HETEROCYCLES, Vol. 68, No. 12, 2006, pp. 2515 - 2525. © The Japan Institute of Heterocyclic Chemistry
Received, 5th September, 2006, Accepted, 23rd October, 2006, Published online, 24th October, 2006. COM-06-10877

RECYCLIZATION OF 7-FLUOROALKYL-4,7-DIHYDROAZOLO[5,1-*c*][1,2,4]TRIAZINES INTO 5-(PYRAZOLINYLHYDRAZONO)AZOLES IN THE REACTIONS WITH HYDRAZIDES AND THIOSEMICARBAZIDE

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Abstract – 7-Fluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines react with hydrazides and thiosemicarbazide to form 5-(5-hydroxy-5-polyfluoroalkyl-2-pyrazoline-4-ylhydrazono)azoles as a result of triazine ring opening at bond C-7–N-8 and followed by *regio*-selective condensation.

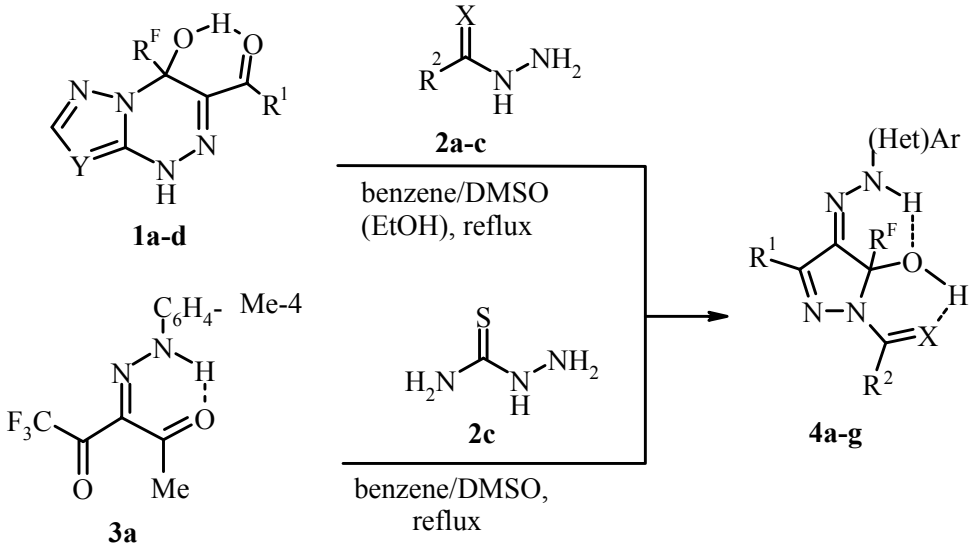
INTRODUCTION

Recently we have developed the one-pot method for preparation of 7-polyfluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**1**) by coupling of fluoroalkyl-containing 1,3-diketones with (4-ethoxycarbonylpyrazol-3-yl)- and (1,2,4-triazol-3-yl)diazonium chlorides. It has been found that azolo[5,1-*c*][1,2,4]triazines (**1**) could generate new heterocyclic systems in the reactions with dinucleophiles. So, heterocycles (**1**) react with hydrazine and its *N*-alkyl(aryl)substituted derivatives *via* open-chain 1,2,3-triketone 2-hetarylhydrazone form to afford 3-CF_3-pyrazoles.[1] Obtained fluoroalkyl-containing pyrazoles are of great interest. These compounds are the structural analogues of *celebrex*, which possesses anti-inflammatory activity and has a little gastric side effect.[2-4] To continue these works we have studied the reactions of azolo[5,1-*c*][1,2,4]triazines (**1**) with hydrazides (**2a,b**) and thiosemicarbazide (**2c**).

RESULTS AND DISCUSSION

Azolo[5,1-*c*][1,2,4]triazines (**1a-d**) react with hydrazides (**2a,b**) and thiosemicarbazide (**2c**) in refluxing benzene/DMSO mixture or in ethanol (Scheme 1) to form the products (**4**). In principle there are four

isomeric structures, which can be considered for these condensation products (Scheme 2). At first, they can be azolo[5,1-*c*][1,2,4]triazines **A**, **B** obtained as a result of the condensation of hydrazide (**2**) on the acyl substituent at the position C-6 of azolo[5,1-c][1,2,4]triazines (**1**) without opening of triazine ring. Secondly, they can be hydrazones **C** or azo-hydrazines **D** (open-chain forms of azolo[5,1-*c*][1,2,4]triazines **A**, **B**). They can also represent hydrazones **E** or azo-hydrazines **F** obtained as a result of the condensation of hydrazide (**2**) primary amino group at polyfluoroacyl group of open-chain 1,2,3-triketone 2-hetarylhydrazone **G** (Scheme 3) or at carbon atom C-7 at fluoroalkyl group followed by triazine ring opening. At last, isomeric 5-(pyrazolinylhydrazono)azoles **H** and 5-(pyrazolinylazo)azoles **I**, **J**, **K** can be obtained.



