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HIGH PERCENTAGES OF SUBSTITUTION META TO OXYGEN IN ELECTROPHILIC BENZYLATION OF 2,6-DIALKYLPHENOLS AND ARYL ETHERS

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Hydroxy and alkoxy groups on aromatic rings are powerful ortho-para directing substituents in electrophilic substitution reactions. We have confirmed, for instance, previous reports[1] that Friedel-Crafts benzylation of phenol, anisole, and ortho-cresol gives solely products of substitution at positions ortho and para to the oxygen substituents. Even in reactions of 2,6-dimethylphenol (1a) and 2,6-dimethylanisole (1b), in which both methyl groups would direct substitution to positions meta to the hydroxy and methoxy functions, a wide variety of electrophilic reagents have been reported to give exclusively the products of substitution para to the oxygens[2], with no reported examples of meta substitution. A Hammett treatment of the data of Olah and co-workers[3] suggested that $TiCl_4$ catalyzed benzylation of 1a and 1b should give just 0.5 and 2.4%, respectively, of meta substitution products.

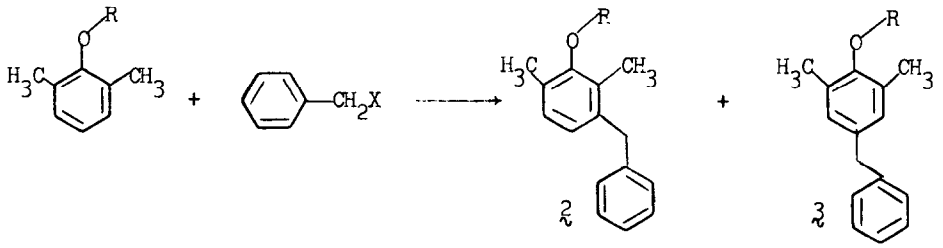
It was with appreciable surprise, therefore, that we observed that Friedel-Crafts benzylation of 1a under a variety of mild conditions gave approximately a 40% yield of the meta-substitution product 2a, while similar reactions of 1b and of isopropyl 2,6-dimethylphenyl ether (1c) gave predominantly the meta-benzyl derivatives. In reactions of the ethers 1b and 1c, the reactivity of each meta-position was actually greater than that of the para-position in the same molecule. These results are summarized in the Table.

The meta and para-benzylated isomers from each reaction could be detected by analytical glpc as overlapping peaks, and mixtures of the two isomers free of starting materials and polybenzylated products could be obtained by preparative glpc, but the isomers could not be separated from each other by glpc, column chromatography, or fractional crystalization. The compositions of the mixtures were determined by nmr analysis from the relative areas of the C-3 (downfield) and C-4 benzylic methylene singlets. They could also be determined (less precisely) from the aromatic regions of the nmr spectra, which showed singlets for protons on the oxygenated rings of 3 superimposed on pairs of doublets (J=8 Hz) for protons of 2. For analysis of the products from 1c, in which the isopropyl methine signals overlapped the benzylic methylene singlets, the ether was cleaved with hydrogen iodide and the relative yields of 2a and 3a in the cleavage products were determined. It was shown that no rearrangement or destruction of either 2a or 3a was caused by

the cleavage process.

To isolate the individual products of the Friedel-Crafts reactions, one mole of bromine per mole of meta-benzylated product was added to the mixtures obtained by benzylation of 1a and 1b. Reaction with bromine in each case resulted in disappearance of the aromatic doublets from the meta-benzyl isomers and caused downfield shifts of their benzylic methylene singlets, but did

