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Improved Synthesis of Secondary Hydroperoxides from Alcohols

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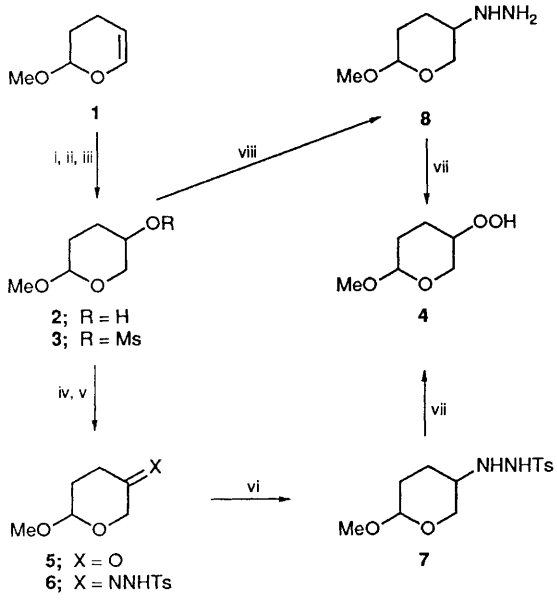
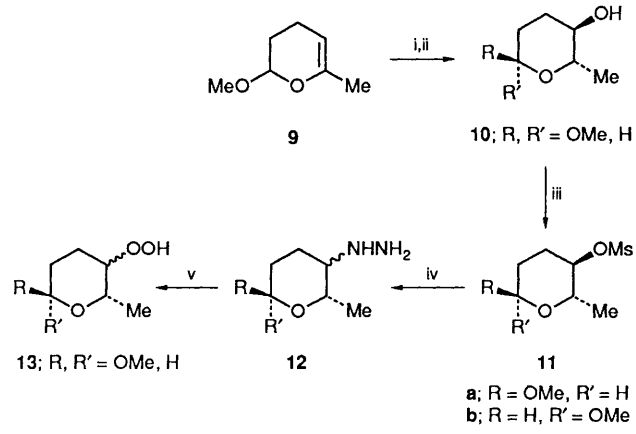
Secondary hydroperoxides have been prepared from secondary alcohols by conversion of the alcohol into its mesylate and subsequent reaction with anhydrous hydrazine followed by hydrogen peroxide and sodium peroxide.

In connection with the isolation of a number of biologically active peroxidic compounds from natural sources in recent years, we recognized that the synthesis of such compounds requires a general and efficient method for incorporating the peroxide linkage. Since classical methods of hydroperoxide synthesis were either impractical or unsuccessful in early studies, we have developed, and now report, an improved, general method for synthesis of secondary hydroperoxides from the corresponding alcohol.

We initially examined the displacement of leaving groups trifloxy, mesyloxy, and phosphite by hydrogen peroxide with no success. The displacement of a tosylhydrazide derivative by hydrogen peroxide was first reported by Caglioti.[1] The necessary hydrazide derivative was prepared from the alcohol **2**. Hydroboration of commercially available **1** with reductive work-up yielded 5-hydroxy-2-methoxytetrahydropyran **2**[2] (Scheme 1). Oxidation of **2** under Swern conditions (oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, −78 °C) gave an 87% yield of ketone **5**. After reaction of **5** with tosylhydrazide in methanol (71%), the resulting hydrazone **6** was reduced to the hydrazide **7** with diborane (BH_3, THF, room temp., 3 h, 38%). Displacement of the hydrazide with hydrogen peroxide and sodium peroxide in tetrahydrofuran gave an 81% yield of the hydroperoxide **4**. Although this hydroperoxide was remarkably stable and easy to characterize, its synthesis was lengthy and the overall product yield was low.



Scheme 1 *Reagents and conditions:* i, BH_3, THF; ii, $NaBO_3$; iii, MsCl, Et_3N, CH_2Cl_2; iv, DMSO, Et_3N, ClCOCOCl, CH_2Cl_2; v, $TsNHNH_2$, MeOH; vi, BH_3; vii, H_2O_2, NaO_2, THF; viii, 96%, NH_2NH_2, heat, 4 d



Scheme 2 *Reagents and conditions:* i, BH_3, THF; ii, $NaBO_3$; iii, MsCl, Et_3N, CH_2Cl_2; iv, 96% NH_2NH_2; v, 30% H_2O_2, Na_2O_2

