# An Efficient Synthesis of *gem*-Dihydroperoxides with Molecular Oxygen and Anthracene under Light Irradiation

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**Abstract:** A new efficient dihydroperoxidation protocol of a wide variety of carbonyl compounds with molecular oxygen, anthracene, and 2-propanol under light irradiation afforded their corresponding *gem*-dihydroperoxides in high yields.

**Keywords:** anthracene; dihydroperoxides; organocatalysis; oxygen; photo-dihydroperoxidation

Organic gem-dihydroperoxides and their derived peroxides have attracted a great deal of attention as potential antimalarial active compounds against the background the increasing resistance of malaria parasites to alkaloid medicine, since artemisinin with an endoperoxide bridge structure shows effective antimalarial activity against multidrug-resistant malaria.<sup>[1]</sup> In addition, from the view point of organic synthesis, gem-dihydroperoxides have been also known to play an important role as key intermediates in the synthesis of various peroxides<sup>[2-4]</sup> as an initiator for radical polymerization,<sup>[5]</sup> and as an oxidant for epoxidation<sup>[6]</sup> and sulfoxidation.<sup>[7]</sup> Generally, gem-dihydroperoxides can be synthesized from carbonyl compounds or their derivative with hydrogen peroxide in the presence of catalysts such as acids, heavy metals and iodine.<sup>[8]</sup> Also we have recently reported the convenient catalyst-free synthesis of gem-dihydroperoxides from ketones and aldehydes with hydrogen peroxide in dimethoxyethane.<sup>[9]</sup> Hydrogen peroxide is an excellent oxidant due to its production of water as the only byproduct in oxidation reactions; however, attention is required for handling due to its corrosive and explosive properties. On the other hand, molecular oxygen has attracted much attention because of its (a) ease of handling, (b) involvement in photosynthesis, and (c) larger atom efficiency than that of other oxidants,<sup>[10]</sup> and higher environmentally benign oxidation processes can be established with it. Based on these considerations, we have reported oxidations with molecular oxygen under light irradiation for various types of reactions.<sup>[11]</sup> In the course of our further studies on applications of aerobic photooxidation, we found that *gem*-dihydroperoxides were obtained from carbonyl compounds when using molecular oxygen as terminal oxidant under light irradiation in the presence of a catalytic amount of anthracene in 2-propanol [Eq. (1)].

$$R^{(n)} \xrightarrow{h\nu, O_2} HOO OOH$$

$$R^{(n)} \xrightarrow{2-\text{propanol}} R^{(n)} \xrightarrow{R^{(n)}} (1)$$

To the best of our knowledge, this reaction is the first example for the preparation of *gem*-dihydroper-oxides from carbonyl compounds with molecular oxygen as a terminal oxidant. Herein, we report our detailed study, including scope and limitations, of this synthesis of *gem*-dihydroperoxides.

The reaction conditions were examined with molecular oxygen and a catalytic photosensitizer under irradiation from a 500 W xenon lamp at room temperature using *tert*-butylcyclohexanone (1) as a test substrate. Among the typical photosensitizers and solvents we have examined, anthracene and 2-propanol were found to be most effective for this reaction, respectively, and even 2 mol% of the catalyst was enough for the smooth progression of this reaction. It is noted that all three factors, light irradiation, anthracene, and molecular oxygen, were necessary for the dihydroperoxydation since the product was not obtained without them.<sup>[12]</sup>

Table 1 indicates the scope and limitations of this synthesis using various ketones under the optimized reaction conditions mentioned above. Cyclohexanone (3) and its derivatives 1, 5, 7, 9 produced the corresponding *gem*-dihydroperoxides 2, 4, 6, 8, 10 in good

	hv a	product		
(0.3 mmol)			2-PrOH (5 mL)	
Entry	Substrate	Time (h)	) Product	Yield [%] <sup>[a]</sup>
1	t-Bu 1	10	OOH t-Bu 2	86
2	G <sup>O</sup> 3	10		62
3	<b>C5</b>	10	OOH OOH 6	67
4	<b>7</b>	10		90
5	↓ <sup>O</sup> 9	10		68
6	0 11	10	HOO OOH	87
7		24	ООН ООН 14	81
8	0 	15	HOO_OOH M <sub>6</sub> 16	84
9		10		77
10	о Ч <sub>6</sub> Н 19	10		33 <sup>[b,c]</sup>
11	MeO 21	10	MeO 22	20 <sup>[b,d]</sup>
12	O 23	30	HOO_OOH	15 <sup>[b]</sup>

<sup>[a]</sup> Isolated yields.

