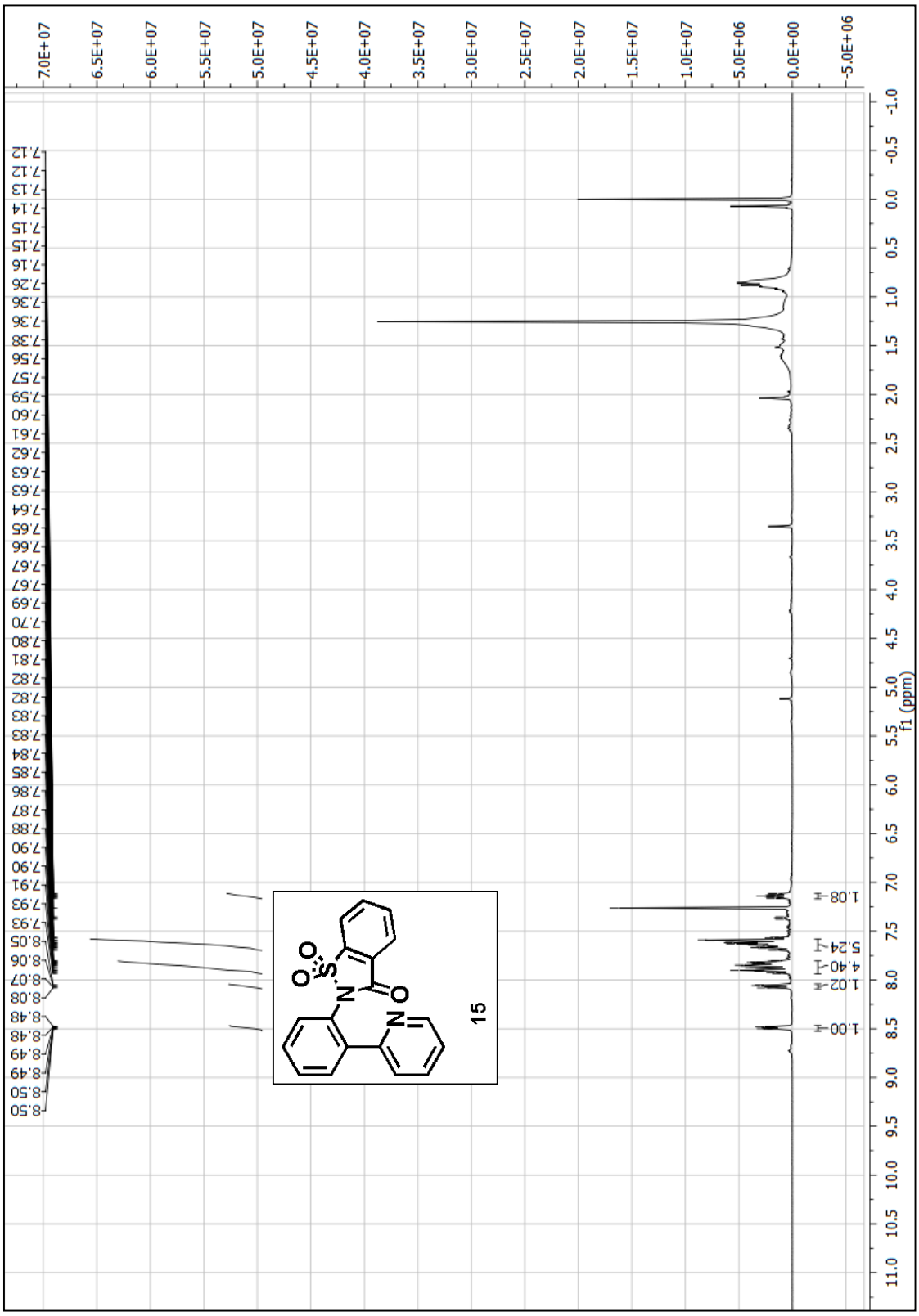
Substrate 2a was subjected to the general procedure as described above. After purification by column chromatography, **15** was obtained (10.5 mg, 88 %).

***R_f*-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.14.

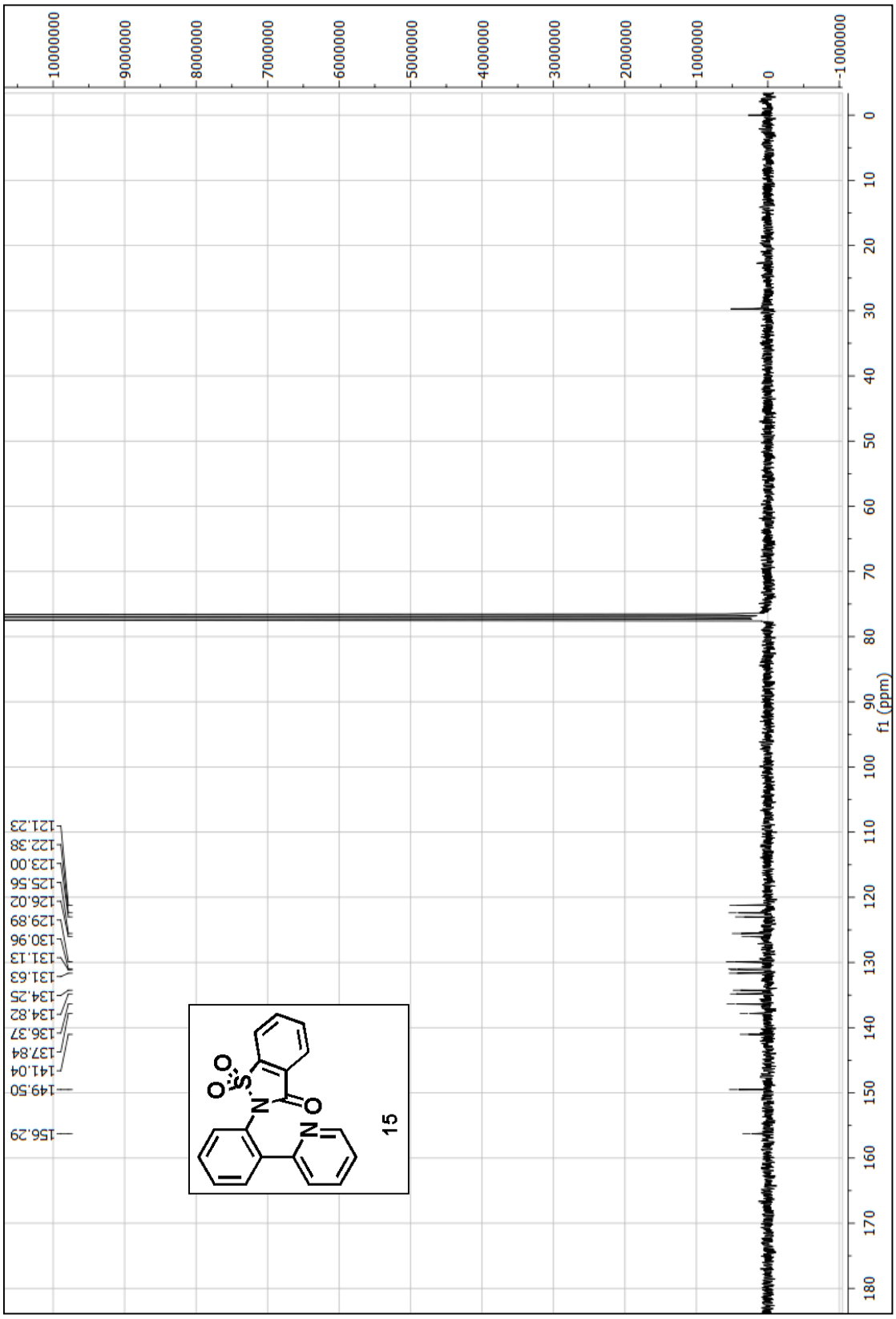
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (dt, *J* = 4.9, 1.4 Hz, 1H), 8.07 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.94 – 7.81 (m, 4H), 7.70 – 7.58 (m, 5H), 7.14 (ddd, *J* = 6.7, 4.8, 2.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.29, 149.50, 141.04, 137.84, 136.37, 134.82, 134.25, 131.63, 131.13, 130.96, 129.89, 126.02, 125.56, 123.00, 122.38, 121.23.

LRMS EI (m/z): [M+] calc'd for $C_{19}H_{11}N_3O_4$ 336.0569, 336.11 observed m/z

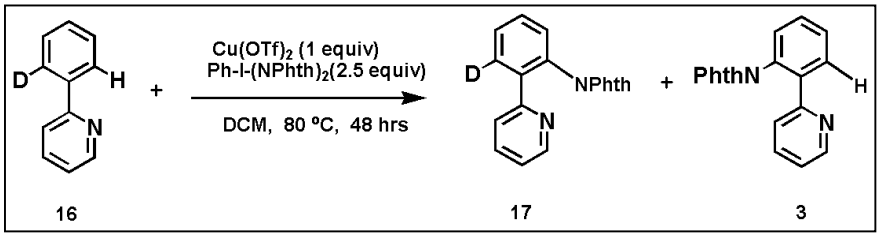


Spectrum 15. ^{1}H NMR of Compound **15**


15
156.29
149.50
141.04
137.84
136.37
134.82
134.25
131.63
131.13
130.96
129.89
126.02
125.56
123.00
122.38
121.23
f1 (ppm)

Spectrum 16. ^{13}C NMR of Compound **15**

Kinetic Isotope Effect

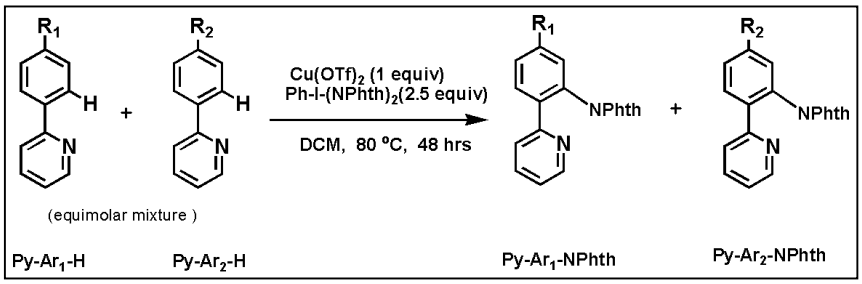


To a solution of 16 (0.0179 g , 0.114 mmol) in 1,2-dichloroethane (4 mL) was added the iodane 2 (0.142 g, 0.286 mmol) and $Cu(OTf)_2$ (0.041 g, 0.114 mmol). The reaction mixture was stirred for 48 h at 80 ^oC in an oil bath. The reaction was then cooled, and an aliquot was removed and analyzed by GC/MS.

GC/MS Conditions: J & W Scientific DB-1, capillary 25.0m x 200μm x 0.33μm, 1.3 mL/min, 40 ^oC, hold 0.50min, 12 ^oC/min to 320 ^oC, hold 6.0min.

$\mathbf{k_H/k_D}$ = 1.15

Competition experiment

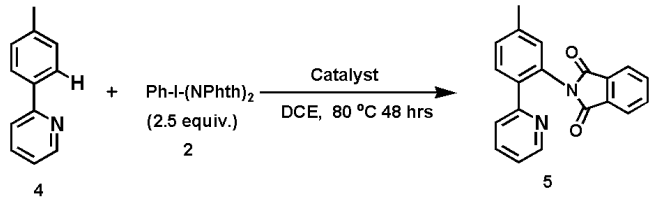


To a solution of equimolar amounts of Py-Ar_1-H (1eq.) and Py-Ar_2-H (1eq.) in 1,2-dichloroethane (4 mL) was added the iodane 2 (2.5 eq) and $Cu(OTf)_2$ (1 eq.). The reaction was mixture was stirred for the 48 h at 80 ^oC in an oil bath. The reaction was then cooled, and an aliquot was removed and analyzed by GC/MS.

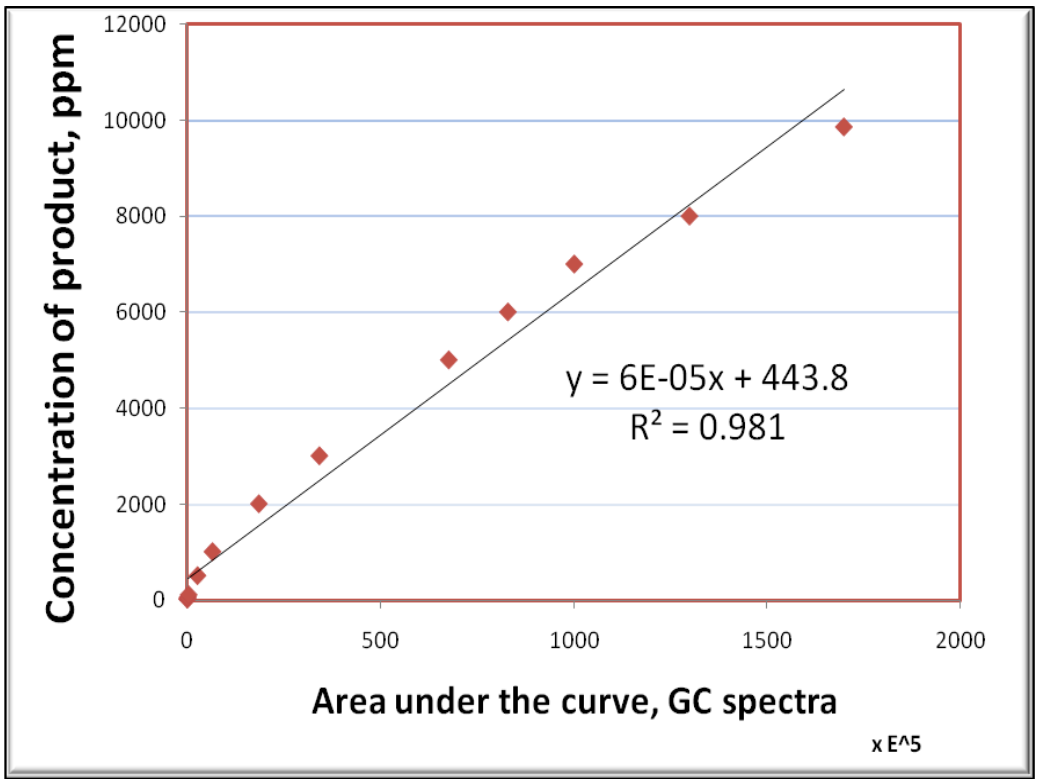
	Py-Ar_1-H **R_1**	**Py-Ar_2-H** **R_2**	**Py-Ar_1-NPhth (%)[a]**	**Py-Ar_2-NPhth (%)[a]**
1	H	Me	42	58
2	H	F	92	8
3	Me	F	94	6

[a] Mole fractions determined by GC/MS

Calibration Curve



The pure product 5 was isolated by column chromatography. Known Concentrations in ppm for (1-100% yield) were prepared in DCE. The plot of various concentrations against their area under the curve from GC-MS spectrum generates the calibration curve.



