ORGANIC LETTERS

2006
Vol. 8, No. 12
2491−2494

Iodine as a Catalyst for Efficient Conversion of Ketones to *gem*-Dihydroperoxides by Aqueous Hydrogen Peroxide

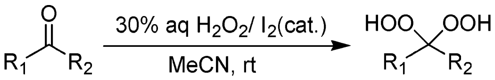
Katja Žmitek,[†] Marko Zupan,[‡] Stojan Stavber,[†] and Jernej Iskra*,[†]

Laboratory of Organic and Bioorganic Chemistry, “Jožef Stefan” Institute, Jamova 39, Ljubljana, Slovenia, and Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, Ljubljana, Slovenia

jernej.iskra@ijs.si

Received March 10, 2006

ABSTRACT



Iodine has been shown to be an efficient catalyst for the selective dihydroperoxidation of ketones with aqueous hydrogen peroxide. Ketones were directly converted to their corresponding *gem*-dihydroperoxides using a “green” oxidant (30% aq H_2O_2) and a simple catalyst (iodine) under neutral conditions in acetonitrile. The yield of hydroperoxidation of various cyclic ketones was 60–98% including androstane-3,17-dione, and acyclic ketones were converted with a similar efficiency.

In recent years, an increasing resistance of malaria parasites to commonly used alkaloidal drugs and the discovery of the antimalarial properties of artemisinin[1] have boosted interest in organic peroxides as potential antimalarials.[2] Dihydroperoxides are key intermediates in the synthesis of many classes of peroxides, such as tetraoxanes[3−6] and other tetraoxacycloalkanes,[7−9] macrocyclic endoperoxides,[10,11]and acyclic analogues with a variety of functional groups.[12] Organic peroxides are also valuable chemicals that serve as radical initiators and oxidants.[13,14]

The three major synthetic paths for the synthesis of *gem*-dihydroperoxides are: (1) ozonolysis of ketone enol ethers or α-olefins in the presence of H_2O_2;[8,9] (2) reaction of ketals with H_2O_2 in the presence of tungstic acid[15] or $BF_3{\cdot}Et_2O$,[16] and (3) peroxidation of ketones using an acidic solvent[17] or, in reactions of cholic acid derivates,[5,6] a catalyst. Synthesis of primary *gem*-dihydroperoxides (DHPs) has been achieved

---

[†] “Jožef Stefan” Institute.

[‡] University of Ljubljana.

[1] *Antimalarial Chemotherapy;* Rosenthal, P. J., Ed.; Humana Press: Totowa, New Jersey, 2001.

[2] Tang, Y. Q.; Dong, Y. X.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425.

[3] Iskra, J.; Bonnet-Delpon, D.; Begue, J. P. *Tetrahedron Lett.* **2003**, *44*, 6309.

[4] Terent’ev, A. O.; Kutkin, A. V.; Starikova, Z. A.; Antipin, M. Y.; Ogibin, Y. N.; Nikishina, G. I. *Synthesis* **2004**, 2356.

[5] Opsenica, D.; Pocsfalvi, G.; Juranic, Z.; Tinant, B.; Declercq, J. P.; Kyle, D. E.; Milhous, W. K.; Solaja, B. A. *J. Med. Chem.* **2000**, *43*, 3274.

[6] Todorovic, N. M.; Stefanovic, M.; Tinant, B.; Declercq, J. P.; Makler, M. T.; Solaja, B. A. *Steroids* **1996**, *61*, 688.

[7] Tsuchiya, K.; Hamada, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H. S.; Shibata, Y.; Wataya, Y. *Tetrahedron Lett.* **1999**, *40*, 4077.

[8] 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.

[9] 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.

[10] McCullough, K. J.; Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M. *Tetrahedron Lett.* **2001**, *42*, 5529.

[11] Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525.

[12] Hamada, Y.; Tokuhara, H.; Masuyama, A.; Nojima, M.; Kim, H. S.; Ono, K.; Ogura, N.; Wataya, Y. *J. Med. Chem.* **2002**, *45*, 1374.

