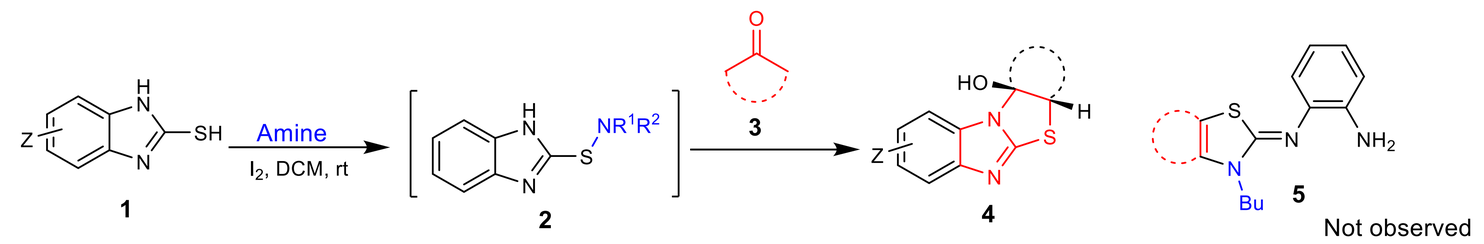
Primary Amine-Promoted Iodine-Mediated Annulation of Mercaptobenzimidazoles and Carbonyls toward Imidazo[2,1-b]thiazoles

Raihan Khaminthong[1], Wong Phakhodee, Mukda Pattarawarapan, Muh Alfliadi

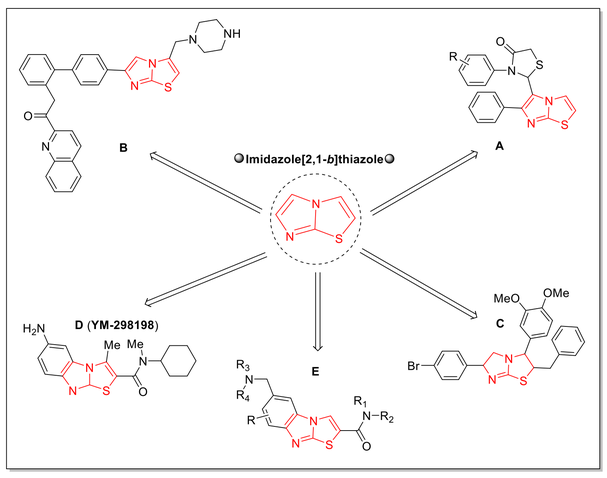
[1]Department of Chemistry, Faculty of Science, Chiang Mai University, Thailand

Student's email: azil357za@gmail.com



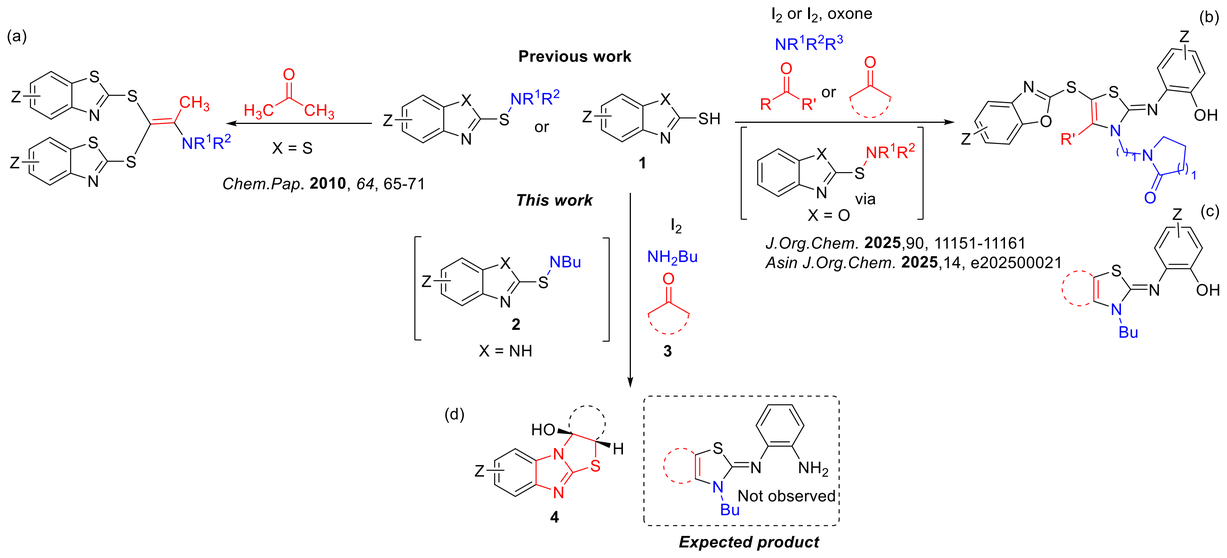
An efficient strategy for the construction of imidazo[2,1-*b*]thiazole frameworks **4** has been developed via a molecular iodine–mediated coupling of 2-mercaptobenzimidazoles **1** with ketones **3**. The transformation proceeds through the in situ generation of highly reactive sulfenamide intermediates **2**, which function as electrophilic sulfenylating species under primary amine catalysis. The ketone substrate subsequently reacts with sulfenamide intermediate **2** to promote C–S bond formation, leading to the corresponding α-sulfenylated ketone species, followed by intramolecular cyclization to furnish the fused heterocyclic scaffold. Notably, the previously reported formation of 2-iminothiazoline derivatives **5** was not observed under the standard reaction conditions.

