Synthesis of pyrimidine derivatives based on ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxopropionates and urea*

*M. V. Goryaeva, Ya. V. Burgart, and V. I. Saloutin**

I. Ya. Postovskii Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22/20 ul. S. Kovalevskoi, 620041 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 5954. E-mail: saloutin@ios.uran.ru

Ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxopropionates under mild conditions undergo regioselective condensation with urea at the ethoxymethylidene substituent giving rise to ethyl 3-polyfluoroalkyl-3-oxo-2-(ureidomethylidene)propionates. Under more drastic conditions, the latter cyclize at the fluoroacyl fragment to form ethyl 4-polyfluoroalkyl-4-hydroxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates.

Key words: ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxopropionates, urea, pyrimidines, cyclization, isomerism.

Important role of pyrimidine derivatives[1—3] in biochemical processes attracts attention of synthetic chemists and stimulates development of new representatives of compounds of this class. A classic method for the construction of pyrimidine framework consists in cyclization of a three-carbon biselectrophilic reagent with 1,1-dinucleophiles.[4] 1,3-Dicarbonyl compounds are widely used as the biselectrophilic reagents. For the preparation of functionalized pyrimidines, it is reasonable to use 1,3-dicarbonyl compounds containing various reactive groups at position 2 (see Refs 5—9). Alternative ways for the formation of pyrimidine skeleton are possible with participation not only of a 1,3-dicarbonyl fragment, but also a functional group at position 2.

Such derivatives of 1,3-dicarbonyl compounds as ethyl 2-ethoxymethylidene-3-oxoalkanoates are suitable building blocks for the preparation of pyrimidines. There is described the reaction of 2-ethoxymethylidene-substituted acetoacetic ester with thiourea leading initially to the monocondensation product at the ethoxymethylidene group, for which a further cyclization at the ester fragment is possible to yield 5-acetyl-4-hydroxypyrimidine-2-thione.[10] However, for ethyl 2-ethoxymethylidene-3-oxoalkanoates the most common is cyclocondensation with urea,[11] morpholine-4-carboxamide,[12] 4-benzyl-1-piperazinecarboxamidine,[13] and creatine[14] at the alkoxymethylideneacyl fragment to form 5-ethoxycarbonylpyrimidine derivatives.

The use of analogous fluoroalkyl-containing biselectrophiles for the synthesis of pyrimidines is much less known. There is described[11] the reaction of ethyl 2-ethoxymethylidene-4,4,4-trifluoro-3-oxobutanoates with urea in the presence of sodium ethoxide leading to ethyl 2-hydroxy-4-(trifluoromethyl)pyrimidine-5-carboxylate.

At the same time, trifluoromethylated pyrimidines are promising objects for the study of their physiological activity, since synthetic inhibitors of various enzymes are found among them.[11,15,16]

In the present work, we studied the reaction of ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxopropionates **1a—c** with urea in order to obtain fluoroalkylated pyrimidine derivatives containing ethoxycarbonyl substituent at position 5, available for subsequent transformations.

For the first time, we have experimentally shown that the reaction of esters **1a—c** with urea proceeds step-wise and, depending on conditions, can give either ethyl 4-polyfluoroalkyl-4-hydroxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **2a—c** or ethyl 3-polyfluoroalkyl-3-oxo-2-(ureidomethylidene)propionates **3a**,**c** (Scheme 1).

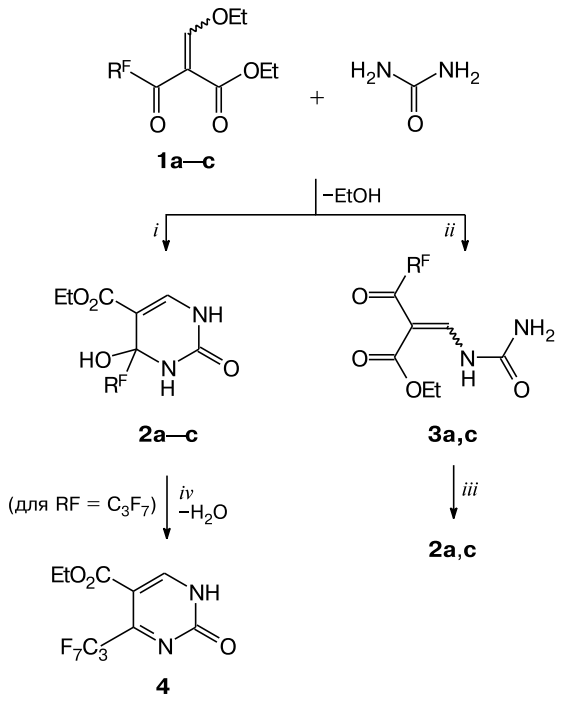
It was found that prolonged heating in DMF at 80 °C promotes cyclization of esters **1a—c** with urea into tetrahydropyrimidines **2a—c** resulting from the cycloaddition of binucleophile at the ethoxymethylidene-fluoroacyl fragment, accompanied by elimination of the ethanol molecule. However, products of monocondensation at the ethoxymethylidene substituent, esters **3a**,**c**, were obtained from esters **1a**,**c** and urea at room tempera-

