Straightforward Access to Ethyl 3-Aminofuropyridine-2-carboxylates from 1-Chloro-2-cyano- or 1-Hydroxy-2-cyano-Substituted Pyridines

Thomas Cailly, Stéphane Lemaître, Frédéric Fabis, Sylvain Rault*

Centre d'Etudes et de Recherche sur le Médicament de Normandie, U.F.R. des Sciences Pharmaceutiques, Université de Caen Basse-Normandie, 5 rue Vaubénard, 14032 Caen Cedex, France
Fax +33(2)31931188; E-mail: sylvain.rault@unicaen.fr

Received 26 June 2007

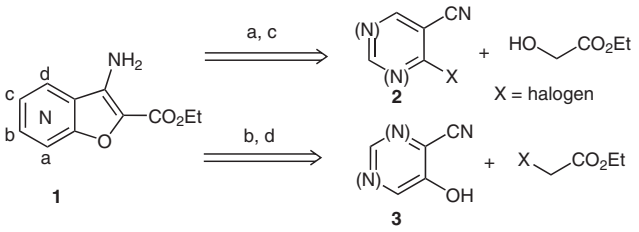
Abstract: The conditions of the synthesis of the four regioisomers of ethyl 3-aminofuropyridine-2-carboxylate are described and discussed in detail. The starting materials are either 1-chloro-2-cyanopyridines or 1-cyano-2-hydroxypyridines.

Key words: fused-ring systems, cyclizations, nitriles, aryl alcohols, nucleophilic aromatic substitutions

ortho-Amino esters are important scaffolds in medicinal chemistry as the precursors of numerous bioactive heterocyclic compounds. Many classes of pharmacologically interesting heterocyclic derivatives such as benzodiazepines,[1] quinazolines,[2] and anthranilics[3] are obtained via *ortho*-amino esters. For example, in our laboratory, they have been used with success for the synthesis of 5-HT_3 partial agonists,[4] 5-HT_4 antagonists,[5] kinase inhibitors,[6] and antitubulin agents.[7] This is why new *ortho*-amino esters are still of great interest as new, potent medicinal chemistry building blocks. In this paper, we wish to describe a straightforward synthesis of the four furopyridine *ortho*-amino esters **1** starting from cyanopyridines (Scheme 1). Whereas several publications have dealt with the synthesis of ethyl 3-aminofuro[2,3-*b*]pyridine-2-carboxylate (**1a**) and its substituted derivatives,[8] only one publication has reported the synthesis of ethyl 3-aminofuro[3,2-*b*]pyridine-2-carboxylate (**1d**),[8a] and, to date, no synthesis has been described for **1b** and **1c** at all.

However, in our hands, none of the previous methods have been able to give the unsubstituted amino esters **1** under acceptable conditions. For this reason, we decided to investigate a general access applicable to the synthesis of all four isomers **1a–d**.

We reasoned that amino esters **1** could be obtained by the use of the correctly substituted cyanopyridines **2** and **3** (Scheme 1). The envisaged strategy to obtain compounds **1a** and **1c** would use the ability of the 2- or 4-halopyridine to undergo nucleophilic aromatic substitution smoothly. By using ethyl glycolate as the nucleophile and 2-chloro-, 4-chloro-, or 4-iodo-3-cyanopyridine (**2a**, **2b**, and **2c**, respectively) as the electrophiles, we wished to obtain isomers **1a** and **1c** in one-pot procedures. Considering that this nucleophilic aromatic substitution would be quite impossible with similar 3-halopyridines, we decided to investigate the synthesis of the corresponding cyano(hydroxy)pyridines **3** to perform a cyclization with ethyl bromoacetate to obtain isomers **1b** and **1d** (Scheme 1).



Scheme 1 Synthetic strategy for the preparation of the ethyl 3-aminofuropyridine-2-carboxylate isomers **1a** and **1c** (a, c) and **1b** and **1d** (b, d)

We decided to start with the preparation of ethyl 3-aminofuro[2,3-*b*]pyridine-2-carboxylate (**1a**) (Scheme 2). Many conditions have been described for the preparation of this amino ester and its substituted derivatives starting from ethyl glycolate and **2a** or its substituted derivatives. These methods included the use of various bases, solvents, and temperatures in one-pot or two-step procedures. We therefore decided to reinvestigate the reaction of commercially available 2-chloro-3-cyanopyridine (**2a**) with ethyl glycolate under various conditions in a one-pot procedure (Scheme 2, Table 1).

