FRIEDEL-CRAFTS ACYLATION STUDIES ON 3-ALKYL-1-(PHENYLsULFONYL)INDOLES USING ALUMINUM CHLORIDE AND BISMUTH TRIFLATE

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

By

VENKATESWARA REDDY KARREPU

B.Sc., Osmania University, 2003

2012

Wright State University

Daniel Ketcha, Ph.D.
Thesis Director

Kenneth Turnbull, Ph.D., Chair
Department of Chemistry
College of Science and Mathematics

Committee on Final Examination

Daniel M. Ketcha, Ph.D.

Eric Fossum, Ph.D.

Vladimir Katovic, Ph.D.

Andrew T. Hsu, Ph.D.
Dean, School of Graduate Studies
ABSTRACT


Using the traditional catalyst, aluminum chloride in stoichiometric amounts, 3-alkyl-1-(phenylsulfonyl)indoles can be regioselectively acylated under Friedel-Crafts conditions at the C-6 position along with 10% of a minor isomer at the C-5 position. Alternatively, using catalytic amounts of the green catalyst, bismuth triflate, C-2 acylation was observed. Therefore, regioselectivity can be controlled by the nature of the Lewis acid catalyst. Moreover, this is the first-time that Friedel-Crafts acylation studies were demonstrated upon 3-alkyl-1-(phenylsulfonyl)indoles.
# TABLE OF CONTENTS

## I. INTRODUCTION

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indole</td>
<td>1</td>
</tr>
<tr>
<td>Indole Synthesis</td>
<td>2</td>
</tr>
<tr>
<td>Reactivity of Indoles</td>
<td>3</td>
</tr>
<tr>
<td>Acidity of Indole</td>
<td>4</td>
</tr>
<tr>
<td>Benzenesulfonylation of Indole</td>
<td>5</td>
</tr>
<tr>
<td>Lithiation of NBSI</td>
<td>5</td>
</tr>
<tr>
<td>Synthesis of Ellipticine</td>
<td>8</td>
</tr>
<tr>
<td>Bromination of NBSI</td>
<td>10</td>
</tr>
<tr>
<td>Chlorination of NBSI</td>
<td>11</td>
</tr>
<tr>
<td>Chlorosulfonation of NBSI</td>
<td>11</td>
</tr>
<tr>
<td>Nitration of NBSI</td>
<td>12</td>
</tr>
<tr>
<td>Nucleophilic Additions on NBSI</td>
<td>13</td>
</tr>
<tr>
<td>Friedel-Crafts Acylations on Indole</td>
<td>14</td>
</tr>
<tr>
<td>Vilsmeier-Haack Reaction on Indole</td>
<td>14</td>
</tr>
<tr>
<td>Indole Grignard Reaction on</td>
<td>15</td>
</tr>
<tr>
<td>Zinc Salts of Indole</td>
<td>16</td>
</tr>
<tr>
<td>Metal Triflates in Friedel-Crafts Acylation Chemistry</td>
<td>22</td>
</tr>
<tr>
<td>Effect of Lithium Perchlorate as an Additive</td>
<td>23</td>
</tr>
<tr>
<td>Alkylation’s on NBSI</td>
<td>23</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION………………………………………………26

1-(Phenylsulfonyl)indole (27)……………………………………………27
1-(Phenylsulfonyl)indole-3-carbaldehyde (109)………………………28
3-Methyl-1-(phenylsulfonyl)indole (110)……………………………28
3-Acetyl-1-(phenylsulfonyl)indole (95)………………………………29
3-Ethyl-1-(phenylsulfonyl)indole (111)……………………………29
6-Acetyl-3-methyl-1-(phenylsulfonyl)indole (112)………………30
6-Acetyl-3-methylindole (114)……………………………………31
2-Acetyl-3-methyl-1-(phenylsulfonyl)indole (76)………………32
2-Acetyl-3-methylindole (74)……………………………………33
6-Propionyl-3-methyl-1-(phenylsulfonyl)indole (115)……………34
6-Acetyl-3-ethyl-1-(phenylsulfonyl)indole (117)…………………35

NMR ANALYSIS…………………………………………………………..35

$^{13}$C NMR Analysis of Indole……………………………………35
$^{13}$C NMR Analysis of Benzenesulfonyl Chloride…………………..36
$^{13}$C NMR Analysis of 27…………………………………………37
$^{13}$C NMR Analysis of 110……………………………………38
$^{13}$C NMR Analysis of 111……………………………………38
$^{13}$C NMR Analysis of 112……………………………………38
$^{13}$C NMR Analysis of 114……………………………………38
$^{13}$C NMR Analysis of 115……………………………………39
$^{13}$C NMR Analysis of 117………………………………………40
$^{13}$C NMR Analysis of 76………………………………………41
$^{13}$C NMR Analysis of 74………………………………………41
II. EXPERIMENTAL .................................................................42

III. REFERENCES ........................................................................66
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR Spectrum of Compound 27</td>
<td>49</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 27</td>
<td>49</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 27</td>
<td>50</td>
</tr>
<tr>
<td>$^1$H NMR Spectrum of Compound 110</td>
<td>50</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 110</td>
<td>51</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 110</td>
<td>51</td>
</tr>
<tr>
<td>$^1$H NMR Spectrum of Compound 95</td>
<td>52</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 95</td>
<td>52</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 95</td>
<td>53</td>
</tr>
<tr>
<td>$^1$H NMR Spectrum of Compound 111</td>
<td>53</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 111</td>
<td>54</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 111</td>
<td>54</td>
</tr>
<tr>
<td>$^1$H NMR Spectrum of Compound 112</td>
<td>55</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 112</td>
<td>55</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 112</td>
<td>56</td>
</tr>
<tr>
<td>$^1$H NMR Spectrum of Compound 113</td>
<td>56</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 113</td>
<td>57</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 113</td>
<td>57</td>
</tr>
<tr>
<td>$^1$H NMR Spectrum of Compound 114</td>
<td>58</td>
</tr>
<tr>
<td>$^{13}$C NMR Spectrum of Compound 114</td>
<td>58</td>
</tr>
<tr>
<td>$^{13}$C dept NMR Spectrum of Compound 114</td>
<td>59</td>
</tr>
</tbody>
</table>
\textsuperscript{1}H NMR Spectrum of Compound 76........................................59
\textsuperscript{13}C NMR Spectrum of Compound 76......................................60
\textsuperscript{13}C dept NMR Spectrum of Compound 76.................................60
\textsuperscript{1}H NMR Spectrum of Compound 74........................................61
\textsuperscript{13}C NMR Spectrum of Compound 74........................................61
\textsuperscript{13}C dept NMR Spectrum of Compound 74.................................62
\textsuperscript{1}H NMR Spectrum of Compound 115.......................................62
\textsuperscript{13}C NMR Spectrum of Compound 115.......................................63
\textsuperscript{13}C dept NMR Spectrum of Compound 115...............................63
\textsuperscript{1}H NMR Spectrum of Compound 117.......................................64
\textsuperscript{13}C NMR Spectrum of Compound 117.......................................64
\textsuperscript{13}C dept NMR Spectrum of Compound 117...............................65
LIST OF TABLES

Page

Screening of Metal Triflates.........................................................32
ACKNOWLEDGEMENTS

Thanks to the department for giving me an opportunity to pursue a career in Chemistry at Wright State University. Especially I would like to thank Dr. Dolson and other admission committee members for offering me admission into MS Chemistry Program.

I am thankful to my advisor Dr. Daniel Ketcha for his excellent guidance in completing NMR analysis successfully since this project relies heavily on NMR for structural characterization of the products and establishing the site of acetylation. Also in many ways I learned many things from his teachings in the lab especially the core and the importance of organic chemistry research. He is a wonderful personality to work with and also challenge the group members at times to live up to their talent to match their potential. In that way I was really forced to learn many things on my own which increased my self-belief as a researcher. And I really learnt the art of synthesis in his lab with his extraordinary advising. Also he has been of immense help when I was going through rough times in my life. Thanks to the group members and especially Charles Clay for his matchless support throughout my Master’s Degree.

Thanks to the Committee members (Dr. Katovic & Dr. Fossum) for their overall support. I learnt a lot from their classes and eventually end up getting A’s. Also I would like to thank Dr. Turnbull, Dr. Pavel, Dr. Aga and Dr. Lunsford for their kind support at times.

Many thanks to my family members especially my Mother, Brother, Aunt Padmavathi and everyone involved in my success.

Finally I am in debt to my BEST FRIEND Pranath Reddy DeviReddy for his matchless support at bad times and helping me to come to USA. Also I am thankful to Srinivas Reddy Vancha for
his great support when I was really going through bad phase of my life. Also I didn’t forget Jaipal Reddy and Sudhakar Mittapalli for their help in the process.
INTRODUCTION

Indole:

Indole $^{1,2}(1)$ is a ubiquitous heterocyclic compound present in biological systems. Molecules possessing this heterocyclic core include serotonin (2), tryptophan (3), melatonin (4), lysergic acid diethylamide (LSD) (5) and indomethacin (6) and represent just a few of the innumerable compounds containing the indole ring in their structures. For example, serotonin (2) is a neurotransmitter in the central nervous system as well as the cardiovascular and gastrointestinal systems of animals. Many proteins contain tryptophan (3) since it is an amino acid. LSD (5) exerts notorious physiological activity, and indomethacin (6) is used to treat rheumatoid arthritis.
Indole Synthesis

Although indole derivatives can be synthesized in a variety of ways\(^3\) the most versatile method is the Fischer-indole synthesis\(^4,5,6,7\). The Fischer-indole synthesis involves the reaction of phenylhydrazine (7) with an enolizable aldehyde or ketone 8 to form the corresponding phenylhydrazone 9. This species undergoes isomerization to the enamine 10 which upon protonation undergoes a cyclic [3,3]-sigmatropic rearrangement to produce an imine intermediate 11. Intramolecular attack by the resultant aniline nitrogen onto the carbon of the imine forms the aminoacetal 12 which undergoes acid catalysis and deamination to finally produce the substituted indole 13.

![Chemical Diagram]

To circumvent the need for variously substituted hydrazines so as to produce indoles with substituents on the benzenoid ring, Buchwald\(^8\) devised a palladium catalyzed process for the Fischer-indole synthesis. In this protocol, benzophenone hydrazine (14) undergoes coupling reaction with aryl bromides in the presence of a Pd(OAc)\(_2\)/(BINAP) catalytic system to produce N-arylbenzophenone hydrazones 16, which on treatment with a ketone and \(p\)-toluenesulfonic acid monohydrate (\(p\)-TsOH, \(H_2O\)) undergo Fischer indolization to produce 2,3-disubstituted indoles.
In terms of substrate scope with respect to both the amine component and the aryl halide, palladium-catalyzed coupling of amines with aryl halides was proven to be general.\textsuperscript{9,10}

Reactivity of Indoles:

Indole usually undergoes aromatic electrophilic substitution reactions at the beta (C-3) position.

