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A facile synthesis of 2,4-diaza-1-borines from anilines

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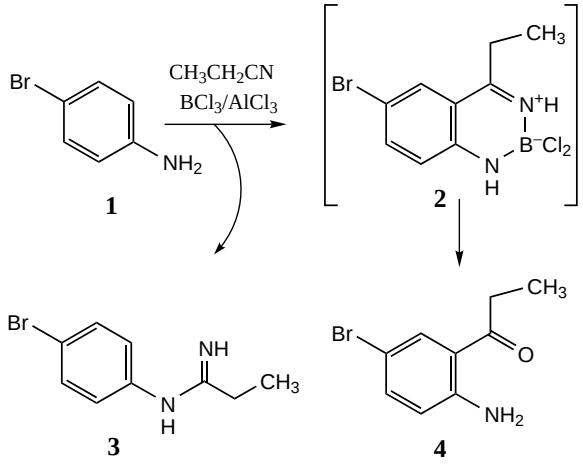
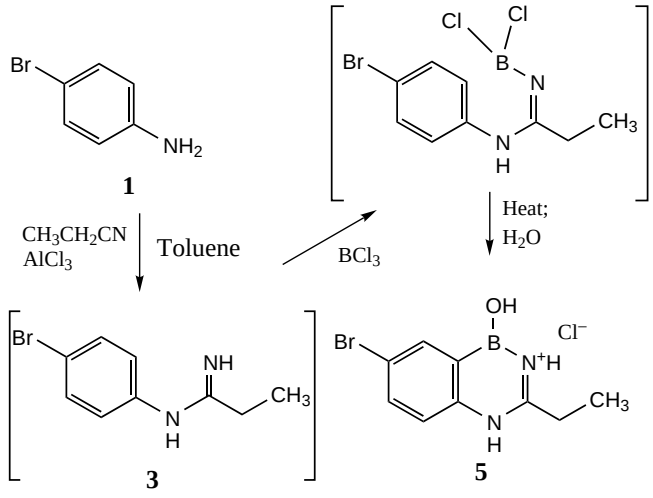
Abstract—A general synthesis of diazaborines is described with the in situ preparation of amidines from anilines using a nitrile and $AlCl_3$, followed by the addition of BCl_3 and heating. The diazaborines were isolated as hydrochlorides in pure form and, in the case of **5**, the structure was confirmed by an X-ray analysis. © 2002 Elsevier Science Ltd. All rights reserved.

The use of boron trichloride/aluminum chloride to transform anilines and nitriles to 2-aminophenyl ketones (Scheme 1) is commonly referred to as the Sugasawa reaction.[1] Under these conditions, amidine **3** is a competing by-product especially when anilines with a deactivating substituent like bromine were used. With the intention of extending the 'Sugasawa *ortho* acylation' to amidines we subjected **3** to $BCl_3/AlCl_3$ conditions and found a product resulting from *ortho* borylation and not *ortho* acylation. The present communication describes the results of these investigations.

The standard methods for making amidines is to heat the neat stoichiometric mixture of aniline and nitrile and $AlCl_3$. In the present study (Scheme 2) we accomplished this in situ in toluene solution. Thus treatment of **1** with propionitrile and $AlCl_3$ in toluene followed by heating to 90°C gave a quantitative yield of **3** as monitored by HPLC. At this stage the reaction mixture was cooled to 0°C, BCl_3 was bubbled in, and refluxed for 2 h. Upon quenching with ice water the precipitated product (55% yield) was collected and characterized further. Elemental analysis indicated a molecular formula of $C_9H_{11}BBrClN_2O$ suggesting incorporation of boron atom into the molecule. ^{11}B NMR showed the chemical shift at 20.71 ppm (DMSO-d_6) which indicates an sp^2 B in an aromatic ring.[2] ^1H NMR indicated the absence of one of the *ortho* protons in the aromatic system. As the original solid was not suitable for X-ray study, attempts were made to find a solvent for crystal-



Scheme 1.



Scheme 2.

Keywords: amidines; *ortho*-borylation; 2,4-diaza-1-borines.

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lization. Finally, water was found to be a suitable solvent, although under these conditions the product retained one equivalent of water as indicated by elemental analysis ($C_9H_{13}BBrClN_2O_2$). Based on X-ray analysis the diazaborine structure (see Fig. 1) was assigned.

The main feature in the crystal packing of **5** is that the chloride ion and water molecules are linked to diazaborine through hydrogen bonding (Fig. 2). The formation of **5** could be rationalized through the intermediacy of amidine **3** as shown in Scheme 2.

