An Easy Access to Unsymmetrical Peroxides

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Dedicated to Dr. K. U. Ingold on the occasion of 60th birthday.

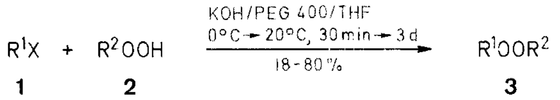
Unsymmetrical peroxides could be prepared easily by reaction of alkyl hydroperoxides with primary and secondary alkyl bromides and methanesulfonates in tetrahydrofuran in the presence of potassium hydroxide and polyethyleneglycol 400.

The discovery of the synthetic applications of the induced decomposition of unsaturated peroxides[1] prompted us to prepare various unsymmetrical peroxides. When we started our study the main general accesses to such compounds were:

- the reaction of an hydroperoxide with a primary or secondary alkyl halide or sulfonate under basic conditions;[2]
- the reaction of a tertiary alcohol with an hydroperoxide under acidic catalysis;[2]
- the reaction of a bromide with an hydroperoxide in the presence of silver trifluoroacetate;[3]
- the reaction of an alkyl triflate with an organometallic peroxide.[4]

As peroxides having hydrogen atoms on the carbons linked to the peroxidic function are sensitive to basic medium,[5] the reaction of a hydroperoxide with an alkyl halide or sulfonate under basic conditions did not always lead to the pure expected peroxide. This remark led Cookson[3] and Salomon[4] to design other procedures operating under neutral conditions, which, however, have the disadvantage of using of expensive reagents. Phase-transfer catalysis appears a good solution avoiding basic decomposition of the peroxide. We decided to use a method based on the phase-transfer properties of benzyltriethylammonium chloride in a dichloromethane solution of hydroperoxide and primary alkyl bromide and solid potassium hydroxide.[6] This reaction was efficient but limited essentially to the reaction of primary alkyl bromides.

The use of crown ethers as catalysts in the preparation of symmetrical secondary peroxides[7] prompted us to check it in the preparation of unsymmetrical ones. The preliminary results confirm their efficiency in such syntheses. Previous replacements of crown ethers by a cheaper substitute, polyethyleneglycol (PEG 400), led us to test this complexing agent. An easy way to unsymmetrical peroxides was developed and the preliminary experiments are reported here.



1	R^1	2	R^2
a	n-C_5H_{11}	**a**	t-C_4H_9
b	$CH_3(CH_2)_3CH(CH_3)$	**b**	$PhC(CH_3)_2$
c	i-Bu	**c**	n-C_5H_{11}
d	$PhCH_2$	**d**	$CH_3(CH_2)_3CHCH_3$
e	$(CH_3)_2C{=}CHCH_2$		

[a] For X, see Table

Table. Preparation of Unsymmetrical Peroxides[a]

Entry	Alkyl (R^1X)	Halide X	Peroxide (R^2OOH)	Reaction Conditions Temp (°C)/Time	Product (R^1OOR^2)	Yield[b] (%)	bp (°C)/mbar and/or n_D^{20}	Molecular Formula[c] or Lit. Data	^{1}H-NMR (CCl_4/TMS)[d] δ, J(Hz)
1	**1a**	Br	**2a**	r.t./2 h	**3aa**	70	55/40	$C_9H_{20}O_2$ (160.3)	0.7–1.8 (m, 18H); 3.8 (t, 2H, J = 6)
2	**1a**	OMs	**2a**	r.t./4 h	**3aa**	63	1.4063[e]		
3	**1a**	I	**2a**	r.t./1 h	**3aa**	50	–		
4	**1a**	Cl	**2a**	r.t./3d	**3aa**	30	–		
5	**1b**	Br	**2a**	r.t./3d	**3ba**	18	62/20	$C_{10}H_{22}O_2$ (174.3)	0.7–1.8 (m, 21H); 3.6–4.1 (m, 1H)
6	**1b**	OMs	**2a**	r.t./3d	**3ba**	50	1.4078[e]		
7	**1c**	Br	**2a**	r.t./2d	**3ca**	45	42/40 1.3960	53/67[10] 1.3959[10]	0.9 (d, 6H, J = 6); 1.2 (s, 9H); 1.4–2.2 (m, 1H); 3.6 (d, 2H, J = 6)
8	**1d**	Br	**2a**	0°/0.5 h	**3da**	70	1.4824[e]	–[f]	1.2 (s, 9H); 4.8 (s, 2H); 7.22 (s, 5H)
9	**1e**	Br	**2a**	0°/0.5 h	**3ea**	65	71/40 1.4275	70/33[1] 1.4283[1]	1.2 (s, 9H); 1.7–1.8 (2s, 6H); 4.3 (d, 2H, J = 7); 5.3 (t, 1H, J = 7)
10	**1a**	Br	**2b**	r.t./2 h	**3ab**	80	1.4837[e]	46/0.01[12] 1.4583[12]	0.7–1.8 (m, 15H); 3.8 (t, 2H, J = 6); 7.0–7.5 (m, 5H)
11	**1a**	Br	**2e**	r.t./2 h	**3ac**	60	54/3 1.4176	42/1.3[11] 1.4168[11]	0.7–1.8 (m, 18H); 3.8 (t, 4H, J = 6)
12	**1a**	Br	**2d**	r.t./2 h	**3ad**	66	66/11 1.4152	$C_{10}H_{22}O_2$ (174.3)	0.7–1.8 (m, 19H); 3.65–4.1 (m, 3H)

