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Synthesis of 3-(Trifluoromethyl)benzo[*c*][1,6]naphthyridines from Substituted 4*H*-Pyran-4-ones via 4-Amino-5-Aryl-2-(trifluoromethyl)pyridines

Vladimir I. Tyvorskii,[a,*] Denis N. Bobrov,[a] Oleg G. Kulinkovich,[a] Wim Aelterman[b] and Norbert De Kimpe[b]

[a]*Department of Organic Chemistry, Belarussian State University, Fr. Scorina Av., 4, 220050 Minsk, Belarus*
[b]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

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Abstract—The cyclization of acylated 4-amino-5-aryl-2-(trifluoromethyl)pyridines under the action of $P_2O_5/POCl_3$ smoothly afforded 3-(trifluoromethyl)benzo[*c*][1,6]naphthyridines in good yields. Intermediate aminopyridines were synthesized in a two-step sequence from the corresponding 4*H*-pyran-4-ones, which were prepared by reaction of 2-acetyl-2-aryloxiranes and 4-dimethylamino-3-(4-methoxyphenyl)-3-buten-2-one with ethyl trifluoroacetate under basic conditions. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Benzannelated [1,6]naphthyridines are currently of interest as structural units of naturally occurring compounds, e.g. the marine alkaloids aaptamines.[1] The bronchodilator drug *benafentrine* has been developed based on the derivatives of partially hydrogenated benzo[*c*][1,6]naphthyridines, which are phosphodiesterase III/IV inhibitors.[2] A number of compounds related to *benafentrine* have a potential application for the treatment of bronchial disorders, dermatoses[3] and thrombosis.[4] Screening of some benzo fused [1,6]naphthyridines also showed potent and often specific antimicrobial properties against the different bacterial strains tested.[5]

The parent benzo[*c*][1,6]naphthyridine was obtained in low yield by photocyclization of 4-(benzylideneamino)pyridine,[6] as well as through the more successful reaction of the corresponding *o*-chlorobenzylidene derivative with potassium amide.[5] Toward this end, photocyclization of 4-(1-cyclohexenylcarboxamido)pyridine was also employed as a key-step.[7] Suitable precursors of substituted benzo[*c*][1,6]naphthyridines can be 4-amino-3-arylpyridines, which still remain rather difficult to access, in contrast with the piperidine congeners.[4] Recently, in order to develop novel chiral catalysts, 3-arylated atropo-isomeric DMAP analogues have been synthesized via a palladium-catalyzed coupling reaction of 3-bromo-4-aminopyridines with arylboronic acids.[8]

Since perfluoroalkylated heterocyclic compounds have received considerable interest mainly because of specific biological activities, in this paper a convenient synthesis of new 4-amino-5-aryl-2-(trifluoromethyl)pyridines **9** and their transformation into 3-(trifluoromethyl)benzo[*c*][1,6]-naphthyridines **11** is disclosed.

Results and Discussion

As shown previously, the dehydration of hydroxydihydropyranone **3a** by the action of thionyl chloride in pyridine is a convenient method for the preparation of 5-phenyl-2-(trifluoromethyl)-4*H*-pyran-4-one (**7a**),[9] which can be used for the synthesis of 4-aminopyridine **9a**. Compound **3a** is formed from the condensation of 2-acetyl-2-phenyloxirane (**1a**) with ethyl trifluoroacetate through cyclization of the intermediate **2a**, occurring via highly regioselective three-membered ring cleavage at the terminal carbon atom.[10] In this reaction, side product **4a** was isolated by column chromatography in very low yield.

The same condensation of 4-(methoxyphenyl)-substituted oxirane **1b**, aimed at the preparation of pyranone **7b**, led to the furanone **4b** as the main reaction product in 44% yield, the desired hydroxydihydropyranone **3b** being obtained only in 11% yield. The predominant formation of

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* Corresponding author. Tel.: +375-0172265609; fax: +375-0172264998; e-mail: tyvorskii@chem.bsu.unibel.by

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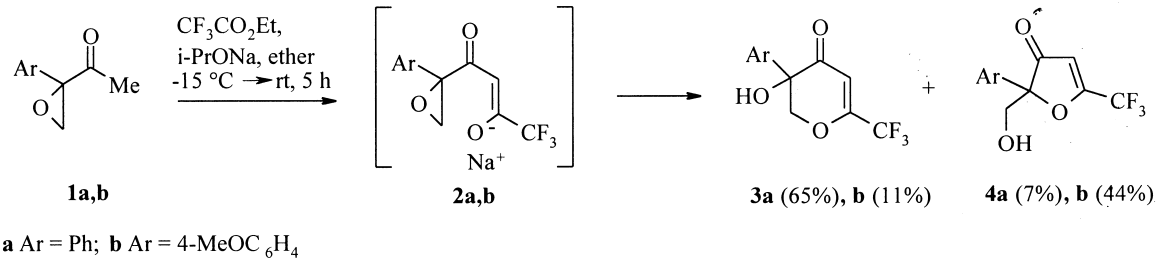


