An Efficient Catalyst-Free Direct Approach to 5-Polyfluoroalkyl-1,2,4-triazole-3-thiones

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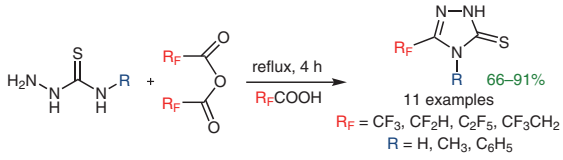

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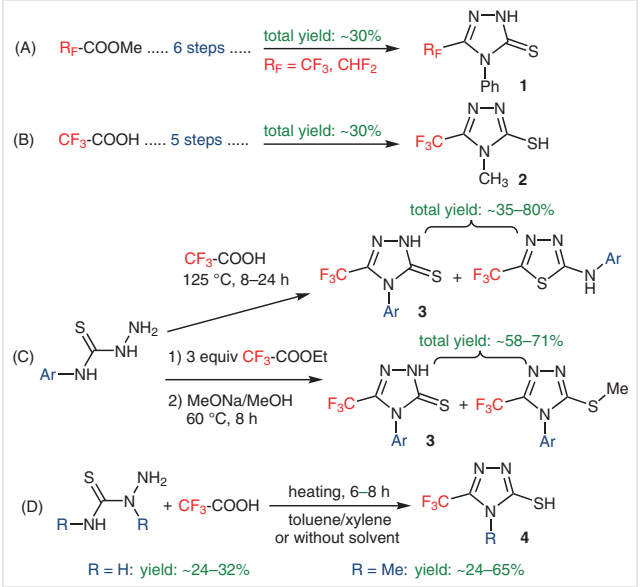
Abstract An easy to handle high-efficient approach to 5-polyfluoroalkyl-1,2,4-triazole-3-thiones (11 examples, up to 91% yield) is reported. The tautomerism of thione and thiol forms for the obtained products is discussed. A one step procedure for 6,6-dimethyl-3-(trifluoromethyl)-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole formation from trifluoroacetic acid and 4-methallylthiosemicarbazide has been developed. The structures of the products were unambiguously determined by complex NMR investigation and by single crystal X-ray diffraction.

Key words thiosemicarbazide, perfluorocarboxylic acid, 1,2,4-triazol-3-thione, fluoroalkyl, [1,3]thiazolo[2,3-*c*][1,2,4]triazole, electrophilic cyclization

Condensed and functional derivatives of 1,2,4-triazole-3-thione attract increasing attention owing to their synthetic importance and significant role in the medicinal, agricultural, and material sciences.[1] These compounds are usually associated with immense biological activities: antibacterial and antifungal,[2a–c] anti-inflammatory and analgesic,[3a–d] antioxidant,[3] antinociceptive,[3c] and ulcerogenic.[3c] They are efficient inhibitors of urease[4] and cationic surfactants.[5] Therefore, a significant part of current scientific investigations on triazole chemistry is devoted to the development of new approaches to biologically active compounds.

It is well documented that polyfluoroalkyl groups are very prospective substituents due to their strong electron-withdrawing properties and high lipophilicity.[6] At the same time, nowadays organofluorine compounds are of particular interest because of their high potential as biologically active compounds.[7] However, to date the number of publications devoted to the synthesis of corresponding perfluoroalkyl-substituted 3-thio-1,2,4-triazole derivatives is quite limited, especially for reliable data concerning 2,4-unsubstituted derivatives of 5-perfluoroalkyl-1,2,4-triazol-3-thiones. Mlostoń and co-workers[8] have reported a 6-step ap-



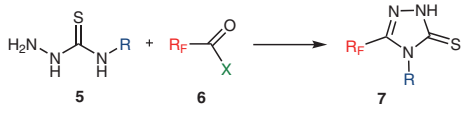
Scheme 1 Synthetic routes to 5-perfluoroalkyl-1,2,4-triazol-3-thiones and -thiols

proach to 5-tri-/difluoromethyl-4-phenyl-1,2,4-triazol-3-thiones **1** starting from the methyl ester of the corresponding fluoroacetic acid (Scheme 1A). Frackenpohl and coworkers[9] have also described multistep synthesis of similar 5-trifluoromethyl-4-methyl-1,2,4-triazol-3-thioles starting from trifluoroacetic acid (TFA), but the authors believed that the product **2** was obtained in the isomeric thiol form (Scheme 1B).

