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SELENIUM DIOXIDE CATALYZED OXIDATION OF SECONDARY AMINES WITH HYDROGEN PEROXIDE. SIMPLE SYNTHESIS OF NITRONES FROM SECONDARY AMINES

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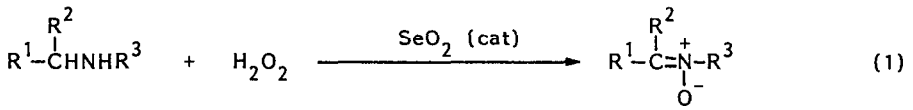
Summary: Oxidation of secondary amines with hydrogen peroxide in the presence of selenium dioxide catalyst at room temperature gives nitrones, which are versatile synthetic intermediates, highly efficiently.

Nitrones are highly versatile synthetic intermediates and excellent spin trapping reagents.[1] The preparation of nitrones has been performed by either condensation of aldehydes or ketones with hydroxylamines[1] or oxidation of the corresponding hydroxylamines.[2] The difficulty of these methods is in the preparation of the starting hydroxylamines. To overcome this difficulty the direct and catalytic oxidation of secondary amines has been required. During the course of our systematic study on the oxidation of amines by simulation of the enzymatic function of flavoenzymes, we have found that the novel transformation of secondary amines to nitrones can be performed upon treatment with hydrogen peroxide in the presence of selenium dioxide catalyst as depicted in Eq 1. The present reaction is advantageous over the previously reported, tungstate catalyzed oxidation reaction of secondary amines.[3]

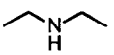
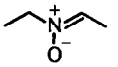
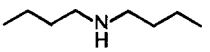
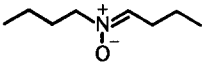
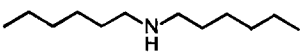
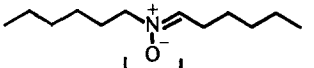
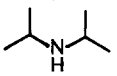
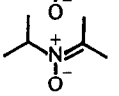
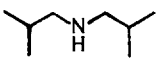
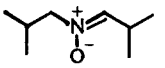
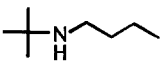
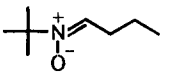
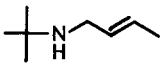
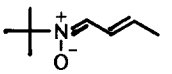
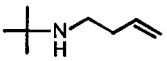
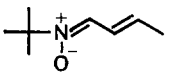
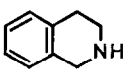
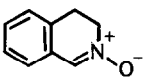
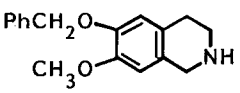
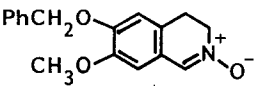
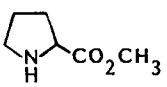
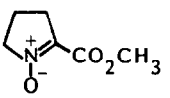
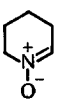
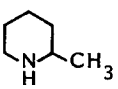
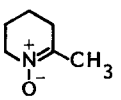
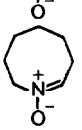


(1)

Generally, secondary amines can be oxidized into the corresponding nitrones upon treatment with 2-3 molar equivalents of hydrogen peroxide in the presence of 4-5 mol % of selenium dioxide at room temperature in a single step. The activity of various oxidants and catalysts has been examined. Hydrogen peroxide has been found to be the best oxidant, and the other oxidants such as t-BuOOH and m-$ClC_6H_4CO_3H$ gave poor results. The reaction proceeds efficiently in a polar solvent such as acetone, methanol, and dioxane.

