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Mechanistic Studies and Derivative Effects In 1, 3, 4- Oxadiazole Synthesis Via Cyclodehydration Reactions

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MECHANISTIC STUDIES AND DERIVATIVE EFFECTS IN 1,3,4-OXADIAZOLE SYNTHESIS VIA CYCLODEHYDRATION REACTIONS

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I also wanted to thank you, the reader, for taking the time to read this thesis. While it involves Organic and Physical Chemistry, I hope you find it as exciting and fascinating as I did.

Abstract

In the world of pharmaceutical synthesis, research to combat foreign pathogens is always necessary. Scientists have been exploring different methods in order to synthesize the most effective compounds in antibacterial, anticancer, anti-inflammatory, and many other treatments. A key component within these versatile compounds are 1,3,4-oxadiazoles. Current methods to synthesize these compounds are inefficient. This research seeks to improve oxadiazole synthesis; however, the mechanism of this reaction is unknown. The goal of this project was to study the mechanistic pathway in the discovered, one-pot cyclodehydration synthesis of 1,3,4-oxadiazoles. In the first part of this study, a diacylhydrazine intermediate was proposed. This commercially available diacylhydrazine was submitted to reaction conditions to test this mechanistic hypothesis. Finally, the laboratory data was combined with thermodynamic computational data in order to observe the Gibbs free energies and equilibrium constants of this reaction. These values can provide key insight into the electron donating and electron withdrawing groups effects on the mechanism of this reaction. This was completed by utilizing various approaches including Molecular Mechanics 2 (MM2) in ChemBio 3D, and PM3 within the Spartan 16 program. Bond dissociation enthalpies were also consulted in order to provide a general investigation of the proposed mechanism.

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Introduction

Background of Heterocycles

Heterocycles are cyclic organic compounds whose rings are composed of more than one element beyond carbon and hydrogen. Several common heterocyclic examples are pyridine, piperidine, adenine, guanine, and adenosine triphosphate (ATP). While many heterocycles exist, these are several common compounds that are constantly utilized for driving certain cellular processes. In Figure 1, some primary examples of heterocycles are shown. Within organic chemistry, these chemicals are frequently studied due to their industrial and biological importance in the development in pharmaceuticals. While there are various classes of heterocycles, the primary purpose of this project is to discuss the synthetic mechanism and derivative effects therein of the synthesis of 1,3,4-oxadiazoles through a cyclodehydration reaction with the assistance of dibromotriphenylphosphorane.

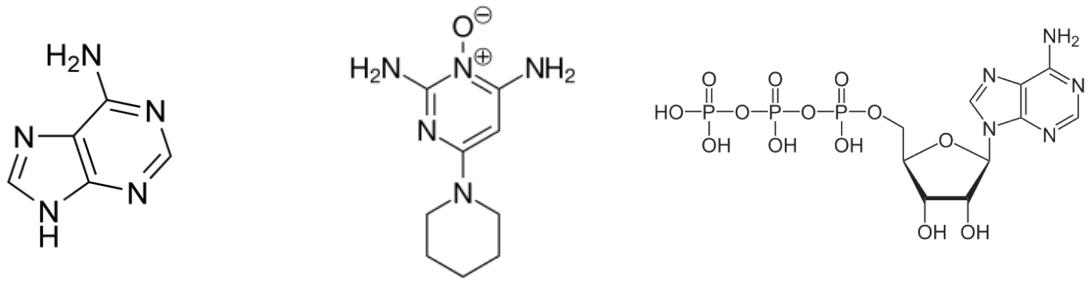


Figure 1: *Adenine (left, one of four nitrogenous bases of DNA), Piperidine (middle, used in cleaving particular nucleotides in DNA), ATP (right, major energy source for many biological pathways.*

A large debate surrounding the research of heterocycles concerns why these compounds are prevalent in nature. In many organisms, heterocycles are crucial for essential biochemical pathways. One reason is that heterocycles are versatile: they can proceed through various types of reactions by acting as acids and bases, cooperating with nucleophiles and/or electrophiles, and

undergoing redox reactions.[1] In addition, heterocycles can manufacture stable complexes with metal ions in order to create biologically stable compounds.[1] These unique characteristics of heterocycles are primarily a result of the electronic distribution within this class of molecules. Ultimately, heterocycles are selected by nature to be one of the essential ingredients to various biological systems because of their adaptable qualities and their abilities to satisfy the demands of these biological systems.

What are 1,3,4-Oxadiazoles?

Two of the most recognized oxadiazoles are 1,2,4-oxadiazoles and 1,3,4-oxadiazoles. The fundamental structure of the 1,3,4-oxadiazole is shown in Figure 2.

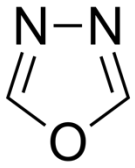


Figure 2: *Base structure of the 1,3,4-oxadiazole.*

The 1,3,4-oxadiazole is a five-membered ring which consists of an oxygen atom in the "1" position, two nitrogen atoms in the "3" and "4" positions, and two carbon atoms in the "2" and "5" positions of the ring. Coming off of the two carbon atoms, a large variety of substituents can be used to provide additional biological functions.

Branching from the 2' and 5' carbons of the oxadiazole structure can be a variety of substituents labeled as R groups in Figure 3.

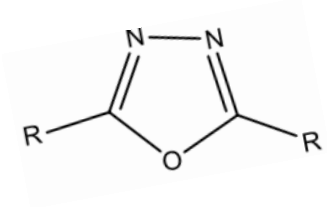


Figure 3: *Oxadiazoles with substituent (R Groups) on the number 2 and 5 carbons of the ring.*

The identity of the R group is incorporated with the 1,3,4-oxadiazole can have various effects on the molecule's overall solubility, activity, and overall yield. One of the most common substituents associated with a 1,3,4-oxadiazole is a benzene ring. There are two types of components that can provide significant changes to the nature of an organic molecule; these are called electron withdrawing groups (EWGs) and electron donating groups (EDGs). In any benzene-containing molecules, EDGs such as alcohols and amines donate electron density into a conjugated ring system by the means of resonance or inductive effects. EDGs are expected to shield the carbon nuclei located at the ortho and para positions on the ring.[2] This leads to a partial negative charge on the benzene on the ring, making it more nucleophilic. On the other hand, EWGs have the opposite effects upon a benzene ring, removing electron density from the conjugated ring system and leaving a partial positive charge upon the benzene ring. This leaves the ring in a more electrophilic state and more susceptible to attack by an electron-rich nucleophile. The act of EWGs withdrawing electrons from a benzene de-shield at the ortho and para positions of a benzene ring.[2]

The effect of EDGs and EWGs on other reaction centers can likewise be explored. The primary attention of this study is their effects of these groups on a carbonyl carbon, since this carbon is the primary reaction center of the cyclodehydration reaction of 1,3,4-oxadiazole synthesis. When an EWG is associated near a carbonyl, the electron density is pulled away from the carbonyl, which initiates a partial positive charge on the carbon of the carbonyl. This makes

the carbon of the carbonyl more electrophilic and easier to be attacked by a nucleophile. When an EDG is associated near the carbonyl, the electron density around the carbonyl increases. As result this region becomes more nucleophilic. It is worth noting that EWGs have been shown in some reports of decreasing the electrophilicity of a carbonyl under certain conditions. In this situation, the ground-state destabilization increases the rate of nucleophilic acyl substitution by decreasing the energetic benefit of the nucleophilic attack.[3] This suggests that not all substituents act as exactly as expected.

In order to begin constructing a potential reaction mechanism, Hammett plots are frequently developed in order to identify linear free energy relationships. The Hammett equation relates changes in equilibrium or rate constants to changes in substituents that originate from EDGs or EWGs. [4] The Hammett equation is presented as Equation 1 and indicates this relationship between the reaction equilibrium constants and two values known as sigma (σ) and rho (ρ).

$$\log\frac{K_X}{K_H} = \sigma\rho \qquad (1)$$

In the Hammett equation, K_X is the equilibrium constant of a molecule with substituent X while K_H is the equilibrium constant for the same molecule where substituent X is a hydrogen. ρ is the slope of the line correlating $\log\frac{K_X}{K_H}$ with the σ values of the substituents.[4] When plotted, the graph is established as $\log\frac{K_X}{K_H}$ versus σ and when a large group of different substituents is surveyed, a plot takes form.[4] The sign of the slope indicates if the reaction rate is accelerated or suppressed by EDGs or EWGs. A negative ρ reflects a positive charge at the reaction center of the transition state of the rate-limiting step which is suppressed by EWGs.[4] A positive ρ reflects

a negative charge at the reaction center in the transition state of the rate-limiting step which is accelerated by EWGs.[4] The substituent constant σ is a measure of the total polar effect exerted by a certain substituent on the reaction center.[4] The σ value ultimately provides critical insight into the reaction mechanism since it will provide the electron manipulating nature of EDGs and EWGs.