* Dedicated to Academician O. N. Chupakhin on the occasion of his 75th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1224—1228, June, 2009.

1066-5285/09/5806-1259

Scheme 1



1—3: R^F = CF_3 (**a**), $H(CF_2)_2$ (**b**), C_3F_7 (**c**)

Reagents and conditions: *i.* DMF, 80 °C, 6—8 days; *ii.* DMF, 22 °C, 3 days; *iii.* EtOH, reflux, 30 min; *iv.* AcOH, reflux, 14 days.

ture in DMF (see Scheme 1). These products easily cyclize on reflux in ethanol due to the nucleophilic addition of the NH group of the aminocarbonyl fragment to fluoroacyl residue, giving tetrahydropyrimidines **2a**,**c**.

When the reaction of esters **1** with urea is performed under classic conditions for obtaining pyrimidine derivatives in boiling acetic acid, a difficult to separate mixture of products is formed.

The data obtained by us testify that the first step of the reaction of esters **1** with urea consists in condensation at the ethoxymethylidene fragment, leading to the formation of the open-chain products **3**. Then, the formation of pyrimidine framework takes place due to the intramolecular cyclization proceeding without elimination of the water molecule, in contrast to the described earlier[11] cyclocondensation of ethyl 2-ethoxymethylidene-4,4,4-trifluoro-3-oxobutanoate into pyrimidine.

Cyclic tetrahydropyrimidines **2a**—**c** and open-chain esters **3a**,**c** are the structural isomers having the same elemental analysis data and different spectral characteristics.

For instance, the IR spectra of esters **3a**,**c** are characterized by the presence of three absorption bands at 1759—1740, 1709—1704, and 1664—1662 cm^{-1} corresponding to the vibrations of three nonequivalent carbonyl groups, as well as absorption bands in the ranges 3405—3402, 3310—3306, and 3226—3213 cm^{-1} related to the stretching vibrations of the NH_2 and NH groups.[17]

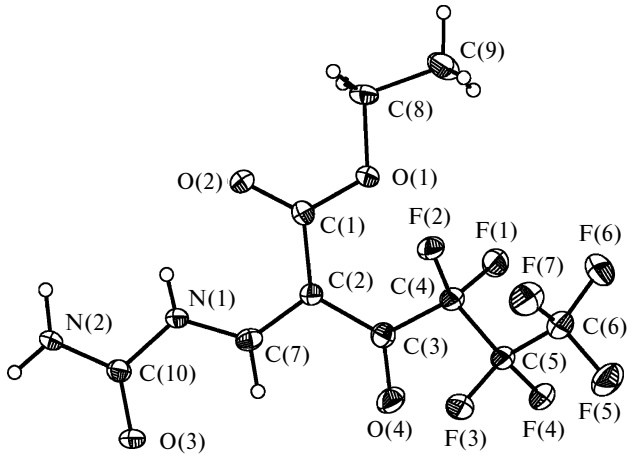


Fig. 1. General view of the molecule of compound **3c**. The thermal ellipsoids of 50% probability are shown.

The structure of ester **3c** in crystal was established using X-ray diffraction analysis (Fig. 1).* According to the X-ray data, the main 3-oxo-2-ureidomethylidenepropionate fragment of the **3c** molecule has approximately plane conformation (the largest deviation of atoms from the plane O(1)C(1)C(2)C(7)N(1)C(10)N(2) is 0.075 Å), whereas the heptafluorobutyryl substituent is the most pulled out of this plane so as atoms C(3), O(4), C(4), C(5), and C(6) deviate from it by 0.171, 0.301, 0.983, 1.645, and 2.742 Å, respectively. In crystal, ester **3c** exists as a *s-cis*,*s-cis*-conformer (*Z*-isomer). The conformation of the molecule is apparently determined by the intramolecular hydrogen bond (IMHB) between atoms O(2)...H(1) and the system of intermolecular hydrogen bonds O(2)...H(2A), O(3)...H(2B), and O(3)...H(1) (Table 1, Fig. 2), forming the molecular chains.

