Abstract

The objective of this project is to synthesize 1-aroyldiaziridine derivatives that contain a variety of different substituents in order to study how the electronic effects of the substituents might affect the bond-breaking selectivity of the diaziridine ring. In other words, will the substituents help to direct C – N, or N – N bond breaking of the ring system. Diazirdines, a class of three-membered ring heterocycles that contain one carbon and two nitrogen atoms, are useful intermediates in the synthesis of more complex heterocyclic compounds, some of which have been utilized in the pharmaceutical industry. Although there are a number of literature studies that address the breaking of the C-N bond to form more complex heterocyclic compounds, there are no reports of N-N bond cleavage. This research project is designed to study the factors that may influence the cleavage of either bond, potentially resulting in the formation of different pharmaceutically active ingredients.

Synthesis and Reactivity of a Variety of 1-Aroyldiaziridine Derivatives

Three-membered ring heterocycles that contain two nitrogen atoms and one carbon atom, referred to as diazirdines, are the main focus of this project. They are useful as intermediates in many therapeutic drugs, and it would be exciting for this work to be incorporated in the pharmaceutical industry. A previous Millersville student started this project, and I am continuing it in order to study the electronics of the rings. First, I must synthesize and characterize a few 1-aroyldiaziridines. Then I will expose the compounds to thermal and basic conditions to study the effects that the conditions have on the molecule.

Background and Significance

Diazirdines are a class of three-membered ring heterocycles that contain one carbon and two nitrogen atoms. (**Figure 1**).

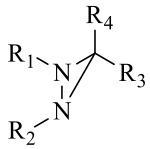

Figure 1: A diaziridine

R can represent any carbon group, which will later be explained. We are interested in using these diaziridine derivatives as intermediates that can be further elaborated into potentially useful pharmaceuticals. Our 1,3,4- oxadiazoline potential product, through the diaziridine intermediates, have a relatively high lipophilicity, which allow them to modify the biological activities (El-Emam et al., 2012). Once they are incorporated in the bodily functions, they have the likelihood of demonstrating anti-anxiety, anti-depressant, anti-fungal, anti-microbial, anti-cancer, and many other therapeutic properties (Stoica et al., 2015). Similarly, the amidine products also have many proven pharmaceutical benefits including, but not limited to, anti-coagulants, anti-microbial, and anti-metastatic drugs (Kotthaus et al., 2011). It will be exciting to see our products used in pharmaceuticals.

Purpose

There are four objectives I hope to accomplish while conducting this research investigation. The first is to finish the synthesis, purification, and characterization of three new 1-aroyldiaziridines started by the previous undergraduate research student. The next objective I hope to achieve is to synthesize, purify, and characterize a few more 1-aroyl-diaziridine derivatives that contain three different substituents from the first three. With the purified 1-aroyldiaziridine derivatives in hand, the third goal is to react them under basic and thermal conditions and to isolate and fully characterize the products by both proton and carbon nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectroscopy, as well as Fourier transform-infrared spectroscopy (FT-IR). The products are anticipated to be oxadiazolines via C – N bond cleavage, and/or amidines *via* breaking of the N – N bond, depending on the electronic influence of the different substituents. Both of these types of products have industrial and pharmaceutical implications. My final, overall purpose of this research project is to increase my knowledge and deepen my understanding of organic chemistry in order to better prepare myself for graduate school in the field of chemistry. This goal will be reached by achieving my three previously stated objectives, which are all hands on, invaluable experiences in an organic research lab. In addition, proposing logical mechanisms for each step of the reaction processes and reading previously published literature on the topic of research is good practice for graduate school.

Study Design

The reaction scheme to prepare the 1-aroyldiaziridines (**6**) is depicted in **Figure 2**. First, a variety of benzaldehydes (**1a-j**) will be reacted with an amine to produce a class of compounds called Schiff bases, or imines (**3a-j**).

