Improved Synthesis of 2,3-Disubstituted Pyridines by Metallation of 2-Chloropyridine: a Convenient Route to Fused Polyheterocycles

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Chemoselective directed metallation of 2-chloropyridine allows the synthesis of 2-substituted 3-carbonylated pyridines, advantage being taken of the metallation *ortho*-directing effect of the halogen, as well as its reactivity towards nucleophiles. Thus (2-chloro-, 2-methoxy-, and 2-amino-3-pyridyl)-ethanones and -arylmethanones as well as carbaldehydes have been prepared. Some of these *ortho*-disubstituted intermediates have been readily cyclized to fused polyheterocycles such as naphthyridines and aza-analogues of coumarins, xanthones, and acridones.

Some 2,3-disubstituted pyridines are molecules of biological interest.[1] Moreover, pyridines bearing a carbonyl function at the C-3 position and a heteroatomic substituent at the C-2 position (halogen, amine, alkoxy, alkylthio, *etc.*) easily lead to various naphthyridines, Hantzsch esters, and aza-analogues of acridines, benzoxazepines, xanthones, and coumarins.[2–6] Synthesis of carbonylated *ortho*-substituted pyridines sometimes involves the intermediate formation of lithiopyridines, which often requires tedious access to the corresponding bromopyridine precursors.

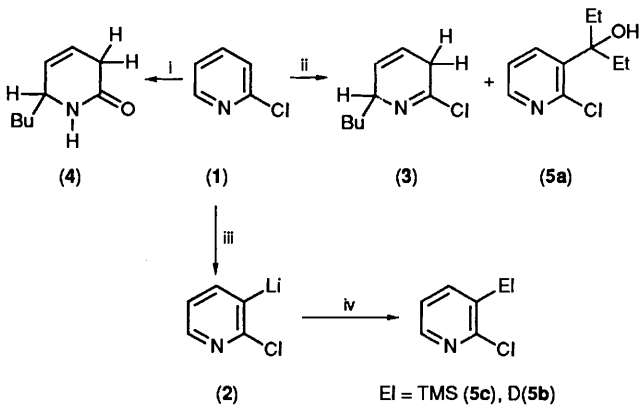
Our experience[7] in the field of directed metallation[8] of electron-poor heteroaromatics prompted us to investigate new pathways to *ortho*-disubstituted pyridines *via ortho*-lithiation of easily accessible material. This has been successfully applied to 2-chloropyridine and a great variety of 3-carbonylated synthons could be prepared by taking advantage of the metallation *ortho*-directing effect of the halogen, as well as its reactivity towards nucleophilic substitution when it is located at the C-2 or C-4 position. Synthons were afterwards cyclized to such polycondensed heterocycles as azacoumarins, naphthyridines, aza- and diaza-xanthones, and aza-acridones.

Results

(I) *Metallation of 2-Chloropyridine.*—The 2-chloropyridine (**1**) metallation parameters were studied first. Metallation was first achieved in tetrahydrofuran (THF) at −70 °C with butyllithium–tetramethylethylenediamine (TMEDA) chelate, but competitive addition of the metallating agent could not be avoided, as had been previously observed with 2-fluoropyridine.[9] The resulting lithiation reaction mixture was quenched by pentan-3-one according to Scheme 1, which led to the metallation product (**5a**) in low yield (13%) together with adduct (**3**) (66%) (Scheme 1).

Other alkyl-lithiums have also been investigated, such as methyl-lithium in THF, which led to the same mixture of addition and metallation products. Reaction of 2-chloropyridine (**1**) with unchelated butyl-lithium in THF, followed by quenching of the lithiation mixture by chlorotrimethylsilane (TMSCl), afforded only 6-butyl-2-oxo-1,2,3,6-tetrahydropyridine (**4**) in 54% yield.

Chemoselective metallation could be achieved when using lithium di-isopropylamide (LDA).[10] The resulting 3-lithiated intermediate (**2**) was characterized as the corresponding 3-trimethylsilyl compound (**5c**) after reaction with TMSCl. The best yield of 2-chloro-3-trimethylsilylpyridine (**5c**) (66%) was observed for a metallation time of 3 h at −70 °C in THF,



Scheme 1. Metallation of 2-chloropyridine (**1**). *Reagents and conditions:* i, BuLi; then TMSCl; ii, BuLi, TMEDA; then EtCOEt; iii, LDA, THF, −70 °C; iv, electrophile.

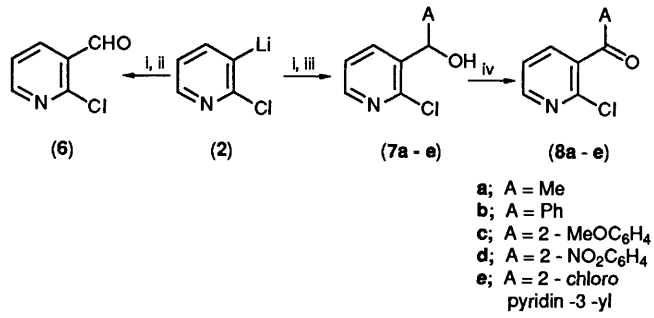
whereas quenching of the lithiation mixture by a solution of DCl in D_2O gave 2-chloro-3-deuteriopyridine (**5b**) in only 47% yield (Scheme 1).

(II) *Synthesis of 2-Substituted Pyridine-3-carbaldehydes and 3-Pyridyl Ketones.*—2-Chloropyridines functionalized by a carbonyl function at C-3 were prepared from 2-chloro-3-lithiopyridine (**2**) by reaction with suitable electrophilic reagents. 2-Chloropyridine-3-carbaldehyde (**6**), a very attractive synthon involved in the synthesis of various pharmaceutical products,[3–5] was readily obtained by reaction of lithiopyridine with ethyl formate,[11] whereas *N*-methylformanilide reacted only slowly at low temperature (Scheme 2).

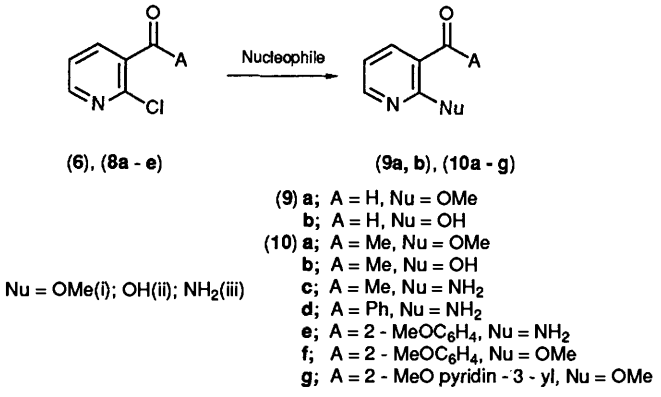
2-Chloro-3-lithiopyridine (**2**) also reacted with aliphatic or aromatic aldehydes to give fair to good yields of the expected secondary alcohols (**7a–e**). These latter compounds were afterwards oxidized to the corresponding (2-chloropyridin-3-yl)-ethanone (**8a**) or aryl(2-chloropyridin-3-yl)methanones (**8b–e**) with manganese dioxide or chromic anhydride.[12,13]

The carbonyl derivatives (**6**) and (**8a–e**) were treated with various nucleophiles to give the corresponding 2-hydroxy, 2-methoxy, or 2-amino derivatives (Scheme 3).

