Photochemistry of Nitrogen Heterocycles: Applications in Amine Sensors and Complex Molecule Synthesis

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PHOTOCHEMISTRY OF NITROGEN HETEROCYCLES: APPLICATIONS IN AMINE SENSORS AND COMPLEX MOLECULE SYNTHESIS

By

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To my Mom and Dad who have loved me and supported me through all my decisions.
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# TABLE OF CONTENTS

List of Tables .......................................................................................................................... vi
List of Equations ....................................................................................................................... vii
List of Figures .............................................................................................................................. viii
List of Schemes ........................................................................................................................... ix
Abstract ......................................................................................................................................... xi

1. YLIDENEMALONONITRILE ENAMINES AS PRIMARY AMINE SENSORS..............1
   1.1 Introduction ......................................................................................................................... 1
   1.2 Results and Discussion ......................................................................................................... 3
   1.3 Conclusions ......................................................................................................................... 25
   1.4 Methods and Characterization ............................................................................................. 25

2. PYRIDAZINE N-OXIDES AS PHOTOCHEMICAL PRECURSORS TO DIAZO
   COMPOUNDS AND PYRAZOLE SYNTHESIS .......................................................................... 46
   2.1 Introduction ......................................................................................................................... 46
   2.2 Results and Discussion ......................................................................................................... 52
   2.3 Conclusions ......................................................................................................................... 63
   2.4 Methods and Characterization ............................................................................................. 63

References ...................................................................................................................................... 119

Biographical Sketch ................................................................................................................... 123
LIST OF TABLES

1.1 Photophysical Properties of Amine Sensors in Solution ..................................................14
1.2 Solid State Photophysical Properties .........................................................................15
LIST OF EQUATIONS

2.1 UHP/TFAA Oxidation of Pyridines..................................................................................56

2.2 Original Suzuki Coupling Conditions.............................................................................57
LIST OF FIGURES

1.1 Common Primary Amines and Primary Amine Containing Compounds........................................1
1.2 Common Sensors Used for Primary Amine Detection.................................................................2
1.3 Two Possible Products from Enamine Reactions with Primary Amines ................................6
1.4 NMR of Propylamine Exchange Reaction with 20..................................................................7
1.5 Crystal Structure of Propylamine Exchange Product ............................................................8
1.6 Photographs of 20 and 26 in Solution under 365 nm Light .......................................................8
1.7 Computational Analysis of HOMO-LUMO Band Gap Possible Fluorescent Sensors........9
1.8 A/B Photographs of Enamine and Amidin under Ambiant and 365 nm Light...................12
1.9 UV Spectrum of Three Propylamine Amidines 26, 29, and 35 .................................................13
1.10 Photographs of 20, 38, and 40 on Filter Paper Under Ambient and 365 nm Light ............14
1.11 Fluorescence Spectra of 34 in Solution at Increasing Concentration ..................................16
1.12 UV Spectra of 34 in Solution Compared to Solid State UV of 34 on Silica .........................17
1.13 Crystal Structure of 28 ............................................................................................................17
1.14 Fluorescence Rate Studies of 37 to 28 on Various Media .......................................................18
1.15 Fluorescence Rate Measurement of 20 to 26 in Solution .....................................................19
1.16 SEM Images of Media .........................................................................................................20
1.17 Selectivity Screening of 43 in Solution .....................................................................................21
1.18 Photographs of 43 Selectivity Screening Under Ambient Light ...........................................21
1.19 Selectivity Screening of 37 on Aluminum Oxide Neutral ......................................................22
1.20 Sensitivity Screening of 37 and 42 on Solid Support ............................................................23
1.21 UV of 42 on Glass Filter Paper at Decreasing Concentration .............................................24
2.1 Pyrazole Containing Biologically Active Compounds .......................................................46
2.2 Methods for the Synthesis of Pyrazoles .................................................................................. 47
2.3 Three types of 1,3-Dipoles .................................................................................................... 49
2.4 General Pyridazine N-Oxide Utilized in this Work ............................................................... 51
2.5 Crystal Structure of Chloropyridazine N-Oxide .................................................................. 54
2.6 Crystal Structure of 3-(benzyloxy)-6-chloropyridazine 1-oxide ........................................ 55
2.7 X-Ray Crystal Structure for 88 Oxidation Product ............................................................... 56
2.8 X-Ray Crystal Structure of Suzuki Coupling Product ......................................................... 58
2.9 Suzuki Coupling Mechanism .............................................................................................. 59
2.10 Suzuki Coupling Substrate Scope ....................................................................................... 60
2.11 S_N_Ar Substrate Scope ..................................................................................................... 61
2.12 X-Ray Crystal Structure of 75 ............................................................................................ 61
2.13 Photochemical Rearrangement Products .......................................................................... 62
LIST OF SCHEMES

1.1 Retrosynthesis of Nevirapine ................................................................................................................... 3
1.2 Baldwin et. al. Pinner Cyclization Conditions .......................................................................................... 4
1.3 Proposed Mechanism for Dimmerization of 11 ......................................................................................... 4
1.4 McQuade Group Original Cyclization Sequence ................................................................................... 5
1.5 Original Functional Group Interconversion Sequence .......................................................................... 5
1.6 McQuade Group Streamlined CAPIC Synthesis .................................................................................... 6
1.7 Synthesis of 2-(3-(dimethylamino)-1,2-diphenylallylidene)malononitrile ......................................... 10
1.8 Synthesis of (E)-2-(2-dimethylamino)methylene)acenaphthaylen-1-(2H)-ylidene) malononitrile ................................................................................................................................................ 11
1.9 Synthesis of 2-imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile ........................................ 11
1.10 Synthesis of 2-imino-4,5-diphenyl-1-propyl-1,2-dihydropyridine-3-carbonitrile ................................ 11
1.11 Synthesis of 9-imino-8-propyl-8,9-dihydroacenaphtho[1,2-c]pyridine-10-carbonitrile ...................... 12
2.1 Mechanism of Condensation Reaction Between Hydrazine and 1,3-Dielectrophiles ....................... 48
2.2 Tandem Cross-Coupling and Electrocyclization ................................................................................... 49
2.3 Vanderwaal Synthesis of Strychnine ..................................................................................................... 50
2.4 Gevorgyan Rh-Catalyzed Transannulation of Pyridotriazoles ............................................................ 51
2.5 Photochemical Ring Opening of Pyridazine N-Oxides ........................................................................ 52
2.6 Katukojvala Rhodium Catalyzed Transannulation of Pyridazine N-Oxides .................................. 53
2.7 Synthesis of Dichloropyridazine N-Oxide .............................................................................................. 53
2.8 Oxidation Reaction Scheme for Amine Substituted Pyridazine .......................................................... 55
2.9 Synthesis of Piperidine Substituted Pyridazine N-Oxide .................................................................... 57
ABSTRACT

Three ylidenemalononitrile enamines were designed as fast and selective primary amine sensors. These sensors were used as both colorimetric and fluorometric sensors for primary amines in solution. Two of the enamines were coated onto various media and were used to detect primary amine vapors. The enamine derived from acenaphthalene was used as a colorimetric sensor when coated on media and a strong fluorescent sensor when dissolved in solution. The enamine derived from 2-phenylacetophenone gave a stronger fluorescent response when coated on media and was used as a fluorescent sensor when coated on media. Each enamine worked to detect primary amines in complex mixtures without intricate sample preparation. Each sensor was generated in short reaction sequences that ranged from three to four steps. These reaction sequences utilized mild reaction conditions, and from inexpensive and commercially available starting material.

Pyridazine N-oxides were used as photochemical intermediates for the synthesis of 3,5-disubstituted pyrazoles. These photochemical precursors were synthesized regioselectively following the oxidation of the commercially available dichloropyridazine. In order to obtain the regioselectivity a Suzuki coupling reaction followed by a nucleophilic aromatic substitution (SNAr) was completed on the molecule using various boronic acids and pyrrolidine. Followed by photochemical ring opening the disubstituted pyridazine N-oxide generated a diazo carbonyl intermediate that could then have cyclized into either a furan or pyrazole. By partitioning between the two mechanisms we were able to selectively synthesize the pyrazole with little to no furan by product.
CHAPTER 1
YLIDENEMALONONITRILE ENAMINES AS PRIMARY AMINE SENSORS

1.1 Introduction

Amines, especially primary amines, are ubiquitous in nature and have utility in various aspects of our everyday lives. This class of compounds are used in the production of various medications, pesticides, paints, and dyes. Primary amines are also given off as byproducts when food products and plants decompose. They are often detected in cases of industrial pollution and used as markers for various disease states. Some examples of these compounds include cadaverine (1), o-toluidene (2), amphetamine (3), direct brown 138 (4) (Figure 1.1). Cadaverine is given off as a byproduct in food spoilage, 2 can be used as a biomarker for lung cancer, 3 is a drug used in the treatment of ADHD, and 4 is a dye used in the coloring of clothes.

Figure 1.1 Common Primary Amines and Primary Amine Containing Compounds.

With the vast prevalence of primary amines in our everyday lives, various methods for their detection have been developed. Traditional methods for amine detection involve chromatographic and electrochemical techniques. These methods have been used to detect primary amines both in complex solutions and in air samples. These two detection methods have the benefit of low detection limits and have the ability to separate complex mixtures. However,
these two methods also suffer from a few drawbacks that limit their use for onsite applications. Some of these drawbacks include: bulky and expensive equipment, intricate sample preparation such as purification from environmental contaminants like sediment, dilution and in some cases the sample needs to be degassed. Another detractor to these methods is the time delay in transporting the sample from the site of collection to the lab for detection. This delay can be problematic for time sensitive samples. Because of these drawbacks new methods for the detection of primary amines need to be developed that allow for real time detection and lend themselves to onsite applications.

Recently there has been an increase in the development of molecular sensors that give a colorimetric and/or fluorescent response when exposed to an analyte. These types of sensors offer low detection limits and give a visual response that can be seen either with the naked eye or by visualization with a hand held UV lamp. Some examples include colorimetric arrays that are comprised of metalloporphyrins, acid/base indicators, and solvatochromatic dyes. Other examples of colorimetric and fluorescent indicators/sensors include ninhydrin (5), water soluble cruciform (6), and epicoconone (7) (Figure 1.2). Each of these sensors enable the detection of

![Figure 1.2 Common Sensors Used for Primary Amine Detection.](image-url)
primary amines, however, they also detect of secondary amines. Another drawback is that some of these sensors require complex syntheses that utilize expensive starting material. Also, the majority of these methods work only for the detection of the analytes in solution or for the detection of analyte vapor.

Herein, I describe three different ylidenemalononitrile derived enamines that can be used for the selective detection of primary amines in solutions. In addition, to the detection of primary amines in solution, when these enamines are coated on solid support can detect primary amine vapors. The compounds described in this chapter undergo both a fluorescent and colorimetric response when exposed to primary amines. This response is rapid, selective, and can discern primary amines from complex mixtures without further sample purification. Importantly these compounds are prepared from inexpensive and commercially available starting material.

1.2 Results and Discussion

Our work towards the development of a selective primary amine sensor began with chemistry that was previously established by the McQuade research group. This chemistry was developed for the synthesis, and subsequent reduction in the production cost for the anti-HIV drug nevirapine (8). After comparing the production cost for 3-amino-2-chloro-4-picoline (CAPIC, 9) and 2-(cyclopropylamino)nicotinic acid (2-CAN, 10), the two pyridine building blocks of 8 (Scheme 1.1), our group found that 9 was the cost driver in the overall synthesis. With this knowledge our group began optimizing the synthesis of 9 to lower its production cost and as a result the cost of 8. Our route to the synthesis of 9 was based off work published by Baldwin, Raab,

![Scheme 1.1 Retro synthesis of Nevirapine.](image-url)
and Ponticello. Baldwin and coworkers showed that the precursor of 9 could be synthesized by cyclizing both a ylidenemalononitrile derived aminal (12) and a ylidenemalononitrile derived enol ether (13) under Pinner conditions (Scheme 1.2). The work accomplished by Baldwin and coworkers suffered from low yields because of the dimmerization of the Knoevenagel condensation product (11). The dimmerization is thought to occur through a Michael type addition between two molecules of 11 (Scheme 1.3). In order to overcome the dimerization and simplify the reaction mixture we chose to run the condensation reaction in chloroform to limit the dimmerization reaction and we changed the C1 source from triethyl orthoformate to dimethylformamide dimethylacetal (DMF-DMA, Scheme1.4). The reason for this change was based on the fact that the reaction with DMF-DMA leads to the formation of one product while the reaction with triethyl orthoformate yields two. The Pinner cyclization worked as described by Baldwin, however we chose to use hydrochloric acid (HCl) gas instead of hydrogen bromide (HBr). The HCl gas was generated by the slow addition of concentrated sulfuric acid to a round bottom flask containing sodium chloride (NaCl). The resulting gas was bubbled into a solution of 20 in acetic acid (AcOH). After the Pinner cyclization the resulting nitrile (21) was then hydrolyzed to the amide (22) under acidic conditions. A Hoffman rearrangement was then performed on 22 to
yield 9 (Scheme 1.5). The seminal work completed by our group lowered the cost of 8 from $170/kg to $110/kg. Our group continued to optimize the synthesis of 9 and lower the price of 8 from $110 to $70 by dividing the synthesis of 9 into two streamlined processes (Scheme 1.6). By using toluene as the solvent we combined the first three steps into the cyclization sequence which contains the Knoevenagel condensation, the enamine formation reaction, and the pinner cyclization. These steps were carried out in one round bottom flask in a sequential order without purification between each step. Utilizing this method we were able to synthesize 21 in 76% yield over three steps. The second sequence contained the two functional group interconversion steps. Following these two sequence we were able synthesize 9 in 76% yield. We found that carrying out the hydrolysis under strong basic conditions prevented the formation of the carboxylic acid which is a common byproduct found in the hydrolysis of amides. It forms when the amide is overhydrolyzed and is generally formed when weak basic conditions are used for the hydrolysis.
While working to further optimize the synthesis of 8, our group wanted to generate 10 in a manor similar to our synthesis of 9 by cyclizing a formaldehyde derived enamine with cyclopropylamine. This hypothesis was based on work published by the groups of Dr. Villemin\textsuperscript{22} and Dr. Škofic\textsuperscript{23}(Figure 1.3). Villemin and coworkers showed that a derivative of 20 (R = Ph) could be cyclized into a pyridine through a reaction with a primary amine. Škofic and coworkers showed that exposure of another derivative of 20 (R = naphthyl) to primary amines exchanged the dimethyl amine of the enamine with that of the primary amine it was exposed to. This amine exchange lead to an isomerization of the olefin to generate a cis enamine. Based on these findings, our group hypothesized we could accomplish two tasks: (1) using Villemin’s work we set out to generate a streamlined synthesis of 10 and (2) following Škofic’s work we could generate a primary amine sensor.

\begin{center}
\includegraphics[width=\textwidth]{synthesis_diagram.png}
\end{center}

\textbf{Scheme 1.6 McQuade Group Streamlined CAPIC Synthesis.}

Figure 1.3 Two Possible Products From Enamine Reactions with Primary Amines.
Our group’s work on the development of a primary amine sensor began with trying to reproduce the work accomplished by Škofic’s group. In order to accomplish this a NMR solution of 20 was generated in deuterated chloroform (CDCl₃) was generated and a proton NMR was obtained at time zero before the addition of propylamine (Figure 1.4). Following the time zero NMR, three equiv of propylamine was added to the NMR tube and a spectra was obtained at 5, 10, 20, 40, 80, and 300 min. We chose to use 19 for this experiment because for our sensor to be competitive it needed to be simple and easy to synthesize in comparison to other primary amine sensors. We monitored the region between 5.5 and 8.0 ppm in the NMR spectrum. This region was chosen because it was isolated from the large signals generated by the excess propylamine. A new set of doublets begins to grow in around 10 min after the addition of propylamine and become the predominant product around 80 min. The resultant product was purified and then crystallized.

