Catalytic Oxidation of Amines Utilizing Binuclear Copper(II) Complex of 7-Azaindole

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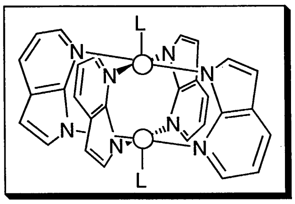
Treatment of benzylamine with a catalytic amount of a binuclear copper(II) complex of 7-azaindole **1** under an oxygen atmosphere at room temperature produced benzylidenebenzylamine and benzonitrile in good yields. This reaction is also applicable to other amines and gives the corresponding imines. Interestingly 1-phenylpyrrolidine was oxidized to cyclic dimers, but, in the presence of triethylamine, it was oxidized to the corresponding γ-lactam.

In recent years, binuclear copper-containing complexes have drawn considerable attention in biochemistry.[1] For example, binuclear copper complexes in hemocyanin and tyrosinase play important roles in oxygen transport and oxidation in organisms. We previously reported that a binuclear copper(II) complex of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) **1** acts as a catalyst for the oxygenation of α-carbon of ethers under molecular oxygen.[2] Since the coordination form of the complex **1** is similar to that of porphyrin, it seems likely that the complex **1** could be utilized for the oxidation of other substrates. Oxidation of amines is of importance from the standpoint of the in vivo metabolism of amines.[3] From these points of view, we report the catalytic oxidation of several amines utilizing complex **1** under molecular oxygen.



○ = Cu(II)

L = DMSO

Cu Complex **1**

Since our earlier studies showed that alkyl benzyl ethers are readily oxidized,[2] benzylamine was initially examined for this oxidation.

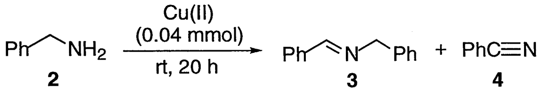
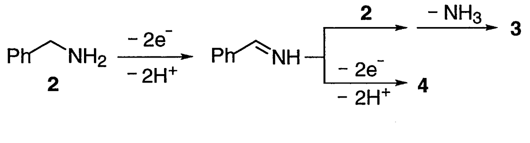


Table 1. Catalytic oxidation of benzylamine

run	Cu(II)	**2** (mmol)	atmosphere (1 atm)	TN[a] (yield/%) **3**	TN[a] (yield/%) **4**
1	**1**	40	O_2	76	152
2	**1**	40	N_2	0	0
3	$Cu(OAc)_2 \cdot H_2O$	40	O_2	0	0
4	**1**	8[b]	O_2	65(65)	86(21)

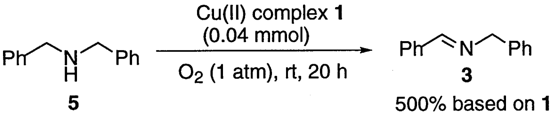
[a]TN = turnover number, based on Cu(II) and determined by ^1H-NMR. [b]solvent: DMF (4 ml).

When benzylamine (**2**; 4.28 g, 40 mmol) was treated with **1** (30 mg, 0.04 mmol) for 20 h under an oxygen atmosphere at room temperature, *N*-benzylidenebenzylamine (**3**) and benzonitrile (**4**) were obtained in 7600% and 15200% yields, respectively, based on Cu(II) (Table 1, run 1). The turnover numbers are calculated on the basis of a two-electron oxidation for **3**[4] and a four-electron oxidation for **4**.



Although treatment of ethers with a catalytic amount of **1** produced oxygenated products (esters),[2] dehydrogenation occurred in the case of the oxidation of amines. The reaction did not proceed under nitrogen or with copper(II) acetate monohydrate, which exists in a dimeric form similar to **1** (runs 2, 3). The reaction in DMF gave the oxidized products in good total yield, based on the substrate (run 4). It is known that the Cu/O_2/pyridine system is capable of efficient dehydrogenation of primary amines.[5] However, the addition of pyridine or 7-azaindole to the reaction, which used $Cu(OAc)_2 \cdot H_2O$ as the catalyst, was not effective. The complex **1** could also catalyze the oxidation of *n*-propylamine to give no propionitrile but the corresponding imine in 5500% yield based on Cu(II).

When dibenzylamine (**5**) was employed in the oxidation, dehydrogenation proceeded to give *N*-benzylidenebenzylamine (**3**) in 500% yield. The lower reactivity of **5** as compared to benzylamine can be explained by the fact that the reactivity of secondary amines toward oxidation is controlled more by steric factors, rather than electronic factors.



Since cyclic secondary amines are expected to have better coordinating ability than acyclic secondary amines, this reaction was applied to pyrrolidine (**6**). In contrast to benzylamine, pyrrolidine was efficiently oxidized to give an equilibrium mixture of 1-pyrroline (**7a**) and its trimer (**7b**) (Table 2, run 1). The catalytic activity of $Cu(OAc)_2 \cdot H_2O$ relative to **6** was different from the case of benzylamine (run 2), and the use of DMF as a solvent retarded the reaction (run 3).

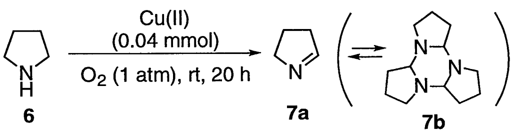


Table 2. Catalytic oxidation of pyrrolidine

run	Cu(II)	**6** (mmol)	TN[a] (yield/%)
1	**1**	50	312
2	$Cu(OAc)_2 \cdot H_2O$	50	168
3	**1**	8[b]	82 (41)

[a]TN = turnover number, based on Cu(II) and determined by ^{1}H-NMR. [b]solvent: DMF (4 ml).

