Tungstate-Catalyzed Oxidation of Secondary Amines to Nitrones. α-Substitution of Secondary Amines via Nitrones

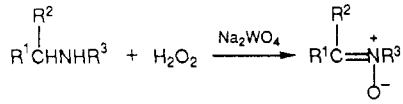
Shun-Ichi Murahashi,* Hitoshi Mitsui, Tatsuki Shiota, Tomoyasu Tsuda, and Shoji Watanabe

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

Received August 22, 1989

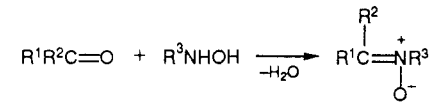
The sodium tungstate catalyzed oxidation of secondary amines with hydrogen peroxide gives the corresponding nitrones. Acyclic and cyclic nitrones can be obtained from secondary amines in a single step in good to excellent yields. The oxidation of secondary amines in the presence of alkenes gives isoxazolidines by 1,3-dipolar cycloaddition of nitrones. Introduction of a substituent at the α-position of secondary amines can be performed upon oxidation of secondary amines and subsequent treatment with various nucleophiles.

Oxidation of amines is of interest in view of metabolism of amines in vivo. Simulation of the enzymatic function of the oxidation of amines has been studied systematically, and various useful metal-catalyzed reactions of amines such as transalkylation of primary, secondary,[1] and tertiary amines,[2] hydrolysis of amines,[3] and transformation of secondary amines to imines[4] have been explored. These reactions may correspond to biological dehydrogenation of amines by mitochondrial monoamine oxidases.[5] Flavin monooxygenase[6] and model compounds, such as 5-ethyl-4a-hydroperoxyflavin (4a-FlEtOOH)[7,8] oxidize secondary amines to nitrones via hydroxylamines. Simulation of this function with metal complex catalysts led to the discovery of tungstate-catalyzed oxidation of secondary amines with hydrogen peroxide to give nitrones (eq 1).[9]

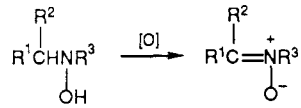


(1)

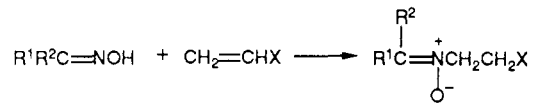
Nitrones are highly valuable synthetic intermediates[10] and excellent spin trapping reagents.[11] In particular, nitrones are excellent 1,3-dipoles and have been utilized for the synthesis of various nitrogen-containing biologically active compounds, e.g., antibiotics,[12] alkaloids,[13] amino sugars,[14] and β-lactams.[15] Generally, nitrones have been prepared mainly by using the following four methods depicted in eqs 2–5. Condensation of carbonyl compounds



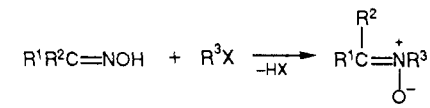
(2)



(3)



(4)



(5)

with N-monosubstituted hydroxylamines (eq 2)[16] and oxidation of N,N-disubstituted hydroxylamines (eq 3)[17,18] are the typical methods. However, preparation of the starting hydroxylamines is generally very tedious. Cyclic hydroxylamines can be prepared by thermal decomposition of the corresponding tertiary amine *N*-oxides.[18] Oximes undergo Michael addition to electronegative alkenes to generate nitrones (eq 4).[19] Alkylation of oximes (eq 5)[20] proceeds

(1) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.
(2) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348.
(3) Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429.
(4) Murahashi, S.-I.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* **1985**, 613.
(5) (a) Silverman, R. B.; Hoffman, S. J.; Catus, W. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 7126. (b) Simpson, J. T.; Krantz, A.; Lewis, F. D.; Kokel, B. *J. Am. Chem. Soc.* **1982**, *104*, 7155 and references cited therein.
(6) (a) Ziegler, D. M.; Mitchell, C. H. *Arch. Biochem. Biophys.* **1972**, *150*, 116. (b) Kadlubar, F. F.; Mckee, E. M.; Ziegler, D. M. *Arch. Biochem. Biophys.* **1973**, *156*, 46. (c) Poulsen, L. L.; Kadlubar, F. F.; Ziegler, D. M. *Arch. Biochem. Biophys.* **1974**, *164*, 774.
(7) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 6498.
(8) Murahashi, S.-I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5002.
(9) The preliminary results were communicated. Mitsui, H.; Zenki, S.; Shiota, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1984**, 874.
(10) For reviews, see: (a) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473. (b) Delpierre, G. R.; Lamchen, M. *Q. Rev.* **1965**, *19*, 329. (c) Sandler, S. R.; Karo, W. In *Organic Functional Group Preparations*; Academic Press: New York, 1972; Vol. 3, p 301. (d) Tennant, G. In *Comprehensive Organic Chemistry*; Barton, D. H., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 2, p 500. (e) Breuer, E. In *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Part 1, p 459. (f) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 83. (g) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988.
(11) (a) Janzen, E. G. *Acc. Chem. Res.* **1971**, *4*, 31. (b) Evans, C. A. *Aldrichimica Acta* **1979**, *12*, 182.
(12) (a) Kametani, T.; Nagahara, T.; Honda, T. *J. Org. Chem.* **1985**, *50*, 2327. (b) Mzengeza, S.; Yang, C. M.; Whitney, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 276. (c) Mzengeza, S.; Whitney, R. A. *J. Org. Chem.* **1988**, *53*, 4074.
(13) (a) Iwashita, T.; Kusumi, T.; Kakisawa, H. *J. Org. Chem.* **1982**, *47*, 230. (b) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1983**, 271. (c) Gribble, G. W.; Bardn, T. C. *J. Org. Chem.* **1985**, *50*, 5900. (d) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1265. (e) Tufariello, J. J.; Winzenberg, K. *Tetrahedron Lett.* **1986**, *27*, 1645. (f) Merlin, P.; Braekman, J. C.; Daloze, D. *Tetrahedron Lett.* **1988**, *29*, 1691. (g) Brandi, A.; Garro, S.; Guarna, A.; Goti, A.; Cordero, F.; De Sarlo, F. *J. Org. Chem.* **1988**, *53*, 2430.
(14) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.
(15) Padwa, A.; Koehler, K. F.; Rodriguez, A. *J. Org. Chem.* **1984**, *49*, 282.
(16) (a) Cope, A. C.; Haven, A. C., Jr. *J. Am. Chem. Soc.* **1950**, *72*, 4896. (b) Utzinger, G. E.; Regenass, F. A. *Helv. Chim. Acta* **1954**, *37*, 1892. (c) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363. (d) Bonnett, R.; Clark, V. M.; Giddey, A.; Todd, A. *J. Chem. Soc.* **1959**, 2087. (e) Robi, J. A.; Hwu, J. R. *J. Org. Chem.* **1985**, *50*, 5913.
(17) Murahashi, S.-I.; Mitsui, H.; Watanabe, T.; Zenki, S. *Tetrahedron Lett.* **1983**, *24*, 1049.
(18) (a) Rupe, H.; Wittwer, R. *Helv. Chim. Acta* **1922**, *5*, 217. (b) Utzinger, G. E.; Regenass, F. A. *Helv. Chim. Acta* **1954**, *37*, 1892. (c) Thesing, J.; Mayer, H. *Chem. Ber.* **1956**, *89*, 2159. (d) Thesing, J.; Mayer, H. *Justus Liebigs Ann. Chem.* **1957**, *609*, 46. (e) Kropf, H.; Lambeck, R. *Justus Liebigs Ann. Chem.* **1966**, *700*, 18. (f) Shono, T.; Matsumura, Y.; Inoue, K. *J. Org. Chem.* **1986**, *51*, 549.

0022-3263/90/1955-1736$02.50/0

with contamination by oxime ethers. The present catalytic oxidation of secondary amines with hydrogen peroxide provides a simple and general method for the preparation of nitrones.

Metal-catalyzed oxidation of tertiary amines with peroxides gives the corresponding *N*-oxides.[21] Primary amines are oxidized to give oximes,[22] nitro compounds,[22b,23] and azoxy compounds[24] depending on the structure of the starting amines. It has been reported that the oxidation of secondary amines with hydrogen peroxide gives the corresponding N,N-disubstituted hydroxylamines in low yields,[22b,25] and the oxidation of strongly hindered secondary amines gives the corresponding nitroxyl radicals.[26] Recently, it has been reported that secondary amines are oxidized with 2-(phenylsulfonyl)-3-aryloxaziridines (Davis' reagents) to give the corresponding nitrones.[27]

Results and Discussion

Oxidation of Secondary Amines to Nitrones. Treatment of secondary amines with hydrogen peroxide in the presence of metal catalysts gave the corresponding nitrones. The catalytic activity of various metal complexes has been examined for the oxidation of dibutylamine with 30% aqueous hydrogen peroxide in methanol. $Na_2WO_4 \cdot 2H_2O$ gave the best yield of *N*-butylidenebutylamine *N*-oxide (**1**). The oxidations with H_2WO_4 and molybdenum complexes gave moderate conversions and yields. WO_3 is not a good catalyst because of low solubility in methanol. Metal complex catalysts of tungsten and molybdenum, which seem to give metallic hydroperoxides (MOOH), are active catalysts for oxidation of secondary amines.

