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INTERACTIONS OF AROYL- AND HETEROAROYLTRIFLUOROACETONES WITH THIOBENZOYLHYDRAZINE*

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The interaction of aroyl(heteroaroyl)trifluoroacetones with thiobenzoylhydrazine may occur at both carbonyl groups. Reaction at the trifluoroacetyl group is facilitated by terminal substituents in the 1,3-dicarbonyl part, which leads can effectively conjugate with the adjacent carbonyl group. The products of condensation at the trifluoroacetyl group are 2-[2-aryl(heteroaroyl)-2-oxoethyl]-5-phenyl-2-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazoles, while condensation at the aroyl(heteroaroyl)group gave 3-aryl(heteroaryl)-5-hydroxy-1-thiobenzoyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles, which are not prone to tautomeric transformations in solution.

Keywords: 5-hydroxy-2-pyrazoline, 1,3,4-thiadiazoline, fluorinated 1,3-diketones.

We have shown previously that interaction of aroylacetaldehydes and aroylacetones with thioacylhydrazines occurs regiospecifically at the formyl or acetyl C=O bond [1, 2]. The condensation products in the crystalline state have the 1,3,4-thiadiazoline structure, formed by the intramolecular attack of the sulfur atom on the C=N bond of the intermediate thioacylhydrazones of the 1,3-dicarbonyl compounds. In solutions the derivatives of the aroylacetaldehydes retain the 1,3,4-thiadiazoline structure, but the derivatives of aroylacetones exist as a tautomeric mixtures of the 1,3,4-thiadiazoline and 5-hydroxy-2-pyrazoline forms; in basic dipolar solvents, DMSO and DMF the conjugated enhydrazine tautomer joins them. This is an example of a rarely achieved equilibrium, in which heterocycles of essentially different nature participate [1-6].

In a continuation of the investigation mentioned above, the interaction of thiobenzoylhydrazine was studied with 1,3-diketones CF_3COCH_2COR **1a-j** in which one of the terminal groups is a trifluoromethyl group while the second is an aryl or heteroaryl ring (Table 1).

We were interested in whether the presence of the acceptor trifluoromethyl group would affect the regioselectivity of the reaction, the structure and the ability of the condensation products to the tautomeric conversions.

The reaction of the 1,3-diketones **1a-j** with thiobenzoylhydrazine occurred under mild conditions: equimolar quantities of the reagents in absolute methanol at room temperature without use of acid catalysts. The end of the reaction was determined by TLC. The reaction occurs very slowly, the complete disappearance of the reagents takes 15-20 days. After removal of the solvent in vacuum at room

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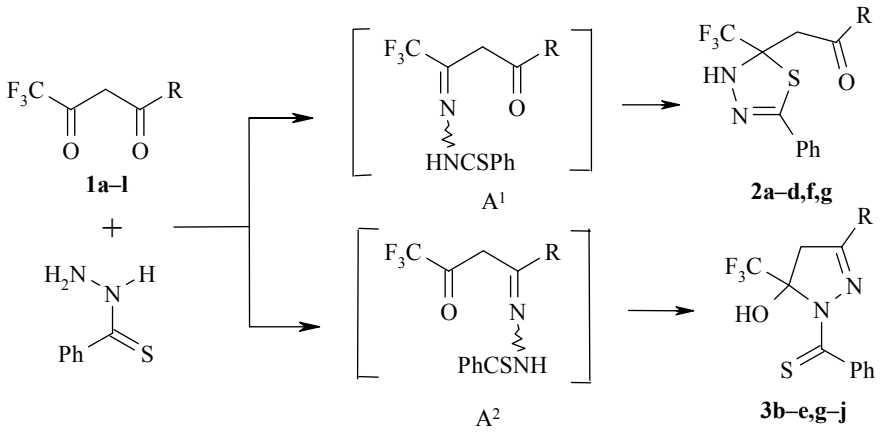
temperature the reaction products were analyzed without recrystallization by ^{1}H NMR spectroscopy. This permitted first of all the determination of the regioselectivity of the reaction.

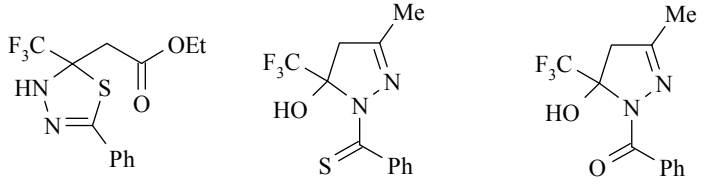
It appeared that in the case of the chosen fluorinated 1,3-diketones the presence of the terminal aryl or heteroaryl substituent did not guarantee that the reaction with thiobenzoylhydrazine occurred in a unique direction. We consider more detailed the results of the interaction of thiobenzoylhydrazine with the diketones **1a** and **1e**, which have strongly electron-donor and electron-acceptor substituents in the aromatic ring



R = 4-XC_6H_4, **a** X = OMe, **b** X = Me, **c** X = H, **d** X = Cl, **e** X = NO_2,
f R = 2- thienyl, **g** R = 2-furyl, **h** R = 2-Py, **i** R = 3-Py, **j** = 4-Py

In the ^{1}H NMR spectra of $CDCl_3$ solutions of the crystalline mass separated after the end of the reaction of 1,3-diketone **1a** with thiobenzoylhydrazine only a single set of resonance signals was observed. This evidently indicates that in the given case the reaction is regioselective and leads to the product of condensation at one of the C=O bonds. The presence in the spectrum of two unsymmetrical doublet signals corresponding to one proton each at 3.65 and 3.86 ppm and with J = 17.0 Hz, forming a typical AB system, indicates the cyclic structure of the derivative of the 1,3-diketone **1a**. Only with a ring structure, either a 1,3,4-thiadiazoline or 5-hydroxy-2-pyrazoline, would the hydrogen atoms be diastereotopic thanks to the presence of a chiral center and corresponds to the presence of AB system in the ^{1}H NMR spectrum.