Ashton[10] and Vasil'eva[11] prepared the 4-aryl-5-trifluoroalkyl-1,2,4-triazol-3-thiones **3** by directly boiling 4-arylthiosemicarbazides in trifluoroacetic acid (TFA) or ethyl trifluoroacetate (Scheme 1C), but later the same authors[11,12] reported that the above procedure also gave isomeric thiadiazoles or methyl thioethers as by-products. Interestingly, the idea of direct interaction between 4-arylthiosemicarbazides and TFA (in a solvent and without it) was transferred to unsubstituted and 2- or 4-methylthiosemicarbazides, but all sources[13–15] reported low yields (24–32%) of unsubstituted triazoles **4** and moderate yields (34–54%) for methyl-substituted triazoles **4** exclusively in the thiol form (Scheme 1D); low yields can be explained by simultaneous formation of isomeric thiadiazoles as by-products (Scheme 1C) – this may also account for the difference in melting point. Noteworthy, no rigorous proofs for the assumed structures were given by authors,[14,15] and, furthermore, patent sources[13] did not contain (or contain incorrect) melting points and spectral data of 5-trifluoromethyl-1,2,4-triazol-3-thiones at all.

Nevertheless, such 5-polyfluoroalkyl-1,2,4-triazole-3-thiones can be considered as perspective building blocks that can be incorporated into a wide variety of potentially biologically active compounds. This requires a thorough study of the conditions of their synthesis and the elaboration of an overall effective method of production for 5-perfluoroalkyl-1,2,4-triazol-3-thiones.

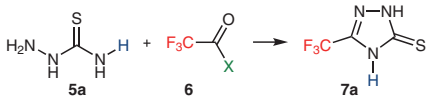
Herein, we examined the reaction of thiosemicarbazides **5** with perfluorocarboxylic acid derivatives **6** at different conditions, and report the concise, efficient, non-catalytic direct approach to either 4-unsubstituted and 4-substituted derivatives of 5-polyfluoroalkyl-1,2,4-triazole-3-thiones **7** (Scheme 2).



Scheme 2 Synthesis of 5-perfluoroalkyl-1,2,4-triazol-3-thiones **7**

Initially we studied the effect of the nature of perfluoro-containing reagents and the nature of solvents on the yield of the product **7a** in the reaction of unsubstituted thiosemicarbazide **5a** (R = H) with TFA derivatives ($R_F = CF_3$) at different reaction conditions (Table 1). We have found that the most effective R_F-reagent is TFA anhydride (the yield of **7a** was 67%, Table 1, entries 9, 10); the described action of TFA[14] gives only 28% (entry 3), and ethyl ester of TFA 32% (entry 22). We also observed a moderate increase in the yield of the desired triazole **7a** when using an excess of anhydride **6a** – optimal conditions are 33% excess of anhydride (entry 10); the decrease in yield when using the action of anhydride without solvent can be explained by the complicated isolation of the final product **7a**. We also noted that the reaction time does not significantly affect the product yield (the optimal time is 4 hours – entry 10) but

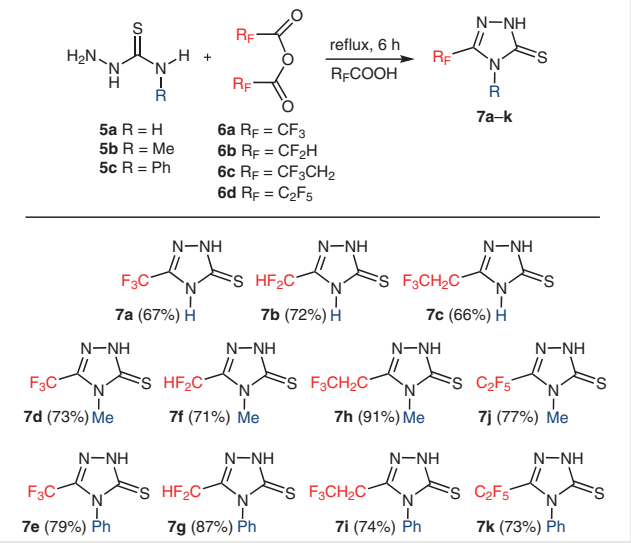
Table 1 Optimization of the Reaction Conditions for the Formation of **7a**



