Selective Reactions using Metal Phenoxides. Part 2.[1] Reactions with Aromatic Alcohols

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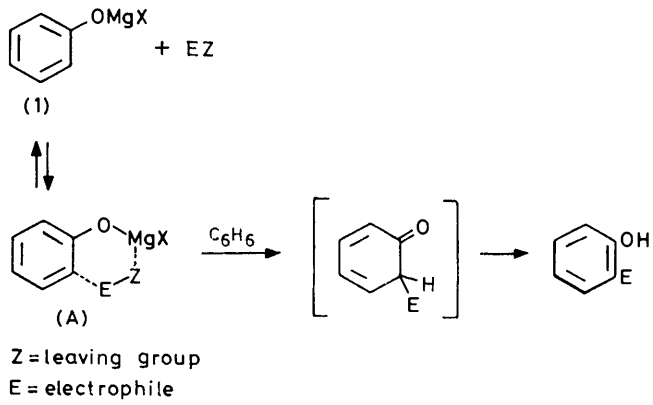
The reactions of aryloxymagnesium bromides (1) with aromatic alcohols in benzene have been studied. In most cases when an *ortho*-OH group is absent in the alcohol, if any reaction occurs at all it is unselective and gives mixtures of *ortho*- and *para*-products. High reactivity and *ortho*-regioselectivity to give 2,2'-dihydroxydi- and triphenylmethanes (3) are achieved with the 2-hydroxybenzyl alcohols (2), especially when the OH group is converted into the magnesium salt. The formation of *ortho*-quinone methides (7) as intermediates has been postulated to account for the high *ortho*-regioselectivity observed.

We have shown [1] that *ortho*-regioselective reactions on the aromatic nucleus of phenols occur in poorly donating solvents like benzene with oxygenated reagents which easily complex magnesium. The subsequent 'intra-complex' reaction occurs exclusively in the *ortho*-position because of the favourable location of the electrophile (E).

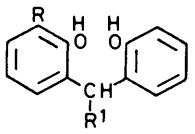


SCHEME 1

It is known [2] that alkylation of phenols with aromatic alcohols in the presence of a variety of acid catalysts is a relatively facile reaction which occurs mainly in the *para*-position. Therefore, it seemed worthwhile to explore the reactivity of these alcohols with magnesium phenoxides; also, we had indirect evidence that in the analogous reactions of aldehydes,[1] 2-hydroxybenzyl alcohols (2) are intermediates which subsequently react *ortho*-selectively with aryloxymagnesium bromides to produce 2,2'-dihydroxydi- and tri-phenylmethanes (3).

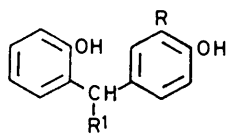
RESULTS

The results are reported in Table 1. No reaction occurs with various benzyl alcohols, but salicyclic alcohol shows high reactivity and *ortho*-selectivity. Predominant *para*-attack is observed with more reactive aromatic alcohols like α-methylbenzyl alcohol, 4-hydroxybenzyl alcohol, and diphenylmethanol and its derivatives; again, *ortho*-attack is observed only with 2-hydroxydiphenylmethanols. The condition of having an OH function in the *ortho*-position of the aromatic nucleus of the alcohol in order to obtain *ortho*-regioselectivity is a necessary but not sufficient one.



(3)

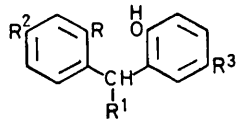
a; R = R¹ = H
b; R = Me, R¹ = H
c; R = Pr^i, R¹ = H
d; R = Bu^t, R¹ = H
e; R = H, R¹ = Ph
f; R = Me, R¹ = Ph
g; R = Pr^i, R¹ = Ph
h; R = Bu^t, R¹ = Ph
k; R = $CH_2C_6H_4OH$-*o*, R¹ = H



(4)

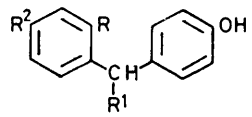
a; R = R¹ = H
b; R = H, R¹ = Ph
c; R = Me, R¹ = H
d; R = Me, R¹ = Ph
e; R = Bu^t, R¹ = H
f; R = Bu^t, R¹ = Ph

Further results in Table 1 show that the conversion of the OH group of the salicyclic alcohol into the magnesium salt has a marked influence on the reaction course (see Experimental section, method B).



