3-11-2018

Synthesis of Oxadiazoles and Examination of Steric Effects in a Cyclodehydration Reaction

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SYNTHESIS OF OXADIAZOLES AND EXAMINATION OF STERIC EFFECTS IN A CYCLODEHYDRATION REACTION

By

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March 11, 2018

Submitted in partial fulfillment of the requirements
For graduation with Honors

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Acknowledgments

First and foremost, I would like to thank my research advisor, Dr. Robin Grote. As my organic chemistry professor for two semesters, she taught me everything that I know about organic chemistry. Supporting my chemistry interests and patiently teaching me new techniques, working under her in the lab has been extremely fulfilling. Without her, none of this would be possible. I would also like to thank my second reader, Dr. Carrigan Hayes. She has been extremely supportive in helping me work through the computational crystallography data involved in this research and is very responsive in answering my questions. Additionally, Dr. Dean Johnston has been extraordinarily helpful in navigating the ConQuest and Mercury software to retrieve experimental crystallography data. Thanks also goes to my parents who have supported my interests all throughout my life and happily listen to me share my excitement for the research I am doing. Additionally, I would like to thank the Otterbein Student Research Fund for funding this research. Lastly, thank you to the reader who has taken the time to share my interest in this research.

Abstract

The objective of this project is to develop a general substrate scope by testing various steric and electronic effects. This is pursued by developing triphenylphosphine dibromide (PPh_3Br_2) as an effective cyclodehydration reagent for use with a variety of hydrazides and sterically and electronically different benzoic acids. The two phases of the experiment include assessing yield through a cyclodehydration reaction and comparing that yield to the steric hindrance and molecular structure recorded in different databases. The cyclodehydration reaction uses ortho-substituted benzoic acid with store bought PPh_3Br_2, and compares those yields to the use of a two step-one pot reaction in place of the PPh_3Br_2. Experimental published data is collected using software ConQuest/Mercury to access Cambridge Crystallographic Data Centre. This data is then then compared to computational data from ChemBio3D Ultra. Because bond length was very similar among the various benzoic acids, it cannot be determined how bond length affects yield. Torsion angle data values differ significantly between the experimental data and the computational data. However, similar trends in data are seen across both methods. In both methods, the 2-Methylbenzoic acid and o-Methoxybenzoic acid show a smaller torsion angle than o-Bromobenzoic acid and o-Chlorobenzoic acid signifying more steric hindrance in 2-Methylbenzoic acid and o-Methoxybenzoic acid. Comparing this to the yield of these benzoic acids show that the smaller the torsion angle, the less reactive the benzoic acid is. Benzoic acid is an exception to this with a small torsion angle and high yield. Due to the lack of an ortho-substituent, the small torsion angle does not increase steric hindrance and therefore does not negatively affect yield.

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Introduction/Background:

Heterocycles:

Heterocycles show significance in not only organic and medicinal chemistry, but also in everyday life. A heterocycle is a broad term for any cyclic compound that contains a heteroatom (an atom that is not carbon). Some common heterocycles found in nature include amino acids used to form proteins, vitamins/co-enzymes essential for human health, Chlorophyll *a* which is crucial for photosynthesis, and DNA/RNA which is the genetic code behind all living things.[1] Outside of nature, heterocycles are extremely important in day-to-day living. Aromatic heterocycles, or benzene derivatives similar to those that are being studied in this experiment, provide a wide variety of uses from industrial applications to medicinal purpose.[1]

These aromatic heterocycles, containing H, O, N and S heteroatoms, can be arranged in a variety of ways producing great diversity between compounds. Not only are these compounds industrially used to form houseware and laminates, but they are also used in creating fireproof clothing, pesticides, and other commonly used products. On top of their industrial significance, heterocycles are the basis of medicinal chemistry. Heterocyclic substances make up about half of the top selling drugs on the market.[1] From cholesterol level reducers to schizophrenia/bipolar disorder treatments, heterocycles are at the center of drug development.[1]

Steric Hindrance and Electronics:

Steric and electronic effects take a large role in affecting the synthesis of heterocycles. Every atom has an electron cloud that surrounds it. Because electrons are negatively charged, they repel one another. When two electron clouds from different atoms are close to one another, they will experience steric strain. This is the strain experienced by a molecule when atoms or groups of atoms are close enough to

each other to have their electron clouds repel one another.[2] This steric strain increases with the size of the interacting atoms/molecules. When steric strain is experienced at the site of a reaction, it is referred to as steric hindrance.[2] Steric hindrance is a steric effect caused by bulky groups at the site of the reaction that make it difficult for reactants to approach one another.[2] In this study, an ortho-substituted benzoic acid is used as a reagent to examine the effect that steric hindrance has on yield of oxadiazole, a specific heterocycle. This benzoic acid is more sterically hindered with the substituent directly next to the carboxyl group compared to the para-substituted benzoic acids previously studied in the Grote Lab.[3,4] The difference between ortho and para-substitution can be seen in Figure 1.

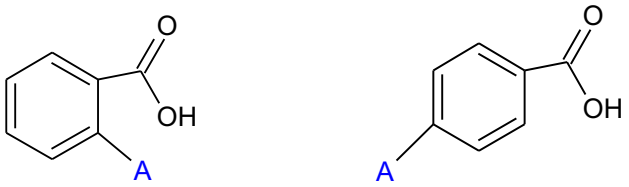

Figure 1. Ortho-substituted benzoic acid (left) is more sterically hindered then para-substituted benzoic acid (right).

In Sn2 reactions, steric hindrance plays a large role in general reactivity because the substituent is still present, creating steric hindrance, when the nucleophile attacks and the reaction takes place. Because of this, it is a general rule that primary alkyl halides (containing one alkyl group off of the carbon) are less sterically hindered and more reactive than secondary and tertiary alkyl halides (containing two or three alkyl groups off of the carbon).[2] In addition to number of alkyl groups attached during nucleophilic attack, the size of the alkyl group also affects steric hindrance and reactivity. The bulkier the alkyl group, the more sterically hindered and less reactive it is.[2] Steric effect is examined in this study comparing the reactivates of o-Methoxybenzoic acid (o-Toluic acid) to o-Bromobenzoic acid and o-Chlorobenzoic acid. Data on steric hindrance is collected using experimental[5] and computational data[6] on bond length and angle torsion, showing how bulky or close to the reaction cite the substituent is.

