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Dialkyl(3-pyridyl)boranes

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Dialkyl(3-pyridyl)boranes (**2**) were synthesized by the iodination of lithium trialkyl(3-pyridyl)borates, prepared from trialkylboranes and 3-lithiopyridine. Although **2** was resistant to quaternization or ate-complex formation, betaines (**4b—e**) were obtained by the reaction of **2a** with cyanide ion and alkylating agents in high yields. Further, protonolysis of **2a** with propionic acid gave 3-pyridylboronic acid (**5**). Proton and carbon-13 nuclear magnetic resonance data for **2a**, **b** and **4b** are presented.

Keywords——dialkyl(3-pyridyl)borane; heteroarylborane; dialkylcyano(1-alkyl-3-pyridinio)borate; 3-pyridylboronic acid; ^{13}C-NMR

Although the potential utility of organoboranes in synthetic chemistry has been well documented, little is known about the chemistry of boranes substituted with heteroaryl groups.[1] In 1975, Nozaki *et al.* reported an efficient ring-opening reaction of (6-bromo-2-pyridyl)tributylborate prepared from 6-bromo-2-pyridyllithium and tributylborane *in situ*.[2a] More recently, the reactions of ate-complexes obtained from trialkylboranes and lithioheteroaromatics have been applied to the synthesis of heterocycles by several groups.[2] Since it is desirable to elucidate the effect of various heteroaryl groups on the properties of substituted boranes, and *vice versa*, we decided as a preliminary study to investigate boranes substituted directly with a pyridyl group as a representative six-membered heteroaromatic. We now wish to report the synthesis and properties of dialkyl(3-pyridyl)boranes (**2**).

The synthesis of the requisite **2** was effected *via* a one-pot procedure from 3-bromopyridine (Chart 1).

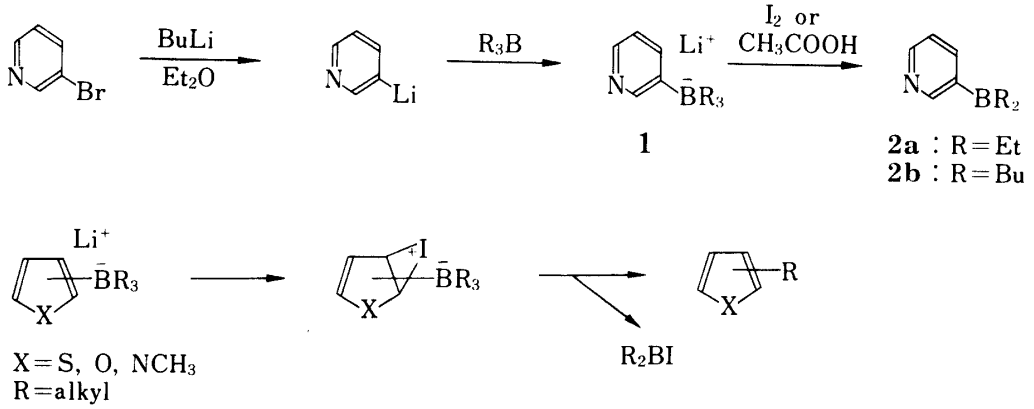

Chart 1

The sequence was initiated by the reaction of 3-lithiopyridine (derived from 3-bromopyridine[3]) with trialkylborane to afford the borate (**1**), which on treatment with iodine gave **2** in excellent yield as very stable crystals.

It should be pointed out that the reaction mode of **1**, which is substituted with an electron-deficient pyridyl group, with iodine is similar to that of tributylphenylborate,[4] and quite different from those of borates substituted with electron-excess five-membered heteroaromatics, in which the reaction proceeds with intramolecular alkyl migration to afford 2- or 3-alkylated products (Chart 1).[2]

Next, we investigated nucleophilic and electrophilic properties of **2**. Several attempts to alkylate **2** with dimethyl sulfate, benzyl chloride or bromide, or to form the ate-complex of **2** with nucleophiles such as butyllithium, the anion of ethyl malonate, acetylacetone or ethyl acetoacetate resulted in recovery of unchanged **2**. These results may be attributable, in part, to the depression of both nucleophilicity of nitrogen and electrophilicity of the boryl group, caused by the interaction of the vacant *p*-orbital of boron and the π-electron system in the pyridine ring.

