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CONVENIENT SYNTHESIS OF AMINOPYRIDINECARBOXYLIC ACIDS

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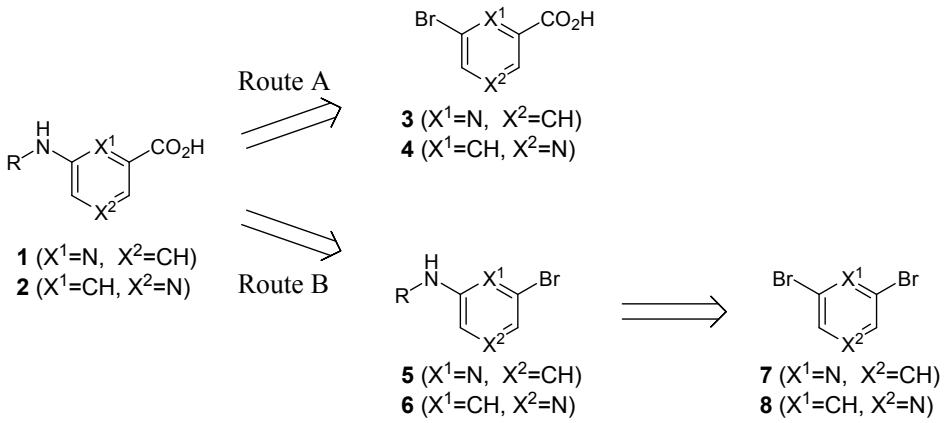
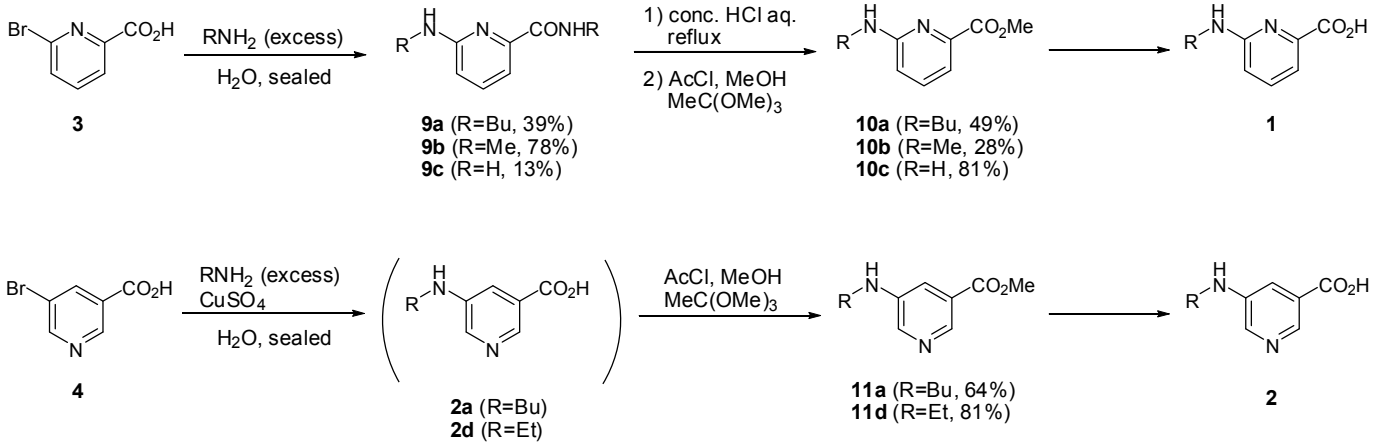
Abstract – 6-(Alkylamino)pyridine-2-carboxylic acids and 5-(alkylamino)pyridine-3-carboxylic acids were conveniently synthesized from dibromopyridine in satisfactory yields.

Pyridine, especially aminopyridinecarboxylic acids, are important structural units of both natural and synthetic bioactive compounds and many types of functional molecules,[1,2] so efficient synthesis of these compounds is an important issue. Many synthetic studies of pyridine derivatives have been reported, and some of them also work well for aminopyridines.[3] However, alkylaminopyridinecarboxylic acids are generally expensive, and their synthesis is troublesome because of their high polarity and water solubility. Herein we report a convenient synthesis of 6-(alkylamino)pyridine-2-carboxylic acids **1** and 5-(alkylamino)pyridine-3-carboxylic acids **2** from dibromopyridines.



