Isoquinoline Alkaloid Synthesis

Abigail K. Frndak
Dr. Carolyn Anderson

My research this summer aimed to further develop the methodology of isoquinoline alkaloid synthesis. Isoquinoline analogues are powerful compounds not only in the natural world but also in the pharmaceutical industry serving as the backbone of drugs like Morphine and Berberine. Our goal was to design a method of synthesis which produced an isoquinoline analogue without sacrificing useful functional groups attached elsewhere on the structure. This would ensure that the structure would retain a high level of both functionality and versatility upon further transformations.

The first step of the synthesis was to perform a Suzuki cross coupling reaction on a particular *N*-alkenylated 2-pyridone of interest. This effectively installed an bromophenyl group capable of undergoing a Heck coupling reaction with the *N*-alkylated pyridine after the tetra-substituted alkene is reduced. This reaction would create a third ring in the compound forming the desired isoquinoline analogue. The first step, however, though already shown to be possible by an earlier member of the Anderson lab, proved difficult for me to accomplish.

After several failed reactions, I concluded that something external must be compromising the system. Several factors presented themselves for evaluation. First, I could be setting up the reaction incorrectly, there by preventing the success of the coupling by exposing the reaction mixture to some contaminant or failing to add catalyst. Second, the reagents used could have degraded over time. Third, the starting material could have been contaminated by some unknown substance. Lastly, my mass calculations could have been slightly off, which, when dealing with 2% mmol catalyst, is not only easily done but also detrimental to the yield of the reaction. It was deduced after evaluating my reaction set-up procedure, testing reagent quality, purifying starting material, and looking closely at my calculations that the later was the barrier to the reaction's success.

The next question to answer is whether or not the internal, tetra-substituted alkene can be reduced in a chiral fashion. In order for such a reduction to be detected, the compound must first undergo an achiral reduction. After such a reduction, the reaction mixture will consist of two enantiomers (non-superimposable mirror-images) in a one-to-one ratio. The HPLC of this reaction mixture will serve as a comparison for future chiral reductions.

This research fellowship has not only fueled my desire to continue on to graduate school but has cultivated a new level of comfort in the laboratory setting. I am now confident that I have developed the skills required to safely and effectively perform the necessary tasks associated with Organic Chemistry research. As the summer progressed, it also became clear that I had an extremely narrow idea of what success and failure looked like when conducting research. Just because a reaction failed, does not mean that you personally have failed in your attempt to unlock answers. Instead, each failure comes with new knowledge which can then be employed to better one's chances of success. That said, this research fellowship has been a definite blessing through both the knowledge imparted and motivation it has produced to continue on this path toward a greater understanding of Chemistry as a whole.