(5)

a; R = R² = R³ = H, R¹ = Me
b; R = OMe, R² = R³ = H, R¹ = Ph
c; R = R² = R³ = H, R¹ = Ph
d; R = R² = H, R¹ = Me, R³ = CHMePh



(6)

a; R = R² = H, R¹ = Me
b; R = R¹ = H, R² = OH
c; R = Me, R¹ = Ph, R² = H
d; R = Cl, R¹ = Ph, R² = H
e; R = OMe, R¹ = Ph, R² = H
f; R = R² = H, R¹ = Ph

Comparison of the data obtained by the two methods A and B shows that when the phenolic group of the salicylic

[1] Part 1, G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Puglia, G. Sartori, and R. Ungaro, preceding paper and references therein.

[2] A. Schriesheim, in 'Friedel–Crafts and Related Reactions,' ed. G. Olah, Wiley, New York, 1964, vol. II, p. 477; J. Mathieu and J. Weil-Raynal 'Formation of C–C Bonds,' Thieme, Stuttgart, 1974, vol. II, p. 314.

alcohol is not converted into a salt, *ortho*-selectivity is decreased and the products of *para*-attack appear.

DISCUSSION

The results show that aromatic alcohols with aryloxymagnesium bromides behave differently from other electrophilic reagents. The lack of reactivity or *ortho*-selectivity of most of the alcohols indicates that a substrate–reagent complex of the type (*A*) is not formed. Perhaps the more reactive alcohols like diphenylmethanols give the normal intermolecular, and therefore unselective, Friedel–Crafts process with the production of both *ortho*- and *para*-compounds. The drastic change observed in the reaction when aromatic alcohols with an *ortho*-OH group are used can be explained with the formation of a new species which reacts *ortho*-selectively with aryloxymagnesium bromides.

It is known [3] that 2-hydroxybenzyl derivatives (2) can generate *ortho*-quinone methides (7) under certain conditions; these species have been observed spectroscopically [4] and trapped with suitable reagents.[5] The generation of *ortho*-quinone methides (7) according to Scheme 2, and the formation of a ' complex ' (8) between this species and magnesium phenoxide with a subsequent ' intracomplex ' reaction, can account for the high *ortho*-regioselectivity observed in this case.

The *ortho*-quinone methide (7) [6] was trapped in the reaction of phenoxymagnesium bromide and 2-hydroxydiphenylmethanol by means of ethyl vinyl ether, which gives 2-ethoxy-4-phenylchroman (9); indirect evidence of the role played by these intermediates in our reactions can be deduced from some data of Table 1.

ortho-Methoxybenzyl alcohols do not react *ortho*-selectively with phenoxymagnesium bromide, although OCH_3 can complex magnesium even better than OH. This fact rules out the hypothesis that *ortho*-attack may be due to a better complexation of the reagent with the substrate, which helps to ' bring together ' the reacting species. Moreover, the noticeable effect of the degree of salt formation, which can be seen by comparing the data of Table 1 (method A and B) and which results in a decrease of *ortho*-regioselectivity when the OH group of the alcohol is not converted into a salt, is in agreement with the hypothesis of the *ortho*-quinone methide intermediate. Magnesium located on the phenolic group of the alcohol can intramolecularly catalyse the generation of the *ortho*-quinone methide so that the *ortho*-regioselective pathway (Scheme 3) overcomes the competing non-selective ' normal ' one.

To show that these species can give selective alkylation with aryloxymagnesium bromides in benzene, we generated 1,2-naphthoquinone 1-methide (10) by thermal depolymerization of its dimer (11) in mesitylene at

TABLE 1

Reaction of aryloxymagnesium bromide with aromatic alcohols.[a]