(III) *Synthesis of Polycondensed Heterocycles.*—The previously prepared 3-carbonylated 2-substituted pyridines are key molecules which allowed us to prepare various fused polyheterocycles such as naphthyridines and aza-analogues of

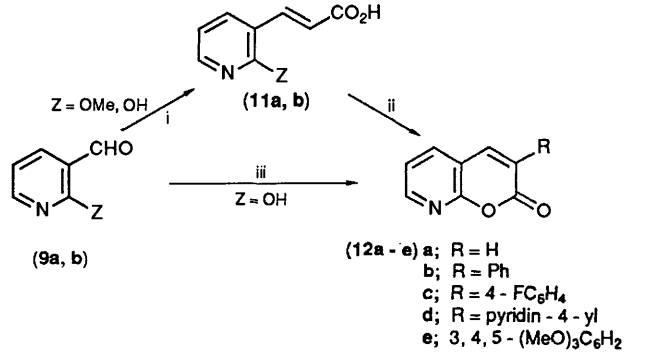


Scheme 2. Synthesis of 2-chloropyridin-3-yl methanols, ketones, and carbaldehyde. *Reagents:* i, LDA; ii, HCO_2Et; iii, A–CHO; iv, MnO_2–PhMe or CrO_3–AcMe.



Scheme 3. Nucleophilic substitutions on (2-chloropyridin-3-yl) carbaldehyde and ketones. *Reagents:* i, MeOH, MeONa; ii, 3M-HCl; iii, aq. NH_3.

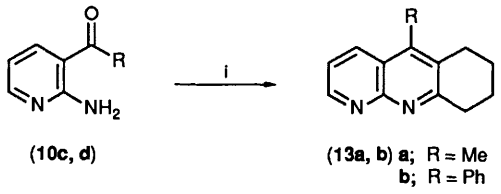
coumarins, xanthones and acridones. 8-Azacoumarin (**12a**) was easily prepared in two steps from 2-hydroxy- or 2-methoxypyridine-3-carbaldehydes (**9a** or **b**).[14] Reaction of these aldehydes with malonic acid under Knoevenagel–Doebner conditions, gave the *E*-isomer of the 3-(pyridin-3-yl)propenoic acids (**11**). Treatment of the latter with boiling pyridinium chloride[15] resulted in isomerization to the *Z*-configuration and cyclization to the expected 8-azacoumarin (**12a**) (Scheme 4).



Scheme 4. Synthesis of 8-azacoumarins. *Reagents:* R = H; i, $CH_2(CO_2H)_2$, pyridine, piperidine; ii, Py, HCl. R = aryl; iii, Perkin conditions (RCH_2CO_2H–Ac_2O, Et_3N).

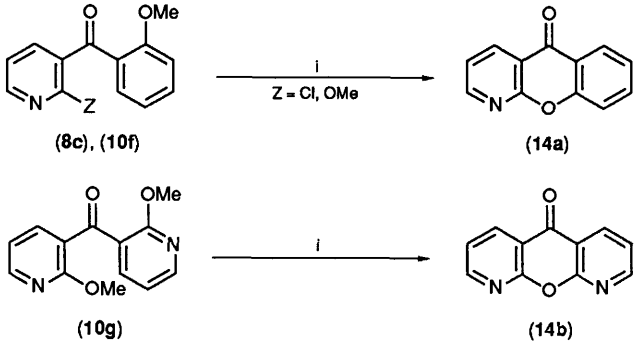
2-Hydroxypyridine-3-carbaldehyde (**9b**) could be transformed in one step into various 3-aryl-8-azacoumarins (**12b–e**) by reaction with the required arylacetic acids following Perkin conditions (Scheme 4).

Naphthyridines were prepared in one step by condensation between 2-aminopyridin-3-yl ketones and cyclohexanone under modified Friedlander conditions using acidic catalysis[16] (Scheme 5).



Scheme 5. Synthesis of 1,8-naphthyridines. *Reagents:* i, cyclohexanone, H_2SO_4, AcOH.

Various diazaxanthones have been previously prepared by us starting from *ortho*-dihalogenopyridines.[11,14] Metallation of 2-chloropyridine (**1**) allowed easier access to the same products. 4,5-Diazaxanthone (**14b**) and 4-azaxanthone (**14a**) were thus prepared by acidic cyclization of *o,o'*-disubstituted diarylmethanones according to Scheme 6.



Scheme 6. Synthesis of azaxanthones. *Reagent:* i, boiling pyridine, HCl.

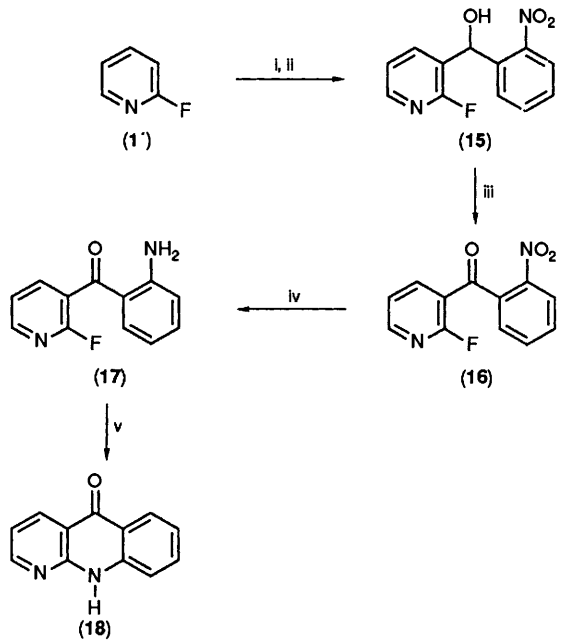
Compound (**14a**) has been also prepared by treatment of (2-aminopyridin-3-yl)-(2-methoxyphenyl)methanone (**10e**) with boiling pyridinium chloride; in this case ring closure occurs only by attack of the methoxy oxygen at C-2, the amino moiety being then the nucleofuge.

(2-Chloropyridin-3-yl)-(2-nitrophenyl)methanone (**8d**) is a precursor of 4-aza-acridone (**18**), but it was more interesting to work on the fluoro series, due to the low yield of formation of the chloro nitro alcohol (**7d**). 2-Fluoro-3-lithiopyridine (**1'**)[7b] was treated with 2-nitrobenzaldehyde and the resulting secondary alcohol (**15**) was oxidized by manganese dioxide to ketone (**16**). Catalytic hydrogenation of the nitro derivative (**16**) afforded the corresponding amino compound (**17**) which spontaneously cyclized on being heated to 4-aza-acridone (**18**). The whole sequence requires 3 steps and has been achieved in 55% overall yield (Scheme 7).

Discussion

Metallation of 2-chloropyridine (**1**) can be achieved with good chemo- and regio-selectivity by LDA in THF at −70 °C. Quenching of the lithio intermediate (**2**) by TMSCl led to a higher metallation yield (66%) than observed after deuteriolysis (47%). As TMSCl reacts slowly with LDA at low temperature, further lithiation of the unchanged 2-chloropyridine is favoured: removal of the 3-lithio intermediate (**2**) by TMSCl causes a metallation equilibrium shift towards lithiation.

