

Synthesis of Oxadiazole Derivatives for Use in Supramolecular Assembly

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Introduction

Supramolecular assembly employing metal-ion ligand bonding is an important emerging field. Supramolecular self-assembly of large molecules from smaller components usually occurs with weak to moderately strong noncovalent bonds working to stabilize the structure of the product. Weak covalent bonding, particularly metal-ligand interactions, also plays an important role in supramolecular design and synthesis (1). Naturally occurring supramolecular self-assemblies are critical to life (i.e. DNA, enzyme structure and function, cell division), and human-designed supramolecular self-assemblies have important potential applications in nanotechnology (2).

To study supramolecular self-assembly with metal-ligand interactions, smaller component molecules must be synthesized and purified, and they must have the desired bond angles and available electrons for ligand bonding to a metal-ion. The purpose of my project was to synthesize and purify four oxadiazole molecules (Figure 1), which will ultimately be used to test the self-assembling properties of these oxadiazole molecules and examine the mechanism of the self-assembly process.

Figure 1: Oxadiazole molecules synthesized in this project

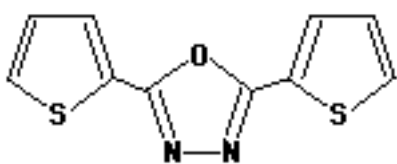


Figure 1A: dithiophen oxadiazole = 2,5-di(thiophen-2-yl)-1,3,4-oxadiazole

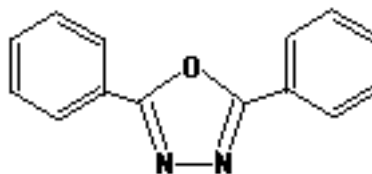


Figure 1B: diphenyl oxadiazole = 2,5-diphenyl-1,3,4-oxadiazole

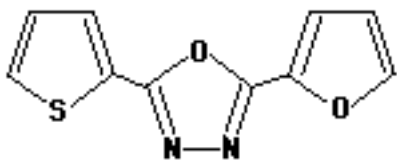


Figure 1C: thiophen/furan oxadiazole = 2-(furan-2-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole

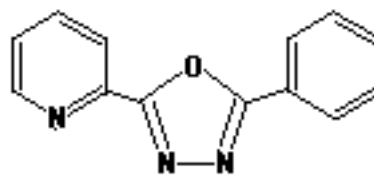


Figure 1D: pyridine/phenyl oxadiazole = 2-pyridine-3-yl-5-phenyl-1,3,4-oxadiazole

My first goal was to modify a method for oxadiazole synthesis reported by Balsells, which had been developed for synthesizing pharmaceuticals (3). I began by synthesizing dithiophen oxadiazole (Figure 1A), and diphenyl oxadiazole (Figure 1B) as test cases to assess and modify the synthesis protocol. Subsequently, I synthesized thiophen/furan oxadiazole (Figure 1C). This series of test cases confirmed that my modifications of the Balsells protocol were effective in preparing oxadiazole derivatives that have similar size and electronic properties to the molecule I needed for self-assembly studies. My second goal was to synthesize pyridine/phenyl oxadiazole (Figure 1D), which has a bond angle between the pyridine nitrogen and one of the oxadiazole nitrogens that I hope is optimal for self-assembly with an appropriate metal complex (2).

For the synthesis protocol, I first used an acylation reaction (Figure 2). Then, I cycloaromatized the resulting products to form the desired oxadiazole structure (Figure 3).

Figure 2: Acylation: benzohydrazide was reacted with benzoyl chloride forming N-benzoylbenzohydrazide

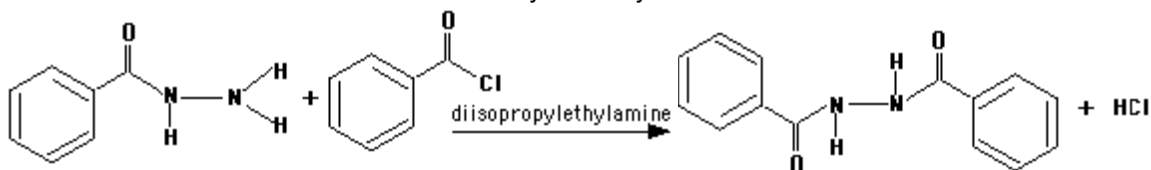
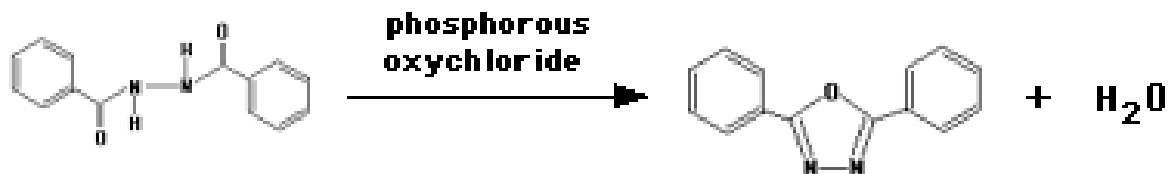


