Selective Reactions using Metal Phenoxides. Part 1. Reactions with Formaldehyde

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The reactions between formaldehyde and a series of aryloxymagnesium bromides (1) and their complexes with hexamethylphosphoramide (HMPA) in benzene have been investigated. In the absence of ligand 2,2'-dihydroxydiphenylmethanes (2) are obtained, while in the presence of stoicheiometric amounts of HMPA 2-hydroxybenzaldehydes (4) are produced in high yield. Both products are the result of an exceptional *ortho*-regioselective attack on the aromatic nucleus of the phenol. The formation of (4) has been shown to occur *via* an oxidation–reduction process, promoted by HMPA, between the 2-hydroxybenzyl alcohol intermediate (5) and formaldehyde. The difference in acidity between the free and HMPA-complexed magnesium counterion is invoked to explain the two reaction pathways.

In spite of the enormous amount of work done on the reaction between phenols and formaldehyde [1] due to its industrial importance, no great success has been achieved so far in the control of its regioselectivity and of the molecular-weight distribution of the products. In order to control the complexity of this reaction and direct it towards synthetic utility, we studied the reactions of formaldehyde with magnesium phenoxides which, as shown by our previous work,[2] tend to react regioselectively with several reagents. We report here the results of these reactions, which were done with magnesium phenoxides or their complexes with hexamethylphosphoramide (HMPA) as substrates in benzene.

RESULTS

The production in high yield (Table 1) of 2,2'-dihydroxydiarylmethane derivatives (2) by means of two successive *ortho*-regioselective reactions on the aromatic nucleus of the phenol is the main feature of the reaction between aryloxymagnesium bromides and formaldehyde in benzene in the absence of ligands. In some cases trinuclear compounds (3) can also be isolated.

No reaction is observed with phenols substituted with electron-withdrawing groups like NO_2 and COMe, and with *ortho*-methoxyphenol, while alkyl-substituted substrates are quite reactive. The results obtained when the same reactions are performed in the presence of stoicheiometric amounts of HMPA are summarized in Table 2.

TABLE 1

Reaction of aryloxymagnesium bromide, RMgBr (1), with formaldehyde (0.5 equiv.) in refluxing benzene (20 h)

R	Recovered phenol (%)	Product [a,b] yields [c] (%) (m.p.) [lit. m.p.] (2)	(3)
(1a) Phenoxy	2	59 (118—119) [118.5—119.5] [1a]	39 (157—158) [161—162] [1a]
(1b) 2-Methylphenoxy	36	61 (120—121) [120—121] [2c]	
(1c) 3-Methylphenoxy	23	46 (125—126) [129—130] [1a]	30 (168—170) [d]
(1d) 4-Methylphenoxy	29	63 (125—126) [126] [e]	4 (213—214) [215] [1a]
(1e) 2-isopropylphenoxy	23	75 (75—76) [75—76] [2c]	
(1f) 2-t-Butylphenoxy	23	69 (105—106) [f]	
(1g) 2,3-Dimethylphenoxy	3	93 (150—151) [g]	
(1h) 3,5-Dimethylphenoxy	43	50 (161—162) [160—161] [1a]	
(1i) 2-t-Butyl-5-methylphenoxy	20	63 (120—121) [h]	
(1j) 4-Methoxyphenoxy	6	64 (86—88) [i]	
(1k) 4-Chlorophenoxy	23	23 (176—177) [178] [j]	
(1l—q) 2-Methoxy-, 2-chloro-, 2- and 4-nitro, 2- and 4-acetyl-phenoxy	100		
(1r) 2-Naphthyloxy	20	73 (198—200) [200] [k]	

