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Copper-promoted decarboxylative direct C3-acylation of N-substituted indoles with α-oxocarboxylic acids†

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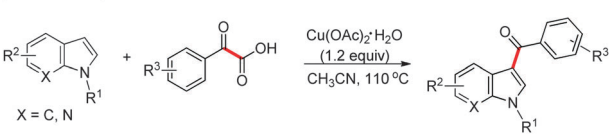
A novel and efficient Cu-promoted decarboxylative direct C3-acylation of N-substituted indoles with α-oxocarboxylic acids for the synthesis of 3-acylindoles was developed.

Transition-metal-catalyzed decarboxylative coupling has attracted a considerable interest in the past decade.[1] It is an effective synthetic method for C–C bond formations because the carboxyl group can direct the regioselectivity and the only waste product from the reaction is CO_2.[2] Extensive studies have been accomplished in this area since Pd-catalyzed decarboxylative Heck-type reactions of benzoic acids of olefination were reported by Meyers *et al.*[3] and Su *et al.*[4] Representative examples are Pd-catalyzed decarboxylative coupling of aryl halides with benzoic acids by Goossen *et al.*,[5] Wagner *et al.*[6] and biaryl coupling of aromatic carboxylic acids by Forgione *et al.*;[7] Cu-catalyzed decarboxylative coupling of potassium polyfluorobenzoates with aryl halides by Liu *et al.*;[8] propiolic acids with aryl halides or amines by Lee *et al.*,[9] You *et al.*,[10] and Jiao.[11] Recently, alternative approaches for decarboxylative acylations of aromatic C–H bonds with α-oxocarboxylic acids used as acyl sources were reported.[12–14] Goossen *et al.* first described Pd-catalyzed decarboxylative acylation of aryl bromides with potassium α-oxocarboxylates to afford diaryl ketones.[12] Shortly thereafter, Ge demonstrated a Pd-catalyzed decarboxylative *ortho*-acylation of acetanilides and phenylpyridines with α-oxocarboxylic acids *via* C–H bond activation.[13] Duan also reported a Pd-catalyzed decarboxylative acylation of cyclic enamides with α-oxocarboxylic acids.[14] Most recently, Kim proposed a Pd-catalyzed decarboxylative acylation of *o*-methyl ketoximes and phenylacetamides with α-oxocarboxylic acids *via* sp^2 C–H bond activation.[15] Meanwhile, Tan *et al.* developed a Pd-catalyzed decarboxylative *ortho*-acylation of *o*-methyl oximes with phenylglyoxylic acids.[16] However, transition-metal-catalyzed decarboxylative acylation on aromatic heterocyclic compounds or C-heteroatom bond formation is rarely explored.[17]

Acylated indoles are ubiquitous among biologically active natural products and pharmaceutical compounds like anti-diabetic, anticancer, and inhibitor of HIV-1 integrase.[18] Additionally, related indoles have even been employed as fulgides and optical switches,[19] and 3-acylindoles are valuable intermediates in a variety of functional group transformations.[20] The synthesis of 3-acylindoles has thus got considerable attention for over a century since the 3-position of indole is the premier site for electrophilic substitution.[21–26] The most classic methods for the preparation of 3-acylindoles are Friedel–Crafts reaction,[21] Vilsmeier–Haack reaction,[22] and indole Grignard reaction.[23] The other significant approaches include Ru-catalyzed formylation and Fe-catalyzed acylation of indoles by using anilines as the carbonyl source,[24] *N*-(2-haloacyl)pyridinium salt with indole,[25] Pd-catalyzed acyl chloride with 3-indolyzinc chloride.[26] These classic reactions require strict exclusion of moisture, stoichiometric Lewis acid promoters,[21c] or a protecting functional group on nitrogen,[21b] or large number of environmental unfriendly $POCl_3$ used.[22a,b] And, they cannot tolerate the sensitive functional group under harsh conditions in some cases.[23]

Herein, we wish to report a novel and mild Cu-promoted decarboxylative direct acylation of C(3)–H of N-substituted indoles with α-oxocarboxylic acids. The protocol has a broad substrate scope, simple reaction conditions, and good yields (Scheme 1).

Our initial efforts focused on the decarboxylation coupling between *N*-methylindole (**1a**) and benzoylformic acid (**2a**) to examine suitable reaction conditions, and the screening results are compiled in Table 1. When $Cu(OAc)_2 \cdot H_2O$ was used as the oxidant, Ag_2CO_3 exhibited the higher reactivity than $Pd(OAc)_2$ (Table 1, entries 1 and 2). According to C-3 arylation of indoles with benzoic acids,[2b] a Pd–Ag catalytic system was used for the



Scheme 1

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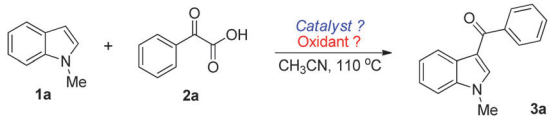
Table 1 Effect of catalyst and oxidant on the model reaction[a]



