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Effect of Electron Withdrawing and Electron Donating Substituents on the Synthesis of 1,3,4-Oxadiazoles using Dibromotriphenylphosphorane

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Abstract

The goal of this project was to determine the effects that electron withdrawing and electron donating substituents have on the synthesis of 1,3,4-oxadiazoles using a hydrazide starting material and dibromotriphenylphosphorane. This investigation involved the synthesis of hydrazide starting material followed by the synthesis of the oxadiazole with electron donating, withdrawing, or neutral substituents. Through this study, one neutral, three electron donating, two electron withdrawing substituents were investigated. Reactions were analyzed through nuclear magnetic resonance spectroscopy. Neutral electronegative substituents were deemed to be more successful through their percent yield and nuclear magnetic resonance spectroscopy data than both electron donating and withdrawing groups. Electron donating groups also produced more consistent and higher yields than electron donating substituents. Neither electron donating nor neutral substituents have enough statistical evidence to declare an affirmative trend, however, evidence from this study supports the hypothesis that electron withdrawing and neutral substituents are more ideal than electron donating substituents.

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Introduction

Heterocycles:

Oxadiazoles are composed of heterocycles, or aromatic rings containing at least one different atom. Heterocycles are important due to their broad range of diversity. Heterocycles are able to be designed to arrange substituents around a center ring.[1] Popular examples of heterocycles can be seen in *Figure 1* and include the nitrogenous bases that compose DNA and also ATP. By applying these features to oxadiazoles, we can generate molecules that act as a scaffold. Oxadiazoles are flat in nature and, by using a heterocycle, we can arrange substituents to generate biologically active molecules that can now be transported throughout the body. Due to these reasons, finding an easy, cost-efficient procedure that produces oxadiazoles in high yield will be beneficial to both medicinal and biochemical research.

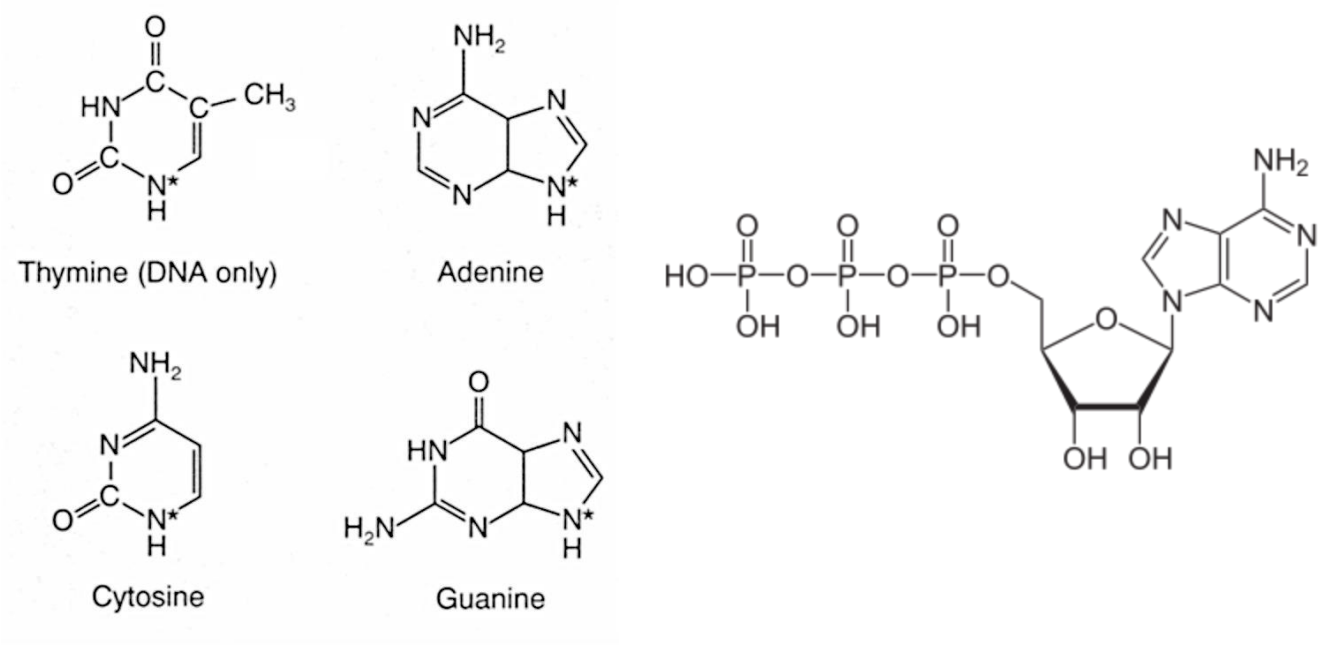


Figure 1: Popular examples of heterocyclic compounds, including the nitrogenous bases of DNA (right) and ATP (left).

1,3,4- Oxadiazoles:

Oxadiazoles are often used in pharmaceuticals due to their biological activity. One such drug can be seen in *Figure* 2.[2]

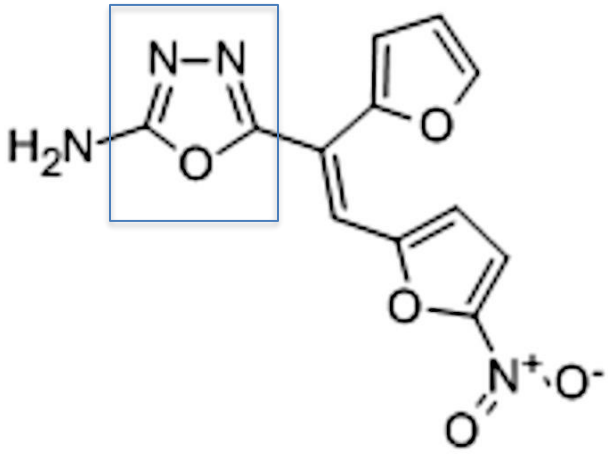


Figure 2: Furamizole, a popular antibacterial agent.[3] The 1,3,4-oxadiazole derivative is highlighted in blue.

In general, the synthesis of 1,3,4-oxadiazoles is relatively simple. The reaction involves a cyclodehydration step in which two carbonyl components are combined to form a ring structure. Cycledehydration reactions occur through an intramolecular mechanism that results in the release of water. The synthesis of 1,3,4-oxadiazoles, in this case, results from the cyclodehydration reaction of a hydrazide and a carboxylic acid, as seen in *Figure 3*. The mechanism requires a cyclodehydrating reagent, which is responsible for catalyzing the reaction by reacting with water molecules released.[4] This is a classic case of Le Chatelier's principle, where adding a cyclodehydrating reagent causes a decrease in the concentration of product water molecules, therefore, favoring the production of more product.