Scheme 1.

furanone **4b** can be attributed to the electron-donating effect of the 4-methoxyphenyl group, which promotes nucleophilic attack at the adjacent carbon atom of the oxirane ring through a borderline S_N2-like transition state (Scheme 1).[11]

As compared with pyranone **3b**, the ^{1}H NMR spectrum of furanone **4b** showed a specific coupling between the proton of the hydroxy group and the diastereotopic methylene protons, appearing as a set of two doublets of doublets at 4.03 (J=4.5, 12.0 Hz) and 4.18 (J=7.0, 12.0 Hz). In the presence of CF_3CO_2H, the signal for the CH_2 group of **4b** collapsed to a pair of doublets with the same geminal coupling constant of 12.0 Hz. In the IR spectrum of furanone **4b**, absorption of the conjugated carbonyl group is observed at 1725 cm^{-1} (cf. 1695 cm^{-1} for pyranone **3b**), which is typical for related 3(2*H*)-furanones.[12]

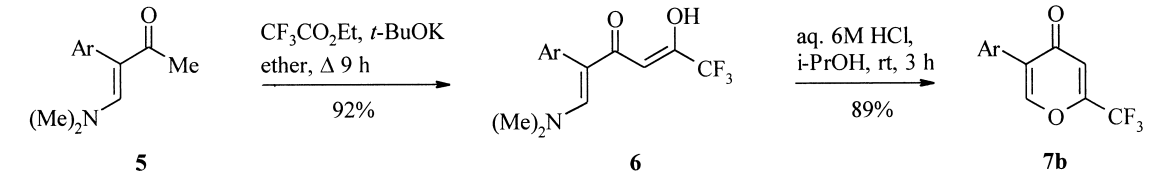
Since difficulties were encountered in the preparation of dihydropyranone **3b**, the alternative way to 5-(4-methoxyphenyl)substituted pyranone **7b** based on the readily available β-dimethylaminoenone **5** was employed (Scheme 2).[13]

Reaction of compound **5** with ethyl trifluoroacetate proceeded in the presence of potassium *tert*-butoxide to give enamino diketone **6** in 92% yield. The latter enaminone was subjected to a workup with aqueous 6 M HCl in *i*-PrOH solution, giving rise to cyclization to the target pyranone **7b** in 89% yield. Although this method for the preparation of compound **7b** is quite simple, the approach starting from acyloxiranes is more versatile and also allows the preparation of the corresponding alkyl substituted pyranones.[9] The structure of pyranone **7b** was confirmed by its spectral data that resemble those of the 5-phenyl analogue **7a**.[9]

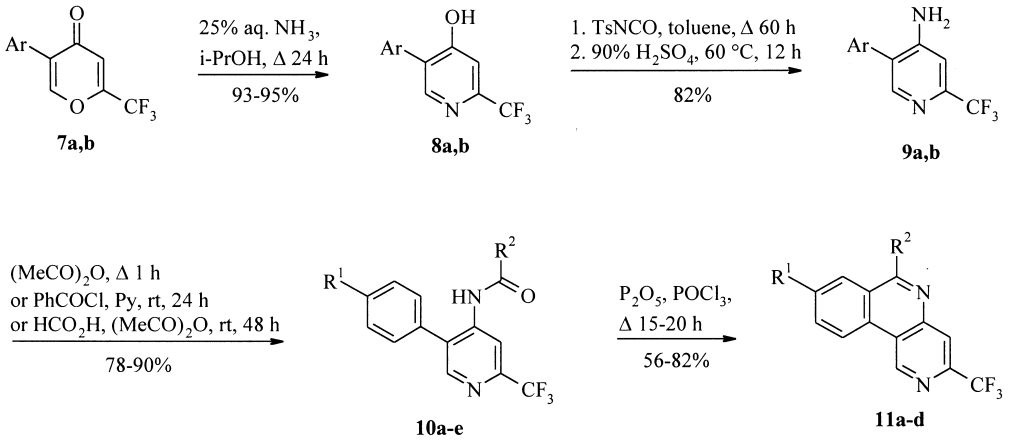
It is known that the three-step reaction involving amination of 4*H*-pyran-4-ones with tosyl isocyanate followed by the addition of ammonia and subsequent hydrolysis of the intermediate *p*-toluenesulfonamide with sulfuric acid provides an efficient and practical route to symmetrical 4-amino-2,6-disubstituted pyridines.[14] However, our attempts to prepare 2-(trifluoromethyl)-4-aminopyridines **9a**,**b** from pyranones **7a**,**b** using the above sequence failed completely. Due to the strong electron-withdrawing character of the trifluoromethyl group, impeding reactions of pyranones **7a**,**b** with electrophiles (such as TsNCO), the reported procedure[14] for the preparation of compounds **9a**,**b** was modified. The sequence applied is given in Scheme 3. Thus, 4-pyridinols **8a**,**b** were prepared in almost quantitative yield upon heating pyranones **7a**,**b** with aqueous ammonia in *i*-PrOH solution at reflux. Treatment of compounds **8a**,**b** with tosyl isocyanate in boiling toluene solution and successive hydrolysis of these reaction products with hot 90% H_2SO_4 led to the formation of the desired 4-aminopyridines **9a**,**b** in 82% overall yield.

