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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Efficient Procedure for Preparing Salicyl Alcohols

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Abstract—A new convenient procedure was developed for selective *ortho*-hydroxymethylation of phenols by reaction of paraformaldehyde with a mixture of phenol and orthoboric acid. The method is general for phenols containing no strong electron-withdrawing substituents; it allows preparation of *o*-hydroxybenzyl alcohols of high purity in a high yield.

Salicyl (*o*-hydroxybenzyl) alcohol and its derivatives are of interest as intermediates in synthesis of many organic compounds: phenylchromones [1], isoflavones [2], etc.

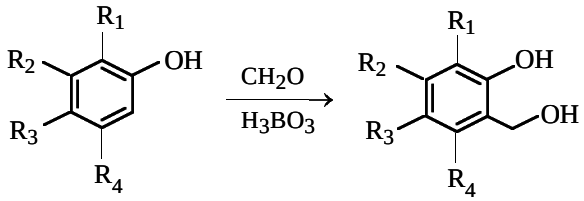
Salicyl alcohol is an aglycone of a number of glycosides found in Salicaceae. Some of them exhibit antihelminth [3] and antiviral [4] activity.

One of the most widely used routes to salicyl alcohol is hydroxymethylation with formaldehyde or compounds generating it of phenyl metaborate PhOB=O (exists as trimers [5]). The initial metaborate is prepared by refluxing equimolar amounts of phenol and boric acid in aprotic aromatic solvents (toluene, xylene) with azeotropic distillation of the released water [5–9]. The yield of the crude target product, according to patents [6–8], depends on the initial phenol and does not exceed 65%; attempts to reproduce the synthesis of salicyl alcohol described in the patent resulted in a yield as low as 35% [5]. The conversion of phenol was incomplete, and polycondensation products formed, complicating purification of the target product [5].

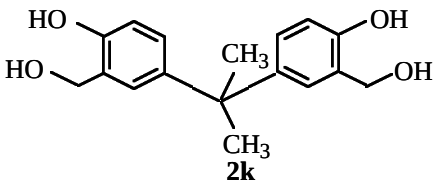
Another route is hydroxymethylation of phenol in the presence of a 1.5-fold excess of arylboronic acids $ArB(OH)_2$. The reaction involves intermediate formation of cyclic esters of hydroxybenzyl alcohol and arylboronic acid. The desired alcohol is released by treatment of these esters with propylene glycol or hydrogen peroxide [10].

A simpler route to salicyl alcohols is reaction of paraformaldehyde with a mixture of phenol and excess boric acid in benzene under conditions of continuous azeotropic distillation of water, without preparing phenyl metaborate in advance. By this method we successfully performed selective *o*-hydroxymethylation of a series of phenols **1a**–**1k** and obtained the corresponding salicyl alcohols **2a**–**2k** (Table 1).

The structures of **2a**–**2k** were proved by the ^1H NMR (Table 2) and IR spectra and by comparison with the authentic samples. The IR spectra of **2a**–**2k** contain two strong absorption bands at 3475–3440 and 3240–3165 cm^{-1} characteristic of the intramolecular hydrogen bond and of O–H stretching vibrations, and also characteristic absorption bands ν(C–O) at 1015–1045 cm^{-1}:



1a–**1j** **2a**–**2j**



2k

where $R^1 = R^2 = R^3 = R^4 = H$ (**a**); $R^2 = R^3 = R^4 = H$, $R^1 = CH_3$ (**b**); $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$ (**c**); $R^2 = R^3 = H$, $R^1 = CH(CH_3)_2$, $R^4 = CH_3$ (**d**); $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$ (**e**); $R^1 = R^2 = R^4 = H$, $R^3 = Cl$ (**f**); $R^1 = R^2 = R^4 = H$, $R^3 = F$ (**g**); $R^1 = R^2 = R^4 = H$, $R^3 = Ph$ (**h**); $R^1 = R^2 = R^4 = H$, $R^3 = OCOPh$ (**i**); $R^1 = R^3 = R^4 = H$, $R^2 = OCOPh$ (**j**).

ortho-Hydroxymethylation of phenols **1a**–**1k** by the suggested procedure occurs at lower temperature (up to 81°C), takes longer time, and requires a larger