An example of a Hammett plot can be seen in Figure 4.[5] In Figure 4, four different reactions are being observed with different substituents. The direction and severity of the slopes vary depending on the state of the reaction center. The sigma value on the x-axis reflects whether an R group on a molecule is an EDG or an EWG with an unsubstituted molecule in the middle at the value zero. A negative sigma value indicates an EDG and a positive sigma value indicates an EWG. The $\log \frac{K_X}{K_H}$ term on the y-axis is the logarithmic relationship of relative equilibrium (K_X) with a specific substituent (X) and general equilibrium with no X group (K_H). For example in reaction A, the line shown possesses a negative slope of -2.69 which indicates that the rate determining step of the reaction will have a more positive charge at the reaction center in the transition state of the given reaction. Also, after observing the initial and ending points of line A, the higher $\log \frac{K_X}{K_H}$ point indicates the rate of reaction is faster with an EDG and the reaction rate will decrease with an EWG. On the other hand, in reaction D, there is a positive slope of 2.51. This indicates that at the rate determining step of the given reaction, there is a negative charge at the reaction center. In addition, based on the initial and end points of the line, an X substituent that is an EDG will decrease the rate of reaction while an EWG will increase the rate of reaction.

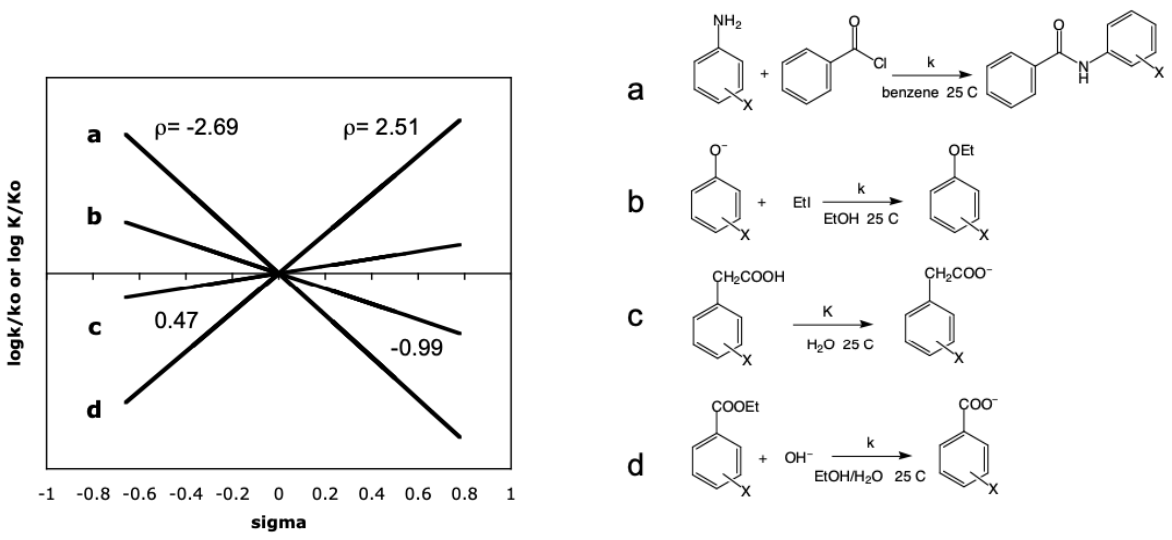


Figure 4: *Example of a Hammett plot observing four different reactions with various substituents.*[5]

Prior to σ being found, the thermodynamic equilibrium constants must be found via experiment or calculated by computational programs.

Biological Applications of 1,3,4-Oxadiazoles

From a biological viewpoint, the 1,3,4-oxadiazole isomer shows an order-of-magnitude lower lipophilicity. This isomer is also favored in respect to metabolic stability, inhibition of the hERH potassium ion channel, and aqueous solubility in comparison to the 1,2,4-oxadiazole isomer.[6] This grants 1,3,4-oxadiazoles to be useful within medical treatments for common ailments. One significant benefit of the 1,3,4-oxadiazole is its ability to serve as a strong anti-inflammatory agent. In comparison the standard reference anti-inflammatory drug, ibuprofen, oxadiazole derivatives have shown to be the most potent and exhibited higher anti-inflammatory activity as seen in Figure 5 (Farghaly A. Omar 1996, Figure 1)[7].

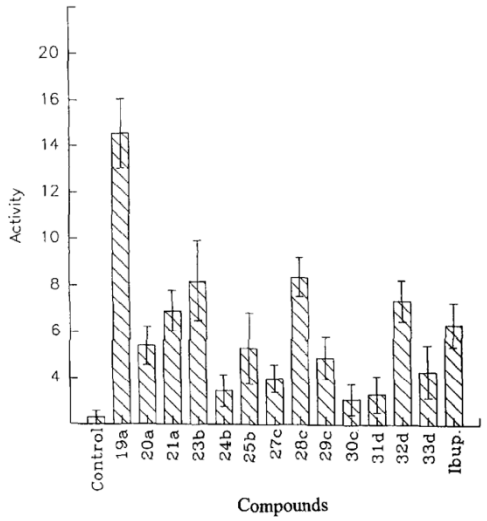


Figure 5: *1,3,4-oxadiazole derivatives 19a, 21a, 23b, 28c, and 32d reveal higher activity in comparison to the standard anti-inflammatory drug, ibuprofen. Activity is measured in mean time (min) +/- standard error.*[7]

Along with the strong anti-inflammatory response, this molecule has also proven to be a resilient instrument against antibacterial activity. Synthesized N-substituted acetamide derivatives of azinane-bearing 1,3,4-oxadiazole nucleus derivatives have been screened and have shown antibacterial activity against *Salmonella typhi, Escherichia coli, P. aeruginosa, S. aureus, and Bacillus subtilis* bacterial strains.[8] These synthesized compounds have shown to be moderate inhibitors against Gram-negative bacteria.[8] These molecules have also been utilized in the production of insect growth regulators (IGRS).[9] IGRs have shown to be safe options in food production while releasing any harmful byproducts to the environment. Instead of implementing ecological disruption and environment interference, IGRs regulate the growth and development

of insect's pest via regulating metamorphosis and breeding. [9] 1,3,4-oxadiazoles have also proven to be active compounds in fighting various fungal infections.

The treatment of cancer has been a common area of research, and numerous remedies have been studied in order to restrain this uncontrolled cell growth. Fortunately, different 1,3,4-oxadiazole derivatives are currently being studied for their effects on Michigan Cancer Foundation-7 breast cells (MCF-7). When MCF-7 cells were subjected to different oxadiazoles, antiproliferative action and growth inhibition in cultured human breast cancer MCF-7 cells are observed.[10] With increasing the concentration of the oxadiazoles, they initiated the loss of cell viability, chromatin condensation, and internucleosomal DNA fragmentation. One compound that displayed the strongest apoptotic effects is 5-ethyl-2-{2-[4-(5-pyridine-3-yl[1,3,4] oxadiazole-2-yl)phenoxy]ethyl}pyridine. [10]

Established Methods in Synthesizing 1,3,4-Oxadiazoles

Currently there are several documented pathways to achieve the synthesis of 1,3,4-oxadiazoles. A traditional pathway to achieve this product is via oxidative cyclization of N-acylhydrazones. Unfortunately, this synthetic approach requires strong oxidants like the Des-Martin Periodinane (DMP) reagent; furthermore, methods similar to this are burdened with significant amounts of byproducts along with the desired oxadiazole; these byproducts must be disposed of properly.[11] Reagents similar to DMP are strong oxidants which ultimately increase the number of carbon and oxygen bonds within a particular molecule. DMP, specifically, is the reagent of choice for the oxidation of primary and secondary alcohols to aldehydes and ketones.[12] Furthermore, oxidative cyclization of N-acylhydrazones with DMP under mild

conditions have shown yields of 1,3,4-oxadiazoles up to 92%.[13] However, the harmful byproducts from this method have initiated additional experimentation to find more green alternatives.

