Efficient Synthetic Strategies using Isatins for Access to Bioactive Small Molecule's Framework

Haye Min Ko

Department of Chemistry, Kookmin University, Seoul, Republic of Korea
Email: hayeminko@kookmin.ac.kr

Spirooxindoles often found in natural products and drug-like compounds have been considered to be important structural moieties. Especially, spirooxindoles with a N-heterocycle at the 3-carbon position can be used in medicinal chemicals according to their biological activities, such as antibacterial, anticancer, and antimicrobial activities. Thus, the synthesis of the spiro[oxindole-3,2′-pyrrolidine] scaffold attaching a nitrogen atom at the spiro-quaternary carbon center has received attention due to its special bioactivity. Because of the important role of these compounds in the pharmaceutical field, many research groups have developed drug candidates on the basis of the privileged spiro[oxindole-3,2′-pyrrolidine] framework that shows antitumor or antibacterial activity. In spite of the many emerging transition-metal-catalyzed reactions for building these frameworks, synthetic strategies involving isatins are still considered to be useful protocols. Multicomponent reactions of isatins with a variety of α-amino acids, 1,3-dipolarophiles, and other electron deficient alkenes have been reported. Among these reactions, the 1,3-dipolar cycloaddition reaction of azomethine ylide is a powerful method for preparing five-membered heterocyclic compounds.

However, remarkably, a survey of the literature reveals that, despite many efforts, it is not easy to construct spiro[oxindole-3,2′-pyrrolidine] with a carbon-carbon double bond in the five-membered ring. To overcome this synthetic limitation, we are interested in the use of benzyne as a new dipolarophile to develop new routes toward the synthesis of spirooxindoles. Here, we report a 1,3-dipolar cycloaddition reaction for the synthesis of spiro[oxindole-3,2′-pyrrolidine] derivatives employing azomethine ylide precursors and benzyne in the presence of a fluoride source.

References

[1] Choi, H. Y.; Jang, C. S.; Kim, J.; Ko, H. M.*, *J. Org. Chem*. **2025**, *90*, 18033-18044.

[2] Park, S. Y.; Kim, J.; Ko, H. M.*, *J. Org. Chem*. **2023**, *88*, 1996-2005.

[3] Jang, W. C.; Jung, M.; Ko, H. M.* *Org. Lett.* **2021**, *23*, 1510-1515.

[4] Jeong, H.; Han, N.; Hwang, D. W.; Ko, H. M.* *Org. Lett.* **2020**, *22*, 8150-8155.

[5] Ryu, H.; Seo, J.; Ko, H. M.* *J. Org. Chem.* **2018**, *83*, 14102-14109.