Entry	Phenol	Alcohol	Method [b]	Reacted phenol (%) [c]	Products [yield %] [c]	Separation technique [d]	Ratio *ortho* : *para*
1	Phenol	Benzyl alcohol	A	0			
2		Benzyl alcohol	B	0			
3		4-Chlorobenzyl alcohol	A	0			
4		α-Methylbenzyl alcohol	A	65	(5a)[19]; (6a)[30]; (5d)[11]	c.c.	41 : 59
5		2-Methoxybenzyl alcohol	A	0			
6		2-Hydroxybenzyl alcohol	A	40	(3a)[18]; (3k)[11]; (4a)[8]	c.c.	78 : 22
7		2-Hydroxybenzyl alcohol	B	74	(3a)[55]; (3k)[18]	c.c.	100 : 0
8		4-Hydroxybenzyl alcohol	B	65	(4a)[12]; (6b)[50]	p.l.c.	20 : 80
9		Diphenylmethanol	A	70	(5c)[14]; (6f)[56]	p.l.c.	20 : 80
10		Diphenylmethanol	B	75	(5c)[13]; (6f)[60]	p.l.c.	19 : 81
11		2-Methyldiphenylmethanol	A	70	(6c)[63]	r.	0 : 100
12		2-Chlorodiphenylmethanol	A	83	(6d)[74]	r.	0 : 100
13		2-Methoxydiphenylmethanol	A	75	(5b)[15]; (6e)[57]	p.l.c.	21 : 79
14		2-Hydroxydiphenylmethanol	A	65	(3e)[35]; (4b)[27]	c.c.	56 : 44
15		2-Hydroxydiphenylmethanol	B	70	(3e)[67]	r.	100 : 0
16	2-Methylphenol	2-Hydroxybenzyl alcohol	A	52	(3b)[45]; (4c)[6]	c.c.	88 : 12
17		2-Hydroxybenzyl alcohol	B	83	(3b)[80]	r.	100 : 0
18		2-Hydroxydiphenylmethanol	A	70	(3f)[29]; (4d)[40]	c.c.	42 : 58
19		2-Hydroxydiphenylmethanol	B	90	(3f)[90]	r.	100 : 0
20	2-Isopropylphenol	2-Hydroxybenzyl alcohol	B	80	(3c)[75]	r.	100 : 0
21		2-Hydroxydiphenylmethanol	B	72	(3g)[69]	r.	100 : 0
22	2-t-Butylphenol	2-Hydroxybenzyl alcohol	A	63	(3d)[50]; (4e)[10]	c.c.	83 : 17
23		2-Hydroxybenzyl alcohol	B	78	(3d)[70]; (4e)[4]	c.c.	94 : 6
24		2-Hydroxydiphenylmethanol	A	75	(3h)[55]; (4f)[12]	c.c.	82 : 18
25		2-Hydroxydiphenylmethanol	B	80	(3h)[65]; (4f)[10]	c.c.	86 : 14
26		2-Hydroxydiphenylmethanol	B [e]	55	(3h)[55]	r.	100 : 0

[a] All the reactions were carried out in anhydrous benzene under reflux for 24 h, with a 1 : 1 molar ratio of phenol to aromatic alcohol. [b] A = reaction with alcohol; B = reaction with monobromomagnesium salt of the alcohol. [c] By g.l.c. [d] c.c. = Column chromatography on Merck 70—230 mesh ASTM silica gel [hexane–ethyl acetate (8 : 2) solvent]; p.l.c. = preparative thin-layer chromatography on silica gel PF_{254} plates; r. = recrystallization (solvent, see Table 2). [e] At 25 °C for 24 h.

[3] A. B. Turner, *Quart. Rev.*, 1964, **18**, 374; G. Decodts, M. Wakselman, and M. Vilkas, *Tetrahedron*, 1970, **26**, 3313; J. C. Robert, G. Decodts, and M. Vilkas, *Bull. Soc. chim. France*, 1973, 1179.

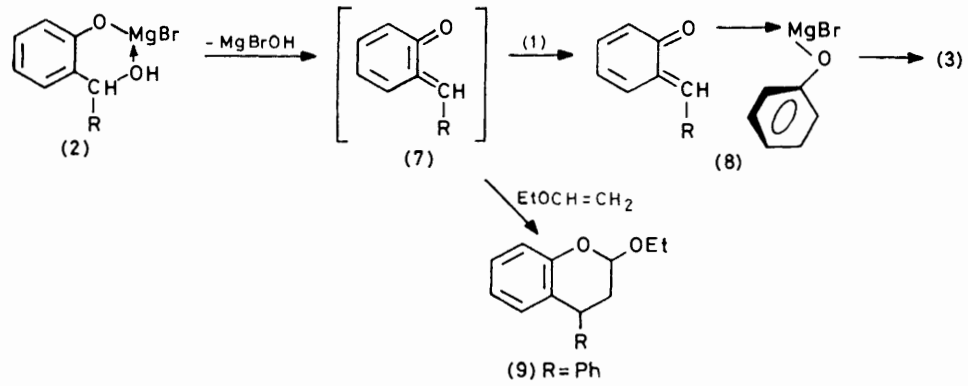
[4] G. L. McIntosh and O. L. Chapman, *Chem. Comm.*, 1971, 771.

