

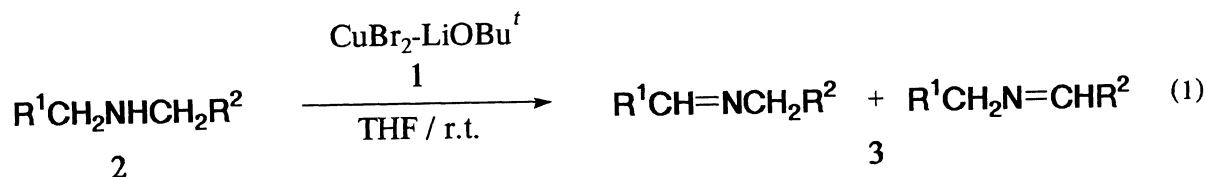
Oxidation of Amines with $\text{CuBr}_2\text{-LiOBu}^t$

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The oxidation of secondary amines with copper(II) reagent, prepared from copper(II) bromide and lithium *t*-butoxide, under mild reaction conditions gave the corresponding imines in high yields. Primary amines were also transformed to the corresponding nitriles.

The conversion of secondary amines into imines is an important process in connection with both biosynthesis and organic synthesis of alkaloids. In the previous paper,¹⁾ we showed that the copper(II) reagent (1) prepared from copper(II) bromide and lithium *t*-butoxide was effective for the oxidation of alcohols to the corresponding carbonyl compounds. Although the detail of the reaction pathway is not clear, we tentatively assume that the oxidation proceeds via the copper(II) alkoxide and the subsequent elimination of copper(II) hydride as similar to the mechanism proposed to account the oxidation of galactose catalyzed by the copper enzyme, galactose oxidase.²⁾ Based on the above hypothesis, it was expected that compounds containing a hydrogen-hetero atom bond would be also oxidized with the copper(II) oxidizing agent (1). In this communication, we wish to report the dehydrogenation of amines to imines and nitriles (Eqs. 1 and 2).



The oxidation of secondary amines (2) was carried out using 2.2 equivalents of the oxidant (1). In most of the reactions examined, amines (2) instantly disappeared when they were added to a THF solution of 1, and the corresponding imines (3) were isolated in quantitative yields (Eq. 1, Table 1). When acyclic unsymmetrical amines (2) were employed, the two possible structurally isomeric imines were produced (runs 3, 4, and 5). In such cases, the benzylidene derivatives always predominated. The oxidation of *N*-benzylaniline derivatives, however, was somewhat complicated by the formation of unidentified by-products (run 9).

Several metal salts, such as MnO_2 ,³⁾ $\text{Hg}(\text{OAc})_2$,⁴⁾ and Ag_2O ,⁵⁾ and other oxidizing agents, such as iodosylbenzene,^{6,7)} iodobenzene diacetate,⁷⁾ and Fremy's salt,⁸⁾ are available for the oxidation of secondary amines. The catalytic oxidations using ruthenium complex,^{6,9)} cobalt complex,¹⁰⁾ and NiSO_4 ¹¹⁾ have been also reported. However, most of these reagents can be applied only for the oxidation of benzylic or allylic amines; to the best of our knowledge, the transformation of 2-substituted pyrrolidines to the corresponding imines with $\text{Hg}(\text{OAc})_2$ ⁴⁾ is the sole example reported as the oxidation of simple aliphatic amine. Considering the fact that the yield of imine is sometimes varied largely with the structure of amine in the conventional reactions, the present

reaction provides a useful synthetic tool for the preparation of imines.

A typical experimental procedure is as follows: To a THF (2 ml) suspension of copper(II) bromide (491 mg, 2.2 mmol) was added a THF solution of lithium *t*-butoxide (3.0 ml, 0.74 ml / mmol, 2.2 mmol) at room temperature under argon, and the mixture was stirred for 15 min. Then a THF (2ml) solution of dibenzylamine (197 mg, 1 mmol) was added to the reaction mixture. After being stirred for 20 min, the reaction was quenched by addition of 3.5% NH₃ aqueous solution. The organic materials were extracted with CH₂Cl₂, and the extract was dried over K₂CO₃. After removal of the solvent, the residue was purified by short column chromatography (Merck aluminum oxide 90 (Brockmann V), hexane : AcOEt = 9:1) and *N*-benzylidenebenzylamine (193 mg) was isolated in 99% yield.

