Polar Effects in Grignard Attack at the Oxygen Atoms of Carbonyl Groups

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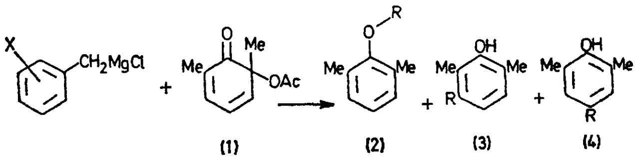
Summary The yields of benzyl ethers relative to those of 4-benzylphenols from reaction of substituted benzylmagnesium chlorides with 6-acetoxy-2,6-dimethylcyclohexa-2,4-dienone are unaffected by the nature of the substituents, but the yields of both products increase, relative to those of 3-benzylphenols, with increasing electron-donating powers of the substituents.

GRIGNARD and lithium reagents commonly add to the carbonyl carbon or the β-carbon atoms of the double bonds in $\alpha\beta$-unsaturated ketones, but the reaction of benzyl and tertiary Grignard reagents with 6-acetoxycyclohexa-2,4-dienones gives ethers resulting from attack at the carbonyl oxygen as the main addition products[1,2] In these reactions the yields of 'normal' conjugate addition at C-3 (or, in a few cases, of addition to the carbonyl group) increased sharply, relative to those of ethers, with secondary Grignard or lithium reagents, while only traces of ethers were obtained with primary Grignards reagents. The relative yields of ethers thus appeared roughly to parallel the expected order of electron-donating abilities of the organometallic reagents, but the relative importance of polar and of steric effects could not be evaluated.[1]

A study of the reactions of 6-acetoxycyclohexa-2,4-dienones with substituted benzyl Grignard reagents now demonstrates that the ratio of attack by Grignard reagents at the carbonyl oxygen compared to attack at C-3 increases with increasing electron-donating powers of the substituents, independently of any steric effects.



The reaction of benzyl Grignard reagents with the acetate (**1**) gives aryl benzyl ethers (**2**), 3-benzyl-2,6-dimethylphenols (**3**), 4-benzyl-2,6-dimethylphenols (**4**), and small amounts of 2,6-dimethylphenol. Yields were determined by g.l.c. analysis of the relative amounts of ethers and phenolic products obtained, and by n.m.r. analysis of the isolated phenolic fractions to determine the relative yields of 3-benzyl- and 4-benzyl-phenols from reaction with (**1a**). For comparison, the ethers were prepared independently from the potassium phenoxides and benzyl chlorides in $\mathrm{Me_2SO}$ solution. The 3-benzylphenols were synthesized by acid-catalysed rearrangements of 6-benzyl-2,6-dimethylcyclohexadienones, or by conjugate addition of the benzyl Grignard to 2,6-dimethylcyclohex-2-enone, followed by chlorination with sulphuryl chloride (2 mol. equiv.) and subsequent dehydrochlorination with LiCl in dimethylformamide (DMF). The 4-benzylphenols were prepared by $AlCl_3$ catalysed condensation of the appropriate benzoyl chlorides with 2,6-dimethylphenyl methyl ether, reduction of the resulting benzophenones to diphenylmethanes with $LiAlH_4$ and $AlCl_3$ and cleavage of the ethers to phenols with PhSK in DMF.

The results in the Table show that the ratios of yields of ethers to those of 3-benzylphenols (**2**):(**3**) increase uniformly as the electron-donating powers of the substituents increase. A plot of the ratio of log k for formation of ether from reaction with (**1**) to that for formation of the phenol (**3**) *vs.* the σ constants for the substituents is a reasonable straight line (ρ — 2·0).

TABLE. Relative yields of products

X	(**2**)	(**3**)	(**4**)
p-Me	100	3·5 ± 0·7	3·1 ± 0·6
H	100	5·0 ± 1·0	4·0 ± 0·8
p-Cl	100	30·4 ± 3·0	3·0 ± 0·4
m-Cl	100	50·5 ± 1·5	2·4 ± 0·7
m,p-di-Cl	100	84·9 ± 11	5·0 ± 0·9

It was suggested previously that ethers were formed by combination of phenoxyl radicals with radicals formed from the Grignard reagents, but a single-step reaction with a transition state in which appreciable electron transfer had occurred could not be discounted. Some insight into this question can be gained by consideration of the relative yields of (**2**) and (**4**) obtained from reaction of Grignard reagents with (**1**). While the mole ratio of (**2**) to (**3**) in the product varies by a factor of nearly 25 over the group of substituents studied, the ratio of (**2**) to (**4**) varies by a factor of *ca.* 2 (barely above the experimental error) and shows no uniform trend with electron-donating power of the substituents. While two completely independent types of reactions leading to (**2**) and to (**4**) could conceivably show such similar variations in rate with changing substituents, a simpler explanation is that both (**2**) and (**4**) are formed from a common intermediate pair of free radicals (R· and 2,6-$Me_2C_6H_3O$·), which combine in highly exothermic reactions with very low activation energies, and therefore show very small substituent effects.

Although this evidence supports the intermediacy of free radicals in the formation of (**2**) and (**4**), the exact sequence of reactions leading to each of the products is not yet clear. We are investigating the possibilities that (**2**) and (**4**) are formed by an initial electron-transfer process, while (**3**) results from nucleophilic addition to the conjugated carbonyl system, or that an initially formed radical anion may either eliminate acetate ion to give a phenoxyl radical, or combine with the radical from the Grignard reagent at C-3 or C-1.

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[1] B. Miller, *J. Amer. Chem. Soc.*, 1973, **95**, 8458.

[2] For an earlier report of a Grignard attack at oxygen in a quinol diacetate, see F. Wessely and J. Kotlan, *Monatsh.*, 1953, **84**, 124.