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AMINOHALOBORANE IN ORGANIC SYNTHESIS. VIII.[1]
A ONE-STEP SYNTHESIS OF 2-AMINOBENZHYDROLS FROM ANILINES

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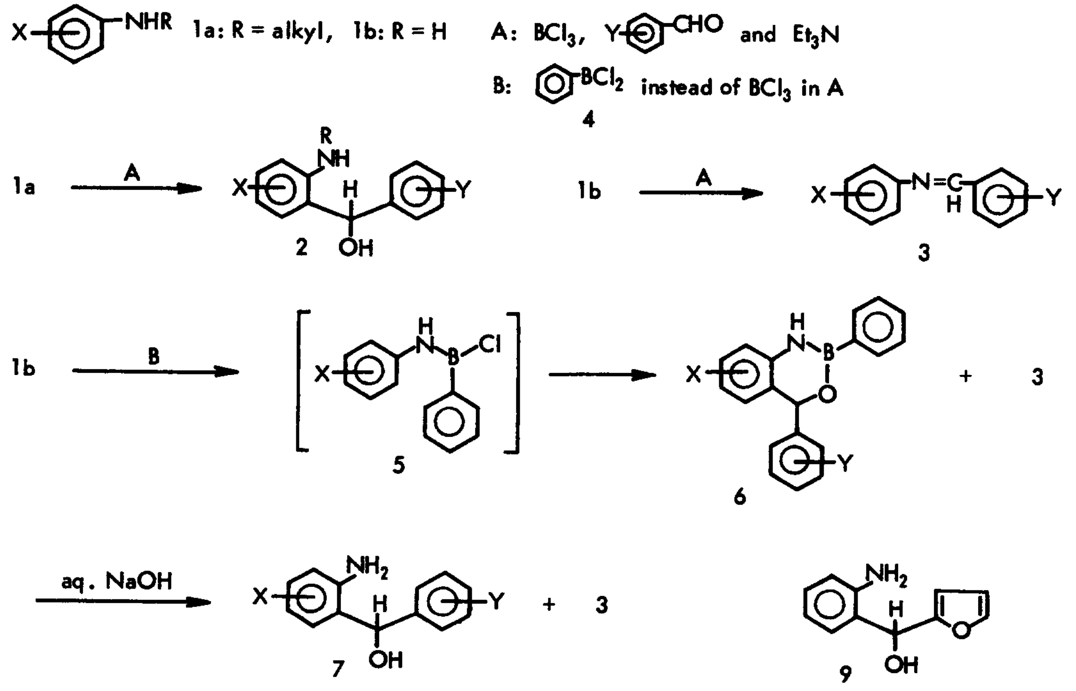
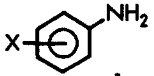
Summary 2-Aminobenzhydrols were obtained regiospecifically from anilines and benzaldehydes with the aid of phenyldichloroborane and triethylamine via N-anilinophenylchloroborane.

We have recently reported a specifically ortho-directed reaction of secondary anilines (1a) with mainly aromatic aldehydes to give 2-sec-aminobenzhydrols (2) using boron trichloride and triethylamine.[2] However, the similar reaction of primary anilines (1b) failed to give mainly aldimine (3) (reaction A). We will report here that the use of phenyldichloroborane[3] (4) instead of boron trichloride has removed this defect (reaction B). The isolation of 2-phenyl-4-(4-nitrophenyl)-1,4-dihydro-3,1,2-benzoxazaborine (6, X = H, Y = 4-NO_2) verified the cyclic reaction path via N-anilinophenylchloroborane (5), although isolation of 5 failed probably due to self-condensation. The work-up with aqueous sodium hydroxide gave the desired product (7) with a lesser amount of 3. Various examples are shown in the Table.