When the atom attached to the aromatic ring is replaced with an electrophile, it is called electrophilic aromatic substitution. The original atom attached to the ring is a substituent, and substituents can be activating or deactivating depending on their electronics. An activating substituent makes the benzene ring more reactive toward electrophilic aromatic substitution, while a deactivating substituent makes the benzene ring less reactive toward electrophilic aromatic substitution. The ability of a substituent to activate or deactivate a reaction directly correlates with its ability to delocalized or pull electrons in and out of the aromatic ring. If a substituent has a lone pair on the atom directly attached to the benzene ring, the pair can be delocalized into the ring and the substituent is an electron donating group. An electron donating group increases the reactivity of the benzene ring, making electrophilic aromatic substitution easier. Contrary to this, if a substituent is attached to the benzene ring through a double or triple bond, the electrons in the ring can be delocalized onto the substituent. These substituents are electron withdrawing groups and decrease the reactivity of the benzene ring. Though halogens have lone pairs, they are electron withdrawing groups due to their high electronegativity. In this study, both electron donating group (OCH3) and electron withdrawing groups (Cl and Br) reactivity levels are observed. Chlorine and bromine are both electron withdrawing groups and their high electronegativity make them slightly deactivating substituents in electrophilic aromatic substitution, while OCH_3 is an electron donating group and an activating substituent in aromatic substitution where the ring is the nucleophile.[2] For the cyclodehydration reaction in this research, the electron withdrawing group is activating and the electron donating group is deactivating because the ring is the electrophile, not nucleophile.

Crystal Structure:

Molecular structure can be assessed in different ways including experimental data based on X-ray crystallography and computational data based on algorithmic data. X-ray crystallography is a technique used to determine the arrangement of atoms within a crystal to obtain experimental data.[2] This technique

can be used to assess molecular shape of any crystal (solid) structure. The ability to view three dimensional atoms and molecules through X-ray crystallography has aided in significant scientific advancements. In 1953, Rosalind Franklin's X-ray images allowed Watson and Crick to accurately describe the structure of DNA.[2] The process of X-ray crystallography is somewhat involved, but for simplistic purposes, it can be summarized into a few steps. Once a crystal of at least 0.5mm long is obtained, it is bombarded with X-rays while being gradually rotated.[2] While most of the X-rays pass through the crystal, there are some that are scattered by the electron clouds of the atoms creating X-ray diffraction.[2] Because of this, computers using complex mathematical methods are used to create a 3D model of the electron density within the crystal.[2] Because X-ray crystallography is a reliable method that is often used to determine crystal structure, data on crystal structure is stored in a variety of databases that give access to experimental data obtained through X-ray crystallography. This research looks at experimental data through the Cambridge Crystallographic Data Centre.[5]

In addition to viewing experimental data on molecular structure to examine bond length and angle torsion, this research also looks at computational data. While experimental data uses X-ray crystallography to obtain results, computational data uses an algorithm to obtain data. Advanced computing technologies have been developed through combining physics, chemistry and mathematics. Different user friendly programs have been developed to obtain computational data. In this research, ChemBio3D Ultra is used to assess bond length and angle torsion of various benzoic acids.[6] ChemBio3D Ultra is a molecular mechanics program that is based in Hooke's Law relating displacement to force.[7] The data collected in the computational software and experimental crystallography database will be compared to each other in addition to being compared to the yield of oxadiazole they produced.

1,3,4-oxadiazoles

Oxadiazoles are 5 membered heterocycles that contain one oxygen and two nitrogen heteroatoms, and have shown promise in treatments for cancer, cystic fibrosis and HIV.[8] These heteroatoms can be arranged around the ring in different ways, denoted by the numbers in the nomenclature. 1,3,4-oxadiazoles, the focus of this study, have been shown to have significant properties including anti-inflammatory capability that is stronger than those of ibuprofen and antitubercular activity. 1,3,4-oxadiazoles also show promise as antidepressants, anticonvulsants, and anti-anxiety medication without the neurotoxicity present in other marketed drugs.[9] Currently, the method used to produce these specific heterocycles is through dehydration reactions using caustic reagents such as phosphorus oxychloride ($POCl_3$) and para-toluene sulfonyl chloride.[10] There is also a patent using triphenylphosphine dibromide (PPh_3Br_2) with other specific reagents for the synthesis of 1,3,4-oxadiazoles.[11] The problem with using these reagents is that soon as they are exposed to air, they release acidic fumes and begin to decompose.

The patent previously mentioned shows triphenylphosphine dibromide (Ph_3PBr_2) being used with a specific hydrazide and benzoic acid to produce an oxadiazole.[3] In order for this reagent to be more useful, a general substrate scope must be developed testing various steric and electronic effects.[4] Following this, a two step-one pot reaction using PPH_3+Br_2 instead of store bought Ph_3PBr_2 can be developed, solving the problem of caustic reagents that create acidic fumes and product decomposition.[12] In this research, the two step-one pot reaction will be further developed by using a general substrate scope, testing steric and electronic effects in correlation with product yield.
In past experiments, benzoic acids and pyrazine-derived hydrazides produced high yields of the oxadiazole.[3,4] The inclusion of a pyrazine ring makes this reaction very specific and not generally useful. When developing new reactions, it is important to test a broad substrate scope.[13,14] This project aims to prove that Ph_3PBr_2 is an effective reagent for a general class of hydrazides, such as aromatic hydrazides and sterically different benzoic acids. Previous research in Dr. Grote's lab used specific substrates that

focused on electronic effects, while this research will primarily focus on steric effects through the use of an ortho-substituted benzoic acid. This benzoic acid is more sterically hindered with the substituent directly next to the carboxyl group compared to the para substituted benzoic acids previously studied in the Grote Lab.[3,4] The effect steric hindrance has on reactivity is shown through the relationship of percent yield in correlation with level of steric hindrance of benzoic acid. Data on steric hindrance is collected using experimental[5] and computational data[6] on bond length and bond angle torsion, showing how bulky or close together the substituents are. Percent yield shows the efficiency of the reaction by comparing the experimental yield with the theoretical yield.

