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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Ambident Properties of 4-Substituted Thiosemicarbazides in Condensations with Fluoroacetic Acids

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Abstract—4-Substituted thiosemicarbazides react with di- and trifluoroacetic acids to give the corresponding 3-fluoroalkyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thiones. Condensation of 4,4-disubstituted thiosemicarbazides with trifluoroacetic acid leads to formation of 2-amino-5-trifluoromethyl-1,3,4-thiadiazoles.

Ambident properties of thioamides, thiohydrazides, and thiosemicarbazides as N,S-difunctional nucleophiles have been well documented and utilized in the synthesis of various heterocyclic compounds, such as thiazoles, pyrazoles, thiadiazoles, triazoles, thiadiazines, triazines, etc. [1–5]. Condensation of thiosemicarbazides with carboxylic acids could lead to formation of both thiadiazoles **III** and dihydrotriazolethiones **IV** [6–8]. Interest in these compounds originates from the fact that 1,3,4-thiadiazole and 1,2,4-triazole derivatives exhibit various kinds of biological activity, including antiphlogistic, analgetic, antiviral, and antibacterial [8]. One of the most effective ways of enhancing biological activity of chemical compounds and/or extending its range is introduction of di- or trifluoromethyl substituents into their molecules, for fluorine atoms and fluoroalkyl groups are characterized by an unusual combination of electronic and steric properties. In addition, the presence of fluorine atoms increases the ability of compounds to penetrate cell membranes due to improved solubility in lipids [9–11].

There are very limited published data on fluorine-containing thiadiazoles and dihydrotriazolethiones. For example, condensation products of nonfluorinated thiosemicarbazides with a series of polyfluorinated acid fluorides [12] and of 2,4-disubstituted thiosemicarbazides with trifluoroacetic anhydride [13] were assigned the structure of polyfluorinated 4,5-dihydro-1,2,4-triazole-5(1*H*)-thiones. However, no rigorous proofs for the assumed structures were given. Ashton *et al*. [7, 8] described reactions of 2-methyl-, 4-(2-pyridyl)-, and 4-(4-nitrobenzyl)thiosemicarbazides with trifluoroacetic acid. The authors believed that the products were the corresponding dihydrotriazolethiones **IV**, but the ^{1}H NMR and mass spectra given therein could equally belong to dihydrotriazolethiones **IV** and thiadiazoles **III**.

In the present work we examined reactions of di- and trifluoroacetic acids with morpholine-4-carbothiohydrazide (**Ia**), piperidine-1-carbothiohydrazide (**Ib**), pyrrolidine-1-carbothiohydrazide (**Ic**), 4-arylthiosemicarbazides **Id**–**Ig**, and 4-piperidinothiosemicarbazide (**Ih**). Hydrazides **Ia**–**Ic** may be regarded as 4,4-disubstituted thiosemicarbazides. The reactions successfully occurred in excess difluoro- or trifluoroacetic acid. The condensation of thiosemicarbazides **Ia**–**Ic** with trifluoroacetic acid afforded exclusively thiadiazoles **IIIa**–**IIIc** (Scheme 1) whose structure was confirmed by the data of elemental analysis, gas chromatography–mass spectrometry, and ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. Compounds **IIIa**–**IIIc** characteristically showed in the ^{19}F NMR spectra a singlet at δ_F 102 ppm from the trifluoromethyl group. Thiadiazoles **IIIa**–**IIIc** can be used as model compounds to distinguish be-

