Synthesis and Characterization of Unique Pyridazines

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Acceptance of Senior Honors Thesis

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Abstract

The field of semiconductive organic chemistry is vast and expanding as numerous applications are being discovered for semiconductors. The research reported in this thesis focuses on the synthesis and characterization of three pyridazines. Pyridazines are organic heterocyclic aromatic semiconductors containing nitrogen and are planar in structure. The three pyridazine compounds were successfully isolated as evidenced by a high percent yield and then characterized by melting point and infrared spectroscopy. The research goal was achieved as a small library of pyridazines was compiled to be further analyzed concerning their potential within various applications in the electronic and industrial world.

Synthesis and Characterization of Unique Pyridazines

Pyridazines: Introduction of the Organic Compound

Pyridazines (Figure 1) are organic six-membered, aromatic heterocyclics that are planar in structure and semiconductive in nature.[1] Organic nomenclature, which defines organic compounds based on their structure, classifies pyridazines as 1,2-diazines or s-diazabenzenes, because they are so similar to the structure of benzene (C_6H_6).[2] The name illustrates that pyridazines contain a benzene ring-like structure in which two adjacent carbon atoms in the benzene ring have been replaced by two nitrogen atoms (Figure 1). Two structures representing the pyridazine were constructed and have since been deemed nonequivalent to each other because of the double bond placement in the respective structures. Knorr first coined the term "pyridazine" for a compound with this structure in his 1885 publication detailing his research.[2] However, it was not until a year after Knorr named the compound that Fischer was able to successfully synthesize the first substituted pyridazines. Nine years following his synthesis, Taüber was able to synthesize a pyridazine with no substituents.[2] Pyridazines are p-electron deficient heteroaromatics because of the strong affinity of both nitrogens (N) for electron density given N's greater electronegativity.[2] This deficiency alters stability, particularly when complexed to a metal system. For instance, (benzene) chromium tricarbonyl is quite stable as the p system of benzene donates its electron density to the chromium atom (Figure 2). However, (pyridazine) chromium tricarbonyl would be expected to be less stable since it cannot freely donate electron density to the chromium atom. Again, this is due to the electronegativity of the N atoms in pyridazine. More recently, pyridazines have shown newfound potential to revolutionize the biological world with their advantageous applications being rapidly elucidated.[3]

Figure 1

General structure of a pyridazine

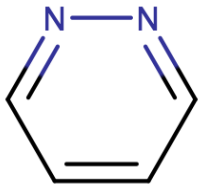
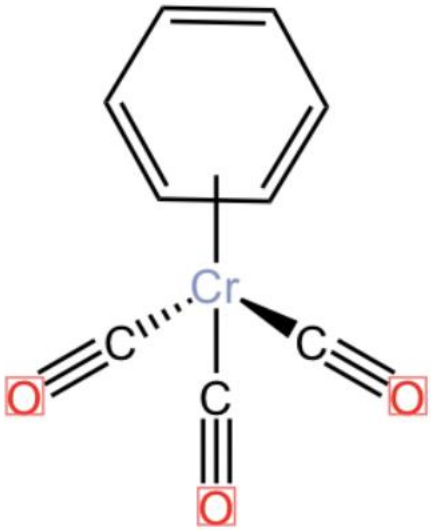


Figure 2

Structure of (benzene) chromium tricarbonyl



After Taüber's synthesis of a pyridazine in the late 19th century, 76 years passed before any significant advancements for applications of the compound occurred. This can be explained by the fact that no naturally occurring pyridazines were found in nature until 1971. During this year, it was discovered that some pyridazines are produced by the *Streptomyces jamaicensis* bacteria. These pyridazines were amino acids classified more formally as hexahydropyridazines (Figure 3).[4] Shortly after, the first antifungal was discovered to be produced by *Streptomyces violaceoniger* called pyridazomycin (Figure 4).[5] This marked the beginning of the usefulness of pyridazine and its derivatives in the pharmaceutical world. However, the amino acids and antibiotics listed above were the only naturally occurring pyridazines. Since their discovery, all the remaining pyridazine derivatives have been chemically synthesized as the derivatives are not harvested from nature.[4] Beyond the pharmaceutical applications of pyridazines, there are numerous agrochemical applications that are on the horizon.[6] An article published in 2020 compiled a list of 10 pyridazine-containing herbicides which included pyridate, credazine, and pyridafol.[7] These pyridazine-containing herbicides act to kill plants by inhibiting photosynthesis. In addition to the herbicidal effects pyridazines exert, they also have exhibited insecticidal properties. Pyridazine-containing insecticides such as pyridazinone-substituted oxadiazoles have shown toxicity toward certain insects, worms, and mites.[7] Further studies in 2021 on the steric and electronic effects on pyridazines continue to emphasize their versatility in a wide range of fields due to their hyperpolarizability.[8]

