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Acylation of primary polyfluoroalkanethioamides

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ABSTRACT

The reaction conditions and the nature of acyl chloride strongly influence the outcome of the primary polyfluoroalkanethioamides acylation. Preparation of *NH*-acetyl polyfluoroalkanethioamides was achieved conducting the reactions in acetonitrile at −20 °C in the presence of pyridine. The reactions of polyfluoroalkanethioamides with 5-hydroperfluoropentanoyl chloride are efficient for the synthesis of *NH*-acyl derivatives when they were carried out in the absence of a base under heating at 100 °C. The obtained *NH*-acyl polyfluoroalkanethioamides enter into cycloaddition reactions with 2,3-dimethylbutadiene at room temperature.

1. Introduction

Thioamides have found a wide variety of synthetic applications over the past decades [1]. Divergent transformations of these compounds employed in organic synthesis arise from the high versatility of the thioamide functionality. At the same time, the additional functionalization of thioamides offers new synthetic possibilities. Among a large number of aliphatic, aromatic and heterocyclic derivatives, fluorinated thioamides remain poorly investigated, although reported procedures indicate their promising synthetic potential as fluorine-containing building-blocks [2]. Recently, we have described novel protocols for the reactions of *N,N*-dialkyl- or *N*-alkyl(aryl)-polyfluoroalkanethioamides with 2,3-dimethyl-butadiene [2e] and trialkyl phosphites [2f]. These reactions were shown to occur under drastic conditions, therefore we decided to increase the reactivity of the thiocarbonyl group by introducing an electron-withdrawing substituent, such as an acyl group, at the nitrogen atom of thioamide.

Among the methods of the synthesis of non-fluorinated *NH*-acyl thioamides [3–9], the direct acylation provides good yields for *NH*-alkanoyl derivatives [3–6], and we have chosen it for the preparation of fluorinated analogs.

To the best of our knowledge, the acylation of polyfluoroalkanethioamides has been described only for *N*-methyl trifluorothioacetamide [2a]. In the present paper, we report on the investigation of the reactions between unsubstituted polyfluoroalkanethioamides and acyl chlorides.

2. Results and discussion

Our initial experiments have shown that the outcome of the acylation of primary polyfluoroalkanethioamides **1a–c** [10] strongly depends on the reaction conditions (solvent, temperature, base) and the nature of acyl chlorides. The treatment of thioamides **1a,c** with acetyl-, benzoyl-, 5-hydroperfluoropentanoyl chlorides in different solvents (diethyl ether, dichloromethane, acetonitrile) at 0 °C in the presence of triethylamine led to complex mixtures of products which hardly undergo any separation and purification.

We have found that the reaction of trifluorothioacetamide **1a** with acetyl chloride in acetonitrile at −20 °C in the presence of pyridine afforded 1,3-dithiethane **3** as a mixture of two stereoisomers (the ratio is 85:15 according to ^{19}F NMR) (Scheme 1). Obviously, the dimerization of the intermediary *NH*-acetyl thioamide **2a** resulted in the formation of compound **3**. NMR (^{19}F, ^{1}H, ^{13}C) and MS data are consistent with the dimeric structure of **3**. It should be noted that only a few examples of spontaneous dimerization of fluorinated thiocarbonyl compounds such as hexafluorothioacetone, perfluorobutane-2-thione, chlorodifluorothioacetyl chloride and trifluoromethyl trifluorodithioacetate have been reported in the literature [11].

In contrast to trifluorothioacetamide **1a**, thioamides **1b,c** reacted with acetyl chloride giving *NH*-acetyl derivatives **2b,c** in good yields (Scheme 1).

As opposed to above mentioned reactions, the treatment of thioamides **1a–c** with 5-hydroperfluoropentanoyl chloride gave mixtures of products. These reactions were carried out in the absence of a base under heating at 100 °C affording *NH*-acyl derivatives **4a–c** in high yields (Scheme 2).

