Synthesis of Nitrones Using the Methyltrioxorhenium/Hydrogen Peroxide System

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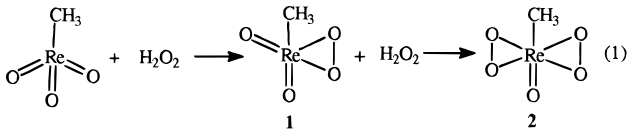
Secondary amines are oxidized by the methyltrioxorhenium/hydrogen peroxide system to the corresponding nitrones in excellent yield. The results provide a further example of the parallel between the chemistry of this metal system and that of the dioxiranes.

Introduction

Nitrones are important organic compounds because of their use in organic synthesis[1] and their use as spin traps.[2,3] The latter usage includes nitrones as scavengers of radicals in the biomedical area. A number of nitrone syntheses have been described.[1,4] Many of these methods involve the oxidation of hydroxylamines which generally are not readily accessible. We have reported[4a] that the oxidation of secondary amines with dimethyldioxirane provides a convenient high-yield synthesis of hydroxylamines. Furthermore, we have demonstrated[5] that some of these hydroxylamines are rapidly and, in most cases, quantitatively converted to nitrones by dimethyldioxirane.

We have become interested in the methyltrioxorhenium/hydrogen peroxide (MTO/H_2O_2) system because of the similarity of its chemistry to that of dioxirane chemistry. This metal system has been shown to oxidize a variety of organic substrates including alkenes,[6] phosphines,[7] arsines,[7] stibines,[7] arenes,[8] sulfur compounds,[9] benzaldehyde,[10] alkynes,[11] anilines,[12] and alcohols.[13] The rhenium system has been shown by Herrmann[14] and Espenson[15] to give two adducts, **1** and **2** (eq 1), either of



(1)

which could be responsible for the chemistry we observe. Under our experimental conditions we expect the major oxidant to be **2**.

We reported earlier[16] that the MTO/H_2O_2 system is capable of accomplishing C−H bond insertion reactions which parallel those of dimethyldioxirane. As part of our effort to further compare this metal system with dimethyldioxirane, we have reported[17] the oxidation of a variety of organonitrogen compounds using the MTO/H_2O_2 system. Again, we observed a remarkable parallel to the dioxirane chemistry. Included in the group of compounds studied was a secondary amine, dibenzylamine, which gave primarily the expected hydroxylamine. However, the reaction also gave a small amount of nitrone which prompted us to study the use of this system as a general preparative method for nitrones. The results of that study are described here.

Results and Discussion

Generally we have followed the procedures described by Herrmann[14] and Espenson[15] to prepare the MTO/H_2O_2

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

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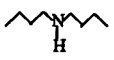
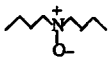
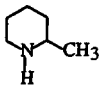
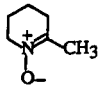
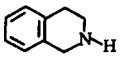
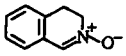
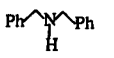
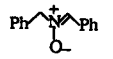
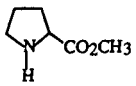
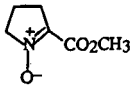
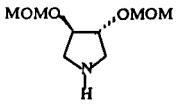
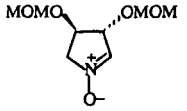
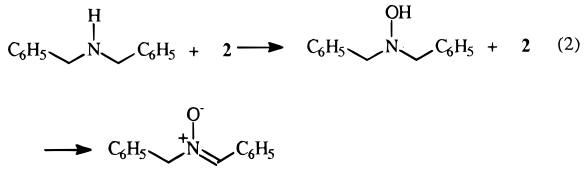
Table 1. Oxidation of Secondary Amines with Hydrogen Peroxide in the Presence of MTO Catalyst[a]

Entry	Substrate	Solvent	Product	% Yield
1		C_2H_2OH		95
2		C_2H_5OH		90
3		C_2H_5OH		90
4		C_2H_5OH		85
5		C_2H_5OH		90
6		C_2H_5OH		80[b]
7		CH_2Cl_2		50[c]
8		CH_2Cl_2		80[b,c]

[a] General experimental procedure followed. [b] Partial decomposition occurs during isolation. [c] Urea-hydrogen peroxide adduct used.

adducts. Oxidations using the adducts generally followed the methods used in our earlier work[17] with organonitrogen compounds. A number of secondary amines of varying structural types were treated with **2**. The reactions were run at room temperature and usually for 30 min. An example of this oxidation is shown in eq 2.



