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Free-Radical Oxidation of *para*-Substituted Phenols by Hypervalent *tert*-Butylperoxyiodane and *tert*-Butyl Hydroperoxide: Synthesis of 4-(*tert*-Butylperoxy)-2,5-cyclohexadien-1-ones

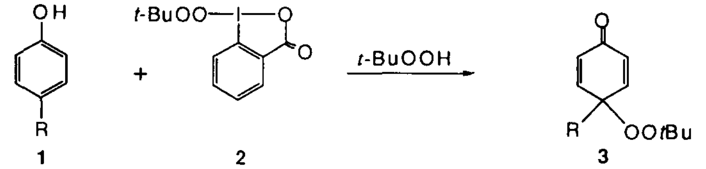
Masahito Ochiai,* Akinobu Nakanishi, and Akiko Yamada

Faculty of Pharmaceutical Sciences, University of Tokushima, 1-78 Shomachi, Tokushima 770, Japan

Abstract: Oxidation of 4-alkylphenols **1** by 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one (**2**) in the presence of *tert*-butyl hydroperoxide affords selectively 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-ones **3** in good yields. Evidence for the involvement of free-radicals is reported.

Free-radical oxidation of phenols has been extensively studied to elucidate the modes of action of phenolic substances in inhibiting autoxidation and olefin polymerization, and the role of this type of reaction in the biogenesis of biologically important compounds such as lignins and alkaloids.[1] In general, the reactions afford a multitude of products as a result of inter- or intramolecular radical-radical coupling between two carbon centers or between an oxygen atom and a carbon atom.

Alkylperoxy radicals or their equivalent species generated by the transition metal-catalyzed decomposition of hydroperoxides or by the thermal decomposition of compounds such as α,α'-azobis(isobutyronitrile) in the presence of dioxygen, the so-called autoxidation, undergo oxidation of 4-alkylphenols to give 4-alkylperoxycyclohexadienones.[2] In the elegant study of Murahashi and his coworkers, 4-alkylperoxycyclohexadienones have been shown to be valuable intermediates for preparing 2-substituted benzoquinones through their Lewis acid-promoted rearrangements.[2a] Recently, we found that 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one (**2**) undergoes homolytic cleavage of the hypervalent *t*-BuOO−I(III) bond at room temperature to generate a *tert*-butylperoxy radical and a σ-iodanyl radical, which act as an efficient radical oxidant for oxidation of benzylic and allylic C−H bonds.[3,4] We report herein selective radical oxidation of 4-alkylphenols **1** by the *tert*-butylperoxyiodane **2** in the presence of *t*-BuOOH yielding 4-(*tert*-butylperoxy)-2,5-cyclohexadien-1-ones **3** under mild conditions in good yields.



The results shown in Figures 1 and 2 indicate that both the peroxyiodane **2** (1.2 equiv) and *t*-BuOOH (6 equiv) are required for effective oxidation of *p*-methylphenol (**1a**) to (*tert*-butylperoxy)cyclohexadienone **3a** in benzene at 50 °C. The oxidation in ethyl acetate resulted in formation of a comparable yield of **3a**, while use of dichloromethane, acetonitrile, or hexane as a solvent gave poor results. The dioxygen was observed to have no effect on the rates of this oxidation and the product yields.[5] The structure of **3a** was determined by comparison with an authentic sample prepared by chromium(VI)-catalyzed oxidation of **1a** with *t*-BuOOH.[2c] The results of phenolic oxidation with the (*tert*-butylperoxy)iodane **2** and *t*-BuOOH in ethyl acetate are summarized in Table 1. The attempted synthesis of 4-(*tert*-butylperoxy)-4-methoxycyclohexadienones by heteropolyacid-catalyzed

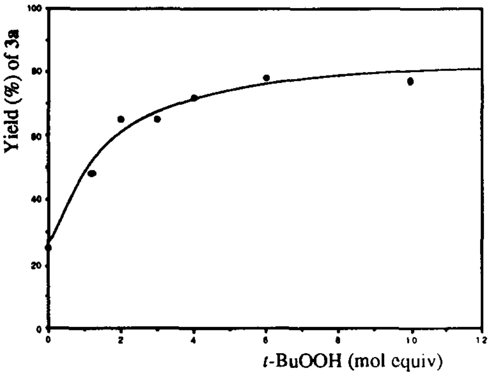


Figure 1. Plots of GC yields of **3a** vs. amounts of *t*-BuOOH for the oxidation of **1a**: **2** (1.2 equiv)/benzene/50 °C.