Scheme 1. Synthetic routes to (alkylamino)pyridinecarboxylic acids

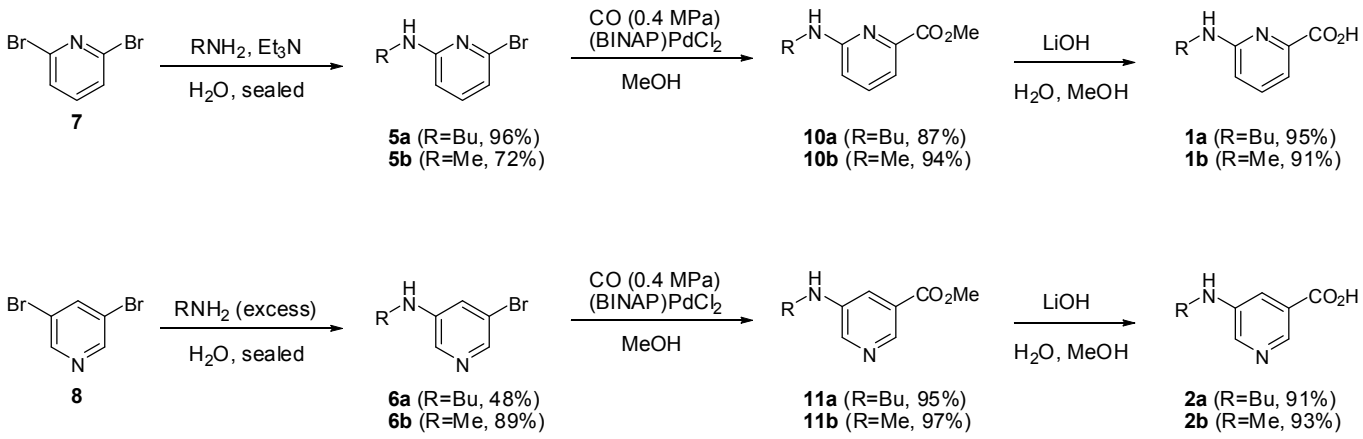
As potential synthetic routes to pyridinecarboxylic acids with various alkylamino groups, we considered two simple approaches using commercially available compounds (Scheme 1). Route A, direct amination of bromopyridinecarboxylic acid **3** or **4**, is expected to be a one-step synthesis, whereas route B, amination and carbonylation, can be started from dibromopyridine **7** or **8**, which is relatively inexpensive. First, we examined route A (Scheme 2). This route is considered to be used generally in syntheses of many kinds of alkylaminopyridinecarboxamides. In order to synthesize in large scale with aqueous solution of amine, such as methylamine, we tried with simple conditions.



Scheme 2. Synthesis of aminopyridinecarboxylic acid from bromopyridinecarboxylic acid (route A)

The amination of **3** and **4** was performed by heating the compounds with an aqueous solution of excess alkyl amine in a sealed tube, to avoid the need to separate a metal catalyst or other additive from the product. Although the amination of 6-bromopyridine-2-carboxylic acid **3** proceeded under this condition, the reaction gave amides **9** instead of carboxylic acids. The reaction of methyl 6-bromopyridine-2-carboxylate, instead of **3**, with butylamine also gave the amide **9a** in quantitative yield. These amides can be purified by chromatography, but their hydrolysis products can not be easily isolated from aqueous solution after acidic or basic hydrolysis. The methyl derivative **1b**, obtained from **9b**, could be isolated by crystallization from the neutralized solution (52%), but (butylamino)pyridinecarboxylic acid **1a**, obtained from **9a**, could not be isolated as a solid. Therefore, in this method, the amides should be converted to methyl esters **10**, which can be purified by chromatography, then hydrolyzed to carboxylic acids **1** (Scheme 2).[4] The reaction with ammonia solution afforded the aminated product **9c**, however the yield was poor. As we can see from these results, the yield varies depending on the amine, probably because of polarity of the amine solution.

In the case of 3-bromopyridine derivatives, it is well known that similar amination requires a copper salt.[4,5] The amination of 5-bromopyridine-3-carboxylic acid **4** in the presence of $CuSO_4$ gave the desired amino acids **2**. However, these compounds could not readily be purified from the copper-containing residue, and had to be converted to the methyl ester **11**, chromatographed, then hydrolyzed to afford the amino acids **2**. Thus, although it is possible to synthesize aminopyridinecarboxylic acids from bromopyridinecarboxylic acid derivatives, purification and handling of the products and intermediates are troublesome.



