Heteroatom Chemistry
Volume 9, Number 3, 1998

Nitroxide Synthesis Using the Methyltrioxorhenium/Hydrogen Peroxide System

Robert W. Murray[1] and Kaliappan Iyanar[1]

[1]*Department of Chemistry, University of Missouri–St. Louis, St. Louis, MO 63121*

Received 1 August 1997; Revised 22 September 1997

ABSTRACT: *Some secondary amines of varying structural type have been oxidized by the methyltrioxorhenium/hydrogen peroxide system to the corresponding nitroxides in excellent yield. These results, coupled with our earlier work using this system, indicate the striking parallel between this chemistry and that of the dioxiranes. While the yields in the dioxirane and methyltrioxorhenium/hydrogen peroxide methods are comparable, the latter method must be regarded as superior since it is catalytic.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:347–350, 1998

INTRODUCTION

Interest in the synthesis of nitroxides continues to grow, largely because of their use [1–3] as spin labels in biochemistry and medicine. A number of oxidants have been used [1] to convert secondary amines to nitroxides. We earlier reported [4] that dimethyldioxirane may be used to carry out this oxidation to give nitroxides in high yield. Recently, we have been studying the chemistry of the methyltrioxorhenium (MTO)–hydrogen peroxide system primarily because of the similarity of this chemistry to that of dimethyldioxirane.

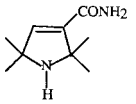
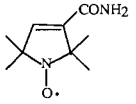
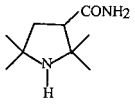
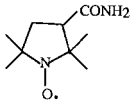
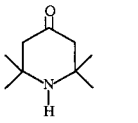
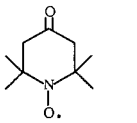
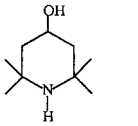
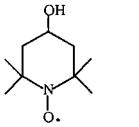
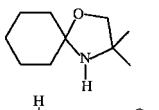
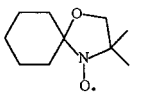
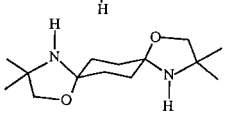
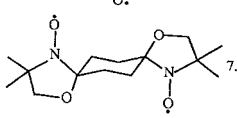
The MTO–H_2O_2 system has been used to oxidize a variety of organic substrates including alkenes [5], phosphines, arsines, and stibines [6], arenes [7], sulfur compounds [8], benzaldehyde [9], alkynes [10], anilines [11], and alcohols [12]. In our work to date, comparing the MTO–H_2O_2 system with dimethyldioxirane, we have shown that the metal system is capable of carrying out a C–H insertion reaction [13] in the same manner as the dioxirane. We have also shown that the metal system can oxidize a variety of organonitrogen compounds [14] and can be used to synthesize nitrones [15] in high yield. In the current work, we extend our studies to the use of the MTO–H_2O_2 system for the synthesis of nitroxides. Again, this work parallels our earlier demonstration [4] that dimethyldioxirane can be used to synthesize nitroxides in high yield.

RESULTS AND DISCUSSION

The rhenium system has been shown by Herrmann [16] and Espenson [17] to give two adducts with hydrogen peroxide, (**1**) and (**2**) (Equation 1), either of which could be responsible for the chemistry described here. Under our experimental conditions, we expect the major oxidant to be **2,** however. We have oxidized a series of secondary amines that have no α-hydrogen atoms so that the oxidation proceeds to the nitroxide (Equation 2). The oxidations followed the methods [14,15] used by us in our earlier work with the metal system. A variety of secondary amine structural types have been oxidized, including a disecondary amine (Table 1). The nitroxides were identified by comparing their physical and spectroscopic properties with literature values. In particular, the

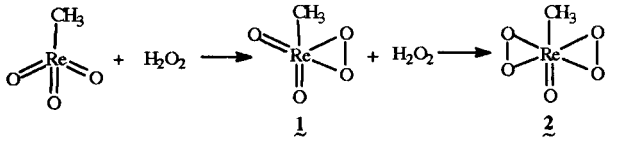
Correspondence to: Robert W. Murray
 CCC 1042-7163/98/030347-04

TABLE 1 Oxidation of Secondary Amines to Nitroxides with Hydrogen Peroxide in the Presence of MTO Catalyst[a]

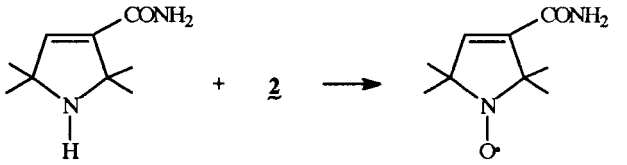
Entry	Substrate	Product	a_N (Gauss)	% Yield
1			15.0	90
2			14.9	95
3			13.0	90
4			16.0	90
5			15.5	90
6[b,c]			7.5[d]	80

