Cationic Control on Competing Reactions: Selective Synthesis of 1,1-Bis[2-hydroxyaryl]alkanes

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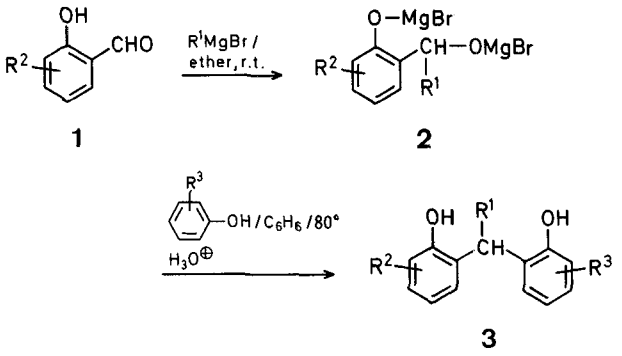
Although diaryl- and triarylalkane derivatives are well known because of their industrial use as antioxidants[1,2], 1,1-bis[2-hydroxyaryl]alkanes **3** have more rarely been described in the literature than the corresponding 1,1-bis[4-hydroxyaryl]alkanes which are well known[3]. The few cases reported are all of the "symmetrical" type ($R^2 = R^3$) which are usually obtained from the condensation of aldehydes with phenols in the presence of acid of alkaline catalysts.

"*Unsymmetrical*" *1,1-bis[2-hydroxyaryl]alkanes* ($R^2 \neq R^3$) are practically unknown substances and no general method of synthesis is available. We now propose a new, general, *one-pot method for the synthesis of both symmetrical and* unsymmetrical compounds of this class starting from 2-hydroxybenzaldehydes **1**.



The simple method consists of treatment of **1** with a suitable Grignard reagent in diethyl ether, addition of a phenol, and refluxing in benzene for 3–4 h. The use of one molar excess of the Grignard reagent and of the phenol (which can be easily recovered after the work up of the mixture)

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allows a complete conversion in the first step **1**→**2** and a higher rate in the second **2**→**3**, which results in a better overall yield in **3** [usually 80–90%].

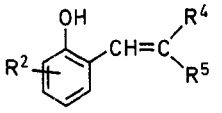
Table 1. 1,1-Bis[2-hydroxyaryl]alkanes (**3**) prepared

3	R^1	R^2	R^3	Yield [%][a]	m.p.[b]	Molecular formula[c]
a	n-C_6H_{13}	3′-H_3C	3-H_3C	78	glass	$C_{21}H_{28}O_2$ (312.4)
b	i-C_3H_7	H	H	75	112–113°	$C_{16}H_{18}O_2$ (242.3)
c	n-C_3H_7	H	3-i-C_3H_7	80	58–59°	$C_{19}H_{24}O_2$ (284.4)
d	i-C_3H_7	H	3-H_3C	80	172–173°	$C_{17}H_{20}O_2$ (256.3)
e	i-C_3H_7	H	4-H_3C	97	80–81°	$C_{17}H_{20}O_2$ (256.3)
f	i-C_3H_7	H	3-i-C_3H_7	87	103–105°	$C_{19}H_{24}O_2$ (284.4)
g	i-C_3H_7	H	3-t-C_4H_9	55	78–79°	$C_{20}H_{26}O_2$ (298.4)
h	i-C_3H_7	3′-H_3C	3-i-C_3H_7	85	104–106°	$C_{20}H_{26}O_2$ (298.4)
i	i-C_3H_7	4′-Cl	3-H_3C	90	98–100°	$C_{17}H_{19}ClO_2$ (290.8)

[a] Yields of pure isolated products based on **1**.
[b] Uncorrected; from light petroleum/benzene 2:1.
[c] All products gave satisfactory microanalyses (C, ±0.35; H, ±0.30; Cl, −0.03).

