Synthesis of 4-(trifluoromethyl)pyrido[4,3-*d*]pyrimidine derivatives

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Earlier unknown 4-alkoxy- and 4-hydroxy-5-methyl-4-trifluoromethyl-1,4-dihydropyrido[4,3-*d*]pyrimidines were obtained by the reaction of 5-acetyl-4-dimethylaminovinyl-6-(trifluoromethyl)pyrimidine with alcoholic (aqueous) solutions of NH_3. The former eliminate alcohol (water) on sublimation *in vacuo* to be converted to 5-methyl-4-(trifluoromethyl)-pyrido[4,3-*d*]pyrimidine. The latter upon the action of alcohols (water) under mild conditions were reverted to the corresponding 4-alkoxy- and 4-hydroxydihydropyrido[4,3-*d*]pyrimidines.

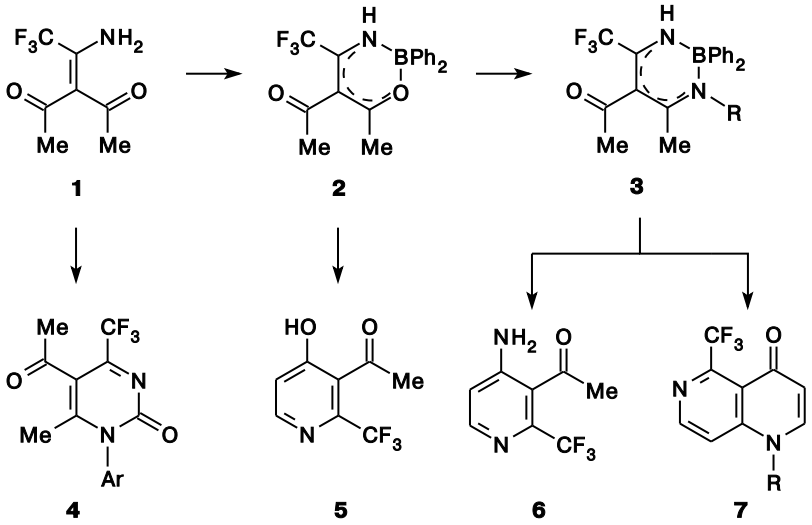
Key words: 4-alkoxy-1,4-dihydropyrido[4,3-*d*]pyrimidines; 4-hydroxy-1,4-dihydropyrido[4,3-*d*]pyrimidine, pyrido[4,3-*d*]pyrimidines, 4-trifluoromethyl-substituted heterocycles.

Introduction of a fluorine-containing substituent usually significantly affects chemical properties of heterocyclic compound and its biological activity.[1—5] Therefore, in the last decades a pronounced interest is directed, in particular, to the synthesis of trifluoromethyl derivatives of various heterocycles. The most preferable seem those approaches, which are based on the construction of cyclic systems from simple and available reagents containing a CF_3 group (see Refs 6—10).

Earlier, for the construction of nitrogen-containing heterocycles we have suggested to use 3-acetyl-4-amino-5,5,5-trifluoro-3-penten-2-one (**1**), readily obtained from acetylacetone and trifluoroacetonitrile,[11] its diphenylboron chelate (**2**)[12], as well as β-diiminates **3** formed upon the action of ammonia and amines on complex **2** (see Ref. 12). Compounds **1—3** were used for the synthesis of 4-(trifluoromethyl)pyrimidinones **4**,[11] 4-hydroxy- and 3-acetyl-4-amino-2-(trifluoromethyl)pyridines **5**, **6**,[13] as well as 1-alkyl-5-trifluoromethyl-1,6-naphthyridin-4(1*H*)-ones **7** (see Ref. 12) (Scheme 1).