The ^{1}H NMR spectra of 4-pyridinols **8a**,**b** and 4-aminopyridines **9a**,**b** showed the expected 0.18–0.68 ppm deshielding for protons 2-H and 5-H in comparison with the starting pyranones **7a**,**b**. In addition, the ^{13}C NMR spectrum of compound **8b** contains the signal due to a quaternary carbon at 162.09, which is consistent with a C-4 atom of 4-pyridinol **8b** rather than the tautomeric 4(1*H*)-pyridinone.[15] The almost complete absence of the carbonyl stretching band in the IR spectra of compounds **8a**,**b** suggests the predominance of the hydroxy tautomer.

With amines **9a**,**b** in hand, their acylated derivatives **10a**–**e** were prepared easily and subjected to a Pictet–Hubert cyclization. To our knowledge, such transformation of 3-aryl-4-(*N*-acylamino)pyridines (like **10**) has not been reported previously. After several initial failures to use $POCl_3$ as standard condensing agent, compounds **10a**–**d** were found to cyclize smoothly under the action of P_2O_5 in boiling $POCl_3$, affording the desired benzo[*c*][1,6]-naphthyridines **11a**–**d** in 56–82% yield (Scheme 3). Unfortunately, all attempts to convert the formyl derivative **10e** (R^2=H) in this reaction were unsuccessful.



Scheme 2.



Scheme 3.

The structural proof of benzonaphthyridines **11a**–**d** was supported by the spectral data and microanalytical results. Compounds **11a**–**d** all exhibit an intensive molecular ion signal (base peak usually) in the GS–MS analysis and have no appreciable $\nu_{C=O}$ absorption in the IR spectra in the 1695–1715 cm^{-1} region, which is typical for amides **10a**–**d**. The distinctive characteristic of the ^1H NMR spectra of **11a**–**d** is the extreme lowfield position of the signal for H-1, appearing as a sharp singlet at 9.87–10.08 in good agreement with the reported data for related systems.[5]

In conclusion, a convenient approach to 3-(trifluoromethyl)-benzo[*c*][1,6]naphthyridines via 4-amino-5-aryl-2-(trifluoromethyl)pyridines was developed, starting from the easily available 2-acetyl-2-(4-methoxyphenyl)oxirane and (*E*)-4-dimethylamino-3-(4-methoxyphenyl)-3-buten-2-one. Both the latter compounds were reacted with ethyl trifluoroacetate in order to prepare the corresponding 4*H*-pyran-4-ones as suitable precursors of the target aminopyridines.

Experimental

IR spectra were measured on a Specord 75 IR (CCl_4 or $CHCl_3$ solution) or a UR 20 (KBr) spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 and 50.3 MHz, respectively, with Me_4Si as the internal standard. Unless otherwise noted, NMR samples were dissolved in $CDCl_3$. Mass spectra were recorded on a Shimadzu QP-5000 GC/MS spectrometer. Melting points were determined in open capillaries and are uncorrected. Preparative column chromatography was carried out on silica gel L Chemapol (40–100 Mesh). All chemicals were reagent grade; solvents were dried and distilled prior to use. (*E*)-4-Dimethylamino-3-(4-methoxyphenyl)-3-butene-2-one (**5**) was synthesized by a known procedure.[13] 5-Phenyl-2-(trifluoromethyl)-4*H*-pyran-4-one (**7a**) was prepared by dehydration of 2,3-dihydro-3-hydroxy-3-phenyl-6-(trifluoromethyl)-4*H*-pyran-4-one (**3a**) as previously reported.[9]

2-Acetyl-2-(4-methoxyphenyl)oxirane (1b). It was synthesized from 2-(4-methoxyphenyl)-3-oxobutyl(trimethyl)-ammonium iodide[16] according to the procedure described previously for the preparation of **1a**.[17] **1b**: (51%), pale yellow oil; IR (CCl_4) 1720 cm^{-1}; ^1H NMR 2.19 (s, 3H), 3.05 and 3.27 (2×d, J=5.5 Hz, 2H), 3.81 (s, 3H), 6.90 and 7.39 (2×d, J=8.5 Hz, 4H). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.97; H, 6.48.