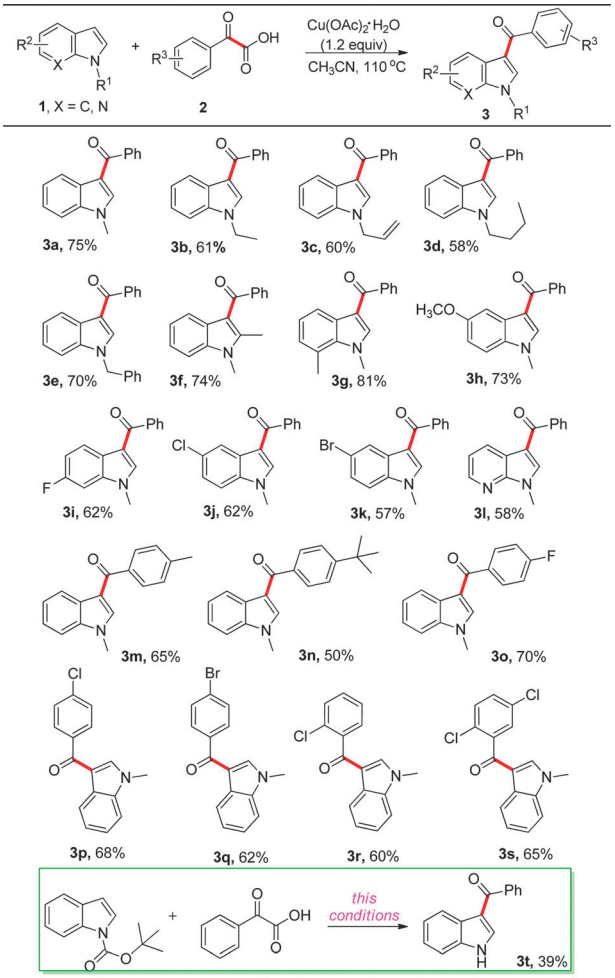
Entry	Catalyst	Oxidant	Yield[b] (%)
1	Ag_2CO_3	$Cu(OAc)_2·H_2O$	68
2	$Pd(OAc)_2$	$Cu(OAc)_2·H_2O$	64
3	$PdCl_2$	Ag_2CO_3	43
4	$Cu(OAc)_2·H_2O$	TBHP	40
5	$Cu(OAc)_2·H_2O$	H_2O_2	38
6	$Cu(OAc)_2·H_2O$	DTBP	35
7	$Cu(OAc)_2·H_2O$	$K_2S_2O_8$	31
8	$Cu(OAc)_2·H_2O$	$(NH_4)_2S_2O_8$	26
9	$Cu(OAc)_2·H_2O$	$PhI(OAc)_2$	NR
10	$Cu(OAc)_2·H_2O$	DDQ	NR
11	$Cu(OAc)_2·H_2O$	BQ	NR
12	—	$Cu(OAc)_2·H_2O$	75

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), catalyst (10 mol%), oxidant (1.2 equiv.), CH_3CN (2.0 mL), 110 °C, 10 h. [b] Isolated yields.

reaction; however, the result was not satisfactory (Table 1, entry 3). Subsequently, further exploration of a number of oxidants indicated that TBHP was superior to the others when $Cu(OAc)_2·H_2O$ was used as catalyst, as is shown in Table 1, entry 4. Other oxidants, H_2O_2, di-*tert*-butyl peroxide (DTBP), $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ showed lower efficiency (Table 1, entries 5–8). No desired product was obtained with $PhI(OAc)_2$, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and 1,4-benzoquinone (BQ) used as oxidants (Table 1, entries 9–11). It is delighted to find that 1.2 equiv. of $Cu(OAc)_2·H_2O$ could promote the reaction efficiently without other transition metal as catalyst (Table 1, entry 12).

Then, various promoters were tested for the reaction and the results are listed in Table S1 (ESI†). The promoter plays an important role in the reaction. Optimization of the promoters demonstrated that $Cu(OAc)_2·H_2O$ was most effective, providing the desired product **3a** in the highest yield. Lower yields of **3a** were obtained by using $Cu(NO_3)_2·3H_2O$, $(NH_4)_2S_2O_8$, Ag_2CO_3 and $CuSO_4·5H_2O$ as promoters. Trace amount of **3a** was obtained in the presence of $CuBr_2$ or $Cu(acac)_2$. No desired product was detected by using $Cu(OH)_2$, $CuCl_2·2H_2O$, Cu, $K_2S_2O_8$, and TBHP (Table S1, ESI,† entries 1–12). Of the solvents tested on the model reaction, CH_3CN proved particularly suitable. Chlorobenzene, methanol, dioxane, DMSO, toluene, *p*-xylene, CH_3CH_2OH and EtOAc were subsequently inferior. Only a trace amount of **3a** was observed when the reaction was carried out in CH_3NO_2 or DCE. No desired product was found in THF, NMP or H_2O (Table S1, ESI,† entries 13–25). Increasing the amount of $Cu(OAc)_2·H_2O$ did not increase the yield of **3a**. The effect of temperature on the reaction was also surveyed and the results showed that the yield of **3a** was not improved when the reaction temperature was increased to 120 °C, but a lower yield was observed when the reaction was performed at less than 100 °C. After surveying a variety of parameters, we found that 1.2 equiv. $Cu(OAc)_2·H_2O$ in CH_3CN at 110 °C for 10 h is the optimal condition (see Table S1, ESI† for details).