Earlier, we have found that unlike compound **3c**, esters of 2-alkyl(aryl, hetaryl)aminomethylidene-3-poly-

Table 1. Parameters of hydrogen bonds N—H...O in the crystal packing of compound **3c**

N—H...O	*d*(N—H)	*d*(H...O)	ω/deg	*d*(N...O) /Å
	Å			
N(1)—H(1)...O(2)	0.796	2.131	127.55	2.691
N(2)—H(2A)...O(2)[a]	0.868	2.025	159.73	2.855
N(2)—H(2B)...O(3)[b]	0.905	1.929	163.30	2.808
N(1)—H(1)...O(3)[c]	0.796	2.417	144.92	3.102

Note. The following notations are used: *d* are the bond lengths or interatomic distances, ω are the corresponding angles N—H...O. The symmetry operations: [a] [−*x* + 1, *y* − 1/2, −*z* + 5/2]; [b] [−*x* + 1, *y* + 1/2, −*z* + 5/2]; [c] [−*x* + 1, *y* + 1/2, −*z* + 5/2].

* We are grateful to P. A. Slepukhin, a research fellow in the I. Ya. Postovskii Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, for the performing the X-ray diffraction experiments.

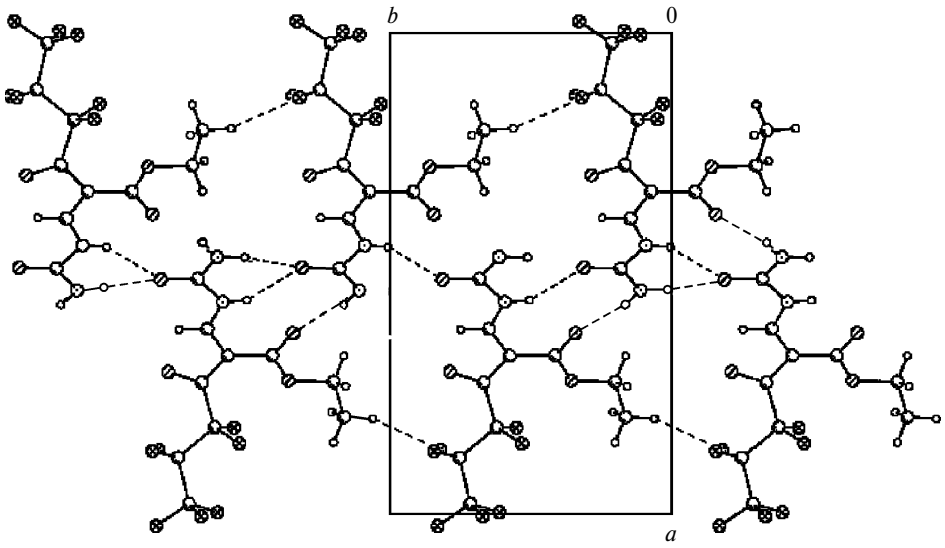
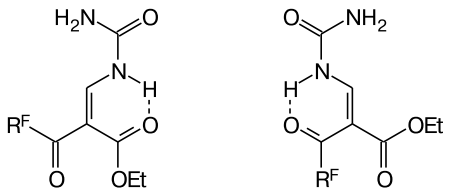


Fig. 2. The molecular packing of compound **3c** along the *c* axis according to the X-ray diffraction data.

fluoroalkyl-3-oxopropionic acid in solid state exist in form of *E*-isomer.[18]

A possibility of *Z*,*E*-isomerism for esters **3a**,**c** exists due to the different positions of substituents with respect to the C=C bond. In this case, in the *Z*-isomer the IMHB is implemented involving the ethoxycarbonyl substituent, whereas in the *E*-isomer it involves the fluoroacyl fragment.



