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REGIOSPECIFIC ORTHO OXYFUNCTIONALIZATION OF SUBSTITUTED BENZENES WITH SINGLET OXYGEN[1]

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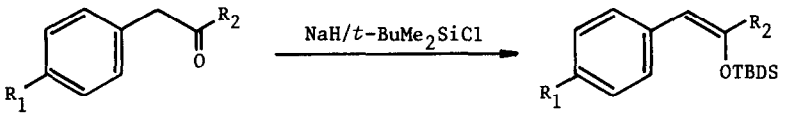
Summary: A new procedure for regiospecific ortho oxyfunctionalization of phenylacetones, phenylacetic acid esters and phenylacetaldehyde has been developed. The method involves tert-butyldimethylsilylation, singlet oxygenation and successive reduction.

Direct hydroxylations of alkylbenzenes are usually accomplished with hydrogen peroxide or organic peroxides as oxidizing agents in the presence of Lewis acids or metal-ions; some of the useful reagents include *t*-BuOOH-$AlCl_3$,[2] H_2O_2-HF-BF_3,[3] and Fe^{+2}-$Na_2S_2O_8$.[4] The major difficulties encountered are the easy of further oxidation of the initially formed products and the lack of high regioselectivity for hydroxylation. To our knowledge, regiospecific ortho monohydroxylation of alkylbenzenes has not been achieved to date. We wish to disclose a new method for regiospecific ortho oxyfunctionalization of substituted benzenes such as phenylacetones, phenylacetaldehyde and phenylacetic acid esters by converting them to silyl enol ethers followed by singlet oxygenation and successive reduction as outlined by Eq. 1.

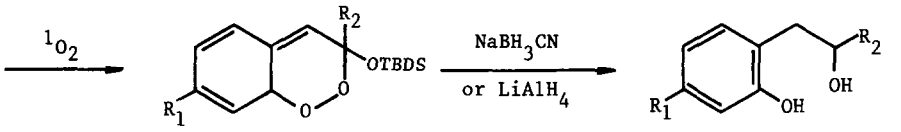
tert-Butyldimethylsilyl (TBDS) enol ethers 2a,b[5] are easily accessible with high regioselectivity from phenylacetones 1a,b by treatment with NaH-*t*-$BuMe_2SiCl$ (room temp, THF) followed by silica gel chromatography. Photooxygenation[6] of 2a (0.1 M) in $CFCl_3$ in the presence of tetraphenylporphine (TPP) at -70 °C[7] afforded the monoendoperoxide 3a[5] in almost quantitative yield.[8] The solution was slowly added to methanolic $NaBH_3CN$ (excess) at 0 °C followed by aqueous workup and subsequent purification with preparative TLC (silica gel, $CHCl_3$-ether 4 : 1) gave 4a[5] (66%). Similarly, singlet oxygenation of 2b under carefully controlled conditions[9] followed by successive $LiAlH_4$[10] reduction in THF provided resorcinol monomethyl ether derivative 4b[5] (27%).

This methodology was successfully applied to the ortho oxyfunctionalization of methyl



1 a, R_1 = H, R_2 = Me
b, R_1 = OMe, R_2 = Me
c, R_1 = H, R_2 = OMe
d, R_1 = R_2 = H

2 a, (94%)
b, (97%)
d, (27%) (Eq. 1)



3 4

phenylacetate (1c) and phenylacetaldehyde (1d). In the case of 1c, the reaction with LDA-*t*-$BuMe_2SiCl$ (HMPA-THF) gave the unstable silyl ketene acetal 2c[11] (80%). Photooxygenation (TPP, CCl_4, 0 °C) of the crude product without purification provided monoendoperoxide 3c[5] in 70% yield as estimated from the NMR spectrum. The photooxygenated mixture was immediately reduced with $NaBH_3CN$ as described above without isolating the endoperoxide 3c. Conventional aqueous workup followed by preparative TLC (silica gel, $CHCl_3$-ether 1 : 1) afforded *o*-hydroxyphenylacetic acid[5] (5) in 34% overall yield starting from 2c. In a similar way *o*-hydroxyphenethyl alcohol[5] (4d) was prepared from 2d in 52% overall yield (Table 1).

