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A simple, efficient and versatile synthesis of primary *gem*-dihydroperoxides from aldehydes and hydrogen peroxide

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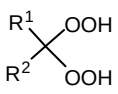
ABSTRACT

Aldehydes were efficiently converted directly into the corresponding *gem*-dihydroperoxides (DHPs) on treatment with aqueous 70% H_2O_2 in a biphasic system with ether catalyzed by camphorsulfonic acid. The synthesis represents the most versatile access to this class of compounds.

The interest in *gem*-dihydroperoxides **1** (DHPs) has increased sharply in recent years due to their relevance to peroxidic antimalaria compounds.[1,2] They are useful intermediates in the synthesis of tetroxanes and their analogues,[3,4] and very recently they have also been utilized as epoxidation reagent for α,β-unsaturated ketones.[5]

The methods for preparing *gem*-DHPs have been reviewed.[6] The most straightforward way for preparing *gem*-dihydroperoxides is the reaction of hydrogen peroxide with ketones or aldehydes. However, in most cases, mixtures of peroxidic products were obtained.[7,8] As the first example of geminal dihydroperoxides, Ledaal and Solbjor[9] isolated 1,1-dihydroperoxycyclododecane when cyclododecanone was treated with 34% aqueous hydrogen peroxide under acidic conditions. Later on, other ketones were used in the presence of formic acid, but DHPs were obtained in lower yields.[10]

A more general way for preparing DHPs from ketones is the use of 30% aqueous H_2O_2 with iodine as catalyst and acetonitrile as solvent.[11,12] This method was also applied to aromatic aldehydes affording 55–76% yield of the corresponding primary DHPs. Das et al.[13] developed an efficient method for the synthesis of *gem*-DHPs from the corresponding ketones and aldehydes using 50% aqueous H_2O_2 and a catalytic amount of ceric ammonium nitrate (CAN). However, for primary *gem*-DHPs the method seems to be limited to aromatic aldehydes, which must not be electron poor. Recently, two other methods for the synthesis of *gem*-DHPs were published by Terent'ev et al., applying a solution of hydrogen peroxide in THF under acid catalysis,[14] and by Dussault et al. using rhenium(VII)oxide in acetonitrile.[15]



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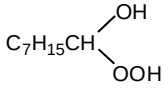

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Remarkably, no conversion of aliphatic aldehydes to DHPs has been reported so far. Using the reaction conditions under which benzaldehyde was transformed into the *gem*-DHP, octanal was converted into corresponding hydroxy-hydroperoxide **2**,[12] that is, just an addition of one molecule of hydrogen peroxide to the carbonyl group occurred. The same compound **2** and additional hydroxy-hydroperoxides were already obtained by Rieche in 1931 on treatment of the corresponding aldehydes with ethereal H_2O_2.[16]

Very few alternative methods to obtain primary *gem*-DHPs have been known so far. We obtained primary DHPs from cyclic benzo-condensed secondary alcohols by acid-catalyzed treatment with H_2O_2 under rearrangement.[17] Ozonolysis of enol ethers in the presence of ethereal H_2O_2 yielded primary *gem*-DHPs.[10] So far, this has been the only more general synthetic procedure described to obtain primary *gem*-DHPs.

The synthesis of DHPs is limited by their stability and depends on their structure. 2,2-Dihydroperoxypropane readily decomposes. However, a stabilization by interaction with diphosphinoyl donors was reported.[18] Very recently, we isolated the hitherto unknown

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ethane-1,1-dihydroperoxide and propane-1,1-dihydroperoxide by reaction of cyclic epoxyketones with hydrogen peroxide.[19] Despite the very high oxygen content (the former has the highest value achieved so far), the compounds are remarkably stable. These findings prompted us to search for a convenient synthesis of primary *gem*-DHPs starting directly from the corresponding aldehydes. Here we report on our preliminary results.

