Notes

2-(2-Methoxyethoxy)prop-2-yl Hydroperoxide: An Easily Handled Reagent for the Synthesis of Alkyl Hydroperoxides

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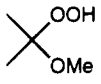
Received June 28, 1994

As part of ongoing studies, we have been interested in methodology for nucleophilic introduction of an aliphatic hydroperoxide group. Traditional methods require prolonged reaction of alkyl sulfonates with excess concentrated hydrogen peroxide under strongly basic conditions.[1,2] Displacements with potassium superoxide often result in production of dialkyl peroxides, alcohols, or ketones.[3] More recently developed alternatives involve complex substitution reactions via intermediate hydrazides and related species.[4-7] We recently introduced 2-methoxyprop-2-yl hydroperoxide (**1**), a hemiketalized version of hydrogen peroxide, as a convenient reagent for nucleophilic introduction of a peroxide group.[8] Reaction between stoichometric amounts of **1** and an alkyl bromide or iodide proceeds rapidly in the presence of CsOH or Cs_2CO_3 to provide good yields of stable monoperoxyketals which undergo subsequent acid hydrolysis to afford the desired hydroperoxides in good overall yield and with excellent purity. We now report the development of a more easily handled alternative, 2-(2-methoxyethoxy)-prop-2-yl hydroperoxide (**2**).



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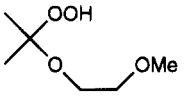
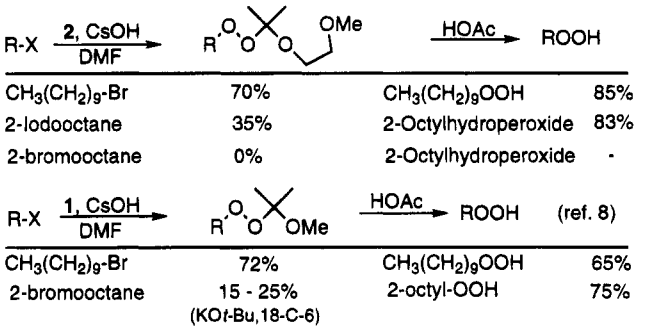


2

Although reagent **1** has been used in our labs on numerous occasions without incident, we have experienced several instances in which isolated samples of hydroperoxide underwent rapid and exothermic decomposition following room temperature removal of solvent *in vacuo*.[9] We therefore sought an alternative reagent with less hazard potential. One approximate indicator

Scheme 1. Synthesis of Hydroperoxides



of relative hazard potential *within* a given class of peroxides is the active oxygen content, the percentage of the total mass formed by the peroxidic or "active" oxygen.[10-12] Hydroperoxide **1** has a high active oxygen content (15%) and was originally assumed to be stable only because of the structural similarity to *tert*-butyl hydroperoxide (active oxygen content = 18%).[13] We reasoned that a decreased active oxygen content should result in a more stable and easily handled reagent. Our first approach, based upon ozonolysis of higher molecular weight alkenes such as methoxymethylenecyclohexane and (−)-β-pinene, furnished alkoxy hydroperoxides which were poorly reactive towards alkyl halides.[14] An alternative approach, ozonolysis of 2,3-dimethylbutene in the presence of higher molecular weight alcohols, produced alkoxyhydroperoxides difficult to separate from residual alcohol.

We next turned to 2-methoxyethanol, a water-soluble primary alcohol. Low temperature ozonolysis of 2,3-dimethyl-2-butene in neat 2-methoxyethanol generated 2-(2-methoxyethoxy)prop-2-yl hydroperoxide (**2**), a reagent with an active oxygen content of only 10%.[15] The reaction mixture was diluted with water and extracted with ethyl acetate; removal of solvent *in vacuo* generated a reagent which was pure by both ^1H and ^{13}C NMR analysis. The experimental procedure given produces **2** in 53% yield with little or no contamination from 2-methoxyethanol; larger scale reactions (caution!) often proceed in higher yield. Dilution of methoxyethanol with CH_2Cl_2 during ozonolysis results in a reduced yield of **2**. The hydroperoxide hydrogen of **2** is observed at ~10 ppm in the ^1H NMR spectrum, apparently as a result of intramolecular hydrogen-bonding.[16]

The similar reactivity of reagents **2** and **1** is illustrated in Scheme 1. Reaction of **2** and a primary bromide in