Figure 1.4 NMR of Propylamine Exchange Reaction with 20.
to obtain a single crystal x-ray diffraction pattern, which showed that in addition to completing an exchange reaction the enamine had cyclized into an amidine (26, Figure 1.5). In addition to the single crystal we generated a solution of 26 in dichlormethane (CH$_2$Cl$_2$) and exposed the solution to a longwave (365nm) UV lamp. When the solution was compared to a similar solution of 20, we observed a fluorescent response had occurred between the starting material and the product. This observation had not been previously reported in the literature and strengthened our hypothesis that ylidenemalononitrile derived enamines could be used as primary amine sensors. Our group came to this conclusion for two reasons: (1) the fluorescent turn-on response is ideal for sensor applications for the reasons listed previously and (2) the fact that the reaction undergoes an irreversible ring closure. This ring formation would prevent false positives from occurring.

**Figure 1.5 Crystal Structure of Product from Propylamine Reaction.**

**Figure 1.6 Photographs of 20 and 26 in Solution Under 365 nm Light.**
With these findings we then began to identify other enamines that would yield amidine products that emit at other wavelengths. In order to accomplish this, computational analysis was used to calculate the band gap for ten different amidines (Figure 1.7). Each of the amidines were chosen for two reasons: (1) they were commercially available for a reasonable price based on Sigma Aldrich listings and (2) they contained extended conjugation which would lower the band gap and lead to the compounds emitting at different wavelengths. The calculations were completed using Spartan computational software with the density functional theorem (DFT) B3LYP and the 6-31G* basis set and CH₂Cl₂ as the solvent. From these ten compounds we chose three substrates. The first substrate we choose was 2-imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile (26), which derived from 19. We chose 26 due to its simplicity and because it had the largest band gap. The second substrate 9-imino-8-propyl-8,9-dihydroacenaphtho[1,2-c]pyridine-10-carbonitrile (35) is derived from acenaphthylene-1(2H)-one and was chosen because it had the smallest band gap. The final amidine chosen was 2-imino-4,5-diphenyl-1-propyl-dihydropyridine-
3-carbonitrile (29), which is derived from 2-phenylacetophenone, because its band gap fell in the middle of the ten substrates.

After the identification of three potential sensors we then synthesized the enamine starting materials. The first enamine we synthesized was 2-(3-(dimethylamino)-1,2-diphenylallylidene)malononitrile (38, Scheme 1.7). We started with the condensation reaction and found that, because of the reactivity of the starting material we could not use basic aluminum oxide instead the reaction was carried out using acetic acid and ammonium acetate. Over the course of the reaction the ylidenemalononitrile product precipitated out of solution and was subsequently filtered off and used in the reaction with DMF-DMA without further purification. Similarly due to solubility 38 precipitated out of the toluene over the course of the reaction, and the product was filtered and collected as an orange solid in 84% yield.

![Scheme 1.7 Synthesis of 2-(3-(dimethylamino)-1,2-diphenylallylidene)malononitrile (38).](image)

The synthesis of (E)-2-(2-((dimethylamino)methylene)acenaphthaylen-1-(2H)-yldene)malononitrile (43) was the most complex synthesis of the three sensors requiring four total synthetic steps and three purifications (Scheme 1.8). In order to generate the 43 in the most cost effective manner we started the synthesis with 1-naphthaleneacetic acid (39). The first synthetic step was the conversion of 39 to the acyl chloride (40) and then utilizing 40 in a Friedel Crafts acylation to generate acenaphthylene-1(2H)-one (41). After purifying 41 by recrystallization we performed the Knoevenagel condensation, utilizing the conditions used to synthesize 37, to synthesize 2-(acenaphthylene-1(2H)-yldene)malononitrile (42). However, the Knoevenagel condensation conditions used to generate 42 yielded a fluorescent by product that needed to be removed through several washes with ethanol, water and hexanes. Using the general DMF-DMA reaction procedure, our group was able to synthesize and collect 43 as a dark purple solid in 61% yield after purification using a silica plug.
Scheme 1.8 Synthesis of (E)-2-(2-((dimethylamino)methylene)acenaphthaylen-1-(2H)-ylidene) malononitrile (43)

After obtaining the three enamine precursors we then synthesized their corresponding amidines using propylamine for the reaction (Schemes 1.9-1.11). Because, of the difference in reaction rates compounds 26 and 35 were both synthesized using CH₂Cl₂ as the solvent while the synthesis of 39 was carried out in acetonitrile (MeCN). The concentration of propylamine used in

Scheme 1.9 Synthesis of 2-imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile.

Scheme 1.10 Synthesis of 2-imino-4,5-diphenyl-1-propyl-1,2-dihydropyridine-3-carbonitrile.
each of the reactions was also variable with the synthesis of 26 needing only three equiv but the synthesis of 29 and 35 used twelve equiv and thirty equiv respectively. By changing the solvent and concentration of amine used the syntheses of 26, 29, and 35 were completed in 24, 5, and 4 hours with yields of 57%, 60%, and 17% respectively. The low yield of 35 can be attributed to problems with the purification of the compound from a minor fluorescent by product that formed over the course of the reaction.

Scheme 1.11 Synthesis of 9-imino-8-propyl-8,9-dihydroacenaphtho[1,2-c]pyridine-10-carbonitrile.

Following the synthesis of both the enamine precursors and the amidine products solutions of each compound were generated using CH$_2$Cl$_2$ as the solvent (Figure 1.8A and B). A photograph was taken of each solution under ambient lighting and when a 365 nm UV lamp was used to excite each of the solutions. Qualitatively we found that our hypothesis had been correct and that each of

Figure 1.8A/B Photographs of Enamines and Amidines under Ambient and UV light.
the enamines chosen emitted at a different wavelength with 26 giving a blue emission and 29 and 35 emitting green and yellow respectively. In addition each sample underwent a fluorescent turn-on from their enamine precursors. In addition observing the fluorescent turn-on we noticed that the conversion of 20 to 26 and the conversion of 38 to 29 lead to amidines that were to close in color to their enamine starting material preventing their use as colorimetric sensors. However, upon conversion of 43 to 35 there was a drastic color change with the compound starting as a purple solid and turning orange once exposed to propylamine. Following these qualitative observations we obtained a UV-Vis spectrum for each amidine in CH$_2$Cl$_2$ (Figure 1.9). The UV-Vis showed a gradual hypsochromic shift of the absorption spectra for each amidine which corresponds to the emission color that was observed.

![Figure 1.9 UV Spectrum of Three Propylamine Amidines 26, 29, and 35.](image)

In order to quantify the strength of each sensor we measured the photophysical properties of both the enamine and the amidine in CH$_2$Cl$_2$ (Table 1.1). The quantum yields ($\Phi_{PL}$) for 20, 38, and 43 were 0.1%, 0.035%, and 0.016% respectively at room temperature. We hypothesized that the lack of emission for 20, 38, and 43 was due to either torsional/vibrational relaxation of the dimethylamine or because of photoinduced electron transfer (PET). To test this hypothesis the emission intensity and lifetimes were measured at 77K in the glassy solvent 2-methyltetrahydrofuran (2-MeTHF). This solvent was chosen because it is a rigid matrix that inhibits the nonradiative pathways from occurring. Both their emission intensity and their lifetime
increased suggesting that our hypothesis of torsional and vibrational relaxation pathways were the primary cause for the loss of emission for these compounds. The $\Phi_{\text{PL}}$ for the corresponding amidines 25, 28, and 34 were found to be 8.0%, 7.0%, and 14.2% respectively. This corresponds to a 80-, 200-, and 900-fold increase in the $\Phi_{\text{PL}}$ upon conversion to the amidine.

**Table 1.1 Photophysical Properties of Amine Sensors in Solution.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorbance $\lambda$ (nm) ($\varepsilon$, x10$^4$ M$^{-1}$ cm$^{-1}$)</th>
<th>Emission at Room Temperature</th>
<th>Emission at 77K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\lambda_{\text{max}}$ (nm)</td>
<td>$\tau$ (ns)</td>
<td>$\Phi_{\text{PL}}$ (%)</td>
</tr>
<tr>
<td>20</td>
<td>388 (4.9), 377 (4.6)</td>
<td>410</td>
<td>-</td>
</tr>
<tr>
<td>38</td>
<td>395 (2.9), 296 (1.0), 261 (1.0)</td>
<td>560</td>
<td>-</td>
</tr>
<tr>
<td>43</td>
<td>541 (1.3), 520 (1.2), 356 (2.8), 300 (1.5), 267 (1.6)</td>
<td>605</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>390 (4.8)</td>
<td>500</td>
<td>8.0</td>
</tr>
<tr>
<td>29</td>
<td>425 (0.5), 276 (2.4)</td>
<td>530</td>
<td>3.3</td>
</tr>
<tr>
<td>35</td>
<td>511 (0.4), 481 (0.5), 390 (1.0), 368 (0.9), 341 (2.9), 325 (2.0)</td>
<td>555</td>
<td>8.5</td>
</tr>
</tbody>
</table>

We hypothesized that upon coating 26, 29, and 35 on solid support we could increase their $\Phi_{\text{PL}}$ and use them as sensors for primary amine vapors. We began by coating 20, 38, and 43 on filter paper and exposing them to 365 nm light (Figure 1.9). We found that 20 was fluorescent when coated onto solid support, and so we focused on 38 and 43, which remained nonfluorescent.

![Figure 1.10 Photographs of 20, 38, and 43 on Filter Paper under Ambient and 365nm Light.](image)
as possible primary amine vapor sensors. We then measured the photophysical properties of 29 and 35 after they were coated onto seven different types of media. As a control we also obtained the photophysical properties for 29 and 35 as a powder. The $\Phi_{\text{PL}}$ of 29 increased significantly both as a free solid as well as when 29 was coated onto solid support. When comparing the $\Phi_{\text{PL}}$ for the solid (45.0 %) to that of the $\Phi_{\text{PL}}$ in solution (7.0 %) there was a 6.4 fold increase. The $\Phi_{\text{PL}}$ stayed around 45.0 % when 29 was coated on silica (46.7%), glass filter paper (44.0%), and reverse phase silica (40.7%). The $\Phi_{\text{PL}}$, dropped slightly when 29 was coated on filter paper (35.4%), filter paper treated with a 1M solution of NaOH (38.0%), and filter paper treated with a 2M solution of NaOH (38.2%). The $\Phi_{\text{PL}}$ for 35 decreased significantly when the powder (0.51%) was compared to the solution (14.%). The $\Phi_{\text{PL}}$ only increased slightly from the powder when coated on silica (1.0%), basic aluminum oxide (4.8%), reversed phase silica (2.4%), and filter paper (1.51%).

Table 1.2 Solid State Photophysical Properties.

