Regiospecificity in Reactions of Metal Phenoxides. Synthesis of 2,2'-alkylidenebisphenols

By Giovanni Casiraghi, Giuseppe Casnati, Andrea Pochini,* and Rocco Ungaro, Istituto di Chimica Organica dell'Università, Via M. D'Azeglio 85, 43100 Parma, Italy

The reactions between aryloxymagnesium bromides (1) with linear aliphatic aldehydes (2) and their acetals (10) in aprotic solvents of variable donicity have been investigated. In benzene high *ortho*-regiospecificity is observed in all cases, although with the aldehyde (2) the yield of 2,2'-alkylidenebisphenols (5) is usually low because of the competing aldehyde self-condensation. This process is avoided using diethyl acetals as electrophilic reagents which give the products (5) in good yields.

ALKYLIDENEBISPHENOLS represent a well known class of compounds of industrial interest.[1] The most widely used are 4,4'-isomers while the analogous *ortho*-(2,2') derivatives are less known because they are difficult to synthesize in good yields.

The most general and simple way for the synthesis of these compounds would be the reaction between aliphatic aldehydes and phenols, provided the numerous competing pathways these reactions usually experience can be controlled.[2]

We have attempted this direct way of synthesis using aryloxymagnesium bromides as substrates since these salts have shown high *ortho*-regiospecificity in the analogous reactions with aromatic aldehydes and formaldehyde giving 2,2'-arylmethylene-[3] and 2,2'-methylenebisphenols[4] in high yields.

We report in this paper the results of these studies.

RESULTS AND DISCUSSION

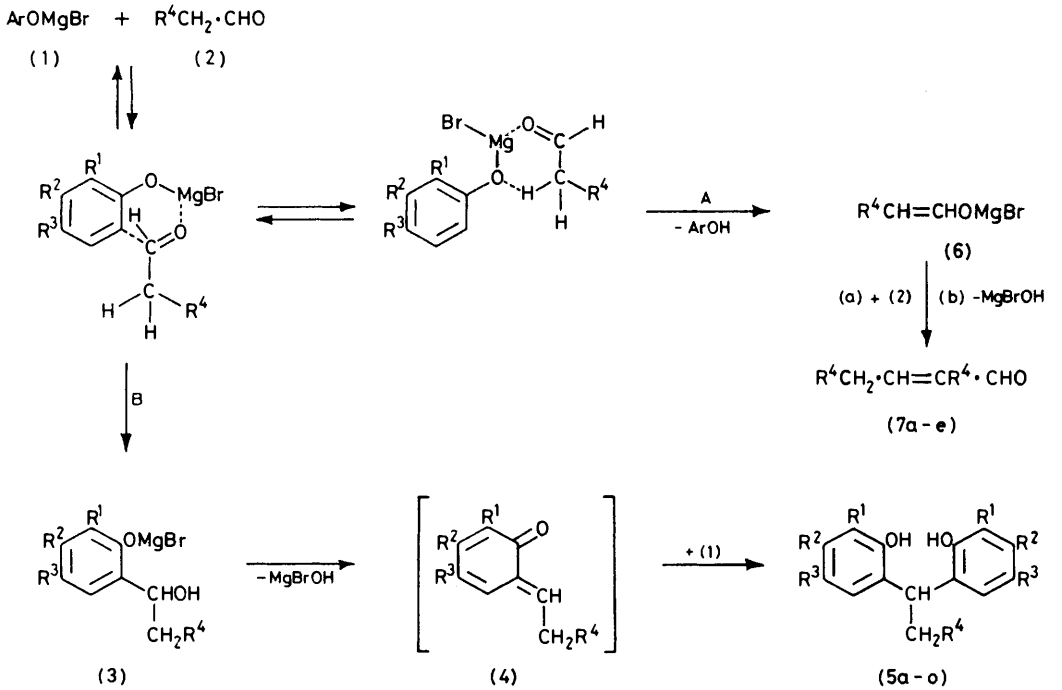
Preliminary results on the direct phenol–aldehyde condensation were obtained using phenoxymagnesium bromide and n-butanal as reagents in benzene (Table 1, entry 2).