References

[1] For recent reviews describing C-C bond formation, see: a) L. Ackermann, R. n. Vicente, A. R. Kapdi, *Angewandte Chemie International Edition* **2009**, *48*, 9792-9826; b) D. Alberico, M. E. Scott, M. Lautens, *Chemical Reviews* **2007**, *107*, 174-238; c) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angewandte Chemie International Edition* **2009**, *48*, 5094-5115; d) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chemical Society Reviews* **2011**, *40*, 5068-5083; e) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chemical Reviews* **2010**, *110*, 624-655; f) O. Daugulis, H.-Q. Do, D. Shabashov, *Accounts of Chemical Research* **2009**, *42*, 1074-1086; g) C.-J. Li, *Accounts of Chemical Research* **2009**, *42*, 335-344; h) T. W. Lyons, M. S. Sanford, *Chemical Reviews* **2010**, *110*, 1147-1169; i) G. P. McGlacken, L. M. Bateman, *Chemical Society Reviews* **2009**, *38*, 2447-2464; j) I. V. Seregin, V. Gevorgyan, *Chemical Society Reviews* **2007**, *36*; k) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chemical Communications* **2010**, *46*; l) C. S. Yeung, V. M. Dong, *Chemical Reviews* **2011**, *111*, 1215-1292.

[2] For recent examples of C-H amination , see: a) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari, T. H. Warren, *Angewandte Chemie International Edition* **2008**, *47*, 9961-9964; b) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *Journal of the American Chemical Society* **2006**, *128*, 6790-6791; c) M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida, T. Katsuki, *Angewandte Chemie* **2011**, *123*, 10058-10061; d) A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano, B. DeBoef, *Journal of the American Chemical Society* **2011**, *133*, 19960-19965;

e) H. J. Kim, J. Kim, S. H. Cho, S. Chang, *Journal of the American Chemical Society* **2011**, *133*, 16382-16385; f) H. Lu, V. Subbarayan, J. Tao, X. P. Zhang, *Organometallics* **2010**, *29*, 389-393; g) A. N. Vedernikov, K. G. Caulton, *Chemical Communications* **2004**, 162-163.

[3] For recent reviews describing C-N bond formation via nitrenoid intermediates , see: a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417-424; b) P. Müller, C. Fruit, *Chemical reviews* **2003**, *103*, 2905-2920; c) C. W. Hamilton, D. S. Laitar, J. P. Sadighi, *Chemical Communications* **2004**, 1628-1629.

[4] For recent examples Pd-catalyzed aminations, see: a) A. R. Dick, M. S. Remy, J. W. Kampf, M. S. Sanford, *Organometallics* **2007**, *26*, 1365-1370; b) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, M. J. Gaunt, *Journal of the American Chemical Society* **2008**, *130*, 16184-16186; c) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *Journal of the American Chemical Society* **2011**, *133*, 1694-1697; d) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *Journal of the American Chemical Society* **2006**, *128*, 9048-9049; e) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7603-7610; f) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *Journal of the American Chemical Society* **2005**, *127*, 14560-14561; g) S. R. Whitfield, M. S. Sanford, *Journal of the American Chemical Society* **2007**, *129*, 15142-15143; h) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *Journal of the American Chemical Society* **2011**, *133*, 1466-1474.

[5] For recent examples of Cu-catalyzed aminations, see: a) I. P. Beletskaya, A. V. Cheprakov, *Coordination Chemistry Reviews* **2004**, *248*, 2337-2364; b) G.

Evano, N. Blanchard, M. Toumi, *Chemical Reviews* **2008**, *108*, 3054-3131; c) T. Kawano, K. Hirano, T. Satoh, M. Miura, *Journal of the American Chemical Society* **2010**, *132*, 6900-6901; d) S. V. Ley, A. W. Thomas, *Angewandte Chemie International Edition* **2003**, *42*, 5400-5449; e) D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Organic Letters* **2009**, *11*, 1607-1610; f) F. Monnier, M. Taillefer, *Angewandte Chemie International Edition* **2009**, *48*, 6954-6971; g) Q. Wang, S. L. Schreiber, *Organic Letters* **2009**, *11*, 5178-5180.

[6] A. John, K. M. Nicholas, *J. Org. Chem.* **2011**, *76*, 4158-4162.

[7] Q. Shuai, G. Deng, Z. Chua, D. S. Bohle, C.-J. Li, *Advanced Synthesis & Catalysis* **2010**, *352*, 632-636.

[8] a) S. H. Cho, J. Yoon, S. Chang, *Journal of the American Chemical Society* **2011**, *133*, 5996-6005; b) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angewandte Chemie International Edition* **2011**, *50*, 8605-8608.

[9] R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman, J. F. Hartwig, *Journal of the American Chemical Society* **2013**, *135*, 8480-8483.

[10] a) C. Röben, J. A. Souto, E. C. Escudero-Adán, K. Muñiz, *Organic Letters* **2013**, *15*, 1008-1011; b) J. A. Souto, C. Martínez, I. Velilla, K. Muñiz, *Angewandte Chemie International Edition* **2013**, *52*, 1324-1328.

[11] N. R. Deprez, M. S. Sanford, *Journal of the American Chemical Society* **2009**, *131*, 11234-11241.

[12] R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593-1597.

[13] L. Hadjiarapoglou, S. Spyroudis, A. Varvoglis, *Synthesis* **1983**, *1983*, 20

[14] C. Liu, W. Yang, *Chemical Communications* **2009**, 6267-6269.

[15] S.-H. Kim, R. D. Rieke, *Tetrahedron Letters* **2009**, *50*, 5329-5331.

[16] C. Liu, N. Han, X. Song, J. Qiu, *European Journal of Organic Chemistry* **2010**, *2010*, 5548-5551.

[17] X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *Journal of the American Chemical Society* **2006**, *128*, 6790-6791.

[18] K. Moriyama, K. Ishida, H. Togo, *Organic Letters* **2012**, *14*, 946-949.

[19] S. Yu, B. Wan, X. Li, *Organic Letters* **2013**, *15*, 3706-3709.

MANUSCRIPT 3

Published in ***Chem. Comm.*** **2011,** *47*, 4679 – 4681

Increasing Synthetic Efficiency via Direct C-H Functionalization: Formal Synthesis of an Inhibitor of Botulinum Neurotoxin

Shathaverdhan Potavathri, Abhishek Kantak

and Brenton DeBoef*

Corresponding author:

Prof. Brenton Deboef

Department of Chemistry,

University of Rhode Island,

Kingston, Rhode Island 02881.

bdeboef@chm.uri.edu

Manuscript 3

Increasing Synthetic Efficiency via Direct C-H Functionalization: Formal Synthesis of an Inhibitor of Botulinum Neurotoxin

Abstract

A new and efficient scheme for the synthesis of one of the best known inhibitors of botulinum neurotoxin serotype A (BoNTA) is reported herein. The synthetic route involves two palladium-catalyzed C-H functionalization reactions, formally activating three C-H bonds.

.

Introduction

Botulinum neurotoxin serotype A (BoNTA) is a protein produced by a spore-forming bacteria called Clostridium botulinum. It is the world's most poisonous protein having a median lethal dose of approximately 1 ng/Kg.[1] The toxin is associated with numerous food-borne illnesses and is a potential bioweapon. Consequently, the synthesis of small molecule inhibitors of BoNTA is of high importance.[2,3] Previous work has shown that devleopment of BoNTA inhibitors is particularly challenging because the enzyme-substrate interface is unusually large. Recently, Pang computationally docked potential inhibitors into the zinc endopeptidase active site of BoNTA and then synthesized and tested the best drug candidates (Figure 1).[4-7] The best inhibitors consisted of two heterocyclic halves: a 2-phenlyindole and a 2-phenylthiophene (**1**, Ki = 15μM).[6] Further computational and synthetic studies recently showed that further elaboration of the 2-aryl thiophene moiety provided increased BoNTA inhibition (**2**, Ki = 5.4μM).[4]

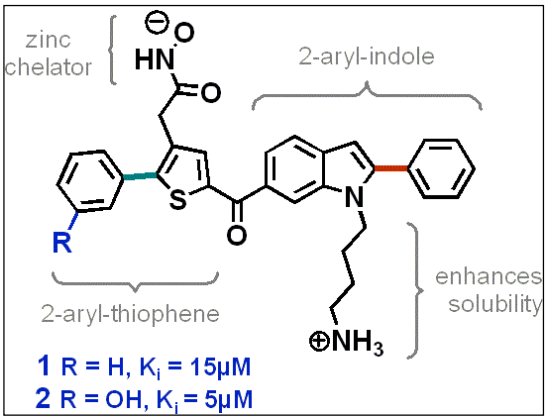
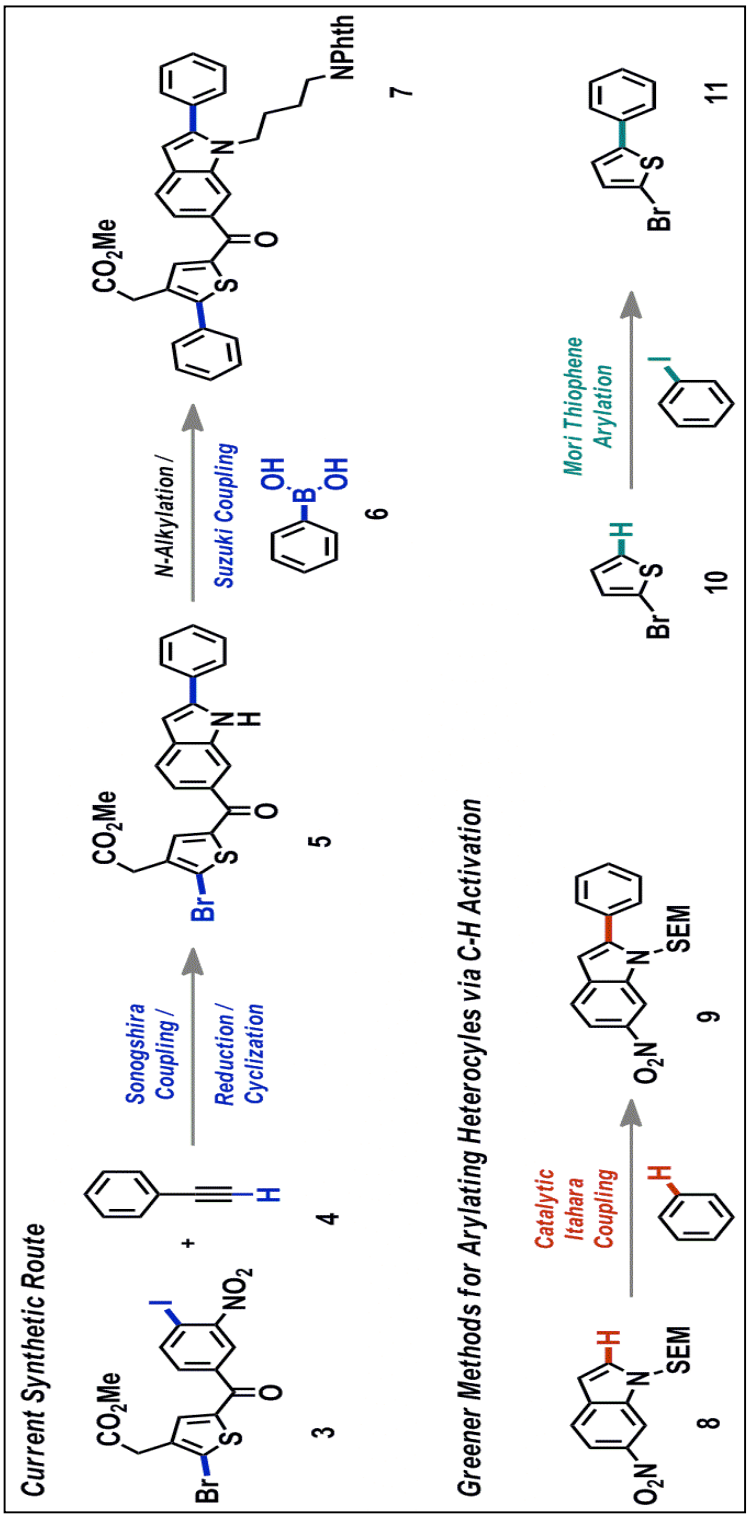


Figure 1 Structure of thiophene-indole BoNTA inhibitors

Results and Discussion

In general, two synthetic strategies can be envisioned for the synthesis of these aryl substituted heterocycles (Scheme 1): the biaryl bond could be synthesized via an organometallic coupling or the heterocycle could be constructed via annulation of an aryl-substituted linear substrate. Pang and co-workers employed both of these paths by cyclizing a 2- alkylaniline to form the 2-arylindole substructure and by arylating a 2-bromothiophene in a Suzuki reaction.[4]



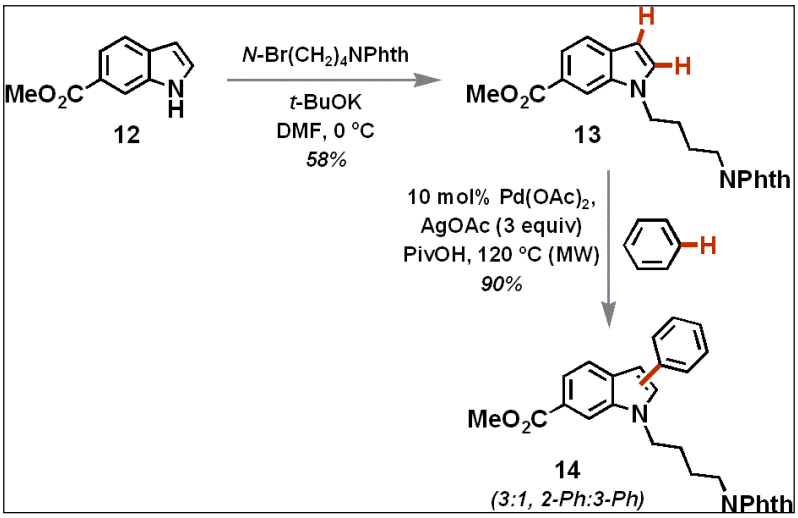
Scheme 1 Comparison of synthetic schemes for constructing arylated heterocycles

Contrastingly, Itahara developed a method for oxidatively coupling heteroarenes such as indoles, pyrroles and furans with benzene in the early 1980's.[8-10] These original reactions required superstoichiometric amounts of palladium acetate. We and others have recently developed catalytic methods for directly arylating heterocycles involving either one or two C-H functionalizations.[11-16] These methods offer the benefit of greater step economy by using readily available hydrocarbon starting materials.[17,18] Herein, we present a novel method for synthesizing inhibitor **1** using two key palladium catalyzed C-H activation steps.

We have recently shown that electron-rich aromatic heterocycles and benzene-derived arenes can be oxidatively cross-coupled by palladium catalysis. For example, both we and the Fagnou group have shown that *N*-acetylindoles can be regioselectively coupled with benzene at either their 2- or 3-position depending on the nature of the oxidant chosen for the reaction.[19-23] We have extended this methodology to include *N*-alkylindoles, a considerably more challenging class of compounds due to their tendency to decompose in the oxidative reaction conditions. In particular, we have found that *N*-alkylindoles bearing electron-withdrawing groups provide high levels of regioselectivity, favoring the 2-aryl-product.[16] Consequently, **1** appeared to be an ideal target for the application of our oxidative coupling technology.