<table>
<thead>
<tr>
<th>Media</th>
<th>Compound</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\Phi_{\text{PL}}$ (%)</th>
<th>$\tau$ (ns)</th>
<th>$k_i$ ($10^7 \text{s}^{-1}$)</th>
<th>$k_{\text{nr}}$ ($10^7 \text{s}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no media</td>
<td>29</td>
<td>522</td>
<td>45.0</td>
<td>18.0</td>
<td>2.49</td>
<td>0.305</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>654</td>
<td>0.51</td>
<td>5.52</td>
<td>0.092</td>
<td>1.80</td>
</tr>
<tr>
<td>silica gel on glass plate</td>
<td>29</td>
<td>524</td>
<td>46.7</td>
<td>22.0</td>
<td>1.36</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>720</td>
<td>1.0</td>
<td>5.0</td>
<td>0.2</td>
<td>1.98</td>
</tr>
<tr>
<td>Al$_2$O$_3$ (basic) on glass plate</td>
<td>29</td>
<td>529</td>
<td>21.8</td>
<td>20.3</td>
<td>1.35</td>
<td>0.358</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>719</td>
<td>4.8</td>
<td>4.6</td>
<td>1.04</td>
<td>2.03</td>
</tr>
<tr>
<td>SiO$<em>2$C$</em>{18}$ on glass plate</td>
<td>29</td>
<td>525</td>
<td>40.7</td>
<td>3.4</td>
<td>1.00</td>
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<td>4.8</td>
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<td>3.60$^d$</td>
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<tr>
<td>filter paper (1 M NaOH)</td>
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<td>20.7</td>
<td>0.937</td>
<td>0.389</td>
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<tr>
<td></td>
<td>35</td>
<td>659</td>
<td>0.44</td>
<td>3.13$^d$</td>
<td>0.141</td>
<td>3.18</td>
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<tr>
<td>filter paper (2 M NaOH)</td>
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<td>38.2</td>
<td>20.7</td>
<td>1.18</td>
<td>0.365</td>
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<td>1.22</td>
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<td>726</td>
<td>0.56</td>
<td>4.75$^d$</td>
<td>0.118</td>
<td>2.09</td>
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there was a decrease in the $\Phi_{PL}$ of 35 still showed a strong colorimetric response, and as such could be used as a colorimetric sensor. We hypothesized the fluorescence quenching of 35 was attributed to the formation of J-aggregates, which occur due to self aggregation of a dye in solution. Because this phenomenon is concentration dependent we generated five solutions of 35 in CH$_2$Cl$_2$ of decreasing concentration. An emission spectrum was obtained for each solution which showed an increase in the emission intensity for each solution as the concentration decreased (Figure 1.10). In addition to the increase in fluorescence intensity there is a bathochromic shift in the emission spectrum, which indicates the formation of J-aggregates. We then obtained a UV-Vis spectrum for the 0.2M solution and the 0.00032M and compared them to the UV-Vis spectrum of 35 coated on silica. We found that the spectrum of the concentrated solution was similar to that of the spectra for when 35 was coated onto silica (Figure 1.11). This similarity in the spectra shows that the J-aggregates form in concentrated solutions and when 35 is coated onto solid support. We hypothesized that 29 could not form J-aggregates because of the orientation of the two phenyl groups. To test this hypothesis we obtained a X-ray crystal structure which showed the phenyl groups were orientent in such a way they would prevent the π-π stacking needed for the formation of J-aggregates (Figure 1.12).
Figure 1.12 UV Spectra of 34 in Solution compared to Solid State

The rates of conversion for the exchange reaction were then obtained to see if the sensors could detect primary amines in a reasonable time window. We began with coating 38 on to various media and using a specialized cuvette an emission spectra was obtained every minute and a half as the exchange reaction progressed (Figure 1.13). In solution the conversion of 38 to 29 was slow taking more that twenty four hours for the conversion to occur in CH2Cl2. However, when coated onto the media there was a significant increase in the rate of the reaction when 38 was coated on aluminum oxide neutral (Al2O3 neutral) and reverse phase silica (SiO2-C18) the turn-

Figure 1.13 Crystal Structure of 28.
on took 30 min and 100 min respectively. Silica had a similar reaction rate to SiO$_2$-C$_{18}$ taking 175 min for a change in fluorescence to be detected. When coated on glass filter paper, filter paper or unsupported by media its rate of conversion was similar to when it was dissolved in CH$_2$Cl$_2$ with no noticeable change in fluorescence with in 800 min. Aluminum oxide basic (Al$_2$O$_3$ basic), and the filter paper that had been treated with one and two molar solutions of NaOH gave median responses with a change in fluorescence taking more than 300 min to be detected. When comparing

![Graph showing fluorescence rate studies of 38 to 29 on various media.](image)

**Figure 1.14 Fluorescence Rate Studies of 38 to 29 on Various Media.**

the three sensors in CH$_2$Cl$_2$ it was established that the conversion of 38 to 29 took more than twenty-four hours for the conversion which prevented its use as a sensor in solution. It was established that the conversion of 20 to 26 took 300 min in chloroform, however when we changed the solvent to MeCN the reaction was completed in 80 minutes with twelve equivalents of propylamine (Figure 1.14). The conversion of 43 to 35 was the fastest, happening within a matter of minutes with low concentrations of primary amines in CH$_2$Cl$_2$. This conversion translated over to the colorimetric response when 43 was coated on to glass filter paper.

With the differences in the reaction rates for 38 on the various medias we obtained scanning electron microscope (SEM, Figure 1.15) images for each type of media. We reasoned that the
difference in the rates was attributed to the surface morphology of the media. After obtaining the images we found a visible change when comparing filter paper (i) to filter paper treated with 0.5 M NaOH (ii) and filter paper treated with 2M NaOH (iii). This increase in the porosity of the filter paper upon treatment could explain the increase in reaction rate by allowing for a faster absorption of the vapor into the media. When we compared silica (iv), aluminum oxide basic (v), aluminum oxide neutral (vi) their surface morphology appeared to be the same. The images for reverse phase

![Figure 1.15 Fluorescence Rate Measurement of 20 to 26 in Solution.](image)

...silica (vii) and glass filter paper (viii) showed that these two media had large surface porosity. Because, the surfaces iv-viii all had similar surfaces but had varying differences in the actual rate of the reaction the actual deciding factor in the reaction rate in the vapor phase must be the ability of the media to absorb the amine vapor to allow for the reaction to take place.

Following the identification of 43 as a solutions based primary amine sensor and 38 as a primary amine vapor sensor, we exposed each sensor to various analytes to test their selectivity (Figure 1.16-1.17). In order to complete the selectivity screening for 43 in solution a 0.9mM solution was prepared in acetonitrile and to each solution twelve equivalents of the appropriate amine was then added. The reactions were allowed to stir at ambient temperature and pressure and aliquots were taken at five minutes and two hours. Before each spectrum was obtained the aliquots were diluted to a concentration of 0.25mM. The emission intensities were obtained at 625nm. The
reaction of 43 was selective when reacted with propylamine (i), isopropylamine (ii), ethanolamine (iii), cyclohexylamine (iv), and benzylamine (v). The conversion for the reaction with propylamine and ethanolamine happened within five minutes. However, with primary amines that had slightly larger substituents surrounding them such as isopropylamine, cyclohexylamine, and benzylamine the conversion took two hours. With more sterically encumbered amines such as t-butylamine and aniline there was no visible response. In addition to primary amines we exposed 43 to the secondary and tertiary amines pyrrolidine (ix), triethylamine (x), and pyridine (xi). Upon exposure to these analytes 43 gave no fluorescent response. We then exposed 43 to a mixture containing propylamine and triethylamine (vi) the fluorescent turn-on was similar to the rate of the pure

Figure 1.16 SEM Images of Media.
propylamine. Because many biogenic amines in nature are diamines we exposed 43 to N,N-dimethyl diamine (DMDA, xii). Upon exposure to DMDA, 43 gave a weak emission that did not increase over the course of two ours. We attributed this weak response to photoinduced electron transfer or (PET), in which the lone pair on nitrogen donates into the $\pi$ system after the fluorophore

The amines used are as follows: (i) propylamine, (ii) isopropylamine, (iii) ethanolamine, (iv) cyclohexylamine, (v) benzylamine, (vi) 1:1 mixture of propylamine and triethylamine, (vii) $t$-butylamine, (viii) aniline, (ix) pyrrolidine, (x) triethylamine, (xi) pyridine

**Figure 1.17 Selectivity Screening of 43 in Solution.**

increase over the course of two ours. We attributed this weak response to photoinduced electron transfer or (PET), in which the lone pair on nitrogen donates into the $\pi$ system after the fluorophore

**Figure 1.18 Photographs of Selectivity Screening Under Ambient Light.**
was excited. In addition to the emission spectra a photo of each solution was obtained under ambient light (Figure 1.17). For each solution where 43 was combined with a primary amine the solution went from a purple color to that of an orange/yellow color which corresponds with the emission spectra. In addition to the emission spectra we obtained a $^1$H NMR spectra which showed that the reaction had gone to full conversion. When we allowed the reactions to stir for twenty-three hours we observed the control reaction went from purple to yellow. This lead us to believe that there may be a stability issue with the enamine sensor in solution.

After screening the selectivity of 43 we then screened 38 coated on neutral aluminum oxide against various biogenic vapors that are detected as common pollutants in the environment. In order to accomplish these studies strips of neutral Al$_2$O$_3$ were dip coated into a 0.5M solution of 37 in DCM. The strip was dip coated three times allowing the CH$_2$Cl$_2$ to evaporate each time. While the strips were drying the appropriate analyte was injected into a specialized chamber (See section 1.4) the chamber was allowed to come to equilibrium and then a strip was inserted into the chamber along with the analyte for one hour. An emission spectrum was obtained after the strip was removed from the chamber and placed under high vacuum to remove the excess vapor from

![Figure 1.19 Selectivity Screening of 37 on Aluminum Oxide Neutral.](image)
the strip (Figure 1.18). When the analyte was exposed to alcohols and thiols there was little to no fluorescent response. However, when a strip of 38 was exposed to a mixture of ethanethiol, methanol, and propylamine there was only a slight fluorescent response and the sensor turned white. This white color change was believed to be associated with the decomposition of the sensor which lead to the slight fluorescent response. The sensor was still selective toward the primary amines propylamine and isopropylamine and the response rates for 38 to these two analytes were the same as those seen for 43. Cadaveriene gave a weak emission because of the same PET interactions that affected the response of 43 with DMDA.

In order for 38 to be used as a fluorescent sensor it needed to work for low concentrations of primary amine vapors. To test this hypothesis, we screened 38 against various concentrations of propylamine when it was coated on neutral Al₂O₃ (Figure 1.19 A/B). In addition to the sensitivity of 38, the sensitivity of 43 was also explored but instead of coating 43 by coating it onto

![Graph](image1)

**Figure 1.20 Sensitivity of 37 and 42 on Solid Support.**
We found that 38 was on able to detect propylamine at concentrations as low as 200 ppm (Figure 1.19A). With concentrations below that point the emission intensity steeply dropped off. When 43 was screened it was found to be more sensitive to the propylamine vapor and was able to detect vapor as low as 29 ppm (Figure 1.19B). The photographs of 43 were obtained under ambient light after exposure to 14 (ii), 29 (iii), 58 (iv), 115 (v), 230 (vi), 345 (vii), 460 (viii), and 575 (ix) ppm for one hour. Each photograph was compared to the control (i) and there was a clear change in the color from the control. In addition to the photographs an absorption spectrum was obtained using the integrating sphere accessory for an Endenburgh Fluorometer (Figure 1.20).

![Figure 1.21 UV of 43 on Glass Filter Paper at Decreasing Concentration.](image)

For each concentration that gave a qualitative response to the propylamine vapor there was a noticeable change in the UV spectrum of the compound. This clear change in the spectrum shows as well as its quick response to the vapor showed the utility of 43 as a colorimetric sensor.
1.3 Conclusions

Throughout this work I have shown the ability of ylidemalononitrile enamines to act as primary amine sensors. The sensors are simple and inexpensive to prepare with the longest synthetic sequence equaling four total steps from commercially available starting material. The sensors also have the ability to detect primary amines in solution as well as detect primary amine vapor. This utility makes them flexible for use both in a laboratory setting and in the field. In addition, the colorimetric response of 43 allows for its use out in the field without the need to purchase extra equipment. For all three sensors the fluorescent turn-on can be seen using a hand held 365nm UV lamp.

By coating 38 onto a solid support we were able to increase the $\Phi_{PL}$ for the fluorescent turn-on allowing for a stronger signal and better sensor. In addition, even though coating 43 onto media lowered the $\Phi_{PL}$ the compound was still sensitive enough to detect propylamine vapor and give a colorimetric response to the analyte. While more work still needs to be done on fully understanding the role of the media in the detection, the data shows that the media doesn’t inhibit the detection so much as the inherent reactivity of the compound does.

1.4 Methods and Characterization

Materials:

Malononitrile was purified by recrystallization in ethanol prior to use. All other reagents were commercially available and were used without further purification.

NMR:

Proton nuclear magnetic resonance ($^{1}$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Bruker 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Chemical shifts are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t= triplet, q = quartet, quin = quintuplet, sext = sextet, m = multiplet), coupling constants are reported in Hertz (Hz), integration.
1.4.1 Synthesis of 19

Isopropylidenemalononitrile was prepared according to the previously reported procedure.\textsuperscript{17} ¹H NMR: (600 MHz, CDCl\textsubscript{3}) δ 2.32 (s, 6H) ppm. ¹³C NMR: (151 MHz, CDCl\textsubscript{3}) δ 178.8, 118.8, 86.1, 24.5 ppm. The spectra for these compounds were identical with those previously reported in the literature.

(E)-2-(4-(dimethylamino)but-3-en-2-ylidene)malononitrile (20) was prepared according to the procedure previously reported with modifications.\textsuperscript{17} To a round-bottom flask containing isopropylidenemalononitrile (5.3 g, 50 mmol) in anhydrous toluene (50 mL) acetic anhydride (0.94 ml, 10 mmol) was added. The reaction was heated to 45°C followed by drop wise addition of N,N-dimethylformamide dimethyl acetal (DMF-DMA) (8.0 mL, 60 mmol). The reaction was maintained for 1 h and the precipitate that formed was collected by vacuum filtration. The solid was rinsed with toluene, and recrystallized using CH\textsubscript{2}Cl\textsubscript{2}/n-heptane, and dried under vacuum to yield the product as a yellow solid in 72 % yield. ¹H NMR: (600 MHz, CDCl\textsubscript{3}) δ 7.25 (d, J=12.7 Hz, 1 H), 5.63 (d, J=12.6 Hz, 1H), 3.23 (s, 3H), 2.99 (s, 3H), 2.23 (s, 3H) ppm. ¹³C NMR: (151 MHz, CDCl\textsubscript{3}) δ 128.3, 152.4, 116.9, 116.1, 97.2, 65.8, 45.9, 37.6, 17.3 ppm. Spectra were in accordance with those previously reported in the literature.

