Synthesis of 6-substituted pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones *via* directed lithiation of 2-substituted 5-aminopyridine derivatives

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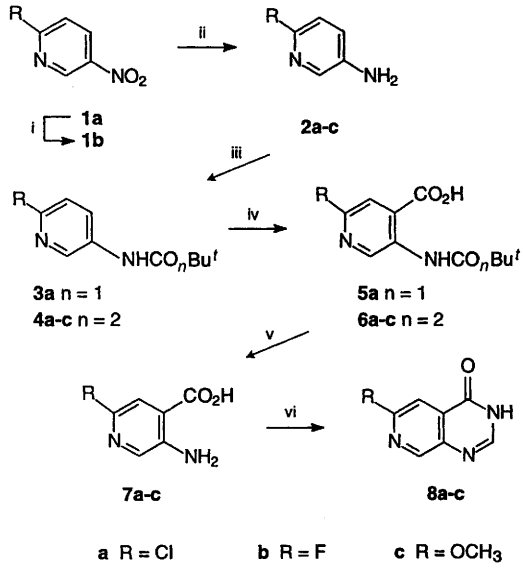
Directed lithiation of Boc or pivaloyl derivatives of 2-substituted 5-aminopyridines with BuLi–TMEDA in diethyl ether at −10 °C gave 4-lithio derivatives which were quenched with CO_2 to give the analogous C-4 carboxylic acids. Hydrolysis of the protecting groups with either TFA or aqueous KOH gave 2-substituted 5-aminopyridine-4-carboxylic acids which were converted to 6-substituted pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones by reaction with formamide or, more optimally, formamidine acetate. Boc protected aminopyridines provided the best overall results, with synthesis of these derivatives best achieved by direct reaction of the aminopyridine with di-*tert*-butyl dicarbonate in the absence of added base.

Introduction

As part of our continuing investigation into 4-anilinoquinazolines and pyrido[*d*]pyrimidines as inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor,[1] we found it necessary to prepare some 6-substituted pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones as intermediates. Since it was also desirable for one of the 6-substituents to be a displaceable group, we initially focused on the synthesis of the 6-chloro derivative **8a** (Scheme 1). Because pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones are readily available from 3-aminoisonicotinic acid derivatives,[2] 5-amino-2-chloropyridine-4-carboxylic acid **7a** became the initial target. Compound **7a** had previously been prepared (as part of an isomer mixture) by direct chlorination of 3-aminoisonicotinic acid,[3] but in order to avoid chromatography at such an early stage we felt that pyridine directed lithiation chemistry[4] would provide a better route. We report on the successful outcome of this investigation *via* directed lithiation and carboxylation of 2-substituted 5-aminopyridine derivatives.



Scheme 1 *Reagents and conditions:* i, F^-; ii, H_2, Pd/C or Raney Ni; iii, $(Boc)_2O$; iv, BuLi–TMEDA–Et_2O −10 °C; v, TFA or KOH–H_2O; vi, $HCONH_2$ 140 °C or formamidine acetate–2-methoxyethanol 120 °C

Results and discussion

Synthesis of 6-chloropyrido[3,4-*d*]pyrimidin-4(3*H*)-one 8a

The directed lithiation and reaction of 6-chloro-3-(pivaloylamino)pyridine **3a** with *N*,*N*-dimethylformamide (DMF) has previously been reported to proceed in poor yield with Bu^{t}Li in tetrahydrofuran (THF),[5] due to nucleophilic addition of the base to the pyridine 4-position, but by using 2.5–3.0 equiv. of BuLi and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in Et_2O at −10 °C, conditions known to minimise nucleophilic addition,[6] we were able to achieve a 51% yield of the desired C-4 acid product **5a** after quenching the reaction with CO_2 gas at −78 °C. The best results were achieved when 3 equiv. of BuLi–TMEDA were used. However, acidic hydrolysis of the pivalamide protecting group proceeded poorly, with appreciable loss of the chloro substituent also occurring, giving rise to a mixture of **7a** and the aminopyridone acid **10** (see later). Although **7a** was the major product, and could be obtained pure by recrystallisation, the method was not optimal. Clean hydrolysis could be achieved under strongly basic conditions however, using aqueous KOH at reflux for 18 h.

To ensure more facile hydrolysis conditions, we also investigated use of the more easily hydrolysed *tert*-butyl carbamate (Boc) group, a protecting group of known utility for the lithiation of related 3-aminopyridines.[7] Formation of the Boc derivative **4a** was best achieved by direct reaction of 2-chloro-5-aminopyridine **2a** with di-*tert*-butyl dicarbonate in 1,4-dioxane at reflux. Although the use of an added base such as sodium bis(trimethylsilyl)amide (NaHMDS) has been reported for the Boc protection of related aminopyridines,[8] in the present case this was not necessary. In fact the reaction was found to be much cleaner in the absence of added bases such as triethylamine or 4-dimethylaminopyridine (DMAP), than when they were present.

Lithiation of **4a** with BuLi–TMEDA in Et_2O as above, followed by quenching with CO_2 gave the C-4 acid **6a** in 57% yield, and reaction of this compound with trifluoroacetic acid (TFA) in CH_2Cl_2 readily gave the amino acid **7a** in 87% yield. Finally, conversion of **7a** to 6-chloropyrido[3,4-*d*]pyrimidin-

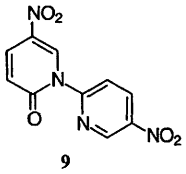
4(3*H*)-one **8a** was readily achieved by reaction with formamide at 140 °C.[2,9] However, subsequent work showed that displacement of the chloro substituent, either of **8a** or derivatives, could not be achieved with a variety of nucleophiles.

