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# Copper-Catalyzed Oxidation of Amines with Molecular Oxygen

**Yasunari Maeda, Takahiro Nishimura, and Sakae Uemura***

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University,
Sakyo-ku, Kyoto 606-8501

Received June 9, 2003; E-mail: uemura@scl.kyoto-u.ac.jp

An improved system for selective aerobic oxidation of amines to imines or nitriles is presented. It involves commercially available and inexpensive copper(I) or (II) chloride as catalyst, toluene as solvent, and MS3A as dehydrating agent under an atmospheric pressure of oxygen. A variety of amines can be used as substrates for this oxidation system to give the corresponding nitriles from primary amines (up to 97% yield; TON, up to 60) and the imines from secondary amines (up to 90% yield; TON, up to 45).

Oxidation of organic compounds with molecular oxygen as a sole oxidant is valuable, because the use of such an inexpensive and clean oxidant, instead of other organic oxidants, has advantages from economical point of view as well as from the viewpoint of green chemistry.[1] For these reasons, efforts have been devoted in recent years to developing the transition metal-catalyzed aerobic oxidation of organic substrates. The direct synthesis of nitriles by the oxidation of primary amines[2,3] is important because nitriles are useful intermediates of medicines or biologically active compounds including heterocycles.[4] Some ruthenium catalysts have been known to work effectively for aerobic oxidation of primary amines to the corresponding nitriles: $RuCl_3$,[5a] $[RuCl_2(RCH_2NH_2)_2(PPh_3)_2]$,[5b,5c] Ru–porphyrin,[5d] Ru–hydroxyapatite,[5e] $[Ru_2Cl(OAc)_4]$,[5f] and $Ru/Al_2O_3$.[5g] Catalytic oxidation using more economical copper salts has also been reported, but the examples are still quite limited. Thus, Capdevielle and co-workers reported that the combination of copper(I) chloride/$O_2$/pyridine/MS4A worked as a good oxidant system for some primary amines.[6a–6c] Unfortunately, however, this system showed only low catalytic activity (TON = 5.5 when applied to piperonylamine (3,4-methylidenedioxybenzylamine)). Komatsu and co-workers used binuclear copper(II) complex of 7-azaindole as a catalyst, which worked efficiently for dehydrogenation of several amines, although the selectivity for the products was sometimes low.[6d] To overcome such drawbacks in direct synthesis of nitriles from primary amines, we have searched for a more effective aerobic oxidation system of primary amines. First, we attempted to use palladium[7a–7f] or vanadium complexes[7g,7h] as catalysts for the aerobic oxidation of primary amines, which were efficient catalysts for the aerobic oxidation of alcohols, but these systems could not be applied to the aerobic oxidation of amines. Next, we carefully examined Capdevielle's system using copper(I) or (II) chloride, and eventually we found that the use of toluene in place of pyridine much improved the yields of the corresponding nitriles (TON: up to 60). Herein, we report the efficient copper-catalyzed oxidation of amines with molecular oxygen (Eq. 1).

$$\mathrm{RCH_2NH_2} \xrightarrow[\mathrm{O_2}]{\text{Cu cat.}} \mathrm{RCN} \qquad (1)$$

## Results and Discussion

First, the oxidation of benzylamine was examined under various reaction conditions (Table 1). Treatment of benzylamine (1 mmol) with an atmospheric pressure of oxygen in toluene (2 mL) in the presence of a catalytic amount of copper(I) chloride (0.01 mmol) and 3 Å molecular sieves (MS3A: 500 mg) at 80 °C for 3 h gave benzonitrile in 34% yield together with a small amount of *N*-benzylidenebenzylamine (entry 1). Other solvents were examined, such as 1,2-dichloroethane, chlorobenzene, 1,2-dimethoxyethane, acetonitrile, *N*,*N*-dimethylformamide, and pyridine, but toluene was revealed to be the solvent of choice (entries 1–7).[8] Next, some copper salts were examined as catalyst for this oxidation system in toluene. Copper(II) acetate, copper(I) oxide, and copper(II) acetylacetonate did not work at all (entries 10–12). When copper(II) nitrate was used as catalyst, benzonitrile was obtained in moderate yield (entry 13). Some copper halides such as copper(I) and (II) chlorides and copper(I) and (II) bromides worked as catalysts to give benzonitrile (entries 1, 8, 14, and 15) in moderate to good yields, among which copper(II) chloride was most effective (entry 14). Some other transition metal chlorides such as $FeCl_2$, $CoCl_2$, $NiCl_2$, $RuCl_3 \cdot 3H_2O$, AgCl, and $IrCl_3$ were not effective under this reaction condition. Then, we investigated the effects of the amounts of the catalyst and MS3A on the selectivity for benzonitrile (Table 2). When the amount of copper(II) chloride doubled, the selectivity for benzonitrile increased (entry 2). Higher concentration of the substrate decreased the yield of benzonitrile (entry 4), while the reaction in lower concentration of the substrate did not improve its yield even after a longer reaction time (entries 5 and 6). Interestingly, MS4A, which was used as a drying agent by Capdevielle et al., was less effective than MS3A (entry 7). Further, the smaller amount of MS3A gave the smaller amount of the corresponding nitrile (entries