Recently,[14] we have found a method for the preparation of 4-amino-3-trifluoroacetimidoyl-3-penten-2-one (**8**)

Scheme 1



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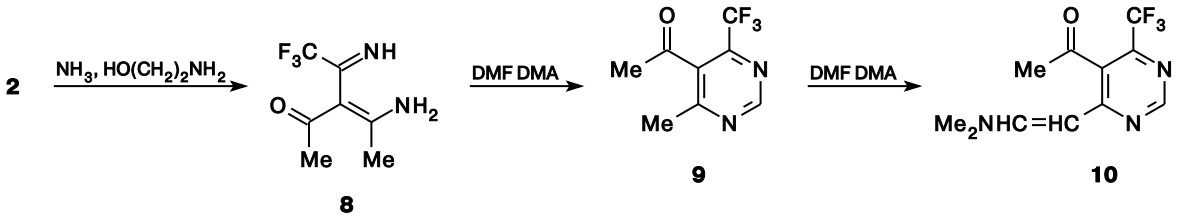
Scheme 2

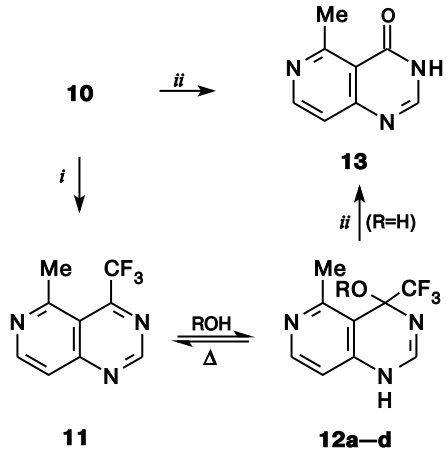


from chelate **2** and suggested a possibility to use this compound as a new building block for the construction of CF_3-containing heterocycles (Scheme 2). For instance, the reaction of aminovinyl imine **8** with dimethylformamide dimethyl acetal (DMF DMA) in the ratio 1:1 led to the formation of (trifluoromethyl)pyrimidine **9**, whereas the use of the acetal in excess amounts allowed us to synthesize dimethylaminovinylpyrimidine **10**.

It is known that one of the principal approaches to the construction of the pyrido[4,3-*d*]pyrimidine system consists in the annulation of a pyridine ring to the corresponding functionally substituted pyrimidines (see, for example, Ref. 15 and references cited therein).

In the present work, in order to obtain trifluoromethyl derivatives of pyrido[4,3-*d*]pyrimidine we studied the action of alcoholic solutions of ammonia on pyrimidine **10**. It was found that heating (75—100 °C) pyrimidine **10** with alcoholic solutions of NH_3 in a sealed tube results in the cyclization to form 5-methyl-4-(trifluoromethyl)pyrido-[4,3-*d*]pyrimidine (**11**). However, 1,4-addition of the solvent (an alcohol) to the pyrimidine ring takes place further under the reaction conditions to result in the formation of 4-alkoxy-5-methyl-4-trifluoromethyl-1,4-dihydropyrido-[4,3-*d*]pyrimidines **12a—c** (Scheme 3).

Scheme 3



i. NH_3, 50—100 °C; *ii*. NH_3/H_2O, ~80 °C, $-CHF_3$.

R = Me (**a**), Et (**b**), *n*-Bu (**c**), H (**d**).

Unexpectedly, it turned out that heating (~80 °C) compound **10** with 20% aqueous NH_3 in a sealed tube leads to 5-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**13**) as a major reaction product (68% yield). Obviously, in this case compound **12d** eliminates CHF_3.

In fact, dihydropyridopyrimidine **12d** upon heating in a sealed tube with 20% aqueous NH_3 at 80 °C for 9 h is by 92% converted to pyridopyrimidinone **13**. If compound **10** is heated in an open vessel with 20% aqueous NH_3 at 50—55 °C, **12d** is obtained in 85% yield. Dihydropyrido[4,3-*d*]pyrimidines **12a—d** at 140—200 °C without melting eliminate alcohol (water) to be converted to pyridopyrimidine **11**. It is more convenient to carry out this process under reduced pressure. Thus, two-fold sublimation of adduct **12a** (7—10 Torr), first at 140—180 °C and then at 80—125 °C, furnished pure (according to the ^1H NMR data) pyridopyrimidine **11** in 82% yield. The latter is capable to add methanol and revert to adduct **12a** already at room temperature. Adduct **12d** is converted to pyridopyrimidine **11** under more drastic conditions (190—210 °C).