Z-**3a**,**c** *E*-**3a**,**c**

The ^{1}H and ^{19}F NMR spectra of esters **3a**,**c** contain two sets of signals related to *Z*- and *E*-isomers. The assignment of isomers was made using the rules found by us for esters of 2-alkyl(aryl, hetaryl)aminomethylidene-3-polyfluoroalkyl-3-oxopropionic acids,[18] according to which the signals for the protons of the CH and NH groups of the *E*-isomer are observed more downfield as compared to the signals for analogous protons of the *Z*-form. In accordance with this, in the ^{1}H NMR spectra of compounds **3a**,**c** the downfield doublet signals for the CH and NH groups with the spin-spin coupling constants 14 Hz at δ_{CH} 8.56—8.69 and δ_{NH} 11.08—11.15 were assigned to the *E*-isomer, whereas the doublets at δ_{CH} 8.37—8.47 and δ_{NH} 10.62—10.63, to the *Z*-form. The ratio of *E*- and *Z*-isomers of compounds **3a**,**c**, according to the NMR spectra in DMSO-d_6, is approximately 1 : 1 (see Experimental).

In the ^{19}F NMR spectra of compounds **3a**,**c**, the signals for the free CF_3 groups and α-CF_2 of the *Z*-isomer (δ_{CF_3} ~91.48, $\delta_{\alpha\text{-}CF_3}$ ~49.77) are downfield shifted as compared to the corresponding signals for the IMHB-bound fluoroacyl group of the *E*-isomer (δ_{CF_3} ~90.19, $\delta_{\alpha\text{-}CF_2}$ ~49.10).

The existence of esters **3a**,**c** in solution as a mixture of *Z*- and *E*-isomers in contrast to the presence of only *Z*-form in crystals is apparently explained by the fact that partial isomeization of the ester molecules occurs on dissolution of the crystals. This is possible for compounds, in the molecules of which there are functional groups neighboring to the double bond, which cause polarization of this bond or make it a part of a conjugated system, resulting in significant reduction of a barrier to rotation around the C=C bond.[19,20] This is especially characteristic of enaminoketones, the so-called *push-pull*-olefins, which, from the one hand, contain electronegative substituents and, from the other hand, electron-donating. In such compound, the formally double C=C bond partially possesses character of a single bond due to the delocalization of an electron. Earlier, we have found that for ethyl 2-alkyl(aryl, hetaryl)aminomethylidene-3-polyfluoroalkyl-3-oxopropionates, the isomeization of the *E*-form into a mixture of *Z*- and *E*-isomers is characteristic on dissolution.[18]

In the IR spectra of tetrahydropyrimidines **2a**—**c**, there are present two absorption bands (at 1716—1702 and 1688—1685 cm^{-1}), related to the vibrations of the carbonyl groups of the ester and ureide fragments, respectively. The low-frequency shift of the absorption bands for the carbonyl groups as compared to the values typical of such groups[17] is explained by the conjugation of the C=O bonds with the C=C bond and their involvement into the IMHB with the hydroxy group. The character of the high-

frequency absorption bands related to the stretching vibrations of the NH and OH groups (3237—3216, 3119—3108 cm^{-1}) in the molecules of compounds **2a—c** also changes with respect to the spectral picture observed for the stretching vibrations of the NH_2 and NH groups of esters **3a**,**c**.

The ^1H and ^{19}F NMR spectra of tetrahydropyrimidines **2a—c** considerably differ from the spectra of their open-chain isomers **3a**,**c**. For instance, the signals for the protons of the CH_2 group of the ethoxy substituent in the ^1H NMR spectra of compounds **2a—c** resonate as an ABX_3-system due to the closeness of the asymmetric center to this substituent.

The ^{19}F NMR spectra of tetrahydropyrimidines **2a**,**c** exhibit the upfield shift of the signals for the fluorine atoms of the CF_3 and α-CF_2 groups (δ_{CF_3} ~79.63, $\delta_{\alpha\text{-}CF_3}$ ~40.71) as compared to analogous signal in the spectra of esters **3a**,**c**. In addition, the signals for the fluorine atoms of the α-CF_2 and β-CF_2 groups in the polyfluoroalkyl substituents of compounds **2b**,**c** resonate as an AB-system, which is due to their closeness to the asymmetric carbon atom.

Tetrahydropyrimidines **2** can undergo dehydration. For instance, a prolonged reflux of ester **2c** in acetic acid leads to ethyl 4-heptafluoro-2-oxopropyl-1,2-dihydropyrimidine-5-carboxylate **4**, resembling the synthesized earlier trifluoromethyl-substituted pyrimidine.[11]

In conclusion, we have shown that the reaction of 2-ethoxymethylidene-3-polyfluoroalkylpropionates **1** with urea has a step-wise character. Under mild conditions, the reaction proceeds at the ethoxymethylidene substituent, leading to 3-polyfluoroalkyl-2-(ureidomethylidene)propionates **3**, which under more drastic conditions cyclize at the fluoroacyl fragment to yield ethyl 4-polyfluoroalkyl-4-hydroxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **2**.

