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Peculiarities of cyclization of ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates with 3-amino-5-hydroxypyrazole

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ABSTRACT

The reactions of ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates with 3-amino-5-hydroxypyrazole result in ethyl 2,7-dihydroxy-7-(polyfluoroalkyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylates under mild conditions. These products undergo recyclization in refluxing ethanol to form ethyl 3-hydroxy-4-(polyfluoroalkyl)-1H-pyrazolo[3,4-*b*]pyridin-5-carboxylates, whereas in refluxing glacial acetic acid they are dehydrated to ethyl 2-hydroxy-7-(polyfluoroalkyl)pyrazolo[1,5-*a*]pyrimidin-6-carboxylates. The non-fluorinated ethyl 2-ethoxymethylene-3-oxo esters in the reactions with 3-amino-5-hydroxypyrazole in ethanol (or glacial acetic acid) under reflux form only ethyl 2-hydroxy-7-phenyl(hydroxy)pyrazolo[1,5-*a*]pyrimidin-6-carboxylates.

1. Introduction

Pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines remain to be tremendously attractive compounds for drug discovery since they exhibit a wide range of biological and pharmaceutical activities. Among their derivatives there are anti-leishmania drugs [1], analgesics [2], selective inhibitors of PDE5 [3], PDE4 [4], HCV polymerase [5], CHK1 [6], cyclin-dependent kinase [7] and B-Raf kinase [8] as well as A1 adenosine [9], glucocorticoid [10] and CRF1 [11] receptor antagonists, antimicrobial [12], anti-tumor [13], antiproliferative [14], and antitubercular agents [15]. The search for new compounds bearing these ring systems seems rather promising.

Cyclocondensation of 1,3-dicarbonyl compounds with aminopyrazoles is of particular value for the synthesis of pyrazolo[1,5-*a*]pyrimidines [16]. The use of 2-ethoxymethylene-3-oxo esters [17,18] and diethyl-2-ethoxymethylenemalonate [18,19] allows obtaining functionalized pyrazolo[1,5-*a*]pyrimidines, which can undergo further transformations. Aminopyrazoles were shown to react as *N*,*N*-binucleophiles in these cyclizations. *N*(1)-Substituted aminopyrazoles react with 2-ethoxymethylene-3-oxo esters [7,20] and diethyl-2-ethoxymethylenemalonate [1,3,4,9,10,20] to yield pyrazolo[3,4-*b*]pyridines. In the latter case, *N*(1)-substituted aminopyrazoles behave as *N*,*C*-binucleophiles.

Previously, we have shown that ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates are very suitable building blocks for the synthesis of azaheterocycles, including condensed pyrimidines [21]. The reactions of ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates with aminoazoles were found to differ from those of non-fluoroalkylated substrates. They react with aminoazoles (including 3-amino-5-methylpyrazole and ethyl 3-aminopyrazole-4-carboxylate) to give stable dihydroazolo[1,5-*a*]pyrimidines bearing a *gem*-aminoalcohol fragment at the polyfluoroalkyl substituent. Polyfluoroalkylated dihydroazolo[1,5-*a*]pyrimidines can be subjected to ring-chain isomerization in solutions [21c].

However, the reactions of ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates with aminopyrazoles bearing both the NH-groups and an activated *C*-center have not been studied previously. In this case, while using such binucleophiles, one can expect a change of the cyclization pathways. The present paper focuses on the cyclization of ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates with 3-amino-5-hydroxypyrazole bearing an additional nucleophilic reaction *C*-center.

2. Results and discussion

It has been established that ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates **1a–c** react with 3-amino-5-hydroxypyrazole in tetrahydrofuran or dimethylformamide under mild

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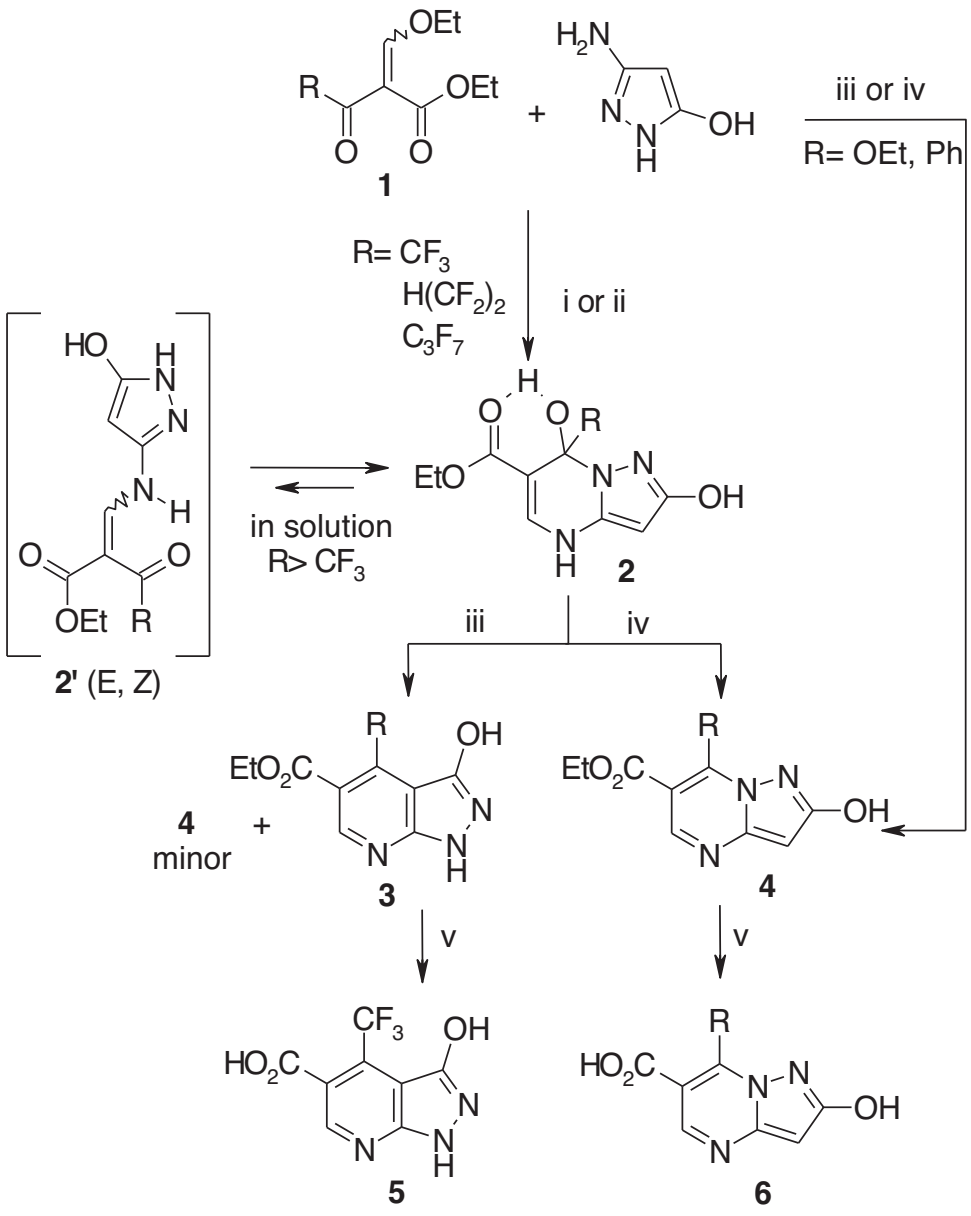