Synthesis of 2-Aminobenzhydrols (7) from Anilines (1) and Benzaldehydes (8)



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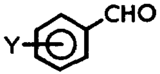

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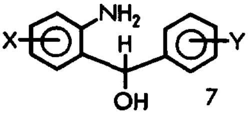

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Run	Compd	X	Compd	Y	Compd	% yield[a,b]	Mp, °C (from)[j]	IR,[k] cm^{-1} ($CHCl_3$)	NMR,[l] δ ($CDCl_3$)
1	1b	H	8a	H	7a[4]	78(16)	115-116, lit[4] 119-120 (EtOH)		5.70
2	1b	H	8a	H	7a	73[c](14)[c]			
3	1b	H	8a	H	7a	26[d](51)[d]			
4	1b	H	8b	4-NO_2	7b	72(16)	142-143	3700, 3610, 3490, 3400	5.85 (1H, d, J = 4Hz)[m]
5	1b	H	8c	2-Cl	7c	96 (4)	91-92	3600, 3480 (br)	6.10
6	1b	H	8d	4-OCH_3	7d[5]	62(29)	61-62 lit[5] 59-60.5	3600, 3480 (br), 3390	5.71, 3.73(3H, s, OCH_3)
7	1c	4-OCH_3	8a	H	7e	65(13)	73-74	3600, 3420, 3380	5.70, 3.64(3H, s, OCH_3)
8	1d	4-Cl	8a	H	7f[6]	26(>50)	105-107 lit[6] 112-113	3600, 3500, 3400	5.68(1H, d, J = 4 Hz)
9	1d	4-Cl	8c	2-Cl	7g	86(9)	101-102	3600, 3480, 3400	6.06
10	1d	4-Cl	8e	3-NO_2	7h	55(17)	155-156	3700, 3620	5.86(br)[m]
11	1e	4-NO_2	8c	2-Cl	7i[7]	16[e](70)	107-108 lit[7] 127-128	3596, 3500, 3400	6.10(1H, d, J = 4 Hz)
12	1f	4-COOEt	8c	2-Cl	7j	60(23)	106-107	3600, 3500, 3400, 1710 (C=O)	6.08(1H, d, J = 4 Hz), 1.23(3H, t, J = 8 Hz, $C\underline{H_3}CH_2O$), 4.17 (2H, q, J = 8 Hz, $CH_3C\underline{H_2}O$)
13	1g	2-CH_3	8c	2-Cl	7k	84(11)	109-110	3600, 3000, 3400	6.13, 2.10(3H, 3, CH_3)
14	1h	2-OCH_3	8c	2-Cl	7l	86(3)	116-117	3595, 3460, 3395	6.16, 3.80(3H, s, OCH_3)
15	1i	3-CH_3	8a	H	7m[f]	18(10)	92-94	3595, 3443, 3390	5.78, 2.23(3H, s, CH_3)
					7n[g]	24	140-141	3612, 3400 (br)	6.18, 2.33(3H, s, CH_3)
16	1j	3-NO_2	8c	2-Cl	7o[h]	2(86)	oil	3600, 3510, 3406	6.24
					7p[i]	11	126-127	3696, 3500, 3380	6.38(1H, d, J = 4 Hz)

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[a] Isolated yield based on aniline used. [b] Yield in parenthesis shows that of the corresponding 3. [c] Yield obtained in the reaction in CH_2Cl_2 and THF (1:1). [d] Reaction using n-butyldichloroborane[9] instead of 4. In this run an epimeric mixture of 2,4-diphenyl-1,3-oxazine (11%) was isolated. Oil, NMR δ 5.50 and 5.82 (1H, d, J = 4 Hz $^{Ph}_{HN}{>}C{<}^{H}_{O-}$), 5.98 and 6.06 (1H, s, $^{Ph}_{Ph}{>}C{<}^{H}_{O-}$). [e] Reaction time 20 hr. [f] 4-Methyl-2-aminobenzhydrol. [g] 6-Methyl-2-aminobenzhydrol. [h] 4-Nitro-2-amino-2'-chlorobenzhydrol. [i] 6-nitro-2-amino-2'-chlorobenzhydrol. [j] CH_2Cl_2- or ether-petroleum ether. [k] NH and OH (taken with JASCO IRS spectrophotometer). [l] Benzyl proton, 1H, s (taken with Varian EM-360-L spectrophotometer). [m] $CDCl_3$ + d_6DMSO (1:1).

