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Facile Ring-Opening of Oxiranes by H_2O_2 Catalyzed by Phosphomolybdic Acid

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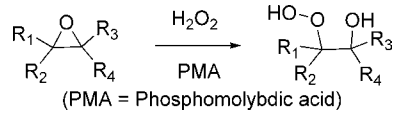
ABSTRACT



At ambient temperature, in the presence of catalytic amounts of phosphomolybdic acid (PMA), ethereal hydrogen peroxide reacted readily with a range of epoxides, giving corresponding *β*-hydroxyhydroperoxides in high yields.

As a simple and readily accessible peroxy bond-containing reagent hydrogen peroxide (H_2O_2) plays an important role in construction of organic peroxides,[1] a class of compounds that in many cases possess significant antimalarial activity as exemplified by qinghaosu[2] (QHS, artemisinin, **1**) and a plethora of derivatives as well as analogues. There have been many different protocols in the literature for incorporation of H_2O_2 into various organic molecular frameworks, including Hg(II) ion[3a] or MeCONHBr[3b] mediated additions to C−C double bonds, acid-catalyzed dehydration of 2-furyl alcohols,[3c,d] alkylation with various mesylates[3e] or a silyloxy group stabilized cation[3f] formed in situ from a silyl enol ether, ring-opening perhydrolysis[1a,b,3g−p] of oxiranes (epoxides) or oxetanes, and perketalization/ketal exchange[1c,d,4] reactions. Among these, the last two categories are of particular importance because the products are related to antimalarial 1,2,4-trioxanes (Figure 1) and 1,2,4,5-tetraoxanes, respectively.

(1) See, for example: (a) Kerr, B.; McCullough, K. J. *Chem. Commun.* **1985**, 590–591. (b) Subramanyam, V.; Brizulela, C. L.; Soloway, A. H. *Chem. Commun.* **1976**, 508–509. (c) Kovac, F. *Tetrahedron Lett.* **2001**, *42*, 5313–5314. (d) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron Lett.* **2003**, *44*, 7359–7363. (e) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Tetrahedron Lett.* **2001**, *42*, 7281–7285. (f) Murakami, N.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 69–72. (g) Liu, H.-H.; Jin, H.-X.; Zhang, Q.; Wu, Y.-K.; Kim, H.-S.; Wataya, Y. *Chin. J. Chem.* **2005**, *23*, 1469–1473. (h) Jin, H.-X.; Wu, Y.-K. *Tetrahedron Lett.* **2005**, *46*, 6801–6803, Cf. also refs 4, 5 below.

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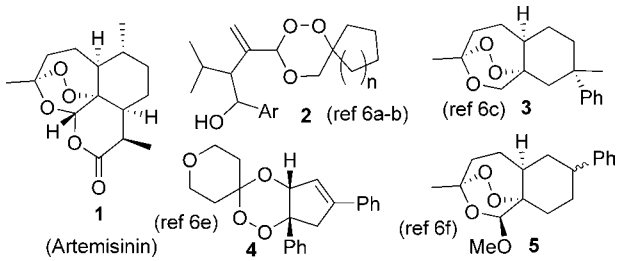
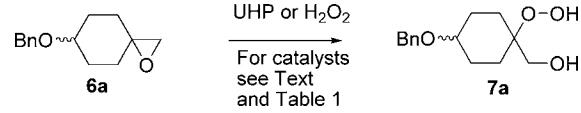


Figure 1. Qinghaosu and some antimalarial 1,2,4-trioxanes.

β-Hydroxyhydroperoxides are apparent precursors for 1,2,4-trioxanes,[3g−i,m,5] the well-known antimalarial core[6] unit of QHS (**1**) and many synthetic peroxide antimalarials. Such hydroperoxides can also be used as protecting groups[5a] for carbonyl groups, which are cleavable under neutral conditions by, for instance, single-electron reduction and thus offer a functionality compatibility profile different from those of classic protecting groups for carbonyl groups. However, as one of the straightforward accesses[7] to the β-hydroxy-hydroperoxides, the ring-opening reaction of oxiranes itself still remain to be improved; mild yet effective protocols are still to be developed.