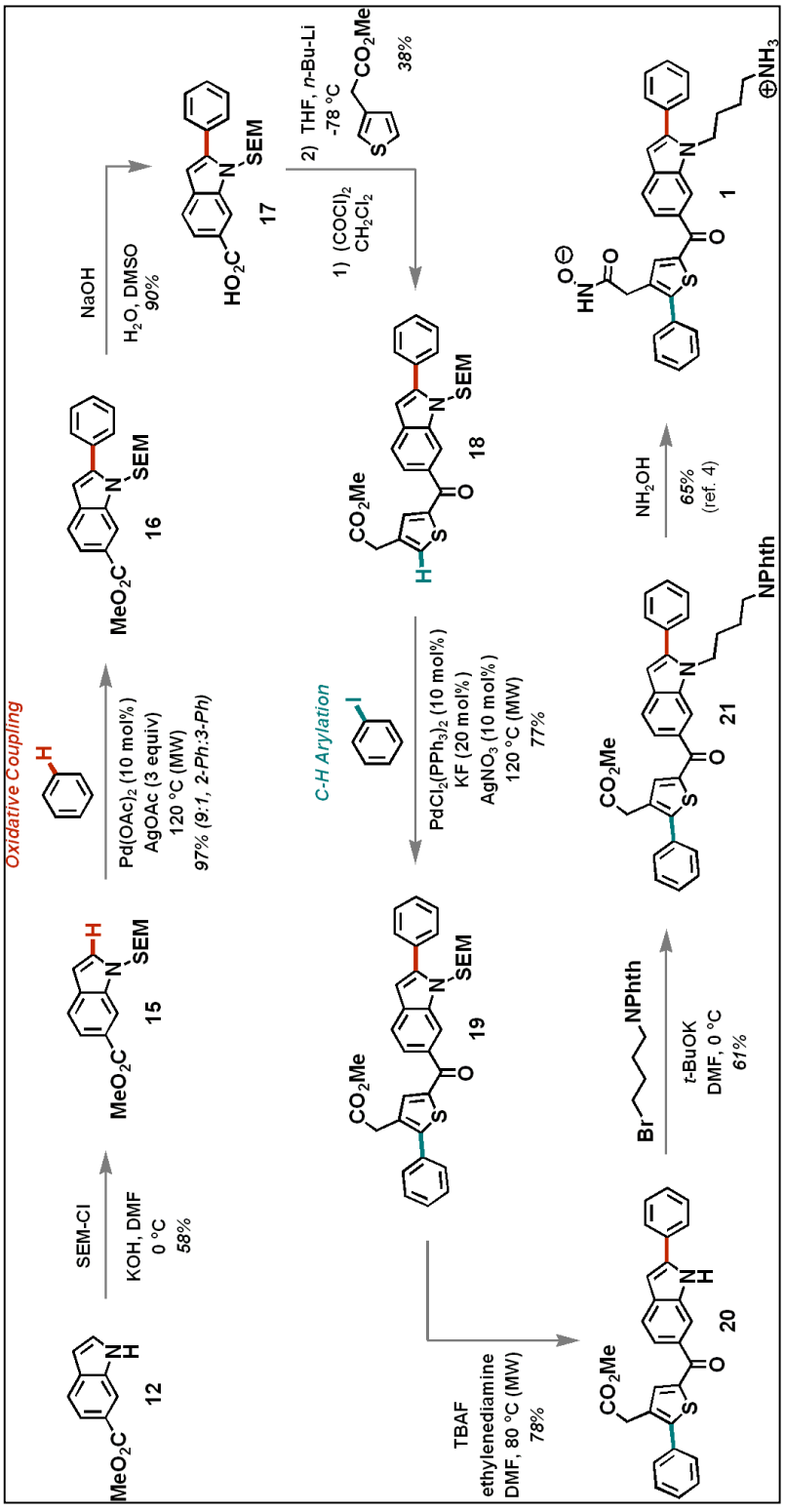
We commenced our study by attempting the oxidative arylation of the butylphthalimide protected ester indole **13**, but low regioselectivity was observed (**14**; 3:1, 2-Ph:3-Ph), and the two regioisomers were inseparable by flash

chromatography (Scheme 2).



Scheme 2 Oxidative arylation of *N*-alkyl protected indole

However, selective oxidative arylation of the SEM-protected indole **15**,[24] using catalytic palladium acetate ($PdOAc_2$) and silver acetate (AgOAc) as an oxidant, afforded **16** in a good yield with a 9:1 regioselectivity favoring arylation at the indole's 2-position, and these regiomers could be separated via flash chromatography. The optimal conditions contained a slight excess of AgOAc (3 equiv) compared to pivalic acid (PivOH, 2.5 equiv), which likely prevents the acid-promoted oxidative decomposition of the indole substrate and products (Scheme 3).[19]



Scheme 3 Synthetic scheme for BoNTA inhibitor **1**

Alkaline hydrolysis of **16** afforded the free acid **17** in a good yield. In situ conversion of **17** to the acid chloride, followed by Friedel-Crafts acylation, as described by Pang,[4] was attempted, but the desired ketone was not observed. Later, the acid chloride was reacted with the anion of methyl-3-thiopheneacetate to afford the desired product **18** in a modest 38% isolated yield. The isomer which is coupled at the thiophene's 2-position (proximal to the ester), was isolated as a minor product (6% yield). We attribute the selectivity favoring the desired product to steric factors (Scheme 3).

In an effort to expand our methodology to form biaryl C-C bonds by activating two C-H bonds, we initially attempted to oxidatively couple benzene to thiophene **18** using our earlier optimization studies as a guide,[19,22] but the starting material failed to convert. This may be the result of the ability of the thiophene to deactivate the palladium catalyst via coordination of its sulfur atom. However, using Mori's conditions, the C-H bond of the thiophene **18** was selectively arylated using both palladium and silver catalysts and iodobenzene as the arene source.[25] The SEM protecting group of compound **19** was cleaved by treatment with tetrabutylammonium fluoride (TBAF) in DMF to afford **20** and subsequent N-alkylation was carried out with *N*-(4-bromobutyl)-phthalimide in the presence of potassium tert-butoxide to afford the *N*-alkylindole **21**. Finally, the BoNTA inhibitor **1** was synthesized following the procedure of Pang by treating **21** with excess hydroxylamine, which simultaneously converts the methyl ester and phthalimide to hydroxamic acid and amine, respectively (Scheme 3).[4]

Conclusion

In conclusion, we have developed a novel synthetic route for the synthesis of an inhibitor of botulinum neurotoxin serotype A (BoNTA). The 4.6% overall yield is nearly identical to that which was reported by Pang, but the step economy of the overall synthesis has been increased due to the incorporation of reactions which do not rely on prefunctionalized starting materials; rather the biaryl C-C bonds were directly formed from the C-H bonds of simple arenes and heteroarenes. It should also be noted that the C-H functionalizing reactions are two of the highest yielding steps in this synthesis. While our initial attempts to form biaryl C-C bonds with thiophene-type substrates such as **18** were not successful, efforts in our laboratory are currently focused on expanding our oxidative coupling methods to encompass these and other classes of heteroarenes for application to the synthesis of more high-value targets.

Experimental Section

Reagents

Substrates, including methylindole-6-carboxylate, 2-(trimethylsilyl)ethoxymethyl chloride, pivalic acid, *n*-butyllithium, *N*-(4-bromobutyl)-phthalimide, oxalylchloride, methyl-3-thiopheneacetate, silver nitrate, potassium fluoride, bis-(triphenylphosphine) palladium (II) chloride, *n*-tetrabutylammoniumfluoride and *n*-bromobutylpthalimide. All the oxidants used were purchased from Acros Chemicals. Flash chromatography was performed on Silicycle silica gel (60Å, 40- 63 μm). All reagents were stored under an inert atmosphere before use.

$Pd(OAc)_2$

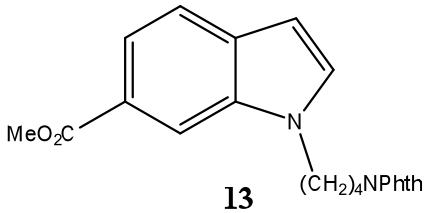
$Pd(OAc)_2$ was obtained from Precious Metals Online (http://www.precmet.com.au/). Upon receipt, it was then dried under vacuum at 100^{o}C for approximately 6 hours.

Instrumentation

Reactions were carried out in CEM Discover Microwave. GC/MS analysis was carried out on an Agilent Technologies 6890 GC System fixed with a 5973 Mass Selective Detector. NMR spectrum were acquired.

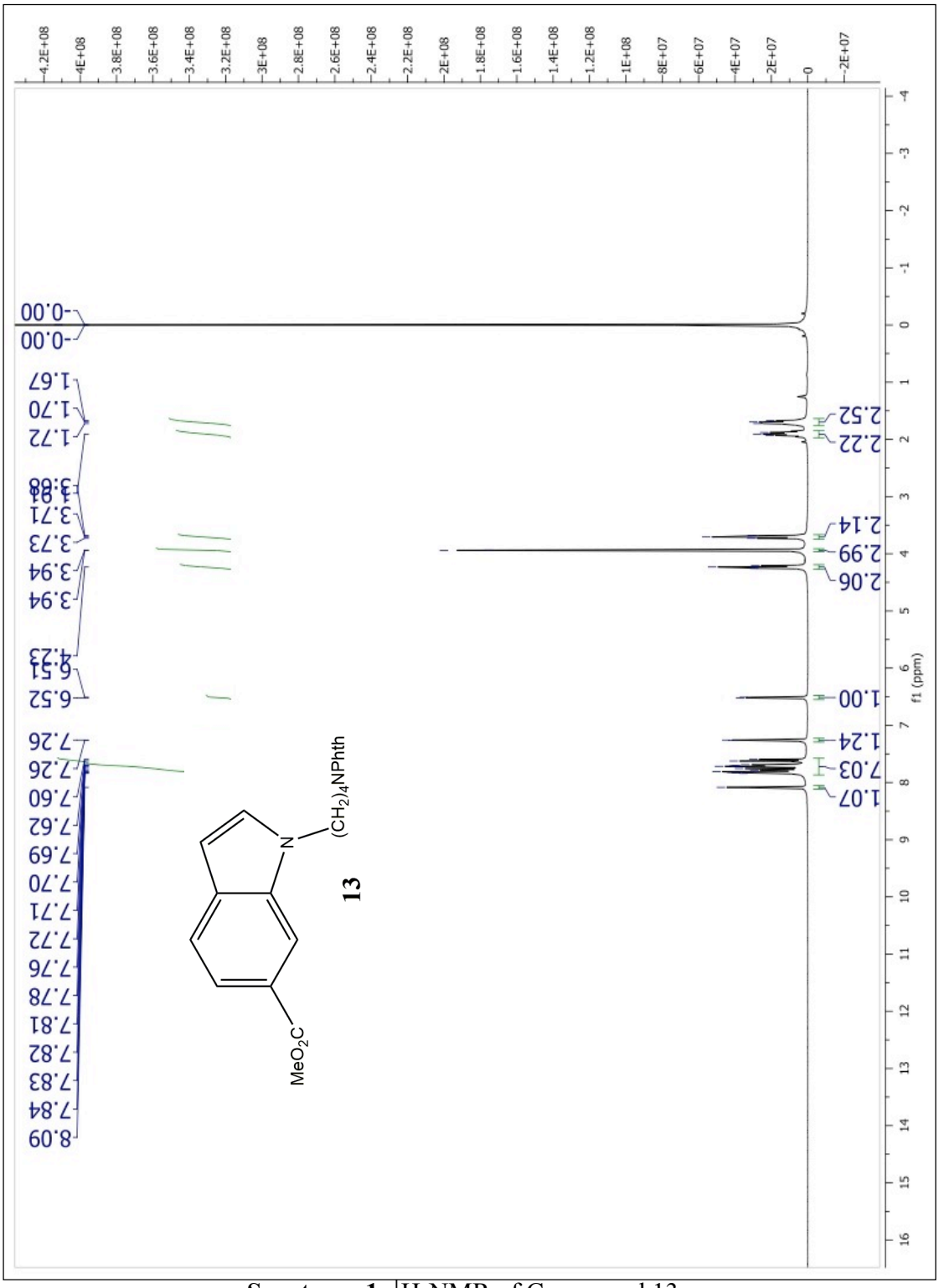
Representative Procedures

Synthesis of methyl-1-(4-(1,3-dioxoisoindolin-2-yl)butyl)-1H-indole-6-carboxylate (13)

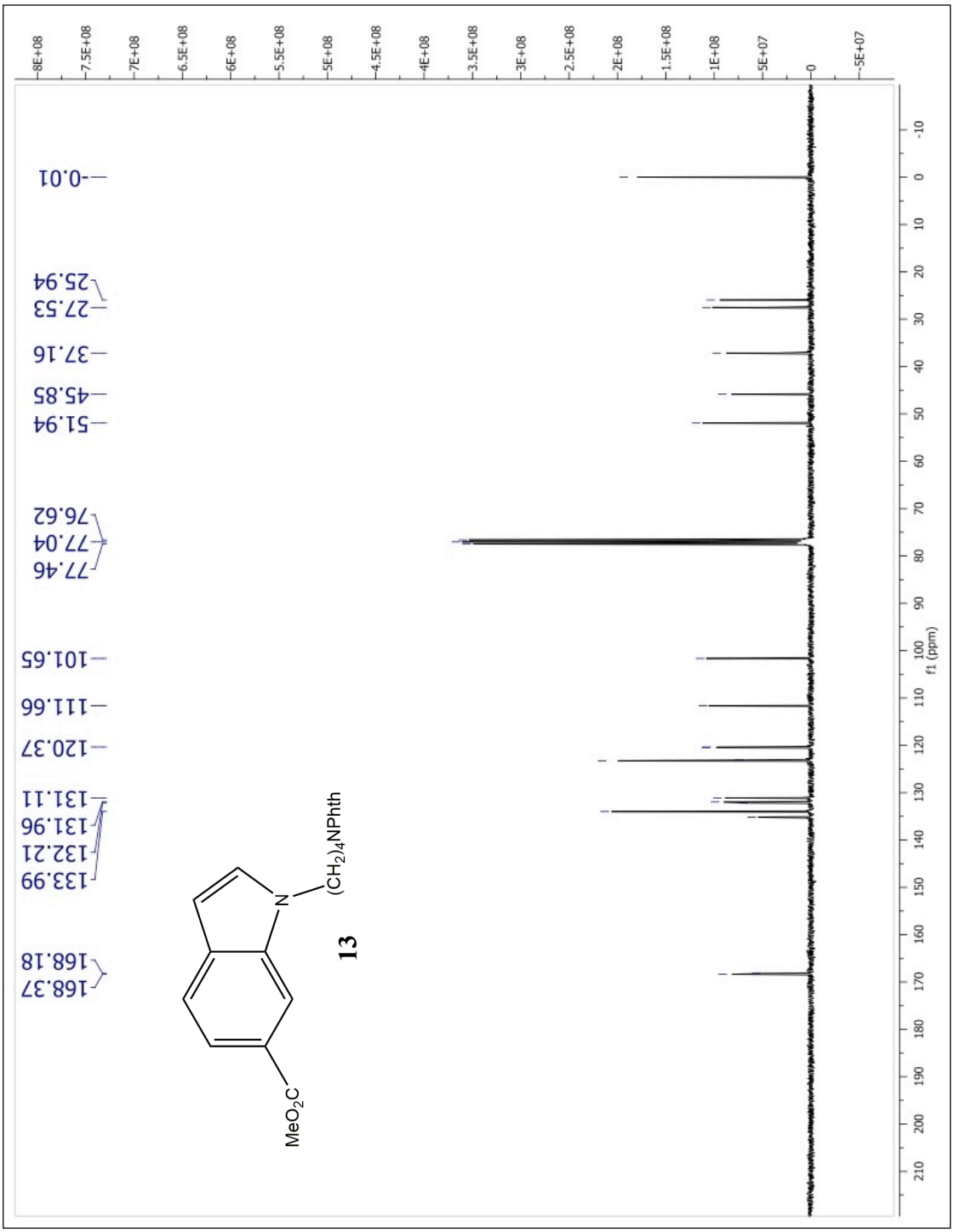


13

To a solution of potassium tert-butoxide (0.143g, 1.28mmol) in 3mL of DMF at 0^{o}C was added a solution of methylindole-6-carboxylate (0.1g, 0.57mmol) in 1mL of DMF and the reaction mixture is stirred for 15min. After stirring for 15mins add a solution of *N*-(4-bromobutyl)-phthalimide (0.264g, 0.93mmol) in 1mL DMF and stirring is continued for 6h. The mixture was diluted with 40mL of water and extracted with three 40mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **13** 0.124g (58%), $\boldsymbol{R_f}$ **-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.26, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 1.68 (m, 2H), 1.88 (m, 2H), 3.69 (t, ^{3}J =3.0 Hz, 2H), 3.91 (s, 3H), 4.21 (t, ^{3}J =6.0 Hz, 2H), 6.49 (d, ^{3}J =3.0 Hz, 1H), 7.60-7.82 (m, 7H),8.06 (d, ^{4}J =3.0 Hz, 1H), **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 25.94, 27.53, 37.16, 45.85, 51.94,101.65, 111.66, 120.37, 120.51, 131.11, 131.96, 132.21, 133.39, 135.18, 168.18, 168.37, **LRMS EI (m/z):** [M+] calc'd for $C_{22}H_{20}N_2O_4$ 376.41, observed 376.20 m/z.