Steric hindrance is the crowding of atoms resulting in a decrease in reactivity. This hindrance is due to bulky groups at the reaction site, not allowing space for other atoms to react.[12] In this experiment, various levels of sterically hindered benzoic acids will be used to see the effect it has on the yield of oxadiazole. Answering how sterics affect product yield allows researchers to further understand the mechanism for how an oxadiazole is formed using Ph_3PBr_2. With information gained on the effect sterics have on percent yield, chemists can more effectively produce oxadiazoles. If it is shown that Ph_3PBr_2 is an effective reagent with a general hydrazide and sterically different benzoic acid substrates, chemists can use this reagent with broader substrates to produce higher yields of oxadiazoles.

Project Description:

The objective of this project is to develop a general substrate scope by testing various steric and electronic effects. This is pursued by developing triphenylphosphine dibromide (PPh_3Br_2) as an effective cyclodehydration reagent for use with a variety of hydrazides and sterically and electronically different benzoic acids. The two phases of the experiment include assessing yield through a cyclodehydration reaction and comparing that yield to the steric hindrance and molecular structure recorded in different databases. The cyclodehydration reaction uses ortho-substituted benzoic acid with store bought PPh_3Br_2,

and compares those yields to the use of a two step-one pot reaction in place of the PPh_3Br_2. Experimental published data is collected using software ConQuest/Mercury to access Cambridge Crystallographic Data Centre. This data is then then compared to computational data from ChemBio3D Ultra.

Results/Discussion:

Bond length C1-CO of experimental data vs. computational data (Table 1)

Name	**Experimental Bond Length[5] (Å)**	**Computational Bond Length[6] (Å)**
2-Methylbenzoic acid (o-Toluic acid)	1.49(1)-1.491(6)[15,16]	1.368
o-Methoxybenzoic acid (o-Anisic acid)	1.481(2)-1.486(2)[17,18]	1.351
o-Bromobenzoic acid	1.492(4)[19,20i]	1.370
o-Chlorobenzoic acid	1.492(3)-1.494(3)[16,20ii,21]	1.351
Benzoic acid	1.43(2)-1.483(3)[22,23]	1.367

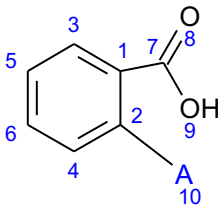

Figure 2. Each carbon is numbered for further reference. The different substituents on benzoic acid are represented by "A." These substituents are CH_3, OCH_3, Br, and Cl. Benzoic acid lacks a substituent off of carbon 2.

Bond length between C1 and CO can be seen in Figure 2 going from carbon 1-7. Rounding and sig figs are done in accordance with software used. Uncertain numbers in experimental data are put in

parenthesis (i.e. o-Bromobenzoic acid has a bond length of 1.492 +/- 0.0004). It is considered standard to round computational data on bond length from ChemBio3D Ultra to the thousandths.[24] All data on bond length is in Ångströms.

The experimental bond lengths are consistently higher than the computational bond lengths. However, within each method, the length does not vary much between different benzoic acids. Computationally, o-Methoxybenzoic acid and o-Chlorobenzoic acid have shortest bond length while experimentally, benzoic acid and o-Methoxybenzoic acid have the shortest bond length. Because the data are all very close together, the bond length is very similar and may not play a large role in steric hindrance in these benzoic acids.

Torsion angle O-C2 of experimental data vs. computational data (Table 2)

Name	**Experimental O-C2 Angle[5] (°)**	**Computational O-C2 Angle[6] (°)**
2-Methylbenzoic acid (o-Toluic acid)	1(1)-1.7(6)[15,16]	0.0(1)
o-Methoxybenzoic acid (o-Anisic acid)	5.6(2)-5.9(2)[17,18]	0.0(0)
o-Bromobenzoic acid	17.0(5)[19,20i]	0.0(3)
o-Chlorobenzoic acid	13.8(4)-14.6(4)[16,20ii,21]	2.5(4)
Benzoic acid	0.0(3)-2(1)[22,23]	0.0(0)

Torsion angle can be seen in in Figure 2 from O to carbon 8-7-1-2. Rounding and significant figures are done in accordance with software used. Uncertain numbers in experimental data are put in parenthesis (i.e. o-Bromobenzoic acid has a torsion angle of 17.0 +/- 0.05). It is considered standard to round computational data on torsion angle from ChemBio3D Ultra to the tenths place.[24] Computational figures

in parenthesis are included in data for comparison purposes but are uncertain. All data on torsion angle is in degrees.

As with table 1, in table 2 the experimental data is much higher than the computational data, but it is more significant in table 2 than in table 1. The experimental and computational data agree that benzoic acid has the smallest torsion angle. Due to the lack of substituent on benzoic acid, the torsion angle should be extremely close to 0. For this reason, the computational data seems more reliable than the experimental data. In both methods, the 2-Methylbenzoic acid and o-Methoxybenzoic acid show a smaller torsion angle than o-Bromobenzoic acid and o-Chlorobenzoic acid signifying more steric hindrance in 2-Methylbenzoic acid and o-Methoxybenzoic acid.

Yield of traditional vs. two step-one pot cyclodehydration reaction (Table 3)

Name	**PPh3Br2 Product % Yield**	**PPh3 + Br2 Product % Yield**
2-Methylbenzoic acid (o-Toluic acid)	_	_
o-Methoxybenzoic acid (o-Anisic acid)	0%	0%
o-Bromobenzoic acid	16%	37%
o-Chlorobenzoic acid	37%	36%
Benzoic acid	_	_

Due to time restrictions, I was unable to run reactions for 2-Methylbenzoic acid and benzoic acid. I was able to run o-Methoxybenzoic acid in both a traditional cyclodehydration reaction and a two step-one pot reaction, and received no yield. O-Bromobenzoic acid and o-Chlorobenzoic acid had yields very similar to each other. The 16% yield for o-Bromobenzoic acid is somewhat low and is possibly attributed to some human/experimental error. Because bromine and chlorine are both electron

withdrawing groups with similar reactivity and level of steric hindrance, it could be expected that they would produce similar yield. The yields between a traditional cyclodehydration reaction and a two step-one pot cyclodehydration reaction are very similar to one another with exception of the error influenced 16% yield with o-Bromobenzoic acid. Though the yields were consistent between methods, they were relatively low overall. This could be due to the ortho-substitution creating too much steric hindrance, decreasing reactivity of the substrates.

