View Article Online / Journal Homepage / Table of Contents for this issue

Published on 01 January 1984. Downloaded by University of Illinois at Chicago on 29/10/2014 15:44:27.

Tungstate Catalysed Oxidation of Secondary Amines with Hydrogen Peroxide. A Novel Transformation of Secondary Amines into Nitrones

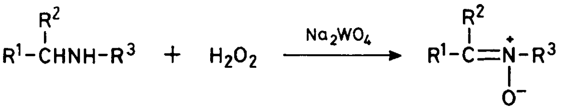
Hitoshi Mitsui, Sei-ichi Zenki, Tatsuki Shiota, and Shun-Ichi Murahashi*

Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka, 560, Japan

The sodium tungstate catalysed oxidation of secondary amines with hydrogen peroxide gives the corresponding nitrones, which are versatile synthetic intermediates and spin trapping reagents, in a single step.

Enzymes as well as the model compounds, 5-alkyl-4a-hydroperoxyflavins, cause facile N-oxidation of secondary amines to give hydroxylamines and, subsequently, nitrones.[1] Simulation of the enzymatic function with metal complex catalysts should provide a method for the oxidation of amines and, as a consequence of these studies, a novel method has been developed for the catalytic oxidation of secondary amines with hydrogen peroxide to give the corresponding nitrones.

Nitrones are highly valuable synthetic intermediates and excellent spin trapping reagents. In particular, nitrones are excellent 1,3-dipoles and have been utilized for the synthesis of various nitrogen containing biologically active compounds, *e.g.* alkaloids[2] and β-lactams.[3] The preparation of nitrones has usually been performed by either condensation of aldehydes with hydroxylamines[4] or oxidation of the corresponding hydroxylamines.[5] The difficulty of these methods is in the preparation of the starting hydroxylamines.

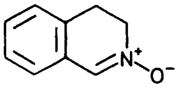


$$R^1\text{-}\overset{R^2}{\overset{|}{C}}HNH\text{-}R^3 + H_2O_2 \xrightarrow{Na_2WO_4} R^1\text{-}\overset{R^2}{\overset{|}{C}}{=}\underset{\underset{O^-}{|}}{\overset{+}{N}}\text{-}R^3 \qquad (1)$$

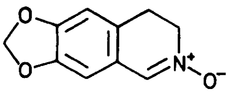
(1) $R^1 = Pr^n$, $R^2 = H$, $R^3 = Bu^n$

(2) $R^1 = R^2 = Me$, $R^3 = Pr^i$

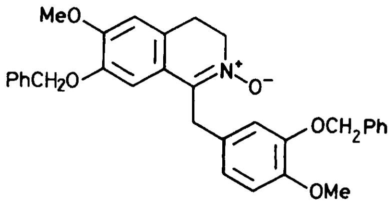
(3) $R^1 = Ph$, $R^2 = H$, $R^3 = CH_2Ph$



(4)

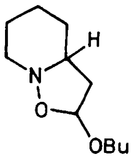


(5)



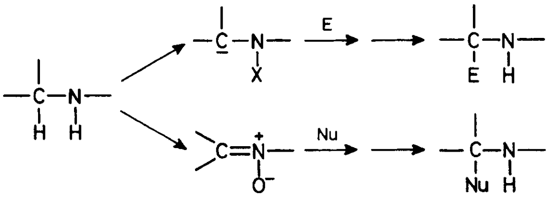
(6)

(7)



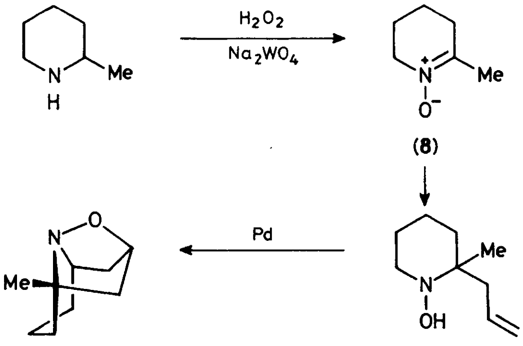
(9)

The tungstate catalysed oxidation of secondary amines with hydrogen peroxide gave nitrones in a single step as depicted in equation (1) and the representative results of the preparation of nitrones are summarized in Table 1. Secondary amines can generally be converted into the corresponding nitrones upon treatment with H_2O_2 in the presence of Na_2WO_4 catalyst. Other catalysts such as $VO(acac)_2$, $Ti(OBu)_4$, and $MoO_2(acac)_2$ (acac = acetylacetonate) gave high yields of nitrones, but their conversions were lower. The efficiency of the present method is apparent from the one-pot preparation of (**4**) (85% yield), which is a useful precursor for the synthesis of isoquinoline alkaloids. Similarly, nitrones (**5**) and (**6**) were obtained in 62 and 60% yields, respectively. 2-Methylpiper-



(2)

(3)



(8) (10) (11)

Table 1. Oxidation of amines with H_2O_2 in the presence of Na_2WO_4.[a]

Nitrone	Solvent	Isolated yield (%)[b]
(**1**)	MeOH	89[c]
(**2**)	MeOH	74[c]
(**3**)	MeOH	85[d]
(**4**)	MeOH	85[d]
(**5**)	MeOH	62[e]
(**6**)	MeOH	60[e]
(**7**)	H_2O	44[d]
(**8**)	H_2O	68[d]

[a] 4 mol% of $Na_2WO_4 \cdot 2H_2O$ and 3 equiv. of H_2O_2 were used at 0 °C for 3 h. [b] Isolated pure products. All compounds have been characterized by spectral data. New compounds have satisfactory elemental analyses and/or mass spectral analyses. [c] Kugelrohr distillation. [d] Column chromatography (silica gel). [e] Preparative t.l.c. (silica gel).

