Electrophilic Aromatic Alkylation by Hydroperoxides. Competition between Ionic and Radical Mechanisms with Phenols

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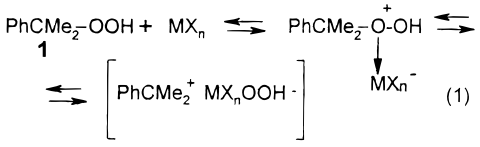
Tertiary hydroperoxides have been utilized for the electrophilic alkylation of activated aromatic substrates, particularly phenols and phenol ethers. Cumyl (**1**) and *tert*-butyl (**2**) hydroperoxides have shown a greatly different behavior as concerns the catalysis and the regioselectivity. The best catalyst for **1** is $TiCl_4$, which is completely inactive with **2**. With the latter an effective catalyst is $FeCl_3$, which, however, can give rise to a combination of electrophilic and radical reactions with alkyl phenols. 2,2′-Dihydroxy-3,3′-di-*tert*-butyl-5,5′-dimethyldiphenyl is obtained in high yields from *p*-cresol.

The acid-catalyzed decomposition of cumyl hydroperoxide **1** is the basis of the industrial production of phenol and acetone[1] (Scheme 1) A similar behavior characterizes other hydroperoxides, such as *t*-BuOOH (**2**), which gives acetone and methanol.

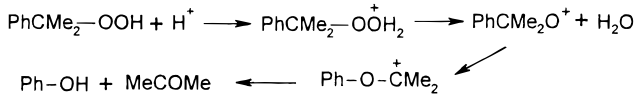
These results indicate that the protonated oxygen is the one directly bonded to hydrogen. The protonated oxygen, R-O-*O*-H, is therefore harder than the oxygen atom bonded to the carbon, R-*O*-O-H. Thus we have investigated the behavior of Lewis acids less hard than the proton, to coordinate the oxygen atom bonded to the carbon, in agreement to the HSAB (hard and soft acids and bases) principle;[2] this would allow the use of tertiary hydroperoxides as sources of carbonium ions useful for electrophilic reactions (eq 1).



(1)

The Friedel−Crafts aromatic alkylation is one of the most important electrophilic aromatic substitutions;[3] alkenes, alkyl halides, and alcohols are the most common sources of the electrophilic species. The development of new catalytic systems is of recent interest.[4,5] The use of hydroperoxides as sources of the electrophilic species was potentially interesting in view of the possibility of obtaining the hydroperoxides by autoxidation of alkanes, such as isobutane and cumene.[6]

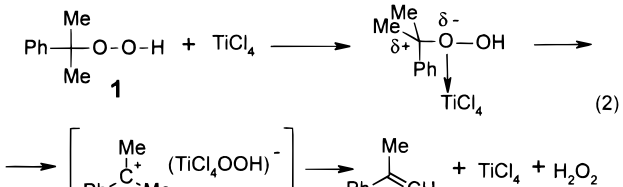
Scheme 1

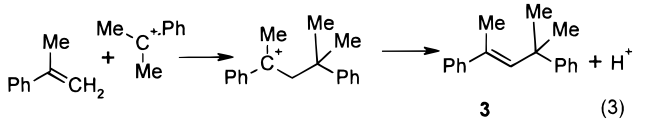


Results and Discussion

We have utilized the commercial cumyl, **1**, and *tert*-butyl, **2**, hydroperoxides and mainly $TiCl_4$ and $FeCl_3$ as Lewis acids. Other Lewis acids, such as $AlCl_3$ and $SnCl_4$, gave much worse results. Phenols and the corresponding ethers were mainly investigated, but also other electron-rich aromatic substrates were tested.

The behavior of **1** in AcOH and CCl_4 solutions was studied in the presence of $TiCl_4$ and $FeCl_3$. In refluxing CCl_4 in the absence of catalyst **1** was unchanged after 2 h. Under the same conditions in the presence of $TiCl_4$ the only substantial reaction product was 2-phenyl-4-methyl-4-phenyl-2-(*Z*)-pentene, **3**, with small amounts of α-methylstyrene. Clearly **3** is formed from the cumyl carbocation through α-methylstyrene (eqs 2 and 3), suggesting a coordination of $TiCl_4$ with the carbon-bonded oxygen atom of the hydroperoxide.