Condensation of acetyloxiranes 1a,b with ethyl trifluoroacetate

To a vigorously stirred suspension of sodium isopropoxide (1.3 g, 15.6 mmol) in dry ether (30 mL) was added dropwise a mixture of acetyloxirane **1a** or **1b** (7.8 mmol) and ethyl trifluoroacetate (1.9 mL, 15.6 mmol) at −15°C over a period of 30 min. The stirred reaction mixture was gradually warmed to ambient temperature over 5 h, then cooled to 0°C and quenched by careful addition of glacial acetic acid (0.9 mL, 15.6 mmol). The aqueous layer was separated and extracted with Et_2O (5 mL×5). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel using hexane–ether (1:11:2), providing subsequently pyranones **3a**,**b** and furanones **4a**,**b**.

2,3-Dihydro-3-hydroxy-3-phenyl-6-(trifluoromethyl)-4*H*-pyran-4-one (3a). (65%). This compound was identical in all aspects with a sample obtained formerly.[9]

2-(Hydroxymethyl)-2-phenyl-5-(trifluoromethyl)-3(2*H*)-furanone (4a). (7%), colourless oil; ^1H NMR 3.92 and 4.29 (2×d, J=12.5 Hz, 2H), 5.17 (br s, 1H), 5.95 (s, 1H), 7.12–7.56 (m, 5H). Anal. Calcd for $C_{12}H_9F_3O_3$: C, 55.82; H, 3.51. Found: C, 55.99; H, 3.68.

2,3-Dihydro-3-hydroxy-3-(4-methoxyphenyl)-6-(trifluoromethyl)-4*H*-pyran-4-one (3b). (11%), colourless oil; IR (CCl_4) 3505, 1695, 1640 cm^{-1}; ^1H NMR 3.76 (s, 3H), 4.47 and 4.91 (2×d, J=12.0 Hz, 2H), 4.57 (br s, 1H), 5.92 (s, 1H), 6.87 and 7.34 (2×d, J=8.5 Hz, 4H). ^{13}C NMR 55.25 (OCH_3), 72.35 (COH), 75.64 (CH_2O), (102.78 (s, $CH{=}CCF_3$)), 114.36 and 127.20 (HC_{ortho} and HC_{meta} or vice versa), 118.44 (q, J=275 Hz, CF_3), 129.33 (C_{quat}), 159.16 (q, J=38 Hz, CCF_3), 160.28 ($COCH_3$), 193.77

(C═O). EIMS (70 eV) *m/z* (rel. int.) 288 (M^+, 2), 151 (10), 150 ([4-$CH_3OC_6H_4COCH_3$]$^+$, 100), 135 (73), 108 (10), 92 (8), 78 (10), 77 (33), 69 (13), 43 (10). Anal. Calcd for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.32; H, 4.03.

2-(Hydroxymethyl)-2-(4-methoxyphenyl)-5-(trifluoromethyl)-3(2*H*)-furanone (4b). (44%), mp 88–89°C (CCl_4); IR (CCl_4) 3625, 1725, 1640 cm^{-1}; ^{1}H NMR 2.08 (m, 1H), 3.81 (s, 3H), 4.03 (d×d, *J*=12.0, 4.5 Hz, 1H), 4.18 (d×d, *J*=12.0, 7.0 Hz, 1H), 6.07 (s, 1H), 6.92 and 7.46 (2×d, *J*=9.0 Hz, 4H). ^{13}C NMR 55.34 (OCH_3), 67.07 (CH_2OH), 95.40 (*C*CH_2O), (106.16 (s, *C*H═CCF_3)), 114.34 and 126.11 (HC_{ortho} and HC_{meta} or vice versa), 118.03 (q, *J*=274 Hz, CF_3), 124.27 (C_{quat}), 160.25 (*C*OCH_3), 173.62 (q, *J*=41 Hz, *C*CF_3), 201.84 (C═O). EIMS (70 eV) *m/z* (rel. int.) 288 (M^+, 2), 259 (13), 258 ([M−CH_2O]$^+$, 100), 257 (30), 243 (28), 215 (12), 135 (41), 121 (12), 107 (7), 92 (12), 79 (6), 77 (35), 69 (14), 63 (11), 53 (10), 51 (11), 39 (10). Anal. Calcd for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.25; H, 3.98.

