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Synthesis of novel 2,7-disubstituted-3-amino-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidines★

B. Narsaiah, A. Sivaprasad, R.V. Venkataratnam*

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract

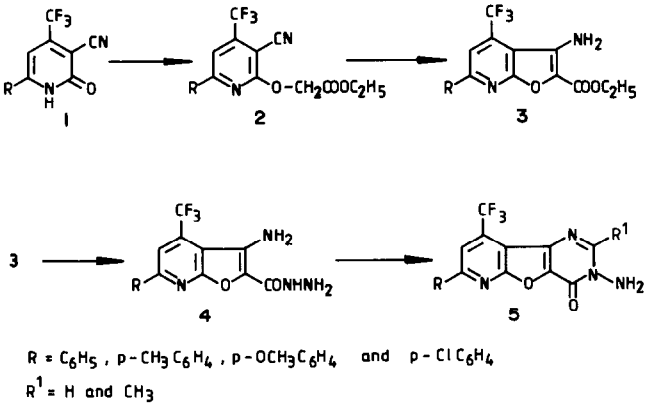
Synthesis of novel 2,7-disubstituted-3-amino-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidines (**5**) from 3-cyano-4-trifluoromethyl-6-substituted 2(1*H*)–pyridones (**1**) via a series of new intermediates such as 2-*O*-ethylacetoxy-3-cyano-4-trifluoromethyl-6-substituted pyridines (**2**), 2-carbethoxy-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-*b*]-pyridines (**3**) and 2-carbohydrazide-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-*b*]-pyridines (**4**) have been described.

Keywords: Synthesis; Substituted pyrido furopyrimidines; Substituted pyridones; Substituted furopyridines; NMR spectroscopy; IR spectroscopy; Mass spectrometry

1. Introduction

Pyrimidines are very important heterocyclic compounds, because of their biological activity. The fluorinated pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidines are considered to be active compounds owing to their enhanced lipophilic nature.

This report is in continuation of our earlier work on the preparation of fluoropyridines [1]. These compounds have been utilized to give new pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidines as shown in Scheme 1.



Scheme 1.

2. Experimental details

2.1. General

Melting points were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz) spectrometer and TMS was used as internal standard. IR spectra were recorded on a Pye- Unicam SP3-200 infrared spectrophotometer. Mass spectra were recorded on a VG-micromass 7070H instrument at 70 eV. Elemental analyses were carried on a Perkin-Elmer 240B instrument.

2.2. Starting materials

The 3-cyano-4-trifluoromethyl-6-substituted-2(1*H*)-pyridones were prepared by a known [1] procedure and all other reagents were obtained from commercial sources.

2.3. 2-*O*-ethylacetoxy-3-cyano-4-trifluoromethyl-6-substituted pyridines (2a–d): general procedure

The 3-cyano-4-trifluoromethyl-6-substituted 2(1*H*)-pyridones (2.6 mmol) were dissolved in dry acetone (50 ml). To the solution was added ethyl bromoacetate

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*Corresponding author.

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(2.6 mmol), potassium carbonate (5.3 mmol) and sodium iodide (0.010 g). The reaction mixture was refluxed for 4 h at 60 °C and cooled to room temperature. The separated salt was filtered off and washed with acetone (20 ml). The total filtrate was concentrated under vacuum and the resultant white residue washed with n-hexane followed by water. The white solid which separated was filtered and dried to obtain good yields of product in pure form.

2-*O*-Ethylacetoxy-3-cyano-4-trifluoromethyl-6-phenylpyridine (**2a**): ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 3H, CH_3); 4.28 (q, 2H, CH_2); 5.12 (s, 2H, OCH_2); 7.75 (s, 1H, H–C(5)); 7.54 (m, 3H, aromatic H); 8.01 (m, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}) 2220; 1740; 1580; 1560; 1130. MS *m/z*: 350(M^+); 305 ($M^+ - OC_2H_5$); 277 (305-CO) (base peak); 248 (277–CHO); 179 (248 – CF_3). Analysis: Calc. for $C_{17}H_{13}F_3N_2O_3$: C, 58.29; H, 3.74; N, 7.99%. Found: C, 58.12; H, 3.70; N, 7.91%.