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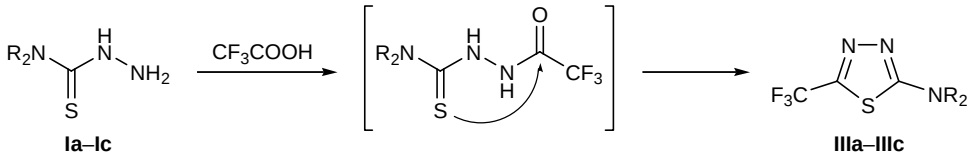
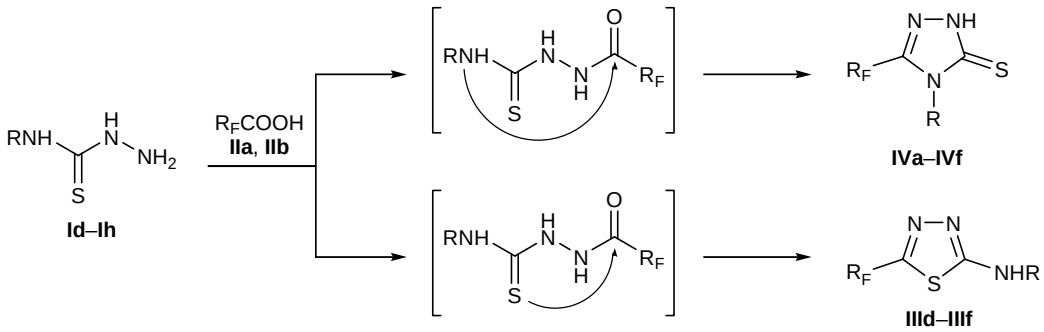
Scheme 1.



Ia–Ic **IIIa–IIIc**

R_2N = morpholino (**a**), piperidino (**b**), 1-pyrrolidinyl (**c**).

Scheme 2.



Id–Ih **IVa–IVf** **IIId–IIIf**

Id, **IIIe**, **IVa**, **IVe**, R = Ph; **Ie**, **IVc**, R = 4-MeC_6H_4; **If**, **IIIf**, **IVb**, R = 3,4-$(MeO)_2C_6H_3$; **Ig**, **IIIe**, **IVd**, R = 4-FC_6H_4; **Ih**, **IVf**, R = piperidino; **IIa**, **IIIf**, **IVa**, **IVb**, R_F = HCF_2; **IIb**, **IIId**, **IIIe**, **IVc**–**IVf**, R_F = CF_3.

tween dihydrotriazolethione and thiadiazole structures **III** and **IV** of the products obtained by condensation of 4-substituted thiosemicarbazides **Id**–**Ih** with fluorocarboxylic acids.

Under analogous conditions, from thiosemicarbazides **Id**–**Ih** and fluoroacetic acid **IIa** and **IIb** we obtained the corresponding 4,5-dihydro-1,2,4-triazole-5(1*H*)-thiones **IVa**–**IVf** as the major products. Thiadiazoles **IIId**–**IIIf** were formed as by-products (3 to 9%) in the condensations of thiosemicarbazides **Id**–**If** with difluoro- and trifluoroacetic acids (Scheme 2). Compounds **IIId** and **IIIe** were identified by the ^{19}F NMR spectra which contained a singlet at δ_F 102 ppm in addition to the signal at δ_F ~98 ppm from the CF_3 group of dihydrotriazolethiones **IVd** and **IVe**. Compound **IVb** showed in the ^{19}F NMR spectrum a doublet at δ_F 44.49 ppm from the HCF_2 group and a doublet at δ_F 47.10 ppm, the latter belonging to thiadiazole **IIIf**.

According to the GC–MS data, the condensation of thiosemicarbazide **Id** with trifluoroacetic acid gives two products, dihydrotriazolethione **IVe** (major peak with a retention time of 15.00 min) and thiadiazole **IIIe** (minor peak; retention time 15.14 min). The mass spectra of both products contain ion peaks with *m*/*z* 246 $[M + H]^+$, 245 $[M]^+$, and 244 $[M - H]^+$, as well as fragment ion peaks with *m*/*z* 176 $[M - CF_3]^+$, 168 $[M - Ph]^+$, 150 $[M - CF_3 - CN]^+$, 77 $[Ph]^+$, and 69 $[CF_3]$. Unlike compound **IVe**, thiadiazole **IIIe** gives rise to much more abundant fragment ion with *m*/*z* 150 (I_{rel} 42% against 3% for **IVe**); this ion is likely to be formed by elimination of CF_3 and CN from the molecular ion.