INTRODUCTION



Imidazothiazoles are biologically active fused N,S-heterocyclic scaffolds with unique electronic and structural properties, making them valuable in medicinal[1], agricultural[2], and materials chemistry[3]. Among them, imidazo[2,1-*b*]thiazole derivatives are recognized as privileged structures in drug discovery due to their rigid bicyclic framework and ability to interact effectively with biological targets[4]. Representative derivatives demonstrate diverse pharmacological activities: compound **A** exhibits anticancer activity[5]; compound **B** shows antidiabetic effects[6]; compound **C** displays anti-inflammatory activity[7]; and compounds **D** and **E** act as noncompetitive mGluR1 inhibitors with relevance to CNS disorders[8]. These examples highlight the broad therapeutic potential of the imidazo[2,1-b]thiazole scaffold as a versatile platform for drug development.

PREVIOUS WORK



- **CHALAENGE**

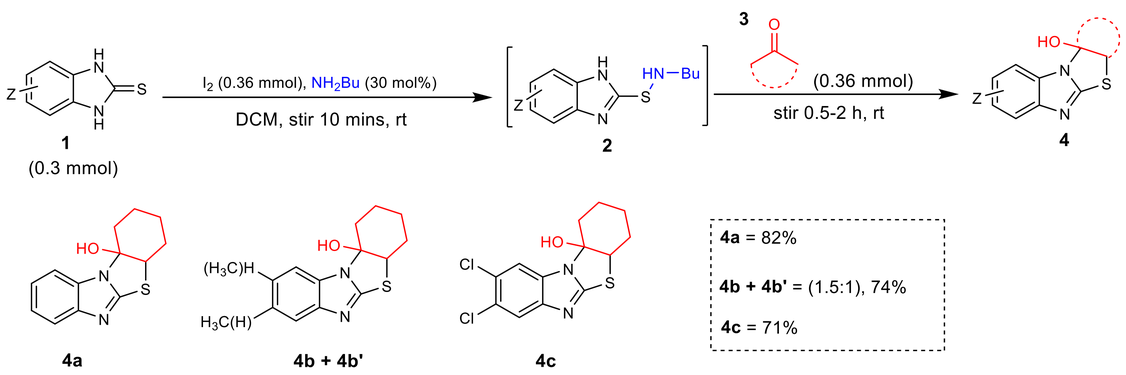
Metal Catalyst | Harmful reagent | Long Period

- **OBJECTIVE**

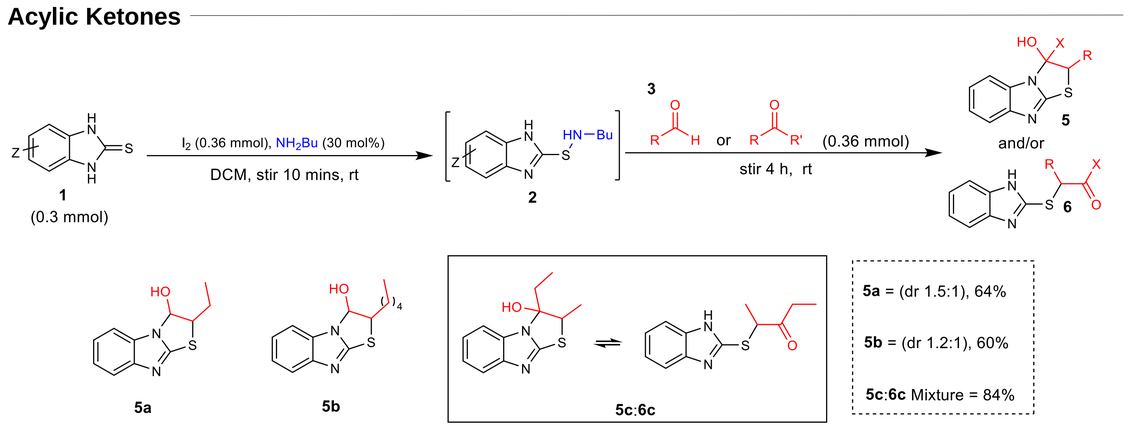
1. To investigate the role of molecular iodine *n*-butylamine as an environmentally friendly catalyst in direct synthesis of the imidazo[2,1-*b*]thiazole derivatives.
2. To explore the role of the sulfenamide intermediate in situ formed in the reaction by using *n*-butylamine.
3. To develop a benign reaction protocol operating under mild conditions, including room temperature and reduced solvent usage.
4. To synthesize imidazo[2,1-*b*]thiazole derivatives bearing a variety of substituents.