2-*O*-Ethylacetoxy-3-cyano-4-trifluoromethyl-6-*p*-tolylpyridine (**2b**): ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3H, CH_3); 2.48 (s, 3H, CH_3); 4.29 (q, 2H, CH_2); 5.11 (s, 2H, OCH_2); 7.72 (s, 1H, H–C(5)); 7.32 (d, 2H, aromatic H); 7.92 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 2225; 1735; 1580; 1560; 1130. MS *m/z*: 364 (M^+) (base peak); 349 ($M^+ - CH_3$); 345 ($M^+ - F$); 319 ($M^+ - OC_2H_5$); 291 (319–CO); 262 (291–CHO); 193 (262 – CF_3). Analysis: Calc. for $C_{18}H_{15}F_3N_2O_3$: C, 59.34; H, 4.15; N, 7.69%. Found: C, 59.21; H, 4.01; N, 7.58%.

2-*O*-Ethylacetoxy-3-cyano-4-trifluoromethyl-6-*p*-anisylpyridine (**2c**): ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 3H, CH_3); 3.80 (s, 3H, OCH_3); 4.18 (q, 2H, CH_2); 4.98 (s, 2H, OCH_2); 6.90 (d, 2H, aromatic H); 7.55 (s, 1H, H–C(5)); 7.88 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 2220; 1735; 1575; 1560; 1135. MS *m/z*: 380 (M^+) (base peak); 365 ($M^+ - CH_3$); 361 ($M^+ - F$); 335 ($M^+ - OC_2H_5$); 307 (335–CO); 278 (307–CHO). Analysis: Calc. for $C_{18}H_{15}F_3N_2O_3$: C, 56.84; H, 3.97; N, 7.36%. Found: C, 56.80; H, 3.86; N, 7.24%.

2-*O*-Ethylacetoxy-3-cyano-4-trifluoromethyl-6-*p*-chlorophenylpyridine (**2d**): ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H, CH_3); 4.22 (q, 2H, CH_2); 5.06 (s, 2H, OCH_2); 7.43 (d, 2H, aromatic H); 7.68 (s, 1H, H–C(5)); 7.91 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 2225; 1730; 1570; 1560; 1135. MS *m/z*: 384 (M^+) (base peak); 356 ($M^+ - C_2H_4$); 312 (356 – CO_2); 282 ($M^+ - OC_2H_5$, CO and CHO); 247 (282–Cl); 228 (247–F); 213. Analysis: Calc. for $C_{17}H_{12}ClF_3N_2O_3$: C, 53.07; H, 3.14; N, 7.28%. Found: C, 52.91; H, 3.01; N, 7.15%.

2.4. 2-Carbethoxy-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-b]-pyridines (3a–d): general procedure

The 2-*O*-ethylacetoxy-3-cyano-4-trifluoromethyl-6-substituted pyridine (1 mmol) was dissolved in dry *N,N*-dimethylformamide (6 ml) and potassium carbonate (2 mmol) was added. The reaction mixture was heated for 3 h with stirring, maintaining the temperature at 110–120 °C. After cooling, it was poured into crushed ice. The separated solid product was filtered, washed with water and dried. The product was purified by passing over neutral alumina in chloroform.

2-Carbethoxy-3-amino-4-trifluoromethyl-6-phenylfuro-[2,3-*b*]-pyridine (**3a**): ^{1}H NMR ($CDCl_3$) δ: 1.43 (t, 3H, CH_3); 4.35 (q, 2H, CH_2); 5.18 (s, 2H, NH_2); 7.40 (m, 3H, aromatic H); 7.83 (s, 1H, H–C(5)); 8.02 (m, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3480; 3360; 1670; 1620; 1135. MS *m/z*: 350 (M^+) (base peak); 331 ($M^+ - F$); 322 ($M^+ - C_2H_4$); 305 ($M^+ - OC_2H_5$); 277 (305–CO); 248 (277–CHO); 179 (248 – CF_3). Analysis: Calc. for $C_{17}H_{13}F_3N_2O_3$: C, 58.29; H, 3.74; N, 7.99%. Found: C, 58.10; H, 3.43; N, 7.72%.

