2,4,6-trimethylcyclohex-3-en-1-one, 61248-71-3; 1-*tert*-butyl-2,3,5-trimethylbenzene, 61248-72-4.

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(10) See E. C. Ashby, J. Laemmle, and H. M. Neumann, *Acc. Chem. Res.*, **7**, 272 (1974), for leading references.
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Substituent Effects on Reactions of Benzylmagnesium Chlorides with *o*-Quinol Acetates[1]

Bernard Miller

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01002

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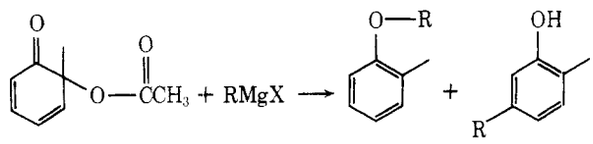
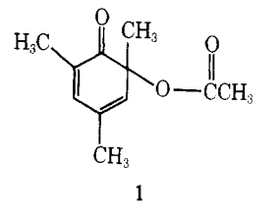
Reaction of 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one with a series of meta- and para-substituted benzylmagnesium chlorides gave decreasing yields of benzyl aryl ethers and increasing yields of *m*-benzylphenols as the electron-withdrawing powers of the substituents increased. Reaction of 6-acetoxy-2,4-dimethylcyclohexa-2,4-dien-1-one with the same Grignard reagents yielded *p*-benzylphenols in addition to aryl benzyl ethers and *m*-benzylpherols. While the ratio of ethers to *m*-benzylphenols increased sharply when more electron-donating substituents were present on the Grignard reagents, the ratio of ethers to *p*-benzylphenols remained almost constant. These results support a mechanism for formation of ethers and of *p*-benzylphenols involving initial electron transfer from the Grignard to the ketone to form phenoxy radicals, and combination of phenoxy and benzyl radicals to form the products.

Grignard and lithium reagents normally react with α,β-unsaturated ketones by addition to the carbon atoms of the carbonyl groups or by conjugate addition to the double bonds. In the preceding paper, however, it was shown that Grignard and lithium reagents react with *o*-quinol acetates (6-acetoxycyclohexa-2,4-dien-1-ones) to give aromatic ethers resulting from attack at the carbonyl oxygen atoms, as well as the "normal" 1,4 and (for primary Grignard reagents) 1,2

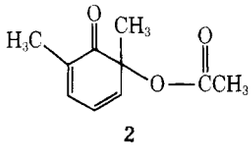


addition to the unsaturated carbonyl systems.[2] While primary Grignard reagents gave only traces of ethers, tertiary and benzylic Grignards yielded ethers as the primary or only addition products. Secondary Grignards gave significant yields of the products of attack at both oxygen and carbon. The relative yields of ethers to those of the "normal" addition products appeared to roughly parallel the expected order of electron-donating abilities of the organometallic reagents. However, the relative importance of the sizes of the carbanionoid reagents and of their electron-donating abilities were difficult to evaluate, since changes in these factors parallel each other for simple alkyl Grignard reagents.[1]

In order to determine whether Grignard attack at oxygen atoms of *o*-quinol acetates is indeed a function of the electron-donating abilities of the Grignards, rather than their steric requirements, we have studied the products obtained from reaction of 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (**1**) and 6-acetoxy-2,6-dimethylcyclohexa-2,4-dien-1-one (**2**) with benzylic Grignard reagents bearing substituents in the meta and para positions.



1



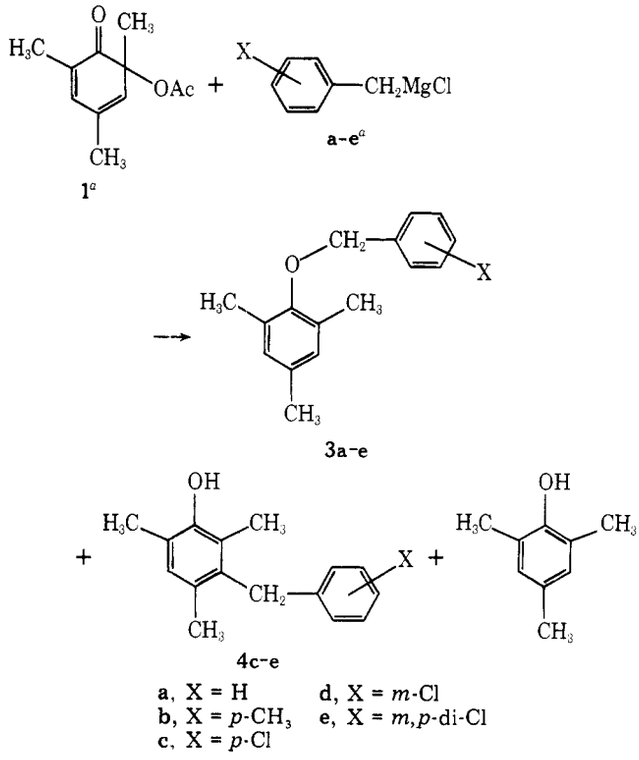
2

Results

A solution of **1** (ca. 2 mmol) in 10 ml of ether was added rapidly to 10 mmol of the Grignard reagent in 10 ml of ether, and the products were analyzed by GLC. Each reaction was carried out two times, using a freshly prepared Grignard solution for each run. The results of these reactions are summarized in Table I.

Benzyl 2,4,6-trimethylphenyl ethers (**3**), which were readily identified by their NMR spectra and by comparison with synthetic samples, were obtained as major products from each reaction. However, neither reaction with benzylmagnesium chloride nor with 4-methylbenzylmagnesium chloride gave a detectable yield of a *m*-benzylphenol. The results obtained with benzylmagnesium chloride agree with those reported in the preceding paper,[2] which differ from those reported here only in that the Grignard reagent was added to the quinol acetate, rather than vice versa.

