One-pot Synthesis of Tetrasubstituted Isoindolinones

by

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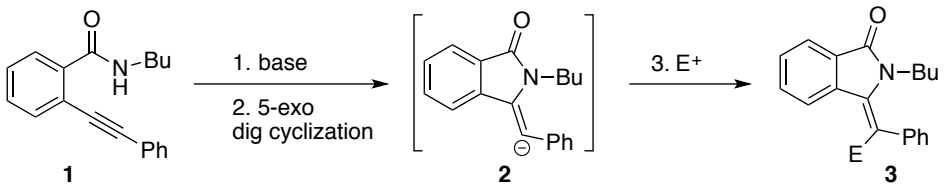
ABSTRACT



The isoindolinone functionality and its derivatives are present in many naturally occurring and biologically active compounds. Tetrasubstituted isoindolinones such as **3**, while a useful building block in materials as well as natural product synthesis, are particularly challenging to make. Current methods to make tetrasubstituted derivatives often require harsh conditions and expensive catalysts. Therefore, we decided to investigate a one-pot synthesis of this functional group using 5-exo-dig cyclization. Our strategy involved the intramolecular cyclization of alkynylbenzamide **1** using anhydrous conditions and trapping intermediate **2** with an electrophile. Several variables were investigated such as solvent, time, temperature, and identity of electrophile. Although the reactivity of intermediate **2** limited our choice with respect to solvents and electrophiles, we were successfully able to obtain target product **3** under certain conditions. Optimization and scope of the reaction will be discussed.

DEDICATION

This thesis is dedicated to my husband. He always believes in me and supports me throughout my studying.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. Sara Eisler, for her scholarly guidance, encouragement and support through the course of my work.

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List of Figures, Tables and Schemes

List of Symbols, Nomenclature or Abbreviations

^{o}C	Degree Celsius
CH_3CN	Acetonitrile
$CDCl_3$	Chloroform-d
DDP	Diketopyrrolopyrrole
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dt	Doublet of triplets
EtOH	Ethyl alcohol
eqiv	Equivalents
g	Gram
Hz	Hertz
h	Hour
^{1}H	Proton
IR	Infrared spectroscopy
J	Coupling in hertz
M	Molar
mmol	Millimole
$MgSO_4$	Magnesium sulfate
m	Multiplet
ml	Milliliter

mg	Milligram
min	Minutes
med	Medium
N	Nitrogen
n-BuLi	N-butyllithium
NH_4Cl	Ammonium chloride
NMR	Nuclear magnetic resonance
NEt_3	Tert-ethyl amine
NaH	Sodium hydride
$NaHCO_3$	Sodium hydride
O	Oxygen
ppm	Parts per million
PPh_3	Triphenylphosphine
Pd	Palladium
q	Quartet
RBF	Round bottom flask
rt	Room temperature
S	Sulfur
st	Strong
s	Singlet
SiO_2	Silica gel
t	Triplet
tt	Triplet of triplets

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TBAF	Tetrabutylammonium fluoride
TPIS	Triisopropylsilyl ether
wk	Weak
δ	Chemical shift in parts per million
%	Percent
π	Pi bond

Chapter 1: Introduction

1.1 Heterocyclic compounds

Heterocyclic compounds represent one of the largest classes of organic compounds. A fundamental feature of a heterocyclic compound is the presence of heteroatoms (O, N, or S), containing at least one lone pair of electrons.[1] These heterocycles have attracted attention in synthetic organic chemistry due to their abundance in natural products such as vitamins, hormones, antibiotics and alkaloids and because of their chemical, biological and commercial importance.[2] They are found in pharmaceuticals, herbicides, dyes and other commercial products such as corrosion inhibitors, anti-aging drugs and stabilizing agents.[3] Isoindolinone derivatives are a type of heterocyclic that has been generally underexplored synthetically, despite strong interest in this group.[4]

1.2 Isoindolinone

Isoindolinone **(**IIN) **1** is a bicyclic molecule, consisting of a six-membered benzene ring fused to a five-membered lactam ring. There are several important derivatives of IINs; compounds **2**, **3**, and **4**, Figure 1.1.[5-10] Methylene IINs **2** have an exocyclic double bond, which could offer interesting physical-electronic properties due to its unique conjugation pathways and potential synthetic handles with the alkene bond position. This double bond could either have one substituent as in trisubstituted derivative **3** or two substituents as in tetrasubstituted derivatives **4,** Figure 1.1.

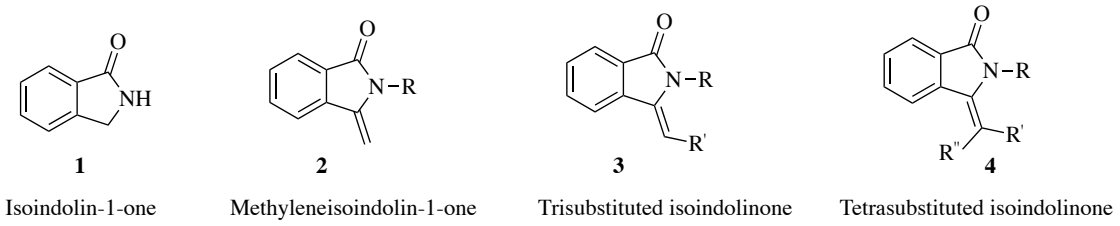


Figure 1.1 Basic isoindolinone units and derivatives of isoindolinone structures

A number of alkaloids containing the IIN group have been isolated, characterized and been found to have biological and pharmacological properties such as antipsychotic, antiulcer, antifungal, antianxiety, anesthetic, antiviral, and antileukemic.[11-18] For example, trisubstituted IIN **5** is a sedative, while trisubstituted IIN **6** was found to inhibit vasoconstriction, Figure 1.2.[19] Tetrasubstituted IINs **7** and **8** are useful as scaffolding intermediates toward complex products. Due to pharmaceutical benefits associated with isoindolinones, they are widely used as building blocks in the synthesis of various drugs and have been recently used as templates for preparation of combinatorial libraries.[20]

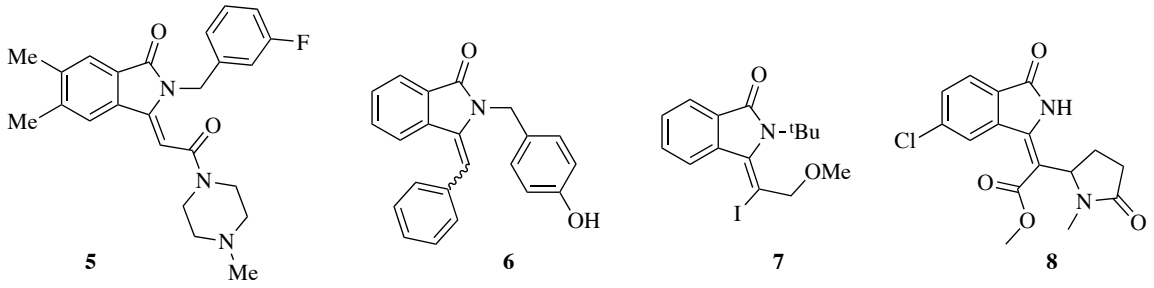


Figure 1.2 Substituted methyleneisoindolinone products

Methylene IINs and related compounds are also found in organic materials with diverse applications such as organic photovoltaics (OPV's) and organic field-effect transistor (OFET) devices.[21-24] Our research group has synthesized trisubstituted IIN **9,** which was found have photo-and chemo-responsive properties.[25] Similar lactam containing molecules, such as DPP **10** with two fused 5-membered aromatic lactam rings and isoindigo **11,** a symmetrical molecule consisting of two indolinone units with strong electron withdrawing character, are known to be important building blocks for the preparation of electroactive materials for organic electronics, Figure 1.3. A variety of molecules with similar structures to isoindolinones have recently appeared in the literature as successful candidates for organic materials. Isoindolinones possess an electron deficient amide functionality in the lactam ring similar to the successful n-type materials isoindigo and DPP derivatives.[26] Also, the planar isoindolinones have protruding carbonyl groups that could allow the formation of intermolecular hydrogen bonds, assisting important molecular order in the crystal packing, which aids in increasing the charge mobility throughout the materials. IINs offer a variety of features that are desirable for organic materials such as being air stable, processable, and easily tunable.[27]

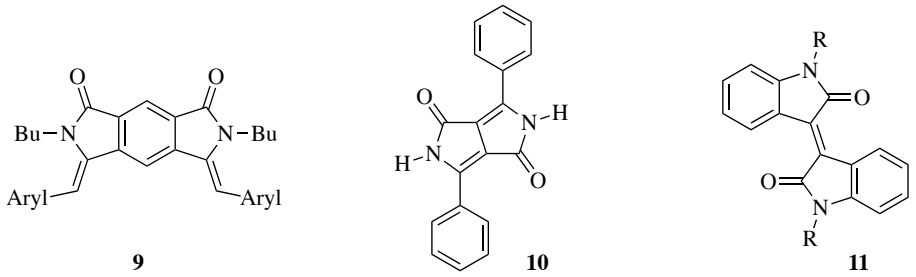


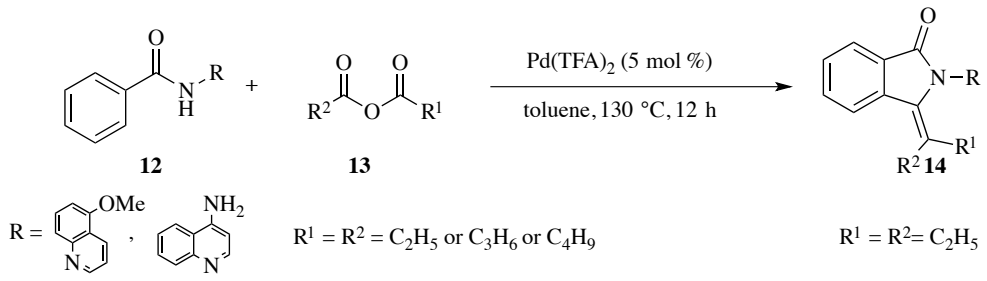
Figure 1.3 Structures of trisubstituted IINs, DPP, and isoindigo

1.3 A review of approaches to the formation of isoindolinones

The properties and applications of isoindolinone-containing molecules with exocyclic alkenes have led to the development of a number of synthetic methods for their preparation.[28-29] Existing methods toward methylene IIN synthesis, such as Wittig and photochemical reactions, often involve phthalimides as starting materials. Other methods in the literature include Horner condensation of 3-(diphenyl-phosphinoyl) isoindolinones with aldehydes, Pd-catalyzed heteroannulations involving 2-iodobenzamides and terminal alkynes, and 5-exo-dig cyclization of alkynylbenzamides.[30-34]

A few methods have also been developed to synthesize tetrasubstituted IINs. These tetrasubstituted IINs have the potential to be building block intermediates toward the synthesis of other more complex molecules and organic materials.[35] However, these methods suffer from one or more disadvantages such as high temperatures, requiring a number of additional synthetic steps, low yields, limited scope and often toxic reagents.

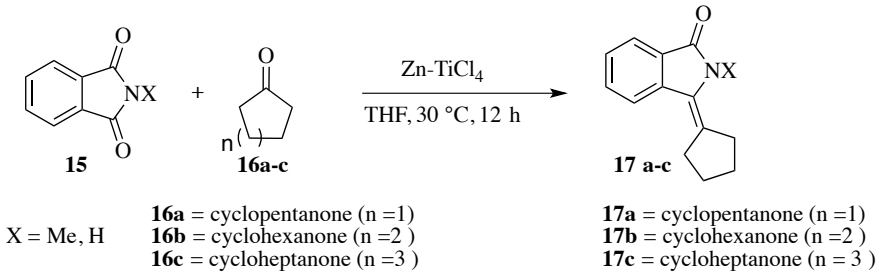
Hong-Wen Liang and co-workers synthesized tetrasubstituted IIN **14** through the reaction of amide **12** with propionic anhydride **13** (R1 = R^2 = C_2H_5) in the presence of $Pd(TFA)_2$, Scheme 1.1.[36] They reported that they used two groups that attach to N-amide and different anhydrides. The tetrasubstituted IINs were formed in various yields (90%, 68%).



Scheme 1.1 Liang's method to synthesize methylene IINs

This synthetic method is relatively simple and has reasonable yields. However, the reaction conditions require high temperature and have limited synthetic scope due to limitations of the anhydride reagents that were used. When symmetrical anhydrides other than **13** ($R^1 = R^2 = C_2H_5$) were used such as isovaleric ($R^1 = R^2 = C_3H_6$) and isobutyric ($R^1 = R^2 = C_4H_9$) anhydrides they obtained trisubstituted IINs instead of product **14**. Due to these significant limitations with the identity of the anhydride reagents, only products with identical alkyl groups at the terminal olefinic position are accessible.

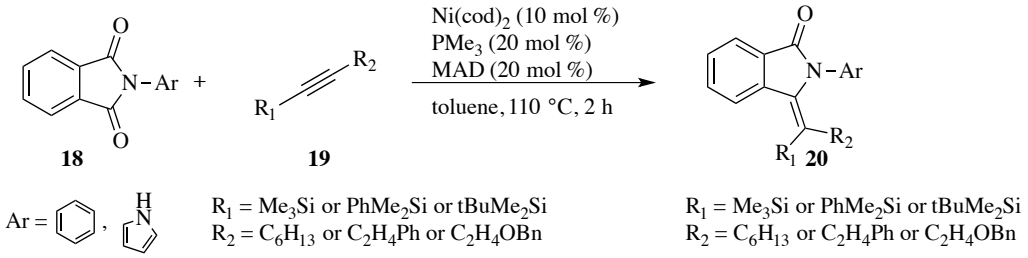
In 2013, Kise and co-workers synthesized tetrasubstituted IINs **17a-c** via reductive coupling of phthalimides **15** with cyclic ketones **16.** They used Zn-$TiCl_4$ and obtained low isolated yields (28%-51%), Scheme 1. 2.[37]



Scheme1.2 Reaction of phthalimides and ketones with Zn-$TiCl_4$

This method also has similar issues with limited scope, where the reaction was applied with cyclic ketones provides products only with identical groups at the terminal alkene position. The isolated yields also were low as product decomposition was observed during isolation. Interestingly, they were able to obtain a high yield (83%) of **17** if they used acetone as the ketone reagent in the reaction.