[a]General experimental procedure followed.
[b]Two equivalents of H_2O_2 and MTO were used.
[c]Urea hydrogen peroxide adduct used.
[d]$a_N/2$.

nitroxides give hyperfine splitting constants (a_N) that are essentially the same as those in the literature. The dinitroxide (entry 6) gives the ESR spectrum of a triplet as previously reported [18]. The dinitroxide has been shown [18] to exist in the *trans* configuration, that is, with the N–O bonds pointed in opposite directions. In addition, the earlier workers [18] concluded that the compound exists in a preferred conformation, namely, a chair conformation with the C–N bonds equatorial. Attempted synthesis of the dinitroxide by the general method proved unsatisfactory. An alternative procedure using urea hydrogen peroxide (UHP) as the source of the hydrogen peroxide, instead of the aqueous solution, provided the dinitroxide in good yield, however. This method allows the use of an organic solvent (methylene chloride) and avoids the use of water, which alters the reaction course. The nitroxides are all highly colored as is usually observed. The nitroxide yields obtained (Table 1) indicate that this synthetic method is superior to many existing methods. While these yields are comparable to those obtained using dimethyldioxirane [4], it should be emphasized that the synthesis described here is catalytic and thus is actually a superior method.



(1)



(2)

We believe that the mechanism of nitroxide formation as observed here is similar to that proposed [4] earlier by us for the corresponding reaction with dimethyldioxirane. In that case, we have shown [19] that the amine is first oxidized to the hydroxylamine. In suitable substrates, the hydroxylamine reacts further to give the nitroxide. We have also shown [15] that the hydroxylamine is produced enroute to nitrone formation in the oxidation of secondary amines by the MTO–H_2O_2 system. This proposal is supported by the observations of Espenson and coworkers. In their studies of the oxidation of a series of anilines by the MTO–H_2O_2 system, Zhu and Espenson [11] used a Hammett plot to show that the reaction was electrophilic in character. Also Al-Ajilouni and Espenson [20] have shown that epoxidation of alkenes by the metal system is an electrophilic process. Indeed, these two linear free-energy results demonstrate dramatically the similarity between the oxidations by dimethyldioxirane and the rhenium system.

EXPERIMENTAL

Materials. Methylrhenium trioxide (MTO) was prepared from Re_2O_7 and $Sn(CH_3)_4$ according to the literature procedure [21]. 2,2,6,6-Tetramethyl-4-piperidone monohydrate (Aldrich), 2,2,6,6-tetramethyl-4-piperidinol (Aldrich), 2,2,5,5-tetramethylpyrrolidine-3-carboxamide (Aldrich), 2,2,5,5-tetramethylpyrrolin-3-carboxamide (Aldrich), *p*-toluenesulfonic acid (Aldrich), 1,4-cyclohexanedione (Aldrich), and 2-amino-2-methyl-1-propanol (Aldrich) were all used as received. Anhydrous sodium sulfate, hydrogen peroxide (50%), urea hydrogen peroxide (UHP), and ethanol were obtained from Fisher and used as such. Benzene (Fisher) and cyclohexanone (Aldrich)

were purified by distillation prior to use. 1,4-Bis(4′,4′-dimethyloxazolidine)cyclohexane and 2-cyclohexyl-4′,4′-dimethyloxazolidine were prepared using the literature methods.

Instrumentation. ^{1}H and ^{13}C NMR spectra were measured on a 300 MHz NMR spectrometer. Mass spectra were recorded on an EI quadrupole mass spectrometer interfaced with a gas chromatograph fitted with a 12 m × 0.2 mm × 0.33 μm ultra-1 (cross-linked methyl silicone) column. Melting points were determined on a capillary melting-point apparatus and are uncorrected.

General Procedure for the Synthesis of Nitroxides. The literature procedure [5a,16] for the preparation of the MTO–H_2O_2 adduct was followed. To a stirred solution of the amine (1 mmol) in ethanol (5 mL) was added dropwise a solution of MTO (0.01 g, 0.04 mmol) in H_2O_2 (3 mL in ethanol, 25 mmol) over a period of 15 minutes at room temperature. Stirring was continued for an additional 1 hour and 45 minutes. Water (10 mL) was added to the reaction mixture followed by saturated aqueous sodium chloride solution (5 mL). The reaction mixture was then extracted with dichloromethane. The organic layer was separated and washed with saturated aqueous sodium chloride. The organic layer was again separated and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent removed on the rotary evaporator. The crude product was then purified by recrystallization.

