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Oxidation of Secondary Amines to Nitrones Using Urea-Hydrogen Peroxide Complex (UHP) and Metal Catalysts.

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Abstract: Secondary amines can be readily oxidized to the corresponding nitrones using urea-hydrogen peroxide complex (UHP) and metal catalysts in methanol at room temperature. Sodium tungstate is the most effective catalyst in several runs and common protecting groups are tolerated in these conditions.

The remarkable importance of nitrones as valuable intermediates and useful spin trapping reagents has stimulated a towering series of synthetic efforts for their direct preparation[1]. Besides the classical condensation of N-substituted hydroxylamines with carbonyls, a number of alternative protocols for the nitrones synthesis are by far become available[2]. Oxidation of N,N-disubstituted hydroxylamines[3] is certainly a very efficient procedure for this purpose, but the preparation of these nitrogeneous precursors is not a trivial task. Direct oxidation of secondary amines is substantially preferable to the latter procedure and several oxidizing systems have been devised[4]. The use of hydrogen peroxide-metal catalysts based procedures offers a practical synthetic tool for nitrones preparation[5]. The above cited techniques employ 30% aqueous hydrogen peroxide as oxidizing source but during the last decade some hydrogen peroxide-base complexes have been introduced in synthesis and constitute a safer alternative to the use of concentrated solutions of hydrogen peroxide[6].

In this communication we describe the utilization of UHP-metal catalyst systems for the direct conversion of secondary amines to nitrones. Mo (VI), W (VI) salts as well as SeO_2 have been tested as metal catalysts for the oxidations with UHP and the results are summarized in the Table . All reactions have been conducted at room temperature in methanol as solvent and the best issues have been obtained using Na_2WO_4 as catalyst, although Na_2MoO_4 in several cases gives comparable results. Acid sensitive protecting groups are usually well tolerated by our reaction conditions. Chiral cyclic nitrone **2b**, an interesting intermediate for the synthesis of polyhydroxylated pyrrolidines[7], is efficiently obtained using various metal catalysts (entry 2). Nitrone **2e** , obtained by oxidation of TBS protected diethanolamine, may represent a good intermediate for the synthesis of polyfunctional molecules[8].

As most of the oxidizing procedures concerning secondary amines this method requires the use of symmetrical substrates in order to avoid regiochemical troubles during nitrone formation[9]. Oxidation of secondary amines with an aromatic ring directly linked to the nitrogen atom usually give disappointing results when peroxopolyoxo complexes are used as catalysts because of the competitive electron transfer from the amine to the oxidant [5d]. In this regard amine **1i** is easily converted to the parent nitrone **2i** in 75% yield using sodium tungstate as catalyst (entry 9). The oxidant activity of these metal catalysts may be ascribed to the generation of peroxo complexes which have been isolated and characterized in several cases[10].

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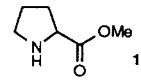
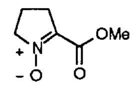
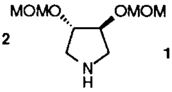
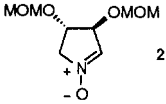
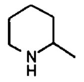
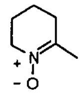
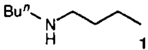
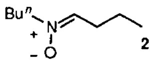
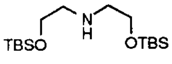
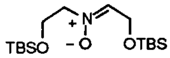
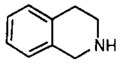
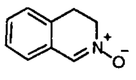
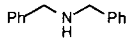
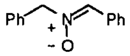
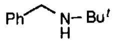
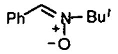
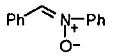
Table: Synthesis of Nitrones by Oxidation of Secondary Amines with UHP-Metal Catalysts in Methanol

Entry	Substrate	Product	Time (h)	Yield ^{a}
1	 1a	 2a	3 3	60 (W) 50 (Mo)
2	 1b	 2b	12 9 12	70 (W) 62 (Se) 55 (Mo)
3	 1c	 2c	4 5	80 (W) 78 (Mo)
4	 1d	 2d	3 5	92 (W) 80 (Mo)
5	 1e	 2e^a	3 3	70 (W) 45 (Mo)
6	 1f	 2f	5 6	80 (W) 76 (Mo)
7	 1g	 2g	4 4	84 (W) 90 (Mo)
8	 1h	 2h	3 4	80 (W) 87 (Mo)
9^b	 1i	 2i	6 7	75 (W) 60 (Mo)

a) Yields of pure, isolated products. Catalysts used are: W = Na_2WO_4; Mo = Na_2MoO_4; Se = SeO_2
b) 6 equivalents of UHP are required for complete oxidation

Synthesis of Nitrones 2a-i: general procedure.

To a stirred solution of the amine (5 mmol) in methanol (10 mL), the metal catalyst (0.25 mmol) and UHP (20 mmol) are successively added at room temperature. After stirring for the appropriate time (see Table 1), the solvent is evaporated and the solid residue is taken up in dichlorometane and filtered to remove urea. Removing of the solvent at reduced pressure affords the crude product that is purified by cristallization or column chromatography.

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3. For a very recent example see: Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571.
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8. Compound 2e : oil, I. R. (cm^{-1}, neat): 1600 (C=N); ^1H-NMR (300 MHz, $CDCl_3$) δ ppm : 0.05 (s, 6H, $SiMe_2$), 0.08 (s, 6H , $SiMe_2$), 0.88 (s, 9H, $SiBu^t$), 0.89 (s, 9H, $SiBu^t$), 3.80 (m, 2H), 4.00 (m, 2H), 4.59 (d, 2H, J= 4.0Hz, CH_2-C=N), 6.88 (t, 1H, J= 4.0Hz, CH=N).
9. These problems have been partially overcome using N-Alkyl α-amino acids as substrates through a regioselective decarboxylative oxidation:Murahashi, S.-I.; Imada, Y.; Ohtake, H. *J. Org. Chem.* **1994**, *59*, 6170.
10. a) Ishii, Y.; Yamawaki, K.; Ura, T.; Yamada, H.; Yoshida, T.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3587. b) Venturello, C.; Aloisio, D. *J. Org. Chem.* **1988**, *53*, 3587. An alternative hypothesis has been elaborated by Murahashi that accounts for the formation *in situ* of peroxytungstate species $HOOWO_3^-$ and $HOOWO_6^-$ (see refs. 5b and 9).

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