Facile Autoxidation of 2-(4-Hydroxy-phenyl)-3,3-dimethylmethylenecyclopropane. The Radical Stabilizing Ability of the Phenoxide Group
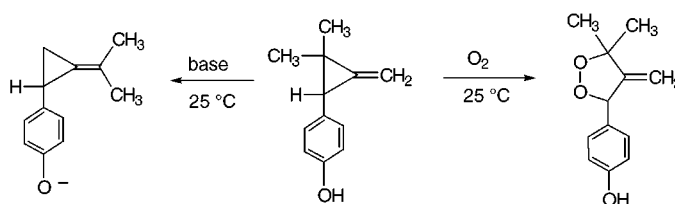
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ABSTRACT

2-(4-Hydroxyphenyl)-3,3-dimethylmethylenecyclopropane undergoes rapid reaction with O_2 at room temperature to give a dioxolane. A chain mechanism involving ring opening of a phenoxy radical is proposed. Conversion of the title compound to the phenoxide results in a remarkably accelerated methylenecyclopropane rearrangement. Computational studies suggest that the intermediate biradical is greatly stabilized by the phenoxide substituent.
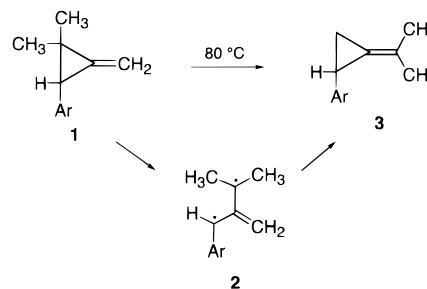
The quantitative ability of substituents to stabilize benzylic radicals has been a topic of interest. A number of free radical stabilization scales have been developed over the years, and these have been recently discussed.[1] A scale developed in our laboratory is based on the thermal rearrangement of substituted methylenecyclopropanes **1** to **3**, which proceeds readily at 80 °C through a biradical (Scheme 1).[2] Absent from our scale is the $\sigma^\bullet$ value for the *p*-OH group and the corresponding deprotonated form. The first report on these groups occurred when Adam used his EPR-based method to evaluate the radical stabilizing effect of a number of substituents, including the *p*-OH and *p*-O⁻ substituents.[3] We now wish to report on the synthesis of the phenol derivative **1** (*p*-OH) as well as the thermal rearrangement of the phenoxide **1** (*p*-O⁻).

Scheme 1

Our initial attempt to prepare the phenol derivative **1** (*p*-OH) involved alkaline hydrogen peroxide oxidation of the boronic acid **4** which we had available from a previous study.[2] However, this led to formation of the peroxide **5** as the major product isolated after an aqueous workup. We next prepared the *tert*-butyldimethylsilyl-protected methylenecy-clopropane **6** by carbenoid addition to 1,1-dimethylallene.[5] However, attempted desilylation of **6** with tetrabutylammo-

(1) Creary, X.; Engel, P. S.; Kavaluskas, N.; Pan, L.; Wolf, A. *J. Org. Chem.* **1999**, *64*, 5634−5643.

(2) Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1987**, *52*, 3254−3263.

(3) Adam, W.; Harrer, H. M.; Kita, F.; Korth, H.-G.; Nau, W. M. *J. Org. Chem.* **1997**, *62*, 1419−1426.

nium fluoride gave, after an aqueous workup, significant amounts of the peroxide **5**, along with the desired **1** (*p*-OH). Careful exclusion of air during the workup is necessary in order to isolate **1** (*p*-OH) (Scheme 2). Further experiments