Bond length and torsion angle affecting yield:

Experimental yields compared to torsion angle (Table 4)

Name	**PPh3Br2 Product % Yield**	**PPh3 + Br2 Product % Yield**	**Experimental Torsion Angle[5] (°)**	**Computational Torsion Angle[6] (°)**
o-Methoxybenzoic acid (o-Anisic acid)	0%	0%	5.6(2)-5.9(2)[17,18]	0.0(0)
o-Bromobenzoic acid	16%	37%	17.0(5)[19,20i]	0.0(3)
o-Chlorobenzoic acid	37%	36%	13.8(4)-14.6(4)[16,20ii,21]	2.5(4)
Benzoic acid	73%[4]	54%[4]	0.03-2(1)[22,23]	0.0(0)

Because bond length was very similar among the various benzoic acids, it cannot be determined how bond length affects yield. Torsion angle data values differ significantly between the experimental data and the computational data. However, similar trends in data are seen across both methods. For comparison purposes and examining trends in yield, data from the Grote lab on benzoic acid yield is included in Table 4. In both methods, the 2-Methylbenzoic acid and o-Methoxybenzoic acid show a smaller torsion angle than o-Bromobenzoic acid and o-Chlorobenzoic acid signifying more steric hindrance in 2-Methylbenzoic acid and o-Methoxybenzoic acid. Comparing this to the yield of these

benzoic acids show that the smaller the torsion angle, the less reactive the benzoic acid is. Benzoic acid is an exception to this with a small torsion angle and high yield. Due to the lack of an ortho substituent, the small torsion angle does not increase steric hindrance and therefore does not negatively affect yield. Comparing product yield to torsion angle suggests that the closer the substituent is to the ring, the more steric hindrance there is causing a lower yield.

Methods/Experimental:

Research began by analyzing the steric parameters of various benzoic acid substrates (2-CH_3, 2-OCH_3, 2-Br, 2-Cl, benzoic acid) through the computer programs Conquest and Mercury. These programs use crystallography data collected from previous research to measure torsion angles and bond lengths.[5] Data was then collected on those same benzoic acids through a computational program ChemBio3D Ultra.[6] This program uses an algorithm based on published work to produce viable data. The benzoic acid substrates were chosen due to their electronic effects and steric hindrance.

No substituent:	Benzoic acid	
Electron donating group:	2-OCH_3	2-CH_3
Electron withdrawing groups:	2-Br	2-Cl

Next, the trends in yield of oxadiazole are compared with the trends in torsion angles and bond length of these various sterically hindered benzoic acids. Two methods were used to synthesize the oxadiazole: a traditional cyclodehydration reaction and a two step-one pot reaction. Due to time restraints, o-Methoxybenzoic acid, o-Chlorobenzoic acid, and o-Bromobenzoic acid were the only substrates ran in these two methods.

<u>Method 1: traditional cyclodehydration reaction</u>

Synthesize hydrazide: To a round bottom flask, add 0.022 mol methyl benzoate and 9mL hydrazine hydrate. Cool product then rotovap to a solid. Add 3 mL ethanol and heat to a clear solution. Cool to

recrystalize, then gravity filter washing with 1 mL of cold ethanol. Press the solid dry between filter paper and scrape product into round bottom flask. Place round bottom flask on vacuum pump to remove residual solvent.

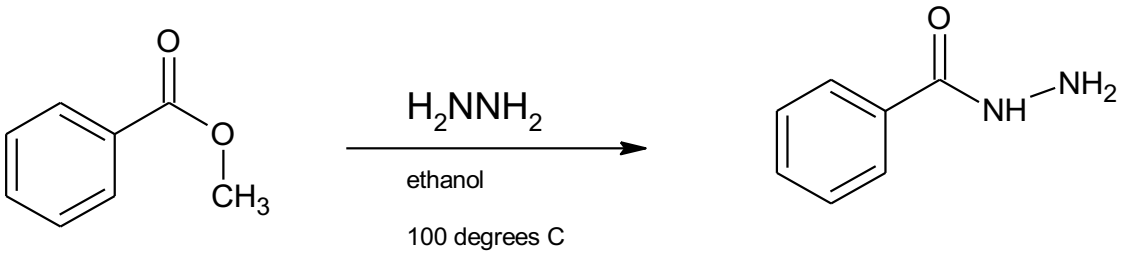

Figure 3. Methyl benzoate and hydrazine hydrate are used to synthesize a hydrazide.

To a 2 5mL round bottom flask, add $0.859x10^{-3}$ mol hydrazide and $0.859x10^{-3}$ mol benzoic acid. Evacuate flask with vacuum pump and fill with nitrogen. Because these reactions are air sensitive, they must be run under a nitrogen atmosphere.[18] Top flask with a nitrogen filled balloon. Add 3 mL acetonitrile (anhydrous) via a syringe. Put reaction on ice and add PPh_3Br_2. Stir reaction for 5 minutes then remove ice. Stir reaction for 1 hour then put flask back on ice to add DiPEA (Diisopropylethylamine). Stir reaction overnight. Once the reaction is complete, purify the product using flash column chromatography.

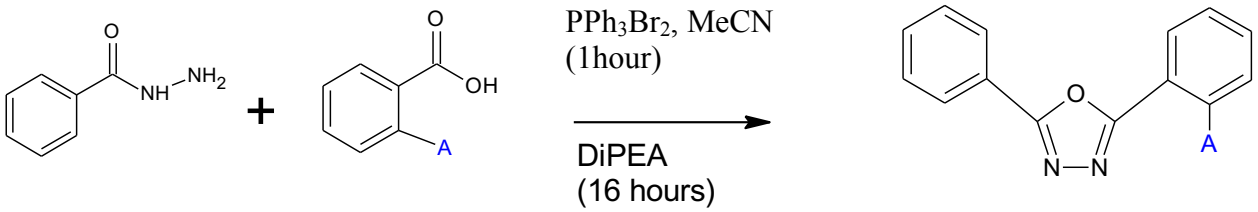

Figure 4. Hydrazide and benzoic acid are used in a traditional cyclodehydration reaction to synthesize an oxadiazole.