[13] *Peroxide chemistry: mechanistic and preparative aspects of oxygen transfer*; Adam, W., Ed.; Wiley-VCH: Weinheim, 2000.

[14] *Organic Peroxides;* Ando, W., Ed.; John Wiley & Sons: Chichester, 1992.

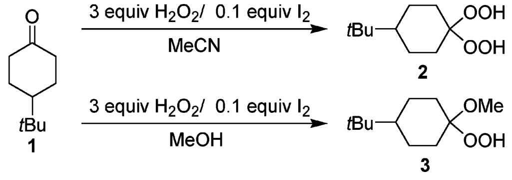
[15] Jefford, C. W.; Li, W.; Jaber, A.; Boukouvalas, J. *Synth. Commun.* **1990**, *20*, 2589.

[16] Terent’ev, A. O.; Kutkin, A. V.; Troizky, N. A.; Ogibin, Y. N.; Nikishin, G. I. *Synthesis* **2005,** 2215.

[17] Ledaal, T.; Solbjor, T. *Acta Chem. Scand.* **1967**, *21*, 1658.

10.1021/ol060590r CCC: $33.50

Scheme 1

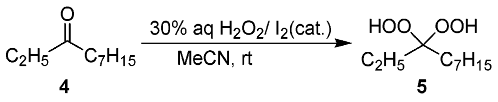


only by ozonolysis[8,9] and by hydroperoxide rearrangement of selected bicyclic alcohols.[18] Drawbacks of these methods are the need for the prior synthesis of the starting substrates, the use of highly concentrated H_2O_2, the need for excess acid, moderate yields, and the restricted substrate range. In addition, the selectivity of ozonolysis is poor and cannot be used for substrates containing ozone-sensitive groups. Because of these limitations, new, more efficient, and broad spectrum methods for the synthesis of DHPs are sought.

Our goal was to find a new approach to synthesize DHPs, starting directly from the carbonyl compound, using commercially available 30% H_2O_2 while avoiding the use of an acid if possible. Because molecular iodine has proven a useful Lewis acid catalyst for the activation of carbonyl compounds, including for acetalization reactions,[19−21] we envisaged that iodine would benefit the peroxidation reactions of such compounds.

An acid and methyltrioxorhenium (MTO) catalyzed reaction of 4-substituted cyclohexanones with 30% H_2O_2 in trifluoroethanol (TFE) led to the formation of tetraoxanes, but only in the case of 4-methylcyclohexanone does a similar reaction without acid yield *gem*-dihydroperoxide.[3,22] Using I_2 instead of (MTO), we performed the reaction with 4-*tert*-butyl cyclohexanone **1** in TFE using 10 mol % of I_2 as the catalyst. DHP **2** was formed in 80% yield as determined from the ^{1}H NMR spectra of the crude reaction mixture. We also investigated whether the use of TFE in combination with I_2 was a requirement of whether other solvents could be used. Therefore, reactions of **1** with 3 equiv of 30% aq H_2O_2 and 10 mol % of molecular iodine in different solvents and without a solvent were performed. After 24 h at room temperature in water, in *N*,*N*-dimethylformamide, and without solvent, the reactions were not selective and yielded varying mixtures of hydroperoxides with low conversion (48%, 55%, and 13%). Surprisingly, the reaction in acetonitrile gave 90% of DHP **2** in the crude reaction mixture (Scheme 1). The reaction in methanol was also selective, but instead of DHP, the monoperoxy ketal **3** was formed in 78% yield (70% after isolation). Given this, acetonitrile was deemed the optimal solvent for the synthesis of DHPs and further optimization of the reaction was made in this solvent.

