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A new synthetic route to fluorinated pyrazolo[3,4-b]pyridines and their use in the preparation of novel pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidines [1]

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Abstract

A single-step synthesis of 3-amino-4-trifluoromethyl-6-substituted-1*H*-pyrazolo[3,4-b]pyridines **(7)** from 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-substituted pyridines **(6)** is described, and their use in the synthesis of novel pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidines **(8)** under microwave irradiation outlined. © 1997 Elsevier Science S.A.

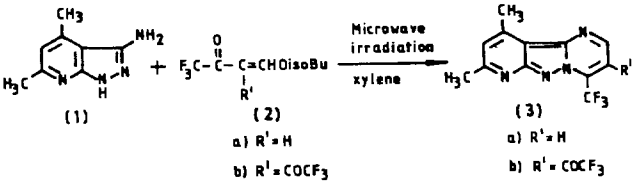
Keywords: Synthesis; Fluorinated pyrazolopyridines; Fluorinated pyridopyrazolo-pyrimidines; Microwave; Irradiation

1. Introduction

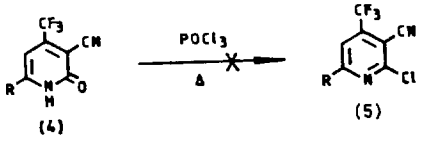
Pyrazolopyridine and pyrazolopyrimidine derivatives are important biologically active compounds. The pyrazolopyridines are found to be active antitubercular agents [1,2], active against gram positive and negative bacteria [3]. The pyrazolopyrimidines [4] are selective inhibitors of cyclic 3′,5′-adenosine mono-phosphate (cAMP) phosphodiesterases *in vitro*, and some of them possess anxiolytic properties comparable to those of benzodiazepines [5]. There is a single report [6] on the synthesis of pyridopyrazolopyrimidines, leaving much scope for extensive study. In view of the growing importance of fluorinated heterocycles as more active agents with better pharmacokinetic properties, we undertook to synthesise some novel fluorinated pyrazolo[3,4-b]-pyridines and pyrido[2′,3′:3,4]pyrazolo[1,5-a]pyrimidines.

2. Results and discussion

Following our earlier work on the utility of microwave irradiation in condensation reactions [7,8], we have found that microwave irradiation of 3-amino-4,6-dimethyl-1*H*-pyrazolo[3,4-b]pyridine **(1)** and 1,1,1-trifluoro-3-(isobutoxymethylene)-2-propanones **(2)** [9] in xylene for a specified time gave exclusively 4-(trifluoromethyl)-pyrido[2′,3′:3,4]-pyrazolo[1,5-a]pyrimidine in high yield.



In adopting the same procedure for the synthesis of trifluoromethylated analogues of **(3)**, we chose 6-aryl-1,2-dihydro-2-oxo-4-trifluoromethyl-3-pyridine-carbonitrile **(4)** [10] as the starting material, compound **4** being subjected initially to chlorination using $POCl_3$. There are conflicting reports in the literature about the formation of the chloro derivative, one favourable [11], the other not [12]. Our experience was that isolation of the required chloro product **(5)** is not possible due to its unstable nature and ready hydrolysis to starting material.



Therefore we have developed a novel high-yield synthetic route to 3-amino-4-trifluoromethyl-6-aryl-pyrazolo[3,4-b]-pyridines **(7)**, namely treatment of 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-aryl-pyridines **(6)** with hydrazine hydrate under reflux conditions:

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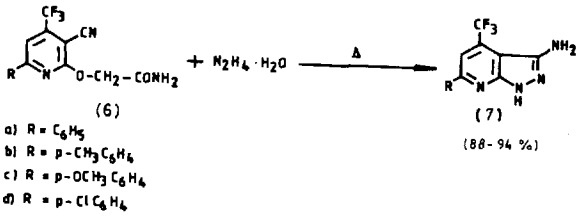
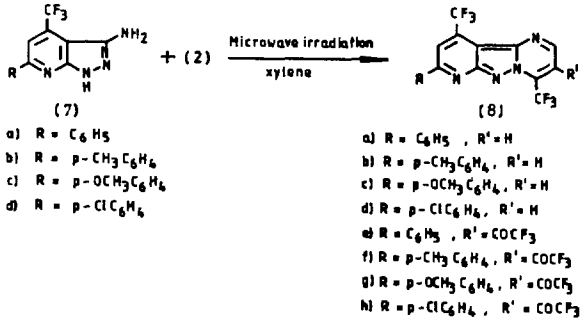


