Regio-controlled dual acetylene incorporation for the one-pot synthesis of pyridoindole scaffolds

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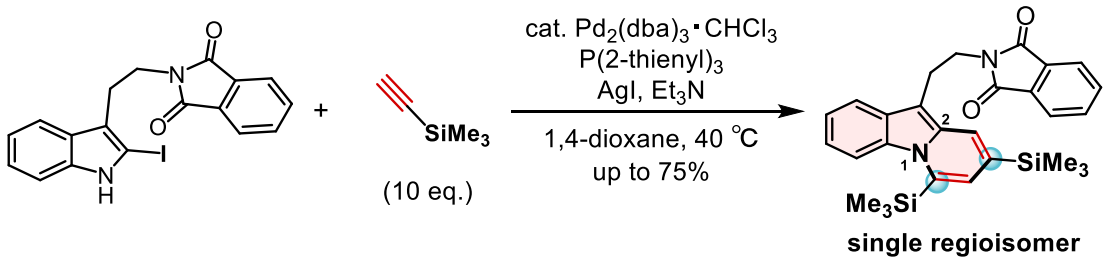
The pyrido[1,2-*a*]indole unit, a tricyclic aromatic scaffold formed by the fusion of indole and pyridine rings, has attracted attention as a privileged structure for developing pharmaceuticals and fluorescent probes. Various synthetic strategies have been explored to access this nitrogen-containing scaffold.[1] Kundu previously reported an annulation approach using symmetrically disubstituted internal alkynes to generate pyridoindole scaffolds.[2] However, one-pot synthetic methodologies that integrate terminal alkynes with precise regioselectivity remain largely unexplored.

In this study, we developed a one-pot synthetic method to construct the pyridoindole scaffold in a single step, featuring a regio-controlled dual acetylene incorporation approach. Using a 2-iodinated tryptamine derivative as the substrate, the palladium-catalyzed reaction regioselectively incorporates two molecules of silyl acetylene along with the formation of a carbon–nitrogen bond at the indole nitrogen. Under optimized conditions with a silver salt additive, the tricyclic pyrido[1,2-*a*]indole scaffold was synthesized with high efficiency, achieving an isolated yield of 75% through a simple and streamlined procedure. In addition, regioselective mono-desilylation of the resulting pyrido[1,2-*a*]indole scaffold was achieved at the carbon adjacent to the indole nitrogen, highlighting the potential utility of this structure as a versatile synthetic intermediate for precise derivatization.



1) Yao, Y.; Alami, M.; Hamze, A.; Provot, O. *Org. Biomol. Chem.* **2021**, *19*, 3509.
2) Samala, S.; Kundu, B, *et al*. *Chem. Eur. J.* **2014**, *20*, 14344.