Heterocyclizations of 3-trifluoroacetyl substituted lactams with cyclic 1,3-bis-nucleophiles

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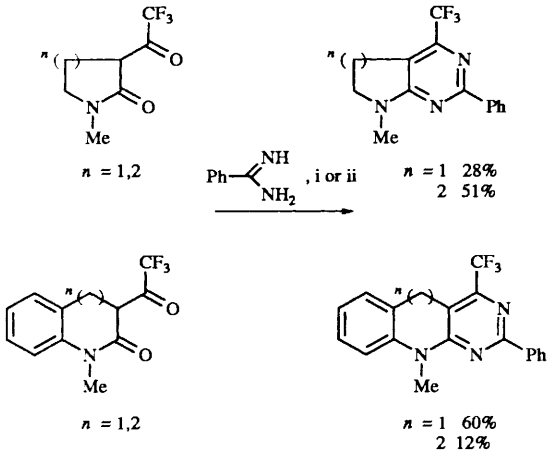
Pyrrolidinone **2**, pyrimido[1,2-*a*]benzimidazoles **3a–c** and 1,2,4-triazolo[4,3-*a*]pyrimidine **4** are prepared by condensation of 3-trifluoroacetyl substituted lactams **1a–c** with cyclic 1,3-bis-nucleophiles. The nature of the nucleophile determines whether the reaction occurs with or without lactam ring opening.

Introduction

The development of new methods for the synthesis of trifluoromethylated pyrimidines and of condensed cyclic derivatives is a topic of continuing interest. One reason for this is their potential biological activity. For example, certain trifluoromethylated deazapurines or 5-deazaflavines are well-known herbicides[1] or plant growth regulators.[2] We have already reported the preparation of related trifluoromethylated polycyclic pyrimidines starting from 3-trifluoroacetyl substituted lactams, benzolactams, γ-butyrolactone or cyclopentanone.[3] These reactions were performed in one step by condensation of benzamidine or guanidine without opening of the lactam structure (Scheme 1).



Scheme 1 *Conditions:* i, neat, 100–180 °C; ii, toluene, reflux

While such condensations with other 3-acyl lactams are apparently unknown, it was reported that α-acetyl-γ-butyrolactone reacts with 2-aminopyridine, 5-amino-3,4-dihydro-2*H*-pyrrole or 2-aminopyrazole with opening of the lactone moiety.[4]

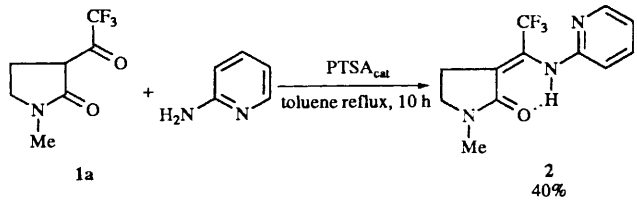
Since 3-trifluoroacetyl lactams **1a–c** have become readily available[5] and cyclize with hydrazines,[6] benzamidine,[3] *o*-aminophenol or *o*-phenylenediamine,[7] we have now examined their reaction with cyclic 1,3-bis-nucleophiles such as 2-aminopyridine, 2-aminobenzimidazole and 3-amino-1,2,4-triazole, in order to find out whether heterocyclizations of 3-trifluoroacetyl lactams **1a–c** can proceed without opening of the lactam structure.

Table 1 Yield of benzimidazoles **3a–c**

Lactam	*n*	Entry	Conv. (%)	Yield **3** (%)
1a	1	**a**	68	23
1b	2	**b**	85	47
1c	3	**c**	90	62

Results and discussion

With 2-aminopyridine and 1-methyl-3-trifluoroacetylpyrrolidin-2-one **1a**, in the presence of a catalytic amount of toluene-*p*-sulfonic acid (PTSA) in refluxing toluene, we obtained selectively the non-cyclized pyrrolidinone **2** (Scheme 2) as shown by the X-ray diffraction analysis of the product.



Scheme 2

Fig. 1 shows a stereoscopic view of one of the two independent molecules which are present in the asymmetric part of the unit cell.[8] The two independent molecules have a very similar geometry, only the planarity of the pyrrolidinone is slightly different (maximum deviation from the mean plane = C4: 0.012 Å, RMS deviation of the fitted atoms 0.009 Å for molecule **2'**; maximum deviation C4: 0.032 Å, RMS deviation 0.022 Å for molecule **2''**). There is an intramolecular hydrogen bond between the carbonyl oxygen and the amino hydrogen with the following geometry: in molecule **2'**: N···O = 2.793(4) Å, H···O = 2.27(4) Å and N–H···O = 138(3)°; for molecule **2''**: N···O = 2.866(3) Å, H···O = 2.31(4) Å and N–H···O = 118(3)°.