When mixtures of these pyrazolo[3,4-b]pyridines (**7**) and 1,1,1-trifluoro-3-(isobutoxymethylene)-2-propanones (**2**) in xylene were exposed to microwave irradiation for short periods (12–24 min), pyridopyrazolopyrimidines (**8**) were obtained in good yields (62–78% after chromatography). Under thermal conditions, only poor yields of these products were achieved (~20%).



3. Experimental details

3.1. General

Melting points were determined in open glass capillaries on a Mettler FP 51 melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer with TMS as the internal standard. IR spectra were recorded on a Pye-Unicam SP3-200 infrared spectrophotometer. Mass spectra were recorded on a VG Micromass 7070H instrument. Elemental analyses were carried out on a Perkin–Elmer 240B apparatus.

3.2. Starting materials

The 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-aryl-pyridines [13] and 1, 1, 1-trifluoro-3-(isobutoxymethylene)-2-propanones [9] were prepared by known procedures. All other reagents were obtained from commercial sources.

3.3. General procedure for the preparation of pyrazolo-[3, 4-b]pyridines (7a–7d)

The 2-*O*-acetamido-3-cyano-4-trifluoromethyl-6-aryl-pyridines (0.01 mol) were suspended in excess of hydrazine monohydrate (15 ml) and the reaction mixture was refluxed for 6 h. It was then cooled to room temperature, poured onto crushed ice and the separated solid was filtered, washed with water, dried over calcium chloride and purified by column chromatography using silica gel (60–120 mesh) and chloroform:hexane (9:1) as an eluant.

3.3.1. 3-Amino-6-phenyl-4-trifluoromethyl-1H-pyrazolo-[3, 4-b]pyridine (7a)

Yield 92%; m.p. 198°C. ^{1}H-NMR (DMSO-d_6) δ: 4.38 (s, br., 2H, NH_2); 7.41 (m, 3H, ArH); 7.60 (s, 1H, H–C(5)); 8.00 (m, 2H, ArH); 12.22 (s, br., 1H, NH) ppm. IR (KBr) (cm^{-1}): 3440, 3340, 1160. MS *m/z*: 278 (M^+) (base peak); 263 (M^+–NH); 77 (C_6H_5); 69 (CF_3). Analysis: Calc. for $C_{13}H_9F_3N_4$: C, 56.11; H, 3.26; N, 20.13%. Found: C, 56.18; H, 3.31; N, 20.19%.

3.3.2. 3-Amino-6-p-tolyl-4-trifluoromethyl-1H-pyrazolo-[3, 4-b]pyridine (7b)

Yield 88%; m.p. 202°C. ^{1}H-NMR (DMSO-d_6) δ: 2.41 (s, 3H, CH_3); 4.50 (s, br., 2H, NH_2); 7.20 (d, 2H, ArH); 7.61 (s, 1H, H–C(5)); 7.92 (d, 2H, ArH); 12.41 (s, br., 1H, NH) ppm. IR (KBr) (cm^{-1}): 3480, 3370, 1170. MS *m/z*: 292 (M^+); 277 (M^+–NH) (base peak); 91 (p-$CH_3C_6H_4$). Analysis: Calc. for $C_{14}H_{11}F_3N_4$: C, 57.53; H, 3.79; N, 19.17%. Found: C, 57.61; H, 3.79; N, 19.25%.