Another method of synthesis is through 1,2-diacylhydrazine using polymer-supported Burgess reagent ([methoxycarbonylsulfamoyl]triethylammonium hydroxide) under microwave conditions. The Burgess reagent has been a valuable component of synthetic chemistry since 1968 by acting as a mild and selective dehydrating reagent.[14] One synthetic route to oxadiazoles couples the Burgess reagent with microwave irradiation. Microwave reactions include polar molecules participating in selective absorption of microwaves while non-polar molecules exhibit passive microwave dielectric loss.[15] As a result, this combination of specific reagents and microwave irradiation allows a large variety of reactions to be completed quickly, with high yield and selectivity without the need for solvents. Regarding 1,3,4-oxadiazole synthesis, 1,2-diacylhydrazine in combination with the polymer-supported Burgess reagent under single-mode microwave conditions can produce the desired molecule with various substituents.[16]

Even though these current methods can synthesize the desired 1,3,4-oxadiazole product, these methods generally have poor efficiency and yield, and some of them have been proven to utilize reagents that are harmful to the environment. In contrast, cyclodehydration synthesis reactions of 1,3,4-oxadiazoles can achieve high yields while minimizing individual and environmental risks, as discussed in the next section.

1,3,4-Oxadiazole Synthesis Via Cyclodehydration

While there are several other methods in the synthesis of 1,3,4-oxadiazoles, a new method of cyclodehydration has been found to improve yield and to restrict the need for additional hazardous reagents. This reaction was the primary study of this project; it consists of the combination of a hydrazide and a benzoic acid to form a heterocyclic ring along with the loss of a molecule of water. Previous research from the Grote laboratory has determined conditions to synthesize the 1,3,4-oxadiazole with the assistance of dibromotriphenylphosphorane (PPh_3Br_2).[17] This reaction can be seen in Figure 6.

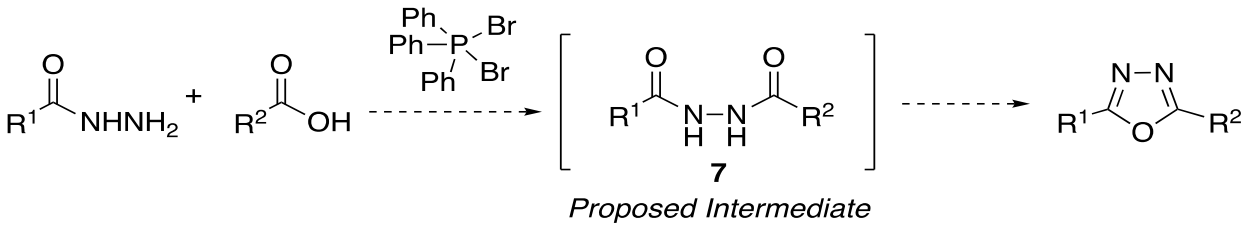


Figure 6: *General reaction scheme for 1,3,4-oxadiazole synthesis via cyclodehydration.*

PPh_3Br_2 has been reported as being used within a two-step, one-pot reaction to brominate alcohols.[18] Previously this reagent has been applied to an analogous 1,3,4-oxadiazole synthesis that uses this *in situ* generated PPh_3Br_2 (in other words: PPh_3Br_2 that is generated in the same reaction flask). This has proven to be an effective strategy in comparison to using commercially purchased PPh_3Br_2, due to the higher decomposition rate of this reactive compound.

While this reaction has proven to be a strong alternative synthesis for 1,3,4-oxadiazoles, both the overall reaction mechanism by which this reaction occurs and the effects of additional substituents are still unknown. Thus, while the first component of this project has explored the

lab bench work of this synthesis, the second component reports on the use of computational chemistry to model substituent effects in the suggested mechanism.[17, 19, 20]

Computational Chemistry via Molecular Mechanics 2 and Spartan 16 with PM3 Methods

One computational approach used in this study was Molecular Mechanics 2 (MM2), available via the ChemBio3D program.[21(a), 21(b)] In order to calculate the thermodynamic equilibrium constant for any reaction, the Gibbs free energy of the reaction being studied is required via the relationship expressed in Equation 2.

$$\Delta G° = -RTlnK \qquad (2)$$

In this relationship between free energy ($\Delta G°$) and equilibrium constant (K), R is the equilibrium gas constant of 8.314 J/K*mol and T is the temperature of reaction in Kelvin. This is where MM2 becomes potentially useful, as it can determine the free energy of the cyclodehydration reactions that synthesize 1,3,4-oxadiazoles.

Within an MM2 analysis, this method elaborates molecules based on the idea of "bonded atoms."[22] In MM2, the overall energy of a molecule is described as a sum of the contributions arising from deviations from "ideal" bond distances (stretch contributions), bond angles (bend contributions), torsion angles (torsion contribution), and with contributions due to "non-bonded" (van der Waals and Coulombic) interactions.[22] This summation of energies is presented in Equation 3 below.

$$E_{steric\ energy} = E_{str} + E_{bend} + E_{str-bend} + E_{VdW} + E_{tor} + E_{qq} \qquad (3)$$

Each of these deviations can be thought of via analogy to Hooke's Law, with distortions from an idealized molecular parameter contributing to the overall steric energy.[22] Because molecular

mechanics methods depend on this simple model, the resulting calculations are efficient.[22] However, some limitations of MM2 are electron distribution (bonding) within molecules, the fact that the force fields used for this method cannot handle non-equilibrium forms (also known as transition states), and describing structures that fall out of scope of the range of MM2.[22] For this study, the steric energies calculated via MM2 were used to calculate the change in Gibbs free energy ($\Delta G°$) previously mentioned and described in Equation 2, thus allowing the calculation of the equilibrium constant (K), which is vital information for the Hammett relationship.

A second type of computational method that can be used, beside MM2, is the semi-empirical method, used in this study through Spartan '16.[23] Overall, the Schrodinger Equation is primarily used for finding the energies and wavefunctions of a quantum mechanical system.[24] *Ab initio* methods involve high levels of theory and seek to directly eliminate empirical "shortcuts" when solving the Schrodinger Equation. Semi-empirical methods are less intense computational pathways to obtaining a solution to the Schrodinger Equation, since some experimental data is simplified to provide faster results (hence, semi-empirical). For example, semi-empirical methods only analyze the valence electrons in a molecule while the core electrons are disregarded.[22] There are a variety of semi-empirical methods available and the one utilized in this study is Parameterized Model 3 (PM3). PM3 can be used to optimize molecular geometries and thus calculate free energies of a reaction. Similarly to MM2, the equilibrium geometry energy found was substituted for Gibbs free energy in Equation 2.

Finally, the overall thermodynamics of this reaction mechanism were studied using the bond dissociation enthalpies (BDEs) of the reactants and products. In the event that MM2 and semi-empirical methods cannot provide an accurate assessment of this cyclodehydration

reaction, an analysis of BDE values can at least provide a general investigation of the proposed mechanism. The BDE calculation involves studying the overall enthalpy of a reaction by comparing the energy differential between bonds formed in the 1,3,4-oxadiazole and the bonds broken from the starting materials of this reaction as well as the diacylhydrazine intermediate. Equation 4 presented shows this relationship. The ΔH_{formed} value is negative because the formation of bonds in a reaction is exothermic, which involves a release of energy; on the other hand, ΔH_{broken} is a positive value as it reflects an endothermic event, which requires an input of energy into the reaction system.

$$\Delta H^{\circ}_{overall} = -\left(\Delta H_{formed}\right) + \Delta H_{broken} \qquad (4)$$

There are two possible, general outcomes from the BDE analysis. If the overall reaction enthalpy for a reaction is positive, this indicates that energy is being absorbed by the system, and we would classify the process as an endothermic reaction. However, if the overall reaction enthalpy for the reaction is negative, and we would classify the process as an exothermic reaction. If the reaction proves to be exothermic via BDE analysis, this will generally support our initial conception of the mechanism, as it generally indicates an energetically favorable process.