Tertiary amines are known to be converted into the corresponding *N*-oxide with hydrogen peroxide or peroxy acids.[6] Furthermore, oxidative dealkylation of tertiary amines is a biologically important process in metabolism of amines.[7] While various aliphatic tertiary amines[8] were nearly inert in the present oxidation system, *N*-phenylpyrrolidine, which has relatively lower ionization potential in comparison with *N*-alkylpyrrolidine, reacted to give oxidative cycloadducts **9a**, **9b** and the oxygenated product, 1-phenyl-2-pyrrolidinone (**10**) (Table 3, run 1). $Cu(OAc)_2 \cdot H_2O$ also catalyzed the reaction to give only cycloadducts (run 2). The addition of triethylamine to the reaction caused very interesting results, namely, the selective formation of pyrrolidinone **10** (run 3). On the contrary, the reaction employing $Cu(OAc)_2 \cdot H_2O$ and triethylamine afforded cycloadducts **9a** and **9b** with no detectable formation of pyrrolidinone **10**. Although it is reported that oxidation of *N*-acyl or *N*-methyl alicyclic tertiary amines by other systems, including the Gif system, leads to the corresponding lactams,[9] there have been no examples of the oxidation of *N*-arylpyrrolidine to our knowledge.

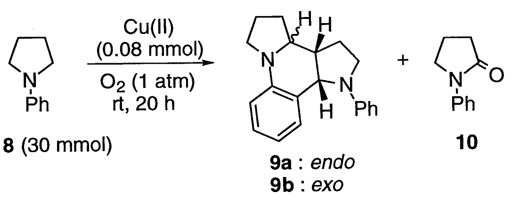
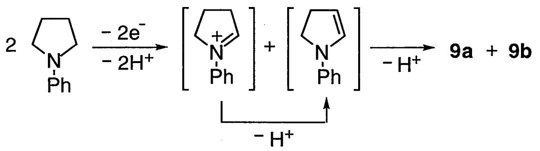


Table 3. Catalytic oxidation of *N*-phenylpyrrolidine

run	Cu(II)	additive (1.6 mmol)	TN[a]		
			9a	**9b**	**10**
1	**1**	—	42	20	12
2	$Cu(OAc)_2 \cdot H_2O$	—	22	31	0
3	**1**	Et_3N	0	0	47
4	$Cu(OAc)_2 \cdot H_2O$	Et_3N	42	55	0

[a]TN = turnover number, based on Cu(II) and determined by ^{1}H-NMR.

The formation of the cycloadducts, **9a** and **9b** is rationalized in the following scheme (below).



In summary, the binuclear copper(II) complex of 7-azaindole **1** catalyzed the oxidation of the α-carbon of amines under molecular oxygen. The efficient dehydrogenation of benzylamine and pyrrolidine with the complex **1** gave the corresponding imines. While 1-phenylpyrrolidine was oxygenated selectively to pyrrolidinone by the complex **1** in the presence of Et_3N, the reaction without Et_3N gave dimeric cycloadducts and pyrrolidinone. The oxidation of other compounds using this system is now underway.

References and Notes

1 B. L. Feringa, "Bioinorganic Chemistry of Copper," ed by K. D. Karlin and Z. Tyeklár, Chapman & Hall, New York (1993), pp306-324.

2 S. Minakata, E. Imai, Y. Ohshima, K. Inaki, I. Ryu, M. Komatsu, and Y. Ohshiro, *Chem. Lett.*, **1996**, 19.

3 R. B. Silverman, S. J. Hoffman, and W. B. Catus, *J. Am. Chem. Soc.*, **102**, 7126 (1980); J. T. Simpson, A. Krantz, F. D. Lewis, and B. Kokel, *J. Am. Chem. Soc.*, **104**, 7155 (1982), and references cited therein.

4 For the reaction mechanism, see; P. Capdevielle, A. Lavigne, and M. Maumy, *Tetrahedron*, **46**, 2835 (1990).

5 L. M. Sayre, W. Tang, K. V. Reddy, and D. Nadkarni, "Bioinorganic Chemistry of Copper," ed by K. D. Karlin and Z. Tyeklár, Chapman & Hall, New York (1993), pp236-248.

6 T. L. Gilchrist, "Comprehensive Organic Synthesis," ed by B. M. Trost, Pergamon Press Oxford (1991), Vol 6, pp735-756.

7 S.-I. Murahashi, T. Naota, and K. Yonemura, *J. Am. Chem. Soc.*, **110**, 8256 (1988); F. Wang and L. M. Sayre, *J. Am. Chem. Soc.*, **114**, 248 (1992).

8 Tribenzylamine was treated with **1** under the conditions (Table 1, run 4) to give a trace amount of benzaldehyde. *N*, *N*-Dimethylbenzylamine was oxidized with the complex **1** (0.04 mmol) under O_2 at 40 °C for 20 h to give a trace amount of benzonitrile. The following tertiary amines were not reactive under the conditions (Table 1, run 1).

$PhNR_2$ (R = Me, Et), NR (R = Me, Et, *i*-Pr, CH_2Ph, COPh)

9 S. Murata, M. Miura, and M. Nomura, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1259; E. Wenkert and E. C. Angell, *Synth. Commun.*, **18**, 1331 (1988); D. H. R. Barton, J. Boivin, D. Gaudin, and K. Jankowski, *Tetrahedron Lett.*, **30**, 1381 (1989).