Scheme 3. Synthesis of aminopyridinecarboxylic acid using carbonylation (route B)

Next, we examined route B (Scheme 3). This method employs 2,6-dibromopyridine **7** or 3,5-dibromopyridine **8** as a starting material. The amination was carried out in a sealed bottle with 1 equivalent of alkylamine and 3 equivalents of triethylamine. The presence of water as a solvent is essential to obtain a good yield. 6-Bromo-2-(alkylamino)pyridines, **5a** and **5b**, were obtained from **7** in this simple way, but 3,5-dibromopyridine **8** reacted more slowly. In the latter case, the use of excess amine gave (butylamino)pyridine **6a** in 48% yield, with 41% recovery of the starting material **8**; and amination to (methylamino)pyridine **6b** proceeded in good yield. These amination reactions were not accompanied with significant formation of the diamino product or other by-product, so this method may be suitable for large-scale synthesis.

Carbonylation of the amines **5** and **6** was performed by Albaneze-Walker's method.[6] Carbon monoxide insertion using $(BINAP)PdCl_2$ afforded the corresponding methyl esters **10** and **11** in almost quantitative yield. These methyl esters were easily purified by chromatography with CH_2Cl_2 then AcOEt as eluents. The amino acids **1** and **2**, which can not be easily purified by chromatography, are obtained by hydrolysis of the methyl esters with LiOH and acidification with an equimolar amount of hydrochloric acid,

followed by recrystallization from water. Thus, these simple sequences afforded (alkylamino)pyridinecarboxylic acids **1** and **2** from dibromopyridine.

In conclusion, we have examined two simple methods for the synthesis of (alkylamino)pyridinecarboxylic acids. Monoamination of dibromopyridine followed by carbonylation using carbon monoxide was found to be convenient, and should be suitable for the synthesis of many alkylaminopyridine compounds.

EXPERIMENTAL

Melting points were determined by using a Yanaco melting point apparatus MP-S3 and are uncorrected. Autoclave reaction was performed in a TVS-1 (Taiatsu Techno Corporation) with a pressure gauge. Elemental analyses were carried out on Thermo Finnigan Flash EA1112, and antipyrine was used as a standard. ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-300, and chemical shifts are expressed in ppm relative to tetramethylsilane. IR spectra were recorded on Shimadzu FTIR-8200A. Mass spectra were measured on JEOL MS700 or HX110. Silica gel [silica gel 40-50 °C μ neutral, (Kanto Chemical Co., Inc.)] was used for all chromatographic procedures. Starting materials, 6-bromopyridine-2-carboxylic acid (**3**, from TCI), 5-bromopyridine-3-carboxylic acid (**4**, from TCI), 2,6-dibromopyridine (**5**, from TCI), 3,5-dibromopyridine (**6**, from TCI), $(MeCN)_2PdCl_2$ (from Aldrich) and *rac*-BINAP (from TCI), were commercial products and were used as received.

(rac-BINAP)PdCl$_2$ [7]

A mixture of $(MeCN)_2PdCl_2$ (5.19 g, 20.0 mmol), *rac*-BINAP (12.46 g, 20.0 mmol) and acetonitrile (160 mL) was stirred at 50 °C for 15 h, then at ambient temperature for 6 h. The bright yellow powder was collected by filtration and washed with acetonitrile to give the complex quantitatively. This complex was used for CO insertion without further purification.

*2-(Butylamino)-6-bromopyridine (**5a**)*

A mixture of 2,6-dibromopyridine (20.1 g, 84.8 mmol), triethylamine (40 mL, 287 mmol), butylamine (10 mL, 101 mmol) and water (50 mL) was heated in a sealed bottle with stirring at 190 °C for 23 h. After cooling, the mixture was poured into sat. $NaHCO_3$ aq., and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated with a rotary evaporator to give the crude product, which was chromatographed (CH_2Cl_2) to give the amine **5a** (18.8 g, 96%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) 7.25 (1H, t, J = 7.7), 6.70 (1H, d, J = 7.3), 6.27 (1H, d, J = 8.1), 4.65 (1H, br-s), 3.20 (2H, q, J = 7.0), 1.59 (2H, quint, J = 7.0), 1.41 (2H, sext, J = 7.0), 0.95 (3H, t, J = 7.3). ^{13}C NMR ($CDCl_3$) 159.0, 140.3, 139.5, 115.5, 103.9, 42.0, 31.4, 20.1, 13.8. IR (KBr) 3360, 2958, 1550, 1433 cm^{-1}. LR-MS (EI)

228, 230 [M^+]. HR-MS (EI) Calcd for $C_9H_{13}N_2Br$: 228.0262, 230.0243; Found: 228.0270, 230.0216.