3.3.3. 3-Amino-6-p-anisyl-4-trifluoromethyl-1H-pyrazolo-[3, 4-b]pyridine (7c)

Yield 91%; m.p. 168°C. ^{1}H-NMR (DMSO-d_6) δ: 3.81 (s, 3H, OCH_3); 4.40 (s, br., 2H, NH_2); 6.89 (d, 2H, ArH); 7.55 (s, 1H, H–C(5)); 7.93 (d, 2H, ArH); 12.20 (s, br., 1H, NH) ppm. IR (KBr) (cm^{-1}): 3480, 3390, 1160. MS *m/z*: 308 (M^+); 293 (M^+–NH) (base peak); 239 (M^+–CF_3); 69 (CF_3). Analysis: Calc. for $C_{14}H_{11}F_3N_4O$: C, 54.54; H, 3.59; N, 18.17%. Found: C, 54.62; H, 3.68; N, 18.25%.

3.3.4. 3-Amino-6-p-chlorophenyl-4-trifluoromethyl-1H-pyrazolo[3, 4-b]pyridine (7d)

Yield 94%; m.p. 220°C. ^{1}H-NMR (DMSO-d_6) δ: 4.58 (s, br., 2H, NH_2); 7.44 (d, 2H, ArH); 7.66 (s, 1H, H–C(5)); 8.08 (d, 2H, ArH); 12.51 (s, br., 1H, NH) ppm. IR (KBr) (cm^{-1}): 3490, 3300, 1180. MS *m/z*: 312 (M^+) (base peak); 297 (M^+–NH); 243 (M^+–CF_3); 69 (CF_3). Analysis: Calc. for $C_{13}H_8ClF_3N_4$: C, 49.93; H, 2.57; N, 17.91%. Found: C, 49.96; H, 2.63; N, 17.98%.

3.4. General procedure for the preparation of pyrido-[2',3':3,4]pyrazolo[1,5-a] pyrimidines (3a–3b) and (8a–8h)

The 3-amino-6-aryl-4-trifluoromethyl-1*H*-pyrazolo[3,4-b]-pyridines (**7**) (15 mmol) and 1,1,1-trifluoro-3-(isobutoxy-methylene)-2-propanones (**2**) (16 mmol) were taken in *o*-xylene (10 ml) and the mixtures exposed to microwave irradiation for a specified time. The mixture was cooled, concentrated partially by removing the solvent by suction and passed through a column of silica gel (60–120 mesh), using chloroform as the eluant.

*3.4.1. 8,10-Dimethyl-4-trifluoromethyl-pyrido[2',3':3,4]-pyrazolo[1,5-a]pyrimidine (**3a**)*

Reaction time 18 min; Yield 82%; m.p. 165°C. ^{1}H-NMR (DMSO-d_6) δ: 2.54 (s, 3H, CH_3–C(10)); 2.70 (s, 3H, CH_3–C(8)); 5.71 (d, 1H, H–C(2)); 6.73 (s, 1H, H–C(9)); 8.23 (d, 1H, H–C(3)); ppm. IR (KBr) (cm^{-1}): 1550, 1170. MS *m/z*: 266 (M^+); 197 (M^+–CF_3) (base peak); 69 (CF_3). Analysis: Calc. for $C_{12}H_9F_3N_4$: C, 54.13; H, 3.40; N, 21.04%. Found: C, 54.28; H, 3.51, N, 21.16%.

*3.4.2. 8,10-Dimethyl-3-trifluoroacetyl-4-trifluoromethyl-pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**3b**)*

Reaction time 12 min; Yield 73%; m.p. 208°C. ^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H, CH_3–C(10)); 2.69 (s, 3H, CH_3–C(8)); 6.75 (s, 1H, H–C(9)); 7.60 (s, 1H, H–C(2)) ppm. IR (KBr) (cm^{-1}): 1680, 1570, 1160. MS *m/z*: 362 (M^+); 293 (M^+–CF_3); (base peak); 97 ($COCF_3$); 69 (CF_3). Analysis: Calc. for $C_{14}H_8F_6N_4O$: C, 46.42; H, 2.22; N, 15.46%. Found: C, 46.51; H, 2.29; N, 15.59%.