Scheme 2
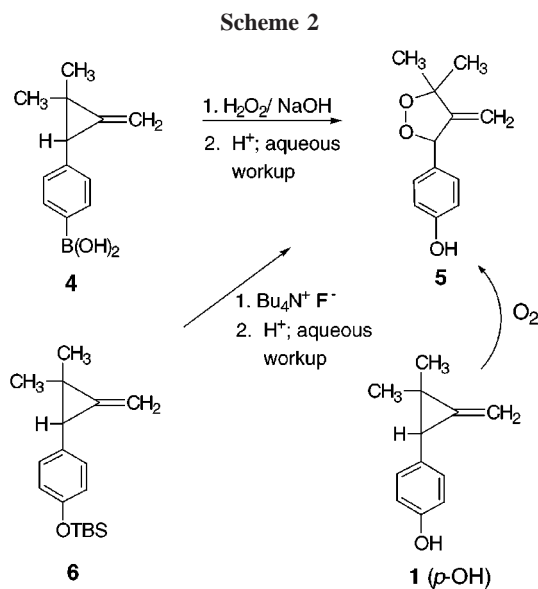
showed that the phenol **1** (*p*-OH) readily absorbs oxygen from air at room temperature, giving the peroxide **5**. This reaction can be easily monitored by NMR in CDCl$_3$ and is complete within an hour when the reaction is carried out under an atmosphere of oxygen.

We felt that this remarkably facile autoxidation warranted further investigation.[6,7] The following mechanism is proposed. The reaction is initiated by hydrogen atom abstraction of the phenolic hydrogen. Ring opening of the strained cyclopropane bond of **7** gives the allylic radical/quinone methide **8**. Capture of molecular oxygen at the center of highest spin density (the tertiary carbon) leads to **9**, which can cyclize in a 5-exo fashion to give the radical **10**. Hydrogen atom abstraction by **10** from the starting material **1** (*p*-OH) generates the observed product and propagates the cycle by regenerating **7** (Scheme 3).

To support this mechanism, methylenecyclopropane **6** was thermally rearranged to isopropylidenecyclopropane **11** and then desilylated. The resultant phenolic product **12** was also found to react rapidly with oxygen at room temperature. The product formed was the identical peroxide **5** that was produced when **1** (*p*-OH) was oxidized (Scheme 4). The proposed common intermediate in the oxidation of both **1** (*p*-OH) and **12** is the radical **8**. This study supports our

(4) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582–584.

(5) Creary, X. *J. Org. Chem.* **1978**, *43*, 1777–1783.

(6) Formation of a dioxolane by reaction of singlet oxygen with tetranisylcyclopropane has been reported. See: Akasaka, T.; Fukuoka, K.; Ando, W. *Tetrahedron Lett.* **1991**, 32, 7695–76.

