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A Broadly Applicable Mild Method for the Synthesis of *gem*-Diperoxides from Corresponding Ketones or 1,3-Dioxolanes

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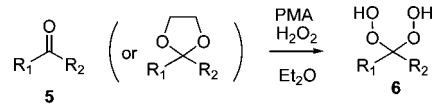
ABSTRACT



(PMA = Phosphomolybdic acid)

Ketones or ketals were readily converted into the corresponding *gem*-dihydroperoxides in high yields by treatment with ethereal H_2O_2 at ambient temperature in the presence of 2−5 mol % of phosphomolybdic acid.

Following the worldwide recognition of qinghaosu[1] (QHS, artemisinin, **1**) as a potent and fast-acting antimalarial agent in the 1980s, many new organic peroxides of various structural types have been designed and synthesized in a global effort to develop novel agents against multidrug resistant malaria. As a consequence, an impressive number of man-made peroxides with high potency in at least in vitro tests were discovered, strongly suggesting that incorporation of peroxy bonds into the structures of organic molecules is indeed a very promising approach to the generation of new antimalarials.

One of the salient structural features[2] shared by many known antimalarial cyclic organic peroxides is the *gem*-peroxy linkage (Figure 1), which presumably is at least one of the main stimuli for the current interest[3] in the synthesis of *gem*-peroxyketals. To date, at least 10 different protocols have been documented in the literature for converting ketones/ketals into corresponding *gem*-peroxides through reaction with H_2O_2. Most of them used a Brönsted or Lewis acid, such as HCO_2H (used as solvent),[3a] F_3CCO_2H (12 mol equiv),[3b] conc. H_2SO_4 (0.3−1.0 mol equiv),[3c] H_2WO_4 (1.0 mol equiv),[3d] $NaHSO_4$−SiO_2 (ca. 0.2 mol equiv),[3e] $F_3B{\cdot}OEt_2$ (0.2−0.4 mol equiv),[3f] or camphorsulfonic acid (CSA, along

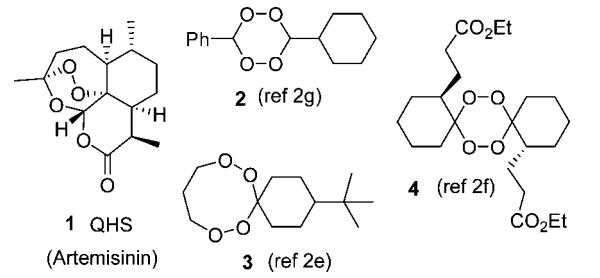


Figure 1. Qinghaosu and some antimalarial *gem*-diperoxides.

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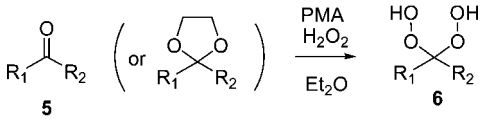
with 70% H_2O_2 and only applicable to aldehydes),[3g] as the catalyst. $Ce(NH_4)_2(NO_3)_6$ (CAN),[3h] I_2,[3i] and methyltrioxorhenium[3j] (MTO, prepared from Re_2O_7) have also been utilized to promote such transformations. However, as noted[3k] by Ghorai and Dussault, none of these methods are mild enough to be generally applicable—they all suffer from one or more of such drawbacks as low yields, slow reactions, requirement for use of high concentration of H_2O_2, and incompatibility with sensitive functionalities.

The recent mild/highly efficient Re_2O_7 protocol of Dussault[3k] does represent a major improvement. However, new mild/effective methods directly applicable to multifunctionalized substrates are still in great need.

In our efforts to develop new antimalarial organic peroxides, we observed that phosphomolybdic acid (PMA, $H_3Mo_{12}O_{40}P{\cdot}xH_2O$, a reagent much cheaper than Re_2O_7) in ethereal H_2O_2[4] could efficiently catalyze the peroxyketalization reaction of ketones/ketals (Scheme 1). The reaction

Scheme 1



5 **6**

(PMA = Phosphomolybdic acid)

usually occurred readily at ambient temperature in the presence of 0.02−0.05 mol equiv (i.e., 2−5 mol %) of PMA and resulted in the desired *gem*-diperoxides in excellent yields within a few hours.

The results are summarized in Table 1. Cyclic ketones of different ring sizes all reacted very well (entries 1−3). Bridged and substituted ketones (entries 4−6 and 9) appeared to be equally reactive. It is interesting to note that even when the carbonyl groups were masked as 1,3-dioxolanes, which usually are more stable/less reactive than dimethyl ketals (the substrates in some of the previous investigations) and therefore are more often used as protecting groups, the *gem*-peroxides were also formed in high yields.

When a free ketone and a ketal functionality are both present in the same molecule, further reactions might follow (entries 10 and 11), leading to also interesting and potentially useful cyclic structures. The conjugated carbonyl group seemed less reactive, and clear-cut discrimination between two types of ketone carbonyl groups was achieved (entry 12).