Experimental

Melting points were measured in unsealed capillary tubes on a Stuart SMP3 apparatus. IR spectra were recorded on a Perkin—Elmer Spectrum One IR Fourier spectrometer in Nujol. NMR spectra were recorded on a Bruker DRX-400 spectrometer (^1H: 400 MHz, relatively to Me_4Si; ^{19}F: 376 MHz, relatively to C_6F_6) in $(CD_3)_2SO$. Elemental analysis was performed using a Perkin—Elmer PE 2400 Series II CHNS-O analyzer. The reaction course was monitored by TLC on Sorbfil plates PTLC-AF-V-UV.

The starting ethyl 2-ethoxymethylidene-3-polyfluoroalkyl-3-oxopropionates **1a—c** were synthesized according to the procedure described earlier.[18]

Monocrystals of compound **3c** were obtained by crystallization from acetone. $C_{10}H_9F_7N_2O_4$, M = 354.19, crystals are monoclinic, space group is $P2(1)/c$, a = 15.5644(12) Å, b = 9.2396(10) Å, c = 9.3890(10) Å, α = 90.00°, β = 95.084(7)°, γ = 90.00°, V = 1344.9(2) Å^3, Z = 4, d_{calc} = 1.749 g cm^{-3}, μ(Mo-Kα) = 0.193 cm^{-1}, $F(000)$ = 712. The total number of reflections was 7061, measured on a XCalibur 3 diffractometer at 293(2) K ($\omega/2\theta$-scanning, Mo-Kα-irradiation, a graphite monochromator, a CCD detector), the number of independent reflections was 2732 (R_{int} = 0.0269), the number of reflections with $F_0 > 4\sigma(F_0)$ was 1810. The structure was solved by the direct method and refined by the least squares method SHELXL-97 [21] to R = 0.0300, wR_2 = 0.0610, and $GOOF$ = 1.000.*

Ethyl 4-fluoroalkyl-4-hydroxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2) (general procedure). ***A.*** Ester **1a—c** (5 mmol) and urea (5 mmol) were heated (80 °C) with stirring in DMF (15 mL) for 6—8 days. The reaction mixture was poured into cold water, a precipitate formed was filtered off and crystallized from EtOH to obtain the corresponding tetrahydropyrimidine **2a—c**.

B. Ester **1a**,**c** (5 mmol) and urea (5 mmol) were stirred in DMF (15 mL) for 3—4 days at 20 °C. The reaction mixture was poured into cold water, a precipitate formed was filtered off and washed with Et_2O to obtain ester **3a**,**c**. Further, ester **3a**,**c** (1 mmol) was refluxed for 30 min in EtOH (10 mL), the reaction mixture was concentrated, a precipitate formed was filtered off to obtain the corresponding tetrahydropyrimidine **2a**,**c**.

Ethyl 4-hydroxy-2-oxo-4-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2a). Method ***A***: the yield was 0.86 g (68%), method ***B***: the yield was 1.23 g (97%), a white powder, m.p. 203—205 °C. Found (%): C, 37.79; H, 3.65; F, 22.38; N, 11.17. $C_8H_9F_3N_2O_4$. Calculated (%): C, 37.80; H, 3.57; F, 22.42; N, 11.02. IR, ν/cm^{-1}: 3216, 3119 (NH, OH); 1702 (CO_2Et); 1685 (C=O); 1665, 1560 (C=C, NH); 1236—1161 (C—O, C—F). ^1H NMR, δ: 1.20 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.1 Hz); 4.10 (m, 2 H, $OC\underline{H}_2CH_3$, ABX_3-system, Δ_{AB} = 0.05, J_{AB} = 10.8 Hz, ^3J = 7.1 Hz); 7.42 (s, 1 H, NH(3)); 7.49 (d, 1 H, H(6), $^3J_{H(6)-NH(1)}$ = 6.3 Hz); 8.46 (br.s, 1 H, OH); 9.89 (br.d, 1 H, NH(1), $^3J_{NH(1)-H(6)}$ = 6.3 Hz). ^{19}F NMR, δ: 79.63 (s, CF_3).

