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Copper-catalyzed decarboxylative C3-acylation of free (N–H) indoles with α-oxocarboxylic acids†

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An efficient Cu-catalyzed decarboxylative C3-acylation of free (N–H) indoles using α-oxocarboxylic acids as acylating agents has been developed. This method was compatible with a variety of functional groups and provided an attractive alternative access to 3-acylindoles in moderate to high yields.

The indole nucleus is one of the most important organic structural motifs found in natural products, pharmaceutically active compounds and agrochemicals.[1] Particularly, 3-acylindoles have been found to exhibit various pharmaceutical activities, such as anticancer, HIV-1 integrase inhibition, and anti-diabetic.[2] Therefore, much effort has been devoted to the preparation of 3-acylindoles. Traditionally, the most common approach is Friedel–Crafts acylation of indole or indole Grignard reagent with acyl chlorides.[3] The other significant approaches include Vilsmeier–Haack acylation of indole with aryl acetamide,[4a] the reaction of indole with a nitrilium salt,[4b] *N*-acylbenzotriazole,[4c] carboxylic acid,[4d] aniline,[4e] or nitrile.[4f,g] Very recently, Wang described a novel and efficient Cu-promoted decarboxylative direct C3-acylation of N-substituted indoles with α-oxocarboxylic acids.[5] Although significant advances have been achieved, there are still some disadvantages, such as strict exclusion of moisture, the use of a stoichiometric Lewis acid promoter or expensive palladium catalyst, the introduction of a protecting group at N-position of indole and a long reaction time. Therefore, development of an efficient approach to obtain 3-acylindoles is highly desirable.

Transition-metal-catalyzed decarboxylative C–C cross-coupling reactions using carboxylic acids or carboxylates instead of organometallic reagents as coupling partners have attracted considerable attention in recent years.[6] Meanwhile, impressive achievements have been made in direct C–H activation using various transition-metal catalysts such as Pd,[7] Ru,[8] Rh,[9] or Cu.[10] Considering the atom- and step-economical features, the combination of decarboxylative coupling with C–H activation could be considered the optimum strategy in the synthetic application. In 2008, Crabtree reported the first Pd-catalyzed decarboxylative C–H arylation.[11] Subsequently, considerable research on the decarboxylative C–H functionalization using aromatic carboxylic acid as a substrate has been reported.[12] Furthermore, α-oxocarboxylic acids were also used as decarboxylative coupling partners for the direct acylation of the arene C–H bond, which provided a new approach to ketones. Firstly, the Ge group demonstrated several Pd-catalyzed decarboxylative acylations including 2-phenylpyridines, acetanilides, potassium aryltrifluoroborates and benzoic acids using α-oxocarboxylic acids as acylating agents.[13] Duan and Guo also reported a Pd-catalyzed decarboxylative acylation of cyclic enamides with α-oxocarboxylic acids.[14] Moreover, Kim *et al.* also reported Pd-catalyzed decarboxylative acylation of *o*-methyl ketoximes, phenylacetamides and *o*-phenyl carbamates with α-oxocarboxylic acids.[15] Most recently, Tan, Zhu and Zhang developed three kinds of strategies of efficient Pd-catalyzed decarboxylative acylations of *o*-methyl oximes, indoles and 2-aryloxypyridines with α-oxocarboxylic acids, respectively.[16] Undoubtedly, the decarboxylative C–H functionalization has emerged as a powerful tool for the construction of C–C bonds in contemporary organic synthesis. Inspired by the recent studies, we report a Cu-catalyzed decarboxylative C3-acylation of free (N–H) indoles with α-oxocarboxylic acids to afford 3-acylindoles in moderate to high yields.

Our investigation started with decarboxylative coupling of 5-methoxyindole (**1a**) with phenylglyoxylic acid (**2a**) in the presence of 20 mol% Pd(II) with 2 equiv. of Ag_2CO_3 in DMF at 90 °C for 3 h. Unfortunately, both $Pd(OAc)_2$ and $PdCl_2$ gave very low yields (Table 1, entries 1 and 2). Surprisingly, when $Cu(OAc)_2{\cdot}H_2O$ co-catalyst was introduced into the $Pd(OAc)_2$-catalyzed reaction system, the yield was significantly enhanced to 60% (Table 1, entry 3). Obviously, $Cu(OAc)_2{\cdot}H_2O$ plays a

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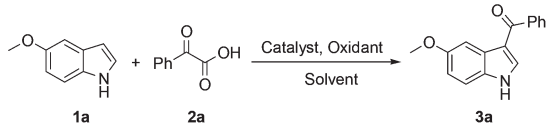
Table 1 Optimization of reaction conditions[a]



