Regiospecificity in Reactions of Metal Phenoxides: 2,2′-Dihydroxytriphenylmethanes from Aryloxymagnesium Bromides and Aromatic Aldehydes

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C-Regiospecific attack of aromatic aldehydes at the *ortho*-position of an aryloxymagnesium bromide in benzene leads to 2,2′-dihydroxytriphenylmethanes in excellent yields. A chelate reaction mechanism is proposed as the basic reason for the exclusive *ortho*-substitution.

ACID-CATALYSED reactions of benzaldehyde and its derivatives with phenols have been extensively studied and shown to be nonregiospecific.[1] Mixtures of isomeric hydroxytriphenylmethanes were obtained. Reactions of aldehydes with metal phenoxides, which are commonly supposed to be unreactive,[2] are as yet unknown.

We found that phenoxymagnesium bromides reacted easily in benzene with aromatic aldehydes giving 2,2′-dihydroxytriphenylmethanes in good yields.[3] Preparative data are summarized in Table 1.

TABLE 1

2,2′-Dihydroxytriphenylmethane derivatives

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	M.p. (°C)	Colour [a]	Yield (%) [b,c]	Solvent [d]
(1)	H	H	H	H	H	H	H	128—129	c	42	A + B
(2)	Me	H	H	H	H	H	H	127—128	c	80	A + B
(3)	H	H	Me	H	H	H	H	158—159	c	80	B + C
(4)	H	Me	H	H	H	H	H	141—142	c	85	A + B
(5)	Pr^i	H	H	H	H	H	H	104—105	c	96	A + B
(6)	H	H	Pr^i	H	H	H	H	Glass	c	88	
(7)	Bu^t	H	H	H	H	H	H	135—136	c	95	C
(8)	H	H	Bu^t	H	H	H	H	Glass	c	79	
(9)	HH	H	OMe	H	H	H	H	130—132	c	78	A + B
(10)	H	NMe_2	H	H	H	H	H	158—160	p	64	B
(11)	Me	H	H	Me	H	H	H	98—100	c	69	A + B
(12)	Pr^i	H	H	Me	H	H	H	112—113	c	87	B
(13)	Me	H	Me	H	H	H	H	106—108	c	70	A + B
(14)	H	NMe_2	H	H	H	H	NO_2	118—120	y	90	B
(15)	H	H	Me	H	H	H	NO_2	230—232	y	90	B
(16)	H	Me	H	H	H	H	NO_2	181—183	y	93	B
(17)	H	H	Bu^t	H	H	H	NO_2	239—240	y	40	B + C
(18)	H	Bu^t	H	H	H	H	NO_2	187—188	y	70	B
(19)	H	H	H	H	H	H	NO_2	173	y	55	B + C
(20)	H	H	Me	H	Cl	H	H	174—175	c	60	B
(21)	H	NMe_2	H	H	Cl	H	H	205—207	p	90	B
(22)	H	H	Me	H	NO_2	H	Cl	172—174	y	80	A + B
(23)	H	H	Me	H	H	H	Me	139—140	c	30	A + D
(24)	H	H	Me	H	H	H	NMe_2	205—206	g	10	B
(25)	H	H	Me	H	Cl	H	NO_2	125—127	y	75	B
(26)	H	H	H	H	H	H	Cl	108—110	c	68	A + D
(27)	H	H	H	H	H	Cl	H	139—140	c	50	B
(28)	H	H	H	H	H	H	Me	107—108	c	25	A + B
(29)	H	H	H	H	Me	H	H	157—159	c	25	B

[a] Colour: c = colourless, p = pink, y = yellow, g = green. [b] Reaction time 20 h in refluxing benzene, mole ratio 1 : 1 of phenoxymagnesium bromide to aldehyde. Yield based on the phenol. [c] Starting material was recovered almost quantitatively in most cases making the effective yield higher. [d] Solvent for recrystallization: A = light petroleum (b.p. 40—70°), B = benzene, C = hexane, D = $CHCl_3$.