<sup>[b]</sup> Determined by <sup>1</sup>H NMR using tetrachloroethane as an internal standard.

<sup>[c]</sup> Octanoic acid (28%) was detected by <sup>1</sup>H NMR.

<sup>[d]</sup> 4-Anisic acid (58%) was detected by <sup>1</sup>H NMR.

to excellent yields (entries 1–5). Cyclooctanone (11) was also converted to the corresponding *gem*-dihydroperoxide 12 in high yield (entry 6). 2-Adamantanone (13), having high steric hindrance, was still reactive and the corresponding *gem*-dihydroperoxide (14) was obtained in 81% yield (entry 7). Furthermore, 2-nonanone (15) and 5-nonanone (17), non-cyclic aliphatic ketones, produced the corresponding *gem*-dihydroperoxides in 84 and 77% yields, respectively (entries 8 and 9). On the other hand, aldehydes 19, 21 produced low yields of products (hydroperoxyhemiacetal 20 or



Scheme 1. Plausible reaction path.

dihydroperoxide **22**) since they were also good substrates for aerobic photo-oxidation to give the corresponding carboxylic acids (entries 10 and 11).<sup>[13]</sup> Unfortunately, acetophenone (**23**) was converted to the corresponding dihydroperoxide only in low yield.

To clarify the mechanism, first we assayed the peroxides in solution by iodometry, and found that large excesses of peroxides were formed in comparison with the substrate.<sup>[14]</sup> This result suggests that hydrogen peroxide or hydroxy peroxide was formed in the solution. In addition, the formation of excess amounts of acetone (2.39 mmol) was detected by <sup>1</sup>H NMR measurements. We have also found that gem-dihydroperoxides can be obtained from the carbonyl compounds and aqueous hydrogen peroxide without any catalyst.<sup>[9]</sup> Scheme 1 shows the plausible path of this reaction, which is postulated by considering all of the results mentioned above and the necessity of 2-propanol, a catalytic amount of anthracene and molecular oxygen. Hydroxy hydroperoxide 25 was generated from 2-propanol in the presence of molecular oxygen and anthracene or dianthracene with irradiation from the xenon lamp.<sup>[15]</sup> Hydroxy hydroperoxide **25** or hydrogen peroxide (26), that is generated from 25 in situ, reacts with ketone to generate the gem-dihydroperoxide.<sup>[16]</sup> It has not been clarified yet which path is operative; however, we believe that hydrogen peroxide was generated in situ since bubbling was observed when catalase was added to this reaction mixture.<sup>[17]</sup>

In conclusion, we have developed a first facile and practical method for preparation of *gem*-dihydroperoxides from various carbonyl compounds in the presence of molecular oxygen and the catalytic amount of anthracene under photo irradiation. This dihydroperoxidation protocol also seems efficient as environment friendly. Further application of this dihydroperoxidation and detailed mechanistic study are now in progress in our laboratory.

### **Experimental Section**

**Caution!** Peroxides generated in the reaction mixture may result in explosion. All preparations should be handled with care on a small scale.

#### **Representative Procedure of Dihydroperoxidation**

A dry 2-propanol solution (5 mL) of 4-*tert*-butylcyclohexanone (46.3 mg, 0.30 mmol) and anthracene (1.07 mg, 0.006 mmol) in a pyrex tube equipped with an O<sub>2</sub>-balloon was stirred and irradiated externally with a 500 W xenon lamp, which was set up at a distance of 30 cm, for 10 h. The temperature of the final stage of this reaction was about 60 °C. The reaction mixture was concentrated under reduced pressure, and the pure product was obtained by purification with preparative TLC: yield: 52.7 mg (86%).

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- [14]  $Na_2S_2O_3$  (4.56 mmol) was consumed for iodometry of the reaction mixture obtained under the optimal conditions (Table 1, entry 1).
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(58%) when dianthracene (0.003 mmol) was used as a catalyst.

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[17] Bubbling was not observed when catalase was added to a 2-propanol solution of dihydroperoxide **2**.