Next, the activity of various oxidants has been examined. Hydrogen peroxide has been found to be the best oxidant. Oxidation of dibutylamine with 70% aqueous *tert*-butyl hydroperoxide in the presence of metal complex catalysts such as $Na_2WO_4 \cdot 2H_2O$, SeO_2, $MoO_2(acac)_2$, $Mo(CO)_6$, and $VO(acac)_2$ (acac = acetylacetonate) gave the corresponding nitrone in low yields. Oxidation with *tert*-butyl hydroperoxide in dry benzene in the presence of catalysts such as $MoO_2(acac)_2$, $Mo(CO)_6$, and $VO(acac)_2$ gave no nitrone. In the presence of $Ti(O\text{-}i\text{-}Pr)_4$ catalyst trace amount of the nitrone was detected. Oxidation with cumene hydroperoxide or *m*-chloroperbenzoic acid gave many products. When NiO_2 was used as an oxidant, the reaction did not proceed.

The solvent effect for the oxidation of dibutylamine with hydrogen peroxide in the presence of $Na_2WO_4 \cdot 2H_2O$ was examined. Methanol gave the best results, and water, dioxane, acetonitrile, and acetone gave good results. The oxidation did not proceed in dimethylformamide and dimethyl sulfoxide because of the decomposition of hydrogen peroxide under the reaction conditions.

Generally, secondary amines can be oxidized to the corresponding nitrones upon treatment with 2–3 molar equiv of hydrogen peroxide in the presence of 1–5 mol % of $Na_2WO_4 \cdot 2H_2O$ at room temperature in a single step. The typical results of the preparation of nitrones are summarized in Table I. Acyclic and cyclic amines are generally converted into the corresponding nitrones in good to excellent yields. The oxidation of dibenzylamine gave *N*-benzylidenebenzylamine *N*-oxide (**3**), which is a useful precursor of *N*-benzylhydroxylamine in 85% yield. *N*-Benzylidene-*tert*-butylamine *N*-oxide (**4**), which is a useful spin trapping reagent, was obtained in 95% yield (entry 4). The oxidation of 1,2,3,4-tetrahydroisoquinolines gave the corresponding nitrones, which are highly versatile intermediates for the synthesis of isoquinoline alkaloids (entries 5–7). It is noteworthy that water is the only solvent that gives satisfactory formation of cyclic nitrones with small molecular weights. The oxidation of secondary amines with hydrogen peroxide in methanol or acetone can be performed by using SeO_2 catalyst.[28] 2-Substituted cyclic amines are converted into thermodynamically stable 2-substituted nitrones. Thus, the oxidation of 2-methylpiperidine gave 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide and 2-methyl-2,3,4,5-tetrahydropyridine *N*-oxide (88:12), but chromatographic separation (SiO_2) gave the former compound in 70% isolated yield. It is noteworthy that esters of α-amino acids such as methyl prolinate can be converted into the corresponding nitrone regioselectively (entry 9).

Oxidation of unsymmetric acyclic amines such as *N*-methylbenzylamine gave *N*-benzylidenemethylamine *N*-oxide and benzaldoxime in 34% and 33% yields, respectively. *N*-Methylaniline was converted into azoxybenzene in 87% yield along with a small amount of nitrosobenzene under the same reaction conditions. These results suggest that nitrones are in equilibrium with carbonyl compounds and N-monosubstituted hydroxylamines under the reaction conditions. In the former reaction, the *N*-methylidenebenzylamine *N*-oxide initially formed undergoes hydrolysis to give formaldehyde and *N*-benzylhydroxylamine, which undergoes further oxidation to give benzaldoxime. Oxidation of *N*-methylaniline proceeds readily to give azoxybenzene quantitatively. *N*-Methylideneaniline *N*-oxide initially formed undergoes hydrolysis to give *N*-phenylhydroxylamine. The oxidation of *N*-phenylhydroxylamine gives nitrosobenzene, which undergoes condensation with *N*-phenylhydroxylamine to give azoxybenzene.

Norreticuline (**12**), which is an important key compound for the biosynthesis of isoquinoline alkaloids,[29] was also oxidized to the corresponding nitrone **14** in 32% yield. The secondary amino group is oxidized chemoselectively in the presence of the phenol group. *O,O'*-Dibenzyl derivative **13** was converted into the corresponding nitrone **15** in 60% yield.

Under phase-transfer conditions,[30] secondary amines are oxidized to nitrones readily. Thus, the treatment of di-

(19) (a) Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1325. (b) Armstrong, P.; Grigg, R.; Surenfrakumar, S.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1327.

(20) (a) Smith, P. A. S.; Robertson, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 1197. (b) Buehler, E. *J. Org. Chem.* **1967**, *32*, 261. (c) Schoenewaldt, E. F.; Kinnel, R. B.; Davis, P. *J. Org. Chem.* **1968**, *33*, 4270.

(21) (a) Thesing, J.; Sirrenberg, W. *Chem. Ber.* **1959**, *92*, 1748. (b) Oswald, A. A.; Guertin, D. L. *J. Org. Chem.* **1963**, *28*, 651. (c) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1968**, *33*, 588.

(22) (a) Kahr, K.; Berther, C. *Chem. Ber.* **1960**, *93*, 132. (b) Burckard, P.; Fleury, J.; Weiss, F. *Bull. Soc. Chim. Fr.* **1965**, *10*, 2730.

(23) (a) Howe, G. R.; Hiatt, R. R. *J. Org. Chem.* **1970**, *35*, 4007. (b) Pagano, A. S.; Emmons, W. D. In *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. 5, p 367.

(24) (a) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Kosswig, K. *Justus Liebigs Ann. Chem.* **1971**, *749*, 206.

(25) (a) Mamlock, L.; Wolffenstein, R. *Chem. Ber.* **1900**, *33*, 159. (b) Sayigh, A. A. R.; Ulrich, H. *J. Chem. Soc.* **1963**, 3144. (c) Toda, T.; Mori, E.; Murayama, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1904.

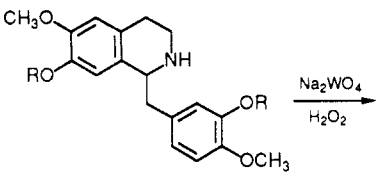
(26) Rozantsev, E. G. In *Free Nitroxyl Radicals*; Hazzard, B. J., Jr.; Ulrich, H., Ed.; Plenum Press: New York, 1970; Chapter III, p 67.

(27) Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856.

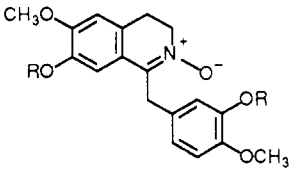
(28) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 2383.

(29) Cordell, G. A. In *Introduction to Alkaloids*; Wiley: New York, 1981.

(30) (a) Venturello, C.; Alneri, E.; Ricci, M. *J. Org. Chem.* **1983**, *48*, 3831. (b) Bortolini, O.; Di Furia, F.; Modena, G.; Seraglia, R. *J. Org. Chem.* **1985**, *50*, 2688. (c) Prandi, J.; Kagan, H. B.; Mimoun, H. *Tetrahedron Lett.* **1986**, *27*, 2617. (d) Bortolini, O.; Conte, V.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1986**, *51*, 2661. (e) Ballistreri, F. P.; Failla, S.; Tomaselli, G. A. *J. Org. Chem.* **1988**, *53*, 830.

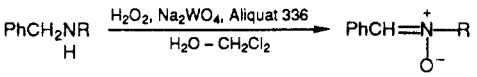


12: R = H
13: R = CH_2Ph



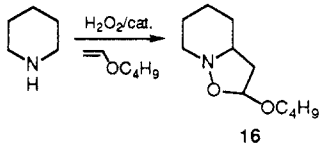
14: R = H
15: R = CH_2Ph

benzylamine with hydrogen peroxide in the presence of 5 mol % of $Na_2WO_4 \cdot 2H_2O$ and 10 mol % of methyltrioctylammonium chloride (Aliquat 336) in water–dichloromethane gave *N*-benzylidenebenzylamine *N*-oxide (**3**) in 71% yield. Under the same conditions *N*-*tert*-butylbenzylamine was converted into nitrone **4** in 83% yield. Water-soluble secondary amines such as dibutylamine can be oxidized readily without Aliquat 336. We have communicated that the oxidation of 1,2,3,4-tetrahydroquinolines with hydrogen peroxide in the presence of sodium tungstate gives the corresponding hydroxamic acids in excellent yields.[31]



3: R = CH_2Ph
4: R = $C(CH_3)_3$

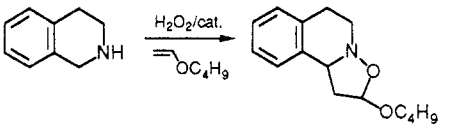
Oxidation of Secondary Amines in the Presence of Alkenes. 1,3-Dipolar cycloaddition of nitrones with alkenes is one of the key reactions for the synthesis of various nitrogen compounds[32] and natural products.[33] The oxidation of cyclic amines in the presence of alkenes gives the corresponding isoxazolidines without isolation of nitrones. Typically, the oxidation of piperidine in the presence of butyl vinyl ether in water gave 2-butoxypiperidino[1,2-b]isoxazolidine (**16**) in 54% yield. Water gave the best



16

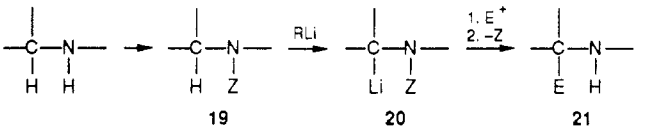
results among the solvents examined. Other solvents, such as ethanol, methanol, and water/methanol (3:1), gave the isoxazolidine in low yields along with many byproducts.

