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Polysubstituted Indole synthesis by Regioselective Introduction of Nucleophiles to Iminoquinone monoacetals

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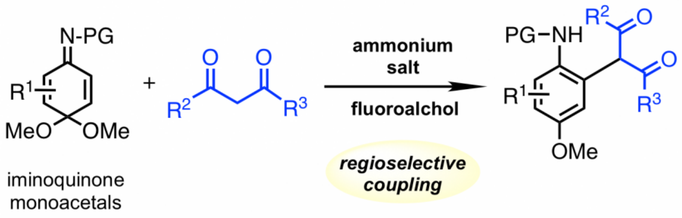
PURPOSE OF THE ABSTRACT

[Purpose] Highly functionalized indole derivatives are important due to their ubiquitousness in building blocks of natural products, pharmaceuticals, and functional materials. Transition metal-catalyzed reactions of pre-functionalized organic substrates are generally utilized for the synthesis of these aromatic compounds. However, increasing the number of steps for preparing the substrate and discharging the stoichiometric metal waste should be improved. Although direct coupling for C-H bond without pre-functionalization is actively studied by various groups as an alternative method, regio- and chemoselective issues remain unsolved. Therefore, the development of a new synthesis method is desired.

[Method] For the synthesis of highly functionalized aromatic compounds, we have studied the original approach using quinone monoacetals (QMAs). In 2011, we reported the regioselective nucleophilic substitutions to alpha-position of QMA carbonyl with the aid of an acid promotor and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent.[1,2] Recently, we have found an efficient method for activating QMAs under neutral conditions using an ammonium salt as an activator, which can expand the substrate scope.[3] However, the control of the regioselectivity of iminoquinone monoacetals (imino-QMAs) is more difficult to achieve. Previously, our group reported the utilization of imino-QMAs[4] and oxidative coupling of aniline derivatives[5] for the synthesis of indoline and indole derivatives. Based on the background, we investigated the reaction conditions for the regioselective introduction of active methylene compounds to imino-QMAs.

[Results] Under the conventional QMA activation conditions, decomposition of imino-QMA predominantly occurred, and no desired product was obtained. On the other hand, it was found that the desired reaction proceeded when a weak acidic ammonium salt was used. Thus, the active methylene compound was regioselectively introduced into the alpha-position of the imino group, and the ortho-substituted aniline derivatives were selectively obtained. Successive intramolecular cyclization of the obtained coupling product led to the synthesis of highly functionalized indole derivatives.

FIGURES



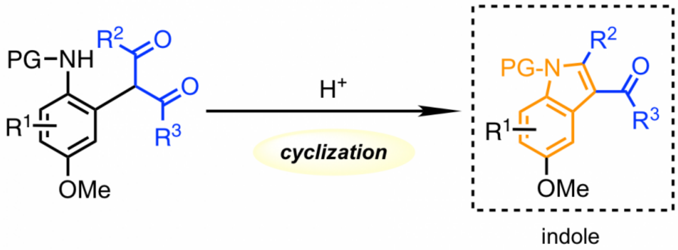


FIGURE 1

Regioselective coupling to imino-QMA

The active methylene compound was regioselectively introduced to the alpha-position of the imino group, and the ortho-substituted aniline derivatives were selectively obtained.

FIGURE 2

Cyclization of ortho-substituted aniline derivatives

Successive intramolecular cyclization of the obtained coupling product led to the synthesis of highly functionalized indole derivatives.

KEYWORDS

Polysubstituted Indoles | Iminoquinone monoacetals | Aniline derivatives | Ammonium salt

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