The following is a typical procedure. To a stirred solution of 4 (3 mmol) in CH_2Cl_2 (3 mL) was added a solution of 1 (R = H) (3 mmol) in CH_2Cl_2 (4 mL) at -20°--15°. To the resulting suspension was added a solution of Et_3N (7.5 mmol) in CH_2Cl_2 (2 mL) and it was stirred for 30 min at the same temperature. Then a solution of benzaldehyde (3 mmol) in CH_2Cl_2 (12 mL) was added and the solution was stirred at room temperature for 4 hr. Ice water was added and the organic layer was separated. The water layer was extracted with CH_2Cl_2 and the combined organic layer was washed with saturated aq. NaCl solution and dried over $MgSO_4$. The NMR spectrum of the extract showed two singlets at about δ 6.1-6.2 (PhC<u>H</u>OBPh) for 6 and at about δ 8.4 (PhN = C<u>H</u>Ph) for a lesser amount of 3. The extract was dissolved in ether (2 mL) and the solution was stirred with 2N NaOH solution (6 mL) at room temperature for 1 hr. The ether layer was separated and concentrated. The residue was dissolved in benzene and chromatographed on Al_2O_3 (Merck, standard, 15 g). The eluate with benzene contained 3 and that with $CHCl_3$ gave 7.

In run 4, 2-phenyl-4-(4-nitrophenyl)-1,4-dihydro-3,1,2-benzoxazaborine (6) was isolated as follows: The CH_2Cl_2-extract (1.0 g) obtained after work-up with ice water was chromatographed (SiO_2 60, prepacked column B, Merck; $CHCl_3$ containing 3% CH_3CN) giving 6 (248 mg). Mp 145-147° (CH_2Cl_2-petroleum ether). Anal. Calcd for $C_{19}H_{15}BN_2O_3$: C, 69.11; H, 4.58; N, 8.48; B, 3.28. Found: C, 68.90; H, 4.78; N, 8.46: B, 3.29. IR 3450 cm^{-1} (NH) ($CHCl_3$). NMR δ 6.30 (1H, s, benzyl H) ($CDCl_3$). MS m/e: 330 (M^+).

The compound 7 series gave reasonable analytical values[10] and spectral data, namely two to three peaks at about 3400 to 3700 cm^{-1} assigned to NH and OH absorptions and a singlet or doublet (coupled with H of OH, J = 4 Hz) at about δ 5.8 to 6.4 assigned to benzyl proton in the IR and NMR spectra, respectively.

Adding tetrahydrofuran to dichloromethane had no substantial influence on the ratio of 6 and 3 (run 2) and changing the solvent to benzene led it to about unity.

The Table shows that our method is widely applicable except for nitroanilines (run 11 and 16), for which the yields are only moderate to poor.

An analogous reaction of 1b with furfuryl aldehyde gave the corresponding 2-aminobenzylalcohol (9) (45%) and aldimine (3) (C_4H_3O instead of Ph, X = H) (33%). 9: mp 64-65° (ether-petroleum ether). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.97; H, 5.84; N, 7.39. IR cm^{-1} 3600, 3380, 3400 ($CHCl_3$). NMR δ 5.75 (1H, s, benzyl H) ($CDCl_3$).

Hitherto, 7 had been obtained by reduction of 2-aminobenzophenones, which were synthesized via several steps from 1,2-disubstituted benzene derivatives[2] or by Grignard reaction of 2-nitrobenzaldehyde followed by reduction.[8] Although we have recently found a simple synthesis of 2-aminobenzophenones,[2] the above mentioned method provides a regiospecific one-step synthesis of 2-aminobenzhydrols (7) from anilines under very mild conditions.

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10) All products except 7o (oil) gave satisfactory elemental analyses (C ± 0.3, H ± 0.1, N ± 0.1, Cl ± 0.5).

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