Open-chain ketones showed similar reactivity under the same conditions, resulting in the expected *gem*-dihydroperoxides in excellent yields (entries 13−15). It is interesting to note that 1,3-dioxolanes, which are more practical protecting groups than those dimethyl ketals, also served very well as the precursors (entries 16−18). Compared with all the previous acid-catalyzed protocols, which were effective only with ketals (mostly dimethyl ones) unless using substantial amounts of strong acids, the present method should have better prospects in application.

That common protecting groups such as TBS (*tert*-butyldimethylsilyl), MOM (methoxymethyl), PMB (*p*-methoxybenzyl), Bn (benzyl), and Bz (benzoyl) groups were tolerated is particularly valuable because construction of *gem*-peroxides by direct peroxy ketalization of ketone/ketals containing common protecting groups in synthetically useful yields has never been achieved before (to the best of our knowledge), and there has been only one[3d] individual example for olefinic substrates.

As a direct comparison, we also tested conversion of **5f** to **6f** under the $NaHSO_4-SiO_2$[3e] conditions. No traces of *gem*-diperoxides could be detected after 2 h, while the TBS protecting group was completely hydrolyzed. Similarly, in an earlier effort to prepare a *gem*-dihydroperoxide from a dimethyl ketal using 20 mol % of $F_3B{\cdot}OEt_2$ as the catalyst, the expected product was formed in 10−40% yield, along with 35−77% of the corresponding ketone which resulted from hydrolysis.

In conclusion, a novel mild method using 2−5 mol % of phosphomolybdic acid (PMA) as the catalyst has been developed for the synthesis of *gem*-diperoxides. The lower acidity and higher catalytic activity of this set of conditions made it possible for the first time to make *gem*-diperoxyketals directly from the ketones/ketals containing such protecting groups as TBS, MOM, PMB, Bn, and Bz and/or C−C double[5] bonds. The yields are generally high, and the reaction time in most cases is 3−4 h. 1,3-Dioxolanes, which are broadly employed protecting groups and might be necessary

(2) (a) Kim, H.-S.; Tsuchiya, K.; Shibata, Y.; Wataya, Y.; Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1867–1870. (b) Hamada, Y.; Tokuhara, H.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Ono, K.; Ogura, N.; Wataya, Y. *J. Med. Chem.* **2002**, *45*, 1374–1378. (c) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2001**, *44*, 2357–2361. (d) Vennerstrom, J. L.; Dong, Y.; Andersen, S. L.; Ager, A. L., Jr.; Fu, H.-n.; Miller, R. E.; Wesche, D. L.; Kyle, D. E.; Gerena, L.; Walters, S. M.; Wood, J. K.; Edwards, G.; Holme, A. D.; McLean, W. G.; Milhous, W. K. *J. Med. Chem.* **2000**, *43*, 2753–2758. (e) Tsuchiya, K.; Hamada, Y.; Masuyama, A.; Nojima, M. *Tetrahedron Lett.* **1999**, *40*, 4077–4080. (f) Dong, Y.; Matile, H.; Chollet, J.; Kaminsky, R.; Wood, J. K.; Vennerstrom, J. L. *J. Med. Chem.* **1999**, *42*, 1477–1480. (g) Kim, H. S.; Tsuchiya, K.; Shibata, Y.; Wataya, Y.; Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1867–1870.

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(5) The only exception was found in ref 3d (a compound similar to **5r** but without the aromatic ring and the oxygen in the six-membered ring).

Table 1. Formation of *gem*-Diperoxides Catalyzed by Phosphomolybdic Acid[a]

