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An Efficient and Practical Protocol for Catalytic Hydrolysis of Nitriles by a Copper(I) Complex in Water

Zhengkai Li,^a Lixia Wang,^a and Xiangge Zhou^{a,b,*}

^a Institute of Homogeneous Catalysis, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China

Fax: (+86)-28-8541-2904; e-mail: zhouxiangge@scu.edu.cn

^b State Key Laboratory of Physical Chemistry of Solid Surface, Xiamen University, Xiamen 361005, People's Republic of China

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Abstract: The cuprous complex $- Cu_4I_4(H_2O)_4 - has$ been isolated and employed for the catalytic hydrolysis of arenecarbonitriles, cinnamonitrile, and arylacetonitriles to the corresponding amides in pure water in high yields of up to 98%. The catalyst can be easily recovered and reused without loss of catalytic activity at least five times. Oxindole could be prepared successfully by one-pot domino protocols based on this method.

Keywords: amides; copper; hydrolysis; nitriles; water

The hydrolysis of nitriles is of synthetic significance for the preparation of amides, which are versatile synthetic intermediates used in the production of pharmacological products, polymers, detergents, lubricants and drug stabilizers.^[1] For instance, more than 2×10^5 ton of acrylamide are produced by the hydrolysis of acrylonitrile every year.^[2] Normally, the classical process of nitrile hydrolysis is carried out in a sequence of distinct steps upon treatment with strong inorganic acid or base, however, further hydrolysis to carboxylic acids is a serious problem in many cases. Meanwhile, the formation of a large amount of salts after neutralization also limits its applications.^[3] Therefore, the catalytic hydrolysis of nitriles seems to be an ideal approach, which fits well for either atom economy or sustainable development. Some metalloenzyme and transition metal catalysts have already been employed for this purpose.^[4-8] For example, Yamada's NHase catalyst,^[5] Murahashi's ruthenium system,^[1d,6b,c] Parkins's platinum complexes,^[6e,g,7] and other Ru^[6p] and Rh catalysts^[8] were reported to exhibit remarkable activities in the catalysis. However, several shortcomings still existed with these catalytic systems: difficulty in catalyst/product separation and necessity of special handling of microorganisms or metal complexes.^[9] Furthermore, the reaction media were in general organic solvents or mixed solvents, and expensive metals such as ruthenium, platinum and rhodium were usually needed. Reports on the homogeneous complex-catalyzed transformation in pure aqueous media are scarce.^[6fg,j,10] To the best of our knowledge, a Cu(I)-catalyzed conversion of nitriles to amides has not been reported.^[2a,11]

In continuation of our studies on copper-catalyzed reactions in water,^[12] herein is reported a highly efficient and practical protocol for the catalytic hydrolysis of nitriles to amides by Cu(I) in water. It has the following advantages compared with the reported methods: water is used as sole solvent without addition of other acids or bases, the product amide can be separated by simple filtration without complicated work-up procedures, the catalyst is easily available with high catalytic abilities and can be easily recovered and reused at least five times without loss of catalytic activities, furthermore, the catalytic system can be applied to large-scale reactions.

Initially, the catalytic hydrolysis of benzonitrile was selected as a model reaction, and the reaction conditions were optimized. As shown in Table 1, CuI exhibited low catalytic abilities to form only traces of amide product, which might be partially caused by the low solubility of the catalyst in water (Table 1, entry 1). Then, several kinds of ligands which were usually applied in coupling reactions and some other transition metals were tested, and the catalyst formed by CuI and ammonia was found to be superior to others in giving a moderate yield of 55% (Table 1, entries 2–10). Interestingly, decreasing the amount of ammonia resulted in an improvement of the catalytic activity. For example, when the molar ratio between Table 1. Catalytic hydrolysis of benzonitrile in water.^[a]