It is interesting to note that the above diazaborine does not add methanol or isopropanol on recrystallization from these solvents. This is in contradiction to the ready but reversible addition of weakly nucleophilic species such as water and methanol to 2,4-diaza-1-borine systems studied in the literature.[3] The hydrochloride salt is very stable and is resistant to H_2O_2 oxidation. Extension of this reaction to *p*-toluidine and 1-aminonaphthalene under the same conditions as with 4-bromoaniline resulted in the isolation of diazaborines **6** and **7** in 70% and 78% yield, respectively. Spectroscopic data and elemental analysis are in complete agreement with the proposed structures.[4]

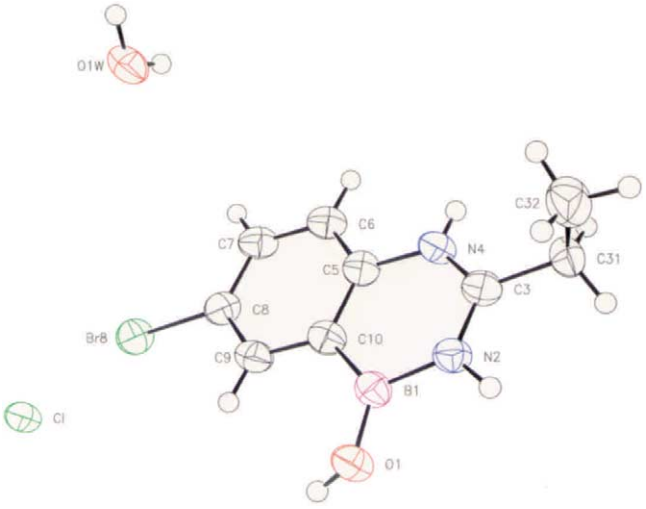


Figure 1. X-Ray structure of **5**.

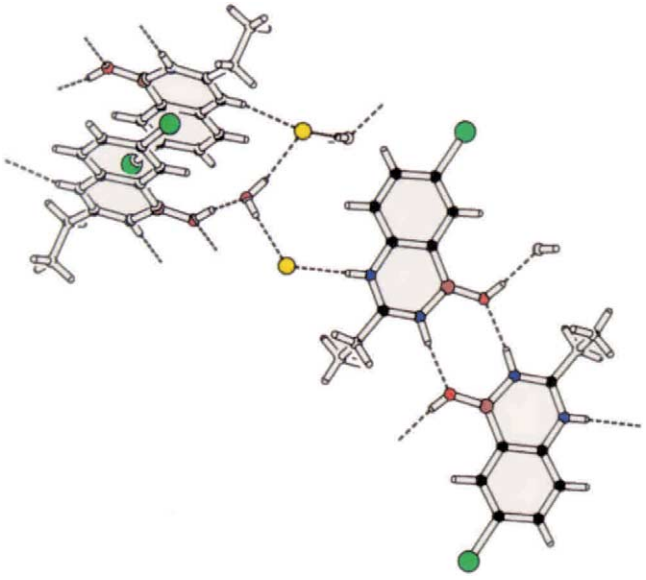
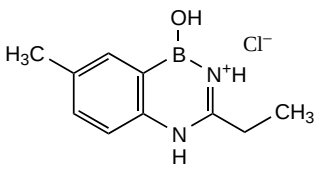


Figure 2. Crystal packing of **5**.



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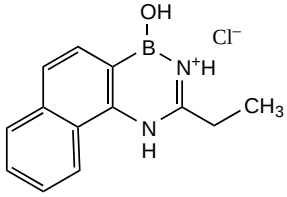

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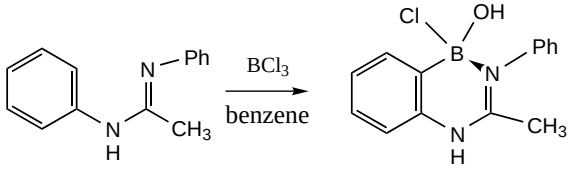
The reaction of *N*,*N*′-diphenylacetamidine **8** with BCl_3 in boiling benzene was reported earlier by Mikhailov and co-workers[3] and the product obtained after quenching with water was proposed to have structure **9**. Based on analogy with our compounds it is tempting to reconsider this compound as a chloride salt, although more evidence is needed to confirm this one way or other.



8 **9**

In conclusion we have demonstrated an efficient synthesis of 2,4-diaza-1-borines from anilines with the in situ intermediacy of amidines.

Acknowledgements

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References

1. Sasakura, K.; Terui, Y.; Sugasawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 1836 and references cited therein.
2. Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597–7605.
3. Boldyrev, O. G.; Dorokhov, V. A.; Mikhailov, B. M. *Izv. Akad. Nauk USSR, Ser. Khim.* **1985**, *2*, 428–430.
4. Representative procedure: 7-Bromo-3-ethyl-1,2-dihydro-1-hydroxy-2,4-benzodiaza-1-borine mono hydrochloride (**5**): A solution of 13.4 g of 4-bromoaniline (0.075 mol) in 21.1 g of propionitrile (0.375 mol) was added to a suspension of 31.4 g of anhydrous $AlCl_3$ (0.16 mol) in 75 mL of toluene at 5–50°C (exothermic). The contents were heated up to 107°C and maintained refluxing for 1.5 h. The reaction mixture was cooled to −5°C; 18 g of boron trichloride gas

