Synthesis of Alkyl Hydroperoxides by Hydroperoxymercuriation and Reduction

A. J. Bloodworth,* Christopher J. Cooksey and Despoina Korkodilos

Chemistry Department, University College London, 20 Gordon Street, London WC1H 0AJ, UK

Alkyl hydroperoxides, $R^1R^2C(OOH)CH_2R^3$, have been prepared from 30% hydrogen peroxide by hydroperoxymercuriation of the corresponding alkenes, $R^1R^2C{=}CHR^3$, followed by addition to 2-methoxypropene, reductive demercuriation with basic sodium borohydride and deprotection of the resultant 2-methoxyprop-2-yl derivatives, $R^1R^2C(OOCMe_2OMe)CH_2R^3$, with aqueous acetic acid.

The preparation of alkyl hydroperoxides (ROOH) is a challenging problem. The most generally applicable route involves the alkylation of hydrogen peroxide. Although a number of variants of this method has been described,[1] none is wholly satisfactory. Harsh conditions and prolonged reaction times are often required leading to decomposition of sensitive hydroperoxides. Yields are frequently low, especially for secondary alkyl compounds. The formation of appreciable amounts of the corresponding dialkyl peroxide (ROOR) is another common problem. In a recent report,[2] 2-methoxyprop-2-yl hydroperoxide was used as a masked form of hydrogen peroxide to try to avoid some of these difficulties. This prompts us to disclose our new preparation of alkyl hydroperoxides since it similarly involves the intermediacy of peroxyacetals, $ROOCMe_2OMe$.

We have previously shown that the alkyl peroxymercuriation of alkenes coupled with reductive demercuriation (Scheme 1) provides a versatile route to dialkyl peroxides.[3] Furthermore it is particularly well suited to the preparation of secondary alkyl compounds ($R^2 = H$).

$$R^1R^2C{=}CHR^3 \xrightarrow{i} R^1R^2C(OOR^4)CH(HgX)R^3 \xrightarrow{ii} R^1R^2C(OOR^4)CH_2R^3$$

Scheme 1 *Reagents*: i, R^4OOH, HgX_2; ii $NaBH_4$, NaOH

Direct extension to the preparation of alkyl hydroperoxides ($R^4 = H$) is not possible because the hydroperoxide group is reduced under the conditions of demercuriation. However, we now find that conversion of the hydroperoxymercurials **1**[4] into the 2-methoxyprop-2-yl derivatives **2** protects the peroxide linkage during borohydride reduction. Subsequent deprotection then affords the alkyl hydroperoxides **4**. The four-step procedure (Scheme 2) is easy to carry out, involves

Table 1 Alkyl hydroperoxides **4**, $R^1R^2C(OOH)CH_2R^3$, obtained *via* Scheme 2

Compound	R^1	R^2	R^3	Yield (%)[a]
a	Ph	H	H	38
b	2-MeC_6H_4	H	H	30
c	4-MeC_6H_4	H	H	40
d	4-$MeOC_6H_4$	H	H	32
e	Bu	H	H	37
f	Ph	Me	H	40
g	H	$-(CH_2)_4-$		33
h	H	$-(CH_2)_3CHMe-$		54[b]

[a] Based on alkene; product hydroperoxides were stabilised by addition of up to 1% of 2,6-di-*tert*-butyl-4-methylphenol. [b] Mixture of 2- and 3-methylcyclohexyl hydroperoxides.

mild conditions and uses readily available reagents including 30% hydrogen peroxide.

$$R^1R^2C{=}CHR^3 \xrightarrow{i} \underset{\mathbf{1}}{R^1R^2C(OOH)CH(HgBr)R^3} \xrightarrow{ii} \underset{\mathbf{2}}{R^1R^2C(OOCMe_2OMe)CH(HgBr)R^3}$$

$$\xrightarrow{iii} \underset{\mathbf{3}}{R^1R^2C(OOCMe_2OMe)CH_2R^3} \xrightarrow{iv} \underset{\mathbf{4}}{R^1R^2C(OOH)CH_2R^3}$$

Scheme 2 *Reagents*: i, 30% H_2O_2, $Hg(OAc)_2$ then KBr; ii, MeOC(Me)=CH_2, cat. $\overset{+}{p}\text{yH}\ \bar{O}\text{Ts}$; iii, $NaBH_4$, NaOH; iv, AcOH, H_2O

The general procedure is described below and the results obtained are presented in Table 1.