2-Carbethoxy-3-amino-4-trifluoromethyl-6-*p*-tolylfuro-[2,3-*b*]-pyridine (**3b**): ^{1}H NMR ($CDCl_3$) δ: 1.47 (t, 3H, CH_3); 2.45 (s, 3H, CH_3); 4.46 (q, 2H, CH_2); 5.30 (s, 2H, NH_2); 7.29 (d, 2H, aromatic H); 7.91 (s, 1H, H–C(5)); 8.05 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3470; 3360; 1665; 1610; 1140. MS *m/z*: 364 (M^+) (base peak); 345 ($M^+ - F$); 336 ($M^+ - C_2H_4$); 319 ($M^+ - OC_2H_5$); 291 (319–CO); 278; 193. Analysis: Calc. for $C_{18}H_{15}F_3N_2O_3$: C, 59.34; H, 4.15; N, 7.69%. Found: C, 59.12; H, 4.08; N, 7.51%.

2-Carbethoxy-3-amino-4-trifluoromethyl-6-*p*-anisylfuro-[2,3-*b*]-pyridine (**3c**): ^{1}H NMR ($CDCl_3$) δ: 1.46 (t, 3H, CH_3); 3.88 (t, 3H, CH_3); 4.45 (q, 2H, CH_2); 5.30 (s, 2H, NH_2); 6.98 (d, 2H, aromatic H); 7.87 (s, 1H, H–C(5)); 8.10 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3490; 3360; 1665; 1590; 1125. MS *m/z*: 380 (M^+) (base peak); 352 ($M^+ - C_2H_5$); 308 (352 – CO_2); 277 (308 – OCH_3); 263; 209 ($M^+ - OC_2H_5$, F and *p*-$OCH_3C_6H_4$); 69 (CF_3). Analysis: Calc. for $C_{18}H_{15}F_3N_2O_4$: C, 56.84; H, 3.97; N, 7.36%. Found: C, 56.81; H, 3.95; N, 7.32%.

2-Carbethoxy-3-amino-4-trifluoromethyl-6-*p*-chlorophenylfuro-[2,3-*b*]-pyridine (**3d**): ^{1}H NMR ($CDCl_3$) δ: 1.37 (t, 3H, CH_3); 4.40 (q, 2H, CH_2); 5.27 (s, 2H, NH_2); 7.42 (d, 2H, aromatic H); 7.86 (s, 1H, H–C(5)); 8.02 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3500; 3370; 1670; 1620; 1130. MS *m/z*: 384 (M^+) (base peak); 356 ($M^+ - C_2H_4$); 312 (356 – CO_2); 282 ($M^+ - OC_2H_5$, CO and CHO); 247 (282–Cl); 228 (247–F); 213 (228–NH). Analysis: Calc. for $C_{17}H_{12}ClF_3N_2O_3$: C, 53.07; H, 3.14; N, 7.28%. Found: C, 53.12; H, 3.12; N, 7.23%.

2.5. 2-Carbohydrazide-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-b]-pyridines (4a–d): general procedure

The 2-carbethoxy-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-*b*]-pyridine (3 mmol) was taken in 95% ethanol (30 ml) and hydrazine hydrate (5 ml) was added. The mixture was refluxed for 2 h and after

cooling to room temperature the ethanol was removed under vacuum. The residue was washed with n-hexane and then water was added to give a yellow solid which was filtered, washed with water and dried.

2-Carbohydrazide-3-amino-4-trifluoromethyl-6-phenylfuro-[2,3-*b*]-pyridine (**4a**): ^{1}H NMR (DMSO-d_6) δ: 4.1 (br., s, 2H, N−NH_2); 5.38 (s, 2H, C−NH_2); 7.51 (m, 3H, aromatic H); 7.7 (s, 1H, CONH); 7.95 (s, 1H, H−C(5)); 8.10 (m, 2H, aromatic H) ppm. IR (KBr) (cm^{-1}): 3440; 3365; 1625; 1360; 1135. MS *m/z*: 336 (M^+); 305 ($M^+ - NHNH_2$) (base peak); 277 (305 − CO); 228 (305 − C_6H_5); 202; 179 (277 − CHO, CF_3); 77 (C_6H_5). Analysis: Calc. for $C_{15}H_{11}F_3N_4O_2$: C, 53.57; H, 3.29; N, 16.66%. Found: C, 53.40; H, 3.26; N, 16.10%.

