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FORMATION OF HIGHLY FUNCTIONALIZED INDOLE THROUGH CARBON-CARBON BOND CLEAVAGE

Ryan A. S. Pike

Ryan A. S. Pike
Candidate

Chemistry and Chemical Biology
Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Dr. Ramesh Giri , Chairperson

Dr. Wei Wang

Dr. Jeffrey Rack

FORMATION OF HIGHLY FUNCTIONALIZED INDOLE THROUGH CARBON-CARBON BOND CLEAVAGE

by

RYAN A. S. PIKE

BACHELOR OF SCIENCE BIOLOGY
BACHELOR OF ARTS CHEMISTRY

THESIS

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DEDICATION

I dedicate my thesis work to my family and friends who have encourage me along my educational studies. A special feeling of gratitude to my loving parents, Richard and Cathie Pike whose words of encouragement and support drove my persistence. In memory of Sal and Kay Marretta, my loving grandparents. This thesis work is also dedicated to my fiancé, Lisa, who has been a constant source of support and encouragement during the challenges of graduate school, work, and life.

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I would also like to recognize Ken Sherrell for running and summarizing the Mass Spectroscopy results.

And finally, I would like to thank my parents Richard and Cathie Pike; your love, encouragement, and support are the greatest gifts I could ask for in the pursuit of my degree.

Formation of Highly Functionalized Indoles through Carbon-Carbon Bond Cleavage

By:

Ryan A. S. Pike

B.S., Biology, University of New Mexico, 2014
B.A., Chemistry, University of New Mexico, 2014

ABSTRACT

Indoles are one of the most abundant heterocycles found in nature and have a wide range of functions. There are a wide variety of indole synthesis methods known both in synthetic chemistry and through biosynthesis. Many of the known indole synthesis routes use a benzene derivative or cyclized ring structure derivative as a starting material. Here, we describe a novel synthetic method utilizing 1, 3-diketones and fumaronitrile with a catalytic amount of base to form a highly functionalized indole as our product. We have isolated and characterized 12 functionalized indoles.

LIST OF ABBREVIATIONS

ºC	Degrees Centigrade
µL	microliters
^{1}H NMR	Proton NMR
^{13}C NMR	Carbon NMR
C_6D_6	Deuterated benzene
cat.	Catalytic amount
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl Acetate
EWG	Electron withdrawing group
equiv	Equivalents
g/mol	Grams per mole
GCMS	Gas Chromatography Mass Spectroscopy
HCl	Hydrochloric Acid
hrs	Hours
K_2CO_3	Potassium Carbonate
K_3PO_4	Potassium Phosphate
$KHCO_3$	Potassium Bicarbonate
KO*t*Bu	Potassium *tert*-butoxide
mg	milligrams
mL	milliliters
mmol	millimole
mol	mole
NaH	Sodium Hydride
NaOMe	Sodium methoxide
NMP	N-Methyl-2-pyrrolidone

NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine

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Chapter 1: Introduction

1. Indoles and Their Uses

Indoles are an aromatic bicyclic organic compound consisting of a benzene ring merged with a pyrrole ring. The basic structure of an indole is shown in figure 1-1 with the numbered positions used for indole nomenclature and describing where substituents are located on the indole ring.

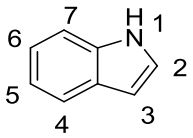
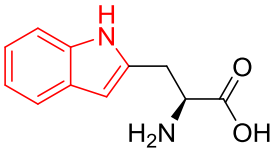


Figure 1-1

Indoles are found extensively in nature and are needed by every living organism to survive.[1] For example, indoles are produced by numerous species of bacteria as an intracellular signal.[1] As an intracellular signal, it is responsible for drug resistance, spore formation, and a pathogen's ability to affect its host.[1] As well as an intracellular signal, indoles are found in proteins of all living organisms as the amino acid tryptophan as shown in figure 1-2. [2]



Tryptophan

Figure 1-2

Indoles are not only found in the environment but also used in common pharmaceutical drugs. Imitrex, Maxalt, and Relpax are pharmaceutical drugs used to treat migraines that are indole derivatives as shown in figure 1-3.[3, 4, 5]

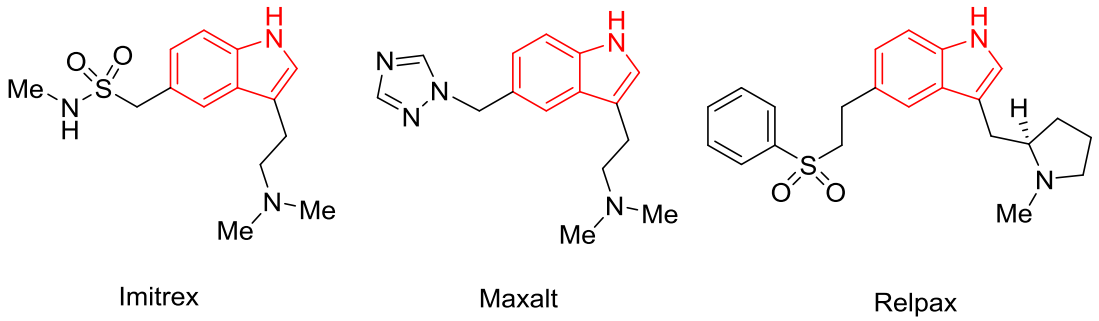


Figure 1-3

Indole derivatives are also used as dyes in solar cells and exhibit efficient photon-to-electron conversion properties.[6] The importance of indoles and their uses cannot be understated as chemists continuously search to develop new methods to synthesize indoles and research possibilities for their application across all sub-divisions of chemistry.

2. Proposed Indole Classification System

There are numerous methods used to synthesize indoles consisting of a wide array of starting materials. In 2011, Taber and Tirunahari proposed an indole synthesis classification system based on the last step in the chemical reaction used to form the indole ring.[7] As shown in figure 1-4, the classification system focuses on distinguishing indole formation reactions based on the last bond formed in the synthesis routes that create the indole ring.[7] Types 1 through 4 (Fischer, Mori, Hemetsberger, and Buchwald respectively) indole synthesis pathways focus on the last bond formed with an aromatic carbon in the benzene ring. Type 1 (Fischer) indole synthesis focuses on a carbon-carbon bond formation with deprotonation of an aromatic carbon.[7] Type 2 (Mori) indole synthesis focuses on a carbon-carbon bond formation with a carbon or heteroatom leaving group [7] Type 3 (Hemetsberger) indole synthesis focuses on a carbon-nitrogen bond formation with a deprotonation of an aromatic carbon.[7] Type 4 (Buchwald) indole synthesis focuses on a carbon-nitrogen bond formation with a carbon or heteroatom leaving group.[7] Type 5

(Sundberg) indole synthesis pathways focuses on the carbon-nitrogen bond formation of the indole ring external to the aromatic ring.[7] Type 6 (Madelung) indole synthesis pathways focuses on the non-aromatic carbon-carbon formation of the indole. [7] Type 7 (Nenitzescu) indole synthesis pathways are derived from a cycloalkane rings, typically utilizing a ketone as the reacting functional group.[7] Type 8 (van Leusen) indole synthesis pathways start with a pyrrole ring and form the benzene ring around the pyrrole ring.[7] Type 9 (Kanematsu) indole synthesis pathways utilize an intramolecular Diels-Alder reaction.[7] Interestingly, six of the nine types of indole forming reaction classifications proposed by Taber and Tirunahari require benzene derivatives as a starting material to form the benzene ring. Additionally, two of the nine require cyclized rings (pyrroles and cycloalkanes) as starting materials for indole synthesis. As shown later in the proposed mechanism, the newly developed indole synthesis method described does not fit clearly into any of the proposed indole classifications from Taber and Tirunahari thus making our indole synthesis pathway even more unique.

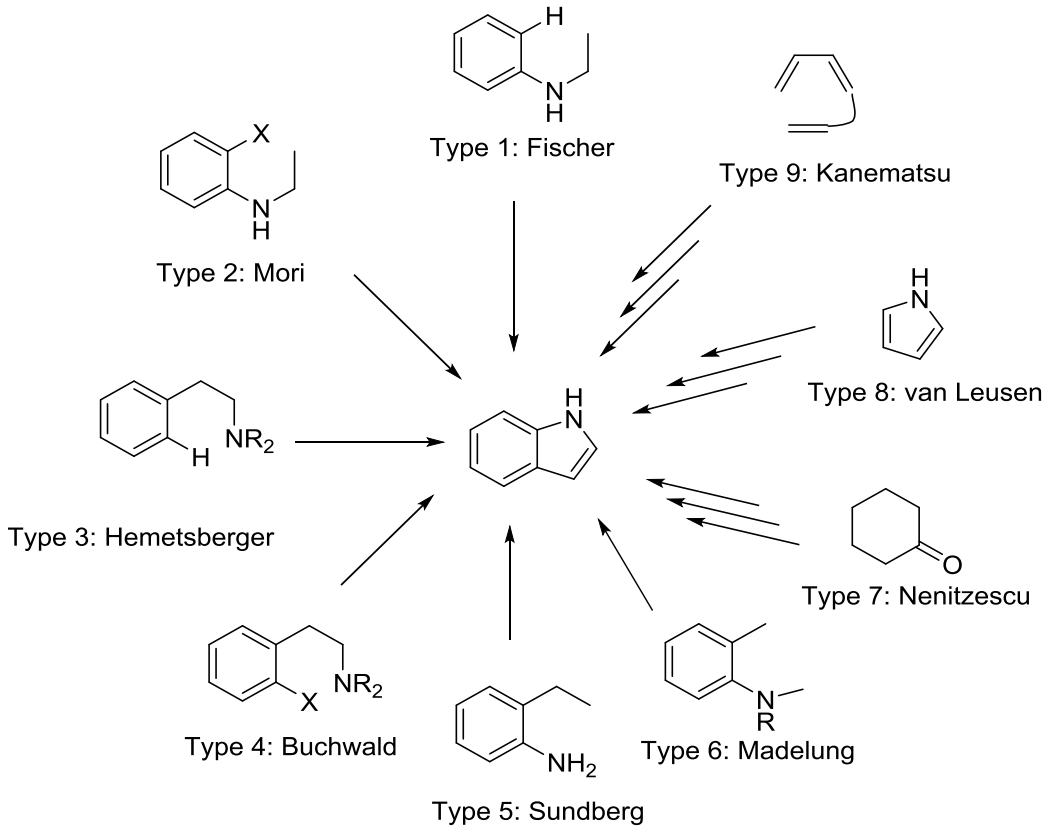


Figure 1-4

3. Known Indole Synthesis Routes

a. Fischer Indole Synthesis

One of the oldest known indole synthesis routes is the Fischer indole synthesis developed by Hermann Emil Fischer in 1883.[8] The Fischer indole synthesis reacts phenylhydrazine with a ketone or aldehyde in acidic conditions (Lewis or Brønsted) to form a phenylhydrazone. Phenylhydrazone will then undergo protonation and a [3, 3] sigmatropic rearrangement producing an imine. The imine produced forms an aminoacetal. Under the necessary acidic conditions, NH_3 of the aminoacetal will be eliminated, forming

the indole product. As shown in figure 1-5 the reaction is not regiospecific forming two isomers. This reaction is an example of a Type 1: Fischer indole synthesis.

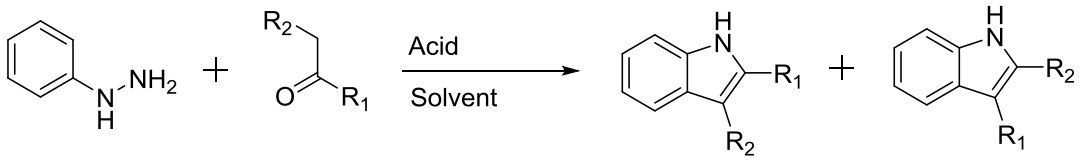


Figure 1-5

b. Larock Indole Synthesis

The Larock indole synthesis (named after Dr. Richard Larock) generates an indole through a reaction with *ortho*-iodoaniline and a di-substituted alkyne with a palladium catalyst using an excess amount of base.[9] The Larock indole synthesis occurs through oxidative addition of *ortho*-iodoaniline to palladium, binding of the alkyne to palladium, insertion of the alkyne into the arylpalladium bond, and formation of the product through reductive elimination. This reaction is regioselective favoring the more sterically hindered R-group inserting near the aryl-palladium bond formed during the generation of an intermediate. This will result in the more sterically hindered R-group to be at the R_1 position as seen in figure 1-6. This reaction is an example of a Type 5: Sundberg indole synthesis.

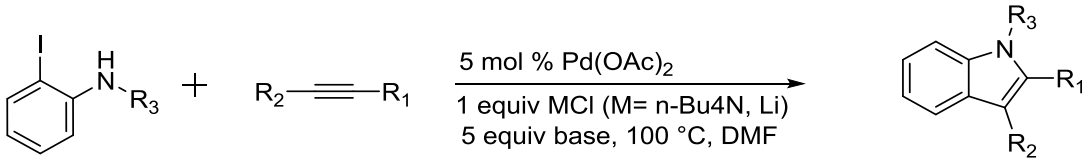


Figure 1-6

c. Intramolecular Diels-Alder Indole Synthesis

First developed by Kanematsu, the Kanematsu indole synthesis approach was the first of its kind to synthesize an indole from an intramolecular Diels-Alder reaction.[7] One

example of an intramolecular Diels-Alder reaction used to create an indole developed by Wipf and coworkers in 2009.[10] As shown in figure 1-7, an alkylaminofuran undergoes an intramolecular Diels-Alder reaction between the two carbon-carbon double bonds of the furan ring and the allylic alcohol carbon-carbon double bond in the molecule. This reaction proceeds with microwave irradiation as a necessary condition under a high temperature environment. This reaction is an example of a Type 9: Kanematsu indole synthesis.

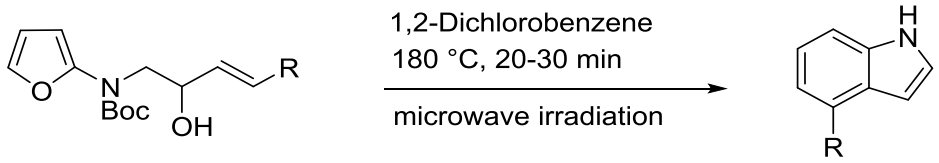


Figure 1-7

d. Borane-catalyzed Indole Synthesis

One of the newest approaches to indole synthesis was developed by Paradies and coworkers at the beginning of 2017. As shown in figure 1-8, the indole synthesis method uses tris-(perfluorophenyl) borane as a Lewis Acid catalyst to drive an intramolecular reaction of a 2-alkynyl aniline to give an indole product.[11] This reaction occurs through an intramolecular hydroamination mechanism under mild reaction conditions. This reaction is an example of a Type 5: Sundberg indole synthesis.

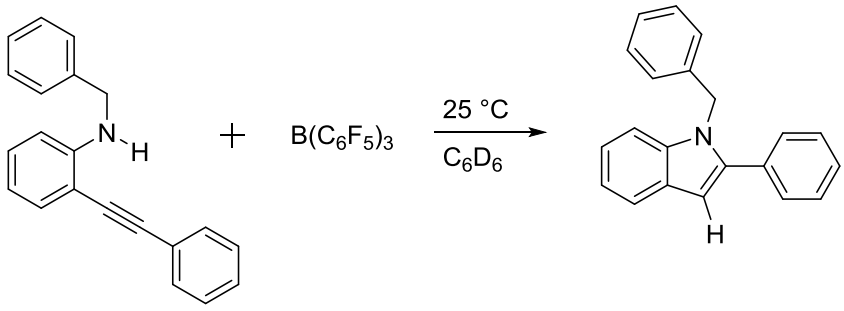


Figure 1-8

e. Biosynthesis

Nature has its own method of producing indoles that are crucial to everyday life. Tryptophan is one of twenty-one amino acids that are used in proteins that execute a wide variety of functions critical to support all living organisms.[2] In plants and bacteria, the biosynthesis starts with shikimic acid or anthranilate as shown in figure 1-9 (shikimic acid can be biosynthesized into anthranilate).[12] Anthranilate will then condense with phosphoribosylpyrophosphate. The ring of the ribose will be opened and undergo decarboxylation. The resulting indole-3-glycerinephosphate in transformed into an indole by removal of glyseraldehyde-3-phosphate. This indole will then go onto react with serine to form the amino acid Tryptophan. Each step of the biosynthetic pathway is catalyzed using an enzyme specific to that reaction. The indole ring forming step of tryptophan biosynthesis is an example of a Type 2: Mori indole synthesis.

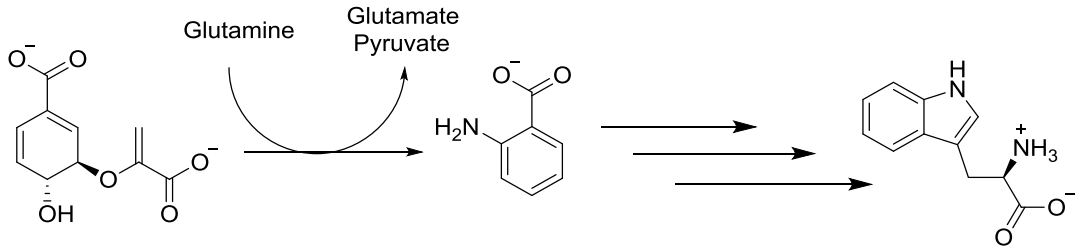


Figure 1-9

4. Conclusions

Indole synthesis reactions are not new to chemists and each year more methods are developed to synthesize indoles. Nature utilizes indoles in a wide variety of functions that are essential to life. There are a wide variety of indole synthesis that utilize different synthetic methods to achieve indole formation. Enzymes, precious metals, and Lewis acids are among the noted catalysts used to synthesize indoles. Many indole synthesis routes use

a cyclized ring as a precursor for the synthesized indole. However, the indole reaction we discovered is unique in comparison to previously described indole synthesis methods because it uses unique, commercially available, and inexpensive starting materials (diketones, fumaronitrile, and no precious metal catalyst) and requires only a catalytic amount of base. Our starting materials for our indole synthesis method are not previously described in the literature to produce the indoles as a product thus making the newly described indole synthesis unique.

Chapter 2: Results and Discussion

1. Initial Research

Initial research for my master's thesis was attempting to create a domino reaction using a copper catalyst, an aryl halide, and alkyne to give a tetra-substituted alkene. Screening proved unsuccessful for the desired tetra-substituted alkene product so we attempted to develop a domino reaction to produce a tetra substituted alkane. We went through screening procedures that utilized DMF, DMSO, DMA, toluene, THF, dioxane, and NMP as solvents and KO*t*Bu, NaOMe, K_2CO_3, K_3PO_4 as bases. The screening reaction shown in figure 2-1 is when we got an unexpected product.

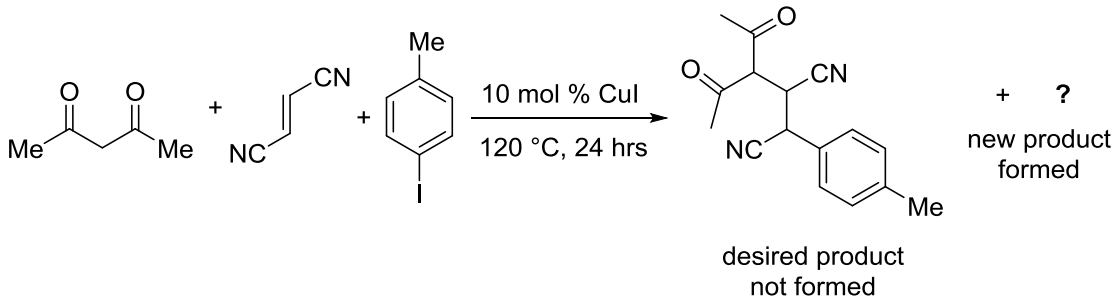


Figure 2-1

Through controlled experiments, we eliminated CuI and 4-iodotoluene as necessary reagents for the new product to form. We were also able to determine that setting the reaction up in the glove box under a controlled environment is unnecessary. We isolated the product and confirmed it as the unknown product through GCMS. The ^{1}H and ^{13}C NMR of the molecule shown in figures 2-2 and 2-3 respectively offered little insight on the nature of the product formed.