In 2013, Takahiro Shiba and co-workers investigated the synthesis of less symmetrical tetrasubstituted IINs **20** via the decarbonylative alkylidenation reaction of phthalimides **18** with silyl-substituted alkynes **19,** in the presence of a nickel-catalyst, Scheme 1.3.[38]

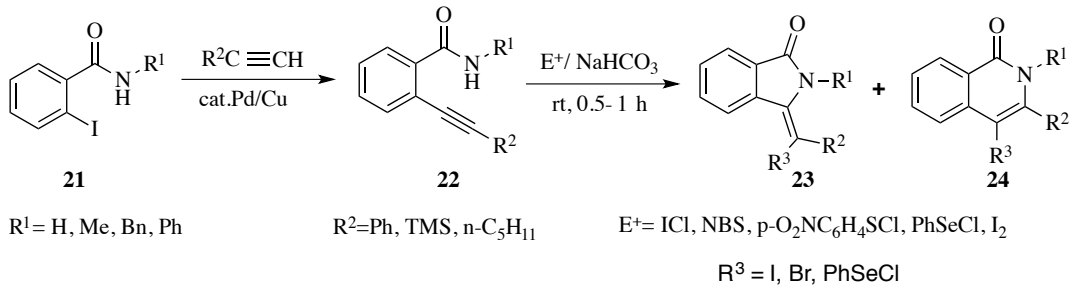


Scheme 1.3 Nickel-catalyzed decarbonylative addition of phthalimides to alkynes

The target product **20** was achieved in various yields (44%-90%) with varying range of scope and functionality where a variety of alkyne R_2 groups and different silyl groups R_1 were used. However, the reaction required high temperature. The least sterically hindered TMS group yielded better results when compared to the bulkier silyl group.

In 2004, Larock and co-workers proposed a method to form tetrasubstituted IINs by using intramolecular electrophilic cyclization of alkynylbenzamide starting materials. The

alkynylbenzamides **22** precursors were readily prepared by Sonogashira coupling reaction of the corresponding iodobenzamides **21** with terminal alkynes. The alkynylbenzamides **22** were cyclized using $NaHCO_3$ in the presence of various electrophiles (ICl, I_2, NBS, p-$O_2NC_6H_4SCl$, and PhSeCl), Scheme 1.4.[39]

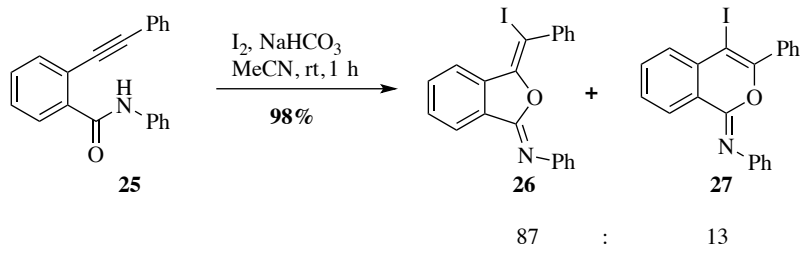


Scheme 1.4. Larock synthesis of tetrasubstituted isoindolinone

IINs **23** were formed via 5-exo-dig cyclization while isoquinolinones **24** were formed via 6-endo-dig cyclization. Product mixtures of **23** and **24** were formed in various yields and ratios (e.g. product **23** when R^1 = Bu, R^2 = Ph and R^3 = I the yield was 85% and product **24** = 8%). The reaction mechanism involves deprotonation of the amide by $NaHCO_3$, followed by nucleophilic attack by the nitrogen of the amide group toward the triple bond, which is activated by the electrophiles via coordination. At the time of publication, this work demonstrated that intramolecular cyclization could be used as a simpler alternative and useful method to synthesize tetrasubstituted IINs.

A few years later, Opatz and co-workers used the Larock procedure to synthesize diglycosylisoindolinones. During their investigation, they discovered that there was a structural misassignment with Larock's tetrasubstituted IIN **23** and isoquinolinone **24**. To test

this hypothesis they used the Larock' procedure to cyclize benzamide **25**. They discovered that the carbonyl oxygen acted as the nucleophiles instead of the nitrogen of the amide functionality to give iminolactones **26** and **27**, Scheme 1.5.[40] Opatz confirmed this problem with the Larock conditions using X- ray crystallography. It is believed that electrophile-alkyne coordination not only promoted 6-endo-dig cyclization, but also facilitated an increase in the carbonyl oxygen's nucleophilicity, which is detrimental toward the formation of the desired lactam.



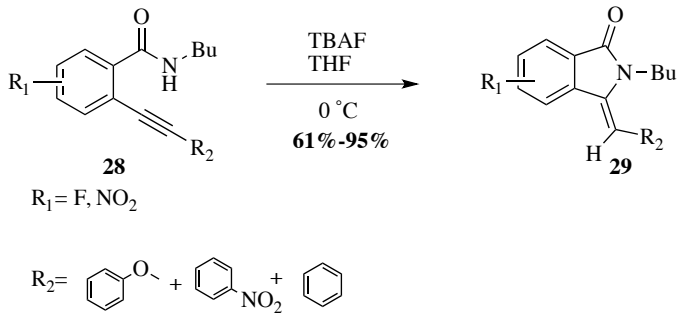
Scheme 1.5 Intramolecular cyclization reaction by Opatz to synthesize iminolactones

This work shows that while cyclization is a potentially powerful method of synthesizing tetrasubstituted IINs, there are a number of issues that need to be considered, including the effect of alkyne coordination on the formation of undesired isomers.

1.4 Previous work on the synthesis of INN derivatives in the Eisler research group

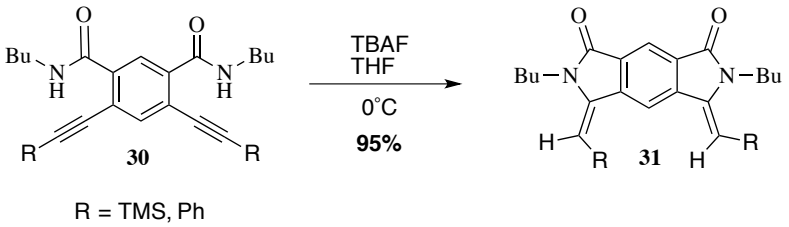
Our research group has developed a very efficient and high yielding synthetic method toward the synthesis of trisubstituted IINs **29** via TBAF-induced intramolecular cyclization of alkynylamides **28**. The TBAF reagent removes the silyl protecting groups and also acts as a base that deprotonates the N-amide proton and induces 5-exo-dig cyclization

toward the target IIN product, Scheme 1.6.[41] This method is regioselective toward 5-exo-dig IIN products as none of the competing 6-endo-dig isoquinolinone products were observed and isolated. Additionally, the absence of alkyne-activating coordination ensures that the desired lactam moiety is formed (methylene IIN).



Scheme 1.6 Synthesis of trisubstituted IINs

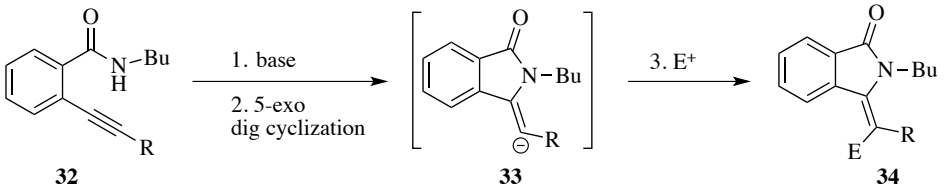
Following the same general steps and changing some of the reaction conditions (i.e TBAF equivalence), cyclization of benzamides with multiple amide-alkyne moieties are also possible, Scheme 1.7.[25]



Schem 1.7 Synthesis of bis-isoindolinones

1.5 Goals

As demonstrated in the literature example, tetrasubsituted IINs have previously been prepared through various methods with varying limitations such as harsh reaction conditions (high temperatures), limited synthetic scope, and low yields. Our goal is to attempt to bypass these limitations and investigate a new methodology for the synthesis of tetrasubsituted IINs **34**. My goal is to synthesize the tetrasubsituted IINs **34** through a one-pot 5-exo-dig cylization of amide **32** and generate intermediate **33** in situ, which would then form target product **34** upon addition of electrophiles**.** The basic reaction conditions will be determined with a number of electrophiles and R groups and it will be investigated to allow access to a variety of structures, Scheme 1. 8.

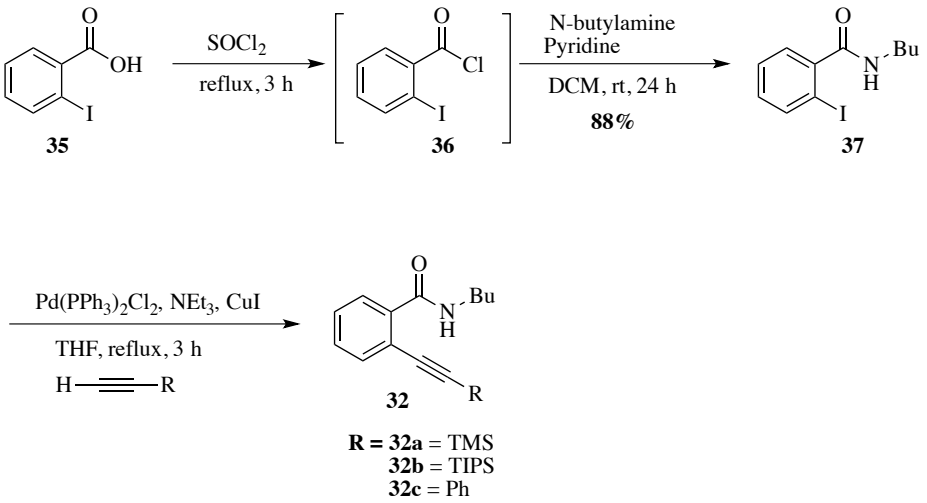


Scheme 1.8 Proposed route for tetrasubstituted IINs

Chapter 2: Results and Discussion

2.1 Synthesis of precursor 32a-c

The first step in achieving my goal was to make compound **32**, as it is not commercially available. Another thing that I needed to ensure was to obtain benzamide **32** in high yields and in large quantities (grams of materials) so that many optimization tests could be performed with relative ease overall. Following the same synthetic route carried out in the Eisler group to synthesize various isoindolinone derivatives, the benzamide **32a-c**-target product could be achieved in two steps from commercially available starting materials, Scheme 2.1.[25]



Scheme 2.1 Synthesis of precursor 32 a-c

Commercially available carboxylic acid **35** was treated with thionyl chloride for 3 h under reflux to generate the respective acyl chloride **36** in situ. After removal of

excess thionyl chloride, the acyl chloride **36** was then dissolved in anhydrous DCM. The n-butyl amine and pyridine were then added in the reaction flask to form the desired amide **37** in 88% yield. Optimization of the Sonogashira coupling reactions were then performed using various corresponding acetylenes **32a-c** in the presence of $Pd(PPh_3)_2Cl_2$ and CuI as co-catalyst. Initial tests, Table 1, entries 1 and 2, involve formation of products **32a** (R = TMS) and **32b** (R = TIPS) with overall acceptable isolated yields. Later test reactions involve the use of commercially available phenylacetylenes to form benzamide **32c**, where room temperature conditions yielded poor results, Table 1, entry 3. Further optimizations of the reaction conditions such as adding heat with shorter reaction times eventually yielded much better results, increasing overall isolated yield up to 85%, Table 1, entry 7.

Entry	R-group	Temp	Time	%
1	TMS	rt - 35 ^{o}C	4 h	68%
2	TIPS	rt - 35 ^{o}C	4 h	54%
3	Ph	rt	24 h	25%
4	Ph	80 ^{o}C	3 h	39%
5	Ph	80 ^{o}C	3 h	56%
6	Ph	80 ^{o}C	3 h	78%
7	Ph	80 ^{o}C	3 h	85%

Table 1. Trials for Sonogashira reaction.

