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One-Pot Synthesis of Amides from Aldehydes and Amines *via* C–H Bond Activation

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ABSTRACT

A one-pot synthesis of amides from aldheydes with *N*-chloroamines, prepared *in situ* from amines, has been developed. Both aliphatic and aromatic aldehydes and many types of mono- and disubstituted amines are tolerant in this transformation. This cross-coupling reaction appears simple and convenient, has a wide substrate scope and makes use of cheap, abundant, and easily available reagents.

The amide bond is the key chemical connection present in many natural important polymers such as peptides and proteins, as well as in synthetic ones such as nylon.[1] The amide functional group is contained in many small-molecule drugs, marketed agrochemical products, and synthetic intermediates for fine chemical industry. Amide bonds are typically synthesized by acylation of amines with carboxylic acid derivatives (acid chloride, anhydride, active esters, etc.): it is the most common methodology used in the synthesis of current pharmaceuticals, accounting for 16% of all reactions. However, this strategy has the innate drawback of producing a stoichiometric amount of waste product and of using highly hazardous reagents.[2] To circumvent these problems, alternative methods for amide synthesis were developed, such as the Staudinger reaction,[3] the Schmidt reaction,[4] the Beckmann rearrangement,[5] aminocarbonylation of haloarenes,[6] iodonium-promoted α-halo nitroalkane amine coupling,[7] direct amide synthesis from alcohols with amines or nitroarenes,[8] hydroamination of alkynes,[9] amidation of thioacids with azides,[10] and transamidation of primary amides.[11]

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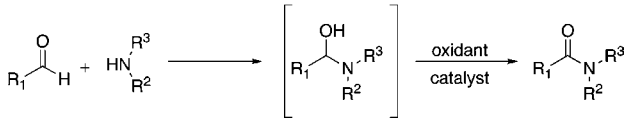
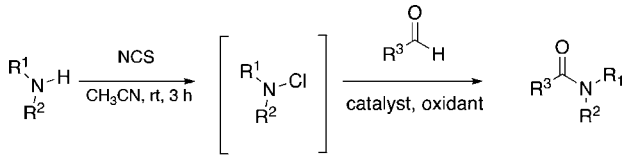
An elegant alternative pathway, which is more atom economic and makes use of cheap and abundant starting materials, is the oxidative amidation of aldehyde with amines.[12] The best accepted mechanism of the oxidative amidation of aldehydes with amines consists of the formation of a hemiaminal intermediate, which is subsequently oxidized to the amide (Scheme 1).

Scheme 1. Accepted Mechanism of the Oxidative Amidation of Aldehydes with Amines



Generally these reactions are catalyzed by metals, such as Cu,[13] Rh,[14] Ru,[15] Pd,[16] Ni,[17] and Fe.[18] Nevertheless, most of the methods outlined above suffer from drawbacks derived from the steric attributes of the amine and the aldheyde, the formation and stability of the hemiaminal intermediate, the use of expensive transition metal catalysts, the limited substrate scope, and the utilization of coreagents. Therefore, the development of different amide formation reactions remains a great goal. The generation of new methods for direct conversion of C−H bonds into C−N bonds appers to be a critical but appealing challenge in organic chemistry, but compared with widely developed and age long C−O and C−C bond formations *via* C−H bond activation, the C−N bond formation from C−H's seems more problematic and was reported just in recent years.[19] Wan[20a] and Wang[20b] recently published two interesting examples of C−N bond formation via C−H aldehyde bond activation. Their papers report on the synthesis of amides through a cross-coupling reaction between aldehydes and *N,N*-disubstituted formamides. Even though the methodologies suffer from some drawbacks,[21] undubitably the amidation of aldehydes *via* C−H bond activation is a fundamentally different method for amide bond formation.[22] Herein, we wish to report on a new and efficient one-pot procedure for the direct amidation of aldehydes with *N*-chloroamines, which were prepared *in situ* starting from the corresponding amines and without any purification, by use of *tert*-butyl hydroperoxide (TBHP) as an oxidant, under base-free conditions and catalyzed by easily accessible copper salts (Scheme 2).

Scheme 2. Synthesis of Amides *via* a Cross-Coupling between Aldehydes and *N*-Chloroamines



Our investigation began by treating dibenzylamine **1a** (1 equiv) with *N*-chlorosuccinimide (NCS) (1.1 equiv) in acetonitrile at room temperature for 3 h. The corresponding *N*-benzyl-*N*-chloro-1-phenylmethanamine **2a** was quantitatively formed (monitored by TLC). This reaction mixture, containing the *N*-chloroamine generated *in situ*, was successively treated, without any purification, with heptaldehyde **3a** (5 equiv), $Cu(OAc)_2$ (0.14 mol %), and *tert*-butyl peroxybenzoate (TBPB 5 equiv) under reflux, for 50 min (the reaction was monitored by TLC until the disappereance of *N*-chloroamine) generating the amide **4a** in 38% yield (Table 1, entry 1). In order to find the optimum reaction conditions various parameters, of the second step, such as catalyst, oxidant, stoichiometric mole ratio of reactants, and temperature, were tested. We performed the same reaction by the use of *tert*-butyl hydroperoxide (TBHP) instead of TBPB obtaining the product with a significant improvement in yield (Table 1, entry 2). No product formation was detected employing H_2O_2 and oxone (Table 1, entries 3 and 4). Then different Cu^{II} and Cu^{I} salts were tested to examine their effect on the formation product. $Cu(Acac)_2$ showed less activity than $Cu(OAc)_2$ giving the desired amide **4a** in 65% yield (Table 1, entry 5). $CuCl_2$ and CuBr showed less activity than $Cu(OAc)_2$ giving the desired amide **4a** in 36% and 47% yields respectively (Table 1, entries 6 and 7). No reaction was observed in the absence of a copper catalyst (Table 1, entry 8).