1,4-Bis(4′,4′-dimethyloxazolidine)cyclohexane. Cyclohexane-1,4-dione (2 g, 0.025 mol) and 2-amino-2-methyl-propanol (5.5 g, 0.061 mol) were refluxed in benzene solution (50 mL) containing 5 mg of *p*-toluenesulfonic acid for 60 hours. Water was removed using a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, anhydrous K_2CO_3 (5 g) was added, and stirring continued for 5 minutes. The solid was filtered off, water (10 mL) was added, and then the reaction mixture was extracted with ether. The organic layer was separated and dried with anhydrous Na_2SO_4. The solvent was evaporated to give white crystals that were recrystallized from ether to give white crystals (3.8 g, 60%), mp 104–105°C, Ref. [18] mp 104–105°C. ^{1}H NMR ($CDCl_3$): 1.27 (s, 12 H), 3.60 (s, 4 H), 1.87 (d, 8 H), 4.62 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ 28.50, 34.78, 58.76, 76.66, 95.07. MS (EI, 70 eV): *m/z* 254 (M^+), 128 (base peak). Calcd for $C_{14}H_{26}N_2O_2$: 254.37.

1,4-Bis(4′,4′-dimethyloxazolidine-3′-oxyl)cyclohexane. The amine (0.254 g, 1 mmol) in ethanol (10 mL) was oxidized using MTO/H_2O_2 (two equivalents) following the general procedure. It was found that this procedure led to the formation of a multi-component reaction mixture. The following alternative procedure was used instead. To a stirred solution of the amine (0.254 g, 1 mmol) and UHP (4.75 g, 50 mmol) in dichloromethane was added MTO (0.02 g, 0.08 mmol). The mixture was stirred for 4 hours (turbidity forms within 1 hour, and then the solution becomes clear after 3 additional hours). The solid was filtered off and the filtrate washed with water and then dried with anhydrous sodium sulfate. Evaporation of the solvent gave a yellow-colored material. This was recrystallized from ether to give yellow-red crystals (0.227 g, 80%), mp 185–190°C, Ref. [18] mp 189–190°C. MS (EI, 70 eV): 284 (M^+, 6.5), 56 (base peak). Calcd for $C_{14}H_{24}N_2O_4$: 284.35.

2-Cyclohexyl-4′,4′-dimethyloxazolidine. Cyclohexanone (4.9 g, 0.05 mmol) and 2-amino-2-methyl-propan-1-ol (4.46 g, 0.05 mmol) were refluxed in benzene (50 mL) for 14 hours using a Dean-Stark apparatus. The solvent was evaporated and the residue distilled at 95°C/20 mm Hg to give a colorless liquid (6.17 g, 73%), Ref. [22] bp 95°C/20 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 6H), 3.57 (s, 2H), 1.45–1.75 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 23.88, 25.31, 28.46, 37.90, 58.67, 76.33, 96.07. MS (EI, 70 eV): 169 (M^+, 5.7), 126 (base peak). Calcd for $C_{10}H_{19}NO$: 169.27.

2-Cyclohexyl-4′,4′-dimethyloxazolidine-3-oxyl. The amine (0.169 g, 1 mmol) was oxidized following the general procedure to give a yellow solid (0.165 g, 90%), mp 59–61°C, Ref. [22] mp 61–62°C. MS (EI, 70 eV): 184 (M^+, 6.3), 99 (base peak). Calcd for $C_{10}H_{18}NO_2$: 184.26.

4-Oxo-2,2,6,6-tetramethylpiperidine-1-oxyl. The general procedure was followed using 0.173 g (1 mmol) of 4-oxo-2,2,6,6-tetramethylpiperidine. Removal of the solvent from the resultant reddish-yellow solution gave a reddish-yellow solid that was recrystallized from the minimum amount of hexane (0.153 g, 90%), mp 32–34°C, Ref. [22] mp 36°C. MS (EI, 70 eV): 170 (M^+, 10.01), 56 (base peak). Calcd for $C_9H_{16}NO_2$: 170.23.

4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl. Oxidation of 4-hydroxy-2,2,6,6-tetramethylpiperidine (0.157 g, 1 mmol) following the general procedure gave a yellow-colored solid (0.155 g, 90%), mp 69–72°C, Refs. [23,24] mp 69–71°C. MS (EI, 70 eV) 172 (M^+, 12.8), 71 (base peak). Calcd for $C_9H_{18}NO_2$: 172.25.