Entry	[Cu]	Ligand	Time [h]	Yield [%] ^[b]
1	CuI	_	21	<2
2	CuI	L1	21	36 ^[c]
3	CuI	L2	21	41 ^[c]
4	CuI	L3	21	32 ^[c]
5	CuI	L4	21	51 ^[c]
6	Complex 1		21	50
7	$CuSO_4 \cdot 5H_2O$	NH ₃ ·H ₂ O	21	33 ^[d]
8	NiCl ₂ ·6H ₂ O	NH ₃ ·H ₂ O	21	38 ^[d]
9	FeCl ₃ ·6H ₂ O	NH ₃ ·H ₂ O	21	25 ^[d]
10	CuI	NH ₃ ·H ₂ O	21	55 ^[d]
11	CuI	NH ₃ ·H ₂ O	21	63 ^[e]
12	CuI	$NH_3 \cdot H_2O$	21	$70^{[f]}$

^[a] Reaction conditions: benzonitrile (1 mmol), Cu-catalyst (0.025 mmol) in H₂O (5 mL).

^[b] Isolated yield.

^[c] [Cu]/ligand = 1:1.

- ^[d] [Cu]/ligand = 1:2.
- [e] [Cu]/ligand = 1:1.
- [f] [Cu]/ligand = 1:0.5.

CuI and ammonia was reduced from 1:2, 1:1 to 1:0.5, the yields increased from 55%, 63% to 70% (Table 1, entries 10–12). This phenomenon suggested to us that the most effective catalytic species during the reaction might not be the complex formed by CuI with ammonia. Thus, the complex formed by CuI and ammonia in a 1: 0.5 molar ratio in water was isolated, and the crystals of the novel complex 2 suitable for X-ray single crystal determination were fortunately obtained.

As shown in Figure 1, the molecular structure revealed that this complex consists of a tetranuclear $[Cu_4(\mu_3-I)_4(H_2O)_4]$ core in which the four copper ions are linked by I bridges, and the remaining coordination sites were occupied by water molecules, respectively.^[12] The addition of small amount of ammonia seemed to be essential for the formation of this complex.

This complex was then applied in the catalysis, and the results are listed in Table 2. As expected, Cu_4I_4



H1WD (

Figure 1. X-ray structure of complex 2.

Table 2. Catalytic hydrolysis of benzonitrile by $Cu_4I_4(H_2O)_4$ in water.^[a]

Entry	Temp. [°C]	Catalyst Loading [mol%]	Yield [%] ^[b]
1	100	2.5	97
2	120	2.5	95
3	80	2.5	87
4	100	2	94
5	100	1	93
6	100	0.5	82

^[a] Reaction conditions: benzonitrile (1 mmol), $Cu_4I_4(H_2O)_4$ (0.025 mmol), H_2O (5 mL), 21 h.

^[b] Isolated yield.

 $(H_2O)_4$ could be easily dissolved in water, and exhibited high catalytic abilities with up to 97% yield. The effects of reaction temperature were studied, and 100 °C was suitable for the catalysis, a lower temperature resulted in a decreased yield (Table 2, entries 1–3). Comparison of different catalyst loadings indicated that 2.5 mol% was suitable for the reaction.

Furthermore, after the reaction, when the mixture had cooled to a low temperature of around 5°C, a number of colorless crystals appeared as shown in Figure 2 (*right*). After simple filtration, the amide product could be obtained in high purity just by washing with a small amount of water and drying under vacuum. The obvious different solubilities of benzamide in hot and cold water and the "clean" reaction mixture without additives and by-products during catalysis made the work-up procedure easy to perform.

On the other hand, the simple work-up procedure also reminded us of the possibility of the reuse of the catalyst. Indeed, after filtration, the filtrate containing the water-soluble catalyst could be reused for the next



Figure 2. Catalytic hydrolysis of benzonitrile to benzamide: (*left*) reaction mixture, (*right*) benzamide crystals appeared after cooling the reaction mixture.

run again, and the yields remained quite stable at around 95% even after reused five times.