Table I. Relative Yields of Products from Reaction of 1 with Benzylmagnesium Chlorides



a, X = H
b, X = p-CH_3
c, X = p-Cl
d, X = m-Cl
e, X = m,p-di-Cl

X	3	4	Mesitol	% 3/% 4
p-CH_3	100	<0.5	16 ± 4	>200
H	100	<0.5	8 ± 3	>200
p-Cl	100	17 ± 6	4 ± 1	5.8
m-Cl	100	42 ± 2	9 ± 2	2.4
m,p-di-Cl	100	101 ± 4	7 ± 4	0.99

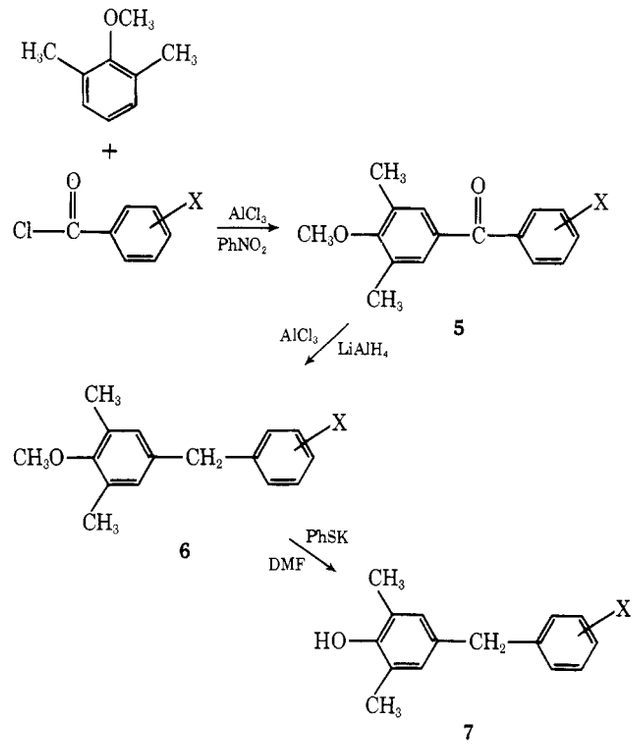
[a] Registry no.: 1, 4906-82-5; a, 6921-34-2; b, 29875-07-8; c, 874-72-6; d, 29874-01-9; e, 61259-69-6.

In contrast, reactions employing Grignard reagents with electron-withdrawing substituents did give phenols (**4c–e**) resulting from conjugate addition to the unsaturated ketone. The yields of conjugate addition products increased with increasing electron-withdrawing power of the substituents, until reaction with 3,4-dichlorobenzylmagnesium chloride gave equal yields of products of attack at oxygen and at C-3 of the ketone.

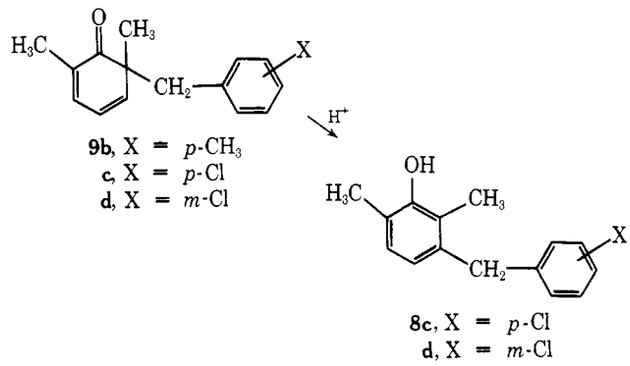
Reaction of substituted benzylmagnesium halides with quinol acetate **2**[3] again gave the expected benzyl 2,6-dimethylphenyl ethers and the reduction product, 2,6-dimethylphenol. Instead of a single *m*-benzylphenol, however, each reaction appeared to give a mixture of phenolic addition products. It proved impossible to isolate the individual components of these mixtures, although the products from reaction with 4-methylbenzylmagnesium chloride and 4-chlorobenzylmagnesium chloride showed two distinguishable, though overlapping, peaks on analytical GLC. The NMR spectra of each of these mixtures was characterized by the presence of two singlets of unequal intensities in the region (δ 3.7–4.0) characteristic of diarylmethylene resonances.

In view of our previous observation that 2,6-dialkyl quinol acetates can give rise to *p*-alkylphenols on reaction with organometallic reagents,[2] it seemed likely that the phenolic products consisted of mixtures of the *m*- and *p*-benzylphenols from each reaction. The *m*- and *p*-benzylphenols were therefore independently synthesized for comparison with the mixtures obtained from the Grignard reactions.

Attempts to prepare the *p*-benzyl isomers by direct Friedel–Crafts benzylation of 2,6-dimethylphenol or of 2,6-dimethylphenyl ether failed, since a mixture of isomers was obtained in each case.[4] Instead, Friedel–Crafts reactions between substituted benzoyl chlorides and 2,6-dimethylphenyl methyl ether gave the 4-methoxybenzophenones (**5**), which were reduced to diphenylmethanes by $LiAlH_4$ and $AlCl_3$. Cleavage of the ethers with potassium thiophenolate in *N,N*-dimethylformamide gave the desired *p*-benzylphenols (**7**).



Synthesis of the *m*-benzylphenols was initially attempted by acid-catalyzed rearrangements of the corresponding o-cyclohexadienones (**9**). This worked reasonably well for syn-



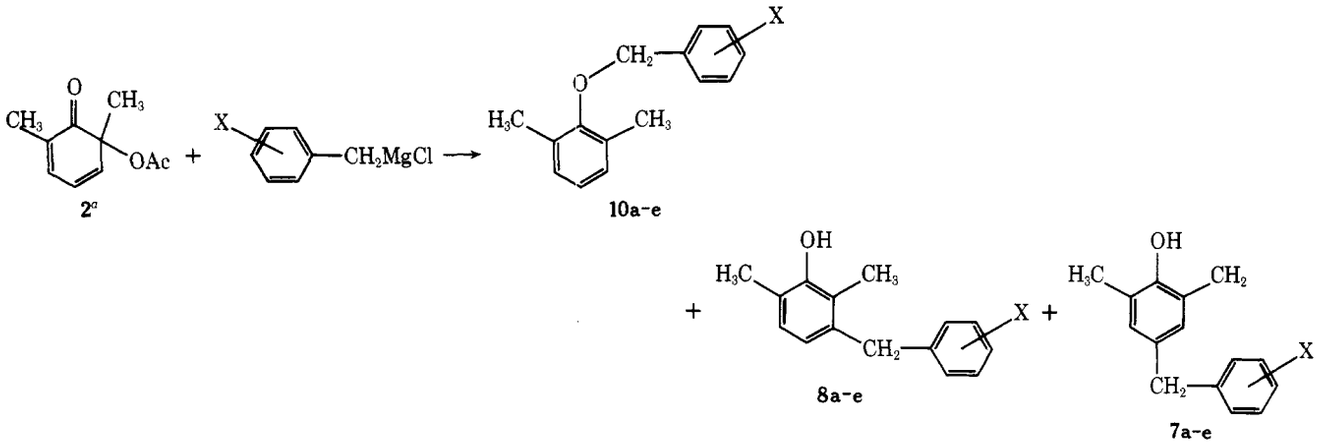
9b, X = p-CH_3
c, X = p-Cl
d, X = m-Cl

8c, X = p-Cl
d, X = m-Cl

thesis of the *m*-chloro and *p*-chloro isomers **8c** and **8d**, although each product was contaminated with small amounts of the *p*-benzyl isomers resulting from [1,3] benzyl migrations.[5]