Metallation of 2-chloropyridine (**1**) offers a convenient access to various 2,3-disubstituted pyridine synthons and therefore to fused polyheterocycles in few steps, starting from readily accessible reagents. This is particularly obvious when it is



Scheme 7. Synthesis of 4-aza-acridone. *Reagents and conditions:* i, LDA; ii, 2-$NO_2C_6H_4CHO$; iii, MnO_2, PhMe; iv, H_2/Pd–C; v, heat.

compared with halogen–metal exchange which needs the tedious synthesis of the required bromo intermediates.

In the synthesis of (2-halogenopyridin-3-yl)methanols, lithiation of 2-fluoropyridine (**1'**)[7b] sometimes gave higher yields than lithiation of 2-chloropyridine (**1**) but the latter reagent is cheaper.

Some (2-substituted pyridin-3-yl)methanones have been previously prepared by the well known Friedel–Crafts acylation using 2-chloronicotinoyl chloride.[4b] Metallation is, however, much more versatile since it allows a greater variety of aryl substituents on the methanone moiety. Moreover, it appears to be the only convenient route to (2-substituted pyridin-3-yl)ethanones and 2-substituted pyridine-3-carbaldehydes.

Experimental

^{1}H NMR spectra were recorded at 60 MHz with tetramethylsilane or hexamethyldisiloxane as internal reference, on a Varian A60 or T60 spectrometer; chemical shifts are given in ppm downfield from Me_4Si. ^{13}C NMR spectra were recorded at 80 MHz with Me_4Si as internal standard, on a Bruker WP 80 FT spectrometer. IR spectra were recorded from potassium bromide disks or thin films in sodium chloride cells on a Beckman IR 4250 spectrometer. Elemental analysis were performed on a Technicon or a Carlo Erba 1106 instrument. Mass spectra were recorded on a JEOL JMS D-100 spectrometer. Diethylether and THF, both distilled from benzophenone–sodium, were stored over molecular sieves (3 Å) under argon. Water content of the solvents was estimated by the modified Karl-Fischer method[17] for Et_2O and THF (respectively) to less than 10 ppm and 45 ppm. Di-isopropylamine (DIA), TMEDA, and TMSCl were redistilled from, and stored over, CaH_2. Butyl-lithium was a commercial hexane solution. 2-Chloropyridine (**1**) of commercial source was distilled and then stored over molecular sieves.

Procedure I: Metallation of 2-Chloropyridine by Butyllithium.—Dry THF (250 ml), BuLi (1.6M in hexane; 31.5 ml, 0.05 mol), and dry TMEDA (5.8 g, 0.05 mol) were introduced into a 500 ml flask under a dry N_2 stream at −70 °C and the resulting solution was stirred for 1 h at −20 °C. The mixture was cooled to −70 °C and a solution of 2-chloropyridine (**1**) (5.68 g, 0.05 mol) in THF (20 ml) was added dropwise and the mixture was stirred at −70 °C for 1 h. A solution of the appropriate electrophilic reagent (0.055 mol) in dry THF (25 ml) was then added dropwise and the mixture was kept for 1 or 3 h at −70 °C. A solution of water (2 ml) in THF (20 ml) acidified by a few drops of conc. hydrochloric acid was added to the mixture at −40 °C and then water (100 ml) was introduced at −10 °C. Extraction with Et_2O (3 × 150 ml), drying over anhydrous magnesium sulphate, and evaporation gave a crude product, which was then purified.

Metallation of 2-chloropyridine (**1**) according to Procedure I followed by reaction of pentan-3-one afforded a mixture of products (**3**) and (**5a**).

2-Butyl-6-chloro-2,5-dihydropyridine (**3**). Yield 5.7 g (66%), b.p. 60 °C (10 mmHg); this compound was difficult to purify in order to obtain an analytical sample because of its partial oxidation into 2-butyl-6-chloropyridine; δ_H(60 MHz; $CDCl_3$) 0.90 (7 H, m, $Me[CH_2]_2CH_2$), 1.40 (2 H, m, $Me[CH_2]_2CH_2$), 3.05 (2 H, m, 5-H_2), 4.30 (1 H, m, 2-H), and 5.7 (2 H, m, 3- and 4-H).

3-(2-chloropyridin-3-yl)pentan-3-ol (**5a**). Yield 1.3 g (13%), m.p. 91 °C (Found: C, 60.3; H, 7.1; N, 7.0. $C_{10}H_{14}ClNO$ requires C, 60.5; H, 7.1; N, 7.0%); ν_{max} 3 340 cm^{-1} (OH); δ_H(60 MHz; $CDCl_3$) 0.75 (6 H, t, *J* 7.3 Hz, $MeCH_2$), 1.85 (2 H, m, $MeCH_2$), 2.4 (2 H, m, $MeCH_2$), 2.9 (1 H, s, OH), 7.26 (1 H, dd, *J* 7.5 and 4.5 Hz, 5-H), and 8.25 (2 H, m, *J* 7.5, 4.5, and 2.5 Hz, 4- and 6-H).

Metallation of 2-chloropyridine (**1**) according to Procedure 1 without TMEDA, followed by reaction of TMSCl (6 g, 0.055 mol), afforded *6-butyl-2-oxo-1,2,3,6-tetrahydropyridine* (**4**), which was purified by distillation (4.1 g, 54%), b.p. 120 °C (0.2 mmHg) (Found: C, 70.3; H, 9.9; N, 9.2. $C_9H_{15}NO$ requires C, 70.6; H, 9.9; N, 9.1%); ν_{max} 3 400 (NH), 1 680 (C=O), and 1 660 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 0.90 (7 H, m, $Me[CH_2]_2CH_2$), 1.40 (2 H, m, $Me[CH_2]_2CH_2$), 2.90 (2 H, m, 3-H_2), 4.05 (1 H, m, 6-H), 5.75 (2 H, m, 4- and 5-H), and 7.85 (1 H, s, NH); δ_C(80 MHz; $CDCl_3$) 13.3 ($Me[CH_2]_3$), 22.2 ($Me[CH_2]_2CH_2$), 23.9 (C-5), 26.8 ($EtCH_2CH_2$), 35.9 ($MeCH_2[CH_2]_2$), 57.9 (C-2), 119.6 (C-4), 129.2 (C-3), and 158.8 (C-6).

Procedure II: Metallation of 2-Chloropyridine (**1**) *by Lithium Di-isopropylamide.*—Dry THF (250 ml) and BuLi (1.6M in hexane; 31.5 ml, 0.05 mol) were introduced into a 500 ml flask under a dry N_2 stream at −70 °C. A solution of dry DIA (5.05 g, 0.05 mol) in THF (25 ml) was added dropwise to the mixture at −70 °C. The mixture was then kept for 1 h at 0 °C. A solution of 2-chloropyridine (**1**) (5.68 g, 0.05 mol) in THF (25 ml) was added dropwise to the mixture at −70 °C and the mixture was stirred for 3 h at this temperature. The reaction procedure was then the same as described in Procedure I.

