ortho-Specific α-Hydroxyalkylation of Phenols with Aldehydes. An Efficient Synthesis of Saligenol Derivatives

Wataru NAGATA*, Kyo OKADA, Tsutomu AOKI

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553 Japan

As is well known, it is not easy to prepare a saligenol derivative directly by the specific condensation of an aldehyde with a phenol at the *ortho* position. Peer[1] has shown the usefulness of boric acid as a catalyst in this condensation, although the reported yield of saligenol was very low (4 %). Some variations involving the use of toluene as solvent in place of benzene[2] and addition of ethylene glycol[3] raised the yield of pure saligenol to 50–60 %. Moreover, the applicability of these methods to substrates other than phenol has not been investigated. We have found that benzeneboronic acid (**2**), when used in the presence of propanoic acid or trichloroacetic acid is a much more effective co-reagent than

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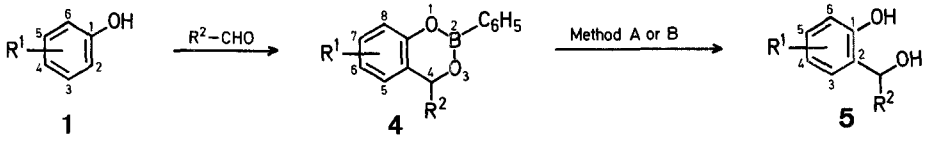
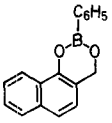
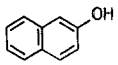
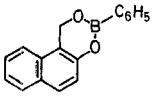
Table 1. *ortho*-α-Hydroxyalkylation of Phenols **1** with Aldehydes **3** in the Presence of Benzeneboronic Acid (**2**) in Benzene



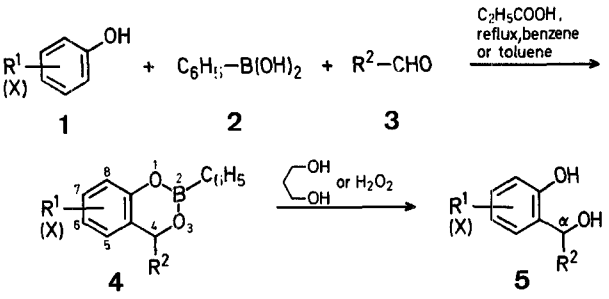
Phenol **1** No.	R^1	Aldehyde **3** R^2 (mol equiv)	Mol equiv of C_2H_5COOH	Reaction time	Yield [%] of **4**	Product **4** No.	R^1
1a	H	H (excess)	0.1	10 h	97	**4a**	H
1b	6-H_3C	H (excess)	0.5	6 h	90	**4b**	8-H_3C
1c	3-H_3C	H (excess)	0.5	6 h	94[a]	**4c**	5-H_3C
						4c'	7-H_3C
1d	4-H_3C	H (excess)	0.5	7 h	97	**4d**	6-H_3C
1e	4-Cl	H (excess)	0.5	15 h	90	**4e**	6-Cl
1f	6-H_3CO	H (excess)	1.0	27 h	47	**4f**	8-H_3CO
1g	3-H_3CO	H (excess)	0.5	5 h	99[c]	**4g**	7-H_3CO
						4g'	5-H_3CO
1h	4-H_3COOC	H (excess)	0.3	20 h	47	**4h**	6-H_3COOC
1i		H (excess)	0.3	6 h	90	**4i**	
1j		H (excess)	0.3	8 h	96	**4j**	
1a	H	H_3C (6)	0.3	6 h	27[e]	**4k**	H
1a	H	*n*-C_5H_{11} (4)	0.3	18 h	82	**4l**	H
1a	H	*n*-C_4H_9—CH(—C_2H_5)— (2)	CCl_3COOH (0.3)	18 h	43[f]	**4m**	H
1a	H	H_3COOC—$(CH_2)_7$— (3.2)	0.3	18 h	62	**4n**	H
1a	H	C_6H_5 (1.0)	CCl_3COOH (0.3)	20 h	49	**4o**	H

[a] 1:1 mixture of **4c** and **4c'**.
[b] Characterized as di-*p*-nitrobenzoate.
[c] 9:2 mixture of **4g** and **4g'**.
[d] Characterized as diacetate.
[e] Reaction in toluene in sealed tube at 100°.
[f] Reaction in toluene.

boric acid and this finding led us to develop an efficient and useful method for preparation of saligenols from phenols as described below.