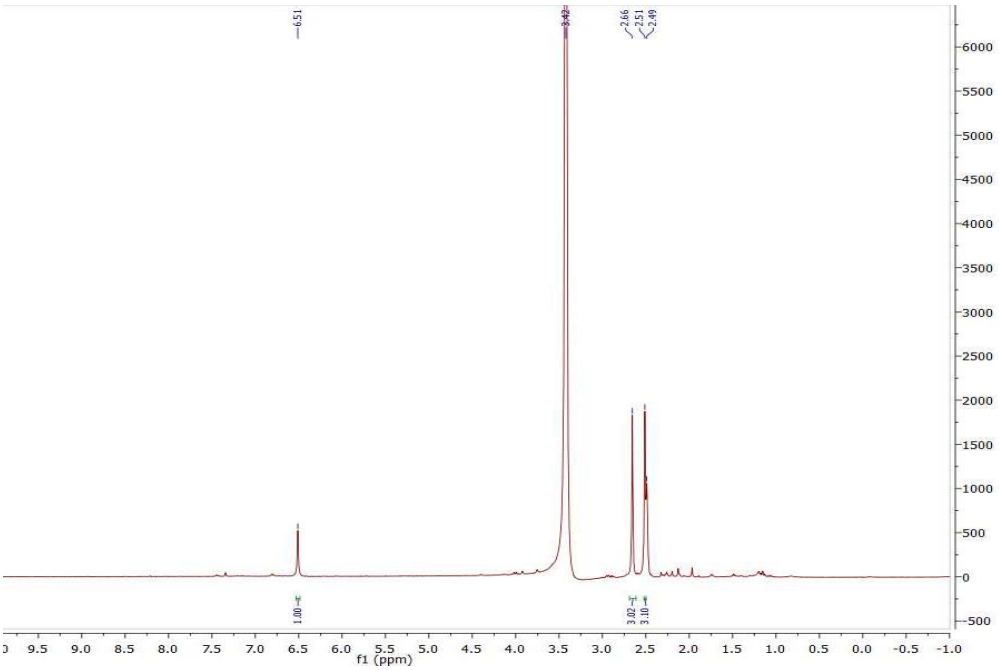


Figure 2-2

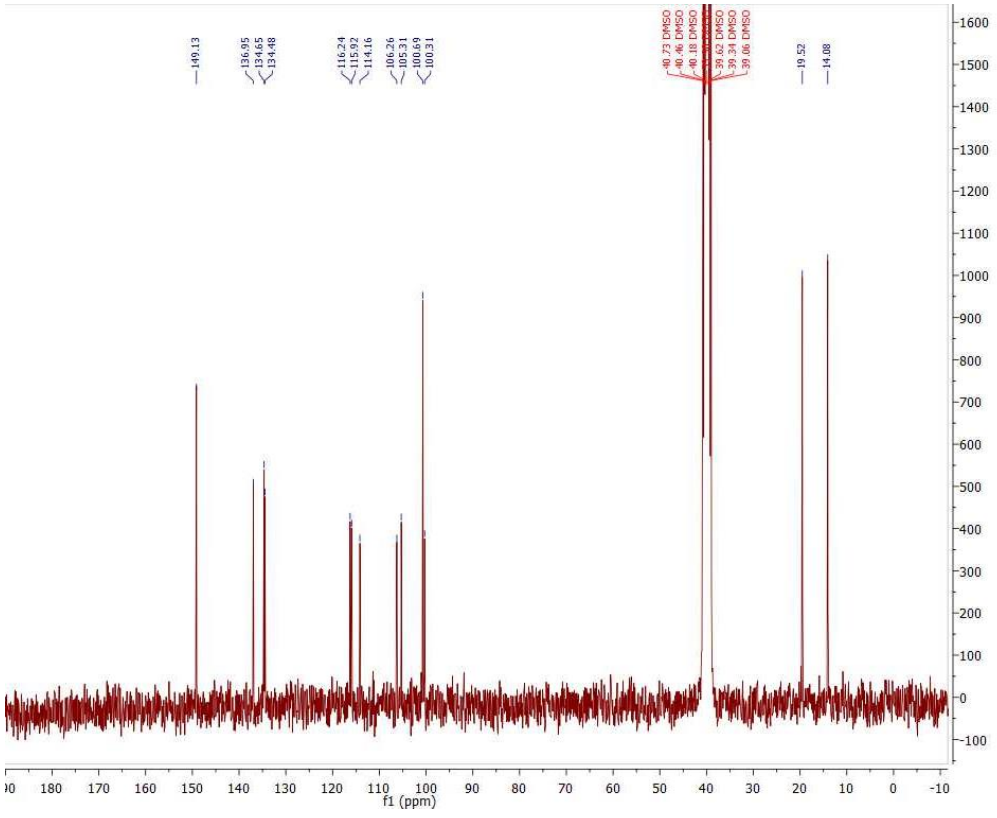


Figure 2-3

As seen in the carbon and proton NMR, 7 protons and 13 carbon atoms are observed in the spectra shown. The ratio of carbon to hydrogen atoms baffled us as we did not know what other atoms were in the molecule. The lack of solid evidence to determine the structure of the product ended when we were able to diffract a single crystal of the product by X-ray.

2. Crystal Structure

After the initial discovery of our indole synthesis, the first evidence collected that provided solid evidence to the structure of our unknown product was the crystal structure shown in figure 2-4. Through slow evaporation in EtOAc a crystal formed during isolation in a test tube. This indole shown below was formed by the initial reaction discovered through reacting 2, 4-pentanedione with fumaronitrile in dioxane with K_2CO_3 as a base. Shown in figure 2-5 is the two-dimensional structure of the molecule seen in the crystal structure. Figure 2-5 is drawn with the correlating carbon and nitrogen numbers from the crystal structure.

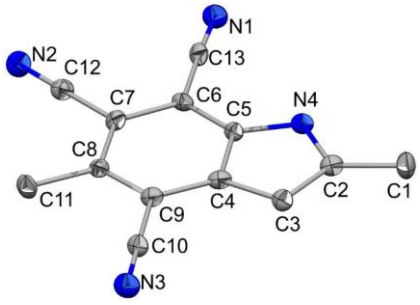


Figure 2-4

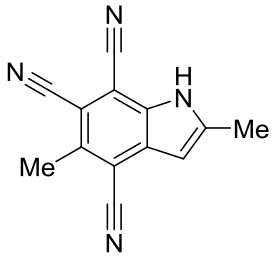


Figure 2-5

The nine-membered ring of the indole structure is visible at the center of the molecule. The blue atoms represent nitrogen and the grey atoms represent carbon while hydrogens are not

represented in this structure for clarity. Three nitrile groups are attached to the benzene of the indole ring at the 4, 6, and 7 positions and two methyl groups are attached at the 2 and 5 positions of the indole ring.

Looking at the crystal structure not only helped us identify our product but also solidified our understanding of the correct stoichiometry needed for the reaction. First, there was an additional hydrogen in the indole that we missed upon analyzing our ^{1}H NMR bringing the total number of hydrogens to 8 from our previously reported 7 (perhaps due to H/D exchange with DCl present in $CDCl_3$). Additionally, the crystal structure provided clues on a possible mechanism to form our product. Since there are four nitrogen atoms in the indole, the indole must require at least two fumaronitrile molecules to form. Also by looking at the crystal structure, we determined that there must be at least one carbon-carbon formation and cleaving step that occurs in the mechanism by the positioning of one of the fumaronitrile molecule fragments. Since there is a fumaronitrile fragment positioned between the carbon skeleton of the diketone, we concluded that there must be at least one carbon-carbon formation and cleaving step in the mechanism. Also by looking at the crystal structure and comparing that structure to the atomic weight, we realized that there are no oxygen atoms in the final structure. Knowing this, we able to determine that the oxygen atoms are lost as a byproduct in the reaction mechanism.

After the discovery of reaction, we looked to optimize the reaction conditions. We used different solvents and bases as seen in table 2-1 below.

Condition	Amount (mg) 0.1 mmol	Desired Product (%)
Normal		86
K_2CO_3 50 mol%	6.9	85
K_2CO_3	13.8	85
K_2CO_3 2 equiv	27.6	86
THF instead of Dioxane		78
DMSO instead of Dioxane		37
Hexane instead of Dioxane		19
$KHCO_3$ (1 equiv) instead of K_2CO_3	10.0	80
$BaCO_3$ (1 equiv) instead of K_2CO_3	19.7	0
$CaCO_3$ (1 equiv) instead of K_2CO_3	10.0	7
$LiCO_3$ (1 equiv) instead of K_2CO_3	7.4	0
$SrCO_3$ (1 equiv) instead of K_2CO_3	14.8	0
Na_2CO_3 (1 equiv) instead of K_2CO_3	10.6	66
K_3PO_4 (1 equiv) instead of K_2CO_3	21.3	67

Table 2-1

Now knowing the proper reaction conditions and the final structure, we could write the complete balanced reaction equation shown in figure 2-6.

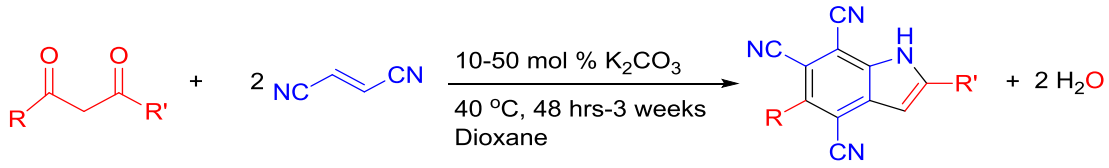


Figure 2-6

After optimizing the reaction conditions, we focused on the formation of the indole product. As stated previously, there are no oxygen atoms in the final molecule and therefore, the oxygen atoms must be lost as a side product during the reaction. We concluded that the oxygen atoms are lost as water based on the stoichiometric analysis of the complete reaction. Now knowing the balance reaction equation, structure of the indole, and with an understanding of the byproducts formed, we proposed a mechanism shown in figure 2-7.

3. Proposed Mechanism

Through structural analysis of the final product's crystal structure, we were able to identify two named reactions as well as other known chemical reactions and processes that possibly occur in the reaction mechanism to give us our product. As shown below in figure 2-7 which proposes a general reaction mechanism involving the Michael addition reaction, the DeMayo reaction, and a series of protonation, deprotonation and dehydration reactions can be used to propose a mechanism that produces our product. Details about these reactions helped us propose a detailed reaction mechanism.

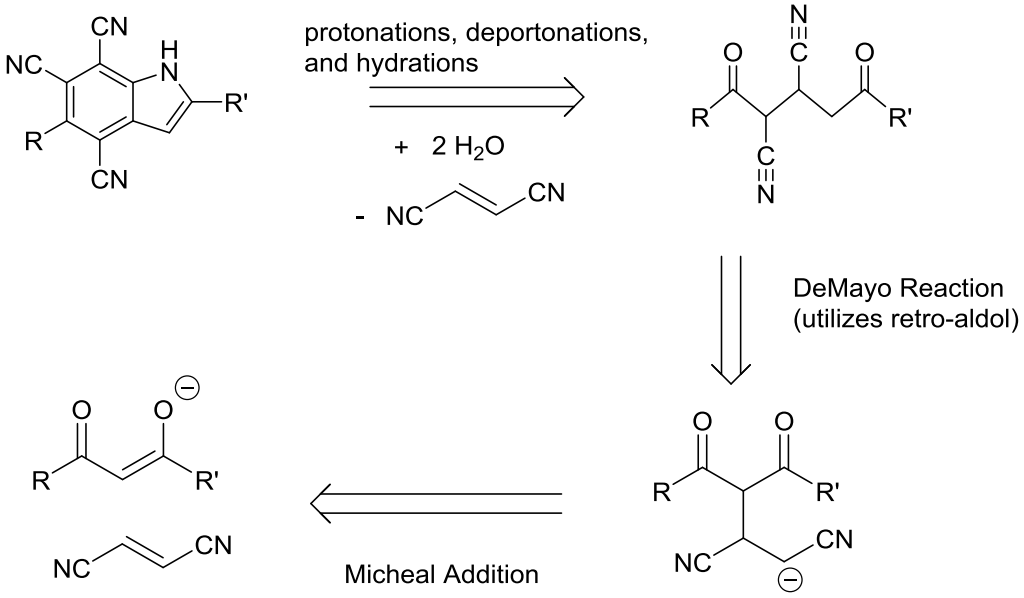


Figure 2-7

a. Reactions Used to Understand the Proposed Mechanism

Through an in-depth literature search, we found multiple reactions and concepts to understand, propose, and support a possible mechanism. The aldol and retro aldol reactions, Michael addition reaction, and DeMayo reaction played crucial roles in proposing a mechanism. Hard-soft Lewis acid and base theory and enolate chemistry were also crucial to our understanding of the proposed mechanism.

i. Aldol and Retro-Aldol Reactions

The Aldol reaction is a carbon-carbon bond forming reaction in which 2 carbonyl compounds react to form a new β-hydroxy carbonyl compound also known as an aldol product (derived from *ald*ehyde and alcoh*ol*).[13] The reaction can proceed under basic or acidic conditions. The reaction proceeds when the enol or enolate form of an aldehyde or ketone reacts with the α-carbon of a different carbonyl molecule. Consequently, the retro-aldol reaction is a carbon-carbon bond breaking reaction. The carbon-carbon bond that will be broken is the bond located between the α-carbon and the β-carbon. The general reaction is shown in figure 2-8.

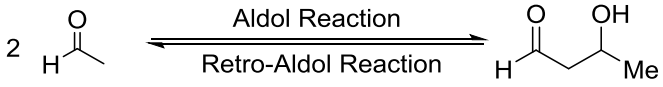


Figure 2-8

When acidic conditions are used for the aldol reaction, the initial step in the reaction mechanism involves protonation of the carbonyl oxygen to a positive charge on the oxygen atom. Through resonance the reactive enolate will form undergoing nucleophilic attack of the partial positive charge on the carbonyl carbon. Then the proton bonded with the positively charged oxygen atom will get deprotonated by a base. The aldol reaction mechanism for acidic conditions is shown in figure 2-9.

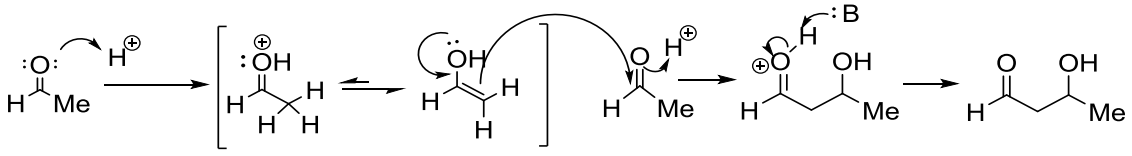


Figure 2-9

If the reaction occurs under basic conditions the aldol reaction occurs through deprotonation of the α-carbon forming an enolate molecule (typically stabilized by a cation

from the base) followed by nucleophilic attack on the carbonyl group of the aldehyde molecule. The aldol reaction mechanism for basic conditions is shown in figure 2-10.

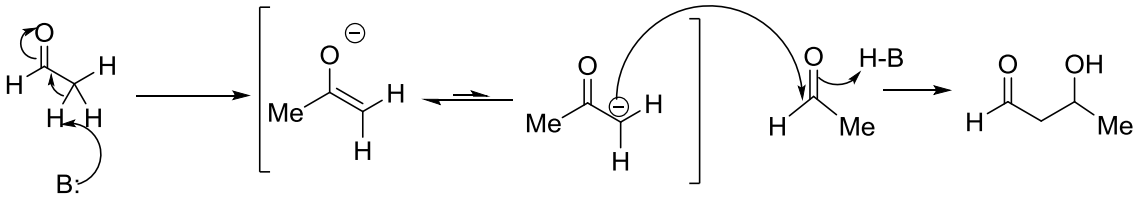


Figure 2-10

Consequently, the retro-aldol reaction breaks the bond located between the α-carbon and the β-carbon. This reaction will proceed under basic conditions with the β-hydroxy getting deprotonated. Through resonance, the bond between the α-carbon and the β-carbon will be broken forming one carbonyl compound and an enolate. Again, through resonance the α-carbon will get protonated forming the second carbonyl compound. The reaction mechanism for the retro-aldol reaction is shown in figure 2-11. The aldol and retro-aldol reactions (a reversible process) and mechanisms are important in understanding the mechanism of our novel indole reaction.

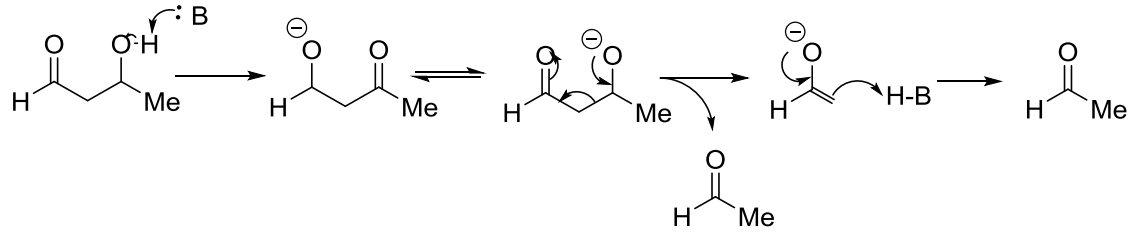


Figure 2-11

The aldol and retro-aldol reactions are crucial for understanding our proposed mechanism. Carbon-carbon bond formation and cleavage through enols and enolates are critical for the formation of the indole ring in our synthesis as well as our understanding of carbon and oxygen interactions. Also, the acid and base catalyzed Aldol reactions provide insights on

protonation and deprotonation of enolates with respect to understanding to our proposed mechanism.

Through hard-soft Lewis acid and base theory and the Aldol reaction, we can further understand the carbon-carbon bond forming interactions and reactions of enolate chemistry. According to the hard-soft Lewis acid and base theory, oxygen atoms are hard and carbon atoms are soft.[1] The hard oxygen atoms prefer to react with other hard bases such as potassium and carbanions prefer to react with a partially positive carbon atoms or unsaturated carbon atoms.[1] When an oxygen anion forms, it is not favorable for it to react with a partially positive carbon atoms or unsaturated carbon atoms even though the oxygen anion is more stable. Instead, it will undergo resonance to form carbanions that are favorable to react with partially positive carbon atoms or unsaturated carbon atoms. These preferred interactions help us understand why carbon-carbon bond formation is preferred over carbon-oxygen bonds forming our indole product.

The aldol reaction is also crucial to our understanding of the mechanism because it occurs under both basic and acidic conditions through proton donors and proton acceptors. The carbon-carbon bond formation of the aldol reaction can occur through protonation with an acid or deprotonation under basic conditions. The reaction conditions for our indole synthesis do not specify the addition of an acid; however, one is formed in the process of our indole synthesis. K_2CO_3 acts as a proton acceptor and $KHCO_3$ acts as a proton donor. Although $KHCO_3$ is not added to the reaction, it is formed when K_2CO_3 deprotonates a molecule shown in the proposed mechanism. The presence of a proton donor and acceptor such as K_2CO_3 and $KHCO_3$ is important to our proposed mechanism because there are numerous steps that involve protonations and deprotonations. These protonations and

deprotonations caused by K_2CO_3 and $KHCO_3$ drive the carbon-carbon bond formation and cleavages as well as hydrolysis reactions that give our indole product.

The retro-aldol Reaction is the carbon-carbon bond cleaving reverse reaction of the aldol reaction. The retro-aldol reaction occurs in part of the mechanism of the DeMayo Reaction as well as our proposed mechanism as necessary to the formation of the indole ring. The retro-aldol reaction is crucial to the formation of the indole ring and its importance will be further explained when discussing the DeMayo Reaction, and how it pertains to our mechanism.

ii. Michael Addition Reaction

The Michael addition reaction is the nucleophilic addition of a carbanion or another nucleophile with an α, β-unsaturated carbonyl compound forming a new carbon-carbon bond as seen in figure 2-12.[14] The nucleophile will react with the olefinic carbon of the α, β-unsaturated carbonyl compound forming a carbon-carbon bond. The nucleophile is called a Michael donor because it donates electrons and the α, β-unsaturated carbonyl compound called a Michael acceptor because it accepts electrons. Typical EWG used in Michael addition reactions are nitrile and acyl groups as seen in our indole synthesis described. This reaction is the probable initial step of the proposed mechanism for the described indole synthesis method.

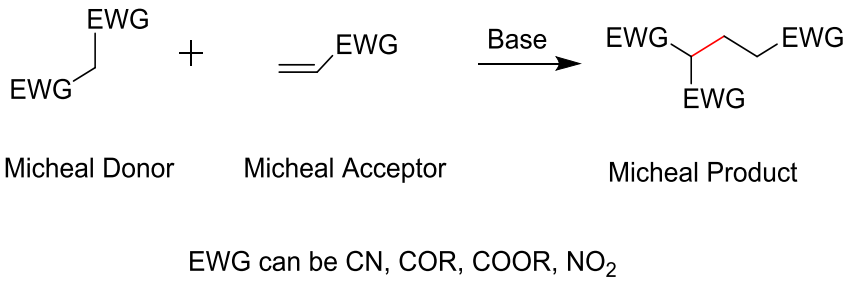


Figure 2-12

The Michael addition reaction is the probable initial step of the proposed mechanism for the described indole synthesis method. Diketones and fumaronitrile provide the necessary EWG needed to proceed through a Michael addition reaction with 2 nitrile groups in fumaronitrile and 2 acyl groups in the diketone starting materials which are the necessary EWGs. In addition, K_2CO_3 provides the base needed to deprotonate the acidic hydrogen and undergo a nucleophilic addition with the α, β-unsaturated carbonyl bond of fumaronitrile. After deprotonation, the enolate will form due to favored stability but the carbanion will react with the carbon-carbon double bond of fumaronitrile due to favorable hard-soft interactions (both the carbanion and carbon-carbon double bonds are soft). The necessary reaction conditions of a Michael addition reaction and the mechanism it undergoes are key to understanding multiple steps of our indole synthesis mechanism.

In addition to the initial step of our proposed mechanism, an additional Michael addition reaction occurs in step 6 of our proposed mechanism. Similar reaction conditions surround the molecule shown in intermediate 6 which has a nitrogen atom, a nitrile group and 2 carbonyl groups adjacent to the carbanion formed on the molecule. This carbanion will react with the carbon-carbon double bond of fumaronitrile giving the second Michael addition reaction of the proposed mechanism.

iii. DeMayo Reaction

The DeMayo Reaction is an ultraviolet light driven reaction between a 1, 3-diketone and an alkene resulting in the formation of a β-hydroxy ketone cyclobutane ring through a [2+2] cycloaddition reaction as shown in figure 2-13.[15] The deprotonation of the β-hydroxy group in the β-hydroxy ketone cyclobutane ring results in a retro-aldol reaction forming a 1, 5-diketone. This reaction is crucial in helping understanding and explaining

the proposed carbon-carbon bond cleavage of the proposed mechanism and formation of the indole ring.

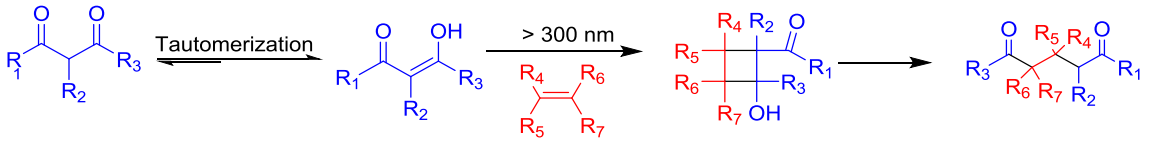


Figure 2-13

Although our reaction does not require ultraviolet light, the carbon-carbon bond cleavage necessary for the indole synthesis is hypothesized to occur through a similar cyclobutane intermediate formed by reacting the necessary starting materials. When the carbanion resulting from the hypothesized Michael addition reaction forms, the lone pair of electrons attack the partial positive charge on the carbonyl functional group in intermediate 4 of our proposed mechanism. The deprotonation of the β-hydroxy group with K_2CO_3 in the cyclobutane ring results in a carbon-carbon bond cleaving retro-aldol reaction forming a 1, 5-diketone shown in intermediate 5 of the proposed mechanism. Shown in figure 2-13 is the general mechanism for the DeMayo Reaction. Shown highlighted in red in figure 2-14 is the carbon skeleton of the diketone. Shown highlighted in blue is a reduced fumaronitrile molecule fragment.

