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Catalytic Oxidation of Imines Based on Methyltrioxorhenium/Urea Hydrogen Peroxide: A Mild and Easy Chemo- and Regioselective Entry to Nitrones

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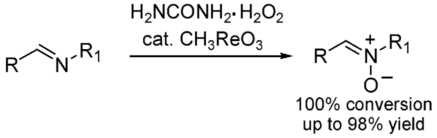
ABSTRACT



The first successful catalytic oxidation procedure for the chemoselective conversion of imines to nitrones is reported. The reaction is general, high yielding, and user and environmentally friendly, and furnishes a solution to the yet unanswered issue of regioselective access to nitrones by oxidation of nitrogen derivatives.

Nitrones **1** are useful and versatile intermediates for organic syntheses. They behave as electrophiles toward organometallics and as 1,3-dipoles in cycloadditions.[1] Recently, novel modes of reaction promoted by metal derivatives have been discovered.[2] Moreover, nitrones have relevant applications as spin traps in biological studies[3] and as therapeutics in age-related diseases.[4] The most common procedures for the preparation of nitrones consist of condensation of aldehydes with *N*-monosubstituted hydroxylamines and oxidation of secondary amines or *N*,*N*-disubstituted hydroxylamines.[1,5] The direct catalytic oxidation of amines[6] is particularly convenient, due to the greater availability of amines compared to hydroxylamines. However, the general viability of oxidation methods has been hampered by unresolved regioselectivity issues when unsymmetrical substrates are involved.[7,8] In this paper, we report the first successful catalytic oxidation procedure for the chemoselective conversion of imines to nitrones. It represents a breakthrough in the chemistry of these compounds, which become accessible regioselectively with a simple and straightforward oxidative approach. The reaction is general and simple, being performed with urea hydrogen peroxide (UHP) and a catalytic amount (2 mol %) of methyltrioxorhenium (MTO, CH_3ReO_3) in MeOH at room temperature. Oxidation of imines **2**, readily available in a regiospecific manner by

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[2] (a) Masson, G.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772−1775. (b) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *26*, 3023−3026. (c) For a brief account, see: Cardona, F.; Goti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7832−7835.

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[4] Floyd, R. A. *Aging Cell* **2006**, *5*, 51−57.

[5] Breuer, E. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; p 459.

[6] (a) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736−1744. (b) Murahashi, S.-I.; Shiota, T.; *Tetrahedron Lett.* **1987**, *28*, 2383−2386. (c) Nannelli, L.; Goti, A. *Tetrahedron Lett.* **1996**, *37*, 6025−6028. (d) Goti, A.; Cardona, F.; Soldaini, G. *Org. Synth.* **2005**, *81*, 204−212.

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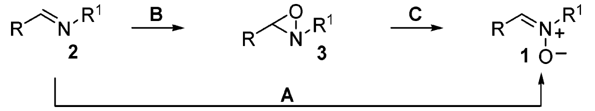
10.1021/ol062862w CCC: \$37.00