The choice between the cyclic structures, 1,3,4-thidiazoline and 5-hydroxy-2-pyrazoline, was determined with the help of ^{13}C NMR spectroscopy by comparison with suitable model compounds. For this we used the products of the condensation of ethyl trifluoroacetate with thiobenzoylhydrazine – **2k**, trifluoroacetylacetone with thiobenzoylhydrazine – **3l** , and with benzoylhydrazine – **4**.



Compound **2k** has a 1,3,4-thiadiazoline structure. In its ^{1}H NMR spectrum in $CDCl_3$ solution there are two unsymmetrical doublet signals at 3.10 and 3.19 ppm with J = 15.3 Hz, corresponding to the diastereotopic protons of the methylene group adjoining the ring. The signal of the NH proton is found at δ 7.06 ppm, which corresponds to the spectral properties of derivatives of 1,3-dicarbonyl compounds with the 1,3,4-thiadiazoline structure [1, 4, 5].

Table 1. Characteristics of Compounds **2a-c,f, g** and **3d,e,g-j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{18}H_{15}F_3N_2O_2S$	56.72 / 56.84	3.89 / 3.97	7.25 / 7.36	98	31
2b	$C_{18}H_{15}F_3N_2OS$	59.26 / 59.33	4.13 / 4.15	7.56 / 7.69	118	42
2c	$C_{17}H_{13}F_3N_2OS$	58.06 / 58.28	3.68 / 3.74	7.89 / 8.00	104	26
2f	$C_{15}H_{11}F_3N_2OS_2$	50.46 / 50.55	3.06 / 3.11	7.78 / 7.86	135	33
2g	$C_{15}H_{11}F_3N_2O_2S$	52.81 / 52.94	3.21 / 3.26	8.13 / 8.23	142	32
3d	$C_{17}H_{12}F_3ClN_2OS$	52.92 / 53.06	3.08 / 3.14	7.16 / 7.28	93	30
3e	$C_{17}H_{12}F_3N_3O_3S$	51.49 / 51.65	2.99 / 3.06	10.52 / 10.63	234	52
3g	$C_{15}H_{11}F_3N_2O_2S$	52.80 / 52.94	3.18 / 3.26	8.11 / 8.23	135	49
3h	$C_{16}H_{12}F_3N_3OS$	54.55 / 54.70	3.34 / 3.44	11.83 / 11.96	142	53
3i	$C_{16}H_{12}F_3N_3OS$	54.60 / 54.70	3.35 / 3.44	11.87 / 11.96	138	48
3j	$C_{16}H_{12}F_3N_3OS$	54.58 / 54.70	3.41 / 3.44	11.83 / 11.96	136	51

In the ^{13}C NMR spectrum of compound **2k** in $CDCl_3$ solution there is a quadruplet (J = 30.9 Hz) signal of the carbon atom in position 2 at 82.53 ppm. Its multiplicity is explained by the neighboring trifluoromethyl group.

The reaction of trifluoroacetone with benzoylhydrazine occurs at the acetyl group; the product of condensation, according to previously obtained ^1H and ^{13}C NMR spectra and X-ray crystallographic data, has the 5-hydroxy-2-pyrazoline structure [7, 8]. In the ^1H NMR spectrum of compound **4** in $CDCl_3$ solution, the signals of the protons of the methylene group have the form of unsymmetrical doublets at δ 3.09 and 3.27 with J = 19.0 Hz, and the signal of the NH proton occurs at 6.70 ppm. In the ^{13}C NMR spectrum the quartet signal (J = 34.0 Hz) of the carbon atom at position 5 is at 92.89 ppm.

In the ^1H NMR spectrum in $CDCl_3$ solution of the product of condensation of thiobenzoylhydrazine with trifluoroacetylacetone **3l** a singlet signal with the intensity for three protons occurs at 1.90 ppm, two unsymmetric doublets at 3.25 and 3.41 with J = 18.9 Hz, and a weak field signal at 8.23 pp. The intensity of the last three signals corresponds to one proton each.

All of these correspond to a cyclic structure of a derivative of trifluoroacetylacetone under discussion. The first signal, naturally, belongs to a methyl group, the next two to the diastereotopic protons of the methylene group, and the last to the proton bonded to the heteroatom.

The form of the ^{13}C NMR spectrum of compound **3l** in $CDCl_3$ solution is in complete agreement with a cyclic structure, and the presence of the quartet signal at δ 95.35 ppm with J =33.9 Hz, after comparison with the spectra of compounds **2k** and **4**, convinces concluded that the product of the reaction of trifluoroacetylacetone with thiobenzoylhydrazine occurs by condensation at the acetyl C=O bond and has the 5-hydroxy-2-pyrazoline structure. Note that the signal of the carbon atom of the C=S group in the ^{13}C NMR spectrum of compound **3l** appears at 200.72 ppm.

Thus the signal of the quarternary carbon atom in the ^{13}C NMR spectrum in position 2 of the 1,3,4-thiadiazoline structure, where this atom is bonded to the trifluoromethyl group and the nitrogen and sulfur atoms, is found at considerably higher fields than the signal of the carbon atom at position 5 in the 5-hydroxy-2-pyrazoline structure, where it is bonded to the same trifluoromethyl group and nitrogen and oxygen atoms.