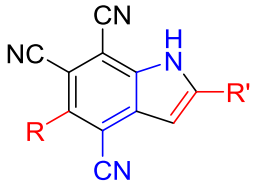


Figure 2-14

For the fumaronitrile molecule fragment to be located where it is in the indole between the carbon skeleton of the diketone, the mechanism must utilize carbon-carbon bond formation and cleavage reactions in order to break the carbon-carbon bonds of the 1, 3-diketone and

insert between those bonds. The hypothesized route the carbon-carbon bond formation and cleavage occurs is through a Michael addition reaction followed by a DeMayo Reaction. The DeMayo Reaction will give a DeMayo product, which is an intermediate for the proposed mechanism.

c. Detailed Reaction Mechanism

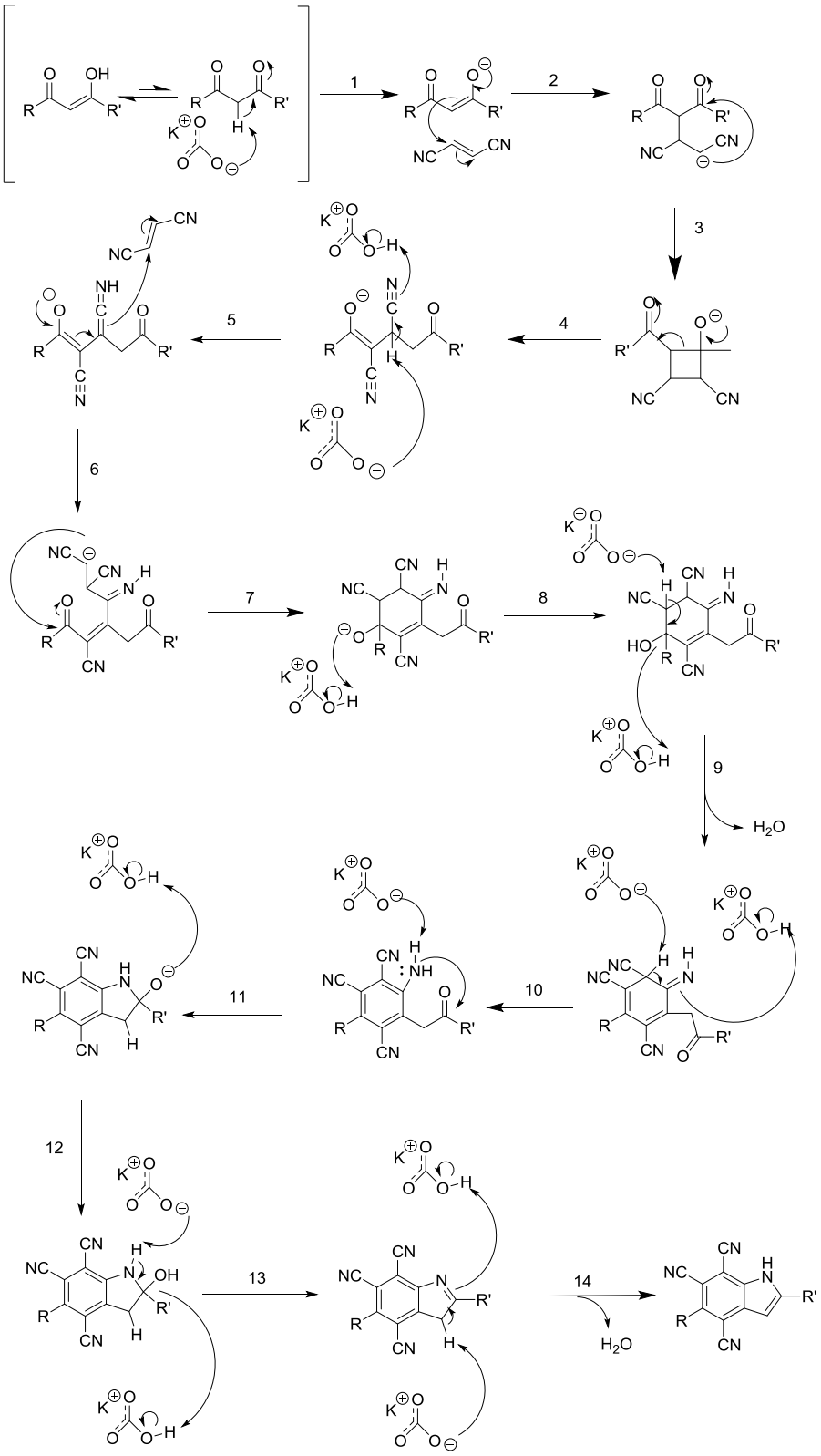


Figure 2-15

The initial tautomerization between the enol and diketone form of the molecule initiates this reaction. K_2CO_3 will deprotonate the diketone over the enol due primarily to two reasons: the decreased pKa value of a sp^3 hybridized carbon hydrogen bond compared to a sp^2 hybridized carbon hydrogen bond and due to a greater probability of being able to deprotonate one of two hydrogens in the diketone compare to just one hydrogen in the enol molecule as shown in step 1. This deprotonation will give resonating structures between a secondary carbanion and an enolate form of the diketone. The enolate is favored due to the electronegativity of oxygen. However, the carbanion will attack the carbon-carbon double bond of fumaronitrile in a Michael addition reaction with electrons from the carbon-carbon double bond forming a secondary carbanion shown in step 2. This carbanion will react with the partial positively charged carbon atom of one of the two carbonyl groups forming a four member cyclobutane ring in a DeMayo reaction with the carbonyl group getting reduced to an alcohol shown in step 3. The deprotonation of the β-hydroxy group with K_2CO_3 in the cyclobutane ring results in a retro-aldol reaction forming a 1, 5-diketone shown in step 4 forming a DeMayo product. Deprotonation of the hydrogen atom adjacent to the carbon-nitrile bond will get deprotonated shown in step 5. Through resonance, a carbanion will form on the imine carbon which will react with the electrophilic carbon-carbon double bond of fumaronitirle undergoing a second Michael addition as shown in step 6. The second fumaronitrile molecule will generate a secondary carbanion on the carbon that did not participate in the new formation of the carbon-carbon bond. This carbanion will react with the partial positively charged carbon atom of the neighboring carbonyl group forming a six-member ring shown in step 7. The negatively charged oxygen atom will get protonated by potassium bicarbonate as shown in step 8. The six-

member ring will get deprotonated while losing a water molecule in the process shown in step 9. Again, the six-member ring will get deprotonated forming the benzene ring of the indole product forming an ortho positioned amine and ketone functional groups shown in step 10. The amino group will get deprotonated and will then immediately react with the partial positively charged carbon atom of the neighboring ketone to form a five-member ring and a negative charge on carbon in step 11 forming the second ring structure. The negatively charged oxygen will then get protonated in step 12. The secondary amine hydrogen is more acidic than the alkane hydrogen so it will get deprotonated as shown in step 13 losing the second water molecule. Finally, the alkane will get deprotonated and through resonance the indole ring will form as shown in step 14 in the reaction mechanism giving the final product shown.

d. Additional Mechanism Support

Multiple attempts to isolate the intermediates in the proposed mechanism proved unsuccessful. Two peaks in the GCMS corresponding to molecular weights of 178.0 g/mol were visible when the reaction was stopped prematurely. The reaction intermediates were visible as seen in figure 2-16 which is the GCMS spectra recorded.

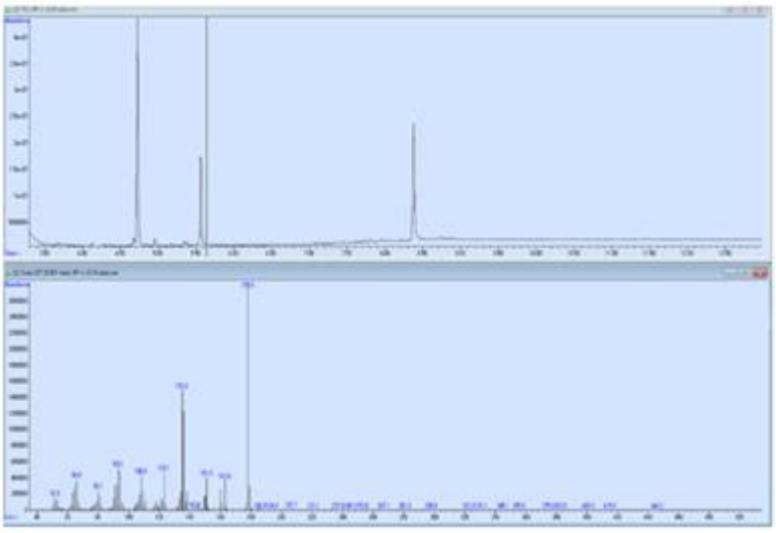


Figure 2-16

These two peaks correspond to 2-(2, 4-dioxopentan-3-yl) succinonitrile (top) and 2-acetyl-3-(2-oxopropyl) (bottom) succinonitrile molecule intermediates in the proposed mechanism. The third peak on the far right is known to be the indole product. These peaks provide additional support that our proposed mechanism is plausible.

4. Substrate Scope

As emphasized in the introduction, indoles are used for numerous applications, are found abundantly in nature, and can be synthesized in a variety of ways. Typically, indoles are synthesized from a closed ring starting material such as benzene or pyrrole and are built around the chosen starting material. Highly functionalized indole also required expensive materials such as a palladium catalyst [16, 17] or a multistep synthesis plan with some reagent that are not commercially available.[18] However, never has an indole been synthesized using a 1, 3-diketone and fumaronitrile in one pot with cheap commercially available starting materials. Now understanding the uniqueness of our discovery, we looked to expand our substrate scope to diversify the application of the discovered indole synthesis using 1, 3-diketones. We successfully expanded our substrate scope with an additional 11 diketones for 12 total indoles shown in figure 2-16. The yields shown in figure 2-16 are isolated yields.

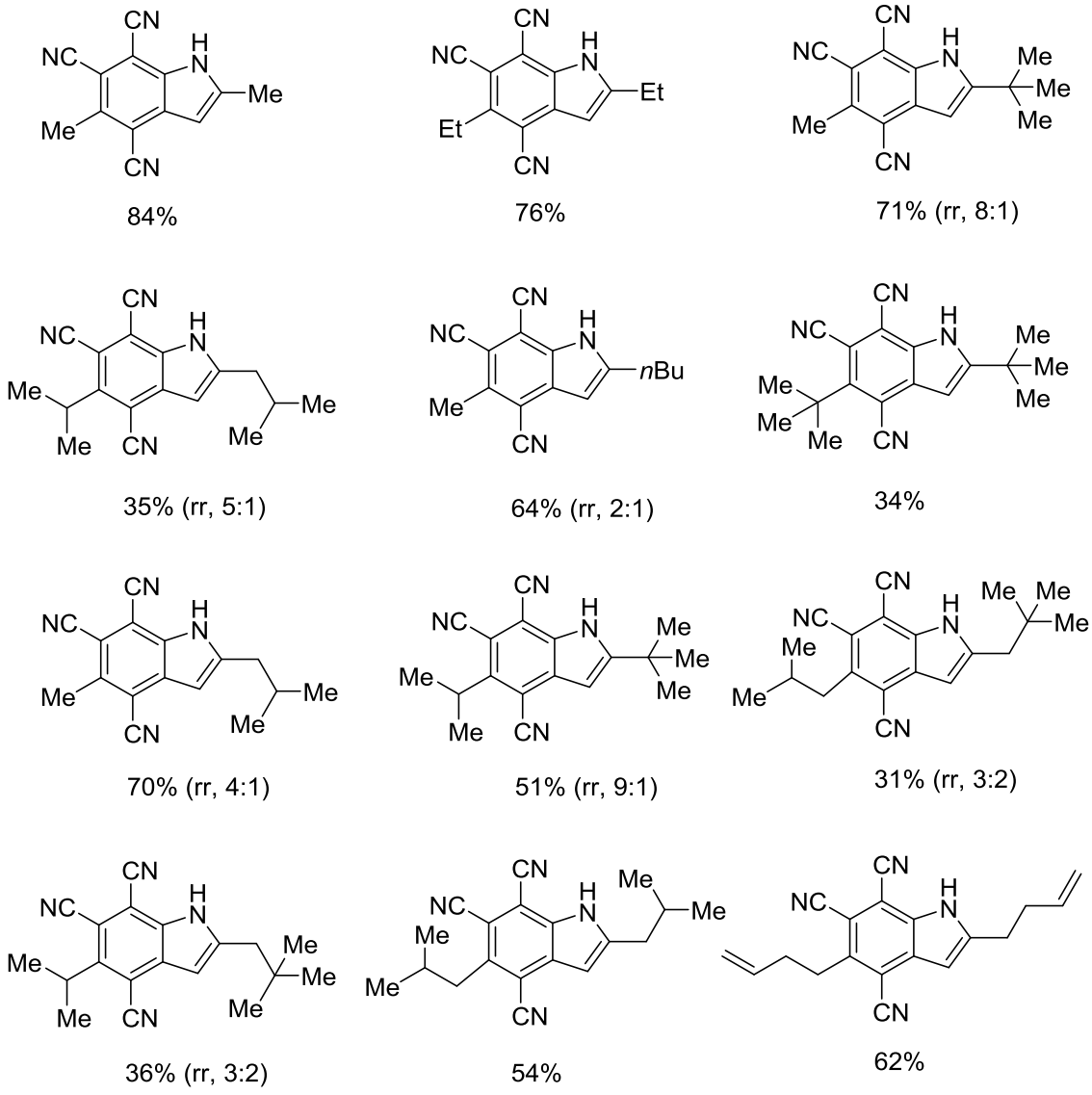


Figure 2-16

Through NOE experiments we determined that the longer and more sterically hindered alkyl chains of unsymmetrical 1, 3-diketones add at the 2 position of the indole. NOE NMR was collected for both the butyl and *t*-butyl side chain at the 2 position of our indole product (reactions with fumaronitrile between 2, 4-octanedione and 2, 2-dimethyl-3, 5-hexanedione respectively).

5. Regioselectivity of Indole Products and Proposed Rate Limiting Steps

As noted in the substrate scope, the longer and more sterically hindered alkyl chains add at the 2 position of the indole. This is due to the sterical interaction that occur during the suspected cyclobutane ring formation of our proposed mechanism. As shown in figure 2-17, we assume that R' is the more sterically hindered alkyl chain.

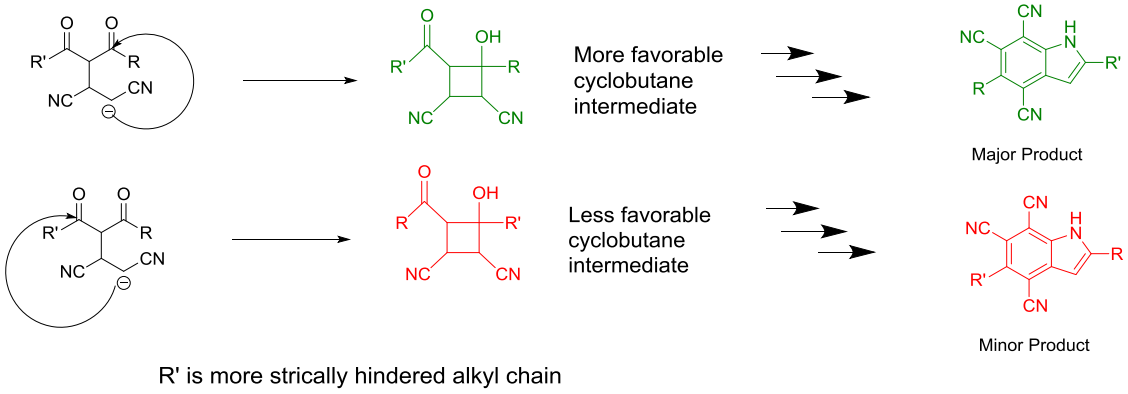


Figure 2-17

The negatively charged secondary carbanion formed from a Michael addition will react with the partial positive charge on the carbonyl carbon. This carbonyl carbon is bonded to two additional alkyl chains depicted as R and R'. If the carbonyl carbon is bonded with a less sterically hindered side chain R, it will make the reaction easier between the secondary carbanion and the carbonyl carbon. If the carbonyl carbon is bonded with a bulky sterically hindered or longer side chain R', it will make the reaction relatively difficult between the secondary carbanion and the carbonyl carbon. If both R and R' are equivalent and sterically bulky, this step of the reaction will have a high-energy barrier to overcome as both carbonyl carbons will be relatively difficult to react with. As stated previously, through NOE NMR we determined that the longer and more sterically hindered alkyl chains add to the 2 position of the indole. NOE NMR determined that the major

product formed had the more sterically hinder and longer side chain on the 2 position of the indole.

Additionally, when 1, 3-diketones are sterically hindered at the carbonyl carbon there is another step where sterics of the 1, 3-diketone will direct the reaction. In intermediate 7 of the proposed mechanism, a carbanion is formed between 2 nitrile functional groups. This carbanion can react with either carbonyl group if the sterics of the 1, 3-diketone are the same. As shown in figure 2-18 there are 2 possible carbonyl reacting sites the carbanion can react with. It the carbanion reacts with the carbonyl carbon adjacent to the enenitrile (highlighted in green) it will proceed to form our indole product. However, if it reacts with the other carbonyl carbon (highlighted in red) it will form an undesired side product. Assuming the sterics are the same, the carbanion reacting will have a similar barrier to overcome but only one will give the desired indole product while the other reaction will give and undesired side product.

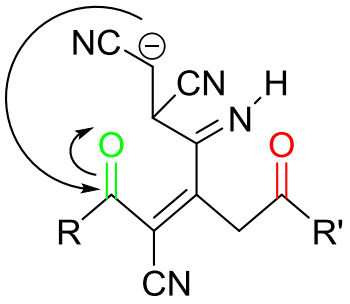


Figure 2-18

Finally, in intermediate 11 of the proposed mechanism, there is an additional barrier the reaction must overcome if R' is sterically hindered. If R' is not sterically hindered than this step of the reaction mechanism will not impose an extra energy barrier. However, if R' is sterically hindered it will provide an additional energy barrier that the reaction must overcome. As shown in figure 2-19, the lone pair of electrons on nitrogen will react with

the partial positive charge on the carbonyl carbon. This step of the reaction mechanism forms the second ring of the bicyclic indole. If R' is sterically bulky this step of the reaction will react slower thus creating a rate limiting step in the reaction for 1, 3-diketones that have steric hindrance at both the 1 and 3 positions.

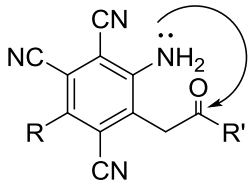


Figure 2-19

6. Future Research

Our newly discovered indole synthesis is the first of its kind. Since it is a newly discover synthesis route, there are numerous opportunities for improvement and expansion on our novel indole synthesis method. We can also attempt to apply the newly discover reaction to create other heterocyclic rings.

a. Expand Substrate Scope

The limits of our substrate scope pose a restricted application of our newly discovered indole reaction in synthesis. Heteroatoms such as oxygen and nitrogen bonded to the carbonyl carbon in the 1, 3 diketone molecules such as diethyl malonate and malonamide shown in figure 2-20 produced no desired product limiting the possibilities of diketone substrates and indole products.

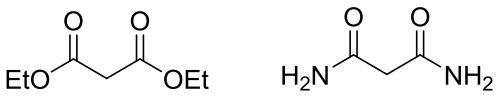


Figure 2-20

In addition to heteroatoms, strong EWG such as RCF_3, RC_2F_5 and $RPhCF_3$ (where R is a 1, 3-diketone) produced no indole. During our current research, attempts were made to accommodate heteroatoms and EWGs bonded to the carbonyl carbon atoms of the 1, 3 diketones, however no progress was made. Future research will include developing reaction conditions that are suitable for these types of heteroatoms and electronic factors. Expanding the substrate scope will increase the application of our new indole synthesis method.

b. Shorten Reaction Times and Increase Yields for Sterically Hindered Diketones

Sterically hindered diketones reacted to produce the desired indoles. However, the reactions required a substantial amount of time to be completed and producing less than desirable yields. The typical reaction conditions for sterically hindered 1, 3-diketones require a minimum of 1 week with some diketones taking up to 3 weeks to react. The sterically hindered 1, 3-diketones typically produce less than 40 % isolated yield which is not desirable for reactions that takes a considerable amount of time. Future research will seek to develop reaction conditions or a catalyst that shortens the reaction time while increasing the yield.

c. Regioselectively React Nitrile Functional Groups of Indole Product at Positions 4, 6, and 7

Selectively reacting each of the nitrile groups to increase substrate diversity will also be a focus of future research. As seen before, there are three nitrile functional groups positioned at the 4, 6, and 7 positions on the indole ring. Nitriles can be readily converted into imines, amides, and primary amines using known reactions which can be further reacted into a wide range of functional groups. Developing reaction conditions that

selectively react one of the three nitrile functional groups and provide regioselective control would increase the application of the indole product. Also, regioslective carbon-carbon bond cleavage of the three nitrile groups would increase the substrate diversity thus increasing the possible applications of our indole product.

d. Selective Regio-control of Alkyl groups at the 2 and 5 positions

In addition to developing reaction conditions that provide regioselective control for the nitrile groups, regioselective control for reactions or carbon-carbon bond cleavage with the alkyl groups at the 2 and 5 positions on the indole would further increase possible applications of the indole product. Typically, in unsymmetrical 1, 3-diktones for our reaction, the longer and/or more sterically hindered chain positions itself in the 2 position of the indole. Developing reaction conditions or a chiral catalyst that regioselectivly places the sterically hindered side of the 1, 3-diketone at the desired 2 or 5 position would allow for selective diversification and expand application of our indole product.

e. Investigate reaction with diacetamide

Another reaction we would aim to pursue in our future research is to determine if a 1, 3-diketone substitution with diacetamide can be used in our reaction to produce benzimidazole derivatives as shown in figure 2-21. The strategy would utilize similar reaction conditions to our indole synthesis method.

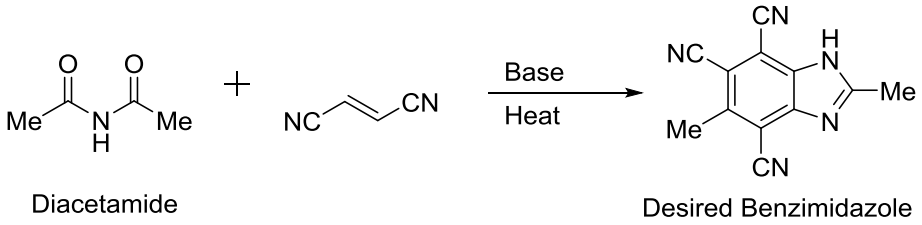


Figure 2-21

Although the electronics and reactivity of carbon and nitrogen differ, the acidic hydrogen in diacetamide creates a similar scenario to begin the reaction. If the remainder of the mechanism would remain the same, the deprotonation of the acidic hydrogen of diacetamide forming a negatively charged nitrogen that would react similar to a carbanion and undergo a Michael addition reaction with fumaronitrile. The difference in reactivity of nitrogen from carbon may produce challenges for this reaction and complications may occur in the multi-step proposed mechanism.

