Tetrahedron Letters, Vol.32, No.40, pp 5445-5448, 1991
Printed in Great Britain

0040-4039/91 $3 00
Pergamon Press plc

OXIDATION OF CATECHOL AND OF 2,6-DI-*TERT*-BUTYLPHENOL BY DIOXIRANES

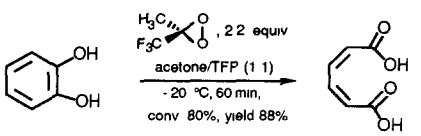
Anna Altamura, Caterina Fusco, Lucia D'Accolti, Rossella Mello, Teresa Prencipe, and Ruggero Curci*

Centro C N R "M I S O", Dipartimento di Chimica, Università di Bari, via Amendola 173, Bari, Italy 70126

Abstract. In a biomimetic transformation, the selective oxidation of catechol (**2**) to Z,Z-muconic acid (**3**) has been achieved under extremely mild conditions using methyl(trifluoromethyl)dioxirane (**1b**) Both dioxirane **1b** and dimethyldioxirane (**1a**) have been applied to the oxidation of 2,6-di-*tert*-butylphenol (**4**), the product natures suggest the incursion of radical pathways

THE oxidation mechanism of phenols and catechols is a topic of continuing interest as a model reaction for oxygenase enzymes.[1] In general, phenol oxidation is relatively facile and it can be carried out using a number of oxidants of widely varying characteristics;[2] however, such processes are rarely selective, as they give rise often to quite complex mixtures of products.[2] With regard to this problem, the opportunity for a new entry into selective oxidation of phenols has recently arisen by the introduction of dioxiranes $R^1R^2CO_2$ (**1**) in synthesis,[3] in fact, these versatile oxidants are extremely efficient in yielding electrophilic O-atom transfer to a variety of substrates, and yet are remarkably selective in their action.[3]

In a study on dioxirane oxyfunctionalization of aromatic hydrocarbons,[4] we found that the highly reactive methyl(trifluoromethyl)dioxirane (**1b**)[5] is capable of bringing about the oxidative cleavage of benzene, yielding the stereomeric *Z,Z*- and *E,E*- muconic dialdehydes in ca. 35% yield. We found, however, that in this reaction other deep seated oxidations gave products that could not be identified Since these might be formed on passing through the sequential mono, di- and polyoxyfunctionalization of the benzene moiety, we deemed it desirable to explore the reactivity of dioxiranes toward phenols and diphenols. Our preliminary findings are reported herein. We have found that, using isolated methyl(trifluoromethyl)dioxirane, the selective conversion of catechol (**2**) into *Z,Z*-muconic acid (**3**) can be achieved under exceptionally mild conditions and in high yield (eq 1) [6]



(1)

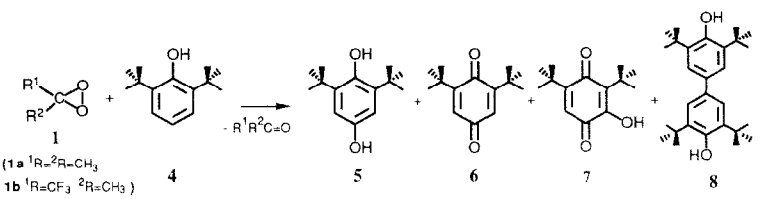
Thus, this dioxirane-mediated transformation neatly mimics oxidative cleavage at C^1-C^2 of catechol promoted by pyrocatechase enzymes [7] It is likely that cleavage of **2** by the powerful dioxirane **1b** proceeds through intermediate oxidation products, such as its semiquinone and/or 1,2-benzoquinone. In fact, the less powerful dimethyldioxirane (**1a**)[8] can carry out the oxidation of several phenols to the *o*-quinone stage [9]

Next, both dioxirane **1b** and **1a** in their isolated form - i e., in 1,1,1-trifluoropropanone (TFP) and acetone solution, respectively - were employed in the oxidation of 2,6-di-*tert*-butylphenol (**4**). This substrate, with both *ortho* positions blocked by bulky t-Bu groups, was expected to yield product mixtures by far less complex than those normally arising from the oxidation of simple, "unprotected" phenols [2,9] Indeed, we found that the reactions of the hindered phenol afforded quite manageable product mixtures (eq 2) [10]

Table 1 Oxidation of 2,6-Di-*tert*-butylphenol (**4**) by Methyl(trifluoromethyl)dioxirane (**1b**) and by Dimethyldioxirane (**1a**) [a]