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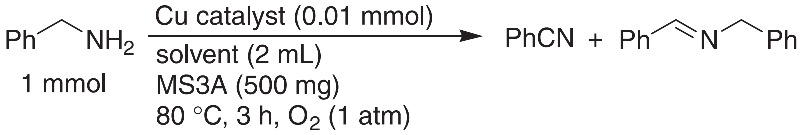
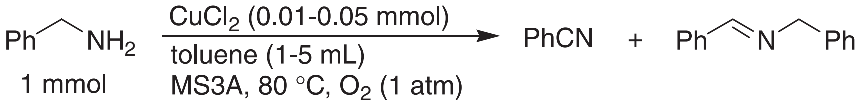
Table 1. Copper-Catalyzed Oxidation of Benzylamine



| Entry | Solvent | Cu catalyst | Yield/%[a)] | |
|---|---|---|---|---|
| | | | Nitrile | Imine[b)] |
| 1 | Toluene | CuCl | 34 | 8 |
| 2 | 1,2-Dichloroethane | CuCl | 16 | 4 |
| 3 | Chlorobenzene | CuCl | 30 | 4 |
| 4 | 1,2-Dimethoxyethane | CuCl | 0 | 10 |
| 5 | Acetonitrile | CuCl | 13 | 70 |
| 6 | *N*,*N*-Dimethylformamide | CuCl | 35 | 65 |
| 7 | Pyridine | CuCl | 1 | 9 |
| 8 | Toluene | $CuBr\cdot SMe_2$ | 32 | 10 |
| 9 | Toluene | CuI | 19 | 44 |
| 10 | Toluene | $Cu(OAc)_2$ | 4 | 6 |
| 11 | Toluene | $Cu_2O$ | 0 | 1 |
| 12 | Toluene | $[Cu(acac)_2]$ | 0 | 0 |
| 13 | Toluene | $CuNO_3\cdot 3H_2O$ | 44 | 24 |
| **14** | **Toluene** | $\mathbf{CuCl_2}$ | **60**[c)] | **18** |
| 15 | Toluene | $CuBr_2$ | 50 | 24 |

a) Based on benzylamine employed (%). b) 0.5 mmol *N*-benzylidenebenzylamine corresponds to 100%. c) TON is 60.