*2-(Methylamino)-6-bromopyridine (**5b**)*

A mixture of 2,6-dibromopyridine (2.59 g, 10.9 mmol), triethylamine (5.0 mL, 35.9 mmol), methylamine solution in water (1.0 mL, 12 mmol) and water (5.0 mL) was heated in a sealed bottle with stirring at 190 °C for 23 h. After cooling, the mixture was poured into sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in a rotary evaporator to give the crude product, which was chromatographed (CH_2Cl_2) to give the amine **5b** (1.47 g, 72%) as colorless needles. Mp 62.0-63.0 °C (hexane). ^{1}H NMR ($CDCl_3$) 7.27 (1H, t, J = 7.7), 6.72 (1H, dd, J = 7.5, 0.6), 6.28 (1H, dd, J = 8.3, 0.4), 4.87 (1H, br-s), 2.90 (3H, d, J = 5.3). ^{13}C NMR ($CDCl_3$) 159.8, 140.2, 139.5, 115.5, 103.7, 29.1. IR (KBr) 3311, 1596, 1558, 1448 cm^{-1}. LR-MS (EI) 186, 188 [M^+]. Anal. Calcd for $C_6H_7N_2Br$: C, 38.53; H, 3.77; N, 14.98. Found: C, 38.53; H, 3.56; N, 14.74.

*Methyl 6-(butylamino)pyridine-2-carboxylate (**10a**)*

An autoclave was charged with a solution of **5a** (18.8 g, 82.1 mmol), triethylamine (15 mL, 108 mmol) MeOH (100 mL), and a stirrer bar, then nitrogen gas was bubbled through for 1 min, followed by addition of (*rac*-BINAP)$PdCl_2$ (115 mg, 0.144 mmol). The autoclave was sealed and air was replaced with CO (by means of several cycles of evacuation and flushing with CO) at a pressure of 0.4 MPa.[6] The mixture was heated at 100 °C with stirring and continuous addition of CO gas to maintain the pressure for 23 h. After cooling, the mixture was filtered and the filtrate was evaporated to give the crude product, which was chromatographed (AcOEt/hexane 1:3) to give the ester **10a** (13.8 g, 87%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) 7.56 (1H, t, J = 8.1), 7.40 (1H, d, J = 7.3), 6.56 (1H, d, J = 8.4), 4.86 (1H, br-s), 3.95 (3H, s), 3.23 (2H, q, J = 7.0), 1.61 (2H, quint, J = 7.7), 1.44 (2H, sext, J = 7.7), 0.95 (3H, t, J = 7.3). ^{13}C NMR (DMSO-d_6) 165.8, 158.7, 145.7, 137.0, 112.7, 111.7, 51.8, 40.3, 30.9, 19.6, 13.6. IR (KBr) 3400, 2954, 1725, 1528, 1270 cm^{-1}. LR-MS (EI) 208 [M^+]. HR-MS (EI) Calcd for $C_{11}H_{16}N_2O_2$: 208.1212; Found: 208.1220.

*Methyl 6-(methylamino)pyridine-2-carboxylate (**10b**)*

Product **10b** was obtained in 94% yield from **5b** (1.125 g, 6.01 mmol) by using a similar method to that employed for **10a**. Mp 49.0-51.0 °C (hexane). ^{1}H NMR (DMSO-d_6) 7.51 (1H, dd, J = 8.4, 7.2), 7.17 (1H, dd, J = 7.2, 0.8), 6.79 (1H, br-q, J = 4.3), 6.64 (1H, dd, J = 8.4, 0.8), 3.79 (3H, s), 2.77 (3H, d, J = 4.9). ^{13}C NMR (DMSO-d_6) 165.8, 159.2, 145.8, 137.1, 112.8, 111.5, 51.8, 27.8. IR (KBr) 3334, 3278, 2949, 1718, 1602, 1521 cm^{-1}. LR-MS (EI) 166 [M^+]. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.78; H, 6.07; N, 16.88.