Entry	**6**: X (equiv)	Solvent	Time (h)	Temp (°C)	Yield (%)
1	OH (solvent)	TFA	4	72.4	22
2	OH (solvent)	TFA	4	0 °C to rt	not isolated
3	OH (solvent)	TFA	6	72.4	28 (24)[14]
4	OH (solvent)	TFA	10	72.4	30
5	OH (solvent)	TFA	24	72.4	24
6	OH (1:1)	xylene	10	138.5	22
7	OH (1:2)	xylene	10	138.5	24
8	$CF_3(CO)O$ (1:1)	TFA	4	72.4	60
9	$CF_3(CO)O$ (1:2)	TFA	4	72.4	67
10	**$CF_3(CO)O$ (3:4)**	**TFA**	**4**	**72.4**	**67**
11	$CF_3(CO)O$ (3:5)	TFA	4	72.4	66
12	$CF_3(CO)O$	$(CF_3CO)_2O$	4	40	65
13	$CF_3(CO)O$ (3:4)	TFA	4	0 °C to rt	21
14	$CF_3(CO)O$ (3:4)	TFA	2	72.4	56
15	$CF_3(CO)O$ (3:4)	TFA	6	72.4	67
16	$CF_3(CO)O$ (3:4)	TFA	10	72.4	64
17	$CF_3(CO)O$ (3:4)	xylene	4	138.5	51
18	$CF_3(CO)O$ (3:4)	xylene	6	138.5	54
19	$CF_3(CO)O$ (3:4)	toluene	6	110.6	50
20	$CF_3(CO)O$ (3:4)	1,4-dioxane	6	101	52
21	CF_3CO_2Et (1:1)	TFA	4	72.4	30
22	CF_3CO_2Et (1:2)	TFA	4	72.4	32
23	CF_3CO_2Et	CF_3CO_2Et	4	61	25
24	CF_3CO_2Et (1:2)	TFA	4	0 °C to rt	not isolated
25	CF_3CO_2Et (1:2)	TFA	10	72.4	30
26	CF_3CO_2Et (1:2)	TFA	24	72.4	28
27	CF_3CO_2Et (1:2)	xylene	4	138.5	20

carrying out this reaction without heating leads to a sharp decrease in yield or makes it impossible to obtain triazole **7a**.

With optimized reaction conditions in hand (Table 1, entry 10), different fluorine-containing carboxylic acid anhydrides **6a–d** were converted into the corresponding 4-unsubstituted 5-perfluoroalkyl-1,2,4-triazol-3-thiones **7a–c** (Scheme 3). Reactions containing a mixture of the thiosemicarbazide **5a** and an excess of anhydrides **6** (3:4) in the medium of the corresponding perfluorocarboxylic acid proceeded smoothly in 4 hours in air under reflux.



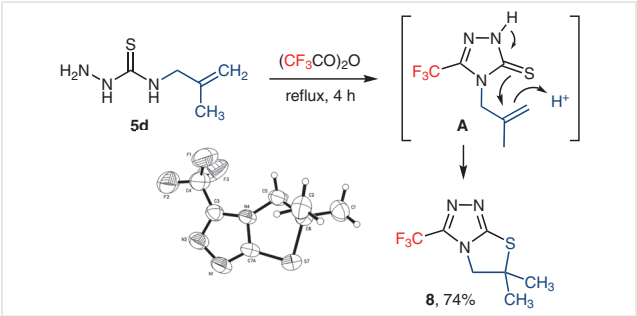
Scheme 3 Scope of the reaction between thiosemicarbazides **5a–c** and carboxylic acids anhydrides **6a–d** under optimized conditions

The developed approach to 4-hydro-5-polyfluoroalkyl-1,2,4-triazole-3-thiones **7a–c** has also been successfully applied to 4-substituted 5-polyfluoroalkyl-1,2,4-trizole-3-thiones **7e–k** (Scheme 3). In total, we have synthesized 11 samples in good to excellent yields.

Hence our approach is simpler, and applicable for different fluorine-containing carboxylic acids and provides high yields of the desired products **7a–k**. Thus, the developed non-catalytic direct approach to 5-polyfluoroalkyl-1,2,4-triazole-3-thione derivatives is applicable for both 4-hydro-, 4-methyl- and 4-phenyl-5-polyfluoroalkyl-1,2,4-triazole-3-thione derivatives.

A comprehensive spectral study of the structure of the obtained triazoles **7** allowed us to clearly answer the question of the tautomeric form of the synthesized products. The broad singlet in the region of 8.21–14.82 ppm in ^{1}H NMR spectra, which corresponds to two protons, indicates that the compounds **7** contain a thioureidic moiety with two NH groups; and the carbon signal at 161.6–171.3 ppm in ^{13}C NMR spectra corresponds to the C=S group (as reported for known 1,2,4-triazol-3-thiones[2a,d,5,16,17]), which fully supports the thionic form of the obtained triazoles **7** (in contrast to the previously reported data[13–15]).