(*E*)-6-Dimethylamino-1,1,1-trifluoro-5-hydroxy-5-(4-methoxyphenyl)-5-hexene-2,4-dione (6). To a vigorously stirred suspension of potassium *tert*-butoxide (4.2 g, 37 mmol) in dry Et_2O (70 mL) was added dropwise a solution of enaminoketone **5** (4.1 g, 19 mmol) and ethyl trifluoroacetate (3.9 mL, 33 mmol) in 10 mL of dry Et_2O at 0°C over a period of 15 min. The reaction mixture was refluxed for 9 h, then cooled to 0°C and quenched by careful addition of glacial acetic acid (2.1 mL, 37 mmol) followed by water (10 mL). The aqueous layer was separated and extracted with Et_2O (10 mL×5). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was recrystallized to afford **6** as yellow-green needles (5.4 g, 92%), mp 118–119°C (hexane–EtOAc, 5:1); IR (CCl_4) 2530 (br), 1580 cm^{-1}; ^{1}H NMR 2.36–3.34 (m, 6H), 3.84 (s, 3H), 5.27 (s, 1H), 6.90 and 7.09 (2×d, *J*=8.5 Hz, 4H), 7.87 (s, 1H), 16.28 (br s, 1H). Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.11. Found: C, 57.25; H, 5.28.

5-(4-Methoxyphenyl)-2-(trifluoromethyl)-4*H*-pyran-4-one (7b). To a stirred suspension of diketone **6** (5.4 g, 17 mmol) in isopropyl alcohol (30 mL) was added 17 mL of 6 M HCl. After 3 h of stirring at room temperature the mixture was deluted with brine (250 mL) and, then, the solid was filtered off, washed with water and air-dried. Recrystallization afforded pyranone **7b** as colourless needles (4.1 g, 89%), mp 118–119°C (hexane–toluene, 2:1); IR (CCl_4) 1670, 1650 cm^{-1}; ^{1}H NMR 3.84 (s, 3H), 6.65 (s, 1H), 6.97 and 7.45 (2×d, *J*=8.5 Hz, 4H), 7.93 (s, 1H). ^{13}C NMR 55.33 (OCH_3), 114.19 and 129.90 (HC_{ortho} and HC_{meta} or vice versa), (115.43 (q, *J*=2.5 Hz, *C*H═CCF_3), 118.35 (q, *J*=274 Hz, CF_3), 121.94 and 130.52 (2×C_{quat}), 151.74 (*C*H═CAr)), 152.13 (q, *J*=40 Hz, *C*CF_3), 160.36 (*C*OCH_3), 176.19 (C═O). EIMS (70 eV) *m/z* (rel. int.) 271 (M^++1, 14), 270 (M^+, 100), 269 (26), 255 (10), 133 (9), 132 (74), 117 (32), 102 (7), 89 (50), 75 (12), 69 (17), 63 (26), 62 (10), 51 (16), 50 (11), 39 (14). Anal. Calcd for $C_{13}H_9F_3O_3$: C, 57.79; H, 3.36. Found: C, 57.95; H, 3.48.

Preparation of pyridinols 8a,b

To a solution of pyranone **7a** or **7b** (10 mmol) in *i*-PrOH (20 mL) was added 25% aqueous ammonia (1.1 mL, 15 mmol). The resulting solution was heated under reflux for 24 h. Then the reaction mixture was poured into 40 mL of water, and the precipitate was filtered off. Pyridinols **8a**,**b** were obtained as a white powder after recryctallization.

5-Phenyl-2-(trifluoromethyl)-4-pyridinol (8a). (95%), mp 238–239°C (toluene–*i*-PrOH, 3:1); IR (KBr) 3445 (br), 1650 (weak), 1615 (weak), 1540 cm^{-1}; ^{1}H NMR (DMSO-d_6) 7.37 (s, 1H), 7.41–7.67 (m, 5H), 8.54 (s, 1H), 11.71 (br s, 1H). EIMS (70 eV) *m/z* (rel. int.) 240 (M^++1, 17), 239 (M^+, 100), 238 (69), 218 (45), 168 (7), 115 (17), 110 (6), 89 (10), 77 (8), 69 (4), 63 (9), 51 (10), 50 (6), 39 (10). Anal. Calcd for $C_{12}H_8F_3NO$: C, 60.26; H, 3.37. Found: C, 60.32; H, 3.53.

