Synthesis and Reduction Ability of Borane Complexes of 2-Aminopyridine Derivative having a Chiral Center at the Amino Nitrogen

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A novel method for synthesis of a chiral amine borane is described and selective reductions of carbonyl compounds with the amine borane are investigated.

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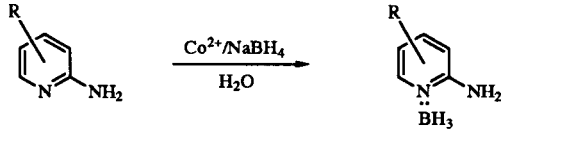
Amine boranes are useful reducing reagents for carbonyl compounds because of their stability and high solubility in ordinary organic solvents [1]. Recently, it has been reported that chemoselective [2], stereoselective [3], and chiral reductions [4] of amine borane reagents are highly dependent on the nature of the amine used in the amine borane complex. However, the synthetic methods of amine boranes are troublesome because the reactions must be done under absolutely anhydrous conditions and, in general in a nitrogen stream [5]. In a previous paper [6], we reported on a simple novel method for the synthesis of borane complexes of 2-aminopyridine and its derivatives, where 2-aminopyridine and its analogs were treated with sodium borohydride in water in the presence of metal ions (Scheme 1).

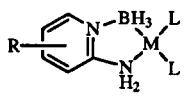
Scheme 1



R=H, 3-CH_3, 4-CH_3, 5-CH_3

The role of metal ions has also been studied [7], and was found to form an intermediate chelate complex with the amine and borane (Chart 1). Moreover, the formation of the intermediate was found to be susceptible to steric hindrance. For example, when a methyl group was introduced at the 6 position of 2-aminopyridine, the corresponding amine borane obtained was very small [6]. On the basis of these facts, we attempted to further develop our method for the synthesis of chiral amine boranes. This report describes the synthesis of borane complexes of 2-aminopyridine having a chiral center at the amino group and their reduction abilities.

Chart 1

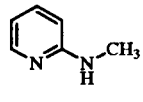
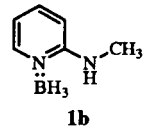
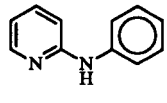
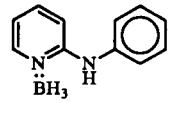
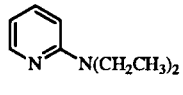
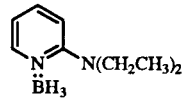
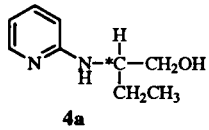
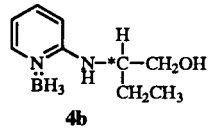
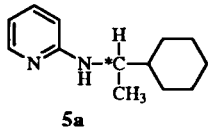
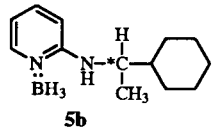


M : Co^{2+}
L : might be OH

Synthesis.

We first studied the effect of a substituent at the exo-nitrogen of 2-aminopyridine for the synthesis of the corresponding amine boranes. When 2-methylaminopyridine (**1a**) was treated by our method, 2-methylaminopyridine borane (**1b**) was obtained in good yield. Nickel(II) ions were found to be superior to cobalt(II) ions in providing the amine borane **1b** (Table I). We surveyed the effect of a more bulky substituent such as phenyl and diethyl groups in place of the methyl group. When 2-phenylaminopyridine (**2a**) and 2-diethylaminopyridine (**3a**) were used as amine-source, the corresponding amine boranes, **2b** and **3b**, were obtained in very low yield and not at all, respectively. We, then,

Table I
Synthesis of Amineborane Using $Ni^{2+}/NaBH_4$ in Water

Starting Amine	Amine Borane	Yield
 **1a**	 **1b**	80%
 **2a**	 **2b**	trace
 **3a**	 **3b**	0%
 **4a**	 **4b**	14%
 **5a**	 **5b**	0%

attempted to introduce 1-hydroxybutan-2-yl and 1-cyclohexylethan-1-yl as a chiral group to the exo-nitrogen of 2-aminopyridine. The reaction of 2-fluoropyridine with chiral 2-aminobutanol and chiral 1-amino-1-cyclohexylethane afforded 2-(1-hydroxybutan-2-yl)aminopyridine (**4a**, *R* and *S*) and 2-(1-cyclohexylethan-1-yl)-aminopyridine (**5a**, *R* and *S*), respectively. These chiral amines were treated with sodium borohydride in water in the presence of nickel(II) ions by our method, and the corresponding amine borane complexes, (*R*)- and (*S*)-2-(1-hydroxybutan-2-yl)aminopyridine boranes (**4b**, *R* and *S*) were obtained in 14% yield, but the 2-(1-cyclohexylethan-1-yl)aminopyridine boranes (**5b**, *R* and *S*) were not obtained. The structures of **4b** (*R* and *S*) were determined on the basis of spectral data. The proton nmr spectra of these amine boranes showed the characteristic broad signals at 2.71-1.37 ppm due to borane protons. In the infrared (ir) spectra, they also showed the characteristic absorption band between 2250-2400 cm^{-1} due to the borane group. Table II shows the specific rotations of compounds **4b** (*R* and *S*).