Next the oxidation of primary amines (4) was examined. It was found that the corresponding nitrile (5a) was produced in 44% yield and the substantial amount of starting material (21%) was recovered by the oxidation of primary amine (4a) with 2.2 equivalents of oxidant (1). The yield of 5a was increased by the use of 4.2 equivalents of the oxidant (1) (Eq. 2, Table 2).

Concerning the transformation of aliphatic amines to nitriles, LTA¹²⁾ and Ni₂O₃¹³⁾ have been used as oxidizing agents. The oxidations of substituted benzylamines with iodosylbenzene,⁷⁾ AgO,¹⁴⁾ and K₂RuO₄¹⁵⁾ were reported. The Co₂O₃-catalyzed oxidation of the same substrates was also examined.¹⁶⁾ As shown in Table 2, the present oxidation gave nitriles in better or comparable yields as compared with those reactions.

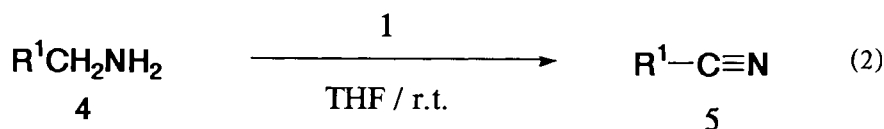
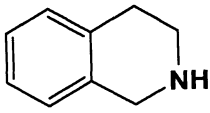
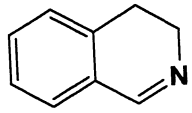


Table 2. The oxidation of primary amines (4) with CuBr₂ - LiOBu^t (1)^{a)}

Run	4	Time min	Product	Yield ^{b)} %
1	Ph(CH ₂) ₃ NH ₂ 4a	25	Ph(CH ₂) ₂ CN 5a	86 ^{c)}
2	CH ₃ (CH ₂) ₁₁ NH ₂ 4b	15	CH ₃ (CH ₂) ₁₀ CN 5b	75 ^{c)}
3	PhCH ₂ NH ₂ 4c	15	PhCN 5c	77 ^{d)}

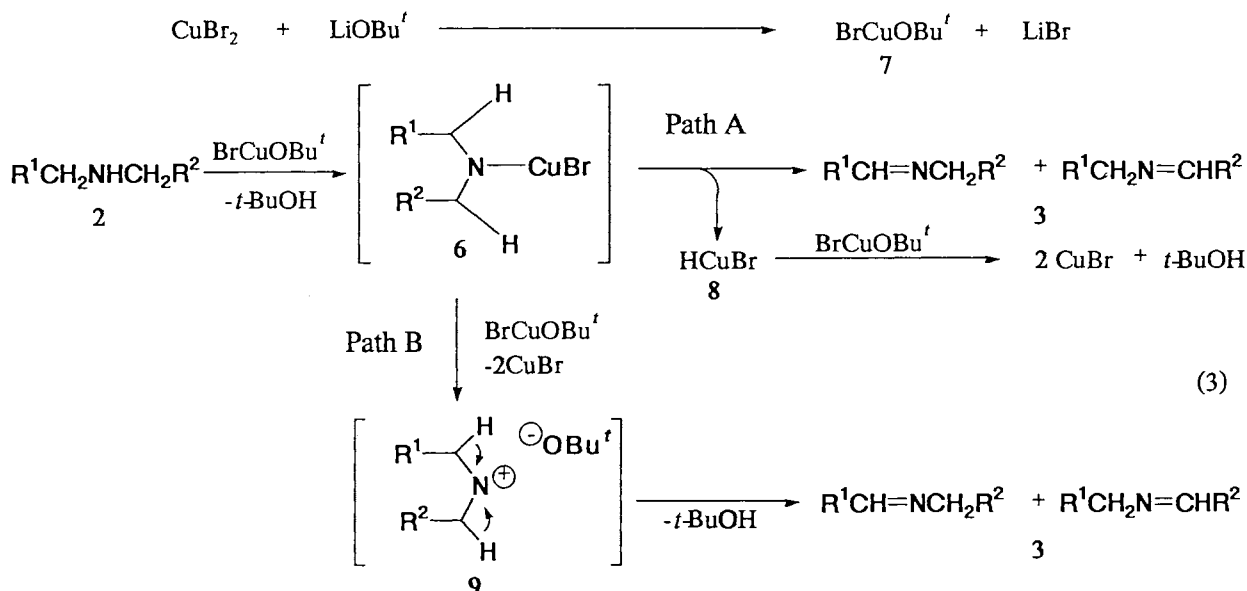
a) All the reactions were performed with a similar procedure as described in the text using 4.2 equivalents of 1, unless otherwise noted. b) Isolated yields. The structures of these compounds were supported by IR and NMR spectra. c) The nitrile (5) was isolated by preparative silica-gel TLC (hexane : AcOEt = 4 : 1). d) The nitrile (5c) was isolated by Kugelrohr distillation (130 °C (bath temp) / 50 mmHg).