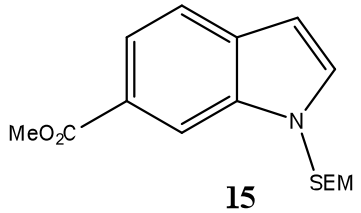


Spectrum 1. ^{1}H-NMR of Compound 13



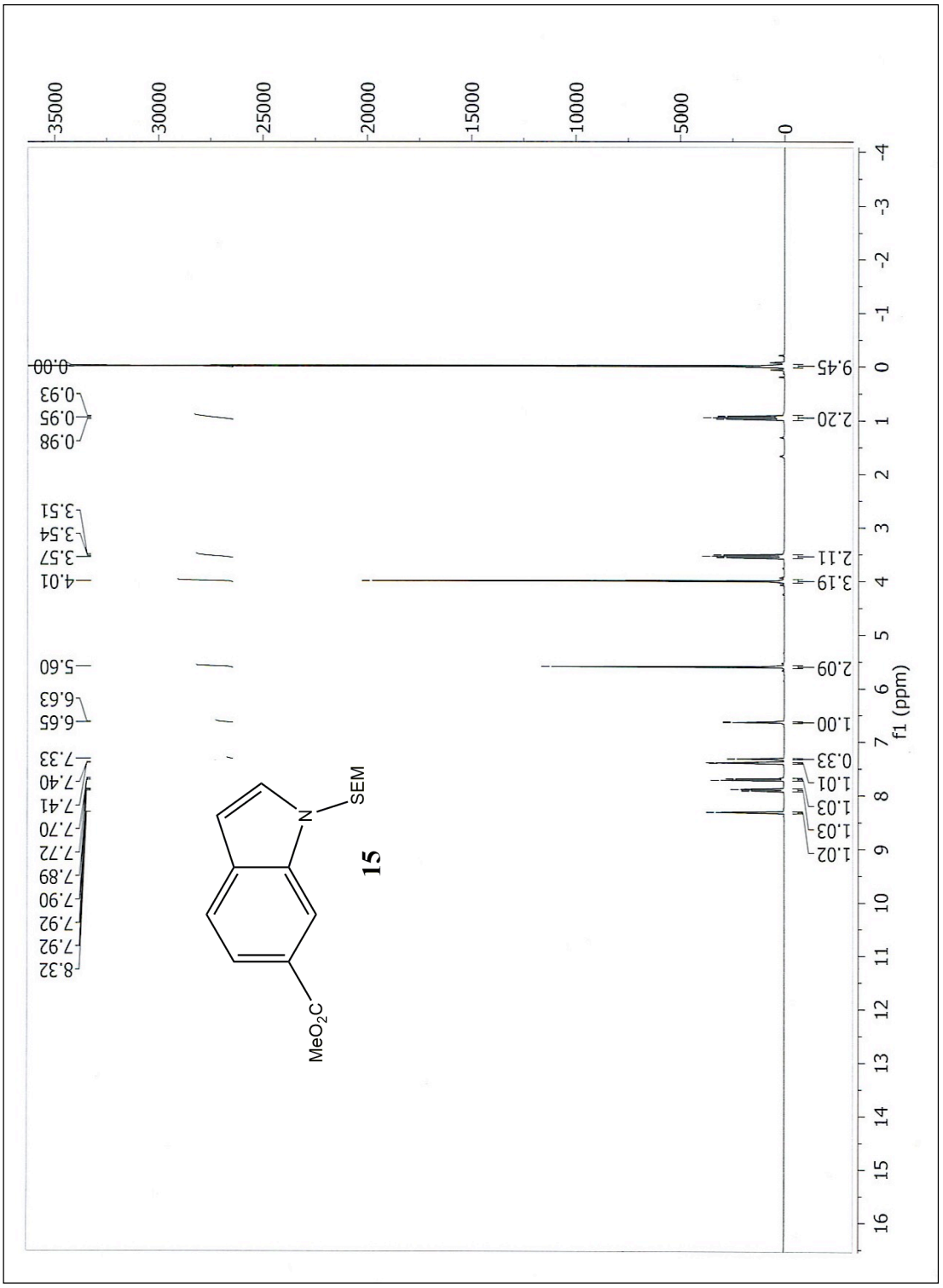
Spectrum 2. ^{13}C-NMR of Compound 13

Synthesis of 1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carboxylate (15)

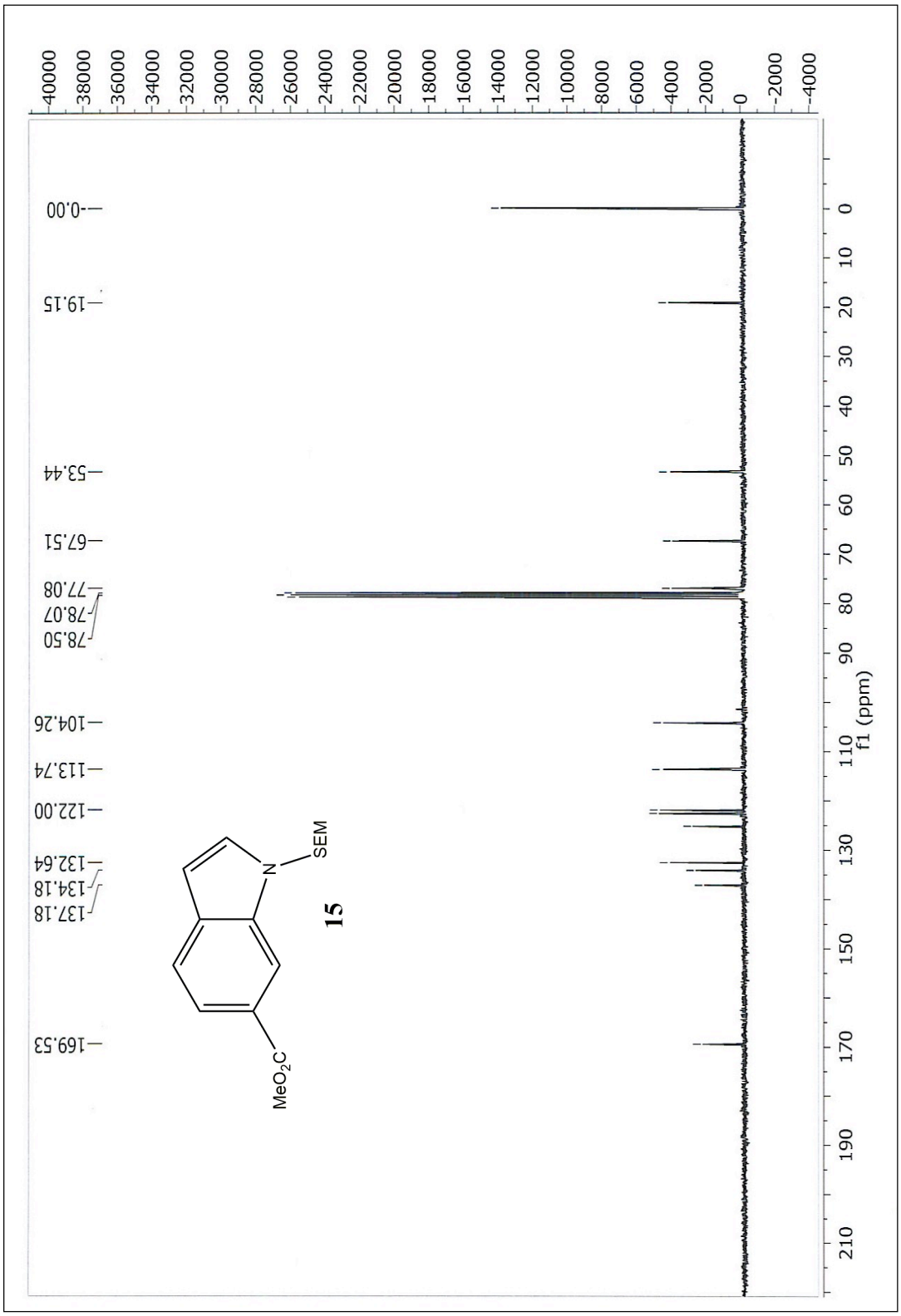


15

To a solution of potassium hydroxide (0.105g, 1.88mmol) in 6mL of DMF at 0^{o}C was added a solution of methylindole-6-carboxylate (0.3g, 1.71mmol) in 2mL of DMF and the reaction mixture is stirred for 15min. After stirring for 15mins add a solution of 2-(trimethylsilyl)ethoxymethylchloride (0.285g, 1.71mmol) in 2mL DMF and stirring is continued for 4h. The mixture was diluted with 40mL of water and extracted with three 40mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **15** 0.309g (59%), $\boldsymbol{R_f}$ **-Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.20, **^{1}H-NMR (300 MHz, CDCl$_3$):** δ = 0.00 (s, 9H), 0.95 (t, ^{3}J =8.28 Hz, 2H), 3.54 (t, ^{3}J = 8.07 Hz, 2H), 4.01 (s, 3H), 5.60 (s, 2H), 6.63 (d, ^{3}J =3.15 Hz, 1H), 7.39 (d, ^{3}J =3.21 Hz, 1H), 7.70 (d, ^{3}J =8.34 Hz, 1H), 7.90 (dd, ^{3}J =8.31 Hz, ^{4}J = 1.26 Hz, 1H), 8.31 (s, 1H), **^{13}C-NMR (75 MHz, CDCl$_3$):** δ = 0.00, 19.15, 53.44, 67.51, 77.08, 104.26, 113.74, 122.00, 122.71, 125.26, 132.63, 134.17, 137.18, 169.53, **LRMS EI (m/z):** [M+] calc'd for $C_{16}H_{23}NO_3Si$ 305.14, observed 305.10 m/z.

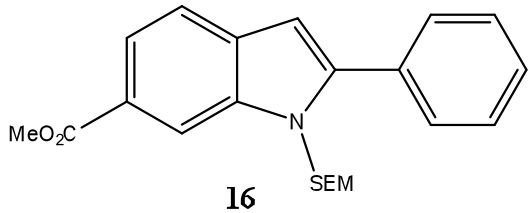


Spectrum 3. ^{1}H-NMR of Compound 15



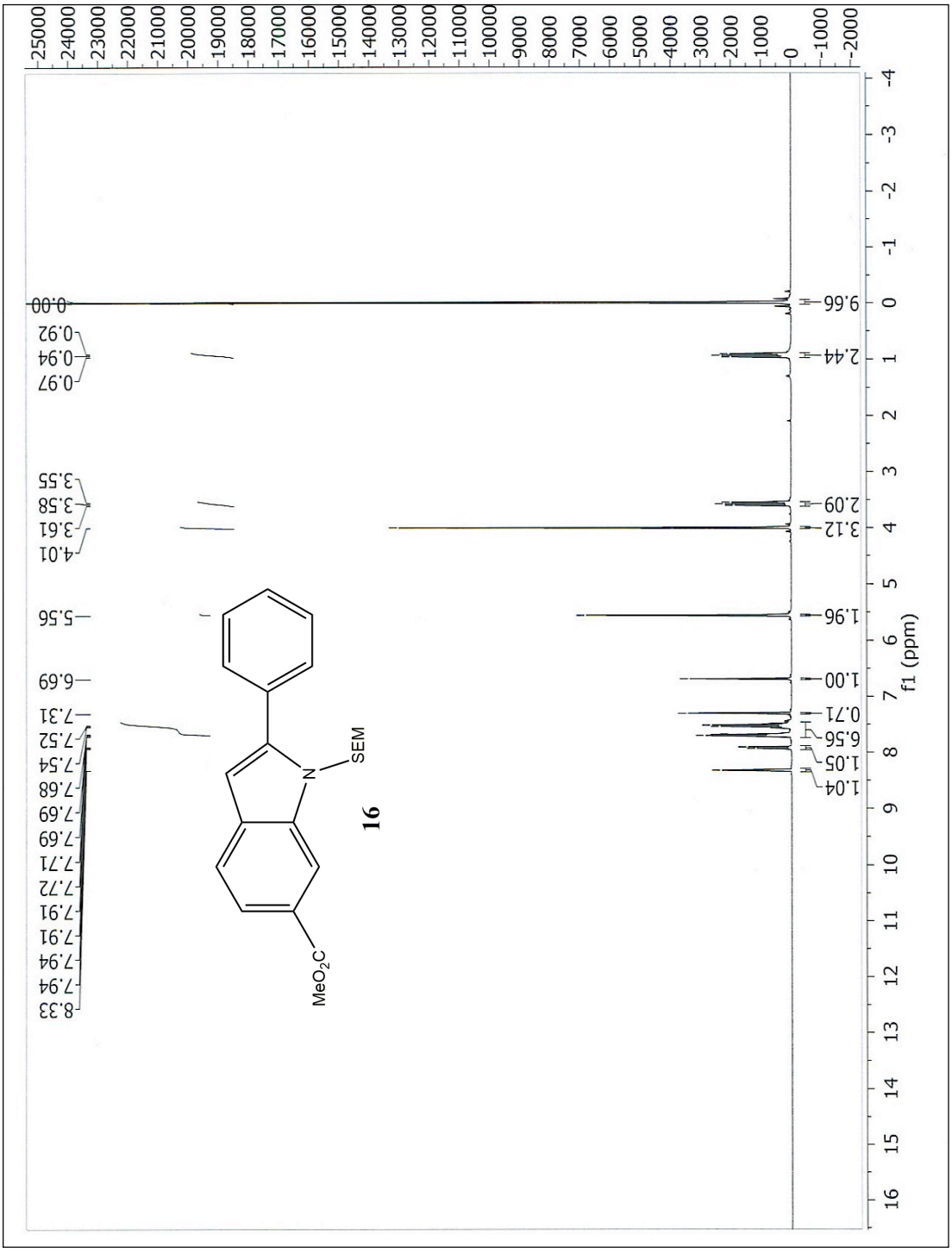
Spectrum 4. ^{13}C-NMR of Compound 15

Synthesis of 2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carboxylate (16)