2.2 5-exo-dig cyclization reactions with n-BuLi as a base

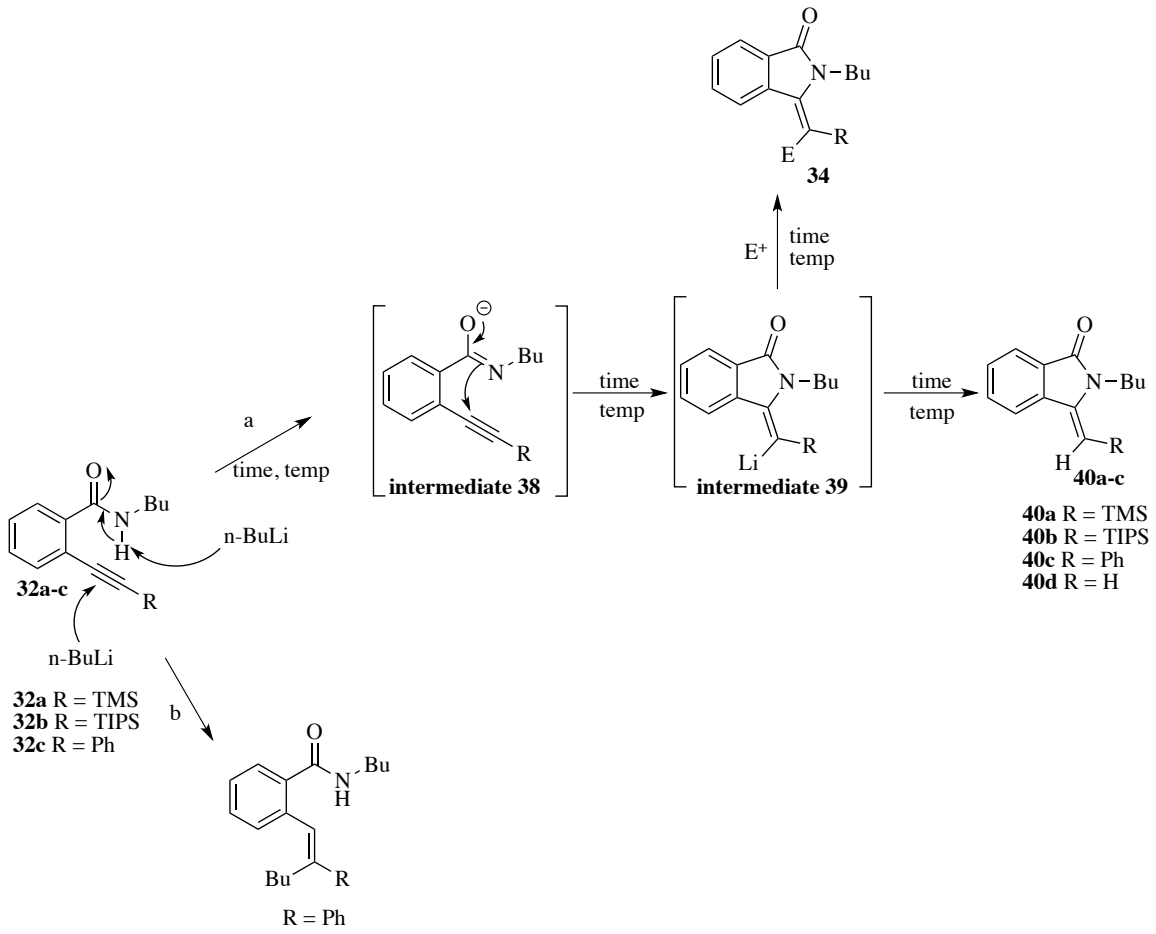
With precursors in hand, it was time to determine the conditions to carry out the one-pot reaction toward target tetrasubstituted IINs. Before performing the synthesis a number of critical questions would need to be addressed and identify possible problems in the synthetic method. These important questions are as follows: 1) Which anhydrous base

should be used to induce 5-exo-dig cyclization in a quantitative manner? 2) What are the appropriate temperatures ranges and reaction times needed to form the anionic cyclic intermediate **39** in situ, while maintaining quantitative cyclization without inducing premature decomposition of reactants? 3) When to add the electrophiles (before or after the anionic cyclization)? 4) How long should the reaction times be to form the tetrasubstituted IINs?

IIN **40** (R = H) was previously synthesized by inducing cyclization of benzamide **32** (R = H) using TBAF in high yield and we can take advantage of this fact by using it as reference when compared with the cyclization using anhydrous base. TLC analysis will aid in monitoring the consumption of benzamide starting materials, and help infer formation of anionic intermediate **39** in situ. As long as the reaction remains anhydrous, the anionic intermediate **39** should remain in the solution and prevent protonation towards **40**. It is critical to identify the time it takes to generate anionic intermediate **39** as well as the right reaction conditions (temperature, solvents) to maintain intermediate stability and prevent overall decomposition. Additionally, the electrophile reagents will be added into the reaction flask after confirming that all of the benzamides underwent cyclization. It is critical to add the electrophile after anionic cyclization to ensure that no other undesired by-products could be formed due to alkyne-electrophile coordination. Similarly, TLC analysis will be used to monitor the reaction between the anionic intermediate **39** and the electrophile, forming the target tetrasubstituted IIN **34**. Premature quenching by H^+ of the reaction at this step will only yield trisubstituted IIN **40**.

As discussed, it is very important to maintain the anhydrous condition of the reaction, which will be the main factor in considering the proper solvents and anhydrous

base to use. Commercially available TBAF typically contains 5% water in THF solution, and the water is very difficult to remove without decomposing the TBAF. The n-BuLi was initially chosen as the base due to its pKa (≥ 50) and should be strong enough to deprotonate the N-H amide proton (pKa = 15), Scheme 2.2.[42]



Scheme 2.2 Testing 5-exo dig cyclization reaction with n-BuLi

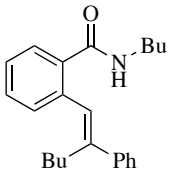
Entry	Addition of n-BuLi	R-group	Temp	Time	Product (% yield)
1	-78 ^{o}C, 20 min	TMS	rt	2 h	**40a** (27%)
2	-78 ^{o}C, 20 min	TIPS	rt	2 h	-
3	-78 ^{o}C, 20 min	Ph	rt	2 h	**40c** (25%)
4	-78 ^{o}C, 20 min	Ph	rt	1 h	**40c** (28%)
5	-78 ^{o}C, 20 min	Ph	0 ^{o}C	1 h	**40c** (33%), **41** (46%)
6	-78 ^{o}C, 20 min	Ph	-10 ^{o}C	1 h	**40c** (7%), **41** (90%)
7	-78 ^{o}C, 20 min	Ph	-20 ^{o}C	1 h	**40c** (10%), **41** (78%)
8	-20 ^{o}C, 20 min	Ph	-10 ^{o}C	1 h	**40c** (80%)
9	-20 ^{o}C, 20 min	Ph	-10 ^{o}C	2 h	**40c** (83%)

Table 2. Investigation of the conditions of cyclization reaction with n-BuLi.

The initial approach was to figure out whether n-BuLi would be an effective anhydrous base to induce 5-exo-dig cyclization. Alkynylamide **32** was first treated with one molar equivalent of n-BuLi at -78 °C for 20 min in THF.[43] The first test reaction was performed with **32a**, R = TMS, Table 2, entry 1, and produced trisubstituted IIN **40a** in poor yield (27%) while the remaining product mixture was the trisubstituted IIN **40d**, which resulted from the removal of the TMS protecting group during the reaction. A bulkier TIPS protecting group, Table 2, entry 2, resulted in a more stable benzamide **32b** product, however when cyclization was performed using n-BuLi, the product mixture was determined to be too crude and messy and was not isolated. It seems that the reaction conditions were a bit harsh for both the silyl protected benzamides and resulted in decomposition and unwanted by-products. When benzamide **32c** (R = Ph) was cyclized in product **40c**, no deprotection was observed, however, initial isolated yields were relatively low, entry 3-4, 25-28%, and further optimization test reactions were performed.

Again alkynylamide **32c** was first treated with one molar equivalent of n-BuLi at -78 °C for 20 min in THF.[43] The temperature was increased to room temperature over 2 h.

While trisubstituted IIN **40c** was formed in 25% yield, Table 2, entry 3, the reaction gave multiple spots as indicated by TLC analysis. In an attempt to increase the yield the reaction was repeated but the reaction mixture was warmed to room temperature for 1 h instead of 2 h, Table 2, entry 4. However, changing the temperature of the reaction didn't translate to better yields when compared with the previous test reaction, Table 2, entry 3. It is likely that the intermediate **39** was reactive and decomposed at higher temperatures. To test this theory n-BuLi was added again at -78 °C but the reaction mixture warmed to either 0 °C, -10 °C, -20 °C, and kept at those temperatures for one hour, Table 2, entries 5-7. Trisubstituted IIN **40c** was again formed in relatively low yields (33%-10%) however, by-product alkene **41** was formed and composed the majority of the product mixture under these conditions, Figure 2.1.

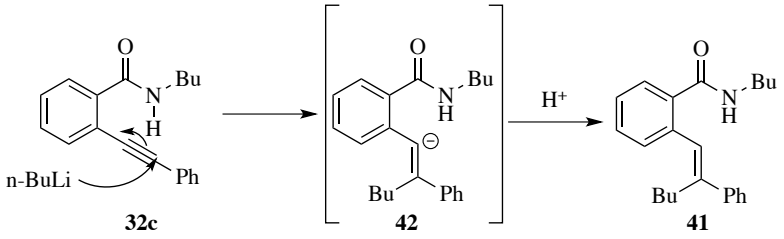


41

Figure 2.1 By-product in n-BuLi reaction

2.3 Analysis of major by-product

Undesired product alkene **41** was formed as the major product when the reaction temperature was warmed to 0 °C, -10 °C, and -20 °C for 1 h, where the n-BuLi acted as a nucleophile instead of as a base in these reaction conditions, Scheme 2.3.



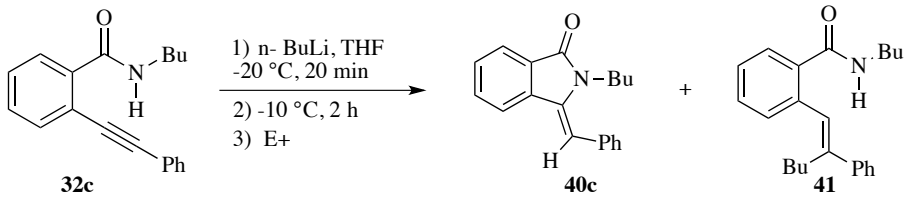
Scheme 2.3 Mechanism of n-BuLi acting as nucleophile

The n-BuLi attacks the triple bond of benzamide **32c** at the position shown in Scheme 2.3, forming intermediate **42,** which after work up and protonation provides alkene **41.** I determined the structure of alkene **41** using ^{1}H NMR and ^{13}C NMR analysis, as well as high-resolution mass spectrometry. Furthermore, a NOESY analysis confirmed the regiochemistry of the nucleophilic attack and the consequential stereochemistry, Figure 2.4 by the observation of a correlation between the hydrogen of alkene and hydrogen amide group. Also the correlation between the hydrogen of alkene and the alkenyl phenyl group in the NOESY spectrum.

To control the basicity of the n-BuLi reagent and its nucleophilicity, n-BuLi was added at -20 °C instead of -78 °C, as suggested by a literature report.[44] As shown in Table 2, entry 8, n-BuLi was added at -20 °C and after the reaction mixture was warmed to -10 °C for 1 h, the trisubstituted **40c** was formed in 80% yield. If the same reaction was warmed to -10 °C for 2 h instead, Table 2, entry 9, a slightly higher yield (83%) of **40c** was isolated. Under these reaction conditions, the undesired product alkene **41** was not synthesized while 5-exo-dig cyclization of the benzamide precursor was induced under anhydrous conditions. I then decided to test the one-pot 5-exo-dig cyclization with several electrophiles to trap intermediate **39** and to form the tetrasubstituted IIN.

2.4 One-pot synthesis with n-BuLi

After several optimization test reactions, Table 2, of the anhydrous anionic 5-exo-dig cyclization of the benzamide precurors, it was time to attempt to add the electrophile reagent and synthesize the target tetrasubstituted IIN **34**. The procedure involved adding one molar equivalent of n-BuLi to a mixture of benzamide **32c** in anhydrous THF at -20 °C for 20 min as the first step**,** followed by stirring the reaction at -10 °C for 2 h, Scheme 2.4.



Scheme 2.4 One-pot reaction with n-BuLi, followed by additon of electrophiles

Entry	Electrophiles(R)	Third step condition	Product
1	Ethyl formate	-10 ^{o}C, 2 h	**40c**
2	Ethyl formate	-10 ^{o}C, 2 h then rt, 5 h	**40c, 41**
3	Iodomonochloride	-10 ^{o}C, 30 min then rt, 3 h	**40c**
4	Iodomonochloride	-10 ^{o}C, 30 min then reflux, 7 h	**40c, 41**
5	Iodomonochloride	-10 ^{o}C, 30 min then reflux, 24 h	**40c, 41**

Table 3. First attempt at the addition of electrophiles.

As the first and second step of the optimized procedure were kept constant, I tried to investigate the conditions for the third step, Table 3, which involves addition of the

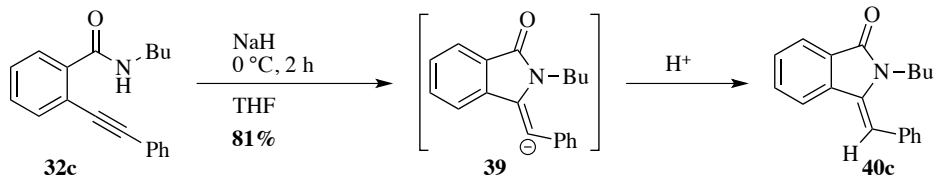
electrophile reagents. Based on similar literature examples and accessibility, I decided to use ethyl formate and iodomonochloride as electrophilic reagents. After complete deprotonation of compound **32c** followed by cyclization toward intermediate **39c**, as indicated by TLC analysis, I added 2 molar equivalents of ethyl formate, at -10 °C for 2 h, Table 3, entry 1. Unfortunately, only trisubstituted IIN **40c** was produced and isolated with none of the target tetrasubstituted IIN observed. After careful consideration, a similar reaction was performed but this time the reaction was left stirring at rt for 5 h, entry 2. Unfortunately, this increase in reaction temperature during the third step yielded unwanted products: the trisubstituted IIN **40c** as well as alkene **41** with no evidence of tetrasubstituted IIN observed. The result could be due to the lack of reactivity of the ethyl formate. Other reasons such as steric hindrance from the phenyl groups in the intermediate structure could have contributed to the lack of reaction between the anionic intermediate and electrophile

Then I decided to use iodomonochloride, a common electrophile used in several similar literature examples. Furthermore, tetrasubsituted IIN with an iodine atom could be a potentially useful precursor and can be elaborated further in future steps. I added 2 equivalents of iodomonochloride at -10 °C for 30 min and left the reaction mixture at rt for 3 h, Table 3, entry 3, however, only trisubstituted IIN **40c** was formed again. Similar experiments were repeated but the reaction was left under reflux for 7 h, and for 24 h, Table 3, entries 4 and 5. Unfortunately, only trisubstituted IIN **40c** as well as alkene **41** were formed again in both cases. In all cases I found that despite the optimized conditions with n-BuLi, significant amounts of alkene **41** were produced, in addition to trisubstituted IIN **40c**. It is apparent that the n-BuLi is a poor choice since it can act as both base and

nucleophile, in which the latter was found to be difficult to mitigate and control. It was therefore time to consider another anhydrous base, preferably non-nucleophilic, to induce 5-exo-dig cyclization.