3 was still the main reaction product with $FeCl_3$ as catalyst, but a significant amount of *p*-cumylphenol, **4**, was also formed. This means that $FeCl_3$ mainly coordinates the oxygen atom of the hydroperoxide bonded to the carbon, leading to **3**, as described by eqs 2 and 3, but

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(1) Van Stevenik, A. W.; Kosymon, E. C. *Recl. Trav. Chim.* **1960**, *79*, 413.
(2) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533; *Science* **1966**, *45*, 581.
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(5) Fu, X.; He, M.; Lei, Q.; Luo, B. *Synth. Commun.* **1991**, *21*, 1273.
(6) Walling, C. In *Active Oxygen in Chemistry, SEARCH series, vol.2*; Foote, C. S. Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Blackie Academic & Professional: London, 1995; p 24.

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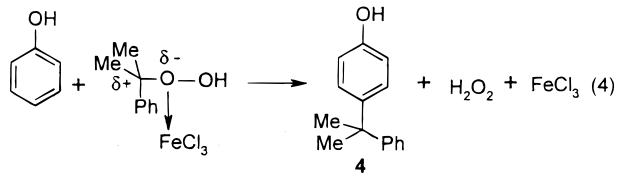
Table 1. Reaction of 1 mmol of 1 with Phenol at Room Temperature

phenol (mmol)	$TiCl_4$ (mmol)	yield (%)[a] 3	4
1	1	36	28
2	1	21	47
2	0.3	16	32
3	1	13	56
5	1	traces	68

[a] Yields based on **1**.

also, to a minor extent, the oxygen atom bonded to the hydrogen, leading, by a mechanism similar to that of Scheme 1, to phenol, which is then alkylated to **4** (eq 4) in competition with the alkylation of α-methylstyrene (eq 3).



In refluxing AcOH, in the absence of catalyst, phenol was substantially the only reaction product (the mechanism of Scheme 1 is operating). Under the same conditions in the presence of $TiCl_4$ or $FeCl_3$ phenol was still the prevailing reaction product, but **3** and **4** were also formed in significant amounts, suggesting that both the mechanisms of Scheme 1 and eqs 2, 3, and 4 were operating.

All these results suggested that in CCl_4 solution, under $TiCl_4$ catalysis, **1** could be utilized for the alkylation of phenols and likely of other electron-rich aromatic substrates as well.

Actually we observed that the decomposition of **1** in CCl_4 solution by $TiCl_4$ in the presence of phenol at room temperature gave **3** and **4**. The ratio between **3** and **4** is strictly related to the ratio between phenol and **1**: an excess of phenol minimizes the formation of **3**, leading to the highest yield of **4** with only traces of **3** (Table 1). The substitution is completely selective in the *para* position of phenol; polar and steric effects appear to be responsible for this selectivity, as will be discussed later on.

If we consider that **1** can be obtained by autoxidation of cumene[6] (eq 5) the interest of this aromatic substitu-

$$PhCHMe_2 + O_2 \rightarrow PhCMe_2OOH \qquad (5)$$

tion is described by the overall eq 6, which is a combination of eqs 4 and 5. The results with a variety of electron-

$$PhOH + PhCHMe_2 + O_2 \rightarrow p\text{-}PhCMe_2C_6H_4OH \qquad (6)$$

rich aromatic substrates are reported in Table 2.

Good results were obtained with α-naphthol, while under the same conditions *β*-naphthol provided only traces of substitution products, which emphasizes again the importance of the steric effect. The diphenol isomers gave poor results: catechol and veratrole gave very low yields, probably because the catalyst is chelated and deactivated by the two *ortho* oxygen atoms, while guaiacol gave moderate yields. The steric effect inhibits the substitution of hydroquinone, while moderate yields were obtained with resorcinol, in which the marked polar effect of both hydroxyl groups balances their steric effect. Better results were obtained with *o*-cresol than with *p*-cresol, always for steric reasons. An attempt of reaction with pyrrole led to low substitution yields.

Table 2. Reaction of 1 mmol of 1 with Aromatic Substrates and $TiCl_4$ in CCl_4 Solution

aromatic substrate (mmol)	*T* (°C)	reaction products (yield %)[a]
o-cresol (4)	20	2-methyl-4-cumylphenol (51)
p-cresol	20	2-cumyl-4-methylphenol (27)
α-naphthol (3)	20	4-cumyl-α-naphthol (81)
β-naphthol	20	1-cumyl-*β*-naphthol (5)
anisole[b]	80	4-cumylanisole (65)
guaiacol (3)	20	2-methoxy-4-cumylphenol (33)
resorcinol (3)	80	4-cumylresorcinol (39)
pyrrole (5)	20	3-cumylpyrrole (26)

[a] Yields based on **1**. [b]Anisole as solvent.