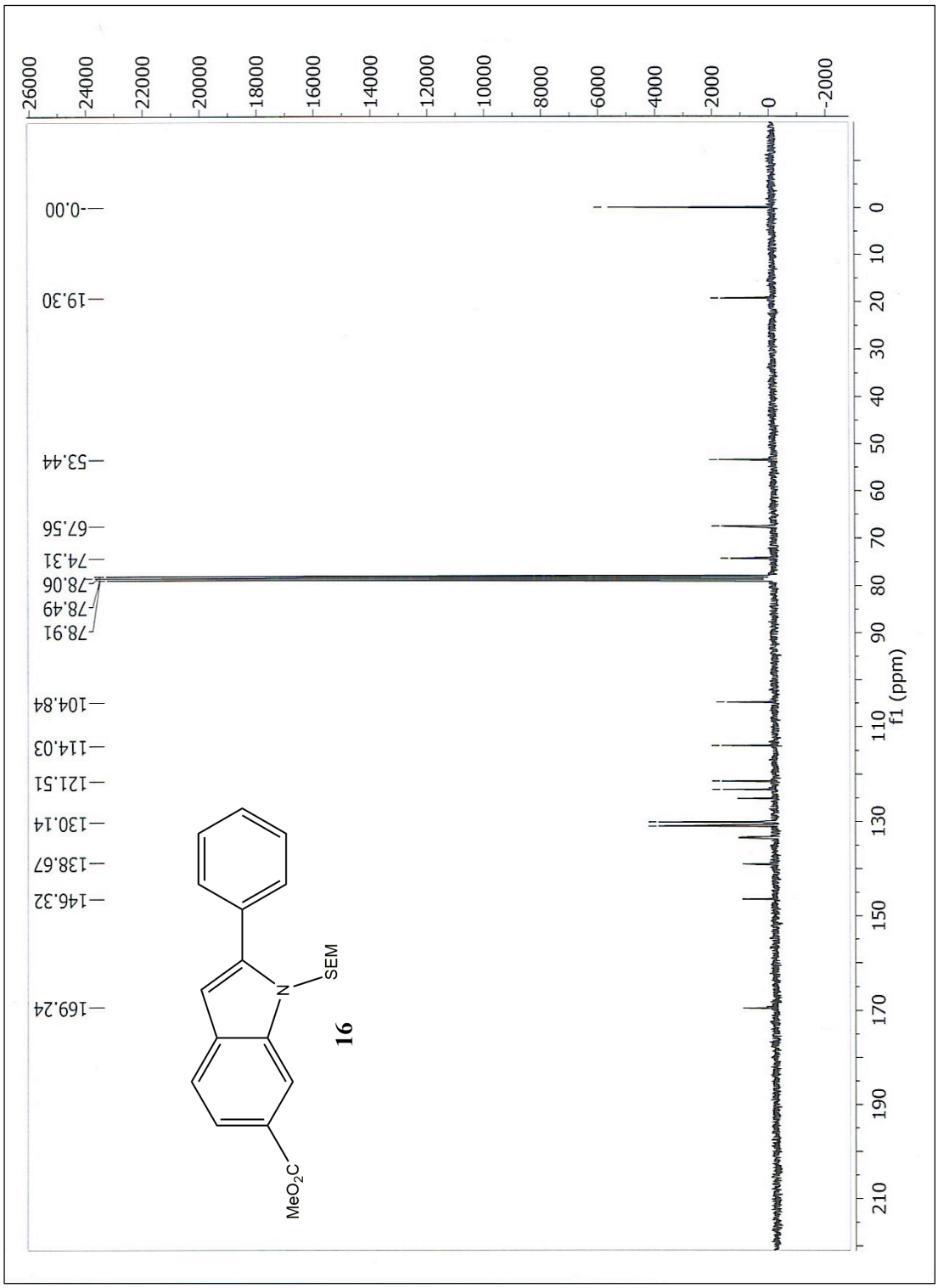


16

A magnetically stirred solution of 1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carboxylate (0.064g, 0.21mmol), palladium acetate (0.0047g, 0.021mmol), silver acetate (0.104g, 0.63mmol), 2,2-dimethylpropanoic acid (0.053g, 0.52mmol) in 5mL of benzene was microwave heated at 120^{o}C for 3h. After evaporation of the solvent, the mixture was diluted with 40mL of water and extracted with three 50mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of brine followed by two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **16** 0.078g (97%), ***R_f* -Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.24, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 0.00 (s, 9H), 0.94 (t, ^{3}J =8.37 Hz, 2H), 3.58 (t, ^{3}J = 8.16 Hz, 2H), 4.01 (s, 3H), 5.56 (s, 2H), 6.69 (s, 1H), 7.52-7.71 (m, 6H), 7.91 (dd, ^{3}J =8.28 Hz, ^{4}J = 1.20 Hz, 1H), 8.33 (s, 1H), **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 0.00, 19.30, 53.44, 67.56, 104.84, 114.03, 121.51, 123.27, 125.16, 130.10, 130.14, 131.00, 133.48, 138.67, 146.32, 169.24, **LRMS EI (m/z):** [M+] calc'd for $C_{22}H_{27}NO_3Si$ 381.18, observed 381.20 m/z.

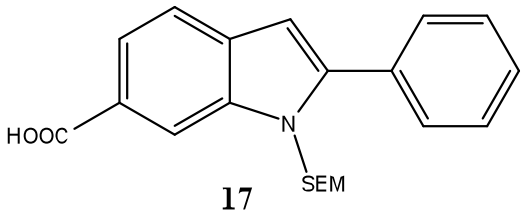


Spectrum 5. ^{1}H-NMR of Compound 16



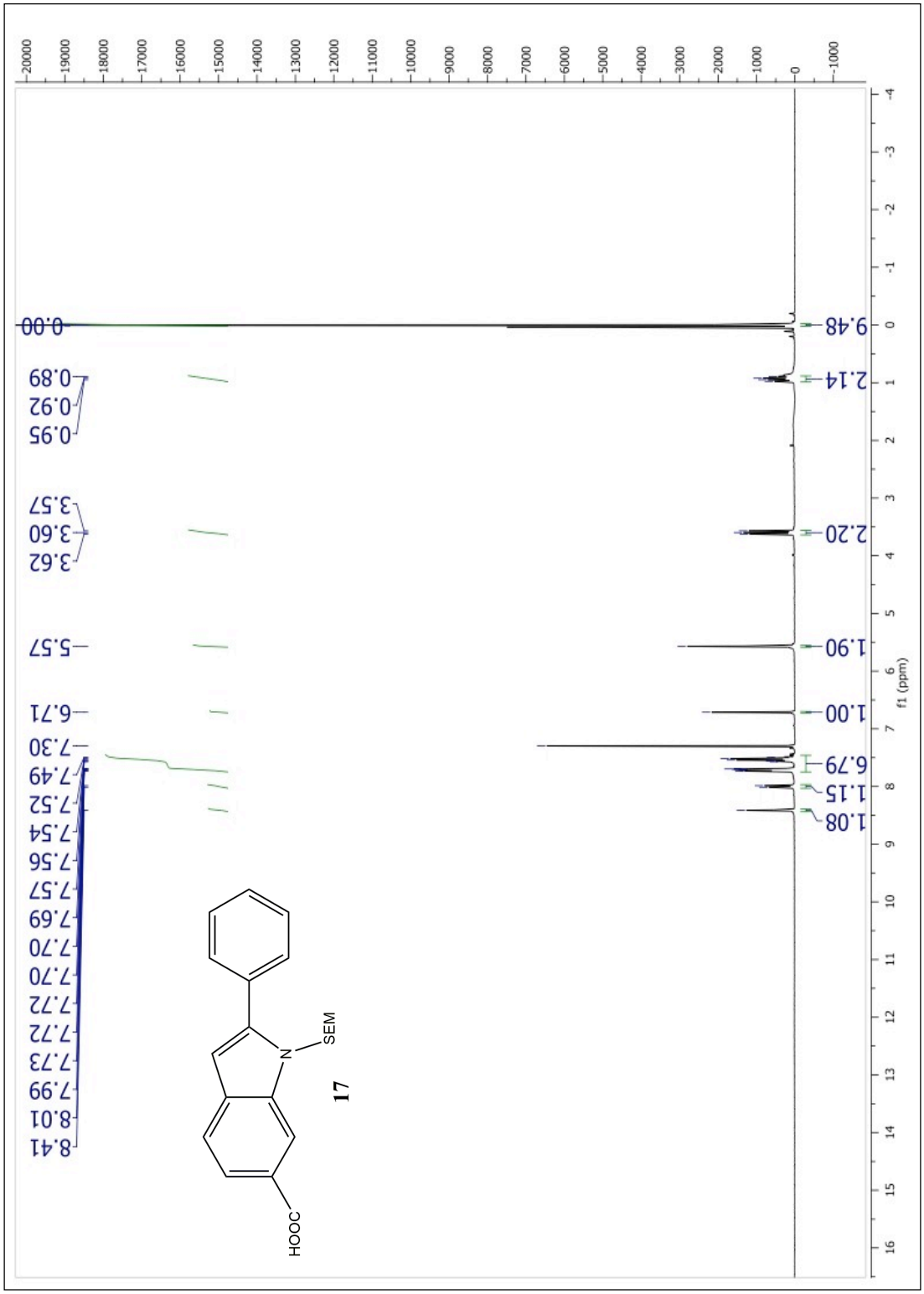
Spectrum 6. ^{13}C-NMR of Compound 16

Synthesis of 2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carboxylic acid (17)

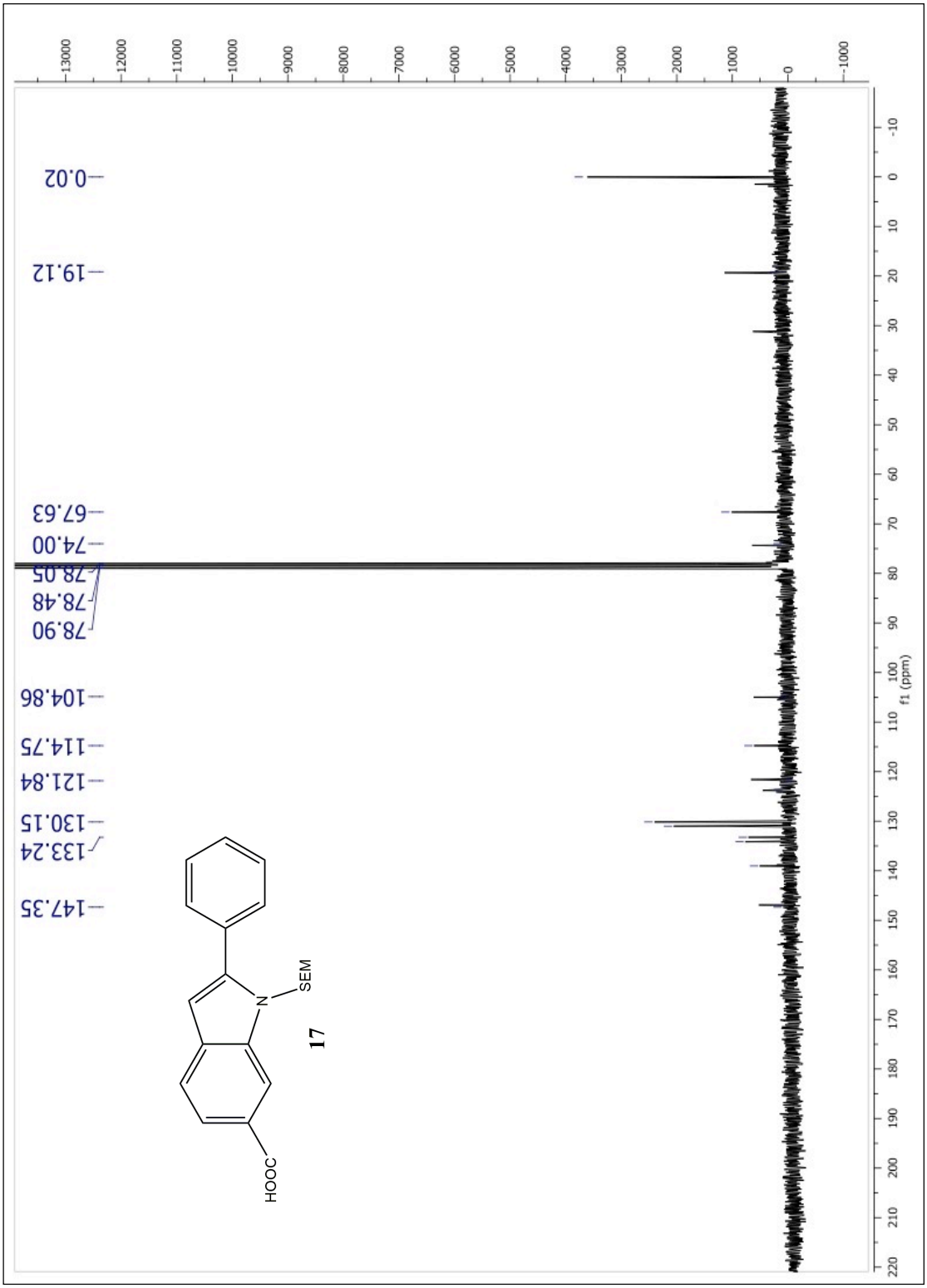


17

A magnetically stirred solution of 2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carboxylate (0.073g, 0.19mmol) and 50% w/w aqueous sodium hydroxide (0.030, 0.38mmol) in 6mL of DMSO was stirred for 2h at room temperature. The mixture was diluted with 40mL of water and extracted with three 60mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **17** 0.063g (90%), $\boldsymbol{R_f}$ **-Value:** Hexane/Ethyl acetate (7:3 *v/v*) = 0.32, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 0.00 (s, 9H), 0.92 (t, ^3J =8.37 Hz, 2H), 3.60 (t, ^3J = 8.16 Hz, 2H), 5.57 (s, 2H), 6.67 (s, 1H), 7.52-7.73 (m, 6H), 7.99 (dd, ^3J =8.28 Hz, ^4J = 1.20 Hz, 1H), 8.33 (s, 1H), **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 0.01, 19.30, 67.61, 74.32, 104.96, 114.74, 121.59, 123.78, 130.14, 131.00, 133.23, 134.14, 139.02, 147.35, **HRMS ESI (m/z):** [M+Na] calc'd for $C_{21}H_{25}NO_3Si$ 390.16, observed 389.96 m/z.