With the respect to the amount of **1a** in the reaction, it was found that 5 equiv was optimal. However, at the end of the reaction (Table 1, entry 2), 60% of unreacted aldehyde was recovered. When less than 5 equiv of aldehyde and TBHP were used the yield of amide **4a** decreased (Table 1, entries 9−11). No product formation was observed when performing the reaction without the oxidant (TBHP) (Table 1, entry 13) or using Bu_4NI as an organocatalyst (Table 1, entry 14).

After the optimized reaction conditions were found, we tested the methodology with an array of commercially available amines and aldheydes. Aliphatic aldehydes provided the resultant amides in good yields (Scheme 3, **4a**−**b**), even when

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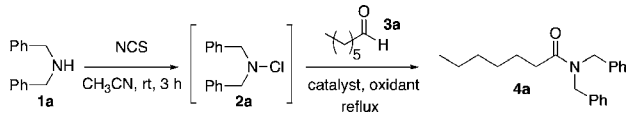
Table 1. Synthesis of Amides: Optimization of the Reaction Conditions



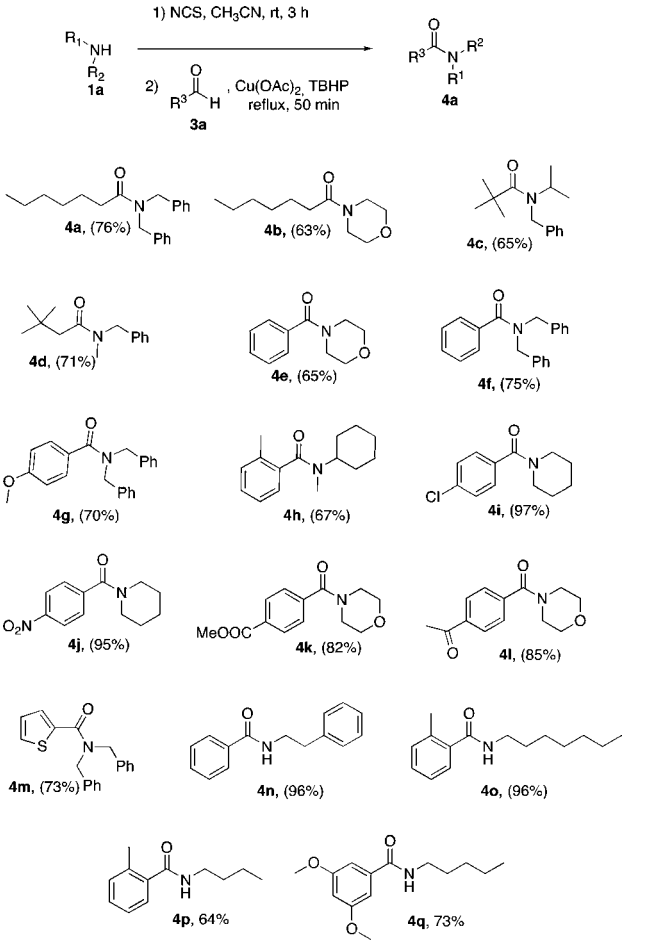
entry[a]	oxidant	catalyst	yield (%)[b]
1	TBPB	$Cu(OAc)_2 \cdot H_2O$	38
2	TBHP	$Cu(OAc)_2 \cdot H_2O$	76
3	H_2O_2	$Cu(OAc)_2 \cdot H_2O$	–
4	oxone	$Cu(OAc)_2 \cdot H_2O$	–
5	TBHP	$Cu(Acac)_2$	65
6	TBHP	$CuCl_2$	36
7	TBHP	CuBr	47
8	TBHP	–	–
9	TBHP[c]	$Cu(OAc)_2 \cdot H_2O$	72
10	TBHP	$Cu(OAc)_2 \cdot H_2O$	65[d]
11	TBHP	$Cu(OAc)_2 \cdot H_2O$	25[e]
12	TBHP	$Cu(OAc)_2 \cdot H_2O$	26[f]
13	–	$Cu(OAc)_2 \cdot H_2O$	–[g]
14	TBHP	Bu_4NI	–[h]

[a] Reaction conditions: dibenzylamine **1a** (1 equiv), *N*-chlorosuccinimide (NCS) (1.1 equiv), in acetonitrile at room temperature for 3 h. To this reaction mixture were added heptaldehyde **3a** (5 equiv), catalyst (0.14 mol %), and oxidant (5 equiv) under reflux, until the disappearance of *N*-chloroamine monitored by TLC. [b] Yield refers to isolated product after column chromatography. [c] TBHP (3.7 equiv). [d] Heptaldehyde **3a** (3.7 equiv). [e] Reaction performed using **3a** (2.5 equiv) and TBHP (2.5 equiv). [f] Reaction performed at room temperature. [g] Reaction performed without TBHP. [h] Reaction performed using Bu_4NI as catalyst.

