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Copper(I)-catalysed aerobic oxidative selective cleavage of C—C bond with DMAP: Facile access to *N*-substituted benzamides

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ABSTRACT

A base/DMAP system for efficient oxidative cleavage of C(CO)–C(alkyl) bond to generate *N*-substituted benzamides has been developed in the presence of copper(I) chloride. The usage of inexpensive copper catalyst, broad substrate scope, mild conditions make this protocol very practical. More importantly, this reaction provides an alternative approach for the construction of useful *N*-substituted benzamides.

The increasing significance of amide in valuable natural products and small organic compounds has prompted chemists to develop novel methods for their efficient synthesis during the past decades [1]. Typically, pyridyl benzamides play an important role in many biological activities, such as luciferase inhibitors, antiulcer agents, antifungal agents, glucokinase activators, etc [2]. Traditional methods of amide synthesis relies on preactivation of carboxylic acid [3] either by using acetyl chloride or coupling reagents. However, these methods have their own drawbacks which include requirements of stoichiometric excess of reagents, expensive coupling reagents, waste production and low yields. Over the past decades, the transition metals [4] and metal-free [5] catalytic C—C bond cleavage for the synthesis of amide have been developed to improve the above issues. Three strategies have been recently reported to cleave the C—C single bonds: (1) developing functional fragments to increase C—C single bond reactivities; [6] (2) finding special catalytic systems to assist C—C single bonds by decreasing activation energy; [7] (3) designing chelation activated method to increase reactivities of C—C bond [8]. Although the great methods have been improved in cleavage of C—C bonds, some developed protocols face the limited substrate scopes, expensive transition-metal catalysts and the harsh reaction conditions[2] (Scheme 1).

The synthesis of pyridyl benzamides have been a booming topic and have had rapid advancement. Recently, the copper catalyzed aerobic oxidation [9] and oxygenation reaction with molecular oxygen has had rapid development. Considering the significance of *N*-heterocyclic amides in different areas, the development of efficient synthetic approaches for their synthesis of ketones through C(CO)—C bond cleavage remains challenging tasks. Last several years, pyridyl benzamides have received considerable attention. In 2014, Huang et al. reported copper(I)-catalysed oxidative C—N coupling of 2-aminopyridine with terminal alkynes featuring bond cleavage promoted by visible light [11]. Subsequently, an elegant work on Cu-catalyzed aerobic oxidative C(CO)—C bond cleavage of phenylacetic acids have been developed [12]. Moreover, Ye group also disclosed a Ce(III)-catalyzed protocol to afford pyridyl benzamides [13]. Despite the fact that several elegant examples have been described, new pathways for ketones promoted C—C bond formation are still highly desirable. In very recent times, a few examples about ketones have been reported to cleave C(CO)-C bond under O_2 atmosphere [14]. Inspired by previous reported protocols and thoughts, we reported a novel strategy for *N*-substituted benzamides formation

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[2] delete (scheme 1)
[3] C(CO)–C(alkyl) bond cleavage

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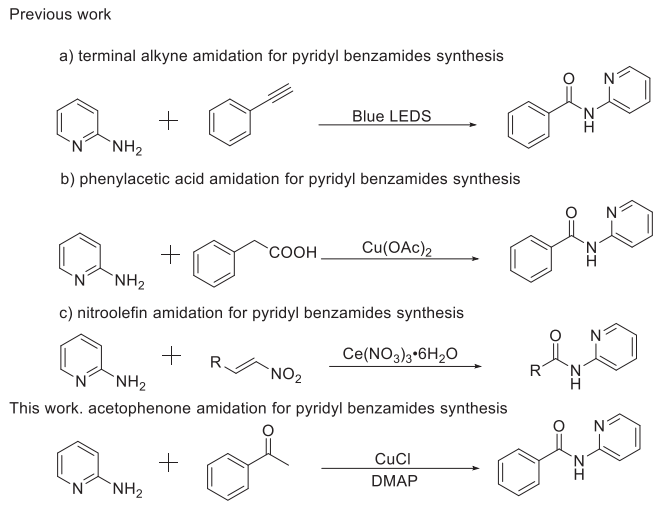