2,2'-Butylidenebisphenol (5b), which derives from two consecutive *ortho* regioselective reactions within the complexes formed from the phenol salt (2) and aldehyde (1)[5] or *ortho*-quinone methide intermediate (4),[6] are the sole phenol–aldehyde condensation products observed.

The structure of compound (5b) has been established on the basis of its ^{1}H n.m.r. spectrum and by comparison with an authentic sample obtained *via* the reaction of 4-chlorophenol and n-butanal under acidic conditions followed by reductive removal of the chlorine.

The regioselectivity was higher than 90% (based on the reacted phenol) although the overall yield of (5b) was low as a result of the self-condensation of the aldehyde, which is the main competing reaction in these conditions.

This process can occur in a co-ordinate manner within the aldehyde-salt complex (Scheme, path A) where the formation of magnesium enolate (6) is competitive with



SCHEME 1 See Tables 1—3 for assignment of R^1, R^2, R^3, and R^4

the co-ordinate electrophilic attack on the aromatic nucleus (path B).*

To verify the limits of this direct synthetic approach we undertook a more extensive study of this reaction. We also examined the effect of the variation of some reaction parameters in order to increase the yields of the product (5).

The results obtained with different aldehydes and aryloxymagnesium bromides in benzene at various aldehyde : salt molar ratios are reported in Table 1.†

As the steric bulkiness of the alkyl groups on the aldehyde increases the yield of 2,2′-alkylidenebisphenols (5) (*R*). An increase in this ratio from stoicheiometric proportions (entry 14; $R = 0.5$) to equimolar (entry 13; $R = 1$) gives a small increase in the yield of products (5). A further increase in this ratio (entries 11 and 12) causes a decrease in the overall yield of the alkylidenebisphenols (5). This is in agreement with our previous results in similar systems which showed that on increasing the aldehyde : ArOMgBr molar ratio the oxygen reactivity of the phenoxide, which in this case leads to products (7), is enhanced because of the co-ordination of the aldehyde to magnesium counterion.[7]

The important role played by the predominant acid or

TABLE 1

Reactions of aryloxymagnesium bromides with linear aliphatic aldehydes [a]

Entry	Phenol (1) R¹	R²	R³	Aldehyde (2) R⁴	Molar ratio (2) (1)	Diphenylalkane (5) [yield (%)] [b]	Crotonic product (7) [yield (%)] [c]
1	H	H	H	Me	0.5	(5a) [57]	(7a) [30]
2	H	H	H	Et	0.5	(5b) [40]	(7b) [48]
3	H	H	H	Pr^n	0.5	(5c) [28]	(7c) [58]
4	H	H	H	Bu^n	0.5	(5d) [25]	(7d) [65]
5	H	H	H	n-C_5H_{11}	0.5	(5e) [10]	(7e) [85]
6	H	H	H	n-C_5H_{11}	1	(5e) [20]	(7e) [74]
7	H	H	Bu^t	Me	1	(5f) [42]	(7a) [47]
8	H	H	Bu^t	Et	1	(5g) [36]	(7b) [58]
9	H	H	Bu^t	Pr^n	1	(5h) [34]	(7c) [57]
10	H	H	Bu^t	Bu^n	1	(5i) [35]	(7d) [52]
11	H	H	Bu^t	n-C_5H_{11}	10	(5j) [27]	(7e) [36]
12	H	H	Bu^t	n-C_5H_{11}	2	(5j) [34]	(7e) [68]
13	H	H	Bu^t	n-C_5H_{11}	1	(5j) [40]	(7e) [60]
14	H	H	Bu^t	n-C_5H_{11}	0.5	(5j) [28]	(7e) [58]
15	Me	H	H	n-C_5H_{11}	1	(5k) [11]	(7e) [78]
16	H	Me	H	n-C_5H_{11}	1	(5l) [58]	(7e) [43]
17	H	H	Me	n-C_5H_{11}	1	(5m) [44]	(7e) [60]
18	Bu^t	H	H	n-C_5H_{11}	1	(5n) [25]	(7e) [73]
19	H	Bu^t	H	n-C_5H_{11}	1	(5o) [63]	(7e) [50]

[a] In refluxing anhydrous benzene for 3 h (conc. = 0.166M for entries 1—6 and 0.05M for entries 7—19). Reacted aldehyde = 100% in all the reactions but entry 11 (= 54%). [b] Calculated on the basis of phenol used. [c] Calculated on the basis of aldehyde used.

decreases, this effect being greater with phenol than with *p*-t-butylphenol as substrate.