First, we performed the reaction of **2a** and ethyl glycolate in *N*,*N*-dimethylformamide at 70 °C in the presence of triethylamine (5 equiv), but, unfortunately, the starting material was recovered completely (Table 1, entry 1). Under the same conditions, but with replacement of triethylamine by potassium *tert*-butoxide or sodium hydride (5 equiv), **1a** and **2a** decomposed (Table 1, entries 2 and 3). Then we retried the use of sodium hydride, but in tetrahydrofuran; this allowed us to isolate **1a** in the very low yield of 3% (Table 1, entry 4). At this stage, we have looked for a base that could effect the deprotonation of the alcoholic moiety, the cyclization, and would not lead to the degradation of amino ester **1a**. Cesium carbonate appeared to us to be a good candidate for this. The first experiment with five equivalents of cesium carbonate (Table 1, entry 5) only led to the formation of side products, mainly due to the production of dimethylamine from *N*,*N*-dimethylformamide (LC/MS monitoring);[9] replacement of *N*,*N*-dimethylformamide by *N*-methylpyrrolidin-2-one result-

SYNTHESIS 2007, No. 20, pp 3247–3251
Advanced online publication: 25.09.2007
DOI: 10.1055/s-2007-990810; Art ID: Z15507SS

ed in degradation of **1a** (Table 1, entry 6), which, in this case, was not the consequence of the reaction of *N*,*N*-dimethylformamide. We then carried out microwave-assisted experiments in the hope to avoid degradation. Two experiments performed in *N*-methylpyrrolidin-2-one with five and three equivalents of cesium carbonate allowed us, finally, to isolate **1a** in 10% and 16% yield, respectively (Table 1, entries 7 and 8). Regarding these two results, we thought that the excess of base employed in all our experiments was the cause of our difficulties, and therefore we undertook a reaction with three equivalents of cesium carbonate in *N*-methylpyrrolidin-2-one at 70 °C for 12 hours; this allowed us to improve the yield to 56% (Table 1, entry 9).

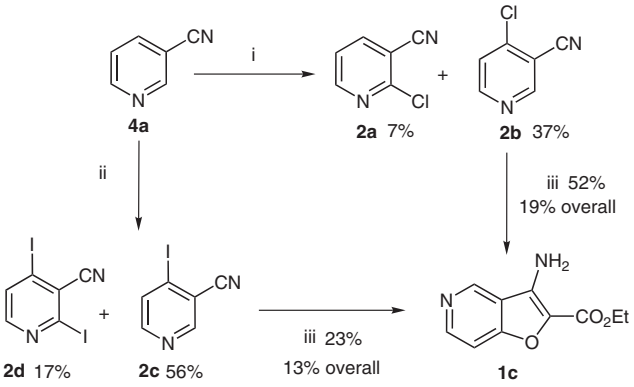
Scheme 2 Synthesis of ethyl 3-aminofuro[2,3-*b*]pyridine-2-carboxylate (**1a**)

Table 1 Conditions Used for the Synthesis of Ethyl 3-Aminofuro[2,3-*b*]pyridine-2-carboxylate (**1a**)

Entry	Solvent	Time (h)	Temp (°C)	Base	Amount base (equiv)	Yield (%)
1	DMF	12	70	Et_3N	5	0
2	DMF	12	70	*t*-BuOK	5	0
3	DMF	12	r.t., then 70 °C	NaH	5	0
4	THF	12	70	NaH	5	3
5	DMF	12	70	Cs_2CO_3	5	0
6	NMP	12	70	Cs_2CO_3	5	0
7	NMP	1.5[a]	150	Cs_2CO_3	5	10
8	NMP	1.5[a]	150	Cs_2CO_3	3	16
9	NMP	12	70	Cs_2CO_3	3	56

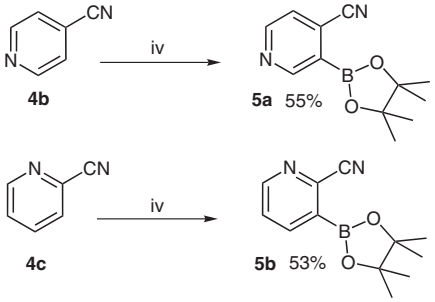
[a] Sealed-tube microwave heating.