(2)

Usually, the product nitrones were obtained in high yield (>80%, Table 1). The products are known materials which were identified by NMR and GC−MS methods. Oxidation of *N*-phenylbenzylamine using the general procedure gave the hydrolysis products nitrosobenzene and benzaldehyde. However, a good yield (50%) of the derived nitrone could be obtained by using urea−hydrogen peroxide (UHP) as the source of hydrogen peroxide and methylene chloride as the solvent. With the proline derivative (entry 6), the nitrone was obtained regiospecifically, presumably because of the acidity of the proton involved. Of particular interest is the synthesis of (3*S*,4*S*)-3,4-bis(methoxymethoxy)-1-pyrroline *N*-oxide (entry 8). This nitrone has proven to be useful in the synthesis of the antibiotic (−)-anisomycin.[18] Generally we have followed the literature procedure[18,19] for the synthesis of the pyrrolidine precursor to the required nitrone. For the nitrone synthesis we used the MTO/H_2O_2 system instead of the SeO_2/H_2O_2 used in the earlier[18] method. The current procedure gave an 80% yield of the nitrone as compared with 60% yield in the earlier synthesis.

We described earlier[5] a synthesis of nitrones using dimethyldioxirane. The method is rapid, simple, and high yield. The results described here using the MTO/H_2O_2 adduct **2** indicate that the latter method is quite competitive with the dioxirane method. Furthermore, it has the advantage of being catalytic as opposed to being stoichiometric, as is the case with the dioxirane method. This new nitrone synthesis further indicates the parallel between the chemistry of **2** and that of the dioxirane systems. The reaction proceeds through the hydroxylamine, as demonstrated in the case of dibenzylamine where we have isolated the hydroxylamine and then oxidized it to the nitrone (eq 2). In their study of the reaction of the MTO/H_2O_2 system with anilines, Zhu and Espenson[12] used a Hammett plot to show that the reaction was electrophilic in character. A number of studies have demonstrated[20] that dimethyldioxirane also behaves in an electrophilic manner in a variety of oxidations. We plan to continue our studies that are directed at a comparison of the dioxirane and MTO/H_2O_2 systems. Results similar to those reported here have been obtained with another metal system. The sodium tungstate/H_2O_2 system oxidizes secondary amines to give the corresponding nitrones in good yield.[21]

Experimental Section

Materials. Methylrhenium trioxide was prepared following the literature procedure[22] using Re_2O_7 and $Sn(CH_3)_4$. Dibenzylamine (Aldrich), 2-methylpiperidine (Aldrich), di-*n*-butylamine (Fisher), 1,2,3,4-tetrahydroisoquinoline (Aldrich), *N*-*tert*-butylbenzylamine (Aldrich), proline methyl ester (Aldrich), *N*-phenylbenzylamine (Aldrich), tetramethyltin (Aldrich), perfluoroglutaric anhydride (Aldrich), dirhenium heptoxide (Aldrich), urea−hydrogen peroxide (Aldrich), L-(+)-tartaric acid (Aldrich), benzylamine (Aldrich), palladium hydroxide on carbon (Aldrich), boron trifluoride etherate (Aldrich), Celite (Aldrich), Florisil (Aldrich), and silica gel 60 (PF254, containing gypsum, Merck) were used as received. Anhydrous sodium sulfate, sodium fluoride, sodium borohydride, sodium chloride, and hydrogen peroxide (50%) were obtained from Fisher and used as such. Ethyl acetate (Fisher), methanol (Fisher), 2-methoxyethyl ether (Aldrich), and ethanol (Fisher) were purified by distillation prior to use. Methylene chloride (Fisher), chloroform (Fisher), and hexane (Fisher) were fractionally distilled over calcium hydride.

Instrumentation. ^1H 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 an Ultra-1 (cross-linked methyl silicone) column. Chromatographic separations on the Chromatotron were accomplished using 2 mm Kieselgel 60PF 254 plates. Melting points were determined on a capillary melting point apparatus and are uncorrected.

