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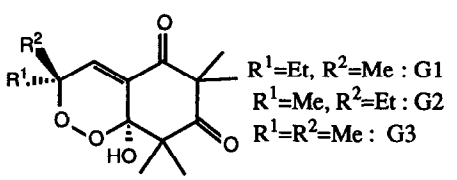
OXYGENATION OF γ,δ-UNSATURATED KETONES IN THE PRESENCE OF THIOPHENOL. EFFICIENT FORMATION OF CYCLIC PEROXIDES.

Jun-ichi Yoshida,* Shogo Nakatani, and Sachihiko Isoe*

Institute of Organic Chemistry, Faculty of Science, Osaka City University, Sugimoto 3-3-138, Sumiyoshi, Osaka 558, Japan

Summary: γ,δ-Unsaturated ketones were found to be oxygenated in the presence of thiophenol to give the corresponding cyclic peroxides. The electrochemical initiation accelerated the reaction markedly.

A number of cyclic peroxides have been isolated from natural sources and some of them exhibit significant biological activities.[1] For example, growth regulators isolated from *Eucalyptus grandis* (**1**) [2] have a six-membered peroxide linkage. Six-membered cyclic peroxides have also been isolated from marine sponges (**2**)[3] and some of them possess antifungal activity. Although there exist several methods for the synthesis of cyclic peroxides,[4] development of a new methodology is still in great demand because of the variety of the structures of naturally occurring cyclic peroxides.



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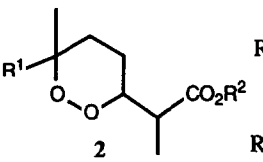

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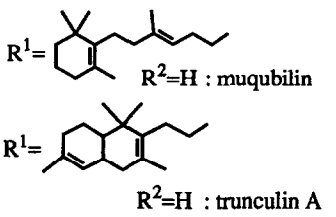
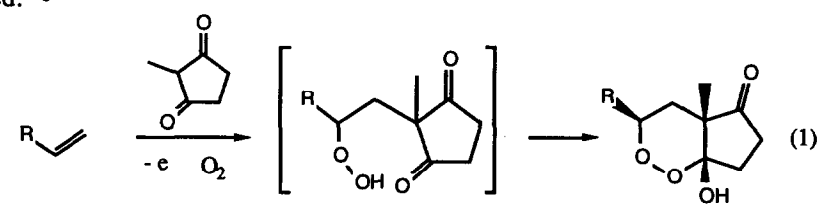


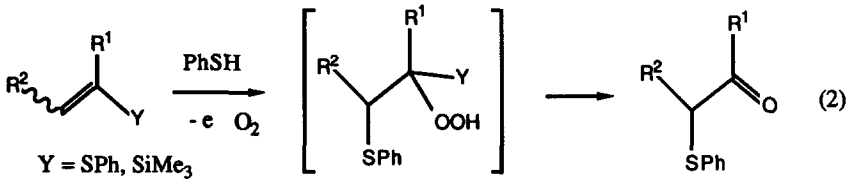
We have recently reported the synthesis of cyclic peroxides by the formal [2+2+2]cycloaddition of 1,3-diketones, olefins, and molecular oxygen (eq 1).[5] A mechanism involving efficient trap of the hydroperoxide (or hydroperoxy radical) intermediate by the carbonyl group located in the appropriate position has been proposed. [6]



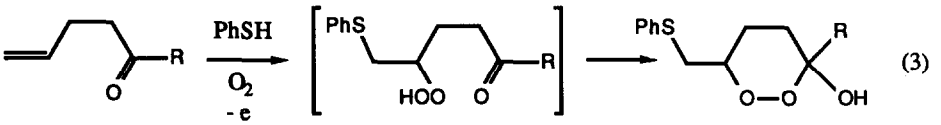
(1)

As for the access to hydroperoxides, addition of phenylthio radical to an olefin followed by the reaction with molecular oxygen is one of the most general and established methods.[7] On the basis of this process we have recently developed the

facile oxygenation of alkenyl sulfides[8] and alkenylsilanes[9] (eq 2). The hydroperoxide intermediate substituted by a phenylthio group or a silyl group at the α position has been suggested to decompose to give the corresponding carbonyl compound.



Herein we wish to report a novel approach to the synthesis of cyclic peroxides by using the combination of the two processes described above, *i. e.* generation of a hydroperoxide by addition of phenylthio radical to an olefin followed by the reaction with molecular oxygen, and intramolecular trapping of the resulting hydroperoxide with a carbonyl group (eq 3).



We first examined the oxygenation of 2-allyl-2-methyl-1,3-cyclopentanedione as the substrate. 2-Allyl-2-methyl-1,3-cyclopentanedione and thiophenol were dissolved in acetic acid and oxygen gas was bubbled through the solution at room temperature (method A). After 19 h, work-up with aq $NaHCO_3$ followed by flash chromatography yielded the corresponding cyclic peroxide in 73% yield. It is rather surprising that the cyclic peroxide was obtained even in the presence of a excess amount of thiophenol, a reducing agent. It is also interesting to note that the product was obtained as a single stereoisomer. The configuration of the cyclic peroxide was determined by X-ray analysis of the corresponding sulfone (Fig. 1).[10]

