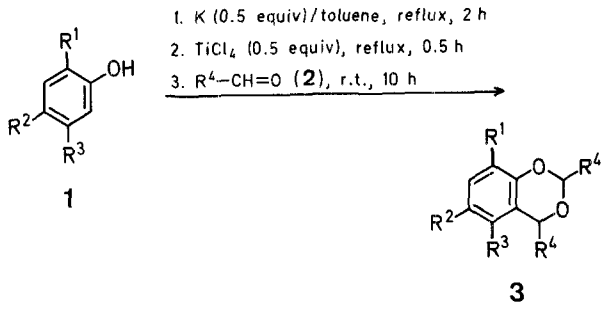
Unusual Friedel-Crafts Reactions; 2[1]. An Improved Synthesis of 2,4-Disubstituted 4*H*-1,3-Benzodioxins from Phenols and Aliphatic Aldehydes

Franca BIGI, Giovanni CASIRAGHI, Giuseppe CASNATI, Giovanni SARTORI*

Istituto di Chimica Organica dell'Università, Via M. D'Azeglio 85, I-43100 Parma, Italy

In the course of our reinvestigations of the reactions between phenols and electrophilic substances, we have devised a promising approach to *ortho*-substituted phenols by the co-operative use of alkali phenolates and Lewis acid systems[2,3].

As a part of this investigation we now report a mild and selective synthesis of 2,4-disubstituted 4*H*-1,3-benzodioxins **3** from phenols **1** and aliphatic aldehydes **2** in the presence of an equimolar combination of potassium phenoxides and a Lewis acid.



Treatment of a 1:1 molar mixture of phenol **1** and its potassium salt in toluene with an aliphatic aldehyde **2** (2 equiv) in the presence of 1 equiv of titanium(IV) chloride at room temperature affords optically inactive 4*H*-1,3-benzodioxins **3a-g** in high yields. Isolation of the product is achieved by quenching with aqueous sodium hydroxide, extraction, evaporation, and distillation in vacuo.

As shown in Table 1, the reaction is of broad applicability with respect to both phenol and aldehyde. Exceptions are due to the lethargy of strongly electron-withdrawing substituted phenols and to the extensive phenol over-alkylation when paraformaldehyde is used.

In the phenol/acetaldehyde reaction, the optimum yield of **3a** is obtained using a 1:1 molar ratio of potassium phenoxide/titanium(IV) chloride. The use of varied combinations such as potassium phenoxide/aluminium chloride, potassium phenoxide/tin(IV) chloride, sodium phenoxide/titanium(IV) chloride, and potassium phenoxide alone cause a significant decrease in yield.

The synthesis of **3** via acid-catalyzed phenol/aldehyde condensation is a well known process[5-8]. However this method, involving strongly acidic catalysts, is conveniently applied only to phenols with the *para*-position hindered and fails in other cases. Here we point out that, in comparison to the above route, our process offers the three major advantages of selectivity, mild conditions, and wider applicability.

The analytical, physical and spectral data of all products **3a-g** (Table 2) are consistent with the 4*H*-1,3-benzodioxin structure[4].

The purity of the products was checked by T.L.C. on silica gel 60 F254, eluent: hexane/ethyl acetate (9:1 v/v) and by G.L.C. (pyrex capillary column, SE 52, 20 m × 3 mm). The latter technique shows that, except for **3g**, one compound predominates between the two possible stereoisomers. The stereochemical assignments of optically inactive compounds **3a-g** have not been performed. The stereoisomer ratios obtained from integrated chromatograms (peak area ratios) are: **3a**, 85:15; **3b**, 96:4; **3c**, 99:1; **3d**, 98:2; **3e**, 97:3; **3f**, 80:20; **3g**, 50:50.

Table 1. 4*H*-1,3-Benzodioxins (**3a-g**) from Phenols (**1**) and Aliphatic Aldehydes (**2**)

Product[a]	R^1	R^2	R^3	R^4	Yield[b] [%]	b.p. [°C]/torr (n_D^{20})	Molecular formula[c]
3a	H	H	H	CH_3	70 (90)	95–98°/16[d] (1.5179)	$C_{10}H_{12}O_2$ (164.2)
3b	H	H	H	*i*-C_3H_7	80 (92)	175–180°/16 (1.4904)	$C_{14}H_{20}O_2$ (220.3)
3c	H	H	H	*n*-C_5H_{11}	78 (88)	195–200°/16 (1.4942)	$C_{18}H_{28}O_2$ (276.4)
3d	H	H	H	$CH(CH_3)$—C_6H_5	65 (90)	205–210°/16 (1.5798)	$C_{24}H_{24}O_2$ (344.4)
3e	CH_3	H	H	CH_3	85 (94)	120–125°/16 (1.5185)	$C_{11}H_{14}O_2$ (178.2)
3f	H	Cl	H	CH_3	55 (95)	145–150°/16 (1.5288)	$C_{10}H_{11}ClO_2$ (198.6)
3g	H		—(CH=CH)$_2$—	CH_3	80 (92)	m.p. 55–58°[e]	$C_{14}H_{14}O_2$ (214.3)

[a] Mixtures of stereoisomers, see text.
[b] Yield of isolated product; value in brackets is yield based on consumed starting phenol.
[c] The microanalyses were in satisfactory agreement with the calculated values (C ±0.25, H ±0.21, Cl +0.12); performed by Istituto di Chimica Farmaceutica dell'Università di Parma.
[d] Lit.[7] b.p. 90–95 °C/15 torr.
[e] Colourless crystals from toluene.