4-Chloro- and 4-iodo-3-cyanopyridine (**2b** and **2c**), not available commercially, were needed to prepare the **1c** isomer (Scheme 3). We recently described an *ortho*-lithiation method leading to these compounds from nicotinonitrile (**4a**) (Scheme 3);[10] thus, **2b** and **2c** can be obtained in 37% and 56% yield, respectively, accompanied by two side products **2a** and **2d** (Scheme 3). From **2b** and **2c**, we then applied the above-described cyclization promoted by cesium carbonate, and could isolate **1c** from **2b** in 52% yield, and **1c** from **2c** in 23% yield. The pathway from **4a** via 4-chloronicotinonitrile (**2b**) in 19% overall yield is slightly better than the pathway from **4a** via 4-iodonicotinonitrile (**2c**) with its 13% overall yield.



Scheme 3 Synthesis of ethyl 3-aminofuro[3,2-*c*]pyridine-2-carboxylate (**1c**). *Reagents and conditions*: (i) LTMP (2 equiv), THF, –80 °C, 0.75 h, then C_2Cl_6 (2.1 equiv), –80 °C, 0.75 h; (ii) LTMP (2 equiv), THF, –80 °C, 0.75 h, then I_2 (2.1 equiv), –80 °C, 0.75 h; (iii) ethyl glycolate (1.1 equiv), Cs_2CO_3 (3 equiv), NMP, 70 °C, 12 h.

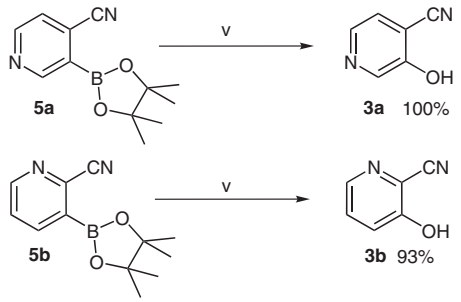
For the preparation of furopyridine isomers **1b** and **1d**, nucleophilic aromatic substitution of the corresponding 3-chloropyridines appeared to us to be problematic, and we therefore decided to study the reactivity of the corresponding cyano(hydroxy)pyridines **3a** and **3b** instead. These compounds in the pyridine series can be obtained easily from the corresponding boronic acid or one of its esters by a hydroxydeboronation reaction. We decided to carry out this reaction on (cyanopyridyl)boronic pinacol esters **5a** and **5b** (Scheme 4), which are easy to handle, and whose synthesis from the corresponding acids we described recently.[11] Begtrup et al. have also published the synthesis of a (2-cyanopyridyl)boronic neopentyl glycol ester, but in a one-pot procedure directly from the cyanopyridines.[12] We used this latter methodology, using pinacol instead of neopentyl glycol, to prepare **5a** and **5b** from the corresponding cyanopyridines **4b** and **4c** in 55% and 53% yield, respectively (Scheme 4).



Scheme 4 One-pot synthesis of (cyanopyridyl)boronic pinacol esters **5a** and **5b**. *Reagents and conditions* : (iv) 1. LTMP (1.2 equiv), $(i\text{-PrO})_3B$ (1.3 equiv), THF, –80 °C, overnight; 2. AcOH (1.4 equiv), pinacol (1.5 equiv), THF, r.t., 2 h.

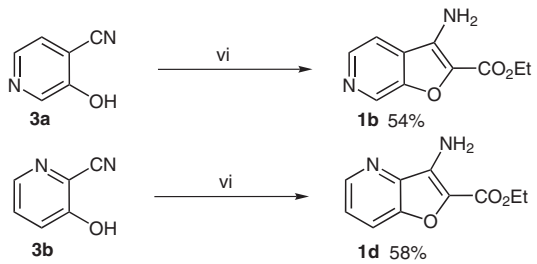
Our research group has recently reported the hydroxydeboronation reaction of pyridineboronic acids or their esters using either hydrogen peroxide or *m*-chloroperoxybenzoic acid.[13] However, the use of these oxidants on **5a** and **5b** only gave mixtures, probably due to the oxidation of the nitrile moiety. We then turned to the proce-

dure of Webb and Levy,[14] who used Oxone as the oxidant in the phenyl series, and we obtained cyano(hydroxy)pyridines **3a** and **3b** in 100% and 93% yield, respectively (Scheme 5), without a trace of oxidized product at the level of the nitrogen atom or the cyano group.