Table 1. Optimization of Reaction Conditions for I_2-Catalyzed Hydroperoxidation of 3-Decanone **4** with 30% aq H_2O_2



	n (mmol)					
entry	**4**	H_2O_2	I_2	concd **4** (M)	time (h)	conv. (%)[a]
1	1	3	0.1	0.5	5	22
2	1	4	0.1	0.5	24	31
3	1	4	0.2	0.5	24	27
4	1	4	0.5	0.5	24	13
5	1	4	0.1	0.1	24	81
6	1	4	0.1	0.1	67	59
7	1	10	0.1	0.1	24	59
8	1	10	0.1	0.1	67	61

[a] Conversions to DHP determined from ^{1}H NMR spectra of the crude reaction mixture.

Because the synthesis of acyclic DHPs is more problematic than that of cyclohexyl DHPs, we selected 3-decanone **4** as a test compound to determine the optimal reaction conditions. The amount of I_2 and H_2O_2, the reaction time, and the concentration of the reagents were varied. The reaction conditions, which worked well for the synthesis of the peroxide **2**, resulted in a low conversion (22%) of **4** into the dihydroperoxide **5** (Table 1, entry 1), and further modification of the conditions was required to enhance the yield. Table 1 shows how an increase in the amount of H_2O_2 and an extended reaction time (24 h) resulted in an increased yield of DHP **5** (entry 2), whereas an increase in the amount of I_2 decreased the yield (entries 3 and 4). Further dilution of the reaction mixture brought about a significant improvement in the conversion of ketone **4** to DHP. In a 0.1 M solution of ketone **4** (entry 5), the conversion was 50% higher than in a 0.5 M solution. A reaction time of 67 h (entry 6) did not bring about any further improvement. On the contrary, it lowered the conversion to DHP, which is probably due to its decomposition with time. A supplementary increase in the amount of H_2O_2 (entry 7) resulted in a deterioration of conversion (lower yield) to DHP **5**.

The best results for the synthesis of DHP **5** were achieved using a 0.1 M solution of ketone **4** in acetonitrile, 4 equiv of 30% aq H_2O_2, and 10 mol % of I_2 at room temperature for 24 h. To determine the limitations of the method, we tested the efficiency of this transformation on various cycloalkanones, acyclic ketones, and aldehydes.

Table 2 gives the results obtained for cyclic ketones. Cyclohexanones show the highest reactivity requiring only 5 h for an efficient conversion to DHPs. Conversion of Me-substituted cyclohexanones was affected by the steric environment around the reaction site, as the yield decreased from 98% for 4-Me-cyclohexyl DHP **12** to 93% for 3-Me **10** and to 80% for 2-Me **8**. Also, 4-*t*-Bu-cyclohexanone **1**, cycloheptanone **14**, cyclododecanone **16**, and androstane-3,17-dione **20** were converted to DHP in good yields, and the cyclopentyl **6** and 2-adamantyl **18** dihydroperoxides required a higher reaction concentration to be formed efficiently.

---

[18] Hamann, H. J.; Liebscher, J. *Synlett* **2001**, 96.

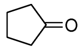
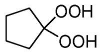
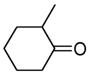
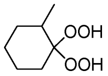
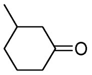
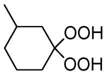
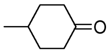
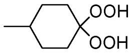
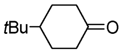
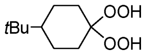
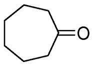
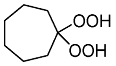
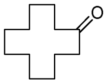
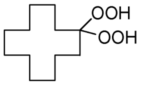
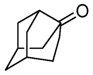
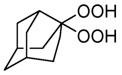
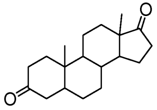
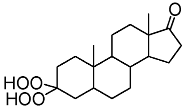
[19] Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Synlett* **2002**, 319.

[20] Karimi, B.; Golshani, B. *Synthesis* **2002**, 784.

[21] Banik, B. K.; Chapa, M.; Marquez, J.; Cardona, M. *Tetrahedron Lett.* **2005**, *46*, 2341.

[22] Zmitek, K.; Stavber, S.; Zupan, M.; Bonnet-Delpon, D.; Iskra, J. *Tetrahedron* **2006**, *62*, 1479.