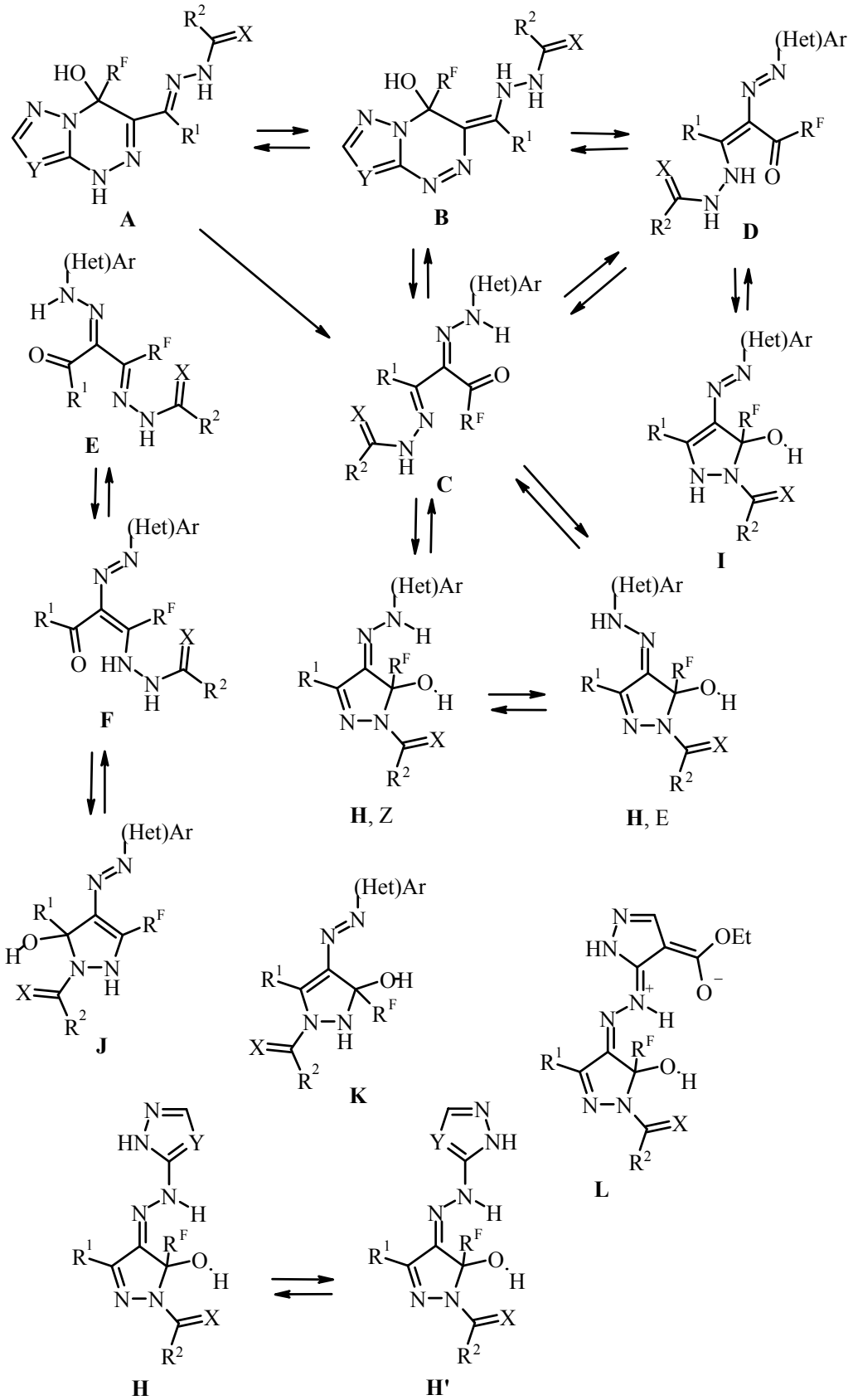
1: R^1 = Ph, Y = N, R^F = CF_3 (**a**); C_3F_7 (**b**); R^F =CF_3, Y = C-CO_2Et, R^1 = Me (**c**); Ph (**d**);
2: X = O, R^2 = Ph (**a**); 4-pyridyl (**b**); X = S, R^2 = NH_2 (**c**);
4: R^1 = Ph, Het = 1*H*-1,2,4-triazol-5-yl, R^F = CF_3, X = O, R^2 = Ph (**a**); pyridyl (**b**);
R^1 = Ph, Het = 1*H*-1,2,4-triazol-5-yl, X = S, R^2 = NH_2, R^F = CF_3 (**c**); C_3F_7 (**d**);
R^F = CF_3, Het = 1*H*-4-ethoxycarbonylpyrazol-5-yl, R^1 = Me, X = O, R^2 = pyridyl (**e**);
R^F = CF_3, Het = 1*H*-4-ethoxycarbonylpyrazol-5-yl, R^1 = Ph, X = S, R^2 = NH_2 (**f**);
R^1 = Me, Ar = C_6H_4-Me-4, R^F = CF_3, X = S, R^2 = NH_2 (**g**)

Scheme 1

Moreover, we have carried out the reaction of 5,5,5-trifluoro-2,3,4-pentanetrione 3-(*p*-tolyl)hydrazone (**3a**) as open-chain analogue of 4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**1**) with thiosemicarbazide (**2c**) (Scheme 1). In this reaction the formation of non-cyclic compounds **C**, **D**, **E**, **F** or pyrazolines **H**, **I**, **J**, **K** could take place.

The structure of five-membered heterocyclic compounds (**4**) was confirmed by ^{13}C NMR spectroscopy in DMSO-d_6 solution. The quartet signal of the carbon atom connected with the trifluoromethyl substituent in the spectra of the products (**4e-g**) is located at 87.3-88.7 ppm (see Experimental) which is typical for a

sp^3-hybridizated quarternary carbon in five-membered 1-(thio)carboxamide-5-fluoroalkyl-5-hydroxy-4*H*-2-pyrazolines in DMSO-d_6 solution.[5,6]



Scheme 2

In the ^{1}H and ^{19}F NMR spectra in DMSO-d_6 solution we observed two signal sets of 2-pyrazolines (**4a-f**) obtained from 7-fluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**1a-d**). We have found that two isomers of the compounds (**4c-e**) have different chemical shifts of NH, CH=, CH_3 protons, fluorine nuclei. The heterocycles (**4a,b,f**), where the second isomer is in quantity of 5 %, are characterized only by the different chemical shifts of NH protons in azole ring and fluorine nuclei (see Experimental). Such changes in the chemical shifts probably can be produced by hydrazono- (**H**), azo- (**I**) tautomerism; *Z*-, *E*-isomerism about C=N bond or restricted rotation about C_{azole}-N bond (conformers **H, H'**) (Scheme 2).