A representative example is the preparation of 1-pyrroline N-oxide (1). To a mixture of SeO_2 (0.014 g, 0.13 mmol) and pyrrolidine (0.184 g, 2.59 mmol) in acetone (5.0 mL) was added dropwise an aqueous 30% hydrogen peroxide solution (0.857 g, 7.56 mmol) at 0 °C under argon. After additional stirring at room temperature for 3 h, acetone was removed under reduced pressure. The

Table 1. Catalytic Oxidation of Secondary Amines with Hydrogen Peroxide[a]

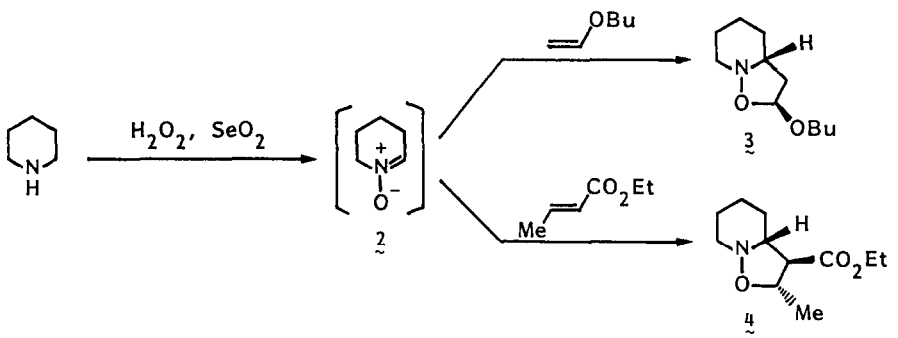
Entry	Amine	Solvent	Product[b]	Yield[c]/%
1		CH_3OH		74
2		CH_3OH		80
3		CH_3OH		85
4		CH_3OH		66
5		CH_3OH		79
6		CH_3OH		64
7		CH_3OH		63
8		CH_3OH		61
9		CH_3OH		89
10		CH_3OH		91
11		$(CH_3)_2C=O$	 1	73
12		$(CH_3)_2C=O$		57
13[d]		$(CH_3)_2C=O$		88
14[d]		$(CH_3)_2C=O$		79
15[d]		$(CH_3)_2C=O$		34

a) The reaction was carried out similar to the procedure described in the text.
b) The products gave satisfactory IR, NMR, and mass spectral data. c) Isolated yield by column chromatography. d) Hydrogen peroxide (2.2 mol equiv) was used.

remaining aqueous solution was extracted with CH_2Cl_2 (20 mL x 4). Column chromatography on Al_2O_3 (eluent; $CHCl_3/CH_3OH$ 9:1) gave nitrone 1 (0.161 g, 73%).

The typical results of the preparation of nitrones are summarized in Table 1. Acyclic and cyclic amines are generally converted into the corresponding nitrones in excellent to good yields. The previously reported tungstate catalyzed oxidation of cyclic amines requires water as a solvent, and hence the isolated yields are low because of difficulty in extracting nitrone. The oxidation of amines bearing a bulky substituent at the α-position proceeds slowly (Entries 4, 6-8). Olefins tolerate the reaction (Entry 7). Hydrogen migration is observed in the oxidation of homoallylic amines such as N-t-butyl-3-butenylamine (Entry 8). The oxidation of 1,2,3,4-tetrahydroisoquinolines gives the corresponding nitrones, which are highly versatile intermediates for the synthesis of isoquinoline alkaloids (Entries 9, 10). It is noteworthy that the esters of α-amino acids, such as methyl prolinate can be converted into the corresponding nitrones (Entry 12).