Triphenylmethanes (1)—(29) were identified mainly by ^1H n.m.r. spectra: the pattern of the aromatic protons is consistent with *ortho*-substitution on the phenol ring, and the chemical shift of the methine proton [δ ($CDCl_3$) 5·75—6·20] is in agreement with analogous results.[4] The singlet of the methine proton in 2,2′-dihydroxytriphenylmethanes appears at lower field than the 2,4′- (δ 5·50—5·70) and 4,4′-dihydroxytriphenylmethane isomers (δ 5·20—5·40).

The structure of (1) was also confirmed by comparison with an authentic sample obtained by condensation of 2,4-dichlorophenol and benzaldehyde under acidic conditions (CH_3CO_2H–H_2SO_4) followed by reductive removal of the chlorine (Raney nickel–sodium hydroxide).

Formation of 2,2′-dihydroxytriphenylmethanes can be rationalized as shown in the Scheme: an initial *C*-regiospecific attack of the aromatic aldehyde at the *ortho*-position of the phenoxymagnesium bromide leads to a bromomagnesium salt of *o*-hydroxydiphenylmethanol [type (30)]; a subsequent *C*-regiospecific attack of a second molecule of aryloxymagnesium bromide on this leads to 2,2′-dihydroxytriphenylmethane.

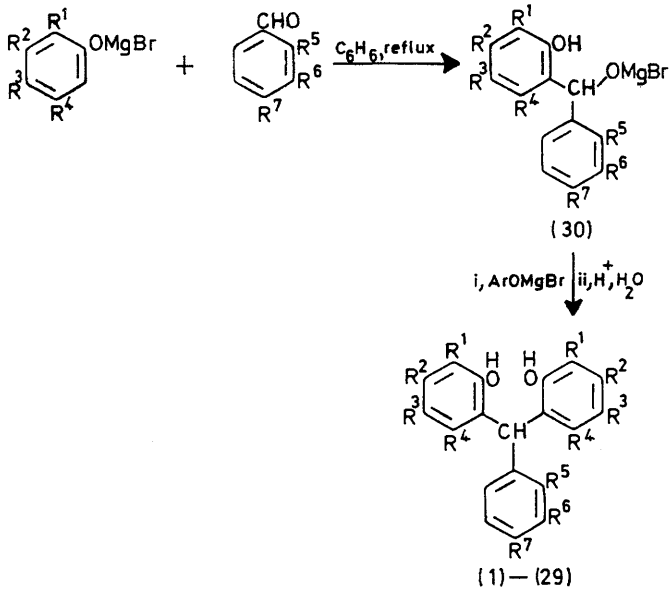
[1] G. A. Olah, 'Friedel–Crafts and Related Reactions,' Interscience, London, 1964, vol. II, part I, p. 597.

[2] R. Gompper, *Angew, Chem. Internat. Edn.*, 1964, **3**, 560; H. Gilman and F. Schulze, *Rec. Trav. chim.*, 1928, **47**, 752.

[3] Preliminary communication, G. Casiraghi, G. Casnati, and G. Sartori, *Tetrahedron Letters*, 1971, 3969.

[4] V. Böhmer and B. Matthiasch, *Makromol. Chem.*, 1971, **148**, 41.

Isolation of the carbinol intermediate (30; $R^1 = R^3 = R^4 = R^5 = R^6 = R^7 = H$, $R^2 = NMe_2$) was achieved from the reaction of *m*-dimethylaminophenoxymagnesium bromide and benzaldehyde under mild



SCHEME

conditions (benzene at room temperature); the subsequent reaction of the bromomagnesium salt of this intermediate with *m*-dimethylaminophenoxymagnesium bromide under the usual conditions leads to product (10), the same as obtained directly from *m*-dimethylaminophenoxymagnesium bromide and benzaldehyde, thus providing evidence for the reaction pathway we have suggested. Furthermore, (1) is the sole product of the reaction of the bromomagnesium salt of *o*-hydroxydiphenylmethanol with phenoxymagnesium bromide.