(0.15 mol) was slowly bubbled into the mixture at −5°C over 15 min (exothermic). The suspension was heated again and refluxed for 4 h (HCl gas evolution). The reaction mixture was cooled to 22°C and poured into a mixture of 400 g of crushed ice and 100 mL of toluene with efficient stirring. The slurry was warmed to 15°C and maintained at this temperature for 0.5 h. The beige solid was filtered, washed with 1000 mL of cold water (5°C) and dried at 40–45°C (15 mbar) overnight to give 11.8 g (55% yield) of **5**; mp 223–224°C; IR (KBr): 3308, 3211, 3070, 2918, 2790, 1651, 1577, 1491, 1455, 1407, 1244, 1168, 1127, 1069, 892, 867, 830, 522 cm^{-1}; UV: λ_{max} (nm) ($\epsilon\times10^4$) (CH_3OH) 264 (1.04), 206 (1.47); ^1H NMR (DMSO-d_6): δ 7.85 (1H, d, $J=2.3$ Hz), 7.63 (1H, dd, $J=2.3$ and 8.6 Hz), 7.25 (1H, d, $J=8.6$ Hz), 4.93 (s, 1H, OH), 2.79 (2H, q, $J=7.7$ Hz), 1.42 (3H, t, $J=7.7$ Hz); ^{13}C NMR (DMSO-d_6): δ 168.16, 141.27, 140.89, 135.80, 134.86, 120.79, 120.41, 29.16, 13.12; MS m/z 491, 489, 487 ($2M-H_2O+H^+$), 255, 253 (MH^+). Anal. calcd for $C_9H_{11}BBrClN_2O$: C, 37.36; H, 3.83; B, 3.74; Br, 27.61; Cl, 12.25; N, 9.68; O, 5.53. Found: C, 37.37; H, 3.65; B, 3.70; Cl, 12.19; N, 9.59; O, 5.62.

Sample for X-ray analysis: 1 g of **5** was dissolved in 25 mL of water at 65°C, filtered, and the filtrate was left overnight. The resulting suspension was filtered, and the filter cake was dried at 22°C (15 mbar) for 16 h to give 0.5 g of a crystalline solid, which was found to be suitable for X-ray analysis, mp 233–234°C. Anal. calcd for $C_9H_{12}BBrClN_2O_2$: C, 35.17; H, 4.26; B, 3.52; Br, 27.61; Cl, 11.53; N, 9.11; O, 10.41. Found: C, 35.31; H, 4.13; B, 3.50; Cl, 11.43; N, 9.02.

Compound **6**: mp 187–188°C; IR (KBr): 3567, 3295, 2922, 2855, 1650, 1582, 1475, 1404, 1291, 1256, 1220, 1200, 881, 863, 828, 761, 528, 481 cm^{-1}; UV. λ_{max} (nm) ($\epsilon\times10^4$) (CH_3OH) 263 (7.16), 204 (1.16); ^1H NMR (DMSO-d_6): δ 7.78 (s, 1H), 7.54 (1H, dd, $J=8.5$ Hz), 7.44 (1H, d, $J=8.5$ Hz), 2.93 (2H, q, $J=7.7$ Hz), 2.44 (s, 1H, OH), 1.44 (3H, t, $J=7.7$ Hz); ^{13}C NMR (DMSO-d_6): δ 168.09, 141.27, 138.49, 135.46, 133.46, 119.37, 28.95, 21.67, 13.26; MS m/z 378, 376 ($2MH^+$), 359 ($2M-H_2O+H^+$), 189 (MH^+). Anal. calcd for $C_{10}H_{14}BClN_2O$: C, 53.50; H, 6.29; B, 4.82; Cl, 15.79; N, 12.48; O, 7.13. Found: C, 53.41; H, 6.21; B, 4.11; Cl, 16.61; N, 12.48; O, 7.18.

Compound **7** (78% yield): mp 188–190°C; IR (KBr) 3405, 3181, 2980, 1644, 1603, 1551, 1520, 1492, 1461, 1392, 823, 751 cm^{-1}; UV: λ_{max} (nm) ($\epsilon\times10^4$) (CH_3OH) 303 (6.63), 234 (2.99); ^1H NMR (DMSO-d_6): δ 8.72 (1H, m), 8.01 (1H, m), 7.88 (2H, m), 7.73 (2H, m), 5.15 (s, 1H, OH), 3.16 (2H, q, $J=7.7$ Hz), 1.52 (3H, t, $J=7.7$ Hz); ^{13}C NMR (DMSO-d_6): δ 169.62, 139.88, 137.25, 130.44, 129.81, 128.91, 128.49, 128.15, 124.58, 122.52, 29.05, 13.92; MS m/z 431 ($2M-H_2O+H^+$), 225 (MH^+). Anal. calcd for $C_{13}H_{14}BClN_2O$: C, 59.93; H, 5.42; B, 4.15; Cl, 13.61; N, 10.75; O, 6.14. Found: C, 60.06; H, 5.49; B, 4.11; Cl, 13.65; N, 10.79; O, 6.44.