Figure 3

Naturally occurring pyridazine found in nature--hexahydropyridazine

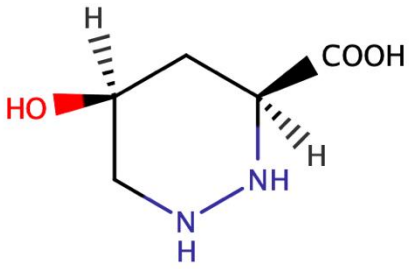
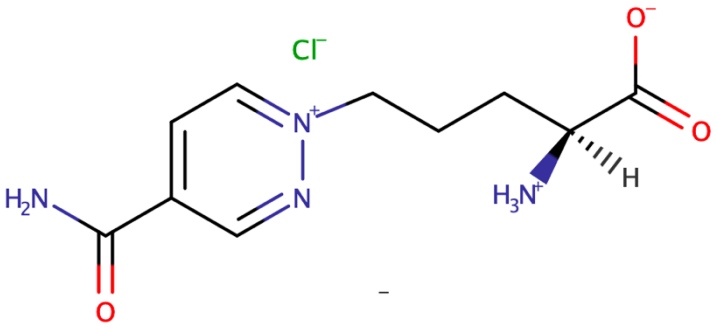


Figure 4

Naturally occurring pyridazine found in nature—pyridazomycin



Applications of Pyridazines

The relatively recent synthesis of pyridazines has led to a drastic expansion of the research surrounding the compound. As a result, numerous medicinal, industrial, and agricultural applications of pyridazines have been implemented because of the large scale of biological and pharmaceutical activities that pyridazine derivatives can achieve.[9] One of the recent medicinal applications of pyridazines was reported in the *Journal of Medicinal Chemistry* in 2020. It was reported that a pyridazine scaffold, which can be further optimized for targeted treatment, demonstrated in vitro evidence of its potential usefulness in the treatment of human African trypanosomiasis, also known as African sleeping sickness.[10] Further research noted a reduction in the presence of parasites in the brains of four out of six mice demonstrating good penetrance of the blood brain barrier.[10] Another medical application involved the use of a Q-tube reactor at high pressure to synthesize thiazolopyridazines. These pyridazines have been shown to be promising as cytotoxic pharmacotherapeutics in cancers of the breast, colon, and lung among others.[11] More studies will be conducted with the thiazolopyridazines investigating their mechanisms of action and exploiting their potential as treatments for cancer.[11] Pyridazine skeletons which make up the backbone of a pyridazine derivative work well in targeting certain cancer cell lines.[12] In addition, it was shown that in addition to pyridazine derivates affecting cancer cells, they also have an epigenetic and immune effect.[12] While prior to this study, pyridazines were known to have a unique structure with potential for medicinal chemistry, this study elucidated the role of pyridazines in cancer treatment.[12] An industrial application for pyridazines has been found in protecting aluminum (Al) alloys from corroding. While oxidation films have previously been used on aluminum alloys, they are not resistant to solutions containing chloride such as hydrochloric acid or even a sodium chloride solution. Three

imidazopyridazines demonstrated success as inhibitors to corrosion on aluminum alloys when they were present in different concentrations of HCl.[13] Also in the industrial realm, a special type of Organic Light Emitting Diodes (OLED) called a phosphorescent OLED has been improved due to research and application of pyridazine derivatives. Pyridazine-based iridium (III) complexes were synthesized and tested for their use and efficiency in these special OLEDs as described previously.[14] They promise advancing the field of OLED technology with a high-yield synthesis, and the fact that with these derivatives, not only are manufacturing costs a fraction of what they previously have been but, OLEDs are more efficient with this derivative due to its unique properties.[14] Early in 2022 a new herbicidal pyridazine derivative, 6-chloro-3-[(4-fluorophenoxy)methyl][1, 2, 4] triazolo [4,3-b] pyridazine, was synthesized, characterized, and tested to determine its ability to target a certain fungus. A docking study in this research after the synthesis and characterization determine it was a suitable compound to target *Fusarium oxysporum.*[15]

Chemistry of Pyridazines

The most basic chemical property of a pyridazine is that is has the odor of the chemical compound pyridine and that it is a colorless liquid at room temperature.[2] Through experimental testing, the boiling point was determined to be 208 °C and the melting point was determined to be -8 ° C. The boiling point of the pyridazines is much higher than water, which can largely be attributed to intermolecular forces.[2] In addition, their polarity due to the C-N bonds in the compound makes them more soluble in water compared to a nonpolar benzene ring.[2]

As previously mentioned, there are two nitrogen atoms in the pyridazine molecule found beside each other in the ring and connected by either a single or a double bond. The structure

allows this classification of compound to exhibit antibiotic, antifungal, antiplatelet, anti-inflammatory, cytotoxic, herbicidal, insecticidal, and numerous other biochemical properties that are characteristic.[16] This structure also allows the nitrogen atoms present at the 1- and 2-positions on the ring to activate all carbons located at the a and g position on the ring. This means that all carbon atoms present in the heterocycle are activated for nucleophilic substitution.[4] Therefore, whereas organometallic stability is negatively affected by pyridazine, the organic chemistry of pyridazines undergo nucleophilic substitution better than benzene.