*6-(Butylamino)pyridine-2-carboxylic acid (**1a**)*

To a solution of ester **10a** (9.91 g, 47.6 mmol) in MeOH (120 mL), a solution of LiOH monohydrate (2.20 g, 52.4 mmol) in water (60 mL) was added. The resulting mixture was stirred at ambient temperature under an argon atmosphere for 17 h. After the addition of 1 mol/L hydrochloric acid (52.4 mL, 52.4 mmol) and stirring for 15 min, volatile materials were removed, first with a rotary evaporator, then under vacuum. Water (10 mL) was added, then the residue was collected by filtration and washed with water to give the product **1a** (8.74 g, 95%) as a pale yellow powder. Mp 153.0-156.0 °C (water). ^{1}H NMR (DMSO-d_6) 7.49 (1H, t, J = 8.1), 7.13 (1H, d, J = 7.3), 6.74 (1H, br-t, J = 5.9), 6.66 (1H, d, J = 8.4), 3.27 (2H, q, J = 6.6), 1.51 (2H, quint, J = 7.0), 1.36 (2H, sext, J = 7.0), 0.90 (3H, t, J = 7.3). ^{13}C NMR (DMSO-d_6) 166.3, 158.3, 146.0, 137.4, 112.1, 111.8, 40.3, 31.0, 19.7, 13.7. IR (KBr) 3280, 3057, 1658, 1586 cm^{-1}. LR-MS (EI) 194 [M^+]. Anal. Calcd for $C_{10}H_{14}N_2O_2$+1/2H_2O: C, 59.10; H, 7.44; N, 13.78. Found: C, 59.18; H, 7.54; N, 13.69.

*6-(Methylamino)pyridine-2-carboxylic acid (**1b**)*

1b was obtained from **10b** in 91% yield by using a similar method to that employed for **1a**. Mp 195.0-196.0 °C (water). ^{1}H NMR (DMSO-d_6) 7.51 (1H, dd, J = 8.4, 7.1), 7.16 (1H, d, J = 7.1), 6.74 (1H, br-q, J = 4.6), 6.65 (1H, d, J = 8.4), 2.80 (3H, d, J = 4.6). ^{13}C NMR (DMSO-d_6) 166.3, 158.9, 146.1, 137.5, 112.3, 111.7, 27.8. IR (KBr) 3481, 3274, 3101, 1647, 1541, 1400 cm^{-1}. LR-MS (EI) 152 [M^+]. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.22; H, 5.43; N, 18.26.

*3-(Butylamino)-5-bromopyridine (**6a**)*

A mixture of 3,5-dibromopyridine (1.015 g, 4.28 mmol), butylamine (4.3 mL, 43.5 mmol) and water (4.3 mL) was heated in a sealed bottle with stirring at 190 °C for 46 h. After cooling, the mixture was poured into sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in a rotary evaporator to give the crude product, which was chromatographed (CH_2Cl_2) to give the amine **6a** (474 mg, 48%), together with recovery of the substrate (413 mg, 41%). Mp 61.0-62.0 °C (hexane). ^{1}H NMR ($CDCl_3$) 7.96 (1H, d, J = 1.8), 7.91 (1H, d, J = 2.4), 6.99 (1H, t, J = 1.8), 3.76 (1H, br-s), 3.10 (2H, q, J = 6.9), 1.62 (2H, quint, J = 7.5), 1.43 (2H, sext, J = 7.8), 0.97 (3H, t, J = 7.5). ^{13}C NMR ($CDCl_3$) 145.3, 138.6, 134.3, 121.1, 120.1, 43.1, 31.2, 20.1, 13.8. IR (KBr) 3261, 2924, 1583 cm^{-1}. LR-MS (EI) 228, 230 [M^+]. Anal. Calcd for $C_9H_{13}N_2Br$: C, 47.18; H, 5.72; N, 12.23. Found: C, 47.20; H, 5.71; N, 12.00.

*3-(Methylamino)-5-bromopyridine (**6b**)*

6b was obtained in 89% yield (17.59 g) from 3,5-dibromopyridine (25.0 g, 105 mmol) and methylamine

solution (40%, 150 mL) by a similar method to that employed for **6a**. Mp 91.5-93.5 °C (hexane), colorless flakes. ^{1}H NMR ($CDCl_3$) 7.99 (1H, d, J = 1.8), 7.93 (1H, d, J = 2.5), 7.00 (1H, t, J = 2.2), 3.88 (1H, br-s), 2.85 (3H, d, J = 5.3). ^{13}C NMR ($CDCl_3$) 146.1, 138.8, 134.1, 121.1, 119.9, 30.0. IR (KBr) 3261, 2924, 1583 cm^{-1}. LR-MS (EI) 186, 188 [M^+]. Anal. Calcd for $C_6H_7N_2Br$: C, 38.53; H, 3.77; N, 14.98. Found: C, 38.60; H, 3.65; N, 14.92.