The more stable intermediate \textbf{18} formed upon an electrophilic attack at C-3 has the positive charge located adjacent to the nitrogen so that it gets stabilized by the interaction with the lone pair electrons on the nitrogen atom. Alternatively, in the case of electrophilic attack at C-2 the
positive charge resides at C-3 (benzylic cation, e.g., 20) and can only derive stabilization from the nitrogen lone pair by disrupting the benzenoid resonance which is unfavorable.

The acidity (pKₐ) of the N-H proton of indole was found to be 16.97,¹¹ and the indolyl anion can be easily generated by the reaction with bases such as sodium hydride (NaH) in dimethylsulfoxide (DMSO) at 0°C.¹² The indolyl anion 22 is an ambient nucleophile which means that electrophiles can attack at either the nitrogen or the C-3 carbon. The ratio of the products has been found to depend on the associated metal, the solvent, polarity and the nature of the electrophile.¹³ If the metal tends to form more ionic bonds (i.e., Li, Na, K) N-substitution is favored, whereas if the metal tends to form more covalent bonds (i.e., Mg) then C-3 substitution is favored. Also, polar solvents such as hexamethylphosphoramide (HMPA) favor N-attack and less polar solvents favor C-3 attack.

The Chemistry of 1-(Phenylsulfonyl)indole (27):
The first synthesis\textsuperscript{12} of 1-(phenylsulfonyl)indole (27) was reported in 1973 by Sundberg and Russell and involved the treatment of 1 with NaH/DMSO (Corey and Cheykovsky reagent\textsuperscript{14}) at 0°C followed by the addition of benzenesulfonyl chloride (PhSO\textsubscript{2}Cl).

\[
\text{1} \xrightarrow{\text{NaH/DMSO, 0°C, PhSO}_2\text{Cl}} \text{27}
\]

Although Illi\textsuperscript{15} initially reported the first phase-transfer catalyzed (PTC) synthesis of 27 using tetrabutylammonium hydrogen sulfate (TBAHS) and 50% sodium hydroxide (NaOH) solution in toluene, it was in 1988 that Bergman and Pelcman reported the now commonly employed PTC method for \(N\)-protection of indole in dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}) in presence of TBAHS, NaOH and benzenesulfonyl chloride at 0°C\textsuperscript{16}.

\[
\text{1} \xrightarrow{1. \text{NaOH, TBAHS, CH}_2\text{Cl}_2, 0°C} \xrightarrow{2. \text{PhSO}_2\text{Cl}} \text{27}
\]

Lithiations:

Although it was reported in 1953 by Shirley and Roussel that \(N\)-methylindole undergoes C-2 lithiations\textsuperscript{17} by \(n\)-butyllithium (\(n\)-BuLi), this methodology is not particularly useful since deprotection of \(N\)-alkylindoles is not an easy task. Since 2-lithioindoles are useful synthetic intermediates to various 2-substituted indoles, \(N\)-protecting groups which can be easily removed were required.
In the original work done by Sundberg it was found that 1-(phenylsulfonyl)indole (27) could be lithiated\textsuperscript{12} at C-2 with tert-butyllithium (t-BuLi) at -12°C to room temperatures to afford the corresponding intermediate 28. Subsequent addition of electrophiles affords the C-2 substituted derivatives 29. While examining other potential N-protecting groups (e.g., methoxymethyl, benzyloxymethyl, benzyl, trimethylsilyl, tert-butyldimethylsilyl), the benzenesulfonyl group\textsuperscript{12} was deemed to be the best among the moieties examined because it can be deprotected easily by alkaline hydrolysis.\textsuperscript{18} In some cases, such as reactions of the 2-lithio species 28 with esters and nitriles, the phenylsulfonyl group is spontaneously cleaved either during the reaction or workup.\textsuperscript{12}

An application of this lithiation strategy was used in the synthesis of the important alkaloid catharanthine,\textsuperscript{19} a precursor of the antimicrotubule drug vinblastine (34). In this sequence, 27 was lithiated at C-2 with t-BuLi followed by the addition of a threefold excess of ethyl pyruvate to afford the alcohol 30, which underwent acid-catalyzed dehydration in the presence of 4 mol\% of p-toluenesulfonic acid to afford the vinyl species 31. Subsequent manipulations (including a Diels-Alder reaction yielding 32) then led to catharanthine 33.
Lithiation at C-2 using Lithium Diisopropylamide (LDA):

In 1982 Gribble\textsuperscript{20} established that lithium diisopropylamide (LDA) is capable of lithiating the C-2 position of 27, which is a remarkable finding given the fact that LDA is easier to handle than t-BuLi. Moreover, this process was found to result in improved yields of C-2 substituted products as well as products of higher purity. Thus, treating 28 with LDA at -75°C to room temperature produces the C-2 lithiated intermediate 28 which upon subsequent addition of electrophiles produces 29.
Synthesis of Ellipticine:

One of the earliest applications of LDA to lithiate the C-2 position of the indole ring was highlighted in the synthesis of the anti-tumor alkaloid ellipticine 39\textsuperscript{21}. In the first step of this synthesis, 27 was lithiated at C-2 using LDA (-75\textdegree C to 0\textdegree C) to afford 28 which underwent regioselective addition to 3,4-pyridinedicarboxylic anhydride (35) to produce the keto-acid 36 as the major isomer. The deprotection of 36 was then effected using potassium carbonate (K$_2$CO$_3$) in the presence of 3:1 mixture of methanol and water under reflux conditions to afford keto-acid 37. Treatment of 37 with acetic anhydride (80-85\textdegree C) afforded the cyclized keto-lactam 38 which upon treatment with excess methyllithium (CH$_3$Li) at -100\textdegree C followed by reduction with sodium borohydride (NaBH$_4$) ultimately yielded ellipticine (39).
Interestingly, generation of a C-3 lithio species can be effected by a somewhat circuitous route also relying upon prior introduction of an N-phenylsulfonyl protecting group. In this protocol, indole is first deprotonated with \( n \)-BuLi at -78\(^\circ\)C, whereupon iodination occurs at the C-3 position yielding 40. Subsequent N-deprotonation with LDA followed by quenching with benzenesulfonyl chloride affords 3-iodo-1-(phenylsulfonyl)indole (41).\(^{20}\)

The 3-iodo species 41 can then undergo halogen-metal exchange on treatment with \( t \)-BuLi at -100\(^\circ\)C in tetrahydrofuran (THF) to produce 3-lithio-1-(phenylsulfonyl)indole (42). When this carbanion is kept at -100\(^\circ\)C, reaction with electrophiles yields the corresponding C-3 functionalized derivatives 43. However, if the temperature brought from -100\(^\circ\)C to 20\(^\circ\)C rearrangement to the more stable 2-lithio-1-(phenylsulfonyl)indole (28) occurs which on further addition of electrophiles produces the 2-substituted indole derivatives 29.
Bromination:

The first synthesis of 3-bromo-1-(phenylsulfonyl)indole (44) was achieved during the synthesis of hobartine (46) in 1985 by Gribble and Barden. In the first step of this synthesis, 1-(phenylsulfonyl)indole (27) reacts with bromine in the presence of propylene oxide at room temperature to produce 3-bromo-1-(phenylsulfonyl)indole (44). This substrate was then subjected to metal-halogen transfer reaction with t-BuLi and subsequent reaction with ethylene oxide in borontrifluoride (BF$_3$) afforded N-(phenylsulfonyl)tryptophol (45) which was subsequently elaborated to hobartine (46).
In 1989, Ketcha et al. synthesized 2-bromo-1-(phenylsulfonyl)indole (47) from 1- (phenylsulfonyl)indole (27) by lithiating at the C-2 position with LDA in THF at -78°C followed by quenching with cyanogen bromide (BrCN).

\[
\text{SO}_{2}\text{Ph} \quad \xrightarrow{\text{LDA/THF, -78°C}} \quad \text{SO}_{2}\text{Ph} \quad \text{BrCN, 85%}
\]

Chlorination:

In 1987, Wenkert synthesized 3-chloro-1-(phenylsulfonyl)indole (48). In this case, indole (1) was allowed to react with methyl magnesium bromide (MeMgBr) in THF at room temperature to produce a magnesium indolate which underwent reaction with benzenesulfonyl chloride to afford 3-chloro-1-(phenylsulfonyl)indole in 45% yield along with 6% of 3-chloroindole (49). In this reaction, benzenesulfonyl chloride acts as a chlorinating agent rather than benzenesulfonylation agent. Also, Wenkert postulated that formation of β-chloroindolenine was the first step in the Grignard reactions. It is also possible that β-chlorination proceeds by an initial electron-transfer step in which indole donates an electron to benzenesulfonyl chloride producing indole radical and benzenesulfonyl chloride radical anion.

\[
\text{SO}_{2}\text{Ph} \quad \xrightarrow{1. \text{MeMgBr/THF, 1h}} \quad \text{SO}_{2}\text{Ph} \quad \text{Cl} \quad + \quad \text{Cl} \quad 45\% \quad 6\%
\]

Chlorosulfonation:

Bergman et al. prepared 1-(phenylsulfonyl)indole-3-sulfonylchloride (50) from 27 by reaction with 3 equivalents of chlorosulfonic acid (HOSO₂Cl) in acetonitrile (CH₃CN).
Expectedly, 50 can easily be converted into a variety of derivatives such as 3-((1H-imidazol-1-yl)sulfonyl)-1-(phenylsulfonyl)-1H-indole (51) by treatment with imidazole in CH₂Cl₂ at room temperature. Likewise, on exposure to an excess of morpholine in CH₂Cl₂ at room temperature 50 afforded sulfonamide 52 in 93% yield. Further, 52 on treatment with potassium carbonate in aqueous methanol at room temperature afforded 4-((1-(phenylsulfonyl)-1H-indol-3-yl)sulfonfyl)morpholine (53) in 92% yield.

