A facile catalyst-free synthesis of *gem*-dihydroperoxides with aqueous hydrogen peroxide†

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***gem*-Dihydroperoxides were easily obtained from the corresponding carbonyl compounds in high yields through a catalyst-free method with aqueous H_2O_2 (35%) in 1,2-dimethoxyethane at room temperature.**

Artemisinin, isolated from *Artemisia annua* which has been used as a traditional Chinese herbal remedy, shows effective antimalarial activity against multidrug resistant malaria.[1] Since the endoperoxide bridge structure of artemisinin is crucial for antimalarial activity,[1d] various types of organic peroxides have been designed and synthesized as candidates for antimalarial drugs.[1c] Thus, organic *gem*-dihydroperoxides and their derived peroxides have attracted a great deal of attention as potential antimalarial active compounds against the background of the building up of resistance of malaria parasites to alkaloid medicines. However, from the view point of organic synthesis, *gem*-dihydroperoxides have been known to play an important role as key intermediates in the synthesis of trioxanes,[2] tetraoxanes[3] and endoperoxides,[4] as an initiator for radical polymerization,[5] and as an oxidant for epoxidation[6] and sulfoxidation.[7] Generally, *gem*-dihydroperoxides can be synthesized from ketone enol ethers, α-olefins, ketones or ketals with hydrogen peroxide in the presence of a catalyst such as acids, heavy-metals or halogens;[8–19] however, we have noticed to the best of our knowledge a lack of reports on catalyst-free synthesis of *gem*-dihydroperoxides from ketones and aldehydes with hydrogen peroxide. Although a catalyst or promoter such as metals and acids have been believed to be essential for preparation of *gem*-dihydroperoxides with hydrogen peroxide, unusually we have found a facile catalyst-free synthetic method for *gem*-dihydroperoxides in dimethoxyethane (DME) with 35% aqueous hydrogen peroxide.[20] Here, we report a detailed study of reaction conditions and scope and limitations of this new synthesis.

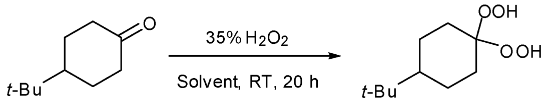
Table 1 shows the results of optimization of reaction conditions for the synthesis of *gem*-dihydroperoxides using 4-*tert*-butylcyclohexanone as a test substrate. The reaction conditions were examined with 5 equiv. of aqueous H_2O_2 (35%) under an argon atmosphere at room temperature, and among our trials, DME was found to be the most suitable solvent. (entries 1–9). Although the reason seems unclear yet, 5 equiv. of hydrogen peroxide was necessary to produce the product in satisfying yield, and lower yields of the product were observed when using 3 or 4 equiv. of hydrogen peroxide (entries 10 and 11).

Table 2 shows the scope and limitations of this synthesis with various carbonyl compounds under the optimized reaction conditions.[21] Cyclic ketones, including 2-adamantanone and aliphatic ketones, except acetophenone, produced the corresponding *gem*-dihydroperoxides in good to excellent yields (entries 1–10 and 13). *p*-Anisaldehyde, an aromatic aldehyde, also produced the corresponding *gem*-dihydroperoxide in high yield; however, dodecanal, an aliphatic aldehyde, showed a varied reactivity, and hydroxyhydroperoxide was obtained in 78% yield as reported in a previous paper (entry 11).[15,19a]

The role of DME is not clear; however, we believe that the nucleophilicity of H_2O_2 for carbonyl compounds is enhanced by the chelating effect of DME with the hydrogen of H_2O_2 to afford the dihydroperoxides.

In conclusion, we have developed a convenient method for the preparation of *gem*-dihydroperoxides with 35% H_2O_2 (5 equiv.) in DME at room temperature without any catalyst. DME is a good solvent for dihydroperoxidation of several carbonyl compounds. This novel synthetic method is environment-friendly and economical due to non-use of catalysts involving metals or acids. Further application of this oxidation and a mechanistic study are in progress in our laboratory.

Table 1 Study of reaction conditions



Entry	Solvent	H_2O_2 (equiv.)	Yield (%)[a]
1	MeOH	5	21
2	CH_2Cl_2	5	24
3	Et_2O	5	49
4	Toluene	5	59
5	AcOEt	5	80
6	*t*-BuOMe	5	82
7	MeCN	5	85
8	*i*-PrOH	5	87
9	DME	5	100
10	DME	4	92
11	DME	3	64

[a] Yields were determined by ^1H NMR spectroscopy with an internal standard (1,1,2,2,-tetrachloroethane).

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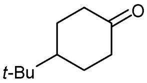
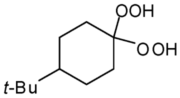
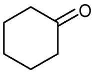
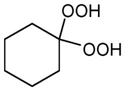
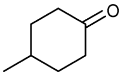
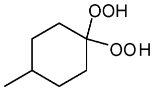
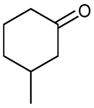
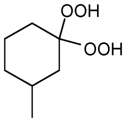
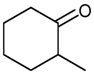
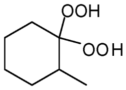
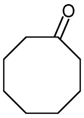
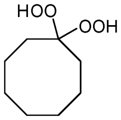
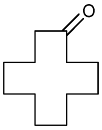
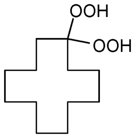
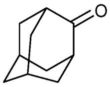
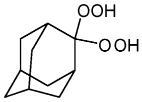
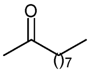
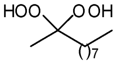
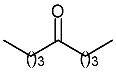
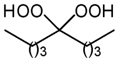
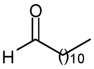
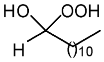
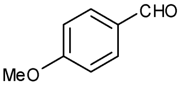
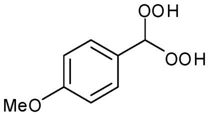
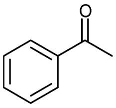
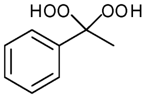
† Electronic supplementary information (ESI) available: Experimental procedure, NMR spectra and ICP analysis data. See DOI: 10.1039/b917056a

Table 2 Synthesis of *gem*-dihydroperoxides

Substrate (0.3 mmol) $\xrightarrow[\text{DME, RT}]{35\%\ H_2O_2\ (5\ \text{equiv})}$ *gem*-Dihydroperoxide

Entry	Substrate	Time/h	Product	Yield (%)[a]
1		20		99
2		10		73
3		10		90
4		15		89
5		15		65
6		1		81
7		1		57
8		20		84
9		5		80
10		5		78
11		5		78[b]
12		5		85
13		5		13[b]

[a] Isolated yields. [b] ^{1}H NMR spectroscopy yields are indicated as the peroxides decomposed under preparative TLC.

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20 We undertook an ICP analysis of the DME, which was purchased from Kanto Chemical, for detection of traces of metal species. The results showed that the amounts of metal species which provided *gem*-dihydroperoxides were not contained in the DME (see ESI†).

21 A typical procedure for the dihydroperoxidation is as follows: To a solution of 4-*tert*-butylcyclohexanone (46.3 mg, 0.30 mmol) in dry DME solution (3 mL) was added 35% H_2O_2 (130 μL, 1.50 mmol) at room temperature. After stirring at room temperature for 20 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC to afford the pure 4-*tert*-butylcyclohexylidenebishydroperoxide (60.7 mg, 99%).