Synthesis of 6-fluoropyrido[3,4-*d*]pyrimidin-4(3*H*)-one 8b

In order to facilitate displacement of the 6-halo substituent, we decided to target the 6-fluoro derivative **8b**, by repeating the procedure of Scheme 1 with the analogous fluoro compounds. Now, although 5-amino-2-fluoropyridine **2b** has been prepared by the Hofmann reaction on 6-fluoronicotinamide,[10] we chose to prepare this compound by reduction of the analogous nitro compound **1b**, which is available *via* fluoride displacement on 2-chloro-5-nitropyridine **1a**.[11,12] However, neither of the two literature procedures[11,12] for this fluoridation was found to be completely suitable for our needs, so we investigated several alternatives. Reaction of **1a** with KF in sulfolane at 120 °C gave a cleaner product than the analogous reaction in DMF,[11] although brief chromatography was necessary to remove sulfolane residues. Reduction of the nitro group of **1b** was successfully achieved using hydrogen and palladium on activated carbon in toluene, in the presence of Na_2SO_4 as a drying agent, after variable results were obtained using a variety of more polar solvents.

Protection of the amino group of **2b** as its Boc derivative **4b** was again achieved in good yield (88%), although lithiation and carboxylation of **4b** to give **6b** proceeded in slightly lower yield (40%) than for **4a**, due to the greater susceptibility of the more electrophilic fluoro system to undergo nucleophilic attack by the butyllithium. Hydrolysis of **6b** to **7b** again proceeded well, but while the conversion of **7a** to pyrimidone **8a** was readily achieved by reaction with formamide,[2] the use of formamidine acetate[9,13] in 2-methoxyethanol was found to give more consistent results for the formation of **8b** from **7b**.

Displacement of the fluorine atom from derivatives of **8b** could readily be achieved,[14] and because of the impressive biological results that were obtained with some of these compounds,[14] **8b** was selected for large scale synthesis. This required a number of synthetic modifications to the various steps in the preparation of **8b** from **1a**. Firstly, the use of CsF in dry monoglyme was found advantageous for the fluoride displacement on **1a**, in terms of a simplified workup procedure, with solvent residues no longer being a problem. By use of this procedure we also isolated a dimeric byproduct which was identified as 5-nitro-1-(5-nitro-2-pyridyl)-2-pyridone **9**. Secondly, reduction of the nitro group of **1b** was found to proceed best using hydrogen and Raney nickel in MeOH, and reaction of the crude amino compound **2b** with di-*tert*-butyl dicarbonate in 1,4-dioxane at 80 °C gave the Boc derivative **4b** in 83% yield over the two steps. The yield for the lithiation of **4b** could be improved slightly by performing the lithiation step at −40 °C for 16 h, with a modified workup giving the acid derivative **6b** in 47% yield. Subsequent steps were performed with only minor modifications compared to the earlier procedure, resulting in the synthesis of multi-gram quantities of the pyridopyrimidone **8b**.



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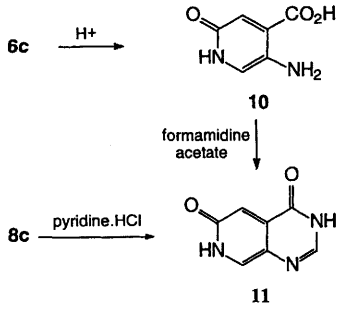
Synthesis of pyrido[3,4-*d*]pyrimidine-4,6(3*H*,7*H*)-dione 11

We also investigated the synthesis of 6-methoxypyrido[3,4-*d*]pyrimidone **8c** since it was expected that the demethylation of **8c** would provide ready access to the analogous pyridopyrimidine-4,6-dione **11**. Protection of the amine **2c** as its Boc derivative **4c** again proceeded well, using di-*tert*-butyl dicarbonate in refluxing 1,4-dioxane, while the lithiation and carboxylation of **4c** to give **6c** actually occurred in significantly better yield (67%) than with the analogous chloro (57%) and fluoro (40%) compounds under the same conditions. This result was not unexpected, as the higher electron density of **4c** will lessen nucleophilic addition of the butyllithium. Hydrolysis of **6c** could be achieved with TFA in CH_2Cl_2 as before, but the product obtained was not completely pure, and a cleaner product was obtained using the base hydrolysis conditions previously employed with the pivalamide **5a**. This base hydrolysis is notable since *tert*-butoxycarbonyl (Boc) groups do not normally cleave under basic conditions.[15] Ring closure of **7c** with formamidine acetate gave **8c** in excellent yield (90%), and subsequent demethylation with pyridine hydrochloride gave the dione **11** (Scheme 2). As an alternative route to dione

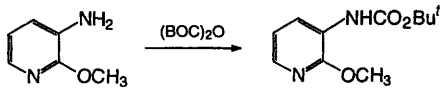


Scheme 2

11 we also investigated the hydrolysis of the methoxy group at an earlier stage. Thus treatment of the Boc derivative **6c** with aqueous HCl resulted in hydrolysis of both the methoxy and Boc groups to give the pyridone acid **10**, which was identical by proton NMR with the byproduct previously seen in the crude product resulting from the acidic hydrolysis of **5a**. Reaction of **10** with formamidine acetate did produce the expected dione **11**, although the product was not as clean as that obtained by demethylation of **8c**.