Nitration:

In 1999, Gribble and Pelkey²⁶ generated a mixture of 3-nitro-1-(phenylsulfonyl)indole (54) and 6-nitro-1-(phenylsulfonyl)indole (55) by reacting 1-(phenylsulfonyl)indole (27) with in situ generated acetyl nitrate with nitric acid/acetic anhydride at room temperature, wherein 3-nitro-1-
(phenylsulfonyl)indole (54) was found to be the major isomer.

\[
\text{N}\begin{array}{c}
\text{O} \\
\text{2} \\
\text{P} \\
\text{h}
\end{array}
\text{N}\begin{array}{c}
\text{O} \\
\text{2} \\
\text{P} \\
\text{h}
\end{array}
+ \\
\text{N}\begin{array}{c}
\text{O} \\
\text{2} \\
\text{P} \\
\text{h}
\end{array}
\text{N}\begin{array}{c}
\text{O} \\
\text{2} \\
\text{P} \\
\text{h}
\end{array}
\]

Nucleophilic Additions to the Indole Nucleus:

Since electron withdrawing groups decrease the electron density in the indole nucleus thereby making the ring susceptible to attack by the nucleophiles, Gribble\textsuperscript{27} reported the nucleophilic substitution of 1,2-bis(phenylsulfonyl)-1\(H\)-indole (56) with organocuprate nucleophiles in THF (-78°C to rt). For instance, treatment of sulfone 56 with dimethyl copper lithium afforded 3-methyl-1,2-bis(phenylsulfonyl)-1\(H\)-indole (57) in 67% although other nucleophiles such as MeMgBr and Me\textsubscript{2}Zn under the same reaction conditions had shown no sign of reaction. The starting material 56 was made in three steps starting from 27 via C-2 lithiation with LDA followed by quenching with diphenyldisulfide (Ph\textsubscript{2}S\textsubscript{2}) producing 2-thiophenylindole (59) which undergoes oxidation with meta-chloroperoxybenzoic acid (\textit{m}-CPBA) to provide 56 in 75% overall yield.
Friedel-Crafts Acylation:

Reportedly, Baeyer\textsuperscript{28} effected the acetylation of indole with acetic anhydride in 1879. In this method indole was reacted with acetic anhydride at 180-200°C to afford varying yields of a mixture of \(N\)-acetyl and 1,3-diacetylinobole. In 1889, Ciamician and Zatti\textsuperscript{29} reported almost the same procedure followed by Zatti and Ferratini\textsuperscript{30} in 1890. Alternative procedures for the acetylation of indole were reported by Oddo and Sessa\textsuperscript{31} in 1911, Majima\textsuperscript{32} in 1922, and Baker\textsuperscript{33} in 1946. In 1952, Saxton\textsuperscript{34} reported the Friedel-Crafts acetylation of indole (1) with acetic anhydride in the presence of 10\% of acetic acid to yield 60\% of 1,3-diacetylinobole (59) along with 5-10\% of 1,1-di-(1-acetyl-3-indolyl)ethylene (60).

\[
\begin{align*}
\text{Indole (1)} & \xrightarrow{\text{AcOH/\text{Ac}_2\text{O}, 147^\circ\text{C}}} \begin{array}{c}
\text{N-acetylindole (59)} \\
\text{1,1-di-(1-acetyl-3-indolyl)ethylene (60)}
\end{array} \\
& \xrightarrow{\text{NaOH/EtOH/H}_2\text{O}} \text{Indole (1)}
\end{align*}
\]

Apart from the aforementioned methods,\textsuperscript{29-34} some of the alternate methods to introduce acyl groups at C-3 positions of indole nucleus are the Vilsmeier-Haack reaction\textsuperscript{35-36}, indole Grignard reactions\textsuperscript{37}, and the reaction of 3-indolylzinc chloride\textsuperscript{38} with acyl chlorides.

Vilsmeier-Haack Reaction:

The Vilsmeier-Haack reaction\textsuperscript{39} was first developed in 1927 by Anton Vilsmeier and Albrecht Haack. In this reaction, electron-rich arenes react with substituted amides and
phosphorous oxychloride (POCl$_3$) to produce aryl aldehydes or ketones. Although Shabica$^{35}$ made indole-3-carbaldehyde (62) from indole (1) by the use of mixture of phosphorous oxychloride and dimethylformamide (DMF) in 55% yield, in 1953 Smith$^{36}$ reported a 95.5% yield of this product using an excess of DMF.

Indole Grignard Reaction:

In 1987, Bergman and Venemalm$^{37}$ reported the use of indolylmagnesium salts 63 in the synthesis of 3-acylindoles 61. Indole Grignard reagent 63 reacts with acryloyl chloride to afford 1-(1H-indol-3-yl)-3-methylbut-2-en-1-one 65. Subsequent intramolecular cyclization of 65 in the presence of sodium chloride (NaCl) and AlCl$_3$ afforded 3,3-dimethyl-2,3-dihydrocyclopenta[b]indol-1-(4$H$)-one (66) whereas in the presence of hydrochloric acid (HCl) in
dioxane 65 underwent a retro aldol to afford 3-acetylindole (61).

Zinc Salts of Indole:

Bergman and Venemalm\textsuperscript{38} also discovered a novel method to synthesize α,β-unsaturated 3-acylindoles. In the first step of this protocol, indole (1) reacts with ethylmagnesium bromide (EtMgBr) in ether to form the corresponding indole Grignard reagent to which anhydrous zinc chloride (ZnCl\textsubscript{2}) was added producing the zinc salt of indole 67. In the next step, zinc salt 67 reacts with 3,3-dimethylacryloyl chloride (64) in ether to produce 3-(3,3-dimethylacryloyl)indole (65) in 70\% yield. In this case yields are higher for the products.
Scope, Limitations and Applications of Indole Friedel-Crafts Chemistry:

Another strategy to synthesize 3-acylindoles is to use N-protected indoles as starting materials. One such strategy was developed by Ketcha and Gribble in 1985 in which 1-(phenylsulfonyl)indole derivatives 27 underwent acylation with various acid anhydrides or acid chlorides to form 3-acyl-1-(phenylsulfonyl)indoles 68, which on subsequent alkaline hydrolysis produced 3-acylindoles 69.

This strategy of using the benzenesulfonyl group as protecting group in Friedel-Crafts acylations was employed in a formal total synthesis of ellipticine 40(39). In this approach, 27 underwent Friedel-Crafts acylation with acid chloride 70 in presence of AlCl3 to afford the keto ester 71. By employing the Comins cyclization methodology followed by reaction with lithium bis(trimethylsilyl)amide, 71 was converted into ellipticine quinone 72 which had already been
converted to ellipticine (39).

In 2004 Pal et al.\textsuperscript{41} developed a method to acylate the C-2-position of 3-methylindole (73) with acetyl chloride in presence of ZnCl\textsubscript{2} (1,2-dichloroethane, 25\textdegree{}C, 36 h) to afford 2-acetyl-3-methylindole (74) in 40\% yield.

Alternatively, Gribble and Jiang\textsuperscript{42} synthesized 2-acetyl-3-methyl-1-(phenylsulfonyl)indole (76). In this reaction 1-(phenylsulfonyl)indole (75) was lithiated at the C-2 position followed by inverse quenching with 5-10 equivalents of acetic anhydride to afford 76 in 81\% yield.
In 1996, Merour et al. discovered an unusual acetylation of 2-methyl-1-(phenylsulfonyl)indole (77). They found that 77 is converted into 6-acetyl-3-chloro-2-methylindole (78) and 6-acetyl-3-chloro-2-methyl-1-(phenylsulfonyl)indole (79) on reaction with excess AlCl₃ and acetic anhydride (Ac₂O) rather than producing the expected 3-acetyl-2-methyl-1-(phenylsulfonyl)indole. They cited the reason as involving the likelihood that chlorination at the 3-position is faster than acetylation in the presence of a large excess of AlCl₃.

![Reactivity Diagram]

In order to prove that acetylation had occurred at the 6-position of 77 they synthesized 5-acetyl-3-chloro-2-methylindole (84) and 3-acetyl-5-chloro-2-methylindole (86). In this structure proving synthesis, 2-methylindoline (80) was N-acetylated and subjected to bromination at C-5 before N-deprotection and oxidation of the C-2 to C-3 bond with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford 81. Treating 81 with PhSO₂Cl and NaOH in CH₂Cl₂ in the presence of catalytic amounts of benzyltriethylammonium chloride (C₆H₅)CH₂N(Cl)(C₂H₅)₃ afforded 5-bromo-2-methyl-1-(phenylsulfonyl)indole (82). Stille coupling of 82 in the presence of palladium tetrakis triphenylphosphine (Pd[P(C₆H₅)₃]₄) and ethoxyvinyltributylstannane (CH₂=CH(OEt)Sn(Bu)₃) afforded 5-acetyl-2-methyl-1-(phenylsulfonyl)indole (83). Then, deprotection of 83 in basic media followed by chlorination with N-chlorosuccinimide (NCS) afforded 5-acetyl-3-chloro-2-methylindole (84).
Acetyl-5-chloro-2-methylindole (86) was synthesized starting from 5-chloroindole (85). In this scheme, 85 was N-protected with PhSO₂Cl and then methylated at the C-2 position with LDA and iodomethane (ICH₃). Cleavage of the benzenesulfonyl group (K₂CO₃/CH₃OH) and acetylation at the 3-position using phosphorous oxychloride (POCl₃) in dimethylacetamide (DMA) afforded 3-acetyl-5-chloro-2-methylindole (86). The ¹H NMR spectra and physical data of 5-acetyl-3-chloro-2-methylindole (84) and 3-acetyl-5-chloro-2-methylindole (86) were different to those of 6-acetyl-3-chloro-2-methylindole (78). Therefore, acetylation of 2-methyl-1-(phenylsulfonyl)indole (77) was not forming either 5-acetyl-3-chloro-2-methylindole (84) or 3-acetyl-5-chloro-2-methylindole (86). Also, debenzenesulfonylation of 6-acetyl-3-chloro-2-methyl-1-(phenylsulfonyl)indole (79) resulted in an observed shielding of 0.89 ppm for the H₇ proton in the resulting compound 6-acetyl-3-chloro-2-methylindole (78). Also they mentioned that the chemical shift of the H₇ proton for 6-acetylindole (8.04 ppm) is higher than the chemical shift of the H₇ (7.45) in the 6-chloroindole. Also, NOESY spectrum of 6-acetyl-3-chloro-2-methylindole (78) showed Nuclear Overhauser interactions between C₂H and C₃H and CH₃CO confirming the acetyl group at 6-position in 6-acetyl-3-chloro-2-methyl-1-(phenylsulfonyl)indole (79).
In 2000 Yoshino et al. developed a method for the Friedel-Crafts acylation of indoles with acid chlorides in the presence of dialkylaluminum chlorides. In this method, N-H indoles bearing various functional groups underwent Friedel-Crafts acylation directly at the C-3 position under mild conditions without the need for prior N-protection. The use of AlCl₃ instead of dialkylaluminum chloride resulted in decomposition and undesirable oligomerization of the indoles probably because of the strong Lewis acidity of AlCl₃ and/or liberated HCl. Thus, in this method, N-protected or N-H indoles react with acid chlorides in the presence of either diethylaluminum chloride (Et₂AlCl) or dimethylaluminum chloride (Me₂AlCl) in dichloromethane at 0°C for 2h to produce 3-acylindoles.

