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Ring-chain isomerism of ethyl 7-polyfluoroalkyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylates

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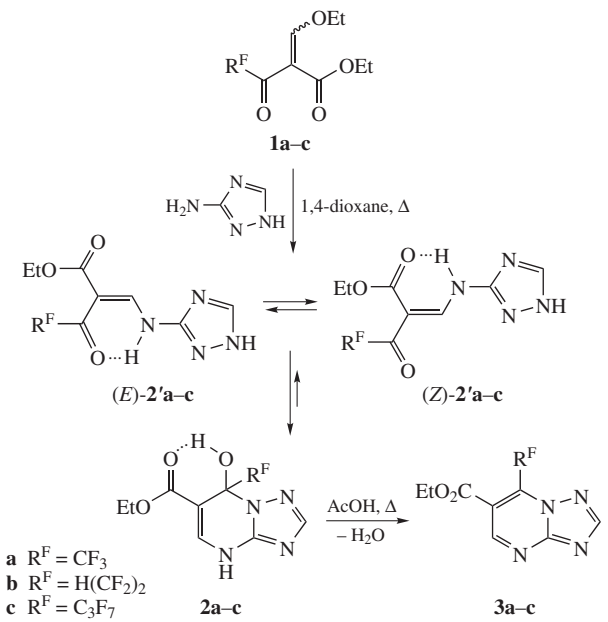
Cyclisation of ethyl 2-ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates with 3-amino-1*H*-[1,2,4]triazole gives ethyl 7-polyfluoroalkyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylates that are subject to ring–chain isomerisation in solution, depending on the solvent and the length of the polyfluoroalkyl substituent, to yield ethyl 3-polyfluoroalkyl-3-oxo-2-{([1,2,4]triazol-3-yl)aminomethylidene}propionates *via* heterocyclic ring opening at the C(7)–N(8) bond.

Azolo[*a*]pyrimidines containing a bridging nitrogen atom are structural analogues (isosteres) of purine bases and can therefore disturb metabolism and hinder protein biosynthesis.[1] New families of antiviral compounds have been found among these compounds.[2] Syntheses of such azolopyrimidines widely employ condensations of 1,3-dielectrophiles with aminoazoles that contain an NH group at the α-position. Convenient 1,3-dielectrophiles include 1,3-dicarbonyl compounds[3] and unsaturated ketones.[4] It is most promising to synthesise azolo[*a*]pyrimidines with functional groups that are capable of various conversions. Compounds suitable for this purpose include 1,3-dicarbonyl compounds functionalised at the 2-position. In fact, 2-arylmethylidene-[5] and 2-ethoxymethylidene-3-oxoesters[6] are suitable for building azolo[1,5-*a*]pyrimidines containing an alkoxycarbonyl fragment. A distinctive feature of polyfluoroalkylated derivatives of 3-oxoesters in these syntheses is that they can form stable tetrahydroazolo[1,5-*a*]pyrimidines with a *gem*-aminoalcohol fragment at the polyfluoroalkyl substituent.[4(*a*),5(*d*)]

In this work, aimed at the synthesis of potential biologically active compounds, we studied the reactions of ethyl 2-ethoxymethylidene-3-oxo-3-polyfluoroalkylpropionates **1a–c** with 3-amino-1*H*-[1,2,4]triazole.



Scheme 1

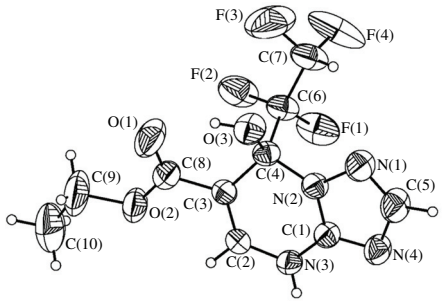


Figure 1 The general view of compound **2b**.

Esters **1a–c** on refluxing in 1,4-dioxane with 3-amino-1*H*-[1,2,4]triazole undergo conjugate substitution at the ethoxymethylidene fragment to give ethyl 7-polyfluoroalkyl-7-hydroxy-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylates **2a–c** (Scheme 1). The reaction could not be repeated by heating to reflux in ethanol or by heating in DMF at ~ 80 °C. Condensation of 2-ethoxymethylidene-substituted acetoacetic ester with 3-amino-1*H*-[1,2,4]triazole alternatively gave 6-ethoxycarbonyl-7-methyltriazolo[1,5-*a*]pyrimidine.[6(*b*)]

The X-ray diffraction analysis of crystalline compound **2b**† (Figure 1) revealed that it is ethyl 7-hydroxy-7-tetrafluoroethyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate, in which XRD data show the existence of an O(1)···H(1) intramolecular hydrogen bond (IMHB). The IMHB parameters for compound **2b** are as follows: distance O(1)···H(1) is 1.89(0) Å; angles O(1)H(1)O(3) and C(8)O(1)H(1) are 148.28° and 99.03°, respectively. The existence of an IMHB in triazolopyrimidine **2b** is also supported by its IR spectrum where a low-field shift

† *Crystallographic data for* **2b**: at 295 K, $C_{10}H_{10}F_4N_4O_3$ (M = 310.22) are monoclinic, space group $P2_1/c$, a = 16.737(2), b = 8.7692(10) and c = 8.8892(10) Å, β = 100.022(10)°, V = 1284.7(3) Å^3, Z = 4, d_{calc} = = 1.604 g cm^{-1}, μ(MoKα) = 0.157 cm^{-1}, $F(000)$ = 632. The intensities of 14817 were measured with a Xcalibur 3 at 295 K ($\omega/2\theta$-scans, MoKα, graphite monochromator, CCD-detector) and 3963 independent reflections (R_{int} = 0.0211) were used in further refinement. The structure was solved by the direct methods with the set programs SHELXL-97[10] and refined by the full-matrix least-squares method. The refinement converged to wR_2 = 0.1885 and GOF = 1.000 for all independent reflections [R_1 = = 0.0633 for 2225 reflections with $F_0 > 4\sigma(F_0)$].