The reactions with various alkenes that have electron-donating substituents gave the corresponding isoxazolidines. Thus, the oxidation of morpholine in butyl vinyl ether gave 2-butoxymorpholino[1,2-*b*]isoxazolidine (**17**). The reaction of 1,2,3,4-tetrahydroisoquinoline afforded 2-butoxy[1,2,3,4]tetrahydroisoquinolino[2,1-*b*]isoxazolidine (**18**) in 77% yield. This procedure cannot be applied to the alkenes bearing an electron-withdrawing substituent because of Michael addition of amines to the alkenes.



18

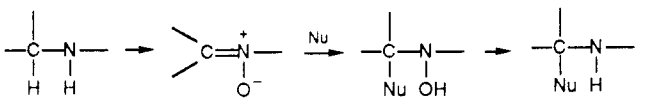
α-Substitution of Secondary Amines via Nitrones. Substitution at an α-carbon adjacent to the nitrogen of secondary amines is of importance in view of synthetic organic chemistry. Introduction of a substituent has been performed by using electrophilic reagents.[34] N-Protected secondary amines (**19**) with electron-withdrawing groups Z such as formamidine (Z = CH=NR),[35] amide (Z = C(O)R),[36] and nitrosoamine (Z = NO)[37] undergo lithiation with organolithium reagents to give carbanions **20**.



19 20 21

Treatment of **20** with electrophiles and removal of the protecting group Z gives α-substituted amines **21**. Asymmetric alkylation α to the nitrogen of secondary amines has been also performed by using chiral formamidines[34a,38] and chiral aminooxazolidines.[39]

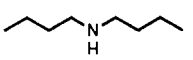
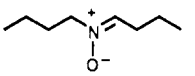
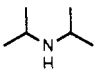
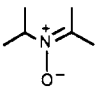
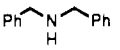
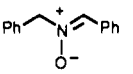
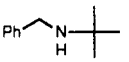
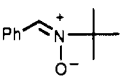
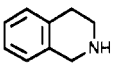
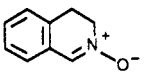
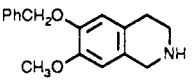
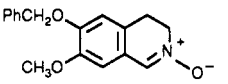
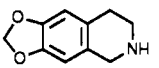
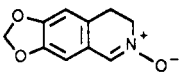
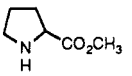
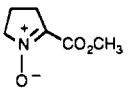
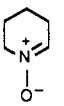
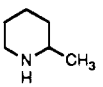
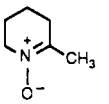
By using the present oxidation of secondary amines, alternative new and general strategy for substitution at the α-position of secondary amine is performed readily. The oxidation of secondary amines gives nitrones, which undergo reaction with various nucleophiles to give α-substituted hydroxylamines.[10] The hydroxylamines thus obtained can be converted into the corresponding amines by either catalytic hydrogenation[40] or reduction with Zn/HCl.[41]



The treatment of nitrones with Grignard reagents and organolithium compounds gives α-substituted hydroxylamines.[10] The reaction of nitrones bearing a sterically bulky substituent also proceeds under mild conditions. Thus, the reaction of *N*-benzylidene-*tert*-butylamine *N*-oxide (**4**) with methylmagnesium bromide gave *N*-*tert*-butyl-*N*-(1-phenylethyl)hydroxylamine (**22**) proceeds in 94% yield. Although phenyl and pyridyl groups cannot be introduced by the previously mentioned electrophilic

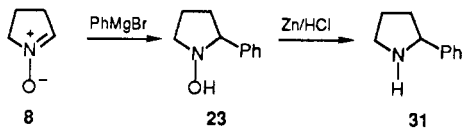
(31) Murahashi, S.-I.; Oda, T.; Sugahara, T.; Masui, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1471.
(32) Murahashi, S.-I.; Kodera, Y.; Hosomi, T. *Tetrahedron Lett.* **1988**, *29*, 5949.
(33) For reviews, see: (a) Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205. (b) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (c) Iida, H.; Kibayashi, C. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 652. (d) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 83.
(34) For a review, see: (a) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
(35) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270.
(36) (a) Wykypiel, W.; Lohmann, J.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1337. (b) Lohmann, J.; Seebach, D.; Syfrig, M. A.; Yoshifuji, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 128. (c) Seebach, D.; Lohmann, J.; Syfrig, M. A.; Yoshifuji, M. *Tetrahedron* **1983**, *39*, 1963. (d) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010.
(37) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15.
(38) (a) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458. (b) Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, 1361. (c) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778.
(39) (a) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076. (b) Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265. (c) Gawley, R. E.; Smith, G. A. *Tetrahedron Lett.* **1988**, *29*, 301. (d) Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381.
(40) Nagasawa, H. T.; Kohlhoff, J. G.; Fraser, P. S.; Mikhail, A. A. *J. Med. Chem.* **1972**, *15*, 483.
(41) Thesing, J.; Mayer, H. *Chem. Ber.* **1959**, *89*, 2159.

Table I. Oxidation of Secondary Amines with Hydrogen Peroxide in the Presence of $Na_2WO_4 \cdot 2H_2O$ Catalyst[a]

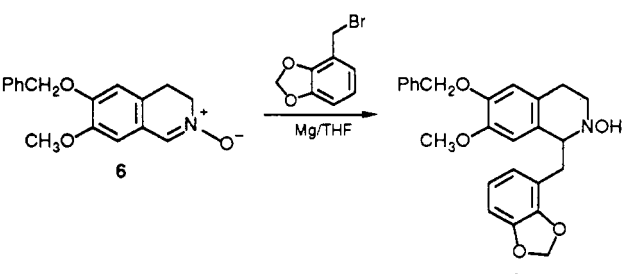
entry	amine	solvent	product	yield,[b] %
1		MeOH	 **1**	89[c]
2		MeOH	 **2**	74[c]
3		MeOH	 **3**	85 (95)[d]
4		MeOH	 **4**	95 (83)[e]
5		MeOH	 **5**	85
6		MeOH	 **6**	86
7		MeOH	 **7**	62
8		H_2O	 **8**	44
9		H_2O	 **9**	42
10		H_2O	 **10**	40
11		H_2O	 **11**	76 (74–76)[d]

[a] Reaction was carried out similar to the procedure described in the Experimental Section. [b] Isolated yield by column chromatography on SiO_2. [c] Isolated yield by Kugelrohr distillation. [d] Yield on large-scale experiment. [e] Under phase-transfer reaction conditions.

substitution reaction, α-phenyl- and α-pyridylhydroxylamines are obtained by the present nucleophilic reaction. Thus, the reactions of nitrone **8** with phenylmagnesium bromide and 3-lithiopyridine, which is derived from 3-bromopyridine directly, gave the corresponding *N*-hydroxylamines **23** and **24** in 53% and 43% yields, respectively. Keto nitrones react with Grignard reagents as well as aldo nitrones. Typically, 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide (**11**) reacts with allylmagnesium bromide to give α,α-disubstituted hydroxylamine **25** in 46% yield. The reactions of 3,4-dihydroisoquinoline *N*-oxides with benzylmagnesium halides give 2-hydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinolines under modified reaction conditions. Typically, treatment of nitrone **6** with 2,3-(methylenedioxy)benzyl bromide in the presence of magnesium at room temperature gave hydroxylamine **28**, which is a precursor of ochotensine.

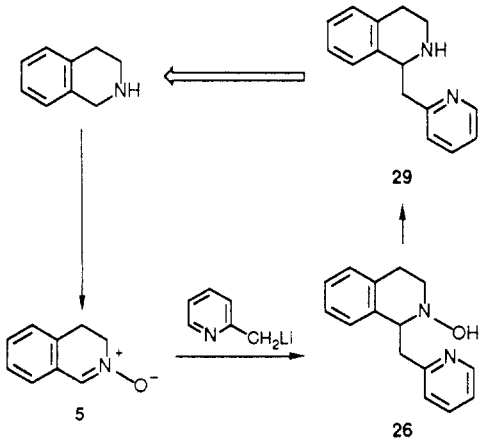


8 **23** **31**



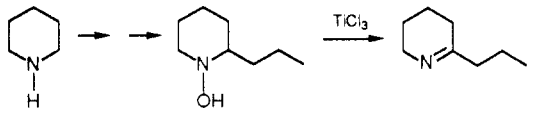
6 **28**

Reduction of the hydroxylamines thus obtained gives the corresponding secondary amines. Palladium-catalyzed hydrogenation of hydroxylamine **26** gave 1-(2-pyridylmethyl)-1,2,3,4-tetrahydroisoquinoline (**29**) (83%), which

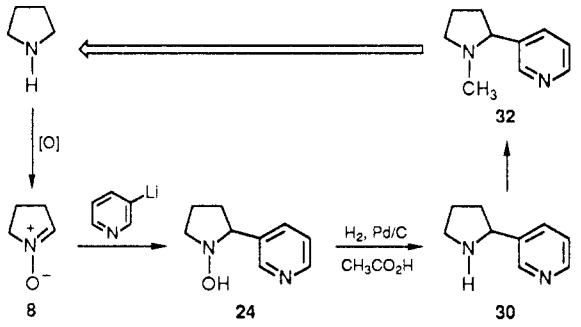


is of interest as a diamine ligand. Usually, the catalytic hydrogenation of hydroxylamines is performed in methanol; however, acetic acid is an excellent solvent for the hydrogenation of hydroxylamines that have strong chelating ability to metals. 2-Phenylpyrrolidine (**31**) was obtained by the reduction of hydroxylamine **23** upon treatment with Zn/HCl in 84% yield. SmI_2, which is an interesting one-electron-transfer reducing agent,[42] and Raney Ni (W-2) also can be used for the reduction of hydroxylamines.