Results and Discussion

During the investigation of this project, mechanistic studies of 1,3,4-oxadiazole synthesis through cyclodehydration were conducted. In the initial stage of this project, tests were performed to confirm the presence of a proposed diacylhydrazine intermediate as well as to analyze the effects of yield by introducing the initial reagents at different stages of the reaction. In the second stage of this project, two computational approaches and a calculation of bond

dissociation energies were studied for additional insight into the mechanistic pathways of this synthetic pathway.

Laboratory Synthesis

To test the hypothesis that a diacylhydrazine was present as an intermediate in this reaction, commercially purchased 1,2-dibenzoylhydrazine was subjected to reaction conditions in order to generate the 1,3,4-oxadiazole. The main idea that was being tested was an intermediate or halfway mark that occurs during this reaction as this can provide useful insight in the flow of electrons within this synthesis. As previously denoted in the Materials and Methods section, the commercially purchased 1,2-dibenzoylhydrazine was subjected to dibromotriphenylphosphorane reaction conditions, analyzed by thin layer chromatography, and purified via column chromatography and characterized via ^{1}H NMR. For each collected sample of 1,3,4-oxadiazole product, the average retardation factor (R_f) was 0.204 while 0.190 g of purified product was collected composing an overall yield of 63.7%. From the ^{1}H NMR evaluation, noticeable chemical shifts were identified at 8.2 and in ^{13}C NMR signals were observed at 165,131, 129, 127, and 125.

Next, to test the effects of hydrazine formation and ultimately, 1,3,4-oxadiazole synthesis, two reactions were performed by subjecting either benzoic acid or benzohydrazide to the dibromotriphenylphosphorane reaction conditions first and then add the other remaining component. By exposing the benzoic acid first to the reaction conditions, the average R_f was 0.185. Unfortunately, the exact yield could not be determined due to a significant loss of product just prior to the final removal of excess solvent from the purified collections. Finally, the same reaction was conducted; however, the benzohydrazide was introduced initially to the standard

reaction conditions while benzoic acid was added shortly later. From all the purified collections, the average R_f was 0.184. In addition, 0.191 g of purified product was recovered to give an overall yield of 63.8%. ^{1}H NMR was performed on the oxadiazole product for both reactions and similar and chemical shifts were found at 8.3 and 7.7.

In the future, it would be beneficial to complete the reaction involving the initial addition of benzoic acid to the reaction conditions in order to calculate the exact yield from this pathway. This would allow to compare the yields from both alternative pathways of the cyclodehydration reaction so the pathway of optimal yield could be uncovered. Finally, additional derivatives can should continue to be evaluated in order to observe a wide array of substituents and their yield effects. This will greatly assist in future Hammett plot construction which can identify unique trends for this mechanism when subjected different derivative effects.

Computational Results

Progressing into the computational stage of this project, the first method that was used to study the mechanistic pathway of this reaction was MM2. The overall Gibbs free energies ($\Delta G°$) for a variety of reactions ranging from the proposed hydrazine intermediate to a variety of R groups were surveyed. Using Equation 2, the equilibrium constant (K) was calculated for each of the given reactions shown in Figure 7 and in Table 1. The primary objective of studying the equilibrium constant (K) is to reveal if the reaction is favored in these reaction conditions and to be utilized in formulating an adequate Hammett plot. Unfortunately MM2 showed that the equilibrium constants were exceptionally small which implies that the reaction favors the reactants or starting materials instead of the products.

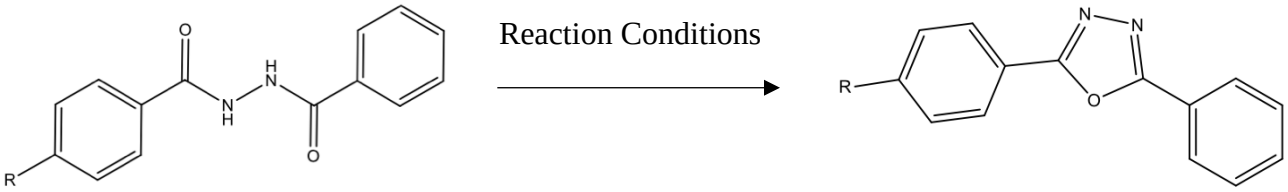


Figure 7: *Reaction scheme for 1,3,4-oxadiazole synthesis with various R groups at the para position of the benzene ring under MM2 analysis.*

R Group	**Energy of Reactants (J/mol)**	**Energy of Products (J/mol)**	**Gibbs Free Energy** $\Delta G°$	**Equilibrium Constant** K	**Relative Constant** K
Standard (H)	-27401.02	39638.17	67157.87	1.69E-12	1
CH_3	-602074.66	24185.61	86260.97	7.57E-16	4.48E-4
Br	-23397.35	42732.03	66130.21	2.56E-12	1.51
Cl	-24034.99	42053.38	66089.21	2.60E-12	1.54
OCH_3	-2728.80	64614.77	67344.20	1.57E-12	9.29E-1
$N(CH_3)$	15670.34	82638.60	66965.76	1.83E-12	1.08

Table 1: *Reaction conditions, EDG or EWG substituents, MM2 computational energies, free energies, and equilibrium constants for reaction in Figure 7.*

However, when comparing the equilibrium constants to the relative equilibrium constants in the table above, most of the values lie around the value of one. This means that MM2 predicts cyclodehydration synthesis of 1,3,4-oxadiazoles is to be thermoneutral, preferring neither the reactants nor the products. While quantitatively these values are not as large as we have hoped, qualitatively, these results do show that the reactions with R groups of Br, Cl, and $N(CH_3)$ are

partially preferred. It is worth noting that with MM2 and other computational programs, qualitative trends can still be deduced as long as the method currently being used is consistently inaccurate: that is, as long as it can reliably predict a qualitative trend. As previously mentioned, qualitative analysis previously mentioned can be observed; however, the MM2 model was unable to provide any definitive quantitative results that could help formulate a Hammett Plot or general mechanism of this reaction. In order to potentially remedy this issue with MM2, PM3 was consulted.

The semi-empirical method of PM3 was the second computational approach in order to address the mechanistic study of this project.[23] Similarly to MM2 analysis, the equilibrium geometry energy was substituted for the overall Gibbs free energy (ΔG°) and the equilibrium constant (K) were found for the given reactions shown in Figure 8 and in Table 2.

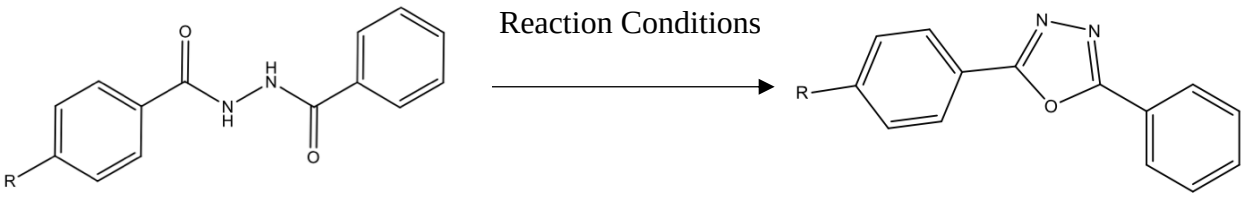


Figure 8: *Reaction scheme for 1,3,4-oxadiaozle synthesis with various R groups at the para position of the benzene ring under PM3 analysis.*

R Group	**Energy of Reactants (J/mol)**	**Energy of Products (J/mol)**	**Gibbs Free Energy** $\Delta G°$	**Equilibrium Constant** K	**Relative Constant** K

Standard (H)	25443.8	61602	36158.2	4.59E-7	1
CH_3	-15460.5	21530.4	36990.9	3.28E-7	7.15E-1
Br	58674.2	95802	37127.8	3.10E-7	6.76E-1
$N(CH_3)$	7354.8	44046.4	36691.6	3.70E-7	8.063E-1

Table 2: *Reaction conditions, EDG or EWG substituents, PM3 computational energies, free energies, and equilibrium constants for reaction in Figure 8.*

While all the R groups from MM2 study were not observed during the PM3 study, a similar result was shown. The equilibrium constants (K) were larger than the MM2 study; however, the values were still fairly small and the relative equilibrium constants for each of the tested R groups produced values close to one. Again, this means that the reaction is neither favored towards the products or reactants. Upon further evaluation of this dilemma, it was concluded that overall simplicity of these two programs could not quantitatively describe energy involved within this cyclodehydration synthesis of 1,3,4-oxadiazoles, but the qualitative trends are still noted due to the consistency of the two programs. In addition, another issue arises with these programs when studying the energetic effects of phosphorus from the dibromotriphenylphosphorane. Due to the lack of standard known values for the effects that phosphorus possesses and since some parameters of both of these methods are guessed, MM2 and semi-empirical methods (PM3) were proven to be ineffective in providing quantitative details about this mechanism.