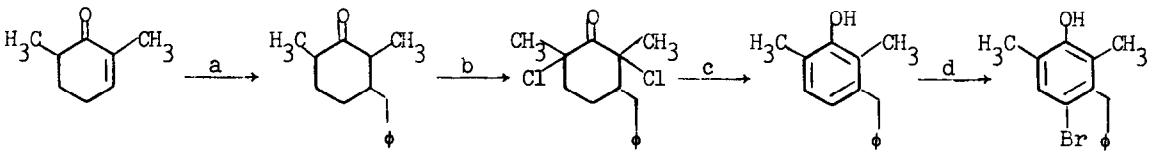
TABLE



Reaction*	R	X	Solvent	Catalyst	Temp (°C)	Time (Hrs.)	%2	Conversion (%)	No. Runs
a	H	Cl	$CHCl_3$	$ZnCl_2$	68	16	37.4 ± 3.1	74 ± 1	2
b	H	Cl	$CHCl_3$	$CaCl_2$	68	16	33	4	1
c	H	OH	EtOEt	H_2SO_4(4M)	ca. 30	2	39.4 ± 2.9	26 ± 1	2
d	CH_3	Cl	$CHCl_3$	$ZnCl_2$	68	16	69.5 ± 2.1	87 ± 4	2
e	CH_3	OH	EtOEt	H_2SO_4(4M)	ca. 30	2	74.2 ± 2.0	14 ± 2	2
f	iPr	Cl	$CHCl_3$	$ZnCl_2$	68	16	70.0 ± 0.9	51 ± 4	2

*All reactions were run using a tenfold molar excess of 1, to minimize dibenzylation.

not affect the peaks assigned to the para-benzyl isomers. Unreacted 3a and 3b and the brominated products (4a and 4b) from 2 were then separated by preparative glpc and identified by comparison with samples synthesized independently. The synthesis of 4a is shown below.



a) CH_2MgCl, Cu_2I_2 b) SO_2Cl_2, CCl_4 c) LiCl, DMF, 100° d) Br_2, $CHCl_3$

The following facts must be considered in deciding on a mechanism for the meta-benzylation of 1a-1c:

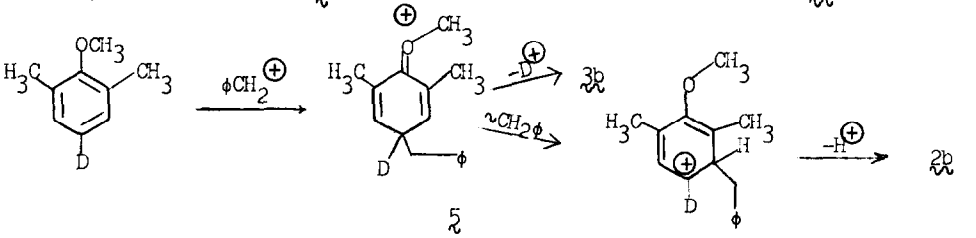
a) Both 3a and 3b were recovered unchanged after refluxing with zinc chloride and hydrogen chloride in chloroform solution for sixteen hours, or after 3 hours in 4M sulfuric acid in ether.

b) 3,4-Dibenzyl-2,6-dimethylphenol (obtained by zinc chloride -- catalyzed reaction of 1a with one molar equivalent of benzyl chloride) was recovered unchanged from reaction with excess 1a under the conditions of reaction a.

c) Benzyl 2,6-dimethylphenyl ether was recovered unchanged after two hours in a 4M solution of sulfuric acid in diethyl ether. When 10 molar equivalents of 1a per mole of the benzyl ether

were added to the reaction mixture, both 2a and 3a were produced in a 1:1 molar ratio. One half of the starting benzyl ether, however, was recovered unchanged after two hours. Since glpc analysis showed no detectable formation of benzyl 2,6-dimethylphenyl ether from benzylation of 1a under the conditions of reaction c, the ether cannot be an intermediate in that reaction, although it can act as an alkylating agent if introduced into the reaction.

d) Benzylation of 2,6-dimethylanisole-4-d under the conditions of reactions d or e gave precisely the same meta/para substitution ratios as benzylation of 1b. (Unreacted starting material was recovered with its deuterium content unchanged.) From the maximum uncertainties in each observation, it can be calculated that if formation of 2b proceeded by benzyl migration in the σ-complex 5, a value of k_H/k_D greater than 1.13 for loss of a proton or deuteron from 5 would have caused a detectable change in the meta/para ratio. Since the expected value for k_H/k_D is much larger than 1.13,[4] we conclude that 5 is not an intermediate in formation of 2b.