2-Chloro-3-deuteriopyridine (**5b**) by *Procedure II.* Electrophilic reagent was a commercial solution of DCl in D_2O; compound (**5b**) was purified by distillation (5.7 g, 47%), b.p. 30 °C (10 mmHg); δ_H(60 MHz; $CDCl_3$) 7.20 (1 H, dd, *J* 7 and 4.5 Hz, 5-H), 7.67 (1 H, dd, *J* 7 and 2 Hz, 4-H), and 8.37 (1 H, dd, *J* 4.5 and 2 Hz, 6-H).

2-Chloro-3-trimethylsilylpyridine (**5c**) *by Procedure II.* Electrophilic reagent was TMSCl (5.98 g, 0.055 mol); *compound* (**5c**) was purified by distillation (6.1 g, 66%), b.p. 117 °C (17 mmHg) (Found: C, 51.7; H, 6.5; N, 7.2. $C_8H_{12}ClNSi$ requires C, 51.7; H, 6.5; N, 7.5%); ν_{max} 1 550 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 0.40 (9 H, s, $SiMe_3$), 7.20 (1 H, dd, *J* 7 and 2 Hz, 5-H), 7.80 (1 H, dd, *J* 7 and 2 Hz, 4-H), and 8.35 (1 H, dd, *J* 5 and 2 Hz, 6-H).

2-Chloropyridine-3-carbaldehyde (**6**).[11a] Electrophilic reagent was HCO_2Et (Procedure II: 21%); product had b.p. 119 °C (30 mmHg) (lit.,[14a] m.p. < 50 °C) (Found: C, 50.6; H, 2.9; N, 9.7. Calc. for C_6H_4ClNO: C, 50.9; H, 2.9; N, 9.9%); ν_{max} 1 700 (C=O) and 1 590 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 7.42 (1 H, ddd,

J 7.5, 4.5, and 0.8 Hz, 5-H), 8.22 (1 H, dd, *J* 7.5 and 2 Hz, 4-H), 8.60 (1 H, dd, *J* 4.5 and 2 Hz, 6-H), and 10.41 (1 H, d, *J* 0.8 Hz, CHO).

General Procedure for the Synthesis of the Alcohols (**7**).—Metallation of 2-chloropyridine (**1**) was achieved according to Procedure II [after addition of the aldehyde (0.055 mol) the mixture was kept for 3 h at −70 °C].

1-(2-*Chloropyridin*-3-*yl*)*ethanol* (**7a**). Reagent was acetaldehyde (2.42 g, 0.055 mol). The *liquid alcohol* (**7a**) was purified by distillation (4.9 g, 62%), b.p. 119 °C (7 mmHg) (Found: C, 53.3; H, 5.2; N, 8.9. C_7H_8ClNO requires C, 53.3; H, 5.1; N, 8.9%); ν_{max} 3 360 (OH), and 1 580 and 1 560 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 1.45 (3 H, d, *J* 7 Hz, Me), 3.90 (1 H, s, OH), 5.15 (1 H, d, *J* 7 Hz, CH), 7.20 (1 H, dd, *J* 8 and 5 Hz, 5-H), 7.95 (1 H, dd, *J* 8 and 2 Hz, 4-H), and 8.15 (1 H, dd, *J* 5 and 2 Hz, 6-H).

(2-*Chloropyridin*-3-*yl*)*phenylmethanol* (**7b**).[4b] Reagent was benzaldehyde (5.84 g, 0.055 mol). The yellow liquid was purified by distillation to give alcohol (**7b**) (4.4 g, 40%), b.p. 160 °C (7 mmHg) (lit.,[4b] m.p. 90 °C) (Found: C, 65.5; H, 4.7; N, 6.4. Calc. for $C_{12}H_{10}ClNO$: C, 65.6; H, 4.6; N, 6.4%); ν_{max} 3 360 (OH) and 1 560 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 4.65 (1 H, s, OH), 6.05 (1 H, s, CH), 7.20 (6 H, m, 5-H and Ph), and 8.00 (2 H, m, 4- and 6-H).

(2-*Chloropyridin*-3-*yl*)-(2-*methoxyphenyl*)*methanol* (**7c**). Reagent was *o*-methoxybenzaldehyde (7.49 g, 0.055 mol). The alcohol was recrystallized from Et_2O to give *compound* (**7c**) as crystals (5.6 g, 45%), m.p. 124 °C (Found: C, 62.3; H, 4.9; N, 5.6. $C_{13}H_{12}ClNO_2$ requires C, 62.5; H, 4.8; N, 5.6%); ν_{max} 3 340 (OH), and 1 600, 1 590, 1 580, and 1 570 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.40 (1 H, d, *J* 4 Hz, OH), 3.85 (3 H, s, MeO), 6.35 (1 H, d, *J* 4 Hz, CH), 7.10 (5 H, m, 5-H and Ph), 7.90 (1 H, dd, *J* 7.5 and 2 Hz, 4-H), and 8.25 (1 H, dd, *J* 5 and 2 Hz, 6-H).

(2-*Chloropyridin*-3-*yl*)-(2′-*nitrophenyl*)*methanol* (**7d**). Reagent was *o*-nitrobenzaldehyde (8.3 g, 0.055 mol). The crude alcohol was purified by chromatography on silica gel with Et_2O–heptane (1:1) as eluant to afford pure *compound*, (**7d**) (3.9 g, 29%), m.p. 127 °C (Found: C, 54.0; H, 3.4; N, 10.2. $C_{12}H_9ClN_2O_3$ requires C, 54.4; H, 3.4; N, 10.6%); ν_{max} 3 230 (OH), and 1 580 and 1 530 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.6 (1 H, br s, OH), 6.53 (1 H, s, CH), 7.33 (4 H, m, 4′-, 5-, 5′-, and 6′-H), 7.90 (2 H, m, 3′- and 4-H), and 8.27 (1 H, dd, *J* 4.5 and 2 Hz, 6-H).

Bis-(2-*chloropyridin*-3-*yl*)*methanol* (**7e**). Reagent was 2-chloropyridine-3-carbaldehyde (**6**) (7.79 g, 0.055 mol). Recrystallization of the alcohol (**7e**) from diethyl ether gave *compound* (**7e**) as a salmon coloured solid (3.2 g, 25%), m.p. 189 °C [Found: C, 50.0; H, 3.55; N, 10.6. $C_{11}H_8Cl_2N_2O$ requires C, 51.8; H, 3.2; N, 11.0%; $(C_{11}H_8Cl_2N_2O)_2H_2O$ requires C, 50.0; H, 3.4; N, 10.6%); ν_{max} 3 140 (OH), and 1 575 and 1 565 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 6.15 (1 H, d, *J* 5 Hz, CH), 6.52 (1 H, d, *J* 5 Hz, OH), 7.42 (2 H, dd, *J* 7.5 and 4.5 Hz, 5- and 5′-H), 7.80 (2 H, dd, *J* 7.5 and 2 Hz, 4- and 4′-H), and 8.33 (2 H, dd, *J* 4.5 and 2 Hz, 6- and 6′-H).