[5] D. A. Bolon, *J. Org. Chem.*, 1970, **35**, 3666.

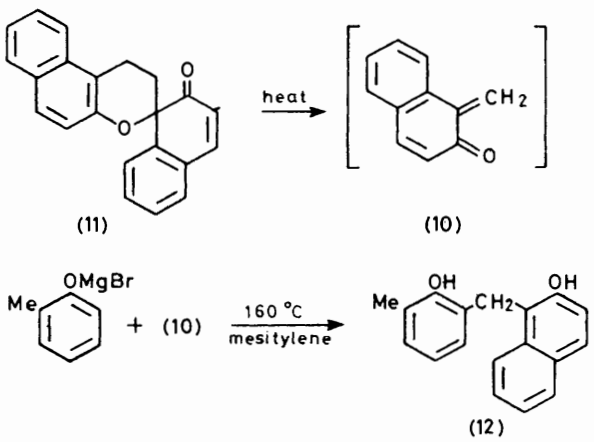
[6] Preliminary communication, A. Pochini and R. Ungaro, *J.C.S. Chem. Comm.*, 1976, 309.

160 °C, and allowed it to react with 2-methylphenoxymagnesium bromide; only the *ortho*-attack product (12) was obtained. There was no *para*-product in spite of the high temperature of the reaction (Scheme 3).

Results in Table 1 (method A) indicate that when the OH group of the alcohol is not converted into the magnesium salt, the two mechanisms are about equally important. *para*-Attack tends to become more important with substrates like 2-t-butylphenol, which also shows less selectivity in the conditions of method B.



SCHEME 2



SCHEME 3

The diminished selectivity of this substrate can be ascribed to less aggregation of its magnesium salts as already observed in other reactions;[1,7,8] at lower temperature, in fact, the reaction is again regioselective (entry 26 of Table 1).

Conclusions.—The results show that, unlike other electrophilic reagents studied so far in our laboratory, aromatic alcohols generally have low reactivity and selectivity with aryloxymagnesium bromides in benzene. To increase the reactivity and to achieve high *ortho*-selectivity with these reagents, an additional OH group is needed in the *ortho*-position of the aromatic nucleus of the alcohol, which then is able to generate an *ortho*-quinone methide (7). This intermediate can be efficiently co-ordinated by the magnesium of the aryloxymagnesium bromide leading to a highly *ortho*-regioselective intracomplex reaction with the production of various types of 2,2'-dihydroxy-di- and -tri-phenylmethane derivatives (3).

Moreover, this study shows once again that the variation (sometimes small) of the donor–acceptor interaction between the substrate and the reagent has a marked influence on the reactivity of salts of organic molecules in media of low polarity.

EXPERIMENTAL

For general directions, see preceding paper.

Reaction of Aryloxymagnesium Bromides with Alcohols (Method A). General Procedure.—A solution of the phenol (20 mmol) in diethyl ether was added dropwise with stirring at room temperature to ethereal ethylmagnesium bromide (20 mmol). The ether was then completely evaporated off *in vacuo* and benzene (50 ml) and the appropriate alcohol (20 mmol) were added. The mixture was heated at reflux with stirring for 20 h, quenched with aqueous NH_4Cl, and extracted with diethyl ether. After drying (Na_2SO_4), the ether was evaporated off to give a residue from which the products were separated by recrystallization, column chromatography, or preparative t.l.c. (see Table 1). Preparative data of isolated compounds are shown in Table 1. Analytical and ^1H n.m.r. spectroscopic data are available in Supplementary Publication No. SUP 22185 (3 pp.).*

Reaction of Aryloxymagnesium Bromides with the Bromomagnesium Salts of Alcohols (Method B). General Procedure.—A mixture of the phenol (20 mmol) and the appropriate alcohol (20 mmol) in diethyl ether was added dropwise with stirring at room temperature to ethereal ethylmagnesium bromide (40 mmol). The ether was then completely evaporated off *in vacuo* and benzene (50 ml) was added. The mixture was heated at reflux with stirring for 20 h, quenched with aqueous NH_4Cl, and extracted with diethyl ether. After drying (Na_2SO_4) the ether was removed

* For details see Notices to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

[7] G. Casiraghi, G. Casnati, M. Cornia, G. Sartori, and R. Ungaro, *J.C.S. Perkin I*, 1974, 2077.