Ethyl 4-(1,1,2,2-tetrafluoroethyl)-4-hydroxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2b). Method ***A***: the yield was 1.00 g (70%), a white powder, m.p. 166—167 °C. Found (%): C, 37.65; H, 3.49; F, 26.32; N, 9.80. $C_9H_{10}F_4N_2O_4$. Calculated (%): C, 37.77; H, 3.52; F, 26.55; N, 9.79. IR, ν/cm^{-1}: 3227, 3108 (NH, OH); 1713 (CO_2Et); 1688 (C=O); 1629, 1500 (C=C, NH); 1233—1125 (C—O, C—F). ^1H NMR, δ: 1.21 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.2 Hz); 4.10 (m, 2 H, $OC\underline{H}_2CH_3$, ABX_3-system, Δ_{AB} = 0.01, J_{AB} = 10.7 Hz, ^3J = 7.2 Hz); 6.55 (dddd, 1 H, $(CF_2)_2H$, $^2J_{H,F(2)_A}$ = 52.0 Hz, $^2J_{H,F(2)_B}$ = 52.7 Hz, $^3J_{H,F(1)_B}$ = 7.4 Hz, $^3J_{H,F(1)_A}$ = 5.6 Hz); 7.41 (dd, 1 H, NH(3), $^4J_{NH(3)-OH}$ = 1.5 Hz, $^4J_{NH(3)-NH(1)}$ = 1.0 Hz); 7.47 (d, 1 H, H(6), $^3J_{H(6)-NH(1)}$ = 6.3 Hz); 8.16 (d, 1 H, OH, ^3J = 1.5 Hz); 9.83 (dd, 1 H, NH(1), $^3J_{NH(1)-H(6)}$ = 6.3 Hz, $^4J_{NH(1)-NH(3)}$ = = 1.0 Hz). ^{19}F NMR, δ: 28.23 (m, 2 F, HCF_2, AB-system, Δ_{AB} = 1.99, J_{AB} = 295.7 Hz); 32.70 (m, 2 F, CF_2, AB-system, Δ_{AB} = 1.49, J_{AB} = 259.2 Hz).

Ethyl 4-(1,1,2,2,3,3,3-heptafluoropropyl)-4-hydroxy-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (2c). Method ***A***: the yield was 1.15 g (65%); method ***B***: the yield was 0.35 g (98%), a white powder, m.p. 198—200 °C. Found (%): C, 34.08; H, 2.32; F, 37.40; N, 7.81. $C_{10}H_9F_7N_2O_4$. Calculated (%): C, 33.91; H, 2.56; F, 37.55; N, 7.91. IR, ν/cm^{-1}: 3237, 3116

* A full set of crystallographic data was deposited with the Cambridge Structural Database (CCDC 692523) and is available at www.ccdc.cam.ac.uk/conts/retrieving.html (or: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

(NH, OH); 1716 (CO_2Et); 1684 (C=O); 1613, 1562 (C=C, NH); 1230—1121 (C—O, C—F). ^{1}H NMR, δ: 1.19 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.0 Hz); 4.11 (m, 2 H, $OC\underline{H}_2CH_3$, ABX_3-system, Δ_{AB} = 0.04, J_{AB} = 10.8 Hz, ^3J = 7.0 Hz); 7.51 (s, 1 H, NH(3)); 7.52 (s, 1 H, H(6)); 8.36 (br.s, 1 H, OH); 9.94 (br.s, 1 H, NH(1)). ^{19}F NMR, δ: 37.41 (m, 2 F, β-CF_2, AB-system, Δ_{AB} = 0.50, J_{AB} = 290.2 Hz); 40.71 (m, 2 F, α-CF_2, AB-system, Δ_{AB} = 33.27, J_{AB} = 275.0 Hz); 82.16 (t, 3 F, CF_3, ^4J = 11.2 Hz).

