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FULL PAPER

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

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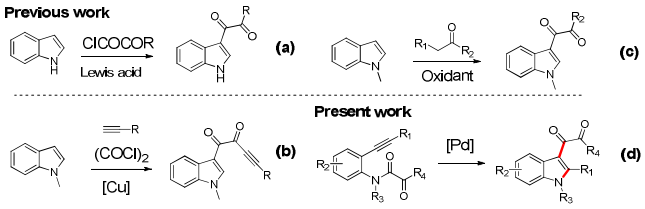
Palladium-catalyzed intramolecular addition of C-N bond to alkynes to synthesize 3-diketoindoles via the construction of indole ring with the migration of the α-ketoacyl group has been achieved. This protocol features operational simplicity, high atom economy, broad substrate scope and high yields, thus 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.[1] 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,[2] benzofuran,[1c,3] benzothiophene,[1k,4] indene[1d,e] and indenone.[5] 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.[2c,6]

The indole moiety is considered as a privileged scaffold owing to its ubiquitous presence in a large number of natural products and pharmaceutical agents.[7] In particular, 3-diketoindoles form an important class of compounds because of their diverse range of pharmacological properties.[8] Consequently, many efforts have been made to synthesize 3-diketoindoles. However, only rare methods have successfully synthesized 3-diketoindoles.[9-14] 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).[9] Glyoxylation/Stephens-Castro coupling sequence reported by Müller'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).[10] 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).[11-13] 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.



Scheme 1 Synthetic methods for 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 $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ 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 $PdCl_2(dppf)_2$, albeit with low yield (entries 3 and 4). Encouraged by this result, various Pd(II) sources were screened (entries 5-9). Among them, $PdCl_2(CH_3CN)_2$ 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).

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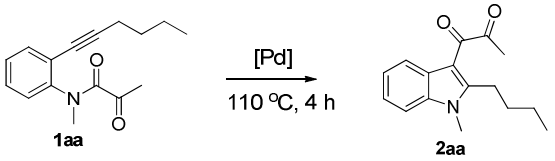
Table 1 Optimization of the reaction conditions [a]

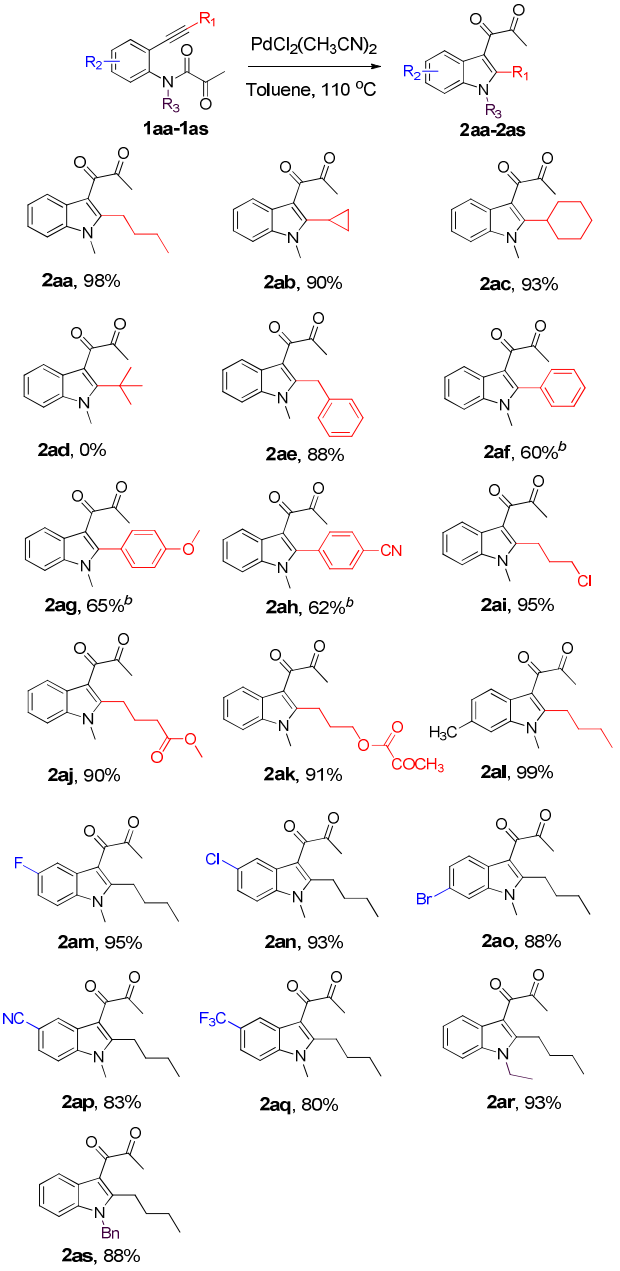


Entry	[Pd]	Solvent	Yield(%)[b]
1	$Pd(PPh_3)_4$	Toluene	0[c]
2	$Pd_2(dba)_3$	Toluene	0[c]
3	$Pd(OAc)_2$	Toluene	15[c]
4	$PdCl_2(dppf)_2$	Toluene	12[c]
5	$Pd_2Cl_2C_6H_{10}$	Toluene	12[c]
6	$PdCl_2(NH_4)_2$	Toluene	11[c]
7	Na_2PdCl_4	Toluene	82
8	$PdCl_2(PhCN)_2$	Toluene	85
9	$PdCl_2(CH_3CN)_2$	Toluene	98
10	$PdCl_2(CH_3CN)_2$	1,2-Dichloroethane	93
11	$PdCl_2(CH_3CN)_2$	1,4-Dioxane	88
12	$PdCl_2(CH_3CN)_2$	CH_3CN	95
13	$PdCl_2(CH_3CN)_2$	EtOH	6[c]
14	$PdCl_2(CH_3CN)_2$	DMSO	11[c]