General Procedure for the Synthesis of Nitrones. The literature procedure[6,14,17] for the preparation of the MTO/H_2O_2

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adduct was followed. To a stirred solution of amine (5 mmol) in ethanol (25 mL) was added MTO (0.04 g, 0.16 mmol) in H_2O_2 (6 mL in ethanol, 50 mmol), and the reaction continued to stir at room temperature for 0.5 h. Water (25 mL) was then added to the reaction mixture followed by the addition of a saturated aqueous solution of NaCl (10 mL). The reaction mixture was then extracted with methylene chloride. The organic layer was separated, washed with saturated NaCl solution (10 mL), and dried over anhydrous sodium sulfate. The drying agent was filtered off, and the solvent was removed on the rotary evaporator. The crude product was purified by either chromatography or crystallization and characterized spectroscopically (^{1}H and ^{13}C NMR spectroscopy and GC−MS).

***N*-Butylidenebutylamine *N*-Oxide.** Oxidation of di-*n*-butylamine (0.646 g, 5 mmol) following the general procedure given above produced a pale yellow liquid. This was purified by distillation at 110−120 °C (2 mmHg), lit.[21] bp 110−120 °C (2 mmHg), to give 0.680 g (95% yield) of product. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H), 0.98 (t, 3H), 1.2−2.0 (m, 6H), 2.47 (dt, 2H), 3.72 (t, 2H), 6.74 (t, 1H). ^{13}C NMR ($CDCl_3$): δ 13.4, 13.8, 18.8, 19.4, 28.4, 29.1, 64.9, 141.9. Mass spectrum (EI, 70 eV): *m*/*z* 143 (M^+, 3.1), 100 (base peak), calcd for $C_8H_{17}NO$ 143.23.

***N*-Benzylidenebenzylamine *N*-Oxide.** The general procedure was followed using dibenzylamine (0.986 g, 5 mmol). Solvent removal gave a solid which was chromatographed on silica gel using ethyl acetate−hexane (15:85) as the eluent. This gave a white solid (0.90 g, 85%), mp 79−81 °C, lit.[4b] mp 82−83 °C. ^{1}H NMR ($CDCl_3$): δ 5.31 (s, 2H), 7.31−7.51 (m, 9H), 8.17−8.25 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 71.2, 128.4, 128.6, 128.9, 129.1, 130.3, 130.4, 133.2, 134.3. Mass spectrum (EI, 70 eV): 211 (M^+, 4.7), 91 (base peak), calcd for $C_{14}H_{13}NO$: 211.26. In a separate experiment the general procedure was used to oxidize 0.213 g (1 mmol) of *N*,*N*-dibenzylhydroxylamine with MTO (10 mg, 0.04 mmol) and hydrogen peroxide (50%, 2 mL, 30 mmol). Removal of the solvent gave a solid which was purified on the Chromatotron using a silica gel plate and ethyl acetate−petroleum ether (15:85) to elute. This gave 0.2 g (94% yield) of the pure product.

***N*-Benzylidene-*tert*-butylamine *N*-Oxide.** Oxidation of *N*-*tert*-butylbenzylamine (0.816 g, 5 mmol) and removal of the solvent gave a white solid. Recrystallization from ethyl acetate-hexane gave the pure nitrone as white crystals (0.80 g, 90% yield), mp 72−74 °C, lit.[23] mp 75−76 °C. ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 9H), 7.38−7.45 (m, 3H), 7.54 (s, 1H), 8.27−8.30 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 28.5, 70.9, 128.4, 128.8, 130.1, 130.2, 131. Mass spectrum (EI, 70 eV): 177 (M^+, 15.5), 57 (base peak), calcd for $C_{11}H_{15}NO$: 177.25.

3,4-Dihydroisoquinoline *N*-Oxide. The general procedure was followed using 0.66 g (5 mmol) of 1,2,3,4-tetrahydroisoquinoline. Removal of the solvent gave a brown, oily liquid. This material was dissolved in ethyl acetate−hexane (80:20) and chromatographed on the Chromatotron using a silica gel plate. Elution with the same solvent combination gave a yellow, oily liquid (0.662 g, 90% yield). The ^{1}H NMR data are the same as those previously reported.[21] ^{13}C NMR ($CDCl_3$): δ 27.7, 57.7, 125.7, 127.2, 127.6, 128, 129.7, 130.2, 134.9. Mass spectrum (EI, 70 eV): 147 (M^+, 100), calcd for C_9H_9NO: 147.17.