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Table 2. Characterization of Products **3a–g**

Product	*m/e*[a] (rel. int. %)	I.R. (film)[b] ν [cm^{-1}]	U.V. (C_2H_5OH)[c] λ_{max} [nm] (log ε)	^{1}H-N.M.R. ($CDCl_3$)[d] δ [ppm]
3a	164 (18), 120 (100), 91 (90)	2857, 1234, 755	273 (3.3), 280 (3.3)	1.51 (d, 6H, 2- and 4-CH_3, J=6 Hz); 5.03 (q, 1H, H-4, J=6 Hz); 5.20 (q, 1H, H-2, J=6 Hz); 6.6–7.3 (m, 4H_{arom})
3b	220 (1), 199 (29), *148 (71)*, *127 (95)*, 94 (100)	2873, 1242, *760*	218 (3.8), 269 (3.0), *275 (4.0)*	0.70 (d, 3H, CH_3, J=7 Hz); 1.03 (d, 6H, CH_3, J=7 Hz); 1.16 (d, *3H, CH_3, J=7 Hz)*; *1.7–2.4* [m, 2H, $\underline{CH}(CH_3)_2$]; *4.78* (d, *1H*, H-4, J=7 Hz); 4.88 (d, 1H, H-2, J=7 Hz); 6.6–7.2 (m, 4H_{arom})
3c	276 (4), 176 (47), 133 (100), 120 (64), 107 (100)	2941, 1234, 755	216 (3.9), 273 (3.3), 280 (3.3)	0.91 (b, 6H, CH_3); 1.0–2.1 (m, 16H, CH_2); 4.96 (t, 1H, H-4, J=5 Hz); 5.03 (t, 1H, H-2, J=5 Hz); 6.7–7.3 (m, 4H_{arom})
3d	344 (2), 239 (12), 149 (24), 121 (100), *105 (88)*	2841, 1227, 755	243 (3.6), 308 (3.2)	1.52 (d, 6H, CH_3, J=7 Hz); 3.32–3.54 (m, 2H, $\underline{CH}-CH_3$); 5.01 (d, 1H, H-4, J=6 Hz); 5.51 (d, 1H, H-2, J=6 Hz); 6.5–7.6 (m, *14H_{arom}*)
3e	178 (22), 134 (100), 119 (12), 91 (28)	2985, 1219, 776	273 (3.3), 280 (3.2)	1.48 (d, 3H, CH_3, J=7 Hz); 1.55 (d, 3H, CH_3, J=7 Hz); 2.2 (s, 3H, CH_3); 5.10 (q, 1H, H-4, J=7 Hz); 5.22 (q, 1H, H-2, J=7 Hz); 6.6–7.2 (m, 3H_{arom})
3f	198 (18), 154 (100), 119 (10), 91 (42)	2941, 1250, 821	228 (3.9), 283 (3.2)	1.52 (d, 6H, CH_3, J=6 Hz); 4.90 (q, 1H, H-4, J=6 Hz); 5.19 (q, 1H, H-2, J=6 Hz); 6.6–7.2 (m, 3H_{arom})
3g	214 (32), 170 (100), *169 (81)*, *153 (17)*, 141 (25)	2985, 1235, 752	224 (3.4), 266 (3.6), *276 (3.7)*, *287 (3.6)*, 317 (3.2), 331 (3.3)	1.4–1.8 (m, 6H, CH_3); 4.8–5.8 (m, 2H, H-4 and H-2); 6.9–7.8 (m, 6H_{arom})

[a] Recorded on a Varian CH-5 instrument.
[b] Recorded on a Jasco UVIDEC-505 instrument.
[c] Recorded on a Perkin-Elmer 475 instrument.
[d] Recorded on a Varian XL-100 instrument at 100 MHz, TMS as internal standard.

4*H*-1,3-Benzodioxin (3a); Typical Procedure:
To an equimolar mixture of the phenol **1** and potassium phenoxide [prepared *in situ* from phenol (**1a**; 9.41 g, 100 mmol) and potassium pellets (1.95 g, 50 mmol) in anhydrous toluene (200 ml)] is added a solution of titanium(IV) chloride (9.49 g, 50 mmol) in toluene (50 ml) at room temperature. The slurry is heated under reflux with stirring for 30 min, while a stream of dry nitrogen is passed. The resulting red suspension is cooled to room temperature and a solution of acetaldehyde (8.81 g, 200 mmol) in toluene (50 ml) is added. The reaction mixture is stirred for 10 h at room temperature then quenched with 10% aqueous sodium hydroxide solution (200 ml). The organic layer is separated, washed with water, and dried with anhydrous sodium sulphate. Evaporation of the solvent gives the crude product which, on bulb to bulb distillation under reduced pressure furnishes pure dioxin **3a**; yield: 11.5 g (70% based on phenol); b.p. 93–96 °C/16 torr, n_D^{20}: 1.5179 (Lit.[6], b.p. 90–95 °C/15 torr).

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