Hydrogen peroxide is commonly used in aqueous form, but ethereal solutions can be prepared and used as well. In the latter case, concentrations are generally lower due to the method of preparation. Since the application of ethereal hydrogen peroxide to aldehydes led only to the formation of perhydrates,[16] that is, only one molecule of hydrogen peroxide entered the aldehyde, we tried now to use aqueous H_2O_2 (70%) and diethylether as a biphasic system in the presence of catalytic amounts of camphorsulfonic acid (CSA). This hitherto unpublished method was originally developed by us for transforming ketones into *gem*-DHPs[20] and was now applied to various aldehydes to obtain the envisaged primary *gem*-DHPs (Scheme 1, Table 1). The reaction was run at room temperature for 16–40 h and worked remarkably well. The reaction mixtures contained some starting material in all cases (except for the lower aldehydes, where probably evaporation occured) even at longer reaction times. This could be explained by the formation of an equilibrium between starting material and product. In addition, the yield might have been further lowered to a small extent by decomposition of the product into the aldehyde **3** during chromatography.

Both acyclic and cyclic aliphatic aldehydes **3** afforded the desired *gem*-DHPs **4** in moderate to good yields. It should be noted that using paraldehyde instead of acetaldehyde did not afford any peroxidic products at all. In most cases, small amounts of bishydroperoxy peroxides **5** were detected as by-products by TLC. In some cases (**5a, 5c** and **5d**), they were also isolated and characterized by NMR spectra.

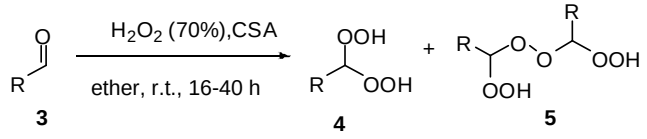
In addition to already known *gem*-dihydroperoxides (**4a, 4b**, **4h** and **4i),** the hitherto unknown 1,1-dyhydroperoxides **4c, 4d**, **4e**, **4f** and **4g** could be obtained in this straightforward way. All *gem*-DHPs **4** show distinctive signals in the NMR spectra, including a signal at ca. 110 ppm in the ^{13}C NMR spectrum and one typical hydroperoxy proton signal (intensity two protons) at ca. 9.0–9.8 ppm in the ^{1}H NMR spectrum. The chemical shift of the hydroperoxy proton can, however, vary due to various reasons, for example, concentration, and the signal can also vary in shape (usually not sharp, but broad in varying extents). The ^{13}C NMR spectra of peroxides **5** are similar to those of the *gem*-DHPs **4**, but most signals are doubled due to the formation of diastereomers. In the ^{1}H NMR spectra of **5,** the intensity relation of the hydroperoxy proton and the CH-proton is 1:1, contrary to the 2:1 ratio of the gem-DHPs **4**.

The products formed from lower aldehydes up to the butanals could be isolated by column chromatography relatively easily. Products **4** derived from higher aliphatic aldehydes were difficult to separate from the substrates and side products. ^{13}C NMR data of such crude mixtures showed also the formation of perhydrates analogous to **3**, which exhibit the typical hydroperoxycarbon signal shifted towards higher field by about 7–10 ppm in comparison with **4**. Changing of the solvent used for chromatography from cyclohexane/ethylacetate to dichloromethane/methanol helped to overcome this problem.

Lowering the concentration of aqueous H_2O_2 from 70% to 40% resulted in lower yields as shown in the case of the DHP **4d** (42% vs 64%, entry 5). The present method was also applied to the hydroperoxidation of aromatic aldehydes such as benzaldehyde (entry 10) leading to 77% yield of **4i**.

The behaviour of chloral **6** under these hydroperoxidation conditions is completely different from that of other aldehydes **3**. Instead of the expected DHP **8,** the dihydroxyperoxide **7** was isolated (Scheme 2). Even by increasing the amount of H_2O_2 (16 equiv instead of 4 equiv), the only product detected was **7**.

The preparation of the peroxide **7** from chloral was first reported by Baeyer and Villiger[21] using Caro's acid or ethereal H_2O_2. Popova et al.[22] described a method for the preparation of the putative DHP **8** by reaction of **6** with a mixture of 30% H_2O_2 and 102% oleum. However, they obviously isolated the peroxide **7** instead as can be deduced by their determined mp (120–123 °C) and content of active oxygen (4.75%) fitting to the structure **7**. The unusual behaviour of chloral **6** can be explained by the presence of the strongly withdrawing trichloromethyl group. The highly electrophilic carbonyl group rapidly undergoes addition of H_2O_2 to form hydroxy-hydroperoxide **9,** which is resistant to ionization and instead undergoes reaction with an additional molecule chloral to form the stable peroxide **7**.