Attempts to prepare the dichlorobenzylcyclohexadienone **9e** as a precursor to the corresponding phenol were fruitless, since the cyclohexadienone appeared to dimerize as quickly as it formed. Attempts to prepare phenol **8b** by rearrangement of **9b** also failed, since, as has previously been reported,[5a] rearrangement of **9b** gave a mixture containing a large amount of the para isomer **7b**. Instead, **8b** was prepared by the synthesis shown below. 3-Benzyl-2,6-dimethylphenol (**8a**) has

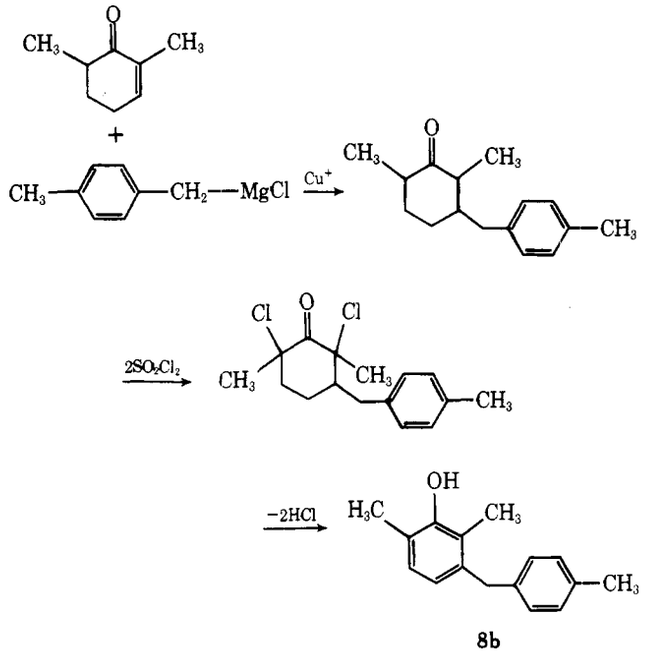
Table II. Relative Yields of Products from Reaction of 2 with Benzylmagnesium Chlorides



a, X = H d, X = *m*-Cl
b, X = *p*-CH_3 e, X = *m,p*-di-Cl
c, X = *p*-Cl

X	10	8	7	2,6-Dimethylphenol	% 10/% 8	% 10/% 7
p-CH_3	100	3.5 ± 0.7	3.1 ± 0.6	11 ± 4	29	32
H	100	4.0 ± 1.0	4.0 ± 0.8	6 ± 1	20	25
p-Cl	100	30.4 ± 3.0	3.0 ± 0.4	8 ± 5	3.3	33
m-Cl	100	50.5 ± 1.5	2.4 ± 0.7	12 ± 5	2.0	42
m,p-di-Cl	100	84.9 ± 11	5.0 ± 0.9	7 ± 2	1.2	20

[a] Registry no.: 2, 7218-21-5.



8b

been prepared in a similar manner by Mr. M. McLaughlin.[4]

Mixtures of the meta and para isomers of each of the substituted phenols 7 and 8 (with the exception of the 3,4-dichloro derivatives) had NMR and IR spectra and GLC retention times which were identical with those of the mixtures obtained from the reactions of Grignard reagents with 2. For each pair of isomers, the peaks for the diarylmethylene groups of the meta isomers appeared ca. 0.15 ppm downfield from those for the para isomers. This enabled us to directly analyze the composition of the phenolic mixtures from the Grignard reactions by comparison of the areas of these peaks.

The relative yields of products obtained from reaction of 2 with substituted benzylmagnesium chlorides are shown in Table II.

Discussion

The yields of benzyl aryl ethers from reactions of *o*-quinol acetates with benzylmagnesium chlorides increase as the electron-donating abilities of the substituents on the Grignard reagents increase. When C-4 of the quinol acetate is unsubstituted, the yields of *p*-benzylphenols similarly increase with electron-donating powers of the substituents.

For reactions with quinol acetate 2, a Hammett plot of the ratio of yields of ethers to those of *m*-benzylphenols vs. the σ values for the Grignard substituents fits a relatively straight line, with a ρ value of −2.0 (s.d. = 0.052) (Figure 2). However, the line which best fits these points shows a moderate curvature, with the more electron-donating substituents giving higher yields of ethers than would be expected on the basis of the straight line plot through the other points.

For reaction with quinol acetate 1, a similar Hammett plot gives a curve which becomes asymptotic to the vertical axis, since no *m*-benzylphenols are obtained when the substituents are H or *p*-CH_3 (Figure 1). For Grignards with electron-donating substituents, the ratio of ethers to *m*-benzylphenols is higher for reaction with 1 than for reaction with 2. For the Grignard reagent with the most electron-withdrawing substituent, however, the relative yield of ether is lower for reaction with 1 than with 2.

These results are consistent with the free-radical mechanism for formation of ethers proposed in the preceding paper,[2] in which the initial step is electron transfer between the Grignard reagent and the quinol acetate (eq 1). The greater curvature of the Hammett plot for reaction with 1 can be attributed to the conflicting steric and electronic effects of the methyl group at C-4 in 1. For Grignard reagents with electron-donating substituents, which can readily donate electrons even to 1, the principal effect of the methyl at C-4 of the quinol acetate is to sterically inhibit formation of *m*-benzylphenols by attack at C-3. For Grignards which bear strong electron-withdrawing substituents, the electronic effect of the methyl group, which inhibits electron donation to 1, is more important, and yields of *m*-benzylphenols are high from reaction

