Alkyl 3-fluoroalkyl-3-oxopropionates in reactions with azolyldiazonium salts

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Alkyl 3-fluoroalkyl-3-oxopropionates react with antipyrinyldiazonium chloride to form 2-antipyrinylhydrazono-3-fluoroalkyl-3-oxopropionates. The use in these reactions of hetaryldiazonium salts, containing NH group in the α position, leads to alkyl 7-fluoroalkyl-7-hydroxy-4,7-dihydroazolo[5,1-*c*]triazine-6-carboxylates. 3-Amino-1*H*-1,2,4-triazole, 3-amino-4-ethoxycarbonyl-1*H*-pyrazole, and 5-amino-4-ethoxycarbonyl-1*H*-imidazole were used as the heterocyclic component.

Key words: 3-fluoroalkyl-3-oxopropionates, azocoupling, azolyldiazonium salts, dihydroazolotriazines, cyclization, isomerism.

Acetyl- and benzoylacetic esters (3-oxo esters) are subjected to the azocoupling reaction with hetaryldiazonium salts at the activated methylene group giving rise to 2-hetarylhydrazono-3-oxo esters,[1—8] some of which are able to undergo various intramolecular cyclizations[2—6] primarily with participation of the acyl substituent and the NH group of the hetaryl fragment to form heteroannulated triazines, including biologically active ones.[1,7] In the literature, there are described examples when the azocoupling reaction of 3-oxo esters with hetaryldiazonium salts directly leads to the fused triazines, resulting from the spontaneous cyclization of 2-hetarylhydrazono-3-oxo esters. Bicyclic pyrazolo[3,2-*c*]-triazines[9,10] and triazolo[5,1-*c*][1,2,4]triazines[11,12], tricyclic triazino[4,3-*b*]indazoles[13,14] and pyrimido-[5′,4′:4,5]pyrazolo[3,2-*c*][1,2,4]triazines[15] were obtained by this way. Among the latter, azolotriazines are of particular interest since they are isosteric to purine bases.

Information on azocoupling of alkyl 3-fluoroalkyl-3-oxopropionates with hetaryldiazonium salts is absent in the literature.

In the present work, reactions of azocoupling of 3-fluoroalkyl-3-oxopropionates **1a—e** with hetaryldiazonium chlorides **2a—d** have been studied. 4-Amino-2,3-dimethyl-5-oxo-1-phenyl-3-pyrazoline (**2a**), 3-amino-1*H*-1,2,4-triazole (**2b**), 3-amino-4-ethoxycarbonyl-1*H*-pyrazole (**2c**), and 5-amino-4-ethoxycarbonyl-1*H*-imidazole (**2d**) have been used as the heterocyclic component.

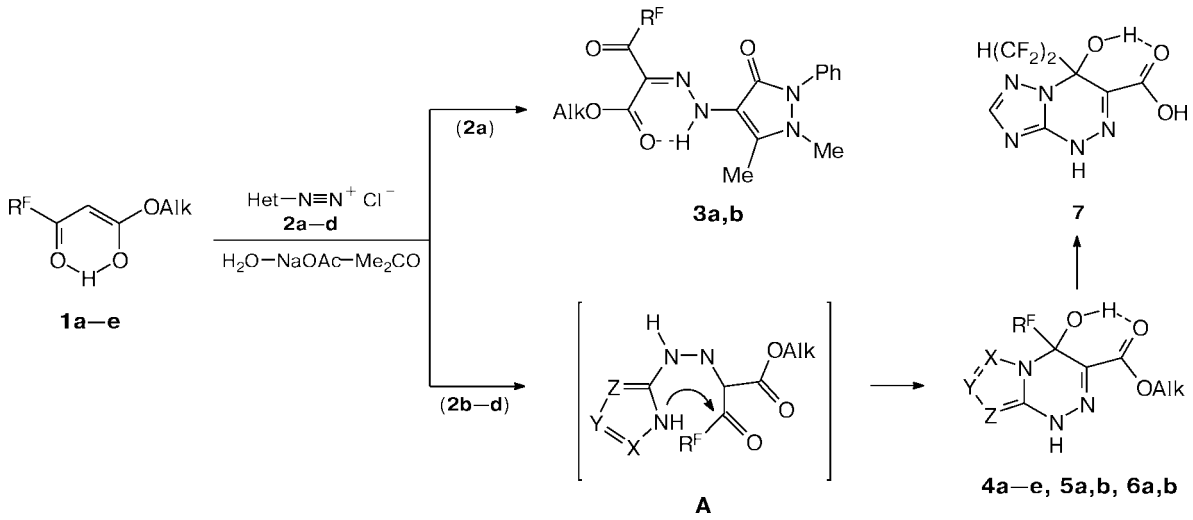
It was found that the azocoupling of 3-oxo esters **1** with hetaryldiazonium salts can be used for the synthesis of both the open-chain and the heterocyclic products depending on the identity of the hetaryldiazonium component. Thus, esters **1a,b** react with antipyrinyldiazonium chloride **2a** to form 2-antipyrinylhydrazono-3-fluoroalkyl-3-oxopropionates **3a,b** similarly to the transformations of acetyl- and benzoylacetic esters.[3] However, when hetaryldiazonium salts **2b—d**, containing an NH group in the α position, are used in these reactions, alkyl 7-fluoroalkyl-7-hydroxy-4,7-dihydroazolo[5,1-*c*]triazine-6-carboxylates **4a—e**, **5a,b**, and **6a,b** are formed. Obviously, that in this case the open-chain 3-fluoroalkyl-2-hetarylhydrazono-3-oxopropionates **A** are the intermediate products, undergoing the intramolecular cyclization through the addition of the NH group to the fluoroacyl fragment (Scheme 1).