Scheme 5 Synthesis of cyano(hydroxy)pyridines **3a** and **3b**. *Reagents and conditions*: (v) Oxone (0.7 equiv), $NaHCO_3$ (7 equiv), H_2O–acetone, 0 °C, 20 min.

From cyano(hydroxy)pyridines **3a** and **3b** thus prepared, we could synthesize furopyridine isomers **1b** and **1d** (Scheme 6). A two-step sequence from salicylonitrile has been reported to give the corresponding aminobenzofuran ester in an overall yield of 50%.[15] To improve this procedure, we decided to transpose the same sequence to a one-pot procedure, using an excess of potassium carbonate and microwave heating. In a sealed tube, with ethanol as the solvent, and at 150 °C, the reaction was complete after half an hour (by TLC). These conditions allowed us to isolate **1b** and **1d** in 54% and 58% yield, respectively (Scheme 6).



Scheme 6 Synthesis of ethyl 3-aminofuro[2,3-*c*]pyridine-2-carboxylate (**1b**) and ethyl 3-aminofuro[3,2-*b*]pyridine-2-carboxylate (**1d**). *Reagents and conditions*: (vi) ethyl bromoacetate (1.1 equiv), K_2CO_3 (2.5 equiv), EtOH, MW, sealed tube, 150 °C, 30 min.

In conclusion, we have described a scalable access to the four isomers **1a–d** of ethyl 3-aminofuropyridine-2-carboxylate. A new, easy synthesis of 2- or 4-cyano-3-hydroxypyridine (**3a** and **3b**) is also reported. We are currently evaluating amino esters **1a–d** as starting materials for the synthesis of potential antitumor agents such as pyridofuropyrrolizinones, but they could also be powerful building blocks for other medicinal chemistry groups.

All commercial reagents were used as received except THF, which was distilled from Na/benzophenone. Melting points were determined on a Kofler melting point apparatus. IR spectra were recorded on a Perkin-Elmer BX FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Jeol Lambda 400-NMR spectrometer. HRMS was carried out on a Jeol JMS GCMate spectrometer. Elemental analyses were performed at the 'Institut de Recherche en Chimie Organique fine' (Rouen, France). The microwave reactions were performed in a Biotage Initiator microwave oven. Temperatures were measured with an IR sensor and the reaction times given are hold times.

Halonicotinonitriles 2; General Procedure

A soln of *n*-BuLi (2.5 M in *n*-hexane; 7.7 mL, 19.2 mmol) was added to a stirred soln of 2,2,6,6-tetramethylpiperidine (3.4 mL, 20.2 mmol) in THF (40 mL) under N_2 at –30 °C. The soln was allowed to reach 0 °C, kept stirring for 15 min, and then cooled to –80 °C. A soln of nicotinonitrile (**4a**; 1 g, 9.6 mmol) in THF (20 mL) was slowly added to the mixture over 15 min. After the mixture had stirred for 30 min at –80 °C, a soln of the chosen electrophile (C_2Cl_6 or I_2) (20.2 mmol) in THF (10 mL) was slowly added over 15 min, and the resulting mixture was stirred for 30 min. The soln was then allowed to warm slowly to r.t. The mixture was quenched with sat. aq NH_4Cl (40 mL). The soln was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, evaporated under vacuum, and purified by chromatography (silica gel).

2-Chloro- and 4-Chloronicotinonitrile (2a and 2b)

Chloronicotinonitriles **2a** (7%) and **2b** (37%) were obtained when hexachloroethane (4.78 g, 20.2 mmol) was used as the electrophile. Chromatography (silica gel, EtOAc–cyclohexane, 1:4).

2-Chloronicotinonitrile (2a)

Yield: 7%; white powder; mp 104 °C.

IR (KBr): 3065, 2236 (CN), 1578, 1554, 1407, 1399, 1145, 1133, 1080, 1071, 809, 736, 673, 571, 471 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, ^3J = 4.9 Hz, ^3J = 7.8 Hz, 1 H), 8.02 (dd, ^3J = 7.8 Hz, ^4J = 1.9 Hz, 1 H), 8.62 (dd, ^3J = 4.9 Hz, ^4J = 1.9 Hz, 1 H).

4-Chloronicotinonitrile (2b)

Yield: 37%; pale yellow powder; mp 86 °C.