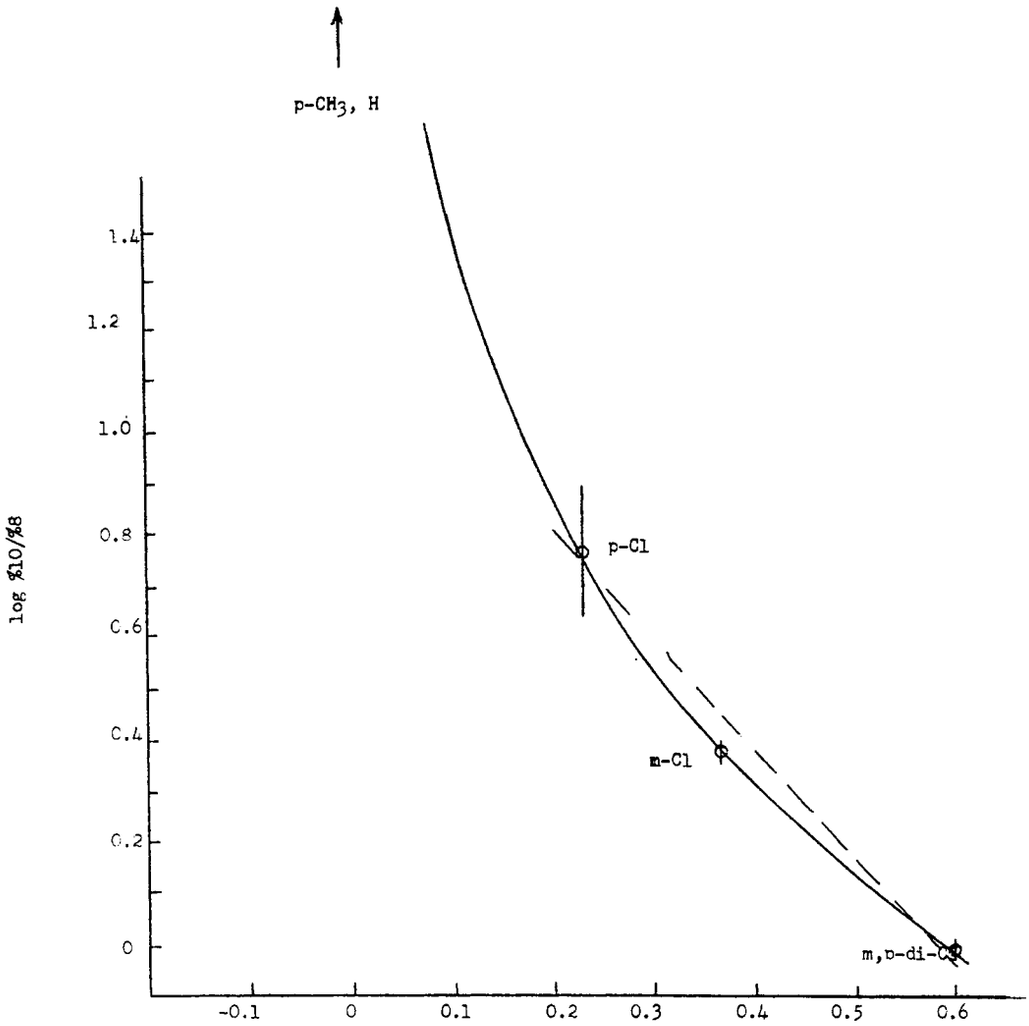
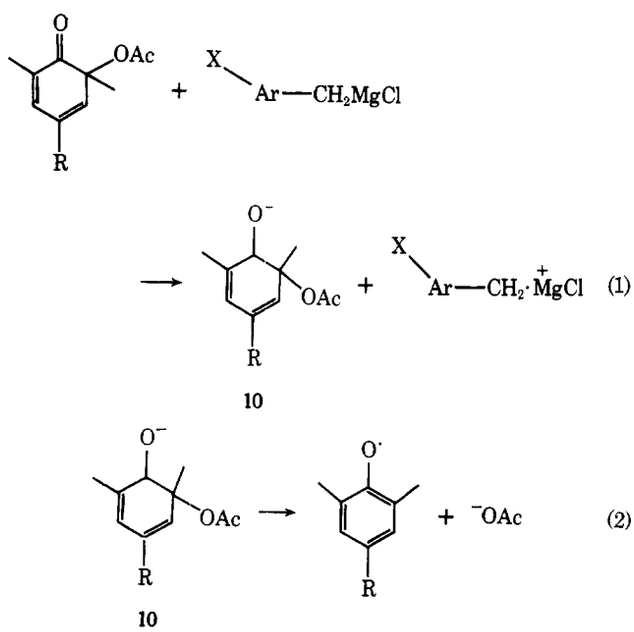


Figure 1. Plot of ratios of yields of benzyl aryl ethers to yields of *m*-benzylphenols from reaction of 1 vs. substituent σ constants. Dashed line is best straight line for Grignards with chlorine substituents.



with 1 in spite of steric interference with their formation. (An additional effect of the *p*-CH_3 group may be to increase the rate of decomposition of ketyl **10** (eq 2), and thus prevent either reverse electron transfer to the benzyl radical or formation of *m*-benzylphenols by reaction between the ketyl and a benzyl radical. Since this effect would increase yields of ethers from all Grignards, however, it cannot be the only electronic effect of the methyl at C-4.)

Of particular interest is the relative constancy of the ratio of yields of ethers to those of *p*-benzylphenols from reaction with **2**. Whereas the ratio of ethers to *m*-benzylphenols varies by a factor of approximately 25 when the substituents on the Grignard ring are changed from *p*-CH_3 to *m,p*-di-Cl, the ratio of ethers to *p*-benzylphenols varies by less than a factor of 2—barely above experimental error—and shows no consistent relationship to the electronic properties of the substituents. (The experimental error in estimating yields of *p*-benzylphenols is relatively high, owing to the fact that they are obtained in low percentages in all reactions.) The fact that formation of *p*-benzylphenols and of ethers show a similar dependence on effects of substituents supports the assumption that the mechanisms for these reactions proceed through the same initial steps, rather than by completely different mechanisms. The hypothesis that ethers and *p*-benzylphenols are both formed by combination of phenoxy and benzyl radicals (eq 3), which was proposed in the preceding paper, is consistent with all our observations.

In contrast to the other products, the yields of the reduction products, mesitol and 2,6-dimethylphenol, from these reactions show no obvious trends with changes in substituents. The yields are quite variable, even for different preparations of the same Grignard reagents. At present, the mechanisms for these reactions remain obscure.