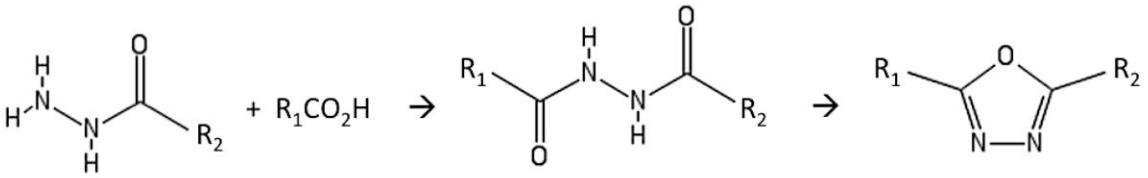


Figure 3: Reaction scheme for the cyclodehydration reaction of a hydrazide and carboxylic acid.

This reaction typically constitutes the use of sulfuric acid or phosphoryl chloride, both of which are extremely harsh reagents.[1] By adjusting the substituents, the electron density near the attack site may be influenced in order to improve yields, all while requiring smaller quantities of reagents. When an electron donating substituent is used, the electron density will be condensed within the center atoms, rather than in the functional group. With electron withdrawing substituents, the electron density will be concentrated within the atoms of the functional group. By influencing the electron field, it is possible to see improvement in the yields of reaction by making specific atoms more prone to nucleophilic attack. As this approach results in valuable insight on the mechanism for the reaction of interest, investigating a survey of substituents is a common approach used when investigating new organic products.

Benzoic acid has a pKa value of approximately 4.20, meaning the molecule primarily exist in its anionic form.[5] When electron withdrawing groups are introduced, the conjugate base of benzoic acid is stabilized. When electron donating groups are introduced, the conjugate base is destabilized. This means that benzoic acid is more acidic with electron withdrawing groups than with electron donating

groups.[6] This increase in acidity caused by electron withdrawing groups will cause benzoic acid to be susceptible to nucleophilic attack.

When applying this thinking to the substituents in question, it is possible to see why some substituents are classified as withdrawing and others are donating. Chlorine, for example, when attached to a benzene ring, pulls the electrons away from the ring. This is because chlorine is highly electronegative (3.16 Pauling units).[7] Chlorine is therefore classified as an electron withdrawing substituent. When placed on benzoic acid, the conjugate base is stabilized and susceptible to nucleophilic attack. On the other hand, groups such as methyl groups, contribute their electron to the ring. This is because methyl groups consist of carbon and hydrogen, elements of which are not very electronegative. Due to this, methyl groups are classified as electron donating and, when placed on benzoic acid, cause the conjugate base to be destabilized. This destabilization causes the acid to be not susceptible to nucleophilic attack. Common substituents and their categorization as either electron withdrawing or donating can be seen in *Table 1.*

Substituent	Classification	Effect on Conjugate Base
-Cl	Withdrawing	Stabilizes
-Br	Withdrawing	Stabilizes
-F	Withdrawing	Stabilizes
-OH	Donating	Destabilizes
-CN	Donating	Destabilizes

Table 1: Common substituents and classification as electron withdrawing or donating.[6]

The 1,3,4-oxadiazoles that will be synthesized in this project are generated from a hydrazide and dibromotriphenylphosphorane using a procedure adapted

from a patent for a molecule that acted as an ATR protein kinase inhibitor. The molecule had a 1,3,4-oxadiazole as the center to which other rings and substituents were attached. The procedure used dibromotriphenylphosphorane in conjunction with anhydrous acetonitrile, N,N-Diisopropylethylamine, and 3-(bromomethyl)benxoic acid to generate 5-bromo-3-(5-3-(bromomethyl)phenyl)-1,3,4-oxidiazole-2-yl)pyrazin-2-amine.[8] Dibromotriphenylphosphorane is a harsh chemical that serves as a dehydrating reagent in the oxadiazole synthesis by reacting with the byproduct water molecules.[3] Dibromortriphenylphosphorane has severe corrosive properties and reacts with the air, decomposing extremely quickly. Due to this, it is more cost effective to commercially purchase the reagent in contrast to synthesizing it fresh. Within this procedure, substituents are interchanged by using the appropriate benzoic acid in order to generate the final oxadiazole.

The mechanistic limitations of this reaction are not yet understood. Currently, it is unknown if changing the electron density will influence the mechanism significantly.[9] By using the final yields in conjunction with the electronegativity data on each of the substituents, ideal substituents can be determined. Yields were taken for the final product for each substituent and used for comparison between functional groups. It was hypothesized that yields will vary between functional groups due to the electronegativity differences. More electronegative atoms should result in a lower yield compared to less electronegative atoms. After synthesis, products were confirmed through melting point data, proton nuclear magnetic resonance, carbon nuclear magnetic resonance,

and infrared spectroscopy. Patterns in the effects of withdrawing and donating substituents were analyzed and ideal substituents were determined for further research.

Materials and Methods

General Procedures:

All solvents and reagents, unless specified, were purchased. All compounds were characterized using a Bruker Fourier 300 MHz nuclear magnetic resonance spectrometer (NMR).

Synthesis of Hydrazide:

Methyl benzoate (2.77ml, 0.022mol) was combined with 30ml of ethanol and 9ml hydrazine anhydrous. The resulting solution was stirred and refluxed in an oil bath at 100°C for four hours. The flask was removed and left to cool to room temperature. The remaining solvent was removed using a rotary evaporator. The resulting solid was recrystallized in 3ml of ethanol and dried.

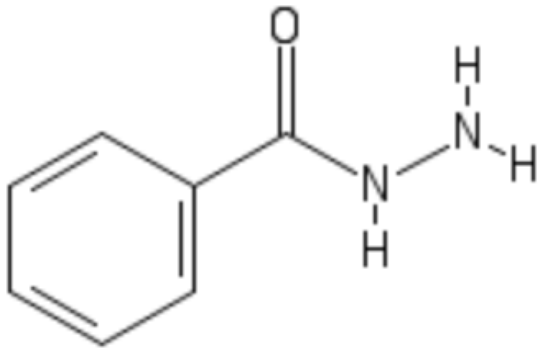


Figure 4: Hydrazide starting material.

Synthesis of Oxadiazoles, 4-nitrobenzoic acid:

Synthesized hydrazide (0.117g, 0.862mmol) was added to 4-nitrobenzoic acid (0.144g, 0.862mmol). Reaction was placed under nitrogen and stirred in ice bath as 3ml of anhydrous acetonitrile was added dropwise. The reaction flask was cracked open to air and 3.34mmol dibromotriphenylphosphorane was added. After three minutes, the ice bath was removed. Reaction continued stirring for one hour. Then, the ice bath was replaced and left for three minutes as 0.9ml of N,N-Diisopropylethylamine was added dropwise while stirring. Ice bath was removed and reaction was left to stir continuously for 12 hours. The resulting mixture was diluted with 25ml H_2O and the separated and washed with dichloromethane (10ml, 2x 15ml). Resulting solution was dried with sodium sulfate. Resulting product was purified through column chromatography (100% petroleum ether to 50% petroleum ether in ethyl acetate) that was tracked through TLC, visualized with UV light/no stain.. 150% yield was collected (0.3493g). **H^1 NMR: page 24**