Boc protection of 3-amino-2-methoxypyridine 12

Finally, we also investigated the direct reaction of 3-amino-2-methoxypyridine **12** with di-*tert*-butyl dicarbonate using our conditions of refluxing 1,4-dioxane (Scheme 3). The Boc



12 **13**

Scheme 3

protection of **12** has been reported to require the use of sodium bis(trimethylsilyl)amide (NaHMDS),[8] but since we had been successful with the direct Boc protection of related aminopyridines, we felt that the same might be true of **12**. This is precisely what we found, with the yield of **13** for the direct reaction in 1,4-dioxane (89%) being comparable (90%) to that reported[8] for the NaHMDS procedure.

Conclusions

We have found that, with the appropriate choice of experimental conditions, the directed lithiation and carboxylation of 2-substituted 5-aminopyridine derivatives at the 4-

position gives synthetically useful yields of product, which can be further converted to 6-substituted pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones in excellent yields, on both a laboratory or semi-industrial scale. Improved procedures have been developed for the fluorination of 2-chloro-5-nitropyridine, and for the Boc protection of certain aminopyridines. Furthermore formamidine acetate has been shown to be a superior reagent to formamide for the ring closure of the aminopyridinecarboxylic acids to the pyrimidone derivatives.

Experimental

Melting points were measured on an Electrothermal 9200 or Gallenkamp digital melting point apparatus, and are uncorrected. NMR spectra were measured on Bruker AM-400 or DRX-400 or Varian Unity 400 MHz spectrometers, and referenced to tetramethylsilane; *J* values are given in Hz. Mass spectra were recorded on a Varian VG 7070 spectrometer at nominal 5000 resolution, or a Fisons VG Trio-2A (CI) spectrometer. Unless otherwise noted, column chromatography was carried out in the flash mode utilising E. Merck 230–400 mesh SiO_2. Analytical TLC was carried out on E. Merck SiO_2 60 F_{254} plates with detection by UV light. All reaction solvents were reagent grade or distilled-in-glass. Diethyl ether was distilled from sodium–benzophenone and TMEDA from CaH_2. CsF was dried at 550 °F in a muffle oven and finely powdered under dry N_2 before use. Anhydrous glyme (ethylene glycol dimethyl ether) was 99.5% grade, Aldrich catalogue no. 25, 952-7.

2-Fluoro-5-nitropyridine 1b

Method A. A stirred mixture of 2-chloro-5-nitropyridine **1a** (25 g, 0.158 mol) and anhydrous KF (27.5 g, 0.474 mol) in sulfolane (75 cm^3) and benzene (50 cm^3) was heated to 120 °C and the benzene was allowed to boil off, to remove azeotropically remaining traces of H_2O. The flask was then fitted with an air condenser and $CaCl_2$ drying tube, and heating was continued for 20 h. After cooling, the reaction mixture was diluted with 700 cm^3 water, saturated with salt, and steam distilled to give an oily product which was extracted with CH_2Cl_2. Chromatography on Al_2O_3 (300 g, activity II-III), eluting initially with hexanes, and then with hexanes–CH_2Cl_2 (4:1), gave the *title compound*[11] **1b** (17.75 g, 79%) as an oil (lit.,[11] bp/7 mmHg 86–87 °C) (Found: C, 42.4; H, 2.2; N, 19.7. $C_5H_3N_2O_2F$ requires C, 42.3; H, 2.1; N, 19.7%); $\delta_H(CDCl_3)$ 9.15 (1 H, dd, *J* 0.7 and 2.7, 6-H), 8.63 (1 H, td, *J* 2.9 and 7.7, 4-H) and 7.15 (1 H, dd, *J* 3.4 and 9.3, H-3); δ_F 57.38 (s); δ_C 165.8 (d, J_{C-F} 250, C-2) 145.0 (dd, J_{C-F} 18, C-6), 142.5 (s, C-5), 136.8 (dd, J_{C-F} 10, C-4) and 110.4 (dd, J_{C-F} 39, C-3); CIMS *m*/*z* 143 (MH^+, 100%).

Method B. A suspension of **1a** (160 g, 1.01 mol) and dry CsF (379 g) was placed in a dry stainless steel bomb which was then charged with 1 dm^3 of anhydrous glyme. The bomb was sealed and the reaction was heated at 130 °C with vigorous stirring for 18 h. The reactor was cooled, vented, and the contents suspended by vigorous agitation. The solid was collected by filtration, then washed well with CH_2Cl_2. The resulting dark brown filtrate was concentrated at 45 °C to give a thick oily brown residue that was distilled through a 4 in Vigreux column at 61 °C/0.05 mmHg to afford **1b** (119.4 g, 83%) as a clear pale yellow oil, > 96% pure by GC. Most of the pot residue is a dimeric side-product. A sample was crystallised from 5:1 EtOAc:hexanes to give 5-*nitro*-1-(5-*nitro*-2-*pyridyl*)-2-*pyridone* **9** as a white solid, mp 166–169 °C (Found: C, 45.7; H, 2.4; N, 21.2. $C_{10}H_6N_4O_5$ requires C, 45.8; H, 2.3; N, 21.4%); $\delta_H(CDCl_3)$ 9.38 (1 H, d, *J* 2.7, 6′-H), 9.34 (1 H, d, *J* 2.9, 6-H), 8.63 (1 H, dd, *J* 9.0, 2.7, 4′-H), 8.31 (1 H, d, *J* 9.0, 3′-H), 8.13 (1 H, dd, *J* 2.9 and 10.2, 4-H) and 6.66 (1 H, d, *J* 10.2, 3-H); $\delta_C([^2H_6]DMSO)$ 160.6 (s), 154.0 (s), 145.2 (d), 144.5 (s), 139.3 (d), 134.8 (d), 134.6 (d), 131.8 (s), 122.7 (d) and 120.9 (d); CIMS *m*/*z* 263 (MH^+, 100%).