Pyridazines can be synthesized several ways; however, the most common involves adding hydrazine to a 1,4-disubstituted carbon chain.[9] When examining the chemistry of the pyridazines and their derivatives, it is important to know and understand the various ways they can be synthesized using different reactants. The first way that will be discussed is the synthetic route that involves the reaction over 20 minutes of pyran-2-ones with boiling hydrazine hydrate. This allows the transformation from pyran-2-one to 1,4-dihydropyridazine to occur in high yield (Figure 5).[17] It was also reported that if one desires to transform 1,4-dihydropyridazines to pyridazine-3-carboxylates, then ammonium cerium (IV) nitrate is an appropriate oxidant.[17]

Another synthetic route involves the use of transition metal catalysis to form the pyridazine derivates. Wu and Wang, 2016 used transition metals individually in the synthetic catalysis. In situ cyclization of an alkyne diol (triple-bonded carbons with 2 alcohol groups) was completed by using the ruthenium catalyst to turn the diols into diketones.[18] After the transformation to the intermediate with ketones, hydrazine hydrate was added (~3 hours). The catalyst was added in the presence of potassium tert-butoxide and yielded a substituted

pyridazine (Figure 6). The palladium-catalyzed reaction involved phenyl rings with functional groups attached and reacted with internal alkynes. The following mixture resulted in a successful formation of a pyridazine product: PdCl2, P(o-Tolyl)3, nBU3N, and DMF all at 90°C. Silica gel plate was used to purify the products that resulted from the reaction (Figure 7).[18]

While there are many synthetic routes for pyridazines due to the large pool of derivatives that can be made, the final synthetic route that will be discussed is one in which diazo esters and MBH carbonates can be reacted to produce highly substituted pyridazines. This reaction scheme utilizes DABCO (10 mol%) (a Lewis Base) in THF at room temperature. After this reaction is complete, it was stirred with P(nBu)$_3$. This stirring was completed in an atmosphere of Argon for 3 hours to achieve evaporation after which the product was purified by flash chromatography.[9] Another variation of this synthesis can be completed with 2,2,2-tri-fluorodiazoethane and MBH carbonates to produce 6-(trifluoro-methyl) pyridazines. This involves reacting the 2, 2, 2-tri-fluorodiazoethane and the MBH carbonates first with DABCO at 0°C for 4 hours. After that is complete the same stirring process is implemented for 3 hours as with the original synthesis (Figure 8).[9]

Figure 5

Pyridazine synthesis involving the transformation of pyran-2-one to 1,4 dihydropyridazine

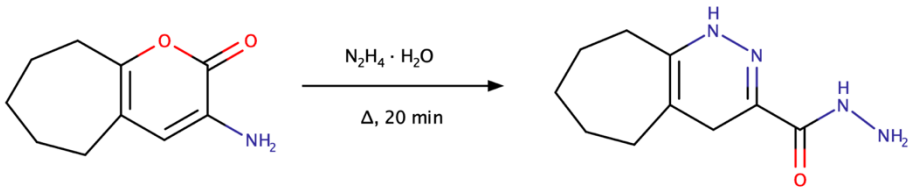


Figure 6

Pyridazine synthesis involving ruthenium catalysis using an alkyne diol as a reactant

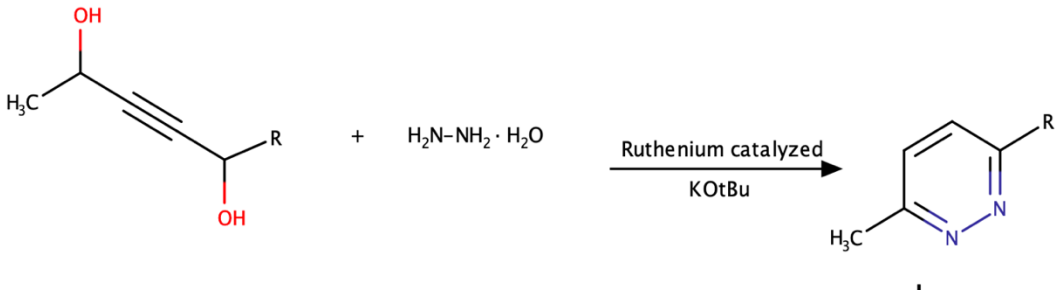


Figure 7

Pyridazine synthesis involving palladium catalysis using internal alkynes as a reactant.