[a] Compounds (2) were crystallized from n-hexane; compounds (3) from benzene. [b] All compounds gave molecular ions in the low-resolution mass spectra corresponding to these molecular formulae. [c] Determined by g.l.c. [d] Found: C, 79.2; H, 6.9. Calc. for $C_{23}H_{24}O_3$: C, 79.3; H, 6.95%. [e] G. T. Morgan and N. J. L. Megson, *J. Soc. Chem. Ind.*, 1933, **53**, 418. [f] Found: C, 80.8; H, 9.0. Calc. for $C_{21}H_{28}O_2$: C, 80.75; H, 9.0%. [g] Found: C, 79.8; H, 7.8. Calc. for $C_{17}H_{20}O_2$: C, 79.75; H, 7.85%. [h] Found: C, 81.1; H, 9.50. Calc. for $C_{23}H_{32}O_2$: C, 81.15; H, 9.45%. [i] Found: C, 68.85; H, 6.1. Calc. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2%. [j] W. S. Gump and Max Luthy, U.S.P. 2,334,408 (*Chem. Abs.* 1944, **38**, 2667). [k] O. Manasse, *Ber.*, 1894, **27**, 2409.

No reaction is observed with phenols substituted with electron-withdrawing groups like NO_2 and COMe, and with *ortho*-methoxyphenol, while alkyl-substituted substrates are quite reactive. The results obtained when the same reactions are performed in the presence of stoicheiometric amounts of HMPA are summarized in Table 2.

[1] (*a*) J. F. Walker, 'Formaldehyde,' Reinhold, New York, 1964, pp. 304—344 and references therein; (*b*) A. M. Partansky, *Amer. Chem. Soc. Div. Org. Coatings Plast. Chem.*, Preprints, 1967, **27**, 115 (*Chem. Abs.* 1967, **66**, 105,412b).

[2] (*a*) G. Casiraghi, G. Casnati, and G. Salerno, *J. Chem. Soc.* (*C*), 1971, 2546; (*b*) G. Casiraghi, G. Casnati, M. Cornia, G. Sartori, and R. Ungaro, *J.C.S. Perkin I*, 1974, 2077; (*c*) G. Casiraghi, G. Casnati, and M. Cornia, *Tetrahedron Letters*, 1973, 679; (*d*) G. Casiraghi, G. Salerno, and G. Sartori, *Synthesis*, 1975, 186.

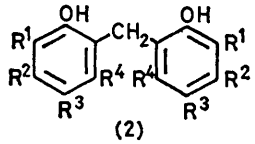
TABLE 2

Reactions of aryloxymagnesium bromides RMgBr and formaldehyde (2.5 equiv.) in refluxing benzene in the presence of HMPA (1 equiv.)

R	Yield of (4) (%) [a]	M.p. (b.p.) [b] (°C)	Lit. m.p. (b.p.) (°C)	Ref.
(1a) Phenoxy	85(98)	(198)	(197)	3
(1b) 2-Methylphenoxy	76(95)	(211)	(208)	3
(1c) 3-Methylphenoxy	67(86) [c]	60—61	60	3
(1d) 4-Methylphenoxy	81(97)	55—56	56	3
(1e) 2-iso-Propylphenoxy	72(90) [d]	(236)		
(1f) 2-t-Butylphenoxy	50(86)	(248)	(78—79/1 mmHg)	6
(1j) 4-Methoxyphenoxy	90(98)	51—52	50—52	*e*
(1k) 4-Chlorophenoxy	75(99)	98—99	99	3
(1m) 2-Chlorophenoxy	58(96)	54—55	54	3
(1s) 2,4-Dimethylphenoxy	85(95)	12—14	11(222)	*f*
(1t) 2,5-Dimethylphenoxy	90(98)	63—64	62—63	*g*
(1u) 2-Methyl-5-isopropylphenoxy	63(87)	(265)	(130/15 mmHg)	3
(1v) 5-Methyl-2-isopropylphenoxy	70(94)	(261)	(130/15 mmHg)	3
(1w) 3-Chlorophenoxy	65(80)	52—53	51—52	*h*
(1y) 4-Hydroxyphenoxy	45(75)	98—99	99	*e*
(1r) 2-Naphthyloxy	60(98)	82	82	3

[a] Yields of pure products; yields in parentheses are based upon starting phenol consumed. [b] Determined at 760 mmHg. [c] In addition, 2% of 2-hydroxy-6-methylbenzaldehyde was formed. [d] Found: C, 73.0; H, 7.15. Calc. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.35%. [e] F. Tiemann and W. H. Müller, *Ber.*, 1881, **14**, 1985. [f] O. Anselmino, *Ber.*, 1902, **35**, 4108. [g] L. Gattermann, *Annalen*, 1907, **357**, 321. [h] H. H. Hodgson and T. A. Jenkinson, *J. Chem. Soc.*, 1927, 1740.