To extend the scope of this reaction, we performed other condensations of **1a–c** with 2-aminobenzimidazole and 3-amino-1,2,4-triazole as nucleophiles.

3-Trifluoroacetyl lactams **1a–c** and 2-aminobenzimidazole furnished the tricyclic structures **3a–c** by a ring closure–ring opening sequence (Scheme 3, Table 1). The structure of benzimidazole **3b** was determined by X-ray diffraction analysis and the same skeleton was assigned to compounds **3a** and **3c** by

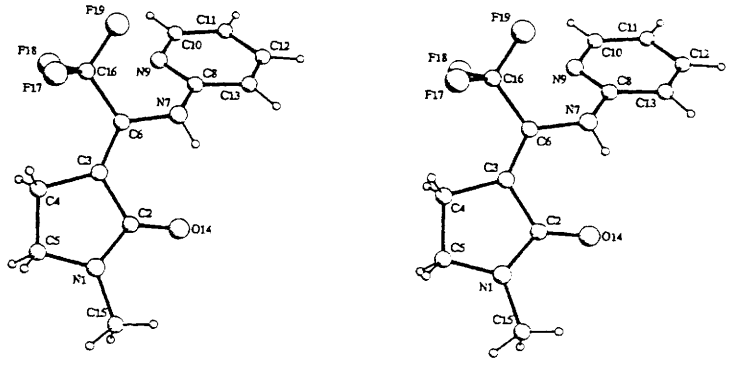


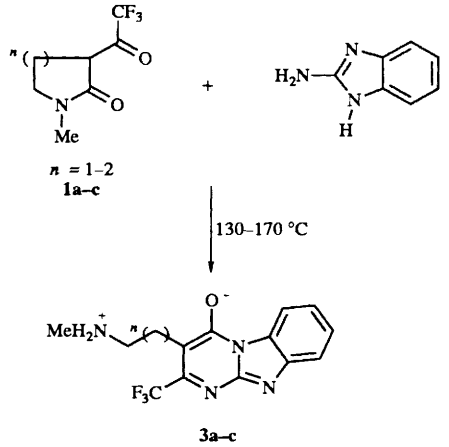
Fig. 1 Stereoscopic view of 2'[8]

Table 2 Intra- and inter-molecular H bond geometries in compound **3b**

	Molecule **3b'**	Molecule **3b''**
intra (O14: x, y, z)		
O14 · · · N22	2.681(6) Å	2.738(5) Å
O14 · · · H22a	1.70(3) Å	1.82(4) Å
O · · · H–N	159(2)°	162(2)°
inter	(N7: 0.5 − x, 1 − y, z − 0.5)	(N7: x, 0.5 − y, z − 0.5)
N7 · · · N22	2.882(6) Å	2.829(6) Å
N7 · · · H22b	1.81(4) Å	1.70(4) Å
N · · · H–N	170(2)°	168(2)°

Table 3 UV–VIS data of heterocycles **4** and **7a–10a**

Compound[ref.]	R^1	R^2	R^3	λ_{max}/nm (ε/10^3)	No. of maxima
4	$MeNH(CH_2)_3$	CF_3	H	216 (3.35), 248 (3.44), 286 (3.50)	3
7a[12]	Me	H	SMe	228 (24.6), 265 (9.6)	2
8a[12]				209 (20.4), 290 (8.8)	2
9a[12]				231 (9.6), 260 (4.3), 309 (4.9)	3
10a[12]				230 (17.3)	1



Scheme 3

comparison of ^{13}C NMR data. It is worth noting that the yields of **3** increase with the size of the lactam ring.

Fig. 2 shows a stereoscopic view of one of the two independent molecules of **3b** which are present in the asymmetric part of the unit cell.[8] The structure is clearly zwitterionic, the two Hs on N22 were located from a difference Fourier and in addition C2–O14 is longer than a normal carbonyl bond. The shape of the two independent molecules of **3b** is similar with a quasi-planar heterocyclic framework. For molecule **3b'**, the RMS deviation of the 13 fitted atoms is 0.017 Å and O14 is 0.08 Å out of this plane. For molecule **3b''**, the RMS deviation is larger (0.037 Å) and O14 is 0.15 Å out of the best mean plane. The C–O^- bond lengths of 1.251(5) and 1.244(4) Å are comparable with those of delocalized double bonds in carboxylate anions (1.254 Å).[9] An intramolecular hydrogen bond between the charged atoms $O14^-$ and $N22^+$ is observed. The same nitrogen (N22) is also an acceptor for an intermolecular H bond with N7 as donor. The geometries of these two H bonds are similar in the two independent entities (Table 2).