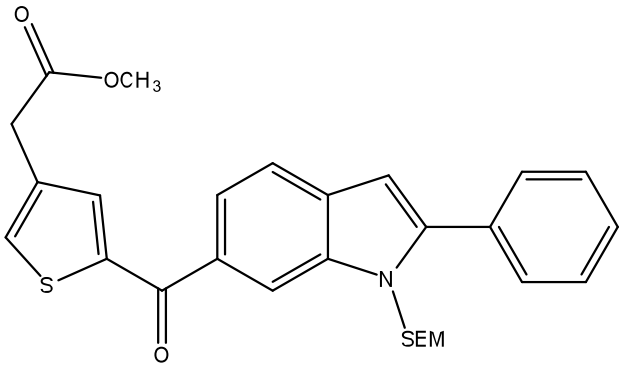


Spectrum 7. ^{1}H-NMR of Compound 17



Spectrum 8. ^{13}C-NMR of Compound 17

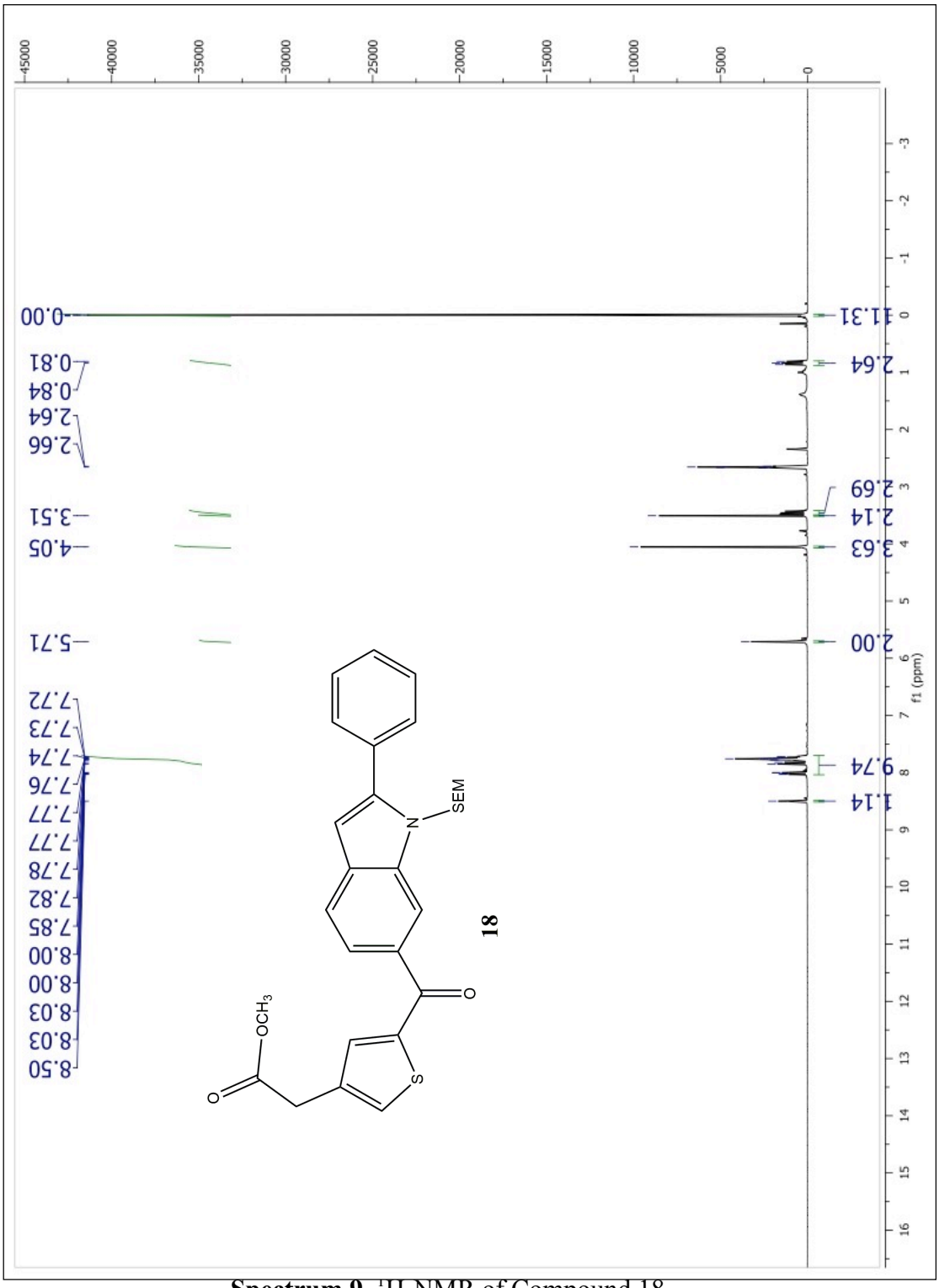
Synthesis of methyl-5-(2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carbonyl)thiophen-3-yl)acetate (18)



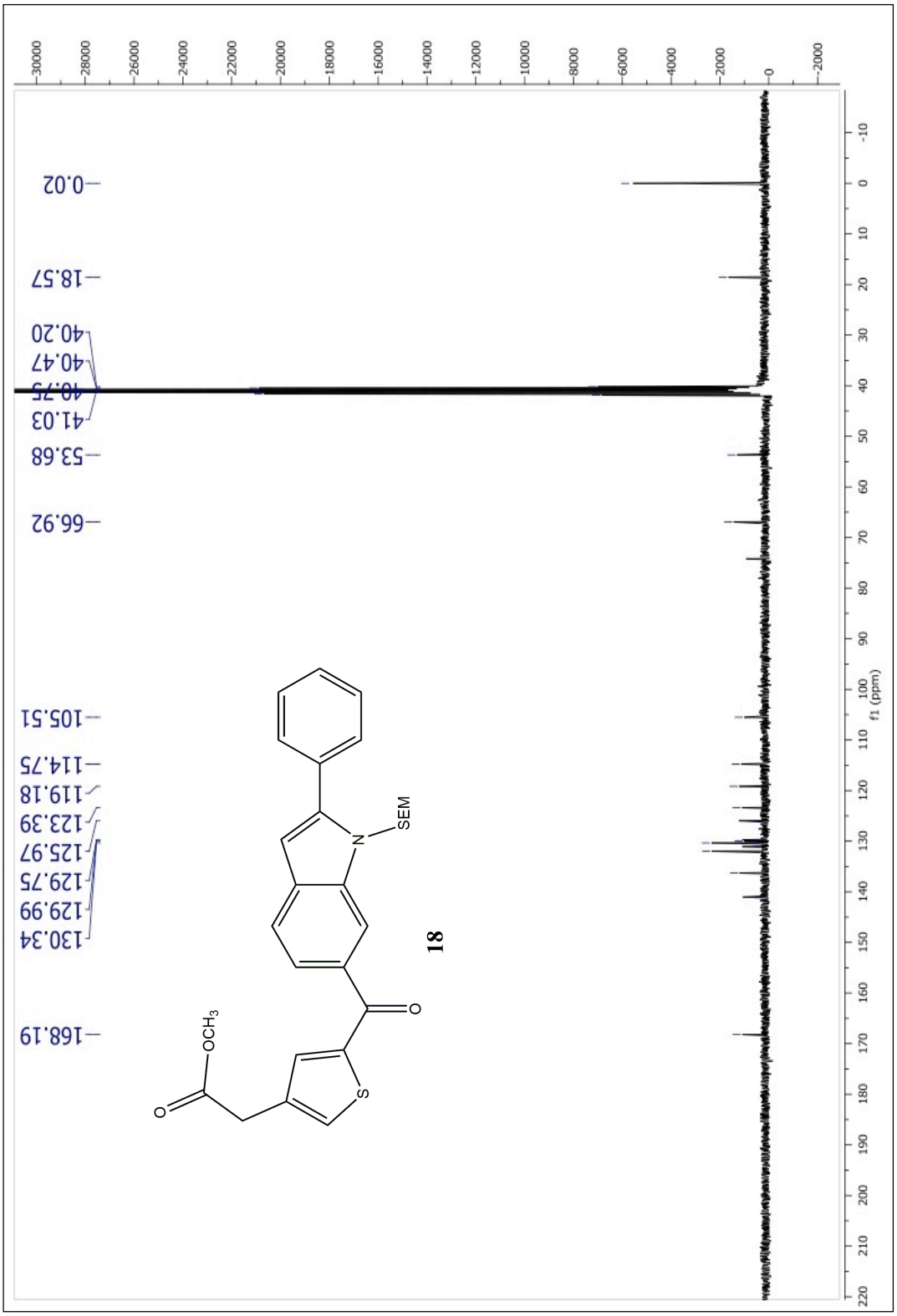
18

A magnetically stirred solution of 2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carboxylicacid (0.560g, 1.52mmol) and oxalyl chloride (0.967g, 7.61mmol) in 10mL of dry dichloromethane was stirred for 2h at room temperature. The solvent was removed at reduced pressure, reaction mixture was re-diluted in 10mL of dry THF and cooled at -78 ^{0}C. The cooled reaction mixture is transferred using a canula to a magnetically stirred solution of methyl-3-thiopheneacetate (0.261g, 1.67mmol) and n-butyl lithium (0.312g, 5.01mmol) at -78 ^{0}C.After stirring the reaction mixture for 2h, the solvent was removed under reduced pressure and the mixture was diluted with 40mL of water and extracted with three 60mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **18** 0.292g (38%). ***R_f* -Value:** Hexane/Ethyl acetate (10:1 *v/v*) = 0.20, **^{1}H-NMR (300 MHz, DMSO-d$_6$):** δ = 0.00 (s, 9H), 0.82 (t, ^3J =8.37 Hz, 2H), 3.46 (t, ^3J = 8.16 Hz,

2H), 3.51 (s, 2H), 4.05 (s, 3H), 5.71 (s, 2H), 7.72 -8.03 (m, 10H), 8.50 (s, 1H), **^{13}C-NMR (75 MHz, DMSO-d$_6$):** δ = 0.02, 18.55, 53.66, 66.90, 74.18, 105.50, 114.74, 119.17, 123.38, 125.93, 129.70, 129.97, 130.33, 131.04, 131.96, 136.27, 141.04, 168.19

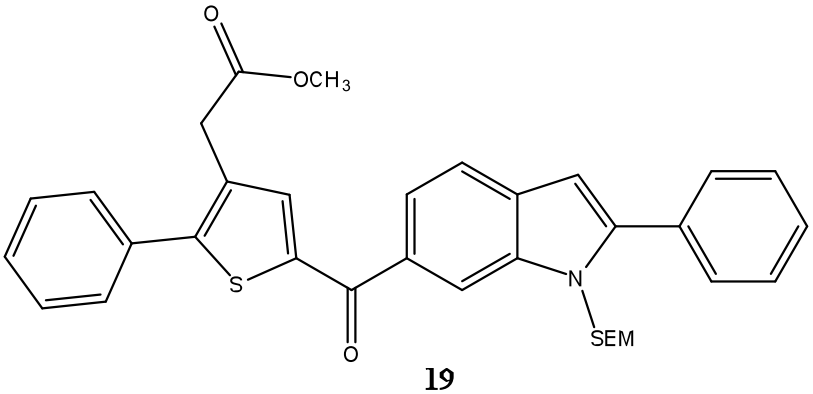


Spectrum 9. ^{1}H-NMR of Compound 18



Spectrum 10. ^{13}C-NMR of Compound 18

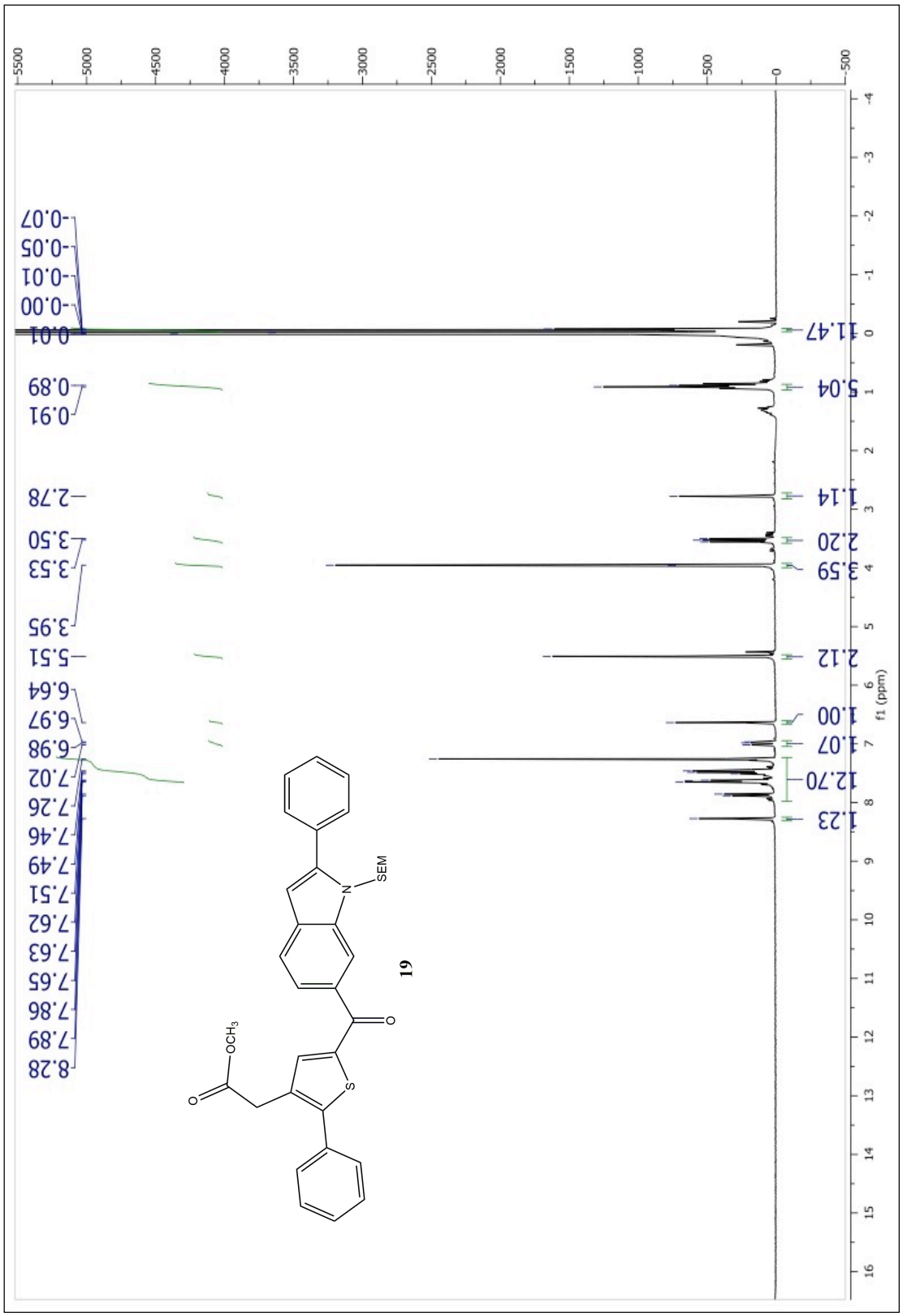
Synthesis of methyl (2-phenyl-5-(2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carbonyl)thiophen-3-yl)acetate (19)