Table 2. Optimization of the Reaction

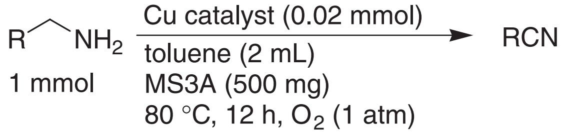


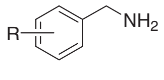
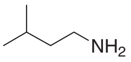
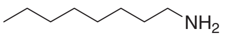
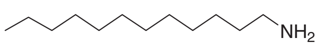
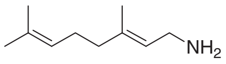
| Entry | Toluene/mL | Time/h | $CuCl_2$/mmol | MS3A/mg | Yield/%[a)] | |
|---|---|---|---|---|---|---|
| | | | | | Nitrile | Imine[b)] |
| 1 | 2.0 | 3 | 0.01 | 500 | 60 | 18 |
| 2 | 2.0 | 3 | 0.02 | 500 | 67 | 14 |
| 3 | 2.0 | 3 | 0.05 | 500 | 60 | 37 |
| 4 | 1.0 | 3 | 0.02 | 500 | 47 | 46 |
| 5 | 5.0 | 3 | 0.02 | 500 | 38 | 16 |
| 6 | 5.0 | 6 | 0.02 | 500 | 65 | 28 |
| 7[c)] | 2.0 | 3 | 0.02 | 500 | 37 | 7 |
| 8 | 2.0 | 3 | 0.02 | 100 | 28 | 17 |
| 9 | 2.0 | 3 | 0.02 | 250 | 40 | 14 |
| 10 | 2.0 | 3 | 0.02 | 750 | 61 | 33 |
| 11 | 2.0 | 3 | 0.02 | 0 | 2 | 2 |
| 12[d)] | 2.0 | 3 | 0.02 | 500 | 2 | 4 |
| 13 | 2.0 | 1 | 0.02 | 500 | 27 | 6 |
| 14 | 2.0 | 2 | 0.02 | 500 | 55 | 10 |
| 15 | 2.0 | 6 | 0.02 | 500 | 71 | 24 |
| **16** | **2.0** | **12** | **0.02** | **500** | **75** | **25** |
| 17 | 2.0 | 24 | 0.02 | 500 | 75 | 25 |

a) Based on benzylamine employed (%). b) 0.5 mmol *N*-benzylidenebenzylamine corresponds to 100%. c) MS4A was used instead of MS3A. d) Under $N_2$.

2, 8, and 9). The presence of MS3A was essential for this oxidation and the oxidation scarcely proceeded at all without MS3A (entry 11). The reaction under nitrogen atmosphere gave very little of the corresponding nitrile (entry 12), indicating that the presence of oxygen is essential for this reaction. In most cases of benzylamine oxidation, *N*-benzylidenebenzylamine was obtained as a by-product. Benzylamine was consumed almost completely after 6 h to give both benzonitrile and *N*-benzylidenebenzylamine (entry 15) and the product ratio did not change much by prolonging the reaction time (entries

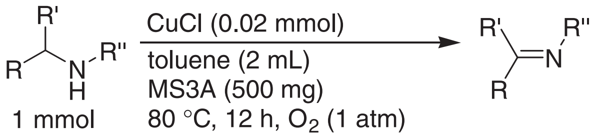
Table 3. Copper-Catalyzed Aerobic Oxidation of Primary Amines

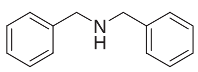
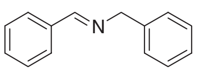
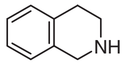
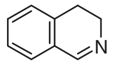
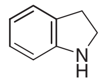
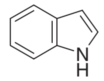
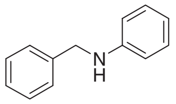
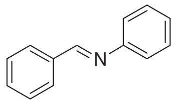
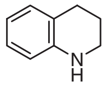
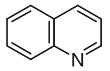


| Entry | Substrate | Cu catalyst | Isolated yield/%[a)] |
|---|---|---|---|
| 1 |  R = H | $CuCl_2$ | 75[b)] |
| 2 | 2-Cl | $CuCl_2$ | 78[b)] |
| 3 | 3-Cl | $CuCl_2$ | 73 |
| 4 | 4-Cl | $CuCl_2$ | 72 |
| 5 | 4-Me | $CuCl_2$ | 66 |
| 6 |  | CuCl | 92[b)] |
| 7 |  | CuCl | 96 |
| 8 |  | CuCl | 97 |
| 9 | | $CuCl_2$ | 17 |
| 10 |  | CuCl | 84 |
| 11 | | $CuCl_2$ | 28 |

a) Based on amine employed (%): In all reactions except for entries 9 and 11, complete consumption of amines was confirmed. b) GLC yield.

Table 4. Copper-Catalyzed Aerobic Oxidation of Secondary Amines



| Entry | Substrate | Product | Isolated yield/%[a)] |
|---|---|---|---|
| 1 |  |  | 90[b)] |
| 2 |  |  | 88 |
| 3 |  |  | 73 |
| 4 |  |  | 24 |
| 5 |  |  | 34 |

a) Based on amine employed (%). b) GLC yield. TON is 45.