Table 1. The oxidation of secondary amines (2) with CuBr₂ - LiOBu^t (1)^{a)}

Run	2	Time min	Product	Yield ^{b)} %
1	$\text{PhCH}_2\text{NCH}_2\text{Ph}$ H 2a	20	$\text{PhCH}_2\text{N}=\text{CHPh}$ 3a	99
2	 3a	20	 3b	89
3	$\text{Ph}(\text{CH}_2)_2\text{NCH}_2\text{Bu}^i$ H 2c	0.1	$\text{PhCH}=\text{NCH}_2\text{Bu}^i$, $\text{PhCH}_2\text{N}=\text{CHBu}^i$ 6 : 4 ^{c)} 3c	92
4	$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{NCH}_2\text{Bu}^i$ H 2d	12	$p\text{-MeOC}_6\text{H}_4\text{CH}=\text{NCH}_2\text{Bu}^i$, $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{N}=\text{CHBu}^i$ 6 : 4 ^{c)} 3d	95
5	$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{N}(\text{CH}_2)_3\text{Ph}$ H 2e	22	$p\text{-MeOC}_6\text{H}_4\text{CH}=\text{N}(\text{CH}_2)_3\text{Ph}$, $p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{N}=\text{CH}(\text{CH}_2)_2\text{Ph}$ 6 : 4 ^{c)} 3e	95
6	$\text{PhCH}_2\text{NBu}^t$ H 2f	5	$\text{PhCH}=\text{NBu}^t$ 3f	96
7	$\text{CH}_3(\text{CH}_2)_7\text{N}(\text{CH}_2)_7\text{CH}_3$ H 2g	5	$\text{CH}_3(\text{CH}_2)_6\text{CH}=\text{N}(\text{CH}_2)_7\text{CH}_3$ 3g	98
8	$t\text{-BuN}(\text{CH}_2)_{11}\text{CH}_3$ H 2h	10	$\text{CH}_3(\text{CH}_2)_{10}\text{CHO}$	88 ^{d)}
9	$p\text{-MeOC}_6\text{H}_4\text{CH}_2\text{NPh}$ H 2i	50	$p\text{-MeOC}_6\text{H}_4\text{CHO}$	52 ^{e)}

a) All the reactions were performed with a similar procedure as described in the text, unless otherwise noted. b) Isolated yields. The structures of these compounds were supported by IR and NMR spectra. c) Determined by NMR spectrum. d) Since it was difficult to isolate the imine (3h) without contamination with the corresponding aldehyde, the product was isolated after hydrolysis. e) Since the imine (3i) could not be purified by chromatography, the product was isolated after hydrolysis.

Similarly to the oxidation of alcohols,¹⁾ it is assumed that the present reaction may proceed through the initial formation of copper(II) amide (6) by the reaction of amine (2) with bromo(*t*-butoxy)copper(II) (7). The copper(II) amide (6), in turn, gives the corresponding imine (3) by the elimination of copper(II) hydride (8) (Path A), or via the cation intermediate (9) (Path B) as illustrated below.



It should be noted that a simple combination of less toxic common reagents which would be stored in laboratories of organic chemistry turned out to be a versatile oxidizing agent for the dehydrogenation of amines.

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