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COMMUNICATION

Copper-catalyzed one-pot oxidative amidation of alcohol to amide *via* C-H activation

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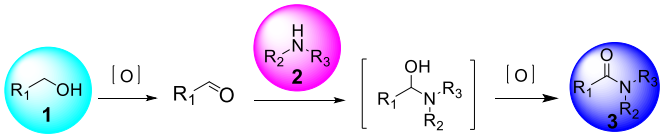
A one-pot oxidative amidation of both aliphatic and aromatic alcohols with *N*-chloroamines, prepared *in situ* from many types of primary and secondary amines, was developed. This cross-coupling reaction integrates alcohol oxidation and amide bond formation, which are usually accomplished separately, into a single operation. And it was green, simple and convenient, which has a wide substrate scope and makes use of cheap, abundant, and easily available reagents. The practical value of this method is highlighted through the synthesis of high-profile pharmaceutical agents, acetylprocainamide.

The formation of amide bonds is one of the most often used organic reactions due to the extensive presence of this functional group in natural products, pharmaceutical compounds, and synthetic polymers.[1] Conventionally, amides are synthesized by the reaction of an amine with carboxylic acid, which needs either coupling reagent [2] or conversion into more reactive derivatives.[3] However, these methods have several common shortcomings, such as poor atom-efficiency, use of hazardous reagents, and generation of wastes which cause environmental problems. To solve these problems, alternative methods for amide synthesis were developed, such as name reactions like the Schmidt reaction,[4] the Beckmann rearrangement,[5] and Ugi reaction.[6] More recent approach has considered the use of direct oxidative amidation from aldehydes.[7] However, these methods require the use of expensive transition metals as catalyst, and the use of aldehydes can be troublesome due to their inherent reactivity.

From the recent perspective of green chemistry, it remains a great challenge to develop a general and efficient method for the synthesis of amide. The direct oxidative amidation of alcohols can be a potentially attractive method due to the use of cheap, abundant and stable starting materials.[8] To date, the oxidative amidation of alcohols is essentially promoted by homogeneous or heterogeneous catalysts, such as Ru- or Rh-based transition metal complexes,[9] and Ag- or Au-based supported catalysts.[10] Usually, these strategies consist of the oxidation of an alcohol to the corresponding aldehyde that reacts with an amine and then further oxidize the hemiaminal to the desired amide (Scheme 1).



Scheme 1 Oxidative amidation of alcohols with amines

In order to compete with those techniques involving expensive metals, studies on zinc- or copper- or iron-catalyzed oxidative amidation of alcohols have been developed.[11-13] In 2013, Wu et al. reported the zinc-catalyzed oxidative amidation of benzyl alcohols (Scheme 2a).[11] Similar approach using copper or iron was developed (Scheme 2b).[12, 13] However, these methods have several drawbacks, such as the formation and stability of the hemiaminal intermediate, the use of expensive transition metal catalysts, and the limited substrate scope. Therefore, it remains a great challenge to develop new methods to synthesis amide. The direct conversion of C-H bonds into C-N bonds appears to be a critical but appealing challenge in organic chemistry. Recently, Wan [14] and Wang [15] reported the formation of C-N bond *via* C-H aldehyde bond activation. In 2013, Gaspa et al. used this method to develop the iron-catalyzed amidation of *N*-chloramines, prepared from amine, which needed the use of 5 equiv of alcohols to obtain good yields (Scheme 2c). [16] However, these methods outlined above shared a common drawback, which was that they showed excellent activity only with benzyl alcohols. Aliphatic alcohols did not perform well in their system. Herein, we report an efficient and green one-pot procedure for the direct amidation of both aliphatic and aromatic alcohols with *N*-

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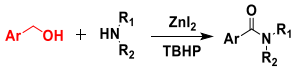
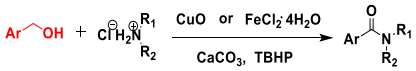
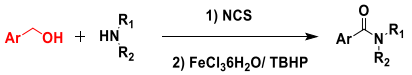
a) Zinc-catalyzed oxidative amidation of benzyl alcohols to amides (Wu et al.) [11]



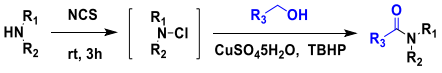
b) Copper- or iron-catalyzed oxidative amidation of benzyl alcohols to amides (Bantreil et al.) [12, 13]



c) Iron-catalyzed oxidative amidation of benzyl alcohols to amides (Gaspa et al.) [16]



d) Copper-catalyzed oxidative amidation of alcohols to amides (this work)



R3=aliphatic and aromatic alcohols
R1, R2=mono- and disubstituted amines

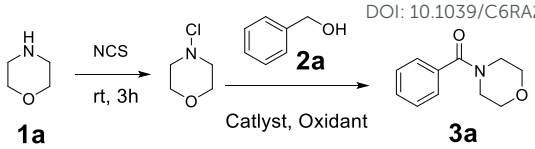
Scheme 2 Metal-catalyzed oxidative amidation of alcohols with amines

chloroamines, which were prepared from amines and without purification, catalyzed by easily accessible copper salts under base-free conditions (Scheme 2d).