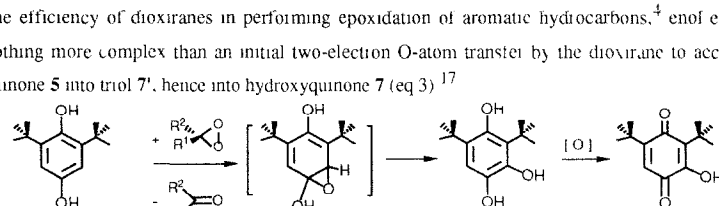
Dioxirane	R (D/S)[b]	T (°C)	Reactn time	Conv (%)[c]	Yield of Products (%)[c] Dimer (**8**)	Hydroquinone (**5**)	Quinone (**6**)	Hydroxyquinone (**7**)
 (**1b**)	1 2	0	7 min	20	– [d]	32	7	37
	3 0	0	3 min	75	– [d]	12	15	60
	4 0	0	1 min	> 96	– [d]	4	24	70
 (**1a**)	3 0	0	40 h	33 [e]	4	– [d]	56	35
	3 0	0	48 h	37	4	– [d]	57	34
	3 0	20	48 h	41	10	– [d]	47	38
	3 0	28	48 h	35	13	– [d]	48	34

[a] In CH_2Cl_2/TFP (oxidations with **1b**) or CH_2Cl_2/acetone (oxidations with **1a**) mixed solvent composition from 20:80 to 50:50, solvents were purged with inert gas prior to use and reactions routinely run under nitrogen (or argon) gas blanket (unless noted otherwise). [b] Ratio of dioxirane to substrate initial concentrations. [c] As determined (± 2%) by gc (SE 30 or OV 101 30 m × 0.25 μm i.d. capillary column) or gc/ms (Hewlett-Packard mod. 5970 mass selective detector and mod. 5890 gas chromatograph); yields are based on the amount of substrate consumed. [d] ≤ 1 %. [e] reaction run in a closed flask, no inert gas blanket.



(2)

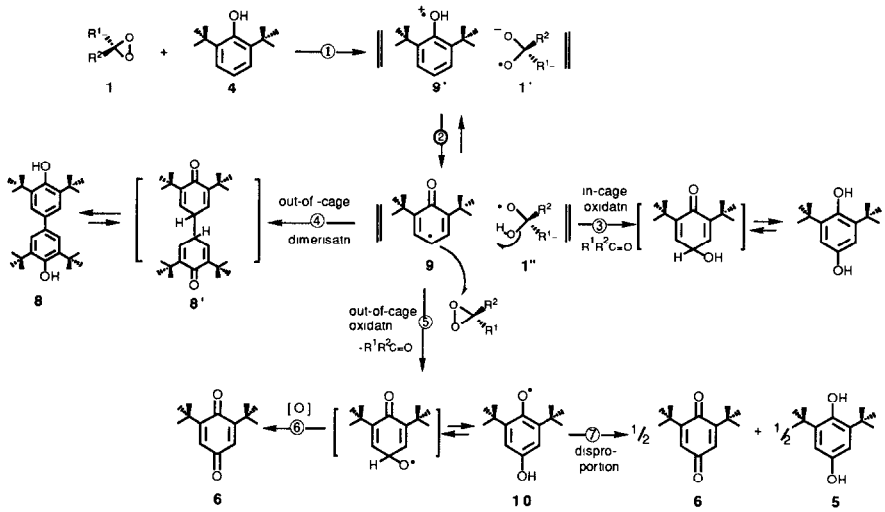
Representative data are collected in Table I. These show (entry 1 to 3) that **1b** is quite effective in performing oxyfunctionalization of the phenol within extremely short reaction times. Using an appropriate oxidant to substrate ratio, the oxidation can be driven to practically complete conversion of the phenol, yielding 3-hydroxy-1,4-benzoquinone (**7**)[11] as the major product. This transformation might provide access to important 3-hydroxyquinones.[12] At low substrate conversion (entry 1) the reaction yields a significant amount of 2,6-*tert*-butylhydroquinone (**5**),[13] a likely precursor of **7**. In fact, control experiments revealed that **5** is rapidly transformed into **7** (g.c. yield ~90%) on treatment with isolated dioxirane **1b**. In parallel, it was verified that 2,6-di-*tert*-butyl-1,4-*benzoquinone* (**6**)[14] is practically unreactive toward isolated dioxirane **1b** (as well as toward **1a**) under the given conditions. In view of the efficiency of dioxiranes in performing epoxidation of aromatic hydrocarbons,[4] enol ethers[15] and enolates,[16] one needs nothing more complex than an initial two-electron O-atom transfer by the dioxirane to account for the transformation of hydroquinone **5** into triol **7'**, hence into hydroxyquinone **7** (eq 3).[17]