Method 2: two step-one pot

Synthesize hydrazide: To a round bottom flask, add 0.022 mol methyl benzoate and 9mL hydrazine hydrate. Cool product then rotovap to a solid. Add 3 mL ethanol and heat to a clear solution. Cool to recrystalize, then gravity filter washing with 1 mL of cold ethanol. Press the solid dry between filter paper and scrape product into round bottom flask. Place round bottom flask on vacuum pump to remove residual solvent. Please reference Figure 3.

To form an oxadiazole through a two step-one pot reaction, triphenylphosphine and bromine can be mixed using acetonitrile as a solvent to give PPh_3Br_2 as a product in solution, ready to use. The detailed procedure for this can be found in *Organic Syntheses.*[25] To a 10 mL round bottom flask, add PPh_3. Evacuate the flask using a vacuum pump and fill flask with nitrogen, topping flask with a nitrogen balloon. Because these reactions are air sensitive, they must be run under a nitrogen atmosphere.[4] Add 3 mL acetonitrile (anhydrous) then put reaction on ice bath to add 4.31 mol bromine dropwise. Remove ice bath after 1 min then let the reaction stir for 1 hour. After the reaction has stirred for 1 hour, put reaction on ice bath and crack flask open to add $0.859x10^{-3}$ mol hydrazide and $0.859x10^{-3}$ mol benzoic acid. Remove ice bath after 1 min and let reaction stir for 1 hour. After the reaction has stirred for 1 hour, put reaction on ice bath to add DiPEA using a syringe. Once the DiPEA is added, the ice bath can be removed and the reaction is set to stir overnight. Once the reaction is complete, the product is purified using flash column chromatography.

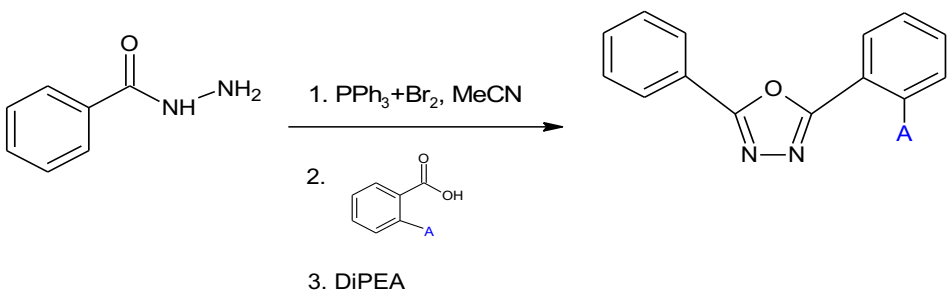

Figure 5. Hydrazide and benzoic acid are used in a two step-one pot cyclodehydration reaction.

H[1]NMR Data:

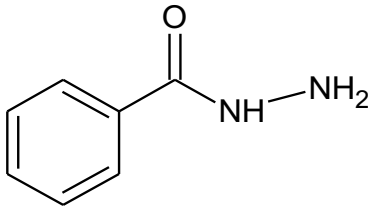

Figure 6. Hydrazide used in both cyclodehydration reaction methods.

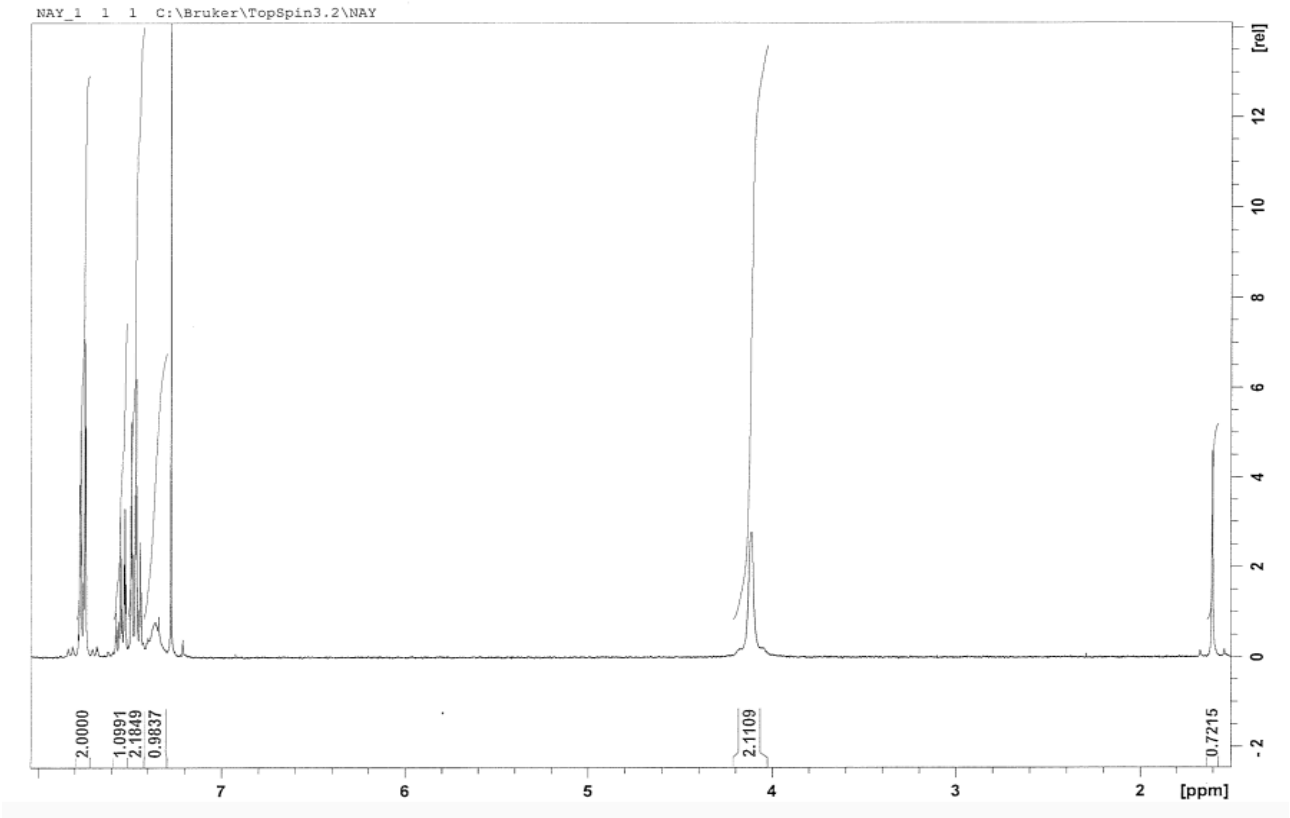

Figure 7. The benzoic hydrazide H[1]NMR shows product with grease as the only contaminant at approximately 1.65ppm.