The reaction of 3-amino-1,2,4-triazole was very similar to that of 2-aminobenzimidazole. Thus, from 1-methyl-3-trifluoroacetylpiperidin-2-one **1b**, 1,2,4-triazolo[4,3-*a*]pyrimidine **4** was formed (Scheme 4). Because of its poor solubility, crystals of good quality for X-ray measurements could not be obtained. Nevertheless the structure of pyrimidine **4** was assigned by comparison with analogues described in the literature.[10–13]

At least ten isomers had to be considered because of the regiochemistry of condensation, stereochemistry and tautomerism of the final products (Scheme 5).

First, we analysed the UV data (Table 3). The isomers **7a**, **8a** and **10a** could be excluded on the basis of their UV–VIS spectra recorded in a neutral medium (EtOH).[12] The shape of the spectrum and the absorption maxima (λ_{max}) suggested the structure **9a** (Table 3) as the most favoured. Next, we

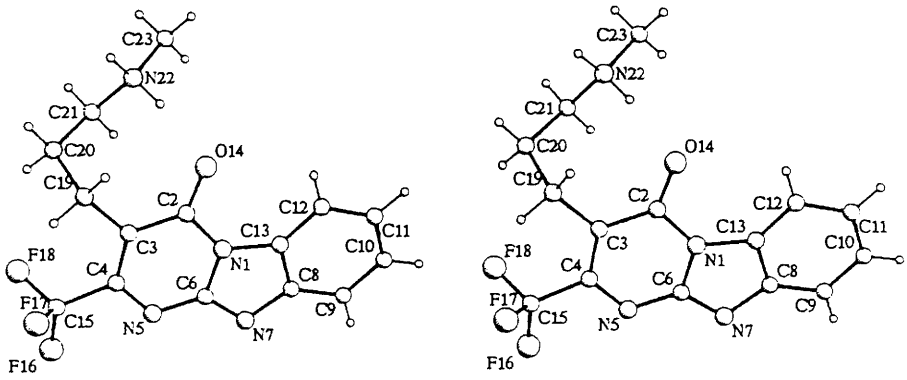
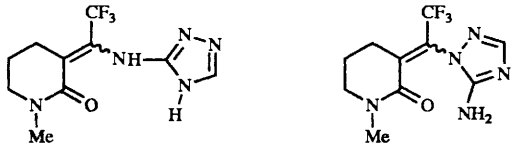


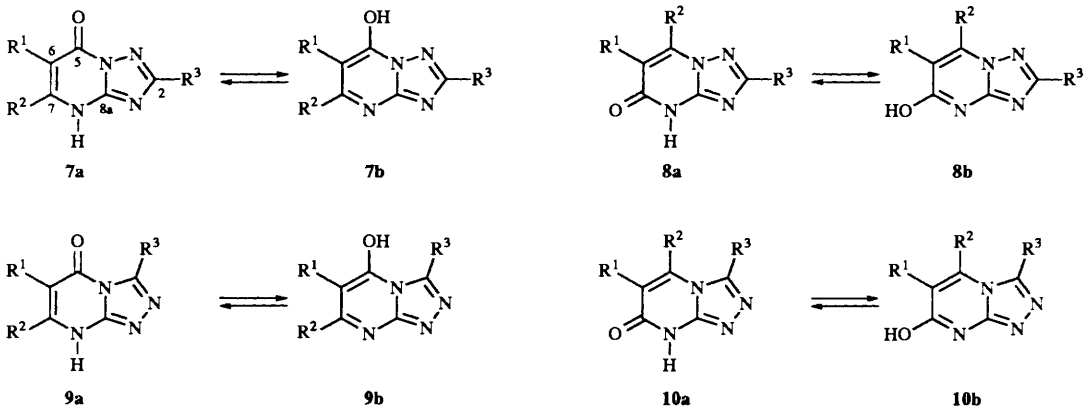
Fig. 2 Stereoscopic view of **3b**'[8]

N—H condensation on the trifluoroacetyl group



5 **6**

Double condensation and lactam ring opening

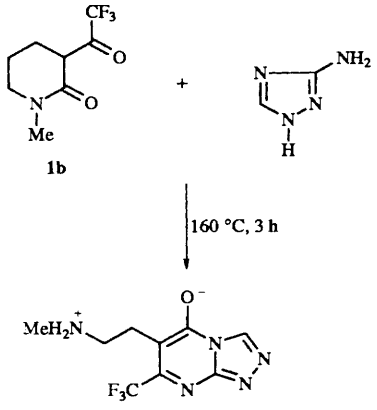


7a **7b** **8a** **8b**

9a **9b** **10a** **10b**

[R^1 = $(CH_2)_3NHMe$, Me; R^2 = CF_3, H; R^3 = H, SMe]