The key step in this procedure is the *ortho*-regioselective reaction of the alcohol **2** with aryloxymagnesium bromides in media of low polarity. We have recently shown[4] that *ortho*-regioselectivity in the reactions of aromatic alcohols with magnesium phenoxides is achieved only with substrates like **2** which can generate orthoquinone methide intermediates on treatment with the appropriate amount of magnesium salt.

Several competing reactions, i.e. *para*-attack, polycondensation, and dehydration of the alcohol **2** to form 2-alkenylphenols **4** or coumarans **5** which occur readily when R^1 is a branched alkyl chain[5], are all suppressed under these conditions in favour of the above reaction scheme to give **3**.



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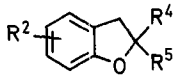

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Moreover, symmetrical 1,1-bis[2-hydroxyaryl]alkanes such as **3a** are usually obtained in low yield even in the reactions of aryloxymagnesium bromides with linear aliphatic aldehydes in media of low polarity[5,6], due to the competing self-condensation reactions of the aldehydes[7].

The structures of all products **3** were established on the basis of their analytical and spectroscopic data (Table 2)

Table 2. Spectroscopic Data of Compounds **3**

Product	Mass Spectra[a] *m/e* (rel. intensity)	I.R.[b] [KBr] ν_{max} [cm^{-1}]	^{1}H-N.M.R.[c] δ [ppm]
3a	312 (100), 227 (90)	750	0.7–1.8 (m, 13H, n-C_6H_{13}); 2.20 (s, 6H, $2ArCH_3$); 4.45 (t, 1H, Ar_2CH—CH_2—, J = 7.5 Hz); 6.6–7.2 (m, 6H_{arom}); 7.70 (bs, 2H, OH)
3b	242 (7), 199 (100), 181 (14), 153 (19)	825, 806 755, 740	0.94 [d, 6H, $(H_3C)_2CH$—, J = 6 Hz]; 2.80 [m, 1H, >CH—$CH(CH_3)_2$]; 4.20 (d, 1H, Ar_2CH—CH<, J = 11 Hz); 6.9–7.6 (m, 8H_{arom}); 7.75 (bs, 2H, OH)
3c	284 (95), 255 (17), 241 (100), 199 (50)	826, 760 745	0.6–2.2 (m, 13$H_{aliphatic}$); 3.2 [m, 1H, $(H_3C)_2CH$—]; 4.45 (t, 1H, Ar_2CH—CH_2—, J = 7.5 Hz); 6.2 (bs, 2H, OH); 6.5–7.3 (m, 7H_{arom})
3d	256 (10), 213 (100)	820, 770, 755, 740, 715	0.90 [d, 6H, $(H_3C)_2CH$—, J = 6 Hz]; 2.18 (s, 3H, $ArCH_3$); 2.75 [m, 1H, >CH—$CH(CH_3)_2$]; 4.18 (d, 1H, Ar_2CH—CH<, J = 11 Hz); 6.9–7.5 (m, 7H_{arom}); 8.3 (bs, 2H, OH)
3e	256 (10), 213 (100), 195 (15), 185 (13)	840, 820, 810, 750, 715	0.94 [d, 6H, $(H_3C)_2CH$—, J = 6 Hz]; 2.24 (s, 3H, $ArCH_3$); 2.75 [m, 1H, >CH—$CH(CH_3)_2$]; 4.10 (d, 1H, Ar_2CH—CH<, J = 11.5 Hz); 6.6–7.5 (m, 7H_{arom}); 6.3 and 7.7 (bs, 2H, OH)
3f	284 (7), 241 (100), 199 (14), 107 (11)	820, 770, 750, 705	0.90 [d, 6H, >CH—$CH(CH_3)_2$, J = 6 Hz]; 1.14 and 1.20 [2d, 6H, $ArCH(CH_3)_2$, J = 7 Hz]; 2.70 [m, 1H, >CH—$CH(CH_3)_2$]; 3.24 [m, 1H, $ArCH(CH_3)_2$]; 4.12 (d, 1H, Ar_2CH—CH<, J = 11.5 Hz); 6.6–7.5 (m, 7H_{arom} + 2OH)
3g	298 (5), 255 (100), 199 (10), 107 (19)	845, 820, 770, 750, 690	0.90 [d, 6H, $-CH(CH_3)_2$, J = 6 Hz]; 1.40 (s, 9H, t-C_4H_9); 2.65 [m, 1H, >CH—$CH(CH_3)_2$]; 4.12 (d, 1H, Ar_2CH—CH<, J = 11.5 Hz); 6.3 (bs, 1H, OH); 6.5–7.5 (m, 7H_{arom} + OH)
3h	298 (6), 255 (100), 213 (14), 121 (10)	826, 810, 780, 762, 750	0.90 [d, 6H, >CH—$CH(CH_3)_2$, J = 6 Hz]; 1.16 and 1.25 [2d, 6H, $ArCH(CH_3)_2$, J = 7 Hz]; 2.2 (s, 3H, $ArCH_3$); 2.65 [m, 1H, >CH—$CH(CH_3)_2$]; 3.25 [m, 1H, $ArCH(CH_3)_2$]; 4.15 (d, 1H, Ar_2CH—CH<, J = 11 Hz); 6.2 (bs, 2H, OH); 6.6–7.4 (m, 6H_{arom})
3i	290 (6), 247 (100), 212 (12), 165 (15)	900, 860, 848, 832, 828, 800, 775, 758	0.90 [d, 6H, $-CH(CH_3)_2$, J = 6 Hz]; 2.20 (s, 3H, $ArCH_3$); 2.65 [m, 1H, >CH—$CH(CH_3)_2$]; 4.0 (d, 1H, Ar_2CH—CH<, J = 11 Hz); 6.6–7.4 (m, 6H_{arom} + 2OH)