Involvement of high concentration H_2O_2 appears to be one of the main drawbacks. For instance, the conditions of Payne and Smith[3g] and those of Adam and Rios[3i] all involved almost neat (90 or 98%) H_2O_2, which is potentially hazardous and strongly discourages broad application. In 2005 a distinct improvement[3m] was made by Vennerstrom and co-workers, who used 50% H_2O_2 with $MoO_2(acac)_2$ as the catalyst. However, only two 2,2-disubstituted oxiranes (*vide infra*) were tested, with the yield being 29 and 59%, respectively. The recent $SbCl_3/SiO_2$/ethereal H_2O_2/sonication[3n] conditions of Zhang and Li generally gave perhydrolysis products in higher yields (72−85%) but are applicable only to the less-hindered 2-mono-substituted oxiranes. Recently, we disclosed[8] that phosphomolybdic acid (PMA) is an excellent catalyst for converting ketones/ketals into corresponding *gem*-hydroperoxides. Here in this communication we wish to report that PMA is also an excellent catalyst for perhydrolysis of oxiranes (epoxides).

Scheme 1



Our investigation on acid-catalyzed perhydrolysis of oxiranes began with the reaction shown in Scheme 1, with **6a** as the substrate. We first utilized urea-H_2O_2 complex (UHP), a commercially available solid reagent with remarkable convenience in storage and handling, as the source of H_2O_2. However, the reaction using up to 10 mol equiv. (with respect to the starting **6a**) of UHP in $MeO(CH_2)_2OMe$ (DME, the best nonaqueous solvent for UHP according to our experience) with a range of potential catalysts, including CSA (camphor-10-sulfonic acid), $SnCl_2$, $Fe(acac)_3$, $BF_3{\cdot}Et_2O$, Ti(*i*-PrO)$_4$, $Cu(acac)_2$, $Co(OAc)_2$, and $MoO_2(acac)_2$, all failed. In most cases, essentially no desired **7a** could be detected.

Table 1. Conversion of **6a** to **7a**[a]

entry	catalyst/reaction time (h)	yield of **7a** (%)
1	$LiClO_4$/12	0[b]
2	CAN/24	12%
3	$Cu(acac)_2$/12	0[b,c]
4	$FeCl_3-SiO_2$/24	21%
5	$SnCl_4$/12	0[d]
6	$TiCl_4$/8	0[d]
7	$Ce(OH)_3OOH$/12	0[b]
8	$ZrCl_4$/12	0[b,c]
9	$MoO_2(acac)_2$/20	62%
10	Salen $Co(OAc)_3$/10min	0[e]
11	Na_2MoO_4/12	0[b]
12	$Sc(OTf)_3$/12	0[b]
13	PMA/6	78%

[a] All runs were performed at ambient temperature in ethereal H_2O_2 containing 0.1 mol equiv (with respect to the added **6a**) of indicated catalyst with the substrate **6a** and H_2O_2 concentration being 0.2 and 1.0 M, respectively. [b] No reactions occurred. [c] A precipitate formed on addition of the catalyst. [d] A complex mixture was formed. [e] On addition of the catalyst H_2O_2 decomposed with violent gas evolving.

Then we switched to ethereal H_2O_2, because it worked very well in our recently reported[8] perketalization reactions. Some of the outcomes in ethereal H_2O_2 are summarized in Table 1. Again, in most cases no desired **7a** could be detected (entries 1,3,5−8, 10−13). However, the reactions with $Ce(NH_4)_2(NO_3)_6$

(4) (a) Ledaal, T.; Solbjor, T. *Acta Chem. Scand.* **1967**, *21*, 1658–1659. (b) Ramirez, A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 4617–4620. (c) Terent'ev, A. O.; Platonov, M. M.; Ogibin, Y. N.; Nikishin, G. I. *Synth. Commun.* **2007**, *37*, 1281–1287. (d) Jefford, C. W.; Li, Y.; Jaber, A.; Boukouvalas, J. *Synth. Commun.* **1990**, *20*, 2589–2596. (e) Das, B.; Veeranjaneyulu, B.; Krishnaiah, M.; Balasubramanyam, P. *J. Mol. Catal. A* **2008**, *284*, 116–119. (f) Terent'ev, A. O.; Kutkin, A. V.; Platonov, M. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron Lett.* **2003**, *44*, 7359–7363. (g) Bunge, A.; Hamann, H.-J.; Liebscher, J. *Tetrahedron Lett.* **2009**, *50*, 524–526. (h) Das, B.; Krishnaiah, M.; Veeranjaneyulu, B.; Ravikanth, B. *Tetrahedron Lett.* **2007**, *48*, 6286–6289. (i) Zmitek, K.; Zupan, M.; Stavber, S.; Iskra, J. *Org. Lett.* **2006**, *8*, 2491–2494. (j) Iskra, J.; Bonnet-Delponb, D.; Begue, J.-P. *Tetrahedron Lett.* **2003**, *44*, 6309–6312. (k) Ghorai, P.; Dussault, P. H. *Org. Lett.* **2008**, *10*, 4577–4579. (l) Zmitek, K.; Zupana, M.; Iskra, J. *Org. Biomol. Chem* **2007**, *5*, 3895–3908 (a review). (m) Ghorai, P.; Dussault, P. H. *Org. Lett.* **2009**, *11*, 213–216.