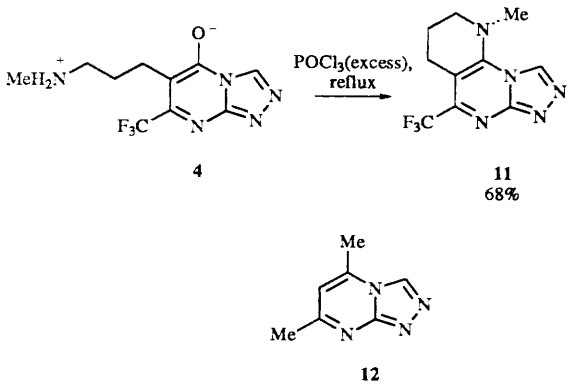
Scheme 5



Scheme 4

substantiated this hypothesis by comparison of ^{13}C NMR data. Table 4 shows that only the chemical shifts of isomer **9a** are in agreement with structure **4**. The carbon–proton coupling constant of the protonated methylamino function ($^1J_{C4'}$ = 142.4 Hz) in compound **4** is characteristic of an aliphatic ammonium salt ($^1J_{MeNH3^+}$ = 145 Hz).[14] Moreover, the chemical shifts $\delta_{C1'-C4'}$ of the side chain and the coupling constant $^1J_{C4'}$ are very similar in **4** and in benzimidazole **3b** (Table 5). Thus, we are able to assign the structure 1,2,4-triazolo[4,3-*a*]pyrimidine to the product **4**.

Chemical proof for this structure of **4** was obtained by cyclization to give pyrimidine **11** upon treatment with phosphorus oxychloride (Scheme 6). The structure of pyrimidine **11** is based on comparison of UV–VIS data with that of the analogue **12**. Except for small variations due to different substitution, the spectra are very similar (Table 6). Consequently, we can assign the structure [1,2,4]-triazolo-[3,4-*b*]pyrimidine to heterocycle **11** and 1,2,4-triazolo[4,3-*a*]-pyrimidine to **4**.



4 11 (68%) 12

Scheme 6

Although the mechanism of the reactions of **1a–c** was not studied in detail, two types of processes are observed with cyclic 1,3-bis-nucleophiles. 2-Aminopyridine condenses only at the trifluoroacetyl group to produce enamine **2**, as has already been observed with guanidine.[3] On the other hand, 2-aminobenzimidazole and 3-amino-1,2,4-triazole condense in close analogy to hydrazines[6] to furnish internal salts of pyrimidine by opening of the lactam structure (compounds **3a–c** and **4**).

Conclusions

Heterocyclizations of cyclic 1,3-bis-nucleophiles (2-aminopyridine, 2-aminobenzimidazole and 3-amino-1,2,4-triazole) give new trifluoromethylated heterocycles such as pyrrolidinone **2** and zwitterionic forms of pyrimidines **3a–c** and **4**. The structure of compounds **2** and **3b** was determined by X-ray diffraction analysis whereas the skeleton 1,2,4-triazolo[4,3-*a*]pyrimidine of **4** was assigned by comparison of UV–VIS and ^{13}C NMR data. Heterocycle **4** was also cyclized to give pyrimidine **11** by treatment with phosphorus oxychloride.

Experimental

Melting points were taken using a Dr Tottoli apparatus and are uncorrected. IR and mass spectra were measured on a Perkin-Elmer 1710 and a Finnigan Mat TSQ 70 apparatus, respectively. The UV spectra were recorded on Perkin-Elmer Lambda 5 UV–VIS spectrometer. The ^1H, ^{13}C and ^{19}F NMR spectra were run on a Bruker AM500 spectrometer at 500.13 MHz (^1H) and 125.77 MHz (^{13}C) or with Varian VXR-200 and Gemini-200 spectrometers at 200 MHz (^1H), 188.2 MHz (^{19}F) and 50.3 MHz (^{13}C), using 5 mm probes. The samples were dissolved in $CDCl_3$ or [$^2H_6$]DMSO. The tetramethylsilane (TMS) signal was taken as internal reference for ^1H and ^{13}C spectra, while $CFCl_3$ was used as an internal reference for the ^{19}F spectra. Most of the ^{13}C NMR spectra were obtained from proton coupled or proton noise decoupled spectra. Chemical shifts are in ppm on the δ scale and coupling constants J are given in Hz. The following abbreviations are used: s singlet, br s broad singlet, d doublet, t triplet, q quartet, qt quintet, sx sextet and m multiplet. In non-decoupled spectra, many signals were observed as multiplets due to long-range coupling to fluorine; J values for these multiplets are marked with an asterisk.