Scheme 1. Synthesis of pyrazolo[1,5-*a*]pyrimidines **2**, **4**, **6** and pyrazolo[3,4-*b*]pyridines **3**, **5**.

conditions to give ethyl 2,7-dihydroxy-7-(polyfluoroalkyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylates **2a–c** (Scheme 1). Nevertheless, the similar synthesis of dihydropyrazolo[1,5-*a*]pyrimidines from 3-amino-5-methylpyrazole and ethyl 3-aminopyrazole-4-carboxylate required more drastic conditions [21c].

X-ray diffraction analysis of crystalline compound **2c** (Fig. 1) confirmed its structure as ethyl 2,7-dihydroxy-7-heptafluoropropyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylate with one intermolecular hydrogen bond between the atoms O(1)...H(3)–O(3). The parameters of this hydrogen bond are as follows: O(1)...H(3) 2.80(2) Å, H(3)–O(3) 0.82(2) Å, O(1)...O(3) 3.133(3) Å, O(1)...H(3)–O(3) 162(2)°.

The comparison of the IR spectra of compounds **2a–c** did not reveal considerable differences in their structure.

The ^{1}H NMR spectra of compounds **2a–c** recorded in $(CD_3)_2SO$ contained the signals corresponding to the resonance of protons in dihydropyrazolo[1,5-*a*]pyrimidines. However, in the ^{1}H and ^{19}F NMR spectra of compound **2c** in $(CD_3)_2SO$, besides a set of signals of heterocyclic form **2** (93%), we observed two additional sets of signals corresponding to **2′** (*Z*) (3%) and **2′** (*E*) (4%) isomers of the

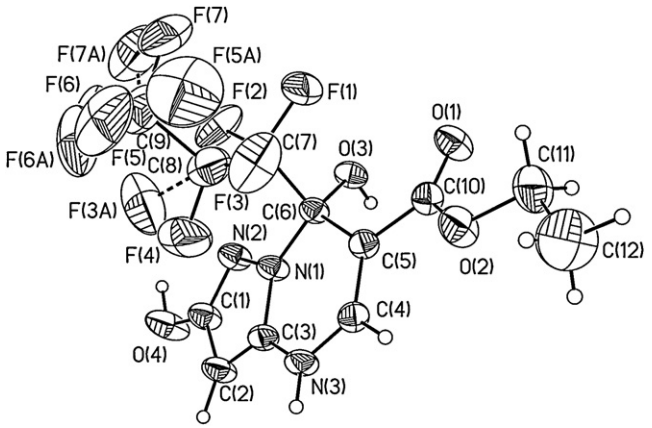

Fig. 1. The general view of compound **2c** (thermal ellipsoids of 50% probability).

open-chain ethyl 4,4,5,5,6,6,6-heptafluoro-2-[(5-hydroxy-1*H*-pyrazol-3-yl)aminomethylene-3-oxohexanoate (Scheme 1).

The ability of dihydropyrazolo[1,5-*a*]pyrimidine **2c** to undergo ring-chain isomerism in $(CD_3)_2SO$ encouraged us to register the ^1H and ^{19}F NMR spectra of compounds **2a–c** in various solvents. The results of this investigation are presented in Table 1. It turned out that the tendency of heterocycles **2a–c** toward opening the pyrimidine ring and formation of the open-chain isomers increases with elongation of the polyfluoroalkyl substituent. Besides, methanol stabilizes the cyclic form regardless of the length of polyfluoroalkyl substituent.

It should be noted that the ring-chain isomerism is not typical for the non-fluorinated analogs viz. 2-Azolylaminomethylene-3-oxoalkanoates. These compounds exhibited irreversible intramolecular condensation with the formation of azolopyrimidines [18a].

Surprisingly, the attempts to crystallize compounds **2a–c** from ethanol led to the formation of pyrazolo[3,4-*b*]pyridines **3a–c** as the main products. We did not observe such transformations when crystallizing other dihydroazolo[1,5-*a*]pyrimidines, including the pyrazolo derivatives [21a,c]. Obviously, it became possible due to the presence of a competitive nucleophilic *C*-center activated by the hydroxy group in 3-amino-5-hydroxypyrazole. These recyclization reactions are regioselective and the pyrazolo[3,4-*b*]pyridines **3** were the predominant products (64–86%), whereas dehydrated pyrazolopyrimidines **4a–c** were isolated as by-products (5–14%) (Scheme 1).

For the recyclization of dihydropyrazolo[1,5-*a*]pyrimidines **2a–c** into pyrazolo[3,4-*b*]pyridines **3a–c**, it is possible to use boiling methanol in addition to ethanol. However, a mixture of products **3a–c** and **4a–c** with the predominance of the latter is formed in *n*-butanol under reflux. The refluxing of heterocycles **2** in polar aprotic solvents such as acetonitrile and dimethylformamide led to an inseparable mixture of the products, in which we did not detected pyrazolo[3,4-*b*]pyridines **3**.

