Some Attempts to Employ the Singlet Oxygen Generated from H$_2$O$_2$[†]

JIN, Hong-Xia(金红霞)   LIU, He-Hua(刘鹤华)   WU, Yi-Kang*(伍贻康)

State Key Laboratory of Bio-organic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Some attempts to employ the singlet oxygen generated from molybdate-catalyzed decomposition of hydrogen peroxide are presented. Reduction of ascaridole with diimide is also described, along with the preliminary results of the cleavage study using Fe-cysteinate as a simple model for Fe—S type redox species. There were strong indications that *S*-alkylation occurred as observed in similar cleavage of the potent antimalarial qinghaosu.

**Keywords**   peroxide, singlet oxygen , free radical, cleavage, mechanism

Organic peroxides have gained a renewed interest[1] as potential antimalarials over the past decades following the historic discovery of qinghaosu[2] (artemisinin) by the Chinese scientists in the 1970s. In studying the relationship between the biological activities and the chemical behavior of organic peroxides we needed facile access to this type of compounds. Because of the nature of our work (involving many different substrates of only small quantities) it was not convenient for us to utilize the traditional photosensitized oxygenation with molecular oxygen. Therefore we had to seek more feasible alternative(s) to introduce[3,4] the critical peroxy bond.

In 1989 Jacobs and co-workers[5] reported a novel type of catalysts (*e.g.*, Mg$_{0.7}$-Al$_{0.3}$-LDH-MoO$_4$) that could effectively decompose H$_2$O$_2$ in essentially neutral methanol solution to yield singlet oxygen at the ambient temperature. They also demonstrated that some conjugated dienes could react smoothly with the "dark" singlet oxygen (generated without irradiation), giving the corresponding peroxides. Unfortunately, the substrates they examined were limited to simple alkenes and aromatics. To find out if the singlet oxygen thus generated also reacted smoothly with other substrates, especially those bearing other functionalities, we carried out the investigations reported below.

The catalyst Mg$_{0.7}$-Al$_{0.3}$-LDH-MoO$_4$ was prepared by following the Jacobs' recipe. To make sure that the catalyst was active, its reaction was first tried with α-terpinene (Scheme 1). The reaction was quite clean and the product ascaridole (±)-**2** was isolated in 51% yield, much higher than that reported in the literature (14.4%, using the same catalyst). The concentration of the H$_2$O$_2$ did not seem to have any discernible effects on the reaction (Table 1).

Scheme 1
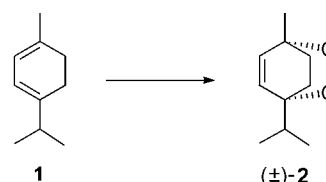
Reagents and conditions: H$_2$O$_2$/Mg$_{0.7}$-Al$_{0.3}$-LDH-MoO$_4$/MeOH, 51%.

Table 1   Experimental outcomes of oxygenation of α-terpinene in H$_2$O$_2$ catalyzed by molybdates

Entry	Catalyst	Solvent	Base	H$_2$O$_2$ concentration/%	Yield/%
1	Mg$_{0.7}$-Al$_{0.3}$-LDH-MoO$_4$	MeOH	—	30	51
2	Mg$_{0.7}$-Al$_{0.3}$-LDH-MoO$_4$	MeOH	—	50	51
3	Na$_2$MoO$_4$	MeOH/H$_2$O	NaOH	30	84
4	Na$_2$MoO$_4$	MeOH/H$_2$O	NaOH	50	85
5	(NH$_4$)$_6$Mo$_7$O$_{24}$•4H$_2$O	MeOH/H$_2$O	NaOH	30	80
6	(NH$_4$)$_6$Mo$_7$O$_{24}$•4H$_2$O	MeOH/H$_2$O	—	—	—

Two other catalysts were also briefly examined. Using Na_2MoO_4 in basic $MeOH/H_2O$ (±)-**2** was obtained in slightly higher yield than that reported[6] (84% vs. 80%) in the literature. Ammonium molybdate ((NH_4)$_6MoO_{24}$·$4H_2O$), which to our knowledge has never been tested before as a catalyst for generating singlet oxygen, could also give **2** in 80% yield under similar conditions (Entry 5).