[a] Purity of the peroxides is checked by GC (Delsi 200, column: CP-sil-5, CB 25 m; oven temperature: 60–100 °C depending on the peroxide) and is always higher than 97%. The preparation of a symmetrical hydroperoxide **3ac** (entry 11) is also achieved. Neopentyl bromide [$(CH_3)_3CCH_2Br$] did not react with *tert*-butyl hydroperoxide (**2a**) under similar reaction conditions (r.t., 6d).

[b] Yield based on the starting alkyl halide or methanesulfonate.

[c] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.2.

[d] Recorded on a Perkin-Elmer R24-B spectrometer.

[e] Purified by column chromatography on silica gel (35–70 mesh). Entries 2 and 6, eluent: pentane; entries 8 and 10, eluent: pentane containing 2% ether.

[f] Physical constants not reported in Ref. 11.

The best conditions have been found out by various trials in the preparation of *tert*-butyl *n*-pentyl peroxide (**3aa**) (*n*-pentyl bromide (**1a**-Br) and *tert*-butyl hydroperoxide (**2a**) as starting materials) leading to the following conclusions:

- PEG 400/potassium hydroxide was the best combination among the possible ones using PEG 300 or PEG 400/potassium or sodium hydroxide;
- an excess of *tert*-butyl hydroperoxide (**2a**) and potassium hydroxide (1.5 mol) was necessary to get total consumption of *n*-pentyl bromide (**1a**-Br) (1 mol);
- rate of formation of peroxide **3aa** was not really increased when molar ratio PEG 400/*n*-pentyl bromide (**1a**-Br) was higher than 0.1;
- PEG 400 was only partially soluble in ether but totally in tetrahydrofuran leading to the choice of this solvent.

Using standard conditions (see experimental) it was noticed that S_N2 reaction occurred with *n*-pentyl bromide, methanesulfonate, iodide and chloride (entries 1–4) but the best yields were obtained with bromide and mesylate as leaving groups (Table). Various peroxides 3 have been prepared by this method using different leaving groups. Reaction conditions and products are described in the Table. Analysis of these results indicates:

- higher yields than ones obtained previously for unsymmetrical peroxides (10–50%);[4]
- a similar efficiency of primary alkyl bromide and mesylate (entries 1 and 2) but a better one for secondary alkyl mesylate than for the corresponding bromide (entries 5 and 6);
- sluggish reactivity of β-substituted alkyl bromides (entries 5 and 7) (no reaction was found to occur in the case of neophyl bromide, Table);
- the mild conditions of the reaction when potassium hydroxide was added slowly at low temperature (entries 8 and 9, only traces of aldehyde are formed from the basic decomposition of the peroxide);
- small effects of the nature of the hydroperoxide (entries 1, 10, 11 and 12).

Alkyl halides, polyethyleneglycols, *tert*-butyl and cumyl hydroperoxides are commercially available. Methanesulfonates are prepared from alcohols,[8] 1-pentyl and 2-pentyl hydroperoxides from alcohols through methanesulfonates.[9]

Preparation of Peroxides 3; General Procedure:

Entries 1–7 and 10–12: The appropriate hydroperoxide **2** (75 mmol) is added dropwise to a suspension of powdered KOH (4.2 g, 75 mmol) in PEG 400 (2 g) and THF (50 mL) at a temperature of 15–20 °C. Then, the corresponding alkyl halide or methanesulfonate **1** (50 mmol) is added slowly using a syringe. Reaction course is followed by GC analysis of the product formed. After completion of the reaction the solid is filtered and THF is removed under vacuum. The residue is diluted with water (5 mL) and extracted with pentane (3 × 20 mL). The pentane phase is washed with a 10% solution of NaOH and water. Organic phase is dried (Na_2SO_4), and the solvent is removed under reduced pressure. The product is purified by vacuum distillation (bath temperature must be kept below 90 °C) or column chromatography on silica gel (35–70 mesh) using the eluents given in the Table.

Entries 8 and 9: KOH (4.2 g, 75 mmol) is added in small fractions to a cold solution (0 °C) of *tert*-butyl hydroperoxide (**2a**; 6.76 g, 75 mmol), PEG 400 (2 g), and the appropriate halide **1d** or **1e** (50 mmol) in THF (50 mL). The temperature is kept at 0 °C 0.5 h, and the product is worked up as given above (Table).

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