Scheme 1. Oxidation of Imines **2** to Nitrones **1** or Oxaziridines **3**



condensation of aldehydes with primary amines,[9] is obviously an attractive way for accessing nitrones. Unfortunately, oxidation of imines to nitrones (Scheme 1, path A) is not an easy task. Only one procedure, employing excess permanganate under phase-transfer conditions,[10] is quite general and affords reasonable yields. However, serious drawbacks concerning selectivity[10,11] and failure to afford the desired nitrones from cyclic imines[12] were reported. Imines may yield several products by oxidation and control of selectivity is challenging.[13] Oxaziridines **3** are the most common oxidation products with a variety of reagents (path B).[13,14] In some instances, they may rearrange to nitrones under acid catalysis (path C).[15] Other oxidants gave amides or rearranged compounds.[11,16] Only a few of these procedures employed environmentally benign oxidants with metal catalysts.[14h−j] It is noteworthy that no catalytic procedure for the oxidation of imines to nitrones has been reported so far. Recently, methyltrioxorhenium (MTO) became popular as a catalyst for alkene epoxidation.[17] Hydrogen peroxide is the usual stoichiometric oxidant, responsible for formation of the catalytically active peroxorhenium species.[17] Several other functional groups have been oxidized by MTO/H_2O_2. During our studies in this area, we noticed that *N*-oxidation of nitrogenated compounds by MTO occurs readily.[6c,d,18] Therefore, we envisaged that MTO might serve as a suitable catalyst for oxidizing imines to nitrones. The results of optimized MTO-catalyzed oxidation of imines **2a**−**v** to the corresponding nitrones **1a**−**v** are shown in Table 1. Imines **2a**−**r** have been prepared by condensation of aldehydes with primary amines and pyrrolines **2s**−**v** by HCl elimination from the corresponding *N*-chloroamines. Remarkably, pyrroline (and tetrahydropyridine) ketimines and aldimines, e.g., **2u** and **2v**, are both accessible regioselectively from the same 2-substituted *N*-chloroamines by elimination with different bases.[19] Oxidations have been performed with 2 mol % of MTO and urea hydrogen peroxide (UHP) as the stoichiometric oxidant. UHP is a solid complex used as a practical and safe source of H_2O_2.[20] It conveniently replaces hydrogen peroxide aqueous solutions when compounds sensitive to hydrolysis, such as **1** and **2**, are involved. All of the substrates reached complete conversion, apart from imine **2q**. This suggested that bulky substituents have detrimental effects on reactivity, as proved by the low yields in entries 17 and 18. *N*-Arylnitrones are known to suffer from low stability under a variety of conditions.[21] This may account for the moderate yield obtained for nitrone **1c** (Table 1, entry 3). The oxidation was highly selective; the crude reaction mixtures showed no trace of oxaziridines or other oxidation products, but only minor amounts of hydrolysis compounds in few cases. Variations in peroxometal catalytic species, H_2O_2 source, and solvent used resulted in poorer conversion and/or yield. MTO was much more effective than other related catalysts: for example, Na_2WO_4/UHP in MeOH did oxidize **2a** to nitrone **1a**, but only 35% conversion was achieved after 21 h. We were surprised at the different chemoselectivity reported for the oxidation of imines with Na_2WO_4/H_2O_2 in acetonitrile, which were claimed to afford oxaziridines only.[14j] However, in our hands, this reaction gave no detectable amount of any oxidation product from imine **2e**. Similarly, MTO/H_2O_2 in acetonitrile gave only 20% conversion of **2e** after 16 h, producing a complex mixture containing only trace amount of nitrone **1e** and oxaziridine **3e**. This finding confirmed the paramount importance of using alcoholic solvents in MTO-catalyzed oxidations of nitrogenated compounds. Our experimental data suggest that nitrones are formed by direct *N*-oxidation,[13] i.e., attack of the lone pair of the imine nitrogen atom to the peroxo moiety of the active Re catalyst. Accordingly, the reaction is only barely sensitive to electronic substituent effects. Intermediate formation of an oxaziridine rearranging to a nitrone was ruled out. Indeed, oxaziridine **3b**, synthesized according to a known procedure,[14f] was unaffected by treatment with MTO or MTO/UHP in MeOH. Concerning the fundamental issue of regioselective formation of nitrones, entries 9, 15, 21, and

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(9) Patai, S. *The Chemistry of the Carbon−Nitrogen Double Bond*; Wiley: New York, 1970.

(10) Christensen, D.; Jørgensen, K. A. *J. Org. Chem.* **1989**, *54*, 126−131.

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(12) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Gallagher, T.; Milán, S. *Tetrahedron: Asymmetry* **2002**, *13*, 437−445.

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(15) Lin, Y.-M.; Miller, M. J. *J. Org. Chem.* **1999**, *64*, 7451−7458.

(16) (a) An, G.-i.; Kim, M.; Kim, J. Y.; Rhee, H. *Tetrahedron Lett.* **2003**, *44*, 2183−2186. (b) Nongkunsarn, P.; Ramsden, C. A. *Tetrahedron* **1997**, *53*, 3805−3830.

(17) For reviews, see: (a) Herrmann, W. A.; Kühn, F. E. *Acc. Chem. Res.* **1997**, *30*, 169−180. (b) Espenson, J. H. *Chem. Commun.* **1999**, 479−488.

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(19) Davis, B. G.; Maughan, M. A. T.; Chapman, T. M.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103−106.

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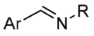
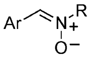
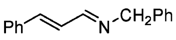
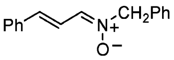
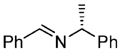
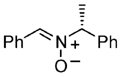
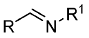
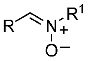
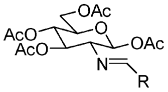
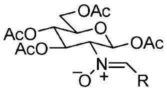
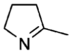
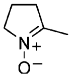
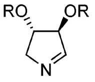
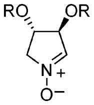
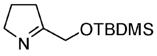
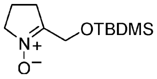
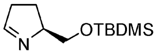
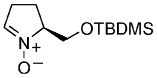
(21) Cordero, F. M.; Barile, I.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. *Synlett* **2000**, 1034−1036.

Table 1. Catalytic Oxidation of Imines **2a**−**v**[a]