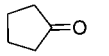
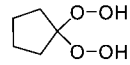
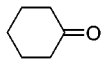
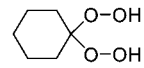
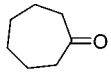
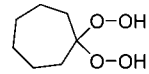
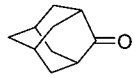
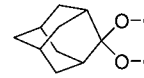
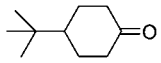
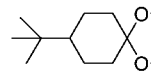
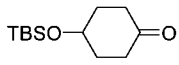
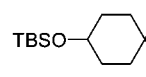
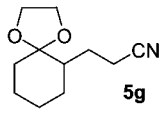
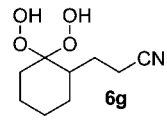
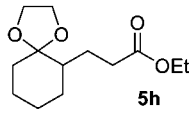
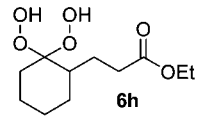
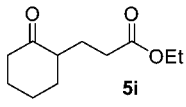
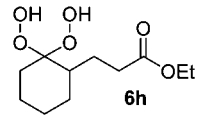
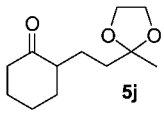
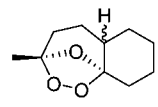
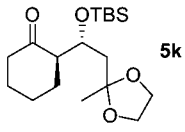
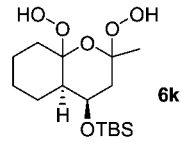
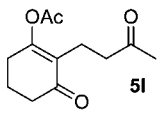
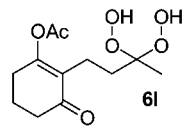
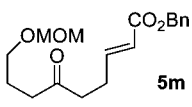
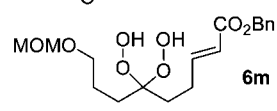
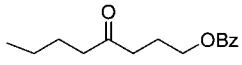
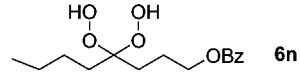
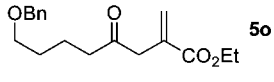
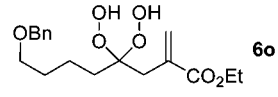
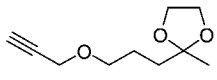
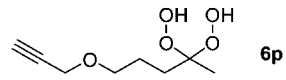
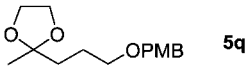
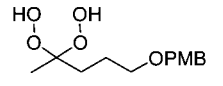
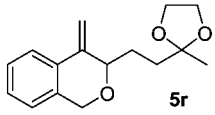
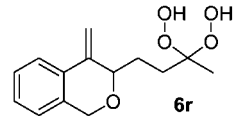
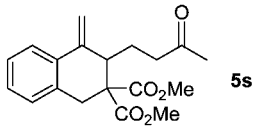
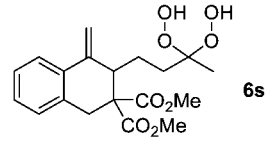
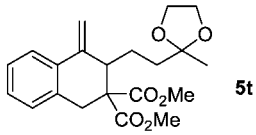
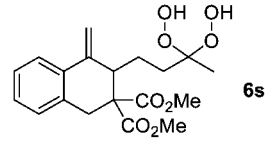
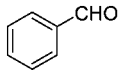
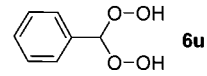
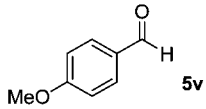
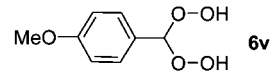
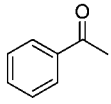
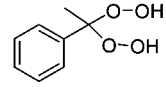
entry	starting material	PMA (mol%)	time (h)	product	isolated yield (%)
1	 **5a**	2	3	 **6a**	95
2	 **5b**	2	2.5	 **6b**	95
3	 **5c**	2	3	 **6c**	93
4	 **5d**	2	4	 **6d**	96
5	 **5e**	2	3	 **6e**	93
6	 **5f**	2	3	 **6f**	95
7	 **5g**	3	5	 **6g**	93
8	 **5h**	3	4	 **6h**	93
9	 **5i**	2	2.5	 **6h**	92
10	 **5j**	3	8	 **6j**	74
11	 **5k**	2	3	 **6k**	70
12	 **5l**	2	2.5	 **6l**	89
13	 **5m**	5	5	 **6m**	90
14	 **5n**	2	6	 **6n**	89
15	 **5o**	5	6	 **6o**	74
16	 **5p**	3	2.5	 **6p**	90
17	 **5q**	3	2.5	 **6q**	97

Table 1 Continued

entry	starting material	PMA (mol%)	time (h)	product	isolated yield (%)
18	 **5r**	3	3.5	 **6r**	96
19	 **5s**	2	3	 **6s**	96
20	 **5t**	2	4	 **6s**	95
21	 **5u**	5	7	 **6u**	74
22	 **5v**	5	6	 **6v**	82
23	 **5w**	5	8	 **6w**	51

[a] All runs were performed at ambient temperature in ethereal H_2O_2 containing the indicated amount (with respect to the starting **5**) of phosphomolybdic acid ($H_3Mo_{12}O_{40}P{\cdot}xH_2O$) with the substrate and H_2O_2 concentration being 0.2 and 1.0 M, respectively.

in the synthesis of such substrates as **5k** and **5r**, could also be directly used in lieu of a free ketone carbonyl group. The chemistry is compatible with a range of functionalities, including ester, nitrile, alkyne, alkene (both isolated and conjugated), and enol ester groups. These advantages, along with the much lower price of PMA compared with that of Re_2O_7, make the present method an attractive means for the synthesis of *gem*-dihydroperoxyketals.

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Supporting Information Available: Experimental procedures, physical and spectroscopic data listing, ^{1}H as well as ^{13}C NMR spectra for all new peroxides, and ^{1}H NMR for the known peroxides **6a**−**c** and **6u**−**w**. This material is available free of charge via the Internet at http://pubs.acs.org.

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