5-Amino-2-fluoropyridine 2b

Method A. Hydrogenation of **1b** (5 g, 35 mmol) was carried out in toluene (100 cm^3) over a mixture of 5% Pd–C and anhydrous Na_2SO_4 (to absorb the H_2O produced) to give **2b** (3.7 g, 94%), mp 89–90 °C (from CH_2Cl_2–hexane) (lit.,[10] mp 87–87.5 °C); $\delta_H(CDCl_3)$ 7.62 (1 H, t, *J* 2.3, 6-H), 7.11 (1 H, td, *J* 3.0 and 7.7, 4-H), 6.72 (1 H, dd, *J* 3.3 and 8.7, 3-H) and 3.74 (2 H, br s, exchangeable with D_2O, NH_2); δ_C 157.1 (d, J_{C-F} 230, C-2), 140.5 (d, J_{C-F} 4, C-5), 132.8 (dd, J_{C-F} 15, C-6), 127.5 (dd, J_{C-F} 7, C-4) and 109.1 (dd, J_{C-F} 39, C-3).

Method B. A stirred solution of **1b** (132.4 g, 932 mmol) in MeOH (1.3 dm^3) was hydrogenated at 50.4 psi† H_2 over Raney nickel (40 g). After 25 h the theoretical amount of H_2 had been taken up. Filtration of the catalyst followed by concentration of the filtrate afforded 135 g of a crude solid that was used directly in the next step.

tert-Butyl *N*-(6-chloro-3-pyridyl)carbamate 4a

A mixture of 5-amino-2-chloropyridine[16] **2a** (10.29 g, 80 mol) and di-*tert*-butyl dicarbonate (19.2 g, 88 mmol) in 1,4-dioxane (100 cm^3) was heated at reflux for 12 h, cooled, and diluted with H_2O to give a precipitate of the *title compound* **4a** (16.25 g, 89%), mp 125–126 °C (from EtOAc–hexane) (Found: C, 52.7; H, 5.5; N, 12.3. $C_{10}H_{13}ClN_2O_2$ requires C, 52.5; H, 5.7; N, 12.3%); $\delta_H(CDCl_3)$ 8.31 (1 H, d, *J* 2.9, 2-H), 7.94 (1 H, dd, *J* 2.6 and 8.6, 4-H), 7.24 (1 H, d, *J* 8.7, 5-H), 7.15 (1 H, m, exchangeable with D_2O, NH) and 1.51 (9 H, s, CMe_3); δ_C 152.5 (s, NCO_2), 144.5 (s, C-6), 139.5 (d, C-2), 134.6 (s, C-3), 128.7 (d, C-4), 124.0 (d, C-5), 81.4 (s, CO) and 28.1 (q, Me).

tert-Butyl *N*-(6-fluoro-3-pyridyl)carbamate 4b

Method A. A solution of **2b** (5.61 g, 50 mmol) and di-*tert*-butyl dicarbonate (14.2 g, 65 mmol) in 1,2-dichloroethane (50 cm^3) was heated at reflux for 16 h using a $CaCl_2$ drying tube. The cooled solution was stirred with 50 cm^3 of H_2O containing a few drops of conc. NH_4OH for 30 min, then extracted with CH_2Cl_2. Chromatography of the residue from the organic layer on SiO_2, eluting first with CH_2Cl_2 and then with CH_2Cl_2–EtOAc (9:1), gave the *title compound* **4b** (9.32 g, 88%), mp 113.5–115 °C (from CH_2Cl_2–hexane) (Found: C, 56.7; H, 6.2; F, 9.1; N, 13.5; M^+, 212.0964. $C_{10}H_{13}FN_2O_2$ requires C, 56.6; H, 6.2; F, 9.0; N, 13.2%; *M*, 212.0961); $\delta_H(CDCl_3)$ 8.07 (1 H, br s, 2-H), 8.05 (1 H, m, 4-H), 6.89 (1 H, dd, *J* 3.3 and 9.2, 5-H), 6.66 (1 H, m, exchangeable with D_2O, NH) and 1.52 (9 H, s, CMe_3); δ_C 159.3 (d, J_{C-F} 235, C-6), 152.8 (s, NCO_2), 137.3 (br dd, J_{C-F} 10, C-2), 133.1 (d, J_{C-F} 4, C-3), 131.9 (br, C-4), 109.2 (dd, J_{C-F} 39, C-5), 81.3 (s, CO) and 28.2 (q, Me).