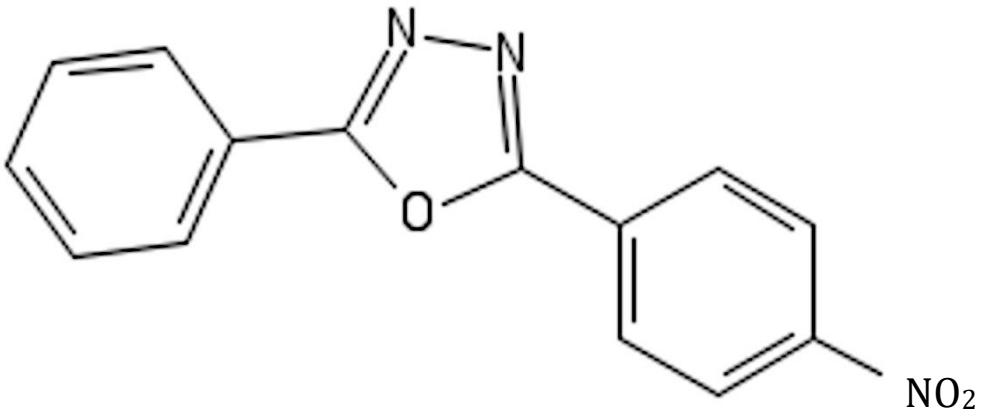


Figure 10: Resulting product from electron withdrawing 4-nitrobenzoic acid.

Synthesis of Oxadiazoles, 4-bromobenzoic acid:

Synthesized hydrazide (0.117g, 0.862mmol) was added to 4-bromobenzoic acid (0.233g, 0.862mmol). Reaction was placed under nitrogen and stirred in ice bath as 3ml of anhydrous acetonitrile was added dropwise. The reaction flask was cracked open to air and 3.34mmol dibromotriphenylphosphorane was added. After three minutes, the ice bath was removed. Reaction continued stirring for one hour. Then, the ice bath was replaced and left for three minutes as 0.9ml of N,N-Diisopropylethylamine was added dropwise while stirring. Ice bath was removed and reaction was left to stir continuously for 12 hours. The resulting mixture was diluted with 25ml H_2O and the separated and washed with dichloromethane (10ml, 2x 15ml). Resulting solution was dried with sodium sulfate. Resulting product was purified through column chromatography (100% petroleum ether to 50% petroleum ether in ethyl acetate) that was tracked through Thin Layer Chromatography (TLC) and visualized with UV light/no stain. 39% yield was collected (0.1014g). **H^1 NMR: page 25**

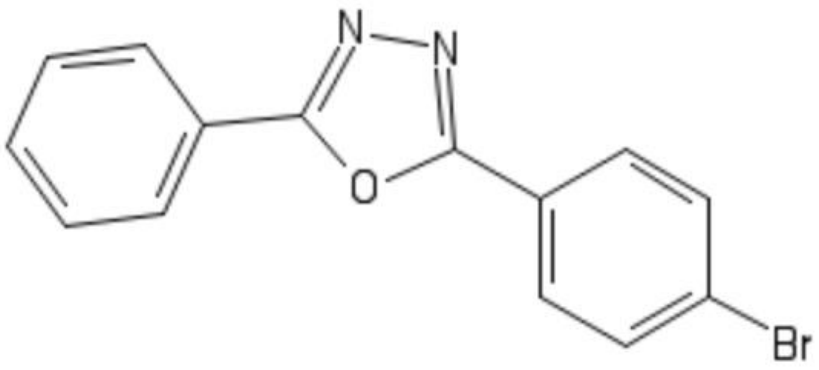


Figure 5: Resulting product from electron withdrawing 4-bromobenzoic acid.

Synthesis of Oxadiazoles, 4-chlorobenzoic acid:

Synthesized hydrazide (0.117g, 0.862mmol) was added to 4-chlorobenzoic acid (0.182g, 0.862mmol). Reaction was placed under nitrogen and stirred in ice bath as 3ml of anhydrous acetonitrile was added dropwise. The reaction flask was cracked open to air 3.34mmol dibromotriphenylphosphorane was added. After three minutes, the ice bath was removed. Reaction continued stirring for one hour. Then, the ice bath was replaced and left for three minutes as 0.9ml of N,N-Diisopropylethylamine was added dropwise while stirring. Ice bath was removed and reaction was left to stir continuously for 12 hours. The resulting mixture was diluted with 25ml H_2O and the separated and washed with dichloromethane (10ml, 2x 15ml). Resulting solution was dried with sodium sulfate. Resulting product was purified through column chromatography (100% petroleum ether to 50% petroleum ether in ethyl acetate) that was tracked through TLC, visualized with UV light/no stain. 52.27% yield was collected (0.1333g). **H^1 NMR: page 26**

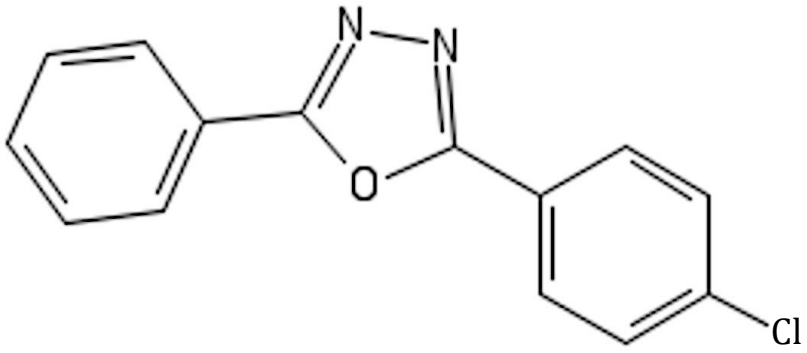


Figure 6: Resulting product from electron withdrawing 4-chlorobenzoic acid.

Synthesis of Oxadiazoles, benzoic acid:

Synthesized hydrazide (0.117g, 0.862mmol) was added to benzoic acid (0.0.105gg, 0.862mmol). Reaction was placed under nitrogen and stirred in ice bath as 3ml of anhydrous acetonitrile was added dropwise. The reaction flask was cracked open to air 3.34mmol dibromotriphenylphosphorane was added. After three minutes, the ice bath was removed. Reaction continued stirring for one hour. Then, the ice bath was replaced and left for three minutes as 0.9ml of N,N-Diisopropylethylamine was added dropwise while stirring. Ice bath was removed and reaction was left to stir continuously for 12 hours. The resulting mixture was diluted with 25ml H_2O and the separated and washed with dichloromethane (10ml, 2x 15ml). Resulting solution was dried with sodium sulfate. Resulting product was purified through column chromatography (100% petroleum ether to 50% petroleum ether in ethyl acetate) that was tracked through TLC, visualized with UV light/no stain.. 73.87% yield was collected (0.0.1414g). **H^1 NMR: page 27**

