Cu-catalyzed cross-coupling of methyl ketones and pyridin-2-amines for the synthesis of N-(2-pyridyl)-α-ketoamides

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Abstract
An efficient copper-catalyzed strategy for the synthesis of α-ketoamides via cross-coupling of methyl ketones and pyridin-2-amines is described. This transformation has provided a simple process for the formation of C−N and C=O bonds to prepare α-ketoamides, which are important substrates and intermediates for the preparation of fine chemicals. The reaction mechanism is investigated, which suggests that the reaction proceeds via a radical pathway.

Keywords
cross-coupling, Cu-catalyzed, methyl ketones, pyridin-2-amines, α-ketoamides

Introduction
Amides are very common in nature and technology as structural materials, and exhibit a wide range of biological functionalities. Many drugs contain amide moieties, including paracetamol, amoxicillin, penicillin, zolpidem, and cephalosporins (Figure 1). Such compounds have attracted the attention of scientists because of their important applications in pharmaceuticals, natural products, agrochemicals, and biologically active molecules. Therefore, it is not surprising that significant effort has been directed toward developing synthetic transformations for the preparation of amides. Several classic and successful synthetic approaches, such as the Beckmann, Ritter, Ugi, and Staudinger reactions, have been developed for the synthesis of amide derivatives. Recently, transition-metal-catalyzed reactions have become powerful tools for the formation of carbon-nitrogen bonds to prepare amides. Ahmed and colleagues reported a unique dimethyl sulfoxide (DMSO)-promoted oxidative amidation approach for synthesis of α-ketoamides from 2-oxoaldehydes and aliphatic amines (Scheme 1(a)); Zhang and Wang⁷ and Wan and colleagues⁸ independently developed a facile TBHP/I₂-promoted oxidative coupling reaction of acetophenones with aliphatic amines for the synthesis of α-ketoamides (Scheme 1(b)); Kaliappan and colleagues⁹ has described a one-pot copper-catalyzed biomimetic route to N-heterocyclic amides from methyl ketones and pyridin-2-amines (Scheme 1(c)). Although numerous investigations in this field have been conducted, the development of a new strategy is still highly desirable for the construction of α-ketoamides, which are an important class of amide compounds with the general structure (R¹C(O)NHR₂).

Very recently, we have developed approaches for the formation of C−C, C−N, and C−O bonds to synthesize heterocycles. Our current interest is focused on the formation of C−N and C−O bonds in order to synthesize N-(2-pyridyl)-α-ketoamides from methyl ketones and pyridin-2-amines (Scheme 1(d)).

Results and discussion
In our initial study, pyridin-2-amine (1a) and acetophenone (2a) were chosen as model substrates to optimize the reaction conditions. The results are summarized in Table 1. In a typical procedure, 1a (0.5 mmol), 2a (0.6

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mmol), Cu(OAc)₂ (5 mol%), and AcOH (5 mol%) were stirred in DMSO using O₂ as the oxidant at 120°C for 8 h. Interestingly, the products 3a and 4a were formed in 18% and 32% yields, respectively (Table 1, entry 1). We next attempted to improve the yield of 3a by using different catalysts. Thus, as catalysts CuCl₂, Cu(OTf)₂, CuI, and CuBr were employed (Table 1, entries 2–5). Among them, Cu(OAc)₂ was the most efficient catalyst. Subsequently, our investigation focused on the synthesis of 3a by testing various additives. The product 3a was formed in 14% and 11% yields by using trifluoroacetate (TFA) or tosylic acid (TsOH) (Table 1, entries 6 and 7).

To our delight, an improved yield was obtained by the addition of KI and acetic acid (AcOH) to the reaction (Table 1, entry 8). When 4a–i were formed in poor yields. A variety of substituents, such as 4-Et, 3-Me, 2-Me, 4-nBu, 3,4-dimethoxy, 3,4-dimethyl, and 4-F, on the benzene ring of the methyl ketones were well-tolerated for the synthesis of the 3 compounds under the optimized conditions. However, the byproduct 4e was formed in 43% yield, while only a trace of 3e was detected. Subsequently, substituted pyridin-2-amines were tested. The product 3j–n were afforded in 53%–73% yields.

Mechanism
To gain insight into the mechanism of the Cu-catalyzed transformation, control experiments were performed. To prove that an organic radical species was involved in the reaction, we carried out the radical trapping reactions by adding a radical-trapping reagent (TEMPO) (Scheme 2(a)). The result indicated that the reaction had been inhibited and that a radical process was involved in this Cu-catalyzed strategy. In addition, the reaction of 1a with 2-oxo-2-phenylacetaldehyde was also carried out and the products were detected by gas chromatography–mass spectrometry (GC-MS) analysis. It was found that 2-oxo-2-phenylacetaldehyde may form as an intermediate in the reaction (Scheme 2(b)). Product 3a' with an 18O in the carbonyl group was not observed in the presence of H₂O. On the basis of the above experiment results, a plausible mechanism is described in Scheme 3. Initially, radical intermediate A is generated from 2a via a single electron transfer (SET) oxidation in the presence of the Cu(II) species and TBHP, which was further oxidized to intermediate B. Next, intermediate C is formed by protonation of intermediate B; subsequent nucleophilic attack of 1a gave the intermediate D. Finally, intermediate D underwent dehydration oxidation to give the product 3a.39,40