The readiness of addition of alcohols and water to compound **11** is apparently due to the combined effect of the electron-withdrawing CF_3 group and the annulated pyridine ring. In any case, (trifluoromethyl)pyrimidine **10** adds methanol neither at room temperature, nor on prolonged reflux. No such reactions are described for pyrido[4,3-*d*]-pyrimidines containing no CF_3 group either.

Compound **11** was isolated as white needles, which are well soluble in most organic solvents, including light petroleum. It is distinguished by volatility and specific strong smell. The structure of pyridopyrimidine **11** was confirmed by ^1H, ^{13}C, and ^{19}F NMR spectra, mass spectra, as well as elemental analysis data. Thus, the ^1H NMR spectrum of compound **11** (in $CDCl_3$) exhibits signals for the Me group (δ 3.09), two doublets for the H(8) (δ 7.79) and H(7) (8.81) atoms, as well as a downfield singlet for the H(2) proton (δ 9.46). The ^{19}F NMR spectrum has a signal at δ −60.7 characteristic of a CF_3 group bound to the sp^2-hybridized C atom. An intensive signal for the molecular ion and a $[M-CF_3]^+$ signal are observed in the mass spectrum.

Dihydropyrimidines **12a—d** were isolated as white powders soluble in ethanol, acetone, DMSO, hot CH_3CN (compound **12d** is also soluble in hot water, whereas adducts **12b,c**, in $CHCl_3$). The structures of compounds

12a—d were confirmed by the ^{1}H, ^{13}C, ^{19}F NMR data, mass spectra, as well as elemental analysis. For instance, the spectrum of compound **12a** (in DMSO-d_6) exhibits three singlets for the Me (δ 2.58), MeO (δ 3.10), and H(2) (δ 7.74), two doublets for the H(8) (δ 6.78) and H(7) (δ 8.30), as well as a broad singlet for the NH group centered at δ 10.7. The signal for the CF_3 group (δ −82.5) in the ^{19}F NMR spectrum (in DMSO-d_6) is upfield shifted as compared to the corresponding signal for compound **12a** of aromatic bicycle **11**, this indicates that the CF_3 group is directly bound to the sp^3-hybridized C atom. Only very weak peak of molecular ion is observed in the mass spectrum of dihydropyridopyrimidine **12a**, rather intensive peaks of $[M - OMe]^+$, $[M - MeOH]^+$, and $[M - CF_3]^+$ are seen. Correlations between the NH and the H(2) and H(8) protons are observed in the {^{1}H,^{1}H} ROESY spectrum of compound **12a**, that confirms that the proton resides on the N(1) atom.

Pyridopyrimidinone **13** is a white powder well soluble in DMSO and hot water and poorly soluble in acetone and $CHCl_3$. Its IR spectrum (KBr) exhibits a sharp band at 1708 cm^{-1} (C=O). No signal for the CF_3 group is found in the ^{19}F NMR spectrum, whereas the mass spectrum has intensive peaks of the $[M]^+$ and $[M - CO]^+$ ions. The NOESY spectrum displays correlations between the NH and H(2) and no correlations between the NH and H(8), this indicates that the H atom resides on the N(3) atom. The ^{1}H and ^{13}C NMR spectra confirm the structure of compound **13** as well.

The spectral data for hydroxypyridopyrimidine **12d** indicate that this compound is analogous in its structure to alkoxy compounds **12a—c**. The ^{1}H NMR spectrum (in DMSO-d_6) exhibits, in addition to the major signals, a minor set of similar signals, that can be due to the presence of small amounts (~10%) of a tautomer, whose H atom resides on the N atom at position 3. The ^{19}F NMR spectrum, in addition to the major signal at δ −83.7, displays a minor signal (~10%) at δ −84.2 as well.

The structure of compound **12d** was unambiguously established by X-ray diffraction study. According to the X-ray data, the N(1) atom has a hydrogen atom (Fig. 1) and the study of the system of hydrogen bonds in the crystal of **12d** indicates the absence of a tautomer with the N(3)H group in the condensed phase.