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(2) Lindstrom, E. G. *J. Am. Chem. Soc.* **1953**, *75*, 5123.
(3) Johnson, R. A.; Nidy, E. G.; Merritt, M. V. *J. Am. Chem. Soc.* **1978**, *100*, 7960.
(4) Collazo, L.; Guziec, F. S., Jr.; Hu, W.-X.; Munoz, A.; Wei, D.; Alvarado, M. *J. Org. Chem.* **1993**, *58*, 6169.
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(8) Dussault, P.; Sahli, A. *J. Org. Chem.* **1992**, *57*, 1009. For a discussion of α-silyloxyhydroperoxides derived from silyl enol ethers, see: Nagata, R; Saito, I. *Synlett* **1990**, 291.
(9) Dussault, P. H. *Chem. Eng. News* **1993**, August 9, 2. The instability appears unrelated to acid-catalyzed formation of the tetroxane or hexoxane and has been observed both in the presence and absence of added stabilizer (BHT). Decomposition may be accelerated by trace metal contaminants and we have received reports that **1** undergoes exothermic decomposition upon exposure to iron salts.
(10) Medard, L. A. *Accidental Explosions: Types of Explosive Substances*; Ellis Horwood Limited: Chichester, 1989; Vol. 2.
(11) Shanley, E. S. In *Organic Peroxides*; D. Swern, Ed.; Wiley-Interscience: New York, 1970; Vol. 3; pp 341.
(12) Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*; Van Nostrand Reinhold: New York, 1992, pp 763.
(13) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(14) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335.
(15) Methyl hydroperoxide (33% active oxygen) is explosive while octyl hydroperoxides (11%) are easily purified on a small scale. However, as is discussed in references 10 and 11, even compounds of low active oxygen content may represent significant hazards on a larger scale.
(16) Richardson, W. H. In *Chemistry of Peroxides*; S. Patai, Ed.; John Wiley & Sons: Chichester, 1983; Vol. 1; pp 129.

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the presence of CsOH results in rapid disappearance of the halide and formation of the corresponding monoperoxyketal in good yield. Reagent **2** is inferior to **1** for displacement of a secondary bromide but displacement of a secondary iodide proceeds in modest yield.[1,8] The intermediate monoperoxyketals are stable towards isolation and purification. Acidic deprotection can be accomplished in even higher yield than for the corresponding peroxyketals derived from **1** to afford pure samples of the desired hydroperoxide.

In conclusion, we have demonstrated that an easily handled higher-molecular weight alkoxyhydroperoxide is an effective hydrogen peroxide synthon for the nucleophilic introduction of the hydroperoxide group.

Caution. We strongly discourage prolonged storage of reagent **2** due to the possibility of intramolecular peroxyl-mediated autoxidation to a dihydroperoxide.[17] Excess reagent can be destroyed with Me_2S, Ph_3P, or $NaHSO_3$. As in any work involving peroxides, standard precautions (use of safety shields, avoidance of heat, light, or metal salts, reactions on minimal scale) should always be observed.[10-12]

Experimental Section

2-(2-Methoxyethoxy)prop-2-yl Hydroperoxide (2). To a −78 °C solution containing 2,3-dimethyl-2-butene (1.0 mL, 8.43 mmol) and Sudan III Red indicator (3 drops of a 0.01% solution in CH_2Cl_2) in distilled 2-methoxyethanol (20 mL) is passed a gaseous solution of O_3/O_2 until the pink color of the Sudan III is discharged. The reaction mixture is poured into distilled water (300 mL) and stirred for 3 min prior to extraction with ethyl acetate (4 × 50 mL). The use of a smaller volume of water leads to increased contamination with 2-methoxyethanol; fewer extractions result in a lower yield of reagent. The organic layer is dried over Na_2SO_4 and concentrated on a rotary evaporator behind a shield to give 668 mg (53%) of alkoxyhydroperoxide **2**: R_f = 0.13 in 11% ethyl acetate/hexanes (EA/hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 1H), 3.67 (dd, 2H, J = 5.7, 4.5), 3.54 (dd, 2H, J = 5.7, 4.2), 3.41 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.1, 72.9, 60.2, 59.0, 22.6; IR (neat) 3307 cm^{-1}. Anal. Calcd for $C_6H_{14}O_4$: C, 47.99; H, 9.39. Found: C, 47.82 ; H, 9.18.