Also, we have tried to transfer the approach to unsaturated derivatives of thiosemicarbazides. But the analogous reaction of trifluoroacetic acid anhydride (**6a**) with 4-methallylthiosemicarbazide (**5d**) surprisingly proceeds with direct one-step formation of condensed 6,6-dimethyl-3-(trifluoromethyl)-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole (**8**) in high yield without isolation of expected the triazole **A** (Scheme 4). Most likely, the interaction of thiosemicarbazide **5d** with trifluoroacetic acid forms the 4-methallyl-triazole **A**, which immediately undergoes the proton-induced electrophilic cyclization under protonation of the unsaturated site of the methallyl substituent by trifluoroacetic acid with thiazoline ring annulation. The proposed mechanism in Scheme 4 is in good agreement with the classical conception electrophilic cyclization[18] and is similar to the protonation of isomeric 3-methallylthio-4-phenyl-1,2,4-triazoles by hexabromotelluric acid.[19] The structure of thiazolotriazole **8** was confirmed by complex NMR data and X-ray crystallography.[20]



Scheme 4 Synthesis of 6,6-dimethyl-3-(trifluoromethyl)-5,6-dihydro[1,3]thiazolo[2,3-c][1,2,4]triazole (**8**)

In conclusion, we have developed an effective non-catalytic direct approach that allows to obtain 4-unsubstituted 5-perfluoroalkyl-1,2,4-triazole-3-thiones from available reagents in a one-step procedure in high yields, which was successfully applied to 4-substituted analogues. For the first time, the possibility of the one-pot synthesis of 6,6-dimethyl-3-(trifluoromethyl)-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole from trifluoroacetic acid and 4-methallylthiosemicarbazide has been found. All prepared compounds have potential to be used as promising building-blocks for the design of bio-active compounds.

All reagents and solvents, and the starting compounds **5a–c** [CAS Reg. Nos. 79-19-6 (**5a**), 6610-29-3 (**5b**), 5351-69-9 (**5c**)], **6a–d** [CAS Reg. Nos. 407-25-0 (**6a**), 401-67-2 (**6b**), 2516-99-6 (**6c**), 356-42-3 (**6d**)] were purchased from commercial sources and used without additional purification. Compound **5d** was synthesized according to the described procedure.[21]

^{1}H NMR spectra were recorded at 400 MHz with Varian UNITY Plus 400 spectrometer. ^{19}F NMR spectra were recorded on Varian UNITY Plus 400 spectrometer at 376.5 MHz. Chemical shifts are given in ppm relative to CCl_3F as external standard. The ^{13}C NMR spectra (proton decoupled) were recorded on a Bruker Avance DRX 500 instrument at 125.7 MHz and on Varian UNITY Plus 400 spectrometer at 101 MHz. Melting points were determined in open capillaries using an SMP3 instrument (Stuart Scientific). Elemental analyses were carried out on an Elementar Vario MICRO analyzer (Germany). The X-ray study of $C_7H_8F_3N_3S$ was carried out using Xcalibur-3 automated diffractometer (Oxford Diffraction Ltd.) (MoKα-radiation, graphite monochromator, Sapphire-3 CCD detector). The powder diffraction study was carried out with Siemens D500 diffractometer (X-ray tube with Cu anode, Bragg–Brentano geometry, graphite monochromator on the diffracted beam, 5°<2θ<60°, Δ(2θ) = 0.02°). The structure was solved with SHELXT/SHELX-2016 program package[22] and refined using full-matrix least squares in the anisotropic approximation. Hydrogen atoms were localized from Fourier D-map and refined using the riding model. The WinGX program[23] was used for the analysis of the structure and preparation of the illustration.

5-Perfluoro-1,2,4-triazol-3-thiones 7; General Procedure

Anhydride of fluorine-containing carboxylic acid **6** (4 mmol) was slowly added to a solution of thiosemicarbazide **5a–c** (3 mmol) in the corresponding fluorine-containing carboxylic acid (5 mL) at rt under stirring. After that, the mixture was refluxed for 4 h, and then cooled to rt. If the product precipitated (in the case of 4-*N*-phenyl derivatives) it was filtered, washed with aq NaOH (pH 8–9) and dried. When it is necessary, target product can be recrystallized from 1,4-dioxane. To the filtrate (or to the reaction mixture when the product is soluble) aq 2 N NaOH was added in portions (2 mL) until the precipitate was observed. Then the mixture was stirred for 5 h, and the precipitate was collected by filtration, washed with H_2O, and crystallized from MeOH and dried.

4-Hydro-5-trifluoromethyl-1,2,4-triazole-3-thione (7a)

White crystals; yield: 0.43 g (67%); mp 180–182 °C (Lit.[14] mp 218 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (br s, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 120.2 (q, $^1J_{C,F}$ = 270.9 Hz, CF_3), 144.1 (q, $^2J_{C,F}$ = 36.5 Hz, N=CCF_3), 172.2 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –59.01 (s, 3 F, CF_3).