At the beginning, morpholine **1a** (1 equiv.) was treated with *N*-chlorosuccinimide (NCS) (1.1 equiv.) in acetonitrile at room temperature for 3h, and then benzyl alcohol **2a** (1.2 equiv.), $Cu(OAc)_2$ (10 mol%) and TBHP (70 wt% in water, 5 equiv.) were added to the reaction mixture under 80°C to generate the amide product **3a** in only 30% yield (Table 1, entry 1). In order to improve the yield of the product, different parameters such as catalyst, oxidant and stoichiometric mole ratio of reactants were examined. Firstly, different catalysts were used instead of $Cu(OAc)_2$ to test the reaction and $CuSO_4{\cdot}5H_2O$ performed best among these catalysts with a yield of 62% (Table 1, entries 1-5). Then different oxidants were used to evaluate the reaction. When we used TBPB as an oxidant, the yield of the product was decreased apparently (Table 1, entry 6). And the product obtained only in trace when we used H_2O_2 or *m*-CPBA as oxidant (Table 1, entries 7-8). In the absence of an oxidant, there was no product observed (Table 1, entry 9). When the amount of catalyst increased to 20 mol%, the yield of product was improved significantly (Table 1, entry 10). And it was unnecessary to continue to increase the amount of catalyst (Table 1, entry 11). The decrease in the amount of TBHP from 5 equiv. to 3 equiv. led to a collapse of the yield (Table 1, entry 12).

With optimized reaction conditions in hand, a wide range of commercial available alcohols was used to test the substrate scope of this reaction. And the results were summarized in Table 2. Aromatic alcohols with both electron-rich group, such as CH_3 (Table 2, **3b**) and OMe (Table 2, **3c**), and electron-deficient group, such as NO_2 (Table 2, **3d**), Cl (Table 2, **3e**) and Br (Table 2, **3f**), were well tolerated to provide the desired amide products in good to excellent yields. Similarly, heterocyclic alcohols **2g** and **2h** gave the corresponding amide products in good yields (Table 2, **3g** and **3h**). Moreover, when

Table 1 Selected results for screening the optimized reaction conditions [a]

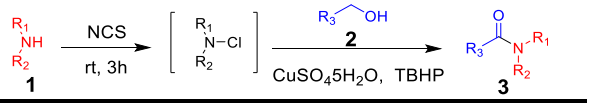


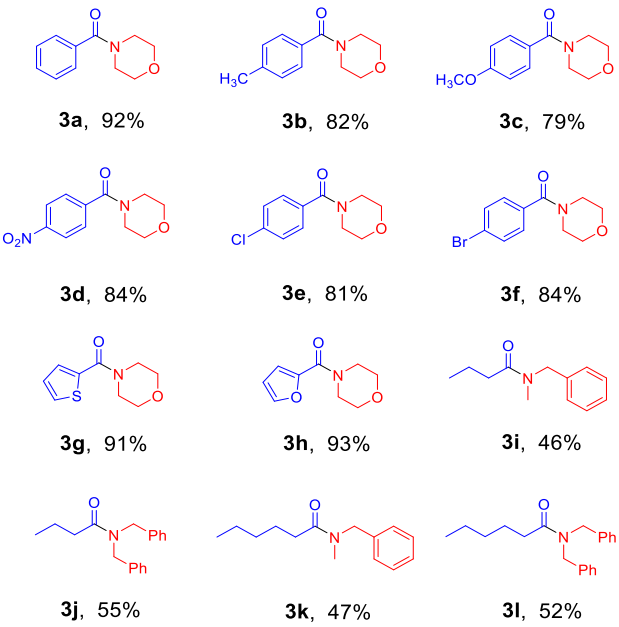
Entry	Catalyst	Oxidant	Yield [b] (%)
1	$Cu(OAc)_2$	TBHP	30
2	$Cu(OAc)_2{\cdot}H_2O$	TBHP	34
3	CuBr	TBHP	42
4	CuI	TBHP	28
5	$CuSO_4{\cdot}5H_2O$	TBHP	62
6	$CuSO_4{\cdot}5H_2O$	TBPB	48
7	$CuSO_4{\cdot}5H_2O$	H_2O_2	Trace
8	$CuSO_4{\cdot}5H_2O$	*m*-CPBA	Trace
9	$CuSO_4{\cdot}5H_2O$	-	-
10[c]	$CuSO_4{\cdot}5H_2O$	TBHP	92
11[d]	$CuSO_4{\cdot}5H_2O$	TBHP	90
12[e]	$CuSO_4{\cdot}5H_2O$	TBHP	44