Table 4 ^{13}C NMR data of heterocycles **4** and **7a–10a**[a]

Compound[ref.]	δ_{C5}	δ_{C6}	δ_{C^-}	δ_{C8a}	δ_{C2}
4	156.8	113.7	146.4	147.9	143.3
7a[12]	154.9	98.4	150.6	151.3	163.2
8a[12]	146.9	104.3	160.6	150.7	162.8
9a[12]	156.7	95.5	158.3	150.4	143.2
10a[12]	145.0	107.9	160.3	150.2	142.7

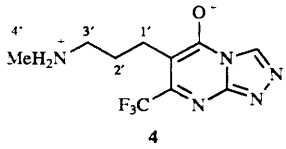
[a] Solvent: [$^2H_6$]DMSO.

Preparation of 1-methyl-3-[2,2,2-trifluoro-1-(2-pyridylamino)-ethylidene]pyrrolidin-2-one 2

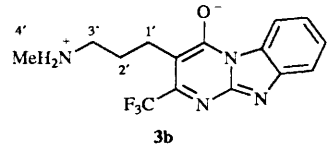
A solution of 1-methyl-3-trifluoroacetyl pyrrolidin-2-one **1a** (0.98 g, 5 mmol), 2-aminopyridine (0.94 g, 10 mmol) and a catalytic amount of toluene-*p*-sulfonic acid (PTSA) in toluene (10 cm^3) was refluxed for 10 h. The solution was then cooled, diluted with diethyl ether (30 cm^3) and washed with water (20 cm^3). The aqueous phase was extracted twice with diethyl ether (2 × 30 cm^3). The combined organic phases were washed with brine (20 cm^3), dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel (eluent: 60% methanol–diethyl ether) gave the title compound **2** as a white solid (0.54 g, 40%), mp 83–84 °C: $\delta_H(CDCl_3)$ 2.92 (3 H, s), 3.01 (2 H, tq, J 6.7, J_F 3.1), 3.45 (2 H, t, J 6.8), 6.8–7.0 (2 H, m), 7.54 (1 H, ddd, J 8.2, 8.1, 1.7), 8.22 (1 H, dd, J 6.8, 1.6) and 9.51 (NH, br s); $\delta_C(CDCl_3)$ 22.8 (t, J 134.4, $^*J_F$ 2.3), 29.9 (q, J 138.8, $^*J_F$ 1.6), 46.9 (t, J 141.0), 113.1 (ddd, J 163.3, 6.7, 1.6), 117.7 (dd, J 165.2, 7.1), 117.9 (s, $^*J_F$ 2.7), 121.8 (qd, J_F 277.5, J 8.4), 135.0 (q, J_F 34.8), 138.1 (ddd, J 161.9, 6.5, 1.6), 148.4 (ddd, J 164.2, 7.3, 2.4), 156.4 (s) and 169.9 (s); $\delta_F(CDCl_3)$ 63.6 (s); $\nu_{max}(CHCl_3)$ cm^{-1} 3270, 3021, 2987, 2954, 1675, 1601, 1587, 1477, 1422 and 1293; λ(EtOH, c 4.723 × 10^{-4} mol dm^{-3}) nm 232 (A 1.49, ε 3160) and 313 (A 2.72, ε 5770); m/z (EI) 272, 271 (M^+), 202 ($M^+ - CF_3$), 200, 180, 172 ($M^+ - NMP$), 131 and 78 (Found: C, 53.25; H, 4.4; N, 15.3. $C_{12}H_{12}F_3N_3O$ requires C, 53.14; H, 4.46; N, 15.49%).

The crystallographic data are as follows: $C_{12}H_{12}F_3N_3O$, M_r = 271.25, triclinic, $P\bar{1}$, a = 8.791(1), b = 11.407(2), c = 13.144(2) Å, α = 82.34(2), β = 73.99(1), γ = 80.34(2)°; V = 1243.7(3) Å^3, D_x = 1.45 g cm^{-3} for Z = 4, Mo-Kα, λ = 0.710 69 Å, μ = 0.126 mm^{-1}, $F(000)$ = 560, T = 291 K, R = 0.056 for 2831 observed reflections [$I \geqslant 2\sigma(I)$] and 0.098 for all 4874 data. The intensities of the 4874 independent reflections were collected from a crystal with approximate dimensions 0.19 × 0.25 × 0.54 mm using a four circle Huber diffractometer: θ range 2.3 to 26°, index ranges $0 \leqslant h \leqslant 10$, $-13 \leqslant k \leqslant 14$, $-15 \leqslant l \leqslant 16$. The structure was solved by direct methods using SHELXS-86[16] and refined by full least-squares on F^2

Table 5 Selected chemical shifts of heterocycles **3b** and **4**[a]



4



3b

Compound	$\delta_{C1'}$	$\delta_{C2'}$	$\delta_{C3'}$	$\delta_{C4'}$	$^1J_{C4'}$
4	22.2	25.1	47.8	32.3	142.4
3b	21.2	26.5	48.2	32.7	141.5

[a] Solvent: [$^2H_6$]DMSO.

