

Bronsted acid catalyzed synthesis of isoxazolidines and their benzylic amide rearrangement

Swati Lekha Mondal* and Mahiuddin Baidya
Indian Institute of Technology Madras, India

The isoxazolidine scaffold featuring an N–O bond connectivity in a ring framework is marked as the core constituent of many pharmaceuticals and natural products. In particular, the cyclopentane-fused isoxazolidine derivatives have received significant attention from the contemporary drug discovery regime owing to their promising bioactivities. They are acknowledged for antibacterial, antifungal, anti-cancer, and other significant therapeutic properties. Furthermore, this unique scaffold can also be utilized as an advanced intermediate towards the synthesis of natural products. Consequently, devising succinct catalytic protocols leading to these high-value scaffolds with enriched substitution patterns is highly desirable. Among the diverse methods to construct isoxazolidine scaffolds, the 1,3- dipolar cycloaddition reaction of nitrones with olefins remained most significant. Classically, nitrones are generated by condensing aldehydes with N-substituted hydroxyl amines with suitable nucleophilic N-center to facilitate the condensation event. However, such N-substitutions often constitute the pivotal burden in post synthetic manipulations. In fact, the recent advancements that account for the three-component coupling of diazo compounds, nitrosoarenes, and activated olefins to forge isoxazolidines also suffer a similar issue of N–aryl bond breaking. Grounded on this research gap, we delineated heretofore unrealized synthesis of cyclopentane-fused isoxazolidine frameworks from distal formyl enones **1** with hydroxycarbamates **2** bearing versatile functionalities such as Cbz, Boc, Troc. etc. The protocol is catalyzed by H₃PO₄ and offers a wide range of desired isoxazolidines **3** in high yields. Of note, these products are isolated as a single observable isomer. The cyclopentane-fused isoxazolidine products were also transformed into valuable cyclopentane-fused γ -lactams through the development of a diastereoselective benzylic amide rearrangement for which literature precedents are currently limited.



Biography

Swati Lekha Mondal is a research scholar, currently pursuing her doctoral studies (PhD) under the supervision of Prof. Md. Mahiuddin Baidya. She joined the Department of Chemistry, IIT Madras in July 2020. Her research studies mainly focus on organocatalytic cascade annulation strategies unraveling the expedient approach towards fused carbocycles and heterocycles.

Received: September 13, 2024; Accepted: September 16, 2024; Published: December 14, 2024