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Table 2. Synthesis of *o*-hydroxybenzyl alcohols **2a**–**2k** by reaction of phenols **1a**–**1k** with paraform

Compound	τ, h	Yield, %	mp, °C
2a	22	53	84–85 (C_6H_6) (85–86 [11])*
2b	37	48	25–27 (hexane) (5 [6], 33–34 [11])
2c	29	63	102–103 (C_6H_6) (104–105 [11])
2d	13	61	83–84 (hexane) (86 [12])
2e	21	40	79–80 ($CHCl_3$) (80–81 [11])
2f	53	54	92–93 (C_6H_6) (92–93 [11])
2g	38	34	69–70 (C_6H_6) (68–70 [13])
2h	46	68	162–163 ($C_6H_5CH_3$) (164–165 [13])
2i	52	60	114–115 (C_6H_6)
2j	33	35	125–126 (C_6H_6)
2k	49	56	144–145 (water)

* In parentheses are published data.

excess of boric acid (up to 1.5 mol) than hydroxymethylation of aryl metaborates [5–9]. Also, fresh portions of paraform should be added at regular intervals to compensate for its removal with the distillate. Nevertheless, there are important advantages: complete conversion of the initial phenol, absence of oligomeric products, and higher yield and purity of the target alcohols **2a**–**2k**.

It is important for practice that in hydroxymethylation of phenyl metaborate the resulting salicyl alcohol, as a rule, is isolated by treatment of the reaction mixture with alkali [5–7, 9], which makes this procedure unsuitable for preparing salicyl alcohols with substituents sensitive to bases. It was found that the boric acid esters formed under conditions of our procedure can be successfully saponified by keeping the reaction mixture in water without adding alkali. This approach allowed us to perform for the first time direct selective hydroxymethylation of phenols **1i** and **1j** containing phenyl benzoate moieties. The resulting alcohols **2i** and **2j** (Table 1) are synthetic equivalents of difficultly accessible dihydroxybenzyl alcohols.

The relatively low yield of **2j** is due to the fact that reaction of phenol **1j** with paraform yields, according to the ^{1}H NMR spectrum, a mixture of **2j** and its isomer, 2-hydroxymethyl-3-benzoyloxyphenol, inseparable by chromatography. In other words, hydroxymethylation occurs at both *o*-positions of the phenolic hydroxyl in **1j**. We were able to isolate only a portion of **2j** by single recrystallization of the mixture from benzene.

It should be noted that pyrocatechol monobenzoate appeared to be almost inert in hydroxymethylation (110 h). This is probably due to a strong intramolecular hydrogen bond blocking the phenolic hydroxyl in the *o*-position relative to the benzoate group.

Reaction of bisphenol **1k** containing two equivalent phenolic hydroxyls with paraform yields bis(hydroxymethyl) derivative **2k** within 49 h. At a shorter reaction time, the reaction mixture contained, according to TLC, unchanged **1k**, the monohydroxymethylation product, and alcohol **2k**; the latter is formed even in early stages of the reaction. Thus, hydroxymethylation of phenol **1k** occurs nonselectively at both phenyl rings.