In 2010, Bull et al. reported the use of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) as a nucleophilic organocatalyst for the regioselective Friedel-Crafts acylation of pyrroles and indoles. In this method, N-methylindole (89) can be acylated with benzoyl chloride (90) in the presence of 15 mol% of DBN in toluene at 115°C for 4h to afford 3-benzoyl-N-methylindole (91) in 65% yield. In this reaction DBN is acting as a nucleophilic catalyst to activate the acyl chloride toward electrophilic attack. X-ray crystal structure of N-acyl-DBN intermediate confirmed that DBN
functions as a nucleophilic catalyst.

Recently Guchhait et al. used zirconium tetrachloride (ZrCl₄) as a Lewis acid catalyst for the regio- and chemoselective Friedel-Crafts acylation of indole. This method minimized or eliminated the common competing reactions that occur due to Lewis/Bronsted acid conditions. A wide range of aroyl, heteroaryl, alkenoyl, and alkanoyl chlorides undergo smooth acylation to afford 3-acylindoles in good to high yields with various indoles without the need for prior N-H protection. In this method, protected or unprotected indoles undergo Friedel-Crafts acylation with various acyl chlorides in the presence of ZrCl₄ in dichloroethane (DCE) to afford 3-acylindoles.

Metal Triflates in Friedel-Crafts Acylations:

Since stoichiometric amounts of AlCl₃ are required for Friedel-Crafts acylation reactions, this catalyst can be deemed environmentally undesirable due to the fact that it cannot be reused and because it must be converted to aluminum hydroxide Al(OH)₃ before disposal. The use of metal triflates in catalytic amounts for Friedel-Crafts acylation reactions has received considerable interest recently especially since they can be recoverable, reusable, and also only
catalytic amounts are required. Though Friedel-Crafts acylations on benzene and naphthalene derivatives using catalytic amounts of metal triflates have been reported in the literature, it was in 2002 that Kobayashi et al reported the Friedel-Crafts acetylation of 27 with acetic anhydride in the presence of 10 mol% of gallium triflate in nitromethane (CH$_3$NO$_2$) at room temperature (24 h) to afford 95 in 93% yield.

Effect of Lithium Perchlorate (LiClO$_4$) as an Additive:

In 2000 Kobayashi et al found that 2-methoxynaphthalene (96) underwent Friedel-Crafts acylation with acetic anhydride (Ac$_2$O) in nitromethane (CH$_3$NO$_2$) in the presence of lithium perchlorate (LiClO$_4$) and catalytic amounts of antimony triflate Sb(OTf)$_3$ or gallium triflate Ga(OTf)$_3$ at room temperature for 4h to produce 2-acetyl-6-methoxynaphthalene (98), a well-known intermediate for the synthesis of naproxen. This is remarkable since without LiClO$_4$ 1-acetyl-2-methoxynaphthalene (97) was obtained as major isomer.

Routes to 3-Alkyl substituted 1-(Phenylsulfonyl)indoles : (Friedel-Crafts acylation Followed by Reductive Deoxygenation)

In 1989 Gribble and Ketcha developed a method to synthesize 3-alkyl-1-(phenylsulfonyl)indoles 92 by first acylating 99 at the C-3 position in the presence of AlCl$_3$ and
acid anhydrides in CH$_2$Cl$_2$ at room temperature to afford 3-acyl-1-(phenylsulfonyl)indoles 100 and then reductively deoxygenating the resultant 3-acyl derivatives with sodium borohydringe (NaBH$_4$) in trifluoroacetic acid (TFA) to produce the corresponding alkyl derivatives.

Alternatively, 2-alkyl-1-(phenylsulfonyl)indoles 104 were synthesized$^{23}$ by first lithiating C-2 of 27 with LDA and then adding trimethylsilyl chloride to yield the C-2 silyl derivatives 102 which then underwent *ipso* substitution with acid anhydrides to yield 103. Reductively deoxygenating$^{23}$ 103 with borane *tert*-butylamine complex (t-BuNH$_2$BH$_3$) in the presence of AlCl$_3$ in CH$_2$Cl$_2$ then afforded 104.

5-Alkyl-1-(Phenylsulfonyl)indoles:

5-Alkyl-1-(phenylsulfonyl)indoles$^{23}$ 108 can be synthesized by a sequence involving acylating C-5 of 1-(phenylsulfonyl)indoline (105) with acid anhydrides in the presence of AlCl$_3$ to afford 5-acyl-1-(phenylsulfonyl)indolines 106 followed by reductively deoxygenating 106 with NaBH$_4$ in TFA or t-BuNH$_2$BH$_3$ in the presence of AlCl$_3$ in CH$_2$Cl$_2$ to afford 5-alkyl-1-(phenylsulfonyl)indolines 107. Oxidizing the C-2 and C-3 bond of the 2,3-dihydro pyrrole ring of
with manganese acetate Mn(OAc)$_3$ in the presence of acetic acid afforded 108.
RESULTS AND DISCUSSION

As described earlier, there are various methods for effecting the Friedel-Crafts acylation of N-protected or unprotected indoles at the C-3 position. Also, the C-2 acetylation\textsuperscript{41} of 3-methylindole and the unusual acetylation\textsuperscript{43} of 2-methyl-1-(phenylsulfonyl)indole to afford 6-acetyl-3-chloro-2-methyl-1-(phenylsulfonyl)indole were discussed in the section on Friedel-Crafts acylation studies. However, there have been no comprehensive studies regarding the scope and limitations of Friedel-Crafts acylations upon 3-alkyl-1-(phenylsulfonyl)indoles although the C-2 acetylation of 3-methyl-1-(phenylsulfonyl)indole by a lithiation route has been described in the literature.\textsuperscript{44} Therefore, it was decided to investigate the Friedel-Crafts acylation reactions of 3-alkyl-1-(phenylsulfonyl)indoles using a range of acidic promoters such as the traditional catalyst AlCl\textsubscript{3} in dichloromethane, as well as non-stoichiometric catalysts such as metal triflates\textsuperscript{50} in nitromethane (CH\textsubscript{3}NO\textsubscript{2}) and/or acetonitrile (CH\textsubscript{3}CN). Moreover, so as to limit steric effects in this process, 3-methyl-1-(phenylsulfonyl)indole was chosen as the prototypical starting material to ascertain optimized conditions for such Friedel-Crafts acylations using the above mentioned catalysts and solvent systems. Moreover, as very little has been done in the past to establish the structural identity of benzene-ring substituted indoles, this thesis will attempt to detail such assignments throughout.

Synthesis of the Starting Materials:

Synthesis of 1-(Phenylsulfonyl)indole (27):

The synthesis of the starting materials for this study normally commenced from the N-protection of indole (1) using the PTC method of Bergman yielding 1-(phenylsulfonyl)indole
(27). To that end, indole (1) was benzenesulfonylated with PhSO₂Cl in the presence of TBAHS and 50% NaOH dissolved in CH₂Cl₂ at 0°C to room temperature. The melting point of 27 was determined to be 77 °C, which was in good agreement with the literature value (lit51 78-79°C).

The chemical shift values for the ¹H NMR spectrum of 27 (figure 1) compared well with those reported in the literature51. Notably, the C-3 H signal occurs at 6.68 ppm split into a doublet ($J = 3.66$ Hz) by the adjacent C-2 H (7.57 ppm, d, $J = 3.66$ Hz) and vice versa.

Protection of Indole-3-carbaldehyde (62):

Generally, the starting materials for this project were obtained in two steps by a sequence involving an initial C-3 acylation of 1-(phenylsulfonyl)indole (27) followed by reductive deoxygenation to the corresponding alkyl derivatives. However, the preparation of 3-methyl-1-(phenylsulfonyl)indole (110) was achieved by initial protection of indole-3-carbaldehyde (62) with PhSO₂Cl in the presence of TBAHS and NaOH in CH₂Cl₂ at room temperature to yield 1-(phenylsulfonyl)indole-3-carbaldehyde (109). The product was recrystallized from methanol and the melting point was found to be 143-145°C (lit52 mp 157-158°C). Although the melting point of 109 was 12-14 degrees off from the literature value, the GC/MS indicated 100% product purity.
and exhibited a peak corresponding to the expected molecular weight at \( m/z \) 285.

![Chemical Structure](image.png)

1. NaOH, TBAHS, CH\(_2\)Cl\(_2\), rt
2. PhSO\(_2\)Cl, 80%

The reductive deoxygenation of 1-(phenylsulfonyl)indole-3-carbaldehyde (109) to 3-methyl-1-(phenylsulfonyl)indole (110) was achieved using borane tert-butylamine complex (t-BuNH\(_2\)BH\(_3\)) in the presence of aluminum chloride (DCM) and the product was recrystallized from methanol. Although GC/MS indicated 100% purity and the spectrum exhibited a peak corresponding to the expected molecular weight at \( m/z \) 273, the melting point was found to be 101\(^\circ\)C (lit\(^53\) 114-121\(^\circ\)C).

The \(^1\)H NMR spectrum of 110 (figure 4) displays a somewhat unusual doublet (\( J = 1.17 \) Hz) at 2.27 ppm which corresponds to an apparent splitting of the \( CH_3 \) group into a doublet, attributable to long range coupling with the proton at the C-2 position. Interestingly, this same splitting was also reported by Baxter et al\(^53\) at 2.25 ppm (3H, d, \( J = 1.20 \) Hz) which must be attributable to the Me group at C-3 although they did not assign peaks.

Using the established method\(^40\), 27 was acetylated at the C-3 position using Ac\(_2\)O in the presence of AlCl\(_3\) in CH\(_2\)Cl\(_2\) at room temperature to afford 3-acetyl-1-(phenylsulfonyl)indole (95). The melting point of 95 was found to be 150-151\(^\circ\)C (lit\(^50\) mp 159-160\(^\circ\)C). Although the melting point of 95 was 9-10 degrees off from the literature value, the NMR spectrum of 95 was found to be in good agreement with the literature spectrum.\(^50\)
The $^1$H NMR spectrum of 95 (figure 7) was also in good agreement with the literature spectrum$^{50}$. The C-2 H peak appears as a singlet at 8.23 ppm, the methyl (-COCH$_3$, 3H) appears as a singlet at 2.59, and the C-4 H appears as a multiplet from 8.33-8.36 (m, 1H).