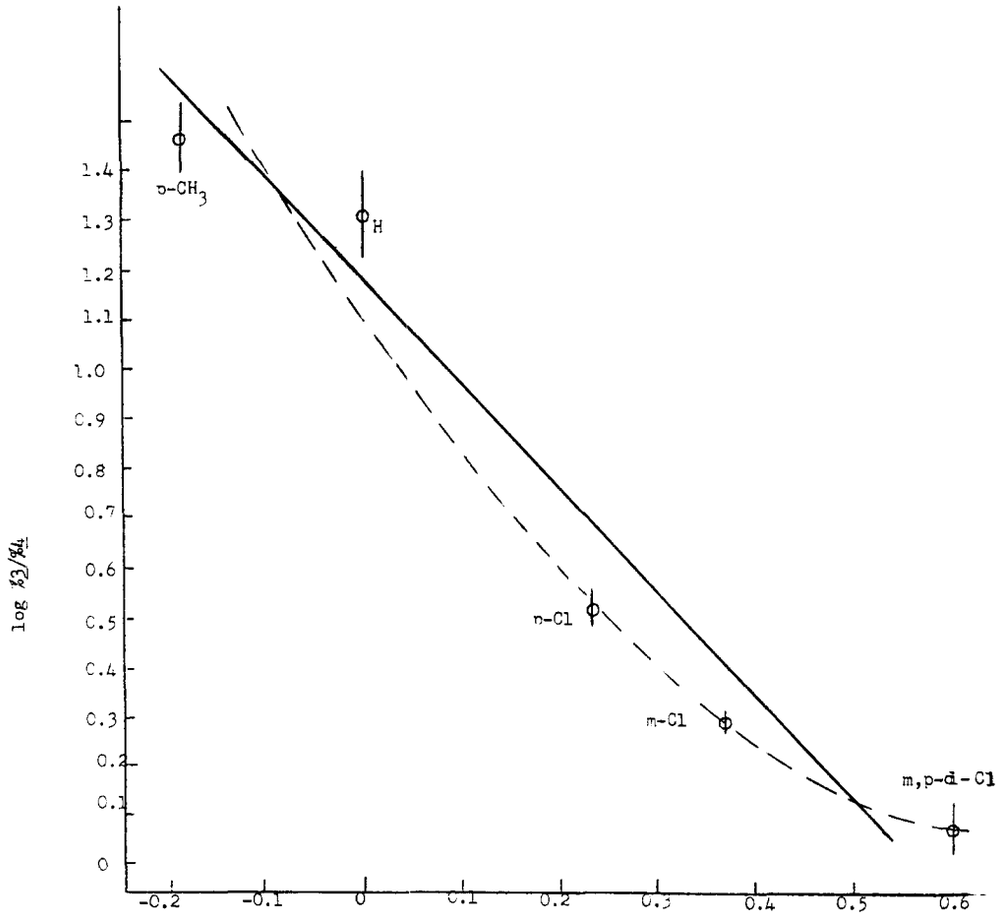
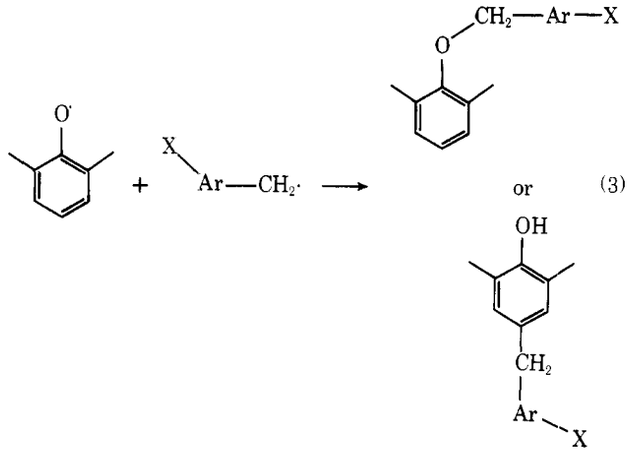


Figure 2. Plot of ratios of yields of benzyl aryl ethers to yields of *m*-benzylphenols from reaction of **2** vs. substituent σ constants. Dashed curve is approximate best fit to all points.



(3)

Experimental Section

General. NMR spectra were taken on Varian A-60 or Perkin-Elmer R12A spectrometers in deuteriochloroform solution, using Me_4Si as an internal standard. IR spectra were taken on Beckman IR-10 or Perkin-Elmer 273B spectrometers.

GLC analyses were carried out on Varian Aerograph Model 202c or Model 2400 instruments, using one of the following columns: column A, 6 ft × 0.25 in., 5% SE-30 on Chromosorb W; column B, 12 ft × 0.125 in., 3% XE-60 on Chromosorb W. Preparative separations were carried out using column C, 5 ft × 0.375 in., 5% SE-30 on Chromosorb W.

Melting points were taken on a Mel-Temp apparatus and are uncorrected.

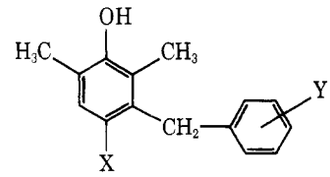
Grignard Reagents. Grignard reagent solutions (ca. 1 M) were prepared by adding a small amount of a benzyl chloride to 1.2 g (0.050 mol) of magnesium in 35 ml of anhydrous ether. When the reaction had started, the remainder of 0.050 mol of the benzyl chloride in 15 ml of ether was added to the reaction mixture as rapidly as possible. The mixture was stirred continuously under a nitrogen atmosphere until reaction was apparently complete, and then refluxed for an additional 15 min. The reaction mixture was then filtered under nitrogen pressure through a sintered glass filter and used immediately.

The Grignard reagents were prepared from magnesium chips of >99.99% purity (grade m4N) obtained from the Ventron Corp. Anhydrous ether was obtained from the Fisher Scientific Co. and used without further purification.

Reaction of Benzylmagnesium Chlorides with 6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (1). A solution of quinol acetate **1** (0.40 g, 2.08 mmol) in 10 ml of anhydrous ether was added rapidly to 10 ml of 1 M Grignard reagent in ether. The mixture was stirred under a nitrogen atmosphere for 10 minutes, and then refluxed for an additional 10 minutes. A solution of ammonium chloride in water was added, the organic layer was separated, washed with water, and dried over magnesium sulfate, and the solvent was evaporated to give a yellow oil. The product was analyzed by GLC on column A. In preparative runs, the product was dissolved in benzene and extracted with Claisen alkali. The alkaline layer was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give a mixture of 2,4,6-trimethylphenol and (for benzyl groups with chlorine substituents) 3-benzyl-2,4,6-trimethylphenols. The products were isolated by preparative GLC on column C. The NMR spectra of the products are summarized in Table III.