Ethyl 4,4,4-trifluoro-3-oxo-2-(ureidomethylidene)butanoate (3a). Method ***B***: the yield was 0.97 g (76%), white crystals, m.p. 185—187 °C. Found (%): C, 37.79; H, 3.55; F, 22.26; N, 11.07. $C_8H_9F_3N_2O_4$. Calculated (%): C, 37.80; H, 3.57; F, 22.42; N, 11.02. IR, ν/cm^{-1}: 3402, 3306, 3213 (NH, NH_2); 1759, 1704, 1664 (C=O); 1621, 1562 (C=C, NH, NH_2); 1237—1162 (C—O, C—F). ^{1}H NMR, δ: *E*-isomer (53%): 1.24 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.2 Hz); 4.20 (q, 2 H, $OC\underline{H}_2CH_3$, ^3J = 7.2 Hz); 7.66, 7.79 (both br.s, 1 H each, NH_2); 8.63 (d, 1 H, CH, ^3J = 13.5 Hz); 11.15 (d, 1 H, NH, ^3J = 13.5 Hz); *Z*-isomer (47%): 1.26 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.2 Hz); 4.26 (q, 2 H, $OC\underline{H}_2CH_3$, ^3J = 7.2 Hz); 7.56, 7.72 (both br.s, 1 H each, NH_2); 8.47 (d, 1 H, CH, ^3J = 13.0 Hz); 10.69 (d, 1 H, NH, ^3J = 13.0 Hz). ^{19}F NMR, δ: *E*-isomer (53%): 90.19 (s, CF_3); *Z*-isomer (47%): 91.48 (s, CF_3).

Ethyl 4,4,5,5,6,6,6-heptafluoro-3-oxo-2-(ureidomethylidene)hexanoate (3c). Method ***B***: the yield was 1.13 g (64%), white crystals, m.p. 196—197 °C. Found (%): C, 34.08; H, 2.32; F, 37.49; N, 7.81. $C_{10}H_9F_7N_2O_4$. Calculated (%): C, 33.91; H, 2.56; F, 37.55; N, 7.91. IR, ν/cm^{-1}: 3405, 3310, 3226 (NH, NH_2); 1740, 1709, 1662 (C=O); 1622, 1571, 1554 (C=C, NH, NH_2); 1285—1191 (C—O, C—F). ^{1}H NMR, δ: *E*-isomer (44%): 1.23 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.2 Hz); 4.20 (q, 2 H, $OC\underline{H}_2CH_3$, ^3J = 7.2 Hz); 7.66, 7.74 (both br.s, 1 H each, NH_2); 8.56 (d, 1 H, CH, ^3J = 13.2 Hz); 11.08 (d, 1 H, NH, ^3J = 13.2 Hz); *Z*-isomer (56%): 1.24 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.1 Hz); 4.26 (q, 2 H, $OC\underline{H}_2CH_3$, ^3J = 7.1 Hz); 7.56, 7.67 (both br.s, 1 H each, NH_2); 8.37 (d, 1 H, CH, ^3J = 13.0 Hz); 10.62 (br.d, 1 H, NH, ^3J = 13.0 Hz). ^{19}F NMR, δ: *E*-isomer (44%): 38.39 (m, 2 F, β-CF_2); 49.10 (m, 2 F, α-CF_2); 82.80 (t, 3 F, CF_3, ^4J = 9.5 Hz); *Z*-isomer (56%): 39.35 (m, 2 F, β-CF_2); 49.77 (m, 2 F, α-CF_2); 82.87 (t, 3 F, CF_3, ^4J = 9.2 Hz).

Ethyl 4-(1,1,2,2,3,3,3-heptfluoropropyl)-2-oxo-1,2-dihydropyrimidine-5-carboxylate (4). Solution of compound **2c** (0.71 g, 2 mmol) in acetic acid (10 mL) was refluxed for 14 days. Then, the reaction mixture was poured into water, the pH was made neutral with aqueous soda. A precipitate formed was filtered off and crystallized from hexane. The yield was 0.38 g (56%), a light beige powder, m.p. 106—108 °C. Found (%): C, 35.39; H, 2.02; F, 39.39; N, 8.12. $C_{10}H_7F_7N_2O_3$. Calculated (%): C, 35.73; H, 2.10; F, 39.56; N, 8.33. IR, ν/cm^{-1}: 3237 (NH); 1750 (CO_2Et); 1668 (C=O); 1627, 1534 (C=C, C=N, NH); 1237—1122 (C—O, C—F). ^{1}H NMR, δ: 1.27 (t, 3 H, $OCH_2C\underline{H}_3$, ^3J = 7.1 Hz); 4.25 (q, 2 H, $OC\underline{H}_2CH_3$, ^3J = 7.1 Hz); 8.69 (s, 1 H, H(6)); 13.40 (br.s, 1 H, NH). ^{19}F NMR, δ: 40.23 (m, 2 F, β-CF_2); 53.27 (m, 2 F, α-CF_2); 83.25 (t, 3 F, CF_3, ^4J = 9.5 Hz).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 09-03-00274a) and the Council on Grants of the President of the Russian Federation (Program for the State Support of Leading Scientific Schools, Grant NSh 3758.2008.3).