Using the established method$^{23}$, 95 was reductively deoxygenated to 3-ethyl-1-(phenylsulfonyl)indole (111) using $t$-BuNH$_2$BH$_3$ in the presence of AlCl$_3$ in CH$_2$Cl$_2$ at room temperature. The melting point of 111 was found to be 108-110°C (lit$^{54}$ mp 121-122°C). Although the melting point of 111 was 10-11 degrees off from the literature value, the NMR spectrum of 111 was found to be in good agreement with the literature spectrum$^{54}$. The C-3-methyl group appears at 1.33 ppm (t, $J$ =7.4 Hz) and the methylene (-CH$_2$CH$_3$, C-3, 2H) appears at 2.70 ppm (q, $J$ = 1.2 Hz).

Friedel-Crafts Acetylation of 3-Methyl-1-(phenylsulfonyl)indole (110):
Using the established method\textsuperscript{40}, \textbf{110} was treated with Ac\textsubscript{2}O (3eq) in the presence of AlCl\textsubscript{3} (6eq) in CH\textsubscript{2}Cl\textsubscript{2} at room temperature to afford a mixture of isomers in 60\% combined yield. GC/MS indicated 92:8 ratio of major to minor isomers. The melting point of the major isomer \textbf{112} and the minor isomer \textbf{113} were found to be 160-162°C and 178°C respectively. Neither of these values are in agreement with the literature melting point of 2-acetyl-3-methyl-1-(phenylsulfonyl)indole\textsuperscript{42} (76) (mp\textsuperscript{42} 115-117°C).

The \textsuperscript{13}C NMR and \textsuperscript{13}C DEPT NMR spectra of major isomer \textbf{112} & \textbf{113} were provided in \textbf{Figure 14, Figure 15, Figure 17 and Figure 18} respectively.

Also, the \textsuperscript{13}C NMR spectra of \textbf{112} and \textbf{113} were not in good agreement with the literature spectra given for 2-acetyl-3-methyl-1-(phenylsulfonyl)indole\textsuperscript{42} (76). In addition to this, the doublet (2.26, $J = 1.17$ Hz) for CH\textsubscript{3} (C-3) of \textbf{110} was retained in the products \textbf{112} and \textbf{113} indicating the presence of the C-2 H. Therefore, it was concluded that the acetylation of \textbf{110} was not taking place at the C-2 position of 3-methyl-1-(phenylsulfonyl)indole (\textbf{110}) but rather on the benzene ring (C-4 or C-5 or C-6 or C-7 positions).

Since the possible benzene ring acetylated products (namely, 4-acetyl-3-methyl-1-(phenylsulfonyl)indole, 5-acetyl-3-methyl-1-(phenylsulfonyl)indole, 6-acetyl-3-methyl-1-(phenylsulfonyl)indole, and 7-acetyl-3-methyl-1-(phenylsulfonyl)indole) were not reported in the literature, deprotection of the major isomer \textbf{112} was conducted in the presence of potassium hydroxide in aqueous methanol under reflux conditions to yield the corresponding deprotected isomer 6-acetyl-3-methylindole (\textbf{114}) in 88\%.
The obtained melting point of 114 was found to be 153-155°C which is not in good agreement with the reported values for 4-acetyl-3-methylindole (mp^{55} 119-120°C), 2-acetyl-3-methylindole (mp^{41} 147-148°C), or 5-acetyl-3-methylindole (mp^{56} 129-130°C).

The $^1$H NMR spectrum of 114 is shown in figure 19. The CH$_3$ (C-3) appears as a singlet at 2.36 ppm, CH$_3$ (-COCH$_3$) appeared as a singlet at 2.68 ppm, the N-H proton appeared as broad singlet at 8.53 ppm, C-2 H appeared as a singlet at 7.18 ppm, C-7 H appeared as singlet at 8.06 ppm, C-5 H was split by C-4 H as a doublet at 7.76 ppm with a coupling constant ($J$) value of 8.25 Hz, C-4 H was split by C-5 H as a doublet at 7.61 ppm with a coupling constant ($J$) value of 8.19 Hz respectively. Acetylation wasn’t happening at C-7 position since the peak for the C-7 carbon (114.2 ppm) of 112 is retained although with slight shielding 114 (112.1 ppm). Therefore it was concluded that the major isomer 112 is 6-acetyl-3-methyl-1-(phenylsulfonyl)indole. Deprotection of the minor isomer was not conducted due to its scarcity. Also, the C-7 carbon exhibited a chemical shift of 113.4 in the minor isomer (113) means C-7 acetylation wasn’t happening.

Screening of Metal Triflates for Friedel-Crafts Acylation of 3-Methyl-1-(phenylsulfonyl)indole:

Inspired by the work of Kobayashi et al\textsuperscript{50} on the Friedel-Crafts acylation of 1-(phenylsulfonyl)indole (27) in the presence of gallium triflate [Ga(OTf)$_3$] (nitromethane, rt) to afford 3-acetyl-1-(phenylsulfonyl)indole (95), It was decided to screen other metal triflates for the Friedel-Crafts acylation reaction of 3-methyl-1-(phenylsulfonyl)indole (110) using the same reaction conditions and monitoring with GC-MS. Thus, on a 0.2 g scale, the starting material 3-methyl-1-(phenylsulfonyl)indole (110) was treated with 10 mol\% of various metal triflates in CH$_3$NO$_2$ or CH$_3$CN at room temperature for 23 h to afford 2-acetyl-3-methyl-1-(phenylsulfonyl)indole (76).
As shown in Table (1), bismuth triflate [Bi(OTf)$_3$] was found to most effectively catalyze the reaction among the five metal triflates screened. It can also be seen that yttrium triflate [Yt(OTf)$_3$] and ytterbium triflate [Yb(OTf)$_3$] were not catalyzing the reaction in CH$_3$NO$_2$ although Yt(OTf)$_3$ gave 7% reaction conversion in CH$_3$CN. Scandium triflate [Sc(OTf)$_3$] gave 16% and 22% reaction conversion in CH$_3$NO$_2$ and CH$_3$CN, respectively, whereas indium triflate [In(OTf)$_3$] gave 29% and 27% reaction and Bi(OTf)$_3$ gave 94 and 97% conversion. Isolation of the product obtained from the bismuth triflate reaction by column chromatography (50:50 hexane: CH$_2$Cl$_2$) followed by recrystallization from MeOH yielded a semi solid compound 0.142 g (72%) of 2-acetyl-3-methyl-1-(phenylsulfonyl)indole (76).

<table>
<thead>
<tr>
<th>M(OTf)$_3$</th>
<th>CH$_3$NO$_2$</th>
<th>CH$_3$CN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% conversion</td>
<td>% conversion</td>
</tr>
<tr>
<td>Bi(OTf)$_3$</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>In(OTf)$_3$</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Sc(OTf)$_3$</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Yt(OTf)$_3$</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Yb(OTf)$_3$</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1: $^a$ determined by GC/MS

In order to unambiguously establish that acetylation was occurring at the C-2 position, deprotection of 76 was pursued. To that end, 2-acetyl-1-(phenylsulfonyl)indole was heated to reflux with KOH in MeOH and H$_2$O to afford 2-acetyl-3-methylindole (74) in 74% conversion. The melting point of 74 was found to be 143$^0$C, which is close to the literature value (m.p $^{41}$ 147-148$^0$C). The $^1$H NMR spectrum was given in Figure 25. The N-H proton appears as a broad
singlet at 9.1 ppm. The H-4 proton appears as doublet \((J = 8.07 \text{ Hz})\) at 7.71 ppm, H-7 & H-6 appear as multiplets at 7.38 ppm, while the H-5 proton appears as a multiplet from 7.19 – 7.13 ppm. The methyl (CH\(_3\), C-3) and methyl (-COCH\(_3\)) appeared at 2.66 ppm respectively.

Friedel-Crafts Acylation on 27 with Propionic Anhydride:

In order to determine the generality of the Friedel-Crafts acylation of 3-alkyl derivatives with various anhydrides in the presence of AlCl\(_3\), propionic anhydride\(^{40}\) was chosen as the acylating agent against 27. When 27 was allowed to react with propionic anhydride in the presence of AlCl\(_3\) (DCM, rt) a mixture of isomers was obtained in the ratio of 92:8 (GC/MS), both exhibiting molecular ions at \(m/z\) 327. The major isomer, assigned the structure of 115 was isolated and found to have a melting point of 150-152\(^{0}\)C and is unknown in the literature.

The \(^1\)H NMR spectrum of major isomer 115 is given in Figure 28. The methyl group of the propionyl group (-COCH\(_2\)CH\(_3\)) occurs as a triplet at 1.27 ppm \((J = 7.23 \text{ Hz})\). The methylene protons (-COCH\(_2\)CH\(_3\)), appears as a quartet at 3.1 ppm \((J = 7.23 \text{ Hz})\). The C-3 methyl group appears as doublet \((J = 1.17 \text{ Hz})\) at 2.27 ppm. The C-2 H appears as a singlet at 7.51 ppm. The C-7 H appears as a doublet at 8.61 ppm \((J = 0.81 \text{ Hz})\) split by the C-5 H. There is also observed a 3 H multiplet at 7.91-7.86 ppm, a 1H multiplet from 7.57-7.53, 2 H multiplet from 7.49–7.42 ppm and one proton multiplet from 7.45-7.41 ppm respectively.
Friedel-Crafts Acylation of 3-Ethyl-1-(phenylsulfonyl)indole (111):

To also demonstrate the generality of this process in regards to 3-alkyl substituents, 3-ethyl-1-(phenylsulfonyl)indole (111) was allowed to react with Ac₂O in the presence of AlCl₃ (DCM/rt) producing a mixture of isomers in 92:8 ratio (GC/MS) both exhibiting molecular ions at m/z 327. The major isomer 117 was separated and the melting point of it was found to be 125-129°C and is an unknown compound in the literature.

The ¹H NMR spectrum of the major isomer 117 is given in Figure 31. The methyl protons (-CH₂CH₃) of the group at C-3 appear as a triplet at 1.33 ppm (J = 7.47 Hz). Similarly, the methylene protons (-CH₂CH₃) appear as a quartet at 2.72 ppm (J = 7.5 Hz). The methyl protons (-COCH₂CH₃) of the acetyl group at C-6 appear as a singlet at 2.69 ppm. The signal for the C-7 H, present at 8.60 ppm (J = 0.93 Hz), is split into a doublet by C-5 H. The C-2 H appears as a singlet at 7.56 ppm. 3 H appeared as multiplet from 7.92-7.86 ppm, one hydrogen appeared as multiplet from 7.54-7.53 ppm, two H’s appears as multiplet at 7.49 ppm, and one H appears as multiplet from 7.47-7.43 ppm respectively.