The alkali-insoluble layer from Claisen alkali extraction of the Grignard reaction product was washed with water and dried over magnesium sulfate, and the solvent was evaporated. The various benzyl 2,4,6-trimethylphenyl ethers were isolated by preparative GLC on column C, and were identified by comparison of their spectra and GLC retention times with those of samples independently prepared

Table III. NMR Spectra of *m*-Benzylphenols[a]



Registry no.	X	Y	Chemical shifts, δ, ppm: $ArCH_3$ (s)	$ArCH_2Ar$ (s)	ArH	−OH (bs)
61259-70-9	CH_3	*p*-Cl	2.07, 2.11, 2.21	3.98	6.86 (s, 1 H) 6.97 (d, *J* = 9 Hz, 2 H) 7.18 (d, *J* = 9 Hz, 2 H)	4.50
61259-71-0	CH_3	*m*-Cl	2.10, 2.13, 2.23	4.00	6.87 (s, 1 H) 6.95–7.30 (m, 9 H)	4.52
61259-72-1	CH_3	*m,p*-di-Cl	2.12, 2.14, 2.26	4.01	6.90 (s, 1 H) 6.90 (dd, *J* = 8, 1 Hz, 1 H) 7.14 (d, *J* = 1 Hz, 1 H) 7.33 (d, *J* = 8 Hz, 1 H)	4.50
55563-88-7	H	*p*-CH_3	2.07, 2.14, 2.25	3.92	6.66 (d, *J* = 8 Hz, 1 H) 7.08 (s, 4–5 H)	4.50
61259-73-2	H	*p*-Cl	2.07, 2.21	3.93	6.66 (d, *J* = 8 Hz, 1 H) 6.85–7.40 (m, 5 H)	4.64
61259-74-3	H	*m*-Cl	2.08, 2.21	3.92	6.67 (d, *J* = 8 Hz, 1 H) 6.75–7.30 (m, 5 H)	4.65
61288-73-1	H	*m,p*-di-Cl	2.07, 2.21	3.92	6.66 (d, *J* = 8 Hz, 1 H) 7.22 (s, 1 H) 6.78–7.40 (m, 3 H)	4.61

[a] Satisfactory C, H analyses were reported for all compounds.

by Williamson syntheses, as described below.

Reaction of Benzylmagnesium Chlorides with 6-Acetoxy-2,6-dimethylcyclohexa-2,4-dien-1-one (2). A solution of quinol acetate **2** (0.40 g, 2.23 mmol) in 10 ml of anhydrous ether was added rapidly to 10 ml of 1 M Grignard reagent in ether. The mixture was stirred under nitrogen for 10 min and then refluxed for an additional 10 min. A solution of ammonium chloride in water was added, the organic layer was separated, washed with water, and dried over magnesium sulfate, and the solvent was evaporated to give a yellow oil. The product was analyzed by GLC on column A. It was then dissolved in benzene and extracted with Claisen alkali. The alkali-insoluble layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give a yellow oil consisting principally of benzyl 2,6-dimethylphenyl ethers. The ethers were isolated by preparative GLC on column C, and identified by comparison with synthetic samples. The alkaline layer was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give a viscous oil. The combined mixture of phenols **7** and **8** was isolated by GLC on column C, and the ratio of *m*- to *p*-benzyl isomers was determined by the ratio of the two methylene peaks in the NMR spectra of the mixture. For phenols **7b** and **8b**, and **7c** and **8c**, the analyses were confirmed by GLC analysis on column B.

Synthesis of Benzyl 2,6-Dimethylphenyl and 2,4,6-Trimethylphenyl Ethers. Potassium *tert*-butoxide (1.0 g, 9.0 mmol) was added to a solution of 2,6-dimethylphenol or 2,4,6-trimethylphenol (9.0 mmol) in 20 ml of dimethyl sulfoxide. The mixture was stirred at room temperature for 10 min and 9.0 mmol of the substituted benzyl chloride was then added. After standing at room temperature for 1 h, the solution was poured into water and extracted with methylene chloride. The organic layer was washed four times with water and dried over magnesium sulfate, and the solvent was evaporated to give 8.0–9.0 mmol of almost pure ethers. Analytical samples were prepared by GLC on column C. The NMR spectra of the ethers are listed in Table IV.

3,4′,5-Trimethyl-4-methoxybenzophenone (5). Anhydrous aluminum chloride (8.0 g, 0.060 mol) was added to a solution of 2,6-dimethylanisole (6.8 g, 0.050 mol) and 4-methylbenzoyl chloride (7.0 g, 0.050 mol) in 20 ml of nitrobenzene. The mixture was stirred at room temperature for 14 h. Water was added cautiously, and then sufficient concentrated hydrochloric acid to dissolve the aluminum hydroxide was added. The mixture was extracted with methylene chloride and the organic layer was washed with dilute hydrochloric acid and then with water. The methylene chloride was evaporated, 300 ml of water was added, and the nitrobenzene was removed by steam distillation employing a Dean-Stark trap. The undistilled residue was extracted with methylene chloride and the organic layer was washed with sodium hydroxide solution and dried over magnesium sulfate. The solvent was evaporated to give 9.1 g (0.036 mol, 72%) of essentially pure **5b** as a yellow oil which crystallized on standing, mp 75–77 °C (from hexane).

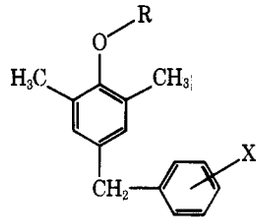
3,5-Dimethyl-4-methoxybenzophenone (**5a**), 3′-chloro-3,5-dimethyl-4-methoxybenzophenone (**5d**), 4′-chloro-3,5-dimethyl-4-methoxybenzophenone (**5c**), and 3′,4′-dichloro-3,5-dimethyl-4-methoxybenzophenone (**5e**) were prepared by the same procedure. Their NMR spectra and melting points are listed in Table V.

3,4′,5-Trimethyl-4-methoxydiphenylmethane (6b). 3,4′,5-Trimethyl-4-methoxybenzophenone (7.50 g, 0.0295 mol) was dissolved in 20 ml of anhydrous ether, and the solution was slowly added to a suspension of lithium aluminum hydride (2.5 g, 0.065 mol) in 20 ml of ether which was stirred by a magnetic stirrer under a nitrogen atmosphere. A mild reaction ensued. After 25 min the reaction was cooled in ice and anhydrous aluminum chloride powder (8.5 g, 0.062 mol) was added cautiously. The reaction mixture was then stirred and refluxed overnight, cooled to room temperature, and water added. Concentrated hydrochloric acid was added, the layers were separated, the organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give 5.2 g of 3,4′,5-trimethyl-4-methoxydiphenylmethane (0.0212 mol, 72%) as a dark brown oil. Its IR spectrum showed no hydroxy or carbonyl peaks.

3,5-Dimethyl-4-methoxyphenylmethane (**6a**), 4-chloro-3,5-dimethyl-4-methoxydiphenylmethane (**6c**), 3′-chloro-3,5-dimethyl-4-methoxydiphenylmethane (**6d**), and 3′,4′-dichloro-3,5-dimethyl-4-methoxydiphenylmethane (**6e**) were prepared in the same way. Their spectra are listed in Table IV.

