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An efficient protocol for the preparation of amides by copper-catalyzed reactions between nitriles and amines in water

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ABSTRACT

The reactions between nitriles and amines catalyzed by $Cu(OAc)_2$ and 2-piperidinecarboxylic acid were carried out in pure water without any other additives. A variety of substituted amides can be obtained in moderate to good yields up to 90%.

Amides represent an important class of compounds found in numerous bioactive products, such as Sorafenib **1**,[1] Lipitor **2,** and Vyvanse **3** (Scheme 1), which have been widely used for the treatment of cancer, hypercholesterolemia, and juvenile hyperactivity, respectively.

Normally, the classical synthetic protocol to obtain amide is the substitution reaction between carboxylic acid and amine,[2] which usually results in the formation of ammonium salt and generally requires a temperature above 160 °C.[3] Further studies revealed that the reaction temperature could be significantly lowered by using specially designed areneboronic acids[4] or heterogeneous silica catalysts.[5] On the other hand, one of the most common methods for amide synthesis employs activated derivatives of the carboxylic acid, such as esters[6] together with carbodiimides, phosphonium, or uronium salts as additives.[7] Other general procedures for amide synthesis include the well-established name reactions such as Ritter,[8] Schmidt,[9] Beckmann,[10] Ugi,[11] Wolff et al.[12] Besides, catalytic procedures have been developed including oxidative amidation of aldehydes[13] or alcohols,[14] aminocarbonylation of aryl halides[15] or terminal alkynes,[16] rearrangement of oximes and coupling with amines,[13a] cross coupling of amides with aryl and alkenyl halides,[17] and transamidation of amides with amines.[18]

Besides these protocols, a less frequently reported synthetic method is the coupling of nitrile with amine, which has been reported to be performed in the presence of ruthenium[19a] or platinum[19b] catalysts. These reactions were unexceptionally carried out in organic solvents such as DME. In continuation of our work on copper-catalyzed hydrolysis of nitrile to amide[20a] and other coupling reactions in water,[20] herein is reported the reaction of nitrile and amine catalyzed by copper to form amide in water.

The initial studies were focused on the optimization of catalytic conditions based on phenylacetonitrile **1a** and aniline **2a** as model substrates. As shown in Table 1, control experiments indicated the catalyst to be essential for the reaction, and only a trace of product was detected in the absence of ligand or metal (Table 1, entries 1 and 2). Seven different ligands **L1**–**L7** were tested, and 2-piperidinecarboxylic acid **L7** seemed to be superior to others in yield of 71% (Table 1, entries 3–9). It is worthy to note that ammonia **L5** gave only 39% yield, which was reported by us to form high catalytic species with CuI during catalytic nitrile hydrolysis (entry 7).[20a] Comparison of different metal sources indicated $Cu(OAc)_2$ to be better than others including $CuCl_2$, CuO, CuI, $NiCl_2$, and $FeCl_3$ (Table 1, entries 9–14). Reaction temperature was another important factor to affect the results. For example, when the reaction temperature was decreased from 100 to 80 °C, the yields of the desired product dropped from 71% to 50% (Table 1, entries 9 and 15). Meanwhile, when the reaction temperature was increased to 120 °C, the yield of the desired product remained quite stable at 70% (Table 1, entry 16). Finally, the catalyst loading was investigated and 10 mol % was found to be fitful for the catalysis (Table 1, entries 17–19). Thus, the optimal catalytic conditions consist of $Cu(OAc)_2$ (10 mol %) and **L7** (20 mol %) in water (5 mL) at 100 °C for 18 h.

Next, the scope and limitation of this protocol were examined by using other substrates under the optimized reaction conditions.

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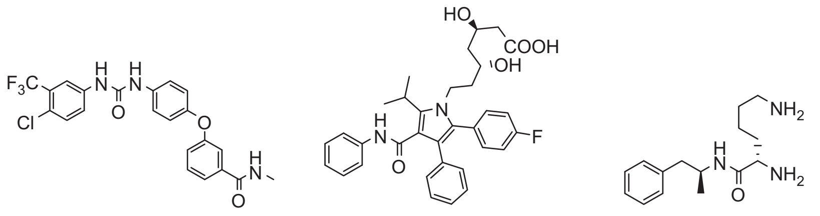
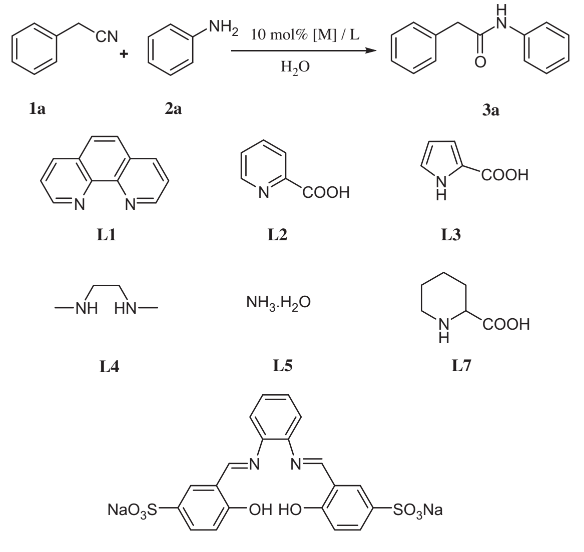


1 **2** **3**

Scheme 1. Selected examples of biologically and therapeutically active amides.