Even though MM2 or PM3 were unable to provide precise details in the mechanism of this cyclodehydration synthesis, the final component which focused on bond dissociation energy supported the proposed mechanism. When using standard known values in order to calculate the overall enthalpy of this reaction, almost all the bonds broken and formed in this reaction were

identical for each scenario. The only variation of bond dissociation energies that were noted was the double bond formation between the oxygen and phosphorus in the reaction's byproduct. As a result, a variety of enthalpies were recorded in Table 3 with the average enthalpy across all three scenarios being roughly -2400kJ/mol. This negative value is insightful because it confirms the theory of this reaction being exothermic. An exothermic reaction simply means that the energy required to start a given reaction is less than the energy released by the reaction itself and the products are at a lower and stable energy level in comparison to the initial reactants. Finally, this reveals that new bonds are being formed through the cyclodehydration synthesis and shows that this reaction is preferred.

Type of P=O Bond Observed (stand in place of $O=PPh_3$)	**Total Energy of Bonds Broken (kJ/mol)**	**Total Energy of Bonds Formed (kJ/mol)**	**Enthalpy ΔH (kJ/mol)**
$Br_3P=O$	1910	-4304.7	-2394.7
$Cl_3P=O$	1910	-4316.7	-2406.7
$F_3P=O$	1910	-4350.7	-2440.7

Table 3: *Overall enthalpy for cyclodehydration synthesis of 1,3,4-oxadiazole synthesis at different observed P=O interactions. It is worth nothing that these three forms of P=O bonds substitute the actual $O=PPh_3$ bonds.*

From the enthalpies previously found, we can conclude that this reaction is preferred and while we cannot quantify this mechanism, the qualitative trends from all this previous data can be noted for the first step of this mechanism. Based on the previous data and general nucleophilic acyl substitution trends, a proposed mechanism for the first step of the

synthesis of 1,3,4-oxadiaozle via cyclodehydration can be seen in Figure 9 to the diacylhydrazine intermediate.

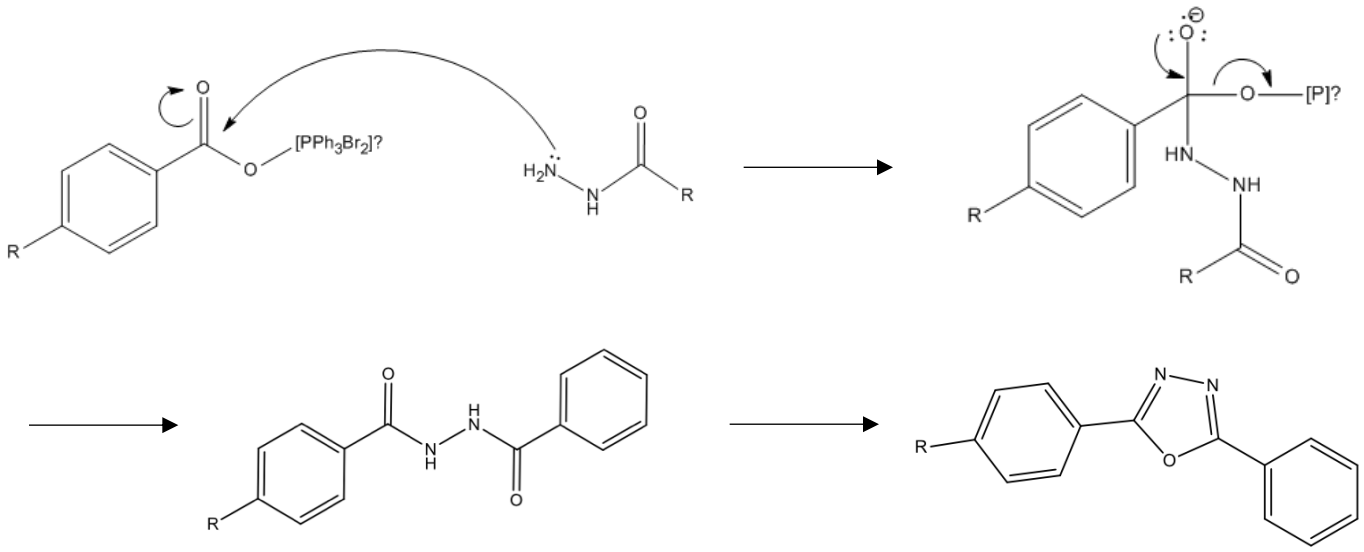


Figure 9: *Proposed mechanism for the first step of 1,3,4-oxadiazole synthesis via cyclodehydration.*

For the initial phases of this mechanism, the lone pair of electrons of the terminal nitrogen of the benzohydrazide acts as the nucleophile and attacks the carbon of the carbonyl in the benzoic acid derivative. This leads to a pair of electrons from the carbonyl to temporarily relocate to the oxygen of the carbonyl and giving the oxygen atom a negative charge as a result. Immediately, a lone pair of electrons collapse back into a double bond carbonyl while ejecting the bulky phosphorus containing leaving group which originates from the dibromotriphenylphosporane. It is worth noting that while the phosphorus is highly suggested to be the leaving group in this reaction, what is bonded to phosphorus during this stage remains unknown. Ultimately, this leads to the synthesis of the diacylhydrazine intermediate. Since the Hammett plot could not be

generated for the latter half of this reaction, the mechanism for this cyclodehydration reaction from the hydrazine intermediate to the 1,3,4-oxadiazole product remains unknown.

In the future, it would be interesting to consult higher levels of theory with this reaction. While the simple nature of MM2 and PM3 can be used for other analyses, full *ab initio* methods, while more time consuming, could possibly provide more in-depth results in this reaction as well as address the phosphorus conflict in the dibromotriphenylphosphorane conflict. Several *ab initio* routes that can be utilized to possibly solve this problem include Hartree Fock and MP2 methods. Using these more thorough methods can potentially provide more quantitative results to reveal the final step of 1,3,4-oxadiazole synthesis from the hydrazine intermediate by developing an adequate Hammett plot. Another way to acquire a more complete study of the mechanism is to study the effects due to additional EDGs and EWGs as these groups will have different influences on the reaction center in 1,3,4-oxadiazole synthesis.

Materials and Methods

General Procedures

All solvents were purchased unless otherwise noted. All reagents that were not synthesized were purchased. All compounds were characterized via a Bruker Fourier 300 MHz nuclear magnetic resonance spectrometer (NMR). Full NMR spectra can be seen in the Appendix below.

Synthesis of 2,5-diphenyl[1,3,4]oxadiazole from commercial 1,2-dibenzoylhydrazine[25]

Reaction and Thin Layer Chromatography: Figure 10

1,2-dibenzoylhydrazine (0.205 g, 0.859 mmol) was added to a flask and was evacuated of air, sealed, and subjected to nitrogen gas. With a syringe, 3 mL of acetonitrile was added and the reaction flask was placed in an ice bath with stirring. Dibromotriphenylphosphorane (1.412 g, 3.39 mmol) was added to the reaction flask and stirred for five minutes. The reaction flask was then removed from the ice bath and stirred for an additional hour. The diisopropylethylamine was added to the mixture and stirred constantly for 16 hours. Thin layer chromatography was performed on silica with an eluant composed of a 9:1 of hexane to ethyl acetate (9 mL hexane, 1 mL ethyl acetate).

