An Improved Synthesis of Salicylaldehydes. No Influence of Steric Hindrance

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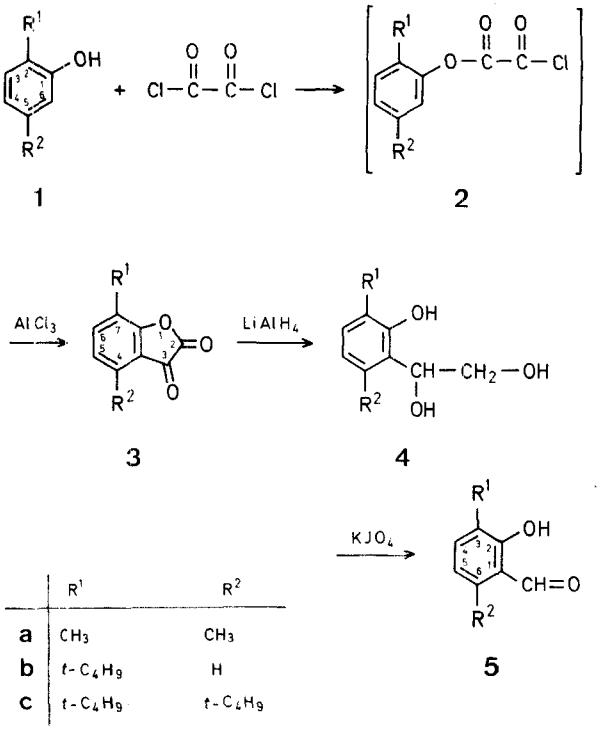
There are several well-known methods for the formylation of phenols to salicylaldehydes[1]. The methods described in the literature give low yields[2,3,4], a mixture of *ortho* and *para* substitution[2,5], only *para* substitution[3,6,7,8], or no[9,10] introduction of a formyl group in phenols. A method for the selective *ortho* formylation of phenols using phenoxymagnesium halides and an excess of ethyl orthoformate[11] gives moderately good yields. However, in 2,5-dialkylphenols, the yields decrease dramatically when a bulky group is present in the 5-position, as it is in the case of 2-methyl-5-isopropylphenol. In this case the yield of the corresponding salicylaldehyde is only 4.5%[11].

In this communication we report a new method for the synthesis of salicylaldehydes which eliminates the influence of bulky groups on the yields (see Table). The synthetic route is outlined in Scheme **A**.

Reaction of the phenols **1** with oxalyl chloride and 4-(*N*,*N*-dimethylamino)-pyridine[12] as catalyst gives the phenoxyoxalyl chlorides **2**; ring closure to the 2,3-dioxo-2,3-dihydrobenzofurans **3** was effected with aluminium chloride in 1,2-dichloroethane. Reduction with lithium aluminium hydride gives the 2-(1,2-dihydroxyethyl)-phenols **4** and oxidation with potassium metaperiodate furnishes the *o*-hydroxybenzaldehydes **5**. In this four-step synthesis the overall yield is more than 50%.



Scheme **A**

Table. Preparation of 4,7-Disubstituted 2,3-Dioxo-2,3-dihydrobenzofurans (**3**), 3,6-Disubstituted 2-(1,2-Dihydroxyethyl)-phenols (**4**), and 3,6-Disubstituted Salicylaldehydes (**5**)

