ORGANIC LETTERS

2001
Vol. 3, No. 15
2387−2390

Oxidative Ring Cleavage of Cyclic Acetals with Hypervalent *tert*-Butylperoxy-λ^3-iodanes

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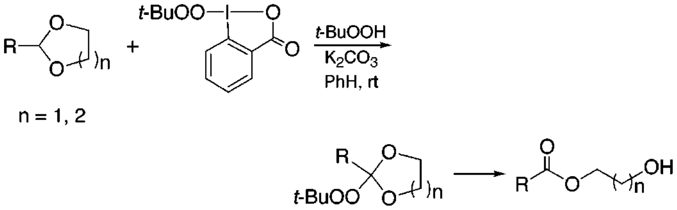
Received May 30, 2001

ABSTRACT

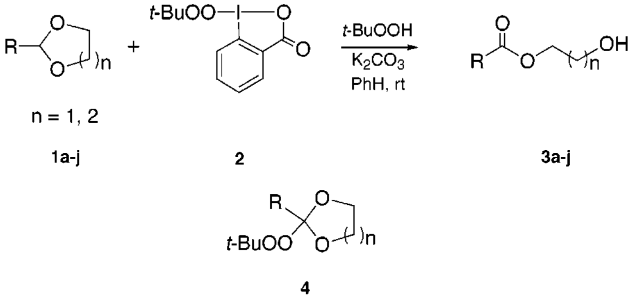


Exposure of cyclic acetals to 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one in the presence of *tert*-butyl hydroperoxide and potassium carbonate in benzene at room temperature results in oxidative ring cleavage to glycol monoesters via intermediate *tert*-butylperoxy ortho esters.

The crystalline alkylperoxy-λ^3-iodane 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one (**2**), prepared from 1-hydroxy-1,2-benziodoxol-3(1*H*)-one by Lewis acid catalyzed ligand exchange with *tert*-butyl hydroperoxide, is stable in the solid state but gradually decomposes in solution at room temperature to generate *tert*-butylperoxy radical.[1,2] The hypervalent (*tert*-butylperoxy)iodane **2** oxidizes benzyl and allyl ethers to esters at room temperature in the presence of alkali metal carbonates via a radical process.[1] A variety of sulfides and 4-alkylphenols are readily oxidized to sulfoxides and 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-ones, respectively, in good yields.[3,4] The (*tert*-butylperoxy)iodane **2** also oxidizes secondary and tertiary amines to imines and *tert*-butylperoxyamino acetals, respectively.[5] Oxidation of amides with **2** affords imides or *tert*-butylperoxyamide acetals, depending on the reaction conditions.[6] We report herein the oxidative conversion of cyclic acetals **1** to hydroxy esters **3** with (*tert*-butylperoxy)iodane **2** in the presence of *tert*-butyl hydroperoxide and potassium carbonate (Scheme 1). Substituent effects for the oxidation of cyclic aryl acetals **1** and the effect of the free-radical scavenger galvinoxyl were also examined.

1,3-Dioxolanes are among the most widely used protective groups for carbonyl compounds and vicinal diols.[7] Oxidation of 2-aryl- and 2-alkyl-1,3-dioxolanes derived from aldehydes provides a useful route for the synthesis of 2-hydroxyethyl esters. Reagents used for direct oxidative cleavage of 1,3-

Scheme 1



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(2) The (*tert*-butylperoxy)iodane **2** is commercially available and was purchased from Tokyo Chemical Industry.

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10.1021/ol016202x CCC: $20.00

dioxolanes include ozone,[8] molecular oxygen−Co(II),[9] hypochlorous acid,[10] potassium permanganate,[11] *N*-hydroxyphthalimide in electrochemical oxidation,[12] and *tert*-butyl hydroperoxide in the presence of Pd(II), Ru(III), or pyridinium dichromate (PDC).[13] 2-Hydroxyethyl esters have found use in selective Diels−Alder reactions, because the functionality can be preferentially activated with Lewis acids by forming a seven-membered chelated structure in the presence of simple ester groups.[14]