Since the synthetic availability of tosylhydrazides is limited, an alternative was sought for the routine preparation of hydroperoxides. The reaction of the mesylate **3** with anhydrous hydrazine provided the hydrazine derivative **8**, which was neither easily purified nor characterized. Reaction of crude **8** with sodium peroxide and hydrogen peroxide gave easy access to **4**. The production of **4** is now quite straightforward. The mesylate **3** was treated with hydrazine (excess of 96% NH_2NH_2, reflux, 4 d) and peroxide (100 mol equiv., 30% aq. H_2O_2, 1.5 mol equiv. Na_2O_2, THF, room temp., 3 d) in turn without purification of the intermediate to give **4** in approximately 23% overall yield. The improved route (through **8** instead of **7**) offers an equivalent overall yield (21% overall compared to 19% from alcohol to hydroperoxide) and the method is much easier with fewer steps and no purification of intermediates from the mesylate to the peroxide is required. This conversion has been scaled up to 8 g of mesylate **3**.

Metallation and methylation of **1**[3] provides an efficient route to another pyran derivative, compound **9** (Scheme 2). Use of **9** in the reaction sequence described above has led to the preparation of the corresponding alcohol **10**,† mesylate **11**, hydrazine **12** and peroxide **13**. Hydroboration of **9** gives a mixture of diastereoisomers in which the hydroxy is *trans* to the methyl group.[2] The diastereomeric mesylates **11** are separable by chromatography; **11a** is an oil and **11b** is a crystalline solid. Reaction of each isomer separately with hydrazine followed by hydrogen peroxide yields a different mixture of two hydro-

† The mixture of diastereoisomeric alcohols **10** has been reported; see ref. 2.

peroxides **13** in each case. These results suggest that the conversion of the mesylates into the hydroperoxides is not stereospecific.

We emphasize the simplicity and apparent generality of the method as examined so far. Mesylates are routinely available from alcohols in high yields. Hydrazine and hydrogen peroxide are common, readily available reagents that do not require any specialized equipment for use. No gaseous reagents are used. Although the yields for the overall transformation are only fair, the reactions have been carried out on a multigram scale. We believe this represents a good general alternative to either photoxygenation methods or enzymatic preparation of peroxide intermediates. Due caution is always recommended, however, when handling oxidants of any type.

Experimental

Two typical procedures are as follows.

5-Hydrazino-2-methoxytetrahydropyran **8**.—2-Methoxy-5-methylsulphonyloxytetrahydropyran **3** (6.0 g, 28.4 mmol) and hydrazine (96%, 30 ml) were refluxed together for 4 days while being protected from moisture by a NaOH drying tube. The reaction mixture was then extracted with ether (3 × 100 ml) and the combined extracts were washed with 50% aqueous KOH (20 ml). The organic layer was dried (Na_2SO_4) and evaporated to give crude product (1.79 g, 43%). This was used in the next step without further purification; δ_H(80 MHz, $CDCl_3$) 2.08–2.5 (m, 4 H), 3.38 (s, 3 H, OMe), 3.43–3.85 (m) and 4.5–4.9 (m).

5-Hydroperoxy-2-methoxytetrahydropyran **4**.—Compound **8** (1.5 g, 9.9 mmol) was stirred with 30% aqueous H_2O_2 (150 ml) and Na_2O_2 (1.3 g, 16 mmol) in THF (100 ml) at room temp. for 3 days. CH_2Cl_2 (100 ml) was added and the layers were separated. The organic layer was washed with saturated brine (100 ml), dried (Na_2SO_4) and evaporated. Purification of the residue by column chromatography over silica gel in 20% EtOAc–hexanes gave a *cis* and *trans* mixture of nearly pure product (740 mg, 56%); δ_H(360 MHz, $CDCl_3$) (all signals are doubled) 1.70–2.05 (m, 4 H), 3.39, 3.40 (s, 3 H, OMe), 3.79–4.06 (m, 3 H), 4.52, 4.84 (t, 1 H), 8.26, 8.38 (s, 1 H, OOH); δ_C(all signals are doubled) 20.78, 23.11, 25.06, 27.81, 55.06, 55.17, 59.48, 62.29, 77.18, 77.51, 98.29 and 98.98; *m/z* (FAB) 149 $(M + 1)^+$; ν_{max}/cm^{-1} 3340 (br OOH), 2937, 2960 and 1133.

Details of the preparation of compounds **3**–**13** together with spectral results for the products are given in a Supplementary Publication [SUP. NO. 56853 (bp.)].*

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* For details of the supplementary publications scheme, see Introduction for Authors (1991), *J. Chem. Soc., Perkin Trans. 1*, 1991, issue 1.

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