Chapter 3: Experimental

1. Materials

All the glassware including the 4-dram borosilicate scintillation (Wheaton), 1-dram borosilicate (Kimble-Chase) vials, and 15 mL pressure tubes were properly cleaned and dried in an oven before use. All glassware was cleaned with soap before being rinsed with acetone and dried in the oven at 150 ^{o}C.

All chemicals (solvents, starting materials, and reagents) used for both diketone and indole synthesis were obtained from commercial sources and used as received. Fumaronitrile (TCI), K_2CO_3 (Fisher Scientific), and dioxane (TCI and Sigma Aldrich) were used as reagents to synthesize indoles. The following diketones were ordered and used as received from their respective vendor to synthesize indoles: 2, 4-pentanedione (99%) (Alfa Aesar), 3, 5-heptanedione (95%) (OxChem), 2, 2-dimethyl-3, 5-hexanedione (97%) (Sigma Aldrich), 6-methyl-2, 4-heptanedione (98%) (Alfa Aesar), 2, 4-octandione (98%) (Alfa Aesar), 2, 2, 6, 6-tetramethyl-3, 5-heptanedione (98%) (Sigma Aldrich). The following diketones were synthesized for indole synthesis: undeca-1, 10-diene-5,7-dione, 2, 8-dimethylnonane-4, 6-dione, 2, 2, 8-trimethylnonane-4, 6-dione, 2, 2, 6-trimethylheptane-3, 5-dione, 2, 2, 8-trimethyloctane-4, 6-dione, and 2, 8-dimethyloctane-4, 6-dione.

The following reagents were purchased and used as received from their respective vendor in order to synthesize diketones: 3-Methyl-2-Butanone (Beantown Chemical), 2-Methyl-4-pentanone (TCI), Ethyl isovalerate (TCI), Ethyl 3,3-dimethylbutanoate (TCI), Ethyl trimethylacetate (Sigma Aldrich), 2, 4- Pentanedione 99% (Alfa Aesar), sodium

hydride (Alfa Aesar), Tetramethylethylenediamine (Sigma Aldrich), *sec*-butyllitium (Sigma Aldrich), and allyl bromide (Sigma Aldrich).

2. Substance Identification

High resolution mass and NMR spectra for new compounds were recorded at the Mass Spectrometry and NMR Facilities in the Department of Chemistry and Chemical Biology at the University of New Mexico.

NMR spectra were recorded on a Bruker instrument spectrometer (300MHz for ^{1}H, 75MHz for ^{13}C) at room temperature. Chemical shifts are recorded in parts per million. ^{1}H NMR shifts are referenced to chloroform-d (d = 7.26) or acetone-d_6 (d =2.05). ^{13}C shifts are referenced to acetone-d_6 (d =29.84 and 206.26) or DMSO-d_6 (39.52). NMR splitting patterns were represented by the following: s for singlet; d for doublet; t for triplet; q for quartet, and m for multiplet. Mass spectroscopy samples were ran using Atmospheric Pressure Photoionization (APPI) in Positive Mode and Electrospray Ionization (ESI) in Positive Mode. 2, 5-Di-*tert*-butyl-4, 6, 7-tricyano-1*H*-indole was the only sample analyzed by ESI method for mass spectroscopy. Infrared (IR) spectra were recorded on a Bruker Alpha-P ATR-IR and ν_{max} is reported in cm^{-1}.

3. Synthesis Procedures of Diketones

a. Synthesis of undeca-1, 10-diene-5, 7-dione

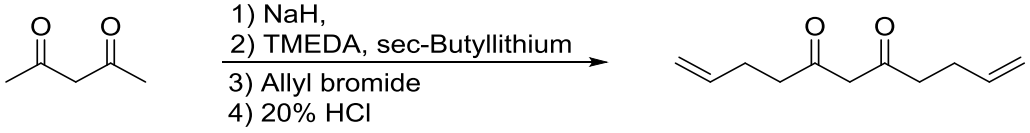


Figure 3-1

The synthesis procedure of undeca-1, 10-diene-5, 7-dione was utilized from the described procedure by Hubbard and Harris.[19] For the synthesis procedure of undeca-1,

10-diene-5, 7-dione, 1.1 g of 2,4-Pentanedione (10 mmol) and 240 mg (1 equiv) of NaH was added to 100 mL of cyclohexane. The mixture was stirred for 30 minutes at room temperature (20 ^{o}C). 2.324 g (2 equiv) of TMEDA was added to the mixture followed with a slow addition of 14.3 mL (2 equiv) of *sec*-butyllithium at 0 ^{o}C. The mixture was stirred for 24 hours at 20 ^{o}C. The reaction was then cooled to -78 ^{o}C for 30 minutes. Once cooled, 2.418 g (2 equiv) of allyl bromide was slowly added dropwise to the solution while stirring. This solution was mixed over night at room temperature. After mixing the reaction overnight, the reaction mixture was slowly neutralized dropwise with 20% HCl solution. The product 1, 10-Undecene-5, 7-dione was purified using column chromatography (silica gel) with EtOAc as the solvent system.

Analytical Data for undeca-1, 10-diene-5, 7-dione: The product was obtained as a yellow oil (631.0 mg, 31% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) 15.41 (s, 1H), 5.77 (m, 2H), 5.49 (s, 1H), 5.01 (t, J = 14.85 Hz, 4H), 2.38 (s, 8H).

b. Synthesis of 2, 8-dimethylnonane-4, 6-dione

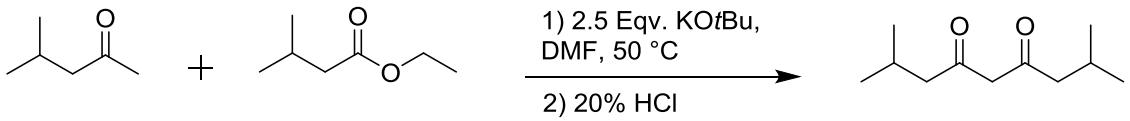


Figure 3-2

The synthesis procedure of 2, 8-dimethylnonane-4, 6-dione was utilized from the described procedure by Nandurkar et al.[20] For the synthesis of 2, 8-Dimethylnonane-4,6-dione, a mixture of 25 mL of DMF and 5.6 g of KO*t*Bu (2.5 equiv) was heated to 50 ^{o}C under nitrogen conditions. 3.485 g of Ethyl isovalerate (30 mmol) was added dropwise to the DMF and KO*t*Bu solution, followed by a solution of 2.036 g of 2-Methyl-4-pentanone

(20 mmol) in 2.5 mL DMF. After the completion of the reaction, the reaction mixture was allowed to cool and slowly neutralized with 20% HCl solution. 25 mL of water was added to separate two layers. The organic layer containing the crude 2, 8-Dimethylnonane-4, 6-dione was purified using column chromatography (silica gel) with EtOAc as the solvent system.

Analytical Data for 2, 8-dimethylnonane-4, 6-dione: The product was obtained as a yellow oil (2.524 g, 70% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) 15.65 (s, 1H), 5.45 (s, 1H), 2.14 (m, 6H), 0.95 (m. 12H).

c. Synthesis of 2, 2, 8-trimethylnonane-4, 6-dione

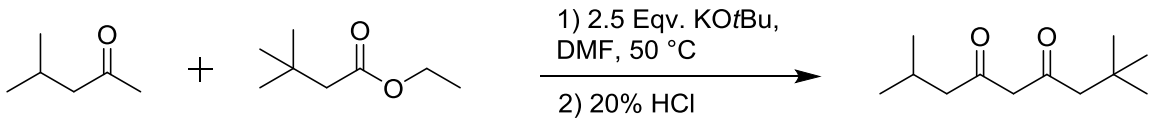


Figure 3-3

The synthesis procedure of 2, 2, 8-trimethylnonane-4, 6-dione was utilized from the described procedure by Nandurkar et al.[20] For the synthesis of 2, 2, 8-trimethylnonane-4, 6-dione, a mixture of 25 mL of DMF and 5.6 g of KO*t*Bu (50 mmol) was heated to 50 ^{o}C under nitrogen conditions. 4.320 g of Ethyl 3, 3-dimethylbutanoate (30 mmol) was added dropwise to the DMF KO*t*Bu solution, followed by a solution of 2.036 g of 2-Methyl-4-pentanone (20 mmol) in 2.5 mL DMF. After the completion of the reaction, the reaction mixture was allowed to cool and slowly neutralized with 20% HCl solution. 25 mL of water was further added to separate two layers. The organic layer containing the crude 2, 2, 8-trimethylnonane-4, 6-dione was purified using column chromatography (silica gel) with EtOAc as the solvent system.

Analytical Data for 2, 2, 8-trimethylnonane-4, 6-dione: The product was obtained as an orange oil (1.135 g, 30% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) 15.73 (s, 1H), 5.40 (s, 1H), 2.08 (m, 5H), 0.99 (s, 9H), 0.93 (d, J = 6.6 Hz, 6H).

d. Synthesis of 2, 2, 6-trimethylheptane-3, 5-dione

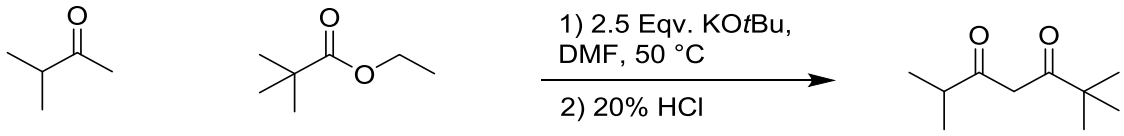


Figure 3-4

The synthesis procedure of 2, 2, 6-trimethylheptane-3, 5-dione was utilized from the described procedure by Nandurkar et al.[20] For the synthesis of 2, 2, 6-trimethylheptane-3, 5-dione, a mixture of 25 mL of DMF and 5.6 g of KO*t*Bu (50 mmol) was heated to 50 ^{o}C under nitrogen conditions. 4.320 g of Ethyl trimethylacetate (30 mmol) was added dropwise to the DMF KO*t*BU solution, followed by a solution of 1.722 g of 2-Methyl-3-butanone (20 mmol) in 2.5 mL DMF. After the completion of the reaction, the reaction mixture was allowed to cool and slowly neutralized with 20% HCl solution. 25 mL of water was further added to separate two layers. The organic layer containing the crude 2, 2, 6-trimethylheptane-3, 5-dione was purified using column chromatography (silica gel) with EtOAc as the solvent system.

Analytical Data for 2, 2, 6-trimethylheptane-3, 5-dione: The product was obtained as a red oil (2.109 g, 62% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) 15.90 (s, 1H), 5.96 (s, 1H), 2.48 (m, 1H), 1.14 (m, 15H).

e. Synthesis of 2, 2, 7-trimethyloctane-3, 5-dione

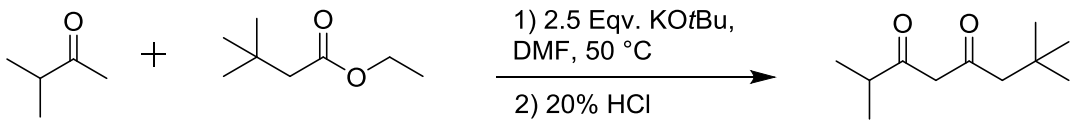


Figure 3-5

The synthesis of 2, 2, 7-trimethyloctane-3, 5-dione was utilized from the described procedure by Nandurkar et al.[20] For the synthesis of 2, 7, 7-Trimethyloctane-3, 5-dione, a mixture of 25 mL of DMF and 5.6 g of KO*t*Bu (50 mmol) was heated to 50 ^{o}C under nitrogen conditions. 4.320 g of Ethyl 3, 3-dimethylbutanoate (30 mmol) was added dropwise to the DMF KO*t*Bu solution, followed by a solution of 1.722 g of 2-Methyl-3-butanone (20 mmol) in 2.5 mL DMF. After the completion of the reaction, the reaction mixture was allowed to cool and slowly neutralized with 20% HCl solution. 25 mL of water was further added to separate two layers. The organic layer containing the crude 2, 2, 7-trimethyloctane-3, 5-dione was purified using column chromatography (silica gel) with EtOAc as the solvent system.

Analytical Data for 2, 7, 7-trimethyloctane-3, 5-dione: The product was obtained as an orange oil (577.2 mg, 15% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) 15.67 (s, 1H), 7.25 (s, 1H), 2.45 (m, 1H), 2.12 (s, 2H), 1.13 (d, J = 6.9 Hz, 6H), 0.99 (s, 9H).

f. Synthesis of 2, 7-Dimethyloctane-3, 5-dione

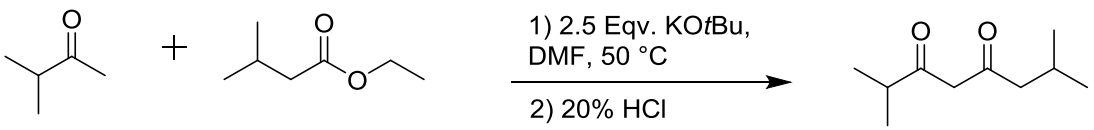


Figure 3-6

The synthesis of 2, 7-Dimethyloctane-3, 5-dione was utilized from the described procedure by Nandurkar et al.[20] For the synthesis of 22, 7-Dimethyloctane-3, 5-dione, a mixture of 25 mL of DMF and 5.6 g of KO*t*Bu (50 mmol) was heated to 50 ^{o}C under nitrogen conditions. 3.485 g of Ethyl isovalerate (30 mmol) was added dropwise to the DMF KO*t*BU solution, followed by a solution of 1.722 g of 2-Methyl-3-butanone (20 mmol) in 2.5 mL DMF. After the completion of the reaction, the reaction mixture was allowed to cool and slowly neutralized with 20% HCl solution. 25 mL of water was further added to separate two layers. The layer containing the crude 2, 7-Dimethyloctane-4, 5-dione was purified using column chromatography (silica gel) with EtOAc as the solvent system.

Analytical Data for 2, 7-Dimethyloctane-3, 5-dione: The product was obtained as a yellow oil (594.2 g, 16% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) 15.61 (s, 1H), 5.47 (s, 1H), 2.44 (m, 1H), 2.12 (m, 3H), 1.13 (d, *J* = 6.0 Hz, 6H), 0.94 (d, *J* = 6.0 Hz, 6H).

4. Synthesis Procedures of Indoles

a. Synthesis of 2, 5-Dimethyl-1*H*-indole-4, 6, 7-tricarbonitrile

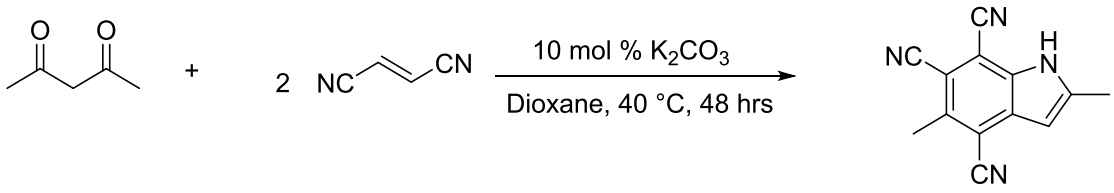


Figure 3-7

For a 1 mmol scale reaction, mix 100.1 mg of 2, 4-pentanedione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol %) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and

heat at 40 ºC for 48 hours while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 20% EtOAc in hexane.

Analytical Data for 2, 5-Dimethyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (138.6 mg, 63% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, Acetone) 11.76 (s, 1H) 6.60 (s, 1H), 2.77 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, DMSO) 14.08, 19.52, 100.31, 100.69, 105.92, 116.24, 134.48, 134.65, 136.95, 149.13 ; IR (Neat): 3298, 2925, 2466, 2227, 1548, 1309, 1263, 797; HRMS (APPI) Calculated for $C_{13}H_8N_4$ $(M+H)^+$ Weight expected 221.0827, found 221.0833.

b. Synthesis of 2, 5-Diethyl-1*H*-indole-4, 6, 7-tricarbonitrile

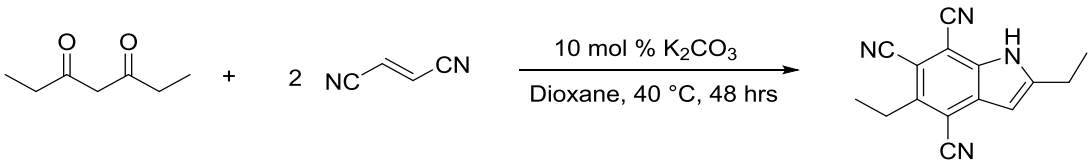


Figure 3-8

For a 1 mmol scale reaction, mix 128.2 mg of 3, 5-heptanedione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol %) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ºC for 48 hours while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 20% EtOAc in hexane.

Analytical Data for 2, 5-Diethyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (153.8 mg, 62% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, Acetone) 11.73 (s, 1H), 6.54 (s, 1H), 3.02 (q, J = 8.0 Hz, 2H), 2.90 (q, J = 8.0 Hz, 2H), 1.29 (t, J = 7.5 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, Acetone) 13.01, 15.49, 22.13, 27.85, 100.06, 101.77, 106.33,

107.22, 114.10, 115.70, 116.00, 135.39, 135.67, 143.75, 154.65; IR (neat): 3297, 2917, 2228, 1544, 1304, 827, 711, 691; HRMS (APPI) Calculated for $C_{15}H_{12}N_4$ $(M+H)^+$ Weight expected 249.1140, found 249.1140.

c. Synthesis of 2, 5-Diisobutyl-1*H*-indole-4, 6, 7-tricarbonitrile

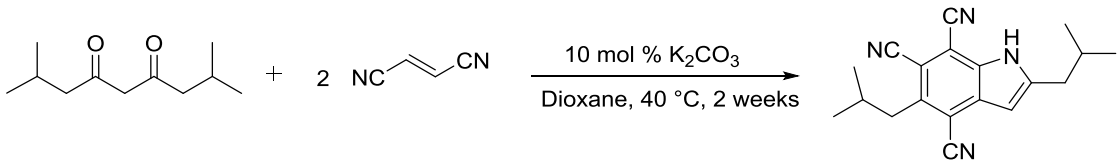


Figure 3-9

For a 1 mmol scale reaction, mix 184.3 mg of 2, 8-dimethylnonane-4, 6-dione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol %) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^oC for 2 weeks while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 30% EtOAc in hexane.

Analytical Data for 2, 5-Diisobutyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (121.6 mg, 40% isolated yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, Acetone) 11.84 (s, 1H), 6.67 (s, 1H), 2.975 (d, J = 9.0 Hz, 2H), 2.85 (d, J = 6.0 Hz, 2H), 2.24-2.06 (m, 2H), 0.99 (q, J = 4.0 Hz, 12H); ^{13}C NMR (75 MHz, Acetone) 22.33, 22.56, 31.49, 37.83, 42.81, 101.63, 101.88, 107.24, 108.02, 114.21, 116.14, 116.39, 135.27, 135.64, 141.20, 152.14; IR (neat): 3275, 2960, 2225, 1545, 1472, 1304, 991, 830, 694; HRMS (APPI) Calculated for $C_{19}H_{20}N_4$ $(M+H)^+$ Weight expected 305.1766, found 305.1773.

d. Synthesis of 2, 5-Di-*tert*-butyl-1*H*-indole-4, 6, 7-tricarbonitrile

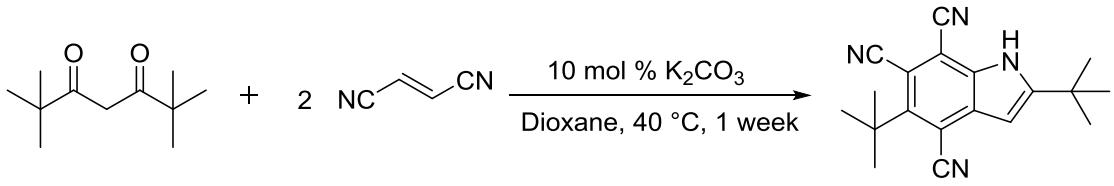


Figure 3-10

For a 1 mmol scale reaction, mix 184.3 mg of 2, 2, 6, 6-tetramethyl-3, 5-heptanedione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol %) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^oC for 1 week while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 25% EtOAc in hexane.

Analytical Data for 2, 5-Di-*tert*-butyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as an orange solid (73.0 mg, 24% isolated yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, Acetone) 11.75 (s, 1H), 6.62 (s, 1H), 1.78 (s, 9 H), 1.50 (s 9H); ^{13}C NMR (75 MHz, Acetone) 31.85, 33.63, 38.57, 99.54, 105.18, 105.93, 107.43, 114.54, 117.90, 118.66, 135.14, 137.13, 148.18, 161.14; IR (neat): 3284, 3236, 2968, 2229, 1532, 1466, 1370, 1269, 1029, 828, 717; HRMS (ESI) Calculated for $C_{19}H_{20}N_4$ $(M+H)^+$ Weight expected 305.1766, found 305.1768.

e. Synthesis of 2, 5-Di(but-3-en-1-yl)-1*H*-indole-4, 6, 7-tricarbonitrile

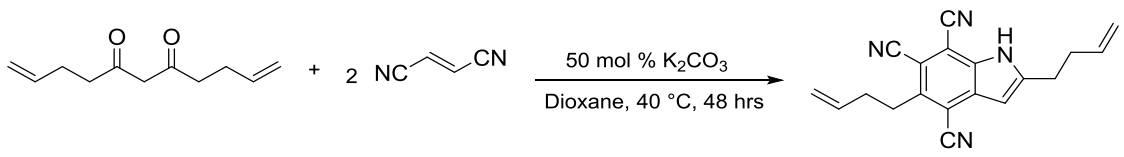


Figure 3-11

For a 1 mmol scale reaction, mix 198.2 mg of undeca-1, 10-diene-5, 7-dione (1.1 equivalents were used due to impurities in the isolation process), 156.1 mg fumaronitrile (2 equivalents), and 69.0 mg K_2CO_3 (50 mol %) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^oC for 48 hours while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 25% EtOAc in hexane.