Table 1
Optimization of reaction conditions[a]



Entry	[M]	Ligand	Yield[b] (%)
1	$Cu(OAc)_2$	–	4
2	–	L7	Trace
3	$Cu(OAc)_2$	L1	16
4	$Cu(OAc)_2$	L2	31
5	$Cu(OAc)_2$	L3	27
6	$Cu(OAc)_2$	L4	22
7	$Cu(OAc)_2$	L5	39[c]
8	$Cu(OAc)_2$	L6	29[d]
9	$Cu(OAc)_2$	L7	71
10	$CuCl_2$	L7	55
11	CuO	L7	29
12	CuI	L7	40
13	$NiCl_2$	L7	23
14	$FeCl_3$	L7	18
15	$Cu(OAc)_2$	L7	50[e]
16	$Cu(OAc)_2$	L7	70[f]
17	$Cu(OAc)_2$	L7	40[g]
18	$Cu(OAc)_2$	L7	56[h]
19	$Cu(OAc)_2$	L7	73[i]

[a] All reactions were carried out by using phenylacetonitrile (1.0 mmol), phenylamine (1.3 mmol), [M] (0.1 mmol), and ligand (0.2 mmol) in H_2O (5 mL) at 100 °C for 18 h.

[b] Isolated yields.

[c] [Cu]/Ligand = 1:4.

[d] [Cu]/Ligand = 1:1.

[e] The reaction temperature was 80 °C.

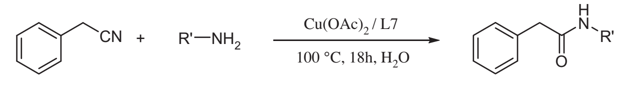
[f] The reaction temperature was 120 °C.

[g] 2.5 mol % catalyst.

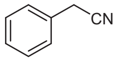
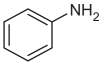
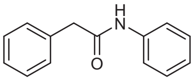
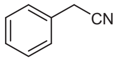
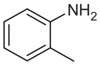
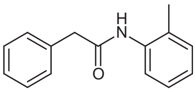
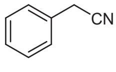
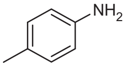
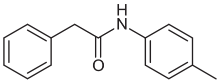
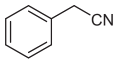
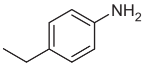
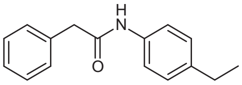
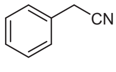
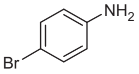
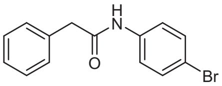
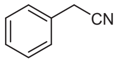
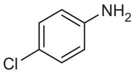
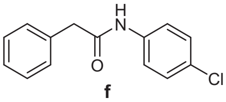
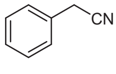
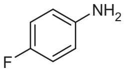
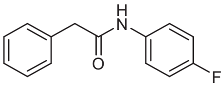
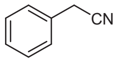
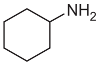
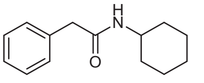
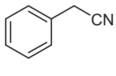
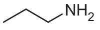
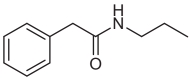
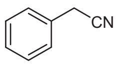
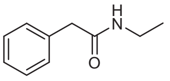
[h] 5 mol % catalyst.

[i] 20 mol % catalyst.

Table 2
Cu-catalyzed reactions between phenylacetonitrile and different amines[a]



1 **2** **3**

Entry	Nitrile	Aniline	Product	Yield[b] (%)
1			 **a**	71
2			 **b**	86
3			 **c**	83
4			 **d**	85
5			 **e**	56
6			 **f**	69
7			 **g**	52
8			 **h**	71
9			 **i**	75
10			 **j**	73

[a] Reaction conditions: **1** (1 mmol), **2** (1.3 mmol), $Cu(OAc)_2$ (0.1 mmol) and 2-piperidinecarboxylic acid (0.2 mmol) in H_2O (5 mL) at 100 °C for 18 h.

[b] Isolated yields.