[a] Recorded on Varian MAT CH5 at 70 eV.
[b] Recorded on a Perkin Elmer 137 instrument. Only out of plane bending absorptions (ν_{max} < 900 cm^{-1}) are reported.
[c] Recorded on Jeol C60 HL instrument at 60 MHz, TMS as internal standard. All spectra were taken in $CDCl_3$; for **3d** acetone-d_6 was used.

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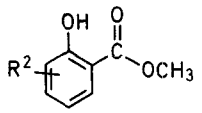
and in few cases (**3b, 3d**) by comparison with their 2,4'- and 4,4'-dihydroxy-isomers obtained by known methods.

Since the starting materials **1** are readily obtained from phenols through a new method discovered in this laboratory[8], the proposed synthesis of 1,1-bis[2-hydroxyaryl]alkanes **3** seems to be valuable.

Attempts to apply the above reaction scheme to 2-hydroxybenzoates **6** in order to obtain compounds **7** were unsuccessful. Even when using a linear Grignard reagent ($R^1 = C_2H_5$) the elimination products **8** were obtained mainly.



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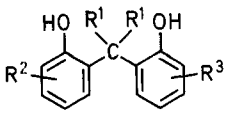

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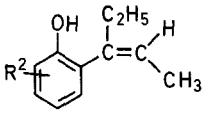

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Preparation of 1,1-Bis[2-hydroxyaryl]alkanes 3; General Procedure:

The 2-hydroxybenzaldehyde **1** (0.02 mol) dissolved in anhydrous diethyl ether (30 ml) is added slowly at room temperature to a stirred solution of the Grignard reagent (0.08 mol) in ether (100 ml). The phenol (0.04 mol) dissolved in anhydrous benzene (50 ml) is then added and the solvent distilled off until the temperature reaches 80° while at the same time more benzene is added to keep the volume at ~150 ml. The reaction mixture is heated under reflux for additional 3 h, cooled, then poured in saturated aqueous ammonium chloride, acidified with dilute hydrochloric acid, and extracted with diethyl ether. The ethereal extracts are washed with water and submitted to steam distillation which separates the excess of the phenol from a residue containing almost pure **3**, which is then extracted and purified by crystallization or preparative thin-layer chromatography (**3a, 3g**) on silica gel using hexane/diethyl ether (9:1).

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