Reaction of phenol (**1**, R^1 = H) with a large excess of paraformaldehyde (R^2 = H) and a slight excess of benzeneboronic acid (**2**) in refluxing benzene in the presence of 0.1 mol equiv of propanoic acid gave 97% of 2-phenyl-4*H*-1,3,2-benzodioxaborin (**4**) as a crystalline product (m.p. 36–38°) and no trace of the *para*-hydroxymethylated product was detected. It is clear from this example that benzeneboronic acid not only accelerates the reaction but also traps the acid-sensitive saligenol as the stable and nicely crystallizable benzodioxaborin **4**. This observation illustrates a principal advantage of the use of benzeneboronic acid. The presence of propanoic acid is critical, otherwise no expected reaction occurred. Trichloroacetic acid was used when a substrate is poorly reactive (see Table 1).

The dioxaborin **4** was subjected to either exchange reaction with a large excess of propylene glycol (method A) or oxidation with hydrogen peroxide[4] in tetrahydrofuran (method B) giving saligenol **5** (R^1 = R^2 = H) in 90 and 80% yields, respectively.



The general applicability of this two-step procedure was examined by varying the phenolic substrate and the aldehydic reactant (Table 1). Whereas electron-rich substrates such as *o*-, *m*-, and *p*-cresols and *m*-methoxyphenol can be converted into the corresponding 2-phenyl-1,3,2-dioxaborin derivatives **4** in high yields, electron-deficient phenols such as *p*-methoxycarbonylphenol show some reluctance. Electron-donating substituents situated *ortho* to the phenolic hydroxy group retard the reaction greatly as is seen from the reaction of *o*-methoxyphenol. Aldehydes other than formaldehyde can also be incorporated in the reaction even if they are secondary (e.g., 2-ethylhexanal) or aromatic (e.g.,

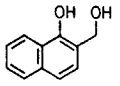
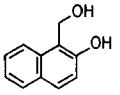
Method for 4→5	Yield [%] of 5	Product 5 No.	R^1
A or B	90 or 80	**5a**	H
B	85	**5b**	6-H_3C
B	71	**5c**	3-H_3C
B	73	**5c'**	5-H_3C
B	77	**5d**	4-H_3C
A or B	91 or 84	**5e**	4-Cl
B	81	**5f**[b]	6-H_3CO
B	75	**5g**[d]	5-H_3CO
		5g'[d]	3-H_3CO
A	75	**5h**	4-H_3COOC
B	84	**5i**[d]	
B	69	**5j**	
B	83	**5k**[b]	H
B	85	**5l**[d]	H
B	60	**5m**[d]	H
B	65	**5n**[d]	H
B	86	**5o**	H

