JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Development of a Synthetic Method for Imidazo[2,1-b]thiazole-Based Heterocycles

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Abstract:

A highly efficient and practical thioamination protocol has been developed for the synthesis of imidazo[2,1-b]thiazole-based heterocycles via the reaction of β-nitroalkenes with 1H-benzo[d]imidazole-2-thiol. This transformation proceeds through a sequential C–N and C–S bond formation cascade under mild conditions, enabling the rapid assembly of N-fused imidazo[2,1-b]thiazole-based frameworks in excellent yields. The methodology exhibits broad functional group tolerance and accommodates a diverse array of β-substituted nitroalkenes, allowing for the synthesis of structurally rich 2,3-disubstituted imidazo[2,1-b]thiazole-based heterocycles. The operational simplicity, scalability, and synthetic versatility of this approach render it a valuable tool for the construction of pharmacologically relevant N,S-heterocycles.

Introduction:

Imidazo[2,1-b]thiazole-based heterocycles constitute a significant class of N,S-fused systems that have garnered increasing attention due to their structural diversity and notable biological activity.[1-4] These polycyclic frameworks have demonstrated various therapeutic applications, including calcium channel modulation, acetylcholinesterase inhibition, SIRT1 activation, and notable antifungal, antitumor, anti-inflammatory, antidiabetic, and antitubercular properties.[5-11] Particularly remarkable are their immunomodulatory and antimetastatic effects, making them privileged scaffolds in medicinal chemistry for the development of innovative drug candidates. Despite their potential, accessing imidazo[2,1-b]thiazole-based heterocycles remains synthetically challenging due to the demand for efficient annulation strategies that enable multi-positional functionalization.[12-14] Conventional protocols typically rely on transition-metal-catalyzed cyclization of 1H-benzo[d]imidazole-2-thiol with halogenated olefins, alkynes, or dihaloalkanes, often suffering from limitations such as reagent sensitivity to moisture, poor regioselectivity, or restricted substitution scope—particularly at the C-2 and C-3 positions of the fused heterocyclic core.[15-17]

β-Nitroalkenes, known for their high electrophilicity and facile synthesis via Henry condensation, serve as attractive building blocks for heterocycle construction.[18-20] Their bifunctional reactivity is ideal for cascade and tandem reactions that allow multiple bond formations in a single synthetic step.[21-23] While β-nitroalkenes have been explored for generating various heterocyclic systems such as pyridines, furans, and imidazoles, their use in the synthesis of imidazo[2,1-b]thiazole-based heterocycles remains largely underutilized. Motivated by these considerations and in pursuit of expanding our nitroalkene-based synthetic strategies, we report a copper(II)-catalyzed thioamination method that enables the efficient construction of imidazo[2,1-b]thiazole-based heterocycles from β-nitroalkenes and 1H-benzo[d]imidazole-2-thiol.[21, 24, 25] This transformation involves a sequential C–N and C–S bond formation under mild conditions, offering excellent substrate scope and high efficiency. The protocol is further validated by its scalability and tolerance to diverse functional groups.[26-29]

Experimental Section:

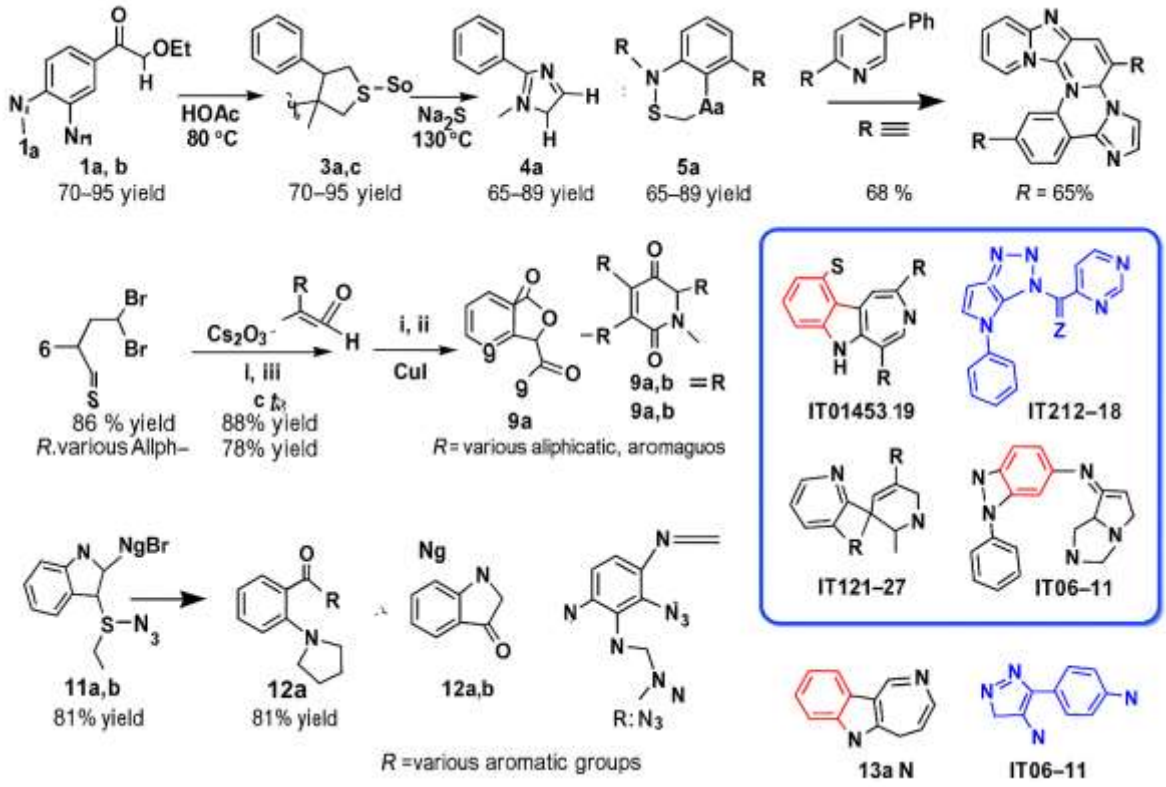
General Procedure: To a stirred solution of 1H-benzo[d]imidazole-2-thiol (0.297 mmol) and the respective β-nitroalkene (0.297 mmol) in anhydrous N,N-dimethylformamide (1.485 mL) was added copper(II) acetate monohydrate ($Cu(OAc)_2 \cdot H_2O$, 14.85 mol%, 8.91 mg). The reaction mixture was heated at 79.2 °C for 7.92 hours under air. After completion (monitored by TLC), the mixture was cooled to room temperature and diluted with water. The aqueous layer was extracted with ethyl acetate (3 × 9.9 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified via silica gel column chromatography using petroleum ether/ethyl acetate (9:1) to obtain analytically pure imidazo[2,1-b]thiazole-based heterocycles.