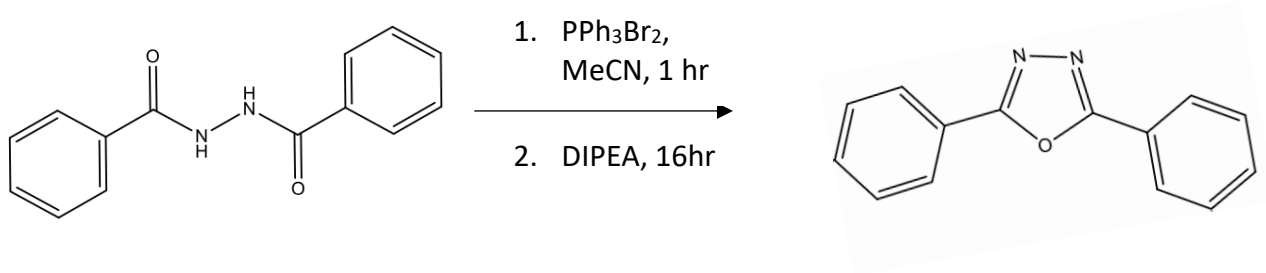


Figure 10: *Synthesis of 2,5diphenyl[1,3,4]oxadiazole from commercial 1,2-dibenzoylhydrazine.*

Work-Up, Column Chromatography, and ^{13}C and ^{1}H NMR

1 mL of deionized water was added to the flask and briefly stirred. The compound was extracted through a separatory funnel and initial reaction was diluted with 10 mL of dichloromethane and 10 mL of deionized water. The organic layer of the mixture was extracted with two additional washes consisting of 15 mL of dichloromethane for each wash. The combined organic mixtures were combined and dried with anhydrous sodium sulfate and immediately gravity filtered into a flask. Organic layer mixture was concentrated via rotary evaporator. The concentrated solution was purified via column chromatography with 200 mL of an eluant with a 9:1 of hexane to ethyl acetate. All collections containing product were combined into a singular flask and excess solvent was removed via rotary evaporation. Product

was dried overnight. Overall yield was 63.7% (0.190 g). A small dry sample of the product was dissolved in chloroform and was characterized by ^{13}C and ^{1}H NMR shown in Figures 13 and 14.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.1, 7.5, 2.2

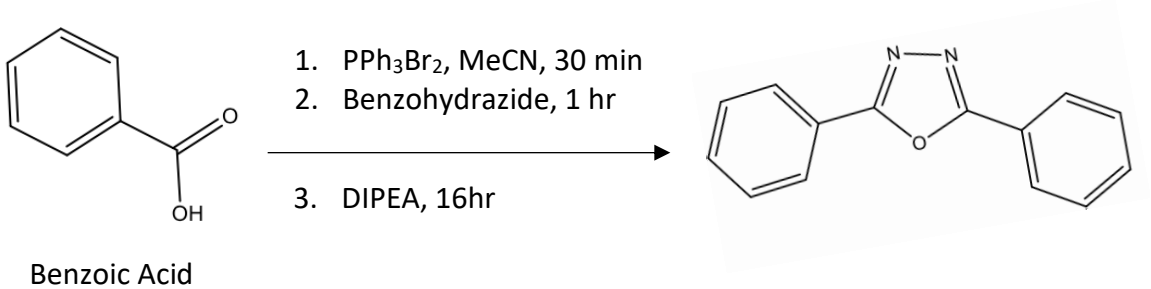
^{13}C NMR: ($CDCl_3$, 300 MHz) δ 207.1, 164.6, 131.8, 129.1, 126.9, 123.9, 31.0

R_f: 0.204

Yield effects of 2,5-diphenyl[1,3,4]oxadiazole synthesis by initially exposing benzoic acid to reaction conditions

Reaction and Thin Layer Chromatography: Figure 11

Benzoic acid (0.105 g, 0.859 mmol) was added to a flask and was evacuated with a pump, sealed, and subjected to nitrogen gas. 3 mL of acetonitrile was added to the flask through the use of a syringe and was immediately placed in an ice bath and stirred for one minute. The reaction mixture was removed from the ice bath and dibromotriphenylphosphorane (1.43 g, 3.39 mmol) was added to the flask and stirred for 30 minutes. Benzohydrazide (0.118 g, 0.859 mmol) was added to the reaction flask and stirred for one hour. 0.9 mL of diisopropylethylamine was added to the flask and the flask was placed within an ice bath to stir for one minute. The ice bath was removed and the reaction mixture was constantly stirred for 16 hours. Thin layer chromatography was performed with an eluant composition of a 9:1 of hexane to ethyl acetate.



Benzoic Acid

Figure 11: *Yield effects of 2,5-diphenyl[1,3,4]oxadiazole synthesis by initially exposing benzoic acid to reaction conditions.*

Work-Up, Column Chromatography, and ^{1}H NMR

1 mL of deionized water was added to the reaction flask and briefly stirred. The compound was extracted through the use of a separatory funnel and the mixture was diluted with 10 mL of dichloromethane and 10 mL of deionized water. The organic layer was extracted along with two additional washes of 15 mL of dichloromethane. The organic extracts were combined to a single flask, immediately dried with anhydrous sodium sulfate, and gravity filtered into another flask. The organic extracts were further concentrated with a rotary evaporator and the solution was purified through column chromatography. The eluant was 200 mL of a 9:1 of hexane to ethyl acetate. All collections containing product from the column were combined and excess solvent was removed via rotary evaporation. During this step, much product was lost so exact yield could not be determined. Remaining product was stored and dried overnight. A small sample of product was dissolved in chloroform in preparation to be analyzed by ^{1}H NMR shown in Figure 15.

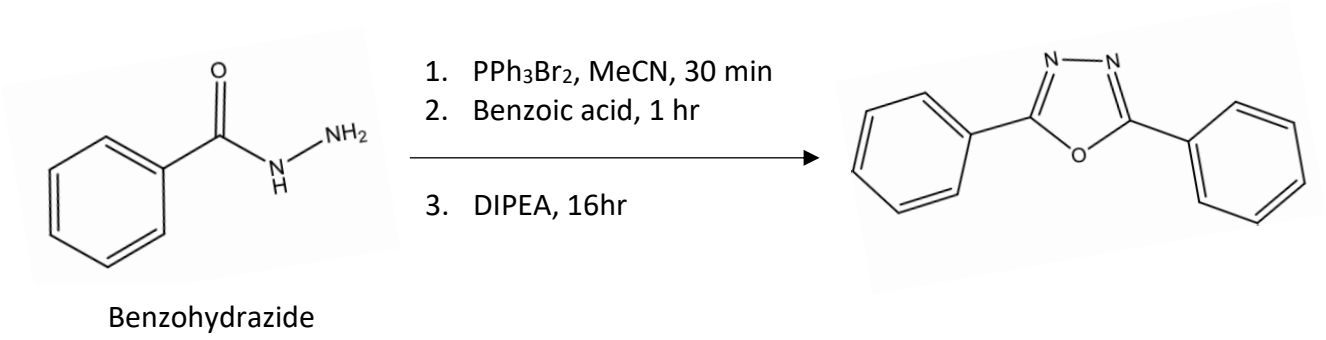
^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.2, 7.6

R_f: 0.185

Yield effects of 2,5-diphenyl[1,3,4]oxadiazole synthesis by initially exposing benzohydrazide to reaction conditions

Reaction and Thin Layer Chromatography: Figure 12

Benzohydrazide (0.117 g, 0.859 mmol) was added to a flask, evacuated with a pump, and filled with nitrogen gas. 3 mL of acetonitrile was added to the flask with a syringe and the flask was placed in an ice bath and stirred for one minute. The ice bath was removed and the dibromotriphenylphosphorane (1.45 g, 3.39 mmol) was added to the flask and was stirred for 30 minutes. Benzoic acid (0.106 g, 0.851 mmol) was added to the flask and stirred for one hour. 0.9 mL of diisopropylethylamine was added to the reaction mixture to be stirred for one minute. The ice bath was removed and the reaction flask was stirred for 16 hours. Thin layer chromatography was performed with a 9:1 eluant of hexane to ethyl acetate.



