Synthesis of Indolizines with a Variety of Aromatic and Aliphatic Methyl Ketones

Rossler, Anderson, NSF

In the Anderson lab this summer I worked with a class of heterocyclic molecular cores called indolizines. An indolizine core is a 5-membered carbon ring fused with a 6-membered carbon ring where one of the carbon atoms is replaced with a nitrogen atom. Our interest in indolizines stems from their pharmacological relevance in the drug industry today; there are several indolizine compounds in double-blind clinical trials as of 2015. Because the indolizine core is medically relevant today, there is a strong desire to determine how efficiently and how diversely these desired products can be synthesized.

In organic chemistry, one of the main goals when it comes to synthesizing a new molecule is to determine the mechanism of formation. If we can understand exactly which bonds are being broken and formed to create the indolizine product, then we can determine the optimal reaction conditions that provide a variety of indolizine products in good yield. That is where I came in this summer; the Anderson lab has a proposed mechanism of formation for the indolizine product, and I was trying to prove just one intermediate in the mechanism. There is no way to actually prove a reaction mechanism, but you can change the reaction scheme in small, controlled ways that cause predictable variations in the product.

My intermediate is called a hemiacetal, and the thing to know about hemiacetals is that they have a lot of electron density. It should then follow that using an electron poor molecule in the reaction scheme should help mediate the extra electron density of the hemiacetal and give a higher yield. So, for the entire summer I played around with various electron donating and withdrawing substituents on the acetophenone (an important reagent in the reaction scheme) to make sure the results corroborated the electron density hypothesis. My results showed that adding electron withdrawing groups to the acetophenone to make it more electron poor increased the yield of the indolizine product. However, I also learned that no appreciable amount of indolizine forms when aliphatic methyl ketones are used; an aromatic substituent must be present, as in acetophenone.

I am very thankful for this opportunity this summer because it has opened a new door for me career-wise. I am currently a Biochemistry major on the pre-dental track here at Calvin, but I became very interested in organic chemistry after taking the class this past year. After spending 400 hours in an organic lab, I realized that this is something I have a passion for and could see myself doing full time. Pursuing a career in dentistry or chemistry both require a lot of schooling, so it is such a blessing to be able to have hands-on experience this early in my education.