Anal. Calcd for $C_3H_2F_3N_3S$: C, 21.30; H, 1.18; N, 28.85; S, 18.93. Found: C, 21.27; H, 1.20; N, 28.87; S, 18.91.

4-Hydro-5-difluoromethyl-1,2,4-triazole-3-thione (7b)

White crystals; yield: 0.40 g (72%); mp 168–170 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.22 (t, $J_{H,F}$ = 53.2 Hz, 1 H, CF_2H), 7.76 (s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 111.4 (t, $^1J_{C,F}$ = 235.6 Hz, CF_2H), 150.7 (t, $^2J_{C,F}$ = 28 Hz, N=CCF_2H), 171.2 (s, C=S). δ = 110.2 (t, $^1J_{C,F}$ = 250.7Hz, CF_2H), 165.5 (t, $^2J_{C,F}$ = 23.9 Hz, C-CF_2H), 171.2 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –108.50 (s, 2 F, CF_2H).

Anal. Calcd for $C_3H_3F_2N_3S$: C, 23.80; H, 1.99; N, 27.81; S, 21.19. Found: C, 23.83; H, 2.01; N, 27.84; S, 21.17.

4-Hydro-5-trifluoroethyl-1,2,4-triazole-3-thione (7c)

White crystals; yield: 0.44 g (66%); mp 176–178 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.41 (q, $J_{H,F}$ = 10.1 Hz, 2 H, CF_3CH_2), 10.22 (s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 38.1 (q, $^2J_{C,F}$ = 25 Hz, CH_2CF_3), 124.2 (q, $^1J_{C,F}$ = 273.2 Hz, CF_3), 150.1 (s, N=CCH_2CF_3), 161.6 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –61.96 (s, CF_3CH_2).

Anal. Calcd for $C_4H_4F_3N_3S$: C, 26.23; H, 2.18; N, 22.95; S,17.49. Found: C, 26.22; H, 2.14; N, 22.93; S, 17.52.

4-Methyl-5-trifluoromethyl-1,2,4-triazole-3-thione (7d)

White crystals; yield: 0.40 g (73%); mp 176–178 °C (Lit.[13d] mp 115 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.61 (s, 3 H, CH_3), 14.43 (br s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 31.3 (s, CH_3), 117.4 (q, $^1J_{C,F}$ = 270.9 Hz, CF_3), 140.9 (q, $^2J_{C,F}$ = 40.32 Hz, N=CCF_3), 170.1 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –65.07 (s, 3 F, CF_3).

Anal. Calcd for $C_4H_4F_3N_3S$: C, 26.23; H, 2.18; N, 22.95; S, 17.49. Found: C, 26.21; H, 2.14; N, 22.92; S, 17.51.

4-Phenyl-5-trifluoromethyl-1,2,4-triazole-3-thione (7e)

White crystals; yield: 0.56 g (79%); mp 138–140 °C (Lit.[8] mp 170–172 °C)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55 (m, 5 H, C_6H_5), 14.74 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 117.1 (q, $^2J_{C,F}$ = 338.9 Hz, CF_3), 128.9 (s, C_6H_5), 129.9 (s, C_6H_5), 130.8 (s, C_6H_5), 132.9 (s, C_6H_5), 140.7 (q, $^1J_{C,F}$ = 50.4Hz, N=CCF_3), 171.3 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –63.21 (s, 3 F, CF_3).

Anal. Calcd for $C_9H_6F_3N_3S$: C, 44.08; H, 2.45; N, 17.14; S, 13.02; found: C, 44.06; H, 2.47; N, 17.16; S, 12.97.

4-Methyl-5-difluoromethyl-1,2,4-triazole-3-thione (7f)

White crystals; yield: 0.35 g (71%); mp 170–172 °C (Lit.[13d] mp 165 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.52 (s, 3 H, CH_3), 7.25 (t, $J_{H,F}$ = 53.4 Hz, 1 H, CF_2H), 14.37 (br s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 30.9 (s, CH_3), 108.2 (t, $^1J_{C,F}$ = 236.9 Hz, CF_2H), 145.1 (t, $^2J_{C,F}$ = 27.7 Hz, N=CCF_2H), 169.3 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –121.05 (d, $J_{F,H}$ = 51.7 Hz, 2 F, CF_2H).

Anal. Calcd for $C_4H_5F_2N_3S$: C, 29.09; H, 3.03; N, 25.45; S, 19.39. Found: C, 29.11; H, 3.01; N, 25.43; S, 19.42.