2-Carbohydrazide-3-amino-4-trifluoromethyl-6-*p*-tolylfuro-[2,3-*b*]-pyridine (**4b**): ^{1}H NMR (DMSO-d_6) δ: 2.43 (s, 3H, CH_3); 4.05 (br., s, 2H, N−NH_2); 5.35 (s, 2H, C−NH_2); 7.32 (s, 2H, aromatic H); 7.05 (s, 1H, CONH); 7.89 (s, 1H, H−C(5)); 8.01 (d, 2H, aromatic H) ppm. IR (KBr) (cm^{-1}): 3435; 3360; 1620; 1370; 1140. MS *m/z*: 350 (M^+); 319 ($M^+ - NHNH_2$) (base peak); 291 (319 − CO); 228 (319-*p*-$CH_3C_6H_4$). Analysis: Calc. for $C_{16}H_{13}F_3N_4O_2$: C, 54.86; H, 3.74; N, 15.99%. Found: C, 54.72; H, 3.69; N, 15.97%.

2-Carbohydrazide-3-amino-4-trifluoromethyl-6-*p*-anisylfuro-[2,3-*b*]-pyridine (**4c**): ^{1}H NMR (DMSO-d_6) δ: 3.82 (s, 3H, OCH_3); 4.11 (br., s, 2H, N−NH_2); 5.41 (s, 2H, C−NH_2); 7.35 (d, 2H, aromatic H); 7.30 (s, 1H, CONH); 7.92 (s, 1H, H−C(5)); 8.12 (d, 2H, aromatic H) ppm. IR (KBr) (cm^{-1}): 3430; 3350; 1615; 1370; 1135. MS *m/z*: 366 (M^+); 335 ($M^+ - NHNH_2$) (base peak); 307 (335 − CO); 228 (335-*p*-$OCH_3C_6H_4$). Analysis: Calc. for $C_{16}H_{13}F_3N_4O_3$: C, 52.46; H, 3.57; N, 15.20%. Found: C, 52.31; H, 3.46; N, 15.13%.

2-Carbohydrazide-3-amino-4-trifluoromethyl-6-*p*-chlorophenylfuro-[2,3-*b*]-pyridine (**4d**): ^{1}H NMR (DMSO-d_6) δ: 4.55 (br., s, 2H, N−NH_2); 5.57 (s, 2H, C−NH_2); 7.6 (d, 2H, aromatic H); 8.25 (d, 2H, aromatic H); 8.3 (s, 1H, H−C(5)); 9.8 (s, 1H, CONH) ppm. IR (KBr) (cm^{-1}): 3440; 3390; 1615; 1350; 1120. MS *m/z*: 370 (M^+); 339 ($M^+ - NHNH_2$) (base peak); 311 (339 − CO); 228 (339-*p*-ClC_6H_4). Analysis: Calc. for $C_{15}H_{10}ClF_3N_4O_2$: C, 48.60; H, 2.72; N, 15.11%. Found: C, 48.52; H, 2.67; N, 15.06%.

2.6. 2,7-Disubstituted-3-amino-9-trifluoromethyl-4-oxo-4H-pyrido-[3′,2′:4,5]-furo-[3,2-d]-(1,3)-pyrimidines (5a–h): general procedure

The 2-carbohydrazide-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-*b*]-pyridine (5 mmol) was taken in toluene (10 ml), and triethyl orthoformate or orthoacetate (5 mmol) and acetic acid (0.2 ml) added. The reaction mixture was refluxed for 3 h, cooled to room temperature and concentrated under vacuum to remove the toluene. n-Hexane was added to the residue; as a result a solid separated which was filtered, washed with n-hexane and dried.

3-Amino-7-phenyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5a**): ^{1}H NMR ($CDCl_3$) δ: 5.32 (br., s, 2H, NH_2); 7.52 (m, 3H, aromatic H); 7.91 (s, 1H, H−C(8)); 8.15 (m, 2H, aromatic H); 8.28 (s, 1H, H−C(2)) ppm. IR ($CHCl_3$) (cm^{-1}): 3435; 3340; 1615; 1350; 1125. MS *m/z*: 346 (M^+) (base peak); 331 ($M^+ - NH$); 316 ($M^+ - (N-NH_2)$); 277 ($M^+ - CF_3$). Analysis: Calc. for $C_{16}H_9F_3N_4O_2$: C, 55.50; H, 2.62; N, 16.18%. Found: C, 55.39; H, 2.51; N, 16.03%.