Molecules in the crystal of **12d** are combined to a centrosymmetric dimers by the hydrogen bond O(1)—H(1O)...N(3) (O...N 2.798(2) Å, OHN 164(1)°), which are packed in layers due to the hydrogen bond N(1)—H(1N)...N(6) (N...N 2.876(2) Å, NHN 166(1)°). Formation of a three-dimensional framework of **12d** is finished by more weak interactions of the type C—H...π, N...π, C—H...F, and F...F.

Earlier, we have synthesized 3-benzyl-5-trifluoromethyl-4(3*H*)-pyrido[4,3-*d*]pyrimidinone containing a CF_3 group in the pyridine ring.[16] Pyrido[4,3-*d*]pyrimidines with a trifluoromethyl group at position 4 have not been described in the literature. Pyrido[4,3-*d*]pyrimidines possess a wide range of biological activity: antimicrobal, antiviral, antimalaria, antitumor, inhibits the EGRF tirasinkinase, exhibit herbicide and fungicide properties (see Ref. 6 and references cited therein).

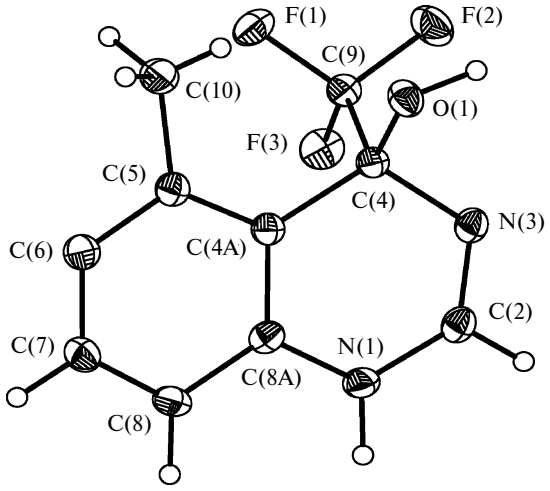


Fig. 1. General view of the molecule of compound **12d** in representation of atoms by probability ellipsoids of thermal vibrations (p = 50%).

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), ^{13}C NMR and {^{1}H, ^{13}C} HMBS, HSQC, {^{1}H, ^{1}H} ROESY, and NOESY two-dimensional spectra were recorded on a Bruker Avance-600 radiospectrometer (600 (^{1}H) and 150 (^{13}C) MHz) using residual signals of a undeuterated solvent as a reference (δ 7.27 for $CDCl_3$ and δ 2.50 for DMSO-d_6 in ^{1}H NMR spectra and δ 39.50 for DMSO-d_6 and δ 77.00 for $CDCl_3$ in ^{13}C NMR spectra). ^{19}F NMR spectra were recorded on a Bruker AC-200 spectrometer (188.29 (^{19}F) MHz) (chemical shifts for F were determined relatively to $CFCl_3$). IR spectra in KBr pellets were obtained on a Specord-M80 spectrometer, mass spectra were recorded on a Kratos MS30 instrument (EI, 70 eV with direct injection of the samples). Assignment of signals in the ^{13}C NMR spectra was performed based on the {^{1}H, ^{13}C} HMBS and HSQC two-dimensional spectra. 5-Acetyl-6-(2-dimethylaminovinyl)-4-(trifluoromethyl)pyrimidine (**10**) was obtained according to the procedure described earlier.[14] Anhydrous alcohols were used in the reactions. Silica gel Kieselgel-60 (0.063—0.200 mm, Merck) was used for column chromatography. A sample of compound **12d** for X-ray diffraction was obtained by crystallization from acetonitrile.

X-ray diffraction study of compound **12d** was carried out on a SMART 1000 CCD diffractometer (MoKα-irradiation, a graphite monochromator, ω-scanning). The structure was solved by the direct method and refined by the least squares method in the anisotropic full-matrix approximation on F^2_{hkl}. The NH and OH hydrogen atoms were localized from differential Fourier-syntheses of electron density. Positions of hydrogen atoms of

methyl and methine groups were calculated geometrically. All the hydrogen atoms were refined in isotropic approximation using the riding model. Calculations were performed by the SHELXTL PLUS program package.[17]

The principal crystallographic data and refinement parameters are given in Table 1.