Preparation of 4-(4-Methylbenzyl)-3,5-dimethylphenol. 3,4′,5-Trimethyl-4-methoxydiphenylmethane (5.0 g, 0.021 mol) was dissolved in 50 ml of *N,N*-dimethylformamide containing a mixture of 8.0 g (0.071 mol) of potassium *tert*-butoxide and 7.7 g (0.070 mol) of thiophenol. The mixture was refluxed under nitrogen for 2 h, and 100 ml of 12 M hydrochloric acid solution was added. The resulting mixture was refluxed for 15 h, and then poured into 100 ml of water. Methylene chloride (50 ml) was added. The solution was extracted with methylene chloride (50 ml) and the organic layer washed three times with water and extracted with Claisen alkali. The alkaline extract was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to leave 2.20 g (0.0098 mol, 46%) of 4-(4-methylbenzyl)-3,5-dimethylphenol

Table IV. NMR Spectra of *p*-Benzylphenols and Ethers[a]



Registry no.	R	X	Chemical shifts δ, ppm: $ArCH_3$ (s)	$ArCH_2$ Ar (s)	ArH	OR (s)	Mp, °C
41772-31-0	H	H	2.18	3.77	6.79 (s, 2 H) 7.06 (m, 5 H)	4.5	68–68.5
55563-86-5	H	*p*-CH_3	2.15 (6 H) 2.28 (3 H)	3.77	6.78 (s, 2 H) 7.06 (s, 4 H)	4.45	90.5–91.0
61259-75-4	H	*p*-Cl	2.18	3.77	6.79 (s, 2 H) 7.11 (d, J = 8 Hz, 2 H) 7.24 (d, J = 8 Hz, 2 H)	4.6	
61259-76-5	H	*m*-Cl	2.17	3.78	6.80 (s, 2 H) 7.0–7.4 (m, 4 H)	4.7	
61259-77-6	H	*m,p*-di-Cl	2.18	3.78	6.78 (s, 2 H) 7.05 (dd, J = 8, 2 Hz, 1 H) 7.27 (d, J = 2 Hz, 1 H) 7.33 (d, J = 8 Hz, 1 H)	4.6	83–85
61259-78-7	CH_3	H	2.20	3.78	6.78 (s, 2 H) 7.03 (s, 5 H)	3.61	
61259-79-8	CH_3	*p*-CH_3	2.18 (6 H) 2.23 (3 H)	3.75	6.79 (s, 2 H) 7.04 (s, 4 H)	3.61	
61259-80-1	CH_3	*p*-Cl	2.20	3.79	6.80 (s, 2 H) 7.10 (d, J = 9 Hz, 2 H) 7.23 (d, J = 9 Hz, 2 H)	3.63	
61259-81-2	CH_3	*m*-Cl	2.19	3.78	6.78 (s, 2 H) 6.95–7.35 (m, 4 H)	3.63	
61259-82-3	CH_3	*m,p*-di-Cl	2.20	3.78	6.78 (s, 2 H) 6.95–7.35 (m, 4 H)	3.65	

[a] Satisfactory C, H analyses were reported for all compounds.

as a dark brown oil which crystallized on standing in ice, mp 90.5–91.0 °C (from hexane).

Other 4-benzyl-3,5-dimethylphenols were synthesized in the same way. Their melting points and NMR spectra are listed in Table IV.

2,6-Dimethyl-3-(4-methylbenzyl)cyclohexanone. Cuprous iodide (1.0 g, 2.6 mmol) was added to a solution of 4-methylbenzylmagnesium chloride formed from 1.55 g (0.064 mol) of magnesium turnings (commercial Grignard grade) and 9.0 g of 4-methylbenzyl chloride (9.0 g, 0.064 mol) in 250 ml of ether. A solution of 2,6-dimethylcyclohex-2-en-1-one (8.0 g, 0.064 mol) in 50 ml of anhydrous ether was immediately added. The reaction mixture was stirred at room temperature for 15 h. Dilute hydrochloric acid was then added and the layers separated. The ether layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give 15.3 g of yellow oil, whose IR spectrum showed strong hydroxy and carbonyl peaks. The product was chromatographed on 600 g of activity II neutral alumina. Elution with 20% methylene chloride in pentane gave 1.70 g (7.4 mmol, 11.5%) of 2,6-dimethyl-3-(4-methylbenzyl)-cyclohexanone as a colorless oil. Its IR spectrum showed a carbonyl peak at 1740 cm^{-1}. Its NMR spectrum showed peaks at δ 1.05 (d, J = 6 Hz, 3 H), 1.20 (d, J = 6 Hz, 3 H) (methyl groups at C-2 and C-6), 2.32 (s, 3 H), 7.07 (s, 4 H), and 3.00 (dd, J = 14, 3 Hz, 1 H, one proton on benzylic methylene group).

2,6-Dimethyl-3-(4-methylbenzyl)phenol. Sulfuryl chloride (1.20 g, 8.9 mmol) was added to a solution of 2,6-dimethyl-3-(4-methylbenzyl)cyclohexanone (1.0 g, 4.38 mmol) in 15 ml of carbon tetrachloride, and the mixture was stirred at room temperature for 16 h. Water was added and the organic layer was washed with sodium bicarbonate solution and dried over magnesium sulfate. The solvent was evaporated to give 1.30 g of yellow fluid whose NMR spectrum showed a methyl singlet (6 H) at δ 1.28 replacing the doublets at δ 1.05/1.20 in the starting ketone. The crude product was dissolved in 15 ml of *N,N*-dimethylformamide. Lithium chloride (150 mg, 3.5 mmol) was added, and nitrogen bubbled through the mixture for 10 min. The mixture was then heated at 135 °C under a nitrogen atmosphere for 1.5 h. It was cooled slightly, and a solution of 5% sulfuric acid was added. The mixture was allowed to stand at room temperature for 18 h, after which methylene chloride was added. The organic layer was washed with water and then with dilute sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was evaporated to give 0.38 g (1.68 mmol, 19%) of 2,6-dimethyl-3-(4-methylbenzyl)phenol as a dark brown oil which crystallized on standing, mp 52–53 °C (from pentane).

6-(4-Chlorobenzyl)-2,6-dimethylcyclohexa-2,4-dien-1-one (9c). *n*-Butyllithium in hexane (48 ml, 0.1 mol) was added to a solution of 2,6-dimethylphenol (12.2 g, 0.1 mol) in 200 ml of benzene. 4-Chlorobenzyl chloride (16.1 g, 0.1 mol) was added and the mixture was refluxed for 24 h. The reaction mixture was cooled, washed with water, and extracted with Claisen alkali. The organic fraction was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give 12.0 g of yellow oil, which was immediately chromatographed on 400 g of neutral alumina (activity III). Elution with 20% methylene chloride in pentane gave 3.0 g of partially purified product, which was rechromatographed on 100 g of alumina. Elution with 10% methylene chloride in pentane gave 0.80 g (3.3 mmol, 3%) of the desired cyclohexadienone as a yellow oil. Its IR spectrum showed an intense carbonyl peak at 1660 cm^{-1}. Its NMR spectrum showed peaks at δ 1.10 (s, 3 H), 1.76 (d, J = 1 Hz), 2.65 (d, J = 13 Hz, 1 H), 3.00 (d, J = 13 Hz, 1 H), 5.8–6.7 (m, 3H), 7.0 (d, J = 8 Hz, 2 H), 7.09 (d, J = 8 Hz, 2 H).