3-Amino-7-*p*-tolyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5b**): ^{1}H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3); 5.30 (br., s, 2H, NH_2); 7.40 (d, 2H, aromatic H); 7.86 (s, 1H, H−C(8)); 8.05 (d, 2H, aromatic H); 8.23 (s, 1H, H−C(2)) ppm. IR ($CHCl_3$) (cm^{-1}): 3430; 3335; 1615; 1345; 1130. MS *m/z*: 360 (M^+) (base peak); 345 ($M^+ - NH$); 318 (345 − HCN); 291 ($M^+ - CF_3$); 91(*p*-$CH_3C_6H_4$). Analysis: Calc. for $C_{17}H_{11}F_3N_4O_2$: C, 56.67; H, 3.07; N, 15.55%. Found: C, 56.56; H, 3.02; N, 15.51%.

3-Amino-7-*p*-anisyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5c**): ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H, OCH_3); 5.36 (br., s, 2H, NH_2); 7.46 (d, 2H, aromatic H); 7.83 (s, 1H, H−C(8)); 7.97 (d, 2H, aromatic H); 8.20 (s, 1H, H−C(2)) ppm. IR ($CHCl_3$) (cm^{-1}): 3430; 3340; 1620; 1345; 1135. MS *m/z*: 376 (M^+) (base peak); 345 ($M^+ - (N-NH_2)$); 307 ($M^+ - CF_3$); 69 (CF_3). Analysis: Calc. for $C_{17}H_{11}F_3N_4O_3$: C, 54.26; H, 2.94; N, 14.89%. Found: C, 54.21; H, 2.81; N, 14.82%.

3-Amino-7-*p*-chlorophenyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5d**): ^{1}H NMR ($CDCl_3$) δ: 5.35 (br., s, 2H, NH_2); 7.56 (d, 2H, aromatic H); 7.97 (s, 1H, H−C(8)); 8.12 (d, 2H, aromatic H); 8.25 (s, 1H, H−C(2)) ppm. IR ($CHCl_3$) (cm^{-1}): 3440; 3340; 1615; 1350; 1120. MS *m/z*/: 380 (M^+); 345 ($M^+ - Cl$); 311 ($M^+ - CF_3$); 69 (CF_3) (base peak). Analysis: Calc. for $C_{16}H_8ClF_3N_4O_2$: C, 50.48; H, 2.12; N, 14.71%. Found: C, 50.37; H, 1.98; N, 14.52%.

2-Methyl-3-amino-7-phenyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-(3,2-*d*]-(1,3)-pyrimidine (**5e**): ^{1}H NMR ($CDCl_3$) δ: 2.62 (s, 3H, CH_3); 5.18 (br., s, 2H, NH_2); 7.45 (m, 3H, aromatic H); 7.92 (s, 1H, H−C(8)); 8.19 (m, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3450; 3360; 1630; 1580; 1370; 1135. MS *m/z*: 360 (M^+) (base peak); 341 ($M^+ - F$); 315 ($M^+ - (N-NH_2$ and $CH_3)$); 289 (315 − CN); 261 (289 − CO); 179; 77. Analysis: Calc. for $C_{17}H_{11}F_3N_4O_2$: C, 56.67; H, 3.07; N, 15.55%. Found: C, 56.40; H, 3.03; N, 15.48%.

2-Methyl-3-amino-7-*p*-tolyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5f**): ^{1}H NMR ($CDCl_3$) δ: 2.45 (s, 3H, CH_3); 2.69 (s, 3H, CH_3); 5.20 (br., s, 2H, NH_2); 7.35 (d, 2H, aromatic

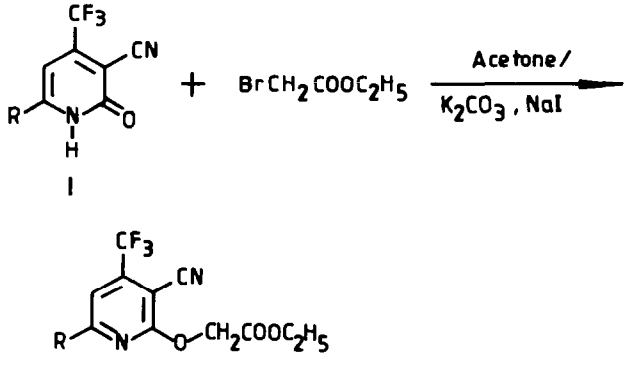
H); 8.05 (d, 2H, aromatic H); 8.12 (s, 1H, H–C(8)) ppm. IR ($CHCl_3$) (cm^{-1}): 3450; 3370; 1625; 1590; 1360; 1130. MS *m/z*: 374 (M^+) (base peak); 359 ($M^+ - CH_3$); 329 (359 – (N–NH_2)); 291; 43. Analysis: Calc. for $C_{13}H_{13}F_3N_4O_2$: C, 57.76; H, 3.50; N, 14.97%. Found: C, 57.68; H, 3.39; N, 14.86%.