(3)

However, results pertaining to the oxidation of the same substrate by dimethyldioxirane **1a** (fourth to seventh entries, Table I) suggest that a more complex oxidation mechanism applies. As expected,[3-5] the less powerful dioxirane **1a** brings about lower conversions of the substrate during much longer reaction times. However, a closer inspection of data in Table I reveals that, in dimethyldioxirane (**1a**) oxidations, the two 'dead alley' oxidation products found when **1b** is used (namely *p*-quinone **6** and its hydroxy derivative **7**) are accompanied by appreciable amounts of the tetra-t-butyl substituted 4,4'-dihydroxybiphenyl **8**.[18] Formation of the latter, a dimer of 2,6-di-*tert*-butylphenoxy radical (**9**),[18b] strongly suggests the incursion of a radical pathway. This might involve several steps and intermediates, for instance as in the simplified sequence sketched in Chart I.

Chart I



The mechanism above finds precedents in the phenolic oxidation effected by oxaziridines,[19] and by one-electron oxidants.[2]

According to this working hypothesis, the oxidation would be triggered by a preliminary one-electron transfer between the hindered phenol and the dioxirane, the resulting phenoxyl cation-radical (**9'**) should readily loose a proton,[2] yielding caged phenoxy radical **9** In-cage oxidation (step ③) would yield hydroquinone **5** However, the phenoxy radical diffusing out of the solvent cage would either dimerize to **8** (via **8'**, step ④) or perform radical attack at the O-O bond of the oxidant (step ⑤), perhaps involving protonated semiquinone **10** The latter might become further oxidized to quinone **6** (step ⑥), or disproportionate (step ⑦) to yield **6** and **5** (which would then proceed to **7**) Then, the actual product distribution would reflect competition among the various steps, and depend upon reaction conditions and oxidant structure For instance, methyl(trifluoromethyl)dioxirane (**1b**) is likely to be more effective than its dimethyl analogue in capturing cage-escaped phenoxy radicals before they dimerize

Concerning this, it is interesting that the oxidation of phenol **4** by dimethyldioxirane (**1a**) generated *in situ*[8c] from acetone and excess peroxymonosulfate $HOOSO_3^-$ yields proportions of quinone **6** over hydroxyquinone **7** in excess of 4 1 , i.e significantly larger than those observed with isolated **1a** (cf , Table I), also, less than 2% dimer is detected in this case It is possible that, with the *in situ* method, dilution and excess peroxide renders dimerization of phenoxy radical **9** unfavored with respect to its oxidation

On the other hand, that dioxiranes are capable of radical oxidation of phenols is reinforced by additional observations, for instance, we find that 2,4,6-tri-*tert*-butylphenol (**11**) (a hindered phenol presenting also the *para* position blocked) on treatment with dioxirane **1a** *in situ* gives 2,6-di-*tert*-butyl-1,4-benzoquinone (**6**) (yield ca 48%), although this reaction is rather slow (i e , ~12% conversion during 24 h) The same transformation was observed to occur much faster (30 min) using isolated dioxirane **1b** Of course, oxidative *para*-dealkylation of **11** is typical of one-electron oxygenations, as catalysed by Co^{II}, Mn^{III} complexes[20] and other transition-metal species.[2]

The formation of phenoxy radicals (**9**) via phenoxyl cation-radicals (**9'**) raises the question of the fate of bisoxy radical-anions **1'** not participating to the cage process (steps ② + ③, Chart I) Recent results seem to indicate that radical ions **1'** generated from dioxirane **1b** and suitable donors might yield TFP (the parent ketone) and superoxide ion $O_2^{-\bullet}$ by a bimolecular process.[21a] Therefore, further studies are warranted in order to unravel these and other important aspects of radical reactivity of dioxiranes.[21] Suffice it to say that, in the system at hand, generation of superoxide should be unimportant, in fact, had this oxidant been generated in any significant amount, one might have expected it to react with quinone **6** to yield the corresponding epoxide [22] This product was not detected

Acknowledgment. Partial support of this research by the Italian Research Council (CNR), in the frame of P.F. "Chimica Fine.II" is gratefully acknowledged. One of us (L. D'A.) wishes to thank Montefluos S.p.A. (Milan, Italy) for making available to her a Fellowship administerd by the "Accademia Nazionale dei Lincei" of Italy.