We also examined compound **4**, one of the simple enones reported by Posner and co-workers.[4] In the present work the starting **4** was prepared from isobutanal and the Wittig reagent[7] derived from α-bromo-acetophenone[8] (Scheme 2). Posner reported that treatment of **4** with singlet oxygen (generated by photosensitization of molecular oxygen) in methanol led to peroxide **5** (with R=Me). Under the Jacobs' conditions, however, no peroxy bond-containing products could be detected, although singlet oxygen was indeed generated. Addition of $CuSO_4$ (Lewis acid) to the reaction mixture did not lead to any improvements.

Scheme 2
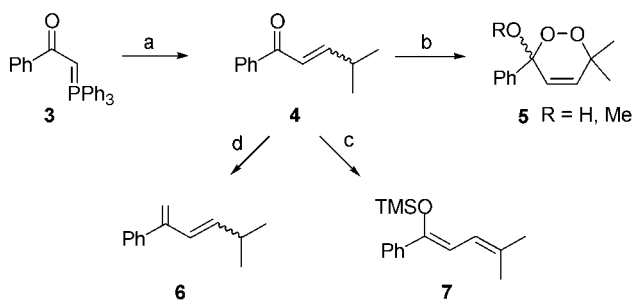
Reagents and conditions: a) isobutanal, 87%; b) see the text; c) $TMSCl/NEt_3$, 90%; d) $Ph_3P=CH_2$, 80%.

Formation of the peroxide **5** from enone **4** required an *in situ* conversion of the enone into its dienol to generate the desired (transient) C=C—C=C partial structure. It appeared that the difficulty encountered here might stem from the disfavored enolization under the given conditions. Therefore, in the subsequent endeavor **4** was converted into diene **6**[9] by a Wittig reaction. This compound was close to α-terpinene as far as the functionality contained in the molecule was concerned. However, the reaction with diene **6** turned out to be very sluggish. When using 30% H_2O_2, essentially no reactions took place. Higher H_2O_2 (50%) concentration appeared to have a promoting effect on the reaction. But still only negligible amounts of products could be detected by TLC after 25 h. It appears that the large difference in reactivity between **6** and α-terpinene can be reasoned only from the conformation of the diene—In α-terpinene the diene is always *s-cis* (the right one for the dioxygen cycloaddition) while in **6** probably the *s-trans* conformer predominates.

We also prepared the known silyl enol ethers **7**[10] and **9**[11] as reported in the literature and tested them under the Jacobs' conditions. Again, in both cases, no reaction

occurred at all when using 30% H_2O_2. Replacing the 30% H_2O_2 with 50% one substantially facilitated the reactions (which were also significantly faster than that with **6**). However, in sharp contrast to the clean cycloaddition of the singlet oxygen to α-terpinene, the product mixture in both cases was very complicated. There were several peroxy bond-containing products in each case, along with many other side products that did not contain a peroxy bond. Most of the products appeared to be rather unstable, making it practically unfeasible to isolate the expected components in synthetically useful quantities (Scheme 3).

Scheme 3
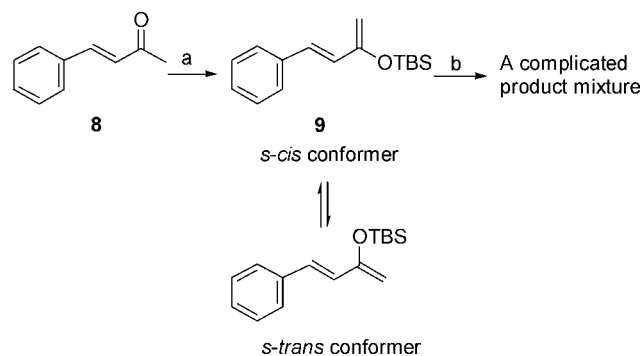
Reagents and conditions: a) $TBSOTf/NEt_3$, 82%; b) $H_2O_2/Mg_{0.7}$-$Al_{0.3}$-LDH-MoO_4/MeOH.

Similar reaction with a known aromatic substrate (**11**, prepared[12] from anthrone **10** by treatment with Me_2SO_4 in the presence of NaOH) proceeded smoothly, yielding only one product (containing peroxy bond, presumably **12**). Compared with the above depressing outcomes with the aliphatic substrates, this result was of course very encouraging. However, when we tried to isolate the product by column chromatography on silica gel, only the decomposition product anthraquinone **13**[13] was obtained (Scheme 4).