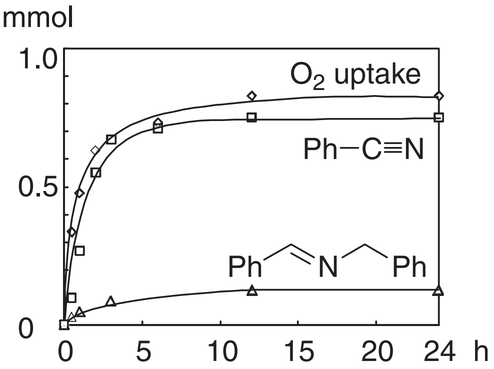


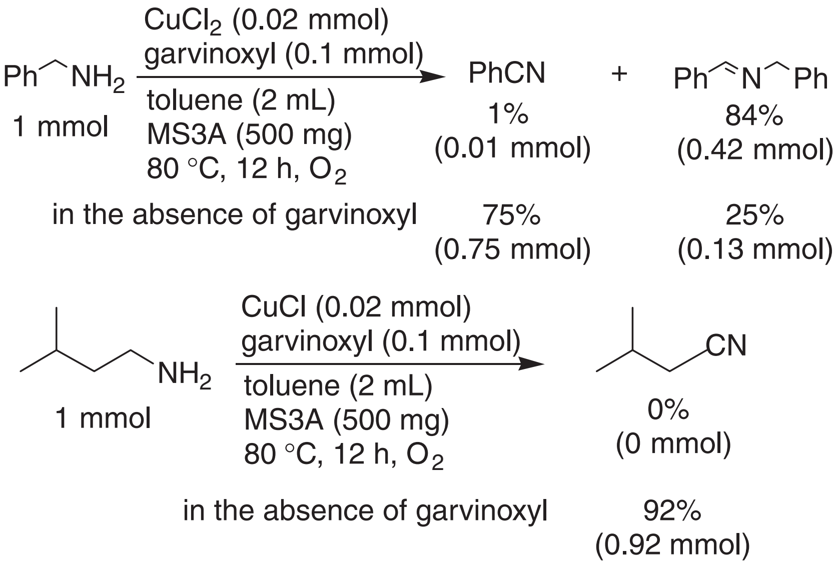
Fig. 1. Correlation between $O_2$ uptake and the product yield. Reaction conditions: benzylamine (1 mmol), $CuCl_2$ (0.02 mmol), toluene (2 mL), MS3A (500 mg), 80 °C, under $O_2$ (1 atm).

16 and 17). Other efforts to improve the selectivity of benzonitrile, such as the change of addition rate of benzylamine, the change of reaction temperature, and so on, were unfortunately in vain.

The oxidation of some other primary amines was examined under the condition of entry 16 of Table 2; typical results are listed in Table 3. Some primary benzylic amines having chloro or methyl substituent on aromatic nuclei were converted to the corresponding nitriles in good yields (entries 1–5). Aliphatic amines including the allylic one were oxidized to give the corresponding nitriles in high yields using copper(I) chloride as catalyst (entries 6–8, and 10); unlike the case of benzylic amines the use of copper(II) chloride was not effective and unreacted amines were recovered under this condition (entries 9 and 11). In the cases of the oxidation of benzylic amines, the corresponding *N*-benzylidenebenzylamines were obtained as by-products in at most 20% yield (entries 1–5).

When this catalytic system was applied to the secondary amines,[9] the corresponding imines were obtained, as summarized in Table 4. Some secondary benzylic amines such as dibenzylamine and 1,2,3,4-tetrahydroisoquinoline were converted to the corresponding imines in high yields (entries 1 and 2). Treatment of indoline as a substrate gave an indole in good yield (entry 3). When *N*-phenylbenzylamine was used as a substrate, the corresponding imine was obtained in low yield (entry 4). 1,2,3,4-Tetrahydroquinoline afforded quinoline with aromatization in moderate yield (entry 5). In the cases of entries 4 and 5, the corresponding unreacted amines were recovered.

The measurement of $O_2$ uptake during the reaction was performed with benzylamine as a substrate to obtain some information about the reaction pathway. The molar amount of observed $O_2$ consumption was found to be equal to the sum of that of benzonitrile and *N*-benzylidenebenzylamine produced in this reaction (Fig. 1). Next, the oxidation of benzylamine and isoamylamine was carried out in the presence of a radical scavenger (Scheme 1). When benzylamine was used as a substrate in the presence of garvinoxyl (0.1 mmol) under the reaction condition of Table 3, *N*-benzylidenebenzylamine was obtained selectively (0.42 mmol: 84% yield) instead of benzonitrile (0.01 mmol: 1% yield; compare with the result of Table 3, entry 1 obtained in the absence of the scavenger). Similarly, the treatment of isoamylamine as a substrate in the presence of garvinoxyl did not produce the corresponding nitrile, while the nitrile was formed in 92% yield in the absence of the scavenger (Table 3, entry 6).[10] These results suggest that this copper-catalyzed aerobic oxidation of amines to nitriles in toluene proceeds through a reaction pathway including an ammoniumyl radical (**A**) and an alkylideneaminyl radical (**B**) (Fig. 2)[11] similar to suggested by Capdevielle et al.,[6b,c] in contrast to the ruthenium catalysis where an ionic pathway has been recognized.[5d,e,g]