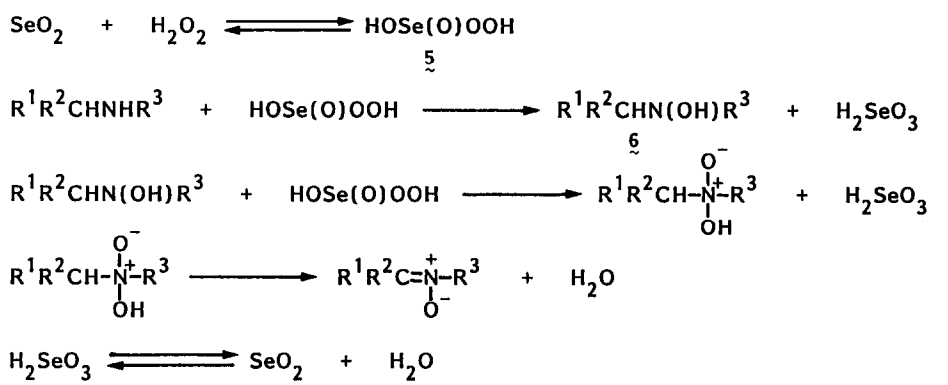
Nitrones are excellent 1,3-dipoles and have been utilized for the synthesis of various nitrogen containing biologically active compounds.[4] Using the present reaction isoxazolidines can be prepared readily without isolation of nitrones. Typical example is the preparation of 2-butoxypiperidino[1,2-b]-isoxazolidine (3). To a mixture of piperidine and SeO_2 (5 mol %) in acetone was added an aqueous 30% H_2O_2 solution (2.2 mol equiv). After stirring for 3 h at room temperature, acetone was removed under reduced pressure. Butyl vinyl ether was added, and the mixture was stirred at 90 °C for 1.5 h. Extraction with CH_2Cl_2 gave 3 (69%).[5] In a similar manner, the reaction of nitrone 2 with (E)-ethyl crotonate gives 3-ethoxycarbonyl-2-methylpiperidino[1,2-b]-isoxazolidine (4)[5] regio and stereoselectively in 56% isolated yield.



The reaction can be rationalized by assuming the mechanism depicted in Scheme 1. The oxidation of secondary amines with peroxyselenious acid (5)[6], which is derived from SeO_2 and H_2O_2, gives hydroxylamines (6). Further oxidation of 6 with 5 followed by dehydration gives nitrones. Selenious acid formed is in equilibrium with selenium dioxide and water[6c] and hence the catalytic cycle is completed. The hydroxylamine intermediates are observed

during the reaction of secondary amines bearing a sterically bulky substituent. The hydroxylamines are readily converted into the corresponding nitrones under the reaction conditions.

Scheme 1



Further work is currently in progress on the extension of this highly efficient reaction to the other system and application to the synthesis of nitrogen containing biologically active natural products.

References and Notes

1) For review of nitrone chemistry, see; a) E. Breuer, "The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives", S. Patai, ed., John Wiley, 1982, p 459; b) G. Tennant, "Comprehensive Organic Chemistry", D. H. R. Barton and W. D. Ollis, ed., Pergamon Press, vol 2, 1979, p 500; c) S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Academic Press, 1972, vol 3, p 301.

2) S.-I. Murahashi, H. Mitsui, T. Watanabe, and S. Zenki, Tetrahedron Lett., 24, 1049 (1983), and references cited therein.

3) H. Mitsui, S. Zenki, T. Shiota, and S.-I. Murahashi, J. Chem. Soc., Chem. Commun., 1984, 874.

4) a) S. Mzengeza, C. M. Yang, and R. A. Whitney, J. Am. Chem. Soc., 109, 276 (1987); b) D. Lathbury and T. Gallagher, J. Chem. Soc., Chem. Commun., 1986, 1017; c) J. J. Tufariello and K. Winzenberg, Tetrahedron Lett., 27, 1645, (1986); d) J. J. Tufariello and J. M. Puglis, ibid., 27, 1489 (1986); e) T. Kametani, T. Nagahara, and T. Honda, J. Org. Chem., 50, 2327 (1985); f) P. DeShong, C. M. Dicken, J. M. Leginus, and R. R. Whittle, J. Am. Chem. Soc., 106., 5598 (1984); g) H. Iida, M. Tanaka, and C. Kibayashi, J. Chem. Soc., Chem. Commun., 1983, 271.

5) The compound gave satisfactory spectroscopic and analytical data.

6) a) Y. Ogata and I. Tabushi, Bull. Chem. Soc. Jpn., 32, 215 (1959); b) N. Sonoda and S. Tsutsumi, ibid., 32, 505 (1959); c) F. J. Hughes and D. S. Martin, Jr., J. Phys. Chem., 59, 410 (1955).

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