1.4.2 Synthesis of 37
2-(1,2-diphenyl)ethylidenemalononitrile was prepared according to the reported procedure.\textsuperscript{17} \textsuperscript{1}H NMR: (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.50-7.03 (m, 10H), 4.25 (s, 2H) ppm. \textsuperscript{13}C NMR: (151 MHz, CDCl\textsubscript{3}) \(\delta\) 177.6, 134.8, 134.3, 132.0, 129.1, 128.9, 127.9, 127.8, 113.0, 112.7, 85.6, 43.4 ppm. Spectra were in accordance with those described in the literature.\textsuperscript{25}

2-(3-(dimethylamino)-1,2-diphenylallylidene)malononitrile (38) was prepared according to the previously reported procedure with the following modifications.\textsuperscript{17} To a solution of 2-(1,2-diphenyl)ethylidenemalononitrile (2.44 g, 10.0 mmol) and Ac\textsubscript{2}O (0.19 mL, 2.0 mmol) in anhydrous toluene (10.0 mL), DMF-DMA (1.6 mL, 12 mmol) was added drop wise. The reaction was stirred at room temperature for 23 h, the solid was collected by vacuum filtration and washed with toluene to yield 1b as an orange solid in 84% yield. \textsuperscript{1}H NMR: (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.39 (m, 3H), 7.32 (m, 5H), 7.18 (m, 2H), 6.76 (br s, 1H), 2.70 (br s, 6H) ppm. \textsuperscript{13}C NMR: (151 MHz, CDCl\textsubscript{3}) \(\delta\) 172.4, 155.1, 137.4, 135.8, 132.5, 130.1, 130.0, 128.4, 128.3, 128.1, 118.2, 116.0, 112.4, 64.3, 47.4, 41.0 ppm. HRMA (EI+): calculated for C\textsubscript{20}H\textsubscript{18}N\textsubscript{3}, 300.14949; found 300.15007.

1.4.3 Synthesis of 42

\begin{equation}
\begin{array}{c}
\text{HO} \\
\text{39} \\
\text{oxalyl chloride cat. DMF} \\
\text{CH}_2\text{Cl}_2, 1 \text{ h} \\
\text{Cl} \\
\text{40} \\
\text{AlCl}_3 \\
\text{CH}_2\text{Cl}_2, 3 \text{ h} \\
\text{41} \\
\text{58\% over two steps}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{NC} \equiv \text{CN} \\
\text{AcOH, NH}_4\text{OAc} \\
\text{Toluene, 120 \text{ oC}, 2 \text{ h}} \\
\text{77\%} \\
\text{NC} \equiv \text{CN} \\
\text{42} \\
\text{DMF-DMA Ac}_2\text{O} \\
\text{Toluene, 18 \text{ h}} \\
\text{61\%} \\
\text{NC} \equiv \text{N} \\
\text{43}
\end{array}
\end{equation}
2-(naphthalene-1-yl)acetyl chloride was prepared according to the literature with the following modifications.\textsuperscript{22} To a solution of 2-(naphthalene-1-yl) acetic acid (14.6 g, 78 mmol) in anhydrous CH$_2$Cl$_2$ (155 mL), oxalyl chloride (9.4 mL, 108 mmol) was added followed by anhydrous DMF (0.15 mL, 2.0 mmol). The reaction mixture was stirred for one hour at room temperature. Following completion of the reaction, the solvent was removed by rotary evaporator, to yield a yellow oil. Oxalyl chloride was removed by diluting the reaction mixture with anhydrous CH$_2$Cl$_2$ (300 mL) and removing it in vacuo. The product was then used in the next step without further purification.

Acenaphthylen-1(2H)-one was prepared following the previously reported literature procedure with the following modifications.\textsuperscript{23} To a solution of 2-(naphthalene-1-yl)acetyl chloride in anhydrous CH$_2$Cl$_2$ (110 mL) aluminum trichloride (17.1 g, 128 mmol) was added in small portions over the course of 30 min. Upon completion of the addition of AlCl$_3$, the reaction turned dark green and was allowed to stir for 3 hours at room temperature. The reaction was then poured over ice, and once the ice melted it was extracted 3 x 50 mL of CH$_2$Cl$_2$. The organic layers were combined and then dried over magnesium sulfate. The solvent was concentrated down in vacuo and then passed through a silica plug using CH$_2$Cl$_2$. The filtrate was then concentrated down on the rotary evaporator and the resulting solid was recrystallized using DCM/hexanes to give the product as a yellow solid in 58% yield. $^1$H NMR: (600 MHz, CDCl$_3$) $\delta$ 8.07 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 6.9 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 3.80 (s, 2H) ppm. $^{13}$C NMR: (151 MHz, CDCl$_3$) $\delta$ 203.1, 143.1, 135.2, 134.8, 131.6, 131.1, 128.5, 128.2, 124.1, 121.2, 42.2 ppm. The spectra were in accordance with those in the literature.\textsuperscript{26}

2-(acenaphthylen-1(2H)-ylidene)malononitrile was prepared according to the previously reported procedure with some modifications.\textsuperscript{17} To a round bottom flask malononitrile (2.36 g, 35.7 mmol), ammonium acetate (0.55 g, 7.1 mmol), acetic acid (2.25 mL, 39.2 mmol), and acenaphthylen-1(2H)-one (6.00 g, 35.7 mmol), and anhydrous toluene (22.5 mL) were added. The flask was attached to a Dean-Stark trap and refluxed for 2 h. The reaction was then cooled in an ice bath, and the resulting precipitate was collected by vacuum filtration and washed using cold ethanol, water, and hexanes. The solid was
then dried under vacuum to give the product in 77% yield as an orange solid. $^1$H NMR: (600 MHz, CDCl$_3$) δ 8.07 (d, J = 8.0 Hz, 1H), 7.95 (d, J=6.9 Hz, 1H), 7.81 (d, J= 8.8 Hz, 1H), 7.70 (t, J=7.7Hz, 1H), 7.58 (t, J=7.5Hz, 1H), 7.45 (d, J= 7.5 Hz, 1H), 3.80 (s, 2H) ppm. $^{13}$C NMR: (151 MHz, CDCl$_3$) δ 203.1, 143.2, 135.2, 134.8, 131.6, 131.1, 128.5, 128.2, 124.1, 121.2, 42.2 ppm.

(E)-2-(2-((dimethylamino)methylene)acenaphthylene-1-(2H)-ylidene)malononitrile (43) were prepared according to the previously reported procedure with the following modifications.\textsuperscript{17} To a slurry of 2-(acenaphthylene-1(2H)-ylidene)malononitrile (6.49 g, 30.0 mmol) and acetic anhydride (0.57 mL, 6.0 mmol) in anhydrous toluene (50.0 mL), DMF-DMA (4.8 mL, 36 mmol) was added dropwise. The reaction was stirred at room temperature overnight and then concentrated down in vacuo. The crude reaction mixture was then passed through a silica plug using 50:50 CH$_2$Cl$_2$/hexanes followed by 100% CH$_2$Cl$_2$ to elute the product. The product was then recrystallized using toluene/hexanes to yield the product as a dark purple solid in 61% yield. $^1$H NMR: (600 MHz, CDCl$_3$) δ 8.58 (d, J = 7.4 Hz, 1H), 8.48 (s, 1H), 7.92 (d, J=8.0 Hz, 1H), 7.58 (m, 2H), 7.48 (t, J=7.7 Hz, 1H), 7.24 (d, J=7.1 Hz, 1H), 3.44 (s, 6H) ppm. $^{13}$C NMR: (151 MHz, CDCl$_3$) δ 162.4, 153.2, 135.8, 135.4, 132.8, 131.2, 130.1, 128.3, 128.0, 125.6, 122.9, 119.6, 118.4, 118.1, 107.0, 45.6 ppm. HRMS (EI+) calcd for C$_{16}$H$_{14}$N$_3$, 272.11905; found, 272.11877.

1.4.4 Preparation and Characterization of the Propylamine Exchange Reaction Products

2-imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile (26). To a round bottom flask containing (E)-2-(4-(dimethylamino)but-3-en-2-ylidene)malononitrile (0.40 mg, 2.5 mmol) was combined with anhydrous CH$_2$Cl$_2$ (2.5 mL). To the reaction mixture propylamine (0.6 mL, 7.44 mmol) was added and then the reaction was allowed to stir for 24 h and the solvent was then removed in vacuo to yield a brown sticky solid. Hexanes was added to the solid and was sonicated for 30 min and the resulting precipitate was collected by vacuum filtration, and the filtrate was concentrated in vacuo. After drying over night 2a was obtained as a yellow solid at 57% yield. The solid was recrystallized in toluene/n-heptane. $^1$H NMR: (600 MHz, CDCl$_3$) δ 7.07 (d, J=7.0 Hz, 1H), 6.43 (br s, 1H), 5.65 (d, J=7.0 Hz, 1H), 3.85 (t, J=7.3 Hz, 2H), 2.28 (s, 3H)m 1.80 (sext, J=7.4 Hz, 2H), 0.97 (t, J=7.4Hz,
2-imino-4,5-diphenyl-1-propyl-1,2-dihydropyridine-3-carbonitrile (29). To a solution of 2-(3-(dimethylamino)-1,2-diphenylallylidene) malononitrile (0.15 g, 0.50 mmol) in acetonitrile (5 mL) propylamine (0.5 mL, 6 mmol) was added. The reaction mixture was allowed to stir for 5 h at which time a yellow precipitate formed. The solid was collected using vacuum filtration and rinsed with cold MeCN to yield the product as a yellow solid in 60% yield. The solid was recrystallized in MeCN for the crystal structure. \(^1\)H NMR: (600 MHz, CDCl\(_3\)) δ 7.27 (m, 4H), 7.13 (m, 5H), 6.86 (m, 2H), 6.70 (br s, 1H), 3.97 (t, J=7.4 Hz, 2H), 1.89 (sext, J=7.3 Hz, 2H), 1.03 (t, J=7.4 Hz, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 156.3, 155.4, 142.2, 135.5, 135.2, 129.2, 129.1, 128.8, 128.3, 128.2, 127.0, 116.9, 116.6, 102.6, 53.5, 21.0, 11.2 ppm.

9-imino-8-propyl-8,9-dihydroacenaphtho[1,2-c]pyridine-10-carbonitrile (35). To a solution of (E)-2-(2-((dimethylamino)methylene)acenaphthaylen-1-(2H)-ylidene) malononitrile (0.067 g, 0.25 mmol) dissolved in anhydrous CH\(_2\)Cl\(_2\) (100 mL) propylamine (0.60 mL, 7.3 mmol) was added. The solution was stirred for 4 hours and then the reaction was concentrated down. The orange solid was recrystallized in CH\(_2\)Cl\(_2\)/n-heptane to yield the product as an orange solid in 17% yield. \(^1\)H NMR: (600 MHz, CDCl\(_3\)) δ 8.33 (m, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.73 (d, J=8.6 Hz, 1H), 7.67 (m, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.52 (m, 1H), 4.01 (t, J=7.4 Hz, 2H), 1.90 (sext, J=7.5 Hz, 2H), 1.05 (t, J=7.4 Hz, 3H) ppm. \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 156.0, 152.1, 135.6, 134.8, 133.0, 132.1, 130.7, 130.6, 128.7, 128.5, 124.8, 124.4, 117.0, 116.2, 115.7, 94.3, 54.3, 21.5, 11.4 ppm. HRMS (EI+): calcd. for C\(_{19}\)H\(_{16}\)N\(_3\), 286.13442; found: 286.13487.
1.4.5 $^1$H and $^{13}$C NMR Spectra of 20

2-Imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile

2-Imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile
1.4.6 $^1$H and $^{13}$C NMR Spectra of 38
1.4.7 $^1$H and $^{13}$C NMR Spectra of 43

(E)-2-[(dimethylamino)methylene]acenaphthylene-1(2H)-ylidene)malonitrile

[NMR spectrum]

(E)-2-[(dimethylamino)methylene]acenaphthylene-1(2H)-ylidene)malononitrile

[NMR spectrum]
1.4.8 $^1$H and $^{13}$C NMR Spectra of 26

2-imino-4-methyl-1-propyl-1,2-dihydropyridine-3-carbonitrile

[Chemical structures and NMR spectra images]

34
1.4.9 $^1$H and $^{13}$C NMR Spectra of 29

2-imino-4,5-diphenyl-1-propyl-1,2,3,4-tetrahydropyridine-3-carbonitrile

[Diagram of NMR spectra with chemical shifts and peak assignments]

2-imino-4,5-diphenyl-1-propyl-1,2,3,4-tetrahydropyridine-3-carbonitrile

[Diagram of NMR spectra with chemical shifts and peak assignments]
1.4.10 $^1H$ and $^{13}C$ NMR Spectra of 35

9-imino-8-propyl-9,9-dihydrosacarosephof1,2-cyridine-10-carbonitrile

9-imino-8-propyl-9,9-dihydrosacarosephof1,2-cyridine-10-carbonitrile
1.4.11 Spartan HOMO-LUMO Mappings of 26

HOMO
(-5.65 eV)

LUMO
(-1.34 eV)

1.4.12 Spartan HOMO-LUMO Mappings of 29

HOMO
(-5.60 eV)

LUMO
(-1.69 eV)

1.4.13 Spartan HOMO-LUMO Mappings of 35

HOMO
(-5.36 eV)

LUMO
(-2.11 eV)
1.4.14 Experimental procedures for vapor detection and solution

Absorption Spectroscopy. The UV-Visible spectra were recorded using the Edinburgh integrating sphere accessory with an Edinburgh FLS980 spectrometer using either a 1 cm cuvette or placing the media on a Benflect plug insert. Solutions Kinetics measurements were acquired with the same instrument and cuvette but the sample was stirred by using a small magnetic stir bar.

Steady-State and Time-Resolved Emission data were collected at room temperature using an Edinburgh FLS980 spectrometer. A housed 450 W Xe lamp with a single grating (1800 l/mm, 250 nm blaze) Czerny-Turner monochromator was used to excite the sample. For 1b and 2b the excitation light was passed through a 0.5 nm bandwidth slit while for 1c and 2c the excitation light was passed through a 2.5 nm bandwidth slit. The resultant emission from the samples was passed through the appropriate long-pass color filter first, followed by a single grating (1800 l/mm, 500 nm blaze) Czerny-Turner monochromator. The emission bandwidth for 1b and 2b was set to 0.5 nm and the emission bandwidth for 1b and 2b was set to 1.0 nm. The resultant emission was detected by a peltier-cooled Hamamatsu R928 photomultiplier tube. The absolute emission quantum efficiency of the samples was measured using the Edinburgh integrating sphere accessory following the De Mello method. No filters were used for the quantum yield measurements.

The emission decays were monitored using the FLS980’s time-correlated single-photon counting capability (1024 channels; 100 ns window). For 2b data collection occurred over 10,000 counts and for 2b data collection occurred over 5,000 counts. Samples were excited by using an Edinburgh EPL-445 picosecond pulsed diode laser (445 nm, 100 ps) operated at 10 MHz. The time-resolved emission data was fit by using an exponential function by using Edinburgh software package.