Oxidations of 2-phenyl-1,3-dioxolane (**1a**; R = Ph, n = 1) with (*tert*-butylperoxy)iodane **2** in benzene were examined at room temperature under a variety of conditions (Table 1). The reaction with the peroxyiodane **2** (1 equiv) was slow, and β-hydroxyethyl benzoate (**3a**; R = Ph, n = 1) was obtained in a low yield (24%) after 24 h at room temperature. The use of potassium carbonate or *tert*-butyl hydroperoxide as an additive increased the yield of benzoate **3a** to more than 60% (compare entries 1, 2, and 7 in Table 1). It has been reported that alkali metal carbonates markedly accelerate benzylic oxidation of benzyl ethers with the peroxyiodane **2**[1b] and that the yields of oxidation of 4-alkylphenols to 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-ones with **2** are significantly improved when *tert*-butyl hydroperoxide is used as an additive.[4] When both of these additives are used in the oxidation of **1a**, the yield of benzoate **3a** increased to 80−94% (Table 1, entries 9−11). No appreciable effects of molecular dioxygen were observed in this oxidative cleavage; thus, reactions carried out under argon and in air gave comparable yields of **3a** (Table 1, entries 3 and 4). The oxidative ring cleavage requires a stoichiometric amount of peroxyiodane **2**, and without **2**, only a trace of **3a** was detected (Table 1, entries 11−13).

Table 1. Oxidative Ring Opening of Cyclic Acetal **1a** with Hypervalent (*tert*-Butylperoxy)iodane **2**[a]

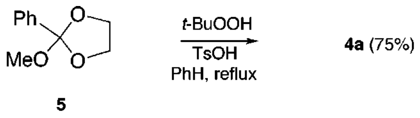
entry	**2** (equiv)	K_2CO_3 (equiv)	*t*-BuOOH (equiv)	time (h)	**3a** yield[b] (%)
1	1			24	24[c]
2	1	2		24	63
3	2	4		11	79
4	2	4		8[d]	73
5	2	4		11[d,e]	0[c]
6	2	4		11[f]	71
7	1		5	24	65
8	1	2	0.5	24	56
9	1	2	1	24	80
10	1	2	3	24	86
11	1	2	5	24	94
12	0.5	2	5	24	50
13		2	5	24	3[c]
14	1	2	5	24[d,e]	0[c]
15	1	2	5	24[f]	58

[a] The reaction was carried out at room temperature in benzene in the air. [b] Isolated yields. [c] **1a** (entry 1, 64%; entry 5, 81%; entry 13, 70%; entry 14, 79%) was recovered unchanged. [d] The reaction was carried under argon. [e] Galvinoxyl (1−2 equiv) was used as an additive. [f] TEMPO (1 equiv) was used as an additive.

The radical nature of this oxidation with **2** was substantiated by complete inhibition of reaction with the added radical scavenger galvinoxyl (Table 1, entries 5 and 14); in these reactions, a large amount of **1a** was recovered unchanged.

A typical experimental procedure is as follows (Table 1, entry 11). To a stirred suspension of 2-phenyl-1,3-dioxolane (**1a**, 0.2 mmol) and potassium carbonate (0.4 mmol) in benzene (3 mL) was added a solution of *tert*-butyl hydroperoxide (4.1 M solution in dichloroethane, 1 mmol) and peroxyiodane **2** (0.2 mmol) at room temperature in air. After 24 h, the reaction mixture was quenched with 5% aqueous potassium carbonate solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by preparative TLC (silica gel, 7:3 hexane/ethyl acetate) gave β-hydroxyethyl benzoate (**3a**, 94%). Very interestingly, in the crude product formation of a large amount of the unstable *tert*-butylperoxy ortho ester **4a** (R = Ph, n = 1) was detected by ^{1}H NMR, in addition to the benzoate **3a**. The ortho ester **4a**, upon exposure to silica gel, readily hydrolyzes to benzoate **3a** in high yield. The structure of **4a** was confirmed by the independent synthesis via acid-catalyzed exchange of ortho ester **5** with *tert*-butyl hydroperoxide (Scheme 2).[15] These results clearly suggest that the primary product of oxidation of 2-phenyl-1,3-dioxolane (**1a**) with (*tert*-butylperoxy)iodane **2** is the ortho ester **4a**.

Scheme 2



The results of oxidation of a variety of acetals with peroxyiodane **2** in the presence of *tert*-butyl hydroperoxide and potassium carbonate are summarized in Table 2. Aromatic and aliphatic 1,3-dioxolanes undergo oxidative ring cleavage, yielding β-hydroxyethyl esters in good yields. The

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Table 2. Oxidation of Acetals with (*tert*-Butylperoxy)iodane **2** and *tert*-Butyl Hydroperoxide[a]