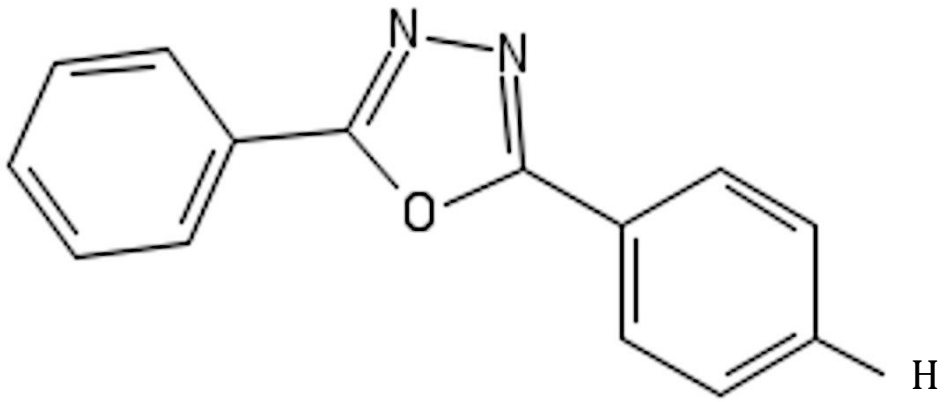


Figure 7: Resulting product from electron neutral benzoic acid.

Synthesis of Oxadiazoles, p-methoxybenzoic acid:

Synthesized hydrazide (0.117g, 0.862mmol) was added to p-methoxybenzoic acid (0.177g, 0.862mmol). Reaction was placed under nitrogen and stirred in ice bath as 3ml of anhydrous acetonitrile was added dropwise. The reaction flask was cracked open to air 3.34mmol dibromotriphenylphosphorane was added. After three minutes, the ice bath was removed. Reaction continued stirring for one hour. Then, the ice bath was replaced and left for three minutes as 0.9ml of N,N-Diisopropylethylamine was added dropwise while stirring. Ice bath was removed and reaction was left to stir continuously for 12 hours. The resulting mixture was diluted with 25ml H_2O and the separated and washed with dichloromethane (10ml, 2x 15ml). Solution was dried with sodium sulfate. Resulting product was purified through column chromatography (100% petroleum ether to 50% petroleum ether in ethyl acetate) that was tracked through TLC, visualized with UV light/no stain.. 60.13%% yield was collected (0.1314g). **H^1 NMR: page 28**

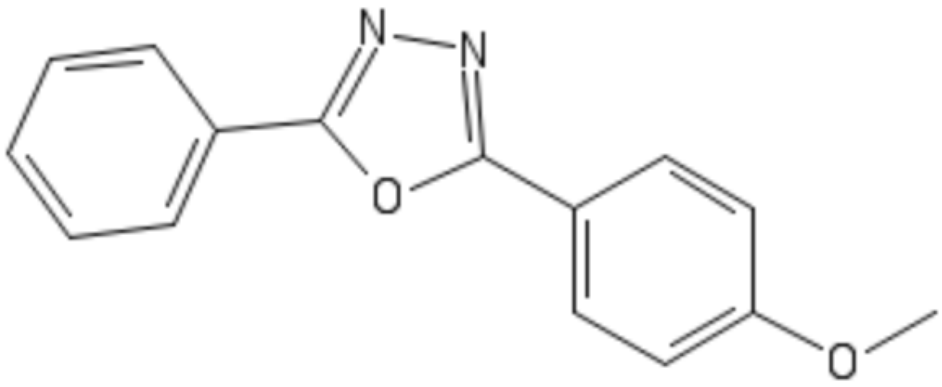


Figure 8: Resulting product from electron donating p-methoxybenzoic acid.

Synthesis of Oxadiazoles, 4-dimethylaminobenzoic acid:

Synthesized hydrazide (0.117g, 0.862mmol) was added to 4-dimethylaminobenzoic acid (0.142g, 0.862mmol). Reaction was placed under nitrogen and stirred in ice bath as 3ml of anhydrous acetonitrile was added dropwise. After three minutes, the ice bath was removed. The reaction flask was cracked open to air 3.34mmol dibromotriphenylphosphorane was added. Reaction continued stirring for one hour. Then, the ice bath was replaced and left for three minutes as 0.9ml of N,N-Diisopropylethylamine was added dropwise while stirring. Ice bath was removed and reaction was left to stir continuously for 12 hours. The resulting mixture was diluted with 25ml H_2O and the separated and washed with dichloromethane (10ml, 2x 15ml). Resulting solution was dried with sodium sulfate. Resulting product was purified through column chromatography (100% petroleum ether to 50% petroleum ether in ethyl acetate). 14.5% yield was collected (0.0332g).

H^1 NMR: page 29

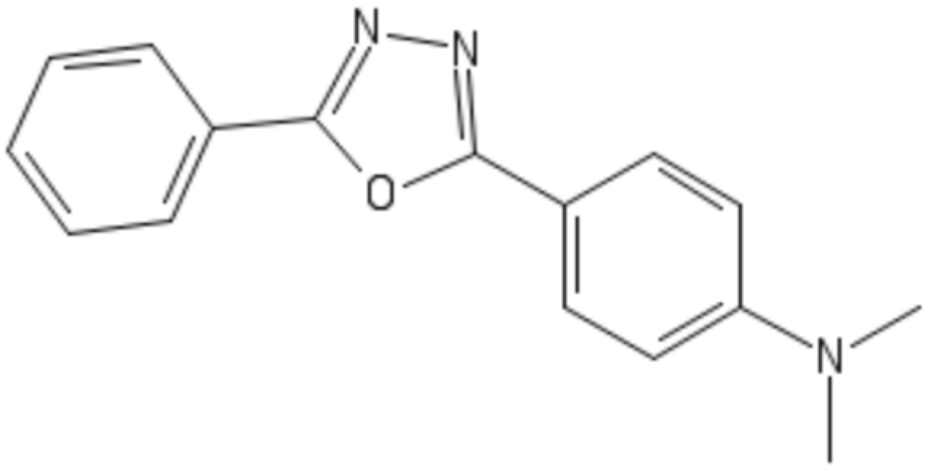


Figure 9: Resulting product from electron donating 4-dimethylaminobenzoic acid.

Results and Discussion

1,3,4-oxadiazoles:

The substituted benzoic acid that yielded the highest percentage was produced using 4-nitrobenzoic acid and resulted in a 150% yield. H-NMR data revealed a highly contaminated product; therefore, 4-nitrobenzoic acid was not be considered a successful reaction. Despite a high yield, the high levels of contamination mean that 4-nitrobenzoic acid is unable to be considered an ideal substrate.