IR (KBr): 3091, 2926, 2236 (CN), 1572, 1549, 1473, 1404, 1291, 1187, 1101, 844, 798, 728, 700, 571, 476 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, ^3J = 5.3 Hz, 1 H), 8.71 (d, ^3J = 5.3 Hz, 1 H), 8.86 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.4, 113.8, 124.6, 146.5, 153.4, 153.8.

Anal. Calcd. for $C_6H_3N_2Cl$: C, 52.01; H, 2.18; N, 20.22. Found: C, 52.31; H, 2.07; N, 19.93.

4-Iodo- and 2,4-Diiodonicotinonitrile (2c and 2d)

Nicotinonitriles **2c** (56%) and **2d** (17%) were obtained when I_2 (5.12 g, 20.2 mmol) was used as the electrophile; sat. aq NH_4Cl (40 mL) and then sat. aq $Na_2S_2O_3$ (40 mL) were used to quench the mixture. Chromatography (silica gel, $CHCl_3$–Et_3N, 99.5:0.5).

4-Iodonicotinonitrile (2c)

Yield: 56%; pale yellow powder; mp 128 °C.

IR (KBr): 3073, 2229 (CN), 1563, 1461, 1396, 1283, 1187, 1061, 935, 847, 722, 661, 462 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, ^3J = 5.3 Hz, 1 H), 8.39 (d, ^3J = 5.3 Hz, 1 H), 8.73 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.7, 117.3, 118.8, 134.1, 152.2, 153.1.

Anal. Calcd. for $C_6H_3N_2I$: C, 31.39; H, 1.31; N, 12.18. Found: C, 31.78; H, 1.12; N, 12.05.

2,4-Diiodonicotinonitrile (2d)
Yield: 17%; white powder; mp 128 °C.

IR (KBr): 3097, 2225 (CN), 1532, 1517, 1415, 1344, 1191, 1180, 1075, 1061, 836, 706, 571, 510 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, ^3J = 5.3 Hz, 1 H), 8.08 (d, ^3J = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.6, 119.1, 121.0, 127.1, 133.2, 151.7.

Anal. Calcd. for $C_6H_2N_2I_2$: C, 20.25; H, 0.57; N, 7.87. Found: C, 20.60; H, 0.20; N, 7.64.

3-Aminofuropyridine-2-carboxylates 1a and 1c from Halonicotinonitriles 2a–c; General Procedure
Cs_2CO_3 (7.05 g, 21.6 mmol), NMP (20 mL), ethyl glycolate (0.76 mL, 7.9 mmol), and one of the halonicotinonitriles **2a–c** (7.2 mmol) were introduced into a round-bottomed flask. The mixture was then heated at 70 °C for 12 h. After cooling, the soln was poured into H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (3 × 20 mL), dried ($MgSO_4$), filtered, evaporated under reduced pressure, and purified by chromatography (silica gel).

Ethyl 3-Aminofuro[2,3-*b*]pyridine-2-carboxylate (1a)
Compound **1a** was prepared from **2a** by the above general procedure and purified by chromatography (silica gel, EtOAc–cyclohexane, 1:4).

Yield: 56%; mp 134 °C.

IR (KBr): 3403, 3353, 2976, 1678 (CO), 1631, 1600, 1443, 1332, 1294, 1214, 1156, 1132, 775, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, ^3J = 7.1 Hz, 3 H), 4.44 (q, ^3J = 7.1 Hz, 2 H), 5.03 (br s, 2 H), 7.25 (dd, ^3J = 7.8 Hz, ^3J = 4.7 Hz, 1 H), 7.95 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1 H), 8.50 (dd, ^3J = 4.7 Hz, ^4J = 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 60.7, 114.2, 118.7, 124.4, 129.7, 137.1, 148.8, 159.9, 161.6.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2O_3$: 206.0691; found: 206.0694.

Ethyl 3-Aminofuro[3,2-*c*]pyridine-2-carboxylate (1c)
Compound **1c** was prepared from **2b** or **2c** by the above general procedure and purified by chromatography (silica gel, EtOAc–cyclohexane, 1:4 + 3% MeOH).

Yield: 52% (from **2b**) and 23% (from **2c**); mp 185 °C.