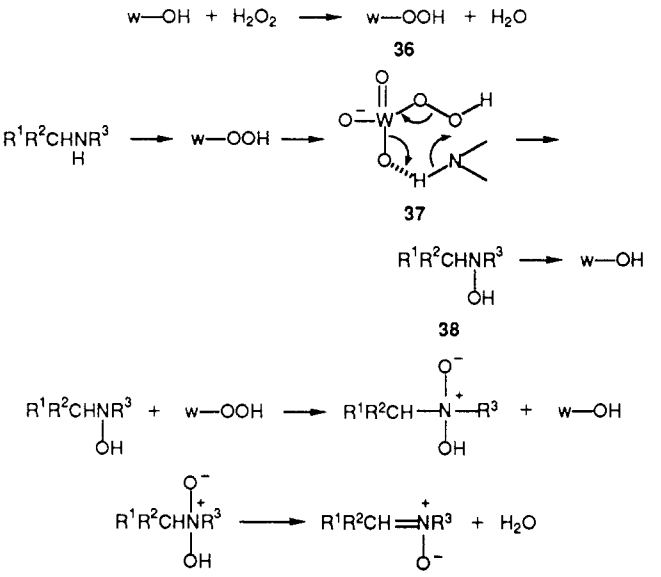
It is noteworthy that the transformation of N,N-disubstituted hydroxylamines thus obtained can be converted into either imines or secondary amines upon treatment with anhydrous or aqueous titanium trichloride.[43]



The usefulness of the present reaction can be demonstrated by the following examples of the synthesis of nitrogen-containing biologically active compounds from parent secondary amines. Nicotine (**32**)[44] can be prepared simply from pyrrolidine. The reduction of the hydroxylamine **24** described above over palladium catalyst gave nornicotine (**30**) (70%), which undergoes reductive N-methylation upon treatment with formaldehyde and subsequently with $NaBH_3CN$ to give nicotine (**32**) in 91% yield.

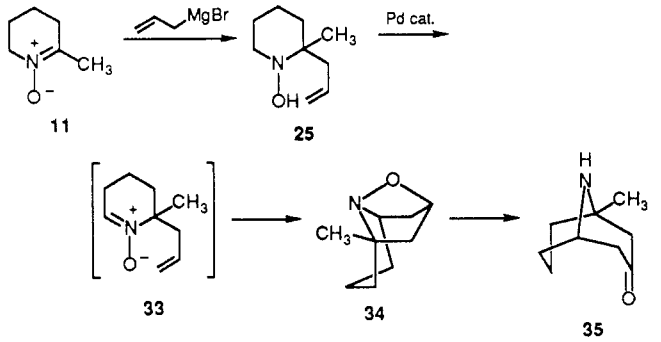


Scheme I[a]



[a] w = WO_3^-, WO_6^-.

The precursor **35** of the alkaloid, isolated from *Euphorbia atoto*,[45] can be prepared from 2-methylpiperidine. Palladium-catalyzed reaction[17] of the hydroxylamine **25** gave intramolecular cycloadduct **34** via nitrone **33** in 43% yield. The cycloadduct **34** can be readily converted into **35**.



Nucleophiles are not limited to Grignard reagents and organolithium compounds. The reaction of cyanide with nitrones gives α-cyano hydroxylamines, which are the key intermediate for synthesis of hydroxyamino acids and amino acids.[46]

Mechanism of Nitrone Formation. The formation of intermediate hydroxylamines was detected when the oxidation of secondary amines was carried out at low temperature. The oxidation of hydroxylamines proceeds faster than that of parent secondary amines. Thus, secondary amines are converted into nitrones via the corresponding N,N-disubstituted hydroxylamines.

The active catalyst may be the peroxytungstate that is formed from sodium tungstate and hydrogen peroxide. The oxidation of dibutylamine does not proceed without a catalyst[47] or without hydrogen peroxide. There are few reports on the tungstate catalysts. Polarographic study revealed that there are two types of peroxytungstates, Na_2WO_5 and Na_2WO_8, in the tungstate-catalyzed oxidation

(42) (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573.
(43) Murahashi, S.-I.; Kodera, Y. *Tetrahedron Lett.* **1985**, *26*, 4633.
(44) Dalton, D. R. In *The Alkaloids*; Marcel Dekker: New York, 1979, p 145.
(45) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1967**, *20*, 561.
(46) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *51*, 6469.
(47) (a) Lebedev, O. L.; Kazarnovskii, S. N. *J. Gen. Chem. USSR* **1960**, *30*, 1629. (b) Lebedev, O. L.; Kazarnovskii, S. N. *J. Gen. Chem. USSR* **1960**, *30*, 3079.

of dimethyl sulfoxide with hydrogen peroxide.[48] The active species for the tungstate-catalyzed epoxidation of olefins seems to be HWO_5^-.[49] The present oxidation of secondary amines can be rationalized by assuming the mechanism depicted in Scheme I. The active species of the present oxidation seems to be $HOOWO_3^-$ and $HOOWO_6^-$. Secondary amines undergo nucleophilic reaction with peroxytungstate (w-OOH) (**36**) (w = WO_3^- or WO_6^-), which is derived from tungstate and hydrogen peroxide, to give hydroxylamines **38** via **37**. Further oxidation of **38** with **36** followed by dehydration gives nitrones.[50] The species w-OH thus formed is readily oxidized with hydrogen peroxide to give w-OOH.

Conclusion

Oxidation of secondary amines with hydrogen peroxide in the presence of sodium tungstate catalyst at room temperature gives nitrones, which are versatile synthetic intermediates, highly efficiently. The oxidation of secondary amines in the presence of alkenes give the corresponding isoxazolidines without isolation of nitrones. General strategy for the introduction of a substituent at the α-position of secondary amines can be performed by the present oxidation and subsequent treatment with various nucleophiles. α-Substituted *N*-hydroxylamines thus obtained are key intermediates of α-substituted amines and nitrogen-containing biologically active compounds.

Experimental Section

General Procedures. All reactions were run under an argon atmosphere unless otherwise noted. All melting points were measured on a Yanagimoto micro melting point apparatus. IR spectra were recorded on a Hitachi 215 spectrometer. ^1H NMR spectra were measured on JEOL JNM-PMX-60 SI (60 MHz), JEOL JNM-GSX-270 (270 MHz), and JEOL JNM-GX-500 (500 MHz) spectrometers. GLC for analysis was carried out on a Shimadzu GC-8APF flame ionization chromatograph by using a 1 m × 3 mm, 10% SE 30 on 60–80-mesh Uniport HP analytical column. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer at 80 eV and a Shimadzu GCMS-QP1000 gas chromatograph–mass spectrometer by using a 1 m × 3 mm, 10% SE 30 on 60–80-mesh Uniport HP glass column at 70 eV. Elemental analyses were carried out on a Yanagimoto MT-3 CHN recorder. Commercially available catalysts were used without further purification except $Mo(CO)_6$, which was sublimated at 80 °C (4 mmHg), and $Ti(O\text{-}i\text{-}Pr)_4$, which was distilled before use. A solution of *tert*-butyl hydroperoxide in dry benzene was prepared and titrated according to the literature procedure.[51] NiO_2,[52] Raney Ni (W-2),[53] SmI_2,[42a] and palladium black[1] were prepared by the literature procedures. Ether and THF were distilled over benzophenone ketyl under argon. Amines were distilled over calcium hydride prior to use. 6-(Benzyloxy)-7-methoxy-1,2,3,4-tetrahydroisoquinoline[54] and 6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline[54] were prepared according to the method for the preparation of 7-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline.[55]

Effect of Various Catalysts, Oxidants, and Solvents on the Oxidation of Dibutylamine. In a 30-mL side-armed flask equipped with a Teflon-coated magnetic stirring bar were placed dibutylamine (2.5 mmol), a catalyst (0.10 mmol), and a solvent (5.0 mL) under argon. To the mixture was added an oxidant (7.5 mmol) dropwise with ice cooling over a period of 3–4 min. After the addition was complete, the reaction mixture was stirred at room temperature for 3 h. The conversions of the starting amine and the yields of *N*-butylidenebutylamine *N*-oxide (**1**) were determined by GLC analysis (10% SE 30, 50–250 °C) using an internal standard (undecane). The oxidations with H_2O_2 in methanol in the presence of various catalysts are as follows: $Na_2WO_4{\cdot}2H_2O$, conversion 100% (yield of **1**, 98%), H_2WO_4 59% (88%), WO_3 18% (34%), $Na_2MoO_4{\cdot}2H_2O$ 80% (59%), $H_2MoO_4{\cdot}H_2O$ 69% (71%), MoO_3 71% (64%), $Mo(CO)_6$ 75% (62%), $MoO_2(acac)_2$ 70% (53%), CeO_3 7% (99%). The oxidations with H_2O_2 in the presence of $Na_2WO_4{\cdot}2H_2O$ in various solvents are as follows: methanol (conversion 100%, yield 98%), 1,4-dioxane (55%, 99%), acetonitrile (48%, 65%), acetone (47%, 46%), DMF (0%), DMSO (0%). The oxidation with *t*-BuOOH did not give nitrone **1**. The oxidation with *m*-chloroperbenzoic acid in benzene in the presence of palladium black or palladium acetate gave **1** (conversion 15%, 50% yield or 75% yield).