[a] Reaction conditions: morpholine (1.5mmol), NCS (1.65mmol, 1.1equiv.), in 4mL acetonitrile, stirring at room temperature for 3 h. To this reaction mixture were added benzyl alcohol (1.8mmol, 1.2equiv.), catalyst (10 mol%) and oxidant (7.5mmol, 5equiv.), stirring at 80°C for 24h. [b] Isolated yield. [c] Reaction performed using 20 mol% of $CuSO_4{\cdot}5H_2O$. [d] Reaction performed using 50 mol% of $CuSO_4{\cdot}5H_2O$. [e] Reaction performed using 20 mol% of $CuSO_4{\cdot}5H_2O$ and 3 equiv. of TBHP.

aliphatic alcohols, such as *n*-butanol and *n*-hexanol, were employed as the substrate, the corresponding amide products were obtained in moderate yield (Table 2, **3i**-**3l**).

Table 2 Scope of alcohols [a]

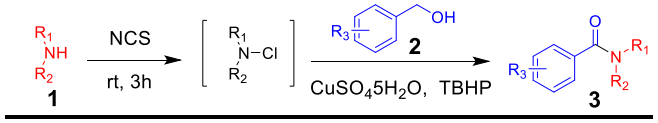


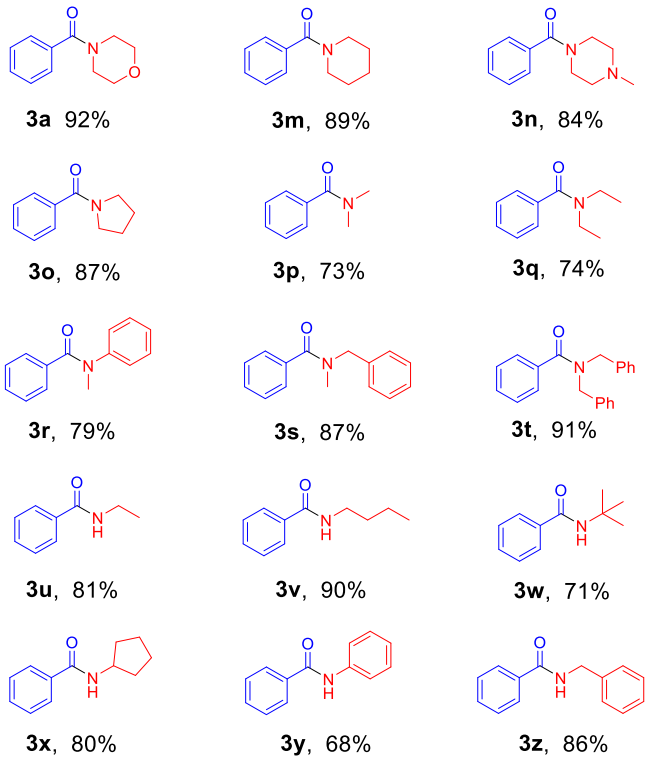


[a] Reaction conditions: amine (1.5mmol), NCS (1.65mmol, 1.1 equiv.), in 4mL acetonitrile, stirring at room temperature for 3 h. To this reaction mixture were added alcohol (1.8mmol, 1.2 equiv.), $CuSO_4{\cdot}5H_2O$ (20 mol%) and TBHP (7.5mmol, 5 equiv.), stirring at 80°C for 24h.

Next, an array of commercially available amines was used to test the substrate scope of this reaction. And the results were shown in Table 3. Disubstituted amines, such as cyclic (Table 3, **3a**, **3m**-**3o**) and acyclic amines (Table 3, **3p**-**3t**), showed great activity to obtain the product in good yields. Furthermore, monosubstituted amines were also showing excellent tolerance (Table 3, **3u**-**3z**), even when they were sterically hindered (Table 3, **3w**).