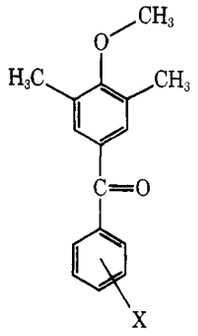
Anal. Calcd for $C_{15}H_{15}ClO$: C, 73.0; H, 6.1. Found: C, 73.0; H, 6.3.

6-(3-Chlorobenzyl-2,6-dimethylcyclohexa-2,4-dien-1-one (9d) was prepared in 5% yield using the same procedure. Its NMR spectrum was essentially identical with that above, except that the aromatic protons appeared as a multiplet.

Anal. Calcd for $C_{15}H_{15}ClO$: C, 73.0; H, 6.1. Found: C, 73.2; H, 6.3.

3-(4-Chlorobenzyl)-2,6-dimethylphenol. One drop of concentrated sulfuric acid was added to a solution of dienone **9c** (0.40 g) in 5 ml of glacial acetic acid. The solution was kept at room temperature for 0.5 h, and then water was added. The mixture was extracted with methylene chloride, and the organic layer washed with sodium bicarbonate solution and dried over methylene chloride. The solvent

Table V. NMR Spectra of 4-Methoxybenzophenones[a]



Registry no.	X	$ArCH_3$ (s)	OCH_3	ArH	Mp, °C
14753-87-8	H	2.29	3.75	7.3–7.9 (m, 7 H)	
61259-83-4	*p*-CH_3	2.30 (6 H) 2.41 (3 H)	3.75	7.48 (s, 2 H) 7.30 (d, J = 8 Hz, 2 H) 7.70 (d, J = 8 Hz, 2 H)	75–77 (hexane)
61259-84-5	*p*-Cl	2.30	3.75	7.45 (s, 2 H) 7.46 (d, J = 9 Hz, 2 H) 7.68 (d, J = 9 Hz, 2 H)	93.5–94.5 (hexane)
61259-85-6	*m*-Cl	2.30	3.74	7.46 (s, H) 7.4–7.7 (m, 4 H)	
61259-86-7	*m,p*-di-Cl	2.30	3.76	7.45 (s, 2 H) 7.57 (d, J = 1 Hz, 2 H) 7.86 (d, J = 1 Hz, 1 H)	101.5–102.5 (hexane)

[a] Satisfactory C, H analyses were reported for all compounds.

was evaporated leaving 0.40 g of dark brown oil. GLC analysis on column A showed the presence of a single major component, which was isolated as a pale yellow oil by preparative GLC on column C. Its NMR spectrum showed peaks at δ 2.02 (s, 3 H), 2.18 (s, 3 H), 3.91 (s, 2 H), 4.4 (bs, 1 H) 6.58 (d, J = 8 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H), 7.01 (d, J = 8 Hz, 2 H), 7.11 (d, J = 8 Hz, 2 H). Small peaks at δ 2.16 and 3.78 showed the presence of some 4-(4-chlorobenzyl)-2,6-dimethylphenol.

3-(3-Chlorobenzyl)-2,6-dimethylphenol. Concentrated sulfuric acid (1 drop) was added to a solution of dienone **9d** (0.30 g) in 5 ml of glacial acetic acid. After 0.5 h, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was evaporated to give 0.26 g of phenol **8d** as a dark brown oil. An analytical sample of the product was isolated as an oil by preparative GLC on column C. Its NMR spectrum showed peaks at δ 2.04 (s, 3 H), 2.19 (s, 3 H), 3.93 (s, 2 H), 4.54 (bs, 1 H), 6.59 (d, J = 8 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H), 7.1 (m, 4 H).

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Registry No.—**9c,** 61259-87-8; **9d,** 61259-88-9; 2,6-dimethylanisole, 1004-66-6; 4-methylbenzoyl chloride, 874-60-2; 2,6-dimethylcyclohex-2-en-1-one, 4079-59-5; 2,6-dimethyl-3-(4-methylbenzyl)cyclohexanone, 61259-89-0; 4-chlorobenzyl chloride, 104-83-6; 2,6-dimethylphenol, 576-26-1; 3-chlorobenzyl chloride, 620-20-2.

References and Notes

(1) Reactions of Cyclohexadienones. 38. For part 37, see ref 2.
(2) B. Miller, *J. Org. Chem.*, preceding paper in this issue.
(3) Part of this work was published as a preliminary communication: B. Miller, *J. Chem. Soc., Chem. Commun.*, 750 (1974).
(4) M. McLaughlin, to be published.
(5) Acid-catalyzed [1,3]benzyl migrations in cyclohexadienones have been reported: (a) B. Miller, *J. Am. Chem. Soc.*, **96,** 7155 (1974); (b) B. Miller and M. R. Saidi, *ibid.*, **98,** 2227 (1976).

Solvent Effects in the Benzylation of Aniline

Francesco P. Ballistreri, Emanuele Maccarone,* Giuseppe Musumarra, and Gaetano A. Tomaselli

Istituto di Chimica Industriale dell'Università di Catania, 95125 Catania, Italy

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Second-order rate constants for the reaction of benzyl chloride with aniline were measured in various solvents: methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2,2-methylpropanol, benzyl alcohol, ethylene glycol, water, *N*-methylformamide, dimethyl sulfoxide, and some mixtures of alcohols with acetonitrile. The kinetic results depend on the dielectric constant and on the electrophilic parameter E_T of the reaction medium. The protic solvent acts also a reaction catalyst, by favoring the displacement of the chloride ion by hydrogen bonding. The reaction is third order overall depending on the concentrations of the substrate, of the nucleophile, and of the protic solvent (electrophile), in agreement with the "push–pull" termolecular mechanism.

Solvent effects on the rate of a bimolecular nucleophilic substitution cannot easily be predicted on the basis of the electrostatic properties of the solvent, considered as a continuum dielectric. The solvent, in fact, can exert many kinds of specific interactions on the reagent and on the transition state.[1] However, if these effects are well understood, the study of the solvent effects is a useful diagnostic tool to elucidate the reaction mechanism.