IR (KBr): 3422, 3317, 3184, 2977, 2927, 1728, 1674 (CO), 1636, 1613, 1462, 1428, 1323, 1299, 1175, 1137, 1106, 885, 815, 760, 659 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, ^3J = 7.3 Hz, 3 H), 4.45 (q, ^3J = 7.3 Hz, 2 H), 5.13 (br s, 2 H), 7.40 (dd, ^3J = 5.8 Hz, ^4J = 0.7 Hz, 1 H), 8.60 (d, ^3J = 5.8 Hz, 1 H), 8.95 (d, ^4J = 0.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 60.8, 108.0, 119.5, 125.7, 137.0, 143.5, 148.0, 158.1, 161.2.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2O_3$: 206.0691; found: 206.0687.

(2-Cyanopyridyl)boronic Esters 5a and 5b; General Procedure
A soln of *n*-BuLi (2.5 M in *n*-hexane; 12 mL, 30 mmol) was added to a stirred soln of 2,2,6,6-tetramethylpiperidine (5.06 mL, 30 mmol) in THF under N_2 (50 mL) at –30 °C. The soln was allowed to reach 0 °C, kept stirring for 15 min, and cooled to –80 °C. (*i*-PrO)$_3$B (8.08mL, 34 mmol) was added and the soln was stirred for 5 min before addition of the appropriate cyanopyridine **4b** or **4c** (25 mmol) in THF (50 mL) over 15 min. The mixture was then allowed to warm slowly to r.t. overnight. The resulting soln was quenched with glacial AcOH (2 mL, 35 mmol) and pinacol (4.43 g, 37.5 mmol). After 2 h, a 10% KH_2PO_4 soln (75 mL) was added. The soln was washed with CH_2Cl_2 (3 × 50 mL), acidified with a 3 M HCl soln, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were then washed with H_2O (3 × 10 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure.

3-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)isonicotinonitrile (5a)
Compound **5a** was prepared from **4b** (2.5 g, 25 mmol).

Yield: 55%; mp 102 °C.

IR (KBr): 2970, 2928, 2231 (CN), 1607, 1542 1469, 1408, 1386, 1374, 1363, 1275, 1189, 1159, 1035, 878, 845, 777, 764, 714, 667, 581 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 12 H), 7.54 (d, ^3J = 5.1 Hz, 1 H), 8.82 (d, ^3J = 5.1 Hz, 1 H), 9.09 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 85.2, 116.7, 125.3, 126.3, 152.3, 156.5 (the quaternary C bonded to B was missing).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}N_2O_2B$: 230.1226; found: 230.1230.

3-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)pyridine-2-carbonitrile (5b)
Compound **5b** was prepared from **4c** (2.5 g, 25 mmol).

Yield: 53%; mp 66 °C.

IR (KBr): 3053, 2979, 2238 (CN), 1582, 1557, 1458, 1361, 1145, 1130, 1074, 1041, 962, 837, 778, 662, 561 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 12 H), 7.48 (dd, ^3J = 4.8 Hz, ^3J = 7.8 Hz, 1 H), 8.18 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1 H), 8.75 (dd, ^3J = 4.8 Hz, ^4J = 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 85.3, 117.2, 125.7, 138.3, 143.4, 152.3 (the quaternary C bonded to the B was missing).

Anal. Calcd. for $C_{12}H_{15}N_2O_2B$: C, 62.65; H, 6.57; N, 12.18. Found: C, 62.41; H, 6.88; N, 11.74.

Cyano(hydroxy)pyridines 3a and 3b; General Procedure
$NaHCO_3$ (0.88 g, 10.4 mmol) and the appropriate boronic ester **5a** or **5b** (0.3 g, 1.5 mmol) were added to a mixture of H_2O (15 mL) and acetone (5 mL), and the mixture was cooled to 0 °C. Oxone (0.72 g, 1.1 mmol) was added dropwise while the temperature of the mixture was maintained between 0 and 8 °C. The mixture was allowed to stir for 20 min at the same temperature, and $NaHSO_3$ (3 g) in H_2O (6 mL) was added. The soln was acidified with a 3 M HCl soln and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure, and purified by chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2–MeOH, 19:1).

3-Hydroxyisonicotinonitrile (3a)
Compound **3a** was prepared from **5a**.

Yield: 100%; mp 166 °C.