Table 1
Content (%) of isomeric forms of compounds **2** in various solvents according to the NMR spectroscopy data.

Compound	R^F	Solvent			
		$(CD_3)_2SO$	CD_3CN	$(CD_3)_2CO$	CD_3OD
2a	CF_3	**2a**, 100	**2a**, 100	**2a**, 100	**2a**, 100
2b	$(CF_2)_2H$	**2b**, 100	**2b**, 96 **2′b** (*E*), 4	**2b**, 94 **2′b** (*Z*), 1 **2′b** (*E*), 5	**2b**, 100
2c	C_3F_7	**2c**, 93 **2′c** (*Z*), 3 **2′c** (*E*), 4	**2c**, 92 **2′c** (*Z*), 3 **2′c** (*E*), 5	**2c**, 82 **2′c** (*Z*), 8 **2′c** (*E*), 10	**2c**, 100

Table 2
The NMR monitoring data for the heterocycle **2a** recyclization in CD_3OD.

Reaction conditions	Content of the starting material and the reaction products (%)		
	2a	**3a**	**4a**
10 min, rt	99	~1	–
6 h, rt	86	14	–
2 weeks, rt	28	70	~1
5 min, reflux	56	43	1
30 min, reflux	–	97	3

While investigating the ring-chain isomerism of dihydropyrazolo[1,5-*a*]pyrimidines **2** in CD_3OD, the open forms were not found (see Table 1). However, the recyclization of dihydropyrazolo[1,5-*a*]pyrimidines **2a–c** into pyrazolo[3,4-*b*]pyridines **3a–c** takes place only in alcohols.

To study this reaction in detail, the recyclization of the heterocycle **2a** in CD_3OD was monitored by NMR, but no intermediates were found (see Table 2). The recyclization proceeded in CD_3OD at room temperature; however, complete conversion of **2a** into **3a** did not occur even after 2 weeks of stirring. When the same reaction was carried out in refluxing CD_3OD, the yield of **3a** was 43% in 5 min. The complete conversion was achieved after refluxing for 30 min.

When ethanol was used as a solvent, the recyclization did not proceed at room temperature. However, refluxing did promote the process, and the TLC monitoring showed complete conversion of **2a** into **3a** in 30 min. Replacement of methanol and ethanol for higher boiling *n*-butanol led to a change in the reaction pathway yielding the dehydrated product **4a**.

A peculiarity of these transformations in alcohols is likely to be due to the solvation effects (hydrogen bonding and others) typical for such polar protic solvents. Solvation effects can lead to redistribution of the electron density in a dissolved compound, which contributes to either the weakening or strengthening of chemical bonds [22].

From the experimental results it can be assumed that an intermediate activated complex of heterocycle **3a** with solvent is formed in methanol and ethanol. The formation of such a complex stabilizes the cyclic form and prevents a fast dihydropyrimidine cycle opening. Therefore, we did not find an open-chain form immediately after dissolution in methanol. However, under the influence of alcohol solvation effects there is the redistribution of electronic density in an intermediate complex resulting in the cleavage of C(7)–N(8) bond. Then, the open-chain form undergoes fast recyclization into a pyridine derivative with a new C(3a)–C(4) bond. Hence, methanol having the smallest size and the greatest dielectric constant compared to other alcohols (MeOH ε 32.6, EtOH ε 24.3, BuOH ε 17.1) is considered to be a more suitable solvent for this recyclization. It is obvious that the recyclization process proceeds faster under the temperature.

The structure of pyrazolo[3,4-*b*]pyridine **3c** was proved by the X-ray diffraction analysis (Fig. 2).

Dehydration of dihydropyrazolo[1,5-*a*]pyrimidines **2a–c** into pyrazolo[1,5-*a*]pyrimidines **4a–c** was successfully performed in glacial acetic acid under reflux for 2–3 days (Scheme 1). The X-ray diffraction analysis proved the structure of heterocycle **4a** (Fig. 3).

The ^1H NMR spectra of compounds **3a–c** are characterized by the singlet of the methine proton H-6 (δ 8.69–8.74 ppm) and two broadened low-field singlets of NH (δ 11.36–11.62 ppm) and OH (δ 13.10–13.21 ppm) protons. These data are in contrast to those published for heterocycles **4a–c**. Their ^1H NMR spectra contained two singlets of methine protons H-3 (δ 6.27–6.32 ppm) and H-5 (δ

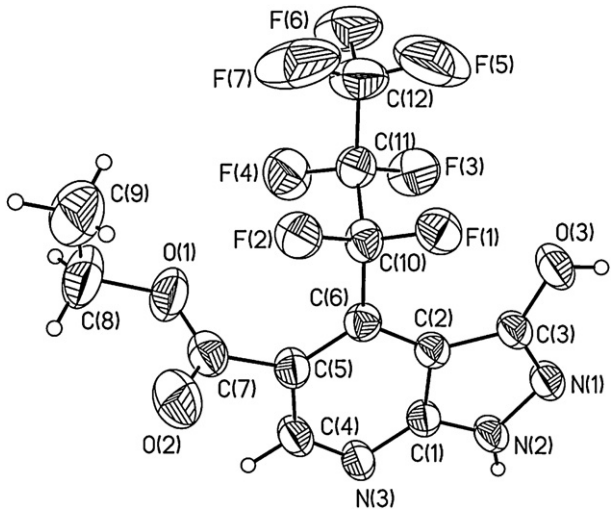

Fig. 2. The general view of compound **3c** (thermal ellipsoids of 50% probability).

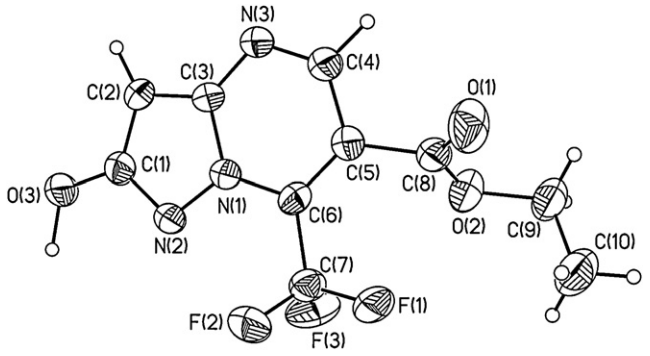

Fig. 3. The general view of compound **4a** (thermal ellipsoids of 50% probability).