2.5 5-exo-dig cyclization reaction with NaH as a base

I decided to use NaH as the new anhydrous base due to its ideal pKa of 38 and it's non-nucleophilicity.[42] Alkynylamide **32c** was added to a solution of 1.1 equivalent of NaH in THF at 0 °C and left to stir for 2 h, Scheme 2.5.[45]

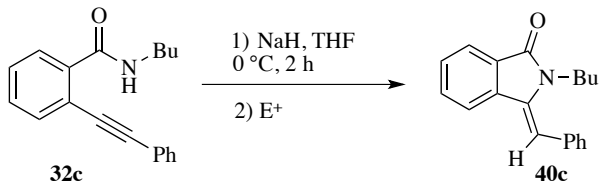


Scheme 2.5 Cyclization reaction with NaH

Preliminary test results show that benzamide **32c** underwent complete cyclization toward product **40c** with a yield of 81%, and no side products were formed. TLC analysis was used to infer formation of anionic intermediate **39c**, indicating that NaH as a base gave better and more efficient results than reactions carried out with n-BuLi.

2.6 One-pot synthesis with NaH

Similar general reaction procedures were performed where the electrophiles were added in the third step, after ensuring complete cyclization of benzamide precursors in situ. Deprotonation of compound **32c** by NaH was followed by adding electrophiles under various conditions, Scheme 2.6.



Scheme 2.6 One-pot reaction with NaH

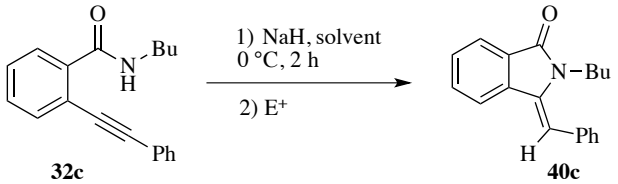
Entry	Electrophiles(R)	Temp/ Time for step 2)	Product
1	Iodomonochloride	0 °C, 15 min then rt, 24 h	**40c**
2	Iodomonochloride	0 °C, 15 min then reflux, 24 h	**40c**
3	Ethyl formate	0 °C, 15 min then 30 °C, 24 h	**40c**
4	NBS	0 °C, 15 min then rt, 24h	**40c**
5	Acetone	0 °C, 15 min then 30 °C , 24 h	**40c**
6	Allyl bromide	0 °C, 15 min then rt, 24 h	**40c**

Table 4. Examination one pot synthesis with different electrophiles.

The first step in the reaction, which was addition of NaH, was kept the same for entries 1-6, Table 4, while the electrophile reagents and temperature were varied. Using iodine monochloride initially the reaction was stirred at rt upon addition of electrophiles for 24 h, entry 1, and refluxed for 24 h, Table 4, entry 2. In both cases trisubstituted IIN **40c** was the only observed product instead of the desired tetrasubstituted IIN. Several other electrophiles were tested such as ethyl formate, NBS, and acetone, Table 4, entries 3-5. In each entry trisubstituted IIN **40c** was formed with no formation of the desired product. It is possible that the result is due to steric effects in either electrophiles or intermediate **39** as mentioned previously or it could be that the electrophiles used were not dry enough.

Fresh and anhydrous allyl bromide was then used. It was added after the NaH induced cyclization and left at room temperature for 24 h, Table 4, entry 6. Unfortunately, again trisubstituted IIN **40c** was formed instead of tetrasubstituted IIN. Despite ensuring that the electrophile reagent was dry, only the quenching reaction of the anionic intermediate toward **40c** was observed. The next likely source of water in the reaction was the THF, which tends to retain moisture if not enough care is taken.

I then decided to change the solvent, which could have a significant effect on the nucleophilic attack of the anionic intermediate toward the electrophile, Scheme 2.7.[46]



Scheme 2.7 Trapping compund 32c with electrophiles in different solvents

Entry	Electrophiles(R)	Temp/ Time for step 2)	Solvent	Product
1	Allyl bromide	0 °C, 4 h then E^+ at rt, 24 h	Ether	**40c**
2	Allyl bromide	0 °C - 30 °C, 7 h then E^+ at 30 °C, 24 h	Hexane	**40c**
3	Allyl bromide	0 °C, 1 h then E^+ at rt, 24 h	Acetonitrile	**40c**
4	Allyl bromide	E^+ in beginning at 0 °C, 1 h then rt, 2 h	Acetonitrile	**40c**

Table 5. Examination of the effect of different solvents on the formation of tetrasubstutited INNs.

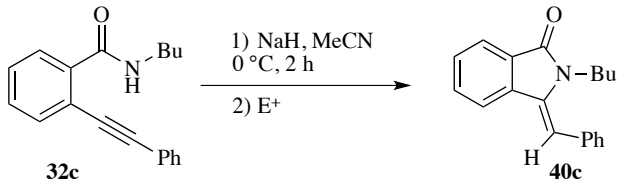
Several solvents were investigated and allyl bromide was used as the electrophile again, since it was sure to be dry and fresh from the bottle. Careful attention was required in the cyclization step as the choice of solvent has a strong affect on the rate of reaction.

Using dry ether, Table 5, entry 1, intermediate **39** was formed after 4 h based on TLC analysis, after which the allyl bromide was then added. Again, the trisubstituted IIN **40c** was, unfortunately, the only product observed in this case**.** When dry hexane was used, Table 5, entry 2, poor solubility of benzamide **32c** was observed. Despite initial solubility issues, all of the benzamide was eventually cyclized and generated intermediate **39** after 7 h. Again only trisubstituted IIN **40c** was formed with no desired product isolated. When anhydrous acetonitrile was used, Table 5, entry 3, complete cyclization was observed after 1 h, followed by the addition of allyl bromide and the reaction ran for 24 h. In all cases the same results were observed where only trisubstituted IIN **40c** was isolated.

As discussed earlier, the electrophile was added in the third step after complete cyclization was ensured. This is because I would like to avoid potential complications in terms of unwanted by-products and potential overall reactivity changes. After much deliberation and careful scrutiny, it seems that the ultimate problem is that the rate of protonation of the anion intermediate **39** is much faster than the rate of electrophile addition reaction. In an attempt to solve this inherent problem, I then decided to add the electrophile from the beginning of reaction with NaH instead, despite the chances of other unwanted reactions also happening. This action provides an advantage, as when intermediate **39** gets generated it could react instantly with electrophile already present in the solution. It was then necessary to ensure that the electrophiles used were known to not coordinate to the triple bond. Allyl bromide was added to solution of NaH and compound **32c** in acetonitrile. Dry acetonitrile was used because the cyclization reaction occurs quickly in this solvent. The reaction was left at rt for 1 h, Table 5, entry 4, but the desired tetrasubstituted IIN product did not form. Again, after much consideration of these results,

an alternative theory was thought of, where the intermediate **39** possibly acted as a strong base and deprotonated any acidic hydrogen on the electrophile reagent, instead of anionic attack toward the electrophilic site.

I then turned my focus toward using electrophiles with no acidic hydrogen, such as benzaldehyde and iodomethane. We made this choice based in literature reports when anions similar to our intermediate **39** reacted as nucleophiles with these electrophiles.[47] Alkynylamide **32c** was then added to solution of 1.1 equivalents of NaH and acetonitrile at 0 °C for 1 h, Scheme 2.8.



Scheme 2.8 One-pot reaction with benzaldehyde and iodomethane as electrophiles

Entry	Electrophiles(R)	Temp/ Time for step 2)	Product
1	Iodomethane	0 °C, 15 min then 30 °C, 2 h	**40c**
2	Iodomethane	E^+ in beginning at 0 °C, 1 h then rt, 3 h	**40c**
3	Benzaldehyde	0 °C, 15 min then 30 °C, 5 h	**40c**
4	Benzaldehyde	E^+ in beginning at 0 °C, 1 h then rt, 24 h	**40c**

Table 6. 5-exo-dig cyclization of compound **32c** with iodomethane and benzaldehyde.

Again, the first step in the reaction was kept the same for all entries. Iodomethane was added to the reaction in two ways. First, it was added after intermediate **39** was formed, Table 6, entry 1. Second, it was added at the beginning of the reaction, Table 6,

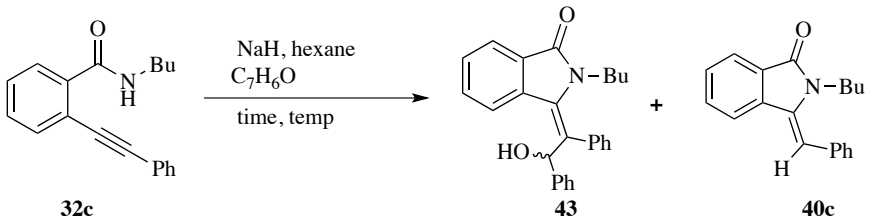
entry 2. The reactions were followed by TLC analysis and only trisubstituted IIN **40c** was observed and isolated. Again, it is possible that the basicity of anionic intermediate **39** could be strong enough deprotonate iodomethane.

Benzaldehyde was then tried. I added benzaldehyde also in two ways, after intermediate **39** was formed, and at the beginning of the reaction, Table 6, entry 3 and 4. Trisubstituted IIN **40c** was again formed. Given this result, it was thought that perhaps the intermediate **39** was deprotonating solvents as well.

2.7 Hypothesis examination

If we assume that the pKa of alkene **39** is around 45, we need to identify electrophiles and solvents that have a higher pKa to ensure that no unwanted acid-base reaction occurs.[42] To test my hypothesis, I decided to use hexane as the solvent due to its pKa of 50 and benzaldehyde as the electrophile. Benzaldehyde has two pKas; one for the aldehyde hydrogen, which is not reactive in acid-base reactions, and the second pKa is for hydrogen on the benzene ring, which is around 45.

To test this hypothesis experimentally further optimization test reactions were performed as described at Scheme 2.9.



Scheme 2.9 Synthsesis of target product by using hexane as solvent

Entry	Temp/ Time	**43**	**40c**
1	0 °C - 30 °C, 8 h then E^+, 48 h	7%	56%
2	E^+ in beginning at 0 °C, 1 h then rt, 24 h	15%	37%
3	E^+ in beginning at 30 °C, 24 h	23%	32%

Table 7. Investigation of the formation of our target product through intermolecular trapping of compound **32 c** with benzaldehyde in hexane.

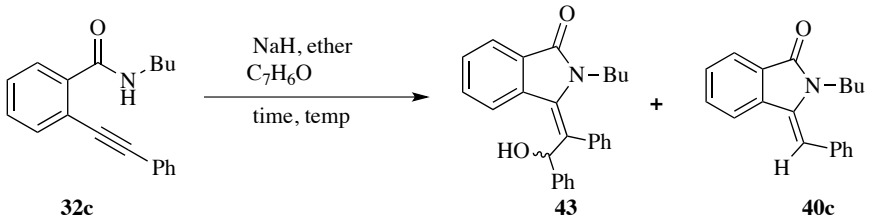
In the first attempt, compound **32c** was added to a solution of 1.1 equivalent of NaH in hexane at 10 °C and it was heated to 30 ^{o}C for 8 h, Table 7, entry 1. Then, after intermediate **39** was formed as indicated by TLC analysis, 2 equivalents of benzaldehyde were added to the mixture and the reaction was left stirring for 48 h at 30 ^{o}C. Finally, the desired tetrasubstituted IIN **43** was formed in 7% yield. Finally I made my target product. The molecular structure of tetrasubstituted IIN **43** was determined and confirmed by using ^{1}H-NMR, ^{13}C-NMR, and HRMS analysis. The rest of the product mixture consisted of trisubstituted IIN **40c**, and starting material **32c**. Encouraged by this result despite the low yield, I decided to add the electrophile from the beginning and see if a higher yield can be obtained. Benzaldehyde **32c** was added with 1.1 equivalent of NaH in hexane with benzaldehyde added at the beginning, Table 7, entry 2. In this case the desired product was formed in 15% yield. From past experience I knew that the starting material **32c** is not very soluble in hexane at room temperature, or at 10 °C, but it is more soluble at 30 °C. In a solution of compound **32c** and NaH in hexane, 2 equivalent of benzaldehyde was added at 30 °C and left for 24 h, Table 7, entry 3. With this condition the isolated product yield increased to 23%. These are all encouraging results, in which further optimization test reactions were performed in search for a higher yield. I then focused my attention on how

to optimize the reaction conditions to give a higher yield and how to provide access to other products.

2.8 Optimizing reaction conditions

As discussed in the previous section, I demonstrated that my target molecule could be made via this one-pot method, although in a relatively low yield. Also mentioned was the solubility issue of the benzamide **32c** starting material in hexane, so a different dry solvent was used. I decided to use ether, as I knew from past experience that the starting material **32c** would dissolve in ether, and due to the fact that the pKa of ether is most likely higher than the pKa of intermediate **39**.

Compound **32c** was added to mixture of NaH (1.1 eqiv) and ether immediately followed by addition of 2 equivalents of benzaldehyde, Scheme 2.10.



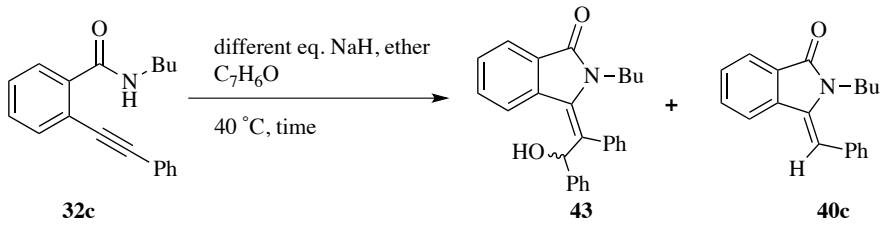
Scheme 2.10 Synthsesis of target product by using ether as solvent

Entry	Temp	Time	**43**	**40c**
1	rt	24 h	22%	52%
2	rt	48 h	32%	48%
3	30 °C	24 h	36%	45%
4	40 °C	24 h	46%	22%
5	40 °C	48 h	57%	20%
6	40 °C	96 h	68%	16%

Table 8. Optimization of reaction conditions using ether.