Scheme 4
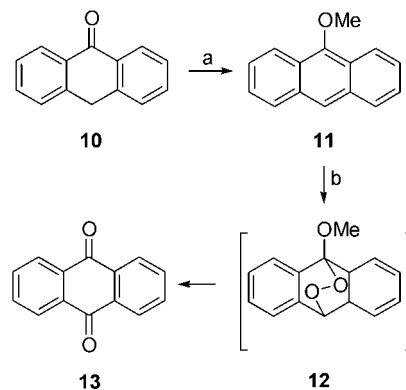
Reagents and conditions: a) Me_2SO_4/aq. NaOH, 60%; b) $H_2O_2/Mg_{0.7}$-$Al_{0.3}$-LDH-MoO_4/MeOH, 60% from **11**.

Our preliminary results suggest that the incorpora-

tion of a peroxy bond with the "dark" singlet oxygen probably can be realized (in synthetically useful yields) only when (1) the C=C—C=C partial structure in the substrates is fixed to a *cis*-conformation (a pre-requisite for cycloaddition) and (2) no other functionality is present (such as α-terpinene) in the molecule. Open-chain dienes do not react so easily as α-terpinene. Silyl enol-dienes react more easily than their open-chain simple alkene counterparts (*i.e.*, those alkenes with no oxygen atoms are directly attached to the carbon-carbon double bonds) but tend to give complicated product mixture under the given (essentially neutral) conditions, perhaps partially caused by the excess H_2O_2 in the system.

Because dihydroascaridole was reported[14] to be a more effective antimalarial (IC_{50}=190 nM) than ascaridole itself (IC_{50} =650 nM), we also briefly studied[15] the cleavage of dihydroascaridole. The double bond in ascaridole was first saturated (Scheme 5) with diimide generated[16] *in situ* from hydrazine hydrate in EtOH in the presence of air. Compound **14** was then cleaved using our[17] cysteine-Fe^{2+} protocol. The main and the only isolable product was the diol **15**, which accounted for 62% of the starting peroxide. Other products were all present in small quantities, making identification extremely difficult. However, it was positive that there were several water-soluble/highly polar products containing amino acid moiety, which according to our earlier results[17,18] were likely to be alkylated cysteine, although the relative quantity seemed to be much less than that of the corresponding product formed in the cleavage of qinghaosu.

Scheme 5
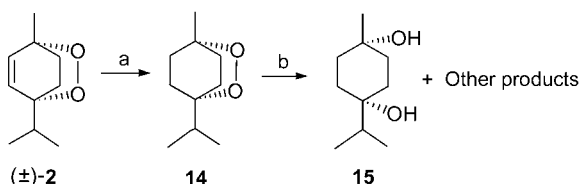
Reagents and conditions: a) N_2H_4-H_2O/EtOH/air, 61%; b) methyl cysteinate/Fe^{2+}/THF-H_2O, 62% for **15**.

Experimental

Chromatography was performed on silica gel (300—400 μ). PE refers to petroleum ether (60—90 ℃). All the products (known compounds) mentioned below were TLC and NMR homogeneous and gave spectroscopic data consistent with those reported in the literature. The Jacobs catalyst $Mg_{0.7}$-$Al_{0.3}$-LDH-MoO_4 was prepared following the literature[4b] procedure. The peroxy bond-containing spots on TLC plates were visualized with freshly prepared $FeSO_4$-NH_4SCN[19] solution. The Fe^{2+} stock solution (*ca.* 3.88 mmol/L) was prepared by dissolving Na_2CO_3 (26 mg, 0.25 mmol), Fe_2-$(SO_4)_3$•nH_2O (49 mg, *ca.* 0.194 mmol), and methyl cysteinate (0.50 mmol) in de-aired distilled water (50 mL) under argon.

Ascaridole (2)

Method A (using $Mg_{0.7}$-$Al_{0.3}$-LDH-MoO_4 as the catalyst): H_2O_2 (30%, 3 mL) was added to a mixture of α-terpinene (2.725 g, 20 mmol) and the Jacobs catalyst $Mg_{0.7}$-$Al_{0.3}$-LDH-MoO_4 (94 mg) in MeOH (100 mL) stirred at the ambient temperature. The white suspension turned red within two minutes. 17 hours later, the red color faded, and the second portion of H_2O_2 (2 mL) was added. The third portion of H_2O_2 (2 mL) along with additional catalyst (52 mg) was introduced 12 h later. The mixture was stirred for 19 h (the starting α-terpinene still did not disappeared) before being diluted with water (150 mL) and extracted with diethyl ether (3×200 mL). The combined organic phases were washed with water (3×60 mL) and brine (2×60 mL), and dried over anhydrous Na_2SO_4. After removal of the drying agent and the solvents, the residue was chromatographed on silica gel (PE：Et_2O, 6：1, *V*：*V*) to give ascaridole as a colorless liquid (1.715 g, yield 51%).