(7) Photosensitized addition of O$_2$ to cyclopropanes to form dioxolanes has also been reported. See: Schaap, A. P.; Siddiqui, S.; Prasad, G.; Palomino, E.; Lopwz, L. *J. Photochem.* **1984**, 25, 167–181.
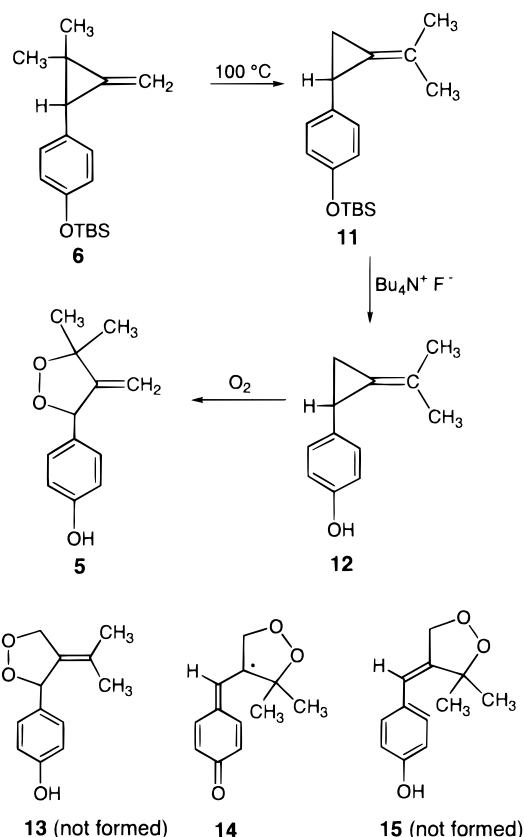
Scheme 3
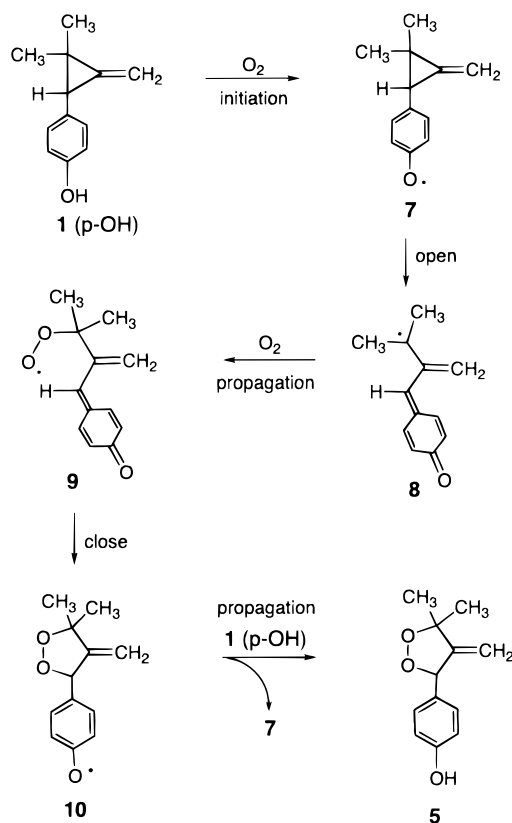
suggestion that this intermediate captures oxygen at the center of highest spin density, i.e., the tertiary center. No product **13** that would have resulted from reaction of oxygen at the primary end of the allylic radical **8** is formed. The intermediate peroxy radical **9** has two potential cyclization modes. The lack of formation of product **15** suggests that the 5-exo cyclization process in **9** to form **10** is significantly faster that the 5-endo cyclization that would have led to **14** (and ultimately **15**).
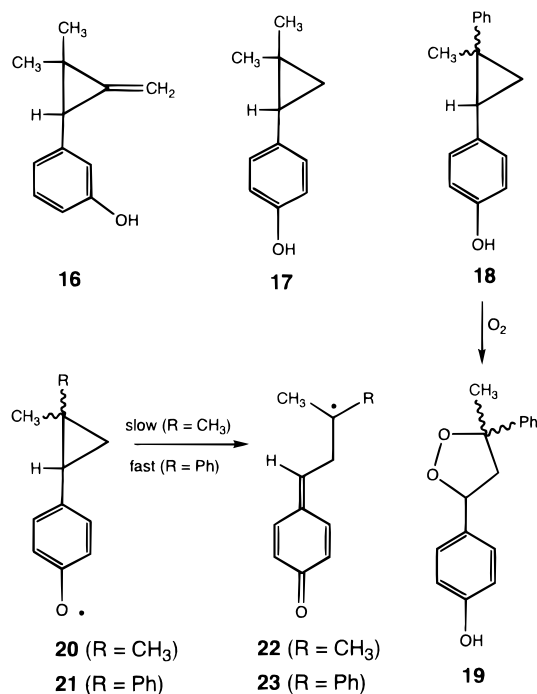
Further insight into this facile autoxidation of **1** (*p*-OH) can be gained by examining the substrates **16**–**18** (Scheme 5). Neither **16** or **17** reacts readily with oxygen at room temperature or even at 80 °C. In the case of the *meta* analogue **16**, this lack of reactivity is attributed to the relatively slow fragmentation of the cyclopropane bond of the *m*-phenoxy radical due to its inability to form a quinone methide structure. In the case of **17**, the fragmentation of the cyclopropane bond of phenoxy radical **20** is relatively slow due to smaller ring strain in **20** (relative to **7**) as well as the decreased spin delocalization in radical **22** relative to allylic radical **8**. Hence, radical chain processes are not readily established for **16** and **17**. By way of contrast, phenol **18** is readily oxidized by molecular oxygen at room temperature to peroxide **19**. This is attributed to facile cyclopropane bond cleavage in phenoxy radical **21** due to the tertiary benzylic nature of radical **23**. Hence a radical chain is readily established.