3-Carbamoyl-2,2,5,5-tetramethylpyrroline-1-oxyl. Oxidation of 2,2,5,5-tetramethylpyrroline-3-carbox-

amide (0.168 g, 1 mmol) following the general procedure gave a bright yellow-colored solid (0.165 g, 90%), mp 202–205°C, Ref. [25] mp 203–204°C. MS (EI, 70 eV): 183 (M^+, 24.53), 153 (base peak). Calcd for $C_9H_{15}N_2O_2$: 183.23.

3-Carbamoyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl. Following the general procedure, oxidation of 0.170 g (1 mmol) of 2,2,5,5-tetramethylpyrrolidine-3-carboxamide and removal of the solvent gave a yellow-colored solid (0.175 g, 95%), mp 170–173°C, Ref. [25] mp 173°C. MS (EI, 70 eV): 185 (M^+, 14.80), 100 (base peak). Calcd for $C_9H_{17}N_2O_2$: 185.25.

ACKNOWLEDGMENTS

This project was supported by Grant Number ES01984 from the National Institute of Environmental Health Sciences, NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH. The Varian XL-300 NMR Spectrometer was purchased with support from the National Science Foundation. We are grateful to Dr. David J. Sloop of the Washington University ESR Group for assistance with the ESR measurements.

REFERENCES

[1] J. F. W. Keana, *Chem. Rev., 78,* 1978, 37.
[2] L. J. Berliner (ed): *Spin Labeling, Theory and Applications,* Academic Press, New York (1976).
[3] J. L. Holzman (ed): *Spin Labeling in Pharmacology,* Academic Press, New York (1984).
[4] R. W. Murray, M. Singh., *Tetrahedron Lett., 37,* 1988, 4677.
[5] (a) W. A. Herrmann, R. W. Fischer, D. W. Marz, *Angew. Chem. Int. Ed. Engl., 30,* 1991, 1638; (b) T. R. Boehlow, C. D. Spilling, *Tetrahedron Lett., 37,* 1996, 2727.
[6] M. M. Abu-Omar, J. H. Espenson, *J. Am. Chem. Soc., 117,* 1995, 272.
[7] (a) W. Adam, W. A. Herrman, J. Lin, C. R. Saha-Moller, R. W. Fischer, J. D. G. Correia, *Angew. Chem. Int. Ed. Engl., 33,* 1994, 2475; (b) W. Adam, W. A. Herrmann, J. Lin, C. R. Saha-Moller, *J. Org. Chem., 59,* 1994, 8281.
[8] (a) P. Huston, J. H. Espenson, A. Bakac, *Inorg. Chem., 32,* 1993, 4517; (b) W. Adam, C. M. Mitchell, C. R. Saha-Moller, *Tetrahedron, 50,* 1994, 13121.
[9] S. Yamazaki, *Chem. Lett.,* 1995, 127.
[10] Z. Zhu, J. H. Espenson, *J. Org. Chem., 60,* 1995, 7728.
[11] Z. Zhu, J. H. Espenson, *J. Org. Chem., 60,* 1995, 1326.
[12] Z. Zhu, J. H. Espenson, *J. Org. Chem., 61,* 1996, 324.
[13] R. W. Murray, K. Iyanar, J. Chen, J. T. Wearing, *Tetrahedron Lett., 36,* 1995, 6415.
[14] R. W. Murray, K. Iyanar, J. Chen, J. T. Wearing, *Tetrahedron Lett., 37,* 1996, 805.
[15] R. W. Murray, K. Iyanar, J. Chen, J. T. Wearing, *J. Org. Chem., 23,* 1996, 8099.
[16] W. A. Herrmann, R. W. Fischer, W. Scherer, M. U. Rauch, *Angew. Chem. Int. Ed. Engl., 32,* 1993, 1157.
[17] S. Yamazaki, J. H. Espenson, P. Huston, *Inorg. Chem., 32,* 1993, 4683.
[18] P. Michon, A. Rassat, *J. Am. Chem. Soc., 97,* 1975, 696.
[19] R. W. Murray, M. Singh, *Synthetic Comm., 19,* 1989, 3509.
[20] A. M. Al-Ajilouni, J. H. Espenson, *J. Org. Chem., 61,* 1996, 3969.
[21] W. A. Herrmann, F. E. Kuhn, R. W. Fischer, W. R. Thiel, C. C. Romo, *Inorg. Chem., 31,* 1992, 4431.
[22] E. M. Hancock, A. C. Cope, *J. Am. Chem. Soc., 66,* 1944, 1738.
[23] E. G. Rozantzev, M. B. Neiman, *Tetrahedron, 20,* 1964, 131.
[24] J. A. Cella, J. A. Kelley, E. F. Kenehan, *J. Chem. Soc., Chem. Commun.,* 1974, 943.
[25] E. G. Rozantzev, L. A. Krinitzkaya, *Tetrahedron, 21,* 1965, 491.