Table 2. ^{1}H NMR Spectra of Solutions of Compounds **2a-d,f,g** and **3b-e,g,i** *

Com-pound*	Chemical shifts, δ, ppm (*J*, Hz)	
	$CDCl_3$	DMSO-d_6
1	2	3
2a	3.65 (1H, d, *J* = 16.4, C<u>H</u>(H)CO); 3.86 (1H, d, *J* = 16.4, CH(<u>H</u>)CO); 3.91 (3H, s, OCH_3); 6.98 (2H, d, $J_{H3',H2'}$ = 8.7, H-3' 4-$CH_3OC_6H_4$); 7.35 (1H, s, NH); 7.38-7.42 (3H, m, H-3',4' C_6H_5); 7.61 (2H, dd, $J_{H2',H3'}$ = 7.3, $J_{H2',H4'}$= 1.4, H-2' C_6H_5); 7.94 (2H, d, $J_{H2',H3'}$ = 8.7, H-2' 4-$CH_3OC_6H_4$)	3.77 (1H, d, *J* = 17.4, C<u>H</u>(H)CO); 3.85 (3H, s, OCH_3); 4.19 (1H, d, *J* = 17.4, CH(<u>H</u>)CO); 7.07 (2H, d, $J_{H3',H2'}$ = 8.7, H-3' 4-$CH_3OC_6H_4$); 7.43-7.48 (3H, m, 2H-3',4' C_6H_5); 7.57 (2H, dd, $J_{H2',H3'}$ = 8.7, $J_{H2',H4'}$ = 1.4, H-2' C_6H_5); 7.98 (2H, d, $J_{H2',H3'}$ = 8.7, H-2' 4-$CH_3OC_6H_4$); 8.75 (1H, s, NH)
2b	2.45 (3H, s, CH_3); 3.70 (1H, d, *J* = 15.9, C<u>H</u>(H)CO); 3.90 (1H, d, *J* = 15.9, CH(<u>H</u>)CO); 7.30 (1H, s, NH); 7.31 (2H, d, $J_{H3',H2'}$ = 8.0, H-3' 4-$CH_3C_6H_4$); 7.37-7.41 (3H, m, H-3',4' C_6H_5); 7.62 (2H, br. d, $J_{H2',H3'}$ = 4.4, C_6H_5); 7.87 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' 4-$CH_3C_6H_4$)	2.38 (3H, s, CH_3); 3.82 (1H, d, *J* = 17.4, C<u>H</u>(H)CO); 4.22 (1H, d, *J* = 17.4, CH(<u>H</u>)CO); 7.36-7.44 (3H, m, H-3',4' C_6H_5); 7.36 (2H, d, $J_{H3',H2'}$ = 8.0, H-3' 4-$CH_3C_6H_4$); 7.56 (2H, d, $J_{H2',H3'}$ = 7.3, H-2' C_6H_5); 7.89 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' 4-$CH_3C_6H_4$); 8.76 (1H, s, NH)
2c	3.74 (1H, d, *J* = 16.0, C<u>H</u>(H)CO); 3.94 (1H, d, *J* = 16.0, CH(<u>H</u>)CO); 7.31 (1H, s, NH); 7.38-7.41 (3H, m, H-3',4' C_6H_5); 7.50-7.54 (3H, m, H-3',4' C_6H_5); 7.63 (2H, dd, $J_{H2',H3'}$ = 6.9, $J_{H2',H4'}$ = 2.7, H-2' C_6H_5); 7.97 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' C_6H_5)	3.86 (1H, d, *J* = 18.2, C<u>H</u>(H)CO); 4.21 (1H, d, *J* = 18.2, CH(<u>H</u>)CO); 7.43-7.61 (8H, m, C_6H_5, 2H-3', H-4' C_6H_5); 8.00 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' C_6H_5); 8.77 (1H, s, NH)
2d	3.67 (1H, d, *J* = 16.5, C<u>H</u>(H)CO); 3.87 (1H, d, *J* = 16.5, CH(<u>H</u>)CO); 7.23 (1H, s, NH); 7.37-7.44 (5H, m, C_6H_5); 7.50 (2H, d, $J_{H3',H2'}$ = 9.3, H-3' 4-ClC_6H_4); 7.91 (2H, d, $J_{H2',H3'}$ = 9.3, H-2' 4-ClC_6H_4)	3.89 (1H, d, *J* = 17.4, C<u>H</u>(H)CO); 4.23 (1H, d, *J* = 17.4, CH(<u>H</u>)CO); 7.43-7.47 (3H, m, 2H-3', H-4' C_6H_5); 7.62 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' C_6H_5); 7.64 (2H, d, $J_{H3',H2'}$ = 8.7, H-3' 4-ClC_6H_4); 8.01 (2H, d, $J_{H2',H3'}$ = 8.7, H-2' 4-ClC_6H_4); 8.75 (1H, s, NH)