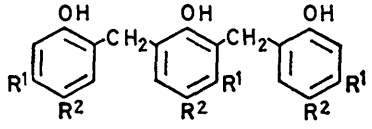
In this case 2-hydroxybenzaldehydes (4) are produced while compounds (2) and (3) are completely absent. The best results are achieved with a formaldehyde : phenol ratio



(2)

a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = Me$, $R^2 = R^3 = R^4 = H$
c; $R^1 = R^3 = R^4 = H$, $R^2 = Me$
d; $R^1 = R^2 = R^4 = H$, $R^3 = Me$
e; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = H$
f; $R^1 = Bu^t$, $R^2 = R^3 = R^4 = H$
g; $R^1 = R^2 = Me$, $R^3 = R^4 = H$
h; $R^1 = R^3 = H$, $R^2 = R^4 = Me$
i; $R^1 = Bu^t$, $R^2 = R^3 = H$, $R^4 = Me$
j; $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
k; $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
r; $R^1 = R^2 = H$, $R^3 = R^4 = -C_4H_4-$

of 2.5 : 1. High yields of (4) are obtained with phenols bearing electron-donating or weakly electron-withdrawing

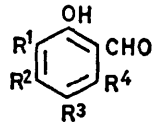


(3)

a; $R^1 = R^2 = H$
c; $R^1 = Me$, $R^2 = H$
d; $R^1 = H$, $R^2 = Me$

groups, but no reaction is observed with 4-acetyl-, 4-nitro-, and 2-methoxy-phenol.

To our knowledge, this process represents the best synthesis of 2-hydroxybenzaldehydes from a variety of phenols, and that with a rather simple procedure. The classical methods for the *ortho*-formylation of phenols



(4)

a; $R^1 = R^2 = R^3 = R^4 = H$
b; $R^1 = Me$; $R^2 = R^3 = R^4 = H$
c; $R^1 = R^3 = R^4 = H$, $R^2 = Me$
d; $R^1 = R^2 = R^4 = H$, $R^3 = Me$
e; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = H$
f; $R^1 = Bu^t$, $R^2 = R^3 = R^4 = H$
j; $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
k; $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
m; $R^1 = Cl$, $R^2 = R^3 = R^4 = H$
r; $R^1 = R^2 = H$, $R^3 = R^4 = -C_4H_4-$
s; $R^1 = R^3 = Me$, $R^2 = R^4 = H$
t; $R^1 = R^4 = Me$, $R^2 = R^3 = H$
u; $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Pr^i$
v; $R^1 = Pr^i$, $R^2 = R^3 = H$, $R^4 = Me$
w; $R^1 = R^3 = R^4 = H$, $R^2 = Cl$
y; $R^1 = R^2 = R^4 = H$, $R^3 = OH$

TABLE 3

Effect of the variation of HMPA : PhOMgBr molar ratio on the reaction between phenoxymagnesium bromide and formaldehyde [a,b]

HMPA : PhOMgBr molar ratio	Conversion (%)	2-Hydroxybenzaldehyde (4a) (%) [c]
0.5 : 1	92	10
1 : 1	75	93
2 : 1	68	86
4 : 1	60	66
20 : 1	27	1.5
30 : 1	0	0

[a] 24 h in refluxing benzene. [b] Molar ratio PhOMgBr : HCHO = 1 : 2.5; conc. of PhOMgBr 0.2 mol l^{-1}. [c] Based upon phenol consumed.