In the case of cyanide ion as a nucleophile, however, **2a** was smoothly converted to the cyanoborate (**3**), which could be isolated and characterized as the betaine (**4a**) after treatment with 10% ethanolic hydrogen chloride, in high yield. In contrast to the former results, the quaternization of nitrogen in the borate (**3**) was successful. Thus, refluxing of an equimolar mixture of borane (**2a**) and potassium cyanide in ethanol for 1 h, followed by reaction with various alkylating agents (1 eq) at an appropriate temperature, gave the betaines (**4b—e**) in high yields. Preparation of the betaines was similarly achieved in a single procedure by the reaction of the mixture of three components under the same reaction conditions, suggesting the formation of cyanoborates in preference to nucleophilic substitution of alkylating agents with cyanide ion. It is assumed that the restoration of the basicity of nitrogen in the pyridine ring resulted from the inhibition of π-interaction between boron and carbon by the formation of the borate.

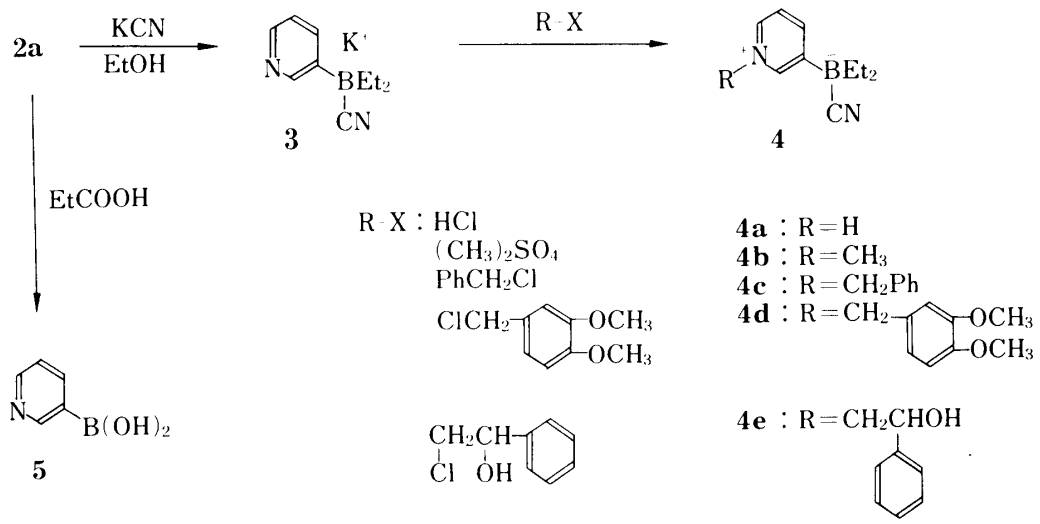

Chart 2

Since the protonolysis of a carbon–boron bond is a well-established process, we examined the reaction of **2** with carboxylic acids. Although **2a** was not affected by boiling acetic acid, upon refluxing in propionic acid, 3-pyridylboronic acid (**5**) was obtained in 25% yield, providing an improved synthesis of **5** (Chart 2).[5]

Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) data for **2a**, **b** and **4b** are summarized in the Table. It is well-known that the resonance of boron-substituted carbon-nuclei in ^{13}C-NMR spectra is characterized by weakening and broadening of the peak due to a large boron–carbon coupling which is incompletely relaxed by the quadrupole