2f	3.64 (1H, d, *J* = 16.0, C<u>H</u>(H)CO); 3.76 (1H, d, *J* = 16.0, CH(<u>H</u>)CO); 7.20 (1H, t, $J_{H3',H2'}$ = $J_{H3',H4'}$ = 4.4, H-3' 2-thienyl); 7.31 (1H, s, NH); 7.39-7.41 (3H, m, H-2',4' 2-thienyl, H-4' C_6H_5); 7.62 (2H, t, $J_{H3',H2'}$ = $J_{H3',H4'}$ = 4.4, H-3' C_6H_5); 7.77 (2H, dd, $J_{H2',H3'}$ = 4.4, $J_{H2',H4'}$ = 1.45, H-2' C_6H_5)	3.69 (1H, d, *J* = 16.4, C<u>H</u>(H)CO); 4.00 (1H, d, *J* = 16.0, CH(<u>H</u>)CO); 7.22 (1H, dd, $J_{H3',H2'}$ = 4.4, $J_{H3',H2'}$ = 3.6, H-3' 2-thienyl); 7.37-7.39 (3H, m, H-3',4' C_6H_5); 7.55 (2H, dd, $J_{H2',H3'}$ = 6.9, $J_{H2',H4'}$ = 2.2, H-2' C_6H_5); 7.92 (1H, d, $J_{H2',H3'}$ = 4.4, 2-thienyl); 7.95 (1H, d, $J_{H4',H3'}$ = 3.6, 2-thienyl)
2g	3.58 (1H, d, *J* = 15.5, C<u>H</u>(H)CO); 3.76 (1H, d, *J* = 15.5, CH(<u>H</u>)CO); 6.62 (1H, d.d, $J_{H3',H2'}$ = 3.65, $J_{H3,H4'}$ = 1.8, H-3' 2-furyl); 7.23 (1H, s, NH); 7.32 (1H, d, $J_{H2',H3'}$ = 3.65, H-2' 2-furyl); 7.38-7.41 (3H, m, 2H-3', H-4' C_6H_5); 7.61 (2H, dd, $J_{H2',H3'}$ = 6.7, $J_{H2',H4'}$ = 2.7, H-2' C_6H_5); 7.67 (1H, $J_{H4',H3'}$ = 1.8, H-4' 2-furyl)	3.77 (1H, d, *J* = 17.4, C<u>H</u>(H)CO); 3.85 (3H, s, OCH_3); 4.19 (1H, d, *J* = 17.4, CH(<u>H</u>)CO); 6.77 (1H, dd, $J_{H3',H2'}$ = 2.9, $J_{H3',H4'}$ = 1.45 H-3' 2-furyl); 7.54-7.62 (5H, m, C_6H_5); 7.92 (1H, d, $J_{H2',H3'}$ = 2.9, H-2' 2-furyl); 8.02 (1H, d, $J_{H4',H3'}$ = 1.45, H-4' 2-furyl); 8.75 (1H, s, NH)
3b	2.39 (3H, s, CH_3); 3.68 (1H, d, J_{AB} = 18.5, H_A-4); 3.88 (1H, d, J_{AB} = 18.5, H_B-4); 7.21 (2H, d, $J_{H3',H2'}$ = 8.4, H-3' 4-$CH_3C_6H_4$); 7.49 (2H, d, $J_{H2',H3'}$ = 8.4, H-2' 4-$CH_3C_6H_4$); 7.60-7.63 (3H, m, H-3',4' C_6H_5); 7.67 (2H, dd, $J_{H2',H3'}$ = 8.4, $J_{H2',H4'}$ = 1.7, H-2' C_6H_5); 8.32 (1H, s, OH)	2.33 (3H, s, CH_3); 3.82 (1H, d, J_{AB} = 19.3, H_A-4); 4.17 (1H, d, J_{AB} = 19.3, H_B-4); 7.28 (2H, d, $J_{H3',H2'}$ = 7.9, H-3' 4-$CH_3C_6H_4$); 7.37-7.49 (5H, m, C_6H_5); 7.61 (2H, d, $J_{H2',H3'}$ = 7.9, H-2' 4-$CH_3C_6H_4$); 8.48 (1H, s, OH)
3c	3.67 (1H, d, J_{AB} = 18.5, H_A-4); 3.87 (1H, d, J_{AB} = 18.5, H_B-4); 7.40 (2H, t, $J_{H3',H2'}$ = $J_{H2',H3'}$ = 8.4, H-3' C_6H_5); 7.41 (2H, t, $J_{H3',H2'}$ = $J_{H3',H4'}$ = 7.6, H-3' C_6H_5); 7.47-7.55 (4H, m, 2H-2', H-3',3' C_6H_5); 7.66 (2H, d, $J_{H2',H3'}$ = 7.6, H-2' C_6H_5); 8.25 (1H, s, OH)	3.88 (1H, d, J_{AB} = 19.6, H_A-4); 4.26 (1H, d, J_{AB} = 19.6, H_B-4); 7.43-7.61 (8H, m, 5H C_6H_5, 2H-3', H-4' C_6H_5); 8.04 (2H, br. d, *J* = 4.4, H-2' C_6H_5); 8.54 (1H, br. s, OH)