Oxidation of Secondary Amines with Hydrogen Peroxide in the Presence of Sodium Tungstate: General Procedure for Synthesis of Nitrones. The preparation of *N*-butylidenebutylamine *N*-oxide (**1**) is described as a typical example. In a 30-mL side-armed flask equipped with a Teflon-coated magnetic stirring bar were placed dibutylamine (0.645 g, 4.99 mmol), $Na_2WO_4{\cdot}2H_2O$ (0.066 g, 0.20 mmol), and methanol (10 mL). To the stirred solution was added 30% aqueous hydrogen peroxide (1.70 g, 15.0 mmol) dropwise with ice cooling. After the addition was complete, the reaction mixture was stirred at room temperature for 3 h. Methanol was removed under reduced pressure. To the residue was added dichloromethane (50 mL) and saturated aqueous sodium chloride solution (20 mL). The organic layer was separated, washed with saturated aqueous sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. Kugelrohr distillation gave nitrone **1** (0.635 g, 89%) as a pale yellow liquid: bp 110–115 °C (2.0 mmHg) (Kugelrohr); IR (neat) 2960, 2880, 1600 (C=N), 1470, 1425, 1387, 1186, 1120, 1069, 941 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.94 (t, J = 6.4 Hz, 3 H, CH_3), 0.97 (t, J = 6.4 Hz, 3 H, CH_3), 1.15–2.21 (m, 6 H, $—CH_2—$), 2.47 (dt, J = 6.0 and 6.5 Hz, 2 H, $—CH_2C=$), 3.73 (t, J = 6.5 Hz, 2 H, $—CH_2N—$), 6.64 (t, J = 6.0 Hz, 1 H, —CH=N—). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.00; H, 11.99; N, 9.84.

***N*-(1-Methylethylidene)-1-methylethylamine *N*-oxide (2)**: IR (neat) 2980, 1593 (C=N), 1470, 1455, 1365, 1305, 1190, 1134, 1073, 920, 747, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.37 (d, J = 6.5 Hz, 6 H, $C(CH_3)_2$), 2.14 (s, 6 H, $N=C(CH_3)_2$), 4.47 (hept, J = 6.5 Hz, 1 H, —CHN—).

***N*-Benzylidenebenzylamine *N*-oxide (3)**:[56] mp 81–83 °C (lit.[16a] mp 81.5–83.5 °C); IR (Nujol) 3070, 1585, 1570, 1500, 1435, 1355, 1320, 1205, 1170, 1150, 1035, 940, 920, 850, 825, 705, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 5.06 (s, 2 H, $ArCH_2$), 7.36–7.51 (m, 9 H, ArH and —CH=N—), 8.17–8.25 (m, 2 H, ArH ortho to CH=N(O)Bn). Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.63; H, 6.29; N, 6.57.

***N*-Benzylidene-*tert*-butylamine *N*-oxide (4)**:[27] IR (Nujol) 2920, 2850, 1580, 1565, 1447, 1410, 1365, 1195, 1114, 1073, 900, 830, 755, 690 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 177 (M^+, 10), 146 (3), 121 (13), 120 (4), 78 (4), 77 (5), 57 (100); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.58 (s, 9 H, $C(CH_3)_3$), 7.20–7.56 (m, 3 H, ArH), 7.48 (s, 1 H, —CH=N—), 8.05–8.41 (m, 2 H, ArH). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.76; H, 8.61; N, 7.87.

3,4-Dihydroisoquinoline *N*-oxide (5): IR (neat) 1594, 1560, 1490, 1453, 1328, 1307, 1286, 1265, 1211, 1180, 1110, 900, 750 cm^{-1}; mass spectrum (80 eV) m/e (rel intensity) 147 (M^+, 86), 129 (100), 103 (35), 91 (46), 77 (43), 51 (41); ^1H NMR ($CDCl_3$, 500 MHz)

(48) Ogata, Y.; Tanaka, K. *Can. J. Chem.* **1981**, *59*, 718.
(49) (a) Stevens, H. C.; Kaman, A. J. *J. Am. Chem. Soc.* **1965**, *87*, 734. (b) Allan, G.; Neogi, A. N. *J. Catal.* **1970**, *16*, 197. (c) Beg, M. A.; Ahmad, I. *J. Catal.* **1975**, 260.
(50) N,N-Disubstituted hydroxylamines can be converted into nitrones upon treatment with a catalytic amount of sodium tungstate at 0–20 °C without any oxidants. However, the rate of the reaction is much slower than that in the presence of hydrogen peroxide, and hence hydroxylamines should be oxidized with peroxytungstate **36** as depicted in Scheme I.
(51) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(52) Nakagawa, K.; Konaka, R.; Nakata, T. *J. Org. Chem.* **1962**, *27*, 1597.
(53) Mozingo, R. In *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, p 181.
(54) Murahashi, S.-I.; Imada, Y.; Hirai, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2968.
(55) Ruchirawat, S.; Chaisupakitsin, M.; Patranuwatana, N.; Cashaw, J. L.; Davis, V. E. *Synth. Commun.* **1984**, *14*, 1221.
(56) Nojima, M.; Takeuchi, K.; Fukui, E.; Tokura, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2202.

δ 3.18 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 4.11 (dt, J = 1.1 and 7.8 Hz, 2 H, $—CH_2N—$), 7.10–7.14 (m, 1 H, ArH), 7.19–7.23 (m, 1 H, ArH), 7.24–7.30 (m, 2 H, ArH), 7.74 (tm, J = 1.1 Hz, 1 H, —CH=N—).

6-(Benzyloxy)-7-methoxy-3,4-dihydroisoquinoline *N*-oxide (6): IR (Nujol) 1598, 1515, 1282, 1226, 1170, 1125, 1026, 1004, 985, 894, 862, 840, 792, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.01 (t, J = 7.6 Hz, 2 H, $ArCH_2$), 3.85 (s, 3 H, CH_3O), 4.03 (t, J = 7.6 Hz, 2 H, $—CH_2N—$), 5.12 (s, 2 H, $PhCH_2$), 6.59 (s, 1 H, ArH), 6.70 (s, 1 H, ArH), 7.32 (s, 5 H, C_6H_5), 7.59 (s, 1 H, —CH=N—).

6,7-(Methylenedioxy)-3,4-dihydroisoquinoline *N*-oxide (7): IR ($CHCl_3$) 2950, 1627, 1606, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.98 (t, J = 8.2 Hz, 2 H, $ArCH_2$), 4.00 (t, J = 8.2 Hz, 2 H, $—CH_2N—$), 5.91 (s, 2 H, OCH_2O), 6.50 (s, 1 H, ArH), 6.60 (s, 1 H, ArH), 7.57 (s, 1 H, —CH=N—).

Oxidation of Cyclic Amines with Hydrogen Peroxide in the Presence of Sodium Tungstate: General Procedure for Synthesis of Cyclic Nitrones. The preparation of 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide (**11**) is described as a typical example. In a 30-mL side-armed flask equipped with a Teflon-coated magnetic stirring bar were placed 2-methylpiperidine (0.495 g, 4.99 mmol), $Na_2WO_4·2H_2O$ (0.066 g, 0.20 mmol), and water (2.0 mL). To a stirring solution was added 30% aqueous hydrogen peroxide (1.6 g, 15 mmol) dropwise with ice cooling. After the addition was complete, the reaction mixture was stirred at room temperature for 6 h and extracted with dichloromethane (50 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. Column chromatography (SiO_2, acetone) gave nitrone **11** (0.429 g, 76%) as a yellow oil: IR (neat) 2930, 1620 (C=N, m), 1450, 1195, 1165, 950, 870, 745 cm^{-1}; mass spectrum (80 eV) m/e (rel intensity) 113 (M^+, 100), 105 (56), 97 (29), 86 (32), 70 (44), 55 (73); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.747 (ddt, J = 5.5, 3.6, and 6.4 Hz, 1 H, H^4), 1.749 (ddt, J = 6.5, 5.5, and 6.4 Hz, 1 H, H^4), 1.949 (ddt, J = 5.5, 3.6, and 6.0 Hz, 1 H, H^3), 1.952 (ddt, J = 6.5, 5.5, and 6.0 Hz, 1 H, H^3), 2.12 (tt, J = 1.6 and 1.1 Hz, 3 H, CH_3), 2.46 (ddtq, J = 6.4, 6.4, 1.7, and 1.1 Hz, 2 H, $—CH_2C=$), 3.81 (ddtq, J = 6.0, 6.0, 1.7, and 1.6 Hz, 2 H, $—CH_2N—$); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.2 (CH_3), 18.3, 22.8, 30.2 (C^5), 57.3 (C^2), 146.2 (C^6).