In conclusion, acylation of 3-methyl-1-(phenylsulfonyl)indole (110) and 3-ethyl-1-(phenylsulfonyl)indole (111) with acetic anhydride and propionic anhydride in the presence of aluminum chloride occurs at the C-6 position (major isomer) and the C-5 position (minor isomer). But in the presence of bismuth triflate, C-2 acylation is found to occur with complete regioselectivity. This conclusion was well supported by ¹H NMR and ¹³C NMR analysis of starting materials and products.
NMR ANALYSIS

Perhaps due to the fact that direct functionalization of the benzene ring of indoles is normally precluded, there has yet to be a definitive study of the NMR spectra of this heterocycle. Thus, the structural assignments of the molecules produced in this study must be derived from first principles using a combination of data from the literature (where available), data from this study, as well as ChemDraw calculations. A comparison of the literature $^{13}$C NMR chemical shift values for indole$^2$ with those obtained from ChemDraw allow for a facile assignment of the chemical shifts obtained on the WSU instrument. The $^{13}$C NMR (CDCl$_3$) chemical shifts for indole (1) occur at 135.9, 127.9, 124.3, 122.0, 120.8, 119.9, 111.2 and 102.6 ppm while the $^{13}$C dept NMR indicated that the peaks at 135.9 and 127.9 corresponded to C-7a and C-3a respectively. An inspection of the assignments below indicates that the most upfield shift should be assigned to C-3, which is expected as the reactivity of this site can be ascribed to a high degree of electron density (shielding). Interestingly, the C-7 carbon is the next most upfield shifted site, and C-2 in the electron-rich heterocyclic ring occurs at 124 ppm, more downfield than C4-C7 of the benzenoid ring.

![Chemical Structures](image)

Having established a baseline for the indole ring carbons, progression to N-phenylsulfonyl substituted indoles requires an inspection of the signals attributable to the protecting group. The $^{13}$C NMR chemical shift values of benzenesulfonyl chloride$^{57}$ were
assigned based on literature and Chem Draw values and the observed spectrum (CDCl$_3$) which exhibits $^{13}$C NMR chemical shifts at 144.4, 135.4, 129.8 and 127.0 ppm. Once again, the strong correlation of literature values with those obtained from ChemDraw allows for a reliable assignment of the carbons of this ring, with the expectation that these values will likely be rather invariant amongst indole derivatives as the sulfonyl group will likely insulate these carbons but a slight variation might appear in comparing alkyl- versus acyl-substituted indoles.

Unfortunately, upon combining the two components, the ChemDraw program apparently fails and its usefulness from this point is questionable. As seen below, upon introduction of the N-phenylsulfonyl group the ChemDraw program depicts the C-2 site as the site of greatest electron density (108.9 ppm), which is inconsistent with the site of reactivity C-3. The observed $^{13}$C (CDCl$_3$) NMR of 1-(phenylsulfonyl)Indole exhibited shifts at 138.3, 134.9, 133.8, 130.7, 129.2, 126.7, 126.3, 124.6, 123.4, 121.4, 113.5, and 109.2 ppm and the $^{13}$C dept NMR suggest that the peaks at 138.3, 134.9, and 130.7 corresponds to ipso-C, C-7a and C-3a, respectively. The assignment of 133.8 ($p$-C), 129.2 (m-C), and 126.7 ($o$-C) is based on Chem Draw and as will detailed later, those peaks remain relatively constant even in 3-methyl-1-(phenylsulfonyl)indole and 3-ethyl-1-(phenylsulfonyl)indole. As will be seen as the arguments progress, substitution of one ring often has little or no effect on the alternate ring. Given that assumption, a reliable assignment of 6-methyl-1-(phenylsulfonyl)indole was reported by Wenkert$^{58}$ and used to aid in the assignment of the $^{13}$C NMR chemical shift values for 1-(phenylsulfonyl)indole.
First, in the ChemDraw calculation for 1-(phenylsulfonyl)indole, it is noted that the two most upfield shifts are assigned to the C-2 and C-3 positions, respectively. Comparison with the 6-methyl derivative suggests that the most upfield shift (109.2 ppm) is more appropriately assigned to the C-3 position, and the next upfield shift is assigned to C-7 (113.5 ppm), which is consistent with the N-unsubstituted case described earlier. Following along, the best correlations involve assigning 126.3 ppm to the C-2 position and 121.4 ppm to the C-4 position. This also firmly establishes the assignments for C-3 and C-2, and indicates that C-7 and C-4 will tend to be upfield of the other benzene ring carbons. Also the following shifts were tentatively assigned based on analogy to the 6-methyl derivative: 124.6 (C-5), 121.4 (C-4), 113.5 (C-7) and 109.2 (C-3).

![Chem Draw (27)](image1)

1-(Benzenesulfonyl)indole (27)

6-Methyl-1-(benzenesulfonyl)indole

Having reliably assigned the carbon shifts for 1-(phenylsulfonyl)indole (27), extension by analogy to the case of the $^{13}$C NMR chemical shift values of 3-methyl-1-(phenylsulfonyl)indole (110) could be attempted. With respect to the parent compound 27, upon alkylation of the C-3 carbon with a methyl group, the C-3 site was observed to be deshielded from 109.2 to 118.8. Alternatively, C-2 is shielded from 126.3 to 123.1 while C-4 was shielded from 121.4 to 119.4. Interestingly, this alkyl substituent induces slight deshielding of C-7a from 134.8 to 135.3 and C-3a from 130.7 to 131.8.
The $^{13}$C NMR chemical shift values of 3-ethyl-1-(phenylsulfonyl)indole (111) can then be assigned similarly, wherein C-3 was deshielded from 109.2 (NBSI) to 125.4 and C-2 was shielded from 126.3 to 123.0, C-4 is shielded from 121.4 to 119.5, C-7a deshielded from 134.8 to 135.5 and C-3a deshielded from 130.7 to 131.1.

Upon acetylation of 3-methyl-1-(phenylsulfonyl)indole (110) at the C-6 position, the C-6 was observed to be deshielded from 123.0 to either 134.9 or 133.9 (both quaternary). It would also appear that the adjacent carbons were slightly deshielded: C-5 from 124.7 to 126.3, and C-7 from 113.7 to 114.2. It also appears as if the carbons meta to the newly introduced acyl substituent remain unchanged.

On debenzenesulfonylation of 6-acetyl-3-methyl-1-(phenylsulfonyl)indole (112) to afford 6-acetyl-3-methylindole (114), this N-unsubstituted indole exhibited $^{13}$C NMR chemical shifts at 198.7, 135.7, 132.0, 131.3, 125.9, 119.5, 118.4, 112.1, 26.8 and 9.5 ppm. The peaks at 135.7,
132.0, and 131.3 correspond to quaternary carbons C-7a, C-3a/C-6 and C-6/C-3a, respectively although the peak for C-3 was not observed. There is substantial ambiguity in assigning peaks for C-7, C-5, C-4 and C-2 respectively. Taking into consideration the ChemDraw assignments as well as the N-protected precursor, the best assignment would be C-7 112.1, C-5 125.9, C-4/C-2 (119.5/118.4).

The $^1$H NMR spectrum of 6-acetyl-3-methylindole exhibited peaks at 8.53 (br s, N-H), 8.06 (s, C-7 H), 7.7 (d, 8.25 Hz, C-5 H), 7.62 (d, 8.1, C-4 H), 7.19 (s, C-2 H), 2.68 (s, 3H, -COCH$_3$), and 2.36 (s, 3H, CH$_3$, C-3) respectively. The ChemDraw simulation is shown below, wherein it is observed that there is rather good correlation, and it is likely that the C-7 H singlet occurs at the most upfield position rather than at 8.06 ppm.

![Chem Draw (114)](image)

On propionylation of 3-methyl-1-(phenylsulfonyl)indole at C-6 position, C-6 is deshielded from 123.0 to 134.9/133.6. C-5 is also deshielded from 124.7 to 126.2 although C-4, C-7 and Carbon atoms retains more or less the same as that of the 3-methyl starting material.

![115](image)
On acetylation of 3-ethyl-1-(phenylsulfonyl)indole (111) at C-6, C-6 was deshielded from 122.0 to 134.7/133.9. As observed for the 3-methyl analog, C-5 was also deshielded from 124.6 to 125.3, C-7 deshielded from 113.7 to 114.3, although C-4 and all other carbon atoms retain more or less the same chemical shifts as that of 3-ethyl-1-(phenylsulfonyl)indole.

As described earlier, in the presence of Bi(OTf)$_3$, acetylation occurs at the C-2 position of 3-methyl-1-(phenylsulfonyl)indole (110). The product, 2-acetyl-3-methyl-1-(phenylsulfonyl)indole (76) is a known compound and the shifts from the literature are given in parentheses. This molecule exhibits $^{13}$C NMR peaks at 195.5 (195.8), 137.4 (137.6), 136.7 (136.9), 135.2 (135.4), 133.8 (134.1), 13.8 (132.1), 128.6 (128.9), 127.5 (127.8), 127.1 (127.4), 127.0 (missing), 124.9 (125.2), 120.8 (121.1), 116.2 (116.5), 32.0 (32.4) and 9.4 (9.7) ppm. According to $^{13}$C dept NMR the quaternary carbon atoms are assigned as follows: ipso-C (137.4), C-7a (136.7), C-3a (135.2/131.8), C-2 (135.2/135.8), and C-3 (127.0). The peaks for the p-C, m-C, and o-C of the benzenesulfonfonyl ring exhibit chemical shifts at 133.8, 128.6 and 127.1, respectively. Since the acetyl group withdraws electron density from nitrogen atom by resonance, chemical shifts for C-5, C-6, C-4 and C-7 increased from 124.7 to 127.5, 123.0 to 124.9, 119.4 to 120.8, and 113.7 to 116.2 respectively.
On debenzenesulfonylation of 2-acetyl-3-methyl-1-(phenylsulfonyl)indole to 2-acetyl-3-methylindole the resulting product exhibits $^{13}$C NMR peaks at 190.4 (190.4$^{41}$), 136.0 (136.0), 132.6 (132.6), 128.7 (128.9), 126.4 (126.4), 121.1 (121.2), 119.9 (120.0), 118.7 (118.7), 111.8 (111.8), 28.9 (29.0) and 11.0 (11.0) respectively and also exactly matching with the literature$^{41}$ chemical shifts given in parenthesis. Therefore acetylation at C-2 is confirmed. According to $^{13}$C dept NMR, quaternary carbon atoms C-7a, C-3a, C-3 and C-2 were assigned peaks at 136.0, 132.6/128.9, 118.7 and 132.6/128.9 respectively. C-5, C-4, C-6 and C-7 were assigned chemical shifts of 126.4, 121.1/119.9, 119.9/121.1 and 111.8 respectively.