When the reaction mixture was stirred in room temperature, tetrasubstituted **43** was synthesized in similar low yields (22-32%) and significant amounts of trisubstituted IIN **40c** (48-52%) were formed despite the longer reaction times, Table 8, entries 1 and 2. When the temperature was increased to 30 ^{o}C for 24 h, the yield increased to 36%, while maintaining a similar yield for **40c**, Table 8, entry 3. Heating the reaction to 40 ^{o}C in ether and increasing the reaction time further increased the yield for **40c** to 46-57% while significantly lower yields (20-22%) were obtained for the trisubstituted IIN **40c** was observed, Table 8, entries 4 and 5. Continuing the reaction for a longer time (96 h) gave an even higher yield of 68% for target tetrasubstituted IIN **43**, Table 8, entry 6. This could be because the 5-exo-dig cyclization occurs slowly in ether. Therefore, the reaction needed to continue for a long time. Also, the starting material required time to convert completely to tetrasubstituted IIN **43**.

Although some amount of compound **32c** did not convert to product, we thought that if we increased the amount of base, a higher yield could be achieved. 1.1 equivalent of base did not convert all of the starting material and when the intermediate **39** is formed, it is possible that deprotonation of the leftover starting material results in formation of trisubstituted IIN **40c**. Use of more equivalents (2 and 3 equiv) could prevent this from happening, Scheme 2.11.



Scheme 2.11 Optimizing condition by using different equivalents of NaH

Entry	NaH. eq	Temp	Time	**43**	**40c**
1	2 eq	40 °C	24 h	58%	32%
2	3 eq	40 °C	24 h	54%	25%
3	3 eq	40 °C	48 h	64%	20%
4	2 eq	40 °C	48 h	66%	24%
5	2 eq	40 °C	72 h	82%	-

Table 9. Optimization of reaction conditions using different equivalents of base.

The reaction was started with 2 equivalent of NaH to deprotonate precursor **32c**. Ether was the solvent. The reaction was heated to 40 ^{o}C and left for 24 h, Table 9, entry 1. The yield was 58%. When 3 equivalents of base were used, Table 8, entry 2, the yield was close to that of entry 1. Keeping the reaction for a longer period of time gave a better result, Table 8, entries 3-5. This result could be because the intermediate of our target product need time to react with electrophiles. The best result was shown in Table 8, entry 5, when the reaction was left for 72 h.

After I optimized the conditions of this synthesis, I turned to investigating the scope of electrophiles that could use. I tried ethyl formate and benzophenone as electrophiles in ether as solvent. The reactions were performed in the same manner as in Table 8, entry 5. Unfortunately, trisubstituted IIN **40c** was formed and with no formation of tetrasubstituted IIN. Then I used hexane as a solvent, which could be heated to more than 40 °C, so I performed the reaction in hexane under reflux for 24 h. Trisubstituted IIN **40c**

was formed again as the major product. In conclusion, I have shown that my one-pot method will work to synthesize tetrasubstituted IINs, and future studies will necessarily have to focus on expanding the scope of this reaction.

2.9 Conclusions and Future work

Tetrasubstituted IIN **43** was synthesized by using a one-pot 5-exo-dig intramolecular cyclization reaction. The synthetic route was started from amidation of the commercially available starting material iodobenzoic acid. Sonogashira coupling reactions were subsequently performed. The target product was then synthesized by using benzaldehyde as the electrophile in either hexane or ether as solvents. I investigated a number of different conditions to carry out the reaction. My methodology will be useful for synthesizing functionalized target products in future.

In order to expand the utility of the one-pot cyclization methodology for tetrasubstituted IINs, several factors such as increasing electrophilicity, changing precursor, and the effect of steric, will need to be investigated more extensively.

Electrophiles are limited as intermediate **39** is a strong base. As ethyl formate and benzophenone as the electrophiles did not work, it is possible that a catalyst could be used to increase the electrophilicity of carbonyl group.

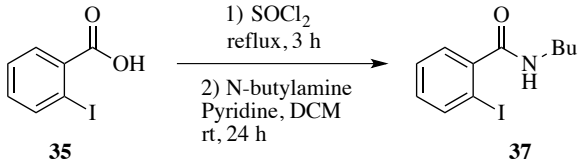
In addition, as I used hexane as solvent but the starting materials **32c** had limited solubility in this solvent, changing the butyl group to a longer alkyl group could help solubility.

Chapter 4: Experimental Methods

4. 1 General Information - All solvents were dried using a Grubbs apparatus prior to use. Amines were dried over molecular sieves and degassed with nitrogen prior to use. All commercially available reagents were purchased from various commercial suppliers and some of them were used with further purification (purification of laboratory chemicals book, Ed,5). All n-BuLi was at a 1.6 M concentration in hexane. All Sonogashira reactions were performed under nitrogen. All NaH was 60% dispersion in mineral oil. One–pot 5-exo-dig cyclization reactions were performed with carefully dried reagents. All temperatures were recorded relative to external bath temperatures. TLC analysis was performed on glass-backed plates (60A) and flash chromatography was performed on ultra-pure flash silica (230-400 mesh size). NMR spectra were recorded using either a Varian Inova 300 MHz (^{1}H: 299.838 MHz, ^{13}C: 75.402 MHz) or an Agilent 400 MR DD2 (^{1}H: 399.945 MHz, ^{13}C: 100.577 MHz) NMR spectrometer with $CDCl_3$ referenced at 7.26 ppm (^{1}H) or 77.16 ppm (^{13}C). IR spectra were recorded using KBr discs on a Nicolet Nexus 470 FTIR spectrometer. High-resolution mass spectra were recorded on a Bruker Daltonics spectrometer using Electrospray Ionization (ESI).

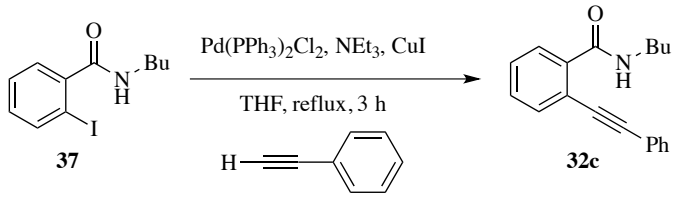
4.2 Experimental procedures

Preparation of *N*-butyl-2-iodobenzamide (37):



35 (1.2 g, 6.6 mmol) was added to a flame dried 2-neck flask fitted with a condenser, stir bar, and drying tube. Thionyl chloride (15 mL) was added. The translucent yellow solution was refluxed for 3 hours. The solution was removed from heat and thionyl chloride was removed which afforded a golden brown solid. To the flask was added dichloromethane (10 mL), *N*-butyl amine (2.3 mL, 5.0 mmol), and 1 mL of pyridine. After stirring at rt for 24 hours, 10 mL of NH_4Cl was added to the reaction and it was extracted with Et_2O (3 x 15 mL). The organic layer was washed with H_2O (3 x 10 mL), brine (2 x 5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and a pale yellow solid was obtained. Yield: 88%. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.93 – 7.71 (m, 1H), 7.41 – 7.29 (m, 2H), 7.15 – 6.90 (m, 1H), 5.89 (s, 1H), 3.55 – 3.26 (m, 2H), 1.71 – 1.51 (m, 2H), 1.46 – 1.32 (m, 2H), 0.93 (td, J = 7.2, 0.9 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.4, 142.5, 139.7, 134.4 – 125.3, 92.4, 39.8, 31.4, 20.2, 13.8.

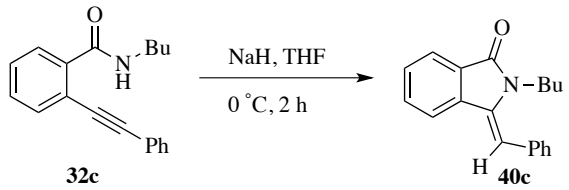
Preparation of *N*-butyl-2-(phenylethynyl)benzamide (32c):



37 (0. 30 g, 0.24 mmol) was added to a flame dried 2-neck flask which was fitted with a stir bar, condenser, and sealed with rubber septa. Tetrahydrofuran and triethylamine (25 mL/1 mL) were added to the flask via syringe. Phenylacetylene (0.06 mL, 2.5 equiv) was added and the solution was degassed with nitrogen for 20 minutes. To the degassed solution was added copper iodide (12 mg, 0.014 mmol) and $Pd(PPh_3)_2Cl_2$ (43 mg, 0.014 mmol). The flask was flushed with nitrogen for one minute and sealed under nitrogen. After heating to 80 ^oC for 3 hours, saturated NH_4Cl (25 mL) was added to the reaction mixture. The organic phase was extracted with diethyl ether (3 x 15 mL), washed with H_2O (3 x 10 mL), brine (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and an orange solid was obtained. The crude product was purified using flash chromatography in 2:1 Hexanes: EtOAc, which afforded an orange solid.

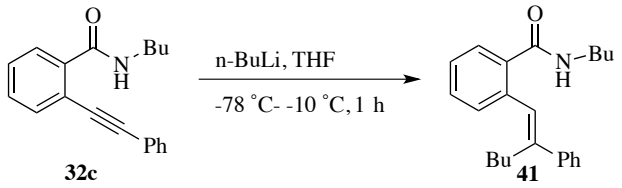
Yield: 85%. 1H NMR (300 MHz, Chloroform-d) δ 8.13 – 8.00 (m, 1H), 7.66 – 7.55 (m, 1H), 7.53 –7.29 (m, 6H), 3.51 (td, J = 7.1, 5.6 Hz, 2H), 1.64 – 1.48 (m, 2H), 1.47 – 1.28 (m, 2H), 0.85(t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 166.3, 140.4, 125.5, 120.8, 95.3, 87.6, 39.9, 31.7, 20.2, 13.7.

Preparation of (*Z*)-3-benzylidene-2-butylisoindolin-1-one (40c):



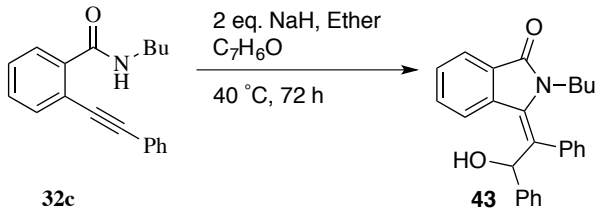
NaH (1.1eqiv) (3.4 mg, 0.1 mmol) was added to a flame dried 2-neck flask, which was fitted with a stir bar and sealed with rubber septa. Tetrahydrofuran (10 ml) was added to the flask via syringe. Then **32c** (20.1 mg, 0.07 mmol) was added to the reaction mixture, and the solution was stirred and cooled in an ice bath to 0 ^{o}C. The stirred solution was protected from light. After 2 h NH_4Cl solution (5 mL) and was added to the solution and the organic layer was extracted with ether (3 x 10 mL), washed with H_2O (5 x 20 mL), brine (2 x 5 mL) and dried over $MgSO_4$, to afford a white solid. Yield: 81%. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.84 (d, J = 0.8 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.63 – 7.56 (m, 1H), 7.54 – 7.49 (m, 5H), 7.41 – 7.33 (m, 1H), 6.78 (s, 1H), 3.81 – 3.58 (m, 2H), 1.18 (d, J = 7.5 Hz, 2H), 0.86 (d, J = 7.5 Hz, 2H), 0.70 – 0.54 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 168.5, 138.2, 134.8 (d, J = 21.5 Hz), 131.6, 130.3 – 126.6 (m), 123.1, 119.1, 106.3, 40.9, 30.1, 19.5, 13.3.

Preparation of (*E*)-*N*-butyl-2-(2-phenylhex-1-en-1-yl)benzamide (41):



32c (20.1 mg, 0.07 mmol) was added to a dry flask that was fitted with a stir bar. Tetrahydrofuran (10 mL) was added to the flask via syringe and followed by adding n-BuLi (0.04 ml, 0.07 mmol) to -78 ° C for 20 min . The solution was stirred and increased the temperature to -10 ° C. The stirred solution was protected from light. After 1 h NH_4Cl solution (5 mL) and was added to the solution and the organic layer was extracted with ether (3 x 10 mL), washed with H_2O (5 x 20 mL), brine (2 x 5 mL) and dried over $MgSO_4$. The crude product was purified using flash chromatography in 2:1 Hexanes: EtOAc, which afforded an yellow oil. Yield: 90%. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.84 – 7.75 (m, 1H), 7.51 – 7.23 (m, 8H), 6.85 (s, 1H), 6.08 (s, 1H), 3.38 (td, J = 7.0, 5.6 Hz, 2H), 2.66 – 2.54 (m, 2H), 1.51 – 1.15 (m, 8H), 0.79, 0.07 (s, 6H).^{13}C NMR (101 MHz, Chloroform-d) δ 168.5, 144.6, 141.7, 135.5 (d, J = 17.8 Hz), 131.2 – 126.2 (m), 39.7, 32.8 – 28.7 (m), 22.7, 20.1, 13.7 (d, J = 11.2 Hz), 1.0. HRMS (ESI+) for $C_{23}H_{28}O_1N_1Na$ [M + Na]$^+$: calcd. 336.1041 found 336.1029.

Preparation of 2-butyl-3-(2-hydroxy-1,2-diphenylethylidene)isoindolin-1-one (43):



NaH (1.1eq) (3.4 mg, 0.1 mmol) was added to a flame dried 2-neck flask which was fitted with a stir bar, condenser, and sealed with rubber septa. Ether (10 ml) was added to the flask via syringe. Then **32c** (20.1 mg, 0.07 mmol) was added to the solution. Followed by adding benzaldehyde (2eq) (0.01 ml, 0.14 mmol) and heat the mixture to 40 °C. After heating to for 72 hours, saturated NH_4Cl (15 mL) was added to the reaction mixture. The organic phase was extracted with diethyl ether (3 x 10 mL), washed with H_2O (3 x 15 mL), brine (2 x 10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and a yellow solid was obtained. The crude product was purified using flash chromatography in (5:2 Hexanes: EtOAc), which afforded **43** in 82%. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.02 – 7.90 (m, 2H), 7.56 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 2H), 7.42 – 7.23 (m, 8H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 1.99 (d, *J* = 7.5 Hz, 1H), 1.22 (d, *J* = 23.0 Hz, 2H), 0.81 – 0.62 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.4, 140.8, 136.6, 135.1, 132.3, 131.7, 129.6, 129.1, 128.4, 128.3, 127.9, 127.8, 127.6, 126.3, 125.9, 124.4, 123.7, 109.9, 77.2, 76.9, 71.9, 41.6, 19.6, 13.6, 1.0. HRMS (ESI+) for $C_{26}H_{25}O_2N_1Na$ $[M + Na]^+$: calcd. 406.1763 found 406.1778.