entry	imine **2**	nitrone **1**	time (h)	yield (%)[b]
1	 **2a**: Ar=Ph, R=PhCH$_2$	 **1a**	6	78
2	**2b**: Ar=Ph, R=*n*-Bu	**1b**	4	85
3	**2c**: Ar=Ph, R=Ph	**1c**	0.5	50
4	**2d**: Ar=4-O$_2$NC$_6$H$_4$, R=PhCH$_2$	**1d**	6	74
5	**2e**: Ar=4-O$_2$NC$_6$H$_4$, R=*n*-Bu	**1e**	3	82
6	**2f**: Ar=2-Naphthyl, R=PhCH$_2$	**1f**	13	73
7	**2g**: Ar=2-Naphthyl, R=*n*-Bu	**1g**	6	76
8	**2h**: Ar=3-MeOC$_6$H$_4$, R=PhCH$_2$	**1h**	4.5	71
9	**2i**: Ar=3-MeOC$_6$H$_4$, R=4-MeOC$_6$H$_4$CH$_2$	**1i**	3	88
10	**2j**: Ar=3-MeOC$_6$H$_4$, R=*n*-Bu	**1j**	3	80
11	**2k**: Ar=4-MeOC$_6$H$_4$, R=PhCH$_2$	**1k**	3.5	81
12	**2l**: Ar=4-MeOC$_6$H$_4$, R=4-MeOC$_6$H$_4$CH$_2$	**1l**	2	80
13	**2m**: Ar=4-MeOC$_6$H$_4$, R= *n*-Bu	**1m**	1.5	68
14	 **2n**	 **1n**	1	76
15	 **2o**	 **1o**	20	60
16	 **2p**: R=*n*-Pr, R^1=PhCH$_2$	 **1p**	1	50
17	**2q**: R=*t*-Bu, R^1=PhCH$_2$	**1q**	5	32[c]
18	 **2r**: R=4-MeOC$_6$H$_4$	 **1r**	72	29[d]
19	 **2s**	 **1s**	2	98
20	 **2t**: R=TBDMS	 **1t**	1.5	50
21	 **2u**	 **1u**	2	95
22	 **2v**	 **1v**	0.5	97

[a] Reaction conditions: imine **2** (1 mmol), CH$_3$ReO$_3$ (2 mol %), H$_2$O$_2$•urea (3 equiv), MeOH (2 mL), rt. All reactions reached complete conversion, unless otherwise stated. [b] Yields of isolated pure nitrones. [c] 50% conversion. [d] 4 mol % of MTO.

22 nicely illustrate the tremendous advantage of this method compared to oxidation of amines or hydroxylamines. Nitrones **1i**, **1o**, **1u**, and **1v** were produced selectively. In contrast, oxidation with MTO/UHP[6c,d] of the amines **4** and **5** gave inseparable equimolar mixtures of regioisomeric nitrones **1i**/**1i′** and **1u**/**1v**, respectively (Scheme 2). This method allowed easy access to chiral nitrones (e.g., **1o**, **1r**, **1t**, **1v**), useful synthetic intermediates,[22] without any loss of optical purity.[23] Particularly meaningful are the syntheses of nitrones **1o** and **1v**. Preparation of nitrones related to **1v** via other oxidation procedures was troublesome and occurred with low yields and an absence of selectivity.[24] *N*-(α-Methyl)benzylnitrones (such as **1o**) have been widely employed in enantioselective syntheses, the *N*-appendage serving as a chiral auxiliary.[22] Their synthesis relies on a lengthy procedure for preparing the chiral hydroxylamine to be reacted with the desired aldehyde.[25] With this method, (α-methyl)benzylamine, inexpensive and available in both

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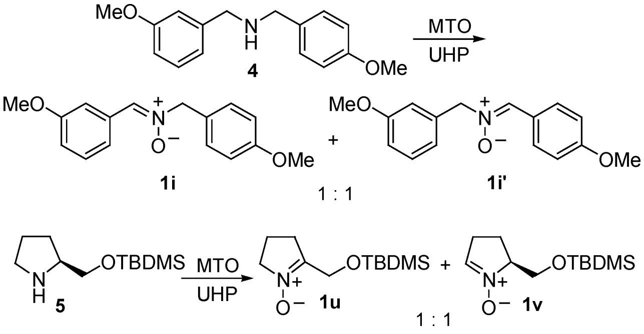
(22) Gothelf, K.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−909.

(23) Comparison of the specific rotation of the known nitrone **1t** with the value reported in the literature (Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1659−1674) proved this assumption: $[\alpha]^{22}_D$ +74.9 (*c* 1.05, CHCl$_3$) [lit. $[\alpha]^{19}_D$ +75.8 (*c* 1.30, CHCl$_3$)].

(24) Closa, M.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1031−1037.

(25) Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron* **1985**, *41*, 3455−3462.

Scheme 2. Oxidation of Secondary Amines **4** and **5** to Nitrones



enantiomeric forms, can be condensed directly with aldehydes to afford imines such as **2o**, which are oxidized to nitrones. In conclusion, we have developed the first catalytic version of the troublesome oxidation of imines to nitrones, which offers a solution to the yet unanswered issue of regiochemical control in the synthesis of nitrones from amine derivatives by oxidative means. This new reaction is user and environmentally friendly, being simple to perform, occurring under mild conditions and with high atom economy, and releasing only water as coproduct. The scope and application of this catalytic procedure is currently being investigated in our laboratories.

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Supporting Information Available: Experimental procedures, characterization data of nitrones, and ^{1}H and ^{13}C NMR spectra of new compounds **1d**−**k**,**m**,**n**,**q**,**r**,**u**,**v**. This material is available free of charge via the Internet at http://pubs.acs.org.

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