1-Pyrroline *N*-oxide (8):[57] IR (neat) 2950, 1590 (C=N, s), 1455, 1355, 1230, 1170, 1065, 1043, 972, 895, 790, 745, 675 cm^{-1}; mass spectrum (80 eV) m/e (rel intensity) 85 (M^+, 100), 69 (5), 55 (47), 41 (38); ^1H NMR ($CDCl_3$, 270 MHz) δ 2.20–2.34 (m, 2 H, H^4), 2.70–2.80 (m, 2 H, H^3), 3.92–4.03 (m, 2 H, H^5), 6.88–6.92 (m, 1 H, —CH=N—).

Methyl 1-Pyrroline-2-carboxylate *N*-Oxide (9). Methyl prolinate[58] was oxidized: IR (neat) 1720 (C=O, s), 1545 (C=N, s), 1300, 1160, 1027, 935, 913, 748, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.17–2.26 (m, 2 H, H^4), 3.052 (ddd, J = 7.50, 7.50, and 1.95 Hz, 1 H, H^5), 3.060 (ddd, J = 7.50, 7.50, and 1.95 Hz, 1 H, H^5), 3.862 (s, 3 H, CH_3O), 4.193 (ddd, J = 8.06, 8.06, and 1.95 Hz, 1 H, H^3), 4.200 (ddd, J = 8.06, 8.06, and 1.95 Hz, 1 H, H^3). Anal. Calcd for $C_6H_9NO_3$: C, 50.03; H, 6.34; N, 9.79. Found: C, 49.89; H, 6.24; N, 9.56.

2,3,4,5-Tetrahydropyridine *N*-oxide (10):[13a] IR (neat) 2940, 2860, 1448, 1375, 1191, 1165, 1100, 987, 928, 874, 855, 795, 748 cm^{-1}; mass spectrum (80 eV) m/e (relative intensity) 99 (M^+, 100), 83 (10), 55 (23), 41 (28); ^1H NMR ($CDCl_3$, 270 MHz) δ 1.6–1.8 (m, 2 H, $—CH_2—$), 1.9–2.1 (m, 2 H, $—CH_2—$), 2.4–2.5 (m, 2 H, $—CH_2C=$), 3.75–3.85 (m, 2 H, $—CH_2N—$), 7.15–7.25 (m, 1 H, —CH=N—). Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.37; H, 9.23; N, 14.00.

Oxidation of *N*-Methylbenzylamine. Preparative TLC (SiO_2, 4:1 hexane/ethyl acetate) gave *N*-benzylidenemethylamine *N*-oxide (34%) and benzaldoxime (33%).

1-(3-Hydroxy-4-methoxybenzyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline *N*-Oxide (14). Norreticuline[59] was oxidized: IR (KBr) 1600, 1517, 1445, 1283, 1133 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO-d_6, 60 MHz) δ 3.02 (t, J = 7.0 Hz, 2 H, $ArCH_2$), 3.72 (s, 3 H, CH_3O), 3.79 (s, 3 H, CH_3O), 4.12 (t, J = 7.0 Hz, 2 H, $—CH_2N=$), 4.13 (s, 2 H, $ArCH_2C=$), 6.56–7.00 (m, 5 H, ArH).

1-[3-(Benzyloxy)-4-methoxybenzyl]-7-(benzyloxy)-6-methoxy-3,4-dihydroisoquinoline *N*-Oxide (15). *O,O'*-Dibenzylnorreticuline[60] was oxidized: mp 160–161 °C; IR (KBr) 3410, 2850, 1600, 1540, 1440, 1375, 1260, 1220 cm^{-1}; mass spectrum (80 eV) m/e 509 (M^+); ^1H NMR ($CDCl_3$, 60 MHz) δ 2.43–3.33 (m, 6 H, $—CH_2—$), 3.83 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 4.00 (s, 4 H, $PhCH_2O$), 6.50–6.90 (m, 5 H, ArH). Anal. Calcd for $C_{32}H_{31}NO_5$: C, 75.42; H, 6.13; N, 2.75. Found: C, 75.08; H, 6.07; N, 2.80.

Oxidation of Secondary Amines with Hydrogen Peroxide under Phase-Transfer Conditions. In a 30-mL side-armed flask equipped with a Teflon-coated magnetic stirring bar were placed dibenzylamine (0.392 g, 1.99 mmol), $Na_2WO_4·2H_2O$ (0.038 g, 0.12 mmol), methyltrioctylammonium chloride (Aliquat 336) (0.084 g, 0.21 mmol), and dichloromethane (2.0 mL). To the solution was added 30% aqueous hydrogen peroxide (0.910 g, 8.02 mmol) with stirring dropwise with ice cooling over a period of 4 min. After 4 h of stirring at room temperature, dichloromethane (10 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. Column chromatography (SiO_2, 1:1 hexane/ethyl acetate) gave *N*-benzylidenebenzylamine *N*-oxide (**3**) (0.299 g, 71%) as colorless crystals.

***N*-Benzylidene-*tert*-butylamine *N*-Oxide (4).** In a 30-mL side-armed flask were placed *N*-*tert*-butylbenzylamine (0.328 g, 2.01 mmol), $Na_2WO_4·2H_2O$ (0.032 g, 0.097 mmol), Aliquat 336 (0.089 g, 0.22 mmol), and dichloromethane (2.0 mL). To the stirred solution was added 30% aqueous hydrogen peroxide (0.683 g, 6.02 mmol) dropwise with ice cooling over a period of 3 min. After 48 h of stirring at room temperature, dichloromethane (20 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. Column chromatography (SiO_2, 1:1 hexane/ethyl acetate) gave nitrone **4** (0.297 g, 83%) as colorless crystals.

Large-Scale Synthesis of Nitrones. 6-Methyl-2,3,4,5-tetrahydropyridine *N*-Oxide (11). A 500-mL, three-necked, round-bottomed flask equipped with a 100-mL pressure-equalizing dropping funnel, a thermometer, and a magnetic stirring bar was placed 2.64 g (8.00 mmol) of sodium tungstate dihydrate. After the flask was flushed with nitrogen, 40 mL of water and 23.5 mL (200 mmol) of 2-methylpiperidine were added. The flask was cooled with an ice–salt bath to −5 °C (internal temperature) and 45.0 mL (440 mmol) of 30% aqueous hydrogen peroxide solution was added dropwise over a period of ca. 30 min. During the period of addition the reaction mixture should be carefully kept at a temperature below 20 °C. The cooling bath was removed, and the mixture was stirred for 3 h. Excess hydrogen peroxide was decomposed by adding ca. 1 g of sodium hydrogen sulfite with ice cooling. The solution was saturated by adding ca. 25 g of sodium chloride and extracted with ten 200-mL portions of dichloromethane. Combined organic extracts were dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the solvent was removed on a rotary evaporator at 40 °C. Crude nitrone **11** was obtained as a pale yellow oil. Further purification of the nitrone was achieved by column chromatography 300 g of silica gel packed in 9:1 ethyl acetate/methanol in a 4.8 cm × 70 cm column. The product was applied to the column in 10 mL of chloroform and the column was eluted with 97:3 chloroform/methanol. After 20 100-mL fractions were collected, the eluent was changed to 8:2 chloroform/methanol, and another ten 100-mL fractions were collected and analyzed by thin layer chromatography. Combination of fractions 16–30 and evaporation provides 13.1–15.0 g (75–77%) of pure nitrone **11** as a pale yellow oil.

***N*-Benzylidenebenzylamine *N*-Oxide (3).** In a 3-L three-necked flask, equipped with a mechanical stirrer, a thermometer, and a dropping funnel were placed dibenzylamine (182 g, 0.923 mol), $Na_2WO_4·2H_2O$ (12.2 g, 3.69 mmol), and methanol (1.8 L). To the stirred solution was added 30% aqueous hydrogen peroxide (314 g, 2.77 mol) dropwise with ice cooling over a period of 2 h. After the addition was complete, the reaction mixture was stirred at room temperature for 18 h. Methanol was removed under

(57) Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047.
(58) Guttmann, S. *Helv. Chim. Acta* **1961**, *44*, 721.
(59) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592.
(60) Hanssen, E. B.; Fu, C. C.; Zgnati, G. *J. Pharm. Sci.* **1971**, *60*, 873.

reduced pressure, and to the residue were added dichloromethane (500 mL × 3) and water (500 mL). The organic layer was separated, washed with saturated aqueous sodium bisulfite (500 mL), and dried over anhydrous sodium sulfate. Removal of the solvent gave nitrone **3** (186 g, 96%) as crystals. Further purification was achieved by recrystallization from petroleum ether/dichloromethane.