The close values of chemical shifts of R^F fluorine nuclei, 3-CH_3 protons and the equal shifts of 3-Ph protons, hydroxyl, benzoyl or 4-pyridinecarbonyl or thiocarboxamide substituents in pyrazoline ring in the ^{1}H and ^{19}F NMR spectra allow us to reject hydrazono- (**H**), azo- (**I**) tautomerism and *Z*-, *E*- isomerism about C=N bond of hydrazone **H**. Moreover, Singh *et al*.[7] reported that 3-methyl protons resonate at 2.09 ppm in 5-hydroxy-2-pyrazoline, while the insertion of *N*-substituent in vicinal position to 5-methyl group in pyrazoline ring resulted in diamagnetic shift of this group signal in ^{1}H NMR spectrum on ~ 0.5 ppm. As the chemical shifts of methyl protons in two isomers of product (**4e**) are equal to 2.08 and 2.11 ppm, respectively, methyl groups are situated at C=N bond in 3 position of 2-pyrazolines.

We made choice in favour of the mixture of conformers **H** and **H'** for the compounds (**4a-f**) also based on dynamic NMR technique. So, we approximately evaluated the barrier to isomerization in 2-pyrazoline (**4e**) by the method[8]. It was 16 kcal mol^{-1} at coalescence temperature 343 K. 2-Dimethylamino-2-imidazolin-4-one is known to exhibit a barrier to rotation about the C-$N(Me)_2$ bond of 15.6 kcal mol^{-1} at 299 K.[9] This value is rather high, probably because of the double-bonded nitrogen bears an acyl group, which stabilizes the dipolar canonical structure of this compound. In the product (**4e**) electron-withdrawing CO_2Et group also stabilizes the canonical structure **L** to enhance the magnitude of the rotational barrier (Scheme 2). In contrast to the restricted rotation about C_{azole}-N bond the barrier to rotation about C=N bond in 2-dimethylhydrazono- 1,3-dimethylimidazolidine is considerably higher, it is equal to 21 kcal mol^{-1} at 410 K.[10] Hence, we could not observe *Z*-, *E*- isomerism in 5-(2-pyrazoline-4-ylhydrazono)pyrazole (**4e**).

The close values of chemical shifts of fluorine nuclei in ^{19}F NMR spectra of the compounds (**4a-c,e,f,g**) allow us to draw a conclusion about 5-(2-pyrazoline-4-ylhydrazono)azole **H** and **H'** structures of two isomers of products (**4a-c,e,f**) obtained from 4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**1a,c,d**). In ^{19}F NMR spectrum of compound (**4d**) in DMSO-d_6, the signals of diastereotopic α-fluorine nuclei in the form of AB-systems also point to the presence of chiral centers of structure **H** in two isomers of substance (**4d**) with heptafluoropropyl substituent (see Experimental).

To determine unambiguously the structure of the products (**4**) the single-crystal X-Ray diffraction analysis of compounds (**4e,g**) was done. The analysis showed that the products (**4e,g**) in the crystals were two crystallographically independent molecules of type **H** pyrazoline (Figure 1, 2).

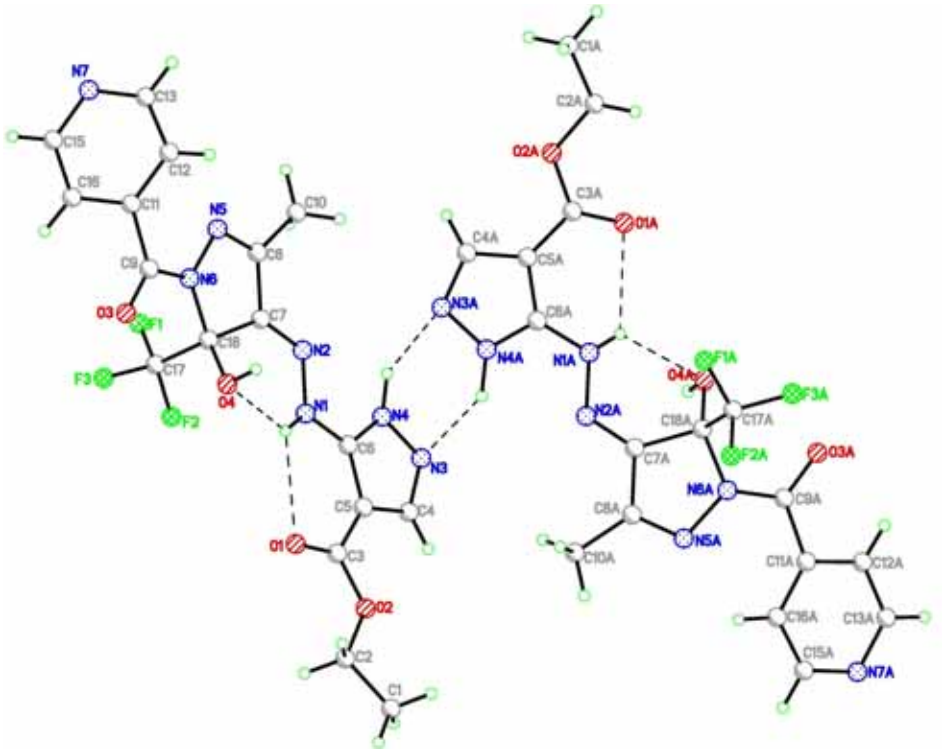


Figure 1. Two crystallographically independent molecules in X-Ray structure of 5-(pyrazolinylhydrazono)azole (**4e**)