In contrast to this, according to the literature data acetyl- and benzoylacetic esters in the reaction of azocoupling with triazolyl-[11,12] and pyrazolyldiazonium salts[9,10] gave the corresponding azolotriazines, while the reaction with imidazolyldiazonium salts initially leads to 2-imidazolylhydrazones, which cyclize to imidazotriazines only under reflux in acidic medium.[6] Attempted dehydration of heterocycles **4a**, **5a**, and **6a** upon heating in acetic acid or acetic anhydride did not lead to their noticeable changes.

The formation of stable 4,7-dihydroazolotriazines, containing *gem*-aminohydroxy fragment, in the reaction of fluoroalkylated 3-oxo esters **1** is their distinguishing feature, caused by the presence of the electron-withdrawing polyfluoroalkyl substituent. From the one hand, this

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 599—603, March, 2008.

Scheme 1



1: Alk = Et, $R^F = CF_3$ (**a**), $H(CF_2)_2$ (**b**); Alk = Me, $R^F = HCF_2$ (**c**), C_3F_7 (**d**), C_4F_9 (**e**)
2: Het is antipyrin-4-yl (**a**), 1,2,4-triazol-3-yl (**b**); 4-EtO_2C-pyrazol-3-yl (**c**), 4-EtO_2C-imidazol-3-yl (**d**)
3: $R^F = CF_3$, Alk = Et (**a**); $R^F = C_4F_9$, Alk = Me (**b**)
4: X = Z = N, Y = CH, Alk = Et, $R^F = CF_3$ (**a**), $H(CF_2)_2$ (**b**); Alk = Me, $R^F = HCF_2$ (**c**), C_3F_7 (**d**), C_4F_9 (**e**)
5: X = N, Y = CH, Z = CCO_2Et, $R^F = CF_3$, Alk = Et (**a**); $R^F = C_3F_7$, Alk = Me (**b**)
6: X = CH, Y = N, Z = CCO_2Et, $R^F = CF_3$, Alk = Et (**a**), $R^F = C_3F_7$, Alk = Me (**b**)

group facilitates addition of a nucleophile (in this case, the NH group of the azole ring) at the neighboring carbonyl atom, but from the other hand, it prevents the ready elimination of a water molecule.

The open-chain 2-hetarylhydrazono-3-oxo esters **3** and dihydroazolotriazines **4—6** are the structural isomers, having an identical elemental analysis and molecular ion peaks. There arises a problem of developing of the strict criteria for the assignment of the open-chain or heterocyclic structures to the products obtained.

X-Ray analysis, performed for a crystal of product **4d**, unambiguously point out its heterocyclic structure. Moreover, it was found that the annulation of the triazole ring occurs with the formation of a single isomer, triazolo[5,1-*c*]triazine. According to the X-ray data, in the molecule of compound **4d** there is an intramolecular hydrogen bond between the oxygen carbonyl atom (O(10)) of the methoxycarbonyl group and the hydrogen atom (H(1)) of the hydroxy substituent. Thus, the intramolecular distance O(10)...H(1) is 2.37(4) Å, the angle O(7)—H(1)...O(10) is 118.77, C(10)—O(10)...H(1) is 108.93° (Fig. 1).