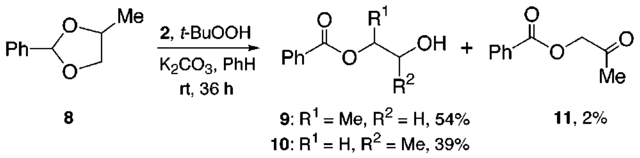
entry	acetal	R	*n*	time (h)	**3**	yield[b] (%)
1	**1b**	*p*-MeC_6H_4	1	24	**3b**	84
2	**1c**	*p*-ClC_6H_4	1	24	**3c**	80
3	**1d**	*m*-ClC_6H_4	1	24	**3d**	78
4	**1e**	2-furyl	1	24	**3e**	77[c]
5	**1f**	PhCH=CH	1	8	**3f**	65
6	**1g**	$PhCH_2$	1	48	**3g**	54[d]
7	**1h**	*n*-C_9H_{19}	1	24	**3h**	71[d]
8	**1i**	*c*-C_6H_{11}	1	24	**3i**	62[d]
9	**1j**	Ph	2	24	**3j**	57[d]
10	**6**[e]			24	**7**	19[d,f]

[a] The reaction was carried out using (*tert*-butylperoxy)iodane **2** (1 equiv) and *tert*-butyl hydroperoxide (5 equiv) in the presence of K_2CO_3 (2 equiv) at room temperature in benzene in the air. [b] Isolated yields. [c] ^{1}H NMR yields. [d] Acetals (entry 6, 12%; entry 7, 22%; entry 8, 10%; entry 9, 27%; entry 10, 47%) were recovered unchanged. [e] Benzaldehyde dimethylacetal (**6**) and methyl benzoate (**7**). [f] 1-(*tert*-Butylperoxy)benzyl methyl ether (13%) was obtained.

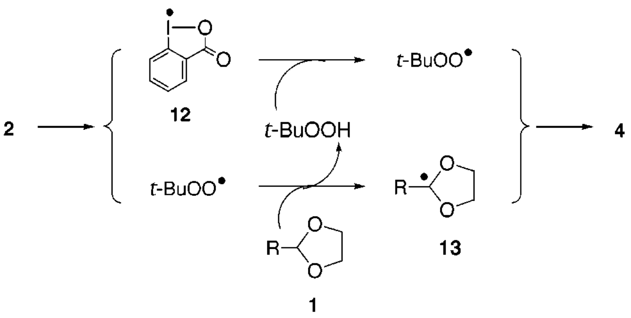
rate of oxidation of aromatic 1,3-dioxolanes appears to be greater than that of aliphatic ones. Oxidation of acetal **1f**, derived from α,*β*-unsaturated aldehyde, affords the conjugated ester **3f** in good yield. As reported in the oxidation with ozone[8] and *N*-hydroxyphthalimide,[12] acyclic dialkoxy acetals react much more slowly than cyclic ones; thus, oxidation of benzaldehyde dimethylacetal (**6**) gave methyl benzoate (**7**) in only 19% yield after 24 h and returned a large amount of unreacted acetal (47%) (Table 2, entry 10). The rates of oxidative cleavage seem to decrease in the order five-membered **1a** > six-membered ring acetal **1j** > acyclic acetal **6**.

Oxidative cleavage of the unsymmetrical cyclic acetal 4-methyl-2-phenyl-1,3-dioxolane (**8**) with **2** favors formation of secondary ester **9** over primary ester **10**, although the degree of regioselectivity is low. A mixture of isomeric hydroxy esters **9** (54%) and **10** (39%) and keto ester **11** (2%) was obtained in this reaction (Scheme 3). The keto ester **11** is probably produced by further oxidation of secondary alcohol **10** under the conditions; this was confirmed by a separate experiment. A slight preference for formation of the secondary ester **9** was observed in oxidative cleavage of **8** with *tert*-butyl hydroperoxide in the presence of PDC[13c] and Pd(II).[13a]

Scheme 3



Scheme 4



As illustrated in Scheme 4, a mechanism for oxidative cleavage of cyclic acetals **1** with peroxyiodane **2** might be assumed to involve the following key steps: (a) homolytic cleavage of the hypervalent iodine(III)−peroxy bond in **2** to give *tert*-butylperoxy radical and [9-I-2] iodanyl radical **12**,[16,17] (b) hydrogen abstraction from acetals **1** by the *tert*-butylperoxy radical to give the carbon-centered acetal radicals **13** and *tert*-butyl hydroperoxide, (c) coupling of 2-dioxolanyl radicals **13** with *tert*-butylperoxy radical, regenerated from *tert*-butyl hydroperoxide by the reaction with iodanyl radical **12**,[4] to give the *tert*-butylperoxy ortho esters **4**, probably via single electron transfer, (d) ring opening of ortho esters **4** to *β*-hydroxyethyl esters **3** by silica gel catalyzed hydrolysis. Formation of acetal radicals **13** via hydrogen abstraction in **1** by iodanyl radical **12** might compete with that by *tert*-butylperoxy radical. Single electron transfer from 2-dioxolanyl radicals **13** to peroxyiodane **2** might also produce the ortho esters **4** with concomitant regeneration of the iodanyl radical **12**.[18,19] The mechanism shown in Scheme 4 is in good agreement with the intermediate formation of the *tert*-butylperoxy ortho esters **4** and the product distribution observed for oxidation of the unsymmetrical acetal **8**. The observation that attempted oxidation of 2-methyl-2-phenyl-1,3-dioxolane, possessing no acetal hydrogens, led to recovery of the acetal (91%) is also compatible with this mechanism.