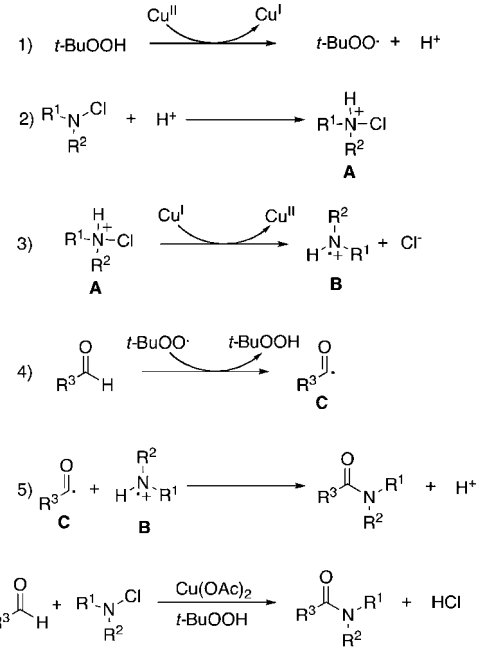
they were sterically hindered (Scheme 3, **4c**–**d**). Aromatic aldehydes with a widespread range of functional groups both an electron-donating group, such as benzylic C–H (Scheme 3, **4h**) and OMe (Scheme 3, **4g** and **4q**), and -withdrawing group, such as NO_2 (Scheme 3, **4j**), were well tolerated providing the desired amides in moderate to excellent yields. Aromatic aldehydes with carbonyl substituents such as ester and ketone gave good results too (Scheme 3, **4k**–**l**).

The reaction carried out on an aldehyde with a halide substituent on the aromatic ring gave the corresponding amide, which could be further transformed by traditional cross-coupling reactions (Scheme 3, **4i**). To prove the synthetic utility of the method, thiophene-2-carbaldehyde was subjected to optimized conditions, giving the desired heteroaryl amide (Scheme 3, **4m**) in good yield. The reaction was tested with a series of *N*,*N*-dialkyl-*N*-chloroamines showing excellent tolerance. Acyclic (Scheme 3, **4a**, **4c**–**d**, **4f**–**h**, and **4m**) as well as cyclic *N*-chloroamines (Scheme 3, **4b**, **4e**, and **4i**–**l**) showed to be effective in this reaction. Furthermore monosubstituted *N*-chloramines gave the corresponding *N*-monosubstituted amides (Scheme 3, **4n**–**q**). With regards to the reaction mechanism, a plausible catalytic cycle is presented in Scheme 4.

Scheme 3. Aldehydes and Amines Diversity



Scheme 4. Proposed Mechanism of Amide Formation



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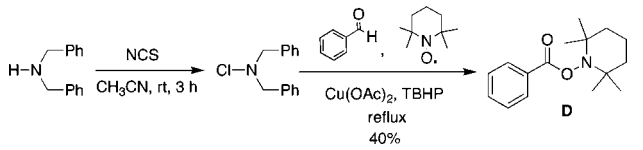
Scheme 5. Trapping of the Acyl Radical



In the first step (Scheme 4, eq 1) Cu^{II} reacts with TBHP forming a *tert*-butylperoxy radical, Cu^{I} and H^{+} following the mechanism proposed in literature.[23] The protonated *N*-chloroamine **A** (Scheme 4, eq 2) is then converted into an amino radical **B** by a redox reaction following Minisci (Scheme 4, eq 3).[24]The aldehyde reacts with the *tert*-butylperoxy radical generating an acyl radical **C** (Scheme 4, eq 4), as reported in literature by Wan[20] and Li.[25] In the end the acyl radical **C** and the amino radical **B** couple to form the desired amide (Scheme 4, eq 5). To confirm this hypothesis, the acyl radical, generated in situ from benzaldehyde under our reaction conditions, was trapped with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), following Wan[20a] and Li,[25] obtaining the TEMPO adduct **D** (Scheme 5).

In conclusion we have reported a novel example of C–N bond formation *via* copper catalyzed C–H aldehyde bond activation. The methodology was employed to prepare amides directly from aliphatic and aromatic aldehydes and variously substituted amines. The procedure reported herein appears to be simple and convenient, has a wide scope, and uses cheap and easily available reagents. Additional studies on the mechanistic details, different catalysts, and expansion of the scope of the reaction are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, characterization of products, and copies of ^{1}H and ^{13}C NMR spectra are provided. The material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.