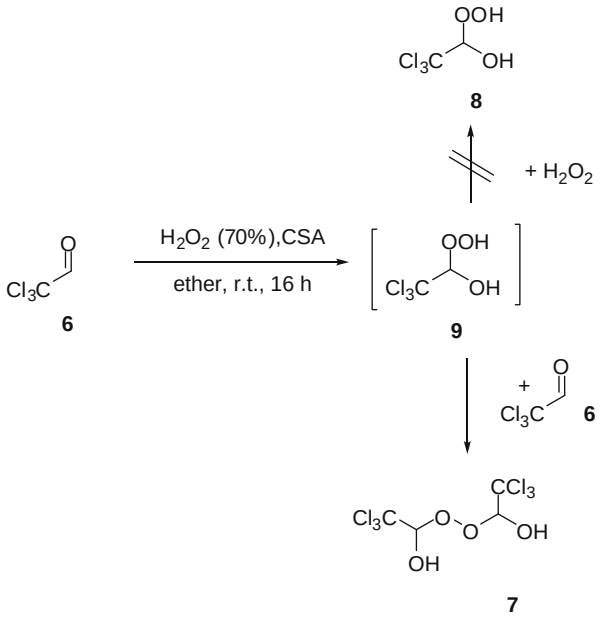


Scheme 1.

Table 1
Synthesis of primary *gem*-dihydroperoxides **4** from aldehydes **3**

Entry	Aldehyde **3**	R	Time (h)	**4**/yield (%)	**5**/yield (%)
1	**3a**	Me	16	**4a**/34	**5a**/10
2	**3b**	Et	16	**4b**/42	Traces
3	**3c**	*n*-Propyl	22	**4c**/63	**5c**/5
4	**3d**	*i*-Propyl	21	**4d**/64	**5d**/5
5			21	**4d**/42[a]	Traces
6	**3e**	*t*-Butyl	40	**4e**/28	0
7	**3f**	*n*-Pentyl	16	**4f**/44	Traces
8	**3g**	*n*-Heptyl	18	**4g**/33	Traces
9	**3h**	Cyclohexyl	16	**4h**/44	Traces
10	**3i**	Phenyl	16	**4i**/77	0

[a] Using aqueous H_2O_2 (40%).



Scheme 2.

In conclusion, we developed an environmentally benign, simple and efficient method for the synthesis of primary aliphatic and aromatic *gem*-dihydroperoxides directly from the corresponding aldehydes by treatment with aqueous H_2O_2 and a catalytic amount of CSA in ether solution. This synthesis represents the most versatile access to this class of compounds. Using this method, we have successfully synthesized several aliphatic primary *gem*-DHPs for the first time.

Presently, we are further optimizing the reaction conditions and investigating the scope and limitations of this method.

Caution : 70% Hydrogen peroxide as well as peroxidic compounds are potentially explosive and should be handled with precautions (shields, fume hoods, avoidance of transition metal salts or heating).

General procedure:[23] The aldehyde **3** (10 mmol) was dissolved in diethylether (2 ml) and cooled in an ice bath. After addition of 70% hydrogen peroxide (2 ml) and camphorsulfonic acid monohydrate (25 mg, 0.1 mmol), the biphasic system was left to stir over night while the temperature gradually rose to room temperature. The mixture was diluted with water (30 ml), extracted with diethyl ether (3×20 ml), and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (20 ml). After drying over sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, cyclohexane–EtOAc or DCM–MeOH) affording pure **4**. Usually traces of **5** were also found, which could be isolated in some cases.