Product	Yield (%)	m.p. (Lit. m.p.)	Molecular formula[a,13]	I.R. (KBr)[16] ν cm^{-1}	^{1}H-N.M.R. ($CDCl_3$)[16] δ ppm
3a	80	135–136° (136°)[14]	$C_{10}H_8O_3$ (176.2)	1820 (2-C=O), 1720, 1580 (3-C=O), 1250, 1130, 1033, 937, 829	2.30 (s, 7-CH_3), 2.57 (s, 4-CH_3), 6.98 (d, H—C-5), 7.45 (d, H—C-6), $J_{5,6}$ = 8 Hz
3b	75	84–86°	$C_{12}H_{12}O_3$ (204.3)	1820 (2-C=O), 1720, 1560 (3-C=O), 1258, 758	1.45 (s, t-C_4H_9), 7.30 (d, H—C-5), 7.64 and 7.58 (q and q, H—C-4 and H—C-6), $J_{5,6}$ = 8 Hz, $J_{4,5}$ = 8 Hz, $J_{4,6}$ = 2 Hz
3c	90	74–76°	$C_{16}H_{20}O_3$ (260.3)	1820 (2-C=O), 1730, 1550 (3-C=O), 1246, 1110, 916, 832	1.42 and 1.43 (s and s, 2 t-C_4H_9), 7.27 (d, H—C-5), 7.71 (d, H—C-6), $J_{5,6}$ = 8 Hz
4a	85	127–128°	$C_{10}H_{14}O_3$ (182.2)	3350, 3230, 3150 (OH's), 1259, 1190, 1060, 1030, 1013, 800	2.20 and 2.24 (s and s, 6-CH_3 and 3-CH_3), 3.82 and 3.88 (q and q, —C<u>H</u>$_2$—OH), 5.22 (q, >C<u>H</u>—OH), 6.60 (d, H—C-4), 6.96 (d, H—C-5), 8.64 (s, 1-OH), 1.64 and 3.50 (broad, other OH's), $J_{4,5}$ = 8 Hz
4b	90	64–66°	$C_{12}H_{18}O_3$ (210.3)	3600–3000 (broad, OH's), 1240, 1070, 1050, 1025, 798, 750	1.40 (s, t-C_4H_9), 3.68 and 3.84 (q and q, —C<u>H</u>$_2$—OH), 4.84 (q, >C<u>H</u>—OH), 6.74 (m, H—C-4), 7.20 (m, H—C-3 and H—C-5), 8.45 (s, 1-OH), 3.12 and 4.22 (broad, other OH's)
4c	90	175–176°	$C_{16}H_{26}O_3$ (266.4)	3430, 3310, 3250 (OH's), 1260, 1228, 1210, 1045, 1003, 813	1.39 and 1.42 (s and s, 2 t-C_4H_9), 3.78 and 4.20 (d and t, —C<u>H</u>$_2$—OH), 6.71 (q, >C<u>H</u>—OH), 6.86 (d, H—C-4), 7.14 (d, H—C-5), 8.70 (s, 1-OH), 2.10 and 3.46 (broad, other OH's), $J_{4,5}$ = 8 Hz
5a	75	59–60° (62–63°)[15]	$C_9H_{10}O_2$ (150.2)	3600–2400 (broad, OH), 1630 (C=O), 1230, 820, 770	2.22 (s, 3-CH_3), 2.56 (s, 6-CH_3), 6.72 (d, H—C-5), 7.25 (d, H—C-4), 10.32 (s, CH=O), 12.17 (2-OH), $J_{4,5}$ = 8 Hz
5b	80	—[b]	$C_{11}H_{14}O_2$ (178.2)	3600–2700 (broad, OH), 1655 (C=O), 1309, 1260, 1220, 1190, 796, 750	1.40 (s, t-C_4H_9), 6.94 (d, H—C-5), 7.31 (q, H—C-4), 7.49 (q, H—C-6), 9.80 (s, CH=O), 11.78 (s, 2-OH), $J_{4,5}$ = 8 Hz, $J_{5,6}$ = 8 Hz, $J_{4,6}$ = 2 Hz
5c	80	81–84°	$C_{15}H_{22}O_2$ (234.3)	3000–2400 (broad, OH), 1620 (C=O), 1260, 820	1.40 and 1.48 (s and s, 2 t-C_4H_9), 6.80 (d, H—C-5), 7.36 (d, H—C-4), 10.73 (s, CH=O), 13.33 (s, 2-OH), $J_{4,5}$ = 8.5 Hz

[a] All compounds except **3a** and **5a** are new and gave satisfactory elemental analyses (C ±0.37%, H ±0.19%).

[b] b.p. 78–79°/1 torr.

2,3-Dioxo-2,3-dihydrobenzofurans (3); General Procedure:
A solution of the phenol **1** (0.1 mol), oxalyl chloride (0.22 mol), and 4-(*N*,*N*-dimethylamino)-pyridine[12] (0.5 g, 4.1 mmol) in chloroform (300 ml) was refluxed for 10 h. During the reaction the colour changed from dark yellow to light yellow. After the reaction time of 10 h, no phenol could be detected with G.L.C. The solution was concentrated, the oily residue was dissolved in 1,2-dichloroethane (100 ml), and at room temperature dropped into a suspension of aluminium chloride (0.3 mol) in 1,2-dichloroethane (300 ml). After a reaction time of 10 h the dark coloured reaction mixture was hydrolysed with water (100 ml). The yellow organic material was collected by extraction with 1,2-dichloroethane, dried (molecular sieves 4 Å), and concentrated. The yellow-red residue was purified by column chromatography (silica 0.05–0.2 mm, eluent: chloroform). After evaporation of the chloroform, the residue was crystallised from petroleum ether (b.p. 40–60°). For yields, m.p.'s, analytical data, and spectral data, see Table.

2-(1,2-Dihydroxyethyl)-phenols (4); General Procedure:
A solution of the compound **3** (0.1 mol) in dry ether (100 ml) was added dropwise to a suspension of lithium aluminium hydride (0.35 mol) in dry ether (200 ml) at room temperature. After refluxing for 1 h, the reaction mixture was cooled in an ice/salt mixture, ethyl acetate (50 ml) was added dropwise, and then hydrochloric acid (200 ml, 2 *N*). The organic material was collected by extraction with ether, dried (molecular sieves, 4 Å) and, after, evaporation of the ether, the residue was crystallised from chloroform and dichloromethane/chloroform. For yields, m.p.'s, analytical data, and spectra data, see Table.

2-Hydroxybenzaldehydes (5); General Procedure:
To a solution of the compound **4** (0.15 mol) in a mixture of water (200 ml) and ethanol (200 ml) was added a suspension of potassium metaperiodate (0.2 mol) in sulphuric acid (200 ml, 3.5 *N*). The mixture was stirred for 4 h at room temperature. The yellow precipitate was filtered off and the filtrate was extracted with ether. After evaporation of the ether, the residue was steam distilled (about 1000 ml of water was used). The organic material in the distillate was collected and, with the precipitate above, crystallised from ethanol/water. For yields, m.p.'s, analytical data, and spectral data, see Table.

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