8.51–8.57 ppm), as well as a broadened singlet of the OH proton (δ 7.62–9.60 ppm) [23]. The difference in the spectral parameters for heterocycles **3a–c** and **4a–c** allowed us to identify all these products even without X-ray diffraction analysis in each case.

The opportunity to obtain three heterocyclic products **2**, **3** and **4** in the reactions of fluoroalkyl esters **1** with 3-amino-5-hydroxypyrazole encouraged us to examine these transformations under various conditions. It has been found that these reactions carried out in ethanol, acetonitrile, 1,4-dioxane, glacial acetic acid or dimethylformamide under reflux are not regioselective and result in inseparable mixtures of the products.

For comparison, we also investigated the reactions of non-fluorinated esters **2d**,**e** with 3-amino-5-hydroxypyrazole. Attempts to implement these transformations under similar mild conditions (tetrahydrofuran or dimethylformamide, at room temperature) were unsuccessful due to the formation of an inseparable mixture of products and an incomplete conversion of the starting reagents. The use of ethanol (or glacial acetic acid) under reflux gave only pyrazolo[1,5-*a*]pyrimidines **4d**,**e** similarly as described in [17b] (Scheme 1).

The ester substituent in heterocycles **3**,**4** made it possible to obtain pyrazolo[3,4-*b*]pyridin-5-carboxylic acid **5** and pyrazolo[1,5-*a*]pyrimidin-6-carboxylic acids **6a–c** by alkaline hydrolysis (Scheme 1).

3. Conclusion

Two types of heterocycles were obtained in the reactions of ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates with 3-amino-5-hydroxypyrazole. In addition, the first example of recyclization of dihydropyrazolo[1,5-*a*]pyrimidines into pyrazolo[3,4-*b*]pyridines was found. The recyclization became possible when 3-amino-5-hydroxypyrazoles with a *C*-nucleophilic center activated by a hydroxy group were used. The revealed recyclization is typical for polyfluoroalkyl-containing pyrazolo[1,5-*a*]pyrimidines and was not found with non-fluorinated analogs.

4. Experimental

4.1. General

Melting points were measured in the open capillaries on a Stuart SMP3 melting point apparatus. The IR diffuse reflectance spectra were recorded on a Perkin Elmer Spectrum One Fourier transform infrared spectrometer in the range from 400 to 4000 cm^{-1}. The ^{1}H (400 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer with $SiMe_4$ and C_6F_6 as internal standards, respectively. The ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 500 spectrometer with $SiMe_4$ as internal standards. The chemical shifts were converted from C_6F_6 to CCl_3F (−162.9 ppm). The microanalyses were carried out on a Perkin Elmer PE 2400 series II elemental analyzer. The column chromatography was performed on Merck silica gel 60 (0.063–0.200 mm).

Ethyl 2-ethoxymethylene-3-oxo-3-(polyfluoroalkyl)propionates **1a–c** were prepared according to the reported procedure [24], 3-amino-5-hydroxypyrazole is commercially available from Alfa Aesar.

4.2. Reactions of esters *1a–e* with 3-amino-5-hydroxypyrazole

Method A. A mixture of the corresponding ester (**1a–c**) (3 mmol) and 3-amino-5-hydroxypyrazole (3 mmol) in dimethylformamide (20 mL) was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was poured into water (50 mL). The resulting precipitate was filtered off and crystallized from acetone (or acetonitrile) to give dihydropyrazolo[1,5-*a*]pyrimidine (**2a–c**).

Method B. A mixture of the corresponding ester (**1a–c**) (3 mmol) and 3-amino-5-hydroxypyrazole (3 mmol) in tetrahydrofuran (20 mL) was stirred for 3–5 days at room temperature. After completion of the reaction, the solvent was evaporated, the residue was crystallized from acetone (or acetonitrile) to give dihydropyrazolo[1,5-*a*]pyrimidines (**2a–c**).

Method C. A mixture of the corresponding ester (**1d**,**e**) (3 mmol) and 3-amino-5-hydroxypyrazole (3 mmol) in glacial acetic acid (10 mL) was refluxed for 4 h (**1d**) and for 3 days (**1e**). After completion of the reaction and cooling the reaction mixture, the resulting precipitate was filtered off and washed with water, then crystallized from dimethyl sulfoxide to give pyrazolo[1,5-*a*]pyrimidine **4d**. In the case of product **4e** the reaction mixture was poured into water (30 mL) and neutralized to pH 7 with sodium hydrogen carbonate. The resulting precipitate was filtered off and crystallized from 50% ethanol.

Method D. A mixture of the corresponding ester (**1d**,**e**) (3 mmol) and 3-amino-5-hydroxypyrazole (3 mmol) in ethanol (15 mL) was refluxed for 2–3 days. After completion of the reaction and cooling the reaction mixture, the resulting precipitate was filtered off and crystallized from dimethyl sulfoxide to give pyrazolo[1,5-*a*]pyrimidine **4d**. In the case of product **4e** the solvent was evaporated and the residue was crystallized from 50% ethanol.

4.2.1. Ethyl 2,7-dihydroxy-7-trifluoromethyl-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-carboxylate (*2a*)

Yield (method A) 580 mg (66%), (method B) 739 mg (84%), white powder, mp 191–192 °C. IR: ν 3323, 3283, 3189 (N–H, O–H), 2985 (C–H), 1680 (C=O), 1609, 1536 (N–C=C–C=N), 1239–1174

(C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 1.22 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.12 (2H, m, CH_2), 5.11 (1H, s, H-3), 7.68 (1H, s, OH), 7.79 (1H, s, H-5), 10.18 (1H, br s, OH), 10.73 (1H, br s, NH). ^{13}C NMR ($(CD_3)_2SO$): δ 14.2 (s, CH_3), 59.4 (s, CH_2), 75.4 (s, C-3), 82.4 (q, C-7, J_{CF} = 33.4 Hz), 93.6 (s, C-6), 123.5 (q, CF_3, J_{CF} = 293.0 Hz), 137.8 (s, C-3a), 138.7 (s, C-5), 161.4 (s, C-2), 164.8 (s, C=O). ^{19}F NMR ($(CD_3)_2SO$): δ −78.45 (s, CF_3). Anal. calcd. for $C_{10}H_{10}F_3N_3O_4$: C, 40.96; H, 3.41; N, 14.33. Found: C, 40.98; H, 3.20; N, 14.47.