It is also worthwhile to point out that thermolysis of monoendoperoxides can give ortho-hydroxylated products but less efficiently.[8a, f] For example, refluxing of 3b in hexane afforded 6b[12] (38%) together with 7b (27%) and 8b (14%) probably via the biradical 9 as depicted in Scheme 1.

In conclusion, the reaction sequence shown in Eq. 1 provides a useful method for the preparation of functionalized *o*-alkylphenols from phenylacetones, phenylacetic acid esters and phenylacetaldehyde without complications from further oxidation, although the overall yields are modest.

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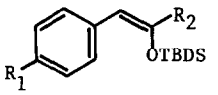
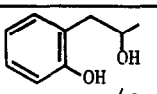
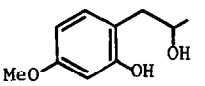
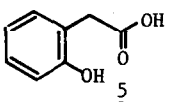
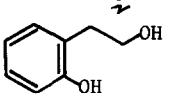
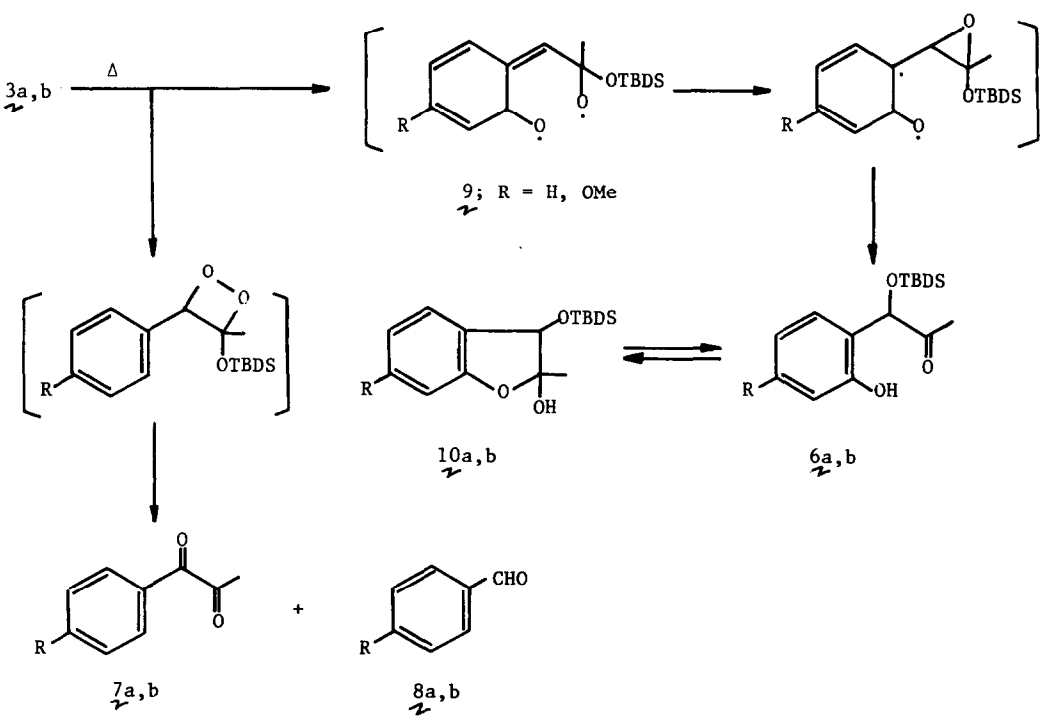
Table 1. Conversion of silyl enol ethers (2) to *o*-alkylphenols

	i) $^1O_2$ ii) reduction	Product (%)[a]
2a	 4a	(66)
2b	 4b	(27)
2c	 5	(34)
2d	 4d	(52)

[a] Yields are for isolated pure products.