A comparative analysis of the IR spectra of compounds **3—6**, recorded in Nujol, showed a distinction in the character of the spectra for the open-chain hetarylhydrazones **3** and for the cyclic azolotriazines **4—6**. Thus, in the IR spectra of 2-antipyrinylhydrazono-3-fluoroalkyl-3-oxopropionates **3a,b**, there are three high-frequency absorption bands in each spectrum, caused by the stretching vibrations of the three nonequivalent carbonyl groups (see Experimental). In contrast to this, the IR spectra of triazolotriazines **4a—e**, having only one alkoxycarbonyl substituent, contain one high-frequency band each, caused by the vibration of this carbonyl group, whereas the spectra of dialkoxycarbonyl-substituted pyrazolotriazines **5a,b**, have two bands, corresponding to the stretching vibrations of the two carbonyl groups. In the IR spectra of imidazotriazines **6a,b**, containing

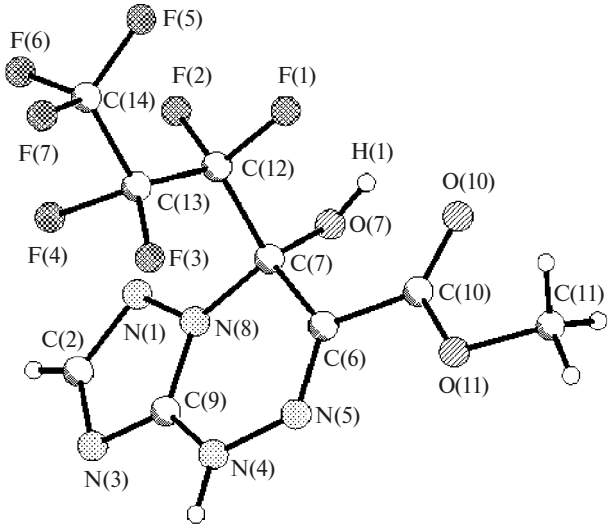


Fig. 1. General view of a molecule of compound **4d**.

also two dialkoxycarbonyl substituents, one broad high-frequency absorption band of the two carbonyl groups are present in each spectrum. In addition, the IR spectra of azolotriazines **4—6** contain two or more intensive absorption bands, caused by the stretching vibrations of the OH and NH groups, whereas in the IR spectra of 2-hydrazono-3-oxo esters **3**, a very weak broad absorption band of the NH group of the hetarylhydrazone fragment is present in the region of 3100 cm^{-1}.

In this way, the X-ray data and the distinctions found by us in the IR spectra allow us to conclude that compounds **4—6** exist in the solid state in a cyclic isomeric form.

The structures of products **3—6** in solutions were investigated by ^{13}C, ^{1}H, and ^{19}F NMR spectroscopy. The NMR spectra of compounds **3a,b**, **4a—e**, **5a,b**, and **6a**, recorded in $CDCl_3$ and DMSO-d_6, contain only one set of signals, pointed out their existence in solution in the form of one from possible isomers. As expected, in the ^{13}C NMR spectrum of ester **3a**, a signal of the carbon atom adjacent to the trifluoromethyl group is found at $\delta \approx 172$, which corresponds to the carbon atom of the trifluoroacetyl fragment, whereas, in the ^{13}C NMR spectrum of triazolotriazine **4a**, a quartet signal of the carbon atom adjacent to the trifluoromethyl group is observed at $\delta \approx 82$, which is characteristic of a quaternary carbon atom.

The ^{1}H NMR spectroscopy data cannot be used for the assignment of a cyclic or open-chain structure to the azocoupling products **3—6** because of the similarities in the spectroscopic characteristics of azolotriazines and hetarylhydrazones. However, we have shown that ^{19}F NMR spectroscopy is a source of reliable criteria for the solution of this problem since the chemical shift values of the fluorine atom signals in the CF_3 and α-CF_2 groups depend on the character of the neighboring to them carbon atoms. Thus, for azolotriazines **4a—e**, **5a,b**, and **6a**, signals of the fluorine atoms in the CF_3 and α-CF_2 group, bonded to the sp^3-hybridized carbon atom, are observed in the more strong region ($\delta_{CF_3} \approx 83—85$, $\delta_{\alpha\text{-}CF_2} \approx 45$) as compared to the corresponding signals of their open-chain analogs, 2-antipyrinylhydrazono-3-fluoroalkyl-3-oxopropionates **3a,b** ($\delta_{CF_3} \approx 90$, $\delta_{\alpha\text{-}CF_2} \approx 49$), and earlier obtained 2-arylhydrazono-3-fluoroalkyl-3-oxopropionates ($\delta_{CF_3} \approx 91—93$, $\delta_{\alpha\text{-}CF_2} \approx 50—52$),[16] in which the CF_3 and α-CF_2 groups are at the sp^2-hybridized carbon atom.