TABLE. NMR, MS and Analysis Data for **2a**, **2b** and **4b**

	mp (°C)	Yield (%)	^{1}H-NMR (in $CDCl_3$) δ	^{13}C-NMR (in $CDCl_3$) δ	Formula	Analysis (%) Calcd (Found) C	H	N	High MS (*m/z*) (Calcd)
2a	160—162	80	0.60 (10H, m), 7.18 (1H, dd, J=6, 7 Hz), 7.53 (1H, s), 7.68 (1H, d, J=7 Hz), 7.97 (1H, d, J=6 Hz)	149.2 (C_2), 155.0 (C_3), 143.9 (C_4), 123.5 (C_5), 140.6 (C_6), 13.0 (BCH_2), 9.2 (CH_3)	$C_9H_{14}BN \cdot 1/4H_2O$	71.34 (71.43	9.64 9.53	9.24 9.13)	146.1255 and 147.1218 (M^+) ($C_9H_{14}BN$: 146.1255 and 147.1288)
2b	116—118	70	0.75 (14H, m), 1.20 (4H, m), 7.18 (1H, dd, J=5, 7 Hz), 7.53 (1H, s), 7.71 (1H, d, J=7 Hz), 8.00 (1H, d, J=5 Hz)	149.3 (C_2), 155.5 (C_3), 143.7 (C_4), 123.5 (C_5), 140.7 (C_6), 24.0 (BCH_2), 28.3, 26.7 and 14.2 ($CH_2CH_2CH_3$)	$C_{13}H_{22}BN \cdot 1/2H_2O$	73.60 (73.42	10.92 10.88	6.60 6.36)	202.1844 and 203.1833 (M^+) ($C_{13}H_{22}BN$: 202.1880 and 203.1844)
4b	96—98	80	0.38 (4H, m), 0.77 (6H, m), 4.27 (3H, s, NCH_3), 7.62 (1H, dd, J=6, 7 Hz), 8.12 (1H, d, J=6 Hz), 8.37 (2H, br s)	149.2 (C_2), 164.6 (C_3), 138.3 (C_4), 125.4 (C_5), 146.0 (C_6), 14.4 (BCH_2), 11.24 (CH_3), 47.6 (NCH_3)	$C_{11}H_{17}BN_2$	70.25 (70.14	9.11 8.91	14.89 14.77)	

mechanism.[6]

Characteristic features of the spectra of **2** as compared to those of pyridine are the upfield shifts of protons at C_2 and C_6 in the ^{1}H-NMR and the deshielding of the C_3 carbon by 30 ppm in the ^{13}C-NMR.

Further work on the reactions and applications of heteroarylboranes is in progress.

Experimental

Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl before use. All melting points were measured with a Yamato MP-1 melting point apparatus and are uncorrected. A Hitachi R-40 and a JEOL JNM-PMX60 spectrometer were used, respectively, to determine ^{1}H- and ^{13}C-NMR spectra with Me_4Si as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are reported in hertz. Mass spectra were measured with a JEOL JMS-QH100 or a JEOL JMS-D300 spectrometer. Infrared (absorption) spectra were measured with a JASCO A-102 spectrometer.

General Procedure for Preparation of 2a, b——A 1 M solution of trialkylborane in hexane (21 ml) was added dropwise to a ethereal solution (30 ml) of 3-lithiopyridine, [prepared from 3-bromopyridine (21 mmol) and BuLi (21 mmol, 13 ml of 1.6 M solution in hexane) according to the reported procedure,[3]] under a nitrogen atmosphere at −78 °C. The whole mixture was stirred at the same temperature for 1 h and at room temperature overnight, then a solution of iodine (21 mmol) in THF (20 ml) was added slowly at room temperature. After being stirred for 1 h, the mixture was diluted with ethyl acetate, and washed with 10% $Na_2S_2O_3$ aq. solution and brine. The organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel with benzene to give almost pure **2** as crystals in 70—80% yield. Further purification of **2** was effected by recrystallization from isopropyl alcohol. The Table summarizes the spectral and analytical data for **2a, b**.

Preparation of Cyanodiethyl(1*H*$^+$-3-pyridinio)borate (4a)——A mixture of **2a** (147 mg, 1 mmol) and KCN (65 mg, 1 mmol) was refluxed for 1 h, then 10% ethanolic hydrogen chloride (10 ml) was added to the mixture at room temperature. After removal of the solvent, the crystalline residue was recrystallized from benzene to give 139 mg (80%) of **4a** as colorless prisms, mp 118—119 °C. IR ν_{max}^{Nujol} cm^{-1}: 2180 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.53 (4H, m), 0.80 (6H, m), 7.56 (1H, dd, J=5 and 8 Hz), 8.05 (1H, d, J=5 Hz), 8.33 (1H, d, J=8 Hz), 8.63 (1H, s). *Anal.* Calcd for $C_{10}H_{15}BN_2 \cdot 1/3H_2O$: C, 66.71; H, 8.77; N, 15.56. Found: C, 66.84; H, 8.78; N, 15.71.