4-Methoxy-5-methyl-4-trifluoromethyl-1,4-dihydropyrido[4,3-*d*]pyrimidine (12a) and 5-methyl-4-(trifluoromethyl)pyrido[4,3-*d*]pyrimidine (11). A mixture of compound **10** (3.30 g, 12.7 mmol) and a solution of NH_3 in methanol (6.7 *M*, 40 mL) was heated for 5—6 h in a sealed tube at 75 °C. Then, methanol with NH_3 was evaporated on a rotary evaporator, the residue was diluted with anhydrous MeOH (25 mL) and refluxed for 1.5 h. The mixture was concentrated to obtain compound **12a** (3.10 g, 99%). According to the ^{1}H NMR data, the purity of compound **12a** obtained was ~95%. Found (%): C, 49.25; H, 3.92; N, 17.39. $C_{10}H_{10}F_3N_3O$. Calculated (%): C, 48.98; H, 4.11; N, 17.14. MS, *m/z* (I_{rel} (%)): 245 $[M]^+$ (7.5), 214 $[M - OMe]^+$ (56), 213 $[M - MeOH]^+$ (72), 176 $[M - CF_3]^+$ (100). ^{1}H NMR (DMSO-d_6), δ: 2.58 (s, 3 H, Me); 3.10 (s, 3 H, MeO); 6.78 (d, 1 H, H(8), *J* = 5.4 Hz); 7.74 (s, 1 H, H(2)); 8.30 (d, 1 H, H(7), *J* = 5.4 Hz); 10.70 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 23.49 (Me); 49.71 (OMe); 85.70 (q, C(4), $^2J_{C,F}$ = 31 Hz); 104.67 (C(4a)); 107.28 (C(8)); 123.91 (q, CF_3, $^1J_{C,F}$ = 287 Hz); 143.65 (C(8a)); 146.39 (C(2)); 149.45 (C(7)); 158.80 (C(5)). ^{19}F NMR (DMSO-d_6), δ: −82.5.

Dihydropyrimidine **12a** (620 mg, 2.5 mmol) was sublimed *in vacuo* of 7—10 Torr initially at 140—180 °C (in an oil bath), and the second time at 80—125 °C to obtain compound **11** (443 mg, 82%), m.p. 53 °C. Found (%): C, 50.63; H, 2.77; N, 19.95. $C_9H_6F_3N_3$. Calculated (%): C, 50.71; H, 2.84; N, 19.71. MS, *m/z* (I_{rel} (%)): 213 $[M]^+$ (100), 144 $[M - CF_3]^+$ (35). ^{1}H NMR ($CDCl_3$), δ: 3.09 (q, 3 H, Me, $J_{Me,F}$ = 1.08 Hz); 7.79 (d, 1 H, H(8), *J* = 5.5 Hz); 8.81 (d, 1 H, H(7), *J* = 5.5 Hz); 9.46 (s, 1 H, H(2)). ^{13}C NMR ($CDCl_3$), δ: 26.56 (q, Me, J_{Me,CF_3} = 7.2 Hz); 116.07 (C(4a)); 119.93 (C(8)); 120.56 (q, CF_3, $^1J_{C,F}$ = 276 Hz); 149.42 (C(7)); 154.25 (q, C(4), $^2J_{C,F}$ = 34 Hz); 155.52 (C(2)); 158.72 (C(5)); 159.99 (C(8a)). ^{19}F NMR ($CDCl_3$), δ: −60.7.