Table 6 UV–VIS data of pyrimidines **11** and **12**[a]

Compound[ref.]	λ_{max} nm (log ε)
11	231 (4.15), 250 (3.79), 259 (3.01), 280 (3.52)
12[15]	247 (3.23), 257 (3.34), 265 (3.36), 285 (3.47)

[a] Solvent: H_2O at pH 6.

with SHELXL93.[17] All atoms, except those of a methyl group, which were calculated, were located from a difference Fourier synthesis and included in the refinement with a common isotropic temperature factor (U = 0.113 Å^2); goodness-of-fit on F^2 0.958, R [$I \geqslant 2\sigma(I)$] = 0.056, R (all data) = 0.098. Largest peak 0.24, largest hole −0.20 e Å^{-3} in final difference Fourier.

General procedure for the preparation of compounds 3a–c and 4

A stirred mixture of 1-methyl-3-trifluoroacetylpyrrolidin-2-ones **1a**, **b** or **c** (10 mmol, 1 equiv.) and an excess of 1,3-bis-nucleophile (11–16 mmol, 1.1–1.6 equiv.) was heated at 100–150 °C for 4–10 h. Diethyl ether (50 cm^3) and methanol (a few drops) were added to the cooled product. The solution was washed twice with brine (2 × 30 cm^3), dried over $MgSO_4$ and evaporated. The resulting oil was purified on silica gel (eluent: methanol–diethyl ether) to give the title compounds.

Reactions with 2-aminobenzimidazole

Preparation of the internal salt of 4-hydroxy-3-(2-methylaminoethyl)-2-trifluoromethylpyrimido[1,2-*a*]benzimidazole 3a. The treatment of 1-methyl-3-trifluoroacetylpyrrolidin-2-one **1a** (0.98 g, 5 mmol) with 2-aminobenzimidazole (0.73 g, 5.5 mmol) gave after chromatography (eluent: 60% MeOH–diethyl ether) the title compound **3a** as a white powder (0.36 g, 23%), mp > 240 °C; δ_H([$^2H_6$]DMSO) 3.0–3.1 (2 H, m), 3.3–3.4 (2 H, m), 3.35 (3 H, s), 4.8–5.0 (NH_2, br s), 7.14 (1 H, ddd, J 8.2, 8.2, 1.0), 7.37 (1 H, ddd, J 8.3, 8.3, 1.2), 7.56 (1 H, d, J 8.3) and 8.47 (1 H, d, J 7.7); δ_C([$^2H_6$]DMSO) 21.9 (t, J 130.2, $^*J_F$ 1.9), 33.0 (q, J 142.0, $^*J_F$ 1.3), 49.0 (t, J 143.2, $^*J_F$ 1.3), 98.1 (s), 115.0 (dd, J 167.1, 7.1), 115.8 (dd, J 161.0, 7.1), 118.3 (ddd, J 160.7, 7.4, 1.3), 122.8 (q, J_F 277.3), 124.1 (ddd, J 159.7, 7.6, 1.4), 127.7 (s), 143.3 (s), 147.9 (q, J_F 30.8), 153.3 (dd, J 3.2, 1.4) and 162.2 (s); δ_F([$^2H_6$]DMSO) −62.4 (s); ν_{max}(KBr)/cm^{-1} 3420–3400, 3046, 3027, 2998, 2926, 1628, 1602, 1533, 1479, 1456 and 1440; m/z (EI) 311, 310 (M$^+$), 267, 266, 247, 238 and 44.