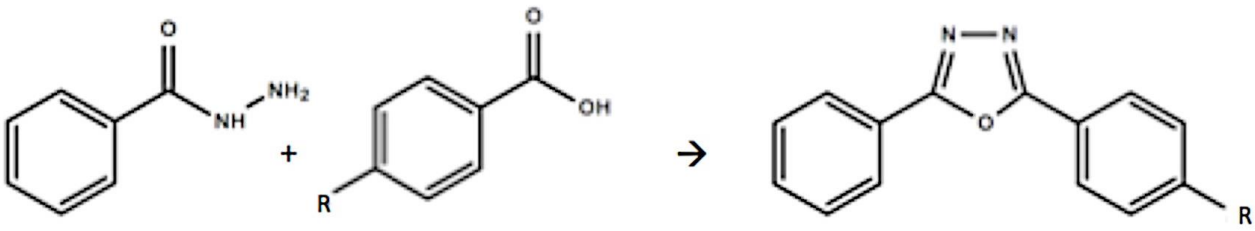
The neutral substituent tested, benzoic acid (substituent -H), resulted in a 73.87% yield. This yield was the highest out of all substituents being considered. H-NMR data revealed that the expected product was produced. The high yield collected and clean analytical data provides evidence to support the claim that neutral substituents are able to react successfully and cleanly to produce desired products.

Electron donating substituent, p-methyoxybenzoic acid, resulted in a 60.13% yield. This yield is higher than both of the electron withdrawing substituents tested and provides contradicting evidence for electronegative substituents being more ideal. However, the electron donating substituent, 4-dimethylaminobenzoic acid, resulted in a yield of only 14.5%. This yield is significantly lower than any of the other substituents. The contradicting results of the two electron donating substituents lends support towards the disfavor of electron donating substituents due to the unpredictability of how they will react.

The reaction of 4-dimethylaminobenzoic acid was repeated multiple times in order to successfully synthesize the product. The first reaction resulted in the formation of green-colored crystals during the aqueous workup phase of the procedure. The resulting product produced a low yield of 9.97% and an H-NMR that contained large amounts of water. It is hypothesized that some of the product solidified during the aqueous workup and was lost during the drying phase with sodium sulfate when the solid was filtered out.

The electron withdrawing substituents, 4-bromobenzoic acid and 4-chlorobenzoic acid, gave 39% and 52.27% yields respectively. H-NMR data confirmed product as expected. 4-Chlorobenzoic acid is more electronegative than 4-bromobenzoic acid, providing evidence that more electronegative substituents provide better outcomes and may be more ideal than the electron donating substituents. However, the reactions of the electron withdrawing substituents were not as successful as the neutral substituent tested.

Overall, there is no statistical trend in the data collected that allows for one type of substituent to be deemed more successful than another, as seen in *Table 2*. In general, the closer to a neutral electronegativity, the better the reactions faired in terms of percent yielded. However, results were not significantly different.



R	Type	% Yield
Br	Withdrawing	39
Cl	Withdrawing	52.27
H	Neutral	73.87
OCH_3	Donating	60.13
$N(CH_3)_2$	Donating	14.5
NO_2	Withdrawing	150

Table 2: Reaction scheme and results for varying substituents for study of electron donating and electron withdrawing substituents for the synthesis of 1,3,4-oxadiazoles. Reaction of 4-nitrobenzoic acid has been labeled in red due to the H-NMR results that revealed a highly contaminated product.

Electron withdrawing and neutral substituents reacted more reliably than electron donating substituents. In theory, it is hypothesized that this is the case as more electronegative atoms have electrons that are closer to the nucleus and shielded far less from the nuclear charge. This means that the electrons within the bonds are more polarized. This polarization of the bonds causes the substrate to be more reactive, allowing the reaction to generate higher yields. Within electron donating substituents, the electrons are not influenced as greatly by the nuclear charge due to shielding that occurs. This means that the electrons are generally further from the nucleus, resulting in nonpolarized bonds and less reactivity.[10]

For future research, the scope of substituents tested should be expanded in order to capture a more diverse spectrum of electronegativity. For example, popular substituents commonly used are other halo, carbonyl, or sulfonyl electron withdrawing groups, along with hydroxyl, ester, or alkoxide electron donating

groups. While the data supports the hypothesis of electron withdrawing and neutral substituents being more ideal than electron donating, there is not enough evidence in order to statistically support this claim. It is hoped that by exploring a broader array of substituents, further evidence to support the trend hypothesized in this study can be collected.

A large majority of the project involved the perfection of the methodology used in order to synthesize the desired 1,3,4-oxadiazole products. Throughout the development of the project, a method was established that produced oxadiazoles consistently and relatively purely. Further research will be able to apply the procedure developed during the beginning stages of the research in order to broaden the scope of substituents more easily.

HNMR Data Figures:

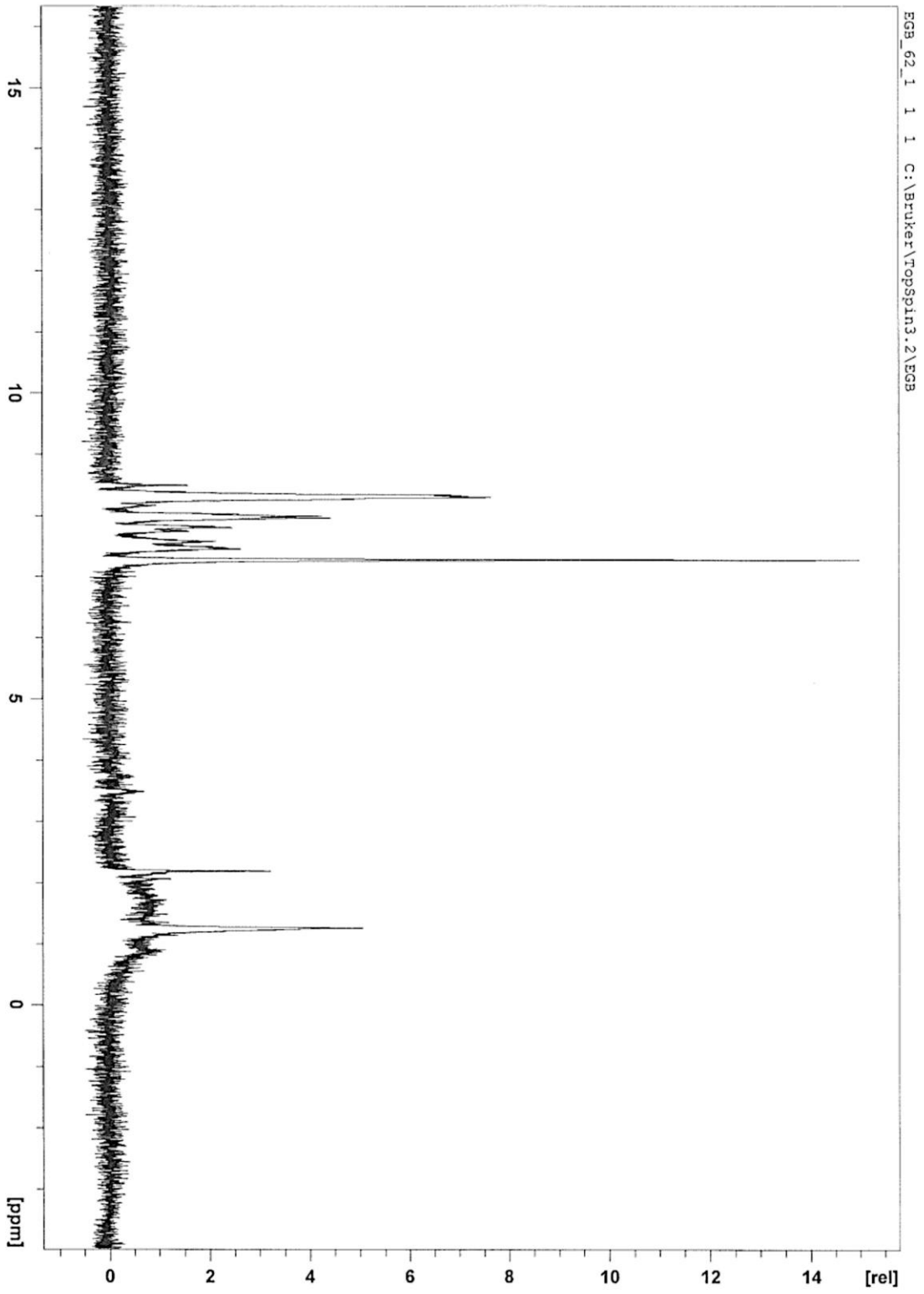


Figure 11: -NO_2

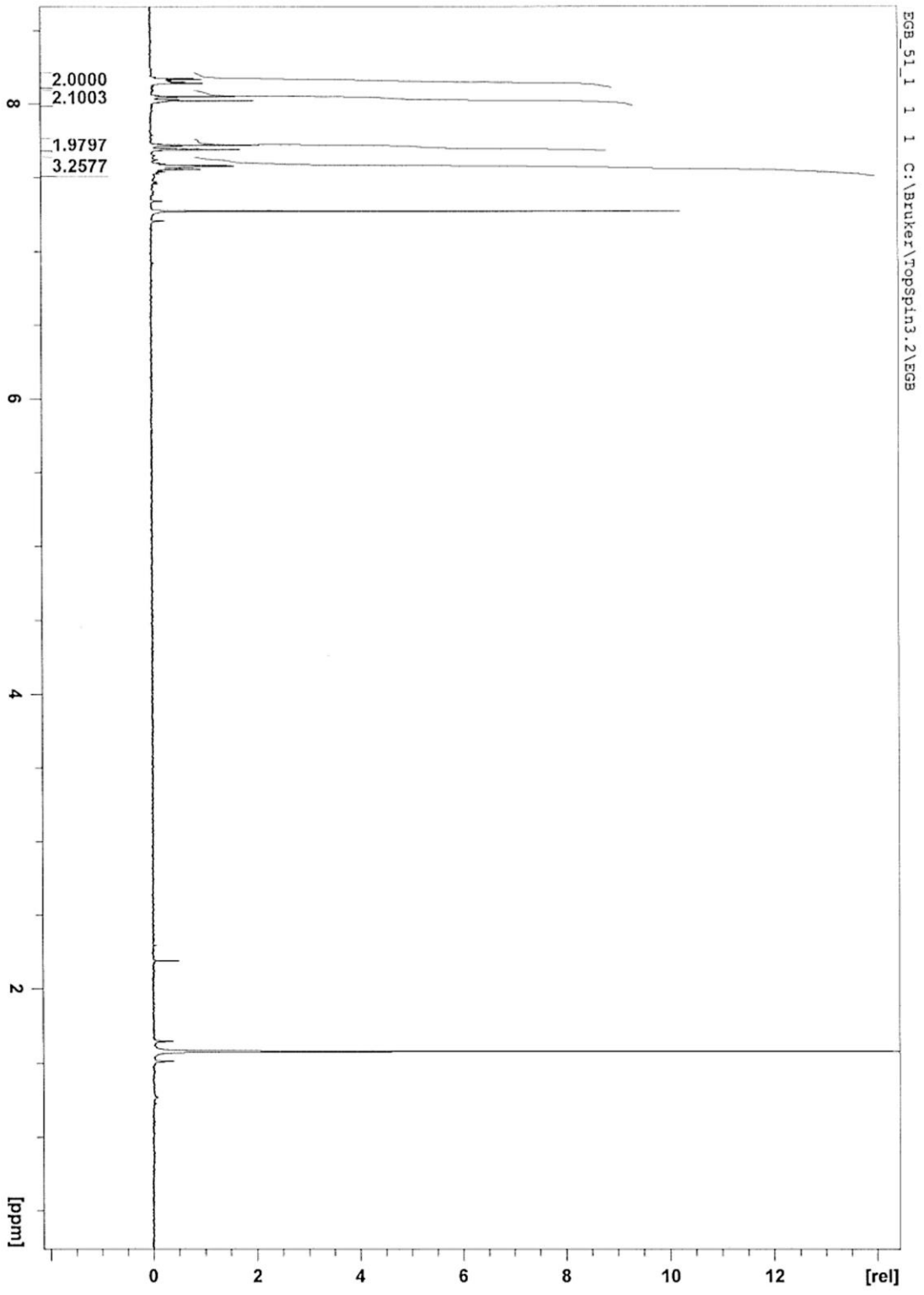

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Figure 12: -Br

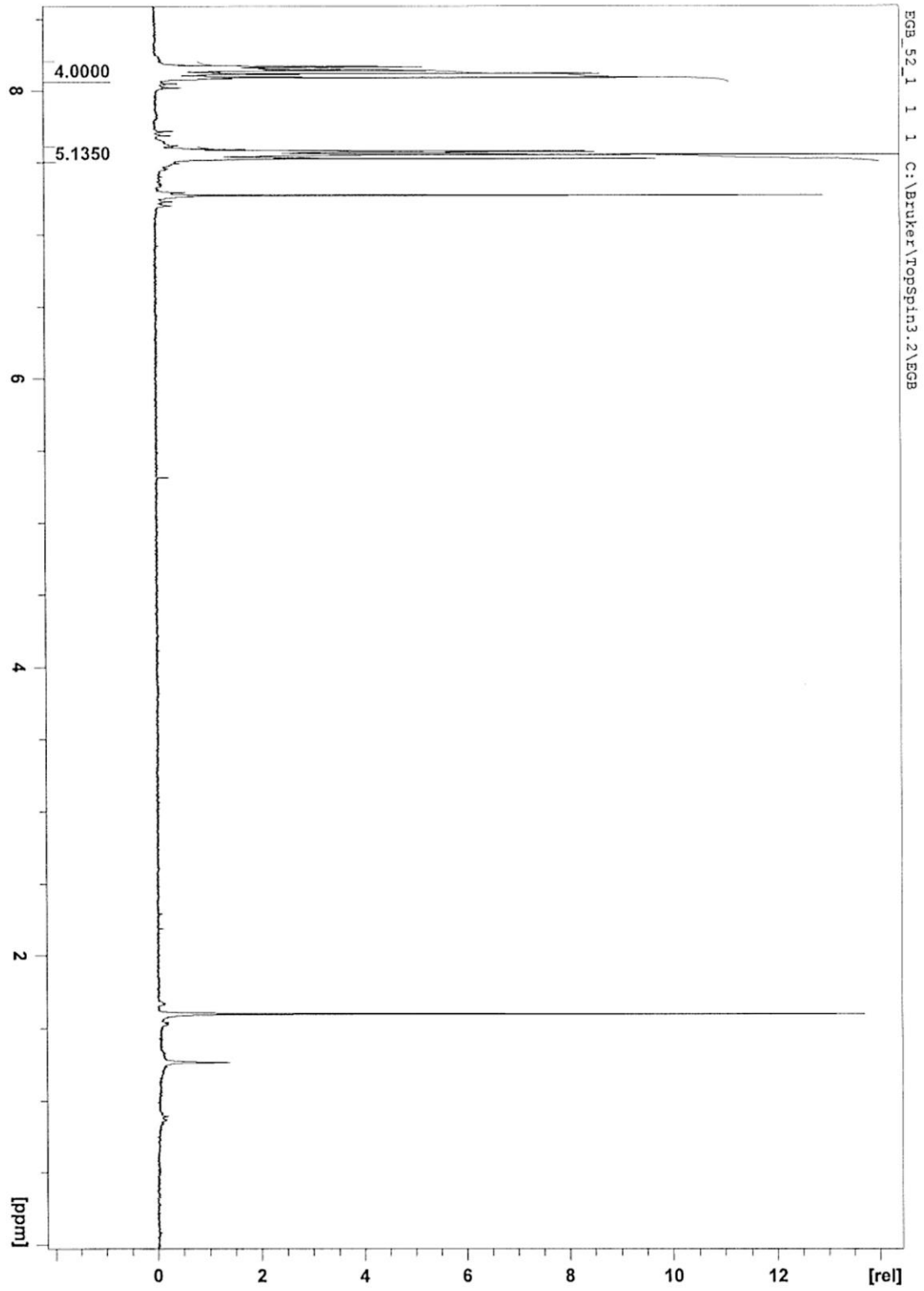
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Figure 13: -Cl