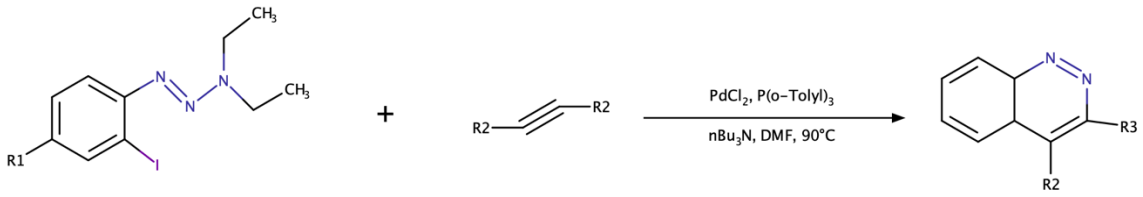
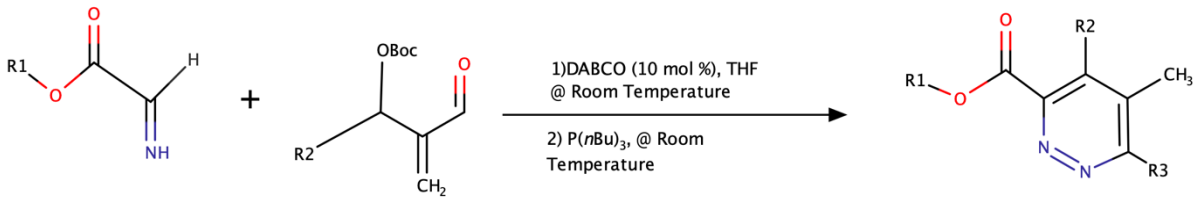


Figure 8

Pyridazine synthesis involving diazo esters reacted with MBH carbonates at room temperature



Novel Pyridazine Research

Our current research is focused on the synthesis and characterization of several unique pyridazines. We have reacted 1,2-diacylcyclopentadienes (fulvenes) in solution with methanol and hydrazine hydrate at room temperature to complete the transformation to 5,6-fused ring pyridazines. After the reactions were complete, separatory extractions were performed to obtain the pyridazine product. We started with three fulvenes (phenyl, thienyl, and tolyl) which were obtained through collaboration with Dr. Nathan Tice, Associate Professor of Chemistry and Chair of the Physical Sciences Department at the University of Findlay. Dr. Tice produced these fulvenes using the reaction scheme outlined in Figure 9. They were completely reacted to produce the three respective unique pyridazines (Figure 10). Our research is primarily concerned with building a small library of pyridazines which are characterized by melting point and infrared spectroscopy. In addition, further reactions of these compounds are planned to make Group VIIB organometallic complexes.

Our Purpose

The interest of our research was birthed out of the knowledge that organic semiconductors are a class of synthesized organic compounds that are exhibiting newfound potential to revolutionize the optoelectronic world as industrial applications are developing rapidly.[19] Our focus is specific to pyridazines given the opportunity to further analyze them for their potential use as semiconductors in the industrial world. With three unique pyridazines that have been synthesized and characterized, the next steps are exhilarating because of the potential that awaits three new compounds not yet analyzed for their usefulness in the industrial world. The opportunity to advance technology through the synthesis of new organic semiconductors is an exciting role.

Figure 9

General synthesis of fulvenes

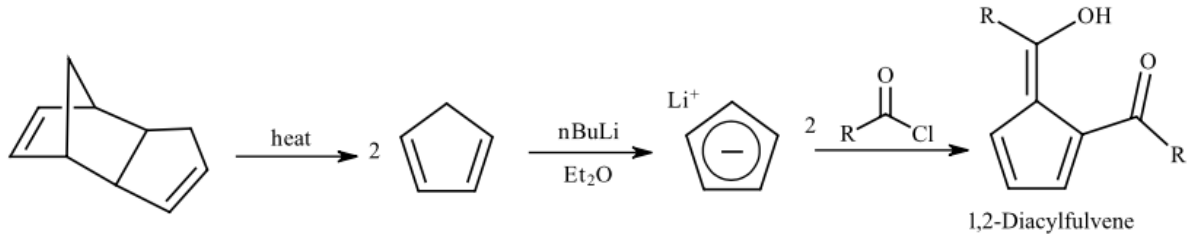
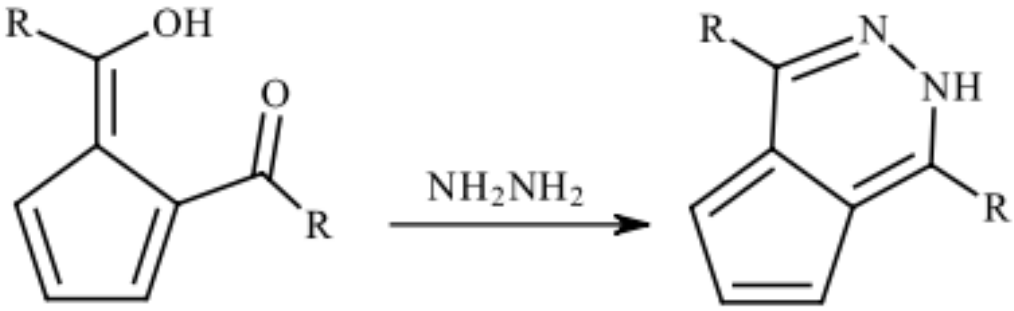