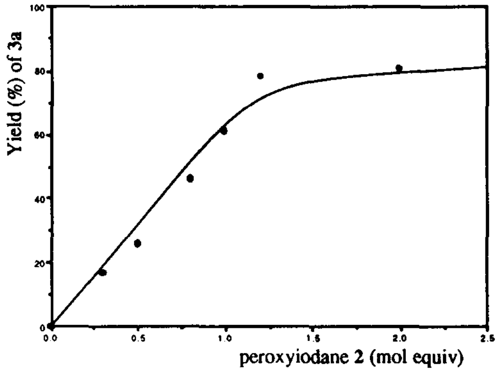
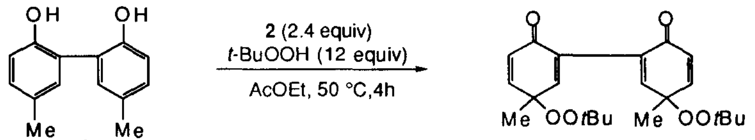


Figure 2. Plots of GC yields of **3a** vs. amounts of **2** for the oxidation of **1a**: *t*-BuOOH (6 equiv)/benzene/50 °C.

oxidation of *p*-methoxyphenols with *t*-BuOOH has been reported to result in exclusive formation of *p*-benzoquinones via their elimination.[6] It is, therefore, to be noted that oxidation of **1f** with **2** and *t*-BuOOH afforded the desired 4-methoxycyclohexadienone **3f** in a reasonable yield, indicating mildness of the reaction conditions (Table 1, entry 6). Methyl podocarpate **1l** and β-estradiol 17-acetate **1m** gave rise to a mixture of diastereoisomers.

Hypervalent organoiodanes have been shown to be useful for oxidation of phenols, and it is generally accepted that the reactions proceed by an ionic mechanism via the formation of some electrophilic reactive intermediates.[7-9] In marked contrast, the radical nature of this phenol oxidation by the peroxyiodane **2** was substantiated by inhibition of the reaction with the added radical scavenger; thus, treatment of **1a** with **2** and *t*-BuOOH in ethyl acetate in the presence of galvinoxyl (1.2 equiv) at 50 °C resulted in formation of the dienone **3a** in less than 5% yield, and more than 92% of the phenol **1a** was recovered unchanged (Compare the result with Table 1, entry 1). The intermediacy of free-radicals in this oxidation was further supported by isolation of a 1:1 mixture of diastereoisomers of 4-(*tert*-butylperoxy)cyclohexadienone dimer **5**[10] in the reaction of *p*-methylphenol (**1a**) with **2** and *t*-BuOOH, albeit in low yield (less than 4%). This dimer **5** is probably produced by simple *o,o*-coupling of **1a** yielding 2,2'-dihydroxy-5,5'-dimethyldiphenyl **4**, followed by further oxidative dearomatization. In fact, reaction of biphenol **4** with **2** and *t*-BuOOH afforded the dimer **5** in 35% yield. This type of *o,o*-coupling of **1a** yielding the biphenol **4** is well precedented in the radical reactions using transition metal oxidants.[1] Furthermore, both the formation of 4-(*tert*-butylperoxy)cyclohexadienone dimers in the cobalt-catalyzed radical oxidations of 2,4-di-*tert*-butylphenol with *t*-BuOOH and the effective oxidation of biphenols to 4-(*tert*-butylperoxy)cyclohexadienone dimers with *tert*-butylperoxy radical have been reported.[2e]