6-Methyl-2,3,4,5-tetrahydropyridine *N*-Oxide. The general procedure was followed to oxidize 0.4959 g (5 mmol) of 2-methylpiperidine. Solvent removal gave a pale yellow oil. This material was chromatographed using the Chromatotron using a silica gel plate and chloroform−methanol (97:3) as the eluent to give 0.509 g (90% yield) of the product. The ^{1}H NMR data are the same as those previously reported.[21] ^{13}C NMR ($CDCl_3$): δ 18.7, 18.9, 23.2, 30.9, 57.5, 148.8. Mass spectrum (EI, 70 eV): 113 (M^+, 100), 54 (79), calcd for $C_6H_{11}NO$: 113.15.

Methyl 1-Pyrroline-2-carboxylate *N*-Oxide. The general procedure was followed using 0.828 g (5 mmol) of L-proline methyl ester. Removal of the solvent gave a pale yellow oil. The oil was purified on the Chromatotron using a silica gel plate and chloroform−methanol (97:3) as the eluent. This process gave 0.573 g (80% yield) of the nitrone. The ^{1}H NMR data are the same as those previously reported.[21] ^{13}C NMR ($CDCl_3$): δ 25.8, 30.7, 48.7, 61.7, 174, 179.1. Mass spectrum (EI, 70 eV): 143 (M^+, 79), 85 (base peak), calcd for $C_6H_9NO_3$: 143.14.

***N*-Benzylidenephenylamine *N*-Oxide.** Oxidation of 0.183 g (1 mmol) of *N*-phenylbenzylamine with urea−hydrogen peroxide (UHP, 2.24 g, 20 mmol) and MTO (20 mg, 0.08 mmol) in CH_2Cl_2 (6 mL) gave a brown-colored mixture after stirring for 2 h at room temperature. The reaction mixture was dried (Na_2SO_4), and the solvent was removed to give a cream-colored solid. This material was purified on the Chromatotron using a silica gel plate and hexane−ethyl acetate (80:20) to elute. This process gave 0.098 g (50% yield) of the pure nitrone, mp 110−112 °C, lit.[24] mp 112−114 °C. ^{1}H NMR ($CDCl_3$): δ 7.45−7.50 (m, 2H), 7.75−7.78 (m, 2H), 7.91 (s, 1H), 8.37−8.41 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 121.8, 128.7, 129.1, 129.2, 130, 130.9, 130.9, 131.0, 134.8, 149.0. Mass spectrum (EI, 70 eV): 197 (M^+, 15), 91 (base peak), calcd for $C_{13}H_{11}NO$: 197.24.

(3*R*,4*R*)-1-Benzyl-3,4-dihydroxy-2,5-pyrrolidindione. Benzylamine (11 mL, 1 mmol) and L-(+)-tartaric acid (15 g, 1 mmol) were mixed in a 300 mL round bottom flask containing 80 mL of xylene. The mixture was heated at reflux for 3 h, and the water (~3.6 mL, 2 mmol) was collected using a Dean−Stark apparatus. Since crystals collect during the reaction, care must be taken to avoid bumping. After the reaction mixture was cooled, the solid was filtered off, washed with acetone, and recrystallized from ethanol (81% yield), mp 196−198 °C, lit.[19] mp 196 °C.

(3*S*,4*S*)-1-Benzyl-3,4-pyrrolidinediol. Boron trifluoride etherate (7.4 mL, 59 mmol) and 2-methoxyethyl ether (30 mL) were combined in a round bottom flask and cooled to 0 °C. The dione (3.3 g, 15 mmol) was added to this mixture. After the reaction mixture was stirred for 10 min, sodium borohydride (1.5 g, 39 mmol) was added slowly. The diborane that was generated was collected by passing it through acetone. After the addition was complete, the mixture was heated to 70 °C and stirred for 2 h. The mixture was cooled to room temperature, and 20 mL of 6 N HCl was added slowly. The mixture was heated to 70 °C and stirred for 15 min. The reaction mixture was cooled to room temperature, and 9.2 g of sodium fluoride was added at once followed by stirring at 100 °C for 30 min. The solution was cooled to 20 °C, and 19 mL of an aqueous sodium hydroxide solution (20%) was added. The aqueous phase was separated, and the organic phase was evaporated to dryness *in vacuo*. The residue was dissolved in 12 mL of water and extracted with ether continuously for 24 h. Evaporation of the ether gave the diol as a crystalline solid (52% yield), mp 98−100 °C, lit.[19] mp 100 °C. $[\alpha]^{20}_D$ +31.4 (*c* 4, methanol), lit.[18] $[\alpha]^{20}_D$ +31.9 (*c* 4, methanol).