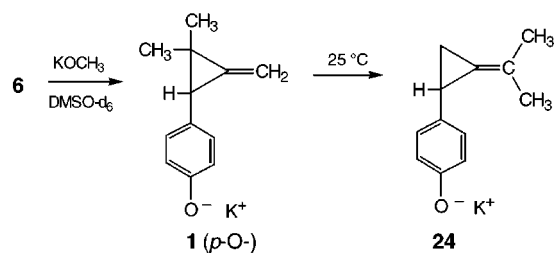Attention was next turned to the thermal rearrangement of phenoxide **1** (*p*-O⁻). This substrate was generated by

Scheme 4

100 °C

6 → **11**

Bu$_4$N$^+$ F$^-$

O$_2$

5 ← **12**

13 (not formed)   **14**   **15** (not formed)

Scheme 5

16   **17**   **18**

O$_2$

slow (R = CH$_3$)
fast (R = Ph)

20 (R = CH$_3$)   **22** (R = CH$_3$)   **19**
21 (R = Ph)   **23** (R = Ph)

reaction of silyl-protected derivative **6** with KOCH$_3$ in DMSO-d_6. This procedure bypassed the need to isolate the

Scheme 6

6   KOCH$_3$ / DMSO-d_6 25 °C

1 (*p*-O-)   **24**

air-sensitive phenol **1** (*p*-OH). The thermal rearrangement of anion **1** (*p*-O$^-$) to isopropylidenecyclopropane **24** occurred readily at room temperature (Scheme 6). By way of contrast, rearrangement of protected material **6** or the parent substrate **1** (Ar = C$_6$H$_5$) required 80 °C for convenient rates. Relative rate data are shown in Figure 1. The rate enhancement of **1**

H   OTBS   OH   O$^-$ N$^+$–O$^-$ O$^-$
1.0   1.9   2.7   1.3   75   2500
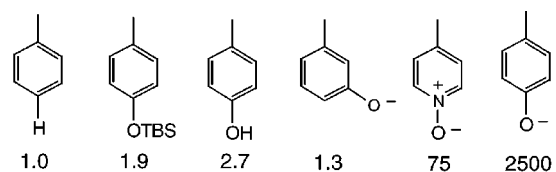
Figure 1. Effect of aryl groups on the relative rearrangement rates of **1** in DMSO-d_6.

(*p*-O$^-$) relative to the unsubstituted (*p*-H) derivative is a factor of 2500 at 25 °C. This is, by far, the largest rate enhancement that we have observed in the methylenecyclopropane rearrangement. The previous record holder was the 4-pyridyl-*N*-oxide substituted methylenecyclopropane, where the rate enhancement was a factor of 75.[8] In this case the intermediate biradical was proposed to derive significant stabilization from spin delocalization involving nitroxyl radical forms.

The facile rearrangement of **1** (*p*-O$^-$) is attributed to significant stabilization in biradical intermediate **25**. Forms such as **25a** and **25b** are recognizable as ketyl radicals, which possess unusual stability.[9]

25   **25a**   **25b**
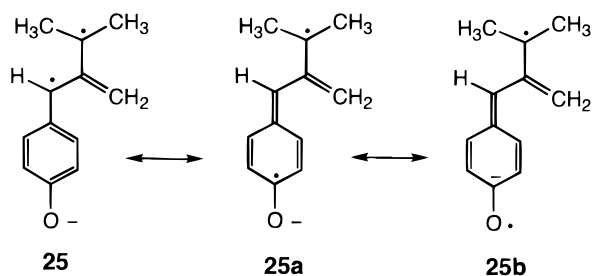
Computational studies have also been carried out in order to gain further insight into the apparently large stabilization