Conclusions
In conclusion, we have developed a novel and straightforward Cu-catalyzed reaction to prepare amides via oxidative coupling of methyl ketones and pyridin-2-amines. This strategy represents a simple process for the formation of C–N and C=O bonds and provides a new route for the synthesis of α-ketoamides which are common structural motifs in natural products and pharmaceuticals. The mechanism was investigated, which suggested that the reaction occurs via a radical pathway. Further studies on the applications and development of amides are underway in our laboratory.
Table 1. Optimization of the reaction conditions.\(^a\)

| Entry | Catalyst     | Additive | Oxidant | Solvent | Yield (%)\(^b\) |
|-------|--------------|----------|---------|---------|-----------------|
| 1     | Cu(OAc)\(_2\) | AcOH     | O\(_2\) | DMSO    | 18 32           |
| 2     | CuCl\(_2\)   | AcOH     | O\(_2\) | DMSO    | <5 19           |
| 3     | Cu(OTf)\(_2\) | AcOH     | O\(_2\) | DMSO    | trace 16        |
| 4     | CuI          | AcOH     | O\(_2\) | DMSO    | – –             |
| 5     | CuBr         | AcOH     | O\(_2\) | DMSO    | – –             |
| 6     | Cu(OAc)\(_2\) | TFA      | O\(_2\) | DMSO    | 14 27           |
| 7     | Cu(OAc)\(_2\) | TsOH     | O\(_2\) | DMSO    | 11 30           |
| 8     | Cu(OAc)\(_2\) | AcOH/KI  | O\(_2\) | DMSO    | 22 25           |
| 9     | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | O\(_2\) | DMSO    | 34 13           |
| 10    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NBr | O\(_2\) | DMSO    | 26 <10          |
| 11    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | TBHP   | DMSO    | 47 20           |
| 12    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | DDQ    | DMSO    | trace trace     |
| 13    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | K\(_2\)S\(_2\)O\(_8\) | DMSO    | trace trace     |
| 14    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | TBHP   | toluene | 62 11           |
| 15    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | TBHP   | dioxane | 33 15           |
| 16    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | TBHP   | DMF     | 36 18           |
| 17    | Cu(OAc)\(_2\) | AcOH/n-Bu\(_4\)NI | TBHP   | DMA     | 31 23           |

\(^a\)Reaction conditions: 1a (0.5 mmol), 2a (0.6 mmol), catalyst (5 mol%), additive (5 mol%), oxidant (2.0 equiv), solvent (2 mL), 120°C, 8 h.

\(^b\)Determined by gas chromatography (GC) analysis.

Table 2. Cu-catalyzed synthesis of amides.\(^a\)

| R          | Ar   | Cu(OAc)\(_2\), AcOH, TBHP, 8 h toluene, n-Bu\(_4\)NI, 120°C | 3a 54 % | 3b 51 % | 3c 42 % | 3d 63 % | 3e < 5 % | 4e 43 % | 3f 40 % | 3g 67 % | 3h 56 % | 3i 49 % | 3j 73 % | 3k 66 % | 3l 70 % | 3m 53 % | 3n 56 % |
|------------|------|-------------------------------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|

\(^a\)Isolated yields

\(^\)Isolated yields.
Experimental section

Commercially available chemicals were purchased from commercial sources and used without further purification. Fourier transform infrared spectra (FTIR) were recorded on a Perkin-Elmer Spectrum 100 Series with pressed KBr pellets. The 1H and 13C NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer (100 MHz for carbon). Mass spectra recorded were obtained on an electro-spray ionization mass spectrometry (ESIMS). Elemental analyses were performed with an elemental analyzer. GC-MS was obtained using electron ionization. Thin-layer chromatography (TLC) was performed using commercially prepared 100–400 mesh silica gel plates.

Synthesis of 3a according to the following procedure: A 25–mL schlenk tube was charged with a stirring bar, and added pyridin-2-amine 1a (0.5 mmol, 1.0 equiv), acetophenone 2a (0.6 mmol, 1.2 equiv), TBHP (2.0 equiv), n-Bu4NI (5 mol%), AcOH (5 mol%), Cu(OAc)2 (5 mol%), and toluene (2 mL). The reaction was allowed to stir at 120°C until the complete consumption of 3a was monitored by TLC analysis. The reaction mixture was purified by TLC silica gel plate (eluent: petroleum ether: ethyl acetate, V: V = 4: 1) and then extracted with EtOAc. The solvents were dried in vacuo to afford the pure product.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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