CCDC 646963 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

Table 1 Compounds **2**, (*Z*)-**2′** and (*E*)-**2′** concentrations in solution according to the NMR data.

Solvent	Compounds		
$(CD_3)_2SO$	**2a**, 100%	**2b**, 100%	**2c**, 80% (*Z*)-**2′c**, 11% (*E*)-**2′c**, 9%
CD_3CN	**2a**, 92% (*Z*)-**2′a**, 3% (*E*)-**2′a**, 5%	**2b**, 68% (*Z*)-**2′b**, 11% (*E*)-**2′b**, 21%	**2c**, 41% (*Z*)-**2′c**, 32% (*E*)-**2′c**, 27%
$(CD_3)_2CO$	**2a**, 100%	**2b**, 59% (*Z*)-**2′b**, 15% (*E*)-**2′b**, 26%	**2c**, 28% (*Z*)-**2′c**, 41% (*E*)-**2′c**, 31%
CD_3OD	**2a**, 100%	**2b**, 100%	**2c**, 100%

of the ethoxycarbonyl group stretching vibration absorption band (1682 cm^{-1}) is observed in comparison with the values typical of C=O groups in α,β-unsaturated esters (1730–1710 cm^{-1}).[7]

A comparison of the IR spectra of compounds **2a**,**c** (Nujol)‡ did not reveal considerable differences in their features.

Based on the above data, it is believed that in the solid state compounds **2a–c** exist as dihydrotriazolo[1,5-*a*]pyrimidines.

The structure of products **2a–c** in solutions was studied by NMR spectroscopy.‡ The ^{1}H NMR spectra of these compounds recorded in $(CD_3)_2SO$ contain signals of ethoxy-group protons, singlet signals of two methine protons H-2, H-5 and broadened low-field singlet signals of NH and OH protons. These signals should be assigned to the resonance absorption of protons in bicyclic form **2**. The ^{19}F NMR spectrum of product **2a** contains a singlet signal of the fluorine atoms at the trifluoromethyl group in the region δ ~83.94 ppm, which is typical of the CF_3 group at the sp^3-hydridised carbon atom in form **2**.[5(*d*)] However, the ^{1}H and ^{19}F NMR spectra of compound **2c** recorded in $(CD_3)_2SO$ contain, in addition to the set of signals belonging to cyclic form **2** (80%), also two additional sets of signals corresponding to (*Z*)-**2′** (11%) and (*E*)-**2′** (9%) isomers. We have recently discovered the existence of *Z*,*E*-isomerism for ethyl 2-(het)arylmethylidene-3-oxo-3-fluoroalkylpropionates.[8]

Furthermore, the ^{13}C NMR spectrum of **2c** in $(CD_3)_2SO$ confirms the presence of bicyclic form **2** and the (*Z*)-**2′** and (*E*)-**2′** open-chain isomers. In this spectrum, the signals of carbon atoms at the heptafluoropropyl substituent are significant; they have the shape of a triplet due to interactions with the nearby fluorine atoms of the α-CF_2 group. The two triplet signals in the low-field region (δ 179.43 and 180.74 ppm) are due to the resonance absorption of the C(3) carbonyl atoms of the (*Z*)-**2′** and (*E*)-**2′** forms, whereas a triplet signal of resonance absorption of the C(7) atom of the predominant cyclic form **2** is observed at 86.53 ppm, which is characteristic of the sp^3-hybridised carbon atom.[5(*d*)]

The assignment of signals from the C(1) and C(3) atoms for the (*Z*)-**2′** and (*E*)-**2′** isomers was performed using principles suggested elsewhere,[8] according to which the signal of the C(1) atom in the ethoxycarbonyl of the (*Z*)-**2′** form is observed in lower field (165.09 ppm) in comparison with the corresponding signal of the (*E*)-**2′** form (164.11 ppm), whereas the signals of the C(3) carbonyl atom at the polyfluoroacyl fragment of isomeric forms (*Z*)-**2′** and (*E*)-**2′** are arranged in the opposite order.[8]

The discovery of the ability of heterocycle **2c** for open-chain isomerism prompted us to study the ^{1}H NMR spectra of compounds **2a–c** in various solvents. Table 1 shows the existence of compounds **2**, (*Z*)-**2′** and (*E*)-**2′** depending on the NMR solvent used.

The dehydration of dihydrotriazolo[1,5-*a*]pyrimidines **2a–c** is hindered. Prolonged refluxing (~60 h) in acetic acid is necessary to obtain ethyl 7-polyfluoroalkyl[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylates **3a–c**.‡

In summary, we can conclude that polyfluoroalkyl-containing dihydroazolopyrimidines **2** are in the bicyclic form in the solid state, whereas in solution, depending on the solvent and the length of the fluoroalkyl substituent, they may also exist in open-chain form **2′**.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.09.017.

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‡ New compounds **2a–c**, **3a–c** were characterised by elemental analyses, IR and ^{1}H (400 MHz, Me_4Si), ^{19}F (400 MHz, C_6F_6) and ^{13}C (100 MHz, Me_4Si) NMR spectroscopy. For these data see Online Supplementary Materials.

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