4.2.2. Ethyl 2,7-dihydroxy-7-(1,1,2,2-tetrafluoroethyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-carboxylate (**2b**)

Yield (method A) 517 mg (53%), (method B) 693 mg (71%), white powder, mp 175–176 °C. IR: ν 3305, 3153 (N–H, O–H), 3089, 2990 (C–H), 1673 (C=O), 1614, 1542 (N–C=C–C=N), 1242–1082 (C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 1.22 (t, 3H, CH_3, J_{HH} = 7.1 Hz), 4.12 (2H, m, CH_2), 5.12 (1H, s, H-3), 6.70 (1H, ddd, J_{HF} = 54.5, 51.8, 11.7 Hz, CF_2H), 7.57 (1H, br s, OH), 7.78 (1H, s, H-5), 10.15 (1H, br s, OH), 10.68 (1H, br s, NH). ^{13}C NMR ($(CD_3)_2SO$): δ 14.1 (s, CH_3), 59.39 (s, CH_2), 75.4 (s, C-3), 83.8 (t, C-7, J_{CF} = 28.8 Hz), 93.9 (s, C-6), 109.8 (tm, HCF_2, J_{CF} = 251.1 Hz), 114.8 (tm, CF_2, J_{CF} = 266.0 Hz), 138.2 (s, C-3a), 138.3 (s, C-5), 161.4 (s, C-2), 165.4 (s, C=O). ^{19}F NMR ($(CD_3)_2SO$): δ −137.02 (1F, ddt, J_{FF} = 292.0, 9.7 Hz, J_{FH} = 54.5 Hz, CF_2H), −131.07 (1F, dm, J_{FF} = 258.5 Hz, CF_2), −130.74 (1F, ddd, J_{FF} = 292.0, 10.7 Hz, J_{FH} = 51.8 Hz, CF_2H), −120.72 (1F, dd, J_{FF} = 258.5, 10.7 Hz, CF_2). Anal. calcd. for $C_{11}H_{11}F_4N_3O_4$: C, 40.62; H, 3.41; N, 12.96. Found: C, 40.56; H, 3.31; N, 12.75.

4.2.3. Ethyl 2,7-dihydroxy-7-(1,1,2,2,3,3,3-heptafluoropropyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-carboxylate (**2c**)

Yield (method A) 578 mg (49%), (method B) 766 mg (65%), white powder, mp 174–176 °C. IR: ν 3319, 3194 (N–H, O–H), 2991 (C–H), 1651 (C=O), 1629, 1609, 1546 (N–C=C–C=N), 1218–1121 (C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ **2c** (93%): 1.22 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.12 (2H, m, CH_2), 5.14 (1H, s, H-3), 7.77 (1H, s, OH), 7.81 (1H, d, J_{HH} = 6.0 Hz, H-5), 10.13 (1H, br s, OH), 10.81 (1H, br d, J_{HH} = 6.0 Hz, NH), **2c′** (*E*) (4%): 1.06 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.17 (2H, q, J_{HH} = 7.1 Hz, CH_2), 5.59 (1H, s, H-4′), 8.61 (1H, d, J_{HH} = 14.6 Hz, CH), 11.01 (1H, s, OH), 11.76 (1H, br d, J_{HH} = 14.6 Hz, NH), 12.16 (1H, br s, NH-1′), **2c′** (*Z*): (3%) 1.28 (3H, t, J_{HH} = 7.0 Hz, CH_3), 4.24 (2H, q, J_{HH} = 7.0 Hz, CH_2), 5.50 (1H, s, H-4′), 8.61 (1H, d, J_{HH} = 14.5 Hz, CH), 10.86 (1H, s, OH), 10.96 (1H, br d, J_{HH} = 14.5 Hz, NH), 12.06 (1H, br s, NH-1′). ^{13}C NMR ($(CD_3)_2SO$): δ **2c** 14.1 (s, CH_3), 59.5 (s, CH_2), 75.6 (s, C-3), 84.3 (t, C-7, J_{CF} = 26.6 Hz), 93.8 (s, C-6), 109.1 (tq, β-CF_2, J_{CF} = 37.6, 268.3 Hz), 114.4 (tt, α-CF_2, J_{CF} = 30.7, 269.9 Hz), 117.7 (qt, CF_3, J_{CF} = 35.0, 289.0 Hz), 137.6 (s, C-3a), 138.5 (s, C-5), 161.2 (s, C-2), 165.4 (s, C=O). ^{19}F NMR ($(CD_3)_2SO$): δ **2c** (93%): −126.55 (1F, ddd, J_{FF} = 288.6, 13.7, 5.4 Hz, β-CF_B), −125.08 (1F, ddd, J_{FF} = 288.6, 12.8, 4.7 Hz, β-CF_A), −117.41 (1F, dm, J_{FF} = 278.0 Hz, α-CF_B), −115.53 (1F, dm, J_{FF} = 278.0 Hz, α-CF_A), −80.58 (t, 3F, J_{FF} = 11.7 Hz, CF_3), **2c′** (*E*): (4%): −123.26 (2F, m, β-CF_2), −113.11 (2F, m, α-CF_2), −79.95 (3F, t, J_{FF} = 9.4 Hz, CF_3), **2c′** (*Z*): (3%): ′124.47 (2F, m, β-CF_2), −112.49 (2F, m, α-CF_2), −79.90 (3F, t, J_{FF} = 9.4 Hz, CF_3). Anal. calcd. for $C_{12}H_{10}F_7N_3O_4$: C, 36.65; H, 2.65; N, 10.69. Found: C, 36.63; H, 2.59; N, 10.75.