Method B. A solution of crude **2b** (135 g) in 1,4-dioxane (1.3 dm^3) was treated with di-*tert*-butyl dicarbonate (225 g, 1.03 mol) and the mixture was heated under N_2 at 80 °C for 3 h. The solution was concentrated to a residue that was dissolved in warm *tert*-butyl methyl ether (350 cm^3). The solution was diluted with light petroleum (bp 35–60 °C) (350 cm^3), then allowed to crystallise in the cold. The solids were collected and dried to give **4b** (138 g), mp 111–113 °C. Concentration and crystallisation of the filtrate afforded an additional 27.5 g of product. Total yield 165 g (83% over two steps).

tert-Butyl *N*-(6-methoxy-3-pyridyl)carbamate 4c

A mixture of 5-amino-2-methoxypyridine[17] **2c** (2.63 g, 21 mmol) and di-*tert*-butyl dicarbonate (5.1 g, 23 mmol) in dry 1,4-dioxane (30 cm^3) was heated under reflux for 30 min, quenched with H_2O, and worked up in EtOAc to give an oil, which was dissolved in boiling hexanes and clarified with charcoal. Concentration and cooling of the solution gave the *title compound* **4c** (4.47 g, 94%), mp 84–85 °C (Found: C, 59.0; H, 7.2: N, 12.5. $C_{11}H_{16}N_2O_3$ requires C, 58.9; H, 7.2; N, 12.5%);

† 1 psi = 6.89 × 10^3 Pa.

$\delta_H(CDCl_3)$ 8.01 (1 H, d, *J* 2.9, 2-H), 7.80 (1 H, br, 4-H), 6.70 (1 H, d, *J* 8.8, 5-H), 6.66 (1 H, br, exchangeable with D_2O, NH), 3.89 (3 H, s, OMe) and 1.50 (9 H, s, CMe_3); δ_C 160.4 (s, NCO_2), 153.2 (s, C-6), 137.4 (br d, C-2), 131.4 (br d, C-4), 129.0 (s, C-3), 110.5 (d, C-5), 80.6 (s, CO), 53.4 (q, OMe) and 28.3 (q, Me).

2-Chloro-5-(*tert*-butylcarbonylamino)pyridine-4-carboxylic acid 5a

A suspension of *N*-(6-chloro-3-pyridyl)-2,2-dimethylpropanamide[5] **3a** (8.51 g, 40 mmol) and TMEDA (14.4 g, 12.4 mmol) in dry Et_2O (300 cm^3) under N_2 was cooled to −78 °C and a 2.5 M solution of BuLi in hexanes (28.8 cm^3, 0.12 mol) was added slowly to give a deep red solution which was allowed to warm to −10 °C, and maintained at that temperature for 2 h. The resulting suspension was recooled to −78 °C and treated with a stream of dry CO_2 gas for several min. The mixture was allowed to warm to room temperature, H_2O containing a small amount of NH_4OH was added, and the aqueous layer was separated, filtered through Celite, and acidified with 2 M aq. HCl to give a precipitate of the *title compound* **5a** (5.27 g, 51%), mp 252 °C (decomp.) (from EtOAc) (Found: C, 51.3; H, 5.2; Cl, 14.1; N, 10.8; M^+, 256.0612/258.0594. $C_{11}H_{13}ClN_2O_3$ requires C, 51.5; H, 5.1; Cl, 13.8; N, 10.9%; *M*, 256.0615/258.0585); $\delta_H([^2H_6]DMSO)$ 10.94 (1 H, s, exchangeable with D_2O, NH), 9.48 (1 H, s, 6-H), 7.82 (1 H, s, 3-H) and 1.26 (9 H, s, CMe_3); δ_C 176.6 (s, NCO), 167.0 (s, CO_2H), 143.4 (s, C-2) 142.6 (d, C-6), 135.2 (s, C-4), 127.5 (s, C-5), 123.8 (d, C-3), 39.4 (s, CMe_3) and 26.9 (q, Me).

2-Chloro-5-(*tert*-butoxycarbonylamino)pyridine-4-carboxylic acid 6a

A solution of **4a** (22.87 g, 0.1 mol) and TMEDA (47 cm^3, 0.31 mol) in dry Et_2O (600 cm^3) was cooled to −78 °C, and BuLi (30 cm^3 of 10 M in hexanes, 0.3 mol) was added dropwise. The solution was allowed to warm to −10 °C and was kept at that temperature for 2 h, before being recooled to −78 °C. Dry CO_2 was then bubbled in, and the resulting mixture was allowed to warm to 20 °C, before being quenched with water (300 cm^3) containing a small amount of NH_4OH. The resulting aqueous layer was washed with EtOAc, then acidified slowly with dil. aq. HCl to give a precipitate of the *title compound* **6a** (15.5 g, 57%), mp 272–278 °C (decomp.) (from EtOAc) (Found: C, 48.8; H, 4.6; N, 10.2. $C_{11}H_{13}ClN_2O_4$ requires C, 48.5; H, 4.8; N, 10.3%); $\delta_H([^2H_6]DMSO)$ 10.00 (1 H, s, exchangeable with D_2O, NH), 9.13 (1 H, s, 6-H), 7.74 (1 H, s, 3-H) and 1.47 (9 H, s, CMe_3); δ_C 166.8 (s, CO_2H), 151.8 (s, NCO), 142.7 (s, C-2), 141.7 (d, C-6), 135.3 (s, C-4), 127.2 (s, C-5), 123.7 (d, C-3), 80.9 (s, CO) and 27.8 (q, Me).