Preparation of the internal salt of 4-hydroxy-3-(3-methylaminopropyl)-2-trifluoromethylpyrimido[1,2-*a*]benzimidazole 3b. The treatment of 1-methyl-3-trifluoroacetylpiperidin-2-one **1b** (0.63 g, 3 mmol) with 2-aminobenzimidazole (0.44 g, 3.3 mmol) gave after chromatography (eluent: 65% MeOH–diethyl ether) the title compound **3b** as a yellow powder (0.46 g, 47%), mp 248–250 °C; δ_H([$^2H_6$]DMSO; 500 MHz; 50 °C) 1.92 (2 H, qt, J 7.2), 2.65 (3 H, s), 2.74 (2 H, t, J 6.7), 2.99 (2 H, t, J 7.4), 5.6–6.3 (NH_2, br s), 7.11 (1 H, dd, J 7.6, 7.6), 7.32 (1 H, dd, J 7.6, 7.6), 7.54 (1 H, d, J 8.0) and 8.49 (1 H, d, J 7.9); δ_C([$^2H_6$]DMSO; 125.8 MHz; 50 °C) 21.2 (t, J 127.6, $^*J_F$ 1.8), 26.5 (t, J 129.3), 32.7 (q, J 140.3), 48.2 (t, J 141.5), 102.0 (s), 115.2 (dd, J 166.8, 8.2), 115.6 (dd, J 159.8, 7.7), 118.2 (dd, J 159.7, 7.7), 123.0 (q, J_F 277.1), 124.2 (dd, J 157.0, 8.3), 127.7 (dd, J 8.7, 8.7), 143.1 (dd, J 9.0, 9.0), 147.5 (qt, J_F 31.0, J 4.3), 153.2 (s) and 162.4 (t, J 5.3); δ_F([$^2H_6$]DMSO) −62.2 (s); ν_{max}(KBr) cm^{-1} 3420–3400, 3032, 2962, 2926, 1626, 1589, 1577, 1533, 1460, 1446 and 1294; m/z (EI) 325, 324 (M$^+$), 281, 278, 267, 266, 238 and 44 (Found: C, 55.35; H, 4.7; N, 17.4. $C_{15}H_{15}F_3N_4O$ requires C, 55.55; H, 4.66; N, 17.27%).

The crystallographic data are as follows: $C_{15}H_{15}F_3N_4O$, M_r = 324.31, orthorhombic, $Pbca$, a = 9.785(2), b = 33.982(6), c = 17.959(6) Å, V = 5972(3) Å^3, D_x = 1.44 g cm^{-3} for Z = 16, Cu-Kα, λ = 1.541 78 Å, μ = 1.031 mm^{-1}, F(000) = 2688. T = 291 K, R = 0.063 for 2739 observed reflections [$I \geqslant 2\sigma(I)$] and 0.120 for all 5385 data. The intensities of the 5385 independent reflections were collected from a crystal with approximate dimensions 0.43 × 0.08 × 0.06 mm using a four circle Huber diffractometer equipped with a RU200 rotating anode generator. θ range of collected data: 2.6 to 68°, index ranges $0 \leqslant h \leqslant 11$, $0 \leqslant k \leqslant 40$, $0 \leqslant l \leqslant 21$. The structure was solved by direct methods using SHELXS86[16] and refined by full least-squares on F^2 with SHELXL93.[17] All atoms, except those of the N22 which were located from a difference Fourier synthesis, were calculated. All the H atoms were included in the refinement with a common isotropic temperature factor (U = 0.087 Å^2); final goodness-of-fit on F^2: 0.926, R [$I \geqslant 2\sigma(I)$] = 0.063, R (all data) = 0.120. Largest peak 0.20, largest hole −0.26 e Å^{-3} in final difference Fourier.

Preparation of internal salt of 4-hydroxy-3-(4-methylaminobutyl)-2-trifluoromethylpyrimido[1,2-*a*]benzimidazole 3c. The treatment of 1-methyl-3-trifluoroacetylazepan-2-one **1c** (0.75 g, 3.4 mmol) with 2-aminobenzimidazole (0.50 g, 3.7 mmol) gave after chromatography (eluent: 80% MeOH–diethyl ether) the title compound **3c** as a yellow powder (0.59 g, 51%), mp 225–227 °C; δ_H([$^2H_6$]DMSO) 1.4–1.7 (4 H, m), 2.50 (3 H, s), 2.5–2.6 (2 H, m), 2.9–3.0 (2 H, m), 5.7–5.8 (NH_2, br s), 7.05 (1 H, dd, J 7.6, 7.6), 7.28 (1 H, dd, J 7.6, 7.6), 7.48 (1 H, d, J 7.8) and 8.44 (1 H, dm, J 7.8); δ_C([$^2H_6$]DMSO) 24.3 (t, J 128.7, $^*J_F$ 3.2), 25.9 (t, J 129.4), 26.9 (t, J 130.1), 32.8 (q, J 141.0), 48.6 (t, J 142.0), 103.5 (s, $^*J_F$ 2.1), 115.1 (ddd, J 166.7, 7.1, 2.1), 115.5 (ddd, J 161.0, 8.0, 1.7), 118.0 (ddd, J 160.0, 7.4, 1.9), 123.2 (q, J_F 276.8), 124.2 (ddd, J 159.8, 8.0, 1.4), 127.8 (s), 143.4 (ddd, J 9.1, 9.1, 1.2), 147.0 (q, J_F 31.5), 153.5 (s, J_F 1.7) and 161.9 (s); δ_F([$^2H_6$]DMSO) −61.9 (s); ν_{max}(KBr)/cm^{-1} 3413, 3099, 3080, 3066, 2938, 2866, 1652, 1634, 1533, 1529, 1519 and 1454; m/z (EI) 339, 338 (M$^+$), 267, 266, 205, 181, 134, 114, 76 ($C_6H_4^+$), 69 (CF_3^+) and 44.