(5) (a) Singh, C.; Malik, H. *Org. Lett.* **2005**, *7*, 5673–5676, but the concept of using peroxy groups as protecting groups was first introduced by Dussault using γ-hydroxyhydroperoxides. (b) Ahmed, A.; Dussault, P. H. *Org. Lett.* **2004**, *6*, 3609–3611.

(6) For some synthetic antimalarial 1,2,4-trioxanes, see: (a) Singh, C.; Gupta, N.; Puri, S. K. *Biorg. Med. Chem.* **2004**, *12*, 5553–5562. (b) Singh, C.; Gupta, N.; Puri, S. K. *Tetrahedron Lett.* **2005**, *46*, 205–207. (c) Haraldson, C. A.; Karle, J. M.; Freeman, S. G.; Duvadie, R. K.; Avery, M. A. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2357–2362. (d) Griesbeck, A. G.; El-Idreesy, T. T.; Fiege, M.; Brun, R. *Org. Lett.* **2002**, *4*, 4193–4195. (e) Jefford, C. W.; Rossier, J.-C.; Milhous, W. K. *Heterocycles* **2000**, *52*, 1345–1352. (f) Posner, G. H.; Oh, C. H. *Heteroatom Chem.* **1995**, *6*, 105–116. (g) Dechy-Canaret, O.; Benoit-Vical, F.; Rober, A.; Meunier, B. *ChemBiochem* **2000**, *4*, 283–284. (h) Jefford, C. W.; Kohmoto, S.; Jaggi, D.; Timari, G.; Rossier, J.-C.; Rudaz, M.; Barbuzzi, O.; Gerard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G. *Helv. Chim. Acta* **1995**, *78*, 647–662. (i) Jefford, C. W.; Verarde, J. A.; Bernardinelli, G.; Bray, D. H.; Warhurst, D. C. *Helv. Chim. Acta* **1993**, *76*, 2775–2788.

(CAN) or $FeCl_3-SiO_2$ as the catalyst afforded the perhydrolysis product in 12% and 21% yield, respectively (Table 1, entries 2 and 4). $MoO_2(acac)_2$ gave **7a** after 20 h in a yield compatible to that of Vennerstrom (entry 9).

Even better result was found with PMA. Thus, with 0.1 mol equiv (with respect to **6a**) of PMA as the catalyst stirring of **6a** at ambient temperature in ethereal H_2O_2[9] gave **7a** in 78% yield (entry 13) within 6 h, indicating for the first time that PMA might also be an excellent catalyst for perhydrolysis of oxiranes.

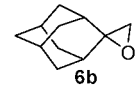
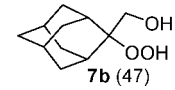
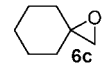
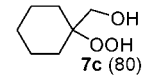
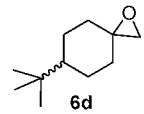
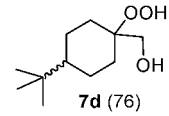
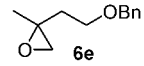
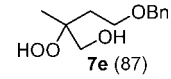
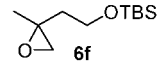
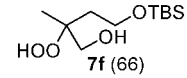
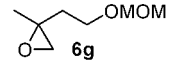
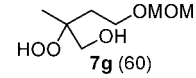
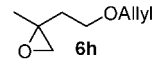
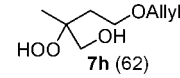
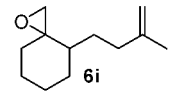
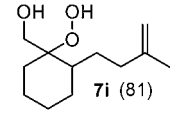
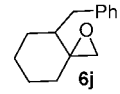
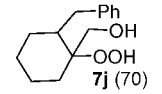
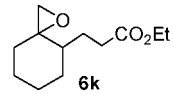
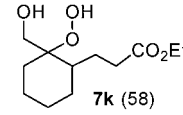
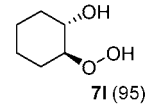
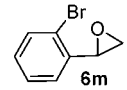
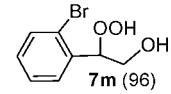
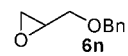
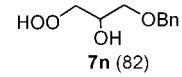
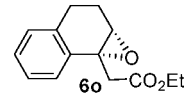
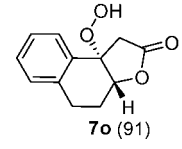
Encouraged by the positive sign, we next examined substrates[3m] (**6b**,**c**) of Vennerstrom for comparison. To our delight, the anticipated **7b** and **7c** were formed in 47% and 80% yield (Table 2, entries 1−2), respectively, confirming that PMA is indeed an excellent catalyst. An array of other 2,2-disubstituted oxiranes were then tested under the same conditions (entries 3−10). In all cases the expected perhydrolysis products were obtained in satisfactory yields. The regioselectivity was the same as under the Vennerstrom's conditions, including those substrates carrying a substituent at the carbon next to the quaternary carbon in the oxirane ring (entries 8−10).