Benzohydrazide

Figure 12: *Yield effects of 2,5-diphenyl[1,3,4]oxadiazole synthesis by initially exposing benzohydrazide to reaction conditions.*

Work-Up, Column Chromatography, and ^{1}H NMR

1 mL of deionized water was added to the reaction flask and briefly stirred. The compound was extracted through the use of a separatory funnel and the mixture was diluted with 10 mL of dichloromethane and 10 mL of deionized water. The organic layer was extracted along with two additional washes of 15 mL of dichloromethane. The organic extracts were combined into a single flask, immediately dried with anhydrous sodium sulfate, and gravity filtered into another flask. The organic extracts were further concentrated with a rotary evaporator and the

solution was purified through column chromatography. The eluant was 200 mL of a 9:1 of hexane to ethyl acetate. All collections containing product from the column were combined and excess solvent was removed via rotary evaporation. Remaining product was stored and dried overnight. Overall yield was 63.8% (0.191 g). A small sample of product was dissolved in chloroform in preparation to be analyzed by ^{1}H NMR shown in Figure 16.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.2, 7.6, 1.6

R_f: 0.184

Computational Studies

Compounds were studied using initially used through MM2 within the ChemBio 3D program. Each compound was built and the summation of free energy was calculated for each reaction.[21] In addition, PM3 was utilized through the Spartan 16 computational program. Each figure was drawn and the equilibrium geometry energy was calculated for each compound of interest.[23] The final component of the computational analysis was to study the overall enthalpy of the cyclodehydration synthesis. Each of the broken and formed bonds of this reaction were calculated using a standard table of bond dissociation energies and Equation 4.[26]

Appendix

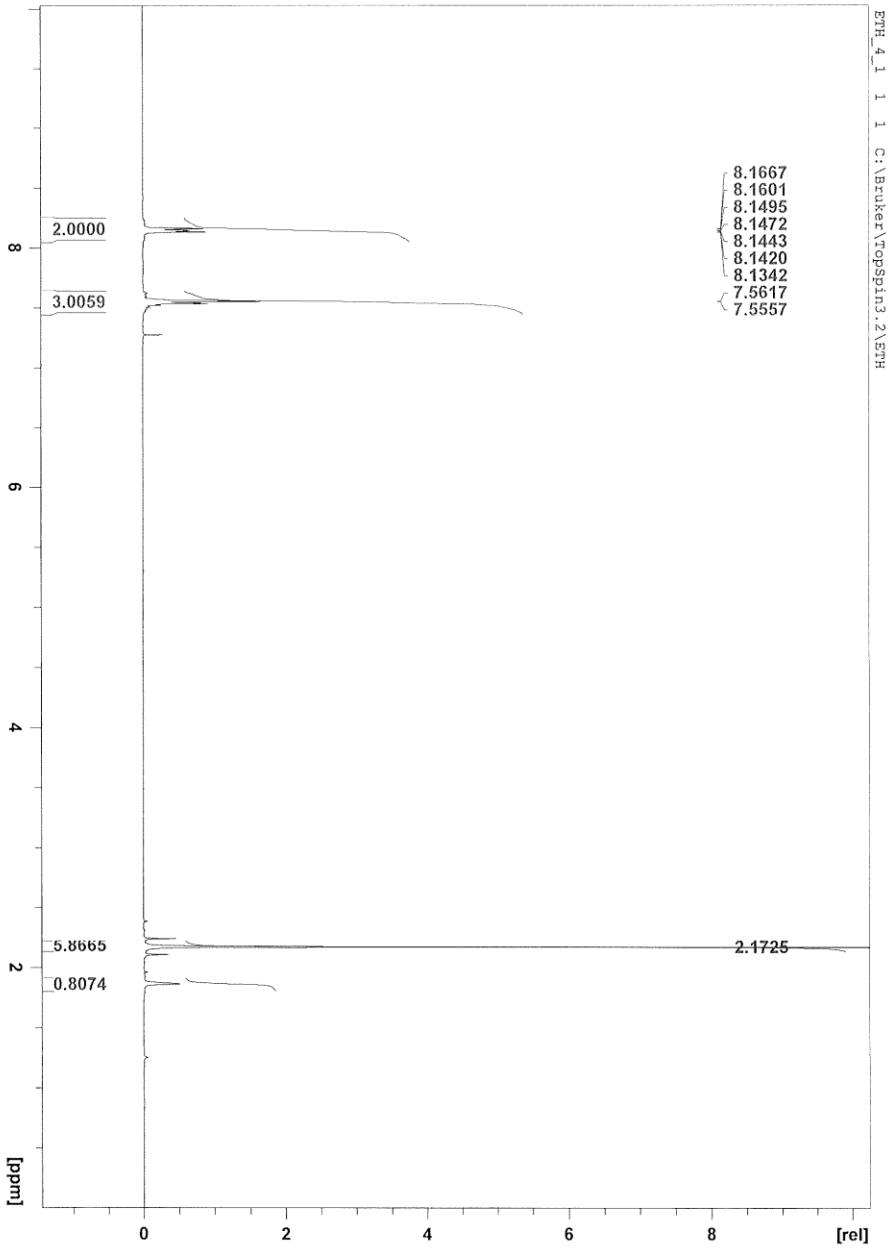


Figure 13: *^{1}H NMR for 1,3,4-oxadiazole product via synthesis from diacylhydrazine intermediate.*

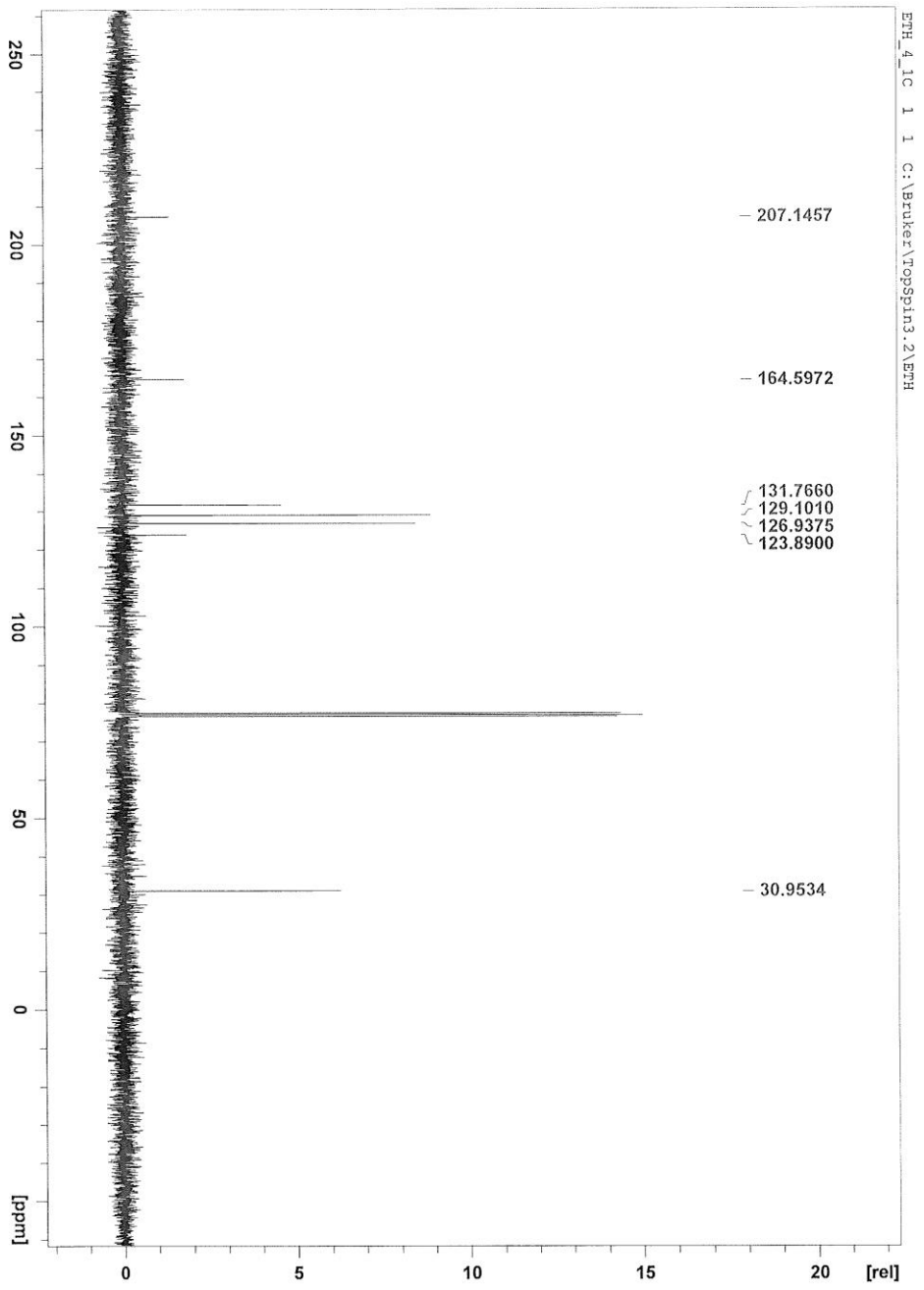


Figure 14: *^{13}C NMR for 1,3,4-oxadiazole product via synthesis from diacylhydrazine intermediate.*