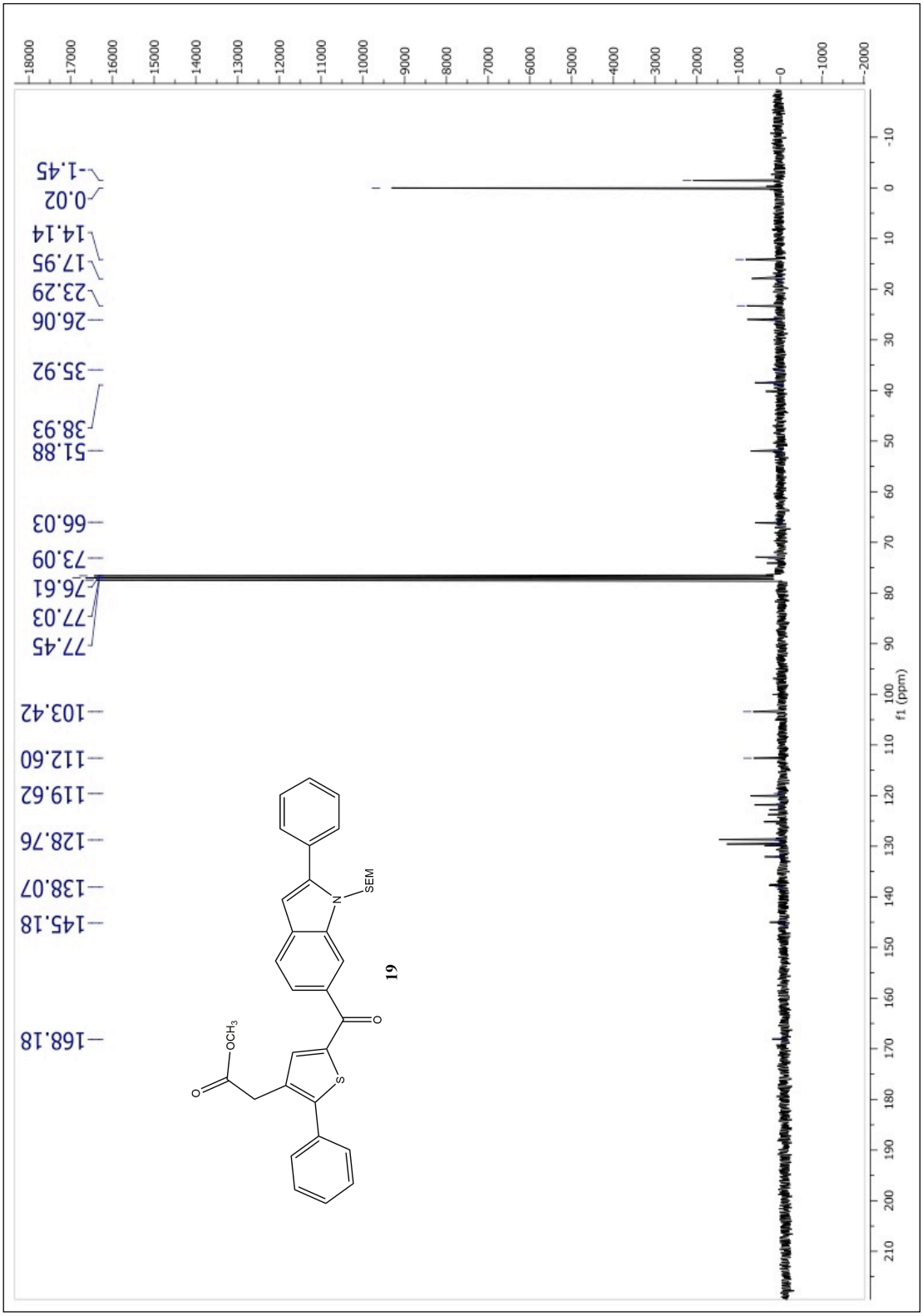
19

A magnetically stirred solution of methyl-5-(2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carbonyl)thiophen-3-yl)acetate (0.067g, 0.132mmol), $PdCl_2(PPh_3)_2$ (0.009g, 0.013mmol), potassium fluoride (0.0015g, 0.026mmol), $AgNO_3$ (0.0022g, 0.013mmol) in 3mL of iodobenzene and 2mL of DMSO was microwave heated at 120^0C for 3h. After evaporation of the solvent, the mixture was diluted with 40mL of water and extracted with three 60mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of brine followed by two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **19** 0.059g (77%), $\boldsymbol{R_f}$ **-Value:** Hexane/Ethyl acetate (9:1 *v/v*) = 0.45, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = -0.01 (s, 9H), 0.86 (t, ^3J =8.37 Hz, 2H), 2.78 (s, 2H), 3.50 (t, ^3J = 8.16 Hz, 2H), 3.95 (s, 3H), 5.51 (s, 2H), 6.64 (s, 1H), 6.98 (m, 1H), 7.26-7.65 (m, 11H), 7.86 (dd, ^3J =8.28 Hz, ^4J = 1.20 Hz, 1H), 8.28 (s, 1H), **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = -0.01, 17.87, 40.15, 51.94, 66.10, 72.88, 103.41, 112.59, 120.05, 121.83, 125.16, 128.67, 129.56, 129.88, 132.06,

137.73, 145.11, 168.07, **HRMS ESI (m/z):** $[M+H]^+$ calc'd for $C_{34}H_{35}NO_4SSi$ 581.21, observed 582.37 m/z.

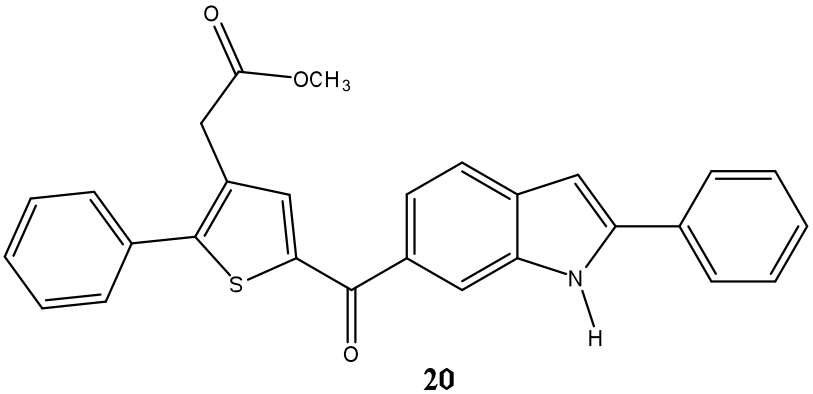


Spectrum 11. ^{1}H-NMR of Compound 19



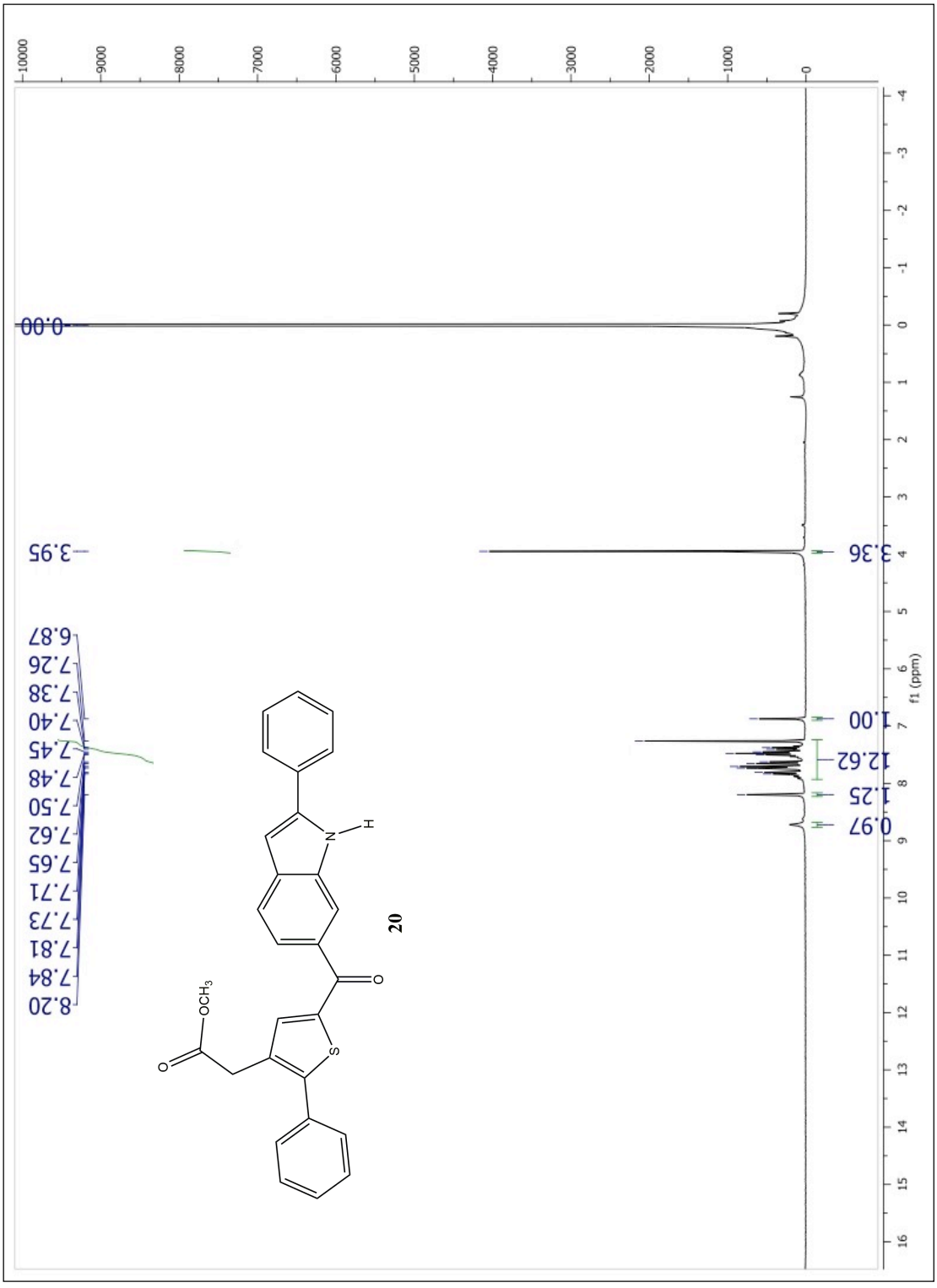
Spectrum 12. ^{13}C-NMR of Compound 19

Synthesis of methyl (2-phenyl-5-(2-phenyl-1-H-indole-6-carbonyl)thiophen-3-yl)acetate (20)

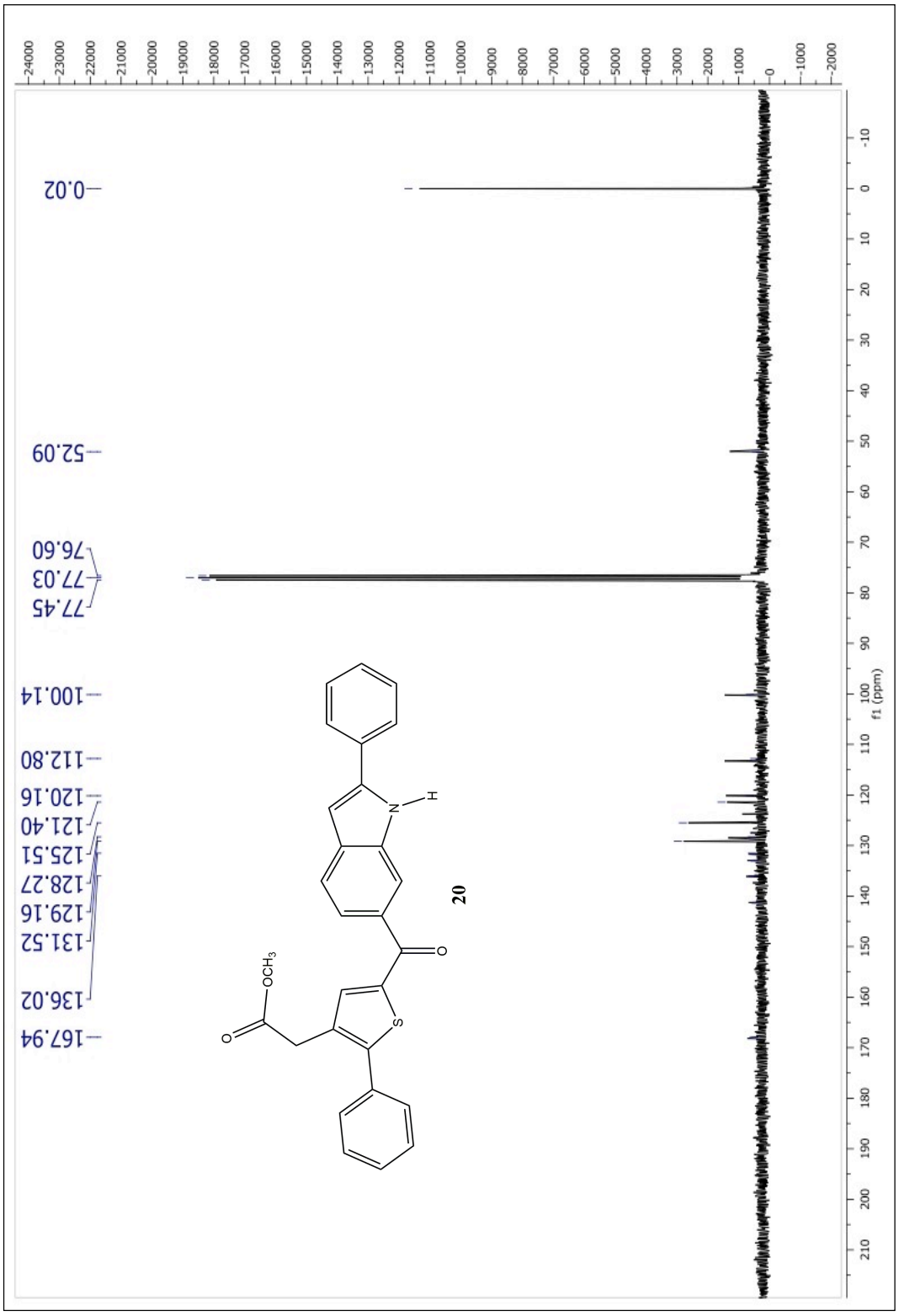


20

A magnetically stirred solution of methyl-(2-phenyl-5-(2-phenyl-1-[2-(trimethylsilyl)-ethoxymethyl]-indole-6-carbonyl)thiophen-3-yl)acetate (0.160g, 0.275mmol), tetra-*n*-butylammoniumfluoride (0.386g, 1.47mmol), DMF (3mL), and ethylenediamine (1.5mL) was microwave heated at 80 ^{o}C for 3h. The mixture was diluted with 40mL of water and extracted with three 60mL portions of ethyl acetate. The extract was washed successively with dilute hydrochloric acid (1N) and 10% sodium bicarbonate solution and after the extract was dried, the solvent was removed in vacuo. The residue was purified by column chromatography to give pure **20** 0.097g (78%), $\boldsymbol{R_f}$ **-Value:** Hexane/Ethyl acetate (8:2 *v/v*) = 0.26, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 3.95 (s, 3H), 6.87 (s, 1H), 7.38-7.84 (m, 14H), 8.20 (bs, 1H), **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 52.09, 100.14, 112.80, 120.16, 121.40, 125.51, 128.27, 129.16, 131.52, 136.02, 167.94, **HRMS ESI (m/z):** $[M+2H]^{2+}$ calc'd for $C_{28}H_{21}NO_3S$ 226.77, observed 227.08 m/z