5-(4-Methoxyphenyl)-2-(trifluoromethyl)-4-pyridinol (8b). (93%), mp 252–253°C (*i*-PrOH); IR (KBr) 3450 (br), 1650 (weak), 1615 (weak), 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6) 3.81 (s, 3H), 7.05 and 7.59 (2×d, *J*=8.0 Hz, 4H), 7.33 (s, 1H), 8.51 (s, 1H), 11.65 (br s, 1H). ^{13}C NMR (DMSO-d_6) 55.17 (OCH_3), (108.52 (s, *C*H═CCF_3)), 113.92 and 130.50 (HC_{ortho} and HC_{meta} or vice versa), 121.82 (q, *J*=274 Hz, CF_3), 126.05 and 126.79 (2×C_{quat}), 146.26 (q, *J*=33 Hz, *C*CF_3), 150.89 (*C*H═CAr), 159.29 (*C*OCH_3), 162.09 (C–OH). EIMS (70 eV) *m/z* (rel. int.) 270 (M^++1, 15), 269 (M^+, 100), 254 (20), 206 (30), 178 (9), 158 (5), 128 (8), 77 (6), 69 (3), 63 (6), 51 (7). Anal. Calcd for $C_{13}H_{10}F_3NO_2$: C, 58.00; H, 3.74. Found: C, 58.12; H, 3.97.

General procedure for the preparation of 4-aminopyridines 9a,b

To a suspension of 4-pyridinol **8a** or **8b** (10 mmol) in 30 mL of dry toluene was added tosyl isocyanate (3.5 mL, 23 mmol) in one portion and the reaction mixture was heated at reflux for 60 h. Then 90% sulphuric acid (4.0 mL) was added to the stirred solution, cooled to 0°C. The two-phase mixture was warmed at 60°C with stirring for 12 h. After cooling to 0°C, crushed ice (5 g) was added followed by 46% aqueous sodium hydroxide (9.5 mL). The precipitated sodium sulphate was then filtered off and washed thoroughly with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (10 mL×5), the combined organic phases being washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the resulting solid was recrystallized to obtain 4-aminopyridines **9a**,**b**.

4-Amino-5-phenyl-2-(trifluoromethyl)pyridine (9a). (82%), mp 93–94°C (cyclohexane–toluene, 1:1); IR (CCl_4) 3495, 3395, 1610 cm^{-1}; ^{1}H NMR 4.59 (br s, 2H), 6.99 (s, 1H), 7.33–7.58 (m, 5H), 8.26 (s, 1H). EIMS (70 eV) *m/z* (rel. int.) 239 (M^++1, 13), 238 (M^+, 100), 237 (52), 217 (50), 167 (7), 140 (9), 115 (11), 109 (11), 89 (8), 77 (8), 75 (6), 71 (8), 69 (6), 63 (9), 51 (11), 49 (7), 39 (12). Anal. Calcd for $C_{12}H_9F_3N_2$: C, 60.51; H, 3.81. Found: C, 60.62; H, 3.95.

4-Amino-5-(4-methoxyphenyl)-2-(trifluoromethyl)pyridine (9b). (82%), mp 101–102°C (cyclohexane–toluene, 1:1); IR (CCl_4) 3505, 3395, 1610 cm^{-1}; ^{1}H NMR 3.86 (s, 3H), 4.67 (br s, 2H), 6.98 (s, 1H), 7.03 and 7.34 (2×d,

J=8.5 Hz, 4H), 8.20 (s, 1H). ^{13}C NMR 55.35 (OCH_3), 106.06 (q, J=2.5 Hz, $CH{=}CCF_3$), 114.84 and 130.05 (HC_{ortho} and HC_{meta} or vice versa), 122.40 (q, J=274 Hz, CF_3), 124.16 and 126.50 (2×C_{quat}), 147.34 (q, J=33.5 Hz, CCF_3), 150.13 ($CH{=}CAr$), 151.96 ($C{-}NH_2$), 160.32 ($COCH_3$). EIMS (70 eV) m/z (rel. int.) 269 (M^++1, 15), 268 (M^+, 100), 253 (33), 249 (6), 205 (36), 178 (6), 155 (7), 128 (5), 102 (4), 89 (4), 77 (6), 69 (4), 63 (7), 51 (8), 39 (8). Anal. Calcd for $C_{13}H_{11}F_3N_2O$: C, 58.21; H, 4.13. Found: C, 58.43; H, 4.32.