References and Notes

1. Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds;* Academic: New York, 1981; Chapter 8 and references cited therein.
2. Mihailovic, M. Lj.; Cekovic, Z., in *The Chemistry of Functional Groups, Hydroxyl Group*; Patai, S., Ed.; Wiley: New York, 1971; Chapter 10, pp 505-592 and references therein.
3. For reviews, see: (a) Curci, R. In *Advances in Oxygenated Processes;* Baumstark, A. L., Ed.; JAI: Greenwich, CT; Vol. 2, Chapter 1, 1990. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Murray, R. W. *Chem Rev.* **1989**, *89*, 1187.
4. Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1990**, *31*, 6097.
5. (a) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (c) R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, R. Curci, *Tetrahedron Lett.* **1990**, *31*, 3067.
6. (a) Addition of an aliquot of standardized[5] dioxirane solution in TFP to substrate **3** dissolved in acetone at -20 °C, and removal of solvent in vacuo yielded **Z,Z-muconic acid** (**3**): m.p. 79-80 °C. Treatment with excess CH_2N_2 in Et_2O at 0° C gave **dimethyl Z,Z-muconate** (**3'**) (yield 88%): m.p. 72 73 °C [lit.[6b]: m.p. 73 °C]. This gave a ^1H NMR ($CDCl_3$, 200 MHz) spectrum presenting a typical *AA'XX'* pattern in agreement with literature data;[6c] ^{13}C NMR ($CDCl_3$, 50 MHz) δ 51.49 (q, J = 147.1 Hz), 123.83 (d, J^1 = 165.6 Hz, J^2 = 2.84 Hz), and 137.9 (d, J^1 = 163.5 Hz, J^2 = 10.72 Hz); MS (EI, 70 eV) *m/z* (rel abund) 170 (2, M^+), 122 (2), 112 (7), 111 (100), 95 (5), 97 (25), 80 (5), 79 (12), 68 (8), 52 (13), 51 (17), 39 (5), 32 (9); IR (KBr) 1712 cm^{-1} (C=O). (b) Tsuji, J.; Takayanagi, H. *J. Am. Chem. Soc.* **1974**, *96*, 7349. (c) Elvidge, J. A.; Ralph, P. D. *J. Chem. Soc. (C)* **1966**, 387.
7. (a) Hamilton, G. A. in *Molecular Mechanisms of Oxygen Activation*; Hayaishi, O. Ed.; Academic, New York, 1974; Chapter 10 and references . (b) Hayaishi, O., Katagiri, M.; Rothberg, S. *J. Am. Chem. Soc.* **1955**, *77*, 5450.
8. (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699. (c) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.
9. Crandall, J. K.; Zucco, M.; Kirsch, R. S.; Coppert, D. M., adjacent article ; we are grateful to Professor Crandall for kindly disclosing to us his results prior to publication.
10. In a typical procedure, an appropriate aliquot (cf., Table I) of standardized dioxirane (**1b** or **1a**) solution (in TFP or acetone, respectively) is rapidly added to phenol **4** (2 mmol) in CH_2Cl_2 (6-8 mL), with stirring and temperature control (Table I). Keeping the mixture under a blanket of inert gas, the reaction is monitored by gc or gc/ms until suitable substrate conversion. Then, products are separated from residual substrate (if any) by column flash-chromatography (silica gel, n-pentane/Et_2O), and identified upon comparison of their spectral characteristics (^1H- and ^{13}C nmr, ir, ms) with those of commercially available or previously synthesized authentic samples. Equipment and instrumentation employed have been described in previous articles.[5]