Considering the broad application and large demand of amides in many fields, especially as a raw material for making pharmacological products and drug stabilizers, we tried to conduct a scale-up preparation study of benzamide based on the above optimized conditions. Actually, the reaction conditions and relevant processing parameters of 100 g of benzo-nitrile in a 1 L volume sealed retort were optimized and the final yield also reached 96%.

Next, the scope of nitrile substrates was surveyed. As exemplified in Table 3, $Cu_4I_4(H_2O)_4$ was in general effective in the selective hydrolysis of different nitriles to the corresponding amide products in good to excellent yields ranging from 63% to 98%. The substrates bearing electron-donating groups gave better results than those bearing electron-withdrawing groups. Furthermore, the catalytic system exhibited tolerance with some functional groups including halides, ether, and nitro groups (Table 3, entries 2, 3, 7, 8, 9 and 14). Hydrolysis of cinnamonitrile also afforded cinnamamide as expected with an intact C=C double bond in 90% yield (Table 3, entry 12). Remarkably, this catalytic system could effectively convert nicotinonitrile to nicotinamide in 95% yield, which was usually more difficult to be hydrolyzed than common nitriles (Table 3, entry 10). Furthermore, as shown in Table 3, the hydrolysis of arylacetonitriles was efficiently (> 87% isolated yield) achieved under the standard reaction conditions (Table 3, entries 13 and 14). We evaluated this catalyst for the hydration of an alphatic nitrile, acetonitrile (Table 3, entry 15), which produced the corresponding acetamide in moderate yield.

Finally, the catalytic system together with the help of our formerly developed C–N coupling catalyst^[13] were successfully applied in the synthesis of oxindole, which is one of the useful lactam derivatives used in

Table 3. Hydrolysis	of various	nitriles	catalyzed	by the	com-
plex Cu ₄ I ₄ (H ₂ O) ₄ in	water. ^[a]				

Entry	Nitrile	Product	Yield [%] ^[b]
1	CN	NH ₂	97
2	CN		86
3	CI	O CI	89
4	CN CH ₃	NH ₂ CH ₃	92
5	CN CH ₃	O NH ₂ CH ₃	95
6	H ₃ C	H ₃ C NH ₂	98
7	H ₃ CO	H ₃ CO NH ₂	95
8			83
9	O ₂ N CN	O ₂ N NH ₂	82
10	CN N	O NH ₂	95
11	CN	O NH ₂	82
12	CN	NH ₂	90
13	CN	NH ₂	95
14	CN	NH ₂	89
15	CH ₃ CN	O NH2	63

^[a] Reaction conditions: nitrile (1 mmol), $Cu_4I_4(H_2O)_4$ (0.025 mmol), H_2O (5 mL), 100 °C, 21 h.

^[b] Isolated yields.



Scheme 1. Synthesis of oxindole by our Cu-catalyzed protocol.

the drug and polymer industry.^[14] As show in Scheme 1, oxindole could be prepared in a total yield of 76% by a one-pot reaction with $Cu_4I_4(H_2O)_4$ and complex 1 as catalysts.

In conclusion, an efficient copper-catalyzed protocol for the hydrolysis of nitriles to amides in water under neutral condition has been disclosed. This approach represents an important complement to the hydrolysis of nitriles and exhibits potential usage in industry. We envision that the fuctionalization of nitrile-containing polymers may be realized using the present hydrolysis strategy.

Experimental Section

General Procedure for the Catalytic Reaction

The corresponding nitrile (1 mmol), the copper catalyst $Cu_4I_4(H_2O)_4$ (2.5 mol%), and water (5 mL) were placed in a sealed tube and the reaction mixture was stirred at 100 °C for the indicated time (see Table 1 and Table 2). then the reaction mixture was cooled to 5 °C. The crystalline product appeared and was collected by simple filtration and dried under vacuum to give analytically pure amide. To the filtrate was added deionized water to 5 mL, and the mixture was employed as the reusable catalytic system.

CCDC 842303 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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