The slow step of this oxidation is probably acetal C−H bond breaking in the cyclic acetals **1** yielding the carbon-centered radicals **13**. This is in good agreement with the relatively large deuterium kinetic isotope effect $k_H/k_D = 8.5$ measured for oxidation of protonated and deuterated 2-phenyl-1,3-dioxolanes **1a** in benzene at 30 °C under argon. A large isotope effect ($k_H/k_D = 13$) has also been reported for the radical oxidation of benzyl *n*-butyl ether with *tert*-butylperoxyiodane **2**, which most likely involves rate-limiting benzylic hydrogen abstraction.[1b]

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(17) The first-order rate constant for decomposition of **2** in dichloromethane at 30 °C is 2.62×10^{-5} s^{-1}.[1b]

(18) Hypervalent [bis(acyloxy)iodo]benzenes act as good electron acceptors: (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (b) Kokkinidis, G.; Papadopoulou, M.; Varvoglis, A. *Electrochim. Acta* **1989**, *34*, 133.

(19) Homolytic cleavage of the iodine(III)−peroxy bond of the peroxyiodane **2** by nucleophilic attack of **13** may also produce the ortho esters **4** and the iodanyl radical **12**.

Relative rates of oxidation for a series of substituted 1,3-dioxolanes **1a**−**d** were measured by competitive reactions, in which a mixture of a 10-fold excess of each of two competing substrates was used. The electron-releasing *p*-Me group increases the rate of oxidation (Table 3). A Hammett plot for the oxidation of 1,3-dioxolanes **1a**−**d**, presented in Table 3, showed a good linear correlation between the relative rate factors and σ-constants of substituents in the aromatic ring and gave the reaction constant $\rho = -0.69$ ($r = 0.97$). This ρ value appears to be comparable to $\rho^+ = -0.30$ for the radical oxidation of benzyl *n*-butyl ethers with *tert*-butylperoxyiodane **2**.[1b]

Table 3. Relative Reactivity of Acetals **1** with **2** in Benzene at 30 °C under Argon

substrate	R	k_{rel}
1a	C_6H_5	1.0
1b	p-MeC_6H_4	1.5
1c	p-ClC_6H_4	0.68
1d	m-ClC_6H_4	0.64

An alternative pathway involving single electron transfer from the cyclic acetals **1** to the peroxyiodane **2** or *tert*-butylperoxy radical, followed by loss of a proton generating 2-dioxolanyl radicals **13**, dose not seem to operate.[20] The peroxyiodane oxidation of **1a** was not retarded by excess amounts of 1,4-dimethoxybenzene, a single electron transfer quencher with oxidation potential $E_{ox} = 1.28$ V (vs SCE in MeCN).[21]

The decrease in the rate of oxidative cleavage in the order of five-membered **1a** > six-membered ring acetal **1j** > acyclic acetal **6** probably reflects differences in the rates of acetal hydrogen abstractions. In fact, it has been reported that the relative rates of hydrogen abstraction with *tert*-butoxy radical at −60 °C in cyclopropane decreases in the order 1,3-dioxolane (1) > 4-methyl-1,3-dioxane (0.06) > dimethoxymethane (0.03).[22] The stereoelectronic effect that a relatively small dihedral angle (<30°) between the C−H bond and the p-type lone pair orbital on the adjacent ethereal oxygen results in high rates of the hydrogen abstraction might play an important role in hydrogen atom abstraction from cyclic and acyclic ethers.[8,22]

In conclusion, we have shown that the (*tert*-butylperoxy)iodane **2** is a useful reagent for oxidative cleavage of five-membered cyclic acetals to the corresponding hydroxy esters under mild conditions. It should be noted that the iodane **2** is very stable in the solid state and an environmentally friendly oxidizing reagent containing no poisonous heavy metals and that the *o*-iodobenzoic acid formed in the reaction can be recycled by oxidation to the hypervalent iodane **2**.

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