A New Method for Preparation of 2-Aminopyridine:Borane and its Analogues

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It has been known that amine:boranes are useful reducing agents for aldehydes and ketones, and also that the reactivity and stereoselectivity of amine:borane reagents is highly dependent on the nature of the amine used in the amine:borane complex[1].

In spite of their remarkable stability, solubility in protic and aprotic solvents, and handling convenience, there is a problem in amine:borane synthesis because of the necessity for strictly dehydrated conditions[2,3]. We now wish to report the first example of amine:borane synthesis in aqueous media. The amine:boranes synthesized here are similar to both primary amine:boranes and pyridine:borane in their reactivity.

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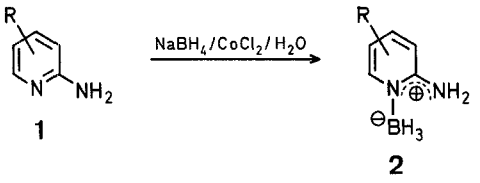
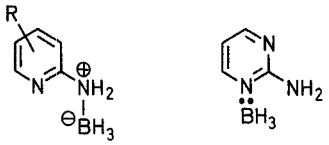
In the course of our studies on the reduction of the amidine group with sodium borohydride[4], we have found that 2-aminopyridine:borane and its analogues **2** were prepared by the treatment of corresponding 2-aminoheterocycles **1** with sodium borohydride in aqueous solvent in the presence of cobalt(II) chloride. The system sodium borohydride/cobalt(II) chloride has already been applied to the reduction of organic functional groups in hydroxylic solvent[5], but not to the preparation of amine:boranes.



1 2

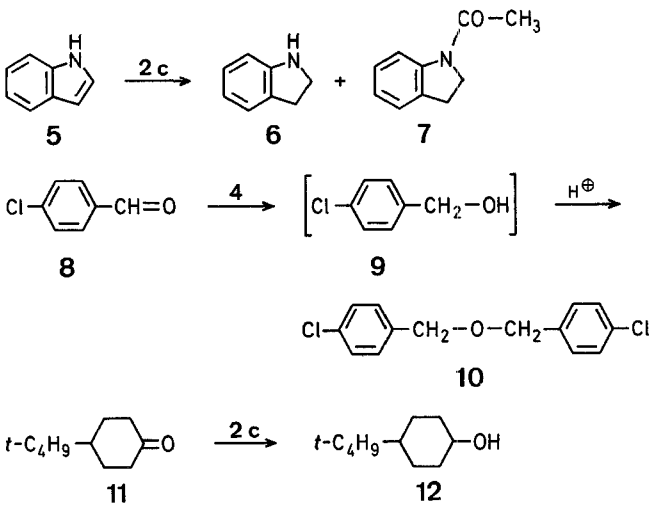
Cobalt(II) chloride and 2-aminopyridine (**1**; R = H) were dissolved in water, sodium borohydride was gradually added to this solution with stirring, subsequent work up gives colorless crystals of 2-aminopyridine:borane **(2a)** in 71% yield. The yield was affected by the amount of cobalt(II) chloride and sodium borohydride, and the amount described here was enough to obtain **2a** in optimum yield. The use of iron(II) sulfate in place of cobalt(II) chloride also gave **2a** in good yield. However, the structure **3a** might be considered along with structure **2a,** though the latter was consistent with M.S. analytical results. In order to clarify this problem, we studied the N.M.R. spectrum of the amine:borane comparing it with that of 2-aminopyridine itself. As shown in Table 1, the signal for the 4-proton of the pyridine ring is observed at a considerably lower field than those of the 5- and 6-protons when the borane complex is formed. These results indicate that the endocyclic nitrogen atom of 2-aminopyridine is quaternized[6,7]. Moreover, no B—N—H coupling was observed in the amine:borane (*cf.* BH_3 in 2-aminopyridine:borane: 2.26 ppm, $J = 93$ Hz, quartet).



3 4

Therefore, the structure **3a** should be out of the consideration. Hereupon, it is worth noting that 4-aminopyridine and 2-aminomethylpyridine did not form the borane complexes under the conditions described above. These results strongly indicate that the amidine moiety in the 2-aminoheterocycles, together with the metal ion, may play an important role for the formation of the amine:boranes. Since diborane is unstable in water, the amidine/metal/borane complex might be considered as an intermediate of the 2-aminoheterocycle:borane. While the basicity of 2-amino-6-methylpyridine (pK_a 7.41 at 21 °C)[8a] is larger than that of 2-aminopyridine (pK_a 6.86 at 20 °C)[8b], the yield of 2-amino-6-methylpyridine:borane **(2e)** is much lower than that of **2a.** This result might be due to a steric hindrance of the 6-methyl group[9]. All amine:boranes obtained by the same method are listed in Table 2. They are like pyridine:borane in reactivity.