*3.4.3. 4,10-Bis(trifluoromethyl)-8-phenyl-pyrido-[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8a**)*

Reaction time 22 min; Yield 78%; m.p. 222°C. ^{1}H-NMR (DMSO-d_6) δ: 7.60 (m, 3H, ArH); 7.90 (d, 1H, H–C(2)); 8.21 (s, 1H, H–C(9)); 8.35 (m, 2H, ArH); 9.10 (d, 1H, H–C(3)) ppm. IR (KBr) (cm^{-1}): 1540, 1160. MS *m/z*: 382 (M^+) (base peak); 313 (M^+–CF_3); 77 (C_6H_5); 69 (CF_3). Analysis: Calc. for $C_{17}H_8F_6N_4$: C, 53.41; H, 2.10; N, 14.65%. Found: C, 53.51; H, 2.18; N, 14.72%.

*3.4.4. 4,10-Bis(trifluoromethyl)-8-p-tolyl-pyrido-[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8b**)*

Reaction time 17 min; Yield 73%; m.p. 172°C. ^{1}H-NMR (DMSO-d_6) δ: 2.43 (s, 3H, CH_3); 7.28 (d, 2H, ArH); 7.37 (d, 1H, H–C(2)); 7.90 (s, 1H, H–C(9)); 8.00 (d, 2H, ArH); 8.22 (d, 1H, H–C(3)) ppm. IR (KBr) (cm^{-1}): 1580, 1160. MS *m/z*: 396 (M^+); 327 (M^+–CF_3) (base peak); 91 (p-$CH_3C_6H_4$); 69 (CF_3). Analysis: Calc. for $C_{18}H_{10}F_6N_4$: C, 54.55; H, 2.54; N, 14.13%. Found: C, 54.68; H, 2.61; N, 14.26%.

*3.4.5. 8-p-Anisyl-4,10-bis(trifluoromethyl)-pyrido-[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8c**)*

Reaction time 21 min; Yield 73%; m.p. 86°C. ^{1}H-NMR (DMSO-d_6) δ: 3.86 (s, 3H, OCH_3); 7.00 (d, 2H, ArH); 7.62 (s, 1H, H–C(9)); 7.90 (d, 1H, H–C(2)); 8.05 (d, 2H, ArH); 8.26 (d, 1H, H–C(3)) ppm. IR (KBr) (cm^{-1}): 1570, 1160. MS *m/z*: 412 (M^+) (base peak); 343 (M^+–CF_3); 69 (CF_3). Analysis: Calc. for $C_{18}H_{10}F_6N_4O$: C, 52.43; H, 2.44; N, 13.58%. Found: C, 52.54; H, 2.56; N, 13.63%.

*3.4.6. 8-p-Chlorophenyl-4,10-bis(trifluoromethyl)-pyrido-[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8d**)*

Reaction time 24 min; Yield 71%; m.p. 208°C. ^{1}H-NMR (DMSO-d_6) δ: 7.05 (d, 1H, H–C(2)); 7.50 (d, 2H, ArH); 7.85 (s, 1H, H–C(9)); 8.10 (d, 2H, ArH); 8.29 (d, 1H, H–C(3)) ppm. IR (KBr) (cm^{-1}): 1580, 1160. MS *m/z*: 416 (M^+); 347 (M^+–CF_3) (base peak); 69 (CF_3). Analysis: Calc. for $C_{17}H_7ClF_6N_4$: C, 48.99; H, 1.69; N, 13.44%. Found: C, 49.07; H, 1.81; N, 13.56%.