Kinetic Experiments:
Media was prepared by dipping it into a solution of 1b (DCM, 0.05M) 2 times allowing for the media to dry after each coating. The media was then dried under high vac to remove the last of the DCM and the media was inserted into a specialized cuvette (shown below) that contained a small test tube of propylamine solution that was (33 v/v% in water) The emission intensity was measured every 3 minutes over the course of 10 h.
**Sensitivity Experiments:**

1b was coated on aluminum oxide neutral and 1c was coated onto glass filter paper. Each media was coated with a solution of the corresponding compound by dipping it into a 0.5 M solution in DCM twice allowing for the media to dry in between coatings. The last of the DCM was removed under vacuum. The media was then inserted into a specialized chamber that already had the amine in the chamber. The amine had been injected ~30min prior to insertion of the media to allow for the chamber to equilibrate. Each media was then left in the chamber for 1 hour to allow for the reaction to occur.
Qualitative Selectivity Experiments

1b on AON was prepared following the procedure described above for the sensitivity experiments. In a 20 mL screw cap vial the media coated in 1b was inserted along with the appropriate analyte and allowed to react for 1 h before emission data was obtained.

X-Ray Crystallography

A single crystal was suspended in Paratone-N oil and mounted on a cryoloop. The crystal was then placed under a stream of cold N$_2$ and the temperature was reduced at a rate of 5 K/min until it reached a temperature of 230 K. The data sets were recorded with ω-scans at 0.3° stepwidth and integrated using a Bruker SAINT software package. For all experiments a multi-scan adsorption correction was performed with XPREP, and the solution refinement of the crystal structures were carried out using the SHELX programs. The final refinement was preformed with anisotropic atomic displacement parameters for all atoms but hydrogen which were placed in calculated positions. Labeled ORTEP plots of 26 and 29 are shown below.
Emission Decay Data of 28 on various media
Emission decay traces of 26 (Ex: 405 nm), 29 (Ex: 400 nm), and 35 (Ex: 445 nm) in CH$_2$Cl$_2$ at 25 °C
Emission decay traces of 20, 26, 38, 29, 43, and 35 in 2-MeTHF at 77K

Absorption spectra of 20 and 26 in CH$_2$Cl$_2$ at 25°C
Absorption spectra of 38 and 29 in CH₂Cl₂ at 25°C

Absorption spectra of 43 and 35 in CH₂Cl₂ at 25°C
Normalized emission spectra of 26 at 25°C in various solvents

Absorption spectra of 26 at 25°C in various solvents
CHAPTER 2
PYRIDAZINE N-OXIDES AS PHOTOCHEMICAL PRECURSORS TO DIAZO COMPOUNDS AND PYRAZOLE SYNTHESIS

2.1 Introduction

Over the past fifteen years interest in the synthesis and reactivity of pyrazole (44) containing compounds has increased steadily.¹ This growing interest can be attributed to the varied biological activity associated with this class of compounds.² Pyrazole derivatives have shown to have activities ranging from antimicrobial, analgesic, and anti-inflammatory to antidepressant and anticonvulsant.³ Some pyrazole derivatives have found utility in the agricultural

Figure 2.1 Pyrazole Containing Biologically Active Compounds.
industry as insecticides. Pyrazoles, five membered heterocycles with two adjacent nitrogen atoms, are also found in a number of active pharmaceutical ingrediants (APIs) currently being sold. Some examples of these APIs include: AM251 (45), dercoxib (46), tepoxalin (47), cyantraniliprole (48), celecoxib (49). AM251 has been found to be an inverse agonist to the CB₁ cannabinoid receptor as well as a μ-opioid receptor antagonist.⁴ Compounds 46 and 47 are both used in veterinary medicine as non-steroidal anti-inflammatory drugs (NSAIDs) used for pain management.⁵,⁶ In addition to being used in the treatment of various inflammatory diseases, such as osteoarthritis and ankylosing spondylitis, 49 has shown to have possible activity in the treatment of psychological disorders.⁷ Cyantraniliprole is used as an insecticide belonging to the ryanoid class, because of its uncommon mechanism of action it is active against insects that have developed resistance to other classes of insecticides.⁸

With the growing interest in pyrazoles derivatives several syntheses have been utilized for their generation (Figure 2.2).⁹ One of the two most common methods used for the synthesis of 44 derivatives is the condensation of hydrazine containing compounds with a 1,3-dielectrophilic speicies (Figure 2.2A).¹⁰ This method utilizes a hydrazine as the neucleophile, and a three carbon

\[ A \]

\[ B \]

\[ C \]

\[ D \]

Figure 2.2 Methods for the Synthesis of Pyrazoles.
unit featuring two electrophilic carbons, that are oriented in a 1,3-relationship. This method suffers from a lack of regioselectivity when an unsymmetrical 1,3-dielectrophile is used with a substituted hydrazine. This substitution on the hydrazine prevents the tautomerization of the compound that could occur with a non-substituted variant (Scheme 2.1). Another limitation to this methodology is the lack of access to 1,3-dielectrophilic building blocks, however there have been new methods to generate these compounds insitu (Figure 2.2 C).

Scheme 2.1 Mechanism of Condensation Reaction between Hydrazine and 1,3-Dielectrophiles.

A second common method for the synthesis of pyrazoles is the 1,3-dipolar cycloaddition (Figure 2.2B). There are three common types of 1,3-dipoles used in this methodology; diazoalkanes (50), nitrilimines (51), and azomethine imines (52, Figure 2.3). This method offers improved regioselectivity than the condensation of 1,3-dielectrophiles, because this method does not rely on the different reactivity of the electrophilic carbons. Instead this methodology relys on the electronegativity difference of the nitrogen and carbon atom in the 1,3-dipole for control of regioselectivity.
Figure 2.3 Three Types of 1,3-Dipoles.

A method that has started to see growing interest and use for pyrazole synthesis is that of multicomponent reactions (Figure 2.2C). This method allows for more than two building blocks to come together in the reaction mixture. The variety of building blocks that can be chosen allows for more diversity in the products. In addition, this method allows for the formation of difficult to obtain 1,3-dielectrophilic compounds. The final example utilizes a diazoacetate and enol triflates in order to complete a tandem cross-coupling and electrocyclization (Figure 2.2D). This method utilizes fully substituted and stereodefined enol triflates along with diazoacetates to synthesize pyrazoles. By going through this method, Frantz and co-workers were able to generate a diazoalkene in situ in the correct conformation that allowed for the electrocyclization to occur (Scheme 2.1).

Scheme 2.2 Tandem Cross-Coupling and Electrocyclization

These methods all utilize acyclic precursors for the synthesis of pyrazoles. However, recently there has been a push to synthesize nitrogen heterocycles using ring opening reactions. These types of reactions allow for the formation of reactive intermediates in situ that are quickly used for the synthesis of complex molecules. One example of this type of chemistry is the work
published by Vanderwaal and co-workers. Utilizing the formation of a Zincke aldehyde they were able to complete the shortest synthesis to strychnine (62).\(^4\) Vanderwal and coworkers reacted an activated pyridine salt (59) with the secondary amine (58) that they had generated through a nucleophilic substitution reaction (S\(_{N}2\)) with allylamine and the appropriate indole (57). Upon reacting 59 with 54 the Zincke aldehyde (56) was formed in the appropriate orrientation needed for an intramolecular Diels Alder reaction. Through this work Vanderwal and co-workers obtained 62, following three additional steps from the intermediate 61, for a total of six total steps. Their group’s utilization of this ring opening chemistry has also allowed them to synthesize norfluorocurarine, dehydrodesacetylretuline, and valparicine, in addition to the synthesis of the antitumor antibiotics porothramycins A and B.

Four years prior to Vandwerwal’s strychnine synthesis Gevorgyan and co-workers showed the utility of pyridotriazoles for transanulations (Scheme 2.4).\(^5\) Their work was based on chemistry previously published by the groups of Davies\(^6\), Padawa\(^7\), and Helequist.\(^8\) These
groups utilized the transannulation of diazocarbonyl compounds with either alkenes or alkynes to form furan and oxazole ring systems. Gevorgyan and co-workers added to this knowledge by utilizing the equilibrium of a pyridotriazole (66) and its open 2-pyridyl diazo form (67). The equilibrium for 66 to 67 lies towards 66 with only small amounts of 67 present in the reaction mixture. This small amount of 67 reacts with the rhodium catalyst to form the reactive metalocarbene species. The formation this species produces more of 67 based on Le chatlier principle. After its formation the metalocarbene then reacts with either an alkyne to form an indolizine, or a nitrile to form an imidazopyridine.

Scheme 2.4 Gevorgyan Rh-Catalyzed Transannulation of Pyridotriazoles.

Here in I describe a new synthetic strategy towards 3,6-disubstitutes pyridazine N-oxides (70). Our group was able to achieve a regioselective synthesis for these pyridazines starting from commercially available dichloropyridazine. Following their formation these disubstituted N-oxides are used as photochemical precursors to a diazocarbonyl intermediate that is then cyclized to form pyrazoles.

Figure 2.4 General Pyridazine N-Oxide Utilized in this Work
2.2 Results and Discussion

Our chemistry is based on work previously published by Buchardt and co-workers (Scheme 2.5). They showed that under photochemical conditions pyridazine N-oxides (71) underwent a ring opening reaction to form the diazocarbonyl species (73). They hypothesized that the ring opening went through the oxaziridine intermediate (72) however, they never isolated or observed its formation. From 73 they were able to form either a furan or a pyrazole based on one of two pathways. The furan is generated through the phtochemical loss of molecular nitrogen to form a carbene. The carbene then reacts with the oxygen of the carbonyl to generate the furan. The pyrazole is formed in a thermal 1,5-cyclization process. This chemistry allowed for the formation of either of these two species under mild conditions. However, there were two main challenges to this chemistry: (1) challenge was the inability to substitute two different functional groups at the third and sixth position on the pyridazine, and (2) it is difficult to partition between the two mechanisms to give only one product. Our group envisioned that by understanding and controlling the reactivity of the diazo intermediate we could better partion between the two mechanisms and form only the pyrazole.

Scheme 2.5 Photochemical Ring Opening of Pyridazine N-Oxides.

The ability to generate new bonds utilizing pyridazine N-oxide generated diazocarbonyls was shown by Katukoivava and co-workers who utilized rhodium catalysis to form alkylindoles (Scheme 2.4). They were able to open the pyridazine by first installing a methyl group on the oxygen and reacting it with potassium hydroxide (KOH) to form intermediate 78. After its formation 78 was then reacted with a rhodium catalyst and a pyrrole. Following the reaction with
the pyrrole the compound undergoes a 6π electrocyclization to form an indole (79). The substrate scope for their work is limited to an aryl group at R^1 and alkyl groups at R^2 and R^3. The substitution pattern for the pyridazine is also another drawback, because it is limited to either 3,5 or 3,4 on the pyridazine. We believed we could improve upon this methodology by utilizing photochemistry to shorten the route to the diazocarbonyl species. Another benefit to our use of photochemistry is our ability to utilize mild reaction conditions to build complexity on our compounds.

Scheme 2.6 Katukojvala Rhodium Catalyzed Transannulation of Pyridazine N-Oxides.

My first goal in developing a regioselective synthesis towards 3,6-disubstituted pyridazine N-oxides was to generate chloropyridazine N-oxide. To generate this species I began with the synthesis of dichloropyridazine (81) by reacting commercially available maleic hydrazine with phosphorus oxychloride (POCl_3) in a dehydration reaction. After the formation of 81 a nucleophilic aromatic substitution (S_NAr) using benzyl alcohol was completed (Scheme 2.7).

Scheme 2.7 Synthesis of Dichloropyridazine N-Oxide
Over the course of the SNAr to form 82 a small amount of by product formed. This by
product was identified as the disubstituted product. The disubstituted product was removed
through column purification. Following the purification of 82, a hydrogenolysis was then
performed to remove the protecting group as well as the chlorine atom and form 83. The difficult
step in this reaction sequence was the formation of chloropyridazine (84) because of its stability
and solubility. However, by limiting the amount of POCl₃ in the reaction and the water used in the
work up I was able to increase the yield from 31% to 85%. The final step in the reaction sequence
was the oxidation of 84 to form 85. Our group hypothesized that this reaction would be
regioselective because of the electron withdrawing effects of chlorine on the adjacent nitrogen.
The NMR for this reaction showed that our hypothesis was correct and a subsequent crystal
structure showed we had formed the desired regioisomer (Figure 2.5).

![Figure 2.5 Crystal Structure of Chloropyridazine N-Oxide](image)

With the knowledge we could regioselectively form simple pyridazine N-oxides my next
goal was to see if I could regioselectively form the desired 3,6-disubstituted pyridazine N-oxide.
To achieve this goal I took 82 and subjected it to the same oxidation conditions that were used to
form 85. My goal was to oxidize the nitrogen adjacent to the benzyl group, hypothesizing that
nitrogen would be the more reactive of the two because of the electron donating ability of the
benzyl group. The NMR for the reaction showed the formation of only one regioisomer, but upon
obtaining the crystal structure for the compound we found that we had oxidized the nitrogen adjacent to the chlorine atom (Figure 2.6).

![Crystal Structure of 3-(benzyloxy)-6-chloropyridazine 1-oxide](image)

**Figure 2.6 Crystal Structure of 3-(benzyloxy)-6-chloropyridazine 1-oxide**

From these results we then hypothesized that utilizing a nitrogen substituent would allow for us to form our desired regioisomer based on its stronger electron donating capabilities. To form the amine substituted pyridazine I took 81 and reacted it with dimethylformamide. The reaction was stopped after forty eight hours and I was able to isolate 88 in 41% yield (Scheme 2.8). This reaction was slow with the majority of the reaction mixture containing starting material after 24 h and even with maintaining the reaction for 48 h, I still had only observed a 50% conversion. Following this reaction I then completed the oxidation using the standard oxidation conditions that were used to form 86 and 85. The reaction for this substrate was slower then the other two oxidations, with the major product that was isolated being unreacted starting material. However, there was only one other product formed and isolated over the course of the reaction and upon obtaining its crystal structure we found that we had again oxidized the position adjacent to the chlorine (Figure 2.7).