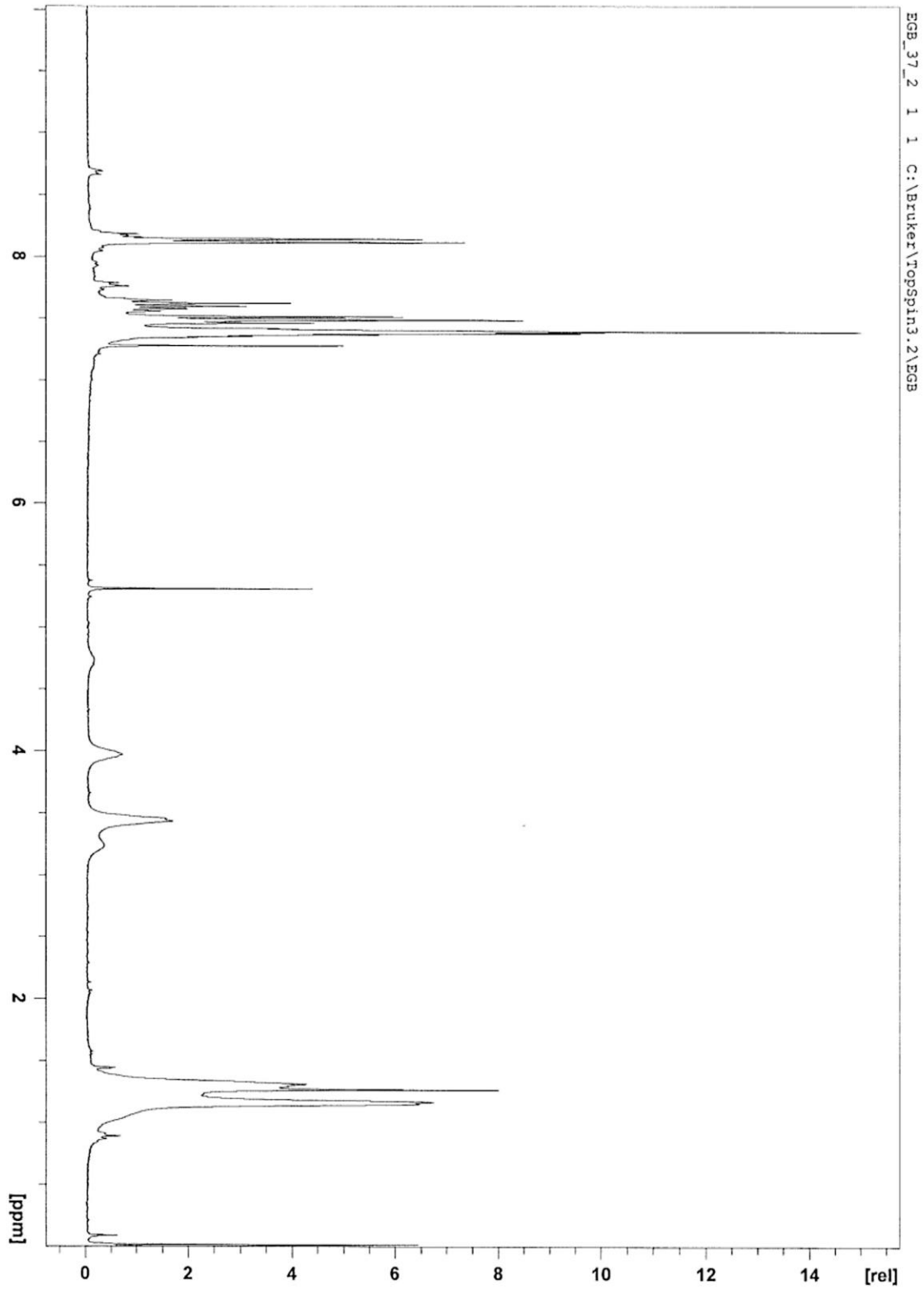

Figure 14: -H

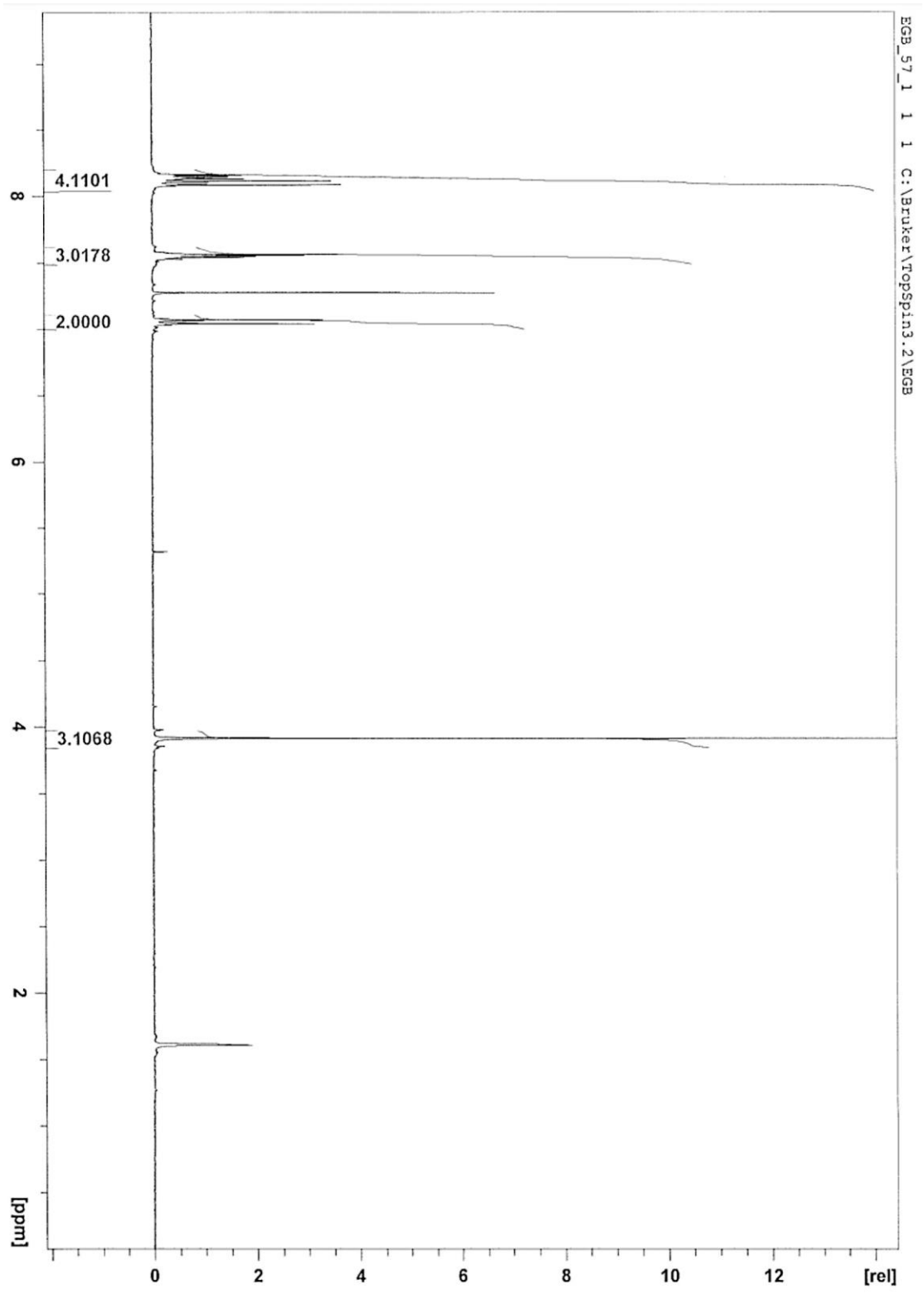

Figure 15: -OCH_3