Results and Discussion:

Optimization of Reaction Conditions: The model reaction between 1H-benzo[d]imidazole-2-thiol (1a) and (E)-1-methyl-4-(2-nitrovinyl)benzene (2a) using 9.9 mol% $Cu(OAc)_2 \cdot H_2O$ in DMSO at 79.2 °C yielded the target imidazo[2,1-b]thiazole heterocycle (3aa) in 34.65% yield. Solvent screening revealed DMF as the optimal solvent, increasing the yield to 67.32%. Raising the catalyst loading to 14.85 mol% further enhanced the yield to 86.13%, while increasing to 19.8 mol% gave no further benefit. Other copper salts and metal acetates were less effective, confirming $Cu(OAc)_2 \cdot H_2O$ (14.85 mol%) in DMF at 79.2 °C for 7.92 h as optimal.

Scope of β-Nitroalkenes: Applying the optimized conditions, a range of β-nitroalkenes with different substituents were examined. Electron-donating groups (e.g., –Me, –OMe) and electron-withdrawing groups (e.g., $–NO_2$, –Cl, –F, –Br) were well tolerated, affording the corresponding 3-substituted imidazo[2,1-b]thiazole-based heterocycles (3aa–3al) in yields ranging from 77.22% to 93.06%. Heteroaryl and polycyclic nitroalkenes, including dioxole- and naphthalene-substituted variants, also performed effectively. However, α-substituted aliphatic nitroalkenes failed to cyclize, highlighting a limitation with non-aromatic substrates.

***Reactions with β-Substituted Nitroalkenes*:** Next, the methodology was extended to β-substituted nitroalkenes bearing alkyl or aryl groups. The resulting 2,3-disubstituted imidazo[2,1-b]thiazole-based heterocycles (5a–5h) were isolated in good yields, underscoring the protocol's capacity to construct multi-substituted fused heterocycles.



Scope of Substituted 1H-Benzo[d]imidazole-2-thiols: Variations in the benzo[d]imidazole ring were also explored. Electron-rich thiol derivatives (–Me, –OMe) yielded regioisomeric mixtures, suggesting non-selective cyclization. Electron-poor derivatives (–Cl, $–NO_2$) failed to deliver the expected products, likely due to reduced nucleophilicity or hindered copper coordination.

Gram-Scale Reaction: To confirm the practicality of this method, a gram-scale synthesis of 3aa was conducted. Under standard conditions, 1.160 g of the imidazo[2,1-b]thiazole-based product was isolated in 73.26% yield, affirming the approach's scalability.

Mechanistic Insights:

The proposed mechanism involves a Michael-type addition of the nitrogen atom of 1H-benzo[d]imidazole-2-thiol (1a) to the β-nitroalkene (2a), generating intermediate A. The thiol coordinates to copper(II), activating sulfur for an intramolecular nucleophilic attack to form a C–S bond, yielding cyclized intermediate B. Elimination of HNO and water subsequently leads to the imidazo[2,1-b]thiazole-based product (3aa). Despite sulfur's higher nucleophilicity, initial N-selectivity likely arises from copper-induced enhancement of nitrogen reactivity.

Conclusion:

We have developed a robust copper(II)-catalyzed thioamination strategy for the synthesis of imidazo[2,1-b]thiazole-based heterocycles. Utilizing readily available β-nitroalkenes and 1H-benzo[d]imidazole-2-thiol, this method proceeds under mild, operationally straightforward conditions. The transformation offers broad substrate compatibility, high functional group tolerance, and is amenable to scale-up, making it a valuable tool for preparing pharmacologically relevant N,S-fused heterocycles. This work significantly expands the scope of nitroalkene-based heterocyclic synthesis and provides a platform for designing novel bioactive molecules.

Acknowledgment

The authors are grateful to the Department of Chemistry, A. M. College, Gaya and Magadh University, Bodh Gaya for providing the necessary laboratory facilities and academic support to carry out this research work. We sincerely thank the faculty members and staff of the department for their valuable assistance and encouragement throughout the course of this study.

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