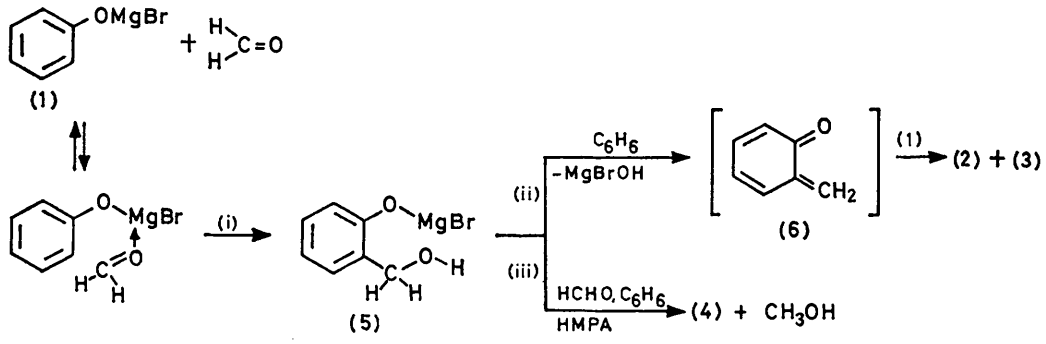
(Duff,[3] Reimer-Tiemann,[4] and Gattermann [5]) give very poor yields: even in procedures recently developed,[6-9] most of

[3] J. C. Duff, *J. Chem. Soc.*, 1941, 547.
[4] H. Wimberg, *Chem. Rev.*, 1960, **60**, 169.
[5] W. E. Truce, *Org. Reactions*, 1957, **9**, 37.
[6] D. J. Zwanenburg and W. A. P. Reynen, *Synthesis*, 1976, 624.
[7] G. Casnati, M. Crisafulli, and A. Ricca, *Tetrahedron Letters*, 1965, 243.
[8] P. G. Gassman and D. R. Amick, *Tetrahedron Letters*, 1974, 3463.
[9] H. Christensen, *Synth. Comm.*, 1975, **5** (1), 65.

which go through several steps, the yield never exceeds 50%. With increases in the amount of HMPA, the reactivity decreases smoothly until no reaction of the phenol is detected (Table 3).

DISCUSSION

The results are consistent with initial formation of a complex between the carbonyl group of the formaldehyde and the magnesium salt. This activates the electrophile and probably the aromatic nucleus as well (Scheme).



SCHEME

The formation of an oriented π-complex has been proposed to explain the first step of the ' anomalous ' reaction of benzylmagnesium chloride with formaldehyde or other carbonyl compounds,[10a] and the reaction of benzylmercury chloride with DCl [10b] which leads to ring *ortho*-substitution products.

The exact nature of this complex and its kinetic relevance in the first step (i) of our reaction, which produces the 2-hydroxybenzyl alcohol (5) both in the presence and in the absence of HMPA, is not fully clear although it accounts for the high *ortho*-regioselectivity of the process. *ortho*-Attack is then a consequence of the favourable location of the substrate and the reagent within the complex. Evidently the magnesium·HMPA complex is still able to co-ordinate formaldehyde and direct the electrophilic attack to the *ortho*-position of the phenol.

Similar behaviour has been observed already in the isomerization of alkyl-substituted [11a] or other [11b] epoxides to aldehydes with a LiBr·HMPA complex; the salt complexes of suitable ligands are capable of co-ordinating the cation but not of occupying all its catalytically active sites.

When all the co-ordination sites of the magnesium are occupied by the donor molecules of the ligand (or by the solvent), the formation of the oriented reactive complex with the formaldehyde is inhibited and the reactivity decreases (see Table 3).

As we previously observed with aromatic aldehydes [2b] and ethyl orthoformates,[2c] and as other authors [12] noted in the reaction of benzylmagnesium chloride with acetaldehyde,[10a] the formation of the magnesium·reagent complex can also be hindered effectively by the presence of a 2-methoxy group, which internally chelates the cation. No reaction occurs in this case; in contrast, 4-methoxyphenol is quite reactive (see Table 2).