4.2.4. Ethyl 2,7-dihydroxypyrazolo[1,5-a]pyrimidine-6-carboxylate (**4d**)

Yield (method C) 395 mg (59%), yield (method D) 308 mg (46%), yellow powder, mp 300–302 °C. IR: ν 3277, 3205, 3147, 3100 (O–H), 3001, 2984, 2939 (C–H), 1715 (C=O), 1661, 1621, 1581, 1551 (C=C–C=N) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 1.27 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.20 (2H, q, J_{HH} = 7.1 Hz, CH_2), 5.58 (1H, s, H-3), 8.44 (1H, s, H-5), 11.04, 12.77 (both 1H, two br s, 2 OH). ^{13}C NMR ($(CD_3)_2SO$): δ 14.3 (s, CH_3), 59.9 (s, CH_2), 77.8 (s, C-3), 99.0 (s, C-6), 140.9 (s, C-3a), 144.2 (s, C-5), 152.2 (s, C-7), 163.7 (s, C-2), 164.1 (s, C=O). Anal. calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.34; H, 3.98; N, 18.70.

4.2.5. Ethyl 2-hydroxy-7-phenylpyrazolo[1,5-a]pyrimidine-6-carboxylate (**4e**)

Yield (method C) 697 mg (82%), yield (method D) 646 mg (76%), light yellow powder, mp 234–236 °C. IR: ν 3131, 3100 (O–H), 3012, 2980 (C–H), 1704 (C=O), 1625, 1539 (C=C–C=N) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 0.91 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.00 (2H, q, J_{HH} = 7.1 Hz, CH_2), 6.09 (1H, s, H-3), 7.45–7.54 (5H, m, Ph), 8.80 (1H, s, H-5), 11.46 (1H, s, OH). ^{13}C NMR ($(CD_3)_2SO$): δ 13.4 (s, CH_3), 60.6 (s, CH_2), 82.2 (s, C-3), 109.3 (s, C-6), 128.0 (s, C_o), 128.7 (s, C_m), 129.5 (s, C_p), 131.0 (s, C_i), 148.2 (s, C-3a), 149.6 (s, C-5), 149.8 (s, C-7), 164.0 (s, C-2), 167.9 (s, C=O). Anal. calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.44; H, 4.53; N, 14.82.

4.3. Recyclization of 4,7-dihydropyrazolo[1,5-a]pyrimidines **2a–c**

Dihydropyrazolo[1,5-*a*]pyrimidine (**2a–c**) (1 mmol) in ethanol (30 mL) was refluxed for 30–40 min. After completion of the reaction, the solvent was evaporated. The residue was washed with chloroform (2 × 20 mL) and crystallized from acetone (or acetonitrile) to give the pyrazolo[3,4-*b*]pyridines (**3a–c**). The chloroform filtrate was evaporated, and the residue was crystallized from hexane to give a small amount (5–14%) of pyrazolo[1,5-*a*]pyrimidines (**4a–c**).

4.3.1. Ethyl 3-hydroxy-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridin-5-carboxylate (**3a**)

Yield 237 mg (86%), light yellow powder, mp 229–231 °C. IR: ν 3171, 3136 (N–H, O–H), 3098, 3989 (C–H), 1714 (C=O), 1590, 1566, 1514 (N–C=C–C=N), 1221–1143 (C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 1.32 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.36 (2H, q, J_{HH} = 7.1 Hz, CH_2), 8.74 (1H, s, H-6), 11.47 (1H, br s, NH), 13.16 (1H, br s, OH). ^{13}C NMR ($(CD_3)_2SO$): δ 13.7 (s, CH_3), 62.1 (s, CH_2), 98.0 (s, C-5), 121.0 (q, C-3a, J_{CF} = 2.9 Hz), 121.9 (q, CF_3, J_{CF} = 274.9 Hz), 128.7 (q, C-4, J_{CF} = 34.9 Hz), 149.2 (s, C-6), 152.5, 153.0 (two s, C-3, C-7a), 166.0 (s, C=O). ^{19}F NMR ($(CD_3)_2SO$): δ −56.91 (s, CF_3). Anal. calcd. for $C_{10}H_8F_3N_3O_3$: C, 43.65; H, 2.93; N, 15.27. Found: C, 43.64; H, 3.05; N, 15.34.

4.3.2. Ethyl 3-hydroxy-4-(1,1,2,2-tetrafluoroethyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate (**3b**)

Yield 218 mg (71%), yellow powder, mp 230–233 °C. IR: ν 3168, 3137 (N–H, O–H), 3098, 3067 (C–H), 1732 (C=O), 1595, 1555, 1506 (N–C=C–C=N), 1231–1072 (C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 1.31 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.35 (2H, q, J_{HH} = 7.1 Hz, CH_2), 6.92 (1H, tt, J_{HF} = 52.0, 5.8 Hz, CF_2H), 8.69 (1H, s, H-6), 11.62 (1H, br s, NH), 13.10 (1H, br s, OH). ^{19}F NMR ($(CD_3)_2SO$): δ −136.40 (2F, dm, J_{FH} = 52.0 Hz, CF_2H), −109.63 (2F, m, CF_2). Anal. calcd. for $C_{11}H_9F_4N_3O_3$: C, 43.01; H, 2.95; N, 13.68. Found: C, 42.80; H, 3.01; N, 13.55.

4.3.3. Ethyl 3-hydroxy-4-(1,1,2,2,3,3,3-heptafluoropropyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate (**3c**)

Yield 240 mg (64%), light yellow powder, mp 251–253 °C. IR: ν 3186, 3126 (N–H, O–H), 3049 (C–H), 1736 (C=O), 1592, 1559, 1500 (N–C=C–C=N), 1239–1110 (C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 1.29 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.35 (2H, q, J_{HH} = 7.1 Hz, CH_2), 8.73 (1H, s, H-6), 11.36 (1H, br s, NH), 13.21 (1H, br s, OH). ^{13}C NMR ($(CD_3)_2SO$): δ 13.6 (s, CH_3), 62.2 (s, CH_2), 98.9 (s, C-5), 108.2 (tq, β-CF_2, J_{CF} = 266.4, 38.8 Hz), 114.9 (tt, α-CF_2, J_{CF} = 258.7, 34.6 Hz), 117.9 (qt, CF_3, J_{CF} = 287.6, 35.9 Hz), 121.0 (t, C-3a, J_{CF} = 4.4 Hz), 126.8 (t, C-4, J_{CF} = 26.2 Hz), 148.9 (s, C-6), 151.9, 153.1 (two s, C-3, C-7a), 166.1 (s, C=O). ^{19}F NMR ($(CD_3)_2SO$): δ −122.28 (2F, m, β-CF_2), −102.79 (2F, m, α-CF_2), −79.87 (3F, t, J_{FF} = 10.1 Hz, CF_3). Anal. calcd. for $C_{12}H_8F_7N_3O_3$: C, 38.41; H, 2.15; N, 11.20. Found: C, 38.43; H, 2.10; N, 11.18.