Preparation of acetamides 10a,b

Compounds **10a**,**b** were obtained by treatment of aminopyridines **9a**,**b** (5 mmol) with acetic anhydride (3.3 mL, 35 mmol) at reflux for 1 h. Excess of anhydride was evaporated, and the residue was recrystallized to give colourless crystalline amides **10a**,**b**.

4-Acetamido-5-phenyl-2-(trifluoromethyl)pyridine (10a). (83%), mp 131.5–132.5°C (*i*-PrOH–cyclohexane, 2:1); IR (CCl_4) 3415, 1715 cm^{-1}; ^{1}H NMR 2.10 (s, 3H), 7.34–7.69 (m, 6H), 8.49 (s, 1H), 8.88 (s, 1H). Anal. Calcd for $C_{14}H_{11}F_3N_2O$: C, 60.00; H, 3.96. Found: C, 60.17; H, 4.09.

4-Acetamido-5-(4-methoxyphenyl)-2-(trifluoromethyl)-pyridine (10b). (78%), mp 170.5–171.5°C (*i*-PrOH); IR ($CHCl_3$) 3410, 1710 cm^{-1}; ^{1}H NMR 2.11 (s, 3H), 3.89 (s, 3H), 7.09 and 7.31 (2×d, J=8.5 Hz, 4H), 7.58 (br s, 1H), 8.46 (s, 1H), 8.84 (s, 1H). Anal. Calcd for $C_{15}H_{13}F_3N_2O_2$: C, 58.07; H, 4.22. Found: C, 58.21; H, 4.35.

Preparation of benzamides 10c,d

Benzoyl chloride (0.6 mL, 5.3 mmol) was added to a solution of amines **9a**,**b** (5 mmol) in 3 mL of pyridine, and the mixture was kept for 24 h at rt. After workup with 10 mL of water, recrystallization of the precipitated crude product afforded amides **10c**,**d**.

4-Benzamido-5-phenyl-2-(trifluoromethyl)pyridine (10c). (86%), mp 123.5–124.5°C (*i*-PrOH–toluene, 2:1); IR (CCl_4) 3425, 1700 cm^{-1}; ^{1}H NMR 7.39–7.71 (m, 10H), 8.38 (br s, 1H), 8.58 (s, 1H), 9.10 (s, 1H). Anal. Calcd for $C_{19}H_{13}F_3N_2O$: C, 66.67; H, 3.83. Found: C, 66.79; H, 3.68.

4-Benzamido-5-(4-methoxyphenyl)-2-(trifluoromethyl)-pyridine (10d). (85%), mp 138.5–139.0°C (*i*-PrOH); IR ($CHCl_3$) 3410, 1695 cm^{-1}; ^{1}H NMR 3.92 (s, 3H), 7.14 (d, J=8.5 Hz, 2H), 7.34–7.71 (m, 7H), 8.40 (br s, 1H), 8.54 (s, 1H), 9.06 (s, 1H). Anal. Calcd for $C_{20}H_{15}F_3N_2O_2$: C, 64.52; H, 4.06. Found: C, 64.75; H, 4.23.

4-Formamido-5-(4-methoxyphenyl)-2-(trifluoromethyl)-pyridine (10e). Compound **10e** was obtained from aminopyridine **9b** (1.3 g, 5 mmol) in dry THF (4 mL) under the action of a formylating mixture prepared from formic acid (0.9 mL, 23 mmol) and acetic anhydride (2.1 mL, 23 mmol). After standing for 48 h at rt the mixture was evaporated to dryness at reduced pressure. The residue was recrystallyzed to afford formamide **10e** (1.3 g, 90%), mp 161–162°C (*i*-PrOH); IR ($CHCl_3$) 3400, 1730 cm^{-1}; ^{1}H NMR 3.89 (s, 3H), 7.09 and 7.31 (2×d, J=8.5 Hz, 4H), 7.64 (br s, 1H), 8.44 (s, 1H), 8.50 (s, 1H), 8.86 (s, 1H). Anal. Calcd for $C_{14}H_{11}F_3N_2O_2$: C, 56.76; H, 3.74. Found: C, 56.94; H, 3.97.

General procedure for the cyclization of acylaminopyridines 10a–d

To a solution of amide **10a**–**d** (3 mmol) in 12 mL of $POCl_3$ was added P_2O_5 (3 g, 21 mmol). After heating for 15–20 h at reflux the excess of $POCl_3$ was distilled off at reduced pressure and the resulting mixture was cooled to 0°C and carefully quenched by the addition of crushed ice (5 g). The pH was adjusted to 10–11 with aqueous ammonia and the mixture was then extracted with CH_2Cl_2 (10 mL×5). The combined organic phases were washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the resulting solid was crystallized to obtain benzo-naphthyridines **11a**–**d**. Compounds **11a**,**b** were sublimated in vacuo (10 mmHg) prior to crystallization.