![Oxidation Reaction Scheme for Amine Susstituted Pyridazine](image)

**Scheme 2.8 Oxidation Reaction Scheme for Amine Susstituted Pyridazine.**
From these results we decided to begin with the oxidation of the symmetrical dichloropyridazine. I began the oxidation by utilizing the standard oxidation procedure that been established in our group. However, over the course of the reaction I found the electron withdrawing effects of the two chlorine atoms slowed the progression of the reaction considerably. Using mCPBA in CH₂Cl₂ at reflux for forty eight hours I was only able to generate a 70% yield of the desired product. While I continued using these conditions to build up starting material a fellow graduate student Michael Maxwell found a paper published by Caron’s group. Caron and co-workers utilized urea hydrogen peroxide (UHP) and trifluoroacetic acid (TFAA) to form a strong peracid that was used to oxidize pyridines under mild conditions (Equation 2.1).\(^\text{21}\) Utilizing these conditions Michael was able to synthesize 3,6-dichloropyridazine \(N\)-oxide (92) within 30 min after the complete addition of the TFAA in a 90% yield (Scheme 2.9).

\[ \text{Equation 2.1 UHP/TFAA Oxidation of Pyridines.} \]
Scheme 2.9 Synthesis of Piperidine Substituted Pyridazine N-Oxide.

With the oxidation product in hand I then attempted to complete the S_NAr with piperidine. I changed the amine so that I could utilize milder reaction conditions that would not affect the oxygen that had been installed. The reaction was completed in tetrahydrofuran (THF) with potassium carbonate (K_2CO_3). After 10 hours there was complete consumption of the starting material and with the formation of one regioisomer. I obtained a crystal structure for the isolated product and found that we had again for the undesired regioisomer.

After this reaction we hypothesized that the chlorine atom located away from the oxidized nitrogen was more reactive, and that in order to obtain the correct regioisomer we needed to react at this position first. To test this hypothesis I began with the Suzuki coupling instead of the substitution reaction (Equation 2.2). This reaction produced only one regioisomer and upon obtaining the crystal structure we found that we had generated the desired product (Figure 2.8). However, using palladium acetate, triphenyl phosphine, and potassium phosphate as the Suzuki coupling condition only gave a 37% yield after eighteen hours with the mass balance being the unreacted starting material.

Equation 2.2 Original Suzuki Coupling Conditions.
After obtaining the desired regioisomer Michael was tasked with optimizing the Suzuki coupling. To begin he looked at the mechanism for the coupling, which involves three main steps the oxidative addition, transmetalation, and reductive elimination, and identified two areas where we could optimize the reaction (Figure 2.9). The first area was the oxidative addition in which palladium(0) inserts into the carbon chlorine of dichloropyridazine N-oxide. This part of the reaction mechanism relies on the bond strength of the aryl halide. Generally aryl chlorides are slow to react under these conditions because strength associated with carbon chlorine bonds compared with carbon iodide and carbon bromide bonds (bond dissociation energies aryl halides: C-Cl = 96 kcal/mol, C-Br = 81 kcal/mol, C-I = 65 kcal/mol). In order to optimize this step in the reaction mechanism we would have to exchange the chlorine atom for either bromine or iodine. However, we wanted to use the least expensive commercially available starting material, we decided to forgo optimizing this step and focus on the second area. The second area we could potentially optimize was the cis/trans ligand isomerization step that precedes the reductive elimination of the product from the palladium. In order to bypass the cis/trans isomerization our group choose to change the ligand from triphenyl phosphine to 1,1’-bis(diphenylphosphino)ferrocene (dppf) in the reaction. Dppf is a bidentate ligand which eliminates the cis/trans ligand isomerization step in the suzuki coupling because the phosphine ligands are tied together by ferrocene. Utilizing this new ligand Michael was able to improve our Suzuki coupling yield from a 37% yield in 10 hours to 92% in one hour.
Figure 2.9 Suzuki Coupling Mechanism.

Michael and I along with another graduate student Maribel Portillo then used these conditions to synthesize seven additional Suzuki coupling substrates in addition to the phenyl substrate (Figure 2.10). Michael and Maribel were able to synthesize compounds 99, 101, 102, and 103, while I worked on the synthesis of 97, 98, and 100. Over the course of these reactions we found that substrates with substituents that were electron donating worked well under these conditions. However, boronic acids that contained electron withdrawing groups or were sterically hindered gave reduced yields.
With the Suzuki coupling substrates we then completed the substitution reaction with pyrrolidine to generate the disubstituted pyridazine N-oxide. The $S_N$Ar was carried out under mild conditions in THF using potassium carbonate as the base. These conditions were optimized by Maribel and the reaction times ranged anywhere from eight to ten hours. These conditions worked moderately well with all the substrates giving yields from 62-94% (Figure 2.9). Compound 101 was low yielding giving a 49% yield, but we hypothesized this was due to the strong electron withdrawing effects of the two chlorine atoms on the phenyl group. Following the substitution reaction we obtained one final crystal structure of 104 to ensure the oxygen had not been removed over the course of the two reactions (Figure 2.10). The crystal structure showed that the oxygen had not been eliminated over the course of the two reactions and we had obtained the desired photochemical precursor.
Following the S\textsubscript{N}Ar addition of pyrrolidine to our substrates and insuring the oxygen was still attached to our compound, Maribel and Maxwell then used a Rayonet photoreactor to carry out the photochemical rearrangement of the pyridazine substrates to their corresponding pyrazoles. To start Maribel wanted to limit the formation of the other by-products that were previously reported. In order to achieve this goal she began with a screening concentrations using THF as the solvent in order to prevent the dimerization of the diazocarbonyl species. She found that running the reaction at 0.1 M and 0.3 M gave roughly the same results with a 90:10 product to by product.
ratio. While at 0.5 M concentration we obtained a 95:5 product to by product ratio. For the purposes of practicality in running the reactions and solubility of our starting material she chose to use 0.3 M for the reaction concentration.

![Figure 2.13 Photochemical Rearrangement Products]

Following the identification of the appropriate concentration she looked into the effects of solvents on the two reaction pathways and found that polar solvents such as methanol and acetonitrile increased the formation of the furan ring as did CH$_2$Cl$_2$ and dioxane. While toluene and tetrahydrofuran limited the formation of the furan ring and generated mainly pyrazole. THF was chosen as the solvent to continue because of solubility issues for some of the substrates in toluene. In addition to solvent and concentration she found that by turning off the fan in the photoreactor and increasing the temperature from 35 °C to 65 °C she could generate more of the desired pyrazole which occurs through a thermal pathway. The photochemical rearrangement
occurred in high yields for all substrates except for 115, 119, and 117 which all gave low yields. Compound 117 was slow to react and after 10 hours mainly starting material was recovered (Figure 2.11) However, after Maribel diluted the sample she was able to obtain the product in an 88% yield. With compounds 115, and 119 we hypothesized the low yield was because of the strong electron donating capabilities of the aromatic substituents.

2.3 Conclusions

Our group has been able to show that one can control the regioselctivity for the substitution of pyridazine N-oxide by beginning with the Suzuki coupling and then completing a S$_{N}$Ar reaction. These conditions work well with both electron donating and electron withdrawing substituents on the aryl ring, though the yield is lower with electron with drawing and sterically encumbered boronic acids. The same trend is seen with the nucleophilic aromatic substitution with pyrrolidine. The reaction time for this step in the sequence is relatively slow when compared to the other two steps, however by generating a harder nucleophile by changing the base our group could possibly improve upon this reaction even further. Through this work we have also demonstrated the ability to partition between the two photochemical pathways of substituted pyridazine N-oxides by controlling the the diazocarbonyl intermediate formed through the photochemical ring opening. In the future our group can capture this diazocarbonyl intermediate with a metal catalysis to generate a metal carbenoid and generate new carbon-carbon and carbon-nitrogen bonds as a new synthetic route for the synthesis of indolizidines.

2.4 Methods and Characterization

Materials:

Trifluoroacetic acid and pyrrolidine were distilled before use each time. All other reagents were commercially available and were used without further purification.

NMR:

Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on either a Bruker 400 or 600 MHz spectrometer.
Chemical shifts for protons are reported in parts per million (ppm) relative to chloroform-d (CDCl$_3$) and dimethylsulfoxide-d$_6$ (DMSO). Chemical shifts are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t= triplet, q = quartet, quin = quintuplet, sext = sextet, m = multiplet, dd= doublet of doublets), coupling constants in Hertz (Hz), integration.

**X-Ray Crystal Structure**

All single crystals were grown out of CH$_2$Cl$_2$/cyclohexanes through slow evaporation. The crystals were suspended in Paratone-N oil and mounted on a cryoloop. The crystal was then placed under a stream of cold N$_2$ and the temperature was reduced at a rate of 5 K/min until it reached a temperature of 230 K. The data sets were recorded with $\omega$-scans at 0.3° stepwidth and integrated using a Bruker SAINT software package. For all experiments a multi-scan adsorption correction was performed with XPREP, and the solution refinement of the crystal structures were carried out using the SHELX programs. The final refinement was preformed with anisotropic atomic displacement parameters for all atoms but hydrogen which were placed in calculated positions.

**Synthesis of Chloropyridazine N-Oxide**

\[
\begin{align*}
\text{POCl}_3 & \quad \rightarrow \quad \text{BnOH, tBuOK} \\
80 & \quad \rightarrow \quad 81 \\
& \quad \rightarrow \quad 82 \\
\text{H}_2(\text{g}), \text{Pd/C} & \quad \rightarrow \quad \text{POCl}_3 \\
81 & \quad \rightarrow \quad 83 \\
& \quad \rightarrow \quad 84 \\
\text{mCPBA} & \quad \rightarrow \quad 85
\end{align*}
\]
**Dichloropyridazine (80).** In a dry 50 mL round bottom flask equipped with a magnetic stir bar maleic hydrazine (5.00g, 44.6 mmol, 1 equiv) and POCl$_3$ (12.4 mL, 44.6 mmol, 3 equiv) were combined and placed under nitrogen. The reaction was heated to 60 °C and maintained for 16 h. The reaction was cooled to room temperature and neutralized with saturated sodium bicarbonate. The reaction mixture was then transferred to a separatory funnel and extracted with an equal volume of ethyl acetate three times. The organic layers were combined, dried with magnesium sulfate, and concentrated under reduced pressure. The product was obtained as a white solid in a 93% yield (6.18 g, 41.5mmol). $^1$H NMR: (400 MHz, CDCl$_3$) δ$_H$ 7.52 (s, 2H). All spectra were in accordance with those previously reported.

**3-(benzyloxy)-6-chloropyridazine (82).** In a dry round bottom flask potassium t-butoxide (0.8263 g, 7.4 mmol) and dioxane (13.4 mL, 0.5M) were combined and placed under nitrogen. Benzyl alcohol (0.69 mL, 6.7 mmol) was then added drop wise, followed by dichloropyridazine (1.00 g, 6.71 mmol). The reaction was then heated to 110 °C and maintained for three hours. The reaction mixture was then cooled to room temperature and quenched with DI water. The reaction mixture was then extracted with ethyl acetate, and the organic layers combined and dried over magnesium sulfate. The organic layer was then concentrated under reduced pressure and purified over silica using hexanes:ethyl Acetate (3:2) to give the product as a white solid in 81% yield (1.20 g, 5.44 mmol). $^1$H NMR: (400 MHz, CDCl$_3$) δ$_H$ 7.49 (t, $J$ = 4.1, 2H), 7.39 (m, 5H), 7.00 (d, $J$ = 9.2, 1H), 5.54 (s, 2H).

**Pyridazin-3-ol (83).** Pd/C (0.25 equiv) was added to a dry round bottom flask equipped with a magnetic stir bar and nitrogen balloon. To this flask a 0.5M solution of 3-(benzyloxy)-6-chloropyridazine (5.00 g, 22.7 mmol) in methanol/ethyl acetate (45.4 mL, 1:1). The reaction flask was then purged with hydrogen and equipped with a hydrogen balloon. The reaction was maintained for two hours and then filtered over celite. The reaction mixture was concentrated under reduced pressure to yield the product as a white solid in 95% (2.07 g, 21.5 mmol). $^1$H NMR: (400 MHz, CDCl$_3$) δ$_H$ 7.83 (d, $J$ = 2.6, 1H), 7.28 (d, $J$ = 3.8, 1H), 7.00 (d, $J$ = 4.8, 1H).
3-Chloropyridazine (84). In a dry round bottom flask equipped with a magnetic stir bar pyridazin-3-ol (0.2026 g, 2.11 mmol) and POCl₃ (0.59 mL, 6.32 mmol) were combined and placed under an inert atmosphere. The reaction was heated to 60 °C and maintained for four hours. The reaction was then cooled to room temperature and neutralized with saturated sodium bicarbonate. The reaction was then extracted with ethyl acetate and dried with magnesium sulfate. The organic layers were then concentrated under reduced pressure to yield the product as a white solid in 85% yield (0.2052 g, 1.79 mmol). ¹H NMR: (400 MHz, CDCl₃) δH 9.15 (dd, J = 2.0, 1H), 7.56 (dd, J = 3.4, 1H), 7.50 (dd, J = 4.4, 1H).

3-Chloropyridazine N-oxide (85). In a dry round bottom flask equipped with a magnetic stir bar 3-chloropyridazine (0.2003 g, 1.75 mmol) was dissolved in CH₂Cl₂ (5 mL, 0.5M). mCPBA (0.4527 g, 2.62 mmol) was then added to the reaction and the flask was placed under an inert atmosphere. The reaction was maintained at 25 °C for 12 h. After full consumption of the starting material potassium carbonate (1.2093 g, 8.75 mmol) was added to the reaction and maintained for an additional 4 h. The reaction was then filtered and the filtrate was concentrated under reduced pressure to yield the product in 90% yield (0.2054 g, 1.57 mmol) as a white solid. ¹H NMR: (400 MHz, CDCl₃) δH 8.07 (d, J = 3.3, 1H), 7.56 (t, J = 4.8, 1H), 7.12 (d, J = 4.1, 1H).