The main features of this reaction are the selectivity in the attack of an aromatic aldehyde at an ambident phenoxide ion and the lack of polyalkylated products. A *C-ortho*-regiospecific attack was always observed although attack at the *para*-position is possible (see Table 1). The exclusive preference of bond formation solely on the *ortho*-carbon of ambident phenoxide ions was shown by the lack of reaction of the *o,o'*-disubstituted phenoxymagnesium bromides (*e.g.* 2,6-dimethyl) under the usual reaction conditions.

An increase of the nucleophilicity of the phenolic substrate always enhanced the reactivity of the system, and poor nucleophilic substrates (*p*-Cl, *o*-NO_2, *p*-NO_2, *o*-CO_2Me, and *p*-CO_2Me phenoxymagnesium bromides) did not react at all under the usual reaction conditions. Analogously, electron-withdrawing substituents on aromatic aldehydes produced an increase and electron-donating substituents a decrease in the reactivity of the system (see Table 2).

Finally, we found that, in contrast with the excellent reactivity of phenoxymagnesium halides in benzene, sodium phenolates exhibited no reactivity; moreover solvents which are especially effective at solvating cations (ether, tetrahydrofuran) strongly reduced the reactivity of phenoxymagnesium halides.

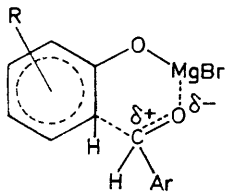
TABLE 2

Effect of substituents in the reactions of some phenoxymagnesium bromides (0·02 mol) with aromatic aldehydes (0·02 mol) in refluxing benzene (100 ml)

Phenol substituent	Benzaldehyde substituent	Time (h)	Conversion (%) *
H	H	20	44·0
2-Me	H	20	83·5
3-Me	H	20	88·1
3-NMe_2	H	20	97·3
4-Cl	H	48	1·5
2- and 4-NO_2	H	48	0·0
2- and 4-CO_2CH_3	H	48	0·0
H	4-NO_2	20	65·0
H	4-Cl	20	72·6
H	4-Me	20	26·8
H	4-NMe_2	20	8·7

* The % conversion of the phenol was determined by g.l.c.

On these bases and according to the mechanism previously proposed for the reaction of benzylmagnesium chloride with aliphatic aldehydes [5] and for selective hydroxymethylation of phenols [6] we suggest a mechanism which involves chelation of the metal counter-ion (MgX^+) with the phenoxy-function and with the electrophilic reagent, thus favouring *C-ortho*-regiospecific attack.



EXPERIMENTAL

I.r. spectra were determined on a Perkin-Elmer 475 spectrophotometer (KCl discs), n.m.r. spectra on a JEOL C-60-HL instrument (Me_4Si as standard), and mass spectra on a Hitachi–Perkin-Elmer 6D spectrometer (70 eV). Elemental analyses were performed at the Istituto di Chimica Farmaceutica e Tossicologica dell'Università di Parma. Satisfactory analytical and i.r. and n.m.r. spectroscopic data were obtained for all the compounds: the data are tabulated in Supplementary Publication No. SUP 21063 (3 pp.).*

Preparation of 2,2'-Dihydroxytriphenylmethanes (1)—(29). —*General procedure.* A solution of phenol (0·2 mol) in anhydrous ethyl ether (200 ml) was added dropwise at room temperature with stirring to a solution of ethylmagnesium bromide (0·2 mol) in dry ether (200 ml). Most of the ether was removed by distillation under nitrogen, then benzene (200 ml) was added. Distillation was continued until the temperature rose to 80° in order to remove completely the ether. Anhydrous benzene (500 ml) was then added and after cooling, a solution of the aromatic aldehyde (0·2 mol) in benzene (200 ml) was added dropwise with stirring.