The substrates containing TBS, MOM, or allyl groups deserve particular mention. Although being placed in an "unshielded" surrounding (i.e., on an unhindered primary hydroxyl group), these protecting groups survived the perhydrolysis (entries 5−7). To the best of our knowledge, these results represent the first examples of using such readily removable protecting groups in this type of reactions.

Apart from 2,2-disubstituted oxiranes, which are most interesting to us because of their potential in malaria chemotherapy, we also briefly examined a few epoxides of other substitution patterns under the newly developed conditions. In all cases, the expected perhydrolysis products were obtained in good to excellent yields. The 2,3-disubstituted oxirane **6l**, for example, afforded the known **7l** in 95% yield within 6 h, substantially better than that (83%) under the previous $SbCl_3/SiO_2$/ethereal H_2O_2/sonication[3n] conditions (Table 2, entry 11).

The reactions with 2-monosubstituted epoxides (**6m** and **6n**) were also high-yielding under the present conditions (Table 2, entries 12−13). In contrast to 2,2-disubstituted oxiranes, which underwent perhydrolysis exclusively at the quaternary carbon, the regioselectivity with 2-monosubstituted epoxides depended critically on the substituent. When one of the two epoxy carbons was at a benzylic position, the predominant product carried the entering hydroperoxyl group at that carbon (Table 2, entry 12) because of stabilization effect of the phenyl group on the intermediate carbocation. In the absence of such a stabilization effect, the ring-opening occurred predominantly at the sterically less crowded terminal carbon presumably via an S_N2 mechanism (Table 2, entry 13).

Table 2. PMA Catalyzed Perhydrolysis of Various Epoxides[a]

entry	substrate **6**	time (h)	product **7** (yield%)
1	 **6b**	6	 **7b** (47)
2	 **6c**	8	 **7c** (80)
3	 **6d**	10	 **7d** (76)
4	 **6e**	5	 **7e** (87)
5	 **6f**	4	 **7f** (66)
6	 **6g**	7	 **7g** (60)
7	 **6h**	8	 **7h** (62)
8[b]	 **6i**	8	 **7i** (81)
9[b]	 **6j**	12	 **7j** (70)
10[b,c]	 **6k**	12	 **7k** (58)
11	 **6l**	6	 **7l** (95)
12	 **6m**	10	 **7m** (96)
13	 **6n**	12	 **7n** (82)
14[d]	 **6o**	2	 **7o** (91)

[a] All runs were performed at ambient temperature in ethereal H_2O_2 containing 0.1 mol equiv (with respect to the starting **6**) of PMA ($H_3Mo_{12}O_{40}P{\cdot}xH_2O$) with the substrate and H_2O_2 concentration being 0.2 and 1.0 M, respectively. [b] The starting **6** was a mixture of diastereomers, but the resulting **7** appeared to be homogeneous in ^1H and ^{13}C NMR. [c] 0.15 Mol equiv of PMA was used. [d] 0.01 Mol equiv of PMA was used.

(7) For an alternative access to β-hydroxyhydroperoxides using O_2 as the source of peroxy bonds, see, for example: (a) O'Neill, P. A.; Pugh, M.; Davies, J.; Ward, S. A.; Park, K *Tetrahedron Lett.* **2001**, *42*, 4569–4571. (b) Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305–1310. (c) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573–576.

(8) Li, Y.; Hao, H.-D.; Zhang, Q.; Wu, Y.-K. *Org. Lett.* **2009**, *11*, 1615–1618.