[8] G. Casiraghi, G. Casnati, and M. Cornia, *Tetrahedron Letters*, 1973, 679.

to give a residue which was worked up as above. Preparative data of isolated compounds are shown in Table 1, and analytical and ^1H n.m.r. spectroscopic data in SUP 22185.

Reaction of 2-Methylphenoxymagnesium Bromide with 1,2-Naphthoquinone 1-Methide.—3,4-Dihydro-2*H*-benzo-[*f*]chromen-2-spiro-1′-naphthalen-2′-one (dimer of 1,2-naphthoquinone 1-methide) (11) was prepared according to the literature [9] and recrystallized from diethyl ether–light petroleum (1 : 4) [m.p. 172—173 °C; i.r. (KBr) 1 680s and 1 230s cm^{-1}].

To a solution of 2-methylphenoxymagnesium bromide (5 mmol) in mesitylene (20 cm^3), the dimer (11) (0.780 g, 2.5 mmol) was added. The mixture was refluxed for 5 min,[10] then worked up as above and the product (12) isolated by preparative t.l.c., yield 0.95 g (72%), m.p. 157 °C; n.m.r. ($CDCl_3$ + $[^2H]_6$DMSO) δ 2.20 (s, 3 H, CH_3), 4.36 (s, 2 H, CH_2), 6.4—7.9 (m, 8 H, aromatic), 8.28 (d, 1 H, aromatic), and 9.50 (s, 2 H, OH); $\nu_{max.}$ (KBr) 3 300, 1 250vs, 1 031, 980, 833, 810vs, 797, 769, and 740vs cm^{-1} (Calc. for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1. Found: C, 81.45; H, 6.35%). This product was identical (mixed m.p. and i.r. spectra) with an authentic specimen prepared from β-naphthol and 2-hydroxy-3-methylbenzyl alcohol.[11] A careful search in the crude material for the corresponding *para*-hydroxy-derivative by t.l.c. and g.l.c. techniques gave negative results.

Trapping of the ortho-*Quinone Methide Intermediate* (7).—Phenol (20 mmol) and 2-hydroxydiphenylmethanol (20 mmol) reacted under the conditions of Method B, in the presence of ethyl vinyl ether (20 mmol) for 20 h at room temperature. After work-up as usual, *2-ethoxy-4-phenylchroman* (9) was isolated by column chromatography on silica gel (hexane as eluant); yield 1.37 g (27%); m.p. 71—72 °C ($C_{17}H_{18}O_2$ requires C, 80.3; H, 7.15. Found: C, 80.05; H, 7.4%), δ(CCl_4) 1.21 (t, 3 H, OCH_2CH_3), 2.0—2.5 (m, 2 H, CH_2), 3.3—3.7 (m, 2 H, OCH_2CH_3), 3.7—4.3 (m, 1 H, $CHPhCH_2$), 5.0—5.3 (m, 1 H, $CHOC_2H_5$), and 6.4—7.5 (m, 9 H, aromatic), *m/e* 254, 208, 207, and 181. Further elution with hexane–ethyl acetate (8 : 2) afforded (3e); yield 1.98 g (36%), m.p. 128—129 °C (from benzene–light petroleum), identical with that prepared according to the above general methods.

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[7/798 *Received*, 9*th May*, 1977]

[9] M. S. Chauhau, F. M. Dean, and M. L. Robinson, *J.C.S. Perkin I*, 1973, 1204.

[10] *Cf.* G. Catteral, *J.C.S. Chem. Comm.*, 1974, 41.

[11] M. I. Bender, A. G. Farnham, and J. W. Guyer, U.S.P. 2,744,882/1956 (*Chem. Abs.* 1957, **51**, 479)