[5] D. V. Joffe and M. I. Mostova, *Russ. Chem. Rev.*, 1973, **42** (1), **56**, and references therein.

[6] H. G. Peer, *Rec. Trav. chim.*, 1960, **79**, 825.

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue (items less than 10 pp. are supplied as full-size copies).

The volume was adjusted to 1 l and the mixture was heated with stirring under reflux for 20 h, then neutralized (pH 7) with 2N-hydrochloric acid and extracted with ether. The solvent was evaporated *in vacuo*. The unchanged phenol was removed by steam distillation and the product was obtained by recrystallization of the residue. Physical data are summarized in Table 1 and i.r. and n.m.r. data in Supplementary Publication No. 21063 (3 pp.).

4-Dimethylamino-2-hydroxydiphenylmethanol (30).—A mixture of *m*-dimethylaminophenoxymagnesium bromide (0·02 mol), prepared as above, and benzaldehyde (0·02 mol) in benzene (100 ml) was stirred at room temperature for 6 h, then neutralized with dilute hydrochloric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and concentrated; the pink precipitate obtained was washed with ether. Recrystallization from benzene of the crude carbinol gave pure product (2·4 g, 49%) as a light pink powder, m.p. 215° (decomp.), $\nu_{max.}$ (KBr) 3150, 1230, and 1020 cm^{-1}, M^+ 243, δ [$(CD_3)_2SO$] 2·8 (6H, s, NMe_2), 5·6 (1H, d, *J* 3·7 Hz, disappeared with D_2O, CH·O*H*), 5·82 (1H, d, *J* 3·7 Hz, collapsed to s with D_2O, C*H*·OH), 6·0—7·3 (8H, m, aromatic), and 9·1 (1H, s, disappeared with D_2O, phenolic OH).

4,4′-Bisdimethylamino-2-2′-dihydroxytriphenylmethane (10).—A mixture of *m*-dimethylaminophenoxymagnesium bromide (0·02 mol) and the bromomagnesium salt of 4-dimethylamino-2-hydroxyphenylmethanol (0·02 mol), prepared as above, was heated with stirring under reflux in benzene (100 ml) for 20 h, then neutralized at pH 7 with 2N-hydrochloric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated *in vacuo*. Recrystallization of the residue from benzene gave (10) (5·5 g, 76%), spectroscopically identical with the product prepared according to the general procedure.

2,2′-Dihydroxytriphenylmethane (1).—(*a*) A mixture of phenoxymagnesium bromide (0·02 mol) and the bromomagnesium salt of 2-hydroxydiphenylmethanol (0·02 mol), prepared as above, was heated with stirring under reflux in benzene (100 ml) for 20 h, then neutralized to pH 7 with 2N-hydrochloric acid and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated *in vacuo*. Recrystallization of the residue from light petroleum–benzene gave (1) (4·8 g, 87%), spectroscopically identical with the product prepared according to the general procedure.

(*b*) A mixture of 2,4-dichlorophenol (0·02 mol) and benzaldehyde (0·01 mol) in glacial acetic acid was stirred at room temperature for 5 h with 96% sulphuric acid (1 ml). The mixture was poured into iced water and extracted with ether. The ether solution was washed with aqueous $NaHCO_3$ and with water, dried (Na_2SO_4), and evaporated *in vacuo*. The oily residue was dissolved in aqueous 10% NaOH (25 ml) and treated with Raney nickel (2·5 g) at 30—35°. The mixture was left overnight, and then neutralized with 2N-hydrochloric acid. Extraction with ether and evaporation of the solvent gave an oily residue which was purified by chromatography on silica gel (0·02—0·05 mm). Elution with hexane–ethyl acetate (95 : 5) gave (1) (1·2 g, 21%), spectroscopically identical with the product prepared according to method (*a*).

[4/468 *Received*, 11*th March*, 1974]