Preparation of Cyanodiethyl(1-methyl-3-pyridinio)borate (4b)——A mixture of **2a** (147 mg, 1 mmol) and KCN (65 mg, 1 mmol) in EtOH (10 ml) was heated under reflux for 1 h, then cooled. Dimethyl sulfate (126 mg, 1 mmol) was added to the reaction mixture and the whole was stirred at room temperature for 4 h. After dilution with benzene, the mixture was washed with brine and dried over $MgSO_4$. The solvent was removed and the residual oil was chromatographed on silica gel with ethyl acetate as the eluent to give 150 mg (80%) of **4b**. Recrystallization of **4b** from benzene–isopropyl ether gave colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 2160 (CN).

General Procedure for Preparation of 4c—e——A mixture of **2a** (1 mmol) and KCN (1 mmol) in EtOH (10 ml) was heated under reflux for 1 h, then cooled. Alkylating agent (1 mmol) was added and the whole mixture was heated under reflux for 5 h. After removal of the solvent, the residue was chromatographed on silica gel with ethyl acetate as the eluent to give **4c—e** in high yield.

Cyanodiethyl(1-benzyl-3-pyridinio)borate (4c)——Colorless viscous oil, 80% yield. IR ν_{max}^{neat} cm^{-1}: 2160 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.44 (4H, m), 0.73 (6H, m), 5.50 (2H, s), 7.33 (5H, m), 7.56 (1H, dd, J=6 and 8 Hz), 8.04 (1H, d, J=6 Hz), 8.38 (1H, d, J=8 Hz), 8.53 (1H, s).

Cyanodiethyl[1-(3,4-dimethoxybenzyl)-3-pyridinio]borate (4d)——Colorless prisms (from benzene), mp 163—165 °C, 70% yield. IR ν_{max}^{Nujol} cm^{-1}: 2190 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.20—0.90 (10H, m), 3.80 (3H, s), 3.83 (3H, s), 5.43 (2H, s), 6.75 (1H, m), 6.84 (2H, s), 7.55 (1H, m), 8.03 (1H, m), 8.35 (1H, m), 8.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{25}BN_2O_2$: C, 70.38; H, 7.77; N, 8.64. Found: C, 70.14; H, 7.91; N, 8.68.

Cyanodiethyl[1-(2-hydroxy-2-phenylethyl)-3-pyridinio]borate (4e)——Colorless leaflets (from benzene), mp 143—145 °C, 70% yield. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 2180 (CN). ^{1}H-NMR (acetone-d_6) δ: 0.10—0.90 (10H, m), 4.50—5.40 (4H, m), 7.10—7.50 (6H, m), 7.50—7.80 (1H, m), 8.20—8.50 (2H, m). *Anal.* Calcd for $C_{18}H_{23}BN_2O$: C, 73.49; H, 7.88; N, 9.52. Found: C, 73.41; H, 7.87; N, 9.52.

Preparation of 3-Pyridylboronic Acid (5)——A mixture of **2a** (402 mg) and propionic acid (10 ml) was heated under reflux for 6 h. Removal of propionic acid under reduced pressure left a crystalline residue, which was collected and washed with benzene to give crude **5**. Recrystallization of crude **5** from methanol gave **5** (84 mg, 25% yield). The spectral data for **5** were identical with those of an authentic sample prepared by the reported method.[4] IR ν_{max}^{Nujol} cm^{-1}: 3200 (OH). ^{1}H-NMR (CD_3OD) δ: 7.29 (1H, m), 8.02 (1H, m), 8.40 (1H, dd, J=2 and 6 Hz), 8.63 (1H, d, J=1 Hz).

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