Table 2. ^{1}H NMR spectra of salicyl alcohols **2a**–**2k** in DMSO-d_6

Compound	δ, ppm
2a	4.70 (s, 3H, CH_2OH), 6.70–7.18 (m, 4H, Ar), 8.80 (s, 1H, ArOH)
2b	2.13 (s, 3H, CH_3), 4.63 (s, 2H, CH_2OH), 6.52–6.95 (m, 3H, Ar)
2c	2.18 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 4.89 (s, 1H, CH_2OH), 6.61–7.07 (m, 3H, Ar), 9.03 (s, 1H, ArOH)
2d*	1.10–1.20 (d, 6H, $C\underline{H}_3$–CH–$C\underline{H}_3$), 2.02 (s, 4H, $ArC\underline{H}_3$, CH_3–$C\underline{H}$–CH_3), 3.28 (m, 1 H, OH), 5.04 (s, 2H, CH_2), 6.65–7.02 (m, 2H, Ar)
2e*	3.10 (s, 1H, OH), 3.60 (s, 3H, OCH_3), 4.63 (s, 2H, CH_2), 6.53–6.66 (m, 3H, Ar)
2f	4.74 (s, 2H, CH_2), 5.20 (s, 1H, $CH_2O\underline{H}$), 6.98–7.54 (m, 3H, Ar), 9.90 (s, 1H, ArOH)
2g	4.50 (s, 2H, CH_2), 4.80 (s, 1H, $CH_2O\underline{H}$), 6.70–7.26 (m, 3H, Ar), 9.40 (s, 1H, ArOH)
2h	4.80 (s, 2H, CH_2), 5.34 (s, 1H, $CH_2O\underline{H}$), 7.05–7.84 (m, 8H, Ar), 9.78 (s, 1H, ArOH)
2i	4.74 (s, 2H, CH_2), 5.30 (s, 1H, $CH_2O\underline{H}$), 7.08–8.36 (m, 8H, Ar), 9.73 (s, 1H, ArOH)
2j**	5.20 (s, 2H, $C\underline{H}_2OH$), 6.91–8.33 (m, 8H, Ar), 9.06 (s, 1H, ArOH)
2k	1.81 (d, 6H, $C\underline{H}_3CC\underline{H}_3$), 4.76 (s, 4H, $C\underline{H}_2OH$), 5.26 (s, 2H, $CH_2O\underline{H}$), 6.90–7.46 (m, 6H, Ar), 9.39 (s, 2H, ArOH)

* In $CDCl_3$. ** In pyridine-d_5.

Phenols with electron-withdrawing substituents in the ring (NO_2, CHO, COOH) remain inert under the reaction conditions and do not give the corresponding salicyl alcohols.

The positive effect reached in hydroxymethylation of phenols in the presence of excess boric acid can be explained as follows. In the case of equimolar amounts of phenol and boric acid [5–9], the presumable precursors of salicyl alcohol are cyclic borates [5]. We can assume with confidence that under the reaction conditions these cyclic borates are in equilibrium with free alcohol **2a** which enters further side transformations (dehydration, condensation with formaldehyde, etc.). Then excess boric acid under the suggested conditions decreases the concentration of free salicyl alcohol owing to shift of the equilibrium. Also, it is significant that the reaction is performed at a lower temperature (81°C) than suggested in the literature (90–95°C) [5–9]. It is known that salicyl alcohol is thermally unstable, and at temperatures above 100°C it rapidly forms polymeric products [14].

EXPERIMENTAL

The IR specrtra were taken on a Specord M-80 spectrophotometer in KBr pellets, and the ^{1}H NMR spectra, on a Bruker AC 200 spectrometer (200 MHz, DMSO-d_6, internal reference HMDS).

The reaction progress was monitored and the product purity checked by TLC on Silufol UV-254 plates, eluent benzene–ethanol (9 : 1). The plates were developed using filtered UV radiation, diazotized sulfanilic acid, or 5% $FeCl_3$ solution.

The typical procedure of hydroxymethylation of phenols **1a**–**1k** with paraform in the presence of boric acid was as follows. A mixture of 40 mmol of appropriate phenol, 3.72 g (60 mmol) of boric acid, and 1.8 g (60 mmol) of paraform in 70 ml of benzene was refluxed in a flask equipped with a Dean–Stark trap with continuous azeotropic distillation of water until the initial phenol was completely converted (TLC). Every 4 h, a fresh 0.45-g (15-mmol) portion of paraform was added. After reaction completion, excess benzene was distilled off under reduced pressure. To the residue 30 ml of water was added, and the mixture was allowed to stand for 5 h to ensure hydrolysis of the intermediate boric acid ester of the salicyl alcohol. The product was extracted with ether (three 40-ml portions), and the combined ether extracts were washed with watedr (20 ml). The solvent was removed, and alcohols **2a**–**2k** were purified by recrystallization.

CONCLUSIONS

(1) Reaction of paraform with phenols in the presence of excess boric acid under conditions of continuous azeotropic distillation of water results in selective *o*-hydroxymethylation of the substrates with complete conversion of the initial phenols and formation of salicyl alcohols.

(2) A general procedure was developed for preparing salicyl alcohols from phenols containing no strong electron-withdrawing substituents.

(3) The suggested procedure allowed for the first time preparation of the synthetic equivalents of dihydroxybenzyl alcohols.

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