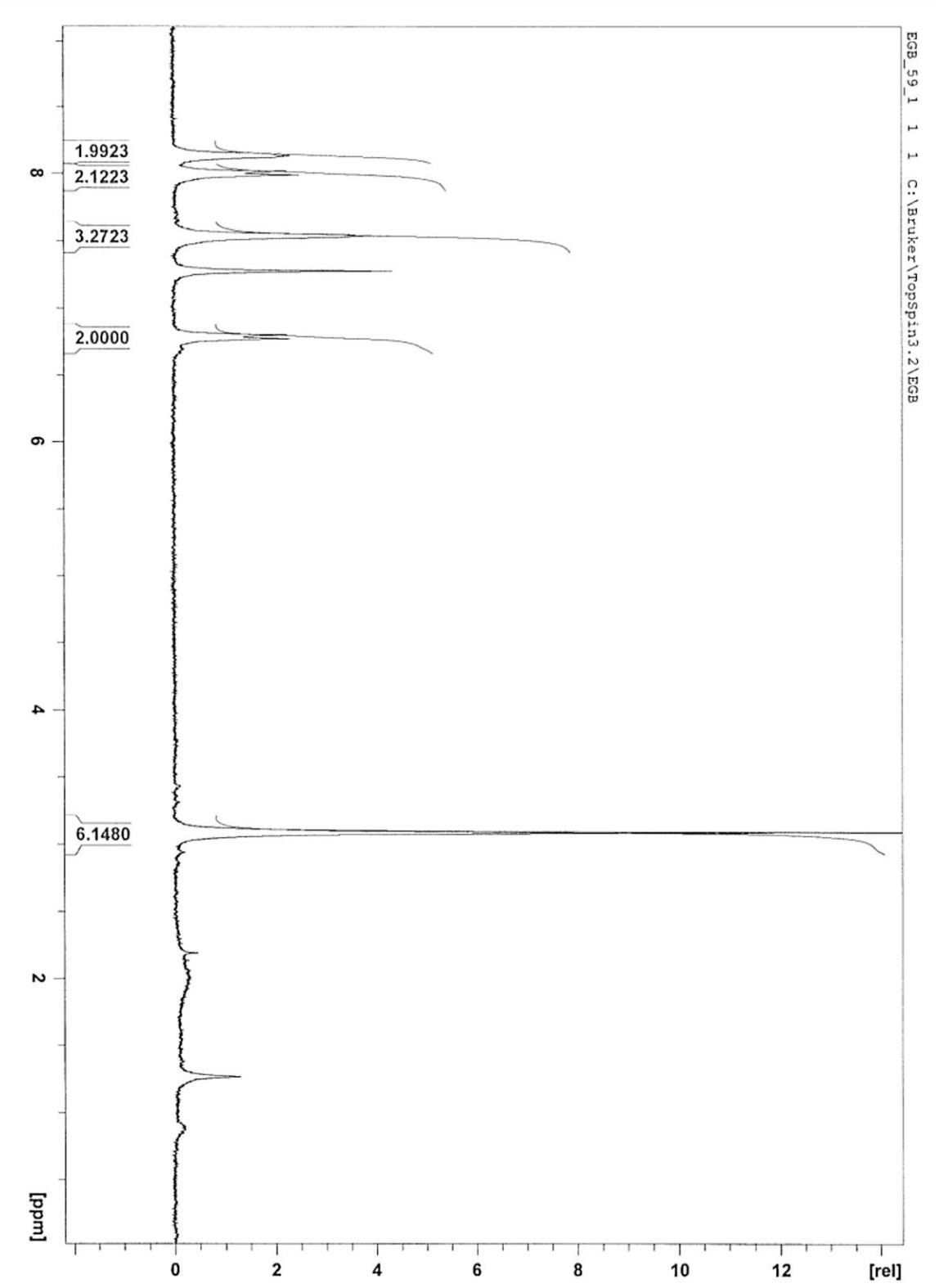

Figure 16: -N(CH$_3$)$_2$

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