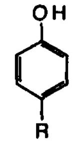
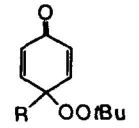
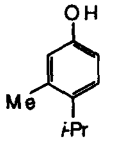
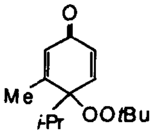
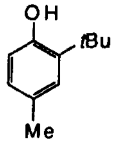
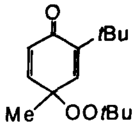
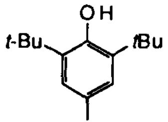
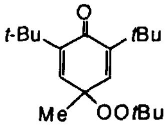
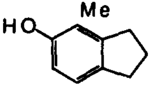
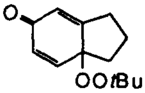
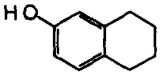
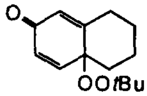
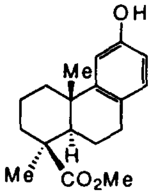
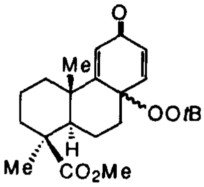
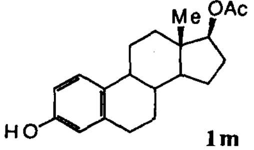
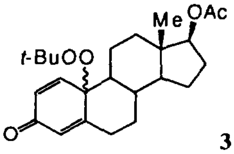
The peroxyiodane **2** decomposes even at room temperature via homolytic bond cleavage of the weak iodine(III)-peroxy bond generating the [9-I-2] iodanyl radical and *tert*-butylperoxy radical.[3] These radicals would be responsible for the oxidation of 4-alkylphenols **1** to 4-(*tert*-butylperoxy)cyclohexadienones **3**. Hydrogen abstraction from phenols **1** by the iodanyl radical and/or *tert*-butylperoxy radical results in the formation of the resonance-stabilized phenoxy radicals.[11] The iodanyl radical could also abstract hydrogen of *t*-BuOOH generating the *tert*-butylperoxy radical. Coupling of the phenoxy radicals with the *tert*-butylperoxy radical is very fast[11b] and gives the cyclohexadienones **3**.[2h,i]



4

5 (35 %)

Table 1 Oxidation of Phenols **1** to 4-(*tert*-Butylperoxy)cyclohexadienones **3** with *tert*-Butylperoxyiodane **2** and *t*-BuOOH[a]

Entry	Phenol 1	Time/h	Dienone 3	Yield[b]/%
1	 **1a** R = Me	3.5	 **3a**	58 (81)[c]
2	**1b** R = *i*-Pr	5	**3b**	53
3	**1c** R = *t*-Bu	5	**3c**	53
4	**1d** R = CH_2Ph	9	**3d**	59
5	**1e** R = Ph	6	**3e**	23[d]
6	**1f** R = MeO	11	**3f**	41[e]
7	 **1g**	5.5	 **3g**	70
8	 **1h**	5	 **3h**	61
9	 **1i**	8.5	 **3i**	85
10	 **1j**	6	 **3j**	65
11	 **1k**	4	 **3k**	68
12	 **1l**	5	 **3l**[f]	56
13	 **1m**	6	 **3m**[g]	63

[a] All the reactions were run with phenols **1** (1 equiv), *tert*-butylperoxyiodane **2** (1.2 equiv), and *tert*-butyl hydroperoxide (6 equiv) in ethyl acetate at 50 °C under an atmosphere. [b] Isolated yields. [c] GC yields. [d] **1e** (10%) was recovered. [e] **1f** (20%) was recovered. [f] A 51:49 mixture of diastereoisomers. [g] A 62:38 mixture of diastereoisomers.

