Development Of New Methodology Towards Accessing 2-Imidazoline Scaffolds For Combatting Tuberculosis And Multiple Myeloma By Proteasome Modulation

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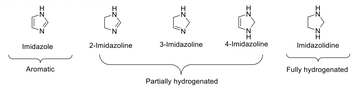
Introduction

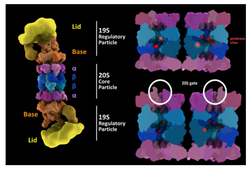
Imidazolines, also known as dihydroimidazoles, are a class of heterocyclic compounds belonging to the imidazole family. Imidazoles when reduced by hydrogen in the presence of a catalyst become one source of the production of imidazolines and imidazolidines. Imidazolines are the products of partial hydrogenation (partial reduction of imidazole). Imidazolidines are the product of complete hydrogenation (full reduction of imidazole). Partial reduction of imidazole gives rise to three imidazoline constitutional isomers, 2-imidazolines, 3-imidazolines, and 4-imidazolines. Of these three constitutional isomers, the most commonly observed and extensively researched isomer is 2-imidazoline.



Imidazolines are versatile heterocycle compounds whose industrial applications as surfactants and anti-corrosion agent, catalysis and ligand potential, as well as pharmacophore abilities have motivated researchers towards developing continuous methods for accessing them. Imidazolines have been experimentally proven to act as proteasome inhibitors, causing the apoptosis in cell systems that are dependent on proteasomal function for cellular viability.

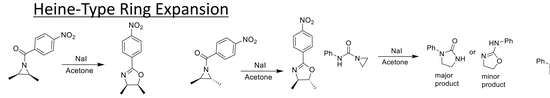
Proteasome Inhibition

The proteasome is a protease responsible for maintaining cell viability, homeostasis and regulation of cellular functions. The human proteasome, commonly referred to as the h26S, is comprised of the catalytic 20S core particle and two 19S regulatory caps. When these three groups assemble the 26S proteasome is formed and its function is to cleave proteins marked for degradation into their resulting amino acids. These amino acids can then be recycled by the cell towards other necessary cellular functions. The 19S caps act as recognition sites, identifying proteins that have been polyubiquitinated and funneling them into the catalytic 20S particle for degradation. Developing molecules that specifically target the proteasome result in modulation of proteasome activity when they bind. This modulation changes the rate of peptide degradation done by the proteasome. Imidazolines scaffolds have been experimentally shown to decrease proteasome activity. This decrease effects the degree to with the proteasome can effectively degrade proteins to maintain intercellular processes. Polyubiquitinated proteins begin to accumulate in the cell and result in downstream apoptosis.

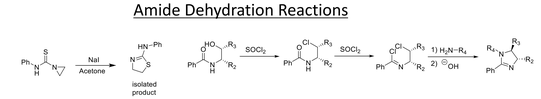


Background on the Synthesis of Imidazolines

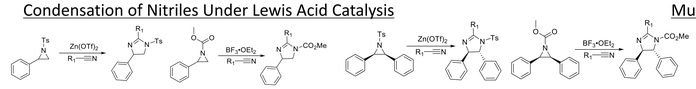
Heine-Type Ring Expansion



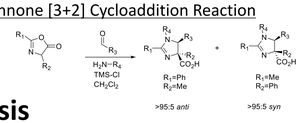
Amide Dehydration Reactions



Condensation of Nitriles Under Lewis Acid Catalysis

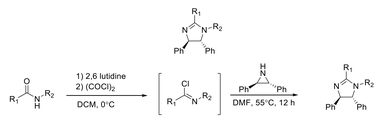


Munchnone [3+2] Cycloaddition Reaction

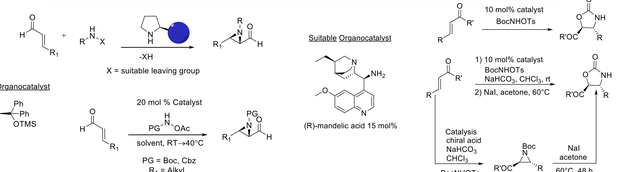


Current Literature on Imidazoline and Aziridine Synthesis

Accessing 2-Imidazolines by Ring Expansion of Imidoylaziridines

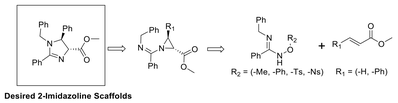


Accessing of Chiral Aziridines by Pyrrolidine Enamine-Iminium Cascade

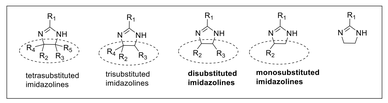


Hypothesis

Diversified 2-Imidazoline scaffolds can be accessed through a tandem enamine-iminium catalyzed Michael addition of O-functionalized N-Hydroxyamidines, in **four steps** from commercially available starting material, to produce a small library of compounds for biological evaluation.