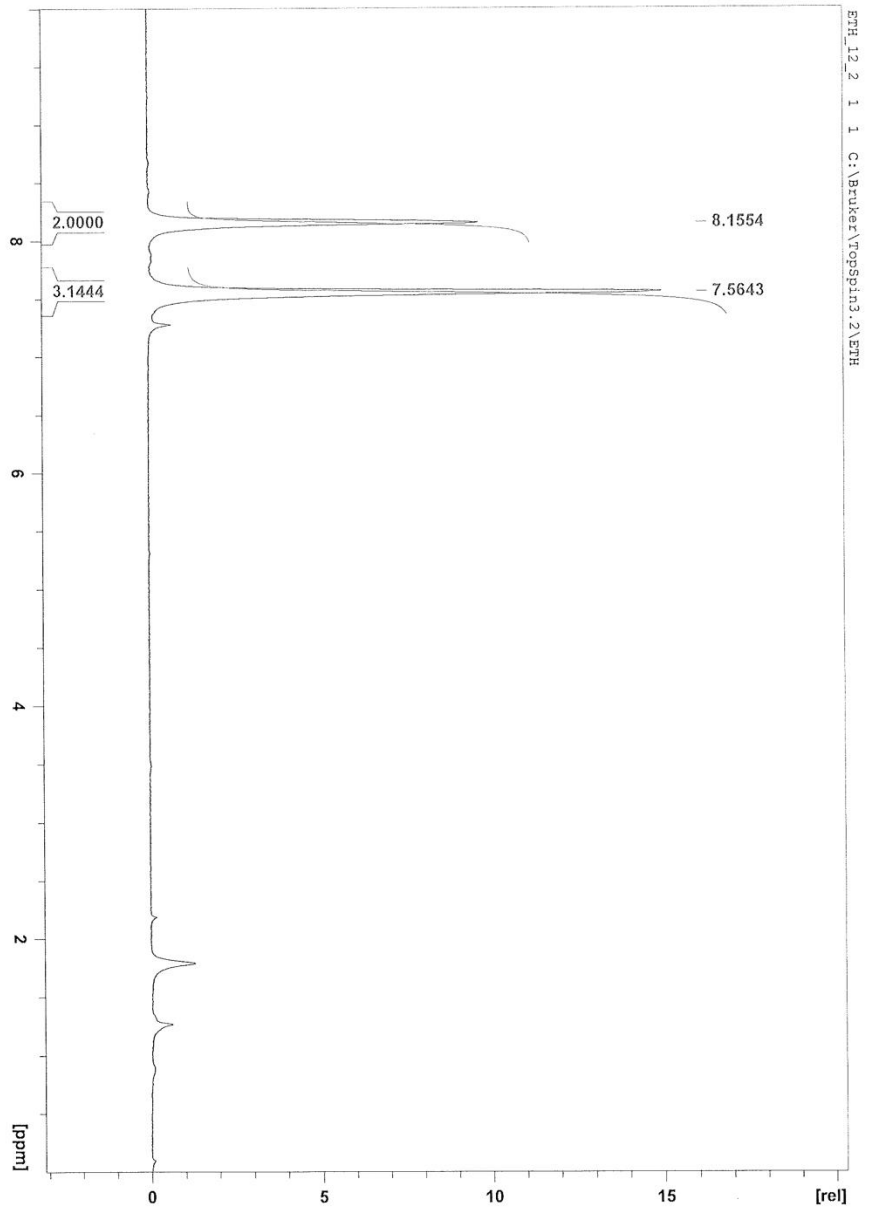


Figure 15: *^{1}H NMR for 1,3,4-oxadiazole product via initial introduction of benzoic acid to reaction conditions.*

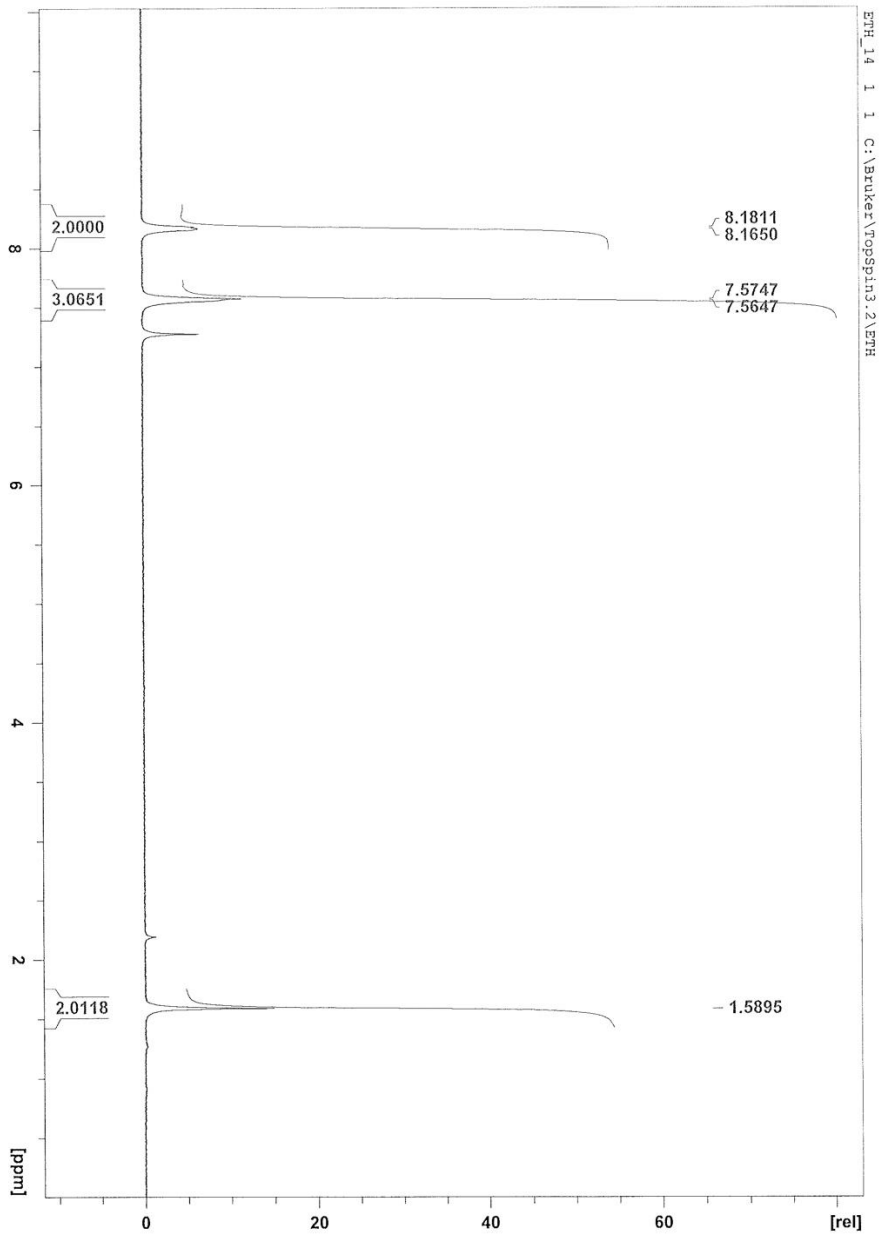


Figure 16: *^{1}H NMR for 1,3,4-oxadiazole product via initial introduction of benzohydrazide to reaction conditions.*

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