IR (KBr): 3227 (OH), 2219 (CN), 2159, 1600, 1537, 1477, 1410, 1281, 1114, 1054, 862, 810, 744, 699, 608, 594, 572, 502, 477 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, ^3J = 4.8 Hz, ^4J = 0.7 Hz, 1 H), 8.16 (d, ^3J = 4.8 Hz, 1 H), 8.41 (s, 1 H), 11.72 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 105.5, 114.8, 125.6, 139.3, 140.5, 154.8.

HRMS (EI): *m*/*z* calcd for $C_6H_4N_2O$: 120.0324; found 120.0324.

3-Hydroxypyridine-2-carbonitrile (3b)
Compound **3b** was prepared from **5b**.

Yield: 93%; mp 205 °C.

IR (KBr): 3078 (OH), 2999, 2893, 2775, 2579, 2238 (CN), 1579, 1467, 1365, 1310, 1277, 1242, 1155, 1119, 1063, 873, 808, 739, 576 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, ^3J = 8.8 Hz, ^4J = 1.9 Hz, 1 H), 7.54 (dd, ^3J = 8.8 Hz, ^3J = 4.5 Hz, 1 H), 8.17 (dd, ^3J = 4.5 Hz, ^4J = 1.9 Hz, 1 H), 11.69 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.2, 120.5, 124.6, 129.1, 142.3, 157.9.

Anal. Calcd. for $C_6H_4N_2O$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.84; H, 3.01; N, 22.93.

3-Aminofuropyridine-2-carboxylates 1b and 1d from Cyano(hydroxy)pyridines 3a and 3b; General Procedure
The appropriate cyano(hydroxy)pyridine **3a** or **3b** (0.3 g, 2.5 mmol), ethyl bromoacetate (0.3 mL, 2.7 mmol), K_2CO_3 (0.86 g, 6.2 mmol), and EtOH (5 mL) were placed in a sealed tube. The resulting mixture was heated at 150 °C for 30 min under microwave irradiation, diluted with H_2O (50 mL), and then extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure, and purified by chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2 + 3% MeOH). The resulting oil was then precipitated with PE.

Ethyl 3-Aminofuro[2,3-*c*]pyridine-2-carboxylate (1b)
Compound **1b** was prepared from **3a**.

Yield: 0.27 g (54%); mp 146 °C.

IR (KBr): 3419, 3309, 3029, 1678, 1645, 1588, 1562, 1475, 1452, 1327, 1292, 1237, 1183, 1133, 1029, 826, 759, 580, 549, 482 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, ^3J = 7.1 Hz, 3 H), 4.46 (q, ^3J = 7.1 Hz, 2 H), 5.00 (br s, 2 H), 7.52 (d, ^3J = 5.3 Hz, 1 H), 8.47 (d, ^3J = 5.3 Hz, 1 H), 8.90 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 61.1, 114.2, 127.2, 127.9, 135.7, 136.8, 141.5, 150.1, 161.4.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2O_3$: 206.0691; found: 206.0694.

Ethyl 3-Aminofuro[3,2-*b*]pyridine-2-carboxylate (1d)
Compound **1d** was prepared from **3b**.

Yield: 0.30 g (58%); mp 117 °C.

IR (KBr): 3447, 3305, 3082, 2980, 1681 (CO), 1633, 1587, 1561, 1478, 1454, 1371, 1337, 1270, 1182, 1106, 1024, 930, 880, 799, 759, 601, 559 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, ^3J = 7.0 Hz, 3 H), 4.46 (q, ^3J = 7.0 Hz, 2 H), 5.23 (br s, 2 H), 7.38 (dd, ^3J = 8.5 Hz, ^3J = 4.6 Hz, 1 H), 7.75 (dd, ^3J = 8.5 Hz, ^4J = 1.2 Hz, 1 H), 8.55 (dd, ^3J = 4.6 Hz, ^4J = 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 60.7, 119.8, 122.9, 140.3, 142.0, 142.9, 145.5, 147.8, 161.3.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.32; H, 4.56; N, 13.28.

Acknowledgment

We thank the Servier Laboratories, the 'Conseil Régional de Basse-Normandie' and 'Les Sapins de l'Espoir' for their financial support. We thank Dr. R. Legay for carrying out the mass analyses.