Pyridinium *p*-toluenesulfonate (5 mg) and 2-methoxypropene (15 mmol) were added to a solution (or solution-suspension) in dichloromethane (20 cm^3) of β-hydroperoxyalkylmercury(II) bromide **1** prepared from the corresponding alkene (10 mmol) as previously described.[4] The mixture was stirred for 40 min and then sodium hydroxide (2.5 mol dm^{-3}; 2 cm^3) was added. Using a Pasteur pipette, this mixture was added a little at a time to an ice-cold solution of sodium borohydride (20 mmol) in sodium hydroxide (2.5 mol dm^{-3}; 8 cm^3). After addition was complete (*ca.* 20 min), the mixture was stirred for 45 min then filtered into a separating funnel. The residue was washed with dichloromethane (10 cm^3) and the combined dichloromethane layer isolated and washed with water (20 cm^3). The dichloromethane was removed at a rotary evaporator and 2,6-di-*tert*-butyl-4-methylphenol (2–5 mg), tetrahydrofuran (6 cm^3), glacial acetic acid (12 cm^3) and water (6 cm^3) were added in that order. The solution was stirred for 24 h, water (30 cm^3) added and the whole extracted with diethyl ether (3 × 15 cm^3). The ether extract was washed with water (2 × 10 cm^3), dried ($MgSO_4$) and the solvent removed at a rotary evaporator. The crude product was chromatographed (SiO_2, CH_2Cl_2) to afford pure alkyl hydroperoxide **4** (yield given in Table 1), which was identified by ^1H and ^{13}C NMR spectra, characteristic oxidising properties and reduction to the corresponding alcohol.

For styrene, the intermediate peroxyacetals **2a** (m.p. 65–66.5 °C) and **3a** (b.p. 38–40 °C/0.04 mmHg) were additionally isolated and their structures confirmed by NMR spectroscopy and elemental analysis.

Care must be taken with the reduction step (**2** → **3**), especially for compounds derived from disubstituted ethenes (Table 1, entries **f–h**), otherwise extensive formation of epoxide takes place as with the related *tert*-butylperoxymercurials.[3]

The method has been shown to work for a tertiary alkyl hydroperoxide (Table 1, entry **f**), but we have concentrated on secondary alkyl hydroperoxides because they are the type most difficult to prepare from hydrogen peroxide by standard methods. Our yields (Table 1), which have not been optimised, compare favourably with those obtained from substitution-based routes, including that (19%) obtained for oct-2-yl hydroperoxide by the new use of 2-methoxyprop-2-yl hydroperoxide.[2] The latter reagent gives excellent yields of primary alkyl hydroperoxides,[2] whereas a general synthesis of these by our route is precluded by the regioselectivity of the hydroperoxymercuriation step (Scheme 2). Thus our method and that of Dussault and Sahli,[2] while both making use of peroxyacetals, are complementary.

It has recently been shown that racemic hydroperoxides can be resolved by chromatographic separation of peroxyacetals derived from a chiral vinyl ether.[5] Thus, by incorporating such a reagent in place of 2-methoxypropene in the procedure, it should prove possible to prepare enantiomerically pure secondary alkyl hydroperoxides from alkenes.

One of us (D. K.) thanks the SERC for the award of a Research Studentship.

Received, 7th April 1992; Com. 2/01843H

References

1 H. Kropf, *Methoden der Organische Chemie* (*Houben-Weyl*), Band E13, Georg-Thieme-Verlag, Stuttgart, vol. 1, 1988.
2 P. Dussault and A. Sahli, *J. Org. Chem.*, 1992, **57**, 1009.
3 A. J. Bloodworth and J. L. Courtneidge, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1797, and earlier parts of the series.
4 A. J. Bloodworth and M. D. Spencer, *J. Organomet. Chem.*, 1990, **386**, 299.
5 N. A. Porter, P. Dussault, R. A. Breyer, J. Kaplan and J. Morelli, *Chem. Res. Toxicol.*, 1990, **3**, 236.