Scheme 1



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2. S. Hashimoto and W. Koike, Bull. Chem. Soc. Jp., 43, 293 (1970).
3. G. A. Olah, A. P. Fung and T. Keumi, J. Org. Chem., 46, 4305 (1981), and references therein.
4. C. Walling and D. M. Camaioni, J. Am. Chem. Soc., 97, 1603 (1975).
5. Selected spectral data. (Z)-2a; ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.90 (s, 9 H), 1.93 (bs, 3 H), 5.31 (bs, 1 H), 6.93-7.53 (m, 5 H). (Z)-2b; ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 6 H), 0.88 (s, 9 H), 1.88 (bs, 3 H), 3.68 (s, 3 H), 5.23 (bs, 1 H), 6.68 (d, 2 H, J = 9 Hz), 7.31 (d, 2 H, J = 9 Hz). (Z)-2d; ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6 H), 0.99 (s, 9 H), 5.28 (d, 1 H, J = 6.8 Hz), 6.40 (d, 1 H, J = 6.8 Hz), 7.03-7.43 (m, 3 H), 7.52-7.75 (m, 2 H). 3a; ^{1}H NMR (C_6D_6) δ 0.07 (s, 6 H), 0.81 (s, 9 H), 1.55 (s, 3 H), 5.05-5.75 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ -2.6, -3.0, 17.6, 25.4, 28.1, 78.4, 101.5, 123.8, 124.6, 125.2, 125.4, 127.1, 135.3; UV (CH_3CN) 315 nm. 3b; ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 3 H), 0.12 (s, 3 H), 0.68 (s, 9 H), 1.60 (s, 3 H), 3.55 (s, 3 H), 4.60 (m, 1 H), 5.55 (dd, 1 H, J = 4, 0.6 Hz), 5.66-5.86 (m, 2 H), 6.16 (d, 1 H, J = 10 Hz). 3c; ^{1}H NMR (CCl_4) δ 0.18 (s, 3 H), 0.19 (s, 3 H), 0.90 (s, 9 H), 3.29 (s, 3 H), 5.31-6.12 (m, 6 H). 3d; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 6 H), 1.02 (s, 9 H), 5.47-6.35 (m, 7 H). 4b; ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6 Hz), 2.63 (d, 1 H, J = 2 Hz), 2.70 (bs, 1 H), 3.83 (s, 3 H), 3.85-4.30 (m, 1 H), 6.33 (dd, 1 H, J = 8, 2.6 Hz), 6.43 (bs, 1 H), 6.87 (d, 1 H, J = 8 Hz). 4a, 4d and 5 were identified by comparison with authentic samples.
6. Irradiation was done externally with tungsten-bromine lamp through 5% *aq* $K_2Cr_2O_7$ filter solution.
7. The photooxygenation at 0 °C gave a mixture of *cis*- and *trans*-diendoperoxides in 33 and 27%, respectively, whose structures were fully confirmed by spectral data.
8. 1,4-Cycloaddition of singlet oxygen to β-alkoxystyrene derivatives leading to monoendoperoxides, see (a) M. Matsumoto and K. Kuroda, Tetrahedron Lett., 1607 (1979); (b) M. Matsumoto, K. Kuroda and Y. Suzuki, *ibid.*, 3253 (1981); (c) D. Ledal and C. S. Foote, *ibid.*, 3227 (1978), (d) W. Adam and J. J. del Firro, J. Org. Chem., 43. 1159 (1978); (e) W. Adam and K. Takayama, *ibid.*, 45, 447 (1980); (f) H. Kotsuki, I. Saito and T. Matsuura, Tetrahedron Lett., 469 (1981).
9. The photooxygenation gave a mixture of mono- and diendoperoxides even at -70 °C. When the reaction was stopped at less than 90% conversion, monoendoperoxide 3b was obtained in improved yield.
10. The use of $NaBH_3CN$ resulted in a complex mixture of products. Addition of the endoperoxide solution to a cold solution of $LiAlH_4$ in THF is crucial.
11. The extremely hydrolytically sensitive product could not be purified without decomposition. ^{1}H-NMR (CCl_4) δ 0.22 (s, 6 H), 0.94 (s, 9 H), 3.58 (s, 3 H), 4.48 (s, 1 H), 6.78-7.63 (m, 5 H).
12. 6 exists in an equilibrated mixture with 10 in $CDCl_3$. 6b; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 3 H), 0.18 (s, 3 H), 0.95 (s, 9 H), 2.01 (s, 3 H), 3.80 (s, 3 H), 5.16 (s, 1 H), 6.49 (d, 1 H, J = 2 Hz), 6.50 (dd, 1 H, J = 9, 2 Hz), 7.15 (d, 1 H, J = 9 Hz), 7.80 (bs, 1 H, OH).

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