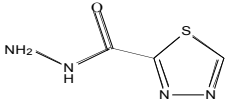
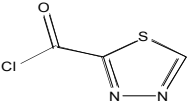
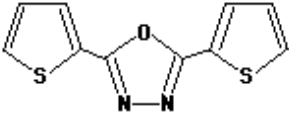
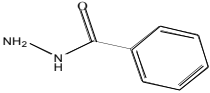
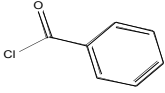
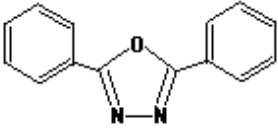
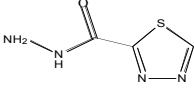
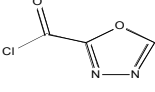
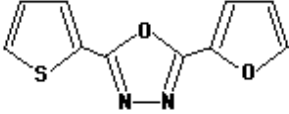
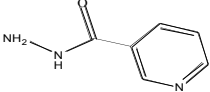
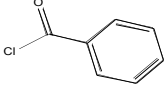
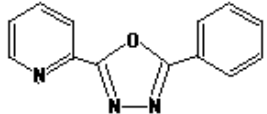
Figure 3: Cycloaromatization: N-benzoylbenzohydrazide was reacted with phosphoryl trichloride to form 2,5-diphenyl-1,3,4-oxadiazole



These acylation reactions involved the addition of a hydrazide to an acid chloride. The hydrazide and acid chloride varied depending on the oxadiazole molecule being

produced (Table 1). The cycloaromatization involved the dehydration of the product from the acylation reaction (3).

Table 1: Hydrazides and acid chlorides used in acylation for specific oxadiazoles

Hydrazide	Acid chloride	Oxadiazole produced
		
		
		
		

Methods

Acylation Reaction: I purged a flask with argon for ten minutes, added 1.05 mmol of hydrazide, and purged the flask for five minutes with argon. Then, I added 1.10 mL of acetonitrile, followed by an addition of 0.000916 mmol of diisopropylethylamine. Next, I added 0.00112 mmol of acid chloride to the flask dropwise over five minutes. For specific masses of hydrazides and specific volumes of acid chlorides used refer to Table 2.

Table 2: Hydrazides and acid chlorides used in the synthesis of each desired oxadiazole molecule

Desired oxadiazole	Hydrazide used	Mass used in acylation	Acid chloride used	Volume used in acylation
Dithiophen oxadiazole	Thiophene-2-carbohydrazide	0.150 g	Thiophene-2-carbonyl chloride	0.13 mL
Diphenyl oxadiazole	Benzohydrazide	0.150 g	Benzoyl chloride	0.13 mL
Thiophen/furan oxadiazole	Furan-2-carbohydrazide	0.150 g	Furan-2-carbonyl chloride	0.13 mL
Phenyl/pyridine oxadiazole	Nicotinohydrazide	0.150 g	Benzoyl chloride	0.13 mL

After stirring the solution vigorously for one hour, I filtered the product with a Hirsch funnel and rinsed it with acetonitrile. I partially dried the product by drawing air through the Hirsch funnel for one hour. Then, I placed the product in a vacuum desiccator overnight before characterizing the products using H-NMR and EI-MS spectra.

Cycloaromatization Reaction: I purged a clean and dry reaction flask equipped with a reflux condenser for ten minutes with argon. Then, I added 0.00198 moles of an acylation product to the reaction flask and again purged the flask with argon for five minutes before adding 10 mL of anhydrous acetonitrile to the flask with stirring. Next, I added 0.0198 moles of phosphorous oxychloride and allowed the reaction to reflux for four hours. I cooled the flask to room temperature and performed a quantitative transfer of the reaction mixture (with the aid of diethyl ether rinses) into an erlenmeyer flask that contained 20 mL of ice-cold ether and 20 mL of ice-cold deionized H₂O. The contents of the erlenmeyer flask were transferred to a separatory funnel. Then, I extracted the product three times with saturated sodium bicarbonate and one time with saturated sodium chloride. I dried the ether layer over anhydrous magnesium sulfate prior to filtering out the magnesium sulfate and running thin-layer chromatography (TLC) analysis, using

silica gel. I rotary evaporated the filtrate and characterized the product using H-NMR and EI-MS.