2-Methyl-3-amino-7-*p*-anisyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5g**): ^1H NMR ($CDCl_3$) δ: 3.83 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3); 5.16 (br., s, 2H, NH_2); 7.28 (d, 2H, aromatic H); 7.89 (d, 2H, aromatic H); 8.05 (s, 1H, H–C(8)) ppm. IR ($CHCl_3$) (cm^{-1}): 3445; 3360; 1630; 1570; 1345; 1135. MS *m/z*: 390 (M^+) (base peak); 371 ($M^+ - F$); 319 (M^+ – (N–NH_2 and CH_3CN); 291 (M^+ – (N–NH_2 and CF_3). Analysis: Calc. for $C_{18}H_{13}F_3N_4O_3$: C, 55.39; H, 3.35; N, 14.35%. Found: C, 55.18; H, 3.21; N, 14.27%.

2-Methyl-3-amino-7-*p*-chlorophenyl-9-trifluoromethyl-4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidine (**5h**): ^1H NMR ($CDCl_3$) δ: 2.65 (s, 3H, CH_3); 5.21 (br., s, 2H, NH_2); 7.5 (d, 2H, aromatic H); 7.96 (s, 1H, H–C(8)); 8.10 (d, 2H, aromatic H) ppm. IR ($CHCl_3$) (cm^{-1}): 3440; 3300; 1610; 1570; 1350; 1120. MS *m/z*: 394 (M^+) (base peak); 375 ($M^+ - F$); 323 (M^+ – (N–NH_2 and CH_3CN); 295 (M^+ – (N–NH_2 and CF_3); 276; 227 (M^+ – (*p*-ClC_6H_4, CH_3CN and NH); 43. Analysis: Calc. for $C_{17}H_{10}ClF_3N_4O_2$: C, 51.73; H, 2.55; N, 14.19%. Found: C, 51.61; H, 2.49; N, 14.07%.

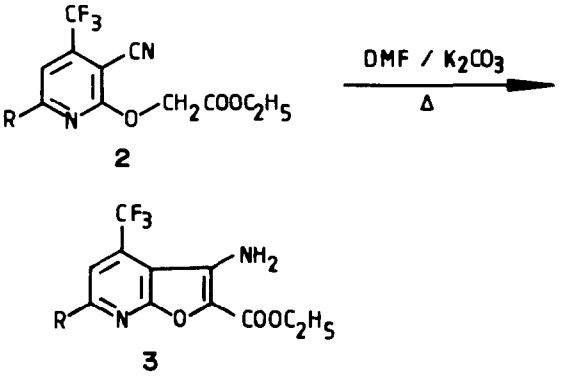
3. Results and discussion

When 3-cyano-4-trifluoromethyl-6-substituted 2(1*H*)-pyridones (**1**) were reacted with ethyl bromoacetate, the 2-*O*-ethylacetoxy-3-cyano-4-trifluoromethyl-6-substituted pyridines (**2**) were formed exclusively. This is in agreement with our experience [2] and the earlier report [3] that when an *ortho* substituent offers steric hindrance, only O-alkylation takes place and not N-alkylation.

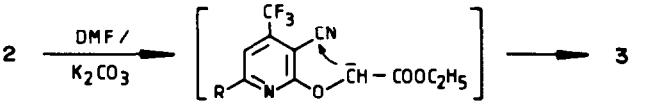


1 2

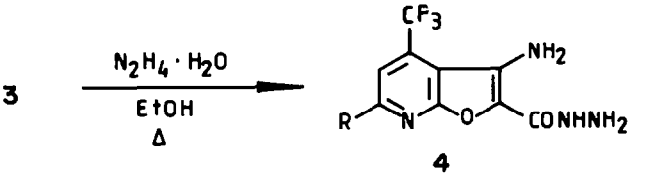
Compounds **2** are cyclized to 2-carbethoxy-3-amino-4-trifluoromethyl-6-substituted furo-[2,3-*b*]-pyridines (**3**) in *N*,*N*-dimethylformamide and potassium carbonate at 110–120 °C.



