Graphical Abstract

Eco-friendly copper sulfate-catalyzed oxidation of amines to imines by hydrogen peroxide in water

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ABSTRACT

Imines are very important compounds in organic synthesis, and therefore, their preparation under mild condition has attracted much attention. In this study, it was found that copper sulfate effectively catalyzes the highly selective oxidation of benzylamines to the corresponding imines with H_2O_2 in water at room temperature for 1.5 h. This mild and eco-friendly oxidation method could be applied to the oxidation of alkylamines. Therefore, convenient procedure for the oxidation of amines to the imines has been developed.

Keywords:

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Imines are important for the synthesis of industrial materials and biologically active compounds such as amides, chiral amines, oxazolidines, hydroxyamines, and nitrones.¹ Numerous methodologies have been developed to synthesize imines, including methods such as oxidation of primary² or secondary³ amines, condensation of amines with aldehydes, and oxidative condensation of amines with alcohols⁴. In particular, extensive efforts have been made to develop efficient methods for imine selective synthesis from primary amines to prevent the formation of other, undesired nitrogen-containing compounds.⁵

Recently, we developed a vanadium-catalyzed oxidation of benzyl alcohols to carbonyl compounds,⁶ and of benzylamines to imines.⁷

Scheme 1. Vanadium-catalyzed oxidation of benzylamines.

During the course of our studies, we found that Cu salts possess good catalytic activity for the oxidation of amines to imines, and herein, we report a convenient copper-catalyzed oxidation of amines to imines with H_2O_2 in water at room temperature. This new method has the following advantages over our previous work; (1) low catalytic load (0.2 mol%), (2) low reaction temperature (room temperature), (3) short reaction time (1.5 h), (4) water as solvent, and (5) substrate scope (aliphatic amines).

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As copper is abundant and inexpensive compared to precious metals such as Pd and Ru, we were prompted by our findings to develop an oxidation method using affordable, readily available, and eco-friendly reagents. The use of water, rather than organic solvents, is advantageous as it is cheap, nontoxic, and inflammable. Furthermore, it is necessary to suppress the use of the organic solvent for the realization of the low-carbon society. Hydrogen peroxide (H_2O_2) is regarded as a green oxidant because the only oxidation byproduct is water.

First, we examined the VO_4 -catalyzed oxidation of benzylamine (**1a**) with H_2O_2 in water at room temperature. However, the reaction did not proceed efficiently and the corresponding *N*-(benzylidene)benzylamine (**2a**) was obtained in only 2% yield (Table 1, entry 1). Next, several metal sulfates were examined and it was found that copper was the most effective of these (entries 2–7). A negligible yield of **2a** was obtained with no catalyst (entry 8). When a variety of Cu(I) and Cu(II) salts were used, imine **2a** was obtained in moderate to high yields (entries 9–16). Of the catalysts employed, CuSO_4 was found to be the most effective for the oxidation of **1a** to **2a**.

Oxidation of substituted benzylamines with H_2O_2 in water at room temperature was investigated using CuSO_4 as the catalyst (Table 2).⁸ Benzylamine derivatives with electron-donating or electron-withdrawing groups could be oxidized to the corresponding imines in good to high yields (entries 2–9). 1-Phenylethanamine (**1i**) could be oxidized to the corresponding imine (**2i**) in moderate yields (entry 10). Oxidation of dibenzylamine (**1j**) proceeded inefficiently, although oxidative

dehydrogenation to give the imine had been expected (entry 11). In general, aliphatic amines undergo oxidation inefficiently compared to aromatic amines. *Very interestingly, the present*