Figure 10

General synthesis of pyridazines from fulvenes



Experimental Design

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All reactions were carried out by using standard organic synthetic techniques under air unless otherwise stated and followed the general scheme outlined in Figure 10. In all the syntheses, hydrazine (Sigma-Aldrich, 98%) and dichloromethane (Fisher Scientific, 99.9%) were used. Infrared spectroscopy was performed using a PerkinElmer Spectrum Two FT-IR Spectrometer. Melting points were taken on a MSRS DigiMelt Melting Point Apparatus. The following syntheses were performed using the same method as previously published.[20]

Synthesis of 1,2-$C_5H_3(CC_6H_5H)(CC_6H_5N)$

Phenyl-fulvene, 1,2-$C_5H_3(COC_6H_5)(COHC_6H_5)$ (**1f**, 250mg, 0.9124mmol), was combined with 50 mL of methanol in a 250 mL round-bottom flask. Excess hydrazine (1 mL) was added before spinning the solution for 24 hours with a stir bar. After 24 hours, 50 mL of water was added, and the formation of a precipitate was observed. The product was extracted (3 x 10 mL of dichloromethane). The organic layers were collected, dried ($MgSO_4$), and filtered. The volatiles were removed *in vacuo*, and the crude product was collected. The product 1,2-$C_5H_3(CC_6H_5H)(CC_6H_5N)$ (**2f**, 178 mg, 0.659mmol) was collected in 71% yield. **M.P.** 202-204.9 °C. **IR (cm^{-1}):** 3319 (C_{sp}-H), C=O (1596), C_{sp2}–H (3035, 3091).

Synthesis of 1,2-$C_4H_4S(COC_6H_5)(COHC_6H_5)$

Thienyl-fulvene, 1,2-$C_4H_4S(COC_6H_5)(COHC_6H_5)$ (**3f**, 254mg, 0.8599mmol), was combined with 50mL of methanol in a 250 mL round-bottom flask. Excess hydrazine (1 mL) was added before spinning the solution for 24 hours with a stir bar. After 24 hours, 50mL of water was added and the formation of a precipitate was observed. The product was extracted (3 x 10 mL of dichloromethane). The organic layers were collected, dried ($MgSO_4$), and filtered. The

volatiles were removed *in* vacuo, and the crude product was collected. The product 1,2-$C_4H_4S(CC_6H_5NH)(CC_6H_5N)$ (**4f**, 110mg, 0.3775mmol) was collected in 43% yield. **M.P.** 164.5-165.9 ℃. **IR (cm^{-1}):** 3096 (N-H), 1594 (C=C aromatic), C_{sp}-H (3235, 3177).

Synthesis of 1,2-$CH_3C_5H_3(CC_6H_5NH)(CC_6H_5N)$

Tolyl-fulvene, 1,2-$CH_3C_5H_3(COC_6H_5)(COHC_6H_5)$ (**5f**, 252mg, 0.8709mmol), was combined with 50 mL of methanol in a 250 mL round-bottomed flask. Excess hydrazine (1 mL) was added before spinning the solution for 24 hours with a stir bar. After 24 hours, 50 mL of water was added and the formation of a precipitate was observed. The product was extracted (3 x 10 mL of dichloromethane). The organic layers were collected, dried ($MgSO_4$), and filtered. The volatiles were removed *in* vacuo, and the crude product was collected. The product 1,2-$CH_3C_5H_3(CC_6H_5NH)(CC_6H_5N)$ (**6f**, 130mg, 0.4556mmol) was collected in 51% yield. **M.P.** 158.5-161.2 ℃. **IR (cm^{-1}):** 3098 (N-H), C=C aromatic (1594, 1538), C_{sp}-H (3235, 3177), C_{sp3}-H (2958).

Results

After the reactions were initiated, images of the fulvenes dissolved in solution and being stirred were obtained (Figures 11, 12, 13). After the purification of the pyridazine products, they were individually observed and analyzed. The phenyl-pyridazine product (Figure 14) was a light-yellow powder with a percent yield of 71.2% and a melting point of 202-204.9 ℃. The IR spectra obtained after IR spectroscopy analysis is found in Figure 15. The thienyl-pyridazine product (Figure 16) was a red, rust color with a percent yield of 43% and a melting point of 164.5-165.9 ℃. The IR spectra obtained after IR spectroscopy analysis is found in Figure 17. The tolyl-pyridazine product (Figure 18) was a deep yellow powder with a percent yield of 51%

and a melting point of 158.5-161.2 ℃. The IR spectra obtained after IR spectroscopy analysis is found in Figure 19. A table outlining the results in a cohesive format is found in Table 1.