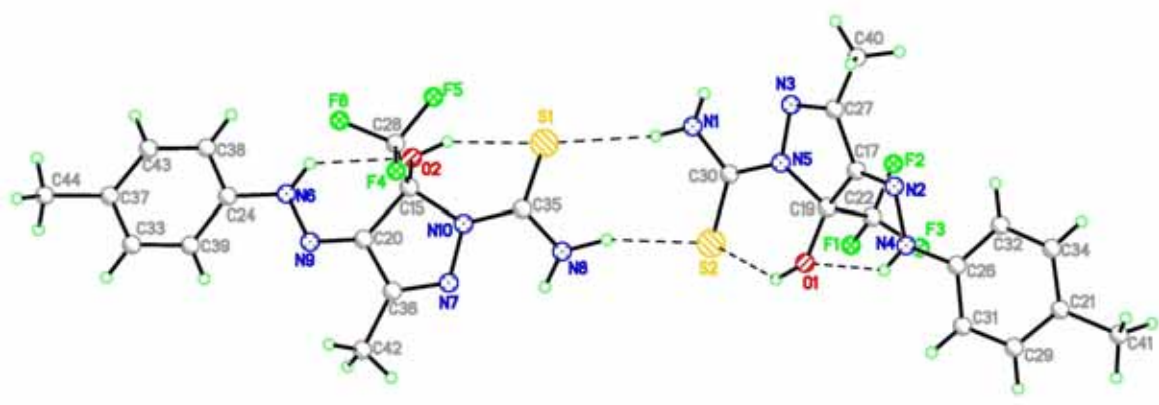
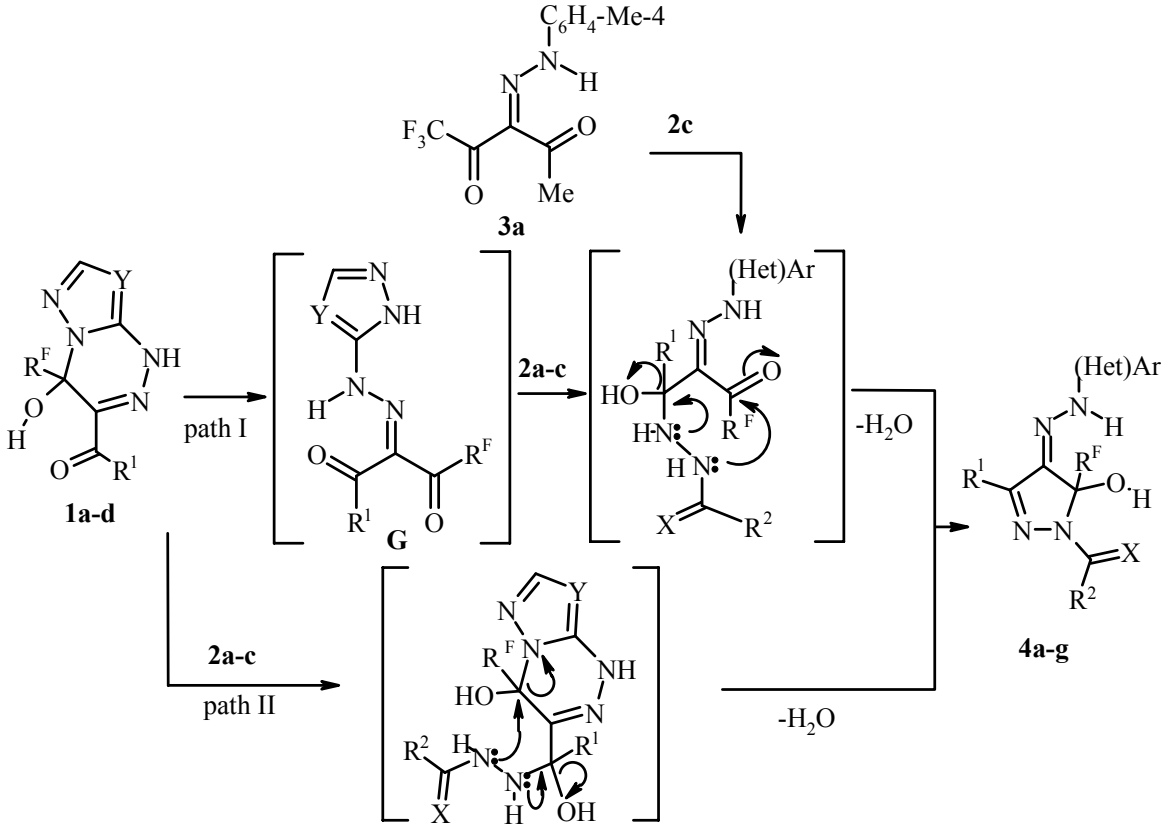


Figure 2. Two crystallographically independent molecules in X-Ray structure of 5-(pyrazolinylhydrazono)azole (**4g**)

The formation of 5-(2-pyrazoline-4-ylhydrazono)azoles (**4a-f**) from azolo[5,1-*c*][1,2,4]triazines (**1a-d**) can proceed *via* path I or path II (Scheme 3). However we suppose that path I is the most probable. In the work[1] it has been found that the ring-chain isomerism is typical for 4,7-dihydroazolo[5,1-*c*]azines (**1**). So, together with ethyl 4,7-dihydropyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylate (**1d**) in MeOD at 25 ºC, DMSO at 100 ºC and pyridine-d_5 at 25ºC we observed the presence of hydrazone **G** (from 0.8 to 10 %) in

the ^{19}F NMR spectra. Thus, primary amino group of dinucleophile (**2**) adds to carbonyl group at non-fluorinated substituent of hydrazone **G** and the reaction proceeds *regio*-selectively *via* path I to yield 5-(2-pyrazoline-4-ylhydrazono)azoles (**4**). Indirect evidence of preferred path I can be similar behaviour azoloazines (**1**) and 1,2,3-triketone 2-arylhydrazones (**3**) in the reactions with hydrazines and hydrazides.