The effect of the substituents on the phenolic nucleus can be seen by comparing entries 6, 13, and 15—19. Although alkyl groups in the *para*-position have little influence on product distribution those in the *meta*-position favour the formation of alkylidenebisphenols (5) over the aldehyde self-condensation products (7); in contrast the latter become predominant with *ortho*-substituted phenols.

Interesting information can be obtained by varying the aldehyde : aryloxymagnesium bromide molar ratio

basic character of the reacting ion-pair in controlling the two competing pathways is evidenced by the solvent effect in these reactions (see Table 2).

In tetrahydrofuran (THF) no aromatic electrophilic attack on the phenol nucleus is observed and self-condensation or oxidation–reduction processes of the aldehydes take place. In a solvent with higher donicity like hexamethylphosphoramide (HMPA) again no nuclear reactivity is observed but 1,3-diol monoesters (8e) and (9e) derived from the aldehyde, are produced in high yields.[7]

$$R^4CH_2{\cdot}CH(OX){\cdot}CH(R^4){\cdot}CH_2{\cdot}OY$$

(8) X = H; Y = $OCOCH_2R^4$

(9) X = $OCOCH_2R^4$; Y = H

From these results it appears that in order to obtain *ortho*-regiospecific attack on the phenolic nucleus,[5] it is necessary to operate in solvents with low donicity, in which the cation acidity is enhanced.

Attempts to increase the cation–anion interaction in the reacting ion-pair by using a less-polar solvent like

* Obviously when all the reactive positions on the phenolic nucleus are substituted, as in 2,4,6-trimethylphenoxymagnesium bromide, condensation products derived from aldehydes are the sole observed products.[7]

† The ^1H n.m.r. spectra of compounds (5) derived from *ortho*-alkylphenols show an AB_2 pattern in the 6.5—7.5 region which clearly indicates the 1,2,6-substitution. Moreover, the chemical shift of the methine proton in $CDCl_3$ (Supplementary material ‡) falls between δ 4.32 and 4.60 for all compounds (5), whereas for their isomers it usually appears at higher field: 3.7—4.0 for 2,4′- and 3.3—3.6 for 4,4′-alkylidenebisphenols.

‡ Results are available as a Supplementary Publication [Sup. No. 23209 (3 pages)]. For details of the Supplementary Publications Scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. I*, 1980, Index issue.

TABLE 2

Solvent effect on the reaction between *p*-t-butylphenoxymagnesium bromide and n-heptanal [a]

Solvent	*T* (°C)	Phenol reacted (%)	Product [yield (%)]	Aldehyde reacted (%)	Product [yield (%)]
Benzene	Reflux	44	(5) [40]	100	(7e) [60]
THF	Reflux	0		78	*b*
HMPT	80	0		100	(8e) + (9e) [80]
Hexane	Reflux	25	(5j) [20]	65	(7e) [40]

[a] Reaction time 3 h; aldehyde : ArOMgBr molar ratio = 1 : 1; conc. 0.166M. Reactions were homogenous in all cases except for that in n-hexane. [b] A complex mixture of products was obtained [(7e), (8e) + (9e), n-heptanal, and heptanoic acid were identified].

n-hexane did not result in any improvement in the yield of 2,2′-alkylidenebisphenols (5), probably because of the high insolubility of the salts and their complexes in this solvent.

From all these results it can be concluded that the reaction of aryloxymagnesium bromides and linear aliphatic aldehydes gives 2,2′-alkylidenebisphenols (5) in good yield only in a few cases, although the reaction is *ortho*-specific.

In order to avoid the self-condensation of the aldehyde and improve the yield of compounds (5), the reactions of acetals (10) with phenoxymagnesium bromides were examined.

The results are reported in Table 3 which shows that

TABLE 3

Reactions between phenoxymagnesium bromide and acetals [a]

Entry	R^4	R	R	Product [yield (%)]
1	Me	Et	Et	(5a) [70]
2	Et	Et	Et	(5b) [60]
3	Pr^n	Et	Et	(5c) [68]
4	n-C_5H_{11}	Et	Et	(5e) [72]
5	n-C_5H_{11}	CH_2–CH_2		(5e) [30]

[a] In refluxing benzene for 24 h; acetal : ArOMgBr molar ratio = 2 : 1; conc. 0.166M.