Tungstate-Catalyzed Oxidation of Cyclic Amines with Hydrogen Peroxide in the Presence of Alkenes: General Procedure for Synthesis of Isoxazolidines. Oxidation of piperidine in the presence of butyl vinyl ether is described as a typical example. In a 30-mL side-armed flask equipped with a Teflon-coated magnetic stirring bar were placed piperidine (0.400 g, 4.70 mmol), $Na_2WO_4 \cdot 2H_2O$ (0.066 g, 0.20 mmol), butyl vinyl ether (1.0 g, 10 mmol), and water (3.0 mL). The mixture was heated at 90 °C, and 30% aqueous hydrogen peroxide (1.7 g, 15 mmol) was added dropwise. After the addition was complete, the reaction mixture was stirred at 90 °C for 1 h. The mixture was cooled to room temperature, and chloroform (100 mL) was added. The organic layer was separated, washed with saturated aqueous sodium chloride (10 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated. Kugelrohr distillation gave 2-butoxypiperidino[1,2-*b*]isoxazolidine (**16**) (0.513 g, 54%): bp 110–115 °C (2.0 mmHg) (Kugelrohr); IR (neat) 2950, 2875, 1449, 1355, 1263, 1092, 1005, 916, 860 cm^{-1}; mass spectrum (80 eV) *m/e* (rel intensity) 199 (M^+, 36), 182 (11), 126 (36), 99 (100), 84 (54), 69 (39); ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.13–2.02 (m, 10 H, $-CH_2-$), 2.02–2.33 (m, 2 H, $-CH_2-$), 2.90–3.93 (m, 5 H, $-CH_2O-$ and $-CH_2NCH-$), 5.16 (t, *J* = 4.0 Hz, 1 H, —OCH(OBu)—).

2-Butoxymorpholino[1,2-*b*]isoxazolidine (17): IR (neat) 2950, 2865, 1420, 1300, 1000, 877 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.95 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.13–1.77 (m, 4 H, $-CH_2-$), 2.22 (dd, *J* = 5.6 and 2.4 Hz, 2 H, $-CH_2-$), 3.03–3.90 (m, 9 H), 5.24 (t, *J* = 4.0 Hz, 1 H, —OCHO—).

2-Butoxy[1,2,3,4]tetrahydroisoquinolino[2,1-*b*]isoxazolidine (18). Preparative TLC on silica gel gave **18** in 77% yield: IR (neat) 2955, 2874, 1600, 1567, 1467, 1330, 1264, 1166, 1090, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.13–1.87 (m, 6 H, $-CH_2-$), 2.33–2.70 (m, 2 H, $ArCH_2$), 3.10–3.40 (m, 2 H, $-CH_2N-$), 3.62 (t, *J* = 6.8 Hz, 2 H, $-CH_2O-$), 4.73 (t, *J* = 7.8 Hz, 1 H, ArCHN), 5.23 (dd, *J* = 5.0 and 2.0 Hz, 1 H, —OCHO—), 7.00–7.42 (m, 2 H, ArH), 7.50–7.90 (m, 2 H, ArH).

***N*-*tert*-Butyl-*N*-(1-phenylethyl)hydroxylamine (22).** To a solution of *N*-benzylidene-*tert*-butylamine *N*-oxide (**4**) (5.36 g, 31.3 mmol) in THF (60 mL) was added a 2.56 M solution of methylmagnesium iodide in ether (18.0 mL, 46.0 mmol) dropwise over a period of 30 min. After stirring at room temperature for 2 h, saturated aqueous ammonium chloride (40 mL) and water (10 mL) were added. THF was removed under reduced pressure, and the residual aqueous layer was extracted with dichloromethane (100 mL × 2). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated. Distillation gave hydroxylamine **22** (5.65 g, 94%): bp 78–95 °C (1 mmHg); IR (neat) 3530, 2970, 1600, 1490, 1480, 1450, 1385, 1360, 1305, 1275, 1220, 1090, 1025, 915, 805, 780, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.06 (s, 9 H, $C(CH_3)_3$), 1.48 (d, *J* = 6.8 Hz, 3 H, CH_3), 3.88–4.96 (br, 1 H, OH), 4.14 (q, *J* = 6.8 Hz, 1 H, ArCHN), 7.03–7.66 (m, 5 H, ArH).

1-Hydroxy-2-phenylpyrrolidine (23). To a solution of PhMgBr, which was prepared from magnesium turnings (3.66 g, 150 mmol) in THF (20 mL) and bromobenzene (23.6 g, 150 mmol) in THF (80 mL), was added a solution of nitrone **8** (4.26 g, 50.0 mmol) in THF (50 mL) dropwise over a period of 10 min. After 2.5 h of stirring at room temperature, saturated aqueous ammonium chloride (60 mL) and water (30 mL) were added. THF was removed under reduced pressure, and the remaining aqueous solution was extracted with dichloromethane (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. Column chromatography (SiO_2, 4:1 hexane/ethyl acetate) gave hydroxylamine **23**[61] (4.28 g, 53%): mass spectrum (70 eV) *m/e* (rel intensity) 163 (M^+, 9), 145 (45), 117 (100), 103 (40), 91 (30), 77 (44), 51 (41); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.47–2.32 (m, 4 H, $-CH_2-$), 2.52–3.45 (m, 2 H, $-CH_2N-$), 3.58–3.93 (m, 1 H, —CHPh—), 6.23 (br s, 1 H, OH), 7.03–7.57 (m, 5 H, ArH).

3-(1-Hydroxy-2-pyrrolidinyl)pyridine (24). 3-Pyridyllithium was prepared by the dropwise addition of 3-bromopyridine (4.74 g, 30.0 mmol) in ether (40 mL) to a mixture of a 1.4 M solution of *tert*-butyllithium in pentane (23 mL, 30.0 mmol) and ether (40 mL) in a −120 °C bath (4:1:1 pentane/2-propanol/acetone, liquid N_2) over 1 h. The resulting yellow slurry was stirred for additional 0.5 h, and a solution of nitrone **8** (1.01 g, 11.8 mmol) in THF (30 mL) was added dropwise at −100 °C over 1 h. The mixture was stirred for additional 1.5 h and warmed to −40 °C over a period of 3 h. Water was added dropwise with sitrring at −40 °C, and the reaction mixture was warmed to room temperature. The ether solution was decanted, and the residue was extracted with ether (15 mL × 3) and dichloromethane (15 mL × 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (SiO_2, 1:1 $CHCl_3$/ether) gave hydroxylamine **24** (0.822 g, 43%): mp 93.0–96.0 °C; IR (KBr) 3200, 2930, 2850, 1600, 1585, 1470, 1435, 1140, 1110, 1090, 1040, 1020, 900, 810, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.40–2.51 (m, 4 H, $-CH_2-$), 2.51–3.97 (m, 3 H, $-CH_2NCH-$), 6.20–6.93 (br, 1 H, OH), 6.93–7.30 (m, 1 H, ArH), 7.58 (dt, *J* = 8.0 and 2.0 Hz, 1 H, ArH), 8.25 (dd, *J* = 5.0 and 2.0 Hz, 1 H, N=CH), 8.43 (d, *J* = 2.0 Hz, 1 H, N=CH). Anal. Calcd for $C_9H_{12}N_2O$: C, 65.81; H, 7.37; N, 17.07. Found: C, 65.66; H, 7.26; N, 16.83.

2-Allyl-1-hydroxy-2-methylpiperidine (25). To a 1.53 M solution of allylmagnesium bromide in ether (31 mL, 47.4 mmol) was added a solution of 6-methyl-2,3,4,5-tetrahydropyridine *N*-oxide (**11**) (2.65 g, 23.4 mmol) in THF (10 mL) at 0 °C over a period of 0.5 h. After 3 h of stirring at 4 °C, a saturated aqueous ammonium chloride solution (35 mL), water (50 mL), and ether (50 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ether (100 mL). The combined organic layers were washed with saturated aqueous sodium chloride (30 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated. Column chromatography (SiO_2, 9:1 hexane/ethyl acetate) gave hydroxylamine **25** (1.67 g, 46%): IR (neat) 3225, 3080, 2945, 2870, 1645, 1455, 1375, 1000, 915 cm^{-1}; mass spectrum (80 eV) *m/e* (rel intensity) 155 (M^+, 0.4), 154 (1.7), 140 (3.3), 114 (100), 97 (12); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.12 (s, 3 H, CH_3), 1.23–1.90 (m, 6 H, CH_2), 2.43 (d, *J* = 7.2 Hz, 2 H, $CH_2C=$), 2.80–3.20 (m, 2 H, CH_2N), 4.82–5.26 (m, 2 H, $C=CH_2$), 5.83 (ddt, *J* = 17.2, 8.8, and 7.2 Hz, 1 H, —CH=C—). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.03; N, 9.02. Found: C, 69.66; H, 10.95; N, 8.88.

2-Hydroxy-1-(2-pyridylmethyl)-1,2,3,4-tetrahydroisoquinoline (26). To a solution of 2-picoline (0.243 g, 2.61 mmol) in THF was added a 1.14 M solution of butyllithium in hexane (2.00 mL, 2.24 mmol) dropwise at −15 °C over a period of 0.5 h, and the resulting deep red solution was stirred for 1 h. A solution of nitrone **5** (0.330 g, 2.24 mmol) in THF (3 mL) was added dropwise over a period of 5 min. After 3 h of stirring at reflux temperature, the mixture was poured onto water (10 mL) and extracted with dichloromethane (10 mL × 3). The combined organic layers were extracted with 2 N hydrochloric acid (10 mL × 3). The aqueous layers were combined, basified with an 8 N aqueous sodium hydroxide solution, and extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated. Column chromatography (SiO_2, 1:1 benzene/ethyl acetate) gave hydroxylamine **26**[62] (0.301 g, 56%): mp 102–104 °C; IR (KBr) 3230, 2910, 1600, 1570, 1495, 1480, 1455, 1430, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.67–3.67 (m, 6 H, $-CH_2-$), 4.43 (t, *J* = 6.0 Hz, 1 H, —CHN—), 6.83–7.67 (m, 8 H, ArH and OH), 8.44 (dd, *J* = 3.0 and 2.0 Hz, 1 H, —CH=N—).