Figure 11

Phenyl-fulvene being reacted with hydrazine hydrate and methanol

Figure 12

Thienyl-fulvene being reacted with hydrazine hydrate and methanol

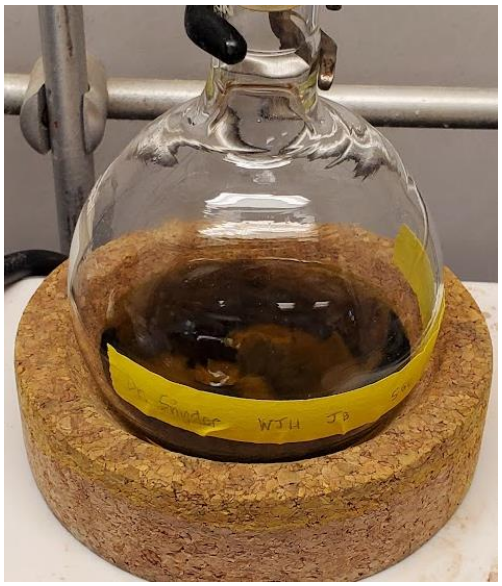


Figure 13

Tolyl-fulvene being reacted with hydrazine hydrate and methanol

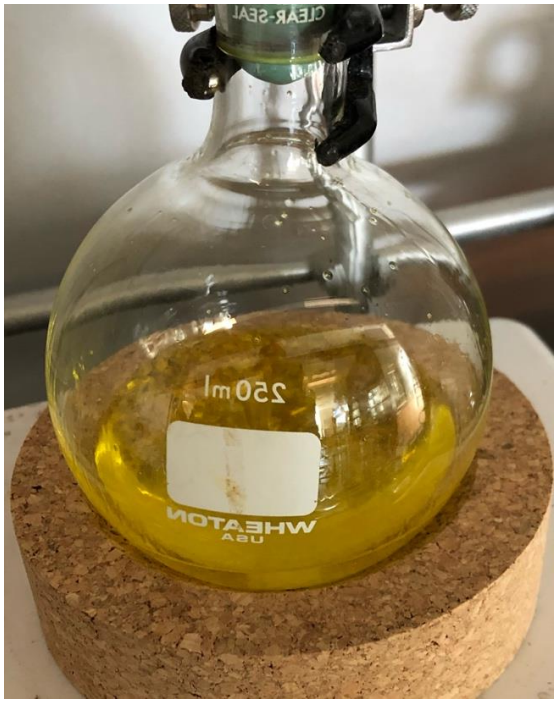


Figure 14

Phenyl-pyridazine product structure

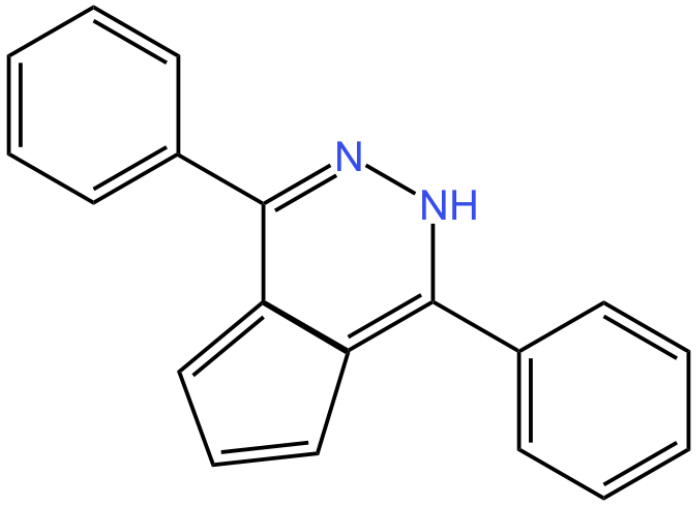


Figure 15

IR Analysis of Phenyl-pyridazine

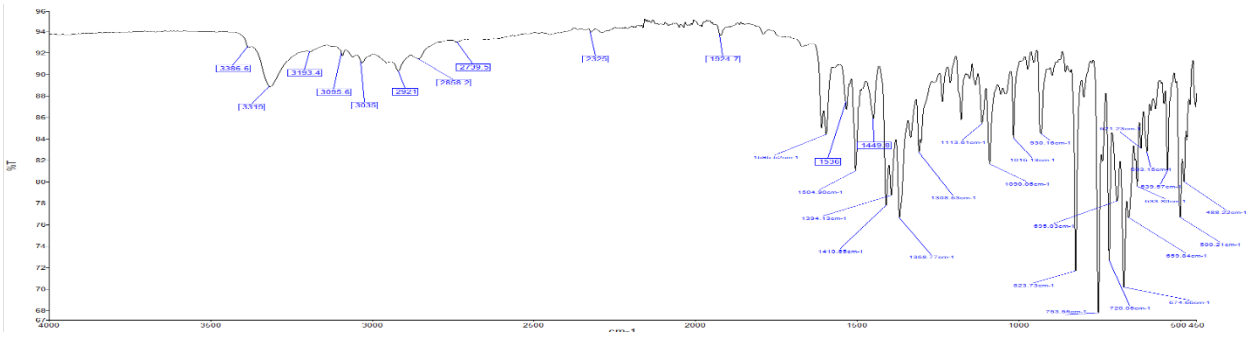


Figure 16

Thienyl-pyridazine product structure

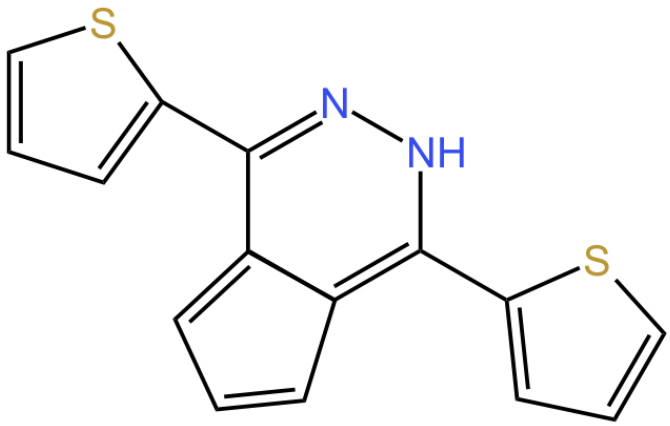


Figure 17

IR Analysis of Thienyl-pyridazine

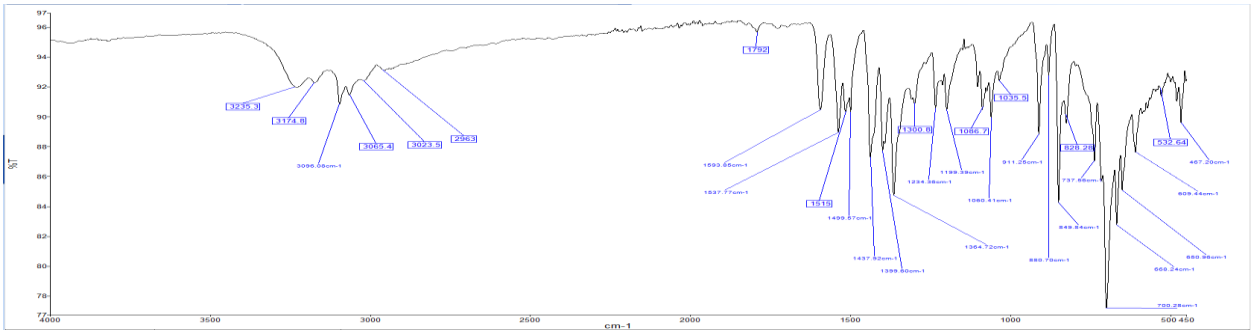


Figure 18

Tolyl-pyridazine product structure

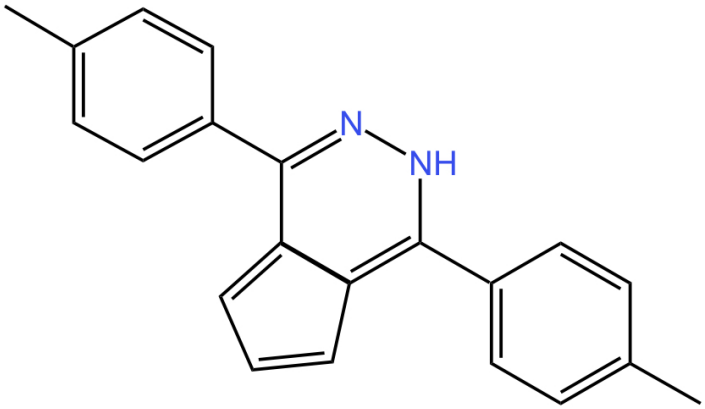


Figure 19

IR Analysis of Tolyl-pyridazine

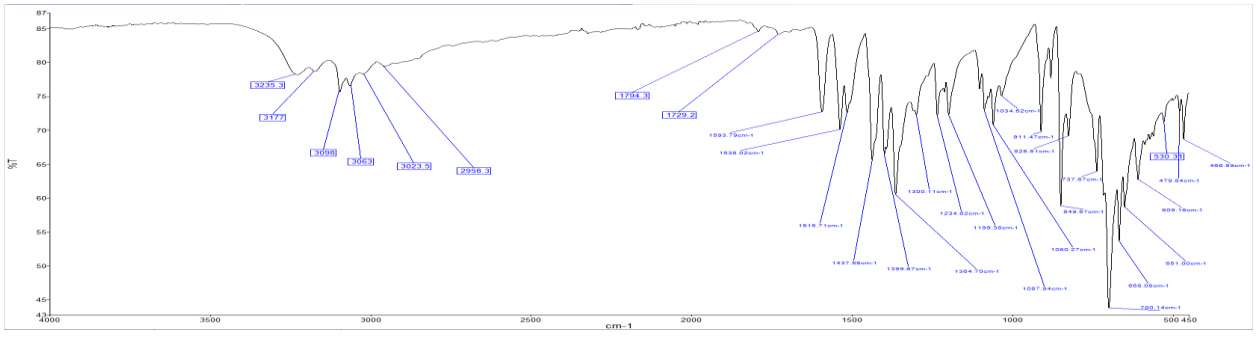


Table 1.

Comparison of the Appearance, Melting Point, and Percent Yield of the three synthesized pyridazines

	Appearance	Melting Point	Percent Yield
Phenyl-pyridazine	light yellow powder	202-204.9 ℃	71.2%
Thienyl-pyridazine	red, rust colored powder	164.5-165.9 ℃	43%
Tolyl-pyridazine	deep yellow powder	158.5-161.2 ℃	51%

Discussion

The fulvene to pyridazine synthesis was successful as evidenced by the results from all three pyridazines. The phenyl and tolyl substituted products were similar color to their parent fulvene whereas the thienyl-pyridazine product was different. The product was a red, rust colored compared to the bright orange color of its parent pyridazine. All three melting points reveal that the products synthesized were pure because the melting point for all three was less than 5°C. The thienyl-pyridazine