11. (a) **3-Hydroxy-2,6-di-*tert*-butyl-1,4-benzoquinone** (**7**)[11b] was isolated (column chromatography) as a yellow oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.275 (s, 9 H), 1.360 (s, 9 H), 6.510 (s, 1 H), 7.252 (s, 1 H, disappears on exchange with D_2O); $\{^1H\}^{13}C$ NMR (CD_2Cl_2, 50 MHz) δ 29.145, 29.830, 35.177, 35.849, 125.00, 128.71, 148.76, 161.96, 184.31, 189.20 ; MS (EI, 70 eV) *m/z* (rel abund) 236 (54, M^+), 221 (72), 193 (53), 165 (55), 151 (22), 138 (27), 111 (26), 97 (67), 43 (46), 41 (100), 39 (50); FT IR 3380, 2970, 1669, 1603, 1391, 1196 cm^{-1}. (b) Que, L., Jr.; Kolanczyk, R. C.; White, L. S. *J. Am. Chem. Soc.* **1987**, *109* , 5373.
12. For example, see: Colson, K. L.; Jackman, L. M.; Jain, T.; Simolike, G.; Keeler, J. *Tetrahedron Lett.* **1985**, *26*, 4579 and references.
13. **2,6-Di-*tert*-butyl-hydroquinone** (**5**) gave : m.p. 108-109 °C [lit.[13b] 110-111 °C]; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.407 (s, 18 H), 4.736 (s, 2 H, disappears on exchange with D_2O), 6.673 (s, 2 H). ; $\{^1H\}^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 32.137 ,36.409, 113.72, 139.46, 149.61, 150.08. (b) Müller, E.; Ley, K. *Chem. Ber.* **1955**, *88*, 601.
14. Commercial (Aldrich) 2,6-di-*tert*-butyl-1,4-benzoquinone (**6**) was re-crystallised from EtOH : m.p. 66-67 °C.
15. For instance, see: (a)Troisi, L.; Cassidei, L.; Lopez, L.; Mello, R.; Curci, R. *Tetrahedron Lett.* **1989**, *30*, 257. (b) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249. (c) Adam, W.; Hadjiarapoglou, L.; Wang, X. *Tetrahedron Lett.* **1989**, *30*, 6497.
16. Guertin, K. R.; Chan, T.-H. *Tetrahedron Lett.* **1991**, *32*, 715.
17. For the analogous transformation of trimethylhydroquinone into 3-hydroxy-2,5,6-trimethyl-1,4-benzoquinone using H_2O_2/heteropolyacid, see: Shimizu, M.; Orita, H.; Hayakawa, T.; Takehira, K. *Tetrahedron Lett.* **1989**, *30*, 471
18. (a) **3,3',5,5'-Tetra-*tert*-butyl-4,4'-dihydroxybiphenyl** (**8**)[18b,c] was obtained by following a literature procedure:[18d] m.p. 185 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.482 (s, 36 H), 5.18 (s, 2 H, disappears on exchange with D_2O), 7.291 (s, 4 H), $\{^1H\}^{13}C$ NMR ($CDCl_3$, 50 MHz) δ 30.325, 34.417, 124.08, 133.89, 135.89, 152.78; MS (EI, 70 eV) *m/z* (rel abund) 410 (70, M^+), 395 (14), 205 (3), 190 (9), 176 (6), 162 (11), 146 (5), 57 (100), 41 (42); IR (KBr) 3631, 3454, 3005, 2970, 2873, 1424, 1389, 1227, 1140, 1104, 871 cm^{-1}. (b) Dewar, M.; Nakaya, T. *J. Am. Chem. Soc.* **1968**, *90*, 7134. (c) Omura, K. *J. Org. Chem.* **1991**, *56*, 921. (d) Karasch, M. S.; Joshi, B. S. *J. Org. Chem.* **1957**, *22*, 1439.
19. Wagner, W. R.; Spero, D. M.; Rastetter, W. H. *J. Am. Chem. Soc.* **1984**, *106*, 1476.
20. Frostin-Rio, M.; Pujol, D.; Bied-Charreton, C.; Perrée-Fauvet, M.; Gaudemer, A. *J. Chem. Soc., Perkin Trans I* **1984**, 1971 and references quoted therein..
21. (a) Adam, W.; Curci, R.; Mello, R.; Gonzales-Nuñes, M. E. *J. Am. Chem. Soc.*, submitted; (b) Adam, W.; Asensio, G.; Curci, R.; Mello, R.; Gonzales-Nuñes, M. E., to be published.
22. (a) Saito, I.; Otsuki, T.; Matsuura, T. *Tetrahedron Lett.* **1979**, *19*, 1693. (b) Frimer, A. A. in *The Chemistry of Functional Groups, Peroxides*; Patai, S., Ed.; Wiley: New York, 1983; Chapter 14, pp 429-461 and references therein.

(Received in UK 27 June 1991)