References

(1) (a) Gogerty, J. H.; Griot, R. G.; Habeck, D.; Iorio, L. C.; Houlihan, W. J. *J. Med. Chem.* **1977**, *20*, 952. (b) Peet, N. P.; Sunder, S. *J. Heterocycl. Chem.* **1977**, *14*, 561. (c) Hirayama, F.; Koshio, H.; Katayama, N.; Ishihara, T.; Kaizawa, H.; Taniuchi, Y.; Sato, K.; Sakai-Moritani, Y.; Kaku, S.; Kurihara, H.; Kawasaki, T.; Matsumoto, Y.; Sakamoto, S.; Tsukamoto, S. *Bioorg. Med. Chem.* **2003**, *11*, 367.
(2) (a) Hennequin, L. F.; Allen, J.; Breed, J.; Curwen, J.; Fennell, M.; Green, T. P.; Lambert van der Brempt, C.; Morgentin, R.; Norman, R. A.; Olivier, A.; Otterbein, L.; Plé, P. A.; Warin, N.; Costello, G. *J. Med. Chem.* **2006**, *49*, 6465. (b) Desroses, M.; Laconde, G.; Depreux, P.; Henichart, J. P. *Org. Prep. Proced. Int.* **2004**, *36*, 445. (c) Wright, S. W.; Carlo, A. A.; Carty, M. D.; Danley, D. E.; Hageman, D. L.; Karam, G. A.; Levy, C. B.; Mansour, M. N.; Mathiowetz, A. M.; McClure, L. D.; Nestor, N. B.; McPherson, R. K.; Pandit, J.; Pustilnik, L. R.; Schulte, G. K.; Soeller, W. C.; Treadway, J. L.; Wang, I. K.; Bauer, P. H. *J. Med. Chem.* **2002**, *45*, 3865.
(3) (a) Barker, J. M.; Huddleston, P. R.; Holmes, D. *J. Chem. Res., Synop.* **1986**, *5*, 155. (b) Elliott, R. L.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron* **1987**, *43*, 3295. (c) Danswan, G.; Kennewell, P. D.; Tully, W. R. J. *Heterocycl. Chem.* **1989**, *26*, 293.
(4) Prunier, H.; Rault, S.; Lancelot, J. C.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D. H.; Misslin, R.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1997**, *40*, 1808.
(5) Hinschberger, A.; Butt, S.; Lelong, V.; Boulouard, M.; Dumuis, A.; Dauphin, F.; Bureau, R.; Pfeiffer, B.; Renard, P.; Rault, S. *J. Med. Chem.* **2003**, *46*, 138.
(6) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Bioorg. Med. Chem.* **2006**, *14*, 8162.
(7) Lisowski, V.; Leonce, S.; Kraus-Berthier, L.; Sopkova-de Oliveira Santos, J.; Pierre, A.; Atassi, G.; Caignard, D. H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448.
(8) (a) Dunn, A. D.; Norrie, R. *J. Prakt. Chem.* **1996**, *338*, 663. (b) Zheng, G. Z.; Bhatia, P.; Daanen, J.; Kolasa, T.; Patel, M.; Latshaw, S.; El Kouhen, O. F.; Chang, R.; Uchic, M. E.; Miller, L.; Nakane, M.; Lehto, S. G.; Honore, M. P.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2005**, *48*, 7374. (c) Sauter, F.; Froehlich, J.; Ahmed, E. K. *Monatsh. Chem.* **1995**, *26*, 945. (d) Narsaiah, B.; Sivaprasad, A.; Venkataratnam, R. V. *J. Fluorine Chem.* **1994**, *69*, 139. (e) Wagner, G.; Prantz, J. *Pharmazie* **1993**, *48*, 250. (f) Kamal El-Dean, A. M.; Abdel Hafez, A. A.; Attallah, A. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1989**, *46*, 1. (g) Gewald, K.; Jaensch, H. J. *J. Prakt. Chem.* **2004**, *318*, 313.
(9) Cho, Y. H.; Park, J. H. *Tetrahedron Lett.* **1997**, *38*, 8331.
(10) Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett.* **2005**, *46*, 135.
(11) Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Sopkova, J.; Rault, S. *Synlett* **2006**, 53.
(12) Hansen, H. M.; Lysén, M.; Begtrup, M.; Kristensen, J. *Tetrahedron* **2005**, *61*, 9955.
(13) Voisin, A. S.; Bouillon, A.; Lancelot, J. C.; Rault, S. *Tetrahedron* **2005**, *61*, 1427.
(14) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117.
(15) Sangapure, S. S.; Agasimundin, Y. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1975**, *14*, 688.