4-*n*-Butoxy-5-methyl-4-trifluoromethyl-1,4-dihydropyrido[4,3-*d*]pyrimidine (12c) was obtained similarly to (**12a**) upon heating compound **10** with a 2.9 *M* solution of NH_3 in *n*-butanol for 10 h at 95—100 °C. A chromatographic column with SiO_2 was used for purification of pyridopyrimidine **12c** ($CHCl_3$—acetone, (5 : 1)—(2 : 1)). The yield of compound **12c** was 63%. Found (%): C, 54.02; H, 5.50; N, 14.87. $C_{13}H_{16}F_3N_3O$. Calculated (%): C, 54.35; H, 5.61; N, 14.63. MS, *m/z* (I_{rel} (%)): 218 $[M - CF_3]^+$ (50), 213 $[M - C_4H_9OH]^+$ (26), 162 $[M - CF_3 - C_4H_8]^+$ (100), 144 $[M - CF_3 - C_4H_9OH]^+$ (11). IR, ν/cm^{-1}: 3240, 3160 (NH); 1376—1112 (CF_3). ^{1}H NMR (DMSO-d_6), δ: 0.85 (t, 3 H, Me, *J* = 7 Hz); 1.35 (m, 2 H, CH_2); 1.58 (m, 2 H, CH_2); 2.65 (s, 3 H, Me); 3.02 and 3.48 (both m, 2 H, CH_2O); 6.85 (d, 1 H, H(8), *J* = 5.5 Hz); 7.72 (s, 1 H, H(2)); 8.28 (d, 1 H, H(7), *J* = 5.5 Hz); 10.70 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 13.77 ($\underline{C}H_3CH_2$); 18.94 ($\underline{C}H_2C$); 23.53 (Me); 31.17 ($OCH_2\underline{C}H_2$); 62.21 (OCH_2); 85.10 (q, C(4), $^2J_{C,F}$ = = 30 Hz); 105.63 (C(4a)); 107.61 (C(8)); 123.92 (q, CF_3, $^1J_{C,F}$ = = 287 Hz); 143.74 (C(8a)); 146.26 (C(2)); 149.45 (C(7)); 158.79 (C(5)). ^{19}F NMR (DMSO-d_6), δ: −82.1.

4-Hydroxy-5-methyl-4-trifluoromethyl-1,4-dihydropyrido[4,3-*d*]pyrimidine (12d). A mixture of compound **10** (0.50 g, 1.9 mmol) and 20% aq. NH_3 (30 mL) was heated at 50—55 °C with stirring in an open vessel for 5 h. Then another portion of 20% aq. NH_3 (15 mL) was added and heating was continued for another 5 h at 50—55 °C (until a precipitate was completely dissolved). Water was evaporated on a rotary evaporator, the residue was subjected to column chromatography on SiO_2 ($CHCl_3$—acetone, first (1 : 1), then from (1 : 2) to (1 : 3)) to obtain hydroxypyridopyrimidine **12d** (380 mg, 85%). Found (%): C, 46.48; H, 3.19; N, 18.38. $C_9H_8F_3N_3O$. Calculated (%): C, 46.76; H, 3.49; N, 18.18. MS, *m/z* (I_{rel} (%)): 231 $[M]^+$ (1.3), 214 $[M - OH]^+$ (21), 213 $[M - H_2O]^+$ (100), 162 $[M - CF_3]^+$ (92). ^{1}H NMR (DMSO-d_6), δ: 2.57 (q, 3 H, Me, J_{Me-F} = = 1.2 Hz); 6.73 (d, 1 H, H(8), *J* = 5.5 Hz); 7.25 (br.s, 1 H, OH); 7.59 (s, 1 H, H(2)); 8.25 (d, 1 H, H(7), *J* = 5.5 Hz); 10.49 (br.s, 1 H, NH). (Minor signals: 6.88, 7.44, 8.31, 8.46, and 9.75). ^{13}C NMR (DMSO-d_6), δ: 25.03 (Me); 81.65 (q, C(4), $^2J_{C,F}$ = = 29.7 Hz); 107.38 (C(8)); 108.93 (C(4a)); 125.32 (q, CF_3, $^1J_{C,F}$ = 290 Hz); 142.24 (C(8a)); 144.30 (C(2)); 149.26 (C(7)); 159.58 (C(5)). ^{19}F NMR (DMSO-d_6), δ: −83.7 and −84.2 (minor tautomer).

Conversion of dihydropyrido[4,3-*d*]pyrimidine 12d to 5-methyl-4-(trifluoromethyl)pyrido[4,3-*d*]pyrimidine (11). Compound **12d** (170 mg, 0.7 mmol) was sublimed at 190—210 °C *in vacuo* first of 15 Torr, then of 2 Torr. The second sublimation was carried out *in vacuo* of 15 Torr at 100—125 °C to obtain pyridopyrimidine **11** (100 mg, 64%).