1a 2a 3a

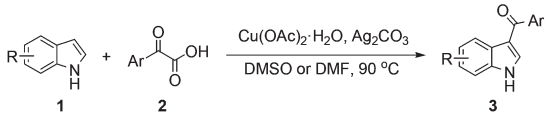
Entry	Catalyst	Oxidant (equiv.)	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	Ag_2CO_3(2)	DMF	8
2	$PdCl_2$	Ag_2CO_3(2)	DMF	22
3[c]	$Pd(OAc)_2$/$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3(2)	DMF	60
4	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3(2)	DMF	71
5	$Cu(OAc)_2$	Ag_2CO_3(2)	DMF	70
6	$CuBr_2$	Ag_2CO_3(2)	DMF	65
7	$CuCl_2{\cdot}2H_2O$	Ag_2CO_3(2)	DMF	59
8	CuO	Ag_2CO_3(2)	DMF	66
9	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3(2)	DMSO	71
10	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3(2)	NMP	70
11	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3(2)	DMAc	68
12[d]	$Cu(OAc)_2{\cdot}H_2O$	Ag_2CO_3(2)	DMSO	64
13	$Cu(OAc)_2{\cdot}H_2O$	—	DMSO	<5
14	—	Ag_2CO_3(2)	DMSO	<5

[a] Conditions: **1a** (0.8 mmol), **2a** (1.6 mmol), catalyst (20 mol%), oxidant, solvent (4 mL), 90 °C, 3 h, under air. [b] Isolated yields. [c] $Cu(OAc)_2{\cdot}H_2O$ (20 mol%) was added. [d] $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) was used.

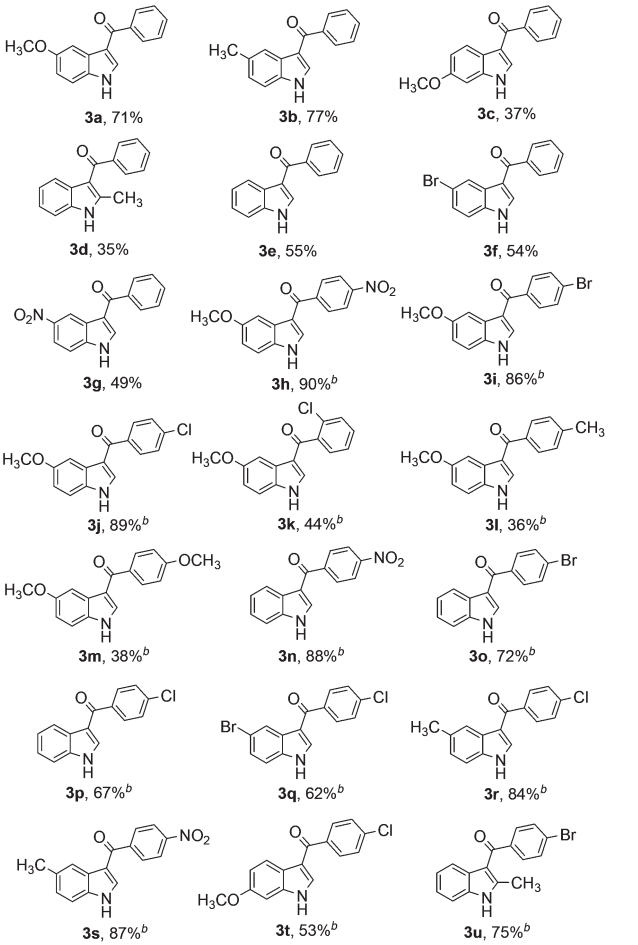
crucial role in the reaction. A subsequent study indicated that the acylation proceeded smoothly only in the presence of $Cu(OAc)_2{\cdot}H_2O$ without $Pd(OAc)_2$ to give the desired product **3a** in 71% yield (Table 1, entry 4). This result encouraged us to find an appropriate copper catalyst. Further studies indicated that $Cu(OAc)_2{\cdot}H_2O$ was superior to the other copper catalysts (Table 1, entries 5–8). Further optimization of solvents demonstrated that DMSO also promoted the reaction drastically (Table 1, entries 9–11). However, the reaction in DMSO resulted in a cleaner conversion into **3a** compared to that in DMF. The use of a reduced amount of catalyst gave rise to slightly low reactivity (Table 1, entry 12). However, no desired product was obtained in the absence of $Cu(OAc)_2{\cdot}H_2O$ or Ag_2CO_3, which indicated that both the copper catalyst and the silver oxidant were necessary for the formation of **3a** (Table 1, entries 13 and 14). Moreover, other silver oxidants, its loading and the reaction temperature were also examined in the reaction. The results are summarized in Table S1 (ESI†). Finally, we found that the reaction proceeds most efficiently in the presence of $Cu(OAc)_2{\cdot}H_2O$ (20 mol%) with 2 equiv. of Ag_2CO_3 in DMSO at 90 °C for 3 h (see Table S1, ESI† for details).