In addition, signals of the fluorine atoms in the α-CF_2 groups of the polyfluoroalkyl substituents in azolotriazines **4b—e** reveal themselves as an AB-system due to the position of this group next to the asymmetric carbon atom.

Thus, the NMR spectroscopic investigations of azolotriazines **4a—e**, **5a,b**, and **6a** showed that they exist in $CDCl_3$ and DMSO-d_6 solutions in a cyclic form.

However, imidazotriazine **6b** is an exception since in its ^{1}H and ^{19}F NMR spectra, recorded in DMSO-d_6 and $CDCl_3$, two sets of signals are present, which correspond to a cyclic and open-chain hydrazone form **A**, and the content of isomer **A** significantly increases in $CDCl_3$ (see Experimental). Apparently, heptafluoropropyl-substituted imidazotriazine **6b** is able to undergo a ring-chain isomerism since it exists as a heterocycle in the solid state and as a mixture of cyclic and hydrazone forms in solution (DMSO-d_6 and $CDCl_3$). The assignment of the isomers was carried out proceeding from the analysis of the chemical shift values of the fluorine atoms of the α-CF_2 group in its ^{19}F NMR spectra.

The synthesized dihydroazolotriazines **4—6** have alkoxycarbonyl substituents in their structure, therefore, they can be converted to the corresponding carboxylic acid. Thus, acid **7** was obtained by the alkali hydrolysis of compound **4c**.

The research carried out by us showed that the azocoupling reaction of fluoroalkylated 3-oxo esters with aryldiazonium salts, containing NH groups in the α-position to the diaza group, can be used as the one-step method for the synthesis of dihydroazolotriazines.

Experimental

IR spectra were recorded on a Perkin Elmer Spectrum One and Thermo Nicolet 6700 Fourier spectrometers in the region 4000—400 cm^{-1} in Nujol. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (^{1}H: 400 MHz; ^{13}C: 100.6 MHz, relatively to $SiMe_4$, ^{19}F: 376 MHz, relatively to C_6F_6). Elemental analysis was performed on a Carlo Erba CHN/S-O EA 1108 elemental analyzer. Column chromatography was carried out on Merck 60 silica gel (0.063—0.200 mm). Melting points were determined in unsealed capillary tubes on a Stuart SMP3 apparatus.

Monocrystals of azolotriazine **4d** were obtained by crystallization from acetone. X-Ray diffraction experiment was performed on a Xcalibur 3 diffractometer with a CCD-detector (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, the temperature was 295(2) °C, ϕ- and ω-scanning technique). An absorption correction was carried out analytically using a multifacet crystal model with the use of the CrysAlis RED 1.171.29.9 program. The crystal structure was solved by the direct method and subsequent Fourier-syntheses using the SHELXS-97 program.[17] The structure was refined by the leasts squares method in anisotropic full-matrix approximation for all the nonhydrogen atoms with the use of the SHELXL-97 program.[17]

The main crystallographic data for compound **4d** and some experimental characteristics are given in Table 1.*

Synthesis of compounds 3a,b, 4a—e, 5a,b, and 6a,b (general procedure). To obtain hetaryldiazonium salt **2**, hetarylamine (10 mmol) was placed into a two-neck flask with a stirrer and dropping funnel followed by addition of a solution of diluted hydrochloric acid (prepared from concentrated HCl (3 mL) and water (10 mL)), then, a solution of sodium nitrite (0.70 g) in water (3 mL) was added dropwise and slowly under vigorous stirring and cooling down to 0 °C. A solution of sodium acetate (4.55 g) in acetone (31 mL)

* Full crystallographic parameters of compound **4d** were deposited with the Cambridge Structural Database (CCDC 652043) and are available at www.ccdc.cam.ac.uk/conts/retrieving.html (CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk).