Table II
Specific Rotations of **4a** and **4b**

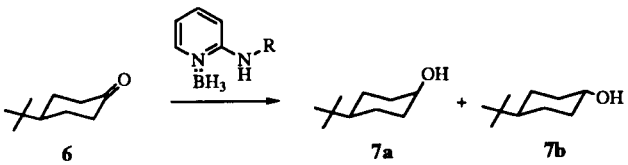
	4a	**4b**
R	+56.7 (0.67)	+62.2 (0.68)
S	-59.2 (0.67)	-61.9 (0.63)

Concentration in parentheses. Solvent: methanol. Temperature is room temperature

Reducing Ability.

Chiral amine boranes **4b**-*R* and **4b**-*S* were examined as to their stereoselective and chiral reductions using 4-*tert*-butylcyclohexanone (**6**) and acetophenone (**8**) as substrates, respectively. The data on these reductions are summarized in Table III and Table IV. When compared with 2-methylaminopyridine borane **1b**, no stereoselectivity or reduction were observed in the use of **4b**-*R* and **4b**-*S*.

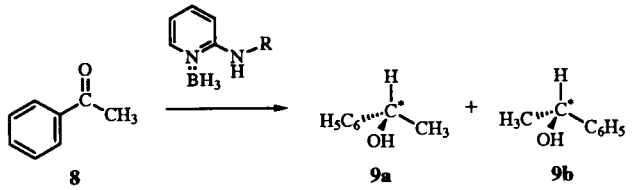
Table III
Stereoselective Reduction



6 **7a** **7b**

R	Time (min.)	Ratio (**7a**:**7b**)	Yield(**7a** + **7b**,%)
CH_3	60	19:81	10.9
$HC(C_2H_5)(CH_2OH)$ (S)	60	3:97	4.7
$HC(C_2H_5)(CH_2OH)$ (R)	60	17:83	9.3

Table IV
Chiral Reduction



8 **9a** **9b**

R	Ratio (**9a**:**9b**)	Yield (**9a** + **9b**, %)
CH_3	54:46	52.2 [a]
CH_3	48:53	99.6
$HC(C_2H_5)(CH_2OH)$ (S)	51:49	53.5
$HC(C_2H_5)(CH_2OH)$ (R)	45:55	18.9

[a] $(C_2H_5)_2OMgBr_2$ was not applied

Conclusion.

Although the yield of amine borane complexes is dependent on the substituents, our method for the synthesis of 2-aminopyridine borane in water could be applied for **1a** and **4a** to provide the corresponding amine borane complexes **1b** and **4b**. The reason why the chiral reducing ability of **4b**-*R* and **4b**-*S* could not be observed may be explained by the fact that the distance between borane and the chiral center is too great to effect selective reduction.

EXPERIMENTAL

The melting points determined on a Yazawa micro melting point BY-2 apparatus are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240B instrument. The ir spectra were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a Varian XL-400 spectrometer using tetramethylsilane as the standard. The uv spectra were measured on a Hitachi U-3200 spectrophotometer with methanol as the solvent. The angles of rotation were measured on a JASCO DIP-140 digital polarimeter with methanol as the solvent. The mass spectra were measured on a JEOL-JMS-O1S spectrometer. Gas chromatography was performed on a Hitachi 163 instrument and the hplc were performed on a JASCO TWINCLE as the pressure pump and a Shimadzu SPD-6A as the detector.

2-Methylaminopyridine Borane **1b**.

A solution of nickel(II)nitrate (24.0 g, 82.5 mmoles) in 100 ml of water was gradually added to a mixed solution of **1a** (24.0 g, 222 mmoles) and sodium borohydride (24 g, 684 mmoles) in 300 ml of water. The mixture was stirred overnight and precipitate was collected by suction filtration. After air-drying, the precipitate was mixed with 300 ml of chloroform with stirring and the mixture was filtered by suction. The filtrate was evaporated to dryness to give **1b** a crude powder which was washed with water to give pure crystals of **1b** in 80% yield (21.6 g), mp 77-78°; ir (potassium bromide pellet): 2250-2400 cm^{-1} (N-BH_3); ms: m/z 121 (M^+-1).