To explore the scope of the acylation reaction, the substituted indoles (**1**) were reacted with phenylglyoxylic acid under the optimized conditions. The results are summarized in Table 2. Notably, a variety of indoles underwent acylation with phenylglyoxylic acid smoothly to afford the corresponding products in moderate to good yields (**3a–g**). It was noticed that indoles with electron-rich groups (5-OCH_3 and 5-CH_3) were found to be favored in the reaction to deliver the desired products in 71% and 77% yield, respectively (**3a** and **3b**). However, 6-methoxyindole provided the target product only in 37% yield

Table 2 Scope of Cu-catalyzed decarboxylative acylation of indole[a]



1 2 3



[a] Conditions: **1** (0.8 mmol), **2** (1.6 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), Ag_2CO_3 (2 equiv.), DMSO (4 mL), 90 °C, 1.5–8 h, under air, isolated yields are given. [b] The reaction was carried out in DMF.

(**3c**). Additionally, 2-methylindole also afforded the product albeit in a relatively low yield due to the steric effect (**3d**). Also the acylation process is compatible with indoles bearing electron-deficient groups such as 5-Br and 5-NO_2, although only moderate yields were obtained (**3f** and **3g**).

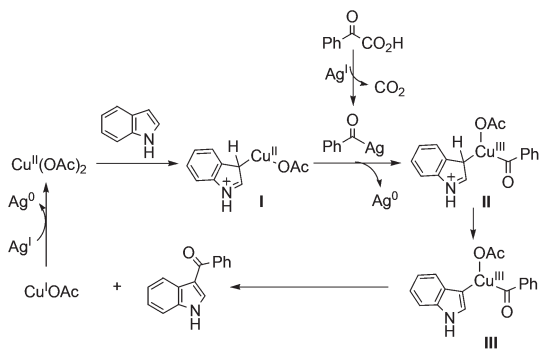
Subsequently, the scope of the α-oxocarboxylic acids (**2**) was also investigated under the optimized conditions. Unexpectedly, the products were obtained as a mixture of isomers with **3h** predominating besides C2-acylated product (4-nitrophenyl)-(5-methoxy-1*H*-indol-2-yl)methanone determined a combination of mixing ^{1}H NMR and ^{13}C NMR (see Fig. S1–S2, ESI†). Similar results were also obtained using other substituted phenylglyoxylic acids as acylating agents. However, the use of DMF instead of DMSO leads to the exclusive acylation at C3-position of indole.

Although the detailed reason was not clear, other reactions were performed in DMF. A series of functional groups including NO_2, Br, Cl, CH_3 and OCH_3 on the phenyl ring were tolerated, and the desired products were obtained in moderate to high yields (**3h–m**). It was observed that electron-deficient groups such as *p*-NO_2, *p*-Br and *p*-Cl exhibited high reactivity and gave high yields (**3h–j**), while electron-rich groups such as *p*-CH_3 and *p*-OCH_3 showed low reactivity and only gave 36% and 38% yield, respectively (**3l** and **3m**). *ortho*-Substituted phenylglyoxylic acid also provided the target product in 44% yield (**3k**). It is worth noting that the bromo and chloro groups on both indole ring and phenyl ring remained untouched, thereby providing an opportunity for further useful transformation. Gratifyingly, the electron-deficient phenylglyoxylic acids with *p*-NO_2, *p*-Br, and *p*-Cl groups proved to be good substrates and were successfully reacted with indoles bearing 5-Br, 5-CH_3, 2-CH_3 and 6-OCH_3 groups under the optimized reaction conditions, thus providing the corresponding products **3n–3u** in moderate to high yields.

To gain further insight into the reaction mechanism, the precipitate was collected by centrifugation and filtration after the reaction and was analyzed by XRD (X-ray powder diffraction). The significant diffraction peak was assigned to Ag^0 (see Fig. S3, ESI†), implying that Ag_2CO_3 additive can be considered as the terminal oxidant in the reaction.

Although the exact mechanism is still not clear, on the basis of the above experimental results and the literature,[13d,17] one plausible mechanism is proposed as shown in Scheme 1. The electrophilic cupration first occurred at the C3-position of indole forming the intermediate **I**, which subsequently underwent a transmetalation step with the acylsilver species formed by the silver-mediated decarboxylation of phenylglyoxylic acid, to afford the Cu(III) intermediate **II**, followed by rearomatization to generate the intermediate **III**. The subsequent reductive elimination provided the desired product and a Cu(I), which was reoxidized by Ag^I to regenerate a Cu(II) to finish the catalytic cycle.

In summary, we have described an efficient Cu-catalyzed decarboxylative C3-acylation of free (N–H) indoles with α-oxocarboxylic acids in combination with Ag_2CO_3 as the terminal oxidant. The reaction can be performed smoothly under air without strict exclusion of moisture and exhibited good functional group tolerance, which provides an attractive alternative to the existing synthetic methods of 3-acylindoles. Further investigation on the detailed reaction mechanism and studies on transition-metal-catalyzed C–H functionalization using α-oxocarboxylic acids as coupling partners are ongoing in our laboratory.



Scheme 1 Plausible reaction mechanism.

Acknowledgements

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