Table 1. Oxidation of **1a** with various catalysts

1a (2.0 mmol) **2a**

entry	catalyst	yield ^a
1	VOSO ₄ •5H ₂ O	2%
2	CuSO ₄ •5H ₂ O	88% ^b
3	FeSO ₄ •7H ₂ O	3%
4	NiSO ₄ •6H ₂ O	1%
5	CoSO ₄ •7H ₂ O	1%
6	Ce(SO ₄) ₂ •4H ₂ O	2%
7	ZnSO ₄ •7H ₂ O	1%
8	None	1%
9	CuCN	76%
10	CuCl	38%
11	CuBr	30%
12	CuI	49%
13	Cu(CH ₃ COO) ₂ •H ₂ O	52%
14	Cu(NO ₃) ₂ •6H ₂ O	54%
15	Cu(CF ₃ SO ₃) ₂ •H ₂ O	63%
16	CuCl ₂	53%

^a Determined by ¹H NMR using an internal standard; Yield of **2a** are based on the substrate **1a**

^b Yield based on H₂O₂ is 44%

Table 2. Oxidation of benzylamine derivatives

1 (2.0 mmol) **2**

entry	substrate	CuSO ₄ (mol%)	yield ^{a,b} (%)
1 ^c	R = H	1a 0.2	2a 84
2	R = H	1a 0.2	2a 91 (72)
3	R = <i>p</i> -Me	1b 0.2	2b 74 (71)
4 ^d	R = <i>p</i> - ^t Bu	1c 0.2	2c 81

5	R = <i>o</i> -OMe	1d	1.0	2d	87
6	R = <i>m</i> -OMe	1e	0.5	2e	99 (90)
7	R = <i>p</i> -OMe	1f	0.5	2f	97
8	R = <i>p</i> -Cl	1g	0.5	2g	85 (84)
9 ^d	R = <i>p</i> -CF ₃	1h	0.2	2h	72
10		1i	0.2	2i	54
11	dibenzylamine	1j	0.2	2a	trace

^a Determined by ¹H NMR using an internal standard (Isolated); Yield of **2** are based on the substrate **1**

^b Yield based on H₂O₂ is as follows; 42% (entry 1), 46% (entry 2), 37% (entry 3), 27% (entry 4), 44% (entry 5), 50% (entry 6), 49% (entry 7), 43% (entry 8), 24% (entry 9), 27% (entry 10)

^c Reaction time: 1.0 h

^d 10% aq. H₂O₂ (3.0 mmol)

mild oxidation method could successfully be applied to aliphatic amines. Aliphatic primary amines could also be oxidized to the corresponding imines efficiently (Table 3, entries 1–5).⁸

Table 3. Oxidation of aliphatic amines

3 (2.0 mmol) **4**

entry	substrate	yield ^{a,b}
1		3a 4a 37%
2		3b 4b 58%
3		3c 4c 75%
4		3d 4d 85%
5 ^c		3e 4e 81%

^a Determined by ¹H NMR using an internal standard; Yield of **4** are based on the substrate **3**

^b Yield based on H₂O₂ is as follows; 19% (entry 1), 29% (entry 2), 38% (entry 3), 45% (entry 4), 27% (entry 5)

^c H₂O₂ (3.0 mmol)

A possible reaction pathway is proposed in Scheme 1.^{2a,9} Firstly, amine complex is formed by reaction of the amine with CuSO₄. Next, the complex reacts with H₂O₂¹⁰ and intermediate imine is generated. The final product is obtained either by transamination of the intermediate imine and the amine substrate, or by hydrolysis of the intermediate imine, followed by condensation of the resulting aldehyde with the amine substrate.

Scheme 1. A possible catalytic cycle for the CuSO_4 -catalyzed oxidation of primary amines with H_2O_2

In conclusion, a convenient procedure for the oxidation of amines to the corresponding imines has been developed. The method is simple to perform, and oxidation of the amines to imines proceeds under mild conditions, using H_2O_2 in water at room temperature for 1.5 h. Studies are currently underway in our laboratory to investigate further synthetic applications.

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- General procedure and supplemental data is shown in supporting information.
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- To get insight into the possible reaction pathway, CuSO_4 -catalyzed oxidation of benzylamine with H_2O_2 was monitored by UV-Vis spectroscopy and spectral changes were observed (See Supporting information SI 1.4).