Reactions with 3-amino-1,2,4-triazole

Preparation of internal salt of 5-hydroxy-6-(3-methylaminopropyl)-7-trifluoromethyl-1,2,4-triazolo[4,3-*a*]pyrimidine 4. The treatment of 1-methyl-3-trifluoroacetylpiperidin-2-one **1b** (1.83 g, 8.7 mmol) with 3-amino-1,2,4-triazole (1.18 g, 13.9 mmol) gave without purification the title compound **4** as a white powder (1.79 g, 75%), mp 153–155 °C; δ_H([$^2H_6$]DMSO) 1.84 (2 H, qt, J 7.6), 2.6 (3 H, overlapped), 2.65 (2 H, t, J 7.6), 2.90 (2 H, tdd, J 7.0, 3.5, 3.5), 8.92 (1 H, s) and 9.0–10.0 (NH_2, br s); δ_C([$^2H_6$]DMSO) 22.2 (t, J 129.8, $^*J_F$ 1.6), 25.1 (t, J 129.7), 32.3 (q, J 142.4), 47.8 (t, J 145.2), 113.7 (s), 122.1 (q, J_F 276.6), 143.3 (d, J 219.0), 146.4 (qt, J_F 32.6, J 4.0), 147.9 (dd, J 5.8, 2.1, $^*J_F$ 1.7) and 156.8 (t, J 5.6); δ_F([$^2H_6$]DMSO) −62.3 (s); ν_{max}(KBr)/cm^{-1} 3500–3300, 3116, 3075, 2959, 1683, 1673, 1608, 1540, 1470 and 1454; λ(EtOH, c 1.01 × 10^{-3} mol dm^{-3})/nm 216 (A 3.38, ε 3350), 248 (A 3.46, ε 3440) and 286 (A 3.52, ε 3500); m/z (FAB) 277, 276, 245, 217, 185, 93 and 44 (Found: C, 43.85; H, 4.3; N, 25.6. $C_{10}H_{12}F_3N_5O$ requires C, 43.64; H, 4.39; N, 25.45%).

Preparation of 1-methyl-5-trifluoromethyl-1,2,3,4-tetrahydropyrido[2,3-*d*][1,2,4]triazolo[3,4-*b*]pyrimidine 11

Compound **4** (0.55 g, 2 mmol) was refluxed in a large excess of $POCl_3$ (20 cm^3) for 1 h. The resulting mixture was evaporated and the residue was diluted with diethyl ether (30 cm^3), washed twice with water (2 × 20 cm^3) and dried over $MgSO_4$. Chromatography of the residue on silica gel using 5% methanol–diethyl ether as eluent gave pyrimidine **11** (0.35 g, 68%), mp 204–206 °C; δ_H($CDCl_3$) 2.09 (2 H, qt, J 7.1), 2.94 (2 H, t, J 6.5), 3.58 (2 H, t, J 5.8), 3.90 (3 H, s) and 8.33 (1 H, s); δ_C($CDCl_3$) 20.2 (tqt, J 131.6, 4.5), 21.4 (ttq, J 131.8, 5.7, J_F 3.1), 42.0 (qt, J 138.0, 1.8), 53.0 (t, J 141.2), 100.3 (td, J 5.6, 1.1), 121.3 (q, J_F 276.9), 147.6 (qt, J_F 33.6, J 2.6), 148.3 (s, $^*J_F$ 1.2), 154.3 (d, J 217.5) and 155.0 (s, $^*J_F$ 2.3); δ_F($CDCl_3$) −66.0 (s); ν_{max}(KBr) cm^{-1} 2978, 2953, 1604, 1574, 1480, 1451, 1436, 1426, 1337 and 1137; λ(H_2O, pH 6, c 5.128 × 10^{-4} mol dm^{-3})/nm 231 (A 2.13, ε 14 130), 250 (A 1.94, ε 6170), 259 (A 1.54, ε 1020) and 280 (A 1.81, ε 3310); m/z (EI) 257 (M$^+$), 238 (M$^+$ − F), 228, 188 (M$^+$ − CF_3), 161, 119, 91, 77 and 69 (CF_3^+) (Found: C, 46.7; H, 3.8; N, 26.9. $C_{10}H_{10}F_3N_5$ requires C, 46.69; H, 3.92; N, 27.22%).

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