(2-*Fluoropyridin*-3-*yl*)-(2′-*nitrophenyl*)*methanol* (**15**). The procedure for the metallation of 2-fluoropyridine has already been described.[7b] Reagent was *o*-nitrobenzaldehyde (8.3 g, 0.055 mol). The alcohol (**15**) was precipitated from EtOH–ice (9.8 g, 79%), m.p. < 50 °C (lit.,[7b] < 50 °C) (Found: C, 57.9; H, 4.0; N, 10.9. Calc. for $C_{12}H_9FN_2O_3$: C, 58.1; H, 3.7; N, 11.3%); ν_{max} 3 280 (OH) and 1 610, 1 590, and 1 530 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.35 (1 H, s, OH), 6.60 (1 H, s, CH), 7.20 (1 H, m, 5-H), and 7.85 (6 H, m, 4- and 6-H and C_6H_4).

General Procedures for the Oxidation of the Pyridyl Alcohols (**7**) *into the Pyridyl Ketones.* (**8**).—*Procedure III: oxidation by manganese dioxide in THF.* A solution of a pyridyl alcohol (0.01 mol) in dry THF (150 ml) was oxidized by active manganese dioxide (MnO_2)[12] (8.7 g, 0.1 mol). The reaction was monitored by IR spectroscopy. Filtration over asbestos, washing of the filter cake by THF, drying, and evaporating gave a crude pyridyl ketone which was then purified.

Procedure IV: oxidation by manganese dioxide in toluene. A solution of a pyridyl alcohol (0.01 mol) in dry toluene (150 ml) was oxidized by active MnO_2[12] (8.7 g, 0.1 mol) at reflux in a Dean–Stark apparatus. The reaction was monitored by measuring the amount of water formed and also by ^1H NMR spectroscopy of samples of the reaction mixture which was first filtered, washed with $CHCl_3$, and then evaporated. When the reaction was complete, the next operations were the same as in Procedure III.

Procedure V: oxidation by chromic anhydride in acetone. A solution of a pyridyl alcohol (0.05 mol) in dry acetone (150 ml) was introduced into a 500 ml flask under a dry N_2 stream. The mixture was cooled to −30 °C and pure, pulverized chromic anhydride (15 g, 0.15 mol) was slowly added. Then the reaction mixture was kept at room temperature for 3 h. Propan-2-ol (100 ml) was added, followed by aq. sodium hydrogen carbonate (to pH 8). After filtration, extraction with $CHCl_3$, drying, and evaporation, the crude pyridyl ketone was purified.

1-(2-*Chloropyridin*-3-*yl*)*ethanone* (**8a**). The crude *ketone* was purified by distillation (Procedure IV: 1.03 g, 66%; Procedure V: 7.39 g, 95%), b.p. 83 °C (1 mmHg) (Found: C, 54.0; H, 4.0; N, 9.1. C_7H_6ClNO requires C, 54.0; H, 3.9; N, 9.0%); ν_{max} 1 690 (C=O), 1 575 and 1 560 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 2.68 (3 H, s, Me), 7.34 (1 H, dd, *J* 7.5 and 5 Hz, 5-H), 7.91 (1 H, dd, *J* 7.5 and 2 Hz, 4-H), and 8.44 (1 H, dd, *J* 5 and 2 Hz, 6-H).

(2-*Chloropyridin*-3-*yl*)*phenylmethanone* (**8b**).[4b] Prepared by Procedure V (9.8 g, 90%) as a green viscous liquid (Found: C, 66.2; H, 3.8; N, 6.6. $C_{12}H_8ClNO$ requires C, 66.2; H, 3.7; N, 6.4%); ν_{max} 1 670 (C=O), and 1 575 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 7.6 (7 H, m, 4- and 5-H and Ph) and 8.55 (1 H, dd, *J* 4.5 and 2 Hz, 6-H).

(2-*Chloropyridin*-3-*yl*)-(2-*methoxyphenyl*)*methanone* (**8c**). Prepared by Procedure IV (2.0 g, 81%) as an *orange liquid*, b.p. 175 °C (Found: C, 63.1; H, 4.2; N, 5.8. $C_{13}H_{10}ClNO_2$ requires C, 63.0; H, 4.1; N, 5.7%); ν_{max} 1 650 (C=O), and 1 595 and 1 575 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.60 (3 H, s, OMe), 7.3 (7 H, m, 4- and 5-H and Ph), and 8.40 (1 H, dd, *J* 5 and 2 Hz, 6-H).

(2-*Chloropyridin*-3-*yl*)-(2-*nitrophenyl*)*methanone* (**8d**). Prepared by Procedure IV (2.4 g, 92%) as a *white solid* (Found: C, 54.7; H, 2.6; N, 10.5. $C_{12}H_7ClN_2O_3$ requires C, 54.9; H, 2.7; N, 10.7%); ν_{max} 1 685 (C=O), and 1 570, 1 560, and 1 525 cm^{-1} (C=C, C=N); δ_H(60 MHz, $CDCl_3$) 7.6 (6 H, m, 4- and 5-H and C_6H_4) and 8.35 (1 H, dd, *J* 4.5 and 2 Hz, 6-H).

Bis-(2-*chloropyridin*-3-*yl*)*methanone* (**8e**). Recrystallization from toluene gave a *white solid* (Procedure IV: 2.1 g, 81%), m.p. 112 °C (Found: C, 52.4; H, 2.65; N, 11.1. $C_{11}H_6Cl_2N_2O$ requires C, 52.2; H, 2.4; N, 11.1%); ν_{max} 1 675 (C=O), and 1 575 and 1 560 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 7.40 (2 H, dd, *J* 7.5 and 4.5 Hz, 5- and 5′-H), 7.97 (2 H, dd, *J* 7.5 and 2 Hz, 4- and 4′-H), and 8.53 (2 H, dd, *J* 4.5 and 2 Hz, 6- and 6′-H).

(2-*Fluoropyridin*-3-*yl*)-(2′-*nitrophenyl*)*methanone* (**16**). Recrystallization from EtOH–ice gave a *beige solid* (Procedure V: 8.6 g, 70%), m.p. < 50 °C (lit.,[7b] < 50 °C) (Found: C, 58.5; H, 2.8; N, 11.4. $C_{12}H_7FN_2O_2$ requires C, 58.5; H, 2.9; N, 11.4%); ν_{max} 1 680 (C=O), and 1 610, 1 580, and 1 530 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 7.50 (4 H, m, 3′-, 4′-, 5-, and 5′-H) and 8.35 (3 H, m, 4-, 6-, and 6′-H).

Nucleophilic Substitutions on 2-*Chloropyridine*-3-*carbaldehyde* (**6**) *and* 2-*Chloropyridinyl Ketones* (**8**).—*Procedure VI: substitution by a methoxy group.* A solution of the chloropyridyl ketone (0.05 mol) in methanol (20 ml) was added dropwise to a methanolic solution of sodium methoxide [Na (3.5 g, 0.15 mol),

solvent (50 ml)]. The reaction mixture was refluxed for 7 h, then cooled, hydrolysed, and extracted with Et_2O. After drying and evaporation the crude methoxylated pyridyl ketone was purified by distillation or recrystallization.

Procedure VII: substitution by an amino group. A mixture of chloropyridyl ketone and an excess of aq. ammonia was heated at 100 °C for 2 h. After cooling, yellow crystals sometimes appeared. If precipitation did not occur, the aqueous solution was extracted with $CHCl_3$; the organic layer was then evaporated.