*3.4.7. 4,10-Bis(trifluoromethyl)-8-phenyl-3-(trifluoro-acetyl)-pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8e**)*

Reaction time 16 min; Yield 69%; m.p. 244°C. ^{1}H-NMR (DMSO-d_6) δ: 7.58 (m, 3H, ArH); 8.27 (s, 1H, H–C(9)); 8.40 (m, 2H, ArH); 8.84 (s, 1H, H–C(2)) ppm. IR (KBr) (cm^{-1}): 1670, 1560, 1160. MS *m/z*: 478 (M^+); 409 (M^+–CF_3) (base peak); 381 (M^+–$COCF_3$); 69 (CF_3). Analysis: Calc. for $C_{19}H_7F_9N_4O$: C, 47.71; H, 1.47; N, 11.71%. Found: C, 47.86; H, 1.54; N, 11.85%.

*3.4.8. 4,10-Bis(trifluoromethyl)-8-p-tolyl-3-(trifluoro-acetyl)-pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8f**)*

Reaction time 15 min; Yield 65%; m.p. 278°C. ^{1}H-NMR (DMSO-d_6) δ: 2.38 (s, 3H, CH_3); 7.31 (d, 2H, ArH); 7.83 (d, 2H, ArH); 8.10 (s, 1H, H–C(9)); 8.62 (s, 1H, H–C(2)) ppm. IR (KBr) (cm^{-1}): 1690, 1570, 1150. MS *m/z*: 492 (M^+) (base peak); 423 (M^+–CF_3); 91 (p-$CH_3C_6H_4$); 69 (CF_3). Analysis: Calc. for $C_{20}H_{99}N_4O$: C, 48.79; H, 1.84; N, 11.38%. Found: C, 48.84; H, 1.96; N, 11.49%.

*3.4.9. 8-p-Anisyl-4,10-bis(trifluoromethyl)-3-(trifluoro-acetyl)-pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8g**)*

Reaction time 18 min; Yield 62%; m.p. 94°C. ^{1}H-NMR (DMSO-d_6) δ: 3.90 (s, 3H, OCH_3); 7.00 (d, 2H, ArH); 7.58 (s, 1H, H–C(9)); 7.85 (s, 1H, H–C(2)); 8.10 (d, 2H, ArH) ppm. IR (KBr) (cm^{-1}): 1670, 1590, 1160. MS *m/z*: 508 (M^+); 439 (M^+–CF_3); 411 (M^+–$COCF_3$) (base peak); 69 (CF_3). Analysis: Calc. for $C_{20}H_9F_9N_4O_2$: C, 47.25; H, 1.78; N, 11.02%. Found: C, 47.39; H, 1.86; N, 11.14%.

*3.4.10. 8-p-Chlorophenyl-4,10-bis(trifluoromethyl)-3-(trifluoroacetyl)-pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidine (**8h**)*

Reaction time 16 min; Yield 62%; m.p. 168°C. ^{1}H-NMR (DMSO-d_6) δ: 7.50 (d, 2H, ArH); 7.70 (s, 1H, H–C(9)); 7.89 (s, 1H, H–C(2)); 8.14 (d, 2H, ArH) ppm. IR (KBr) (cm^{-1}): 1690, 1580, 1160. MS *m/z*: 512 (M^+); 443 (M^+–CF_3); 416 (M^+–$COCF_3$); 69 (CF_3) (base peak). Analysis: Calc. for $C_{19}H_6ClF_9N_4O$: C, 44.80; H, 1.17; N, 10.92%. Found: C, 44.86; H, 1.29; N, 10.98%.

3.5. Spectra

The infrared spectra of products (**7**) and (**8**) were fully consistent with the structures assigned.

^{1}H-NMR spectra of the pyrazolopyridines (**7**) contained signals for NH_2 and NH protons as a broad singlets in the range 4.38–4.58 and 12.20–12.51 ppm respectively. The presence of C(2) and C(3) protons adjacent to each other in compounds (**3a**) and (**8a–8d**) resulted in two doublets, the downfield signal being assigned to C(3) protons since they

are adjacent to C carrying the CF_3 group. The single C(2) proton present in compounds **(3b)** and **(8e–8h)** gave rise to a singlet absorption. Signals from other aromatic protons in all the products appeared in appropriate regions. The mass spectra of the products showed the stable molecular ion with characteristic fragmentation patterns; details are provided above, together with assignments.

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