*Methyl 5-(butylamino)pyridine-3-carboxylate (**11a**)*

11a was obtained in 95% yield from **6a** by a similar method to that employed for **10a**. **11a**: Mp 111.5-113.0 °C (AcOEt/hexane), colorless needles. ^{1}H NMR (DMSO-d_6, 60 °C) 8.26 (1H, br-s), 8.16 (1H, br-s), 7.33 (1H, dd, J = 2.6, 1.8), 6.02 (1H, br-t, J = 5.1), 3.84 (3H, s), 3.06 (2H, q, J = 6.6), 1.55 (2H, quint, J = 7.0), 1.39 (2H, sext, J = 7.0), 0.92 (3H, t, J = 7.3). ^{13}C NMR (DMSO-d_6, 150 °C) 165.2, 114.2, 138.4, 136.5, 125.2, 116.6, 50.7, 41.7, 30.1, 18.7, 12.3. IR (KBr) 3269, 2928, 1724, 1601 cm^{-1}. LR-MS (EI) 208 [M^+]. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.51; H, 7.89; N, 13.31.

*Methyl 5-(methylamino)pyridine-3-carboxylate (**11b**)*

11b was obtained in 97% yield from **6b** by a similar method to that employed for **10a**. **11b**: Mp 124.0-124.5 °C (AcOEt/hexane), pale yellow prisms. ^{1}H NMR ($CDCl_3$) 8.48 (1H, br-s), 8.11 (1H, br-s), 7.37 (1H, dd, J = 2.8, 1.6), 4.11 (1H, br-s) 3.86 (3H, s), 2.83 (3H, s). ^{13}C NMR 166.5, 144.8, 139.5, 139.3, 126.1, 117.9, 52.2, 30.2. IR (KBr) 3271, 3065, 1716, 1593 cm^{-1}. LR-MS (EI) 166 [M^+]. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 58.02; H, 6.02; N, 16.63.

*5-(Butylamino)pyridine-3-carboxylic acid (**2a**)*

2a was obtained in 91% yield from **11a** by a similar method to that employed for **1a**. **2a**: Mp 168.0-170.5 °C (water). ^{1}H NMR (DMSO-d_6, 60 °C) 8.25 (1H, br-s), 8.12 (1H, br-d, J = 2.2), 7.32 (1H, dd, J = 2.6, 1.8), 5.95 (1H, br-s), 3.06 (2H, t, J = 7.0), 1.55 (2H, quint, J = 7.3), 1.39 (2H, sext, J = 7.3), 0.92 (3H, t, J = 7.3). ^{13}C NMR (DMSO-d_6, 120 °C) 166.1, 144.3, 138.1, 136.9, 126.2, 117.0, 41.8, 30.2, 18.9, 12.7. IR (KBr) 3300, 2960, 1701, 1597 cm^{-1}. LR-MS (EI) 194 [M^+]. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.72; H, 7.34; N, 14.25.

*5-(Methylamino)pyridine-3-carboxylic acid (**2b**)*

2b was obtained in 93% yield from **11b** by a similar method to that employed for **1a**. **2b**: Mp 262.0-266.5 °C (water). ^{1}H NMR (DMSO-d_6, 60 °C) 8.24 (1H, d, J = 1.5), 7.82 (1H, d, J = 3.0), 7.32 (1H, br-t, J = 1.5), 5.45 (1H, d, J = 4.5), 2.70 (3H, d, J = 4.8). ^{13}C NMR (DMSO-d_6) 167.0, 145.6, 138.3, 137.2,

126.5, 116.9, 29.2. IR (KBr) 3298, 1608 cm^{-1}. LR-MS (EI) 152 [M^+]. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.25; H, 5.20; N, 18.33.