Anal. Calcd. for $C_6H_{11}BN_2$: C, 59.08; H, 9.09; N, 22.97. Found: C, 59.01; H, 9.12; N, 22.85.

Chiral 2-(1-Hydroxybutan-2-yl)aminopyridine **4a**.

A mixture of 2-fluoropyridine (2.5 g, 2.57 mmoles) and chiral 2-amino-1-butanol (2.3 g, 2.58 mmoles) was refluxed for 25 hours without a solvent. The reaction products were purified by column chromatography using silica gel (chloroform as the eluant) and chiral **4a** was obtained as an oil in 79% yield (3.8 g); pmr: 1.07 (3H, CH_3), 1.68 and 1.85 (2H, CH_2CH_3), 3.48-3.69 (2H, CH_2OH), 3.95 (1H, CH), 4.86 (1H, OH), 6.39 (1H, NH), 6.60 (1H, C_3-H), 6.67 (1H, C_5-H), 7.50 (1H, C_4-H), 8.10 (1H, C_6-H); ms: m/z 166 (M^+).

Anal. Calcd.for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.99; H, 8.54; N, 16.58.

Chiral 2-(1-Hydroxybutan-2-yl)aminopyridine Borane **4b**.

A solution of nickel(II)nitrate (1.05 g, 3.61 mmoles) in 10 ml of water was gradually added to a mixture of **4a** (1.75 g, 1.05 mmoles) and sodium borohydride (1.05 g, 2.80 mmoles) in 100 ml of water with stirring. After 20 hours stirring, the reaction mixture was extracted three times with 60 ml of dichloromethane. The extract was evaporated under reduced pressure and the residue was purified by column chromatography using a silica gel (chloroform as eluant) to give 0.26 g (14%) of **4b** as oil; ir (silver chloride plate): 2250-2400 cm^{-1} (N-BH_3); pmr: 0.91 (3H, CH_3), 1.34-2.58 (3H, BH_3), 1.52 and 1.66 (2H, CH_2CH_3), 3.43-3.64 (3H, $CHCH_2$), 4.98 (1H, OH), 6.29 (1H, NH), 6.64 (1H, C_3-H), 6.95 (1H, C_5-H), 7.73 (1H, C_4-H), 8.04 (1H, C_6-H); ms: m/z 179 (M^+-1).

Anal. Calcd. for $C_9H_{17}N_2BO$: C, 60.04; H, 9.52; N, 15.56. Found: C, 59.98; H, 9.81; N, 15.32.

Reduction of 4-tert-Butylcyclohexanone (Table III).

To a solution of **6** (0.17 g, 1.10 mmoles) in 30 ml of methanol/water (2/1) was added an equimolecular amount of **4b**. After stirring for 1 hour at room temperature, the solution was neutralized with 1 mol/dm3 of hydrochloric acid, followed by extraction with 10 ml of chloroform. The extract was evaporated under reduced pressure to give 4-*tert*-butylcyclohexanol (**7**).

The stereochemistry of **7** was analyzed as follows: Product **7** (1 mg) was placed in a test tube with a screw cap and dissolved in 100µl of pyridine. *N,O*-Bis(trimethylsilyl) trifluoroacetamide, 300µl was added to the solution and the mixture was heated at 100° for 10 minutes. After cooling, the mixture was extracted with 2 ml of chloroform/water(1/1). The organic layer was concentrated at room temperature using nitrogen stream, and ethyl acetate was added to the residue. The solution was analyzed by gas chromatography (glass column: 3% OV-101,ø3 mm x 2m; temperature: 120°; detection; FID).

Reduction of Acetophenone (Table IV).

To a mixture of 8 (0.2 g, 1.66 mmoles) and magnesium bromide diethyl etherate (0.4 g, 1.66 mmoles) in 30 ml of tetrahydrofuran was added an amine borane (1.66 mmoles). The mixture was stirred at room temperature for 3 hours and evaporated under reduced pressure, then acidified with 10 ml of 1 mol/l of hydrochrolic acid. The mixture was extracted with chloroform three times and the organic solvent was evaporated to give 1-phenylethanol (9) as an oil.

The chirality of **9** was analyzed by hplc [column: CHIRAL OB (Daicel Chemical Industries Ltd.), ø0.46 x 25 cm; mobile phase: *n*-hexane/2-propanol(9/1); detection: uv 254 nm].

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