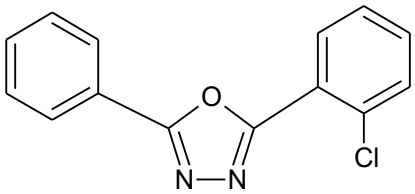

Figure 8. 1,3,4-oxadiazole synthesized using o-Chlorobenzoic acid.

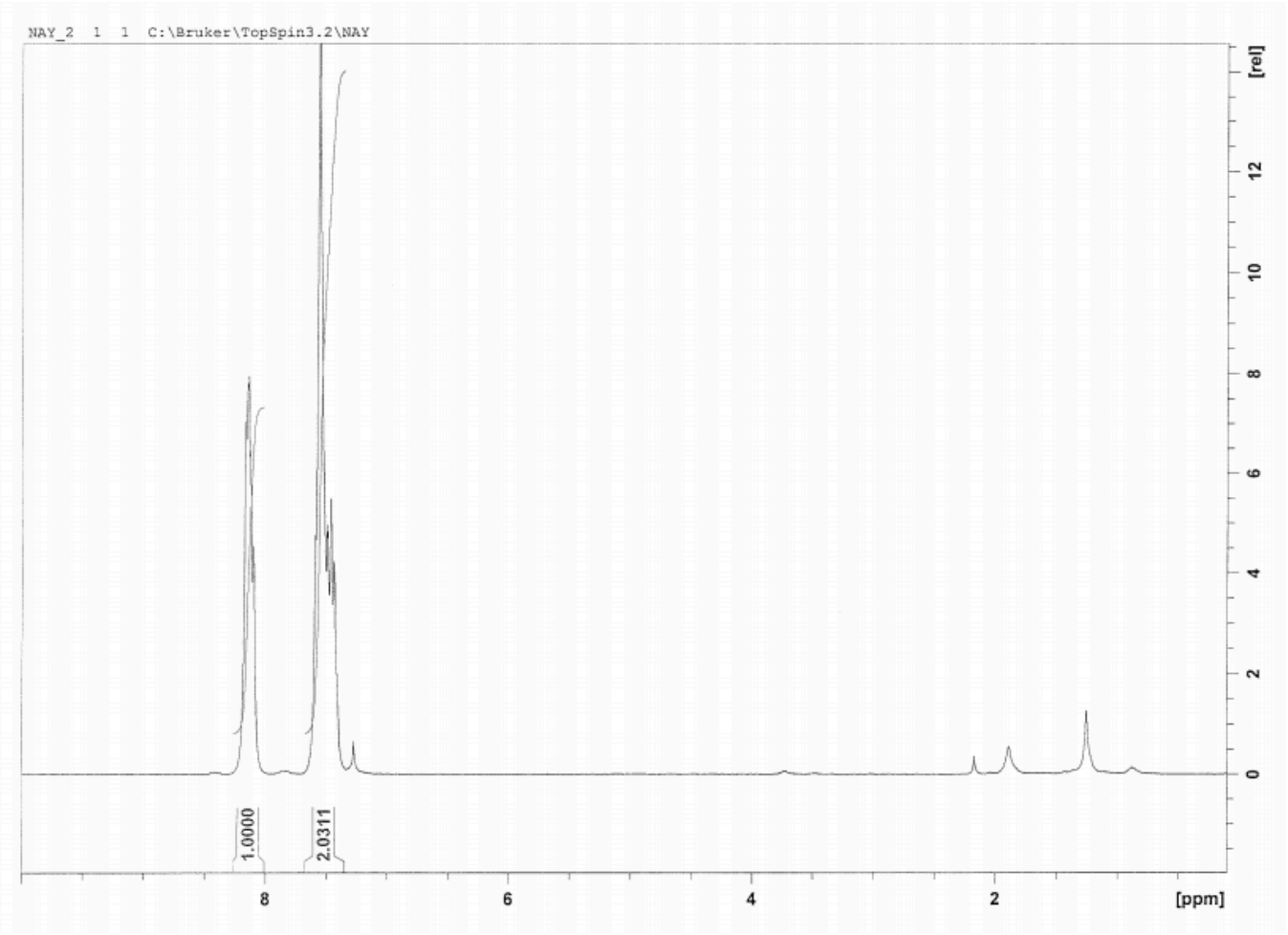

Figure 9. H[1]NMR of 1,3,4-oxadiazole synthesized using o-Chlorobenzoic acid is from the two step-one pot cyclodehydration method. Product is consistent with product shown in NAY_2, but is not conclusive. This may be due to contaminants or rotamers. In the future, the H[1]NMR can be heated up to view potential product.