I attempted synthesis of the oxadiazole molecules in which both reactions were carried out in a single flask (one-pot procedure) without any purification after the first reaction, thinking the one-pot procedure would be more efficient and rapid. However, impurities that occurred in the first reaction were carried into the second reaction, reducing the yields of the desired oxadiazole molecules. When I continue this research, I will use the two-pot protocol to synthesize the desired oxadiazole molecules.

Results

Synthesis of dithiophen oxadiazole yielded a white crystalline solid. TLC, showed a single product. The $^1\text{H NMR}^*$, as seen in Figure 4 (all NMR figures are in the Appendix), shows a singlet with a chemical shift of 7.92 ppm corresponding to the two “a” protons on the molecule, a doublet with a chemical shift of 7.25 ppm corresponding to the two “b” protons and a doublet of doublets at 6.69 ppm, which corresponds to the two “c” protons on the thiophenes. The NMR results were supported by EI-MS that gave a molar mass of 234 gmol^{-1} , which is the expected molar mass of dithiophen oxadiazole.

Synthesis of diphenyl oxadiazole yielded a white crystalline solid. TLC, showed a single product. The $^1\text{H NMR}$, seen in Figure 5, shows a chemical shift from 8.12 to 8.18 ppm, which corresponds to the four “a” protons on the oxadiazole molecule. The chemical shift from 7.50 to 7.60 ppm corresponds to the four “b” protons. The chemical shift from 7.50 to 7.58 ppm corresponds to the two “c” protons. EI-MS gave a molar mass of 222 gmol^{-1} , which is the expected molar mass of diphenyl oxadiazole.

* In all figures containing NMR data, the singlet with the chemical shift of 7.26 ppm corresponds to the solvent, deuterated chloroform.

Synthesis of thiophen/furan oxadiazole yielded a white crystalline solid. TLC, identified a single product. The ^1H NMR, seen in Figure 6, shows a doublet of doublets with a chemical shift of 8.82 to 8.85 ppm that relates to the “d” proton on the oxadiazole molecule. A chemical shift of 8.66 to 8.68 ppm corresponds to the “a” proton. The doublet of doublets with the chemical shift of 8.56 to 8.60 ppm corresponds to the “e” proton. The chemical shifts from 8.18 to 8.27 ppm relate to the “c” and “f” protons. Finally, the quartet with the chemical shift of 7.61 to 7.64 ppm corresponds to the “b” proton on the molecule. EI-MS gave a molar mass of 218 gmol^{-1} , which is the expected molar mass of thiophen/furan oxadiazole.

Synthesis of phenyl/pyridine yielded a white crystalline solid. TLC identified a single product. The ^1H NMR, seen in Figure 7, shows a singlet with the chemical shift of 9.5 ppm that represents the “a” proton on the oxadiazole. The singlet with the chemical shift of 8.9 ppm relates to the “d” proton. The chemical shift from 8.6 to 8.7 ppm represents the “c” proton. Finally, the chemical shift from 7.6 to 8.2 ppm corresponds to the “b” proton on pyridine ring as well as the protons on the phenyl ring of the molecule. EI-MS supported the NMR data with a molar mass of 223 gmol^{-1} , which is the expected molar mass of phenyl/pyridine oxadiazole.

Conclusion

The first phase of my research was successful. I synthesized four oxadiazole derivatives and developed my own protocol based on modifications of a published procedure. Results also showed that the purification procedure I used yielded pure products. However, the one-pot procedure did not produce a pure product, most likely due to the lack of purification between the two steps of the synthesis.

The next step in my research will be to examine the self-assembling properties of pyridine/phenyl oxadiazole. I will use the pyridine/phenyl oxadiazole with various palladium (II) or platinum (II) complexes. This future research will be used to understand the ways in which oxadiazole molecules can coordinate to palladium (II) and platinum (II) ions, which is the first step in understanding oxadiazole self-assembly.

Acknowledgments

Dr. Ronald G. Brisbois and Macalester College provided a lab for me and supervised my research. Dr. Brisbois also provided me with literature on organic synthesis, and metal-aided ligand bonding in supramolecular self-assembly. Lillian Nordahl, Sarah Miller, Johann Bergholz at Macalester College helped me gain a better understanding of the techniques pertinent to my research. Ms. Lois Fruen aided me as I wrote my paper. Finally, the Breck School research class was a source of constant support and encouragement.