Table 3. Reaction of 1 mmol of *t*-BuOOH with Aromatic Substrates and $FeCl_3$ Catalysis

aromatic substrate (mmol)	$FeCl_3$ (mmol)	*T* (°C)	*tert*-butylation (yield)[a]	
phenol (4)	0.5	80	*ortho* (27)	*para* (35)
phenol (4)	0.5	20	*ortho* (6)	*para* (8)
phenol (4)	2	80	*ortho* (2)	*para* (56)
phenol (4)	2	20	*ortho* (−)	*para* (66)
anisole (3)	0.5	80	*ortho* (11)	*para* (35)
anisole (3)	2	80	*ortho* (2)	*para* (43)
anisole (3)	2	20	*ortho* (−)	*para* (65)
p-cresol (4)	0.5	80	*ortho* (67)	
2-*t*-Bu-4-Me-phenol[b] (2)	0.5	80		
benzene (3)	2	80	25	
benzene (10)	2	80	57	
toluene (10)	2	80	*ortho* (18)	*para* (46)

[a] Yields based on *t*-BuOOH. [b]**5** was obtained in 96% yield.

Lower yields of phenol substitution were obtained by using $FeCl_3$ as catalyst, while benzene, toluene, biphenyl, and naphthalene did not react with either $TiCl_4$ or $FeCl_3$ catalysts.

The behavior of *t*-BuOOH, **2**, was greatly different from that of **1** in that $TiCl_4$ is completely ineffective as alkylation catalyst, while $FeCl_3$ is effective also with nonactivated aromatic substrates, such as benzene and toluene. The results are summarized in Table 3. $AlCl_3$ as catalyst is completely ineffective, while $SnCl_4$ gave very low alkylation yields.

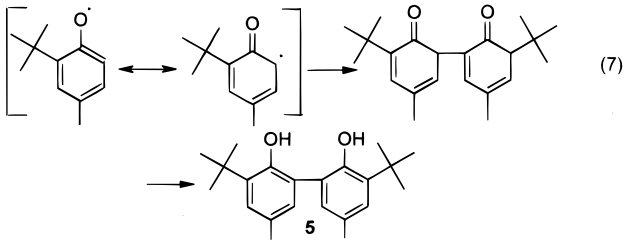
Also the regioselectivity with **2** is different from that observed with **1**: the *tert*-butylation of phenol is not selective in the *para* position, as it was with **1**, but considerable amounts of *ortho* isomer are also formed. This can be explained by the larger steric effect, the lower reactivity, and the higher selectivity (reactivity−selectivity principle)[7] of the benzyl compared to *tert*-butyl carbonium ion.

However, as the results of Table 3 indicate, the regioselectivity is strongly affected by the amount of catalyst. An excess of catalyst makes the *tert*-butylation completely selective in the *para* position, likely because the coordination of the phenol group with the catalyst increases the steric hindrance of the *ortho* positions. The same trend was observed with anisole.

These results prompted us to try to synthesize 2,6-di-*tert*-butyl-4-methylphenol (BHT), one of the most important industrial antioxidants,[8] from *p*-cresol by this new procedure. However, we obtained quite unexpected re-

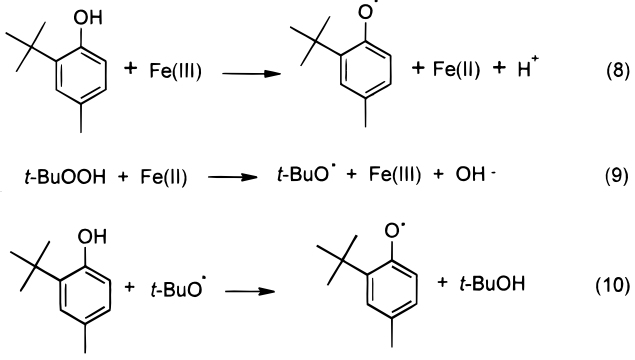
(7) Olah, G. A.; Krishnamurti, R.; Surya, G. K. *Compr. Org. Synth.* **1991**, *3*, 293.

sults. By using an excess of *p*-cresol, 2-*tert*-butyl-4-methylphenol was the only substantial reaction product; by using an excess of **2** in an attempt to prepare BHT, the latter was not formed in significant amount, while an almost quantitative yield of 2,2′-dihydroxy-3,3′-di-*tert*-butyl-5,5′-dimethyldiphenyl, **5**, was obtained. The formation of **5** certainly involves the coupling of the phenoxyl radical (eq 7).