(9) Prepared by extracting the commercially available aqueous 30% H_2O_2 with Et_2O. (a) Saito, I.; Nagata, R.; Yuba, K.; Matsuura, T. *Tetrahedron Lett.* **1983**, *24*, 1737–1740. (b) Terent'ev, A. O.; Krylov, I. B.; Borisov, D. A.; Nikishin, G. I. *Synthesis* **2007**, 2979–2986, For a modified procedure, see ref 8 above.

Similar regioselectivity had been reported[3n] previously. However, no experimental evidence was provided therein. This deficiency, along with a literature example[10] of similar ring-opening reaction that occurred with different regioselectivity, urged us to check the identity of **7n** more carefully. Finally, with the assistance of DEPT, HMQC, and NOESY experiments performed on the acetonide of **7n** it was proven beyond all doubt that the structure of **7n** was indeed as depicted (cf. Figure S in the Supporting Information).

The phenomenon observed with **6o** also deserves a few more words. When using the same amount of PMA (0.1 mol equiv) as in other cases, a deep-blue color appeared immediately and the reaction system became very complex as shown by TLC. However, a clean reaction could be achieved by reducing the amount of added PMA to 0.01 mol equiv. Under such conditions, the desired **7o** was isolated in 91% yield after 2 h.

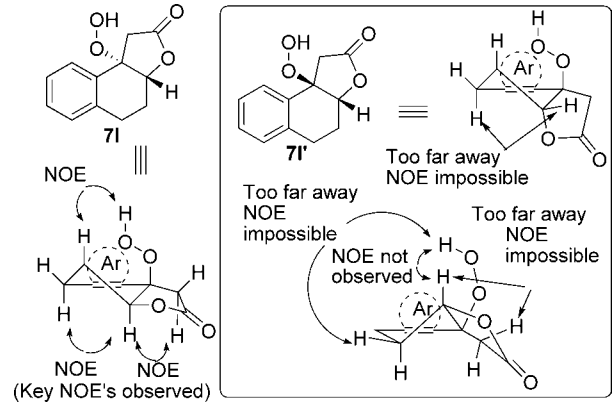


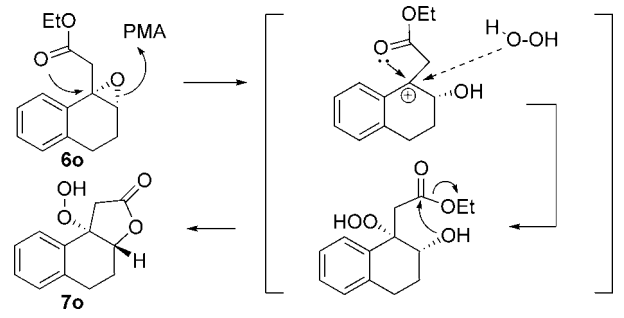
Figure 2. Key NOE's observed in 2D NOESY spectrum, which are compatible with **7o**, but not **7o′** (boxed).

The relative configuration of **7o** was established according to the detected key NOE's shown in Figure 2. This unexpected stereochemistry along with the peculiar phenomena observed during the reaction suggested that the **7o** was not formed via a simple S_N1 mechanism.

A possible mechanism that may lead to the unexpected stereochemical outcome with **6o**/**7o** is shown in Scheme 2. The ring-opening of the oxirane is greatly facilitated because of stabilization of the carbocation by the carbonyl group from

(10) Dussault, P. H.; Xu, C. *Tetrahedron Lett.* **2004**, *45*, 7455–7457.

Scheme 2



the backside of the leaving epoxy group. Then, the hydroperoxyl group enters from the other face. Finally, a lactonization occurs, leading to **6o**/**7o**.

In brief, phosphomolybdic acid (PMA) is shown to be a mild yet highly efficient catalyst for perhydrolysis of oxiranes (epoxides). A range of β-hydroxyhydro-peroxides, immediate precursors for 1,2,4-trioxanes, were readily prepared from corresponding oxiranes using the newly developed protocol. The reaction typically took ca. 10 h to complete at ambient temperature in ethereal H_2O_2 with 0.1 mol equiv (with respect to the substrate) of PMA as the catalyst. The regioselectivity for 2,2-disubstituted oxiranes was very high, with the entering hydroperoxyl group always attached to the quaternary carbon. 2,3-Disubstituted and 2-monosubstituted oxiranes also reacted well, but the regioselectivity depended significantly on the nature of the substituents. Finally, the tolerance of readily cleavable protecting groups in such reactions for the first time observed in this work may open up new access to a diverse of β-hydroxyhydroperoxides and consequently the corresponding 1,2,4-trioxanes.

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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 β-hydroxyperoxides **7b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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