View Article Online

Published on 01 January 1984. Downloaded by University of Illinois at Chicago on 29/10/2014 15:44:27.

idine was converted into thermodynamically stable (**8**) in 68% yield. Water is the only solvent which results in the satisfactory formation of cyclic nitrones.

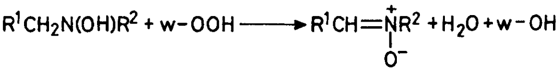
The following procedure for the preparation of (**8**) is representative. To a solution of $Na_2WO_4{\cdot}2H_2O$ (0·92 g, 28 mmol) and 2-methylpiperidine (6·94 g, 70 mmol) in water (13 ml) was added a 30% H_2O_2 solution (17.4 g, 154 mmol) at 0 °C under argon. After additional stirring at 20 °C, $NaHSO_3$ and NaCl were added. The reaction mixture was then extracted with CH_2Cl_2. Column chromatography on silica gel (eluant 5% MeOH in CH_2Cl_2) gave (**8**) (5.37 g, 68%).

1,3-Dipolar cycloadducts are conveniently and directly obtained by the oxidation of secondary amines in the presence of alkenes with an electron-donating group. Thus, oxidation of piperidine in the presence of butyl vinyl ether gave (**9**) in 54% yield.

Although substitution α to the nitrogen of amines is of importance, the available methods are limited to a few cases which involve deprotonation and electrophilic reaction at the α-carbon of amines, equation (2).[6] The present reaction provides an alternative method which involves nucleophilic substitution at the α-position of secondary amines, equation (3).[7] Typically, the benzylation of 3,4-dihydroisoquinolines is performed by oxidation followed by a modified Grignard reaction. Thus, nitrone (**5**) was allowed to react with 3,4-dimethoxybenzyl bromide in the presence of magnesium. The hydroxylamine thus obtained (65%) was converted into canadine by reduction and subsequent condensation with formaldehyde. The precursor of pellefierine alkaloid can be prepared in a similar way. Allylation of nitrone (**8**) with allylmagnesium bromide gave (**10**) (86%), which undergoes a palladium catalysed reaction[5] to give the cycloadduct (**11**).

The present reaction can be rationalized by assuming that the N-oxidation of secondary amines with tungstate peracid (w-OOH)[8] (w = WO_3^-, WO_4^-, WO_6^-) to give hydroxylamines, which undergo further oxidation to give nitrones, occurs as shown in equations (4) and (5).

$$R^1CH_2NHR^2 + w\text{-}OOH \longrightarrow R^1CH_2N(OH)R^2 + w\text{-}OH \qquad (4)$$



$$R^1CH_2N(OH)R^2 + w\text{-}OOH \longrightarrow R^1CH{=}\underset{O^-}{\overset{+}{N}}R^2 + H_2O + w\text{-}OH \qquad (5)$$

Received, 14th February 1984; Com. 205

References

1 S. Ball and T. C. Bruice, *J. Am. Chem. Soc.*, 1980, **102**, 6498.

2 J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396; W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 10; S. Takano and K. Shishido, *J. Chem. Soc., Chem. Commun.*, 1981, 940; T. Iwashita, T. Kusumi, and H. Kakisawa, *J. Org. Chem.*, 1982, **47**, 230; H. Iida, M. Tanaka, and C. Kibayashi, *J. Chem. Soc., Chem. Commun.*, 1983, 271.

3 A. Padwa, K. F. Koehler, and A. Rodriguez, *J. Am. Chem. Soc.*, 1981, **103**, 4974; T. Kametani, S.-P. Huang, A. Nakayama, and T. Honda, *J. Org. Chem.*, 1982, **47**, 2328; R. V. Stevens and K. Albizati, *J. Chem. Soc., Chem. Commun.*, 1982, 104; P. DeShong and J. M. Leginus, *J. Am. Chem. Soc.*, 1983, **105**, 1686.

4 G. Tennant, in 'Comprehensive Organic Chemistry,' eds. D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 2, ch. 8, p. 500.

5 S.-I. Murahashi, H. Mitsui, T. Watanabe, and S. Zenki, *Tetrahedron Lett.*, 1983, 1049, and references cited therein.

6 D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 15; U. Schöllkopf, *ibid.*, 1977, **16**, 339; P. Beak and R. A. Brown, *J. Org. Chem.*, 1982, **47**, 34; A. I. Meyers and S. Hellring, *ibid.*, p. 2229.

7 See, S.-I. Murahashi and T. Watanabe, *J. Am. Chem. Soc.*, 1979, **101**, 7429.

8 Y. Ogata and K. Tanaka, *Can. J. Chem.*, 1981, **59**, 718.