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Palladium-Catalyzed Intramolecular Addition of C-N Bond to Alkynes: A Novel Approach to 3-Diketoindoles†

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Palladium-catalyzed intramolecular addition of C-N bond to alkynes to synthesize 3-diketoindoles via the construction of indole ring with the migration of the α-ketoacyl group has been achieved. This protocol features operational simplicity, high atom economy, broad substrate scope and high yields, thus affording a versatile approach to highly functional 3-diketoindoles.

Transition metal-catalyzed addition of X-Y (X, Y = H, B, C, N, O, Si, S, Cl, Se) bonds to alkynes is an important strategy for the functionalization of carbon–carbon triple bonds. These catalytic addition reactions construct one new C-X bond and one new C-Y bond in an atom-economic way. Especially, the intramolecular addition of X-Y bonds to alkynes has become one of the most efficient methods to synthesize functional heterocycles such as indole, benzofuran, benzothiophene, indene and indenone. Among the reported methods, the intramolecular addition of C-N bond to alkynes has attracted considerable attention because of its high efficiency in constructing highly functional indoles.

The indole moiety is considered as a privileged scaffold owing to its ubiquitous presence in a large number of natural products and pharmaceutical agents. In particular, 3-diketoindoles form an important class of compounds because of their diverse range of pharmacological properties. Consequently, many efforts have been made to synthesize 3-diketoindoles. However, only rare methods have successfully synthesized 3-diketoindoles.

Traditional Friedel-Crafts acylation between indoles and oxalyl chloride achieved the synthesis of 3-diketoindoles but suffered from poor selectivity and low yield (Scheme 1a). Glyoxylation/Stephens-Castro coupling sequence reported by Müllers’s group also realized the dicarbonylation of indoles, but the utility of the reaction is limited by requiring strict exclusion of moisture, operational complexity and moderate yield (Scheme 1b). The oxidative cross-coupling of indoles developed by Li and Wu offered an interesting route for the synthesis of 3-diketoindoles, but this process was accompanied by disadvantages such as limited substrate scope and low atom economy (Scheme 1c). In addition, all these methods achieved the synthesis of 3-diketoindoles through the modification rather than construction of the indole ring. Herein, we present our efforts to synthesize 3-diketoindoles via the construction of the indole ring using palladium-catalyzed intramolecular addition of C-N bond to alkynes with the migration of the α-ketoacyl group (Scheme 1d). Our protocol features operational simplicity, high atom economy, broad substrate scope and high yields, thus affording a versatile approach to highly functional 3-diketoindoles.

Initial screening experiments were performed using 1aa as the model substrate to optimize the reaction conditions for catalysts and solvents (Table 1). Treatment of 1aa with Pd(0) catalysts such as Pd(PPh3)4 and Pd2(dba)3 in toluene at 110 °C for 4 hours did not give the desired product at all (entries 1 and 2). Pleasingly, the desired product 2aa was achieved when 1aa was subjected to Pd(II) catalysts such as Pd(OAc)2 and PdCl2(dppf), albeit with low yield (entries 3 and 4). Encouraged by this result, various Pd(II) sources were screened (entries 5-9). Among them, PdCl2(CH3CN)2 was found to be the most effective catalyst, providing product 2aa with 98% yield (entry 9). A further screening of the solvents revealed that the reaction yield was strongly influenced by the solvent used, and toluene was demonstrated to be the best choice for this transformation (entries 10-14).
After determining the optimal reaction conditions, we then examined the general applicability of the process (Scheme 2). The reactions of 1aa-1ac carrying alkyl groups at R₁ afforded the corresponding products 2aa-2ac in excellent yields (90-98%), while the reaction of 1ad bearing a bulky tert-butyl group did not give the desired product due to steric hindrance. A high yield (88%) was also achieved from 1ae with a benzylic group at R₁ (2ae). Substrates with aromatic rings at R₁ furnished the corresponding products in moderate yields (2af-2ah). To our delight, the protocol was also compatible with various functional groups such as halide and ester at the alkynyl moiety with high yields (2ai-2ak). Subsequently, substrates at R₂ were investigated, substrates bearing an electron-donating substituent (Me), halides (F, Cl, Br), and electron-withdrawing substituents (CN, CF₃) at R₂ afforded the products in 80-99% yields. In addition, different substituents at R₂ were also explored, the reaction of substrates having an ethyl or benzyl group at R₂ also produced the desired products in high yields (88-93%).

Next, various migrating groups on the nitrogen were investigated (Scheme 3). The reaction of substrates bearing an ethyl or isopropyl group at R₄ proceeded smoothly and gave the corresponding products in excellent yields. It is worth noting that substrates carrying sterically congested groups such as tert-butyl and phenyl at R₄ also furnished the desired products in high yields (85-90%). Interestingly, an indole dimer product was achieved in 90% yield when substrate (1ax) was subjected to the optimal reaction conditions (Scheme 4).
Mechanistic studies were also carried out with the crossover experiments, as shown in Scheme 5. No crossover products of the migrating group were observed when equimolar 1aa and 1ay were mixed under the standard reaction conditions, indicating that this palladium-catalyzed addition of the C3N bond to alkynes proceeds in an intramolecular manner.

Based on the above results, a plausible mechanism as outlined in Scheme 6 was proposed. Coordination of alkyn to PdCl2(CH3CN)2 furnishes intermediate A, followed by nucleophilic attack of nitrogen to the alkyne, producing the intermediate B. An intramolecular [1, 3]-migration of the pyruvoyl group then gives intermediate C, which affords the product and regenerates the catalyst.

An efficient and practical protocol has been developed to synthesize 3-diketoindoles by palladium-catalyzed intramolecular addition of C-N bond to alkynes. The operational simplicity, high atom economy, broad substrate scope and high yields demonstrate the great potential of this method for the synthesis of highly functional 3-diketoindoles. We anticipate that these 3-diketoindole derivatives may find pharmaceutical applications after further investigations.

Notes and references