[a] Reaction conditions: **1aa** (0.5 mmol), [Pd] (0.05 mmol), and solvent (2.0 mL) under argon atmosphere at 110 °C for 4 h. [b] Isolated yield. [c] **1aa** was recovered.

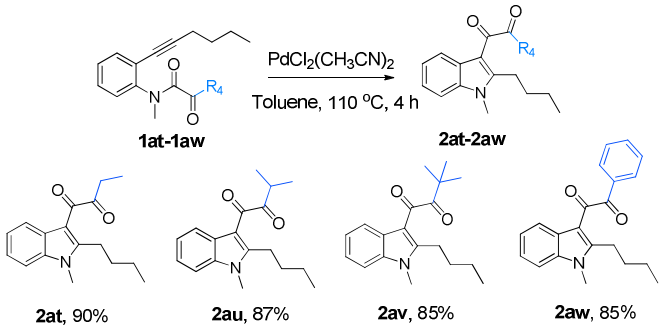
After determining the optimal reaction conditions, we then examined the general applicability of the process (Scheme 2). The reactions of **1aa-1ac** carrying alkyl groups at R_1 afforded the corresponding products **2aa-2ac** in excellent yields (90-98%), while the reaction of **1ad** bearing a bulky *tert*-butyl group did not give the desired product due to steric hindrance. A high yield (88%) was also achieved from **1ae** with a benzyl group at R_1 (**2ae**). Substrates with aromatic rings at R_1 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, substituents at R_2 were investigated, substrates bearing an electron-donating substituent (Me), halides (F, Cl, Br), and electron-withdrawing substituents (CN, CF_3) at R_2 afforded the products in 80-99% yields. In addition, different substituents at R_3 were also explored, the reaction of substrates having an ethyl or benzyl group at R_3 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 R_4 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 R_4 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).

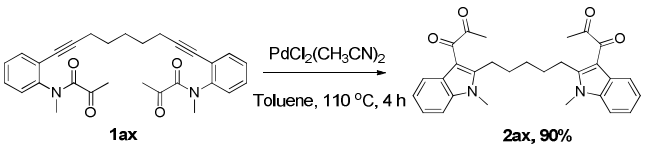


[a] Reaction conditions: **1** (0.5 mmol), $PdCl_2(CH_3CN)_2$ (0.05 mmol), and Toluene (2.0 mL) under an argon atmosphere at 110 °C for 4 h. [b] The reaction was performed in toluene at 110 °C for 24 h.

Scheme 2 Pd-catalyzed synthesis of 3-diketoindoles. [a]

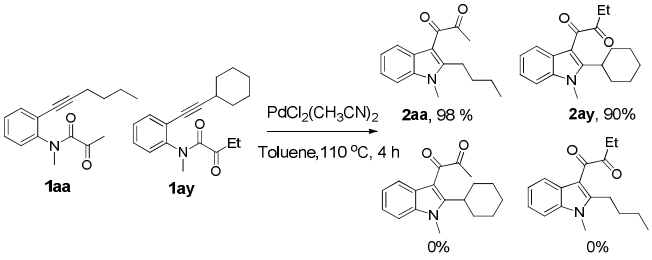


Scheme 3 Pd-catalyzed Synthesis of 3-diketoindoles.



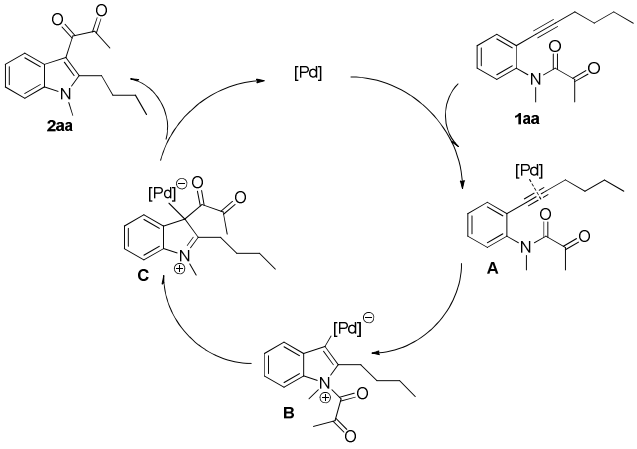
Scheme 4 Pd-catalyzed synthesis of 3-diketoindole dimer.

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 C-N bond to alkynes proceeds in an intramolecular manner.



Scheme 5 Mechanistic studies of Pd-catalyzed synthesis of 3-diketoindole.

Based on the above results, a plausible mechanism as outlined in Scheme 6 was proposed. Coordination of alkyne to $PdCl_2(CH_3CN)_2$ 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.



Scheme 6 Proposed reaction mechanism.

Conclusions

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.

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