Analytical Data for 2, 5-Di(but-3-en-1-yl)-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (93.0 mg, 31% isolated yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, Acetone) 11.82, (s, 1H), 6.67 (s, 1H), 5.84-6.00 (m, 2H), 5.05-5.14 (m, 2H), 4.98-5.02 (m, 2H), 3.205 (t, *J* = 7.2 Hz, 2H), 3.093 (t, *J* = 7.5 Hz, 2H), 2.60 (q, *J* = 10.8 Hz, 2H), 2.50 (q, *J* = 11.1 Hz, 2H); ^{13}C NMR (75 MHz, Acetone) 27.27, 32.28, 32.86, 34.52, 100.91, 100.10, 106.13, 106.92, 113.20, 114.92, 115.19, 115.90, 134.29, 134.72, 136.06, 136.82, 140.41, 151.42; IR (neat): 3239, 2919, 2409, 2227, 1643, 1543, 1307, 995, 921, 819, 705; HRMS (APPI) Calculated for $C_{19}H_{16}N_4$ $(M+H)^+$ Weight expected 301.1453, found 301.1452.

f. Synthesis of 2-(*tert*-butyl)-5-methyl-1*H*-indole-4, 6, 7-tricarbonitrile and 5-(*tert*-butyl)-2-methyl-1*H*-indole-4, 6, 7-tricarbonitrile

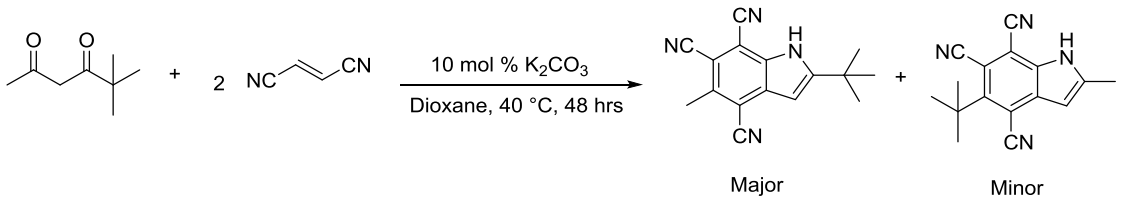


Figure 3-12

For a 1 mmol scale reaction, mix 142.2 mg of 2, 2-dimethyl-3,5-hexanedione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^oC for 48 hours while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 20% EtOAc in hexane.

Analytical Data for 2-(*tert*-butyl)-5-methyl-1*H*-indole-4, 6, 7-tricarbonitrile and 5-(*tert*-butyl)-2-methyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (138.9 mg, 53% isolated yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, Acetone) 11.67 (s, 1H), 6.54 (s, 1H), 2.68 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, Acetone) 19.45, 31.89, 33.67, 98.47, 101.65, 107.49, 108.57, 114.23, 115.88, 116.16, 134.88, 135.74, 137.65, 161.44; IR (neat): 3256, 2966, 2927, 2414, 2228, 1531, 1308, 1273, 821, 720; HRMS (APPI) Calculated for $C_{16}H_{14}N_4$ $(M+H)^+$ Weight expected 263.1297, found 263.1294.

g. Synthesis of 5-Butyl-2-methyl-1*H*-indole-4, 6, 7-tricarbonitrile and 2-Butyl-5-methyl-1*H*-indole-4, 6, 7-tricarbonitrile

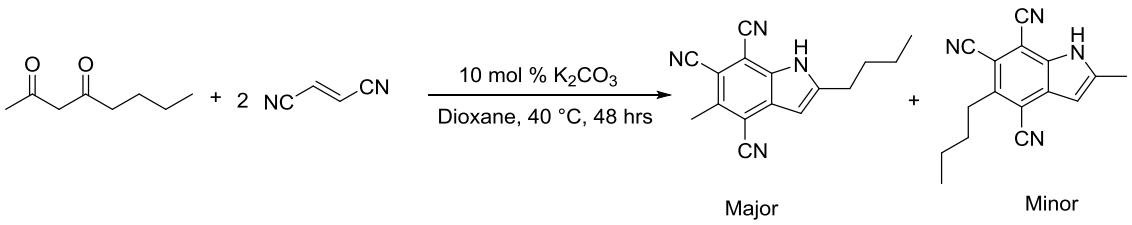


Figure 3-13

For a 1 mmol scale reaction, mix 156.2 mg 2, 4-octanedione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL and heat at 40 ^oC

for 48 hours while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 20% EtOAc in hexane.

Analytical Data for 5-Butyl-2-methyl-1*H*-indole-4, 6, 7-tricarbonitrile and 2-Butyl-5-methyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as an orange solid (138.6 mg, 60% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, Acetone) 11.82 (s, 0.5x1H) 6.67 (s, 0.55x1H), 6.65 (s, 0.45x1H), 3.15 (t, *J* = 7.5 Hz, 0.44x2H), 3.02 (t, *J* = 7.5 Hz, 0.55x2H), 2.81 (s, 0.56x3H), 2.67 (s, 0.44x3H), 1.70-1.85 (m, 0.5x2H), 1.39-1.56 (m, 0.5x2H), 0.95-1.03 (m, 0.5x3H); ^{13}C NMR (75 MHz, Acetone) 13.93, 19.47, 22.95, 31.44, 100.61, 101.39, 107.03, 107.88, 114.10, 115.88, 116.13, 135.13, 135.46, 137.61, 153.29; IR (neat): 3249, 2931, 2871, 2418, 2230, 1541, 1307, 821; HRMS (APPI) Calculated for $C_{16}H_{14}N_4$ $(M+H)^+$ Weight expected 263.1297, found 263.1302.

h. Synthesis of 2-Isobutyl-5-methyl-1*H*-indole-4, 6, 7-tricarbonitrile and 5-Isobutyl-2-methyl-1*H*-indole-4, 6, 7-tricarbonitrile

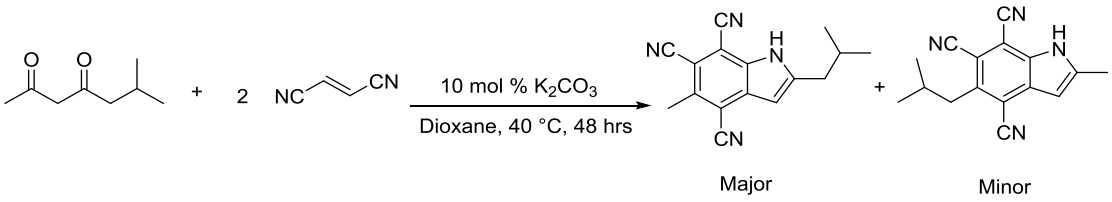


Figure 3-14

For a 1 mmol scale reaction, mix 142.2 mg of 2-methyl-3, 5-heptanedione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^{o}C for 48 hrs while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 20% EtOAc in hexane.

Analytical Data for 2-Isobutyl-5-methyl-1*H*-indole-4, 6, 7-tricarbonitrile and 5-Isobutyl-2-methyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (133.6 mg, 51% isolated yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, Acetone) 11.83 (s, 0.5x1H), 6.68 (s, 0.88x1H), 6.67 (s, 0.12x1H), 3.04 (d, *J* = 6 Hz, 0.14x2H), 2.89 (d, *J* = 6 Hz, 0.86x2H), 2.82 (s, 0.87x3H), 2.68 (s, 0.13x3H), 2.28-2.14 (m, 0.5x1H), 1.03 (d, *J* = 6.0 Hz, 0.14x6H), 1.01 (d, *J* = 6.0 Hz, 0.86x6H); ^{13}C (75 MHz, Acetone) NMR 19.44, 22.59, 37.89, 101.55, 107.13, 107.99, 114.19, 115.96, 116.19, 135.18, 135.52, 137.72, 152.18; IR (neat): 3259, 2955, 2425, 2228, 1542, 1306, 830, 692; HRMS (APPI) Calculated for $C_{16}H_{14}N_4$ $(M+H)^+$ Weight expected 263.1297, found 263.1299.

i. Synthesis of 5-Isobutyl-2-isopropyl-1*H*-indole-4, 6, 7-tricarbonitrile and 2-Isobutyl-5-isopropyl-1*H*-indole-4, 6, 7-tricarbonitrile

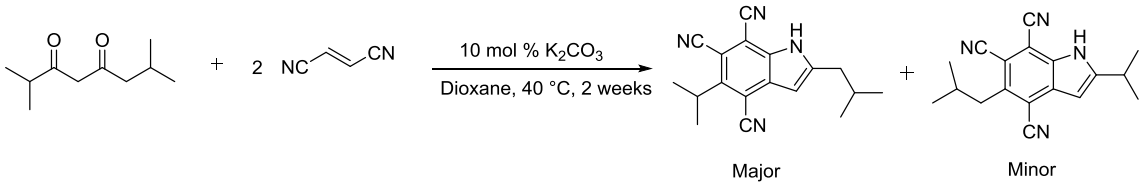


Figure 3-15

For a 1 mmol scale reaction, mix 170.3 mg of 2, 7-dimethyloctane-3, 5-dione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^{o}C for 2 weeks while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 25% EtOAc in hexane.

Analytical Data for 5-Isobutyl-2-isopropyl-1*H*-indole-4, 6, 7-tricarbonitrile and 2-Isobutyl-5-isopropyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (69.6 mg, 24% isolated yield) after purification by silica gel column

chromatography. ^{1}H NMR (300 MHz, Acetone) 11.81 (s, 0.5x1H), 6.64 (s, 0.5x2H), 3.73 (m, 0.55x1H) 3.32 (m, 0.45x1H), 2.97 (d, *J* = 7.5 Hz, 0.48x2H) 2.85 (d, *J* = 7.5 Hz, 0.52x2H), 2.15 (m, 0.5x2H), 1.57 (d, *J* = 7.2 Hz, 0.52x6H), 1.29 (d, *J* = 6.9 Hz, 0.48x6H), 0.98 (t, *J* = 6.2 Hz, 0.5x12H) ^{13}C NMR (75 MHz, Acetone) 21.54, 22.18, 22.33, 22.55, 31.52, 34.44, 37.83, 42.84, 101.82, 102.85, 105.45, 106.57, 114.28, 116.34, 116.63, 135.58. 136.27, 147.22, 152.23; IR (neat): 3248, 2959, 2871, 2228, 1756, 1538, 1464, 1305, 1079, 798, 719; HRMS (APPI) Calculated for $C_{18}H_{18}N_4$ $(M+H)^+$ Weight expected 291.1610, found 291.1610.

j. Synthesis of 5-Isobutyl-2-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile and 2-Isobutyl-5-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile

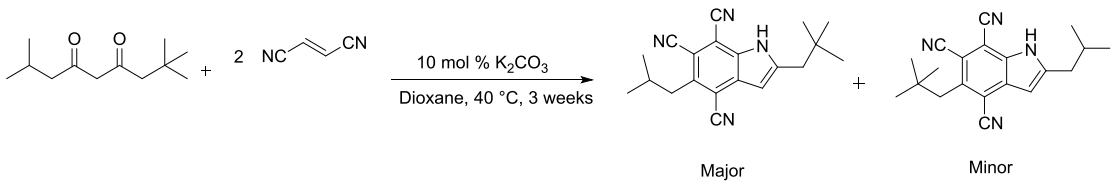


Figure 3-16

For a 1 mmol scale reaction, mix 198.3 mg of of 2, 2, 8-trimethylnonane-4, 6-dione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^{o}C for 3 weeks while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 30% EtOAc in hexane.

Analytical Data for 5-Isobutyl-2-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile and 2-Isobutyl-5-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (66.8 mg, 21% isolated yield) after purification by silica gel column

chromatography. ^{1}H NMR (300 MHz, Acetone) 11.85 (s, 0.5x1H), 6.68 (s 0.18x1H), 6.66 (s, 0.82x1H), 3.12 (s, 0.24x1H), 3.015 (d, *J* = 9.0 Hz, 0.29x2H), 2.885 (d, *J* = 9.0 Hz, 0.71x2H), 2.84 (s, 0.76x2H), 2.18-2.07 (m, 0.5x1H), 1.07-0.98 (m, 0.5x15H); ^{13}C (75 MHz, Acetone) NMR 22.37, 29.70, 31.55, 32.80, 42.65, 42.87, 102.05, 107.33, 108.20, 114.32, 116.23, 116.47, 135.17, 135.39, 141.30, 150.53; IR (neat): 3246, 2958, 2872, 2227, 1539, 1466, 1307, 1228, 990, 804, 751, 681; HRMS (APPI) Calculated for $C_{20}H_{22}N_4$ $(M+H)^+$ Weight expected 319.1923, found 319.1930.

k. Synthesis of 2-Isopropyl-5-(*tert*-butyl)-1*H*-indole-4, 6, 7-tricarbonitrile and 5-(*tert*-butyl)-2-Isopropyl-1*H*-indole-4, 6, 7-tricarbonitrile

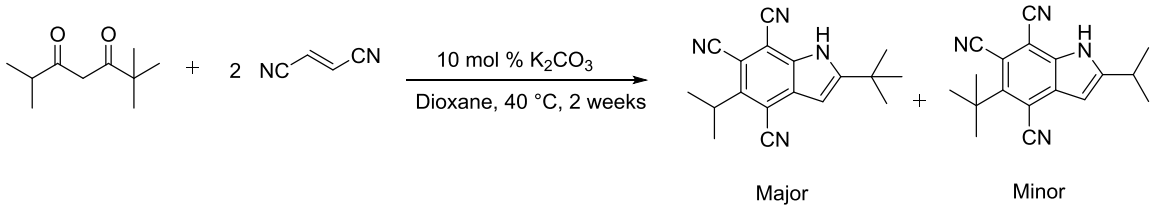


Figure 3-17

For a 1 mmol scale reaction, mix 170.1 mg 2, 2, 6-trimethylheptane-3, 5-dione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^{o}C for 2 weeks while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 25% EtOAc in hexane.

Analytical Data for 2-Isopropyl-5-(*tert*-butyl)-1*H*-indole-4, 6, 7-tricarbonitrile and 5-(*tert*-butyl)-2-Isopropyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (98.6 mg, 34% yield) after purification by silica gel column

chromatography. ^{1}H NMR (300 MHz, Acetone) 11.77, (s, 0.5x1H), 6.64 (s, 0.63x1H), 6.61 (s, 0.37x1H), 3.79-3.65 (m, 0.64x1H), 3.38-3.25 (m, 0.36x1H), 1.77 (s, 0.37x9H), 1.56 (d, *J* = 7.2 Hz, 0.63x6H), 1.50 (s, 0.63x9H), 1.43 (d, *J* = 6.9 Hz, 0.37x6H); ^{13}C (75 MHz, Acetone) NMR 21.52, 33.65, 34.42, 98.75, 102.93, 105.85, 107.21, 114.33, 116.28, 116.61, 135.81, 135.98, 147.21, 161.44; IR (neat): 3282, 3234, 2970, 2229, 1536, 1371, 1297, 1271, 1072, 824, 717; HRMS (APPI) Calculated for $C_{18}H_{18}N_4$ $(M+H)^+$ Weight expected 291.1610, found 291.1609.

l. Synthesis of 2-Isopropyl-5-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile and 5-Isopropyl-2-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile

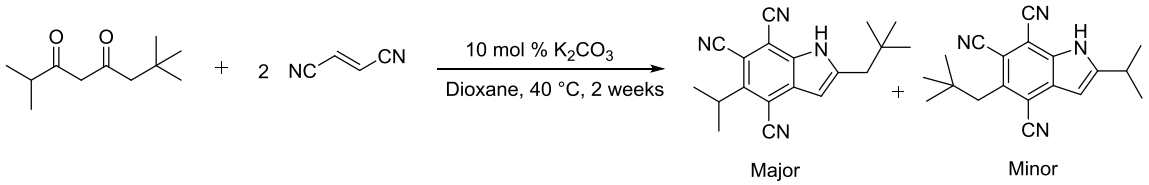


Figure 3-18

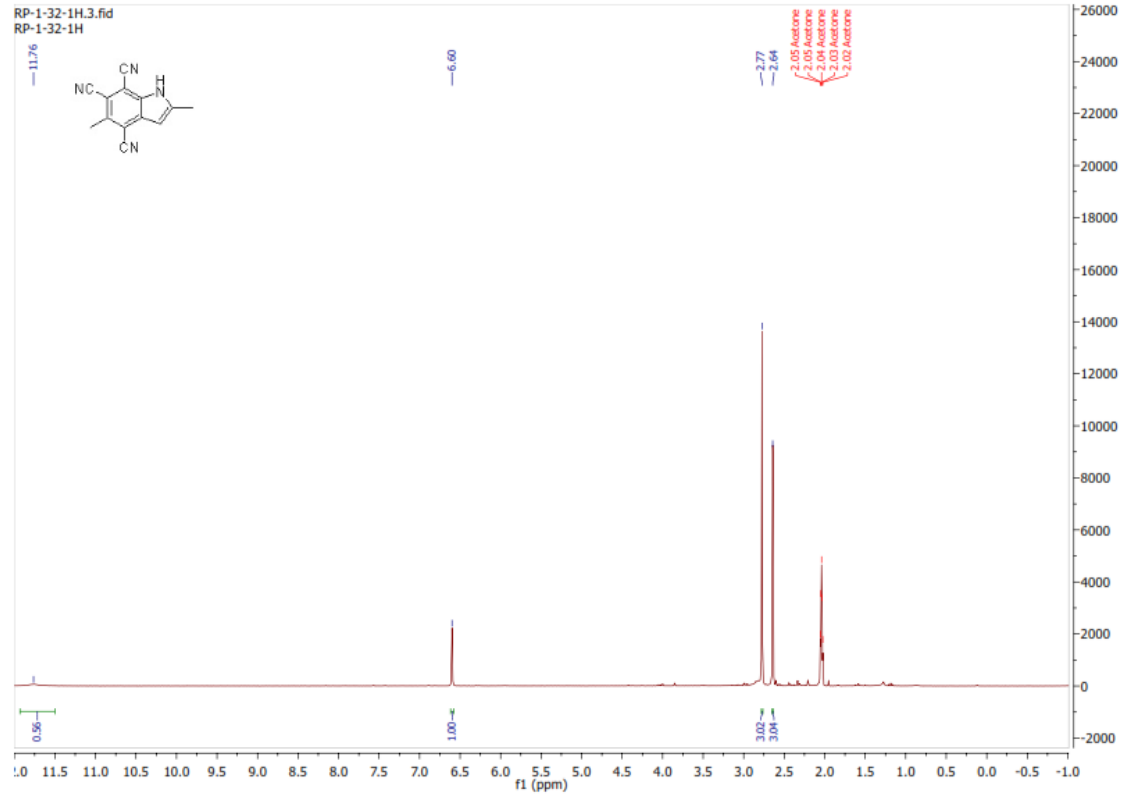
For a 1 mmol scale reaction, mix 184.3 mg of 2, 2, 8-trimethyloctane-3, 5-dione, 156.1 mg fumaronitrile (2 equivalents), and 13.8 mg K_2CO_3 (10 mol%) into 5 mL of dioxane in a 15 mL sealed tube under normal atmospheric conditions. Seal the 15 mL sealed tube and heat at 40 ^{o}C for 2 weeks while rapidly stirring the mixture. The molecule was isolated by silica gel column chromatography with a solvent system of 25% EtOAc in hexane.

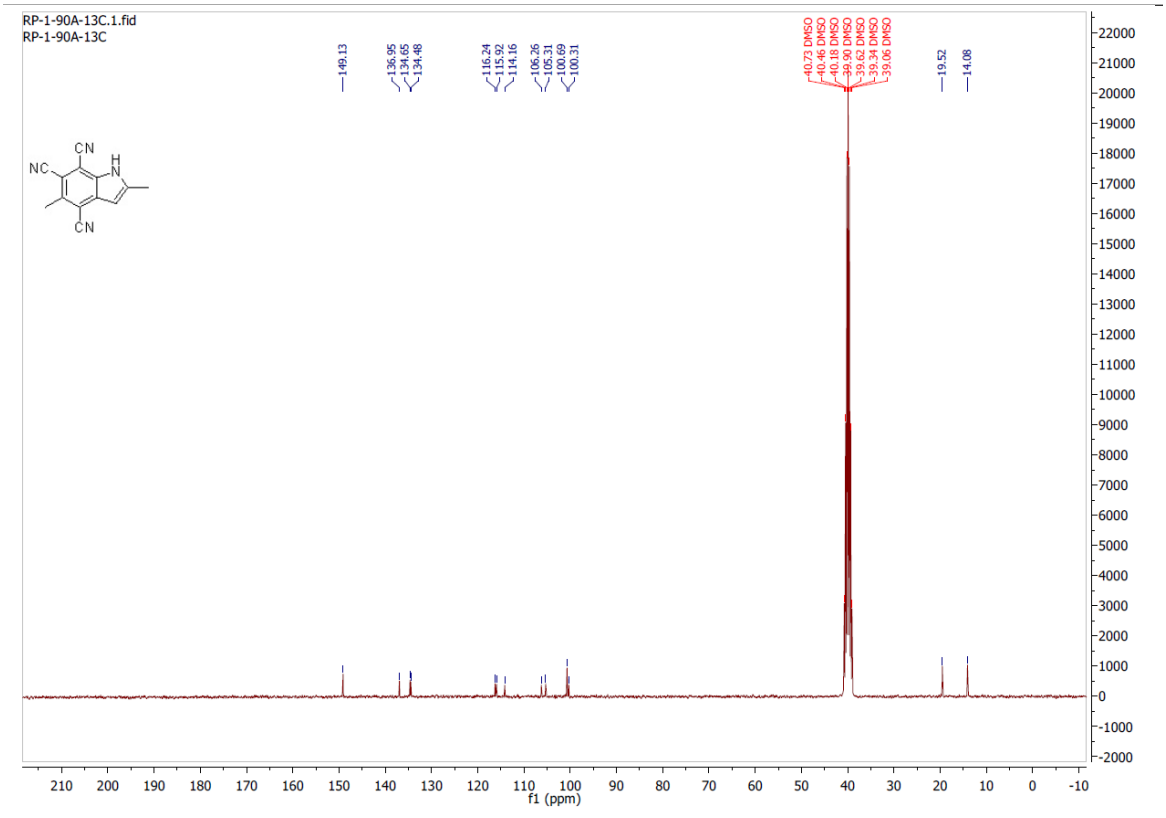
Analytical Data for 2-Isopropyl-5-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile and 5-Isopropyl-2-neopentyl-1*H*-indole-4, 6, 7-tricarbonitrile: The product was obtained as a yellow solid (69.6 mg, 23% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, Acetone) 11.84 (s, 0.5x1H), 6.67 (s, 0.61x2H), 6.65 (s, 0.39x2H),

3.79-3.70 (m, 0.6x1H), 2.90 (s, 0.61x4H) 2.88 (s, 0.39x4H), 2.26-2.11 (m, 0.4x1H) 1.58 (d, *J* = 6 Hz, 0.61x6H), 1.04 (s, 0.5x9H), 0.985 (d, *J* = 9.0 Hz, 0.39x6H), 0.97 (s, 0.5x3H); ^{13}C NMR (75 MHz, Acetone) 21.58, 32.81, 34.51, 42.67, 103.01; IR (neat): 3241, 2957, 2236, 1538, 1463, 1368, 1304, 1075, 993, 797, 766, 693; HRMS (APP) Calculated for $C_{19}H_{20}N_4$ $(M+H)^+$ Weight expected 305.1766, found 305.1774.