Table. X-Ray crystallographic data and parameters for compound **4d**

Parameter	**4d**
Molecular formula	$C_9H_6F_7N_5O_3$
Molecular weight	369.15
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	11.398(1)
b/Å	16.380(1)
c/Å	7.231(1)
α/deg	90
β/deg	94.12(1)
γ/deg	90
V/Å^3	1346.5(5)
Z	4
d_{calc}/g cm^{-3}	1.801
μ/mm^{-1}	0.197
Total number of reflections	2711
Number of independent reflections	2006
R_1-factor	0.048
Number of refined parameters	275

and 3-oxo ester **1** (10 mmol) were mixed in another flask. A solution of hetaryldiazonium salt **2** was added dropwise and slowly to thus obtained mixture at 10 °C. A precipitate was filtered off, recrystallized from ethanol, and dried *in vacuo*.

Ethyl 2-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-hydrazono-4,4,4-trifluorobutyrate (3a). The yield was 57%, m.p. 158—160 °C. The product was purified by column chromatography (chloroform was the eluent). IR, ν/cm^{-1}: 3100 (NH^{str}); 1695, 1670, 1650 (C=O); 1595, 1530, 1495 (NH^{bend}, C=N, C=C); 1295—1150 (C—F). ^{1}H NMR ($CDCl_3$), δ: 1.39 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 2.52 (s, 3 H, Me); 3.15 (s, 3 H, NMe); 4.39 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.35—7.51 (m, 5 H, Ph); 13.37 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 90.81 (s, 3 F, CF_3). ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 2.48 (s, 3 H, Me); 3.20 (s, 3 H, NMe); 4.31 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.38—7.58 (m, 5 H, Ph); 13.18 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.49 ($OCH_2\underline{Me}$); 13.86 (Me); 35.13 (NMe); 61.22 ($O\underline{CH_2}Me$); 111.42 (C(4′)); 117.03 (q, C(4), $^1J_{C,F}$ = 292.7 Hz); 121.23 (C(2)); 124.94 (*o*-C); 127.60 (*p*-C); 129.34 (*m*-C); 133.74 (*ipso*-C); 144.04 (C(3′)); 158.00 (C(5′)); 162.87 (C(1)); 172.39 (q, C(3), $^2J_{C,F}$ = 31.3 Hz). Found (%): C, 51.38; H, 4.35; F, 14.20; N, 14.10. $C_{17}H_{17}F_3N_4O_4$. Calculated (%): C, 51.26; H, 4.30; F, 14.31; N, 14.06.

Methyl 2-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-hydrazono-4,4,5,5,6,6,7,7,7-nonafluorohexanoate (3b). The yield was 68%, m.p. 129—131 °C. The product was purified by column chromatography (chloroform was the eluent). IR, ν/cm^{-1}: 3090 (NH^{str}); 1690, 1675, 1655 (C=O); 1595, 1530, 1490 (NH^{bend}, C=N, C=C); 1280—1130 (C—F). ^{1}H NMR ($CDCl_3$), δ: 2.49 (s, 3 H, Me); 3.16 (s, 3 H, NMe); 3.91 (s, 3 H, OMe), 7.34—7.52 (m, 5 H, Ph); 13.40 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 36.88 (m, 2 F, β-CF_2); 40.49 (m, 2 F, γ-CF_2); 49.56 (m, 2 F, α-CF_2); 80.75 (m, 3 F, CF_3). Found (%): C, 42.76; H, 2.66; F, 31.69; N, 10.50. $C_{19}H_{15}F_9N_4O_4$. Calculated (%): C, 42.71; H, 2.83; F, 32.00; N, 10.49.

Ethyl 7-trifluoromethyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (4a). The yield was 52%, m.p. 164—166 °C. The product was purified by column chromatography (chloroform was the eluent). IR, ν/cm^{-1}: 3270, 3205, 3120, 3070 (NH^{str}, OH); 1710 (CO_2Et); 1610, 1560, 1540, 1480, 1465 (C=N, C=C, NH^{bend}); 1275—1110 (C—F). ^{1}H NMR (DMSO-d_6), δ: 1.27 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 4.26 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 8.06 (s, 1 H, =CH); 9.30 (s, 1 H, OH); 13.34 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 10.49 ($OCH_2\underline{Me}$); 61.33 ($O\underline{CH_2}Me$); 82.00 (q, C(7), $^2J_{C,F}$ = 35.0 Hz); 121.71 (q, CF_3, $^1J_{C,F}$ = 290.4 Hz); 126.29 (C(6)); 146.08 (CH); 151.35 (C(9)); 160.91 (C(=O)OEt). ^{19}F NMR (DMSO-d_6), δ: 85.24 (s, 3 F, CF_3). Found (%): C, 34.62; H, 2.99; F, 20.30; N, 25.00. $C_8H_8F_3N_5O_3$. Calculated (%): C, 34.42; H, 2.89; F, 20.42; N, 25.09.

