Application Details

Manage Application: Support for Faculty Scholars Award (SFSA)

Award Cycle: March 1, 2017 - February 28, 2018
Internal Submission Deadline: Tuesday, January 31, 2017 at 5:00 PM

Application Title: Biomimetic Synthesis of 3-Substituted Pyridines
Application ID: #000072
Applicant First Name: James
Applicant Last Name: Kiddle
Department: Chemistry
College: Arts and Sciences
Faculty Rank: Associate Professor
Email: james.kiddle@wmich.edu

Proposal Title: Biomimetic Synthesis of 3-Substituted Pyridines
Amount requested ($2,000 Maximum Request): 2,000

Date and title of any previous SFSA or FRACAA project(s):

Unexpected reaction of Nheterocyclic carbenes in water. $2,000, Support for Faculty Scholars Award (SFSA), 2014.

Stereoselective Lewis Base-Activated Boronic Ester Additions. $10,000, Faculty Research and Creative Activities Award (FRACAA), 2012.

Development of New Cancer-Treatments to Reduce Patient Toxicity. $10,000, Faculty Research and Creative Activities Support Fund, 2007.

Provide an abstract/succinct summary of the proposal (50 words or less):

The proposal describes a synthesis of 3-substituted pyridines, an important building block in many drugs, that mimics how nature produces these molecules. The proposed route has previously never been reported. The reactions occur under mild conditions providing a large number of the target 3-substituted pyridines in a simple approach.

Describe your proposed work (e.g., objectives or goals, activities, timeline, outcomes, products, or other relevant information), including the connection, if one exists, with any previous award(s):
Introduction and Background The pyridine ring (blue, Figure 1) is the second most common heterocycle in drug molecules. It is present in more than 100 of the currently marketed drugs, including esomeprazole (Nexium, acid reflux), pioglitazone (Actos, diabetes), and imatinib (Gleevec, leukemia). As a result of the immense value of pyridines, for decades methods to access 3-substituted pyridines have been highly sought. The reactions of the isoelectronic carbocycle benzene (Scheme 1) are dominated by electrophilic (positively charged species) substitution. In general these reactions occur under mild conditions that can be assessed by the temperature, time of the reaction and the percentage of the product produced. Pyridine is itself about a million times less reactive than benzene in electrophilic substitution reactions based on the significantly increased temperature, time of the reaction and very poor production of the product. A promising approach to developing new methods in chemistry to construct molecules is by mimicking nature. In biomimetic chemistry, chemists take what is observed in nature and apply its principles to the discovery of new routes to synthetic compounds. For example, the tobacco plant efficiently produces nicotine, a 3-substituted pyridine, under mild conditions that suggest an electrophilic substitution like those illustrated in Scheme 1. However, all experience from the chemistry of pyridine indicates such a reaction would only be possible under drastic conditions. So, how does a tobacco plant synthesize nicotine from the known starting molecule nicotinic acid? The tobacco plant achieves the right result by taking an ingenious chemical detour (Scheme 2). The detour the tobacco plant takes to accomplish its synthesis of nicotine utilizes a nucleophilic (negatively charged species) hydride (green) to temporarily change the electronics of the ring and cause it to lose carbon dioxide (red). Once the carbon dioxide is lost the negative charge on the ring (structure highlighted in gray) can efficiently react with the necessary electrophile and subsequent loss of the hydride (green) and acid (blue) results in the production of large amounts of nicotine at 20-25 °C. The production of nicotine by the tobacco plant suggests an unexplored biomimetic route to 3-substituted pyridines using simple hydride nucleophiles. We propose to investigate this biomimetic synthetic route to 3-substituted pyridines and optimize the reactions conditions to offer a mild competitive alternative to these important drug building blocks. Objectives for the Proposed Project The development and optimization of any new synthetic method focuses on an iterative examination of the experimental conditions for the specific transformation and include for the biomimetic synthesis of 3-substituted pyridines (Scheme 3): The type and quantity of the reagent that delivers the nucleophilic hydride species. The type, quantity and need for an acid in the reaction. The time, temperature and solvent used in the reaction. The tobacco plant uses water as a solvent and room temperature for the reaction, but this might not be the case for the biomimetic reaction proposed. The scope of the electrophiles (E+, purple), specifically what variations in this species will produce 3-substituted pyridine building blocks. Timeline Shown below is a timeline for the proposed project. Initially the focus will be on hydride optimization for the reaction. This portion of the project will be iterative, and overlap with condition optimization and the scope of the proposed reaction.
There have been no published reports of a biomimetic synthesis of 3-substituted pyridines. Therefore, this will be an original contribution to the field of organic synthetic methodologies.

The research results from the proposed study will be submitted in a peer-reviewed American Chemical Society journal.

Since the proposed study focuses on a previously never utilized reaction pathway it will produce a premier article on the use of this approach and would enhance the profile of both the investigator and the institution within the field of synthetic organic chemistry methodologies.

In general, the development of a novel methodology is partly a trial-and-error experiment. Therefore many specific details about the exact nature of supplies cannot be predetermined. The proposed research is only asking for support of the materials necessary to fully develop this new methodology.

Minimally five to seven hydride reagents will be examined to find the optimal reagent for the reaction conditions. Each reagent costs between $50 and $200 of material. To fully generalize the reaction approximately ten electrophiles will be required to complete the scope of the reaction study (cost $50/10grams). Disposables are the vials necessary for the reactions, acids for the development of the conditions and solvents that are required for the analyses of the reaction products to determine purity that are imperative for the publication of the research.