Thus 4-substituted thiosemicarbazides exhibit ambident properties in the condensation with di- and trifluoroacetic acids. The described reactions provide a convenient synthetic route to 3-difluoromethyl- and 3-trifluoromethyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thiones **IV**. Isomeric heterocyclic systems, thiadiazoles **III**, are formed as by-products (3–9%).

EXPERIMENTAL

The ^1H, ^{19}F, and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on Tesla BS-567A (80 MHz for ^1H and 75 Hz for ^{19}F) and Bruker DRX-400 spectrometers (400 MHz for ^1H, 376 MHz for ^{19}F, and 100 MHz for ^{13}C); the chemical shifts were measured relative to tetramethylsilane (^1H and ^{13}C) and hexafluorobenzene (^{19}F) as internal references. The IR spectra were obtained on a Perkin–Elmer Spectrum I instrument from samples dispersed in mineral oil. Gas chromatography–mass spectrometry was performed on a Varian Saturn 2100T GC/MS system (GC 3900); VF-5ms capillary column, 30 m×0.25 mm; carrier gas helium, flow rate 1 ml/min; oven temperature programming from 40°C (3 min) to 200°C at a rate of

20 deg/min. Thiosemicarbazides **Ia**–**Ih** were synthesized by the procedure reported in [14].

General procedure for condensation of thiosemicarbazides with di- and trifluoroacetic acids. Di- or trifluoroacetic acid, 0.04 mol, was added dropwise under stirring to 0.02 mol of thiosemicarbazide **Ia**–**Ih**, and the mixture was heated for 8 h under reflux. The mixture was poured into water, and the precipitate was filtered off and recrystallized from water or hexane–chloroform (3:1).

2-Morpholino-5-trifluoromethyl-1,3,4-thiadiazole (IIIa). Yield 84%. Colorless crystals, mp 94–95°C (from water). IR spectrum, ν, cm^{-1}: 1464 (C=N); 1135, 1114, 1026 (C–F). ^1H NMR spectrum, δ, ppm: 3.61 t (4H, CH_2O, $^2J_{CH}$ = 5.1 Hz), 3.85 t (4H, CH_2N, $^2J_{CH}$ = 5.1 Hz). ^{19}F NMR spectrum: δ_F 102.23 ppm, s (CF_3). ^{13}C NMR spectrum, δ_C, ppm: 49.88 s (CNC), 65.80 s (COC), 119.38 q (CF_3, $^1J_{CF}$ = 271.8 Hz), 146.36 q (C^5, $^2J_{CF}$ = 39.2 Hz), 174.13 s (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 240 (100) $[M]^+$, 86 (11), 84 (14), 69 (36). Found, %: C 35.17; H 3.34; F 23.80; N 17.78; S 13.56. $C_7H_8F_3N_3SO$. Calculated, %: C 35.15; H 3.37; F 23.83; N 17.57; S 13.40.

2-Piperidino-5-trifluoromethyl-1,3,4-thiadiazole (IIIb). Yield 32.8%. Yellow crystals, mp 37–38°C (from hexane–chloroform, 3:1). IR spectrum, ν, cm^{-1}: 1464 (C=N); 1182, 1139, 1030 (C–F). ^1H NMR spectrum, δ, ppm: 1.73 m (6H, CH_2), 3.58 m (4H, NCH_2). ^{19}F NMR spectrum: δ_F 102.21 ppm, s (CF_3). ^{13}C NMR spectrum, δ_C, ppm: 23.90 s, 24.99 s, 51.42 s (CH_2); 119.60 q (CF_3, $^1J_{CF}$ = 271.4 Hz); 145.37 q (C^5, $^2J_{CF}$ = 38.8 Hz), 174.01 s (C^2). Found, %: C 40.54; H 3.34; F 23.92; N 17.75. $C_8H_{10}F_3N_3S$. Calculated, %: C 40.50; H 4.25; F 24.02; N 17.71.