For example, indole **(5)** was reduced with 2-amino-4-methylpyridine:borane **(2c)** to indoline (**6**; 47%) and *N*-acetylindoline (**7**; 27%)[10], and *p*-chlorobenzaldehyde **(8)** was converted with 2-aminopyrimidine:borane **(4)** to bis[*p*-chlorobenzyl] ether **(10)** in 67% yield[11]. Also, these tertiary amine:boranes sometimes behave like primary amine:boranes. For example, 4-*t*-butylcyclohexanone **(11)** was reduced with **2c** to its alcohol **12** (total yield, 99%; *trans*:*cis* = 96:4) under the conditions described in the literature[1]. However, pyridine:borane **(2a)** is not suitable for the reduction of 4-*t*-butylcyclohexanone[1]. Studies on the stereo- and chemo-selective reductions of aldehydes and ketones with these 2-aminoheterocycle:boranes are in progress.



2-Amino-4-methylpyridine:Borane (2c); Typical Procedure:
Sodium borohydride (0.50 g, 13 mmol) is gradually added to a solution of cobalt(II) chloride hexahydrate (0.5 g, 2.1 mmol) and 2-amino-4-methylpyridine (**1c**; 0.45 g, 4.2 mmol) in water (50 ml) with stirring. After 3 h, the mixture is extracted with chloroform (3 × 20 ml). The extract is dried with sodium sulfate and evaporated at 40 °C under reduced pressure to give crystals which are purified by passage through a silica gel (Woelm) column using chloroform as an eluent; yield: 0.36 g (71%); m.p. 88–89 °C (plates from cyclohexane/chloroform).

2-Amino-4-methylpyridine:Borane (2c); Typical Preparative Scale Procedure:
2-Amino-4-methylpyridine (**1c**; 10 g, 92 mmol) and cobalt(II) chloride (10 g, 42 mmol) are dissolved in water (300 ml) in a 1-l beaker. Since vigorous foam formation occurs when sodium borohydride (10 g, 264 mmol) is gradually added to the solution, isopropyl alcohol is occasionally added dropwise to defoam. About 2 ml of isopropyl alcohol are necessary for this purpose. After stirring for 3 h, the mixture is extracted with chloroform (3 × 100 ml). The organic layer is dried with sodium sulfate and evaporated to dryness. Purification is carried out as described above.

2-Aminopyrimidine:Borane (4):
2-Aminopyrimidine (5 g, 53 mmol) and cobalt(II) chloride (5 g, 21 mmol) are dissolved in water (200 ml) in a 1-l beaker. Sodium borohydride (5 g, 132 mmol) is gradually added, and isopropyl alcohol is occasionally added dropwise to the mixture (about 2 ml). After stirring for 3 h, the mixture is extracted with chloroform (3 × 70 ml). The organic layer is dried with sodium sulfate and evaporated to dryness. Recrystallization from ethanol/water gives prisms of **4**; yield: 2.5 g (43%); m.p. 111–112 °C.

Reduction of Indole with 2c:
To a solution of indole (**5**; 70 mg, 0.6 mmol) in acetic acid (8 ml) is added **2c** (300 mg, 2.5 mmol). The mixture is stirred for 18 h, then made alkaline (pH > 13) by addition of 10% sodium hydroxide solution and sodium hydroxide pellets with cooling. The aqueous layer is extracted with benzene (3 × 10 ml) which is then evaporated under reduced pressure. To the residue is added 10% hydrochloric acid to decompose excess **2c**. The aqueous layer is made alkaline (pH > 13) with 10% sodium hydroxide and sodium hydroxide pellets with cooling, and then

Table 1. Chemical Shifts [ppm] of Pyridine Ring Protons[a]

Compound	H-3	H-4	H-5	H-6
1a (R=H)	6.44	7.36	6.58	8.03
1a: BH_3 (**2a**; R=H)	6.67	7.53	6.60	8.07
Difference	0.23	0.17	0.02	0.04
1b (R=3-H_3C)	—	7.23	6.58	7.93
1b: BH_3 (**2b**; R=3-H_3C)	—	7.42	6.58	8.03
Difference	—	0.19	0.00	0.10

[a] $CDCl_3$ solvent, TMS as internal standard.