2-*Methoxypyridine*-3-*carbaldehyde* (**9a**).[3] Chloro aldehyde (**6**) was refluxed with a 3-fold excess of sodium methoxide in methanol for 5.0 h. Evaporation to dryness, hydrolysis, extraction with Et_2O, and evaporation of the ethereal solution gave a crude liquid, which was then vacuum distillated to afford compound (**9a**) (yield 90%), b.p. 95 °C (16 mmHg) [lit.,[3] 105–110 °C (15 mmHg)] (Found: C, 61.1; H, 5.0; N, 10.1. Calc. for $C_7H_7NO_2$: C, 61.3; H, 5.1; N, 10.2%); ν_{max} 1 680 (C=O) and 1 580 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 4.05 (3 H, s, OMe), 6.99 (1 H, ddd, *J* 7.5, 5, and 0.8 Hz, 5-H), 8.10 (1 H, dd, *J* 7.5 and 2 Hz, 4-H), 8.38 (1 H, dd, *J* 5 and 2 Hz, 6-H), and 10.37 (1 H, d, *J* 0.8 Hz, CHO).

2-*Hydroxypyridine*-3-*carbaldehyde* (**9b**).[18] A mixture of chloro aldehyde (**6**) (5 g, 0.035 mol), hydrochloric acid (3M; 20 ml), and hydrogen peroxide (3%; 4 drops) was refluxed for 2 h. After cooling and neutralization with potassium carbonate, the solution was filtered. The yellow solid was purified by recrystallization (aq. EtOH) to give the title compound as a white solid (3.4 g, 80%), m.p. 224 °C (lit.,[14] 224 °C) (Found: C, 58.6; H, 4.4; N, 11.6. Calc. for $C_6H_5NO_2$: C, 58.5; H, 4.1; N, 11.4%); ν_{max} 1 675 (C=O), 1 640 (C=O pyridone), and 1 590 and 1 555 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 6.39 (1 H, td, *J* 7, 6.5, and 0.7 Hz, 5-H), 7.83 (1 H, dd, *J* 6.5 and 2.5 Hz, 6-H), 8.00 (1 H, dd, *J* 7 and 2.5 Hz, 4-H), and 10.10 (1 H, d, *J* 0.7 Hz, CHO). This compound has a pyridone structure.

1-(2-*Methoxypyridin*-3-*yl*)*ethanone* (**10a**). The crude *ketone* was purified by distillation (Procedure VI: 90%), b.p. 62 °C (9 mmHg) (Found: C, 63.8; H, 6.0; N, 9.2. $C_8H_9NO_2$ requires C, 63.6; H, 6.0; N, 9.3%); ν_{max} 1 650 (C=O), and 1 580 and 1 560 cm^{-1} (C=C, C=N); δ_H(60 MHz; CCl_4) 2.50 (3 H, s, Me), 4.03 (3 H, s, OMe), 6.90 (1 H, dd, *J* 7.5 and 5 Hz, 5-H), 8.08 (1 H, dd, *J* 7.5 and 2 Hz, 4-H), and 8.23 (1 H, dd, *J* 5 and 2 Hz, 6-H).

1-(2-*Hydroxypyridin*-3-*yl*)*ethanone* (**10b**).[19] A mixture of chloro ketone (**8a**) (5.2 g, 0.033 mol), hydrochloric acid (3M; 40 ml), and hydrogen peroxide (3%; 4 drops) was refluxed for 20 h. After cooling, neutralization with potassium carbonate, evaporation to dryness, and extraction with ethanol, the extract was filtered and evaporated. The pale yellow solid was purified by sublimation to give the title compound as a white solid (3.3 g, 72%), m.p. 162 °C (lit.,[19] 164 °C) (Found: C, 61.0; H, 4.8; N, 9.9. Calc. for $C_7H_6NO_2$: C, 61.3; H, 5.1; N, 10.2%); ν_{max} 1 670 (C=O), 1 640 (C=O pyridone), and 1 600 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 2.74 (3 H, s, Me), 6.43 (1 H, dd, *J* 7 and 6 Hz, 5-H), 7.65 (1 H, dd, *J* 6 and 2 Hz, 6-H), 8.20 (1 H, dd, *J* 7 and 2 Hz, 4-H), and 12.75 (1 H, m, NH). This compound has a pyridone structure.

1-(2-*Aminopyridin*-3-*yl*)*ethanone* (**10c**). Obtained as *yellow crystals* (Procedure VII: 90%), m.p. 136 °C (Found: C, 61.6; H, 5.7; N, 20.3. $C_7H_8N_2O$ requires C, 61.75; H, 5.9; N, 20.6%); ν_{max} 1 640 (C=O), and 1 610 and 1 540 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 2.55 (3 H, s, Me), 6.65 (1 H, dd, *J* 8 and 5 Hz, 5-H), 6.90 (2 H, s, NH_2), 8.00 (1 H, dd, *J* 8 and 2 Hz, 4-H), and 8.25 (1 H, dd, *J* 5 and 2 Hz, 6-H).

(2-*Aminopyridin*-3-*yl*)*phenylmethanone* (**10d**).[2] Obtained as yellow crystals (Procedure VII: 90%), m.p. 147 °C (lit.,[7b] 147 °C) (Found: C, 72.4; H, 5.1; N, 14.2. Calc. for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1%); ν_{max} 1 640 (C=O), and 1 620, 1 580, and 1 550 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 6.55 (1 H, dd, *J* 8 and 5 Hz, 5-H), 7.15 (2 H, s, NH_2), 7.50 (5 H, m, Ph), 7.70 (1 H, dd, *J* 8 and 2 Hz, 4-H), and 8.20 (1 H, dd, *J* 5 and 2 Hz, 6-H).

(2-*Aminopyridin*-3-*yl*)-(2-*methoxyphenyl*)*methanone* (**10e**). Obtained as *yellow crystals* from Et_2O–hexane (Procedure VII: 75%), m.p. 160 °C (Found: C, 68.4; H, 5.25; N, 12.3. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%); ν_{max} 1 630 (C=O), 1 600, 1 580, and 1 550 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.75 (3 H, s, OMe), 6.50 (1 H, dd, *J* 8 and 5 Hz, 5-H), 7.10 (4 H, m, C_6H_4), 7.50 (1 H, dd, *J* 8 and 2 Hz, 4-H), and 8.15 (1 H, dd, *J* 5 and 2 Hz, 6-H), and no signal for NH_2.

(2-*Methoxyphenyl*)-(2′-*methoxypyridin*-3′-*yl*)*methanone* (**10f**). Obtained as *white crystals* from $CHCl_3$–Et_2O (Procedure VI: 73%), m.p. 110 °C (Found: C, 68.9; H, 5.5; N, 5.6. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.8%); ν_{max} 1 640 (C=O), and 1 595 and 1 580 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.60 (3 H, s, 2-OMe), 3.80 (3 H, s, 2′-OMe), 7.2 (5 H, m, 5-H and C_6H_4), 7.80 (1 H, dd, *J* 7.5 and 2 Hz, 4-H), and 8.20 (1 H, dd, *J* 5 and 2 Hz, 6-H).