2-(1-Pyrrolidinyl)-5-trifluoromethyl-1,3,4-thiadiazole (IIIc). Yield 35.8%. Yellow crystals, mp 68–69°C (from hexane–chloroform, 3:1). IR spectrum, ν, cm^{-1}: 1478 (C=N); 1182, 1134, 1094, 1030 (C–F). ^1H NMR spectrum, δ, ppm: 2.12 m (4H, CH_2), 3.56 m (4H, NCH_2). ^{19}F NMR spectrum: δ_F 102.40 ppm, s (CF_3). ^{13}C NMR spectrum, δ_C, ppm: 25.72 s, 51.02 s (CH_2); 119.56 q (CF_3, $^1J_{CF}$ = 271.2 Hz); 144.48 q (C^5, $^2J_{CF}$ = 38.9 Hz); 169.91 s (C^2). Found, %: C 37.55; H 3.80; N 18.75; S 14.32. $C_7H_8F_3N_3S$. Calculated, %: C 37.67; H 3.61; N 18.82, S 14.36.

3-Difluoromethyl-4-phenyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thione (IVa). Yield 45%. Yellow crystals, mp 198–199°C (from hexane–chloroform, 1 : 3). IR spectrum, ν, cm^{-1}: 3088, 3039, 2744 (NH); 1594 (C=N); 1126, 1077, 1056 (C–F). ^1H NMR spectrum, δ, ppm: 6.53 t (1H, HCF_2, $^2J_{CF}$ = 51.5 Hz), 7.39–7.61 m (5H, C_6H_5), 11.96 br.s (1H, NH). ^{19}F NMR spectrum: δ_F 44.76 ppm, d (HCF_2, $^2J_{FH}$ = 51.5 Hz). Found, %: C 47.30; H 2.88; F 16.72; N 18.61; S 14.08. $C_9H_7F_2N_3S$. Calculated, %: C 47.57; H 3.11; F 16.72; N 18.49; S 14.11.

3-Difluoromethyl-4-(3,4-dimethoxyphenyl)-4,5-dihydro-1,2,4-triazole-5(1*H*)-thione (IVb) and 5-difluoromethyl-2-(3,4-dimethoxyphenylamino)-1,3,4-thiadiazole (IIIf). Yield 35%. Yellow crystals, mp 215–216°C (from hexane–chloroform, 1:3). IR spectrum, ν, cm^{-1}: 3090, 3040, 2750 (NH); 1590 (C=N); 1170, 1130, 1050 (C–F). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.90 s (3H, OCH_3), 3.95 s (3H, OCH_3), 6.51 t (1H, HCF_2, $^2J_{CF}$ = 51 Hz), 6.68–7.26 m (3H, C_6H_3), 11.54 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: **IVb**: 44.09 d (HCF_2, $^2J_{FH}$ = 51.3 Hz); **IIIf**: 47.09 d (HCF_2, $^2J_{FH}$ = 51.9 Hz); signal intensity ratio **IVb**:**IIIf** ≈ 10:1. Found, %: C 45.64; H 3.64; F 12.72; N 14.25; S 11.28. $C_{11}H_{11}F_2N_3O_2S$. Calculated, %: C 45.99; H 3.86; F 13.23; N 14.63; S 11.16.