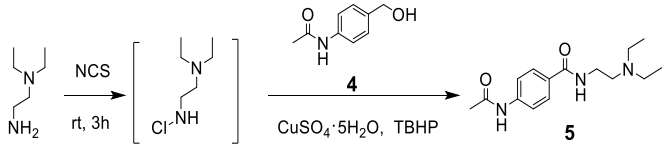
Table 3 Scope of amines [a]



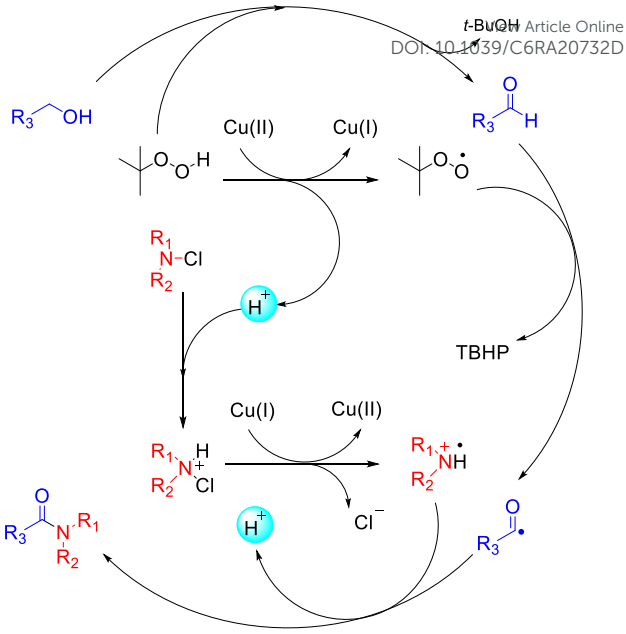


[a] Reaction conditions: amine (1.5mmol), NCS (1.65mmol, 1.1 equiv.), in 4mL acetonitrile, stirring at room temperature for 3 h. To this reaction mixture were added benzyl alcohol (1.8mmol, 1.2 equiv.), $CuSO_4 \cdot 5H_2O$ (20 mol%) and TBHP (7.5mmol, 5 equiv.), stirring at 80°C for 24h.

In order to show the application of this new methodology, the Cu-catalyzed one-pot oxidative amidation was used as a key step to synthesis the biologically active *N*-acetylprocainamide **5**, which was an antiarrhythmic agent, from commercial available 4-acetamidobenzyl alcohol **4** in 68% yield (Scheme 3).

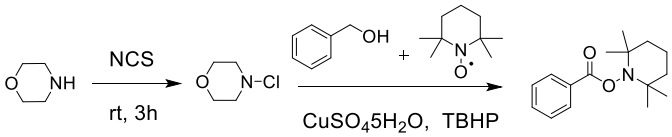


Scheme 3 Synthesis of *N*-acetylprocainamide



Scheme 4 Proposed mechanism for amide synthesis

On the basis of previous studies, [7h, 16] a possible mechanism was proposed as shown in Scheme 4. Firstly, alcohol is oxidized to aldehyde by TBHP. And Cu (II) reacts with TBHP to form a tert-butylperoxy radical, Cu (I) and H^+ following the mechanism proposed in literature.[17] Then the tert-butylperoxy radical captures hydrogen from aldehyde to generate an acyl radical, as reported by Wan.[14] And the protonated *N*-chloroamine is then converted into an amino radical by a redox reaction as well documented by Minisci.[18] Finally, the acyl radical and the amino radical couple to form the desired amide. To confirm this hypothesis, the acyl radical, generated from benzyl alcohol under our reaction conditions, was trapped with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), obtaining the TEMPO adduct, , which was detected by HRMS (Scheme 5).



Scheme 5 Trapping of the acyl radical

In conclusion, we have developed an efficient and green one-pot procedure for the synthesis of amides *via* copper-catalyzed direct oxidative amidation of aliphatic and aromatic alcohols with *N*-chloroamines, prepared *in situ* from variously substituted amines. This method integrates alcohol oxidation and amide bond formation, which are usually accomplished separately, into a single operation. And the use of copper as a catalyst, TBHP as sole oxidant under mild reaction conditions makes this methodology novel and environmentally benign. More importantly, it has a wide substrate scope, and uses cheap, abundant, and easily available reagents.

Acknowledgements

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Copper-catalyzed one-pot oxidative amidation of both aliphatic and aromatic alcohols with *N*-chloroamines, prepared *in situ* from many types of primary and secondary amines, to form amides under mild conditions.