Method B (using Na_2MoO_4 as the catalyst): To a mixture of MeOH (28 mL) and H_2O (12 mL) were added α-terpinene (110 mg, 0.8 mmol), NaOH (160 mg, 4 mmol), Na_2MoO_4 (96 mg, 0.4 mmol), and H_2O_2 (30%, 0.98 mL). The red-brown mixture, which turned gradually to bright yellow, was stirred at the ambient temperature for 50 min before being diluted with water (50 mL) and extracted with diethyl ether (4×50 mL). The combined organic phases were washed with water (3×20 mL) and brine (2×20 mL), and dried over anhydrous Na_2SO_4. After removal of the drying agent and the solvents, the residue was chromatographed on silica gel (PE：Et_2O, 6：1, *V*：*V*) to give ascaridole as a colorless liquid (112 mg, yield 84%).

Method C [using $(NH_4)_6Mo_7O_{24}$•$4H_2O$ as the catalyst]: The procedure was the same as that in Method B, except that the Na_2MoO_4 was replaced by $(NH_4)_6Mo_7$-O_{24}•$4H_2O$. Yield 80%.

Anthraquinone (13)

H_2O_2 (30%, 2 mL) was added to a mixture of anthranone (198 mg, 0.95 mmol) and $Mg_{0.7}$-$Al_{0.3}$-LDH-MoO_4 (80 mg) in MeOH (50 mL) stirred at the ambient temperature. 10 hours later, the red color faded, and the second portion of H_2O_2 (2 mL) was added. The mixture was stirred for another 9 h. The solids were filtered off. The filtrate was diluted with water (70 mL) and extracted with diethyl ether (3×180 mL). The combined organic phases were washed with water (3×40 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. After removal of the drying agent and the solvents, the residue was chromatographed on silica gel (CH_2Cl_2：PE, 1：2, *V*：*V*) to give **13** as a yellow solid (138 mg, 60% yield).

Dihydroascaridole (14)

A solution of (±)-**2** (516 mg, 3 mmol), N_2H_4•H_2O (1.47 mL, 30 mmol) in EtOH (75 mL) was stirred at the ambient temperature in a flask open to the air for 4 h,

1002 *Chin. J. Chem.*, 2004, Vol. 22, No. 9

JIN, LIU & WU

when TLC showed disappearance of the starting material. The reaction mixture was concentrated on a rotary evaporator and the residue was diluted with diethyl ether, washed with water and brine, dried over anhydrous Na_2SO_4. After removal of the drying agent and the solvent, the residue was chromatographed on silica gel (hexane：EtOAc, 15：1, *V*：*V*) to give **14** as an essentially colorless oil (317 mg, 61% yield).

Cleavage of dihydroascaridole with Fe^{2+} in the presence of excess methyl cysteinate

To a solution of **14** (200 mg, 1.15 mmol) and methyl cysteinate (437 mg, 2.30 mmol) in deaired distilled water (23 mL) and deaired THF (23 mL) stirred at the ambient temperature (*ca*. 29 ℃) under argon were added NEt_3 (0.32 mL, 2.3 mmol) and Fe^{2+} stock solution (11.5 mL). The purple mixture was stirred at the ambient temperature for 5 h before being acidified with 2 mol/L HCl to pH 2—3. The stirring was continued for 3 h. The mixture was extracted with EtOAc (3×50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (3×20 mL) and brine (2×30 mL), and dried over anhydrous Na_2SO_4. Removal of the drying agent and the solvents gave a sticky yellow-green oil, which was chromatographed on silica gel (PE：EtOAc, 2：1, *V*：*V*) to give **15** as a yellowish solid (124 mg, 62% yield).

References

1 See, for example:
(a) Ziffer, H.; Highet, R. J.; Klayman, D. L. *Prog. Chem. Org. Nat. Prod.* **1997**, *72*, 121.
(b) Bhattacharya, A. K.; Sharma, R. P. *Heterocylces* **1999**, *51*, 1681.
(c) Wu, Y.-K. *Acc. Chem. Res.* **2002**, *35*, 255 and the references cited therein.
(d) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73.