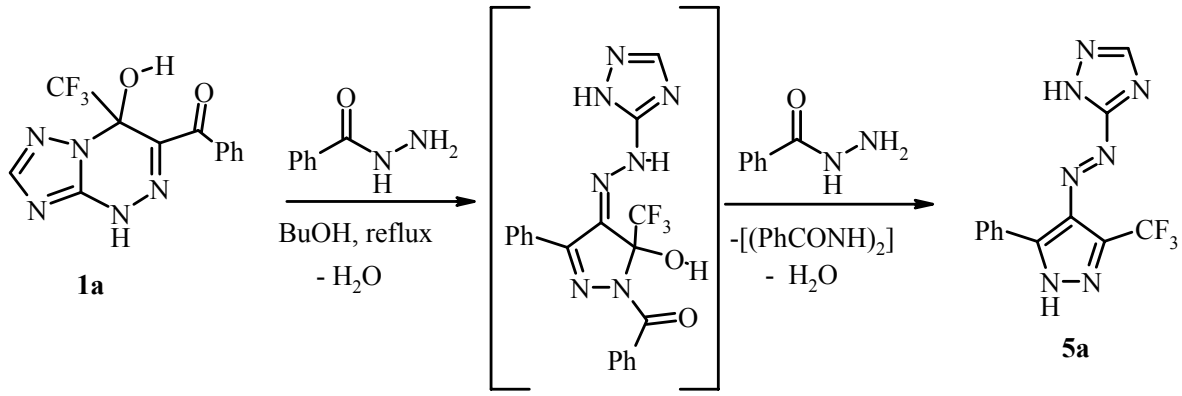


Scheme 3

It is worth mentioning that the reactions of azolo[5,1-*c*][1,2,4]triazines (**1**) and 1,2,3-triketone 2-(het)arylhydrazones (**3**) with *N*-alkyl(aryl)substituted hydrazines led to the formation of 3-R^f-pyrazoles as a result of initial addition of primary amino group at the polyfluoroacyl fragment.[1,11] In these cases the reactions proceed *via* 1*H*-3-pyrazolines **K**, which were not isolated due to the easy elimination of water under the reaction conditions. The differences in the reactivity of compounds (**1**, **3**) towards hydrazides (**2a,b**) (thiosemicarbazide (**2c**)) and hydrazines may be explained according to the *Pearson* concept.[12]

It has been found that the interaction of azoloazine (**1a**) with benzoic acid hydrazide (**2a**) in refluxing butanol leads to pyrazole (**5a**) as a result of the cyclocondensation, elimination of benzoyl substituent and dehydration (Scheme 4). Evidently after cyclocondensation elimination takes place at first and then 5-hydroxy-5-trifluoromethyl-1*H*,2*H*-3-pyrazoline dehydrates readily to pyrazole (**5a**). So, the stable pyrazolines (**4**) are cleaved much easier than they are dehydrated. Earlier pyrazole (**5a**) have been obtained by the reaction of asoloazine (**1a**) with hydrazine hydrate. Azo-hydrazone tautomerism can occur in the compound (**5a**) in contrast to *N*-1-substituted pyrazoles existing in the azo form. However,

the same character of absorption bands in the UV spectra of pyrazole (**5a**) and 3-(1,5-diphenyl-3-trifluoromethylpyrazol-4-ylazo)-1*H*-1,2,4-triazole provides evidence in favor of pyrazol-4-ylazo form of compound (**5a**).[13]



Scheme 4

Thus, we showed that 7-polyfluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**1**) can be used for the synthesis of new heterocycles due to the opening of triazine ring at the C-7–N-8 bond in the reaction with diamines and followed by condensation at 1,3-dicarbonyl fragment of open-chain form.

EXPERIMENTAL

The infrared spectra were recorded on Perkin Elmer Spectrum One FT-IR spectrometer at 4000-400 cm^{-1} in nujol mulls. UV spectra were recorded on a Shimadzu UV-2401 PC spectrophotometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker DRX-400 spectrometer (^1H, 400 MHz, ^{13}C, 100.6 MHz) relative to $SiMe_4$. The ^{19}F NMR spectra were obtained on a Bruker DRX-400 spectrometer (^{19}F, 376 MHz) using C_6F_6 as an internal standard. The chemical shifts were converted from C_6F_6 to CCl_3F. Mass spectra were measured on a Varian MAT-311A spectrometer. Elemental analyses (C, H, N, S) were conducted using the elemental analyser Perkin Elmer PE 2400 series II. The column chromatography was performed on silica gel L 100/250.

The X-Ray studies were performed for the compounds (**4e,g**) on a Xcalibur 3 CCD diffractometer with $\omega/2\theta$ scanning and graphite monochromatic Mo-K_α radiation (0.71073 Å). The crystal structures were solved by direct methods followed by Fourier synthesis with SHELXS-97 and refined by full-matrix least-squares methods for all non-hydrogen atoms with SHELXL-97 software packages.[14] The coordinates of H-atoms were found experimentally and refined in an isotropic approximation.

7-Fluoroalkyl-4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**1**) were prepared *via* a known procedure.[1] Polyfluorinated 1,2,3-triketone 2-arylhydrazone (**3**) were prepared by the method described previously.[11]

Reactions of 4,7-dihydroazolo[5,1-c]azines and 1,2,3-triketone 2-arylhydrazone with hydrazides and thiosemicarbazide (general procedure). A mixture of 4,7-dihydroazolo[5,1-*c*][1,2,4]triazine (**1a-d**) or 1,2,3-triketone 2-arylhydrazone (**3a**) (2 mmol) and hydrazide (**2a,b**) or thiosemicarbazide (**2c**) (2 mmol) in ethanol (30 mL) (benzene/DMSO (5:1) mixture for (**4c,d,g**) and butanol for (**5a**) obtaining) was refluxed for 20 h.