Ethyl 7-tetrafluoroethyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (4b). The yield was 72%, m.p. 170—172 °C. IR, ν/cm^{-1}: 3265, 3205, 3050 (NH^{str}, OH); 1715 (CO_2Et); 1610, 1565, 1530, 1475, 1460 (C=N, C=C, NH^{bend}); 1235—1120 (C—F). ^{1}H NMR (DMSO-d_6), δ: 1.27 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 4.26 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 6.73 (dddd, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 51.7 Hz, $^3J_{H,F}$ = 8.9 Hz); 8.05 (s, 1 H, =CH); 9.10 (br.d, 1 H, OH, $^4J_{H,F}$ = 2.4 Hz); 13.24 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 27.77 (m, 2 F, CF_2, AB-system, Δ_{AB} = 2.98, $^2J_{AB}$ = 297.1 Hz, $^2J_{F,H}$ = 51.7 Hz, $^2J_{F,F}$ = 10.7 Hz, $^4J_{F,H}$ = 2.4 Hz); 34.84 (m, 1 F, HCF_2, $^2J_{AB}$ = 266.2 Hz, $^2J_{F,F}$ = 9.9 Hz); 41.00 (m, 1 F, HCF_2, $^2J_{AB}$ = 266.2 Hz, $^2J_{F,F}$ = 10.2 Hz). Found (%): C, 34.60; H, 2.71; F, 24.35; N, 22.43. $C_9H_9F_4N_5O_3$. Calculated (%): C, 34.72; H, 2.92; F, 24.42; N, 22.50.

Methyl 7-difluoromethyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (4c). The yield was 54%, m.p. 212—214 °C. The product was purified by column chromatography (chloroform was the eluent). IR, ν/cm^{-1}: 3275, 3210, 3110, 3075 (NH^{str}, OH); 1705 (CO_2Me); 1615, 1570, 1540, 1450 (C=N, C=C, NH^{bend}); 1215—1145 (C—F). ^{1}H NMR (DMSO-d_6), δ: 3.81 (s, 3 H, OMe); 6.77 (t, 1 H, HCF_2, $^2J_{H,F}$ = 54.5 Hz); 7.99 (s, 1 H, =CH); 8.60 (d, 1 H, OH, $^4J_{H,F}$ = 3.0 Hz); 13.17 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 33.85 (m, 2 F, HCF_2, AB-system, Δ_{AB} = 3.47, $^2J_{AB}$ = 282.1 Hz, $^2J_{F(A),H}$ = 55.0 Hz, $^2J_{F(B),H}$ = 54.8 Hz, $^4J_{F(A),H}$ = 3.0 Hz). Found (%): C, 34.15; H, 2.80; F, 15.48; N, 28.18. $C_7H_7F_2N_5O_3$. Calculated (%): C, 34.02; H, 2.85; F, 15.37; N, 28.33.

Methyl 7-heptafluoropropyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (4d). The yield was 74%, m.p. 198—200 °C. IR, ν/cm^{-1}: 3290, 3210, 3120, 3080 (NH^{str}, OH); 1725 (CO_2Me); 1615, 1560, 1540, 1475 (C=N, C=C, NH^{bend}); 1215—1100 (C—F). ^{1}H NMR (DMSO-d_6), δ: 3.79 (s, 3 H, OMe); 8.07 (s, 1 H, =CH); 9.43 (br.s, 1 H, OH); 13.40 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 36.99 (m, 2 F, β-CF_2); 45.31 (m, 2 F, α-CF_2, AB-system, Δ_{AB} = 1.08, $^2J_{AB}$ = 283.4 Hz); 82.37 (t, 3 F, CF_3, J = 11.2 Hz). Found (%): C, 29.84; H, 1.66; F, 36.42; N, 19.28. $C_9H_6F_7N_5O_3$. Calculated (%): C, 29.60; H, 1.66; F, 36.42; N, 19.18.