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23. *Spectral data for new compounds*: Bis(1-hydroperoxyethyl)peroxide **5a**: colourless oil (10%); 1:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$): 9.72 (s, 2H), 5.47–5.40 (m, 2H), 1.47–1.44 (m, 6H); ^{13}C NMR ($CDCl_3$): 106.6, 106.5, 14.7, 14.6; HRMS (ESI) calcd for $C_4H_{14}O_6N$: 172.0816 ($M+NH_4^+$); found 172.0814. *Butane-1,1-dihydroperoxide* **4c**: colorless oil (63%); ^{1}H NMR ($CDCl_3$): 9.84 (s, 2H), 5.30 (t, 1H, J = 6.1 Hz), 1.71 (dd, 2H, J = 6.3, 15.2 Hz), 1.48 (dd, 2H, J = 7.5, 15.2 Hz), 0.95 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$): 111.1, 30.5, 18.0, 13.7; HRMS (ESI) calcd for $C_4H_{10}O_4Cl$: 157.0273 ($M+Cl^-$); found 157.0267. *Bis(1-hydroperoxybutyl)peroxide* **5c**: colorless oil (5%); 1:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$): 9.69 (s, 2H), 5.24–5.29 (m, 2H), 1.73–1.82 (m, 4 H), 1.52 (dd, 4H, J = 7.6, 15.1 Hz), 0.98 (t, 6H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$): 109.8, 30.4, 30.3, 18.1, 13.7; HRMS (ESI) calcd for $C_8H_{18}O_6Na$: 233.0996 ($M+Na^+$); found 233.0997. *2-Methyl-propane-1,1-dihydroperoxide* **4d**: white waxy solid (64%); ^{1}H NMR ($CDCl_3$): 8.92 (s, 2H), 4.99 (d, 1H, J = 7.9 Hz), 2.05–2.17 (m, 1H), 1.03 (d, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): 115.5, 28.5, 18.2. HRMS (ESI) calcd for $C_4H_{10}O_4Cl$: 157.0273 ($M+Cl^-$); found 157.0271. *Bis(1-hydroperoxy-2-methyl-propyl)peroxide* **5d**: colorless oil (5%); 1:1 mixture of diastereomers; ^{1}H NMR ($CDCl_3$): 9.81 (s, 2H), 4.89 (dd, 2H, J = 5.1, 8.6 Hz), 2.12–2.25 (m, 2H), 1.07 (d, 12H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$): 114.4, 114.3, 28.3, 28.2, 18.6, 18.5; HRMS (ESI) calcd for $C_8H_{18}O_6Na$: 233.0996 ($M+Na^+$); found 233.0995. 2,2-*Dimethylpropane-1,1-dihydroperoxide* **4e**: white solid (28%), already melting at room temperature; ^{1}H NMR (C_6D_6): 7.51 (br s, 2H), 5.10 (s, 1H), 0.95 (s, 9H); ^{13}C NMR (C_6D_6): 117.1, 35.6, 25.7; ^{1}H NMR ($CDCl_3$): 9.80 (br s, 2H), 5.14 (s, 1H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$): 117.1, 35.6, 25.5; HRMS (ESI) calcd for $C_5H_{12}O_4Cl$: 171.0430 ($M+Cl^-$); found: 171.0424. *Hexane-1,1-dihydroperoxide* **4f**: colorless oil (44%); ^{1}H NMR ($CDCl_3$): 9.82 (s, 2H), 5.27 (t, 1H, J = 6.0 Hz), 1.71 (dt, 2H, J = 9.0, 6.3 Hz), 1.47–1.38 (m, 2H), 1.33–1.24 (m, 4H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): 111.3, 31.3, 28.4, 24.3, 22.3, 13.8; HRMS (ESI) calcd for $C_6H_{14}O_4Cl$: 185.0586 ($M+Cl^-$); found: 185.0586. *Octane-1,1-dihydroperoxide* **4g**: colorless oil (33%); white solid when stored in the freezer (−30 °C); ^{1}H NMR ($CDCl_3$): 9.73 (s, 2H), 5.28 (t, 1H, J = 6.0 Hz), 1.72 (dt, 2H, J = 9.0, 6.0 Hz), 1.49–1.38 (m, 2H), 1.31–1.22 (m, 8H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): 111.3, 31.7, 29.2, 29.0, 28.5, 24.6, 22.6, 14.0; HRMS (ESI) calcd for $C_8H_{18}O_4Cl$: 213.0899 ($M+Cl^-$); found: 213.0892.