2-Fluoro-5-(*tert*-butoxycarbonylamino)pyridine-4-carboxylic acid 6b

Method A. A solution of **4b** (3.8 g, 0.112 mol) and TMEDA (40 g, 0.344 mol) in Et_2O (600 cm^3) was cooled to −78 °C and treated slowly with 2.5 M BuLi (134 cm^3, 0.336 mol). The resulting deep red solution was allowed to warm to −10 °C and maintained at that temperature for 3 h. After recooling to −78 °C, dry CO_2 gas was bubbled into the stirred solution until all of the colour disappeared. The resulting suspension was allowed to warm to room temperature before being diluted with 1 dm^3 of H_2O. The separated organic layer was washed with dil. NH_4OH solution, and the combined aqueous layers were then washed with a 1:1 mixture of EtOAc and hexane. The aqueous layer was filtered through Celite and acidified with dil. aq. HCl. The resulting precipitate was dissolved in EtOAc, and the solution was filtered through Celite, concentrated and cooled, to give the *title compound* **6b** (11.6 g, 40%), mp 252–254.5 °C (Found: C, 51.9; H, 5.1; F, 7.1; N, 11.1; M^+, 256.0855. $C_{11}H_{13}FN_2O_4$ requires C, 51.6; H, 5.1; F, 7.4; N, 10.9%; *M*, 256.0859); $\delta_H([^2H_6]DMSO)$ 9.84 (1 H, s, exchangeable with D_2O, NH), 8.84 (1 H, s, 6-H), 7.49 (1 H, d, $^3J_{H-F}$ 2.8, 3-H) and 1.48 (9 H, s, CMe_3); δ_C 166.8 (d, J_{C-F} 4, CO_2H), 158.2 (d, J_{C-F} 232, C-2), 152.2 (s, NCO_2), 139.4 (dd, J_{C-F} 15, C-6), 134.0 (d, J_{C-F} 5, C-4) 130.4 (d, J_{C-F} 7, C-5), 109.4 (dd, J_{C-F} 41, C-3), 80.7 (s, CO) and 27.9 (q, Me).

Method B. A mechanically stirred solution of **4b** (63.67 g, 300 mmol), TMEDA (115 cm^3) and dry Et_2O (1.8 dm^3) was cooled to −78 °C in a Nestar refrigeration unit. BuLi (10 M in hexanes; 72 cm^3) was added dropwise at such a rate so as to maintain the internal reaction temperature below −60 °C. The resultant red solution was stored at −40 °C for 16 h, recooled to −78 °C, then charged for *ca.* 20 min with dry CO_2 gas introduced *via* a sparge tube with the rate of bubbling adjusted so as to maintain the internal reaction temperature below −40 °C. The reaction flask was removed from the bath and allowed to warm to room temperature over *ca.* 1 h. The orange mixture was poured into cold dil. aq. NaOH (700 cm^3) (final pH 12.5). The layers were separated and the aqueous layer was further extracted with 2 × 400 cm^3 of Et_2O. The aqueous layer was ice-cooled and acidified to *ca.* pH 6 with aq. HCl. A sticky precipitate was filtered off, then the filtrate was again ice-cooled and further acidified to pH 3.0. A light yellow precipitate was collected by filtration, washed with H_2O (200 cm^3), then redissolved in 5% aq. NaOH (1 dm^3). Insoluble matter was removed by filtration and the two-stage acidification–precipitation described above was repeated on the filtrate to provide **6b** (36.9 g, 47%) as a beige solid, mp 253–257 °C (decomp.) (Found: C, 50.4; H, 5.0; N, 10.6. $C_{11}H_{13}N_2O_4F{\cdot}0.3\ H_2O$ requires C, 50.5; H, 5.2; N, 10.7%).

5-(*tert*-Butoxycarbonylamino)-2-methoxypyridine-4-carboxylic acid 6c

Treatment of **4c** with 3 equiv. of BuLi–TMEDA as before, followed by quenching with CO_2 gave the *title compound* **6c** (4.50 g, 67%), mp 192 °C (decomp.) (from EtOAc) (Found: C, 53.8; H, 6.2; N, 10.6. $C_{12}H_{16}N_2O_5$ requires C, 53.7; H, 6.0; N, 10.4%); $\delta_H([^2H_6]DMSO)$ 13.74 (1 H, br, exchangeable with D_2O, CO_2H), 9.44 (1 H, br s, exchangeable with D_2O, NH), 8.71 (1 H, br s, 6-H), 7.14 (1 H, s, 3-H), 3.86 (3 H, s, OMe) and 1.47 (9 H, s, CMe_3); δ_C 167.2 (s, CO_2H), 159.3 (s, C-2), 152.5 (s, NCO_2), 152.4 (s, C-4), 139.9 (br d, C-6), 129.0 (s, C-5), 109.9 (d, C-3), 79.8 (s, CO), 53.5 (q, OMe) and 27.9 (q, Me).

5-Amino-2-chloropyridine-4-carboxylic acid 7a

Method A. A solution of **6a** (2.57 g, 10 mmol) and KOH (5.6 g, 0.1 mol) in water (50 cm^3) was heated at reflux for 18 h, cooled, and acidified with conc. HCl to give a white precipitate. The solid was collected, washed with H_2O and then CH_2Cl_2 (to remove traces of pivalic acid), and dried to give the *title compound* **7a** (1.27 g, 74%), mp 279–281 °C (from aqueous EtOH) (Found: C, 42.3; H, 2.9; Cl, 20.3; N, 16.3. $C_6H_5ClN_2O_2$ requires C, 41.8; H, 2.9; Cl, 20.5; N, 16.2%); $\delta_H([^2H_6]DMSO)$ 9.01 (2 H, m, exchangeable with D_2O, NH_2), 8.03 (1 H, s, 6-H) and 7.48 (1 H, s, 3-H); δ_C 167.3 (s, CO_2H), 145.2 (s, C-2), 140.1 (d, C-6), 134.6 (s, C-4), 123.0 (d, C-3) and 117.8 (s, C-5).