is the purest product with a melting point range of 1.4°C. The melting point for these pyridazines ranged from about 155°C to 205°C. The percent yields calculated for all pyridazine products were greater than 40%. The phenyl-pyridazine was the most robust product with a 71% yield. The goal of these organic synthesis reactions was ring-closure on the fulvenes. Ring-closure in organic compounds is fighting entropy as the reactant has less order and more rotational movement than the product. Through synthesis, one is trying to generate a product that has more order and less rotational movement which is against the natural tendencies of chemical reactions. Therefore, the percent yield of 43% and 51% for the thienyl and tolyl substituted pyridazines was expected and not considered low for this reaction. Pyridazine products all contain the same general structure, and this was confirmed for these products as the IR analyses of each product had many similar peaks in the same locations as the other products. More specifically, analysis by IR spectroscopy confirmed the presence of expected functional groups on the phenyl-pyridazine (Figure 15). 3° Hydrogens are seen at approximately 3319 cm^{-1} and the N-H stretch is seen at approximately 3095 cm^{-1}. The aromatic rings are seen in a double peak around 1596 cm^{-1}. Analysis by IR spectroscopy confirmed the presence of expected functional groups on the thienyl-pyridazine (Figure 17). The N-H stretch is

seen at approximately 3096 cm^{-1}, the aromatic C=C bond is seen at approximately 1594 cm^{-1}, and the C_{sp}-H stretch is seen at both 3235 cm^{-1} and 3177 cm^{-1}. Analysis by IR spectroscopy confirmed the presence of expected functional groups on the tolyl-pyridazine (Figure 19). 1° Hydrogens are seen at approximately 2958 $cm^{-1}$and the aromatic rings are seen in a double peak around 1593 cm^{-1}. Like the other compounds the 2° hydrogens are seen at approximately 3063 and 3098 cm^{-1}.

Conclusion

In summary, a series of aryl substituted pyridazines were made in high yield starting from 1,2-diacyl fulvenes and hydrazine hydrate. These compounds were characterized by their melting points and IR spectroscopy. The research goal was achieved as a small library of pyridazines was built with the data collected through synthesis and characterization of these three unique pyridazines. With the industrial potential of organic semiconductors, there are several possibilities in the future for these compounds. These compounds could either be further reacted to make Group VIIB organometallic complexes, polymerized as organic compounds, further analysis, and testing for their possible use as semiconductors or in optoelectronic devices. Our future work includes the isolation and characterization of other pyridazine compounds.

Acknowledgements

As I come to the end of my undergraduate studies, I want to first and foremost thank my Lord and Savior, Jesus Christ for his faithfulness, steadfast love, and never-ending mercies (Lamentations 3:22-23). I would like to acknowledge the Liberty University Department of Biology and Chemistry for the opportunity to learn under their direction and for the facilities and resources that I have been able to use for the past three and a half years. This research project

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