Scheme 1. Copper-catalyzed aerobic oxidation of primary amines in the presence or absence of a radical scavenger.

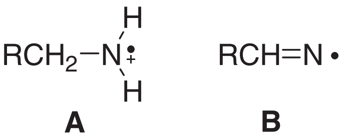


Fig. 2. Ammoniumyl radical (**A**) and alkylideneaminyl radical (**B**).

In summary, we found that copper(I) or (II) chloride, which was a commercially available and inexpensive compound, worked efficiently as a catalyst in toluene for the aerobic oxidation of primary amines to the corresponding nitriles in good yields and selectivity. Especially, the oxidation of aliphatic primary amines gave the corresponding nitriles in excellent yield (up to 97% yield; TON, up to 60). This catalytic system could also be applied to secondary amines to give the corresponding imines (up to 90% yield; TON, up to 45).

## Experimental

**General Procedures.** NMR spectra were recorded on JEOL EX-400 ($^1$H NMR, 400 MHz; $^{13}$C NMR, 100 MHz) and JNM-AL-300 ($^1$H NMR, 300 MHz; $^{13}$C NMR, 75.5 MHz) instruments for solutions with $Me_4Si$ as an internal standard. GLC analyses were performed on a Shimadzu GC-14A instrument (25 m × 0.33 mm, 5.0 mm film thickness, Shimadzu fused silica capillary column HiCap CBP10-S25-050) with a flame-ionization detector and helium as carrier gas. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F-254 plates. Column chromatography was performed with Merck silica gel 60 or ICN alumina N. Commercially available organic and inorganic compounds were used without further purification except for the solvent. Commercial MS3A (powder) (Nacalai Tesque) was activated by calcination just before use. All amines and the corresponding nitriles or imines were commercial products and were purified by normal methods just before use.

**Typical Procedure for the Oxidation of Primary Amines with Molecular Oxygen.** To a suspension of CuCl or $CuCl_2$ (0.02 mmol) in toluene (1.5 mL) in a 10 mL two-necked round-bottomed flask was added MS3A (500 mg, powder). A solution of primary amine (1 mmol) in toluene (0.5 mL) was then added and the resulting mixture was stirred. Oxygen gas was then introduced into the flask from an $O_2$ balloon under atmospheric pressure and then the mixture was stirred vigorously for 3–12 h at 80 °C under oxygen. After the reaction, the mixture was cooled to room temperature and MS3A was separated by filtration through a glass filter. The amount of the product was determined by GLC analysis using bibenzyl as an internal standard. For isolation of the product the solvent was evaporated and the residue was purified by column chromatography (hexane–ethyl acetate as an eluent) and identified by $^1$H NMR and $^{13}$C NMR.

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8 Although Capdevielle and co-workers used pyridine as solvent in the presence of a stoichiometric amount of Cu(I) chloride [Refs. 6a–c], almost no reaction proceeded using a catalytic amount of it in our hand.

9 Metal-catalyzed aerobic oxidation of secondary amines to the corresponding imines, see Refs. 3e (Ru), 3f (Ru), and 4d (Cu), and also: a) (Co); A. Nishinaga, S. Yamazaki, and T. Matsuura, *Tetrahedron Lett.*, **29**, 4115 (1988). b) (Cu); M. Simizu, H. Orita, T. Hayakawa, K. Suzuki, and K. Takehira, *Heterocycles*, **41**, 773 (1995).

10 Isoamylamine was completely consumed under this reaction condition. The use of *n*-octylamine as a substrate in the presence of garvinoxyl gave a mixture of unidentified compounds among which the presence of the corresponding imine (around 20% yield) was confirmed by $^{1}$H NMR and $^{13}$C NMR.

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