5-(1-Benzoyl-5-hydroxy-3-phenyl-5-trifluoromethyl-2(*Z*)-pyrazoline-4-ylhydrazono)-1*H*-1,2,4-triazole (**4a**). Yield after filtration of precipitated residue, 593 mg (69%), mp 241°C, white powder; ^{1}H NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 95:5): δ = 7.46-8.11 (m, 2 Ph), 8.43 (broadened s, CH=), 9.76 (broadened s, NH), 10.21 (s, OH); **H**: δ = 13.75 (broadened s, NH); **H'**: δ = 13.27 (broadened s, NH) ppm; ^{19}F NMR (DMSO-d_6) **H**: δ = -74.5 (s, CF_3) ppm; IR (Nujol mulls): $\overline{\nu}$ = 3290 (OH), 3160, 3100, 1550 (NH), 1680 (C=O), 1620, 1600, 1490 (C=N, C=C), 1170-1200 (C-F) cm^{-1}; UV-Vis (DMSO, c =5×10^{-5} mol dm^{-3}): λ_{max} (ε) = 207 (8853), 254 (10216), 280 (11722), 346 (19697) nm (mol^{-1} dm^3 cm^{-1}); Anal. Calcd for $C_{19}H_{14}N_7O_2F_3$: C, 53.15; H, 3.29; N, 22.84. Found: C, 52.97; H, 3.06; N, 22.90.

5-[5-Hydroxy-3-phenyl-1-(4-pyridinecarbonyl)-5-trifluoromethyl-2(*Z*)-pyrazoline-4-ylhydrazono]-1*H*-1,2,4-triazole (**4b**). Yield after filtration of precipitated residue, 611 mg (71%), mp 219°C, white powder; ^{1}H NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 98:2): δ = 7.47-8.8 (m, Ph, C_6H_4), 8.36 (broadened s, CH=), 9.88 (broadened s, NH), 10.31 (s, OH); **H**: δ = 13.8 (broadened s, NH); **H'**: δ = 13.3 (broadened s, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 88.3 (q, $^2J_{C\text{-}F}$ = 36 Hz, C-3), 122.7, 122.9 (q, $^1J_{C\text{-}F}$ = 291 Hz, C-3-*C*F_3), 127.8, 128.2, 128.4, 128.7, 130.8, 133.4, 141.6, 148.3, 149.8, 160, 164 (C=O) ppm; ^{19}F NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 98:2) **H**: δ = -74.7 (s, CF_3); **H'**: δ = -75 (s, CF_3) ppm; IR (Nujol mulls): $\overline{\nu}$ = 3360 (OH), 3130, 3070, 1530 (NH), 1680 (C=O), 1610, 1570 (C=N, C=C), 1170-1180 (C-F) cm^{-1}; MS (70 eV): *m/z* = 77 (Ph^+, 6), 78 (C_6H_6, 71), 106 ($[C_5H_4N\text{-}C{=}O]^+$, 100), 306 (M^+ -C_5H_4NCO -H_2O, 10), 361 (M^+ -CF_3, 33), 430 (M^+, 6); Anal. Calcd for $C_{18}H_{13}N_8O_2F_3$: C, 50.24; H, 3.04; N, 26.04. Found: C, 50.12; H, 3.12; N, 26.06.

5-(5-Hydroxy-3-phenyl-1-thiocarboxamide-5-trifluoromethyl-2(*Z*)-pyrazoline-4-ylhydrazono)-1*H*-1,2,4-triazole (**4c**). Benzene was removed. Yield after precipitation from DMSO by water, filtration and recrystallization from chloroform, 446 mg (58%), mp 174°C, yellow powder; ^{1}H NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~8:2): δ = 7.49-7.59 (m, H-*p*, 2 H-*m*), 8.39 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2 H-*o*), 8.61, 8.97 (2 s, NH_2), 9.37 (s, OH); **H**: δ = 8.47 (broadened s, CH=), 10.21, 13.77 (2 broadened s, 2 NH); **H'**: δ = 7.82 (broadened s, CH=), 10.8, 13.28 (2 broadened s, 2 NH) ppm; ^{19}F NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 8:2) **H**: δ = -74.3 (s, CF_3); **H'**: δ = -75.4 (s, CF_3) ppm; IR (Nujol mulls): $\overline{\nu}$ = 3425 (OH), 3400, 3300, 3260, 3100, 3060, 1530 (NH), 1600 sh, 1590, 1500 (C=N, C=C), 1185-1200 (C-F) cm^{-1}; MS (70 eV): *m/z* = 60 ($[S{=}C\text{-}NH_2]^+$, 40), 69 (CF_3^+, 14), 77 (Ph^+, 45), 306 (M^+ -NH_2CS -H_2O,

2), 315 (M^+-CF_3, 57), 384 (M^+, 26); Anal. Calcd for $C_{13}H_{11}N_8OF_3S$: C, 40.63; H, 2.88; N, 29.15; S, 8.34. Found: C, 40.33; H, 2.98; N, 29.42; S, 8.62.