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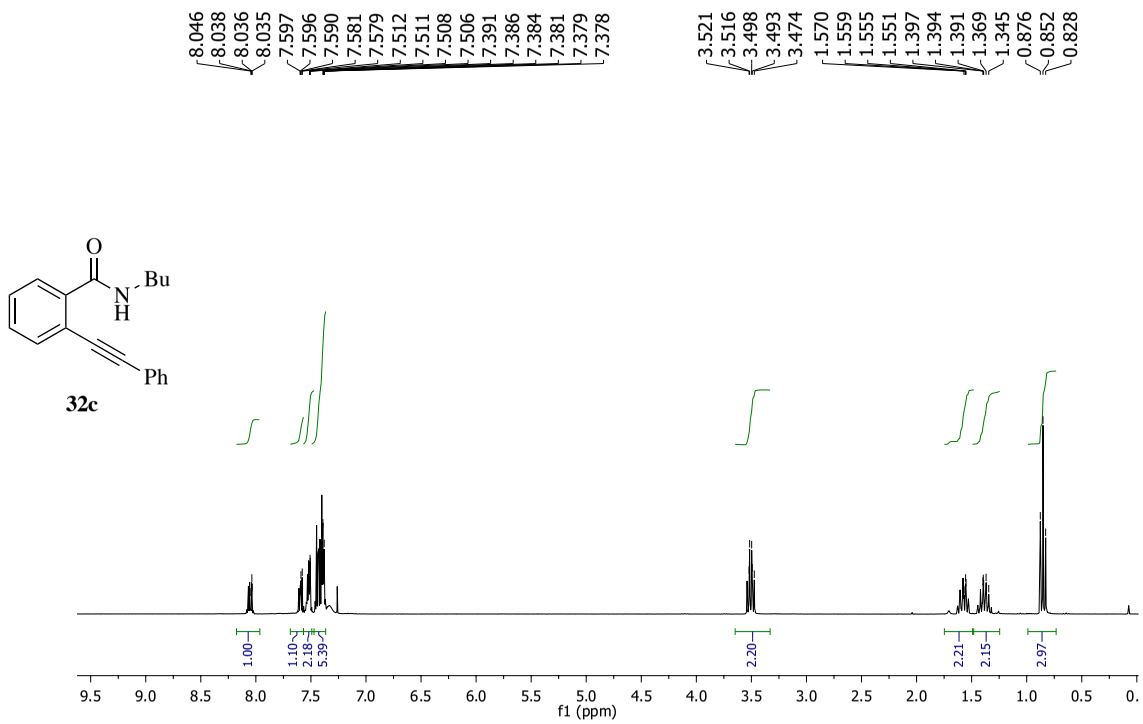
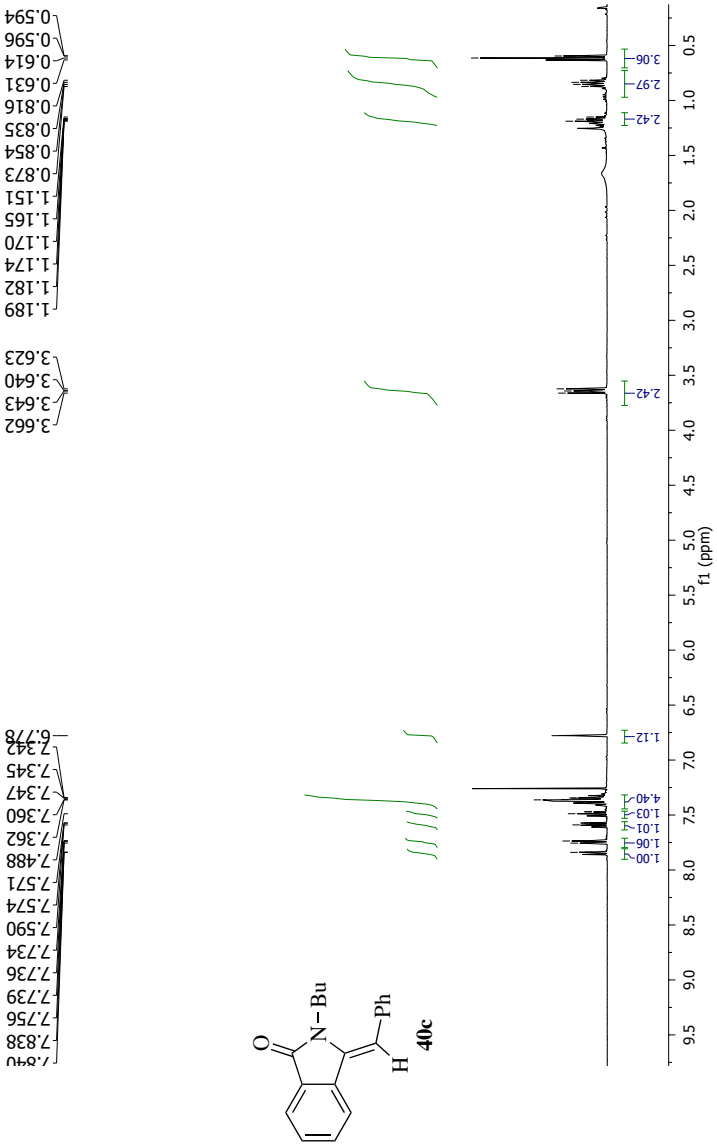
Appendix A: ^{1}H NMR Spectra

37
f1 (ppm)
7.793
7.792
7.324
7.322
7.319
7.318
7.316
7.314
7.045
7.037
7.036
7.033
7.031
3.435
3.419
3.415
3.411
1.585
1.580
1.565
1.562
1.557
1.417
1.414
1.396
1.393
1.390
0.959
0.956
0.935
0.908
1.05
2.17
1.10
1.00
2.28
2.12
2.11
3.16


8.046
8.038
8.036
8.035
7.597
7.596
7.590
7.581
7.579
7.512
7.511
7.508
7.506
7.391
7.386
7.384
7.381
7.379
7.378
3.521
3.516
3.498
3.493
3.474
1.570
1.559
1.555
1.551
1.397
1.394
1.391
1.369
1.345
0.876
0.852
0.828
O
N
H
Bu
Ph
32c
1.00
1.10
2.18
5.39
2.20
2.21
2.15
2.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)


O
N–Bu
Ph
H
40c
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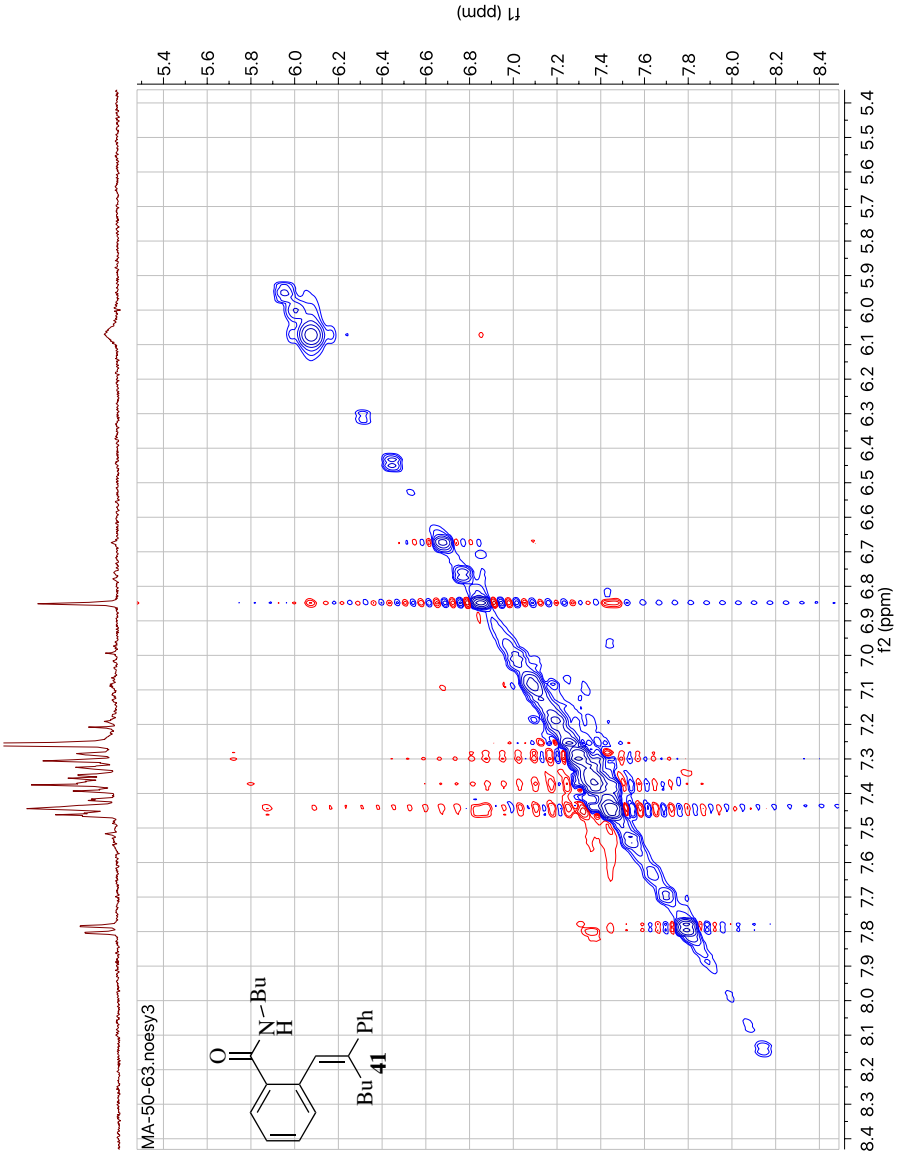
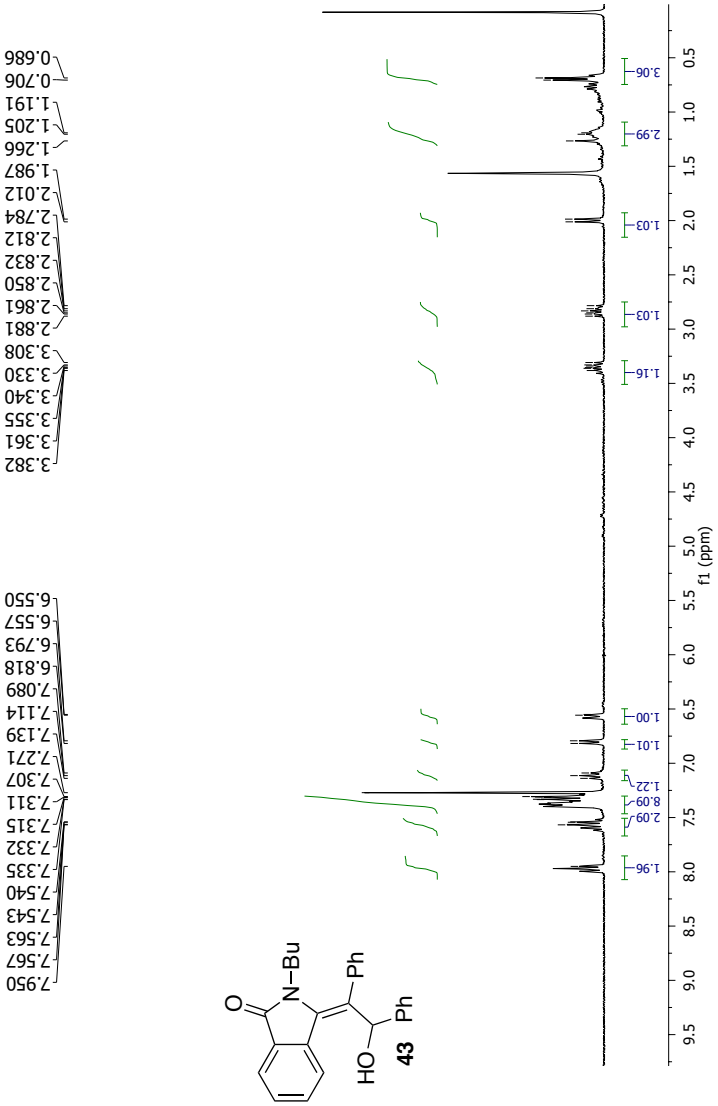
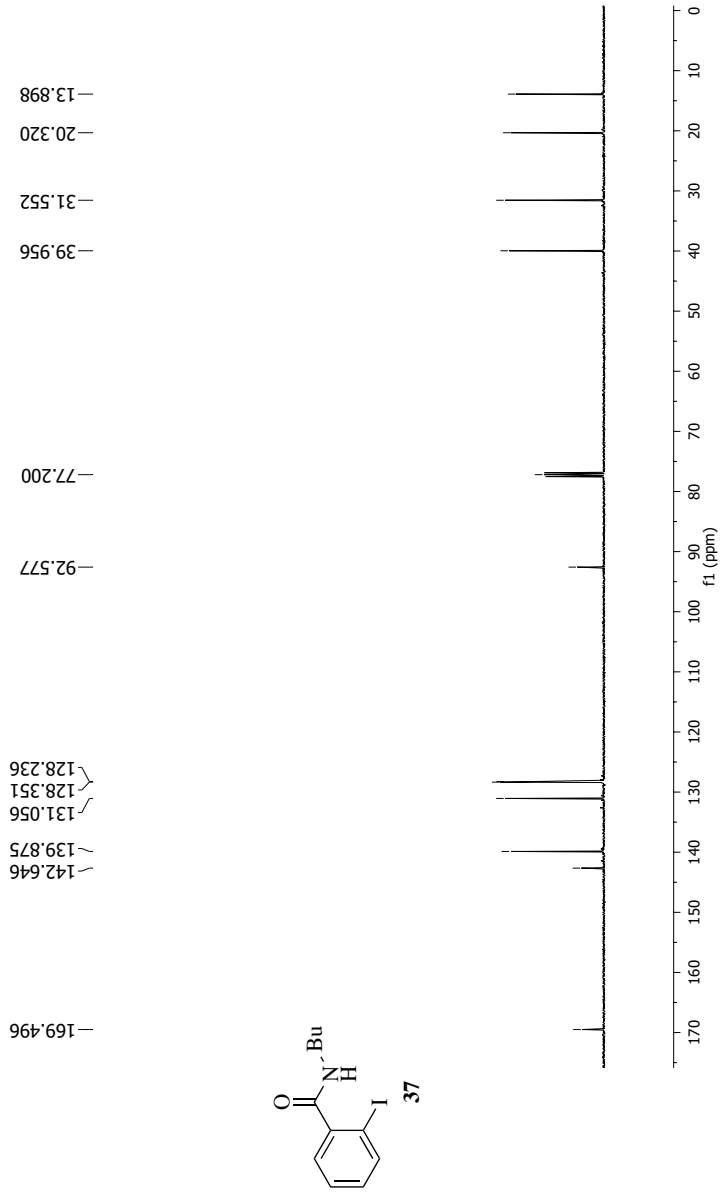
7.838
7.756
7.739
7.736
7.734
7.590
7.574
7.571
7.488
7.362
7.360
7.347
7.345
7.342
6.778
3.662
3.643
3.640
3.623
1.189
1.182
1.174
1.170
1.165
1.151
0.873
0.854
0.835
0.816
0.631
0.614
0.596
0.594
1.12
1.00
1.06
1.01
1.03
4.40
2.42
2.42
2.97
3.06
f1 (ppm)