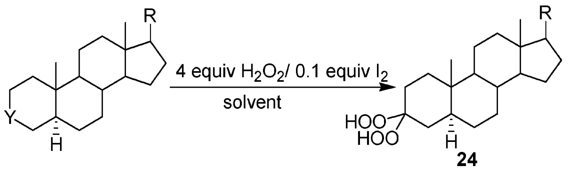
Table 2. Synthesis of Dihydroperoxides from Cycloalkanones with I_2/30% aq H_2O_2

substrate		t (h)	product	yield (%)^{a}
	**6**	24^{c}		**7**: 70
	**8**	5^{b}		**9**: 80
	**10**	5^{b}		**11**: 93
	**12**	5^{b}		**13**: 98^{d}
	**1**	5^{b}		**2**: 91
	**14**	24^{b}		**15**: 90
	**16**	24^{b}		**17**: 60
	**18**	24^{c}		**19**: 92
	**20**	5^{b}		**21**: 77

[a] Yield after column chromatography. [b] Conditions: 1 mmol of ketone, 4 mmol of 30% aq H_2O_2, 0.1 mmol of I_2, 10 mL of MeCN, rt. [c] 2 mL of MeCN. [d] DHP **13** was synthesized on a few gram scale without any apparent complications.

Because many synthetic methods for making DHPs start from ketals, we tested whether there was a difference in the reactivity between ketones and ketals when using our method. Conversion of 4-Me-cyclohexanone **12** and its dimethoxy ketal was determined from the ^{1}H NMR spectra of the crude reaction mixture. The ketal yielded a slightly lower amount of DHP (88%) than the ketone (94%). It seems that reactive ketones and their ketals show similar reactivity for DHP formation. We also tested the use of ketals for less reactive 5α-cholestan-3-one **22**. Its low reactivity is likely to originate from its low solubility because improved results were obtained by increasing the reaction time or by adding CH_2Cl_2 to improve solubility (Scheme 2). To overcome this problem, we used dimethoxy cholestane **23**, which is more soluble than the parent ketone. The result was a good conversion in a shorter reaction time as determined by ^{1}H NMR of the crude reaction mixture.[6]

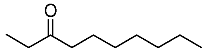
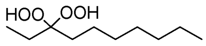
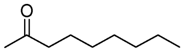
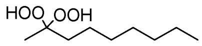
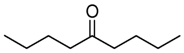
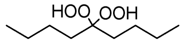
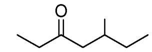
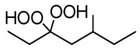
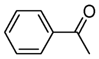
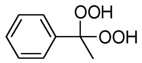
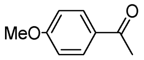
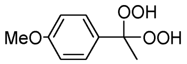
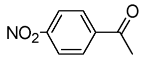
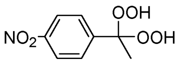
Scheme 2



24

22, Y: C=O:	MeCN, 5 h:	29%
	MeCN, 24 h:	51%
	MeCN/CH_2Cl_2 (9:1), 5 h:	42%
23, Y: $C(OMe)_2$:	MeCN, 5 h:	44%

Table 3. Synthesis of Dihydroperoxides with I_2/30% aq H_2O_2

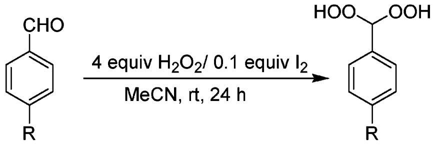
substrate		product	yield (%)^{a,b}
	**4**		**5**: 91
	**25**		**26**: 96
	**27**		**28**: 78
	**29**		**30**: 50
	**31**		**32**: 16
	**33**		-
	**34**		-

[a] Yield after column chromatography. [b] Conditions: 1 mmol of ketone, 4 mmol of 30% aq H_2O_2, 0.1 mmol of I_2, 10 mL of MeCN, rt, 24 h.