Table 2 (continued)

1	2	3
3d	3.67 (1H, d, J_{AB} = 18.9, H_A-4); 3.87 (1H, d, J_{AB} = 18.9, H_B-4); 7.38 (2H, t, $J_{H3',H2'} = J_{H3',H4'}$ = 8.0, H-3' C_6H_5); 7.42 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' C_6H_5); 7.51-7.53 (3H, m, 2H-3' 4-ClC_6H_4, H-4' C_6H_5); 7.66 (2H, d, $J_{H2',H3'}$ = 8.0, H' 4-ClC_6H_4); 8.25 (1H, s, OH)	3.84 (1H, d, J_{AB} = 19.6, H_A-4); 4.22 (1H, d, J_{AB} = 19.6, H_B-4); 7.37-7.49 (7H, m, 2H-3' 4-ClC_6H_4, 5H C_6H_5); 8.06 (2H, d, $J_{H2',H3'}$ = 8.7, H-2' 4-ClC_6H_4); 8.54 (1H, br. s, OH)
3e	3.73 (1H, d, J_{AB} = 18.5, H_A-4); 3.93 (1H, d, J_{AB} = 18.5, H_B-4); 7.43 (2H, t, $J_{H3',H2'} = J_{H3',H4'}$ = 7.6, H-3' C_6H_5); 7.53 (1H, t, $J_{H4',H3'}$ = 7.6, H-4' C_6H_5); 7.66 (2H, d, $J_{H2',H3'}$ = 7.6, H-2' C_6H_5); 7.76 (2H, d, $J_{H2',H3'}$ = 9.3, H-2' 4-$NO_2C_6H_4$); 8.27 (2H, d, $J_{H3',H2'}$ = 9.3, H-3' 4-$NO_2C_6H_4$); 8.12 (1H, s, OH)	3.89 (1H, d, J_{AB} = 19.6, H_A-4); 4.30 (1H, d, J_{AB} = 19.6, H_B-4); 7.37-7.49 (5H, m, C_6H_5); 7.87 (2H, d, $J_{H2',H3'}$ = 8.7, H-2' 4-$NO_2C_6H_4$); 8.29 (2H, d, $J_{H3',H2'}$ = 8.7, H-3' 4-$NO_2C_6H_4$); 8.63 (1H, s, OH)
3g	3.71 (1H, d, J_{AB} = 18.3, H_A-4); 3.87 (1H, d, J_{AB} = 18.3, H_B-4); 6.53 (1H, dd, $J_{H3',H2'}$ = 3.7, $J_{H3',H4'}$ = 1.8, H-3' 2-furyl); 6.87 (1H, d, $J_{H2',H3'}$ = 3.7, H-2' 2-furyl); 7.37–7.45 (4H, m, H-2',3' C_6H_5); 7.57 (1H, m, H-4' C_6H_5); 7.66 (1H, d, $J_{H4',H3'}$ = 1.8); 8.32 (1H, s, OH)	3.75 (1H, d, J_{AB} = 18.9, H_A-4); 4.09 (1H, d, J_{AB} = 18.9, H_B-4); 6.70 (1H, dd, $J_{H3',H2'}$ = 2.9, $J_{H3',H4'}$ = 1.45, H-3' 2-furyl); 7.21 (1H, d, $J_{H2',H3'}$ = 2.9, H-2' 2-furyl), 7.37–7.45 (5H, m, H C_6H_5); 7.90 (1H, d, $J_{H4',H3'}$ = 1.45, H-4' 2-furyl); 8.55 (1H, br. s, OH)
3h	3.72 (1H, d, J_{AB} = 18.7, H_A-4); 3.98 (1H, d, J_{AB} = 18.7, H_B-4); 7.42 (2H, t, $J_{H3',H2'} = J_{H3',H4'}$ = 7.3, H-3' C_6H_5); 7.51 (1H, t, $J_{H4',H3'}$ = 7.3, H-4' C_6H_5); 7.62 (2H, d, $J_{H2',H3'}$ = 7.3, H-2' C_6H_5); 7.72 (1H, td, $J_{H5',H4'} = J_{H5',H6'}$ = 8.0, $J_{H5',H3'}$ = 1.45, H-5' 2-pyridyl); 7.34 (1H, dd, $J_{H4',H5'}$ = 8.0, $J_{H4',H3'}$ = 5.1, H-4' 2-pyridyl); 7.93 (1H, d, $J_{H6',H5'}$ = 8.0, H-6' 2-pyridyl); 8.33 (1H, s, OH); 8.63 (1H, br. d, J = 5.0, H-3' 2-pyridyl)	3.90 (1H, d, J_{AB} = 19.6, H_A-4); 4.28 (1H, d, J_{AB} = 19.6, H_B-4); 7.39-7.49 (5H, m, C_6H_5); 7.50 (1H, br. s, H-4' 2-pyridyl); 7.77 (1H, br. d, J = 7.3, H-6' 2-pyridyl); 7.88 (1H, t, $J_{H5',H4'} = J_{H5',H6'}$ = 8.0, H-5' 2-pyridyl); 8.61 (1H, s, OH); 8.65 (1H, d, $J_{H3',H4'}$ = 4.4, H-3' 2-pyridyl)
3i	3.75 (1H, d, J_{AB} = 18.6, H_A-4); 3.95 (1H, d, J_{AB} = 18.6, H_B-4); 7.23 (2H, dd, $J_{H3',H2'}$ = 8.0, $J_{H3',H4'}$ = 7.3, H-3' C_6H_5); 7.30 (1H, $J_{H4',H3'}$ = 7.3, H-4' C_6H_5); 7.35 (1H, dd, $J_{H5',H6'}$ = 7.6, $J_{H5',H4'}$ = 4.2, H-5' 3-pyridyl); 7.61 (2H, d, $J_{H2',H3'}$ = 8.0, H-2' C_6H_5); 7.93 (1H, d, $J_{H6',H5'}$ = 7.6, H-6' 3-pyridyl); 8.21 (1H, s, OH); 8.72 (1H, d, $J_{H4',H5'}$ = 4.2, H-4' 3-pyridyl); 8.85 (1H, br. s, H-2' 3-pyridyl)	3.88 (1H, d, J_{AB} = 19.3, H_A-4); 4.29 (1H, d, J_{AB} = 19.3, H_B-4); 7.40-7.47 (3H, m, H-3' C_6H_5, H-5' 3-pyridyl); 7.48 (1H, t, $J_{H4',H3'}$ = 6.9, H-4' C_6H_5); 7.59 (2H, d, $J_{H2',H3'}$ = 6.9, H-2' C_6H_5); 8.25 (1H, ddd, $J_{H6',H5'}$ = 8.0, $J_{H6',H4'}$ = 2.2, $J_{H6',H2'}$ = 1.45, H-6' 3-pyridyl); 8.56 (1H, s, OH); 8.86 (1H, d, $J_{H4',H5'}$ = 3.6, H-4' 3-pyridyl); 9.19 (1H, br. s, H-2' 3-pyridyl)
3j	3.69 (1H, d, J_{AB} = 18.9, H_A-4); 3.90 (1H, d, J_{AB} = 18.9, H_B-4); 7.41 (2H, t, $J_{H3',H2'} = J_{H3',H4'}$ = 7.6, H-3' C_6H_5); 7.52 (1H, t, $J_{H4',H3'}$ = 7.6, H-4' C_6H_5); 7.50 (2H, br. s, H-2' 4-pyridyl); 7.61 (2H, d, $J_{H2',H3'}$ = 7.6, H-2' C_6H_5); 8.72 (2H, br. s, H-3' 4-pyridyl); 8.20 (1H, s, OH)	3.87 (1H, d, J_{AB} = 19.3, H_A-4); 4.29 (1H, d, J_{AB} = 19.3, H_B-4); 7.35-7.45 (3H, m, H-3',4' C_6H_5); 7.57 (2H, d, $J_{H2',H3'}$ = 6.9, H-2' C_6H_5); 7.60 (2H, d, $J_{H2',H3'}$ = 5.8, H-2' 4-pyridyl); 8.67 (2H, br. s, H-3' 4-pyridyl); 8.62 (1H, s, OH)