*N-Butyl-6-(butylamino)pyridine-2-carboxamide (**9a**)*

A mixture of 6-bromopyridine-2-carboxylic acid (10.05 g, 49.8 mmol), butylamine (40 mL, 4.5 mmol), $CuSO_4$ (1.25 g, 5.0 mmol) and water (40 mL) was heated in a sealed bottle with stirring at 170 °C for 22 h. After cooling, the mixture was poured into sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in a rotary evaporator to give the crude product, which was chromatographed (AcOEt/CH_2Cl_2 0:1 then 1:1) to give the product **9a** (4.85 g, 39%) as a brown oil. ^{1}H NMR (DMSO-d_6, 60 °C) 8.13 (1H, br-s), 7.47 (1H, dd, J = 8.4, 7.3), 7.11 (1H, d, J = 7.3), 6.61 (1H, d, J = 8.1), 6.53 (1H, br-t, J = 5.9), 3.30 (4H, m), 1.54 (2H, quint, J = 7.3), 1.51 (2H, quint, J = 7.3), 1.35 (4H, m), 0.92 (3H, t, J = 7.3), 0.91 (3H, t, J = 7.3). ^{13}C NMR (DMSO-d_6) 164.2, 157.7, 147.8, 137.3, 111.3, 109.1, 40.1, 38.1, 31.3, 31.1, 19.7, 19.5, 13.7, 13.5. IR (KBr) 3347, 2958, 1670, 1608, 1508 cm^{-1}. LR-MS (EI) 249 [M^+]. HR-MS (EI) Calcd for $C_{14}H_{23}N_3O$: 249.1841; Found: 249.1846.

*N-Methyl-6-(methylamino)pyridine-2-carboxamide (**9b**)*

A mixture of 6-bromopyridine-2-carboxylic acid (10.2 g, 50.3 mmol) and methylamine solution in water (160 mL, 1.8 mol) was heated in a sealed bottle with stirring at 200 °C for 19 h. After cooling, the mixture was poured into sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in a rotary evaporator to give the crude product, which was chromatographed (AcOEt/hexane 1:1) to give the product **9b** (6.55 g, 78%) as a colorless solid. Mp 69.0-70.0 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$) 8.34 (1H, br-s), 7.47 (1H, dd, J = 8.4, 7.2), 7.11 (1H, dd, J = 7.2, 0.7), 6.67 (1H, br-s), 6.58 (1H, dd, J = 8.3, 0.7), 2.84 (3H, d, J = 4.9), 2.80 (3H, d, J = 4.9). ^{13}C NMR (DMSO-d_6) 165.0, 158.3, 148.0, 137.2, 111.2, 109.2, 27.6, 25.7. IR (KBr) 3388, 3323, 2896, 1668, 1602 cm^{-1}. LR-MS (EI) 165 [M^+]. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.30; H, 6.72; N, 25.42.

*6-Aminopyridine-2-carboxamide (**9c**)*

A mixture of 6-bromopyridine-2-carboxylic acid (5.2 g, 25.6 mmol) and ammonia solution in water (160 mL, 2.6 mol) was heated in a sealed bottle with stirring at 200 °C for 17 h to give the product **9c** (456 mg, 13%), using a similar method to that employed for **9b**. Mp 149.5-153.0 °C (AcOEt/hexane). ^{1}H NMR (DMSO-d_6) 7.62 (1H, br-s), 7.50 (1H, t, J = 8.1), 7.43 (1H, br-s), 7.14 (1H, dd, J = 7.2, 0.9), 6.60 (1H, dd, J = 8.4, 0.9), 6.08 (2H, s). ^{13}C NMR (DMSO-d_6) 166.4, 158.5, 148.3, 137.9, 111.1, 109.9. IR (KBr) 3361, 3200, 1705, 1680, 1618 cm^{-1}. LR-MS (EI) 137 [M^+]. HR-MS (EI) Calcd for $C_6H_7N_3O$: 137.0589; Found:

137.0585.

*Methyl 6-aminopyridine-2-carboxylate (**10c**)*

A mixture of **9c** (457 mg, 3.34 mmol) and conc. hydrochloric acid (20 mL) was heated at reflux with stirring for 19 h, and volatile materials were removed under reduced pressure to give a colorless solid. This crude product was dissolved in MeOH (5 mL), and a mixture of MeOH (12 mL) and acetyl chloride (1.65 mL, 23 mmol) was added, followed by the addition of trimethyl orthoacetate (1.65 mL, 13.0 mmol). The resulting mixture was heated at reflux for 17 h, then evaporated under reduced pressure. Sat. $NaHCO_3$ aq. was added to the residue, and the mixture was extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$, then evaporated to give the crude product, which was chromatographed (AcOEt) to give the ester **10c** in 81% yield. Mp 88.0-91.5 °C (AcOEt/hexane). ^{1}H NMR (DMSO-d_6) 7.50 (1H, dd, J = 8.0, 7.3), 7.17 (1H, dd, J = 7.1, 0.7), 6.63 (1H, dd, J = 8.4, 0.7), 6.28 (2H, s), 3.78 (3H, s). ^{13}C NMR (DMSO-d_6) 165.7, 159.6, 145.7, 137.6, 113.1, 112.2, 51.8. IR (KBr) 3437, 3300, 3166, 1714, 1629 cm^{-1}. LR-MS (EI) 152 [M^+]. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.04; H, 5.25; N, 18.27.