Reaction of 5-methyl-4-(trifluoromethyl)pyrido[4,3-*d*]pyrimidine (11) with alcohols and water. Reaction of **11** with MeOH. A solution of pyridopyrimidine **11** (44 mg, 0.21 mmol) in an-

Table 1. Principal crystallographic data and refinement parameters for compound **12d**

Parameter	Value
Molecular formula	$C_9H_8F_3N_3O$
Molecular mass	231.18
T/K	120
Crystal system	Monoclinic
Space group	$P2_1/n$
Z	4
a/Å	5.9677(4)
b/Å	17.5381(11)
c/Å	9.5325(6)
β/deg	104.852(5)
V/Å^3	964.36(11)
d_{calc}/g cm^{-3}	1.592
μ/cm^{-1}	1.47
F(000)	472
$2\theta_{max}$/deg	58
Number of measured reflections	10462
Number of independent reflections	2552
Number of reflections with $I > 2\sigma(I)$	1955
Number of refining parameters	146
R_1	0.0485
wR_2	0.1223
GOOF	1.000
Residual electron density, e Å^{-3}(d_{max}/d_{min})	0.393/−0.295

hydrous methanol (10 mL) was kept for 20 h at ~20 °C, the solvent was evaporated on a rotary evaporator to obtain compound **12a** (50 mg, 99%), which was pure according to the ^{1}H NMR data.

Reaction of **11** with EtOH. Compound **11** (310 mg, 1.5 mmol) and anhydrous ethanol (10 mL) were refluxed for 3 h, then ethanol was evaporated on a rotary evaporator, the residue was subjected to column chromatography on SiO_2 ($CHCl_3$—acetone (2 : 1)) to isolate 4-ethoxy-5-methyl-4-trifluoromethyl-1,4-dihydropyrido[4,3-*d*]pyrimidine (**12b**) (340 mg, 90%). Found (%): C, 50.66; H, 4.47; N, 15.92. $C_{11}H_{12}F_3N_3O$. Calculated (%): C, 50.96; H, 4.67; N, 16.21. MS, *m*/*z* (I_{rel} (%)): 259 $[M]^+$ (44), 214 $[M - C_2H_5O]^+$ (49), 213 $[M - C_2H_5OH]^+$ (63), 190 $[M - CF_3]^+$ (80), 162 $[M - CF_3 - C_2H_4]^+$ (100), 144 $[M - CF_3 - C_2H_5OH]^+$ (44). ^{1}H NMR (DMSO-d_6), δ: 1.2 (t, 3 H, Me, J = 7 Hz); 2.6 (q, 3 H, Me, J_{Me-F} = 1.2 Hz); 3.04—3.10 and 3.50—3.56 (both m, 2 H, OCH_2); 6.80 (d, 1 H, H(8), J = 5.5 Hz); 7.25 (s, 1 H, H(2)); 8.31 (d, 1 H, H(7), J = 5.5 Hz); 10.70 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 14.87 ($\underline{C}H_3CH_2$); 23.49 (Me); 58.23 (OCH_2); 85.20 (q, C(4), $^2J_{C,F}$ = 31 Hz); 105.62 (C(4a)); 107.63 (C(8)); 123.89 (q, CF_3, $^1J_{C,F}$ = 282 Hz); 143.80 (C(8a)); 146.28 (C(2)); 149.41 (C(7)); 158.77 (C(5)). ^{19}F NMR (DMSO-d_6), δ: –83.57.

Reaction of **11** with water. A mixture of pyridopyrimidine **11** (900 mg, 4.2 mmol) and water (100 mL) was heated for 3—4 h with stirring at 50—55 °C, the substance initially melted and then solidified while the reaction progress. A precipitate of **12d** (640 mg) was separated, the filtrate was concentrated to additionally obtain compound **12d** (250 mg). The total yield of dihydropyridopyrimidine **12d** was 890 mg (92%).