Table 2. Physical and Analytical Data for Compounds **4** and **5**

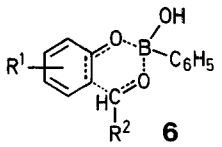
Product	M.p.[a] or b.p./torr	Molecular formula[b] or lit. m.p.	^{1}H-N.M.R. ($CDCl_3$ or DMSO-d_6) δ [ppm]
4a	36–38° 114–117°/0.5	$C_{13}H_{11}BO_2$ (210.0)	5.15 (s, 2H); 6.9–7.53 (m, 7H); 7.9–8.07 (m, 2H)
4b	48–39°	$C_{14}H_{13}BO_2$ (224.1)	2.36 (s, 2H); 5.13 (s, 2H); 6.63–7.16 (m, 3H); 7.43–7.60 (m, 3H); 7.90–8.06 (m, 2H)
4c	79.5–80.5°	$C_{14}H_{13}BO_2$ (224.1)	2.15 (s, 3H); 5.13 (s, 2H); 6.70–7.57 (m, 6H); 7.83–8.03 (m, 2H)
4c'	58–59.5°	$C_{14}H_{13}BO_2$ (224.1)	2.33 (s, 3H); 5.15 (s, 2H); 6.8–7.47 (m, 6H); 7.83–8.0 (m, 2H)
4d	83–84°	$C_{14}H_{13}BO_2$ (224.1)	2.28 (s, 3H); 5.17 (s, 2H); 6.77–7.53 (m, 6H); 7.90–8.07 (m, 2H)
4e	101–102°	$C_{13}H_{10}BClO_2$ (244.5)	5.13 (s, 2H); 6.78–7.57 (m, 6H); 7.83–8.0 (m, 2H)
4f	68–69.5°	$C_{14}H_{13}BO_3$ (240.1)	3.93 (s, 3H); 5.17 (s, 2H); 6.45–7.45 (m, 6H); 7.87–8.03 (m, 2H)
4g	40–41°	$C_{14}H_{13}BO_3$ (240.1)	3.77 (s, 3H); 5.10 (s, 2H); 6.45–7.50 (m, 6H); 7.83–8.0 (m, 2H)
4g'	113–114°	$C_{14}H_{13}BO_3$ (240.1)	3.80 (s, 3H); 5.17 (s, 2H); 6.50–7.57 (m, 6H); 7.87–8.03 (m, 2H)
4h	153–154°	$C_{15}H_{13}BO_4$ (268.1)	3.90 (s, 3H); 5.25 (s, 2H); 7.0–8.1 (m, 8H)
4i	90–92°	$C_{17}H_{13}BO_2$ (260.1)	5.31 (s, 2H); 6.8–8.5 (m, 11H)
4j	167–168°	$C_{17}H_{13}BO_2$ (260.1)	5.56 (s, 2H); 7.15–8.15 (m, 11H)
4k	118–120°/0.6	$C_{14}H_{13}BO_2$ (224.1)	1.63 (d, 3H); 5.73 (q, 1H); 6.9–7.6 (m, 7H); 7.85–8.1 (m, 2H)
4l	150–155°/0.5	$C_{18}H_{21}BO_2$ (280.2)	0.65–2.1 (m, 11H); 5.23 (t, 1H); 6.9–7.55 (m, 7H); 7.85–8.1 (m, 2H)
4m	143–147°/0.6	$C_{20}H_{25}BO_2$ (308.2)	0.5–1.8 (m, 15H); 5.36 (bs, 1H); 6.8–7.6 (m, 7H); 7.8–8.1 (m, 2H)
4n	—	$C_{22}H_{27}BO_4$ (366.3)	1.0–2.5 (m, 14H); 3.6 (s, 3H); 5.21 (t, 1H)
4o	96–97°	$C_{19}H_{15}BO_2$ (286.1)	6.22 (s, 1H); 6.8–7.5 (m, 12H); 7.85–8.1 (m, 2H)
5a	86–87°	Lit.[2] 86–87°	—
5b	35–36°	Lit.[2] 32°	—
5c	83–84°	Lit.[8] 80°	—
5c'	106–108°	Lit.[8] 103°	—
5d	104–105°	Lit.[2] 104.5°	—
5e	91–92°	Lit.[10] 92–93°	—
5f	172–173°	$C_{22}H_{16}N_2O_9$ (452.4)	3.81 (s, 3H); 5.37 (s, 2H); 7.0–7.27 (m, 3H); 8.03–8.30 (m, 8H)
5g	100–105°/ 0.3–0.5	$C_{12}H_{14}O_5$ (238.2)	2.02 (s, 3H); 2.30 (s, 3H); 3.77 (s, 3H); 4.98 (s, 2H)
5g'	—	—	2.05 (s, 3H); 2.32 (s, 3H); 3.83 (s, 3H); 5.13 (s, 2H)
5h	153–154°	$C_9H_{10}O_4$ (182.2)	3.78 (s, 3H); 4.51 (s, 2H); 6.75–8.05 (m, 3H)
5i	95–100°/0.01	$C_{15}H_{14}O_4$ (258.3)	2.06 (s, 3H); 2.46 (s, 3H); 5.21 (s, 2H); 7.3–8.0 (m, 6H)
5j	88–89°	Lit.[9] 88–89°	—
5k	169–171°	$C_{22}H_{16}N_2O_8$ (436.4)	1.72 (d, 3H); 6.36 (m, 1H); 7.2–7.8 (m, 4H); 8.15 (d, 4H); 8.33 (s, 4H)
5l	80–90°/0.01	$C_{16}H_{22}O_4$ (278.3)	0.6–1.8 (m, 11H); 2.01 (s, 3H); 2.32 (s, 3H); 5.93 (t, 1H); 6.8–7.6 (m, 4H)
5m	71–74°	$C_{28}H_{28}N_2O_8$ (520.5)	0.5–2.2 (m, 15H); 6.27 (d, 1H); 7.2–7.8 (m, 4H); 8.1, 8.3, 8.4 (s, 8H)
5n	140–145°/ 0.007	$C_{20}H_{28}O_6$ (364.4)	1–2.5 (m, 14H); 2.0 (s, 3H); 2.31 (s, 3H); 3.64 (s, 3H); 5.91 (t, 1H); 6.8–7.6 (m, 4H)
5o	84–85°	$C_{13}H_{12}O_2$ (200.2)	5.95 (s, 1H); 6.7–7.4 (m, 9H)