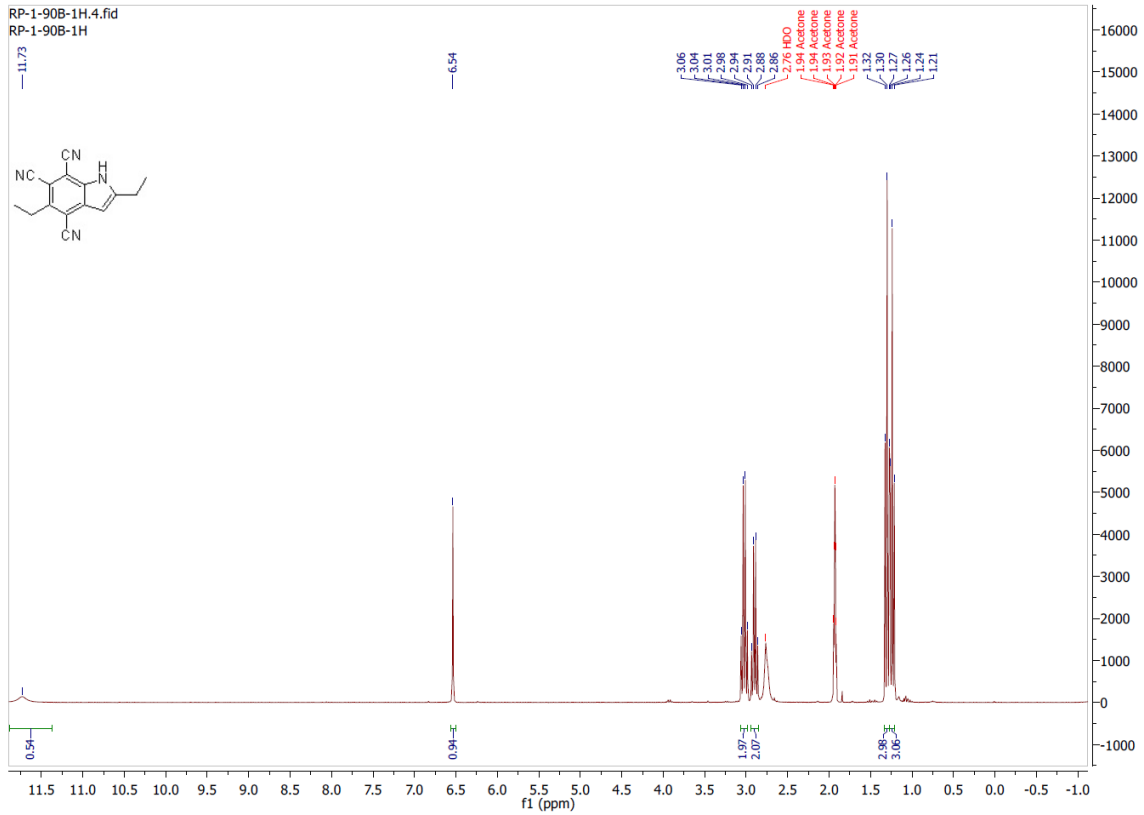
Appendices

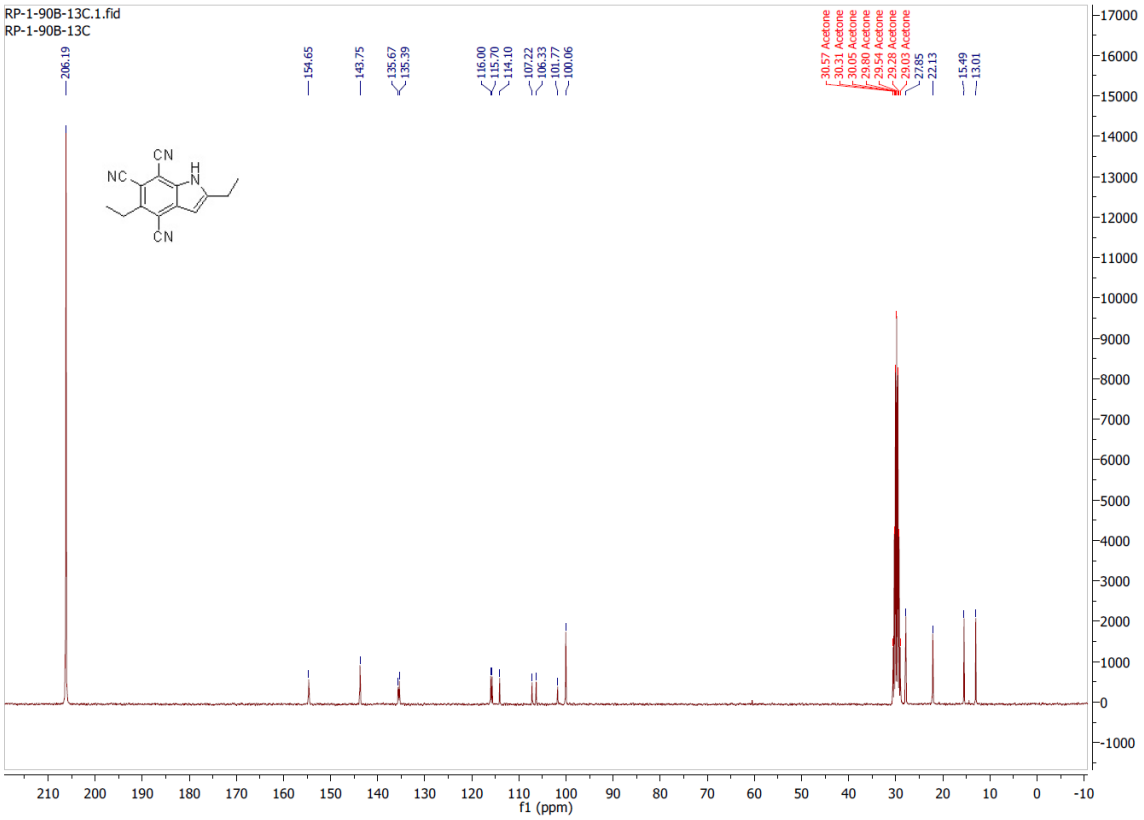
1. ^{1}H and ^{13}C NMR Data: 2, 5-dimethyl-1H-indole-4, 6, 7-tricarbonitrile



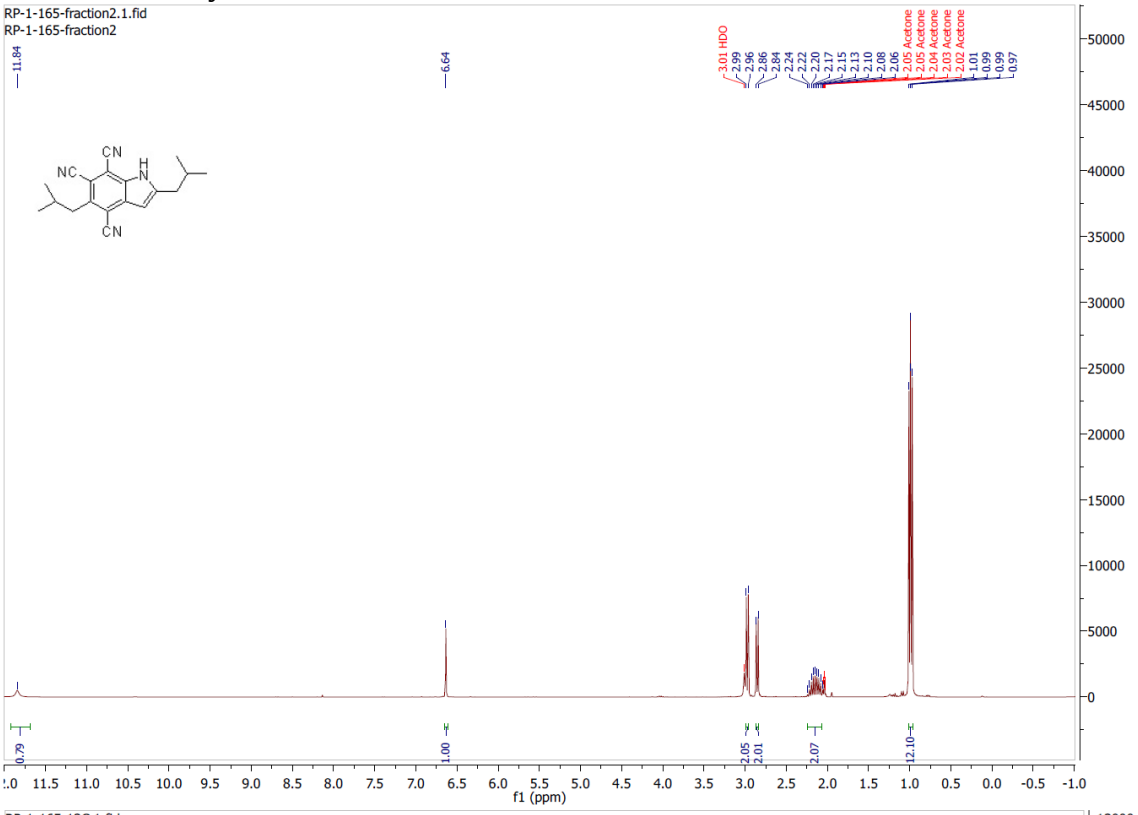


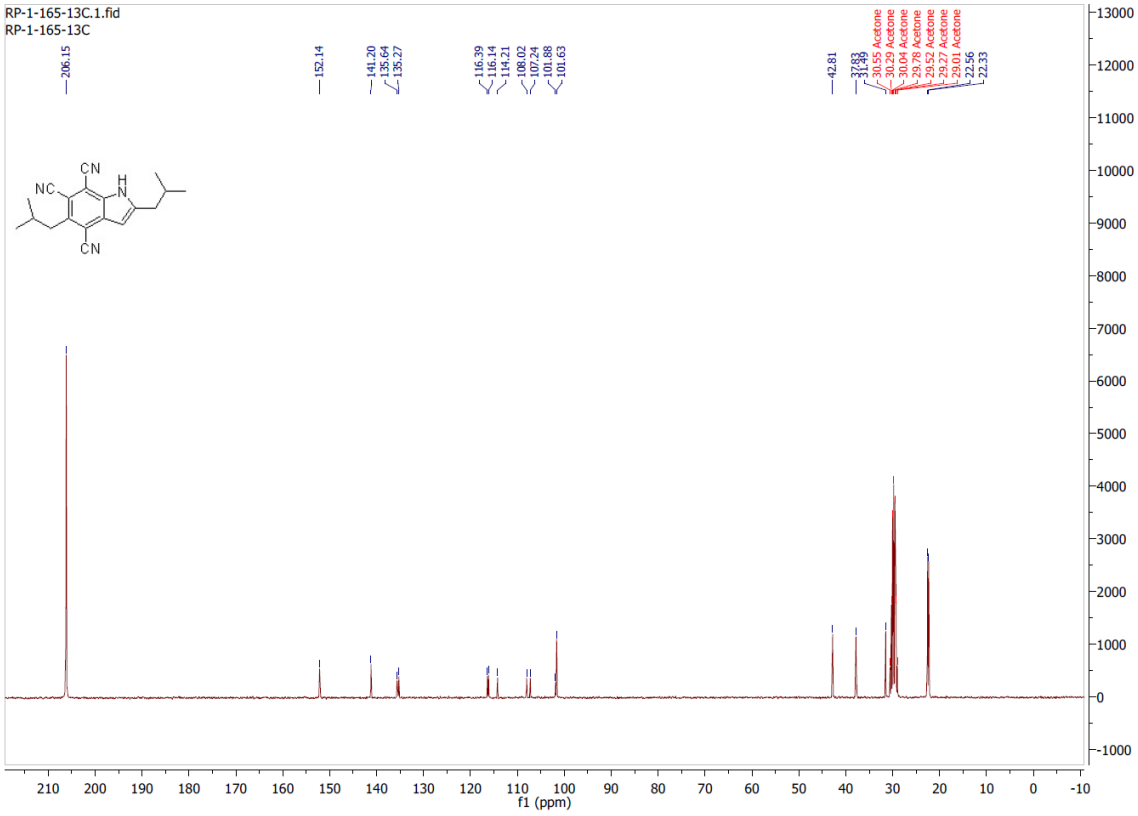
2. 2, 5-diethyl-1*H*-indole-4, 6, 7-tricarbonitrile NMR Data



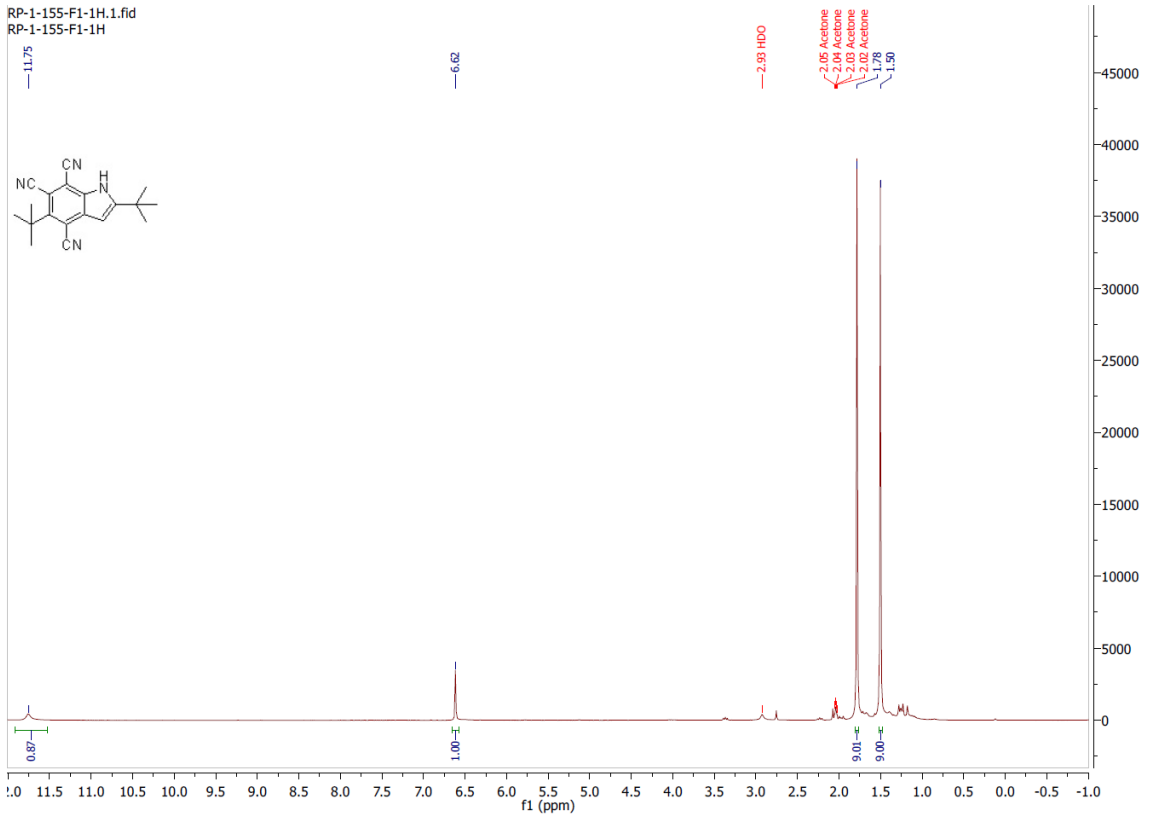


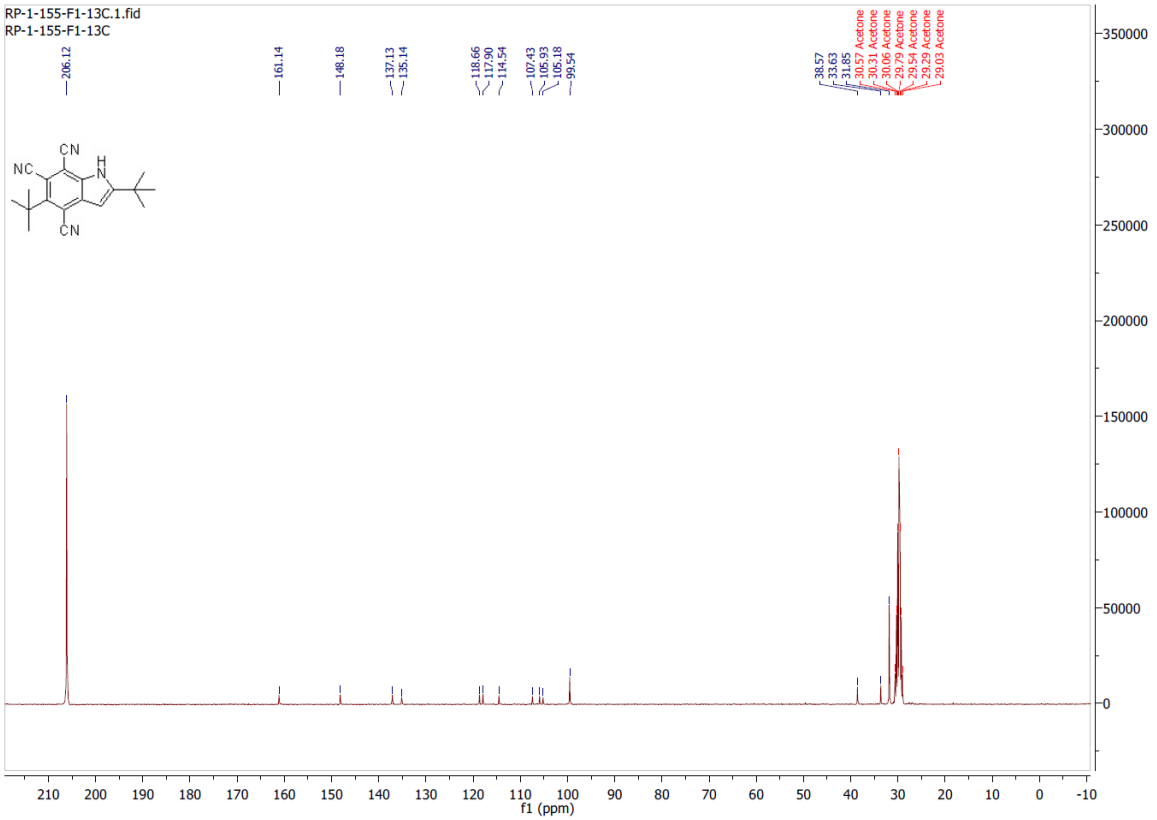
3. 2, 5-diisobutyl-1*H*-indole-4, 6, 7-tricarbonitrile NMR Data



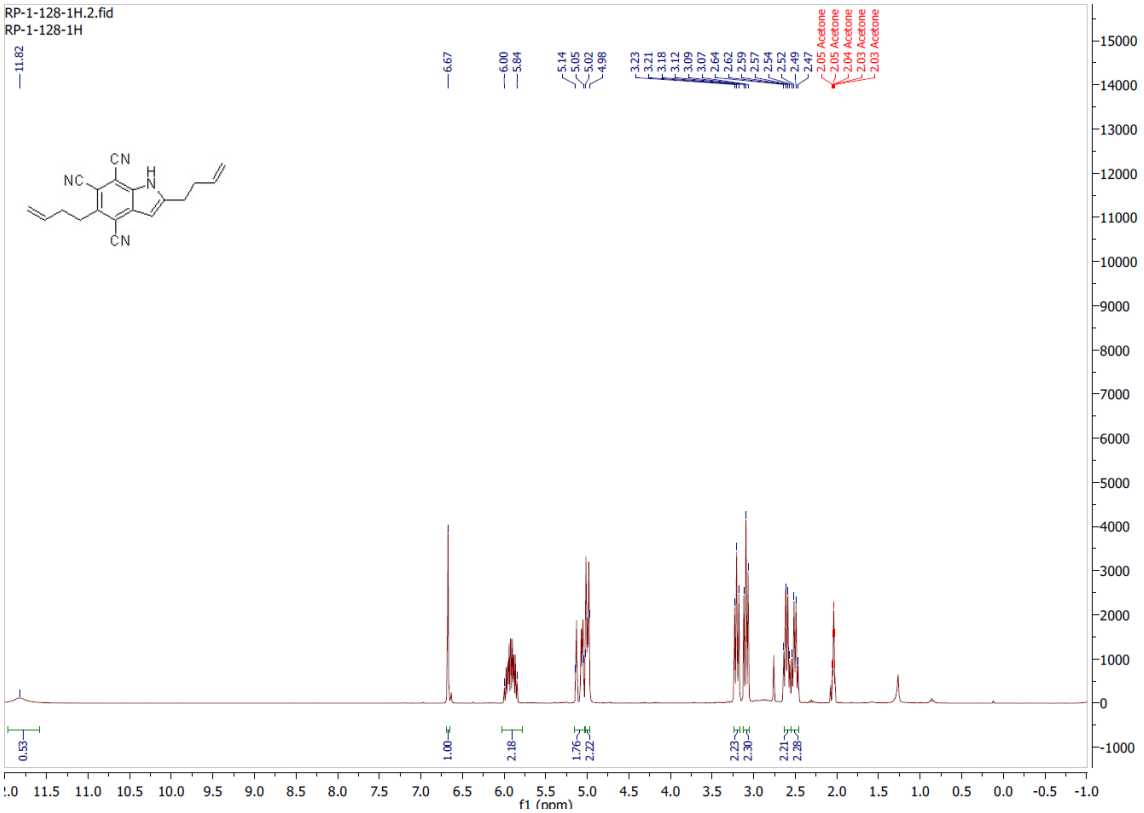


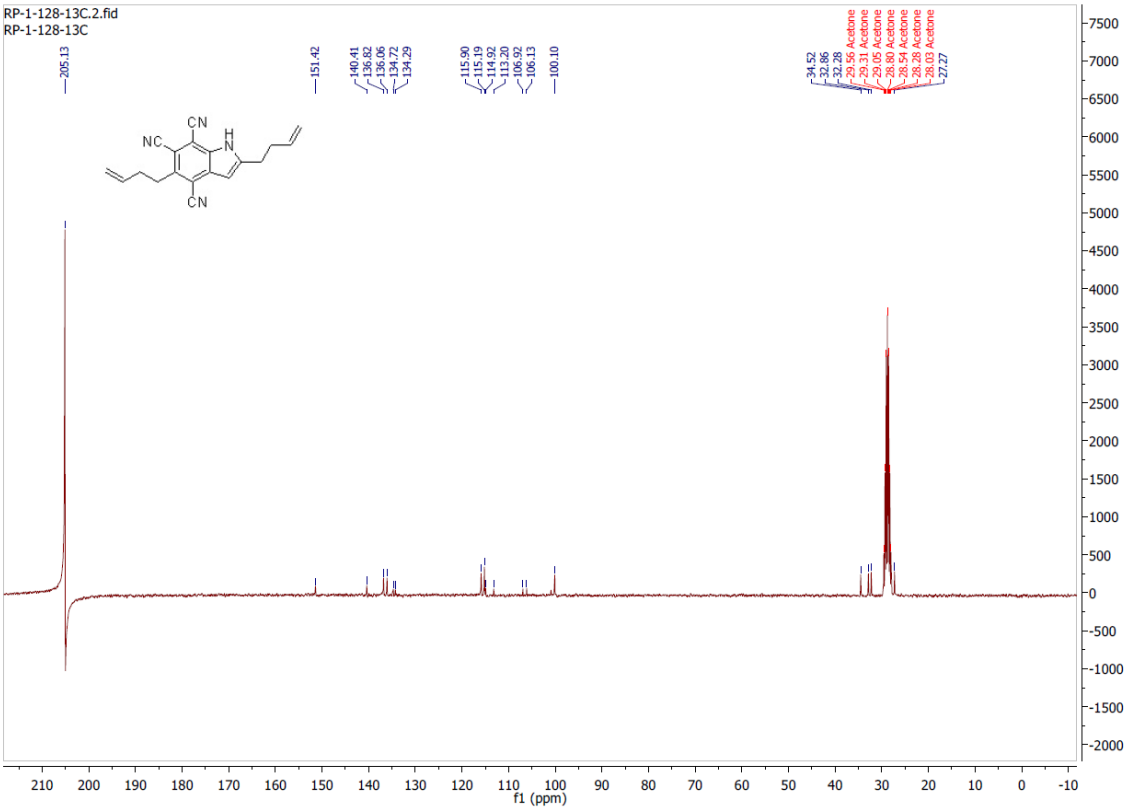
4. 2, 5-di-*tert*-butyl-1*H*-indole-4, 6, 7-tricarbonitrile NMR Data