4-Phenyl-5-difluoromethyl-1,2,4-triazole-3-thione (7g)

White crystals; yield: 0.46 g (87%); mp 137–139 °C (Lit.[8] mp 187–189 °C)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.03 (t, $J_{H,F}$ = 53.2 Hz, 1 H, CF_2H), 7.49 (m, 5 H, C_6H_5), 14.45 (br s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 107.9 (t, $^1J_{C,F}$ = 238.1 Hz, CF_2H), 128.7 (s, C_6H_5), 129.9 (s, C_6H_5), 130.5 (s, C_6H_5), 144.9 (t, $^2J_{C,F}$ = 27.7 Hz, N=CCF_2H), 169.3 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –119.73 (s, 2 F, CF_2H).

Anal. Calcd for $C_9H_8F_2N_3S$: C, 47.37; H, 3.51; N, 18.42; S, 14.03. Found: C, 47.35; H, 3.52; N, 18.41; S, 13.99.

4-Methyl-5-trifluoroethyl-1,2,4-triazole-3-thione (7h)

White crystals; yield: 0.38 g (91%); mp 108–110 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.32 (s, 3 H, CH_3), 3.41 (q, $J_{H,F}$ = 10.1 Hz, 2 H, CF_3CH_2), 10.51 (s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 37.2 (s, CH_3), 38.2 (q, $^2J_{C,F}$ = 28.1 Hz, CH_2CF_3), 124.2 (q, $^1J_{C,F}$ = 273.2 Hz, CF_3), 144.3 (s, N=CCH_2CF_3), 167.9 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –61.98 (s, 2 F, CF_3CH_2).

Anal. Calcd for $C_5H_6F_3N_3S$: C, 30.46; H, 3.04; N, 21.32; S, 16.24. Found: C, 30.44; H, 3.07; N, 21.29; S, 16.27.

4-Phenyl-5-trifluoroethyl-1,2,4-triazole-3-thione (7i)

White crystals; yield: 0.57 g (74%); mp 192–194 °C.

^{1}HNMR (400 MHz, CD_3OD): δ = 3.33 (q, $J_{H,F}$ = 12.2 Hz, 2 H, CF_3CH_2), 7.31 (m, 5 H, C_6H_5).

^{13}CNMR (101 MHz, CD_3OD): δ = 39.3 (q, $^3J_{C,F}$ = 29.2 Hz, CH_2CF_3), 119.6 (s, C_6H_5), 123.7 (s, C_6H_5), 125.5 (q, $^1J_{C,F}$ = 273.3 Hz, CF_3), 130.8 (s, C_6H_5), 141.3 (s, C_6H_5), 165.2 (s, N=CCH_2CF_3), 185.0 (s, C=S).

^{19}F NMR (376 MHz, CD_3OD): δ = –64.54 (t, $^2J_{C,F}$ = 12 Hz, 3 F, CF_3CH_2).

Anal. Calcd for $C_{10}H_8F_3N_3S$: C, 46.33; H, 3.09; N, 16.22; S, 12.35. Found: C, 46.35; H, 3.11; N, 16.25; S, 12.34.

4-Methyl-5-pentafluoroethyl-1,2,4-triazole-3-thione (7j)

White crystals; yield: 0.48 g (77%); mp 107–109 °C (Lit.[13d] mp 77 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.58 (s, 3 H, CH_3), 14.72 (br s, 1 H, NH).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 31.8 (s, CH_3), 108.0 (tq, $J_{C,F}$ = 232.1, 38.4 Hz, CF_2), 118.0 (qt, $J_{C,F}$ = 286.5, 36.3 Hz, CF_3),139,7 (t, $J_{C,F}$ = 28.9 Hz, N=CC_2F_5), 170.4 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –82.45 (s, 3 F, CF_3), –113.70 (s, 2 F, CF_2).

Anal. Calcd for $C_5H_4F_5N_3S$: C, 25.75; H, 1.72; N, 18.03; S, 13.73. Found: C, 25.73; H, 1.71; N, 18.06; S, 13.77.

4-Phenyl-5-pentafluoroethyl-1,2,4-triazole-3-thione (7k)

White crystals; yield: 0.64 g (73%); mp 165–167 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.51 (m, 5 H, C_6H_5), 14.86 (br s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 107.5 (tq, $J_{C,F}$ = 256.4, 36.5 Hz, CF_2), 117.5 (qt, $J_{C,F}$ = 267.3, 36.1 Hz, CF_3), 128.7 (s, C_6H_5), , 129.3 (s, C_6H_5), 130.4 (s, C_6H_5), 132.8 (s, C_6H_5), 139.0 (t, $^3J_{C,F}$=29.2 Hz, N=CCF_2CF_3), 171.0 (s, C=S).

