University of Louisville
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Research Seminar

When: March 9, 2023
Time: **12:00 p.m**.
Location: CBLL-16

Recent Studies on the Reactions and Synthesis of Nitrogen-containing Heterocycles

ABSTRACT:

The isoindolinone core comprises an aromatic ring fused to a five-membered lactam. The substructure is present in several organic compounds including natural products, agrochemicals and medicinal compounds.[1] As a unique class of alkaloids which are extracted and isolated from plants, the fused five-membered lactam substructure provides interesting leads to molecules with diverse biological activities such as anti-tumor, anti-malaria, anti-leukemia, anti-inflammatory, anti-anxiety, and anti-infectives.[2] The *N*-phthaloyl (phthalimide) group is an established amine protecting group and also a means of introducing nitrogen into a molecule via the Gabriel synthesis. However, to its detriment, the *N*-phthaloyl group may undergo partial reduction to form the corresponding hydroxylactam or lactam during multi-step synthesis. While the partial reduction is an unwanted side reaction, since the hydroxylactam cannot be removed, it is demonstrated that the hydroxylactam may be oxidized back to the easily removable phthalimide. Presented herein is the oxidation of hydroxylactam into the corresponding imides using nickel peroxide (NiO_2) in refluxing toluene as an oxidation system. Control studies have established that the iron-mediated systems compare favorably to the more common alcohol oxidants PCC and IBX systems.[3] We envisioned that a more environmentally benign iron reagent which is not a common oxidant for hydroxyl groups in multi-step synthesis was adopted. A catalytic iron-system [Iron III trifluoroacetate/TBHP and anhydrous $FeCl_3$/TBHP] in acetonitrile as solvent is reported that oxidizes both hydroxylactams and the methylene of lactams to the corresponding phthalimides.[4] A novel aza-tetracyclic indolizidine moiety has been constructed via the utility of the *N*-acyliminium ion chemistry to afford unique derivatives of this novel compound with similar scaffolds as several known alkaloids which have shown biological activities including aloperine a parent member of a rare family of C_{15} lupine alkaloids derived from the seeds and leaves of *Sophora alocuperoides L*.[5] The novel aza-tetracyclic compounds and their derivatives described herein may be of interest for their neuroleptic potential and other drug-like properties using established bioassays.

References:

1. Wang, H.; Xie, Z.; Lu, B.; Zhong, K.; Lu, J. "One-pot Method to Construct Isoindolinones and its Application to the Synthesis of DWP205109 an Intermediate of Lenalidomide. *Tetrahedron Lett.* **2021**, *74*, 153152-153157.
2. Dempster, R. K.; Luzzio, F. A "A Direct Arylation-Oxidation Route to 3-Arylisoindolinone Inhibitors of MDM2-p53 Interaction." *Tetrahedron Lett*. **2011**, *52*, 4992 - 4995.
3. Adjei, B. L.; Luzzio, F. A. "An Oxidation Study of Phthalimide-Derived Hydroxylactams" *Molecules* **2022**, 27, 548-558.
4. Adjei, B. L.; Luzzio, F. A. "Iron-Catalyzed Oxidation of Phthalimide-Derived Hydroxylactams and Isoindolinones" *Tetrahedron* **Manuscript in final preparation**.
5. (a) Brosius, A. D.; Overman, L. E. "Aloperine: Stereocontrolled Synthesis of Two Stereoisomers and Determination of Absolute Configuration." *J.Org. Chem*. **1997**, *62*, 440-441. (b) Dijkink, J., Schoemaker, H.E., Speckamp, W.N. Biomimetic Heterocyclization reactivity of rigid unsaturated systems. *Tetrahedron Letters*. **1975**, 46, 4043 - 4046.