1-[2-(Methoxyethoxy)-1-methylethyl]-1-decyl Peroxide (3). To a 0 °C solution of **2** (385 mg, 2.57 mmol) in DMF (20 mL) is added CsOH (431 mg) followed by 1-bromodecane (567 mg, 2.57 mmol). The reaction is stirred for 2.5 h whereupon distilled water (50 mL) is added. After 5 min, the reaction is extracted with hexanes (3 × 50 mL) and the organic layer is dried over Na_2SO_4. Following concentration on a rotary evaporator, the crude oil is subjected to flash chromatography using 5% EA/hex to afford 527 mg (70%) of monoperoxyketal **3**: R_f = 0.40 in 11% EA/hex; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, 2H, 6.7 Hz), 3.65 (dd, 2H, J = 6.4, 5.7), 3.54 (dd, 2H, J = 6.2, 5.5), 3.35 (s, 3H), 1.56 (m, 2H), 1.38 (s, 6H), 1.35−1.15 (15H), 0.89 (t, 3H, $J \approx$ 6−7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.6, 75.1, 72.0, 60.8, 59.0, 31.86, 29.5, 29.4, 29.3, 26.1, 23.2, 22.6, 14.0. Anal. Calcd for $C_{16}H_{36}O_4$: C,65.71; H,12.40. Found C, 65.66; H,12.51.

1-Decyl Hydroperoxide (4). Monoperoxyketal **3** (94 mg, 0.32 mmol) is dissolved into a freshly prepared 0 °C solution of AcOH:H_2O (90:10, 10 mL) containing four drops of a 0.1 M solution of BHT in dichloromethane. After 1 h, the reaction mixture is allowed to warm to room temperature. After 5 h, the reaction is quenched with sufficient saturated aqueous $NaHCO_3$ to bring the solution to pH 7 and extracted with ethyl acetate (4 × 25 mL). The organic layer is dried over Na_2SO_4 and concentrated on a rotary evaporator. Purification with flash chromatography using 10% EA/hex affords 48 mg (85%) of **4**: R_f = 0.34 in 11% EA/hex; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 3.99 (t, 2H, J = 6.4 Hz), 1.65 (m, 2H), 1.42−1.10 (14H), 0.85 (t, 3H, J = 6−7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.4, 31.7, 29.3, 29.2, 29.1, 27.3, 25.7, 22.4, 13.8; IR (neat) 3396 cm^{-1}.

1-[2-(Methoxyethoxy)-1-methylethyl]-1-methylheptyl Peroxide (5). To a 0 °C solution of **2** (400 mg, 2.67 mmol) in DMF (15 mL) is added CsOH (430 mg) followed by 2-iodooctane (492 mg, 2.05 mmol). After 2.5 h, the reaction is quenched with water (50 mL) and warmed to room temperature. Following extraction with hexanes (3 × 50 mL), the organic layer is dried with Na_2SO_4 and concentrated on a rotary evaporator. Purification with flash chromatography using 5% EA/hex gives 189 mg (35%) of monoperoxyketal **5**: R_f = 0.35 in 11% EA/hex; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (m, 1H), 3.61 (dd, 2H, J = 5.8, 4), 3.48 (broad t, 2H, J = 4.8−5.5), 3.32 (s, 3H), 1.54 (m, 2H), 1.344 (s, 3H), 1.366 (s, 3H), 1.118 (d, 3H, J = 6.2), 1.3−1.15 (8H), 0.81 (t, 3H, $J \approx$ 6−7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 79.5, 72.0, 60.7, 58.9, 34.5, 31.67, 29.3, 25.4, 23.4, 23.1, 22.5, 18.6, 13.9. Anal. Calcd for $C_{14}H_{30}O_4$: C, 64.09; H, 11.52. Found C, 64.13 ; H, 11.66.

2-Octyl Hydroperoxide (6). Monoperoxyketal **5** (28 mg, 0.11 mmol) is deprotected in a similar manner as before. Chromatographic purification using 5% EA/hex gives 13 mg (83%) of **6**: R_f = 0.46 in 13% EA/hex; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 4.09−3.89 (m, 1H), 1.7−0.8 (16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.7, 34.0, 31.8, 29.3, 25.4, 22.6, 18.1, 14.1; IR (neat) 3397 cm^{-1}.

Acknowledgments. This work was supported by funding from the American Cancer Society. We thank Mr. Tom Baiga (UCSD) for communicating observations regarding the stability of **1** in the presence of iron salts.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **2**, **3**, and **5** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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