4.4. Dehydration of 4,7-dihydropyrazolo[1,5-a]pyrimidines **2a–c**

Dihydropyrazolo[1,5-*a*]pyrimidine (**2a–c**) (1 mmol) in glacial acetic acid (10 mL) was refluxed for 2–3 days. After the completion of the reaction, the reaction mixture was poured into water (20 mL) and neutralized to pH 7 by sodium hydrogen carbonate. The resulting precipitate was filtered off and crystallized from hexane to give corresponding pyrazolo[1,5-*a*]pyrimidine (**4a**,**c**). In the case of product **4b** after neutralization, the reaction mixture was extracted with chloroform (2 × 50 mL). The organic layer was concentrated and the residue was purified by column chromatography (eluent–chloroform).

4.4.1. Ethyl 2-hydroxy-7-trifluoromethylpyrazolo[1,5-a]pyrimidin-6-carboxylate (**4a**)

Yield 245 mg (89%), yellow powder, mp 139–141 °C. IR: ν 3159 (O–H), 3008, 2971 (C–H), 1741 (C=O), 1629, 1534 (C=C–C=N), 1266–1163 (C–F) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.59 (2H, q, J_{HH} = 7.1 Hz, CH_2), 6.32 (1H, s, H-3), 8.57 (1H, s, H-5), 9.60 (1H, br s, OH). ^{19}F NMR ($CDCl_3$): δ −65.64 (s, CF_3). Anal. calcd. for $C_{10}H_8F_3N_3O_3$: C, 43.65; H, 2.93; N, 15.27. Found: C, 43.58; H, 2.82; N, 15.47.

4.4.2. Ethyl 2-hydroxy-7-(1,1,2,2-tetrafluoroethyl)pyrazolo[1,5-a]pyrimidin-6-carboxylate (**4b**)

Yield 258 mg (84%), yellow powder, mp 129–131 °C. IR: ν 3140 (O–H), 3050, 2986 (C–H), 1728 (C=O), 1629, 1538 (C=C–C=N), 1257–1086 (C–F) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.40 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.44 (2H, q, J_{HH} = 7.1 Hz, CH_2), 6.27 (1H, s, H-3), 6.95 (1H, tt, J_{HF} = 53.3, 5.8 Hz, CF_2H), 7.62 (1H, s, OH), 8.53 (1H, s, H-5). ^{19}F NMR ($CDCl_3$): δ −138.13 (2F, dm, J_{FH} = 53.3 Hz, HCF_2), −118.55 (2F, m, CF_2). Anal. calcd. for $C_{11}H_9F_4N_3O_3$: C, 43.01; H, 2.95; N, 13.68. Found: C, 43.17; H, 2.99; N, 13.60.

4.4.3. Ethyl 7-(1,1,2,2,3,3,3-heptafluoropropyl)-2-hydroxypyrazolo[1,5-a]pyrimidin-6-carboxylate (**4c**)

Yield 289 mg (77%), yellow powder, mp 130–131 °C. IR: ν 3151 (O–H), 3049, 2938 (C–H), 1737 (C=O), 1625, 1530 (C=C–C=N), 1243–1124 (C–F) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38 (3H, t, J_{HH} = 7.1 Hz, CH_3), 4.42 (2H, q, J_{HH} = 7.1 Hz, CH_2), 6.29 (1H, s, H-3), 8.19 (1H, br s, OH), 8.51 (1H, s, H-5). ^{13}C NMR ($CDCl_3$): δ 13.7 (s, CH_3), 63.2 (s, CH_2), 66.0 (s, C-3), 83.3 (s, C-6), 109.3 (tq, β-CF_2, J_{CF} = 269.6, 36.7 Hz), 113.4 (tt, α-CF_2, J_{CF} = 263.4, 36.0 Hz), 117.7 (qt, CF_3, J_{CF} = 288.4, 33.9 Hz), 131.5 (t, C-7, J_{CF} = 27.4 Hz), 147.7 (s, C-5), 150.4 (s, C-3a), 164.0 (s, C-2), 167.3 (s, C=O). ^{19}F NMR ($CDCl_3$): δ −122.61 (2F, m, β-CF_2), −109.81 (2F, m, α-CF_2), −81.59 (3F, t, J_{FF} = 8.8 Hz, CF_3). Anal. calcd. for $C_{12}H_8F_7N_3O_3$: C, 38.41; H, 2.15; N, 11.20. Found: C, 38.21; H, 2.10; N, 11.22.

4.5. Hydrolysis of ethyl pyrazolo[3,4-b]pyridin-5-carboxylate **3a** and ethyl pyrazolo[1,5-a]pyrimidin-6 carboxylates **4b**,**d**,**e**

Pyrazolo[3,4-*b*]pyridine **3** (or pyrazolo[1,5-*a*]pyrimidine **4**) (0.3 mmol) and sodium hydroxide (0.6 mmol) in the mixture of ethanol–water 3:2 (15 mL) were refluxed for 6–8 h. After completion of the reaction, the reaction mixture was poured into water (40 mL) and acidified to pH 3–4 with 10% hydrochloric acid. The resulting precipitate was filtered off, washed with water and crystallized from ethanol to give acid (**6a–c**). In the case of product **5** after acidification, the reaction mixture was extracted with acetonitrile (2 × 50 mL). The solvent was removed under reduced pressure; the residue was crystallized from ethanol.

4.5.1. 3-Hydroxy-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridin-5-carboxylic acid (**5**)

Yield 71 mg (96%), light yellow powder, mp 290–292 °C. IR: ν 3261, 3213 (O–H, N–H), 3058, 2985 (C–H), 1702 (C=O), 1592, 1558 (N–C=C–C=N), 1224–1124 (C–F) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 8.73 (1H, s, H-6), 11.68, 13.09, 13.40 (all of 1H, three br s, 2 OH, NH). ^{19}F NMR ($CDCl_3$): δ −56.87 (s, CF_3). Anal. calcd. for $C_8H_4F_3N_3O_3$: C, 38.88; H, 1.63; N, 17.00. Found: C, 38.93; H, 1.66; N, 16.94.