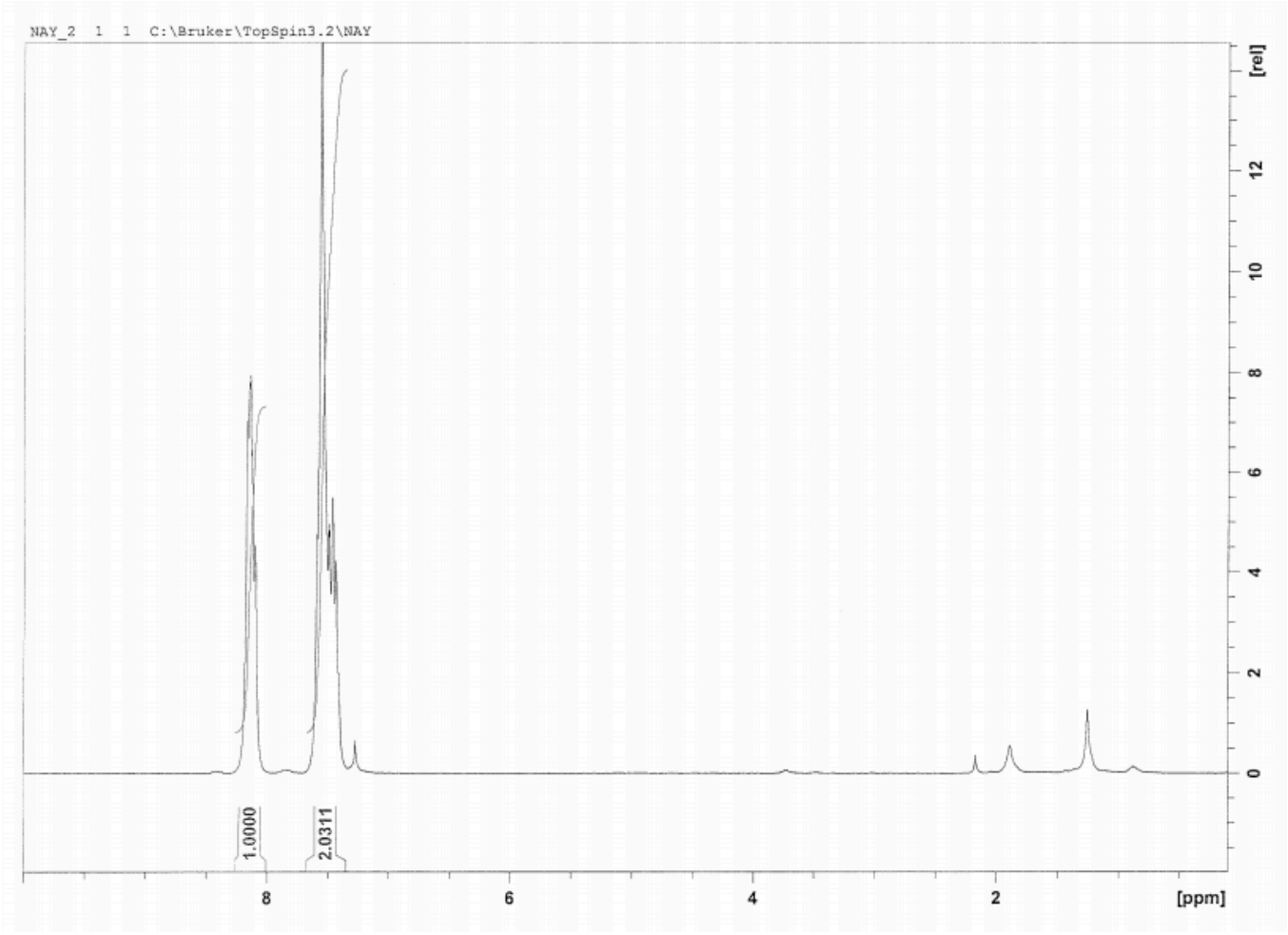

Figure 10. H^1NMR of 1,3,4-oxadiazole synthesized using o-Chlorobenzoic acid is from the traditional cyclodehydration method. Product is consistent with product shown in NAY_3, but is not conclusive. This may be due to contaminants or rotamers. In the future, the H^1NMR can be heated up to view potential product.

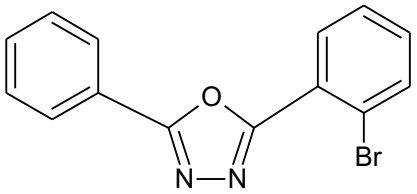

Figure 11. 1,3,4-oxadiazole synthesized using o-Bromobenzoic acid.