The $^1$H NMR spectrum of 2-acetyl-3-methylindole exhibits NH peak at 9.1 (br s, N-H), 7.71 (d, 8.0 Hz, C-4 H), 7.38 (m, 2H), 7.19-7.13 (m, 1H), 2.66 (s, 3H, COCH$_3$) and 2.66 (s, 3H, CH$_3$, C-3).
Experimental

Synthesis of 1-(Phenylsulfonyl)indole\textsuperscript{44} (27):

To a suspension of indole (1) (5.0 g, 43 mmol), 50 % NaOH (40 mL) and TBAHS (0.15 g, 0.43 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (80 mL) at 0°C was added benzenesulfonyl chloride (5.5 mL, 43 mmol) dropwise for 1 h and stirring was continued overnight and the reaction mixture was then poured into water. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 25 mL) and the combined organic layers were washed with water, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. Recrystallization of the resulting solid from MeOH afforded pure 27 (7.5 g, 70 %); mp 77 °C (lit\textsuperscript{44} mp: 77.5-79 °C); $R_f = 0.70$ (CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 6.67 (d, $J = 3.66$, 1H, H\textsubscript{3}), 7.20-7.35 (m, 2H), 7.38-7.45 (m, 2H), 7.48-7.55 (m, 2H), 7.57 (d, $J = 3.66$ Hz, 1H, H\textsubscript{2}), 7.86-7.91 (m, 2H), 8.01 (d, $J = 8.31$, 1H, H\textsubscript{7}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 109.2, 113.5, 121.4, 123.3, 124.6, 126.3, 126.7, 129.2, 130.7, 133.7, 134.8, 138.2; MS m/z (% base) 257 (M\textsuperscript{+}, 100); Anal. Calcd for C\textsubscript{14}H\textsubscript{11}NO\textsubscript{2}S: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.16; H, 4.90; N, 4.49

Synthesis of 1-(Phenylsulfonyl)indole-3-carboxaldehyde\textsuperscript{109} (109):

To a suspension of indole-3-carboxaldehyde (62) (4.0 g, 27 mmol), NaOH pellets (3.3 g, 24 mmol) and TBAHS (0.37 g, 1.07 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (34 mL), benzenesulfonyl chloride (4.1 mL, 32 mmol) dissolved in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) was added dropwise and stirring was continued for 10 h at room temperature. After TLC indicated disappearance of starting material, the reaction mixture was poured into water (100 mL) and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 30 mL). The combined organic layers were washed with water, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. Recrystallization of the resulting solid from MeOH afforded pure 109 (6.30 g, 80 %); mp
143-145 °C (lit42 mp 158-158.8 °C); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.46 (m, 2H), 7.50-7.56 (m, 2H), 7.60-7.66 (tt, 1H), 7.97-8.01 (m, 3H), 8.26-8.30 (m, 1H), 10.1 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 113.2, 122.5, 122.6, 125.1, 126.3, 126.4, 127.1, 129.7, 134.7, 135.2, 136.1, 137.4, 185.2; MS m/z (% base) 285 (M⁺, 100); Anal. Calcd for C\(_{15}\)H\(_{11}\)NO\(_3\)S: C, 63.14; H, 3.89; N, 4.91

3-Methyl-1-(phenylsulfonyl)indole (110):

To a magnetically stirred solution\(^{24}\) of AlCl\(_3\) (33.0 g, 242 mmol) and t-BuNH\(_2\)BH\(_3\) (42.0 g, 484 mmol) in CH\(_2\)Cl\(_2\) (416 mL) was added a solution of 1-(phenylsulfonyl)indole-3-carboxaldehyde (109) (23.0 g, 80 mmol) dissolved in CH\(_2\)Cl\(_2\) (100 mL) and the mixture was allowed to stir overnight. After TLC indicated disappearance of starting material, the reaction mixture was poured over ice and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 30 mL). The combined organic layers were washed with 3M HCl (3 x 30 mL), saturated aqueous NaHCO\(_3\) (3 x 30 mL), and brine (3 x 30 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product subjected to flash chromatography using hexanes-CH\(_2\)Cl\(_2\) (70:30) to afford pure 110 (18.0 g, 71%); mp 101°C (lit\(^{20}\) mp 117-118.5°C); \(R_f = 0.62\) (CH\(_2\)Cl\(_2\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.26 (d, \(J = 1.17\) Hz, 3H, CH\(_3\)), 7.24-7.33 (m, 1H, H\(_{arom}\)), 7.34 (s, 1H, H\(_2\)), 7.36-7.55 (m, 5H, H\(_{arom}\)), 7.86-7.91 (m, 2H, H\(_6\) & H\(_5\)), 8.02 (d, \(J = 8.19\) Hz, 1H, H\(_7\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.6, 113.6, 118.8, 119.4, 123.0, 123.0, 124.6, 126.6, 129.1, 131.8, 133.5, 135.3, 138.4; MS m/z (% base) 271 (M⁺, 18), 130 (100).

3-Acetyl-1-(phenylsulfonyl)indole\(^{31}\) (95):

Acetic anhydride (13 mL, 137 mmol) was added to a magnetically stirred suspension of AlCl\(_3\) (37.0 g, 273.6 mmol) in CH\(_2\)Cl\(_2\) (100 mL) and stirred at rt for 15 min followed by the drop wise addition of 1-(phenylsulfonyl)indole (27) (11.68 g, 45.6 mmol) and the mixture was stirred for 3 h. After TLC indicated disappearance of starting material, the reaction mixture was poured over
ice and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were washed with 3M HCl (3 x 30 mL), saturated aqueous NaHCO$_3$ (3 x 30 mL), and brine (3 x 30 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Recrystallization from MeOH afforded pure 95 (9.5 g, 70%); mp 150-151 °C (lit$^{31}$ mp 159-160 °C); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.59 (s, 3H), 7.33-7.43 (m, 2H), 7.48-7.55 (m, 2H), 7.58-7.65 (tt, 1H), 7.93-7.99 (m, 3H), 8.24 (s, 1H), 8.31 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 27.7, 113.0, 121.8, 123.1, 124.9, 125.8, 127.0, 127.5, 129.6, 132.1, 134.5, 134.9, 137.6, 193.3; MS m/z (% base) 299 (M$^+$, 24), 77 (100); Anal. Calcd for C$_{16}$H$_{13}$NO$_3$S: C, 64.20; H, 4.38; N, 4.68. Found: C, 63.95; H, 4.38; N, 4.70

3-Ethyl-1-(phenylsulfonyle)Indole$^{20}$ (111):

To a magnetically stirred solution of AlCl$_3$ (12.2 g, 91 mmol) and t-BuNH$_2$BH$_3$ (42.0 g, 484 mmol) in CH$_2$Cl$_2$ (150 mL) was added a solution of 95 (9.1 g, 30 mmol) dissolved in CH$_2$Cl$_2$ (50 mL) and the mixture was allowed to stir overnight. After TLC indicated disappearance of starting material, the reaction mixture was poured over ice and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were washed with 3M HCl (3 x 30 mL), saturated aqueous NaHCO$_3$ (3 x 30 mL), and brine (3 x 30 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Recrystallization from MeOH afforded 111 (6.07 g, 70%); mp 108-110°C (lit$^{20}$ mp 118-119 °C); $R_f$ = 0.67 (CH$_2$Cl$_2$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.32 (t, $J = 7.47$, 3H), 2.70 (q, $J = 1.23$, 2H), 7.22-7.36 (m, 3H), 7.39-7.47 (m, 2H), 7.48-7.56 (m, 2H), 7.86-7.91 (m, 2H), 8.03 (d, $J = 8.22$, 1H, H$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 13.23, 18.16, 113.75, 119.48, 121.99, 123.03, 124.65, 125.47, 126.67, 129.15, 131.08, 133.56, 135.47, 138.43; Anal. Calcd for C$_{16}$H$_{15}$NO$_3$S: C, 67.34; H, 5.30; N, 4.91

6-Acetyl-3-methyl-1-(phenylsulfonyle)indole (112) and 5-acetyl-3-methyl-1-(phenylsulfonyle)indole 113:
Acetic anhydride (2.09 mL, 22.11 mmol) was added dropwise to a magnetically stirred suspension of AlCl₃ (5.9 g, 44.22 mmol) in CH₂Cl₂ (74 mL) and the mixture was allowed to stir for 15 min followed by the dropwise addition of 111 (2.0 g, 7.37 mmol). The resulting mixture was then stirred for an additional 3 h and quenched with ice. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (3 x 30 mL), and brine (3 x 30 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford a mixture of acylated products (112:113) in a ratio of 92:8 by GC-MS. Recrystallization from MeOH afforded 0.64 g of major isomer 112 and 0.06 g of the minor isomer 113 and 1.0 g of an inseparable mixture of both (total yield 1.7 g, 71%). TLC shown major isomer 112 was not fluorescent while the minor isomer 113 as fluorescent.