Bis-(2-*methoxypyridin*-3-*yl*)*methanone* (**10g**).[11a] Obtained as white crystals from Et_2O–hexane (Procedure VI: 74%), m.p. 82 °C (lit.,[11a] 82 °C) (Found: C, 63.9; H, 5.0; N, 11.8. Calc. for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 5.0; N, 11.5%); ν_{max} 1 650 (C=O), and 1 590 and 1 580 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.75 (6 H, s, OMe), 6.94 (2 H, dd, *J* 7.5 and 5 Hz, 5- and 5′-H), 7.90 (2 H, dd, *J* 7.5 and 2 Hz, 4- and 4′-H), and 8.25 (1 H, dd, *J* 5 and 2 Hz, 6- and 6′-H).

General Procedures for the Synthesis of 8-*Azacoumarins* (**12**).—*Procedure VIII: Knoevenagel–Doebner reaction. Procedure VIIIa: condensation reaction.* A mixture of *ortho*-substituted pyridine-3-carbaldehyde (0.01 mol), malonic acid (1.15 g, 0.011 mol), piperidine (0.8 ml), and pyridine (20 ml) was refluxed for 3 h. Evaporation of the amines gave a crude oil, which was crystallized from methanol (10 ml). The solid was filtered off and washed with Et_2O.

Procedure VIIIb: cyclization reaction. The above formed substituted propenoic acid was then treated for 20 min at 220 °C with pyridinium chloride (20 g) and the hot reaction mixture was poured onto ice. Extraction with $CHCl_3$, drying, and evaporation gave a crude solid, which was purified by sublimation.

Procedure IX: synthesis using modified Perkin reaction. A mixture of 2-hydroxypyridine-3-carbaldehyde (0.5 g, 0.004 mol), substituted phenylacetic acid (0.01 mol), triethylamine (0.6 g, 0.006 mol), and acetic anhydride (3.1 g, 0.03 mol) was refluxed for 4 h. After cooling, neutralization with conc. aq. ammonia, and filtration, the solid was then purified by recrystallization.

(E)-3-(2′-*Methoxypyridin*-3-*yl*)*prop*-2-*enoic acid* (**11a**). Prepared by Procedure VIIIa (78%): *white crystals* from EtOH–Et_2O, m.p. 191 °C (Found: C, 60.3; H, 5.4; N, 7.7. $C_9H_9NO_3$ requires C, 60.3; H, 5.1; N, 7.8%); ν_{max} 1 680 (C=O), and 1 620 and 1 580 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 3.97 (3 H, s, OMe), 6.63 (1 H, d, *J* 16 Hz, 2-H), 7.06 (1 H, dd, *J* 7.5 and 5 Hz, 5′-H), 7.73 (1 H, d, *J* 16 Hz, 3-H), 8.09 (1 H, dd, *J* 7.5 and 1.5 Hz, 4′-H), 8.23 (1 H, dd, *J* 5 and 1.5 Hz, 6′-H), and 9.22 (1 H, m, CO_2H).

(E)-3-(2′-*Hydroxypyridin*-3′-*yl*)*prop*-2-*enoic acid* (**11b**). Prepared by Procedure VIIIa (64%): white crystals from MeOH, m.p. >250 °C (Found: C, 58.5; H, 4.6; N, 8.7. $C_8H_7NO_3$ requires C, 58.2; H, 4.3; N, 8.5%); ν_{max} 1 670 (C=O) and 1 620 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 6.29 (1 H, dd, *J* 7 and 6.5 Hz, 5′-H), 6.98 (1 H, d, *J* 16 Hz, 2-H), 7.49 (1 H, dd, *J* 6.5 and 2 Hz, 6′-H), 7.53 (1 H, d, *J* 16 Hz, 3-H), and 7.84 (1 H, dd, *J* 7 and 2 Hz, 4′-H).

2-*Oxo*-2H-*pyrano*[2,3-b]*pyridine* (**12a**). Prepared by Procedure VIIIb [71% from (**11a**); 50% from (**11b**)], 8-*azacoumarin* had m.p. 135 °C (Found: C, 65.2; H, 3.6; N, 9.5. $C_8H_5NO_2$ requires C, 65.3; H, 3.4; N, 9.5%); ν_{max} 1 725 (C=O), and 1 630

and 1 600 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 6.52 (1 H, d, *J* 9.5 Hz, 3-H), 7.33 (1 H, dd, *J* 7.5 and 5 Hz, 6-H), 7.78 (1 H, d, *J* 9.5 Hz, 4-H), 7.97 (1 H, dd, *J* 7.5 and 2 Hz, 5-H), and 8.55 (1 H, dd, *J* 5 and 2 Hz, 7-H).

2-*Oxo*-3-*phenyl*-2H-*pyrano*[2,3-b]*pyridine* (**12b**). The brown solid was recrystallized from aq. EtOH (80:20) to give a *white solid* (Procedure IX: 80%), m.p. 202 °C (Found: C, 75.1; H, 4.3; N, 6.3. $C_{14}H_9NO_2$ requires C, 75.3; H, 4.1; N, 6.3%); ν_{max} 1 710 (C=O) and 1 590 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 7.40 (5 H, m, Ph), 7.77 (1 H, dd, *J* 7 and 4.5 Hz, 6-H), 8.29 (1 H, dd, *J* 7 and 2 Hz, 5-H), 8.30 (1 H, s, 4-H), and 8.54 (1 H, dd, *J* 4.5 and 2 Hz, 7-H).

3-(4′-*Fluorophenyl*)-2-*oxo*-2H-*pyrano*[2,3-b]*pyridine* (**12c**). The brown solid was recrystallized from MeOH to give a *white solid* (Procedure IX: 61%), m.p. 254 °C (Found: C, 69.7; H, 3.5; N, 5.6. $C_{14}H_8FNO_2$ requires C, 69.7; H, 3.3; N, 5.8%); ν_{max} 1 710 (C=O) and 1 600 cm^{-1} (C=C, C=N); δ_H(60 MHz; CF_3CO_2H) 7.17 (2 H, t, 3′- and 5′-H), 7.74 (2 H, dd, 2′- and 6′-H), 8.00 (1 H, dd, *J* 7.5 and 6 Hz, 6-H), 8.18 (1 H, s, 4-H), 8.71 (1 H, dd, *J* 6 and 1.8 Hz, 7-H), and 8.86 (1 H, dd, *J* 7.5 and 1.8 Hz, 5-H).

2-*Oxo*-3-(*pyridin*-4-*yl*)-2H-*pyrano*[2,3-b]*pyridine* (**12d**). The solid was recrystallized from EtOH–acetone to give a *white solid* (Procedure IX: 64%), m.p. 283 °C (Found: C, 69.7; H, 3.8; N, 12.3. $C_{13}H_8N_2O_2$ requires C, 69.6; H, 3.6; N, 12.5%); ν_{max}1 710 (C=O) and 1 600 cm^{-1} (C=C, C=N); δ_H(60 MHz; CF_3CO_2H) 8.05 (1 H, dd, *J* 7.5 and 5.5 Hz, 6-H) and 8.8 (7 H, m, other H).