(7)

Equations 8−10 account for the phenoxyl radical formation.



Since the reactivity of *p*-cresol and 2-*tert*-butyl-4-methylphenol toward electrophilic alkylation should not be very different, we suggest that the introduction of a *tert*-butyl group onto the *p*-cresol ring decreases the redox potential of the phenol derivative, thus making its electron-transfer oxidation by Fe(III) salt[9] (eq 8) easier. The high yield and the simple and cheap procedure for the synthesis of **5** suggest its potential application as phenolic antioxidant.

The most interesting conclusions of Tables 1−3 concern (i) the possibility to utilize tertiary hydroperoxides for electrophilic aromatic alkylation, even if the range of useful applications is, at present, more restricted compared to other alkylating reagents (alkenes, alkyl halides, alcohols);[3−5] (ii) the nature of the used acid affects the course of acid-catalyzed decomposition of hydroperoxides; (iii) **1** and **2** require different catalysts; (iv) the regioselectivity (*ortho*:*para* ratio) in the alkylation of phenol or anisole by **2** is affected by the amount of catalyst; and (v) $FeCl_3$ can act as an electrophilic or free-radical catalyst with different phenolic derivatives, allowing the synthesis in high yields of **5**, an antioxidant of potential industrial interest.

Experimental Section

Materials and General Methods. All the chemicals were reagent grade and obtained from Aldrich Chemical Co. and were used without further purification.

(8) Perkins, M. J. *Radical Chemistry*; Ellis Horwood: New York, 1994; p 122.

(9) ref 8, p 91.

^{1}H NMR spectra were recorded at 250 and 400 MHz in $CDCl_3$ using TMS as internal reference. Mass spectra were performed on a GLC−MS instrument equipped with an SBP-1 fused silica column (30 m × 0.2 mm i.d., 0.2 μm film thickness) and with He as carrier gas. GC analyses were performed on a capillary gas-chromatograph equipped with an SB-5 fused silica column (25 m × 0.25 mm i.d., 1 μm film thickness) at a hydrogen flow rate of 8 cm^3 min^{-1}, PTV injector, and flame ionization detector. Most of the reaction products were commercially available and were analyzed by comparison of GC−MS spectra with authentic samples.[10] In numerous experiments no violent decomposition or explosion took place. In any case, it is opportune to use safety precautions when working with hydroperoxides.

Decomposition of 1. (A) A 5 mmol sample of **1** was unchanged after refluxing for 2 h in 10 mL of CCl_4.

(B) A 5 mmol sample of **1** in 10 mL of CCl_4 and 5 mmol of $TiCl_4$ were refluxed for 2 h. The solution was washed with 10% HCl aqueous solution and analyzed by GC−MS. 2,4-Diphenyl-4-methyl-2(*Z*)-pentene was the only substantial reaction product, as it results by comparison with an authentic sample (87% yield). MS (*m*/*z*) peaks at 236 (M$^+$), 221, 143.

(C) A 5 mmol sample of **1** in 10 mL of CCl_4 and 2.5 mmol of $FeCl_3$ were refluxed for 2 h. GC−MS analysis revealed that **3** was the main reaction product (56%), but **4** (18%) and acetophenone (7%) were also obtained as byproducts.

(D) A 5 mmol sample of **1** in 10 mL of AcOH was refluxed for 2 h. HPLC analysis revealed that 83% of **1** had reacted, giving 75% yield of phenol.

(E) A 5 mmol sample of **1** in 10 mL of AcOH and 5 mmol of $TiCl_4$ were refluxed for 2 h. Conversion of **1** was complete (HPLC analysis); GC−MS analysis revealed the formation of phenol (35%), **3** (7%), and **4** (12%).

(F) A 5 mmol sample of **1** in 10 mL of AcOH and 2.5 mmol of $FeCl_3$ were refluxed for 2 h. Conversion of **1** was complete (HPLC analysis); GC−MS revealed the formation of phenol (15%), **3** (18%), **4** (31%), and acetophenone (8%).