* The ratios of the regioisomeric products of condensation, %: **2b**:**3b**, 80:20; **2c:3c**, 34:66; **2d**:**3d**, 31:69; **2g**:**3g**, 68:32.

These differences permit reliable identification of the cyclic forms in which the products of the interaction of fluorinated 1,3-diketones with thiobenzoylhydrazines can exist.

In the ^{13}C NMR spectra of compound **2a** in $CDCl_3$ solution – the product of the condensation of the 1,3-diketone **1a** with thiobenzoylhydrazine – which has a cyclic structure according to the ^{1}H NMR spectrum, a quartet signal is observed at 82.11 ppm with J = 30.4 Hz (Table 3). The multiplicity of this signal shows the presence of a neighboring trifluoromethyl group, but the position of the signal, after comparison with those of the model compounds **2k**, **3l**, and **4**, shows that it has the 1,3,4-thiadiazoline structure formed by intramolecular cyclization of the intermediate hydrazone **A**[1] at the C=N bond.

The only product of condensation at the trifluoroacetyl C=O bond, having the 1,3,4-thiadiazoline structure **2f**, according to analogous spectroscopic study (Tables 2 and 3), is formed from reaction of thiobenzoylhydrazine with the 1,3-diketone **1f**, where the thiophene ring serves as the terminal substituent.

Note that the ^{1}H and ^{13}C spectra of solutions of compounds **2a** and **2f**, recorded directly after solution and after prolonged storage of the solutions, coincide completely; new sets of signals are not observed. Consequently tautomeric transitions do not occur in the potentially possible hydrazone and conjugated enhydrazine, nor in the alternative cyclic 5-hydroxy-2-pyrazoline forms.

In the ^{1}H NMR spectrum of the solution of the crystalline mass, isolated after reaction of thiobenzoylhydrazine with the 1,3-diketone **1e**, there is also just one set of resonance signals (Table 2), and in this case just one condensation product **3e** with a cyclic structure. The form of the spectrum, the presence of the unsymmetric doublets at 3.73 and 3.93 ppm with J = 18.9 Hz shows that it is unique.

In the ^{13}C NMR spectrum of the $CDCl_3$ solution of compound **3e** a quartet signal is observed at 96.40 ppm (J =3.7 Hz) (Table 3). Comparison with the ^{13}C NMR spectra of the model compounds confirms that interaction of the 1,3-diketone **1e** with thiobenzoylhydrazine leads to the product of condensation at the aroyl C=O bond, which has the 5-hydroxy-2-pyrazoline structure, thanks to cyclization of hydrazone **A**[2] at the trifluoroacetyl function.

On interaction of thiobenzoylhydrazine with the 1,3-diketones **1h-j**, in which the terminal substituent is a pyridine ring, all of the observed products are formed by condensation at the heteroaryl C=O bond and possess the 5-hydroxy-2-pyrazoline structure according to ^{1}H and ^{13}C NMR spectral data.

The ^{1}H and ^{13}C NMR spectra of compounds **3e**,**h-j** in $CDCl_3$ and DMSO-d_6 do not change with time, possible tautomeric transitions do not occur, and the 5-hydroxy-2-pyrazoline forms are completely dominant.

Reactions of thiobenzoylhydrazine with the remaining 1,3-diketones **1b-d**,**g** lead to mixtures of products of condensation at both C=O bonds. The ratio of the regioisomers is given in Table 2. In ^{1}H NMR spectra of solutions of the crystalline masses isolated after conclusion of the reaction have two sets of resonance signals. One set corresponds to the 1,3,4-thiadiazolines **2b-d**,**g**, formed by condensation at the trifluoroacetyl group, while the second corresponds to the 5-hydroxy-2-pyrazolines **3b-d**,**g**, obtained by condensation at the C=O bond adjacent to the aryl and heteroaryl groups (Table 2). Assignment of the signals in the ^{1}H and ^{13}C NMR spectra (Tables 2 and 3) was carried out by comparison with the spectra of the model compounds **2k**, **3l**, and **4** and derivatives of 1,3-diketones for which the reaction occurred regiospecifically at the trifluoroacetyl function (**2a**,**f**) and at the alternative heteroaryl C=O bond (**3e**,**h-j**). Note that the ^{1}H and ^{13}C NMR spectra of the condensation products with the 1,3-diketones **1b-d**,**g** did not change with time, no new tautomeric forms appeared for either derivatives of the trifluoroacetyl group or the aroyl or heteroaroyl C=O bonds.

The results obtained showed that introduction in the aromatic nuclei of the 1,3-diketones of electron-donor substituents, or use of 2-furyl and especially 2-thienyl groups as terminal groups, capable of conjugation with the neighboring C=O group, facilitated the formation of products of condensation at the trifluoroacetyl group. Introduction of a strongly electron-accepting substituent in the aromatic ring, and also 2-, 3-, and 4-pyridyl rings, increasing the electrophilicity of the carbon atom of the adjacent C=O group, can lead and leads to the complete predominance of condensation products at the aroyl or heteroaroyl carbonyl groups.