4-(4-Methylphenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thione (IVc). Yield 55%. Yellow crystals, mp 141–143°C (from hexane–chloroform, 1:3). IR spectrum, ν, cm^{-1}: 3034, 2742 (NH); 1606 (C=N); 1220, 1179, 1156 (C–F). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.65 s (3H, CH_3), 7.09–7.48 m (4H, C_6H_4), 10.53 br.s (1H, NH). ^{19}F NMR spectrum ($CDCl_3$–C_6F_6): δ_F 99.91 ppm, s (CF_3). Found, %: C 46.50; H 3.20; F 21.54; N 16.11; S 12.30. $C_{10}H_8F_3N_3S$. Calculated, %: C 46.33; H 3.11; F 21.98; N 16.21; S 12.37.

4-(4-Fluorophenyl)-3-trifluoromethyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thione (IVd) and 2-(4-fluorophenylamino)-5-trifluoromethyl-1,3,4-thiadiazole (IIId). Yield 88%. Colorless crystals, mp 139–140°C (from water). IR spectrum, ν, cm^{-1}: 3083, 3039, 2747 (NH); 1599 (C=N); 1276, 1197, 1164 (C–F). ^1H NMR spectrum, δ, ppm: 7.26–7.38 m (4H, C_6H_4F), 12.50 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: **IVd**: 53.61 s (1F, 4-FC_6H_4), 98.31 s (3F, CF_3); **IIId**: 102.14 s (3F, CF_3), 47.04 s (1F, 4-FC_6H_4); signal intensity ratio **IVd**:**IIId** ≈ 10:1. Found, %: C 41.10; H 2.00; N 16.01; S 12.25. $C_9H_5F_4N_3S$. Calculated, %: C 41.07; H 1.91; N 15.96; S 12.18.

4-Phenyl-3-trifluoromethyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thione (IVe) and 2-phenylamino-5-trifluoromethyl-1,3,4-thiadiazole (IIIe). Yield 70%. Yellow crystals, mp 153–154°C (from chloroform). IR spectrum, ν, cm^{-1}: 3071, 3032, 2743 (N–H); 1618

(C=N); 1251, 1176, 1150 (C–F). ^{1}H NMR spectrum, δ, ppm: 7.25–7.61 m (5H, C_6H_5), 11.00 br.s (1H, NH). ^{19}F NMR spectrum, δ_F, ppm: **IVe**: 98.34 s (CF_3); **IIIe**: 102.17 s (CF_3); signal intensity ratio **IVe**:**IIIe** ≈ 30:1. ^{13}C NMR spectrum, δ_C, ppm: 116.52 q (CF_3, $^1J_{CF}$ = 271.8 Hz); 127.83 s, 130.04 s, 130.98 s, 131.92 s (C_{arom}); 141.67 q (C^3, $^2J_{CF}$ = 41.4 Hz); 171.28 s (C^5). Mass spectrum, *m*/*z* (I_{rel}, %): **IVe**: 246 (100) $[M + H]^+$, 245 (36) $[M]^+$, 244 (64), 150 (3), 77 (16), 69 (13); **IIIe**: 246 (41) $[M + H]^+$, 245 (100) $[M]^+$, 244 (69), 150 (42), 92 (4), 77 (38), 69 (31). Found, %: C 44.08; H 2.25; F 23.19; N 17.23; S 13.12. $C_9H_6F_3N_3S$. Calculated, %: C 44.08; H 2.47; F 23.24; N 17.14; S 13.07.

4-Piperidino-3-trifluoromethyl-4,5-dihydro-1,2,4-triazole-5(1*H*)-thione (IVf). Yield 50%. Yellow crystals, mp 155–156°C (from hexane–chloroform, 1:3). IR spectrum, ν, cm^{-1}: 3060, 3100, 2740 (NH); 1598 (C=N); 1219, 1160, 1155 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.48–1.74 m (10H, CH_2), 8.25 br.s (1H, NH). ^{19}F NMR spectrum: δ_F 101.88 ppm, s (CF_3). Found, %: C 38.56; H 4.01; F 22.62; N 22.23. $C_8H_{11}F_3N_4S$. Calculated, %: C 38.09; H 4.40; F 22.59; N 22.21.

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