[a] Melting and boiling points are uncorrected.

[b] All the new compounds gave satisfactory microanalysis (C ±0.29 %, H ±0.29, N ±0.26 %, Cl ±0.16 %).

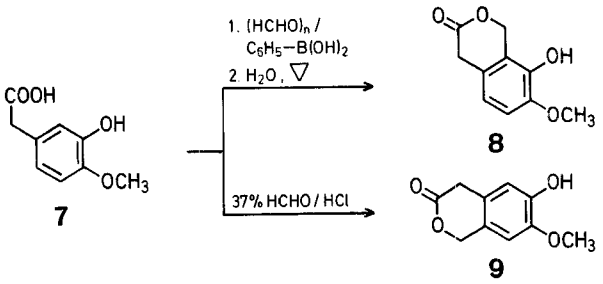
benzaldehyde). Acetaldehyde showed an exceptionally low reactivity probably due to its high tendency to self-polymerize.

Mechanistically, coordination of an aldehyde molecule to the boron atom of a probable intermediate, i.e. (substituted) phenyl benzeneboronate, followed by [3,3] sigmatropic rearrangement as indicated in **6** to give the benzodioxaborin **4** may be suggested.



6

The usefulness of the method was nicely demonstrated by regiospecific, high-yield (85 %) conversion of homoisovanillic acid (**7**) into 8-hydroxy-7-methoxy-3-isochromanone (**8**). This conversion should be contrasted to the exclusive formation of the isomeric isochromanone **9** in hydrochloric acid-catalyzed hydroxymethylation of **7**[5,6].



7 **8** **9**

2-Phenyl-4*H*-1,3,2-dioxaborins 4:

A solution of a phenol **1** (10 mmol), benzeneboronic acid (**2**; 10–12 mmol), an aldehyde **3** (10–80 mmol), and propanoic acid (or trichloracetic acid) (2–5 mmol) in dry benzene (or toluene) is heated under reflux with azeotropic removal of water using a Dean-Stark type separator for 5–26 h depending upon the reactivity of the substrate or the reactant. In case of *ortho*-hydroxymethylation a large excess of paraformaldehyde (50–80 mmol) should be added portionwise at intervals of 1.5–2 h. Evaporation of the solvent, extraction with dichloromethane or ether, washing with aqueous sodium carbonate and water, and evaporation of the solvent after drying gives a residue which is either distilled or crystallized from a mixture of ether and petroleum ether to afford the 2-phenyl-4*H*-1,3,2-dioxaborin derivative **4**.

Conversion of 2-Phenyl-4*H*-1,3,2-dioxaborins 4 into Saligenol Derivatives 5:

Method A: A mixture of the dioxaborin **4** (5 mmol), propylene glycol (0.1 mol), and dry benzene (8 ml) is heated under reflux for 2 h. The solvent is evaporated and the residue mixed with *n*-pentane and water. The organic layer containing 2-phenyl-1,3,2-dioxaborinane is removed[7]. Extraction of the aqueous layer with ether, washing with water, and evaporation of the solvent after drying gives a crude product which is either distilled or crystallized from *n*-pentane or benzene/petroleum ether to yield the pure saligenol derivative **5**.

Method B: A mixture of the dioxaborin **4** (2 mmol), 30 % hydrogen peroxide solution (2 ml), and tetrahydrofuran (2 ml) is stirred at 0–25° for 0.5–2 h. The reaction mixture is poured into ice/water and extracted with ether several times. The extracts are washed with sodium hydrogen sulfite solution to decompose excess hydrogen peroxide and dried. Removal of the solvent and distillation or crystallization (usually from *n*-pentane) of the residue gives the pure saligenol derivative **5**.

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