2,2′-alkylidenebisphenols (5) are produced in good yields using these aldehyde derivatives.

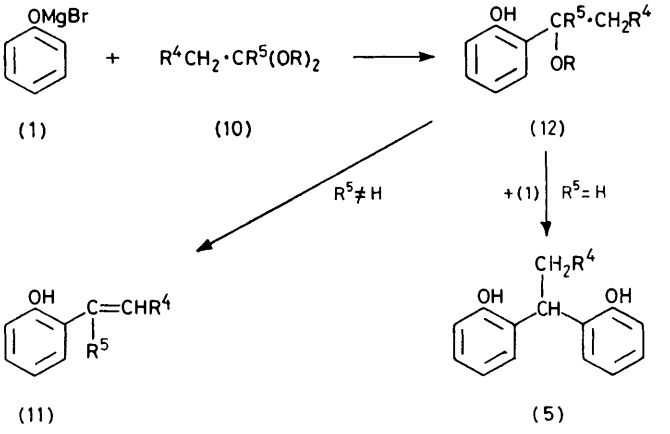
Acetals like ketals studied previously [8] give *ortho*-regiospecific processes with magnesium phenoxides * although they produce mainly 2,2′-alkylidenebisphenols (5) instead of *ortho*-alkenylphenols (11) which are obtained with ketals. Evidently, the presence of two alkyl groups on the double bond of the products favours the elimination process from the ether intermediate (12) in the case of ketals † (Scheme 2).

Special mention deserves the type of acetal used. Diethyl acetals are more reactive and selective than cyclic ones (2-alkyl-1,3-dioxolans) which were also studied.

Conclusions.—The results obtained confirm that linear aliphatic aldehydes and their acetals give *ortho*-regiospecific processes with phenol magnesium salts in benzene as observed with other electrophilic reagents.

With aldehydes the yield of 2,2′-alkylidenebisphenols (5) is usually low because of the competing aldehyde self-condensation which cannot be avoided.

However, this reaction can also be useful when the yields are not very high, since the starting materials are



SCHEME 2

usually simple and the reaction products (5) are easily isolated in a pure form. On the other hand, the diethyl acetals of linear aliphatic aldehydes under the same conditions give 2,2′-alkylidenebisphenols in good yields. These are two complementary synthetic routes and represent a more direct approach to the synthesis of alkylidenebisphenols of the 'symmetrical' type compared with the method we have recently proposed,[10] which uses 2-hydroxybenzaldehyde as starting material.

The behaviour of diethyl acetals compared with ketals, which mainly give 2-alkyenylphenols, and with 1,3-dioxolans (much less reactive and selective) shows that in co-ordinated reactions of metal phenoxides small structural variations can substantially modify the reaction course.

EXPERIMENTAL

For general directions and analytical instrumentation see refs. 3 and 4.

All phenols were reagent grade and were used without further purification. Aldehydes were distilled before use and stored under nitrogen. Diethyl acetals [12] and 1,3-dioxolans [13] were prepared following known procedures.

Reactions of Aryloxymagnesium Bromides (1) *with Linear*

* Crombie *et al.*[9] have observed *ortho*-regiospecific processes during the chromenylation of magnesium phenoxides with α,β-unsaturated aldehyde dimethyl acetals.

† This seems to be quite general behaviour in the reactions of aryloxymagnesium bromides in media of low polarity, since it has also been observed by us using 2-hydroxybenzyl alcohols [10] and α-branched aldehydes [11] as reagents.