5-Methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (13). Method *A*. A mixture of pyrimidine **10** (480 mg, 1.85 mmol) and 20% aq. NH_3 (30 mL) was heated for 6 h at 80 °C in a sealed tube, then water with NH_3 were evaporated on a rotary evaporator, the residue was subjected to column chromatography on SiO_2 (first $CHCl_3$, then $CHCl_3$—acetone from (3 : 1) to (1 : 3)) to sequentially isolate pyridopyrimidinone **13** (203 mg, 68%), m.p. >300 °C (from CH_3CN, with decomp. and sublimation) and dihydropyridopyrimidine **12d** (81 mg, 18.5%).

Compound **13.** Found (%): C, 59.34; H, 4.24; N, 25.93. $C_8H_7N_3O$. Calculated (%): C, 59.60; H, 4.38; N, 26.07. MS, *m*/*z* (I_{rel} (%)): 161 $[M]^+$ (83), 133 $[M - CO]^+$ (100). IR, ν/cm^{-1}: 3000—2000 (NH), 1708 (C=O). ^{1}H NMR (DMSO-d_6), δ: 2.90 (s, 3 H, Me); 7.55 (d, 1 H, H(8), J = 5.5 Hz); 8.20 (s, 1 H, H(2)); 8.58 (d, 1 H, H(7), J = 5.5 Hz); 12.45 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 25.88 (Me), 116.58 (C(4a)), 119.08 (C(8)), 149.59 (C(2)), 151.44 (C(7)), 155.37 (C(8a)), 160.70 (C(5)), 161.25 (C=O).

Compound **12d.** ^{1}H NMR is identical to that described above.

Method *B*. A mixture of compound **12d** (320 mg, 1.39 mmol) and 20% aq. NH_3 (15 mL) was heated in a sealed tube for 9 h at 80 °C. Water was evaporated on a rotary evaporator to obtain pyridopyrimidinone **13** (230 mg) (according to the ^{1}H NMR data, the compound purity is 92%).

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References

1. L. M. Yagupol´skii, *Aromaticheskie i geterotsiklicheskie soedineniya s ftorsoderzhashchimi zamestitelyami* [*Aromatic and Heterocyclic Compounds with Fluorine-containing Substituents*], Naukova Dumka, Kiev, 1988, p. 275—282 (in Russian).
2. J. Mann, *Chem. Soc. Rev.*, 1987, **16**, 381.
3. J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
4. K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013.
5. M. A. McClinton, D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.
6. W. Mo, G. Liao, T. Wang, H. He, *J. Fluorine Chem.*, 2008, **129**, 519.
7. A. S. Kiselyov, L. Strekowski, *Org. Prep. Proced. Int.*, 1996, **28**, 289.
8. S. V. Druzhinin, E. S. Balenkova, V. G. Nenajdenko, *Tetrahedron*, 2007, **63**, 7753.
9. M. T. Cocco, C. Congin, V. Onnis, *Tetrahedron Lett.*, 1999, **40**, 4407.
10. J. Elguero, A. Fruchier, N. Jagerovic, A. Werner, *Org. Prep. Proced. Int.*, 1995, **27**, 33.
11. V. A. Dorokhov, A. V. Komkov, L. S. Vasil´ev, O. G. Azarevich, M. F. Gordeev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 2639 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1991, **40**, 2311].
12. L. S. Vasil´ev, F. E. Surzhikov, O. G. Azarevich, V. S. Bogdanov, V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1510 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1994, **43**, 1431].
13. L. S. Vasil´ev, F. E. Surzhikov, O. G. Azarevich, V. S. Bogdanov, V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2715 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1996, **45**, 2574].
14. L. S. Vasil´ev, M. A. Prezent, A. V. Ignatenko, V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 2313 [*Russ. Chem. Bull., Int. Ed.*, 2008, **27**, 2359].
15. A. V. Komkov, V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2212 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2290].
16. L. S. Vasil´ev, F. E. Surzhikov, V. A. Dorokhov, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 2221 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 2319].
17. G. M. Sheldrick, *SHELXTL-97, Version 5.10*, Bruker AXS Inc., Madison,WI-53719, USA.

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