2 (a) Liu, J.-M.; Ni, M.-Y.; Fan, J.-F.; Tu, Y.-Y.; Wu, Z.-H.; Wu, Y.-L.; Chou, W.-S. *Acta Chim. Sinica* **1979**, *37*, 129 (in Chinese).
(b) Li, Y.; Wu, Y.-L. *Curr. Med. Chem.* **2003**, *10*, 2197.
(c) Li, Y., Wu, Y.-L. *Med. Trop.* **1998**, *58*, *Suppl. 3*, 9.

3 For some examples of introducing peroxy bond with singlet oxygen generated by classical photosensitization, see:
(a) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624.
(b) Xu, X.-X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron* **1986**, *42*, 819.
(c) Xu, X.-X.; Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039.

4 Posner, G. H.; O'Dowd, H.; Ploypradith, P.; Cumming, J. N.; Xie, S.-L.; Shapiro, T. A. *J. Med. Chem.* **1998**, *41*, 2164.

5 (a) van Laar, F.; De Vos, D.; Vanoppen, D.; Sels, B.; Jacobs, P. A.; Del Guerzo, A.; Pierard, F.; Kirsh-De Mesmaeker, A. *J. Chem. Soc., Chem. Commun.* **1998**, 267.
(b) Sels, B. F.; De Vos, D. E.; Grobet, P. J.; Pierard, F.; Kirsch-De Mesmaeker, F.; Jacobs, P. A. *J. Phys. Chem. B* **1999**, *103*, 11114.

6 Aubry, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 5844.

7 Stille, J. K.; Lau, K. S. Y. *J. Am. Chem. Soc.* 1**976**, *98*, 5841.

8 Ganesh, T.; Kumar, C. H.; Krupadanam, G. L. D. *Synth. Commun.* **1999**, *29*, 2069.

9 Mulzer, J.; Bruentrup, G.; Kuehl, U.; Hartz, G. *Chem. Ber.* **1982**, *115*, 3453.

10 Fleming, I.; Iqbal, J. *Tetrahedron Lett.* **1983**, *24*, 2913.

11 Ohkata, K.; Lee, Y.-G.; Utsumi, Y.; Ishimaru, K.; Akiba, K. *J. Org. Chem.* **1991**, *56*, 5052.

12 Itamar, U.; Marc, H. *Synthesis* **1979**, 177.

13 (a) Bowlus, S. B. *Synth. Commun.* **1984**, *14*, 391.
(b) Bovicelli, P.; Sanetti, A.; Bernini, R.; Lupattelli, P. *Tetrahedron* **1997**, *53*, 9755.

14 Posner, G. H.; Tao, X.-L.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 7225.

15 The peroxide type antimalarials with qinghaosu as the best known example are currently believed by many investigators to exert their parasiticidal effects through transient radical-mediated processes such as alkylations. The radical generating and subsequent radical evolution processes were therefore studied by cleavage experiments. For further information, see, for instance, the Refs. 1(c) and 2(b) and many references cited therein.

16 Roush, W. R.; Hoong, J. L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.

17 (a) Wu, Y.-K.; Yue, Z.-Y.; Wu, Y.-L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2580.
(b) Wu, Y.-K.; Liu, H.-H. *Chem. Res. Toxicol.* **2003**, *16*, 1202.
(c) Wu, Y.-K.; Liu, H.-H. *Helv. Chim. Acta* **2003**, *86*, 3074.
(d) Wu, Y.-K.; Yue, Z.-Y.; Liu, H.-H. *Helv. Chim. Acta* **2001**, *84*, 928.
(e) Liu, H.-H.; Wu, Y.-K.; Shen, X. *Chin. J. Chem.* **2003**, *21*, 875.

18 (a) Wang, D.-Y.; Wu, Y.-L. *J. Chem. Soc., Chem. Commun.* **2000**, 2193.
(b) Wang, D.-Y.; Wu, Y.-L.; Wu, Y.-K.; Liang, J.; Li, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 605.
(c) Wu, W.-M.; Chen, Y.-L.; Zhai, Z.; Xiao, S.-H.; Wu, Y.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1645.

19 Touchstone, J. C. *Practice of Thin Layer Chromatography*, John Wiley, New York, **1992**, p. 170.