REFERENCES AND NOTES

1. For reviews of phenolic oxidations, see: (a) Kametani, T.; Fukumoto, K. *Phenolic Oxidation*; Gihodo: Tokyo, 1970. (b) Lewis, J. R. *Chem. Ind.* **1964**, 1672. (c) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic Press: London, 1985; Chapter 5. (d) Musso, H. *Angew. Chem.* **1963**, 965. (e) Kametani, T.; Fukumoto, K. *Synthesis* **1972**, 657. (f) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229
2. (a) Murahashi, S.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc.* **1996**, *118*, 2509. (b) Maruyama, K.; Kusukawa, T.; Mashino, T.; Nishinaga, A. *J. Org. Chem.* **1996**, *61*, 3342. (c) Muzart, J. *J. Chem. Research (s)* **1990**, 96. (d) Nishinaga, A.; Yamazaki, S.; Nogusa, H.; Shimoyama, T.; Matsuura, T. *Nippon Kagaku Kaishi* **1985**, 378. (e) Horswill, E. C.; Ingold, K. U. *Can. J. Chem.* **1966**, *44*, 269. (f) Horswill, E. C.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1966**, *44*, 985. (g) Boozer, C. E.; Hammond, G. S.; Hamilton, C. E.; Sen, J. N. *J. Am. Chem. Soc.* **1955**, *77*, 3233. (h) Bickel, A. F.; Kooyman, E. C.; Lau, C. L. *J. Chem. Soc.* **1953**, 3211. (i) Campbell, T. W.; Coppinger, G. M. *J. Am. Chem. Soc.* **1952**, *74*, 1469.
3. Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716.
4. For synthesis of the *tert*-butylperoxyiodane **2**, see; (a) Ochiai, M.; Ito, T.; Masaki, Y.; Shiro, M. *J. Am. Chem. Soc.* **1992**, *114*, 6269. (b) Moss, R. A.; Zhang, H. *J. Am. Chem. Soc.* **1994**, *116*, 4471.
5. The rate of combination of phenoxy radicals with dioxygen is very slow. See: Nishinaga, A.; Tomita, H.; Nishizawa, K.; Matsuura, T. *J. Chem. Soc., Dalton* **1981**, 1504.
6. (a) Shimizu, M.; Orita, H.; Hayakawa, T.; Watanabe, Y.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2583. (b) Shimizu, M.; Orita, H.; Hayakawa, T.; Watanabe, Y.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1835. (c) Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126.
7. For reviews of phenolic oxidations with organoiodanes, see: (a) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431. (b) Kita, Y.; Tohma, H.; Yakura, T. *Trends in Organic Chemistry* **1992**, *3*, 113. (c) Kita, Y.; Tohma, H. *Farumashia* **1992**, *28*, 984. (d) Varvoglis, A. *The Chemistry of Polycoordinated Iodine*; VHC Publishers: New York, 1992. (e) Stang, P. J.; Zhdankin, V.V. *Chem. Rev.* **1996**, *96*, 1123.
8. (a) Rengarajan, K.; Mathai, I. M. *Indian J. Chem.* **1978**, *16B*, 1097. (b) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (c) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (d) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (e) Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119. (f) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435. (g) Hara, H.; Inoue, T.; Nakamura, H.; Endoh, M.; Hoshino, O. *Tetrahedron Lett.* **1992**, *33*, 6491. (h) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891. (i) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047.
9. For radical oxidation of phenol ethers, see: Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.
10. **5**: a 1:1 mixture of diastereoisomers; IR ($CHCl_3$) 1679, 1665, 1649, 1639, 1364, 1197, 1069, 843 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 7.02 (d, J = 3.1 Hz, 1H), 6.98 (d, J = 3.1 Hz, 1H), 6.46 (dd, J = 10.1, 3.1 Hz, 1H), 6.44 (dd, J = 10.1, 3.1 Hz, 1H), 6.19 (d, J = 10.1 Hz, 1H), 6.18 (d, J = 10.1 Hz, 1H), 1.16 (s, 9H), 1.14 (s, 9H), 1.10 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 183.12 (s), 183.04 (s), 149.76 (d), 149.59 (d), 149.54 (d), 149.39 (d), 135.06 (s), 134.58 (s), 129.39 (d), 79.93 (s), 79.84 (s), 76.62 (s), 76.58 (s), 26.43 (q), 23.29 (q); MS (CI, isobutane) *m/z* (rel intensity) 391 (100, $M^+ + 1$), 302 (13), 301 (9); HRMS, calcdfor $C_{22}H_{31}O_6$ ($M^+ + 1$) 391.2121, found 391.2162.
11. *tert*-Butylperoxy radical reacts very quickly with phenols with a rate constant $k = 10^4 - 10^6 M^{-1}s^{-1}$ at 25 °C. See: (a) Ingold, K. U. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 2. (b) Mahoney, L. R.; DaRooge, M. A. *J. Am. Chem. Soc.* **1970**, *92*, 4063.

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