I_2-catalyzed hydroperoxidation with 30% aq H_2O_2 was effective for acyclic ketones (Table 3). DHPs were formed in excellent yields from 3-decanone **4** and 2- and 5-nonanone **25** and **27**. Steric effects are again important, and the yield of DHP from an acyclic ketone with a methyl substituent on the β-position **30** is lower. Surprisingly, acetophenone **31** was also converted to its DHP, although until now hydroperoxidation of acetophenone derivatives was not reported. Although we also investigated the influence of electron-donating (**33**, MeO−) and -withdrawing groups (**34**, NO_2−) on conversion, no DHP was isolated.

Hydroperoxidation of aldehydes is more problematic, and there exists no corresponding efficient synthetic method to our knowledge. Thus, we were glad when, with our hydroperoxidation protocol, benzaldehyde was converted into the *gem*-dihydroperoxide **36a** in a 55% yield (isolated). The effect of electron-donating (**35b**, MeO−) and -withdrawing groups (**35c**, NO_2−) on the conversion to DHP proved remarkable (Scheme 3). The methoxy group in **35b** improved the yield of the isolated DHP **36b** to 76%, and the nitro group in **35c** inhibited the reaction with no dihydroperoxide being isolated.

Scheme 3. Formation of Dihydroperoxides **36** from Benzaldehydes **35**

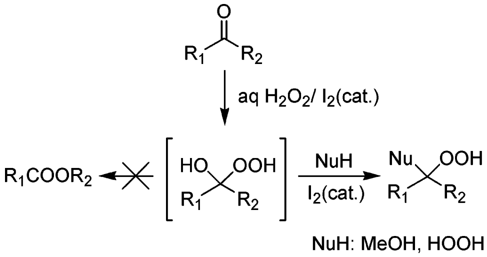


35

R= H **36a**: 55%
MeO **36b**: 76%
NO_2 **36c**: 0%

Iodine could be playing a double role as a catalyst, enhancing the electrophilic character of the carbonyl C-atom and enhancing the nucleophilic character of hydrogen

Scheme 4



peroxide. Furthermore, iodine assists in the rehybridization of the sp^3 C-atom into the sp^2 one and thus enables the second addition of a nucleophile or rearrangement (Scheme 4). The neutral conditions of this reaction seem to be crucial for further substitution by a nucleophile (H_2O_2 and MeOH) and do not lead to a Baeyer−Villiger rearrangement of this Criegee intermediate as proposed for acid- and BF_3-catalyzed reactions.[23,24] Neutral conditions also prevent the acid-catalyzed enolization of the starting ketone that would otherwise lead to α-iodination of ketone.[25]

In conclusion, iodine-catalyzed hydroperoxidation of cyclic and acyclic ketones with aqueous H_2O_2 in acetonitrile is a straightforward and efficient method for the synthesis of *gem*-dihydroperoxides and the reaction is conducted directly from carbonyl compounds in a neutral medium with a readily available low-cost oxidant and catalyst. Further work on this method and transformations of DHP to potentially bioactive endoperoxides is underway, and studies with ^{18}O-labeled H_2O_2 and other nucleophiles will provide further insight into the mechanism of this interesting reaction.

Acknowledgment. This research has been supported by the Ministry of Higher Education, Science and Technology of the Republic of Slovenia and the Young Researcher program (K.Ž.) of the Republic of Slovenia. The authors are grateful to I. Pravst, the staff of the National NMR Centre at the National Institute of Chemistry in Ljubljana (A. Gačeša and J. Plavec), and the staff of the Mass Spectroscopy Centre at the JSI (B. Kralj, D. Žigon) and to T. Stipanovič and Prof. B. Stanovnik for some elemental combustion analysis.

Supporting Information Available: Data on general synthetic procedures for DHP and characterization of substances. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060590R

---

(23) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, *737*, 7.
(24) Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* **2001**, *66*, 1193.
(25) Jereb, M.; Iskra, J.; Zupan, M.; Stavber, S. *Lett. Org. Chem.* **2005**, *2*, 465.