(8) Creary, X.; Mehrsheikh-Mohammadi, M. E.; McDonald, S. *J. Org. Chem.* **1989**, *54*, 2904–2910.

of benzylic type radical **25** by the *p*-O⁻ substituent. Density functional calculations[10] (B3LYP/6-31+G*) have been carried out on simple benzylic radical **26** as well as compounds **27**−**29**. The isodesmic reaction energy is 10.0 kcal/mol (9.8
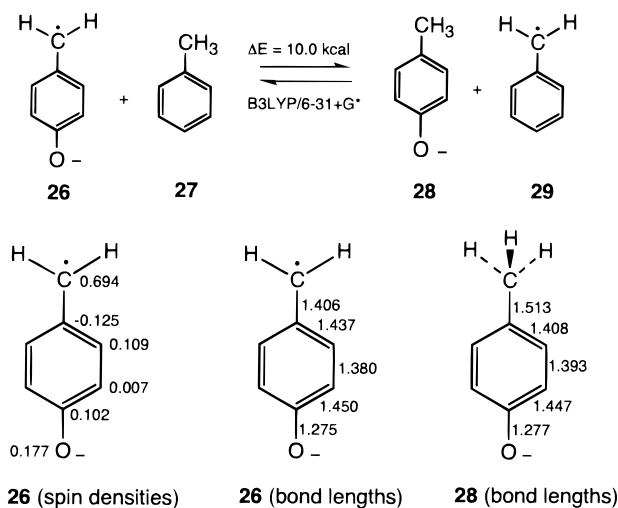
kcal/mol at B3LYP/6-31G*) and is indicative of a large radical stabilization by the *p*-O⁻ substituent. By way of contrast, the analogous isodesmic reaction energy of the

p-methyl benzyl radical with toluene is only 0.4 kcal/mol at the B3LYP/6-31+G* level and the reaction energy of the highly stabilized 4-pyridyl-*N*-oxide radical [$^{\bullet}$CH$_2$−C$_5$H$_4$NO] with toluene is 5.5 kcal/mol. Calculated spin densities also support the ketyl nature of radical **26**, as reflected by a large amount of positive spin density on the oxygen atom of **26**. Radical anion **26** is isoelectronic with the semiquinone radical anion, [$^{\bullet}$O−C$_6$H$_4$O $^-$]. However, the isodesmic reaction of the semiquinone radical anion with toluene gives a calculated reaction energy of 40.1 kcal/mol. This suggests that **26** (which is 10 kcal/mol more stable than the benzyl radical) is substantially less stable than the semiquinone radical anion. The stability order is therefore [$^{\bullet}$O−C$_6$H$_4$O $^-$] > [$^{\bullet}$CH$_2$−C$_6$H$_4$O $^-$] > [$^{\bullet}$CH$_2$−C$_6$H$_5$].

Our findings are in contrast to those of Adam,[3] who reported no unusual radical stabilization by the phenoxide group. We are uncertain of the reason for this large discrepancy, but both our experimental and computational studies indicate that the *p*-O⁻ substituent is the best radical stabilizer examined to date.

In summary, certain phenols substituted in the *p*-position with cyclopropyl groups undergo room-temperature oxidation with molecular oxygen to give dioxolanes. The reaction is believed to involve fragmentation of the strained cyclopropane bond of the intermediate phenoxy radical. In a related study, the anionic phenoxy substituent provides an enormous rate enhancement in the methylenecyclopropane rearrangement and this has been attributed to large stabilization of the radical-like transition state.

(9) For a discussion, see: Hirota, N. In *Radical Ions*; Kaiser, E. T., Kevan, L., Eds.; Interscience: New York, 1968; pp 35−85.

(10) Frisch, M, J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision B.3, Gaussian, Inc., Pittsburgh, PA, 1995.