Table 3. ^{13}C NMR Spectra of Compounds **2a-d,f,g** and **3b-e,g-j**

Compound	Chemical shifts, $CDCl_3$ δ, ppm (*J*, Hz)
2a	40.86 (CH_2); 55.98 (OCH_3); 82.11 (q, *J* = 30.4, C-2); 114.53, 125.02 (q, *J* = 284.2, CF_3); 127.50, 129.02, 129.79, 130.53, 130.67, 131.33, 147.55 ($C_{(5)}$); 164.81, 193.90 (C=O)
2b	22.01 (CH_3); 41.26 (CH_2); 82.99 (q, *J* = 30.4, C-2); 124.25 (q, *J* = 290.8, CF_3); 127.50, 129.00, 130.02, 130.54, 130.66, 131.53, 134.30, 145.69, 147.47 (C-5); 195.07 (C=O)
2c	41.61 (CH_2); 82.88 (q, *J* = 29.9, C-2); 125.03 (q, *J* = 284.7, CF_3); 127.48, 127.85, 128.35, 128.84, 129.08, 129.60, 131.21, 132.19, 147.35 (C-5); 195.45 (C=O)
2d	41.65 (CH_2); 82.90 (q, *J* = 30.4, C-2); 125.04 (q, *J* = 284.3, CF_3); 127.56, 127.98, 128.23, 128.95, 129.16, 129.38, 130.56, 134.55, 147.38 (C-5); 195.64 (C=O)
2f	42.18 (CH_2); 82.16 (q, *J* = 29.9, C-2); 124.85 (q, *J* = 284.2, CF_3); 127.52, 128.98, 129.04, 130.55, 130.60, 133.88, 136.28, 144.00, 147.37 (C-5); 187.89 (C=O)
2g	40.98 (CH_2); 83.03 (q, *J* = 30.9, C-2); 113.50, 119.42, 124.83 (q, *J* = 283.2, CF_3); 127.51, 129.02, 130.47, 130.59, 147.52 (C-5); 148.02, 152.58, 183.83 (C=O)
3b	22.12 (CH_3); 44.50 (CH_2); 96.01 (q, *J* = 33.2, C-5); 128.10 (q, *J* = 290.8, CF_3); 126.82, 127.15, 128.35, 129.99, 130.86, 132.72, 133.38, 143.11, 154.76 (C-3); 200.53 (C=S)
3c	44.52 (CH_2); 96.51 (q, *J* = 33.2, C-5); 124.23 (q, *J* = 290.3, CF_3); 127.50, 128.29, 129.32, 130.37, 130.85, 131.59, 132.70, 133.10, 154.64 (C-3); 200.99 (C=S)
3d	44.44 (CH_2); 96.14 (q, *J* = 33.7, C-5); 124.15 (q, *J* = 290.8, CF_3); 127.47, 128.12, 129.06, 129.71, 130.24, 131.32, 138.39, 143.02, 153.40 (C-3); 201.24 (C=S)
3e	44.44 (CH_2); 96.40 (q, *J* = 33.7, C-5); 124.04 (q, *J* = 290.8, CF_3); 124.55, 128.04, 128.33, 129.11, 131.68, 135.54, 142.91, 149.72, 151.93 (C-3); 202.40 (C=S)
3g	44.26 (CH_2); 95.56 (q, *J* = 33.9, C-5); 112.91, 115.11, 126.78 (q, *J* = 290.8, CF_3); 127.91, 129.03, 131.26, 142.95, 146.13, 146.43 (C-3); 200.81 (C=S)
3h	44.59 (CH_2); 95.59 (q, *J* = 33.9, C-5); 123.93 (q, *J* = 287.8, CF_3); 121.70, 125.44, 128.29, 130.86, 132.45, 136.87, 149.79, 150.43, 155.53 (C-3); 201.61 (C=S)
3i	44.26 (CH_2); 95.32 (q, *J* = 33.9, C-5); 124.63 (q, *J* = 290.8, CF_3); 124.25, 126.62, 128.23, 129.61, 129.75, 134.45, 135.37, 148.19, 150.63, 151.53 (C-3); 202.02 (C=S)
3j	44.48 (CH_2); 95.42 (q, *J* = 33.9, C-5); 121.39, 124.09 (q, *J* = 287.8, CF_3); 128.86, 130.13, 132.31, 135.49, 138.17, 151.28, 151.33 (C-3); 201.42 (C=S)

It may be concluded that regioselectivity of the rection of thiobenzoylhydrazine with the fluorinated 1,3-diketones **1a-j** is determined by the electronic properties of the terminal substituent of the 1,3-dicarbonyl component, the structure of the ultimately formed cyclic compounds depends on the position of the trifluoromethyl group in the structure of the hydrazone intermediate, and intramolecular cyclization occurs exclusively at the multiple bond adjacent to the trifluoromethyl radical.

By successive recrystallization we succeeded in isolating in pure form the 1,3,4-thiadiazolines **2b**,**c,g** and the 5-hydroxy-2-pyrazolines **3d**,**g**. We did not succeed in isolating in pure form both cyclic isomers of each of the 1,3-diketones. In the best cases we obtained a mixture of condensation products in both directions with up to 90-95% of one isomer, which, however, was sufficient to identify the signals of the rings in the mixture. Both regioisomers were obtained for the 1,3-diketone **1g**, with the 2-furyl ring as the terminal substituent. It should be noted that compounds **2g** and **3g,** kept in the reaction mixture for a long time, did not undergo interconversion. This indicates that they are formed by independent routes, but the regioselectivity of the reaction is the result of kinetic control.