2-Hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (27). To a C_6H_5MgBr solution, derived from magnesium turnings (0.24 g, 10 mmol) in THF (10 mL) and bromobenzene (1.57 g, 10.0 mmol) in THF (5 mL) at 0 °C, was added dropwise a solution of nitrone **5** (1.47 g, 10.0 mmol) in THF (5 mL) at 0 °C, and the

(61) Schopf, C. *Chem. Ber.* **1959**, *92*, 1748.

(62) Tsuge, O.; Sone, K.; Urano, S. *Chem. Lett.* **1980**, 977.

reaction mixture was stirred for 4 h at ambient temperature. To the mixture was added a saturated aqueous ammonium chloride solution (50 mL) and ether (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether (50 mL). The combined organic layers were dried over sodium sulfate. Removal of the solvent and column chromatography (SiO_2, dichloromethane) gave hydroxylamine **27** (1.40 g, 67%): IR (neat) 3400, 3080, 1605, 1570, 1460, 1335, 1265, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.87-3.39 (m, 4 H, $-CH_2-$), 4.76 (s, 1 H, ArCHN), 6.88-7.88 (m, 10 H, ArH and OH).

6-(Benzyloxy)-2-hydroxy-7-methoxy-1-[2,3-(methylenedioxy)benzyl]-1,2,3,4-tetrahydroisoquinoline (28). To a mixture of magnesium turnings (0.352 g, 14.5 mmol) and THF (5 mL) were added dropwise a solution of 2,3-(methylenedioxy)benzyl bromide (2.97 g, 13.8 mmol) in THF (20 mL) and nitrone **6** (0.617 g, 2.18 mmol) in THF (10 mL) dropwise at room temperature, and the reaction mixture was stirred for 5 h. To the mixture were added a saturated aqueous ammonium chloride solution (20 mL), water (10 mL), and chloroform (30 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform (30 mL × 2). The combined organic layers were dried over magnesium sulfate. Removal of the solvent and column chromatography (SiO_2, 3:1 hexane/ethyl acetate) gave hydroxylamine **28** (0.524 g, 57%): mp 147-148 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.53-3.50 (m, 6 H, $-CH_2-$), 3.68 (s, 3 H, CH_3O), 4.23 (t, J = 6.5 Hz, 1 H, ArCHN), 5.07 (s, 2 H, $PhCH_2O$), 5.85 (s, 2 H, OCH_2O), 6.45 (s, 1 H, ArH), 6.58 (s, 1 H, ArH), 6.67 (s, 3 H, ArH), 7.23-7.62 (m, 6 H, ArH and OH). Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.36; H, 5.98; N, 3.27.

1-(2-Pyridylmethyl)-1,2,3,4-tetrahydroisoquinoline (29). A mixture of hydroxylamine **26** (0.240 g, 1.00 mmol), 5% palladium on charcoal (0.076 g), and acetic acid (20 mL) was vigorously stirred under H_2 for 60 h. The catalyst was separated by filtration through Celite, and the filtrate was evaporated. A hydrochloric acid (1 N, 10 mL) was added to the residue, and the solution was washed with ether (5 mL). The aqueous layer was basified with an 8 N aqueous sodium hydroxide and extracted with dichloromethane (5 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give amine **29** (0.185 g, 83%): IR (neat) 3300, 3020, 2930, 2840, 1600, 1570, 1500, 1480, 1460, 1440, 1380, 1320, 1120, 1000, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.07-2.40 (br, 1 H, NH), 2.60-3.60 (m, 6 H, $-CH_2-$), 4.33-4.73 (m, 1 H, ArCHN), 6.93-7.76 (m, 7 H, ArH), 8.53 (d, J = 4.0 Hz, 1 H, CH=N—).

2-Phenylpyrrolidine (31). To a mixture of hydroxylamine **23** (0.163 g, 1.00 mmol), water (5.8 mL), and HCl (1.4 mL) was added zinc powder (0.468 g, 7.16 mmol), and the mixture was stirred at 100 °C for 2 h. The mixture was made basic with 30% aqueous sodium hydroxide and extracted with ether (15 mL × 5). The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to afford cyclic amine **31**[63] (0.123 g, 84%) as a colorless liquid.

3-(1-Methyl-2-pyrrolidinyl)pyridine (Nicotine) (32). Catalytic hydrogenation of **24** over palladium on charcoal in acetic acid under H_2 gave **30**[63] in 70% yield. To a solution of **30**, aqueous formaldehyde, and sodium cyanoborohydride in acetonitrile was added acetic acid dropwise until the solution becomes neutral. The usual treatment gave **32**[45] in 91% yield.

1-Methyl-10-oxa-9-azatricyclo[3.3.1.1^{3,9}]decane (34). A mixture of hydroxylamine **25** (0.311 g, 2.0 mmol) and Pd black (0.043 g, 0.4 mmol) in toluene (5 mL) was stirred for 40 h at reflux temperature. To the mixture was added ether (10 mL), and the mixture was filtered through Celite. The filtrate was evaporated, and Kugelrohr distillation gave isoxazolidine **34** (0.171 g, 56%): bp 77-86 °C (4 mmHg) (Kugelrohr); IR (neat) 2975, 2940, 2880, 1480, 1455, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.20 (s, 3 H, CH_3), 1.33-2.34 (m, 10 H, $-CH_2-$), 3.40-3.83 (m, 1 H, —CHN—), 4.80 (t, J = 5.0 Hz, 1 H, —CHO—).

Registry No. **1**, 86544-58-3; **2**, 94143-77-8; **3**, 3376-26-9; **4**, 3376-24-7; **5**, 24423-87-8; **6**, 98809-70-2; **7**, 94143-78-9; **8**, 24423-88-9; **9**, 113123-23-2; **10**, 34418-91-2; **11**, 55386-67-9; **12**, 4781-58-2; **13**, 16249-34-6; **14**, 94617-77-3; **15**, 94143-79-0; **16**, 94143-80-3; **17**, 94617-79-5; **18**, 94617-80-8; **22**, 102564-44-3; **23**, 99075-08-8; **24**, 125198-33-6; **25**, 94143-81-4; **26**, 75997-56-7; **27**, 125198-34-7; **28**, 125198-35-8; **29**, 125198-36-9; **30**, 13450-58-3; **31**, 1006-64-0; **32**, 75202-10-7; **34**, 94143-82-5; CH_3MgI, 917-64-6; PhBr, 108-86-1; $HNBu_2$, 111-92-2; $HN(Pr\text{-}i)_2$, 108-18-9; $PhCH_2NHCH_2Ph$, 103-49-1; $PhCH_2NHBu\text{-}t$, 3378-72-1; $PhCH_2NHMe$, 103-67-3; PhCH=N(=O)Me, 3376-23-6; H_2C=CHOBu, 111-34-2; H_2C=$CHCH_2BrMg$, 1730-25-2; 3-bromopyridine, 626-55-1; 1,2,3,4-tetrahyrdoisoquinoline, 91-21-4; 6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 98809-69-9; 6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline, 94143-83-6; pyrrolidine, 123-75-1; methyl 2-pyrrolidinecarboxylate, 2577-48-2; piperidine, 110-89-4; 2-methylpiperidine, 109-05-7; benzaldoxime, 932-90-1; morpholine, 110-91-8; 2,3-(methylenedioxy)benzyl bromide, 101417-40-7; 2-picoline, 109-06-8.

(63) Seeman, J. I. *Synthesis* **1977**, 498.

Tungstate-Catalyzed Oxidation of Tetrahydroquinolines with Hydrogen Peroxide: A Novel Method for the Synthesis of Cyclic Hydroxamic Acids

Shun-Ichi Murahashi,* Tetsuya Oda, Toshiaki Sugahara, and Yoshiyuki Masui

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

Received August 23, 1989

The sodium tungstate catalyzed oxidation of 1,2,3,4-tetrahydroquinolines (**1**) with 30% aqueous hydrogen peroxide solution in methanol gives 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-ones (**2**), which are important biologically active compounds, in good to excellent yields. The cyclic hydroxamic acid **7** is also obtained in good yield. Since reduction of **2** thus obtained gives 3,4-dihydroquinolin-2(1*H*)-ones (**4**), the present reaction provides a convenient method for synthesis of **4** from **1**.

Flavin monooxygenase[1] and model compounds, such as 5-ethyl-4a-hydroperoxyisoalloxazines[2,3] effect oxidation of secondary amines to give nitrones. Simulation of this function with transition metal complex catalysts led the

(1) (a) Ziegler, D. M.; Mitchell, C. H. *Arch. Biochem. Biophys.* **1972**, *150*, 116. (b) Kadlubar, F. F.; Mckee, E. M.; Ziegler, D. M. *Arch. Biochem. Biophys.* **1973**, *156*, 46. (c) Poulsen, L. L.; Kadlubar, F. F.; Ziegler, D. M. *Arch. Biochem. Biophys.* **1974**, *164*, 774.

(2) (a) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 6498. (b) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4017.

(3) Murahashi, S.-I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc.* **1989**, *111*, 5002.

0022-3263/90/1955-1744$02.50/0