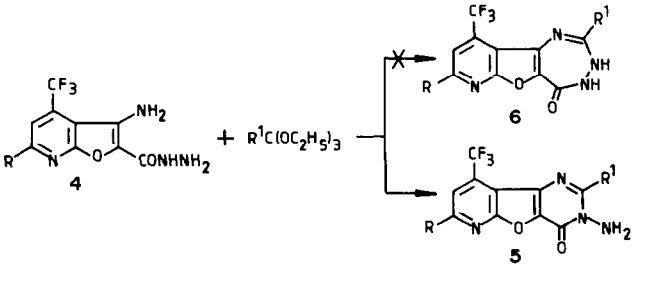
The mode of cyclization is through the formation of an anion by abstraction of a proton from the active methylene group by the base. The generated anion attacks the carbon of the nitrile (C≡N) function in situ to give the cyclized product **3**. This type of cyclization is also known as the Thorpe–Ziegler reaction [4].



Compounds **3** when reacted with hydrazine hydrate in refluxing ethanol resulted in the corresponding hydrazides **4**.



Hydrazides **4** are selectively cyclized to 4-oxo-4*H*-pyrido-[3′,2′:4,5]-furo-[3,2-*d*]-(1,3)-pyrimidines (**5**) [5] when reacted with orthoformate and orthoacetates in toluene acetic acid. The alternative triazepin **6** was not formed.



The results of the reactions are tabulated in Tables 1 and 2.

Table 1
Trifluoromethyl substituted pyridines and furo pyridines

Product	R	Yield (%)	M.p. (°C)
2a	C_6H_5	94.5	121
2b	p-$CH_3C_6H_4$	87.0	186
2c	p-$OCH_3C_6H_4$	93.0	132
2d	p-ClC_6H_4	90.5	150
3a	C_6H_5	82.3	158
3b	p-$CH_3C_6H_4$	96.2	162
3c	p-$OCH_3C_6H_4$	81.6	183
3d	p-ClC_6H_4	76.8	183
4a	C_6H_5	82.0	202
4b	p-$CH_3C_6H_4$	86.8	227
4c	p-$OCH_3C_6H_4$	77.8	211
4d	p-ClC_6H_4	91.8	251

Table 2
Trifluoromethyl substituted pyrido furo pyrimidines

Product	R	R′	Yield (%)	M.p. (°C)
5a	C_6H_5	H	90.5	242
5b	p-$CH_3C_6H_4$	H	89.7	265
5c	p-$OCH_3C_6H_4$	H	90.7	251
5d	p-ClC_6H_4	H	81.6	248
5e	C_6H_5	CH_3	52.0	243
5f	p-$CH_3C_6H_4$	CH_3	50.8	268
5g	p-$OCH_3C_6H_4$	CH_3	53.1	247
5h	p-ClC_6H_4	CH_3	54.0	284

3.1. Spectra

The infrared spectra of products **2** show the presence of the nitrile (C≡N) function as a sharp peak at 2220 cm^{-1} and the absence of the lactam carbonyl at 1680 cm^{-1}. Products **3** show the presence of amine (NH_2) functions as two doublet shoulders at 3480 and 3360 cm^{-1} and the disappearance of the nitrile (C≡N) at 2220 cm^{-1}. The presence of hydrazide carbonyl in products **4** and the ring carbonyl in products **5** are observed via peaks in the region 1615–1620 cm^{-1}.

The ^1H NMR spectra of products **2** show the presence of active methylene protons as a sharp singlet in the range δ 4.98–5.12 ppm, which are absent from the spectra of products **3** where the presence of NH_2 protons as a broad singlet at δ 5.18–5.30 ppm is observed instead. The presence of $C^2-CONHNH_2$ protons and C^3-NH_2 protons appeared as a broad singlets in the spectra of products **4** while the presence of N^3-NH_2, C^2-H or C^2-CH_3 protons were observed in the spectra of products **5**. The aromatic protons in all the products appeared in their appropriate aromatic regions. The mass spectra of the products showed the stable molecular ion with characteristic fragmentation patterns. The number of fragments shown by each product is given in detail in the Experimental section together with the proper assignment.

4. Conclusion

The synthetic sequence adopted affords a series of new fluorinated pyrido furopyrimidine heterocycles. Studies on their chemical reactivity and potential biological activity are in progress.

Acknowledgement

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