2-Hydroxybenzyl alcohol (5) is the first intermediate of the process and has been, in fact, isolated in the reaction between phenoxymagnesium bromide and formaldehyde in benzene under milder conditions. In addition, its bromomagnesium salt reacts selectively at the 2-position with phenoxymagnesium bromide in benzene to produce a mixture of (2a) and (3a). The subsequent behaviour of this intermediate is highly dependent on the reaction conditions and particularly on the presence or absence of HMPA.

Recently, evidence has been obtained in our laboratory showing that *ortho*-quinone methide intermediates (6) have to be generated in order to have *ortho*-selectivity in the reactions between benzylic alcohols and aryloxymagnesium bromides in benzene.[13] Other evidence (see following paper) shows their generation to be facilitated by intramolecular assistance by the magnesium salt, which also justifies the rather mild conditions under which they are produced. On this basis we can hypothesize the formation of the intermediate (6) as an essential step for the production of dinuclear (2) and trinuclear (3) derivatives which occurs in benzene in the absence of ligands. The formation of an *ortho*-quinone methide intermediate is inhibited by the presence of HMPA, which probably reduces the acidity of the magnesium. In fact, in the reaction of 2-hydroxybenzyl alcohol (5) and phenoxymagnesium bromide with 1 mole of HMPA, starting materials are recovered quantitatively in the presence of ethyl vinyl ether; this has been used to trap *ortho*-quinone methide intermediates.[13,14]

The formation of aldehydes (4) can now be explained: the favoured reaction pathway (*ii*) is blocked by the presence of the ligand, and a competitive oxidation–reduction process can occur between benzylic alcohol (5) and formaldehyde to give the aldehydes (4) and methanol through a hydride shift.

[10] (*a*) D. V. Joffe and M. I. Mostova, *Russ. Chem. Rev.*, 1973, **42**, 1 and references therein; (*b*) V. A. Nikaronov, V. I. Rozenberg, M. A. Bazeed, Y. U. G. Bundel, and O. A. Reutov, *J. Organometallic Chem.*, 1976, **108**, 325.

[11] (*a*) B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, 1971, **93**, 1693; (*b*) G. Magnusson and S. Thoren, *J. Org. Chem.*, 1973, **38**, 1381.

[12] F. Bernardon and J. Bourdois, *Tetrahedron Letters*, 1970, 4711.

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

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

The reaction between the bromomagnesium salt of 2-hydroxybenzyl alcohol complexed with 1 mole of HMPA and formaldehyde in benzene gave, in fact, (4) and methanol showing the hypothesis to be correct. Further investigations, however, are needed in order to clarify the details of mechanism of this oxidation–reduction process.

Conclusions.—The results show that the reactions between phenols and formaldehyde can be controlled and directed towards an *ortho*-regioselective pathway by the use of a cation with high co-ordinating power ($MgBr^+$) located on the phenolic oxygen and a solvent with a low dielectric constant and basicity (benzene) in which the necessary cation–reagent interaction is enhanced.

A further control leading to the regioselective synthesis of 2-hydroxybenzaldehydes is achieved when the reaction is done in the same reaction medium but with the aryloxymagnesium bromide–HMPA 1 : 1 complex. The high yield and selectivity of this reaction make it particularly attractive from a synthetic point of view, since other known methods are less selective or pass through several steps.

EXPERIMENTAL

For general directions, see also ref. 2. All reactions were carried out under dry conditions in nitrogen. Analytical g.l.c. analyses were carried out on a Varian Aerograph 1400 flame ionization instrument with nitrogen as carrier gas and column (5 ft × 1/8 in) packed with 5% Silicone SE-30 (Methyl) or 5% diethylene glycol succinate (DEGS) on silanized Chromosorb W (80—100 mesh).

Absolute yields of products were calculated from peak areas by the use of internal-standard techniques with response factors obtained from pure samples. For column chromatography, silica gel 60 (Merck; 70—230 mesh ASTM) was used. Paraformaldehyde was purchased from Fluka AG Buchs (Switzerland); however no significant differences were observed when paraformaldehyde from seven other commercial sources was used.