*Methyl 5-(ethylamino)pyridine-3-carboxylate (**11d**)*

A mixture of 5-bromonicotinic acid (9.44 g, 46.7 mmol), ethylamine solution (70% in water, 100 mL) and $CuSO_4$ (0.76 g, 3.05 mmol) was heated in a sealed bottle with stirring at 170 °C for 21 h. After cooling, the mixture was evaporated to give a green viscous oil. To this crude mixture, MeOH (30 mL) and then a mixture of 100 mL of MeOH and 25 mL of acetyl chloride were added, followed by the addition of trimethyl orthoacetate (20 mL). The resulting solution was heated at reflux for 17 h, then evaporated under reduced pressure. Sat. $NaHCO_3$ aq. was added to the residue, and the mixture was extracted with CH_2Cl_2. The organic solution was dried over $MgSO_4$, then evaporated to give the crude product, which was chromatographed (CH_2Cl_2 then AcOEt/hexane 1:1) to give the ester **11d** in 81% yield. Mp 104.0-106.5 °C (AcOEt/hexane), colorless needles. ^{1}H NMR ($CDCl_3$) 8.54 (1H, d, J = 1.5), 8.15 (1H, d, J = 2.6), 7.43 (1H, dd, J = 2.9, 1.8), 3.93 (3H, s), 3.81 (1H, br-s), 3.22 (2H, dq, J = 7.0, 5.5), 1.30 (3H, t, J = 7.0). ^{13}C NMR ($CDCl_3$) 166.4, 144.0, 139.5, 139.1, 126.1, 118.2, 52.1, 38.0, 14.5. IR (KBr) 3273, 1716, 1598 cm^{-1}. LR-MS (EI) 180 [M^+]. Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.86; H, 6.82; N, 15.49.

*5-(Ethylamino)pyridine-3-carboxylic acid (**2d**)*

2d was obtained in 93% yield from **11d** by a similar method to that employed for **1a**. **2d**: Mp 199-245 °C (dec) (water), colorless powder. ^{1}H NMR (DMSO-d_6) 8.25 (1H, br-s), 8.11 (1H, br-s), 7.30 (1H, dd, J =

2.6, 1.8), 6.07 (1H, br-s), 3.08 (2H, dq, *J* = 7.0, 4.8), 1.17 (3H, t, *J* = 7.0). ^{13}C NMR (DMSO-d_6) 167.0, 144.7, 138.5, 137.1, 126.5, 117.2, 36.9, 14.0. IR (KBr) 3319, 2977, 1608 cm^{-1}. LR-MS (EI) 166 [M$^+$]. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.80. Found: C, 57.57; H, 6.01; N, 16.65.

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REFERENCES

1. M. T. H. Khan and A. Ather, *Top. Heterocycl. Chem.*, 2007, **10**, 99.
2. 'Foldamers,' ed. by S. Hecht and I. Huc, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2007; V. Balzani, A. Credi, and Venturi, 'Molecular Devices and Machines,' Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2003.
3. V. Caprio, 'Comprehensive Heterocyclic Chemistry III,' Vol. 7, 101, Elsevier Ltd., 2008; 'Heterocyclic Compounds: Synthesis, Properties and Applications,' ed. by K. Nylund, and P. Johansson Nova Science Publishers, Inc., New York, 2010.
4. H. H. Jensen, L. Lyngbye, A. Jensen, and M. Bols, *Chem. Eur. J.*, 2002, **8**, 1218.
5. J. Lindley, *Tetrahedron*, 1984, **40**, 1433.
6. J. Albaneze-Walker, C. Bazaral, T. Leavey, P. G. Dormer, and J. A. Murry, *Org. Lett.*, 2004, **6**, 2097.
7. J. Albaneze-Walker, R. Raju, J. A. Vance, A. J. Goodman, M. R. Reeder, J. Liao, M. T. Maust, P. A. Irish, P. Espino, and D. R. Andrews, *Org. Lett.*, 2009, **11**, 1463.