Synthesis of 6-chloro-3-(dimethylamino)pyridazine-1-oxide

6-chloro-Ν,Ν-dimethylpyrazidin-3-amine (88). In a 100 mL round bottom flask equipped with a magnetic stir bar 3,6-dichloropyridazine (1.00 g, 6.71 mmol, 1 equiv) and dimethylformamide (19. mL, 0.34 M) were combined and heated to 170 °C. The reaction was maintained for 48 h. Following the reaction, the excess dimethylformamide was distilled away from the reaction mixture. The resultant solid was then purified over silica using a solution of hexanes:ethyl acetate (3:2) as the eluent. The product was
obtained as a white solid in 41% yield (0.4337 g, 2.75 mmol). ¹H NMR: (400 MHz, CDCl₃) δ (H) 7.16 (dt, J = 2.7, 1H), 6.77 (d, J = 9.4, 1H), 3.15 (t, J = 1.9, 6H).

**6-chloro-3-(dimethylamino)pyridazine-1-oxide (89).** In a dry round bottom flask equipped with a magnetic stir bar chloro-NN-dimethylpyridazin-3-amine (0.1 g, 0.63 mmol) was dissolved in CH₂Cl₂ (0.5M). mCPBA (0.16, 0.95 mmol) was then added to the reaction and the flask was placed under an inert atmosphere. The reaction was maintained at 25 ºC for 12 h. After full consumption of the starting material potassium carbonate (0.44 g, 3.15 mmol) was added to the reaction and maintained for an additional 4 h. The reaction was then filtered and the filtrate was concentrated under reduced pressure to yield the product in 31% yield (0.034 g, 0.19 mmol) as a white solid. ¹H NMR: (400 MHz, CDCl₃) δ (H) 7.42 (d, J = 9.2, 1H), 6.44 (d, J = 9.3, 1H), 3.10 (s, 6H). ¹³C NMR: (150 MHz, CDCl₃) δ (C) 171.1, 159.1, (CH) 128.4, 115.3, (CH₃) 46.2, 25.3.

**Synthesis of Dichloropyridazine N-Oxide**

![Synthesis of Dichloropyridazine N-Oxide](image)

In a dry two neck round bottom flask equipped with a magnetic stir bar, reflux condenser, and addition funnel dichloropyridazine (1.00g, 6.7 mmol) and UHP (2.52g, 26.85 mmol) were dissolved in anhydrous CH₂Cl₂ and placed under inert atmosphere. TFAA (5.64 g, 26.85 mmol) was then added drop wise through the addition funnel and following complete addition of TFAA the reaction was maintained for 30 min. The reaction was then quenched with sodium thiosulfate and HCl and transferred to a separatory funnel. The aqueous layer was then back extracted with CH₂Cl₂ and the organic layers were combined and washed with saturated sodium bicarbonate. The organic layer was then dried over sodium sulfate and concentrated down to yield 92 as a yellow solid in 90% (0.99 g, 6.03 mmol). mp: 118-119 ºC.
Synthesis of 6-chloro-3-(piperidin-1-yl)pyridazin-1-oxide (94)

In a dry round bottom flask equipped with a magnetic stir bar 3,6-dichloropyridazine N-oxide (0.1g, 0.61 mmol), potassium carbonate (0.25g, 1.82 mmol), piperidine (0.091 mL, 0.92 mmol), and tetrahydrofuran (0.2 M) were all combined. The flask was equipped with a reflux condenser and placed under a nitrogen balloon. The reaction was then heated to reflux for 8 to 10 hours. After consumption of the starting material the reaction was diluted in CH$_2$Cl$_2$ and filtered to yield the product as a yellow solid in 71% yield (0.092g, 0.43 mmol). $^1$H NMR: (400 MHz, CDCl$_3$) $\delta$H 7.36 (d, $J$ = 9.2, 1H), 6.51 (d, $J$ = 9.3, 1H), 3.49 (d, $J$ = 5.1, 4H), 1.59 (quin, $J$ = 8.2, 6H). $^{13}$C (150 MHz, CDCl$_3$): $\delta_c$ (C) 157.9, (CH) 134.1, (C) 125.1, (CH) 104.7, (CH$_2$) 46.2, 25.2, 24.2 ppm.

Synthesis and Characterization of Suzuki Coupling Precursors

*General Procedure*: In a dry shlenck flask equipped with a magnetic stir bar dichloropyridazine N-oxide (1 equiv), boronic acid (1.1 equiv), potassium phosphate tribasic (2 equiv), and Pd$_2$Cl$_2$dpff (0.03 equiv) were all combined. The flask was backfilled with nitrogen three times and placed under a nitrogen balloon. 10:1 dioxane:water (0.3 M) was added to the flask and the reaction was heated to 95 °C and the reaction monitored by TLC until starting material was consumed one to ten hours. The reaction was filtered over a silica plug, concentrated down via rotary evaporator, and purified via column chromatography.
6-Chloro-3-phenylpyridazine-1-oxide (96) Synthesized according to the general Suzuki coupling procedure. Collected as a white solid in 92 % yield. mp: 133-135 °C. $^1$H NMR: (400 MHz, CDCl$_3$) $\delta$H 7.96 (dd, $J$ = 7.9, 2 H), 7.84 (d, $J$ = 8.5, 1 H), 7.50 (m, 3 H), 7.43 (d, $J$ = 8.5, 1 H). $^{13}$C (100 MHz, CDCl$_3$): $\delta$C (C) 157.8, 136.4, (CH) 134.6, (CH$_2$) 132.9, 131.2, 129.1, 127.1, 114.. IR: 3064.1, 1600.7, 1550.98, 1412.87, 1123.4 cm$^{-1}$. HRMS (EI+): calcd for C$_{10}$H$_7$ClN$_2$O 229.0163, found 229.0159

6-Chloro-3-(p-tolyl)pyridazine-1-oxide (98) Synthesized according to the general Suzuki coupling procedure. Collected as a yellow solid in 79 % yield. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.86 (d, $J$ = 8.0, 2 H), 7.80 (d, $J$ = 8.5, 1 H), 7.40 (d, $J$ = 8.5, 1 H), 7.30 (d, $J$ = 7.9, 2 H), 2.42 (s, 3 H). $^{13}$C (151 MHz, CDCl$_3$): $\delta$ (C) 157.8, 141.8, 136.0, (CH) 134.6, (C) 130.2, (CH) 129.9, 127.1, 114.1, (CH$_3$) 21.42. IR (thin film) 3070, 1610, 1554, 1422, 1398, 1118 cm$^{-1}$. HRMS (EI+): calcd for C$_{11}$H$_9$ClN$_2$O 243.0301, found 243.0304

6-Chloro-3-(4-methoxyphenyl)pyridazine-1-oxide (97) Synthesized according to the general Suzuki coupling procedure. Collected as a tan solid in 84 % yield. mp: 166.2-167.5 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.94 (q, $J$ = 2.98, 2 H), 7.78 (d, $J$ = 8.58, 1 H), 7.38 (d, $J$ = 8.58, 1 H), 7.00 (q, $J$ = 2.98, 2 H), 3.88 (s, 3 H). $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ (C)162.2, 157.5, 135.5, 134.4, (CH) 128.8, 125.4, 114. 6, 113.6, (CH$_3$) 55.5. IR (thin film): 2963, 2035, 1606, 1511, 1405, 1288 cm$^{-1}$. HRMS (EI+): calcd for C$_{11}$H$_7$ClN$_2$O$_2$, 237.04308; found 237.04404.

6-Chloro-3-(4-fluorophenyl)pyridazine-1-oxide (100) Synthesized according to the general Suzuki coupling procedure. Collected as a white solid in 67 % yield. mp: 167.5-168.8 °C. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$H 7.97 (quin, $J$ = 3.51, 2 H), 7.84 (d, $J$ = 8.52, 1 H), 7.39 (d, $J$ = 8.52, 1 H), 7.20 (t, $J$ = 8.58, 2 H). $^{13}$C NMR (151 MHz, DMSO): $\delta$C (C) 164.6, 162.9, 155.7, (CH) 135.9, 129.5, 129.4, 116.2, 116.1, 115.0. IR: 3383, 3069, 2256, 1655, 1504 cm$^{-1}$. HRMS (EI+): calcd for C$_{10}$H$_7$ClFN$_2$O 247.0043, found 247.0045
6-Chloro-3-(4-(dimethylamino)phenyl)pyridazine-1-oxide  (99)
Synthesized according to the general Suzuki coupling procedure. Collected as a green/yellow solid in 38 % yield. mp: 224.5-227.3 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.89 (d, $J = 8.9, 2$ H), 7.67 (d, $J = 8.6, 1$ H), 7.32 (d, $J = 8.6, 1$ H), 6.71 (d, $J = 8.9, 2$ H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): δ (C) 157.9, 152.2, 134.1, (CH) 128.3, (C) 119.7, (CH) 113.2, 111.8, (CH$_3$) 40.1 ppm. IR (thin film): 1604, 1519, 1418, 1403, 1285 cm$^{-1}$. HRMS (EI+): calcd for C$_{12}$H$_{12}$ClN$_3$O 272.0566; found 272.05647.

3-(benzo[d][1,3]dioxol-5-yl)-6-chloropyridazine-1-oxide  (103)
Synthesized according to the general Suzuki coupling procedure. Collected as a beige solid in 36 % yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.77 (d, $J = 8.5$ Hz, 1 H), 7.46 (br. d, $J = 8.7$ Hz, 2 H), 7.32 (d, $J = 8.5$ Hz, 1 H), 6.89 (d, $J = 7.9$ Hz, 1 H), 6.05 (s, 2 H) ppm. $^{13}$C NMR (151 MHz, DMSO): δ (C) 156.7, 150.2, 148.7, (CH) 136.1, (C) 135.5, 127.4, (CH) 122.4, 115.2, 109.2, 107.2, 102.4 ppm. IR (thin film) 3029, 1605, 1509, 1417, 1362, 1339, 1265 cm$^{-1}$. HRMS (EI+): calcd for C$_{11}$H$_7$ClN$_2$O 273.0038; found 273.0033

6-Chloro-3-(2,4-dichlorophenyl)pyridazine-1-oxide  (101)
Synthesized according to the general Suzuki coupling procedure. Collected as a white solid in 22 % yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.86 (d, $J = 8.4$ Hz, 1 H), 7.61 (d, $J = 8.3$ Hz, 1 H), 7.54 (br s, 1 H), 7.41 (t, $J = 8.9$ Hz, 2 H) ppm. IR (thin film): 3113.4, 3067, 2923, 2691, 2146, 1592, 1544, 1322 cm$^{-1}$. HRMS (EI+): calcd for C$_{10}$H$_5$Cl$_3$N$_2$O 296.9365; found 296.9360.

6-Chloro-3-(naphthalene-2-yl)pyridazine-1-oxide  (102)
Synthesized according to the general Suzuki coupling procedure. Collected as a white solid in 77 % yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.98 (m, 2 H), 7.90 (m, 2 H), 7.65 (d, $J = 7.0$ Hz, 1 H), 7.54 (m, 3 H), 7.30 (d, $J = 8.3$ Hz, 1 H) ppm. $^{13}$C NMR (151 MHz, CDCl$_3$): δ (C) 159.6, 136.7, (CH)134.3, 133.8, 131.9, 130.9,
130.3, 128.7, 128.3, 127.5, 126.49, 125.2, 124. 4, 118.7 ppm. IR (thin film): 3040, 1542, 1418, 1340, 1246, 1116 cm⁻¹. HRMS (EI⁺): calcd for C₁₄H₉ClN₂O; 264.1113, found 264.1114.

Synthesis and Characterization of S₉Ar Precursors

**General Procedure:** In a dry round bottom flask equipped with a magnetic stir bar aryl chloride (1.0 equiv), potassium carbonate (3 equiv), pyrrolidine (2 equiv), and tetrahydrofuran (0.2 M) were all combined. The flask was equipped with a reflux condenser and placed under a nitrogen balloon. The reaction was then heated to reflux for 8 to 10 hours. After consumption of the starting material the reaction was diluted in CH₂Cl₂ and filtered. The filtrate was concentrated down and the resultant solid was triterated in ethylacetate.

3-phenyl-6-(pyrrolidin-1-yl)pyridazine-1-oxide (104) Synthesized according to the general S₉Ar reaction procedure. Collected as a yellow solid in 94 % yield. ¹H NMR (400 MHz, CDCl₃): δH 7.77 (d, J = 7.3, 2H), 7.44 (q, J = 6.5, 3H), 6.37 (d, J = 8.9, 1H), 3.50 (br. s, 4 H) 2.02 (br. s, 4H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ (C)156.6, 134.4, (CH) 132.6, 132.5, 128.6, 128.5, 128.2, 103.7, (CH₂) 46.8, 25.2. IR (thin film): 3064, 2972, 1591, 1457, 1435 cm⁻¹ HRMS (EI⁺): calcd for C₁₄H₁₅N₃O 264.11128; found 264.11142.

6-(pyrrolidin-1-yl)-3-(p-tolyl)pyridazine-1-oxide (106) Synthesized according to the general S₉Ar reaction procedure. Collected as a yellow solid in 62 % yield. ¹H (400 MHz, CDCl₃): δH 7.82 (d, J = 8.2,
2H), 7.39 (d, J = 8.76, 1H), 7.24 (s, 2H) 7.04 (d, J = 8.7, 1H), 3.71 (t, J = 6.7, 4H), 2.38 (s, 3H), 2.00 (m, 4H).

3-(4-methoxyphenyl)-6-(pyrrolidin-1-yl)pyridazine-1-oxide (105)

Synthesized according to the general S_N_Ar reaction procedure. Collected as a yellow solid in 69% yield. mp: 191.3-192.7 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.87 (d, J = 8.8, 2H), 7.34 (d, 8.7, 1H), 7.02 (d, J = 8.8, 1H), 6.96 (d, J = 8.8, 2H), 3.85 (br. s, 3H), 3.68 (t, J = 6.7, 4H), 2.00 (quin, J = 3.1, 4H). ^13C NMR (100 MHz, CDCl_3): δ (C) 160.5, 148.4, 146.2, 127.0, (C) 127.5118.9, (CH) 115.1, 114.0, (CH_3) 55.2, (CH_2) 49.8, 25.1 ppm. IR (thin film): 2967, 2849, 1606, 1510, 1453, 1327, cm^-1. HRMS (EI+): calcd for C_{15}H_{17}N_3O_2 294.12185; found 294.12195.