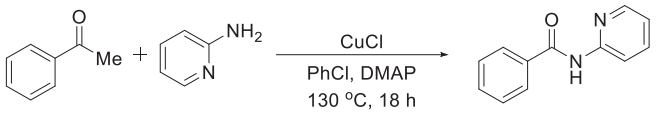
Scheme 1. Different transformations for pyridyl benzamides.

from aryl ketones and 2-aminopyridine under Cu(I)-catalyzed aerobic oxidative in the presence of DMAP[1]. DMAP is one of the most important organic mild bases, which can promote the cleavage of C—C bond efficiently. Fortunately, numerous aryl ketones have been demonstrated to be active substrates in this novel strategy, thus greatly broaden the substrate scope. A novel mechanism and the detailed mechanistic studies are also presented.

We firstly selected acetophenone (**1a**) and 2-aminopyridine (**2a**) as the model substrates to examine various reaction conditions (Table 1). It was found that the catalyst and solvent critically affect the reaction efficiency. As we can see, copper salts demonstrated good activities on this novel transformation. The reaction of **1a (**0.2 mmol, 1 equiv) with **2a** (0.4 mmol, 2 equiv) was conducted in the presence 0.04 mmol of CuCl as catalyst, 3.0 equiv of pyridine in PhCl under O_2 at 130 °C, and the desired product (**3aa**) was obtained in 56% yield (Table 1, entry 1). Then a variety of copper salts were attempted, the results showed that CuCl was more efficient than other copper salts such as CuBr and $CuCl_2$ (Table 1, enties 1–3). We also studied whether the reaction could conduct under N_2 or in air atmosphere. The results showed that O_2 was better than N_2 and air, and small amount or no product was detected under air or N_2 (Table 1, entries 1, 4–5). When the solvent was changed into DMSO or DMF, only trace desired product **3aa** was detected, while xylene gave the desired product in 50% yield, showing that PhCl was the optimal choice (Table 1, entry 6–8). When temperature was decreased to 110 °C, the yield of desired product **3aa** reduced correspondingly (Table 1, entry 9). Next, we optimized the ligand, the result indicated that pyridine was the superior choice to 1,10-phenanthrolin and L-proline (Table 1, entry 10–12). Among the various additives we screened, DMAP was the most effective, affording **3aa** in the highest yield of 78% (Table 1, entry 13–16). We speculate that the alkalinity of the reaction system was enhanced after introduction of DMAP which was suitable for this reaction. Finally, the optimized reaction conditions are as follows: acetophenone **1a** (0.2 mmol), 2-aminopyridine **2a** (0.4 mmol), CuCl (20 mol%), pyridine (3 equiv), and DMAP (1 equiv) in PhCl (2 mL) at 130 °C under oxygen.

With the optimized reaction conditions in hand, we then investigated the substrate scope of the acetophenone derivatives as a coupling partner (Scheme 2). Both electron-rich and electron-withdrawing groups on the ring of acetophenone could be performed smoothly to afford the corresponding products in available yields

Table 1
Optimization of reaction conditions[a].



1a **2a** **3aa**

Entry	Catalyst	Ligand	Solvent	Additive	Yield (%)[b]
1	CuCl	Py	PhCl		56
2	CuBr	Py	PhCl		nd
3	$CuCl_2$	Py	PhCl		35
4[c]	CuCl	Py	PhCl		nd
5[d]	CuCl	Py	PhCl		17
6	CuCl	Py	DMSO		Trace
7	CuCl	Py	DMF		Trace
8	CuCl	Py	Xylene		50
9[e]	CuCl	Py	PhCl		39
10	CuCl	1,10-Phen	PhCl		28
11	CuCl	L-Proline	PhCl		35
12	CuCl	none	PhCl		45
13	CuCl	Py	PhCl	DMAP	78
14	CuCl	Py	PhCl	HOAc	12
15	CuCl	Py	PhCl	Na_2CO_3	27
16	CuCl	Py	PhCl	$NaHCO_3$	39