Method B. A stirred suspension of **6a** (1.91 g, 7 mmol) in CH_2Cl_2 (200 cm^3) was treated slowly with TFA until homogeneous (*ca.* 12 cm^3). The solution was stirred overnight and extracted with dil. NH_4OH, and the aqueous layer was acidified with dil. aq. HCl to give a precipitate of **7a** (1.05 g, 87%).

5-Amino-2-fluoropyridine-4-carboxylic acid 7b

Method A. A suspension of **6b** (2.56 g, 10 mmol) in CH_2Cl_2 (100 cm^3) was diluted with TFA (20 cm^3) and stirred at room temperature for 12 h. The mixture was evaporated to dryness, and the resulting solid was partitioned between H_2O and EtOAc. After being dried (Na_2SO_4) the organic layer was concentrated, diluted with 1,2-dichloroethane, and concen-

trated further to give the *title compound* **7b** (1.19 g, 76%), mp 259 °C (decomp.) (from EtOAc) (Found: C, 46.0; H, 2.9: F, 12.1; N, 18.1. $C_6H_5FN_2O_2$ requires C, 46.2; H, 3.2; F, 12.2; N, 17.9%); δ_H([$^2H_6$]DMSO) 8.86 (3 H, m, exchangeable with D_2O, NH_2 and CO_2H), 7.81 (1 H, d, J_{H-F} 1.1, 6-H) and 7.20 (1 H, d, J_{H-F} 2.3, 3-H); δ_C 167.4 (d, J_{C-F} 4, CO_2H), 154.5 (d, J_{C-F} 222, C-2), 144.5 (d, J_{C-F} 3, C-4), 136.4 (dd, J_{C-F} 14, C-6), 119.8 (d, J_{C-F} 6, C-5) and 107.7 (dd, J_{C-F} 40, C-3); CIMS *m/z* 157 (MH^+, 100%).

Method B. A suspension of crude **6b** (36.6 g, 140 mmol), hydrated with 0.3 equiv. of H_2O, in CH_2Cl_2 (280 cm^3) was cooled in an ice-bath then treated dropwise over 15 min with TFA (140 cm^3). The bath was removed and the resultant mixture was stirred at room temperature for 14 h, then concentrated. The yellow orange solid was triturated in warm 1:1 Et_2O:CH_2Cl_2 (125 cm^3). After cooling, the solid was collected, washed with 1:1 Et_2O:CH_2Cl_2 mixture (100 cm^3), and dried to afford crude **7b** (18.9 g). Processing of the filtrate afforded a second crop (1.6 g). Total yield 20.5 g (94%).

5-Amino-2-methoxypyridine-4-carboxylic acid 7c

A solution of **6c** (1.68 g, 6.3 mmol) and KOH (3.5 g, 63 mmol) in H_2O (50 cm^3) was heated at reflux for 18 h, cooled, and acidified with conc. HCl to give the *title compound* **7c** (0.99 g, 93%), mp 217–221 °C (decomp.) (from EtOH) (Found: C, 50.1; H, 4.8; N, 16.6. $C_7H_8N_2O_3$ requires C, 50.0; H, 4.8; N, 16.7%); δ_H([$^2H_6$]DMSO) 8.49 (3 H, br, exchangeable with D_2O, NH_2 and CO_2H), 7.87 (1 H, s, 6-H), 7.00 (1 H, s, 3-H) and 3.77 (3 H, s, OMe); δ_C 168.0 (s, CO_2H), 155.0 (s, C-2), 140.7 (s, C-4), 136.0 (d, C-6), 120.4 (s, C-5), 108.2 (d, C-3) and 53.3 (q, OMe).

6-Chloropyrido[3,4-*d*]pyridin-4(3*H*)-one 8a

A stirred solution of **7a** (8.1 g, 4.7 mmol) in formamide (100 cm^3) was heated at 140 °C for 12 h. Dilution of the cooled mixture with H_2O gave a precipitate of the *title compound* **8a** (7.3 g, 86%), mp 318–326 °C (decomp.) (from EtOH) (Found: C, 46.6; H, 1.9; Cl, 19.8; N, 22.9; M^+, 181.0036/183.0012. $C_7H_4ClN_3O$ requires C, 46.3; H, 2.2; Cl, 19.5; N, 23.1%; *M*, 181.0043/183.0013); δ_H([$^2H_6$]DMSO) 12.73 (1 H, m, exchangeable with D_2O, NH), 8.90 (1 H, d, *J* 0.7, 8-H), 8.23 (1 H, s, 2-H) and 7.97 (1 H, d, *J* 0.7, 5-H); δ_C 159.0 (s, C-4), 151.0 (d, C-8), 147.8 (d, C-2), 146.2 (s, C-6), 142.9 (s, C-8a), 130.6 (s, C-4a) and 118.5 (d, C-5).