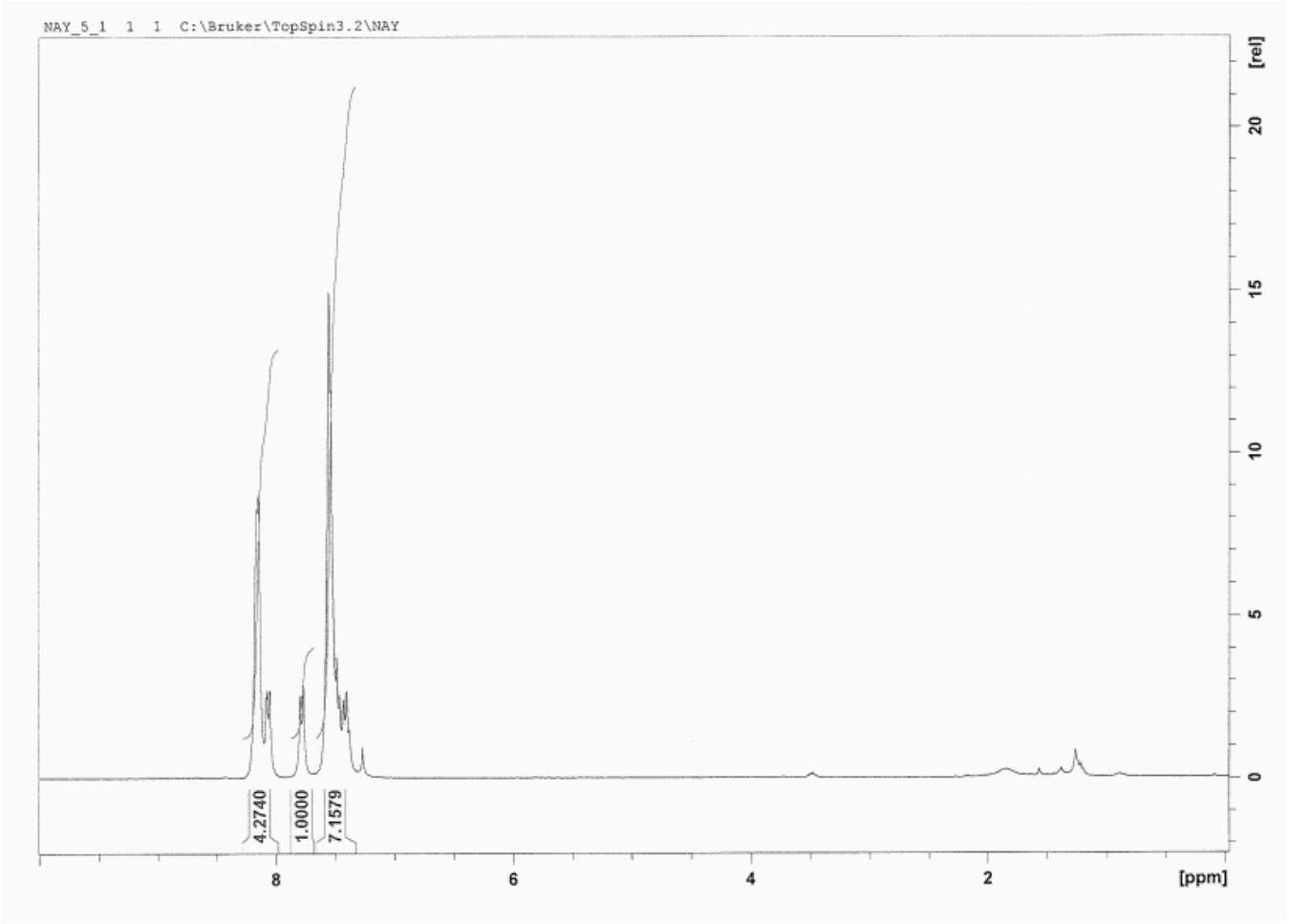

Figure 12. H[1]NMR of 1,3,4-oxadiazole synthesized using o-Bromobenzoic acid in a two step-one pot cyclodehydration reaction shows a contaminated product that may contain rotamers. In the future, the HNMR can be heated up to view potential product.

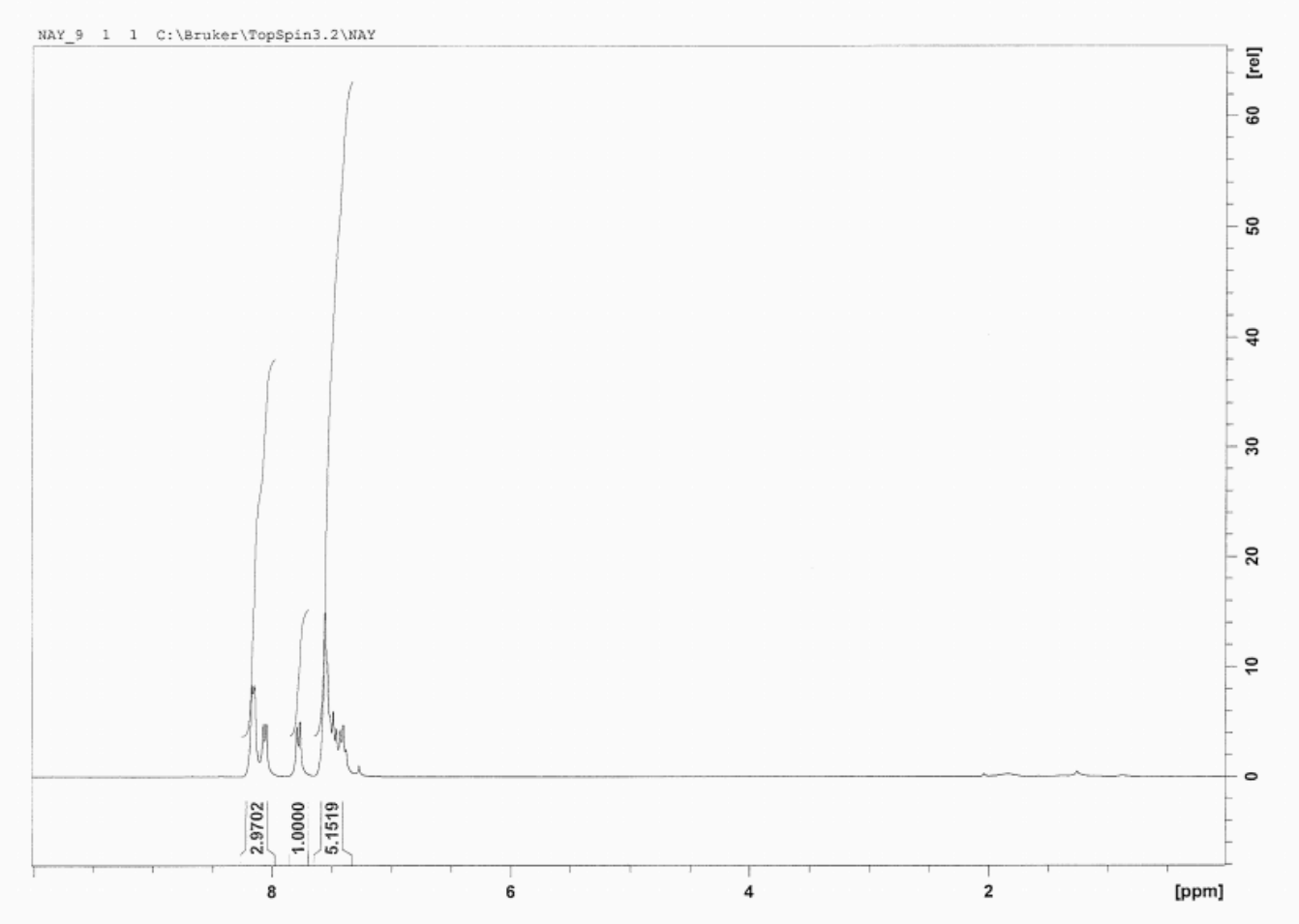

Figure 13. H^1NMR of 1,3,4-oxadiazole synthesized using o-Bromobenzoic acid in a traditional cyclodehydration reaction is inconclusive, showing consistence with product having possible rotamers. In the future, the H^1NMR can be heated up to view potential product.

Future Work

Future work would entail heating up NMR to check for rotamers. Because I did not get a yield above 60%, it would be wise to run all of my reactions over again to ensure the poor yield is not due to error. Additionally, running o-Methylbenzoic acid would be beneficial towards this research, seeing if it's torsion angle effects yield. Separating variables by running a reaction using a less bulky EDG on the benzoic acid would be helpful in determining electronic effects on substrate scope. Because ortho-substituted benzoic acid produced a poor yield, it could be useful to see how reactive meta-substituted benzoic acid is. It would be interesting to compare experimental and computational crystallography data to a broad substrate scope yield, examining any trend that may present.

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