2-*Oxo*-3-(3′,4′,5′-*trimethoxyphenyl*)-2H-*pyrano*[2,3-b]*pyridine* (**12e**). The brown solid was recrystallized from MeOH to give a *white solid* (Procedure IX: 61%), m.p. 164 °C (Found: C, 65.3; H, 5.1; N, 4.4. $C_{17}H_{15}NO_5$ requires C, 65.2; H, 4.8; N, 4.5%); ν_{max} 1 720 (C=O) and 1 580 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 3.90 (9 H, s, OMe), 6.35 (2 H, s, 2′- and 6′-H), 7.29 (1 H, dd, *J* 7.5 and 4.8 Hz, 6-H), 7.73 (1 H, s, 4-H), 7.98 (1 H, dd, *J* 7.5 and 2 Hz, 5-H), and 8.46 (1 H, dd, *J* 4.8 and 2 Hz, 7-H).

General Procedure for the Synthesis of Substituted Benzo[b][1,8]*naphthyridines* (**13**). *Procedure X.*—We used Friedlander's annelation under Fehnel's conditions. The aminopyridyl ketone (0.01 mol) was dissolved in a mixture of cyclohexanone (2 g, 0.02 mol) and acetic acid (10 ml), before addition of sulphuric acid (0.1 ml) and warming at reflux temperature during 4 h. The cold solution was poured on a mixture of conc. aq. ammonia (40 ml) and ice (20 g), which gave a brown tarry product. After extraction with $CHCl_3$, drying, evaporation and addition of Et_2O, the brown solid was purified by recrystallization or by chromatography on silica gel.

5-*Methyl*-6,7,8,9-*tetrahydrobenzo*[b][1,8]*naphthyridine* (**13a**). Purification by chromatography with Et_2O–EtOH (95:5) gave a beige powder (82%), m.p. 148 °C; ν_{max} 3 050, 3 030, 3 020, 2 930, 2 920, 2 860, 1 650, 1 595, 1 585, 1 545, 1 485, 1 450, and 1 425 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.90 (4 H, m, 7-H_2 and 8-H_2), 2.45 (3 H, s, Me), 2.80 (2 H, m, 6-H_2), 3.15 (2 H, m, 9-H_2), 7.30 (1 H, dd, *J* 9 and 4 Hz, 3-H), 8.20 (1 H, dd, *J* 9 and 2 Hz, 4-H), and 8.75 (1 H, dd, *J* 4 and 2 Hz, 2-H); *m*/*z* 198 (M^+, 100%).

5-*Phenyl*-6,7,8,9-*tetrahydrobenzo*[b][1,8]*naphthyridine* (**13b**). Purfication by chromatography with $CHCl_3$–EtOH (90:10) gave a beige powder (73%), m.p. 161 °C; ν_{max} 3 050, 3 020, 2 930, 2 850, 1 650, 1 625, 1 600, 1 575, 1 550, 1 495, 1 475, and 1 450 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 1.85 (4 H, m, *J* 6 Hz, 7-H_2, and *J* 6.5 Hz, 8-H_2), 2.60 (2 H, t, *J* 6 Hz, 6-H_2), 3.25 (2 H, t, *J* 6.5 Hz, 9-H_2), 8.0 (7 H, m, 4- and 5-H and Ph), and 8.90 (1 H, dd, *J* 4 and 2 Hz, 2-H); *m*/*z* 260 (M^+, 100%).

Synthesis of Azaxanthones (**14**)—5-*Oxo*-5H-*benzopyrano*[2,3-b]*pyridine* (**14a**).[4a] Reaction according Procedure VIIIb gave a white solid [from (**8c**) 92%; from (**10f**) 100%], m.p. 185 °C (lit.,[4a] 178–182 °C) (Found: C, 72.8; H, 3.8; N, 7.0. Calc. for $C_{12}H_7NO_2$: C, 73.1; H, 3.6; N, 7.1%); ν_{max} 1 660 (C=O), and 1 605 and 1 590 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 7.6 (4 H, m, 3-, 4-, 7-, and 8-H), 8.3 (1 H, ddd, 6- or 9-H), 8.7 (2 H, m, 2- and 9- or 6-H).

5-*Oxo*-5H-*pyrano*[2,3-b:6,5-b′]*dipyridine* (**14b**).[11a] Ketone (**8e**) was treated according to Procedure VIIIb to give compound (**14b**) as a white solid (78%), m.p. 240 °C (lit.,[11a] 240 °C) (Found: C, 66.3; H, 3.4; N, 14.0. Calc. for $C_{11}H_6N_2O_2$: C, 66.5; H, 3.1; N, 14.1%); ν_{max} 1 660 (C=O), and 1 610 and 1 590 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 7.57 (2 H, dd, *J* 7.5 and 4.5 Hz, 3- and 7-H), 8.52 (2 H, dd, *J* 7.5 and 2 Hz, 4- and 6-H), and 8.77 (2 H, dd, *J* 4.5 and 2 Hz, 2- and 8-H).

Synthesis of Aza-acridone.—(2-*Aminophenyl*)-(2′-*fluoropyridin*-3′-*yl*)*methanone* (**17**). Catalytic hydrogenation (20 °C; 1 atm) of a solution of compound (**16**) (1.6 g, 0.0065 mol) in MeOH (150 ml) was very fast with palladium (0.7 g) on activated carbon (10%). After filtration and washing of the catalyst, the methanolic solution was very cautiously evaporated to afford ketone (**17**); if the methanolic solution was evaporated to dryness, only the aza-acridone was isolated. Compound (**17**) showed ν_{max} 3 460 and 3 360 (NH_2), 1 640 (C=O), and 1 600 and 1 550 cm^{-1} (C=C, C=N); δ_H(60 MHz; $CDCl_3$) 5.00 (2 H, s, NH_2), 7.00 (4 H, m, 3-, 4-, 5-, and 5′-H), 7.90 (2 H, m, 4′- and 6-H), and 8.30 (1 H, ddd, 6′-H).

5-*Oxo*-5,10-*dihydrobenzo*[b][1,8]*naphthyridine* (**18**). Evaporation to dryness of the aforementioned methanolic solution of compound (**17**) gave the aza-acridone (**18**). Recrystallization from Et_2O–AcOEt and sublimation (0.5 mmHg) gave a white solid (1.3 g, 100%), m.p. 270 °C (lit.,[20] 278–279 °C) (Found: C, 73.4; H, 4.0; N, 14.0. Calc. for $C_{12}H_8N_2O$: C, 73.5; H, 4.1; N, 14.3%); ν_{max} 3 430 (NH_2), 1 650 (C=O), and 1 625, 1 595, 1 530, and 1 480 cm^{-1} (C=C, C=N); δ_H[60 MHz; $(CD_3)_2SO$] 7.20 (1 H, m, 9-H), 7.25 (1 H, dd, *J* 4.5 and 8 Hz, 3-H), 7.60 (2 H, m, *J* 8 Hz, 7- and 8-H), 8.15 (1 H, dd, *J* 8 Hz, 6-H), 8.55 (1 H, dd, *J* 8 and 2 Hz, 4-H), 8.70 (1 H, dd, *J* 4.5 and 2 Hz, 2-H), and 12.20 (1 H, s, NH).

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