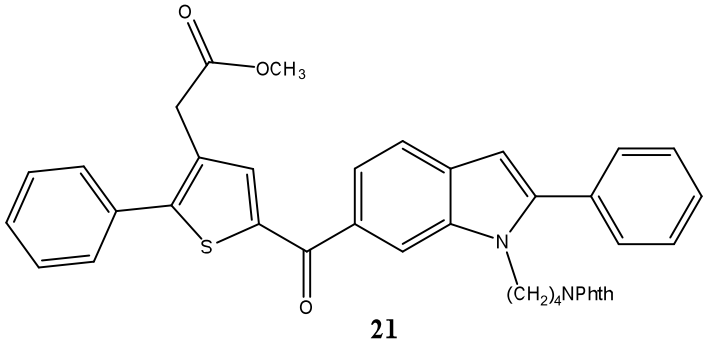


Spectrum 13. ^{1}H-NMR of Compound 20



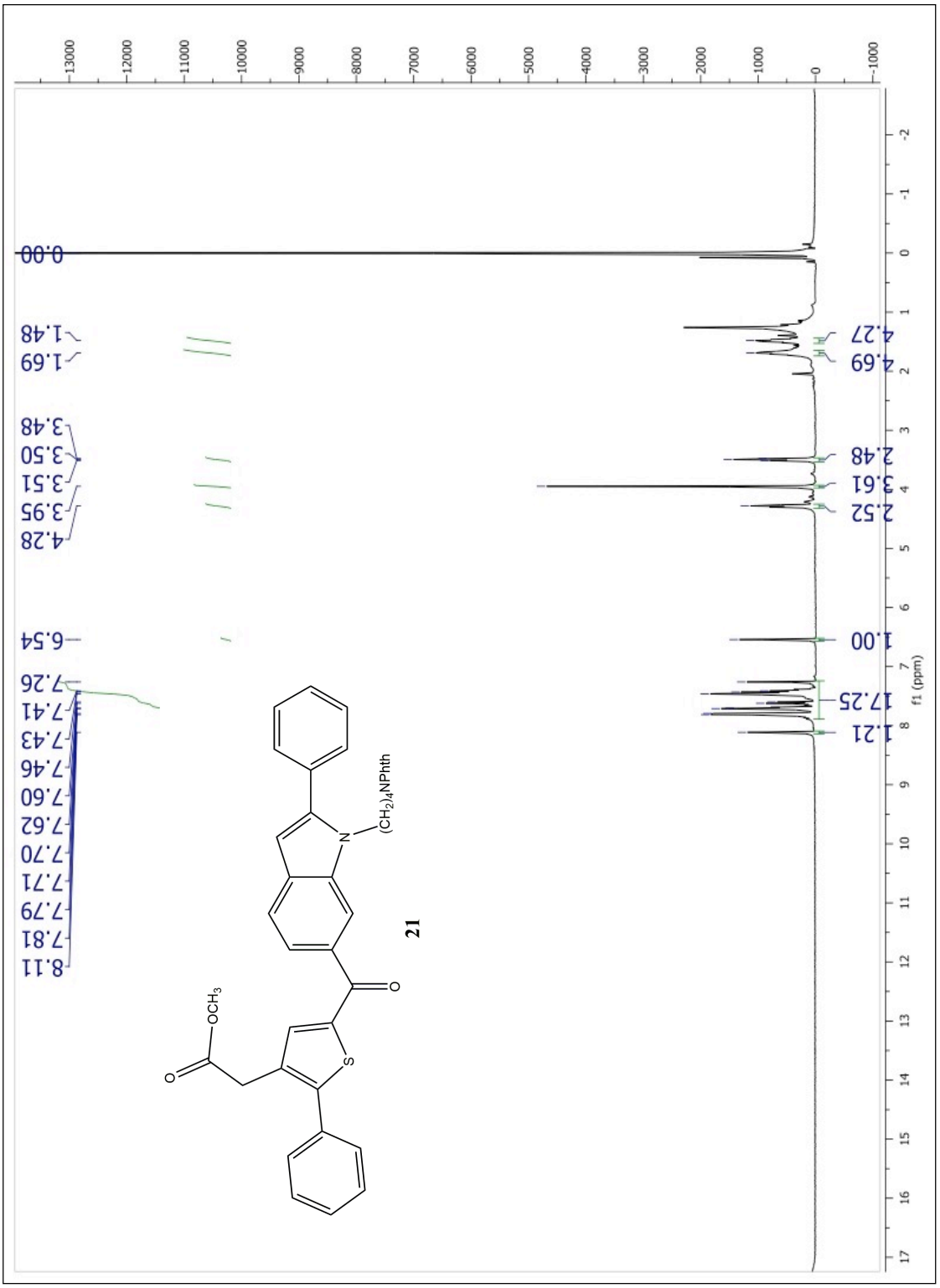
Spectrum 14. ^{13}C-NMR of Compound 20

Synthesis of methyl 2-(5-(1-(4-(1,3-dioxoisoindolin-2yl)butyl)-2-pheny-1H-indole-6-carbonyl-2-(3-phenyl)thiophen-3-yl)acetate (21)

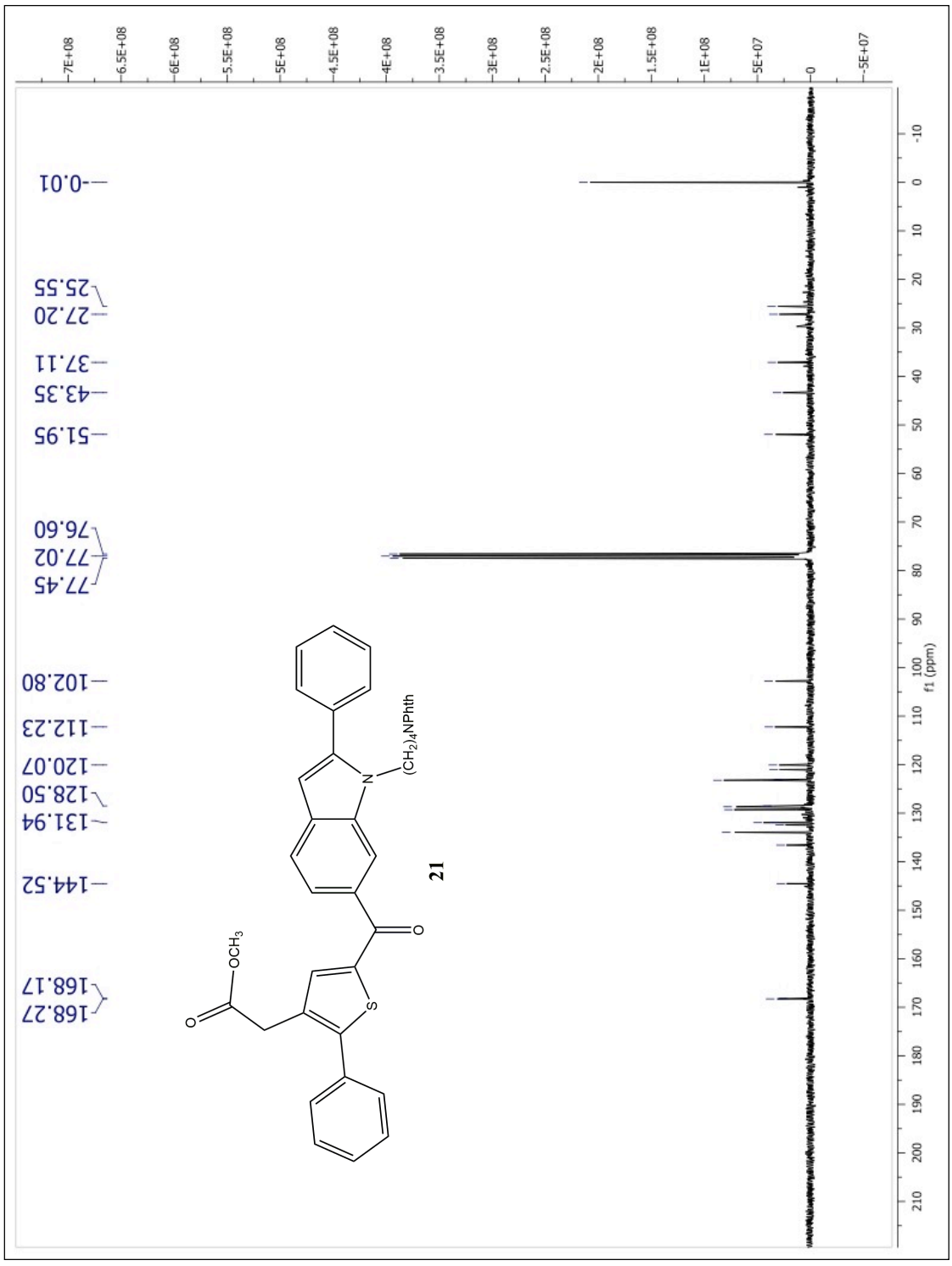


21

To a solution of potassium tert-butoxide (0.018g, 0.16mmol) in 4mL of DMF at 0^{o}C was added a solution of methyl (2-phenyl-5-(2-phenyl-1-H-indole-6-carbonyl)thiophen-3-yl)acetate (0.038g, 0.084mmol) in 1mL of DMF and the reaction mixture is stirred for 15min. After stirring for 15mins add a solution of *N*-(4-bromobutyl)-phthalimide (0.035g, 0.12mmol) in 1mL DMF and stirring is continued for 10h. The mixture was diluted with 40mL of water and extracted with three 50mL portions of ethyl acetate. The combined organic extracts were washed with two portions of 40mL of water and dried with anhydrous magnesium sulfate. After filtration, the solvent is removed at reduced pressure and crude product was purified by column chromatography to give pure **21** 0.033g (61%), $\boldsymbol{R_f}$ **-Value:** Hexane/Ethyl acetate (8:2 *v/v*) = 0.20, **^{1}H-NMR (300 MHz, $CDCl_3$):** δ = 1.48 (m, 2H), 1.69 (m, 2H), 3.49 (t, ^{3}J = 6.8 Hz, 2H), 3.95 (s, 3H) 4.28 (t, ^{3}J = 7.0 Hz, 2H), 6.54 (s, 1H), 7.43-7.81 (m, 17H), 8.11 (s, 1H), **^{13}C-NMR (300 MHz, $CDCl_3$):** δ = 22.57, 27.23, 37.15, 43.38, 51.97, 102.83, 112.25, 120.09, 121.02, 123.06, 123.24, 128.52, 128.69, 129.30, 131.88, 131.96, 132.45, 133.95, 136.61, 144.54, 168.20, 168.29, **HRMS ESI (m/z):** $[M+H]^+$ calc'd for $C_{40}H_{31}O_5N_2S$ 652.76, observed 653.24 m/z



Spectrum 15. ^{1}H-NMR of Compound 21



Spectrum 2. ^{13}C-NMR of Compound 21

References

[1] Fleming, D. O. P.; Hunt, D. L. *Biological Safety: Principles and Practices*; 4th ed.; ASM Press, 2006.

[2] Cote, T.; Mohan, A.; Polder, J.; Walton, M.; Braun, M. *J. Am. Acad. Derm.* **2005**, *53*, 407-415.

[3] Kessler, K. R.; Benecke, R. *Neurotoxicology* **1997**, *18*, 761-770.

[4] Tang, J.; Park, J. G.; Millard, C. B.; Schmidt, J. J.; Pang, Y. *PLoS ONE* **2007**, *2*, e761.

[5] Pang, Y.; Vummenthala, A.; Mishra, R. K.; Park, J. G.; Wang, S.; Davis, J.; Millard, C. B.; Schmidt, J. J. *PLoS ONE* **2009**, *4*, e7730.

[6] Park, J. G.; Sill, P. C.; Makiyi, E. F.; Garcia-Sosa, A. T.; Millard, C. B.; Schmidt, J. J.; Pang, Y. *Bioorg. Med. Chem.* **2006**, *14*, 395-408.

[7] Pang, Y.; Davis, J.; Wang, S.; Park, J. G.; Nambiar, M. P.; Schmidt, J. J.; Millard, C. B. *PLoS ONE* **2010**, *5*, e10129.

[8] Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, 254.

[9] Itahara, T.; Kawasaki, K.; Ouseto, F. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3488-3493.

[10] Itahara, T. *The Journal of Organic Chemistry* **1985**, *50*, 5272-5275.

[11] McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447-2464.

[12] Chen, X.; Engle, K.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 5094-5115.

[13] Joucla, L.; Djakovitch, L. *Adv. Synth. Cat.* **2009**, *351*, 673-714.

[14] Li, C. *Acc. Chem. Res.* **2009**, *42*, 335-344.

[15] Li, B.; Yang, S.; Shi, Z. *Synlett* **2008**, *2008*, 949-957.

[16] Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238.

[17] Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259-281.

[18] Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233-1246.

[19] Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676-14681.

[20] Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050-4053.

[21] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am Chem. Soc.* **2007**, *129*, 12072-12073.

[22] Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137-3139.

[23] Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172 -1175.

[24] Touré; Lane, B. S.; Sames, D. *Organic Letters* **2006**, *8*, 1979-1982.

[25] Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083-5085.

Appendix I: Common Abbreviation and Symbols

AcOH	acetic acid
AgOAc	silver acetate
bs	broad singlet
BoNTA	botulinum nerurotoxic inhibitor A
BoNT	botulinum nerurotoxic inhibitor
n-BuLi	*n*-butyllithium
Bz	benzyl
$CDCl_3$	deuterated chloroform
$((CD_3)_2CO)$	deuterated acetone
CO_2Me	carboxylate group
$Cu(OAc)_2$	copper acetate
$Cu(OTf)_2$	copper triflate
^{13}C-NMR	carbon nuclear magnetic resonance
DMSO-d_6	deuterated dimethylsulfoxide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
d	doublet
dd	doublet of doublets
EtOAc	ethylacetate
FG	functional group
GC/MS	gas chromatography/ mass spectrometry
^{1}H-NMR	proton nuclear magnetic resonance

HRMS ESI	high resolution mass spectrum electrospray ionization
LRMS EI	low resolution mass spectrum electron impact
MOM	methoxymethyl
Me	methyl
MW	microwave
MHz	megahertz
MeO	methoxy
m	multiplet
NaOH	sodiumhydroxide
NPhth	phthalimide
$Pd(OAc)_2$	palladium acetate
PivOH	pivalic acid
PhH	benzene
PhI	iodobenzene
R_f	retention factor
s	singlet
SEM	(trimethylsilyl)ethoxy methyl
SEMCl	(trimethylsilyl)ethoxy methyl chloride
t	triplet
TBAF	tetra-*n*-butylammoniumfluoride
TLC	thin layer chromatography
TMS	trimethylsilane
Tos	tosyl