6-Acetyl-3-methyl-1-(phenylsulfonyl)indole (112): mp 160-162°C; Rf = 0.19 (CH₂Cl₂); (¹H NMR (300 MHz, CDCl₃) δ 2.27 (d, J = 1.2 Hz, CH₃), 2.69 (s, 3H, -COCH₃), 7.42-7.49 (m, 4H, Hₐrom), 7.52 (s, 1H, H₂), 7.54-7.58 (m, 1H, Hₐrom), 7.86 (d, J = 1.47, 1H, H₄ or H₅), 7.88 (d, J = 1.47 Hz, 1H, H₃ or H₄), 8.6 (br s, 1H, H₇); ¹³C NMR (100 MHz, CDCl₃) δ 9.6, 26.8, 114.2, 118.6, 123.1, 126.3, 126.7, 129.4, 133.9, 133.9, 134.9, 135.4, 138.1, 197.6; MS m/z (% base) 313 (M⁺, 100); Anal. Calcd for C₁₇H₁₅NO₃S: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.16; H, 4.90; N, 4.49

Minor Isomer 113: mp 178°C; Rf = 0.19 (CH₂Cl₂); (¹H NMR (300 MHz, CDCl₃) δ 2.30 (d, J = 1.17 Hz, 3H), 2.66 (s, 3H), 7.38-7.49 (m, 3H), 7.52-7.59 (tt, 1H), 7.86-7.91 (m, 2H), 7.96 (dd, J = 1.56 Hz, 8.73 Hz, 1H), 8.05 (d, J = 8.7, 1H), 8.11 (d, J = 1.02 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 9.6, 26.7, 113.4, 119.3, 120.5, 124.3, 124.5, 126.7, 129.3, 131.7, 132.6, 134.0, 137.8, 138.1, 197.6; Anal. Calcd for C₁₇H₁₅NO₃S: C, 65.16; H, 4.82; N, 4.47; MS m/z (% base) 313 (M⁺, 100); Anal. Calcd for C₁₇H₁₅NO₃S: C, 65.16; H, 4.82; N, 4.47.
6-Acetyl-3-methyl-1-(phenylsulfonyl)indole (112) (0.5 g, 1.6 mmol) and KOH (0.23 g, 4 mmol) were dissolved in aqueous MeOH (25 mL) and the mixture was refluxed for 2 h. After TLC indicated disappearance of starting material, the solution was extracted with CH₂Cl₂ (3 x 20 mL) and the organic extracts washed with brine (3 x 25 mL), dried over Na₂SO₄ and evaporated in vacuo. Purification by column chromatography (CH₂Cl₂: Hexane 50:50) afforded 6-acetyl-3-methylindole (114) (0.22 g, 80%) as a light yellow solid; mp 153-155°C; Rf = 0.097 (CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 2.36 (s, 3H, CH₃), 2.68 (s, 3H, -COCH₃), 7.18 (s, 1H, H₂), 7.18 (s, 1H, H₂), 7.61 (d, J = 8.19 Hz, 1H, H₄), 7.76 (d, J = 8.25, 1H, H₅), 8.06 (s, 1H, H₇), 8.53 (br s, NH); ¹³C NMR (100 MHz, CDCl₃) δ 9.5, 26.8, 112.0, 112.1, 118.4, 119.5, 125.9, 131.2, 132.0, 135.7, 198.7; MS m/z (% base) 173 (M⁺, 58), 158 (100); Anal. Calcd for C₁₁H₁₁NO: C, 76.28, H, 6.40, N, 8.09

2-Acetyl-3-methyl-1-(phenylsulfonyl)indole (76):

3-Methyl-1-(phenylsulfonyl)indole (110) (0.21 g, 0.77 mmol), Ac₂O (0.22 mL, 2.31 mmol), Bi(OTf)₃ (0.05 g, 0.077 mmol) were dissolved in CH₃NO₂ (1.8 mL) and stirred for 24 h at rt. After TLC demonstrated near completeness of reaction (GC/MS indicated the 8% of the starting material left unreacted) the mixture was evaporated and the residue subjected to column chromatography (Hexane/CH₂Cl₂: 40:60) to provide 77 (0.142 g, 60 %) as a yellow viscous semi solid; Rf = 0.12 (CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.99-7.95 (d, J = 8.25 Hz, H-7), 7.54-7.50 (m, 2H, H-4 & H-6), 7.37-7.29 (m, 3H), 7.24-7.17 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 9.4, 32.0, 116.2, 120.8, 124.9, 127.0, 127.1, 127.5, 128.6, 131.8, 133.8, 135.2, 136.7, 137.4, 195.4; MS m/z (% base) 313 (M⁺, 48), 172 (100); Anal. Calcd for C₁₇H₁₃NO₃S: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.24; H, 4.88; N, 4.43

2-Acetyl-3-methylindole (74):
2-Acetyl-3-methyl-1-(phenylsulfonyl)indole (76) (0.71 g, 2.27 mmol) and KOH (0.31 g, 5.6 mmol) were dissolved in aqueous MeOH (35 mL) and refluxed for 2 h. The aqueous layer was extracted with CH₂Cl₂ and the organic extracts washed with brine (3 x 25 mL), dried over Na₂SO₄ and evaporated in vacuo to give 74 as a white solid of (0.28 g, 72 %); mp 143 °C (lit mp 147-148°C); ¹H NMR (300 MHz, CDCl₃) δ 9.10 (br s, N-H), 7.71 (d, J = 8.07 Hz, H-4), 7.38 (m, H-7 & H-6), 7.19-7.13 (m, H-5), 2.66 (CH₃, C-3, 3H), 2.66 (CH₃, -COCH₃, C-6, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 11.08, 29.01, 111.87, 118.75, 120.03, 121.22, 126.47, 128.89, 132.66, 136.07, 190.44; MS m/z (% base) 173 (M⁺, 79), 158 (100); Anal. Calcd for C₁₁H₁₁NO: C, 76.28, H, 6.40, N, 8.09; Found: C, 76.40; H, 6.46; N, 7.99

3-Methyl-6-propionyl-1-(phenylsulfonyl) indole (115):

Propionic anhydride (2.84 mL, 22.11 mmol) was added to a magnetically stirred suspension of AlCl₃ (5.9 g, 44.22 mmol) in dichloromethane (74 mL) and the mixture was stirred for 15 min followed by the dropwise addition of 110 (2.0 g, 7.37 mmol). After 2 h, TLC indicated disappearance of starting material and the reaction was quenched with ice. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), saturated aqueous NaHCO₃ (3 x 20 mL), brine (3 x 20 mL) and concentrated in vacuo. Recrystallization from MeOH gave the major isomer 115 (0.50 g) and 0.7 g of a mixture of the major 115 and minor 116 isomers. Total yield after recrystallization is 1.2 g (50 %). For the major Isomer 115; mp 150-152⁰C; Rf = 0.19 (CH₂Cl₂);

¹H NMR (300 MHz, CDCl₃) δ 1.27 (t, J = 7.23 Hz, 3H, -COCH₃), 2.27 (d, J = 1.17 Hz, 3H, CH₃), 3.1 (q, 2H, J = 7.23 Hz, -CH₂), 7.49-7.41 (m, 4H, H₄arom), 7.51 (s, 1H, H₂), 7.57-7.53 (m, 1H, H₃arom), 7.87 (d, J = 1.32 Hz, 1H, H₅ or H₆), 7.9 (d, J = 1.44 Hz, 1H, H₅ or H₄), 8.61 (br s, 1H, H₇); ¹³C NMR (100 MHz, CDCl₃) δ 8.4, 9.5, 31.2, 113.8, 118.6, 119.4, 122.8, 126.2, 126.7, 129.3, 133.6, 133.9, 134.9, 135.2, 138.1, 200.3; MS m/z (% base) 327 (M⁺, 29), 298 (100); Anal. Calcd for C₁₈H₁₇NO₃S: C, 66.03; H, 5.23; N, 4.28. Found: C, 63.06; H, 5.21; N, 4.29.
6-Acetyl-3-ethyl-1-(phenylsulfonyl)indole 117:

Acetic anhydride (2.0 mL, 21 mmol) was added to a magnetically stirred suspension of AlCl₃ (5.64 g, 42 mmol) dissolved in CH₂Cl₂ (80 mL) and stirred for 15 min followed by the dropwise addition of 3-ethyl-1-(phenylsulfonyl)indole (111) (2.0 g, 7.0 mmol) and stirred for 2 h until TLC indicated disappearance of starting material. The reaction was quenched with ice, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x20 mL). The combined organic layers were washed with brine (3 x 20 mL), saturated aqueous NaHCO₃ (3 x20 mL), brine (3 x 20 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Recrystallization from MeOH gave 6-acetyl-3-ethyl-1-(phenylsulfonyl)indole 117 (0.5 g) and 1.12 g of a mixture of 117 and 118 (GC/MS 117/118: 92/8). Total yield of the reaction after recrystallization from MeOH was 70% (1.62 g).

6-Acetyl-3-ethyl-1-(phenylsulfonyl)indole (117): (Major isomer) mp 125-129°C; ¹H NMR (300 MHz, CDCl₃) δ 1.27 (t, J = 7.47, 3 H, -CH₃), 2.26 (s, 3 H, -COCH₃), 2.75-2.67 (q, J = 1.2 Hz, 2H, -CH₂), 7.54-7.43 (m, 5H, H₅, H₆, H₇), 7.88 (s, 1H, H₁), 7.96-7.86 (m, 2H, H₄ & H₅), 8.50 (br s, 1H, H₇); ¹³C NMR (100 MHz, CDCl₃) δ 13.22 (one peak overlapped), 18.0, 26.8, 114.2, 119.4, 123.0, 125.3, 125.3, 126.7, 129.3, 133.9, 134.6, 135.0, 138.1, 197.6; MS m/z (% base) 327 (M⁺, 43), 144 (100); Anal. Calcd for C₁₈H₁₇NO₃S: C, 66.03; H, 5.23; N,
NMR SPECTRA

Figure 1. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 27

Figure 2. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 27
Figure 3. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 27

Figure 4. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 110
Figure 5. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 110

Figure 6. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 110
Figure 7. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 95

Figure 8. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 95
Figure 9. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 95

Figure 10. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 111
Figure 11. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 111

Figure 12. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 111
**Figure 13.** 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 112

**Figure 14.** 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 112
Figure 15. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 112

Figure 16. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 113
Figure 17. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 113

Figure 18. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 113
Figure 19. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 114

Figure 20. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 114
Figure 21. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 114

Figure 22. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 76
Figure 23. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 76

Figure 24. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 76
Figure 25. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 74

Figure 26. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 74
Figure 27. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 74

Figure 28. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 115
Figure 29. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 115

Figure 30. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 115
Figure 31. 300 MHz $^1$H NMR spectrum (CDCl$_3$) of 117

Figure 32. 75 MHz $^{13}$C NMR spectrum (CDCl$_3$) of 117
Figure 33. 75 MHz $^{13}$C dept NMR spectrum (CDCl$_3$) of 117
REFERENCES


4. Fischer, E.; Jourdon, F. Uber die Hydrazine der Brenztraubensaure. Ber. 1883, 16, 2241-2245


27. Qian, D. C; Alford, P. E; Kishbaugh, T. L. S; Jones, S. T; Gribble, G. W. 1,2-Bis(phenylsulfonyl)-1H-indole as an acceptor of organocuprate nucleophiles. *ARKIVOC*, **2010**, 66-73


34. Saxton, J. E; The reaction between indole and acetic anhydride. *J. Chem. Soc.* **1952**, *3592-3594*


45. Taylor, J. E; Jones, M. D; Williams, J. M. J; Bull, S. D. Friedel-Crafts acylation of pyrroles and indoles using 1,5-diazabicyclo[4.3.0]non-5-ene (DBU) as a nucleophilic catalyst. *Org. Lett,* 2010, 12, 5740-5743