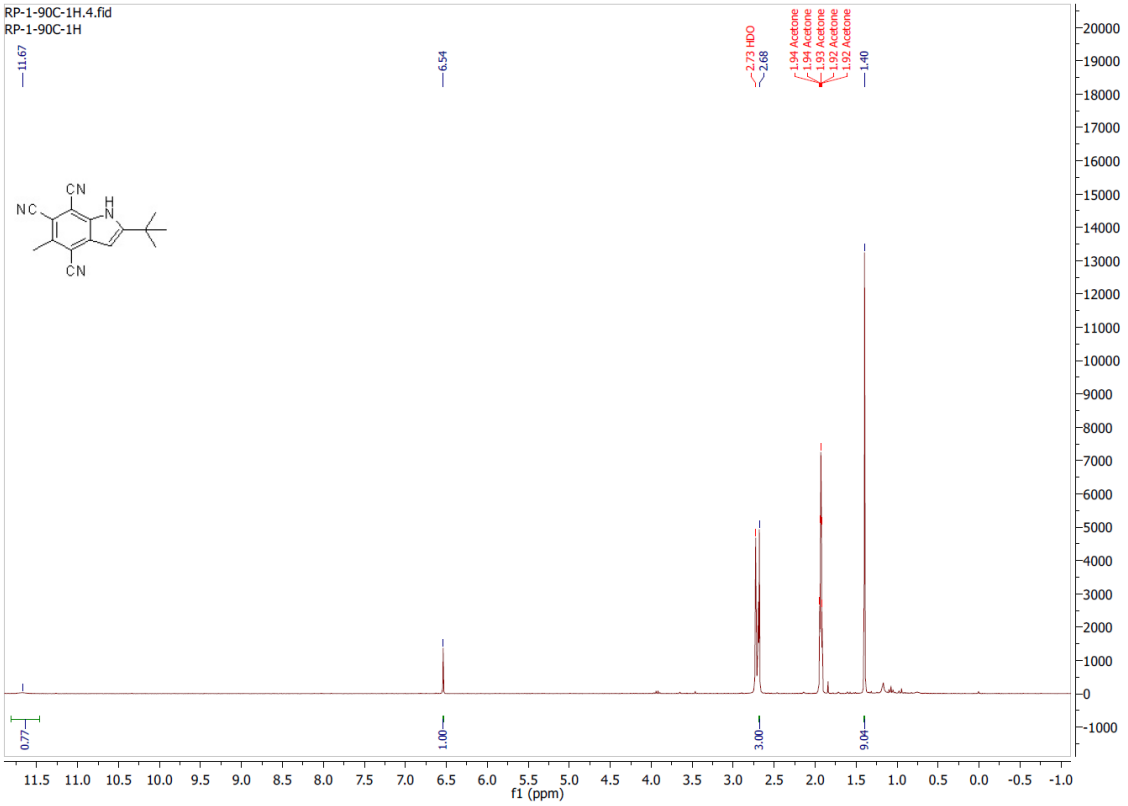


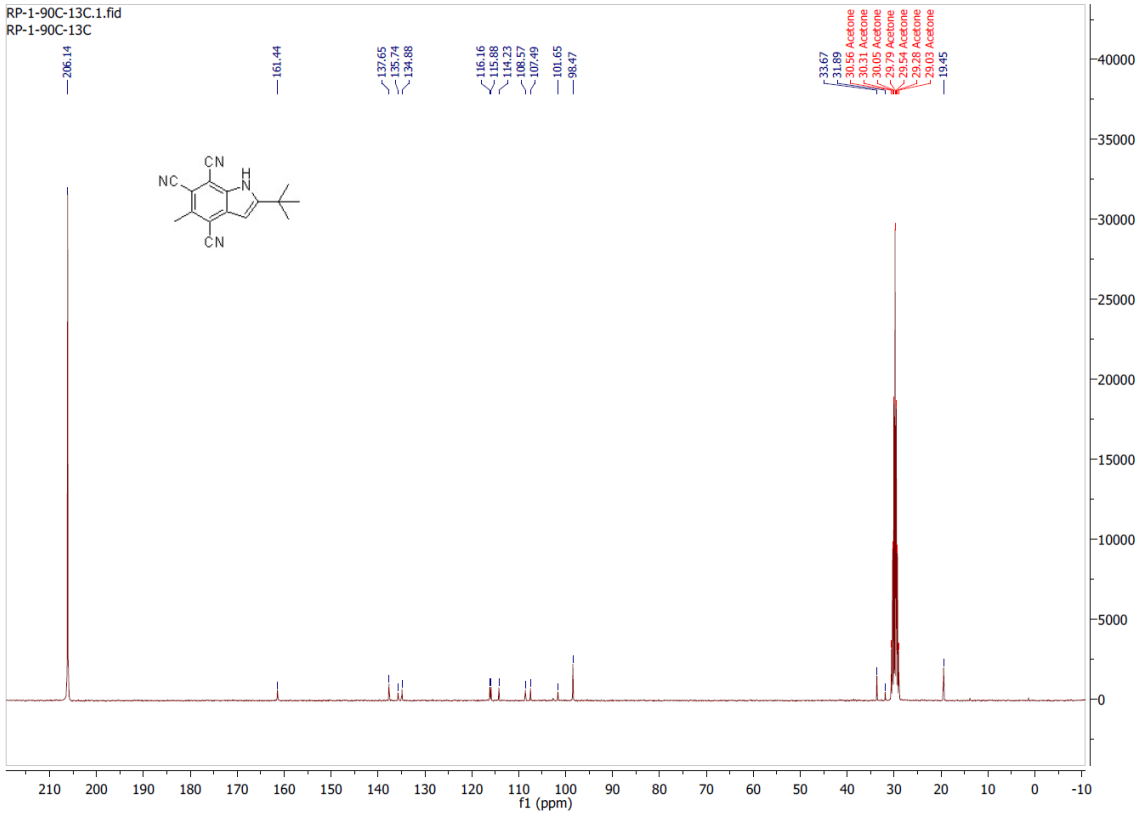
5. 2, 5-di(but-3-en-1-yl)-1*H*-indole-4, 6, 7-tricarbonitrile NMR Data



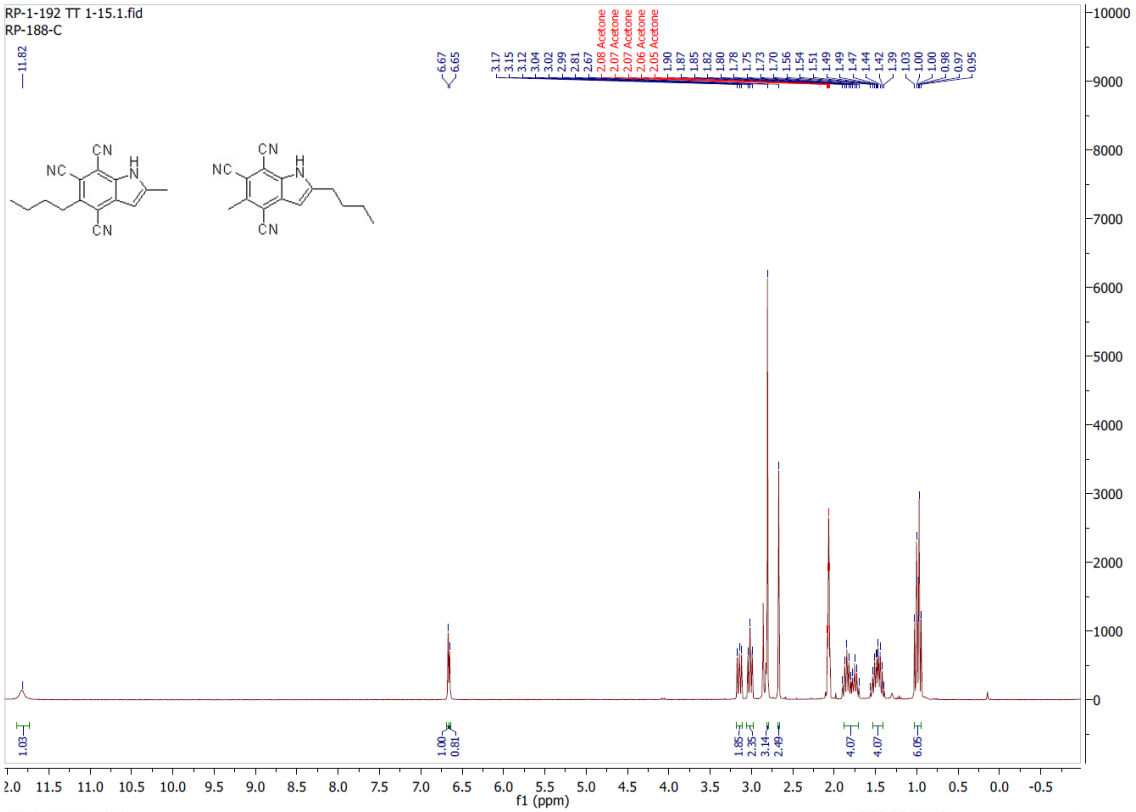


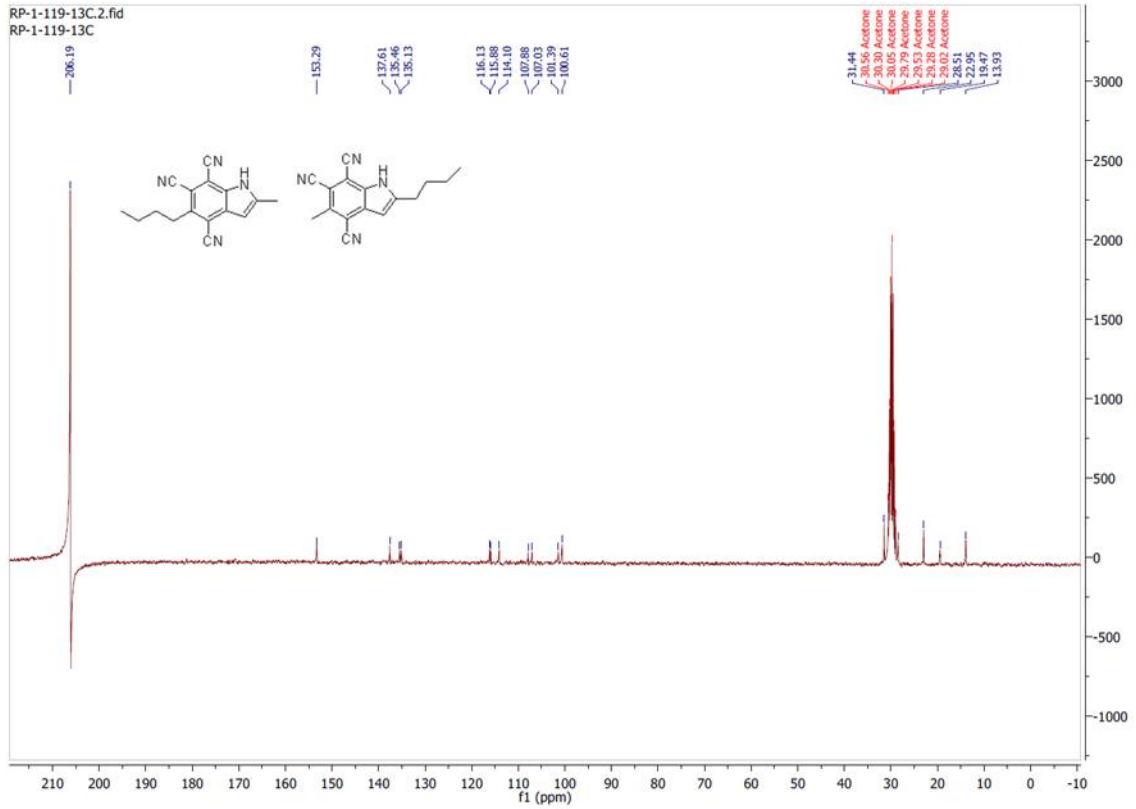
6. 2-(tert-butyl)-5-methyl-1H-indole-4, 6, 7-tricarbonitrile and 5-(tert-butyl)-2-methyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data



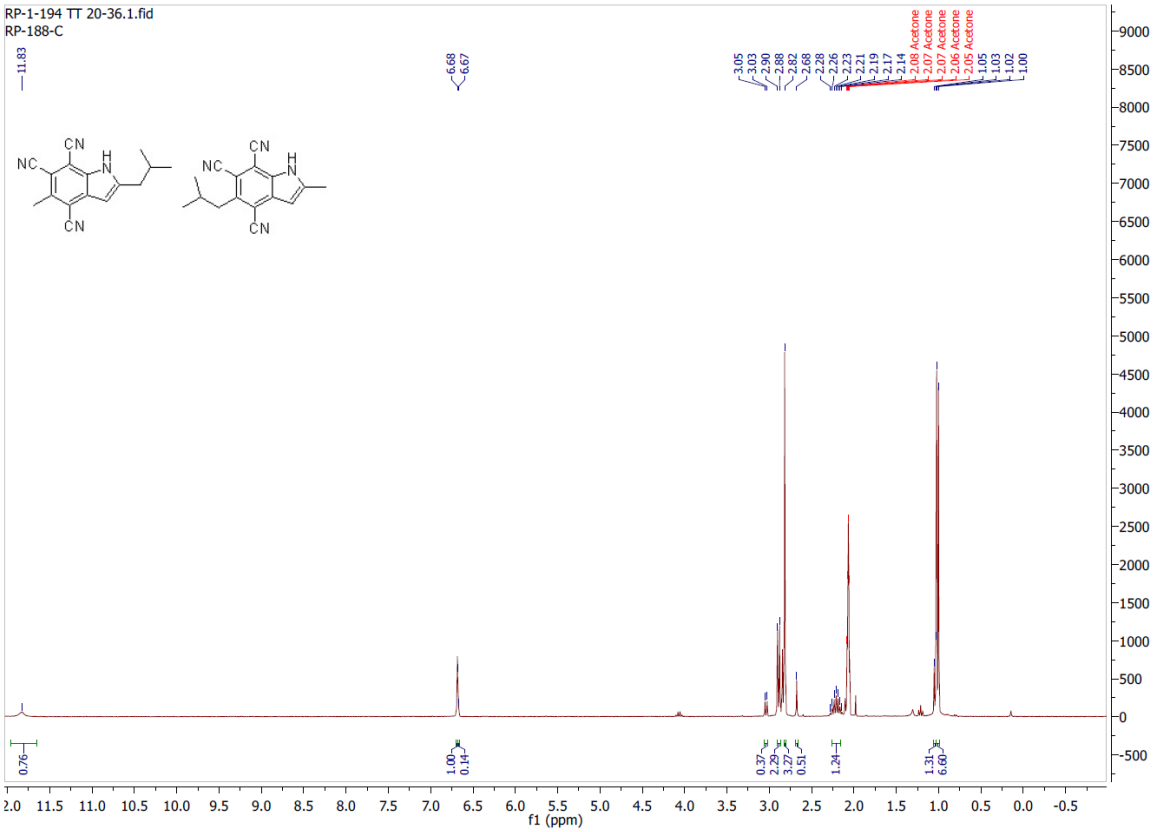


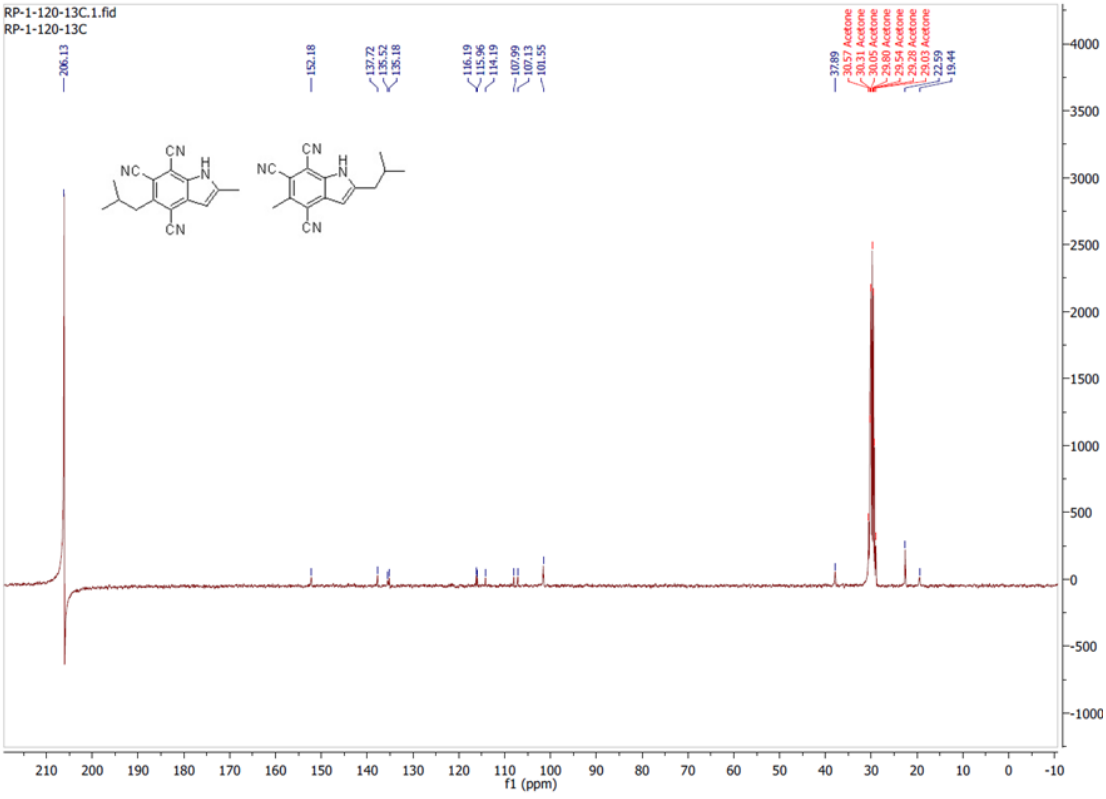
7. 5-butyl-2-methyl-1H-indole-4, 6, 7-tricarbonitrile and 2-butyl-5-methyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data