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Appendix

Figure 4: NMR of the Dithiophene Oxadiazole

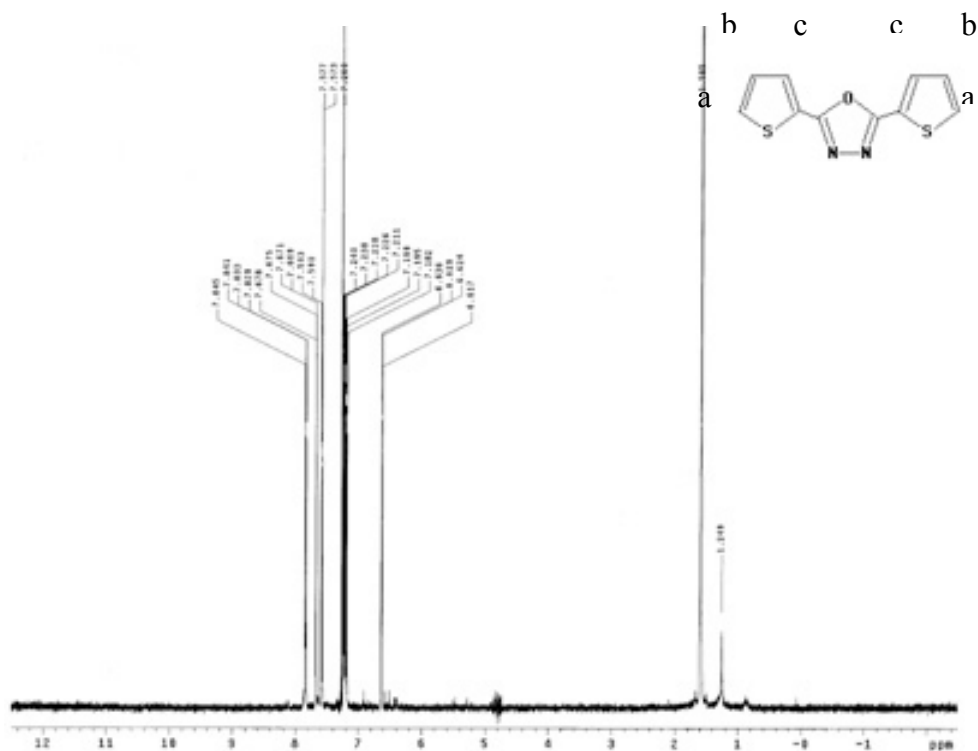


Figure 5: NMR of the Diphenyl Oxadizole

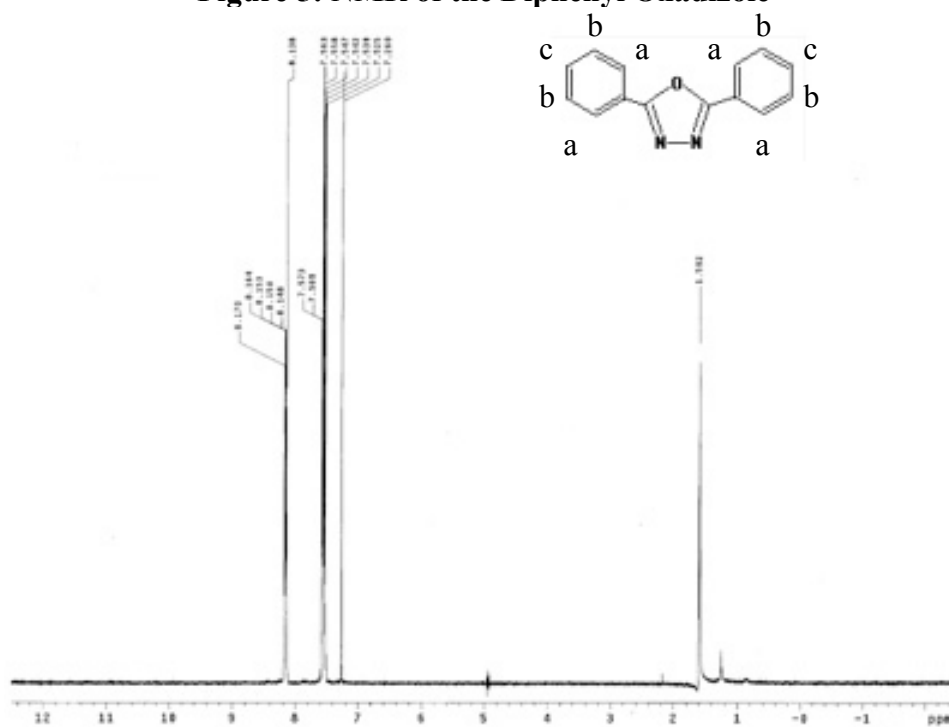


Figure 6: NMR of the Thiophene/furan Oxadiazole