6-Methyl-3-(trifluoromethyl)benzo[*c*][1,6]naphthyridine (11a). (68%), mp 165.0–165.5°C (heptane–*i*-PrOH, 5:1); IR (CCl_4) 1615, 1585 cm^{-1}; ^{1}H NMR 3.11 (s, 3H), 7.82–7.90 (m, 1H), 7.96–8.04 (m, 1H), 8.30 (s, 1H), 8.32 (d, J=8.0 Hz, 1H), 8.76 (d, J=8.0 Hz, 1H), 9.95 (s, 1H). EIMS (70 eV) m/z (rel. int.) 263 (M^++1, 15), 262 (M^+, 100), 247 (5), 243 (4), 241 (6), 227 (4), 200 (4), 193 (7), 178 (1), 166 (3), 164 (3), 152 (3), 140 (3), 131 (5), 106 (4), 101 (3), 96 (2), 87 (2), 82 (2), 77 (3), 75 (6), 69 (8), 63 (5), 51 (5), 50 (4), 39 (5). Anal. Calcd for $C_{14}H_9F_3N_2$: C, 64.12; H, 3.46. Found: C, 64.34; H, 3.61.

8-Methoxy-6-methyl-3-(trifluoromethyl)benzo[*c*][1,6]-naphthyridine (11b). (71%), mp 205–206°C (EtOH–toluene, 2:1); IR ($CHCl_3$) 1630, 1585 cm^{-1}; ^{1}H NMR 3.07 (s, 3H), 4.04 (s, 3H), 7.56–7.66 (m, 2H), 8.27 (s, 1H), 8.66 (d, J=9.5 Hz, 1H), 9.87 (s, 1H). EIMS (70 eV) m/z (rel. int.) 293 (M^++1, 18), 292 (M^+, 100), 277 (8), 262 (7), 250 (9), 249 (62), 179 (10), 146 (9), 126 (2), 121 (3), 113 (2), 99 (2), 86 (3), 75 (4), 68 (4), 63 (5), 51 (3). Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79. Found: C, 61.83; H, 3.91.

6-Phenyl-3-(trifluoromethyl)benzo[*c*][1,6]naphthyridine (11c). (56%), mp 238.0–238.5°C (toluene); IR ($CHCl_3$) 1610, 1575, 1560 cm^{-1}; ^{1}H NMR 7.29–7.68 (m, 6H), 8.00–8.08 (m, 1H), 8.26 (d, J=8.0 Hz, 1H), 8.47 (s, 1H), 8.87 (d, J=8.0 Hz, 1H), 10.08 (s, 1H). EIMS (70 eV) m/z (rel. int.) 325 (M^++1, 8), 324 (M^+, 45), 323 (100), 283 (4), 254 (5), 253 (19), 226 (7), 202 (4), 200 (3), 152 (21), 138 (2), 126 (21), 113 (23), 101 (5), 100 (19), 94 (3), 88 (4), 87 (5), 77 (4), 75 (5), 74 (3), 69 (4), 51 (7). Anal. Calcd for $C_{19}H_{11}F_3N_2$: C, 70.37; H, 3.42. Found: C, 70.55; H, 3.60.

8-Methoxy-6-phenyl-3-(trifluoromethyl)benzo[*c*][1,6]-naphthyridine (11d). (82%), mp 217–218°C (toluene); IR (CCl_4) 1625, 1570 cm^{-1}; ^{1}H NMR 3.88 (s, 3H), 7.55–7.82 (m, 7H), 8.43 (s, 1H), 8.76 (d, J=9.0 Hz, 1H), 9.98 (s, 1H). EIMS (70 eV) m/z (rel. int.) 355 (M^++1, 21), 354 (M^+, 100), 353 (99), 340 (10), 339 (48), 338 (27), 335 (7), 324 (20), 311 (16), 310 (38), 290 (8), 269 (7), 253 (10), 241 (10), 214 (13), 188 (5), 176 (7), 170 (15), 167 (6), 160 (28), 155 (13), 145 (21), 135 (6), 130 (13), 127 (7), 120 (18), 113 (14), 107 (20), 100 (10), 93 (10), 87 (6), 69 (5), 63 (7), 51 (8).

Anal. Calcd for $C_{20}H_{13}F_3N_2O$: C, 67.80; H, 3.70. Found: C, 67.98; H, 3.93.

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