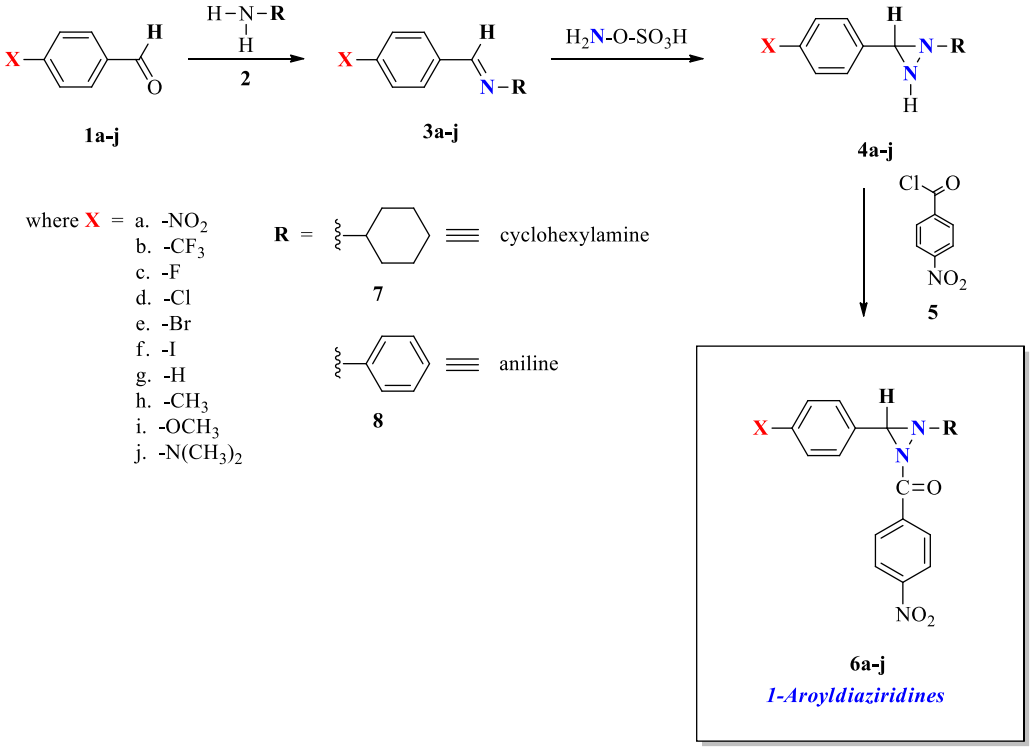

Figure 2: Pathway to make the 1-Aroyldiaziridines (**6**)

Different substituents with either electron-donating (i.e.: **1h-j**) or electron-withdrawing (i.e.: **1a-f**) capabilities will be placed on the 6-membered ring of the benzaldehydes (**1**), with a hydrogen substituent (**1g**) as the control. These groups are all being added in order to study the reactivity and chemistry of the diaziridine ring system, as well as to try and understand how the electronics of the diaziridine system affects the therapeutic properties of the overall molecule. Treatment of the imines (**3a-j**) with hydroxylamine-O-sulfonic acid should produce diaziridines (**4a-j**). Subsequent reaction with 4-nitrobenzoylchloride (**5**) should afford the target 1-aroyldiaziridines (**6a-j**). All of these 1-aroyl-diazirdines will vary based on the groups added to the original benzaldehyde and amine.

Since the project is still a work in progress, currently **3a**, **3i** and **4g** have been successfully synthesized and characterized. The next step is to react **3a** and **3i** with the hydroxylamine-O-sulfonic acid to produce two more diaziradine rings (**4a** and **4i**). After the three diaziradine ring have been characterized, they will be treated with the 4-nitrobenzoylchloride (**5**) in order to obtain three desired 1-aroyldiaziridines (**6a**, **6i** and **6g**). These three diaziridine rings include the control, an electron withdrawing group, and electron donating group. Due to time constraints, the electronic effects will be tested based off of these three only. It would be interesting for a prospective student to prepare and test the rest of the substituents mentioned in order to gain a larger set of data.

Expected Results

With the successfully synthesized **6a-j**, attention will turn towards subjecting **6a-j** to base treatment, as well as to heat treatment in order to determine whether the C – N or the N – N bond breaks. It is fun to speculate that breaking of the C – N side-bond might lead to the formation of oxadiazolines (**9**), while amidines (**10**) might form under thermal treatment (see **Figure 3**) (Heine et al., 1976).

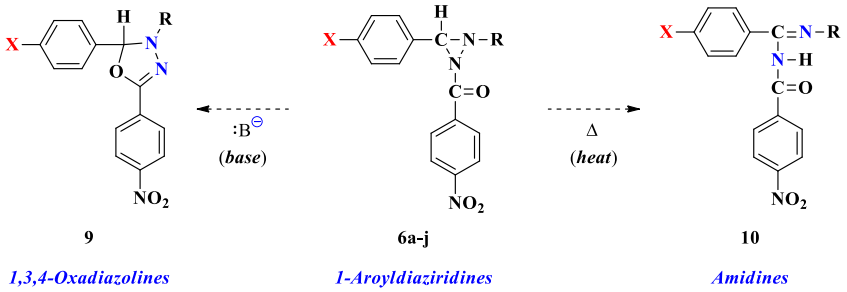

Figure 3: Predicted products resulting from the treatment of 6a-j with either base or heat

Conclusion

The next step of the project is to synthesize the diaziradine rings with the methoxy ($HOCH_3$) and nitro (NO_2) group substituents. Then I will react all three of them with 4-nitrobenzoylchloride in order to obtain my library of 1-aroyldiaziridines. With my unique library complete, and correctly characterized, I will expose them each to basic and thermal conditions to

determine the electronic tendencies on the individual molecules. Some future work for myself is to complete the reaction scheme shown in **Figures 2 and 3**. Also, future work for other undergraduate students is to increase the size of the library of 1-aroyldiaziridines to develop a larger data set and improve the conclusions made by the three diaziridines that I will synthesize.

References

El-Emam, A. A., Alrashood, K. A., Al-Omar, M. A., & Al-Tamimi, A.S., Molecules, 2012, 17, 3475-3483.

Heine, H. W., Bachlawski, L. M., Bonser, S. M., & Wachob, G. D., *J. Org. Chem*., 1976, 41(20), 3229-3232.

Kotthaus, J., Steinmetzer, T., van de Locht, A., & Clement, B., *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2011, 26(1), 115–122.

Stoica, C. I., Ionu, I., Pîrnău, A., Pop, C., Rotar, A., Vlase, L., Oniga, S., Oniga, O., *Clujul Medicinal*, 2015, 88(4), 421-429.