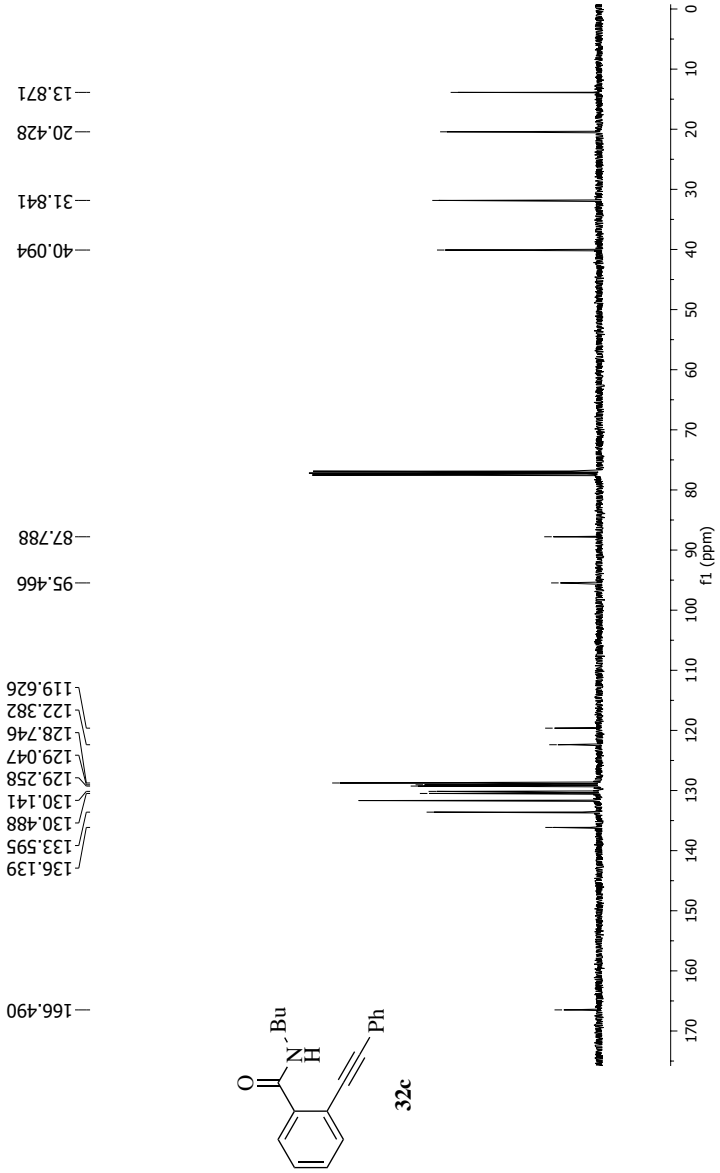
O
N
H
Bu
Bu
Ph
41
7.785
7.780
7.401
7.380
7.377
7.371
7.353
7.350
7.345
7.330
7.311
7.308
7.306
7.260
6.854
3.396
3.392
3.373
3.368
3.349
2.627
2.603
2.576
1.256
1.254
1.249
1.245
1.227
0.789
0.783
0.764
0.759
0.98
8.12
1.00
0.96
2.14
2.11
8.75
6.26
f1 (ppm)


MA-50-63.noesy3
O
N
H
Bu
Ph
Bu
41
f2 (ppm)
f1 (ppm)

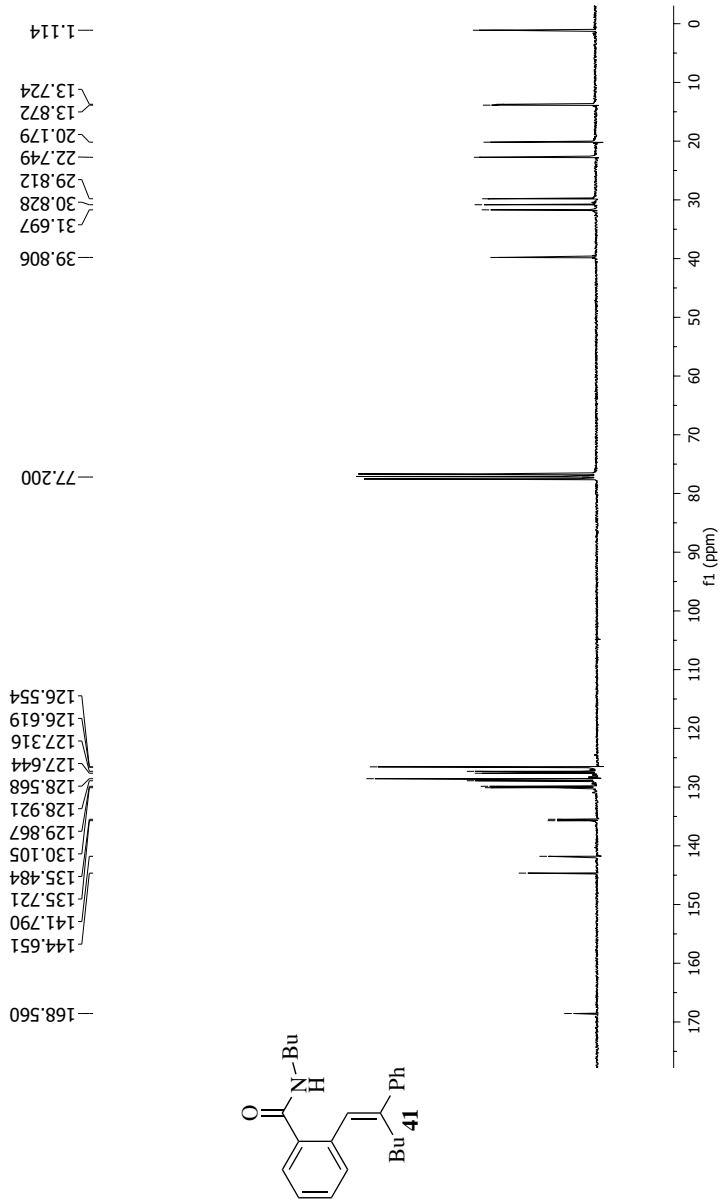

O
N–Bu
Ph
HO
Ph
43
7.950
7.567
7.563
7.543
7.540
7.335
7.332
7.315
7.311
7.307
7.271
7.139
7.114
7.089
6.818
6.793
6.557
6.550
3.382
3.361
3.355
3.340
3.330
3.308
2.881
2.861
2.850
2.832
2.812
2.784
2.012
1.987
1.266
1.205
1.191
0.706
0.686
1.96
2.09
8.09
1.22
1.01
1.00
1.16
1.03
1.03
2.99
3.06
f1 (ppm)

Appendix B: ^{13}C NMR Spectra


169.496
142.646
139.875
131.056
128.351
128.236
92.577
77.200
39.956
31.552
20.320
13.898
f1 (ppm)
37


O
N
H
Bu
Ph
32c
166.490
136.139
133.595
130.488
130.141
129.258
129.047
128.746
122.382
119.626
95.466
87.788
40.094
31.841
20.428
13.871
f1 (ppm)

O
N-Bu
Ph
H
40c
168.490
138.205
134.887
134.673
131.628
129.395
128.768
127.924
127.387
123.056
119.084
106.276
77.200
40.989
30.120
19.487
13.340
f1 (ppm)