^{19}F{H} NMR (376 MHz, DMSO-d_6): δ = –81.64 (s, 3 F, CF_3), –110.31 (s, 2 F, CF_2).

Anal. Calcd for $C_4H_2F_5N_3S$: C, 21.92; H, 0.91; N, 19.18; S, 14.61. Found: C, 21.93; H, 0.88; N, 19.21; S, 14.64.

6,6-Dimethyl-3-(trifluoromethyl)-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole (8)

Trifluoroacetic anhydride (**6a**; 4 mmol) was slowly added to a solution of thiosemicarbazide **5d** (3 mmol) in TFA (5 mL) at rt under stirring. After that, the reaction mixture was heated at 72 °C for 4 h, and then cooled to rt. To the reaction mixture was added aq 2 NaOH in portions (2 mL) until a precipitate was observed. Then the mixture was stirred for 5 h, the precipitate was filtered, washed with H_2O, and purified by crystallization from MeOH; white crystals; yield: 0.49 g (74%); mp 105–107 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67 (s, 6 H, CH_3), 4.31 (s, 2 H, CH_2).

^{13}C (126 MHz, DMSO-d_6): δ = 28.88 (s, CH_3), 57.63 (s), 66.32 (s), 117.36 (q, $^1J_{C,F}$ = 270.9 Hz, CF_3), 140.89 (q, $^2J_{C,F}$ = 36.5 Hz, N=CCF_3), 161.15 (s, C=S).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –62.78 (s, 3 F, CF_3).

Anal. Calcd for $C_7H_6F_3N_3S$: C, 38.01; H, 2.71; N, 19.00; S, 14.21. Found: C, 37.99; H, 2.74; N, 19.03; S, 14.24.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751401.

References

(1) (a) Kucukguzel, S.; Cikla-Suzgun, P. *Eur. J. Med. Chem.* **2015**, *97*, 830. (b) Korol, N.; Slivka, M. *Chem. Heterocycl. Comp.* **2017**, *53*, 852. (c) Sathyanarayana, R.; Poojary, B. *J. Chin. Chem. Soc.* **2020**, 1. (d) Song, M.-X.; Deng, X.-Q. *J. Enzym. Inhib. Med. Chem.* **2018**, *33*, 453. (e) Aggarwal, R.; Sumran, G. *Eur. J. Med. Chem.* **2020**, *205*, 112652. (f) Slivka, M. V.; Korol, N. I.; Fizer, M. M. *J. Heterocycl. Chem.* **2020**, *57*, 3236.

(2) (a) Barbuceanu, S.; Draghici, C.; Barbuceanu, F.; Bancescu, G.; Saramet, G. *Chem. Pharm. Bull.* **2015**, *63*, 694. (b) Saundane, A.; Manjunatha, Y. *Arab. J. Chem.* **2016**, *9*, S501. (c) Tratat, C.; Haroun, M.; Paparisva, A.; Geronikaki, A.; Kamoutsis, Ch.; Ciric, A.; Glamoclija, J.; Sokovic, M.; Fotakis, Ch.; Zoumpoulakis, P.; Bhunia, S. S.; Saxena, A. K. *Arab. J. Chem.* **2018**, *11*, 573. (d) Slivka, M. V.; Korol, N. I.; Pantyo, V.; Baumer, V. M.; Lendel, V. G. *Heterocycl. Commun.* **2017**, *23*, 109. (e) Fizer, M.; Sukharev, S.; Slivka, M.; Mariychuk, R.; Lendel, V. *J. Organomet. Chem.* **2016**, *804*, 6.

(3) (a) Naseer, Md. A.; Husain, A. *J. Drug Deliv. Ther* **2019**, *9*, 236. (b) Sarigol, D.; Uzgoren-Baran, A.; Tel, B.; Somuncuoglu, E.; Kazkayasi, I.; Ozadali-Sari, K.; Unsal-Tan, O.; Okay, G.; Ertan, M.; Tozkoparan, B. *Bioorg. Med. Chem.* **2015**, *23*, 2518. (c) Cristina, A. *Farmacia* **2018**, *66*, 883. (d) Toma, A.; Mogoşan, C.; Vlase, L.; Leonte, D.; Zaharia, V. *Med. Chem. Res.* **2017**, *26*, 2602.

(4) Khan, I.; Khan, A.; AhsanHalim, S.; Saeed, A.; Mehsud, S.; Csuk, R.; Al-Harrasi, A.; Ibrar, A. *Int. J. Biol. Macromol.* **2020**, *142*, 345.

(5) Fizer, M.; Slivka, M.; Fizer, O. *Biointer. Res. Appl Chem.* **2021**, *6*, 13885.