Aliphatic Aldehydes (2) *and their Acetals* (10): *General Procedure*.—The benzene solution of aryloxymagnesium bromides was prepared as previously described.[3] The aldehydes or their acetals were added at room temperature to this solution and the reaction mixture heated under reflux with stirring for the time required (see Tables 1 and 3). After cooling the reaction mixture was poured into an excess of a saturated aqueous solution of NH_4Cl, extracted with diethyl ether, and the combined ethereal extracts dried over Na_2SO_4. Known aliquots of this solution were submitted to quantitative g.l.c. analysis [5% DEGS for phenols; 20% Carbowax 1000 and 20 M for aldehydes; 3% SE 30 for 2,2-alkylidenebisphenols (5). For the analysis of the aldehyde crotonization products see ref. 7]. Ether solvent was removed from the remaining solution and the oily residue submitted to steam distillation which usually gives crude compound (5) of good purity. Further purification of products (5) was performed by preparative t.l.c. (hexane–ethyl acetate, 9 : 1). The preparative detail in respect of compounds (5) is summarized in Tables 1 and 3 and ^1H n.m.r. spectral data in Supplementary Publication No. 23209 (3 pages).* All products are glassy materials except (5f) (m.p. 65 °C). Elemental analyses were in agreement with calculated ones (C $\pm$0.28; H $\pm$0.18%; see Supplementary Publication).

Reaction of p-*t-Butylphenoxymagnesium Bromide with n-Heptanal in Different Solvents*.—The reaction in THF was performed on the salt obtained by exchange between *p*-t-butylphenol and EtMgBr prepared in the same solvent. Reactions in HMPA and hexane were carried out preparing first an ethereal solution of the salt as described for benzene solution, removing diethyl ether under reduced pressure and replacing it with the higher boiling solvents.

Synthesis of 2,2′-*Butylidenebisphenol* (5b).—To a stirred solution of 4-chlorophenol (0.1 mol) in 75% sulphuric acid (60 ml) at 0 °C n-butanal (0.05 mol) was added. After 3 h the solution was neutralized and extracted with diethyl ether. Removal of the solvent gave an oil which was treated overnight with nickel–aluminium alloy (5 g) suspended in 5% NaOH solution (100 ml).[14] After filtration and neutralization the reaction mixture was extracted with diethyl ether and submitted to steam distillation after evaporation of the solvent. The product, compound (5b), was further purified by preparative t.l.c. and showed the same chromatographic behaviour and spectral data as for the product obtained in the reaction between phenoxymagnesium bromide and n-butanal or its diethyl acetal.

* For details of the Supplementary Publication Scheme, see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, Index issue, 1980.

This work was partially supported by a grant from C.N.R., Italy.

[1/572 *Received*, 10*th April*, 1981]

REFERENCES

[1] See *e.g.* H. Schnell and H. Krimm, *Angew. Chem.*, 1963, **75**, 662; *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 373; H. W. B. Reed, 'Alkylphenols' in 'Kirk-Othmer Encyclopedia of Chemical Technology,' Wiley–Interscience, New York, 1978, 3rd edn., vol. 2, p. 72.

[2] K. D. Bode, in 'Houben–Weil Methoden der Organischen Chemie,' G. Thieme Verlag, Stuttgart, 1976, Phenole Teil 2, vol. 6/1c, p. 1054.

[3] G. Casiraghi, G. Casnati, M. Cornia, G. Sartori, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2077.

[4] G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Puglia, G. Sartori, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 1*, 1978, 318.

[5] E. Dradi, A. Pochini, and R. Ungaro, *Gazz. Chim. Ital.*, 1980, **110**, 353.

[6] G. Casiraghi, G. Casnati, M. Cornia, A. Pochini, G. Sartori, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 1*, 1978, 322.

[7] G. Casnati, A. Pochini, G. Salerno, and R. Ungaro, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1527.

[8] G. Casiraghi, G. Casnati, G. Sartori, and G. Terenghi, *J. Chem. Res.*, 1977, (*S*), 96; (*M*) 1123.

[9] G. O. Asgill, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1978, 59.

[10] A. Pochini and R. Ungaro, *Synthesis*, 1978, 617.

[11] G. Casnati, A. Pochini, G. Terenghi, and R. Ungaro, unpublished results.

[12] J. A. Van Allan, *Org. Synth.*, Coll. Vol. 4, 1963, 21; S. M. McElvein, R. L. Clark, and G. D. Jones, *J. Am. Chem. Soc.*, 1942, **64**, 1966.

[13] V. I. Stenberg, G. F. Vesley, and D. Kubik, *J. Org. Chem.*, 1971, **36**, 2551.

[14] S. R. Finn, J. W. James, and C. G. S. Standen, *Chem. Ind.* (*London*), 1954, 188.