5-(5-Heptafluoropropyl-5-hydroxy-3-phenyl-1-thiocarboxamide-2(*Z*)-pyrazoline-4-ylhydrazono)-1*H*-1,2,4-triazole (**4d**). Benzene was removed. Yield after precipitation from DMSO by water, filtration and recrystallization from chloroform, 460 mg (54%), mp 194°C, yellow powder; ^{1}H NMR (DMSO-d_6/CCl_4, a mixture of isomers **H**:**H'** ~ 78:22) : δ = 7.46-7.54 (m, H-*p*, 2 H-*m*), 8.34 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2 H-*o*), 8.60, 9.05 (2 s, NH_2), 9.43 (s, OH), 10.01 (broadened s, NH); **H**: δ = 8.23 (broadened s, CH=), 13.68 (broadened s, NH); **H'**: δ = 7.70 (broadened s, CH=), 13.21 (broadened s, NH) ppm; ^{19}F NMR (DMSO-d_6/CCl_4, a mixture of isomers **H**:**H'** ~ 78:22): δ = -112.7 (m, AB-system, Δν= 4.24, J = 281 Hz, α-CF_2), -80.4 (m, CF_3); **H**: δ = -126.7 (m, β-CF_2); **H'**: δ = -126.9 (m, β-CF_2) ppm; IR (Nujol mulls): $\overline{\nu}$ = 3420 (OH), 3360, 3250, 3100, 3040, 1530 (NH), 1610 sh, 1590, 1500 (C=N, C=C), 1180-1220 (C-F) cm^{-1}; Anal. Calcd for $C_{15}H_{11}N_8OF_7S$: C, 37.20; H, 2.29; N, 23.13; S, 6.62. Found: C, 37.49; H, 2.29; N, 22.80; S, 6.37.

5-[5-Hydroxy-3-methyl-1-(4-pyridinecarbonyl)-5-trifluoromethyl-2(*Z*)-pyrazoline-4-ylhydrazono]-1*H*-4-ethoxycarbonylpyrazole (**4e**). Ethanol was removed. Yield after chloroform washing, 633 mg (72%), mp 232°C, yellow powder; ^{1}H NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 1:1): δ = 1.31 (t, ^3J = 7 Hz, OCH_2CH_3), 4.29 (m, ^3J = 7 Hz, OCH_2CH_3), 8.24 (m, C_6H_4), 10.69 (s, OH); **H**: δ = 2.08 (s, Me), 8.29 (broadened s, CH=), 9.54, 13.06 (2 broadened s, 2 NH); **H'**: δ = 2.11 (s, Me), 7.77 (broadened s, CH=), 9.79, 13.47 (2 broadened s, 2 NH); ppm; ^{19}F NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 1:1) **H**: δ = -74.7 (s, CF_3); **H'**: δ = -74.8 (s, CF_3) ppm; UV-Vis (DMSO, c = 5×10^{-5} mol dm^{-3}): λ_{max} (ε) = 205 (8094), 247 (8739), 265 (10915), 347 (26480) nm (mol^{-1} dm^3 cm^{-1}); IR (Nujol mulls): $\overline{\nu}$ = 3320 (OH), 3230, 3140, 1550 (NH), 1680 (C=O), 1610, 1560, 1540 (C=N, C=C), 1175 (C-F) cm^{-1}; Anal. Calcd for $C_{17}F_3H_{16}N_7O_4$: C, 46.47; H, 3.67; N, 22.32. Found: C, 46.32; H, 3.67; N, 22.35.

Main crystallographic data for **4e**: $C_{17}H_{16}N_7O_4F_3$, M = 439.37, space group $P2_1/c$, monoclinic, a = 18.543(3), b = 15.3799(14), c = 14.2644(12) Å, α = 90°, β = 100.371(9)°, γ = 90°, V = 4001.5(7) Å^3, T = 295(2) K, Z = 8, D_{calc} = 1.459 g/cm^3, μ(Mo-K_α) = 0.125 mm^{-1}, 12795 reflections measured, 3313 reflections with I ≥ 2σ(I). The final R is 0.0491. CCDC 604171 contains the supplementary crystallographic data for this compound. [1]

5-[5-Hydroxy-3-phenyl-1-thiocarboxamide-5-trifluoromethyl-2(*Z*)-pyrazoline-4-ylhydrazono]-1*H*-4-ethoxycarbonylpyrazole (**4f**). Ethanol was removed. Yield after recrystallization from chloroform, 501 mg (55%), mp 169°C, yellow powder; ^{1}H NMR (DMSO-d_6, mixture of isomers **H**:**H'** ~ 96:4): δ = 1.31 (t,

[1] These data can be obtained free of charge *via* 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).

^3J = 7 Hz, OCH_2CH_3), 4.28 (m, ^3J = 7 Hz, OCH_2CH_3), 7.49-7.58 (m, H-*p*, 2 H-*m*), 8.22 (broadened s, CH=), 8.41 (dd, ^3J = 8 Hz, ^4J = 1 Hz, 2 H-*o*), 8.65, 9.02 (2 s, NH_2), 9.51, 10.91, (2 s, OH, NH); **H**: δ = 13.20 (broadened s, NH); **H'**: δ = 12.68 (broadened s, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.2 (OCH_2CH_3), 60 (OCH_2CH_3), 88.7 (q, $^2J_{C\text{-}F}$ = 35 Hz, C-3), 98.7, 123.1 (q, $^1J_{C\text{-}F}$ = 293 Hz, C-3-CF_3), 128.2, 128.4, 130.9, 133.2, 133.8, 146.8, 150.7, 161.4, 163.1 (CO_2Et), 175.1 (C=S) ppm; ^{19}F NMR (DMSO-d_6, a mixture of isomers **H**:**H'** ~ 96:4) **H**: δ = -74.6 (s, CF_3); **H'**: δ = -75 (s, CF_3) ppm; IR (Nujol mulls): $\overline{\nu}$ = 3400 sh (OH), 3340, 3280, 3160, 3070, 1560 (NH, NH_2), 1710 (CO_2Et), 1630, 1590, 1500 (C=N, C=C), 1180-1200 (C-F) cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_7O_3F_3S$: C, 44.84; H, 3.54; N, 21.53; S, 7.04. Found: C, 44.72; H, 3.45; N, 21.59; S, 6.88.