References

1. *Comprehensive Organic Chemistry*, Eds S. D. Barton, W. D. Ollis, Pergamon Press, New York, 1979.
2. N. A. Tyukavkina, Yu. I. Baukov, *Bioorganicheskaya khimiya* [*Bioorganic Chemistry*], Drofa, Moscow, 2005, 542 pp. (in Russian).
3. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicines*], 14th ed., Novaya Volna Publ. Ltd, Moscow, 2002, vol. **1**, 540 pp.; vol. **2**, 608 pp. (in Russian).
4. T. L. Gilchrist, *Heterocyclic Chemistry*, 2nd ed., John Wiley and Sons, New York, 1992.
5. J. J. Van den Eynde, N. Hecq, O. Kataeva, C. O. Kappe, *Tetrahedron*, 2001, **57**, 1785.
6. B. C. O´Reilly, K. S. Atwal, *Heterocycles,* 1987, **26**, 1185.
7. K. S. Atwal, G. C. Rovnyak, B. C. O´Reilly, J. Schwartz, *J. Org. Chem*., 1989, **54**, 5898.
8. K. S. Atwal, *Bioorg. Med. Chem. Lett*., 1991, **1**, 291.
9. M. V. Pryadeina, Ya. V. Burgart, V. I. Saloutin, M. I. Kodess, E. N. Ulomskii, V. L. Rusinov, *Zh. Org. Khim.*, 2004, **40**, 938 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2004].
10. Jpn Pat. 77151182; *Chem. Abstrs*, 1978, **88**, 136666w.
11. M. S. S. Palanki, P. E. Erdman, L. M. Gayo-Fung, G. I. Shevlin, R. W. Sullivan, M. E. Goldman, L. J. Ransone, B.L. Bennet, A. M. Manning, M. J. Suto, *J. Med. Chem.,* 2000, **43**, 3995.
12. Ger. Pat. 143615; *Chem. Abstrs*, 1981, **95**, 97833w.
13. Jpn Pat. 6143173; *Chem. Abstrs*, 1986, **105**, 42843u; Eur. Pat. 188094; *Chem. Abstrs*, 1986, **105**, 208919a.
14. G. Menichi, M. Hubert-Habart, R. Royer, *Eur. J. Med. Chem.-Chim. Ther.*, 1974, **9**, 11.
15. D. P. Walker, F. C. Bi, A. S. Kalgutkar, J. N. Bauman, S. X. Zhao, J. R. Soglia, G. E. Aspnes, D. W. Kung, J. Klug-McLeod, M. P. Zawistoski, M. A. McGlynn, R. Oliver, M. Dunn, J.-Ch. Li, D. T. Richter, B. A. Cooper, J. C. Kath, C. A. Hulford, C. L. Autry, M. J. Luzzio, E. J. Ung, W. G. Roberts, P. C. Bonnette, L. Buckbinder, A. Mistry, M. C. Griffor, S. Han, A. Guzman-Perez, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6071.
16. N. Zanatta, S. S. Amaral, J. M. dos Santos, D. L. de Mello, L. S. da Fernandes, H. G. Bonacorso, M. A. P. Martins, A. D. Andricopulo, D. M. Borchhardt, *Bioorg. Med. Chem.*, 2008, **16**, 10236.
17. E. Pretsch, P. Buhlmann, C. Affolter. *Structure Determination of Organic Compounds. Tables of Spectral Data*, Springer-Verlag, Berlin—Heidelberg, 2000.
18. M. V. Pryadeina, Ya. V. Burgart, V. I. Saloutin, P. A. Slepukhin, O. N. Kazheva, G. V. Shilov, O. A. D´yachenko, O. N. Chupakhin, *Zh. Org. Khim.*, 2007, **43**, 945 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2007, **43**].
19. V. M. Potapov, *Stereokhimiya* [*Stereochemistry*], Khimiya, Moscow, 1988, p. 262 (in Russian).
20. M. Oki, *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Publishers, Inc, 1985, p. 76, 112.
21. G. M. Sheldrick, *SHELXS-97, A Software Package for the Solutions and Refinement of X-ray Data*, Göttingen University, Germany, 1997.

Received July 29, 2008;
in revised form February 20, 2009