SUBSTRATE SCOPE

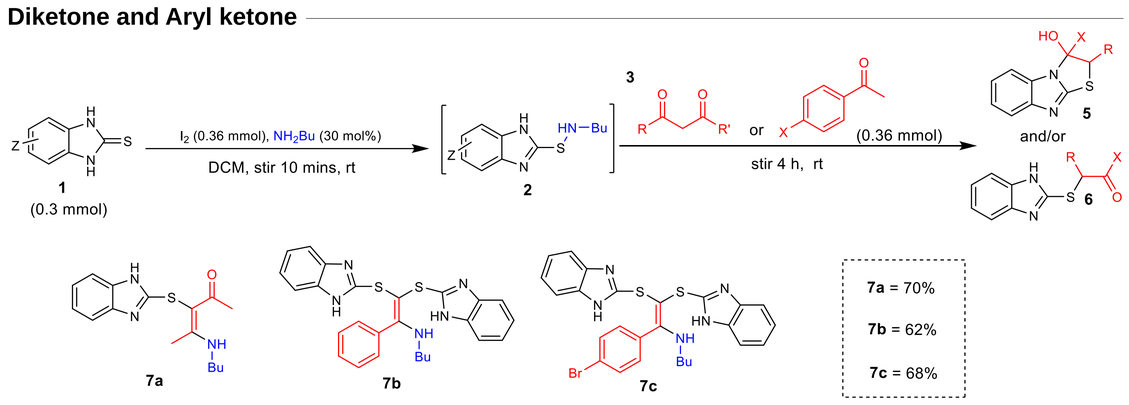
Cylic Ketones



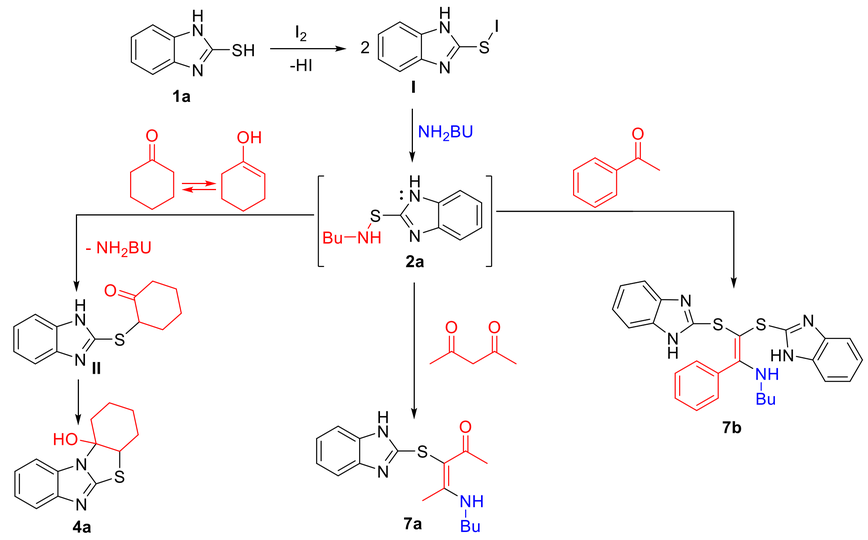
Acylic Ketones



Diketone and Aryl ketone



PROPOSED MECHANISM



CONCLUSION

A mild and efficient annulative strategy for the construction of benzimidazo[2,1-b]thiazole frameworks has been developed. This transformation proceeds through in situ generation of sulfenamide intermediates from 2-mercaptobenzimidazoles, enabling sequential C–S and C–N bond formation with ketones under aerobic, transition-metal-free conditions. The protocol accommodates a wide range of structurally diverse substrates, exhibits good functional-group tolerance, and employs readily available and operationally simple starting materials.

Mild Reaction Condition | **High yield** | **Mechanistic Study**

REFERENCE

[1] Guo, M.; Yu, X.; Zhu, Y. Z.; Yu, Y. *Molecules* **2023**.
[2] Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Andreani, F.; Gehret, J.-C. *Pharm. Acta Helv.* **1996**.
[3] Cherif, A.; Alzahrani, A. Y. A.; Hammoudan, I.; Saddik, R.; Tighadouini, S. *Materials Today Sustainability* **2023**.
[4] Hu, F.; Zhang, L.; Nandakumar, K. S.; Cheng, K. *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* **2021.**
[5] Kamboj, P.; Anjali; Imtiyaz, K.; Rizvi, M. A.; Nath, V.; Kumar, V.; Husain, A.; Amir, M. *Sci. Rep.* **2024.**
[6] Vu, C. B.; Bemis, J. E.; Disch, J. S.; Ng, P. Y.; Nunes, J. J.; Milne, J. C.; Carney, D. P.; Lynch, A. V.; Smith, J. J.; Lavu, S.; Lambert, P. D.; Gagne, D. J.; Jirousek, M. R.; Schenk, S.; Olefsky, J. M.; Perni, R. B. *J. Med. Chem.* **2009**.
[7] Shetty, N. S.; Khazi, I. A. M.; Ahn, C. *Bull. Korean Chem. Soc.* **2010**.
[8] Kohara, A.; Toya, T.; Tamura, S.; Watabiki, T.; Nagakura, Y.; Shitaka, Y.; Hayashibe, S.; Kawabata, S.; Okada, M. **2005**.