4.5.2. 2-Hydroxy-7-(1,1,2,2-tetrafluoroethyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**6a**)

Yield 80 mg (96%), white powder, mp 291–293 °C. IR: ν 3162, (O–H), 3095 (C–H), 1698 (C=O), 1649, 1625, 1578, 1564 (C=C–C=N), 1234–1101 (C–F) cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.73 (1H, s, H-3), 7.10 (1H, tt, J_{HF} = 52.6, 5.8 Hz, CF_2H), 8.58 (1H, s, H-5), 11.27, 13.59 (both 1H, two br s, 2 OH). ^{13}C NMR ($(CD_3)_2SO$): δ 80.0 (s, C-3), 103.9 (s, C-6), 109.3 (tt, HCF_2, J_{CF} = 249.8, 29.1 Hz), 110.7 (tt, CF_2, J_{CF} = 260.3, 26.3 Hz), 133.8 (t, C-7, J_{CF} = 27.1 Hz), 140.7, 146.7 (two s, C-3a, C-5), 152.8 (s, C-2), 164.6 (s, C=O). ^{19}F NMR ($CDCl_3$): δ −137.89 (2F, dm, J_{FH} = 52.6 Hz, HCF_2), −121.99 (2F, m, CF_2). Anal. calcd. for $C_9H_5F_4N_3O_3$: C, 38.72; H, 1.81; N, 15.05. Found: C, 38.77; H, 1.84; N, 14.98.

4.5.3. 2,7-Dihydroxypyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**6b**)

Yield 57 mg (98%), beige powder, mp 293–295 °C. IR: ν 3149 (O–H), 3063, 2934 (C–H), 1693 (C=O), 1629, 1580, 1544 (C=C–C=N) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 5.72 (1H, s, H-3), 8.59 (1H, s, H-5), 11.37, 13.37 (both 1H, two br s, 2 OH). ^{13}C NMR ($(CD_3)_2SO$): δ 78.90 (s, C-3), 97.57 (s, C-6), 141.50, 144.58 (two s, C-3a, C-5), 157.21 (s, C-7), 164.65 (s, C-2), 165.18 (s, C=O). Anal. calcd. for $C_7H_5N_3O_4$: C, 43.09; H, 2.58; N, 21.53. Found: C, 42.92; H, 2.56; N, 21.45.

4.5.4. 2-Hydroxy-7-phenylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid (**6c**)

Yield 76 mg (99%), light yellow powder, mp 283–285 °C. IR: ν 3454, 3129 (O–H), 3059, 2972 (C–H), 1699 (C=O), 1615, 1598 (C=C–C=N) cm^{-1}. ^1H NMR ($(CD_3)_2SO$): δ 6.07 (1H, s, H-3), 7.49 (5H, m, C_6H_5), 8.82 (1H, s, H-5), 11.39, 12.89 (both 1H, two br s, 2 OH). ^{13}C NMR ($(CD_3)_2SO$): δ 81.9 (s, C-3), 109.9 (s, C-6), 127.95 (s, C_o), 128.8 (s, C_m), 129.4 (s, C_p), 131.1 (s, C_i), 148.2 (s, C-7), 149.8, 150.2 (two s, C-3a, C-5), 165.3 (s, C-2), 167.7 (s, C=O). Anal. calcd. for $C_{13}H_9N_3O_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 60.99; H, 3.57; N, 16.39.

4.6. Crystallographic details

The single crystals of compounds **2c**, **3c** and **4a** were obtained by crystallization from acetone–ethanol 2:1, acetone and $CHCl_3$ respectively. The X-ray studies were performed on an Xcalibur 3 CCD diffractometer at 295(2) K (Mo Kα irradiation, graphite monochromator, CCD detector, $\omega/2\theta$ scanning). The crystal structures were solved by direct methods followed by Fourier synthesis with SHELXS-97 and refined with full-matrix least squares methods for all non-hydrogen atoms with SHELXL-97 software packages [25].

4.6.1. Crystallographic data for **2c**

$C_{12}H_{10}F_7N_3O_4$ (M =393.23) are triclinic, space group P-1, a =6.8890(9) Å, b =10.3836(17) Å, c =11.3313(10) Å, α =96.243(13)°, β =100.022(10)°, γ = 108.867(12), V =756.75(17) Å^3, Z = 2, Dcalc = 1.726 g/cm^3, μ(Mo Kα) = 0.183 mm^{-1}, F(0 0 0) =396, 5346 reflections measured, 2562 unique reflections which were used in all calculations. The final R is 0.0473, number of refined parameters 285.

4.6.2. Crystallographic data for **3c**

$C_{12}H_8F_7N_3O_3$ (M = 375.21) are triclinic, space group P-1, a = 5.3342(13) Å, b = 9.125(2) Å, c = 15.453(4) Å, α = 86.80(3)°,

β = 81.50(2)°, γ = 75.953(18), V = 721.5(3) Å^3, Z = 2, Dcalc = 1.727 g/cm^3, μ(Mo Kα) = 0.183 mm^{-1}, F(0 0 0) = 376, 6788 reflections measured, 2960 unique reflections which were used in all calculations. The final R is 0.0353, number of refined parameters 238.

*4.6.3. Crystallographic data for **4a***

$C_{10}H_8F_3N_3O_3$ (M = 275.19) are monoclinic, space group $P2_1$, a = 4.9635(6) Å, b = 11.4886(16) Å, c = 10.1451(16) Å, $\alpha = \gamma = 90°$, β = 95.690(11)°, V = 575.66(14) Å^3, Z = 2, Dcalc = 1.588 g/cm^{-3}, μ(Mo Kα) = 0.150 mm^{-1}, F(0 0 0) = 280, 4259 reflection measured, 1482 unique reflections which were used in all calculations. The final R is 0.0377, number of refined parameters 184.

CCDC Nos. 869663, 869664 and 869662 contain the supplementary crystallographic data for **2c**, **3c** and **4a**, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e mail: deposit@ccdc cam ac uk.

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