O
N
H
Bu
Bu
Ph
41
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141.790
135.721
135.484
130.105
129.867
128.921
128.568
127.644
127.316
126.619
126.554
77.200
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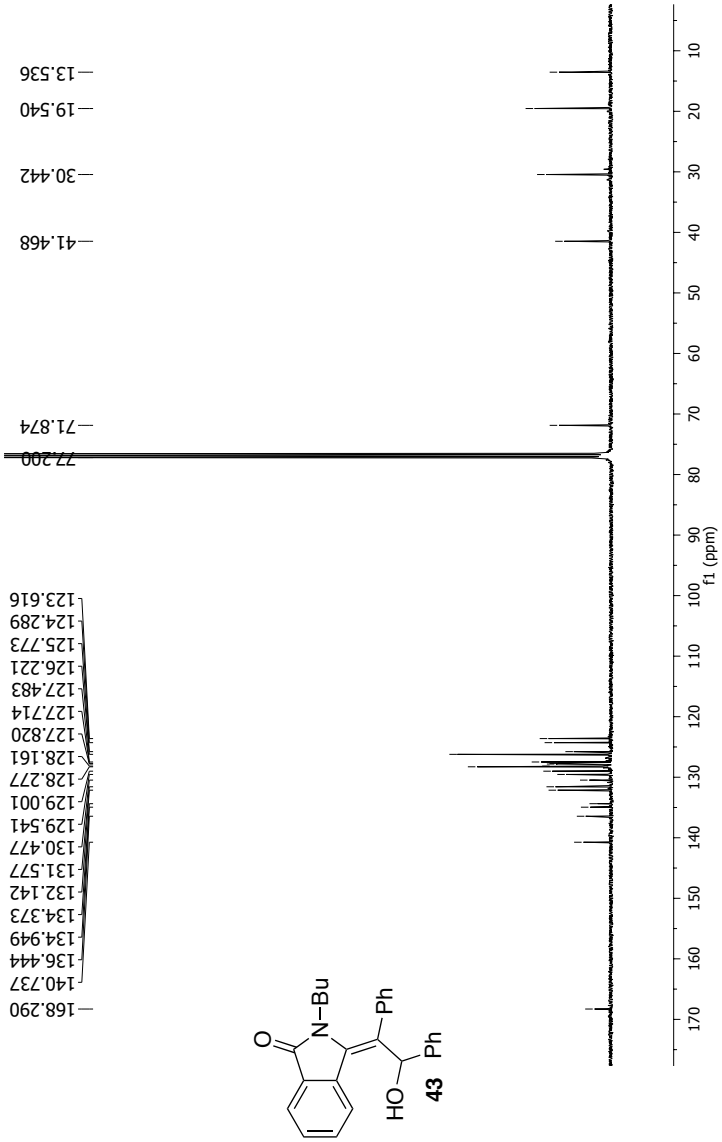
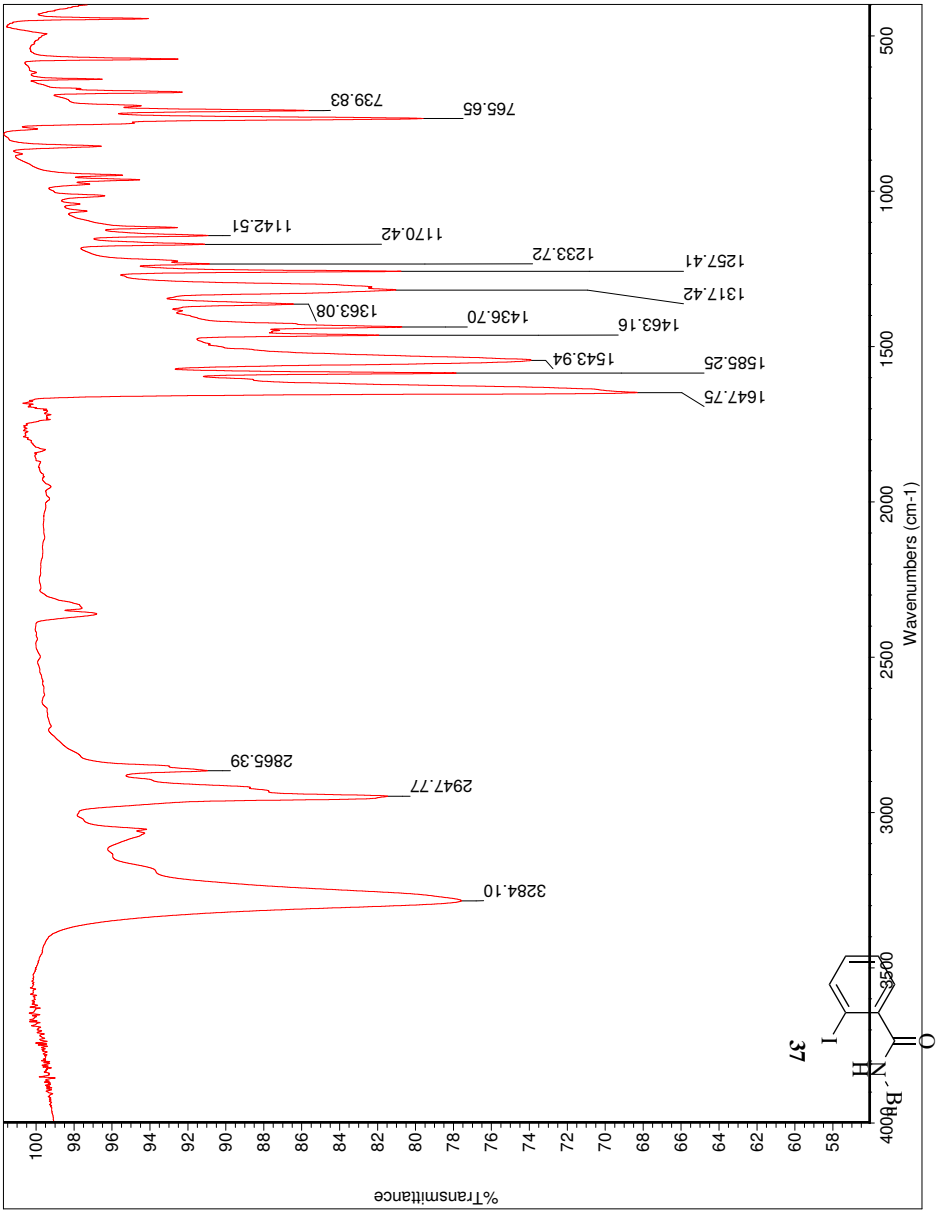
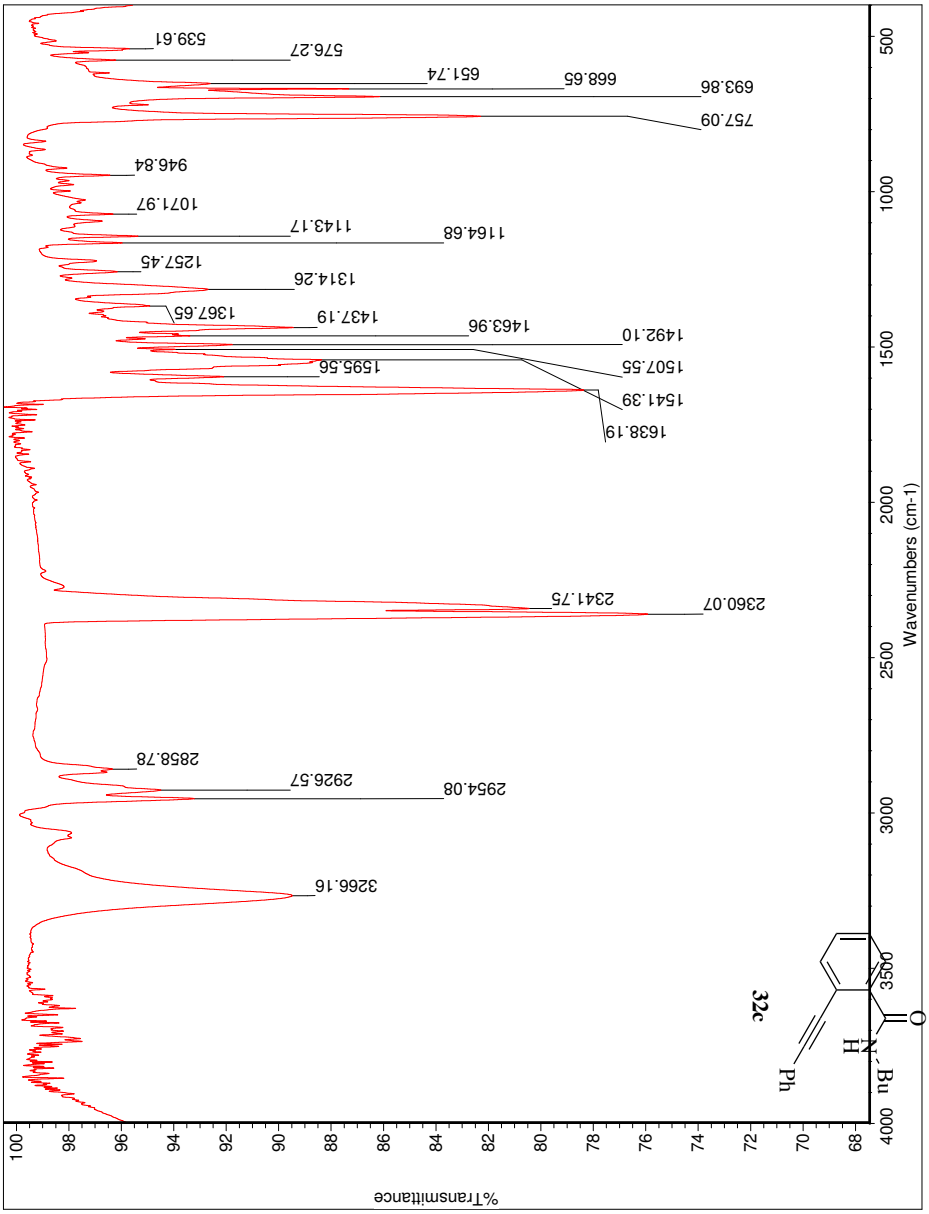
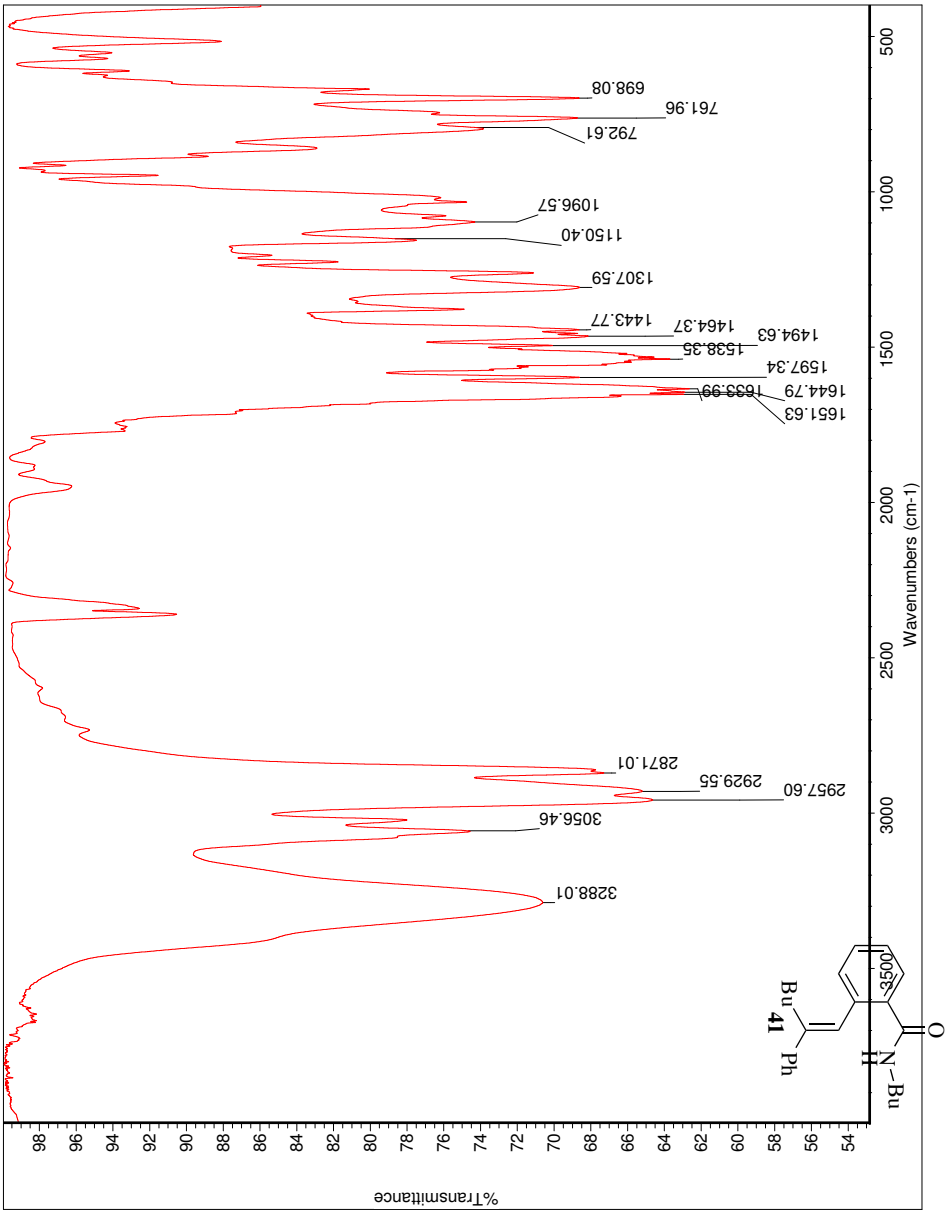
31.697
30.828
29.812
22.749
20.179
13.872
13.724
1.114
f1 (ppm)


O
N–Bu
Ph
HO
Ph
43
168.290
140.737
136.444
134.949
134.373
132.142
131.577
130.477
129.541
129.001
128.277
128.161
127.820
127.714
127.483
126.221
125.773
124.289
123.616
77.200
71.874
41.468
30.442
19.540
13.536
f1 (ppm)

Appendix C: IR Spectra


%Transmittance
Wavenumbers (cm-1)
3284.10
2947.77
2865.39
1647.75
1585.25
1543.94
1463.16
1436.70
1363.08
1317.42
1257.41
1233.72
1170.42
1142.51
765.65
739.83
37


32c
Ph
H
N
Bu
O
%Transmittance
Wavenumbers (cm-1)
3266.16
2954.08
2926.57
2858.78
2360.07
2341.75
1638.19
1541.39
1507.55
1595.56
1492.10
1463.96
1437.19
1367.65
1314.26
1257.45
1164.68
1143.17
1071.97
946.84
757.09
693.86
668.65
651.74
576.27
539.61


%Transmittance
Wavenumbers (cm-1)
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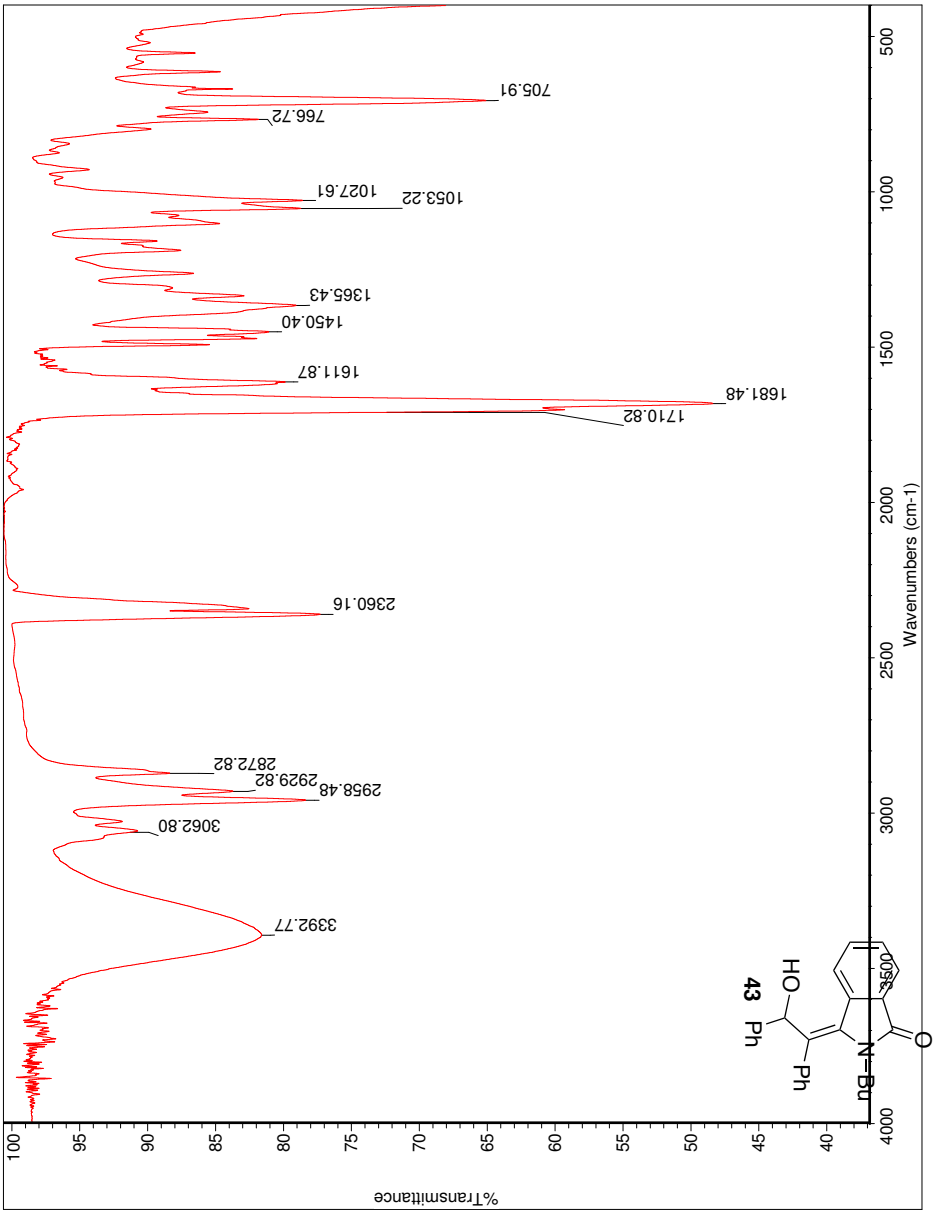
2929.55
2871.01
1651.63
1644.79
1633.99
1597.34
1538.35
1494.63
1464.37
1443.77
1307.59
1150.40
1096.57
792.61
761.96
698.08
41


%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3392.77
3062.80
2958.48
2929.82
2872.82
2360.16
1710.82
1681.48
1611.87
1450.40
1365.43
1053.22
1027.61
766.72
705.91
43
Ph
HO
Ph
N-Bu
O

Curriculum Vitae

Candidate's full name: Milhah Almansour

Universities attended: B.Sc. Najran University, 2006