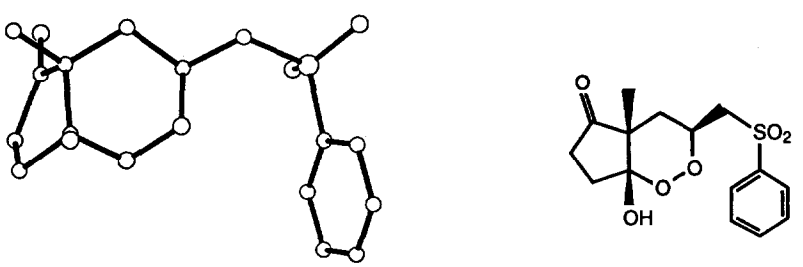
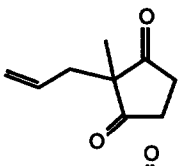
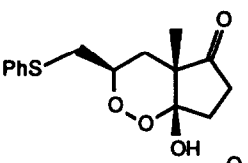
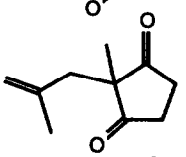
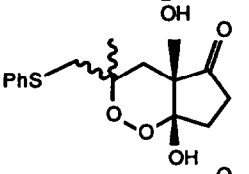
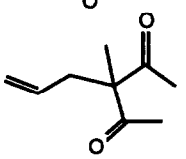
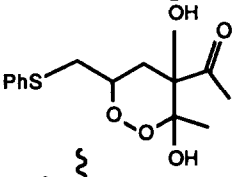
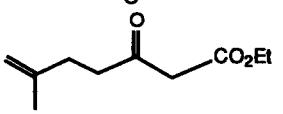
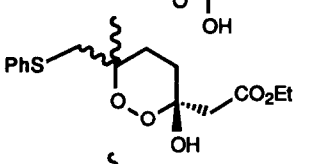
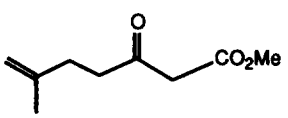
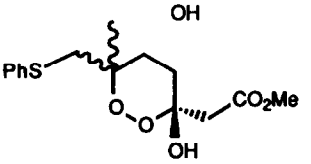
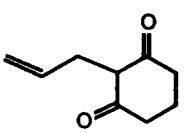
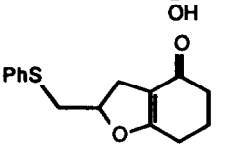


Fig. 1. X-ray structure of the cyclic peroxide

The reaction also took place with other γ,δ-unsaturated ketones as shown in Table I. In the case of the formal [2+2+2]cycloaddition of 1,3-diketones, olefins, and molecular oxygen (eq 1), the reaction is applicable only to cyclic 1,3-diketones. In the present reaction, however, this limitation is overcome. Acyclic 1,3-diketones and ketoesters were oxygenated under the conditions to give the corresponding cyclic peroxides.

Table I. Oxygenation of γ,δ-Unsaturated Ketones in the Presence of Thiophenol

substrate	method	electricity F/mol	time h	product	% yield
	A	-	19		75
	B	0.397	6.5		42
	A	-	39		62
	B	0.423	5.5		71
	A	-	37		29
	B	0.948	8		36
	A	-	66		40
	B	0.250	5		51
	A	-	44		56
	A	-	40		16

The reactions were normally carried out with 1.0 mmol of γ,δ-unsaturated ketones in the presence of 4 equiv of thiophenol in 10 ml of acetic acid.

The reaction can be accelerated significantly by the electrochemical means (method B). In the electro-initiated reaction, a γ,δ-unsaturated carbonyl compound and thiophenol were dissolved in 0.2 M Et_4NOTs/AcOH and constant electric current was passed with bubbling of oxygen for 2 min. The electrolysis was repeated several times at an interval of 30 min until the most of the γ,δ-unsaturated carbonyl compound was consumed. The results are also listed in Table I.

The following radical chain mechanism seems to be reasonable. A phenylthio radical generated from thiophenol by the reaction with molecular oxygen or by the electrochemical oxidation adds to the carbon-carbon double bond. The resulting carbon radical reacts with molecular oxygen to give the peroxy radical which abstracts hydrogen from another molecule of thiophenol to regenerate a phenylthio

radical. The hydroperoxide reacts with the carbonyl group intramolecularly to give the cyclic peroxide.

It is interesting that 2-allyl-1,3-cyclohexanedione gave the dihydrofuran derivative instead of the corresponding cyclic peroxide. Since the 1,3-diketone moiety seems to be present as its enol form predominantly, the hydroperoxide intermediate cannot be trapped effectively by the carbonyl group. Therefore the hydroperoxide might be reduced with the excess thiophenol to the corresponding alcohol which forms the dihydrofuran on aqueous work-up. However, more data should be accumulated before elucidation of the detailed mechanism.

Acknowledgement

We thank Dr. Ken Hirotsu, Osaka City University for determination of the X-ray structure of the cyclic peroxide. We also thank the Ministry of Education, Science and Culture, Japan for a Grant-in-Aid for Scientific Research on Priority Area (No. 01607003) for financial support of this work.

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(6) Intramolecular trapping of a hydroperoxide by a carbonyl group: For example, (a) Pierrot, M.; El Idrissi, M.; Santelli, M. *Tetrahedron Lett.* **1989**, *30*, 461. (b) Oku, A. Yokoyama, T.; Harada, T. *Tetrahedron Lett.* **1983**, *24*, 4699. (c) Adam, W.; Griesbeck, A. *Synthesis*, **1986**, 1050.

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(10) The sulfide was converted into the sulfone by the treatment with oxone: Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287. Crystal data: $C_{15}H_{18}O_6S$, triclinic, space group $P\bar{1}$, a = 11.168(3), b = 10.373(4), c = 7.060(2) Å, α = 100.10(3), β = 106.31(2), γ = 97.34(3) °, z = 2. The structure was solved using MULTAN.[11] Full-matrix least-squared refinement with anisotropic temperature factors for non-hydrogen atoms converged to R = 0.046.[12] Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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