(3*S*,4*S*)-1-Benzyl-3,4-bis(methoxymethoxy)pyrrolidine. The diol (0.3 g, 1.55 mmol) in dimethoxymethane (10 mL) was cooled to 0 °C, and P_2O_5 (1.1 g, 7.75 mmol) was added slowly with stirring over a period of 1 h. The reaction mixture was then stirred at room temperature for 2 days. The solvent was evaporated, and the residue was again cooled to 0 °C. The residue was treated with 20% methanolic KOH (7.5 mL). The resulting suspension was filtered over Florisil, and the methanol was evaporated. The crude residue was purified on the Chromatotron using silica gel and eluting with hexane/ethyl acetate (3:2) to give the diether as a colorless oil. The ^{1}H NMR spectrum is essentially the same as that in the literature.[18] ^{13}C NMR ($CDCl_3$): δ 138.1, 129.1, 128.4, 127.2, 95.8, 81.7, 60.5, 58.8, 55.7. Mass spectrum (EI, 70 eV): 281 (M+, 0.36), 91 (base peak), calcd for $C_{15}H_{23}O_4N$: 281.35.

(3*S*,4*S*)-3,4-Bis(methoxymethoxy)pyrrolidine. The diether (0.229 g, 0.812 mmol) and $Pd(OH)_2$ on carbon (0.05 g) were mixed in methanol (10 mL). The suspension was hydrogenated at room temperature and 1 atm for 3 h. The catalyst was removed by filtration through Celite and was washed with methanol. The solvent was evaporated to give the crude product which was purified on the Chromatotron using silica gel and elution with hexane/ethyl acetate/ethanol/NH_4OH (4:4:1.8:0.2) to give 0.109 g (70%) of pure material.

(23) Emmons, W. D. *J. Am. Chem. Soc.* **1957,** *79*, 5739.

(24) (a) Utzinger, G. E. *Ann.* **1944**, *556*, 50. (b) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.

The ^{1}H NMR spectrum is essentially the same as that in the literature.[18] ^{13}C NMR ($CDCl_3$): δ 95.6, 81.8, 55.7, 52.0. Mass spectrum (EI, 70 eV): 191 (M+, 0.12), 45 (base peak), calcd for $C_8H_{17}NO_4$: 191.23.

(3*S*,4*S*)-3,4-Bis(methoxymethoxy)-1-pyrroline *N*-Oxide. Urea-hydrogen peroxide (0.146 g, 1.57 mmol) and methyltrioxorhenium were mixed in CH_2Cl_2 (5 mL), and the mixture was stirred for 5 min. The solution became yellow colored. (3*S*,4*S*)-3,4-Bis(methoxymethoxy)pyrrolidine (30 mg, 0.157 mmol) was dissolved in CH_2Cl_2. This solution was added to the UHP−MTO solution, and the combined solution was stirred for $^1/_2$ h. The general workup procedure was used followed by solvent removal. The crude product was purified by column chromatography on silica gel with elution by hexane/ethyl acetate/ethanol (4:5:1) which gave 25 mg (80% yield) of pure product. The ^{1}H NMR spectrum is essentially the same as that in the literature.[18] ^{13}C NMR ($CDCl_3$): δ 132.6, 95.2, 81.3, 55.2, 51.6. Mass spectrum (EI, 70 eV): 205 (M^+, 0.7), 45 (base peak), calcd for $C_8H_{15}NO_5$: 205.21.

Note Added in Proof: Since submission of this paper a report has appeared describing similar results; see: Gobi, A.; Nanelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025.

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