4-(*p*-Tolyl)hydrazono-5-hydroxy-3-methyl-1-thiocarboxamide-5-trifluoromethyl-2(*Z*)-pyrazoline (**4g**). Benzene was removed. Yield after precipitation from DMSO by water, filtration, drying and column chromatography (with chloroform:hexane (1:1) mixture as an eluent), 407 mg (61%), mp 132°C, yellow powder; ^{1}H NMR (DMSO-d_6): δ = 2.19, 2.26 (2 s, 2 Me), 7.13 (d, J = 8 Hz, 2 H-*m*), 7.34 (d, J = 8 Hz, 2 H-*o*), 8.24, 8.78 (2 s, NH_2), 9.13, 10.22 (2 s, OH, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 11 (Me), 20.3 (C_6H_4-CH_3-4), 87.3 (q, $^2J_{C\text{-}F}$ = 35 Hz, C-3), 114.4 (C-*m*), 123.3 (q, $^1J_{C\text{-}F}$ = 294 Hz, C-3-CF_3), 129.5 (C-*o*), 131.2, 131.5, 140.8, 151.7, 174.6 (C=S) ppm; ^{19}F NMR (DMSO-d_6): δ = -74.4 (s, CF_3) ppm; UV-Vis (powder, reference filter with $BaSO_4$, integrating sphere): λ_{max} (D) = 207 sh (0.06306), 235 (0.07016), 248 sh (0.06625), 269 (0.05938), 307 (0.05057), 373 (0.04269) nm (mol^{-1} dm^3 cm^{-1}); UV-Vis (DMSO, c = 5×10^{-5} mol dm^{-3}): λ_{max} (ε) = 204 sh (8252), 236 sh (7966), 259 (11726), 303 (6938), 372 (28176) nm (mol^{-1} dm^3 cm^{-1}); IR (Nujol mulls): $\overline{\nu}$ = 3440, 3420, 3340, 3290, 3220, 3120, 1595 (OH, NH, NH_2), 1565, 1530, 1500 (C=C), 1160-1270 (C-F) cm^{-1}; Anal. Calcd for $C_{12}H_{14}N_5OF_3S$: C, 57.45; H, 4.02; N, 14.89. Found: C, 57.74; H, 4.34; N, 14.71.

Main crystallographic data for **4g**: $C_{13}H_{14}F_3N_5OS$, M = 345.35, space group $P2_1/c$, monoclinic, a = 18.069(2), b = 18.832(2), c = 9.3735(7) Å, α = 90°, β = 97.969(9)°, γ = 90°, V = 3158.6(6) Å^3, T = 295(2) K, Z = 8, D_{calc} = 1.452 g/cm^3, μ(Mo-K_α) = 0.247 mm^{-1}, 10085 reflections measured, 2497 reflections with I ≥ 2σ(I). The final R is 0.043. CCDC 603123 contains the supplementary crystallographic data for this compound. [2]

5-(5-Phenyl-3-trifluoromethyl-1*H*-pyrazol-4-ylazo)-1*H*-1,2,4-triazole (**5a**). Butanol was removed. Yield after recrystallization from mixture of chloroform:ethanol (10:1), 326 mg (53%), mp 167-168°C, yellow powder (Ref.[13] mp 167-168°C).

[2] These data can be obtained free of charge *via* 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).

ACKNOWLEDGEMENTS

This work was supported by the State Programme for supporting leading scientific schools of Russian Federation (grant 9178.2006.3) and Russian Science Support Foundation.

REFERENCES

1. O. G. Khudina, E. V. Shchegol'kov, Y. V. Burgart, M. I. Kodess, O. N. Kazheva, A. N. Chekhlov, G. V. Shilov, O. A. Dyachenko, V. I. Saloutin, and O. N. Chupakhin, *J. Fluorine Chem.*, 2005, **126**, 1230.
2. D. B. Reitz and P. C. Isakson, *Curr. Pharm. Des.*, 1995, **1**, 211.
3. D. B. Reitz and K. Seibert, *Annu. Rep. Med. Chem.*, 1995, **30**, 179.
4. T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1347.
5. K. I. Pashkevich, O. G. Khomutov, and D. V. Sevenard, *Zh. Org. Khim.*, 2000, **36**, 1180.
6. A. V. Sanin, V. G. Nenaidenko, V. S. Kus'min, and E. S. Balenkova, *Khim. Geterotsikl. Soed.*, 1998, 634.
7. S. P. Singh, J. K. Kapoor, D. Kumar, and M. D. Threadgill, *J. Fluorine Chem.*, 1997, **83**, 73.
8. M. Oki, 'Applications of Dynamic NMR Spectroscopy to Organic Chemistry,' VCH Publishers, Florida, 1985, p. 5.
9. R. F. Dietrich, G. L. Kenyon, J. E. Douglas, and P. A. Kollman, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1592.
10. H. Kessler and D. Leibfritz, *Justus Liebigs Ann. Chem.*, 1970, **737**, 53.
11. Y. V. Burgart, A. S. Fokin, O. G. Kuzueva, O. N. Chupakhin, and V. I. Saloutin, *J. Fluorine Chem.*, 1998, **92**, 101.
12. R. D. Chambers, A. R. Edwards, A. Batsanov, and J. A. K. Howard, *J. Fluorine Chem.*, 1998, **88**, 95; R. J. Pearson, *Usp. Khim.*, 1971, **40**, 7, 1259.
13. E. V. Shchegol´kov, Y. V. Burgart, O. G. Khudina, V. I. Saloutin, and O. N. Chupakhin, *Russ. Chem. Bull.*, 2004, **53**, 1.
14. G. M. Scheldrik, 'SHELXS 97 and SHELXL 97', University of Gottingen, Germany, 1997.