To examine the scope of the substrates, the reactions of N-substituted indoles with benzoylformic acid (**2a**) were performed under the optimized reaction conditions. The results are summarized in Scheme 2. As can be seen from Scheme 2, the reactions of **2a** with different N-substituted indoles could proceed well and offered

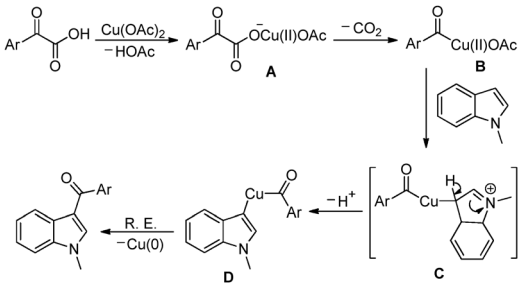


[a]Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), $Cu(OAc)_2·H_2O$ (0.30 mmol), CH_3CN (2.0 mL), 110 °C, 10 h. [b] Isolated yields.

Scheme 2 The reactions of N-substituted indoles with 2-oxo-2-arylcarboxylic acids.[a]

the desired products in good yields. A wide range of indoles bearing substituents on the N-atom and aromatic rings were investigated. The results demonstrated that both electron-donating and electron-withdrawing groups were tolerated. *N*-Methylindole, *N*-ethylindole, *N*-allylindole, *N*-*n*-butylindole and *N*-benzylindole coupled with **2a** smoothly and gave the desired products in 58–75% yields (Scheme 2, **3a–e**). Notably, the *N*-methylindoles with a methyl group in the C-2 or C-7 position were well tolerated and the desired products (**3f** and **3g**) were obtained in 74% and 81% yields, respectively. 5-Methoxy-*N*-methylindole, 6-fluoro-*N*-methylindole, 5-chloro-*N*-methylindole, and 5-bromo-*N*-methylindole could also couple with **2a** to give the desired products (**3h–k**) in 57–73% yields. It is important to note that *N*-methyl-pyrrolo[2,3-b]pyridine gave the corresponding product **3l** in 58% yield. However, a high electron-deficient *N*-methyl-5-cyanoindole was ineffective in the reaction. Notably no desired product was observed when free NH-indole was used under the present reaction conditions.

The reactions of various 2-oxo-2-arylacetic acids with *N*-methylindole (**1a**) are also presented in Scheme 2. 2-Oxo-2-arylacetic acids with an electron-donating group, such as Me or *t*-Bu on the *para*-position of the benzene ring could react with **1a** and afford the corresponding decarboxylative acylation products **3m** and **3n**



Scheme 3 Proposal reaction mechanism.

in 65% and 50% yields respectively. A series of functional groups including F, Cl and Br were tolerated on the 2-oxo-2-arylacetic acids under the optimal reaction conditions, and the desired products (**3o–q**) were obtained in 62–70% yields. The reaction was not sensitive to steric hindrance as the reaction of **1a** with 2-(2-chlorophenyl)-2-oxoacetic acid, and 2-(2,5-dichlorophenyl)-2-oxoacetic acid, providing the corresponding products **3r** and **3s** in 60% and 65% yields respectively. When *tert*-butyl 1*H*-indole-1-carboxylate was used, a product **3t** was generated in 39% yield (Scheme 2). It should be noted that the reactions of methyl-2-oxo-2-phenylacetate and ethyl-2-oxo-2-phenylacetate with *N*-methylindole also generated **3a** in 41% and 38% yields under the present reaction conditions. Meanwhile, we found that the esters can be partially hydrolyzed into the corresponding acids under the present reaction conditions. In all cases, the decarboxylative acylation occurred exclusively in the C-3 position of indoles determined by ^{1}H NMR.

Although the exact mechanism of this decarboxylative coupling is still not clear, on the basis of our results and literature,[2b,27] a plausible mechanism is proposed and shown in Scheme 3. α-Oxocarboxylic acid initially reacts with $Cu(OAc)_2{\cdot}H_2O$ to form a Cu(II) carboxylate **A**, and then an acyl Cu(II) species **B** is generated *via* a decarboxylation process. The obtained **B** can undergo attack at the C3-position of indole to generate **C**, which is followed by a rearomatization *via* C–H bond cleavage to **D**. The reductive elimination of **D** affords the C3-acylation product and Cu(0).

In summary, we have demonstrated a novel and efficient Cu-promoted decarboxylative direct acylation of indoles with α-oxocarboxylic acids. In the presence of $Cu(OAc)_2{\cdot}H_2O$, a variety of α-oxocarboxylic acids reacted with N-substituted indoles to generate the corresponding C-3 acylated indoles exclusively in good yields. The protocol has a broad substrate scope and simple reaction conditions. The detailed reaction mechanism and further applications are currently under way.

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