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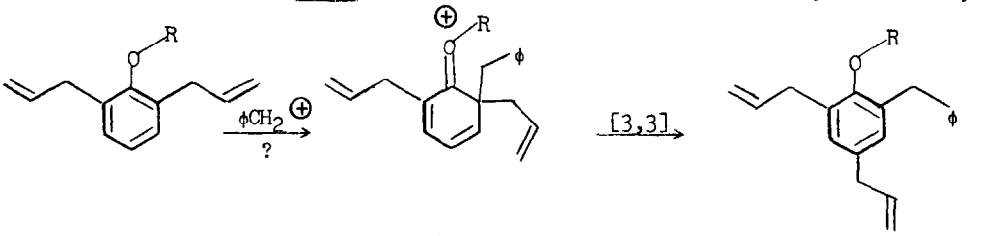
e) Under the conditions of reaction a, benzylation of phenol, anisole, and isopropyl phenyl ether gives products containing, respectively, 60%, 40%, and 34% of the ortho-benzyl isomers -- a sequence consistent with increasing steric hindrance to attack at the ortho positions with increasing size of the substituents on oxygen. This sequence is very different from the changes in percent meta benzylation of 1 with increasing size of the substituents on oxygen. Meta-benzylation of 1 is thus difficult to rationalize on the basis of initial ortho benzylation followed by acid-catalyzed benzyl migrations to meta-positions.

As a further test of the possibility that meta-benzylation products were formed by initial ortho-attack, we examined the benzylation of 2,6-diallylanisole under the conditions of reaction d. A mixture of benzyldiallylanisoles was obtained whose components could not be separated by glpc or column chromatography. To identify the components of the mixture, the allyl groups were reduced to propyl groups (to simplify the nmr spectra) and the effects of added $Eu(fod)_3$ on the chemical shifts of the benzylic methylene peaks were examined. It was found that the effects of the shift reagent on the product mixture were identical with its effects on the shifts of a synthetic 60:40 mixture of 3-benzyl-2,6-dipropylanisole and 4-benzyl-2,6-dipropylanisole. Products with ortho-benzyl groups, which show very large shifts on addition of $Eu(fod)_3$, would have been easily detected, but no evidence for their presence was observed.

If benzylation of 2,6-diallylanisole initially occurred at an ortho position, the O-methylated cyclohexadienone 6b would be the first intermediate in the reaction. Allyl groups at the quaternary carbons of ortho-cyclohexadienones have been found to undergo predominant or exclusive [3,3] migrations in the presence of a wide variety of electrophilic agents, at rates much greater than migrations of benzyl groups.[5] In accord with these observations, dienone 6a was found to give exclusively phenol 7a on reaction with zinc chloride in chloroform at room temperature. In

contrast, the absence of any ortho-benzyl groups in the products of benzylation of 2,6-



6a, R = H
6b, R = CH_3

7a, R = H
7b, R = CH_3

diallylanisoles would require, if 6b were an intermediate in the reaction, that substitution of a methyl group for a proton on oxygen in 6 not only prevent any [3,3] migration of the allyl group, but result in quantitative migration of a benzyl group rather than the allyl. Since such behaviour would be quite unprecedented, we conclude that ortho attack does not precede meta benzylation to any significant extent.

Since all other reasonable mechanisms have been eliminated, formation of meta-substitution products during Friedel-Crafts benzylation of 2,6-dimethylphenol and its ethers must proceed by direct attack of electrophilic agents at the meta-positions.

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