These investigations show that the fluorinated 1,3-diketones **1a-j** occupy a special position in the reactions with thiobenzoylhydrazine. For them the choice of a terminal substituent in the 1,3-dicarbonyl component may direct the reaction to the regioselective formation of functionalized derivatives of 2,3-dihydro-1,3,4-thiadiazole or 4,5-dihydro-1H-pyrazole. The trifluoromethyl group determines a definite cyclic structure, which is incapable of tautomeric transformation. In this connection the condensation products of fluorinated 1,3-diketones with thiobenzoylhydrazine differ from the derivatives of related aroylacetones [2] which exist in solution as ring-ring tautomeric mixtures.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solutions with TMS as internal standard with a Bruker DX-300 instrument (300 and 75 MHz respectively).

The 1,3-diketone starting materials were made by condensation of methyl aryl or methyl heteroaryl ketones with ethyl trifluoroacetate with NaH as condensing agent.

Reaction of 1,3-diketones with Thiobenzoylhydrazine. A solution of thiobenzoylhydrazine (3 mmol) in absolute methanol (15 ml) was added to a solution of a 1,3-diketone **1a-l** in absolute methanol (15 ml) and the reaction mixture was kept at 20-25°C. The course of the reaction was monitored by TLC on Silufol-254 plates (eluent $CHCl_3$). At the end of the reaction the solvent was evaporated in vacuum. The crystals formed were recrystallized from hexane. The following were obtained pure by this method: the 2-[2-aryl(heteroaryl)-2-oxoethyl]-5-phenyl-2-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazoles **2a-c**,**f**,**g** and 3-aryl(heteroaryl)-5-hydroxy-1-thiobenzoyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles **3d,e,g-j**.

Ethyl 2-(5-phenyl-2-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazol-2-yl)acetate (2k). A solution of thiobenzoylhydrazine (0.456 g, 3 mmol) in absolute methanol (10 ml) was added to a solution of ethyl 4,4,4-trifluorobutan-3-oate (0.552 g, 3 mmol). The mixture was kept for 20 days at ~20°C and part of the solvent was removed in vacuum. The precipitated crystals were recrystallized from ethanol. Yield of compound **2k** 0.82 g, (86%); mp 38-39°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 1.28 (3H, t, *J* = 7.3, $OCH_2C\underline{H}_3$); 3.10 (1H, d, *J* = 15.3, C<u>H</u>(H)CO); 3.19 (1H, d, *J* =15.3, CH(<u>H</u>)CO); 4.23 (2H, q, *J* = 7.3, $OC\underline{H}_2CH_3$); 7.06 (1H, br. s, NH); 7.40-7.42 (3H, m, H_{Ph}); 7.61-7.64 (2H, m, H_{Ph}). ^{13}C NMR spectrum ($CDCl_3$); δ, ppm (*J,* Hz): 14.26 ($OCH_2\underline{C}H_3$); 39.48 (CH_2); 62.20 ($O\underline{C}H_2CH_3$); 82.53 (q, *J* = 30.9, C-2); 124.79 (q, *J* = 283.2, CF_3); 127.42, 129.07, 130.47, 130.63, 147.15 (C-5); 168.42 ($\underline{C}O_2C_2H_5$). Found, %: C 48.89; H 4.05; N 8.69. $C_{13}H_{13}F_3N_2O_2S$. Calculated, %: C 49.05; H 4.12; N 8.80.

5-Hydroxy-3-methyl-1-thiobenzoyl-4,5-dihydro-1H-pyrazole (3l). 1,1,1-Trifluorobutane-2,4-dione (0.462 g, 3 mmol) was added to a solution of thiobenzoylhydrazine (0.456 g, 3 mmol) in chloroform (5 ml). The solvent was removed at ~20°C over 20 min in vacuum. Yield of compound **3l** 0.58 g (67%); mp 41°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.86 (3H, s, CH_3); 3.25 (1H, d, J_{AB} = 18.9, H_A-4); 3.41 (1H, d, J_{AB} = 18.9, H_B-4); 7.27-7.50 (5H, m, C_6H_5); 8.23 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J,* Hz): 43.34 (CH_2); 47.93 (CH_3); 95.35 (q, *J* = 33.9, C-5); 122.55 (q, *J* = 285.2, CF_3); 127.72, 128.21, 128.87, 129.49, 157.68 (C-3); 200.72 (C=S). Found, %: C 49.84; H 3.76; N 9.60. $C_{12}H_{11}F_3N_2OS$. Calculated, %: C 50.00; H 3.85; N 9.72.

1-Benzoyl-5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazole (4). A solution of benzoylhydrazine (1.36 g, 10 mmol) in absolute methanol (10 ml) was added to a solution of 1,1,1-trifluropentane-2,4-dione (1.48 g, 9.6 mmol) in absolute methanol (10 ml), part of the solvent was removed in vacuum at ~20°C over 1 day. Yield of compound **4** 2.03 g (76%); mp 105-106°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.06 (3H, s, CH_3); 3.09 (1H, d, *J* = 19.0, H_A-4); 3.27 (1H, d, *J* = 19.0, H_B-4); 6.70 (1H, s, OH); 7.42-7.57 (3H, m, C_6H_5); 7.93 (2H, d, *J* = 7.3, C_6H_5). ^{13} C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 16.09 (CH_3); 47.17 (C-4); 92.89 (q, *J* = 34.0, C-5); 123.86 (q, *J* = 286.9, CF_3); 128.23, 130.51, 132.53, 133.47, 155.08 (C-3); 171.56 (C=O). Found, %: C 52.78; H 4.10; N 10.32. $C_{12}H_{11}F_3N_2O_2$. Calculated, %: C 52.94;, H 4.04; N 10.29.

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