6-Fluoropyrido[3,4-*d*]pyrimidin-4(3*H*)-one 8b

Method A. A mixture of **7b** (1.17 g, 75 mmol) and formamidine acetate (1.56 g, 150 mmol) in 2-methoxyethanol (25 cm^3) was heated at reflux for 12 h before the solvent was removed under vacuum. The solid residue was washed with dil. aq. $NaHCO_3$, collected by filtration, washed with H_2O, and dried, to give the *title compound* **8b** (1.10 g, 89%), mp 287 °C (decomp.) (from MeOH) (Found: C, 51.3; H, 2.6; F, 10.8; N, 25.2; M^+, 165.0339. $C_7H_4FN_3O$ requires C, 50.9; H, 2.4; F, 11.5; N, 25.4%; *M*, 165.0338); δ_H([$^2H_6$]DMSO) 12.68 (1 H, m, exchangeable with D_2O, NH), 8.78 (1 H, s, 8-H), 8.20 (1 H, s, 2-H) and 7.67 (1 H, d, J_{H-F} 3, 5-H); δ_C 160.4 (d, J_{C-F} 238, C-6), 159.2 (d, J_{C-F} 4, CO), 148.9 (dd, J_{C-F} 15, C-8), 146.3 (d, C-2), 142.1 (d, J_{C-F} 4, C-8a), 132.6 (d, J_{C-F} 8, C-4a) and 103.0 (dd, J_{C-F} 40, C-5).

Method B. A suspension of crude **7b** (38.4 g, 246 mmol), formamidine acetate (52.01 g, 500 mmol) and 2-methoxyethanol (500 cm^3) was heated at reflux for 6 h, then concentrated to a solid. The solids were treated carefully with 10% aq. $NaHCO_3$ (100 cm^3) while maintaining vigorous stirring. The resultant suspension was filtered and the collected brown solid was washed well with H_2O, then dried over P_2O_5 to afford **8b** (31.3 g, 77%), which was sufficiently pure for subsequent work.[14]

6-Methoxypyrido[3,4-*d*]pyrimidin-4-(3*H*)-one 8c

A mixture of **7c** (1 g, 5.95 mmol) and formamidine acetate (1.25 g, 12 mmol) in 2-methoxyethanol (20 cm^3) was heated at reflux for 8 h, cooled, and diluted with H_2O to give the *title compound* **8c** (0.95 g, 90%), mp 258–260 °C (from EtOH) (Found: C, 54.3; H, 3.9; N, 23.9. $C_8H_7N_3O_2$ requires C, 54.2; H, 4.0; N, 23.7%); δ_H([$^2H_6$]DMSO) 12.35 (1 H, br, exchangeable with D_2O, NH), 8.73 (1 H, s, 8-H), 8.03 (1 H, s, 2-H), 7.26 (1 H, s, 5-H) and 3.95 (3 H, s, OMe); δ_C 161.6 (s, C-6), 159.6 (s, C-4), 148.2 (d, C-8), 144.1 (d, C-2), 138.4 (s, C-8a), 131.2 (s, C-4a), 102.2 (d, C-5) and 54.0 (q, OMe).

5-Amino-2-hydroxypyridine-4-carboxylic acid hydrochloride 10

A suspension of **6c** (2.52 g, 10 mmol) in 6 M aq. HCl (50 cm^3) was heated under reflux for 4 h, to give a clear solution which was evaporated to dryness to give the *title compound* **10** (2.02 g, 89%), mp 215 °C (decomp.) (from EtOH) (Found: C, 38.0; H, 3.7; Cl, 18.5; N, 14.4. $C_6H_7ClN_2O_3$ requires C, 37.8; H, 3.7; Cl, 18.6; N, 14.7%); δ_H([$^2H_6$]DMSO) 7.84 (1 H, s, 6-H) and 6.99 (1 H, s, 3-H); δ_C 165.6 (s, CO_2H), 158.7 (s, C-2), 133.2 (br s, C-4), 132.4 (d, C-6), 120.4 (br s, C-5) and 117.9 (br d, C-3).

Pyrido[3,4-*d*]pyrimidine-4,6(3*H*,7*H*)-dione 11

A mixture of pyridine (7.9 g, 0.1 mol) and conc. HCl (8.3 cm^3, 0.1 mol) was heated to 220 °C to drive off H_2O, and **8c** (0.5 g, 2.8 mmol) was added to the hot mixture. After a further 15 min at 220 °C the solution was concentrated under vacuum and triturated with a minimum volume of H_2O to give **11** (0.31 g, 67%), mp 348–353 °C (decomp.) (from EtOH) (Found: C, 51.8; H, 3.1; N, 25.9. $C_7H_5N_3O_2$ requires C, 51.5; H, 3.1; N, 25.8%); δ_H([$^2H_6$]DMSO) 11.90 (2 H, br, exchangeable with D_2O, NH), 8.43 (1 H, s, 2-H), 7.86 (1 H, s, 5-H) and 7.01 (1 H, s, 8-H); δ_C 161.6 (s, C-6), 159.6 (s, C-4), 144.8 (br d, C-2), 142.5 (d, C-8), 134.7 (s, C-8a), 132.5 (s, C-4a) and 104.8 (br, d, C-5).

tert-Butyl *N*-(2-methoxy-3-pyridyl)carbamate 13

A mixture of 3-amino-2-methoxypyridine[17] **12** (1.0 g, 80.6 mmol) and di-*tert*-butyl dicarbonate (2.11 g, 96.7 mmol) in dry 1,4-dioxane (25 cm^3) was heated at reflux for 18 h, and H_2O was added to quench the excess reagent. The solvent was removed and the product was worked up in EtOAc to give an oil which was chromatographed on SiO_2, eluting with CH_2Cl_2–hexanes 1:1, to give **13** (1.60 g, 89%) as an oil; δ_H($CDCl_3$) identical to reference 8; δ_C 152.6 (2 s, C-2 and NCO_2), 138.7 (d, C-6), 124.4 (d, C-4), 123.2 (s, C-3), 117.1 (d, C-5), 80.8 (s, CO), 53.5 (q, OMe) and 28.2 (q, Me).

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