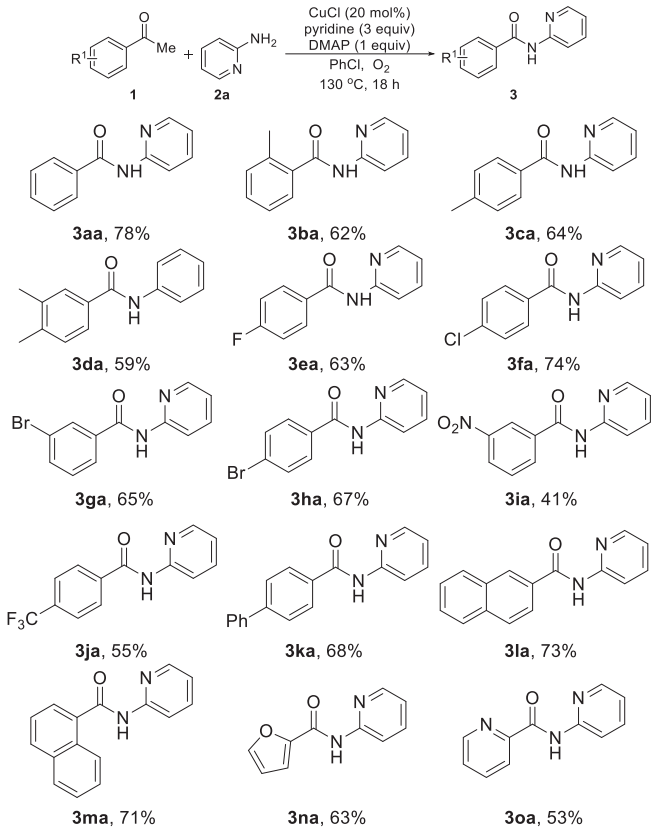
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (20 mol%), ligand (0.6 mmol) and additive (0.2 mmol) in solvent (2 mL) was stirred at 130 °C for 18 h.
[b] Isolated yields.
[c] Under N_2 atmosphere.
[d] Under air atmosphere.
[e] At 110 °C. Py = pyridine; 1,10-phen = 1,10-phenanthrolin; DMAP = 4-dimethylaminopyridine.

(Scheme 2, 3aa-3oa). Whether mono methyl acetophenone or multi methyl acetophenone were all well tolerated in this system (Scheme 2, 3ba-3da). We found that a variety of halogen-containing acetophenones are compatible with the reaction conditions, such as fluorine acetophenone, chlorine acetophenone and bromine acetophenone (Scheme 2, 3ea-3ha). As a challenging substrate, acetophenones bearing NO_2-, CF_3- and Ph- groups afforded the corresponding amides in moderate to good yields (Scheme 2, 3ia-3ka). In addition, naphthalene moieties also underwent the reaction to furnish the corresponding products, affording the corresponding products in 73% and 71% yields respectively (Scheme 2, 3la-3ma). Moreover, other heteroaryl ketones including 1-(2-furanyl)-ethanon, 1-(2-pyridinyl)-ethanon also successfully endured the reaction to furnish the desired pyridyl-amide products (Scheme 2, 3na-3oa).

Next, the substrate scope of various 2-aminopyridines was also investigated by using **1a** as a partner (Scheme 3). 2-aminopyridines with electron-withdrawing group or electron-donating group on the phenyl ring also could be performed, and yields of corresponding products range from 35% to 83% (Scheme 3, 3aa-3al). Interestingly, highly fluorinated 2-aminopyridine was also proved to be reactive (Scheme 3 **3aj**). As a challenging substrate, 2-aminopyridine with a nitro substituent was successfully applied to the reaction (Scheme 3 **3ak**).