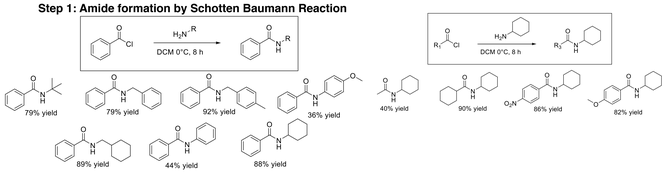


Desired 2-Imidazoline Scaffolds

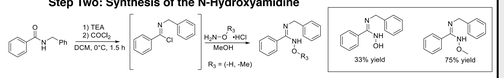


Experimental Results

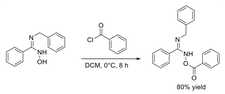
Step 1: Amide formation by Schotten Baumann Reaction



Step Two: Synthesis of the N-Hydroxyamidine

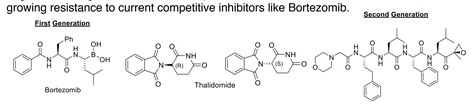


Step Three: O-Functionalization of the N-hydroxyamidine



Understanding Multiple Myeloma

Multiple myeloma is a malignant cancer of the plasma cells, found in blood. Although largely incurable, the lifespan of patients can be prolonged through the use of drug therapy. The target of synthetic drugs and polypeptide therapies is the proteasome, which has been identified as the linchpin for activating cell death. Bortezomib, is the one of leading proteasome inhibitors, and has been approved in the U.S. for the treatment of multiple myeloma. Drugs like Bortezomib, exhibit activity though competitive inhibition of the proteasome. This causes proteolysis to stop, thereby causing the accumulation of redundant and damaged proteins in the cell which result in cell death. This ability directly translates to the molecules' potent anticancer activity. However over time random mutations occur in cancer cells proteasomes that result loss of efficacy for Bortezomib and similar therapies. Apart from loss of activity, extended use of Bortezomib has resulted in severe off-target effects, due to lack of specificity for the proteasome of cancerous cells. In response to this, research has begun to investigate other methods of proteasome inhibition in an effort to combat the growing resistance to current competitive inhibitors like Bortezomib.

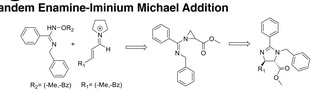


Understanding Tuberculosis

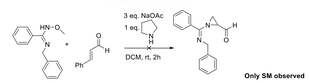
Tuberculosis is an infectious disease that is spread by *mycobacterium tuberculosis* (mTB). The emergence of multidrug and extensive drug resistant forms of TB have revitalized the need for novel scaffolds for TB inhibition. Often miseducation about TB and its behavior result in patients abruptly stopping treatments like Isoniazids as soon as visible symptoms disappear, instead of continuing the drug regiment in its entirety. The normal treatment time for a TB infection is 6-8 months to insure there is no secondary infection. One of the key factors that is being targeted in an attempt to combat TB is the inhibition of the proteasome. When mTB switches from its active mode to its passive or persistent mode, it is forced to use different metabolic pathways to survive in a low nutrient environment. One of the key factors to that survival is the recycling of proteins to make the amino acids available for other cellular operations, which the proteasome is responsible for.

Ongoing Research and Conclusions

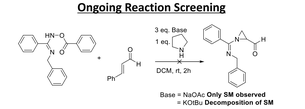
Step Four: Tandem Enamine-Iminium Michael Addition



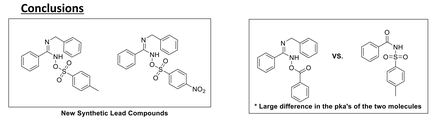
Negative Control



Ongoing Reaction Screening



Conclusions



New Synthetic Lead Compounds

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Acknowledgments

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