Table 2. 2-Aminoheterocycle : Boranes **2a–e, 4**

Product No.	R	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	M.S. *m/e* for $M^+ - 1$ (calc.)
2a	H	71	36–38° (c-C_6H_{12}/$CHCl_3$)	$C_5H_9BN_2$ (108.0)	107.078 (107.078)
2b	3-H_3C	72	65–66° (c-C_6H_{12}/$CHCl_3$)	$C_6H_{11}BN_2$ (122.0)	121.098 (121.094)
2c	4-H_3C	71	88–89° (c-C_6H_{12}/$CHCl_3$)	$C_6H_{11}BN_2$ (122.0)	121.100 (121.094)
2d	5-H_3C	75	94–95° (c-C_6H_{12}/$CHCl_3$)	$C_6H_{11}BN_2$ (122.0)	121.098 (121.094)
2e	6-H_3C	2	51–52° (c-C_6H_{12}/$CHCl_3$)	$C_6H_{11}BN_2$ (122.0)	121.096 (121.094)
4	—	43	111–112° (C_2H_5OH/H_2O)	$C_4H_8BN_3$ (109.0)	108.076 (108.073)

[a] Satisfactory microanalyses (C ±0.19, H ±0.30, N ±0.36), N.M.R., I.R., M.S., and T.L.C. (silica gel, chloroform/methanol, 1 : 0, 9 : 1, or 4 : 1) data obtained.

extracted with benzene (3 × 20 ml). The extract is washed with saturated sodium chloride solution and dried with sodium sulfate. After evaporation of benzene, the residue is submitted to preparative T.L.C. (silica gel, Merck) using chloroform/methanol (9/1) for development to give a mixture of indoline **(6)** and *N*-acetylindoline **(7)**. The mixture is acidified (pH 2) with 0.1 normal hydrochloric acid solution and extracted with chloroform (3 × 10 ml). The organic layer is dried with sodium sulfate and evaporated to give *N*-acetylindoline **(7)**; yield: 26.7 mg (28%); m.p. 102 °C (dec) (Lit.[12], m.p. 101.5 °C).

The aqueous layer is made alkaline (pH 12) and extracted with chloroform (3 × 10 ml). The organic layer is dried with sodium sulfate and evaporated under a reduced pressure to give indoline **(6)** as an oil; yield: 33.6 mg (47%); identical to an authentic sample[10].

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[1] G. C. Andrews, T. C. Crawford, *Tetrahedron Lett.* **21,** 693 (1980).
G. C. Andrews, *Tetrahedron Lett.* **21,** 697 (1980).
[2] G. W. Schaeffer, E. R. Anderson, *J. Am. Chem. Soc.* **71,** 2143 (1949).
H. Nöth, H. Beyer, *Chem. Ber.* **93,** 928 (1960).
[3] M. D. Taylor, L. R. Grant, C. A. Sands, *J. Am. Chem. Soc.* **77,** 1506 (1955).
[4] Y. Okamoto, T. Kinoshita, *Chem. Pharm. Bull.* **29,** 1165 (1981).
[5] T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, Z. Imai, *Tetrahedron Lett.* **1969,** 4555.
[6] N. Nakagawa, *Interpretation of NMR Spectra,* Kyoritsu Shuppan Co., Ltd., Tokyo, 1966, p. 91.
[7] Y. Okamoto, A. Takada, T. Ueda, *Chem. Pharm. Bull.* **19,** 764 (1971).
[8] (a) F. Fastier, M. McDowall, *Aust. J. Exp. Biol.* **36,** 491 (1958); *C. A.* **53,** 4550 (1959).
(b) A. Albert, R. Goldacre, N. Phillips, *J. Chem. Soc.* **1948,** 2240.
[9] H. C. Brown, H. I. Schlessinger, S. Z. Cardon, *J. Am. Chem. Soc.* **64,** 325 (1942).
[10] Y. Kikugawa, K. Saito, S. Yamada, *Synthesis* **1978,** 447.
[11] Y. Kikugawa, *Chemistry Lett.* **1979,** 415.
[12] G. M. Bennet, M. M. Hafez, *J. Chem. Soc.* **1941,** 287.

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