Reaction of Phenoxymagnesium Bromides (1) *with Paraformaldehyde* (1 : 0.5 *Molar Ratio*). *Synthesis of* (2) *and* (3); *General Procedure.*—An ethereal solution of the phenol (100 mmol) was added dropwise to a solution of ethylmagnesium bromide (100 mmol) in diethyl ether (200 ml) with stirring at room temperature. Most of the ether was distilled off and anhydrous benzene was added. Distillation was continued until the temperature rose to 80 °C in order to remove the ether completely. The volume was then adjusted to 500 ml with benzene and finally powdered paraformaldehyde (50 mmol) was added; the mixture was heated under reflux with stirring for 10 h. After cooling, the mixture was poured into an excess of saturated aqueous ammonium chloride and extracted with ether. The organic phase was washed with water, dried over magnesium sulphate, and filtered, and the volume adjusted to 500 ml. Analytical g.l.c. analysis was carried out at this point. The ether was then distilled off *in vacuo* and the unchanged phenol was removed by steam distillation. The products were separated as follows. (*i*) If the residue contained only crude (2), this was recrystallized from benzene–light petroleum. (*ii*) If the residue contained a mixture of (2) and (3), this was separated by column chromatography on silica gel with n-hexane–ethyl acetate (9 : 1 v/v). Physical and preparative data are summarized in Table 1 and spectral data (i.r., u.v., ^1H n.m.r.) in Supplementary Publication No. SUP 22184 (2 pp.).*

Reaction of Phenoxymagnesium Bromide (1a) *with Paraformaldehyde* (1 : 0.5 *Molar Ratio*). *Isolation of 2-Hydroxybenzyl Alcohol.*—A mixture of phenoxymagnesium bromide (1a) (10 mmol) and paraformaldehyde (5 mmol) in benzene (50 ml) was heated at 50 °C for 1 h. After cooling the mixture was quenched with aqueous NH_4Cl and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give an oily residue which was chromatographed on silica gel. Elution with n-hexane afforded phenol (370 mg) and 2,2′-dihydroxydiphenylmethane (2a) (215 mg). Further elution with n-hexane–ethyl acetate (9 : 1 v/v) afforded 2,6-bis-(2-hydroxybenzyl)phenol (3a) (93 mg) and 2-hydroxybenzyl alcohol (180 mg, 14%) identical with an authentic sample.

Reaction of Phenoxymagnesium Bromide (1a) *and 2-Hydroxybenzyl Alcohol.*—A mixture of phenoxymagnesium bromide (1a) (10 mmol) and the bromomagnesium salt of 2-hydroxybenzyl alcohol (10 mmol) in benzene (50 ml) was heated under reflux with stirring for 10 h. After cooling, it was quenched with aqueous NH_4Cl and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to give a residue from which (2a) (881 mg, 40%) and (3a) (550 mg, 16%) were separated by column chromatography as in the above general procedure for the synthesis of (2) and (3).

Reaction of Phenoxymagnesium Bromide (1) *with Paraformaldehyde* (1 : 2.5 *Molar Ratio*) *in the Presence of HMPA* (1 *Equiv.*). *Synthesis of* (4); *General Procedure.*—A mixture of the phenoxymagnesium bromide (1) (20 mmol), HMPA (20 mmol), and paraformaldehyde (50 mmol) in anhydrous benzene (100 ml), was heated under reflux for 3 h, then acidified with aqueous 10% hydrochloric acid and extracted with ether. Removal of the solvent *in vacuo* gave crude (4) which was purified by steam distillation and subsequent recrystallization or high-vacuum distillation.

Preparative data for all the aldehydes are summarized in Table 2.

2-Hydroxybenzaldehydehyde (4a) *from 2-Hydroxybenzyl Alcohol and Paraformaldehyde.*—A mixture of the bromomagnesium salt of 2-hydroxymethylphenol (20 mmol) [from 2-hydroxymethylphenol (20 mmol) and ethylmagnesium bromide (40 mmol)], HMPA (20 mmol), and paraformaldehyde (20 mmol) in benzene (100 ml) was heated under reflux for 3 h. The product was worked up as above to give (4a) (2.3 g, 98%).

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