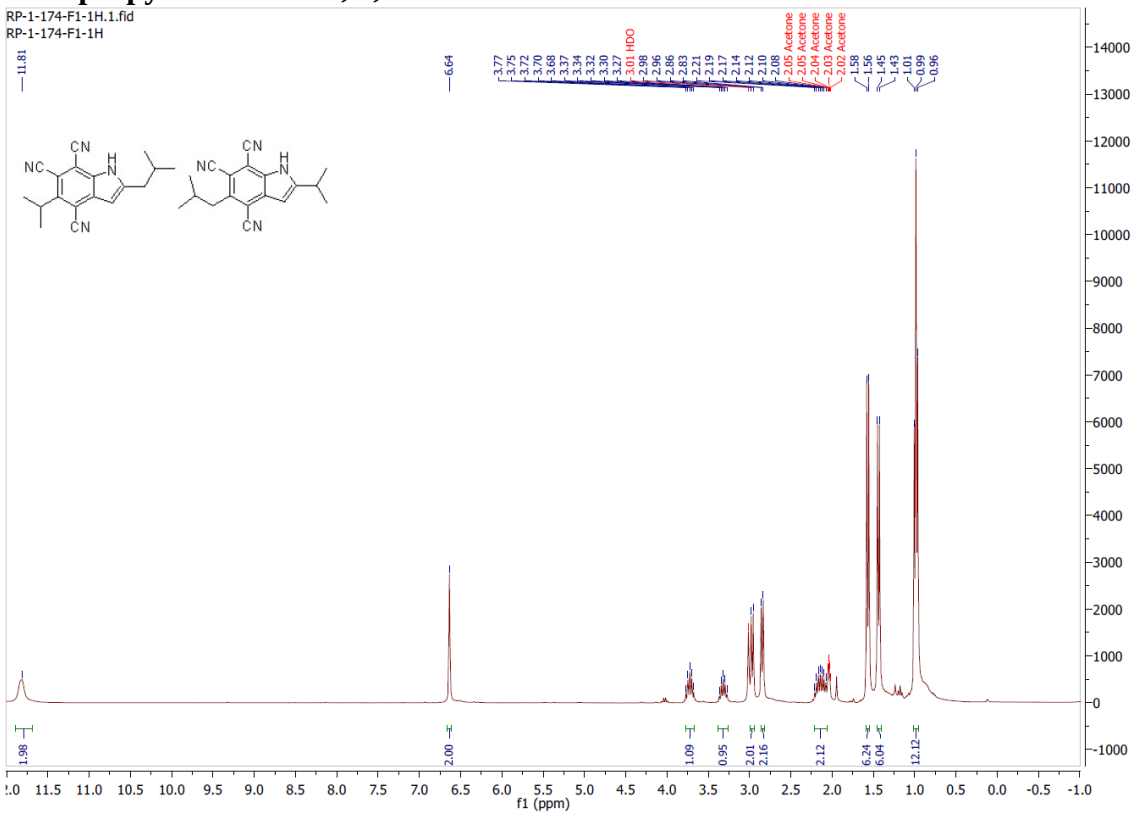


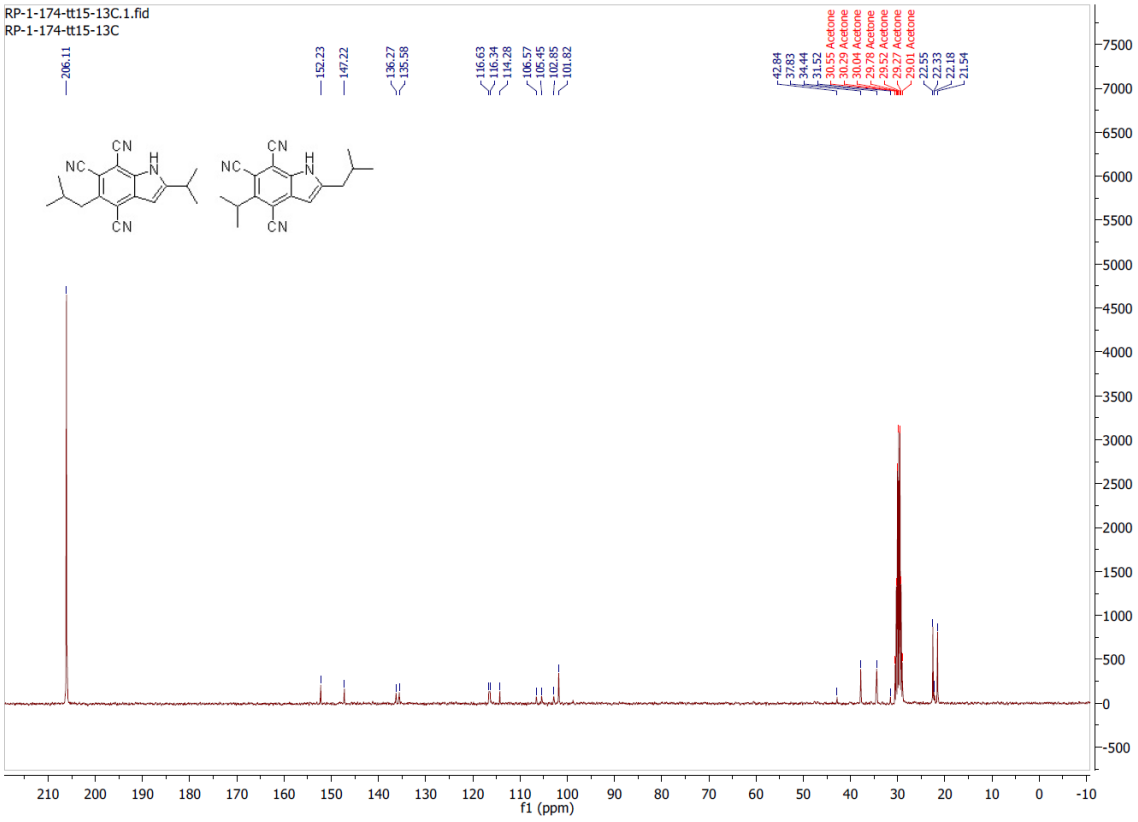
8. 2-isobutyl-5-methyl-1H-indole-4, 6, 7-tricarbonitrile and 5-(isobutyl)-2-methyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data



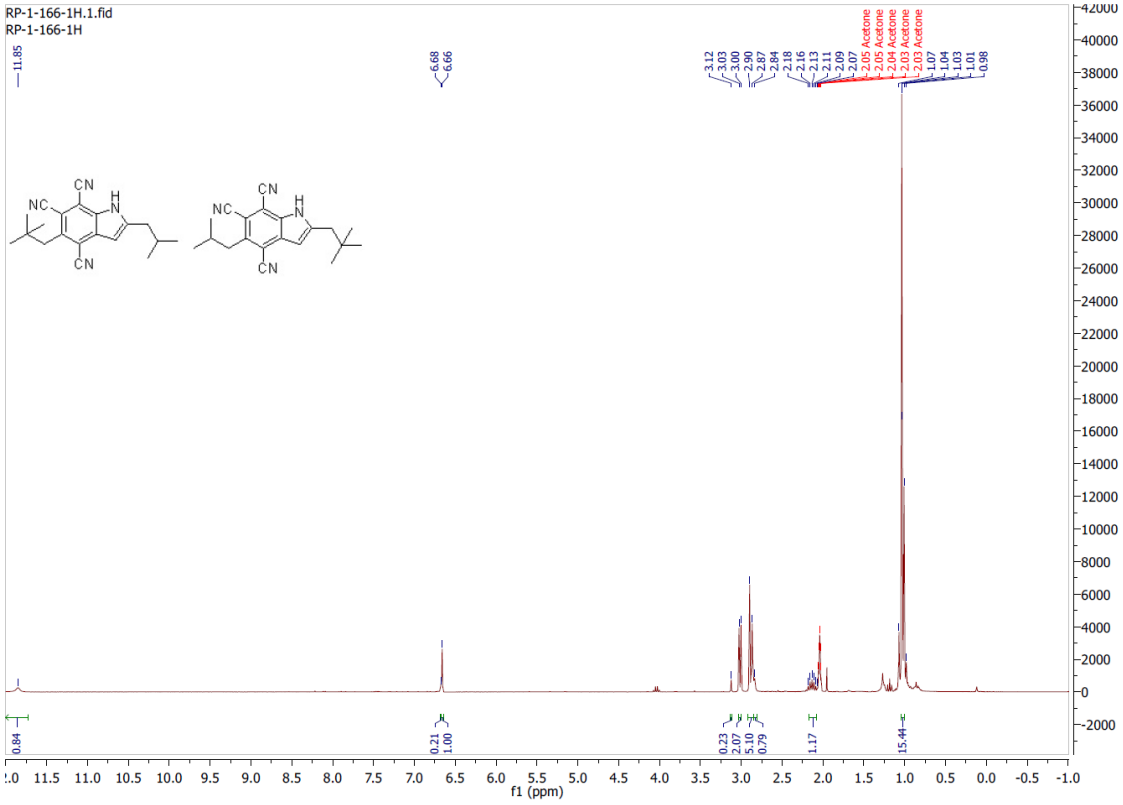


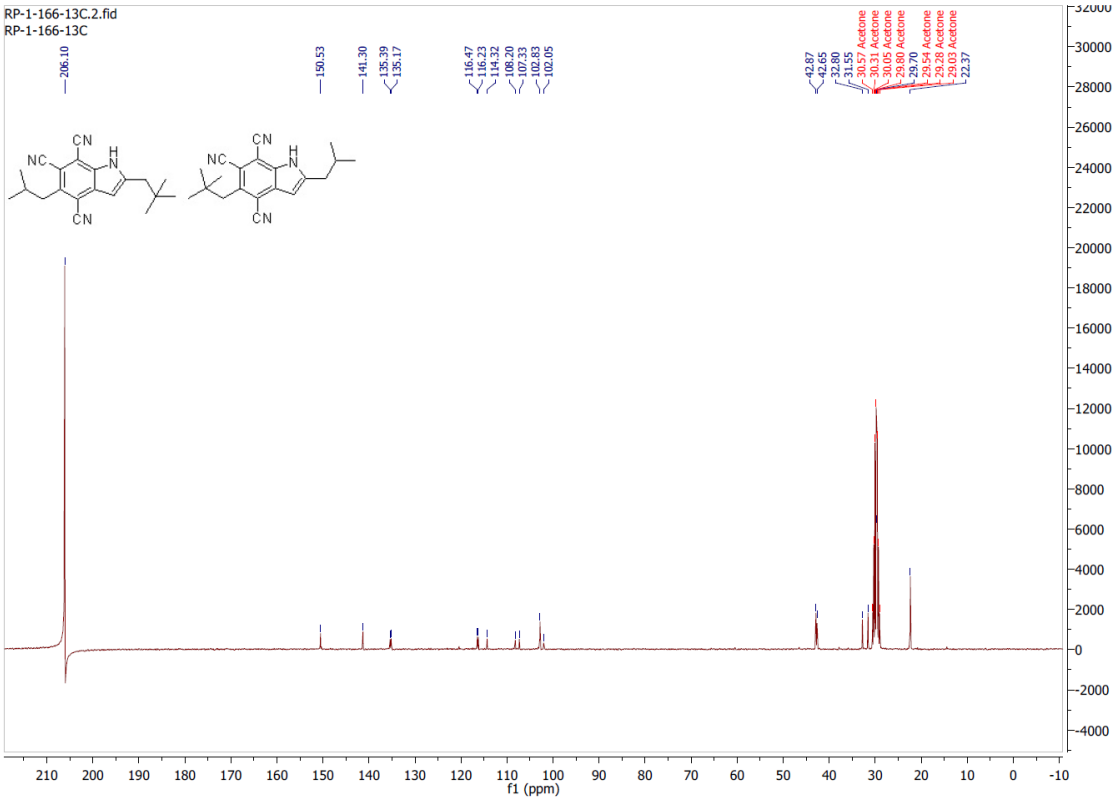
9. 5-isobutyl-2-isopropyl-1H-indole-4, 6, 7-tricarbonitrile and 2-isobutyl-5-isopropyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data



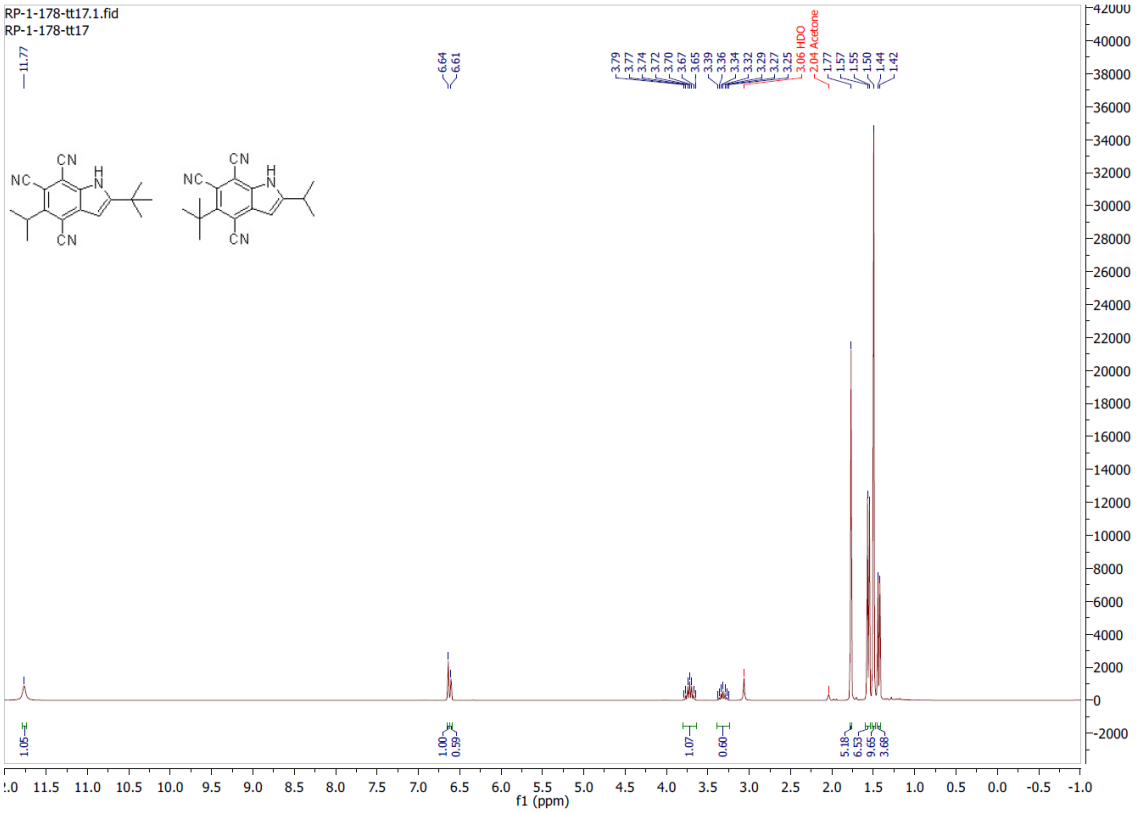


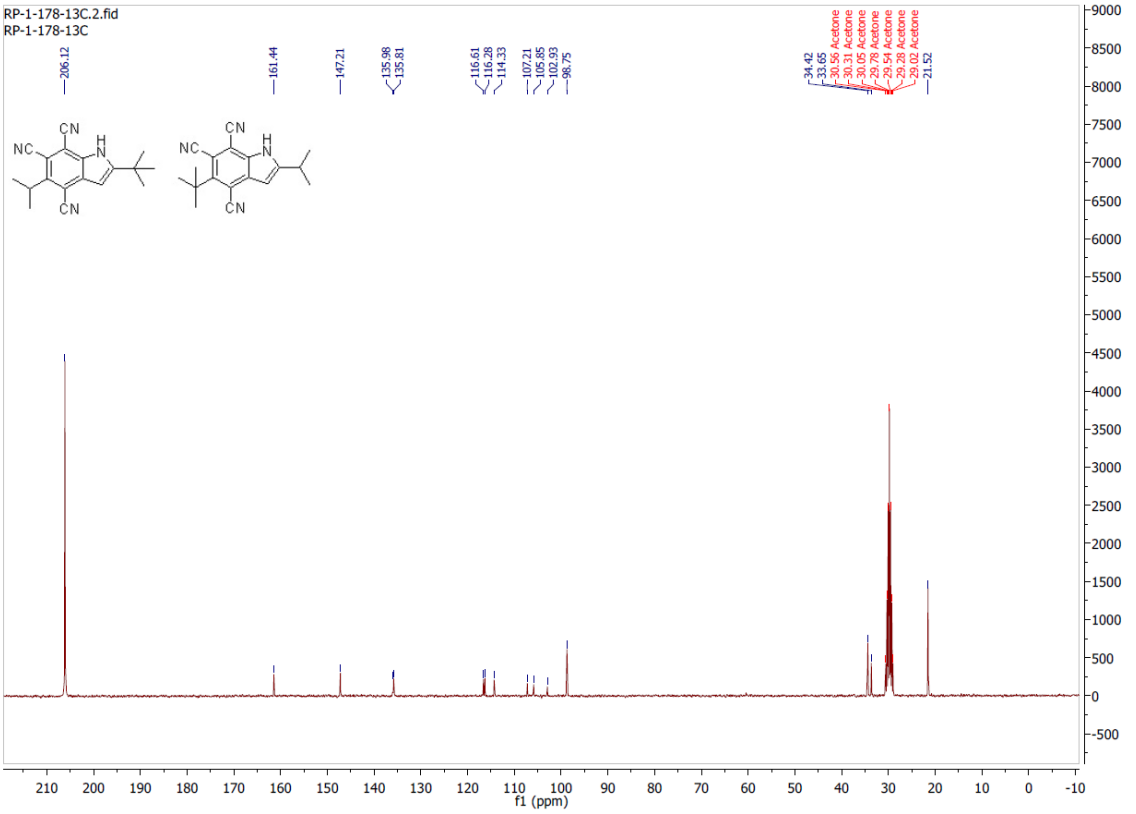
10. 5-isobutyl-2-neopentyl-1H-indole-4, 6, 7-tricarbonitrile and 2-isobutyl-5-neopentyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data



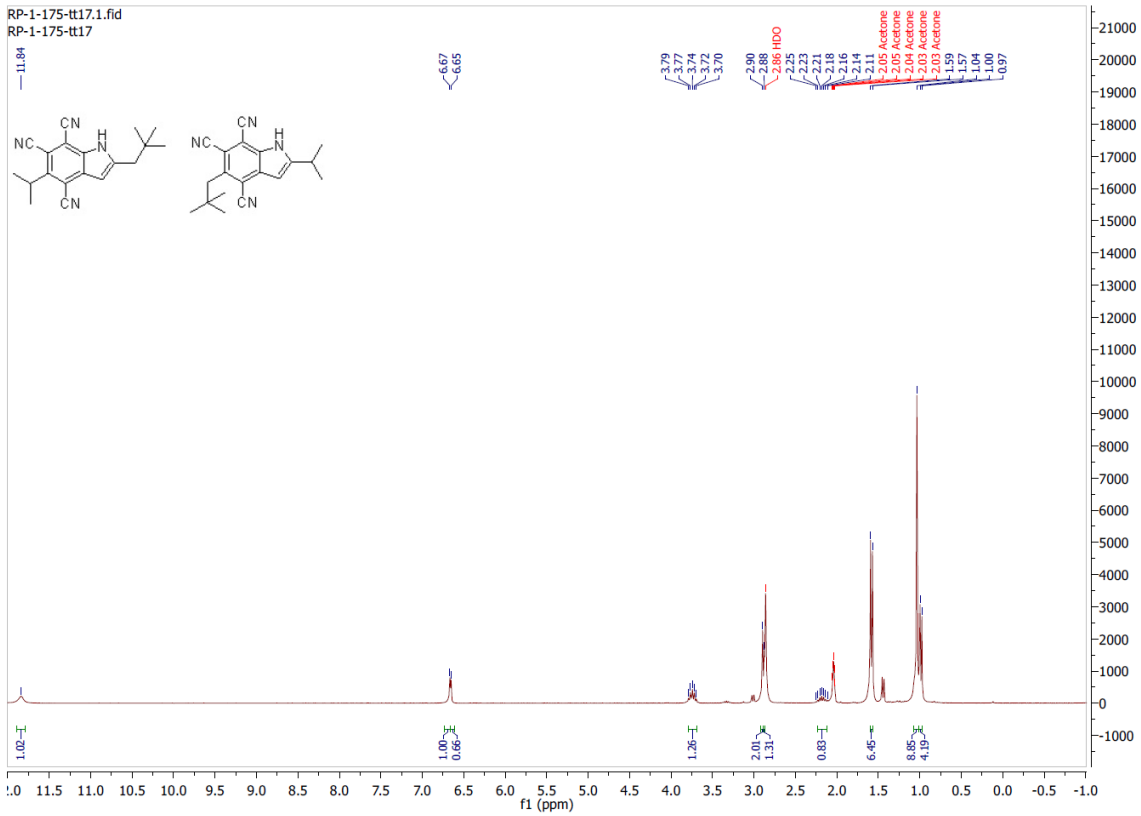


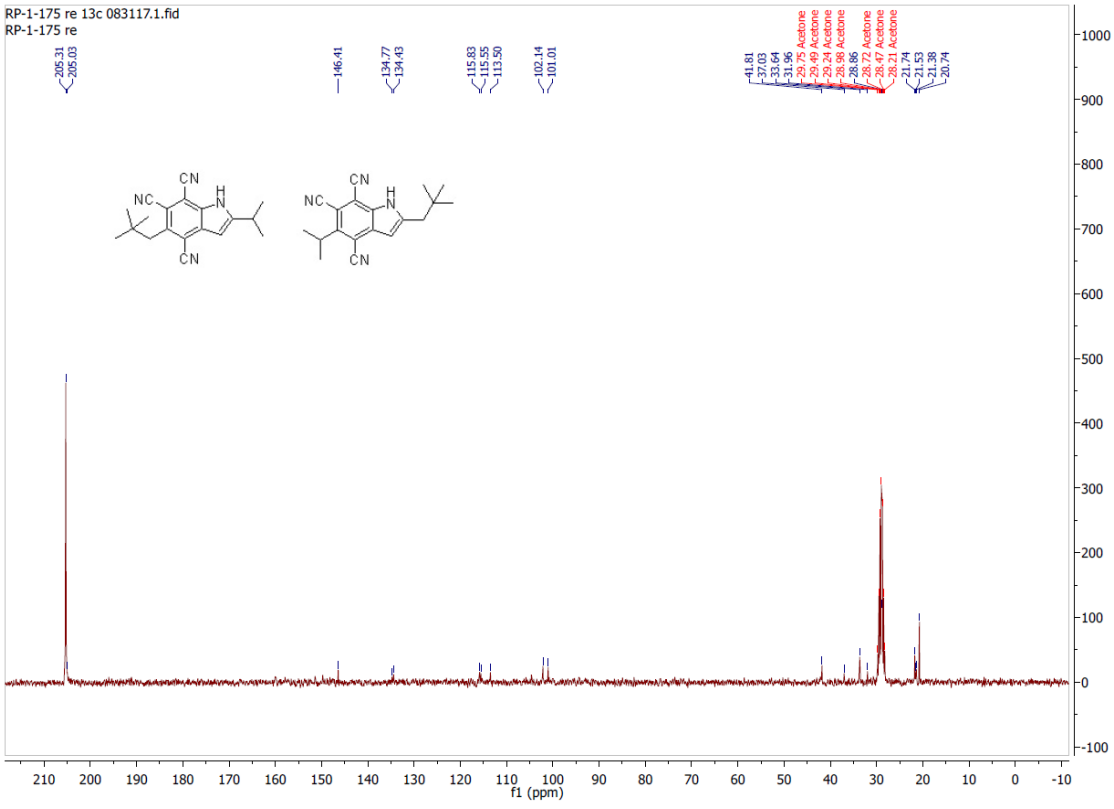
11. 2-isopropyl-5-(tert-butyl)-1H-indole-4, 6, 7-tricarbonitrile and 5-(tert-butyl)-2-isopropyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data





12. 2-isopropyl-5-neopentyl-1H-indole-4, 6, 7-tricarbonitrile and85-isopropyl-2-neopentyl-1H-indole-4, 6, 7-tricarbonitrile NMR Data





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