Methyl 7-nonafluorobutyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (4e). The yield was 77%, m.p. 179—181 °C. IR, ν/cm^{-1}: 3275, 3215, 3115, 3080 (NH^{str}, OH); 1710 (CO_2Me); 1615, 1565, 1540, 1440 (C=N, C=C, NH^{bend}); 1275—1115 (C—F). ^{1}H NMR (DMSO-d_6), δ: 3.79 (s, 3 H, OMe); 8.07 (s, 1 H, =CH); 9.45 (br.s, 1 H, OH); 13.41 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 37.05 (m, 2 F, β-CF_2, AB-system, Δ_{AB} = 0.86, $^2J_{AB}$ = 284.8 Hz); 40.23 (m, 2 F, γ-CF_2); 45.69 (m, 2 F, α-CF_2, AB-system, Δ_{AB} = 0.96, $^2J_{AB}$ = 284.1 Hz); 82.26 (m, 3 F, CF_3). Found (%): C, 29.09; H, 1.28; F, 41.22; N, 16.88. $C_{10}H_6F_9N_5O_3$. Calculated (%): C, 28.93; H, 1.46; F, 41.18; N, 16.87.

Diethyl 7-trifluoromethyl-7-hydroxy-4,7-dihydropyrazolo[5,1-*c*][1,2,4]triazine-3,6-dicarboxylate (5a). The yield was 65%, m.p. 203—205 °C. IR, ν/cm^{-1}: 3340, 3150, 3070 (NH^{str}, OH);

1735, 1705 (2 CO_2Et); 1615, 1565, 1465 (C=N, C=C, NH^{bend}); 1230—1125 (C—F). ^1H NMR (DMSO-d_6), δ: 1.27, 1.29 (both t, 6 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.0 Hz); 4.26 (m, 4 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.0 Hz); 8.03 (s, 1 H, =CH); 9.22 (br.s, 1 H, OH); 12.68 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 85.40 (s, 3 F, CF_3). Found (%): C, 41.60; H, 3.52; F, 16.07; N, 15.79. $C_{12}H_{13}F_3N_4O_5$. Calculated (%): C, 41.15; H, 3.74; F, 16.27; N, 16.00.

Methyl 3-ethoxycarbonyl-7-heptafluoropropyl-7-hydroxy-4,7-dihydropyrazolo[5,1-*c*][1,2,4]triazine-6-carboxylate (5b). The yield was 78%, m.p. 193—195 °C. IR, ν/cm^{-1}: 3340, 3150, 3075 (NH^{str}, OH); 1740, 1715 (CO_2Et, CO_2Me); 1620, 1570, 1465 (C=N, C=C, NH^{bend}); 1230—1125 (C—F). ^1H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 3.80 (s, 3 H, OMe); 4.28 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 8.07 (s, 1 H, =CH); 9.35 (s, 1 H, OH); 12.75 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 36.95 (m, 2 F, β-CF_2); 45.65 (m, 2 F, α-CF_2); 82.41 (m, 3 F, CF_3). Found (%): C, 35.61; H, 2.73; F, 30.28; N, 12.79. $C_{13}H_{11}F_7N_4O_5$. Calculated (%): C, 35.79; H, 2.54; F, 30.48; N, 12.84.

Diethyl 7-trifluoromethyl-7-hydroxy-4,7-dihydroimidazo-[5,1-*c*][1,2,4]triazine-3,6-dicarboxylate (6a). The yield was 62%, m.p. 95—96 °C. The product was purified by column chromatography (chloroform—ethanol (10 : 1) was the eluent). IR, ν/cm^{-1}: 3340, 3225, 3135 (NH^{str}, OH); 1680 br (CO_2Et); 1610, 1565, 1480 (C=N, C=C, NH^{bend}); 1225—1095 (C—F). ^1H NMR (DMSO-d_6), δ: 1.27, 1.29 (both t, 6 H, 2 $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 4.25, 4.28 (both q, 4 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.88 (br.s, 1 H, OH); 9.57 (br.s, 1 H, =CH); 12.60 (br.s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 82.95 (s, 3 F, CF_3). ^1H NMR ($CDCl_3$), δ: 1.43, 1.44 (both t, 6 H, 2 $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 4.44 (m, 4 H, $O\underline{CH_2}Me$); 7.47 (br.s, 1 H, OH); 7.64 (s, 1 H, =CH); 10.17 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 78.80 (d, 3 F, CF_3, J = 0.9 Hz). Found (%): C, 41.25; H, 3.68; F, 16.16; N, 15.89. $C_{12}H_{13}F_3N_4O_5$. Calculated (%): C, 41.15; H, 3.74; F, 16.27; N, 16.00.