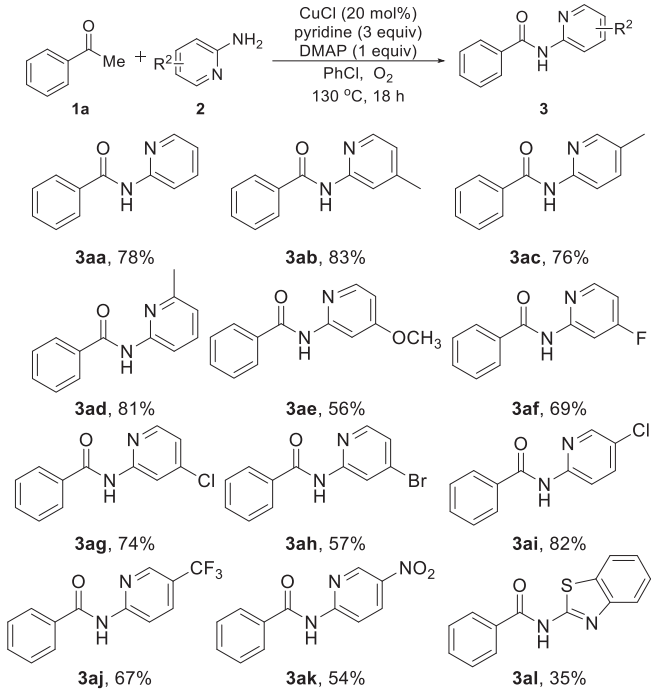
In order to further explore possible reaction mechanism, a set of control experiments were performed (Scheme 4). To examine the absence of radical involvement, the reaction was performed under the standard conditions in the presence of di-*tert*-butylhydroxytoluene (BHT) and 2,2,6,6 tetramethylpiperidine-1-oxyl (TEMPO) as a radical trapping reagent. The oxidation was greatly suppressed and only a trace amount of **3aa** was observed, which might indicate the possibility of a radical mechanism.

[1] (Scheme 1).

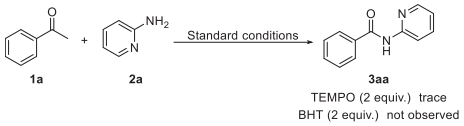


Scheme 2. Substrate scope of the reaction with aryl ketones.

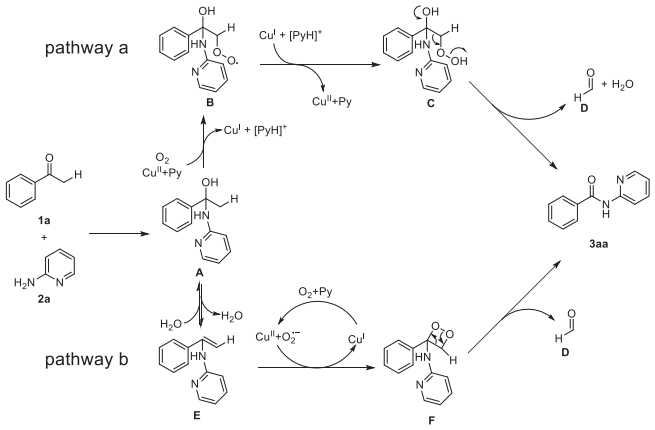
On the basis of the above results and previous reports [15], two possible reaction pathway was proposed for the reaction of acetophenone with 2-aminopyridine in the synthesis of pyridyl benzamides (Scheme 5). Initially, acetophenone (**1a**) and 2-aminopyridine (**2a**) generate intermediate **A** by the nucleophilic addition [16]. In pathway a, superoxide intermediate **B** is formed in the presence of Cu salt and oxygen *via* single electron transfer (SET). Then, the SET reduction and subsequent protonation of intermediate **B** gives hydroperoxide intermediate **C** [17] by Cu^{I} and $[PyH]^{+}$. The cleavage of the C—C bond occurred during the rearrangement of intermediate **C** [18], resulting in the desired product **3aa** along with aldehyde **D** and H_2O. In pathway b, enamine **E** is generated reversibly by the dehydration of intermediate **A**. Subsequently, dioxetane intermediate **F** is produced from enamine **E** in a Cu(II)/oxygen system in the presence of pyridine. Eventually, the desired product **3aa** and byproduct aldehyde **D** are formed by the C—C bond and O—O bond cleavage of dioxetane intermediate **F**.



Scheme 3. Scope of the reaction with 2-aminopyridines.



Scheme 4. Controlled experiments.



Scheme 5. Plausible mechanistic pathway.

In summary, a facile and highly efficient method has been successfully developed for efficient oxidative cleavage of C(CO)—C (alkyl) bond to generate *N*-substituted benzamides. The synthesis was carried out *via* copper(I)-catalysed aerobic oxidative of acetophenone and 2-aminopyridine in the presence of DMAP under mild conditions. A series of structurally diverse products could be effectively obtained using DMAP as additive in the presence of CuCl. The usage of inexpensive copper catalyst, broad substrate scope, mild conditions make this protocol be very practical.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153199.

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