General Procedure for the Alkylation of Aromatic Substrates by Cumyl Hydroperoxide, 1. The aromatic substrate and **1** in the amounts reported in the tables were added to a solution of $TiCl_4$ in 5 mL of CCl_4. The solution was stirred for 4 h at 20 °C (in a few cases at 80 °C, Table 2). The solution was washed with 10% aqueous HCl and analyzed by GC−MS by using authentic samples as references. When these were not available, the reaction products were isolated by flash-chromatography (hexane/ethyl acetate, 9:1) and analyzed by NMR and MS. The results are reported in Tables 1 and 2.

4-Cumylphenol (4). Anal. Calcd for $C_{15}H_{16}O$: C, 84.91; H, 7.55. Found: C, 84.83; H, 7.51.[10a]

2-Cumyl-4-methylphenol. Anal. Calcd for $C_{16}H_{18}O$: C, 84.96; H, 7.96. Found: C, 84.87; H, 7.99.[10b]

2-Methyl-4-cumylphenol. Anal. Calcd for $C_{16}H_{18}O$: C, 84.87; H, 7.96. Found: C, 85.11; H, 7.91.[10b]

4-Cumylresorcinol. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.95; H, 7.02. Found: C, 78.79; H, 6.98.[10c]

4-Cumyl-α-naphthol. MS: *m*/*z* 262 (M$^+$); 247; 169. Anal. Calcd for $C_{19}H_{18}O$: C, 87.02; H, 6.87. Found: C, 86.88; H, 6.86. ^{1}H NMR ($CDCl_3$): δ 1.65 (s, 6H), 6.72 (d, 1H), 7.14 (d, 1H), 7.24 (m, 5H), 7.53 (m, 2H), 7.96 (m, 1H), 8.20 (m, 1H).

3-Cumylpyrrole. MS: *m*/*z* 185 (M$^+$); 170; 108. Anal. Calcd for $C_{13}H_{15}N$: C, 84.32; H, 8.11. Found: C, 84.19; H, 8.04. ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 6H), 6.05 (m, 1H), 6.48 (m, 1H), 6.61 (m, 1H), 7.22 (m, 5H).

2-Methoxy-4-cumylphenol. MS: *m*/*z* 242 (M$^+$); 227; 212; 165; 133. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.44. Found: C, 79.48; H, 7.51.

(10) For **4**, MS: Iida, Y.; Daishima, S.; Shibata, A. *Org. Mass Spectrom*. **1993**, *28*, 433. ^{1}H NMR: Koshchii, V. A.; Kozlikovskii, Ya. B.; Matyusha, A. A. *J. Org. Chem. USSR (Engl. Transl.)* **1988**, 1358−1361. (b) For 2-methyl-4-cumylphenol and for 4-methyl-2-cumylphenol, ^{1}H NMR: Rosevear, J.; Wilshire, J. F. K. *Aust. J. Chem*. **1985**, *38*, 1163−1176. (c) For 4-cumylresorcinol, ^{13}C NMR: Yamamura, T.; Nishiwaki, K.; Tanigaki, Y.; Terauchi, S.; Tomiyama, S.; Nishiyama, T. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 2955.

General Procedure for the Alkylation of Aromatic Substrates by *t*-BuOOH, 2. A 1 mmol sample of *t*-BuOOH was added to the solution of the aromatic substrate and $FeCl_3$ in 5 mL of CCl_4 in the amounts reported in Table 3. The solution was stirred for 4 h at 80 °C (in a few cases at 20 °C, Table 3). The solution was washed with 10% aqueous HCl and analyzed by GC−MS by using authentic commercial samples as references. The results are reported in Table 3.

Oxidation of 2-*t*-Butyl-4-methylphenol by *t*-BuOOH and $FeCl_3$. The same procedure described above has been utilized. Compound **5** was obtained practically pure in 96% yield by evaporation of the CCl_4 solution.

Compound 5. ^{13}H NMR ($CDCl_3$): δ 7.14−7.12 (d, J_m = 1.25 Hz, 2H); 7.00−6.88 (d, J_m = 1.25 Hz, 2H); 5.18 (s, 2H); 2.30 (s, 6H); 1.242 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 149.87; 136.92; 129.53; 128.80; 128.42; 122.69; 60.40; 34.90; 29.64. MS: *m*/*z* 326 (M^+); 311; 255. Anal. Calcd for $C_{32}H_{34}O_2$: C, 85.33; H, 7.56. Found: C, 85.11; H, 7.52.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for 4-cumylphenol, 2-cumyl-4-methylphenol, 4-cumyl-2-methylphenol, and 4-cumylresorcinol. This material is available free of charge via the Internet at http://pubs.acs.org.

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