Methyl 3-ethoxycarbonyl-7-heptafluoropropyl-7-hydroxy-4,7-dihydroimidazo[5,1-*c*][1,2,4]triazine-6-carboxylate (6b). The yield was, 69%, m.p. 70—72 °C. The product was purified by column chromatography (chloroform was the eluent). IR, ν/cm^{-1}: 3270, 3100 (NH^{str}, OH); 1710 (br. CO_2Me, CO_2Et); 1610, 1590, 1555, 1530, 1460 (C=N, C=C, NH^{bend}); 1225—1120 (C—F). ^1H NMR (DMSO-d_6), δ: ring (90%): 1.30 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 3.79 (s, 3 H, OMe); 4.29 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.86 (s, 1 H, =CH); 9.72 (s, 1 H, OH); 12.65 (s, 1 H, NH); hydrazone (10%): 1.38 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 3.86 (s, 3 H, OMe); 4.37 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.90 (s, 1 H, =CH); 13.47 (br.s, 1 H, OH); 13.88 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: ring (90%): 36.88 (m, 2 F, β-CF_2); 44.07 (m, 2 F, α-CF_2); 82.40 (m, 3 F, CF_3); hydrazone (10%): 40.79 (m, 2 F, β-CF_2); 50.93 (m, 2 F, α-CF_2); 83.32 (m, 3 F, CF_3). ^1H NMR ($CDCl_3$), δ: ring (75%): 1.43 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 4.00 (s, 3 H, OMe); 4.41 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.64 (br.s, 1 H, OH); 7.67 (s, 1 H, =CH); 10.18 (br.s, 1 H, NH); hydrazone (25%): 1.46 (t, 3 H, $OCH_2\underline{Me}$, $^3J_{H,H}$ = 7.1 Hz); 3.96 (s, 3 H, OMe); 4.47 (q, 2 H, $O\underline{CH_2}Me$, $^3J_{H,H}$ = 7.1 Hz); 7.63 (br.s, 1 H, OH); 7.65 (s, 1 H, =CH); 14.08 (br.s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: ring (75%): 36.05 (m, 2 F, β-CF_2); 41.10 (m, 2 F, α-CF_2); 81.12 (m, 3 F, CF_3); hydrazone (25%): 37.64 (m, 2 F, β-CF_2); 49.13 (m, 2 F, α-CF_2); 81.49 (m, 3 F, CF_3). Found (%): C, 35.95; H, 2.42; F, 30.57; N, 12.89. $C_{13}H_{11}F_7N_4O_5$. Calculated (%): C, 35.79; H, 2.54; F, 30.48; N, 12.84.

7-Tetrafluoroethyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo-[5,1-*c*][1,2,4]triazine-6-carboxylic acid (7). Azolotriazine **4c** (1 mmol) was dissolved in 2*N* NaOH (10 mL) and kept for 16 h at ~20 °C. Then, conc. HCl was added to pH ~1, a precipitate formed was filtered off, washed with water, and dried *in vacuo*. The yield was 87%, m.p. 199—201 °C. IR, ν/cm^{-1}: 3325, 3310 (NH^{str}, OH); 1720 br. (CO_2H); 1605, 1555, 1500 (C=N, C=C, NH^{bend}); 1210—1080 (C—F). ^1H NMR (DMSO-d_6), δ: 3.41 (s, 1 H, COOH); 6.73 (dddd, 1 H, $H(CF_2)_2$, $^2J_{H,F}$ = 52.2 Hz, $^3J_{H,F}$ = 8.6 Hz); 8.02 (s, 1 H, =CH); 9.10 (br.s, 1 H, OH); 13.10 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 27.87 (m, 2 F, CF_2, AB-system, Δ_{AB} = 2.93, $^2J_{AB}$ = 296.4 Hz, $^2J_{F,H}$ = 52.2 Hz, $^2J_{F,F}$ = 10.7 Hz, $^4J_{F,H}$ = 3.2 Hz); 35.29 (m, 1 F, HCF_2, $^2J_{AB}$ = 265.7 Hz); 40.81 (m, 1 F, HCF_2, $^2J_{AB}$ = 265.7 Hz). Found (%): C, 29.78; H, 1.80; F, 26.54; N, 24.62. $C_7H_5F_4N_5O_3$. Calculated (%): C, 29.69; H, 1.78; F, 26.84; N, 24.73.

This work was financially supported by the Ural Branch of the Russian Academy of Sciences (Program for Support of Young Scientists and Postgraduate Students of UB RAS), the Russian Foundation for Basic Research (Project No. 05-03-32384), the American Civilian Research and Development Foundation (CRDF), and the Ministry of Education and Science of the Russian Federation (Joint Grant Y3-C-05-15).

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Received July 27, 2007;
in revised form December 21, 2007