(6) (a) Piccionello, A. P.; Pibiri, I.; Buscemi, S.; Pace, A. *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*; Elsevier Inc: Amsterdam, **2019**, 213. (b) Nenajdenko, V. *Fluorine in Heterocyclic Chemistry*; Springer: Cham, **2014**.

(7) (a) Inoue, M.; Sumii, Y.; Shibata, N. *ACS Omega* **2020**, *5*, 10633. (b) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. *iScience* **2020**, *23*, 101467.

(8) Mlostoń, G.; Obijalska, E.; Żurawik, A.; Heimgartner, H. *Chem. Heterocycl. Comp.* **2016**, *52*, 133.
(9) Frackenpohl, J.; Schneider, L.; Decker, L.; Dittgen, J.; Fenkl, F.; Fischer, C.; Franke, J.; Freigang, J.; Getachew, R.; Gonzalez, F.-N.; Susana, M.; Helmke, H.; Hills, M. J.; Hohmann, S.; Kleemann, J.; Kurowski, K.; Lange, G.; Luemmen, P.; Meyering, N.; Poree, F.; Schmutzler, D.; Wrede, S. *Bioorg. Med. Chem.* **2019**, *27*, 115142.
(10) Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchine, S. M.; Strelitz, R. A.; MacCoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 591.
(11) Vasil'eva, E. B.; Sevenard, D. V.; Khomutov, O. G.; Kuznetsova, O. A.; Karpenko, N. S.; Filyakova, V. I. *Russ. J. Org. Chem.* **2004**, *40*, 874.
(12) Vasil'eva, E. B.; Filyakova, V. I.; Sidorova, L. P.; Filatov, I. E.; Charushin, V. N. *Russ. J. Org. Chem.* **2005**, *41*, 1522.
(13) (a) Erdman, D. T. Patent US6472535, **2002**. (b) Watanabe, Y.; Mihara, J.; Yamazaki, D.; Shibuya, K.; Shimojo, E.; Emoto, A. Patent EP 2006/002262, **2006**. (c) Michot, C. Patent US7919629, **2011**. (d) Linker, K.-H.; Haas, W.; Findeisen, K.; Diehr, H.-J. Patent EP 0661277A1, **1994**.
(14) Faridoon Hussein, W. M.; Vella, P.; Islam, N. U.; Ollis, D. L.; Schenk, D.; McGeary, R. P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 380.
(15) Ashton, W. T.; Cantone, C. L.; Meurer, L. C.; Tolman, R. L.; Greenlee, W. J.; Patchett, A. A.; Lynch, R. J.; Schorn, T. W.; Strouse, J. F.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 2103.
(16) (a) Fizer, M.; Slivka, M.; Sidey, V.; Baumer, V.; Fizer, O. *J. Mol. Struct.* **2021**, *1241*, 130632. (b) Korol, N.; Slivka, M.; Fizer, M.; Baumer, V.; Lendel, V. *Monatsh. Chem.* **2020**, *151*, 191.
(17) (a) El Ashry, E. S. H.; Awad, L. F.; Soliman, S. M.; Al Moaty, M. N. A.; Ghabbour, H. A.; Barakat, A. *J. Mol. Struct.* **2017**, *1146*, 432. (b) Özdemir, N.; Türkpençe, D. *Comput. Theor. Chem.* **2013**, *1025*, 35. (c) Davari, M. D.; Bahrami, H.; Haghighi, Z. Z.; Zahedi, M. *J. Mol. Model.* **2021**, *16*, 841.
(18) (a) Danilkina, N. A.; Kulyashova, A. E.; Khlebnikov, A. F.; Bräse, S.; Balova, I. A. *J. Org. Chem.* **2014**, *79*, 9018. (b) Andrade, V. S.; Mattos, M. C. *Synthesis* **2019**, *51*, 1841. (c) D'Hollander, A. C. A.; Peilleron, L.; Grayfer, T. D.; Cariou, K. *Synthesis* **2019**, *51*, 1753. (d) Slivka, M.; Onysko, M. *Synthesis* **2021**, *53*, 3497.
(19) Fizer, M.; Slivka, M.; Baumer, V. *J. Organomet. Chem.* **2021**, *952*, 122044.
(20) CCDC 2026192 (**8**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures
(21) Fizer, M. M.; Slivka, M. V.; Lendel, V. G. *Chem. Heterocycl. Compd.* **2019**, *55*, 478.
(22) (a) Sheldrick, G. M. *Acta Crystallogr., Sect. C* **2015**, *71*, 3. (b) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2015**, *71*, 3.
(23) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.