3-(4-fluorophenyl)-6-(pyrrolidin-1-yl)pyridazine-1-oxide (108)

Synthesized according to the general S_N_Ar reaction procedure. Collected as a yellow solid in 67 % yield. mp: 163-170 °C. ^1H NMR (400 MHz, CDCl_3): δ_H 7.88 (q, J = 5.3 Hz, 2H), 7.36 (d, J = 8.7, 1H), 7.12 (t, J = 8.6 Hz, 2H), 7.04 (d, J = 8.7 Hz, 1H), 3.71 (t, J = 6.4 Hz, 4H), 2.01 (t, J = 6.6, 4H). ^13C NMR (100 MHz, CDCl_3): δ (C)164.3, 162.6, 147.4, 146.6, 130.7, (CH) 128.0, 127.9, 118.7, 115.8, 115.6, 115.4, (CH_2) 49.9, 25.2 ppm. IR (thin film): 3031, 2971, 2874, 1601, 1504, 1325 cm^-1. HRMS (EI+): calcd for C_{14}H_{14}FN_3O 282.1019; found 281.1020.

3-(4-dimethylamino)phenyl)-6-(pyrrolidin-1-yl)pyridazine-1-oxide (107) Synthesized according to the general S_N_Ar reaction procedure. Collected as a yellow solid in 75 % yield. mp: 215-216 °C. ^1H NMR (400 MHz, CDCl_3): δ_H 7.82 (d, J = 8.73, 2 H), 7.31 (d, J = 8.7, 1H), 6.99 (d, J = 8.7, 1H), 6.73 (d, J = 8.7, 2H), 3.64 (t, J = 6.2, 4H), 3.00 (s, 6H), 1.98 (t, J = 6.2, 4 H) ppm. ^13C NMR (100 MHz, CDCl_3): δ (C) 151.1, 149.4, 145.8, (CH) 127.2, (C) 122.1, (CH) 119.29, 114.78, 112.02, (CH_2) 49.78, (CH_3) 40.26, (CH_2) 25.15 ppm. IR (thin film): 2842, 1605, 1516, 1452, 1352, 1272 cm^-1. HRMS (EI+): calcd for C_{16}H_{26}N_4O 279.0301; found 279.0304.
3-(benzo[d][1,3]dioxol-5-yl)-6-(pyrrolidin-1-yl)-1-oxide (111)

Synthesized according to the general S$_{N}$Ar reaction procedure. Collected as a yellow solid in 64 % yield. mp: 194-195 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 7.68 (d, $J = 8.4$ Hz, 1H), 7.50 (s, 2H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.05 (d, $J = 7.7$ Hz, 1H), 6.13 (s, 2H), 3.59 (s, 4H), 1.92 (s, 4H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_C$ (C) 148.7, 148.5, 147.6, 146.8, 129.1, (CH) 120.5, 120.3, 115.5, 109.1, 106.4, (CH$_2$) 101.9, 49.8, 25.1 ppm. IR (thin film): 2900, 1584, 1556, 1489, 1456, 1259 cm$^{-1}$. HRMS (EI+): calcd for C$_{15}$H$_{15}$N$_3$O$_3$ 286.1191; found 286.1190.

3-(2,4-dichlorophenyl)-6-(pyrrolidin-1-yl)pyridazine-1-oxide (109)

Synthesized according to the general S$_{N}$Ar reaction procedure. Collected as a yellow solid in 49 % yield. mp: 195-201 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 7.62 (d, $J = 8.3$ Hz, 1H), 7.47 (br s, 1H), 7.35 (m, 2H), 7.00 (d, $J = 8.7$, 1H), 3.75 (br s, 4H), 2.00 (br s, 4H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_C$ (C) 146.9, 146.3, 135.3, 132.8, 132.7, (CH) 132.5, 129.8, 127.4, 120.0, 117.4, (CH$_2$) 50.1, 25.2 ppm. IR (thin film) 3055, 2976, 1552, 1457, 1320, 1268, 1101 cm$^{-1}$. HRMS (EI+): calcd for C$_{14}$H$_{13}$Cl$_2$N$_3$O 332.0326; found 332.0325.

3-(naphthalene-2-yl)-6-(pyrrolidin-1-yl)pyridazine-1-oxide (110)

Synthesized according to the general S$_{N}$Ar reaction procedure. Collected as a yellow solid in 88 % yield. mp: 179.5-180.7 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 8.08 (d, $J = 2.4$, 1H), 7.91 (q, $J = 4.6$, 2H), 7.63 (d, $J = 7.0$, 1H), 7.48-7.54 (m, 3H), 7.25 (d, $J = 7.5$, 2H), 7.10 (d, $J = 8.6$, 1H), 3.77 (t, $J = 6.6$, 4H), 2.03 (quin, $J = 2.9$, 4H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_C$ (C) 149.7, 146.6, 133.7, 133.3, 130.7, (CH) 129.4, 128.3, 127.6, 126.6, 125.9, 125.1, 124.9, 120.2, 118.3, (CH$_2$) 49.9, 25.2 ppm. IR (thin film): 2867, 1578, 1448, 1396, 1320, 1268, 1114 cm$^{-1}$. HRMS (EI+): calcd for C$_{18}$H$_{17}$N$_3$O 314.1269; found 314.1264.
Synthesis and Characterization of Pyrazole Products

General Procedure: In a 4 mL vial equipped with a magnetic stir bar the appropriate N-oxide was dissolved in THF (0.3M) and placed in the Rayonet photoreactor that had been heated to 65 °C and excited with 350 nm light. The reaction was monitored by TLC and maintained until all starting material was consumed. The reaction was then purified over SiO$_2$ to yield the pyrazole products.

(3-phenyl-1H-pyrazol-5-yl)(pyrrolidin-1-yl)methanone (112)
Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 92 % yield. mp: 183.4-184.4 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 11.34 (br s, 1H), 7.80 (d, $J = 7.24$, 2H), 7.43 (t, $J = 6.56$, 2H), 7.35 (d, $J = 5.7$, 1H), 6.89 (s, 1H), 3.87 (t, $J = 5.7$, 2H), 3.71 (t, $J = 5.8$, 2H), 2.07 (m, 2H), 1.97 (m, 2H) ppm. IR (thin film): 3115, 2972, 1581, 1456, 1404, 1185 cm$^{-1}$. HRMS (EI+): calcd for C$_{14}$H$_{15}$N$_3$O 264.1113; found 164.1110.

Pyrrolidin-1-yl(3-(p-tolyl)-1H-pyrazol-5-yl)methanone (114)
Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 80 % yield. mp: 203-204 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 7.67 (d, $J = 8.0$, 2H), 7.23 (d, $J = 7.9$, 3H), 6.87 (s, 1H), 3.87 (t, $J = 6.7$, 2H), 3.71 (t, $J = 6.7$, 2H), 2.38 (s, 3H), 2.05 (m, 2H), 1.97 (m, 2H) ppm. IR (thin film): 3115, 2948, 1588, 1456, 1417, 1178, 1001 cm$^{-1}$. HRMS (EI+): calcd for C$_{15}$H$_{17}$N$_3$O 278.1269; found 278.1269.
(3-(4-methoxyphenyl)-1H-pyrazol-5-yl)(pyrrolidin-1-yl)methanone (113) Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 84 % yield. mp: 183-184 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 7.72 (d, $J = 8.76$, 2H), 6.96 (d, $J = 8.76$, 2H), 6.82 (br s, 1H), 3.85 (d, $J = 4.5$, 5H), 3.71 (t, $J = 6.84$, 2H), 2.06 (m, 2H), 1.96 (m, 2H) ppm. IR (thin film): 3113, 2923, 2691, 1896, 1592, 1544, 1413, 1322, 1099 cm$^{-1}$. HRMS (EI+): calcd for C$_{15}$H$_{16}$N$_2$O$_2$ 294.1234; found 2294.1232.

(3-(4-fluorophenyl)-1H-pyrazol-5-yl)(pyrrolidin-1-yl)methanone (116) Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 90 % yield. mp: 211-212 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 7.77 (q, $J = 4.7$, 2H), 7.11 (t, $J = 8.7$, 2H), 6.82 (s, 1H), 3.85 (t, $J = 6.8$, 2H), 3.71 (t, $J = 6.8$, 2H), 2.08 (m, 2H), 1.97 (m, 2H) ppm. IR (thin film): 3173, 1592, 1447, 1209, 1151 cm$^{-1}$. HRMS (EI+): calcd for C$_{14}$H$_{14}$FN$_2$O 282.1019, found 282.1011.

(3-(benzo[\(d\)][1,3]dioxol-5-yl)-1H-pyrazol-5-yl)(pyrrolidin-1-yl)methanone (118) Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 88 % yield. mp: 245-246 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H 7.30 (s, 4H), 6.88 (d, $J = 7.9$, 1H), 6.80 (s, 1H), 6.02 (s, 2H), 3.86 (m, 2H), 3.73 (m, 2H), 2.09 (m, 2H), 1.99 (m, 2H) ppm. IR (thin film): cm$^{-1}$. HRMS (EI+): calcd for C$_{15}$H$_{15}$N$_3$O$_3$ 308.1011; found 308.1006.
(3-(2,4-dichlorophenyl)-1H-pyrazol-5-yl)(pyrrolidin-1-yl)methanone (117) Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 88% yield. mp: 202-203 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 7.77 (d, $J = 8.4$, 1H), 7.48 (d, $J = 2.0$, 1H), 7.32 (dd, $J = 3.4$, 1H), 7.09 (s, 1H), 3.84 (t, $J = 6.7$, 2H), 3.71 (t, $J = 6.8$, 2H), 2.06 (m, 2H), 1.96 (m, 2H) ppm. IR (thin film): 3090, 2977, 1876, 1595, 1404, 1187, 1107 cm$^{-1}$. HRMS (EI+): calcd for C$_{14}$H$_{13}$Cl$_2$N$_3$O 332.0328; found 332.0329.

(3-(naphthalen-2-yl)-1H-pyrazol-5-yl)(pyrrolidin-1-yl)methanone (119) Synthesized according to the general photochemical reaction procedure. Collected as a white solid in 89% yield. mp: 212.5-213.7 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ 8.33 (br s, 1H), 7.89 (d, $J = 7.2$, 2H), 7.64 (d, $J = 6.7$, 1H), 7.52 (t, $J = 6.3$, 3H), 6.94 (s, 1H), 3.89 (t, $J = 6.4$, 2H), 3.72 (t, $J = 6.3$, 2H), 2.04 (t, $J = 6.3$, 2H), 1.95 (t, $J = 6.4$, 2H). IR (thin film): 3119, 2865, 1579, 1509, 1388, 1338 cm$^{-1}$. HRMS (EI+): calcd for C$_{18}$H$_{17}$N$_3$O 314.1269; found 314.1264.
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Diagram showing chemical structure with peaks at various ppm values.
REFERENCES

Chapter One References


Chapter Two References


BIOGRAPHICAL SKETCH

Rebecca Ryann Chandler

EDUCATION

Florida State University – Tallahassee, FL
M. Sc.: Organic Chemistry
Advisor: Dr. James H. Frederich
Aug. 2013 – Present

University of West Florida – Pensacola, FL
Bachelor of Science: Chemistry and Biochemistry
Advisor: Dr. Michael T. Huggins
Aug. 2009 – May 2013

RESEARCH EXPERIENCE

Florida State University: Organic Chemistry
Using computational and synthetic methods to optimize yields and generate new small molecules. Primary amine sensor applications of enamine based compounds. Regioselective synthesis of pyridazine N-Oxides as photochemical precursors to diazo-compounds.
Dec. 2013 – Present

Reduction of Key Target Molecules for Segetis Corporations
Investigated new methods to generate purify three target molecules and generate .5Kg quantities of each, using GC/MS and NMR analysis to monitor reaction progress
August 2012-July 2013

Generation of New Fluorescent Liquid Crystal
Prove purity and understand properties through multiple analytical methods such as DSC, GC/MS, NMR, and TGA.
August 2012-July 2013

Synthesis of Target Polymers for Pall Corporation
Generated multistep pathway to generate key molecules starting from PEG that would be polymerized to form water filters, using Electrospray, and NMR analysis to monitor reaction
August 2011-July 2012

Synthesis and Study of New Hydrogen Bonding Dipyrrinones
Discover/ optimize pathway to generate key dipyrrinone compounds, and use multiple methods to disrupt the self-association attributed to the molecules hydrogen bonding, IR, NMR and GC/MS were used for characterization
May 2011-August 2011

PUBLICATIONS

Longstreet, A. R.; Chandler, R. R.; Banerjee, T.; Hanson, K.; Miller, L.Z.; McQuade, D. T.; Ylidemalononitrile Enamines as Fluorescent “Turn-On” Probes (Manuscript Submitted)


PRESENTATIONS


AWARDS

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<td>American Institute of Chemists Foundation Award</td>
<td>University of West Florida</td>
<td>April 2013</td>
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<td>Grace Po-Yuen Chiu Scholarship</td>
<td>University of West Florida</td>
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<td>The Pall Corporation Scholarship</td>
<td>University of West Florida</td>
<td>August 2012</td>
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<td>MERK Research Fellowship</td>
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TEACHING AND PROFESSIONAL EXPERIENCE

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<td>Teaching Assistant</td>
<td>Florida State University</td>
<td>2013-Present</td>
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<td>Courses: Organic Chemistry 1</td>
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<td>Laboratory Teaching Assistant</td>
<td>Florida State University</td>
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<td>Lecture Teaching Assistant/ Grader</td>
<td>University of West Florida</td>
<td>2011 – 2013</td>
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<tr>
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<tr>
<td>Laboratory Teaching Assistant</td>
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<tr>
<td>Courses: General Chemistry 1 and Organic 1</td>
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LEADERSHIP AND SERVICE ACTIVITIES

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<tr>
<td>Participant – University of West Florida Chemistry Club, and University of West Florida Chemistry Scholars to recruit and aid chemistry students in classes</td>
<td>2011 – 2013</td>
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<td>Volunteer – Volunteered as tutor for the chemistry department at the University of West Florida</td>
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