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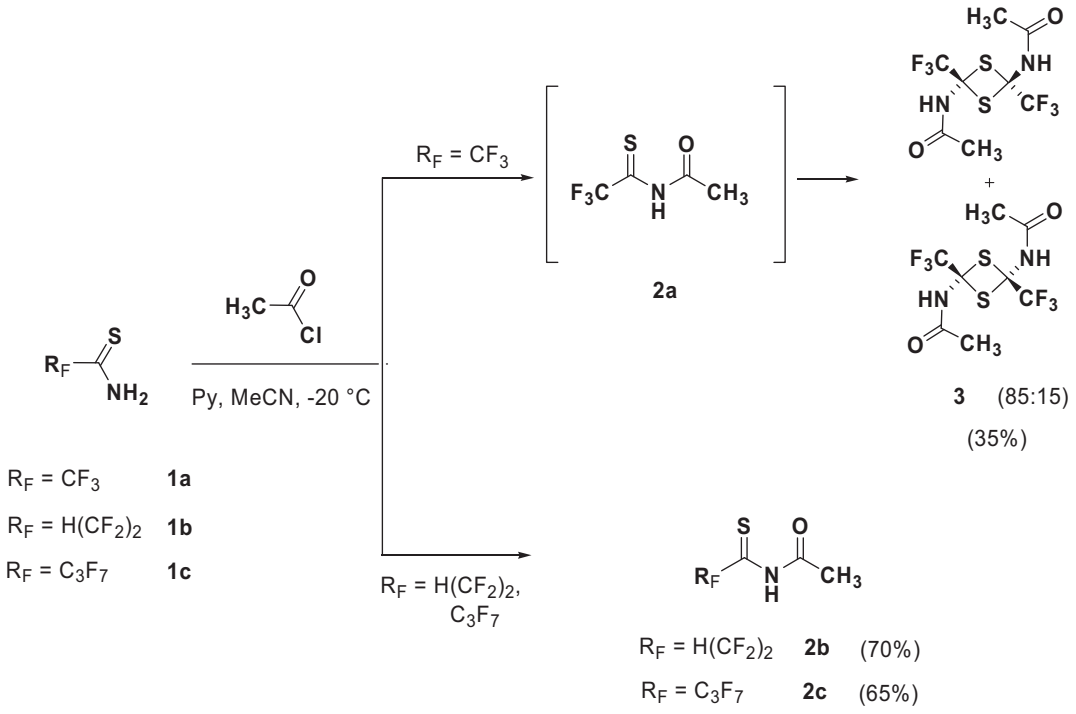
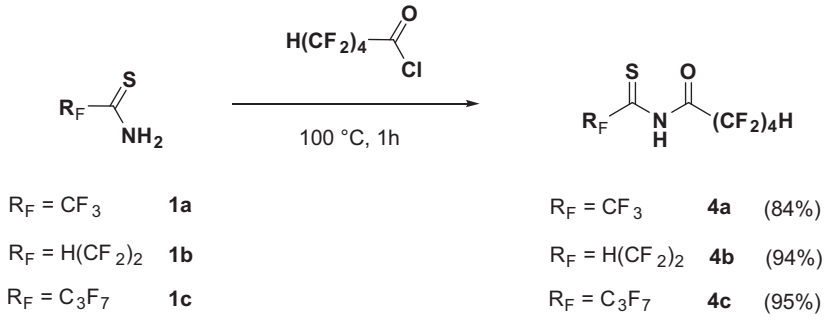
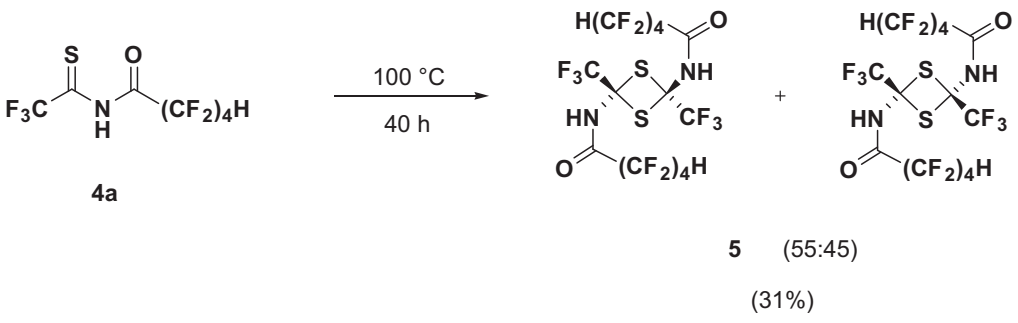


Scheme 1.



Scheme 2.



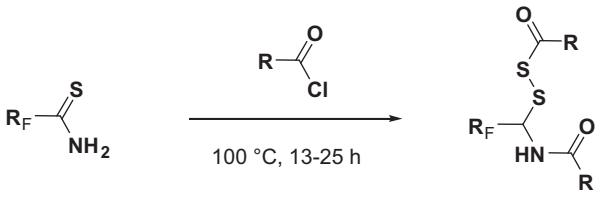
Scheme 3.

In the ^{13}C NMR spectra of *NH*-acyl thioamides **2b,c** and **4a–c** the signals in the ranges of 178.4–186.5 ppm and 155.1–170.3 ppm were attributed to the C=S and C=O groups, respectively.

Compounds **4b,c** appeared to be stable at room temperature, while trifluoromethyl-substituted *NH*-acyl thioamide **4a** slowly undergoes dimerization into a mixture of stereoisomeric 1,3-dithiethane **5** (the ratio is 55:45 according to ^{19}F NMR). The total conversion of **4a** to **5** was achieved by heating the compound **4a** at 100 °C for 40 h (Scheme 3).

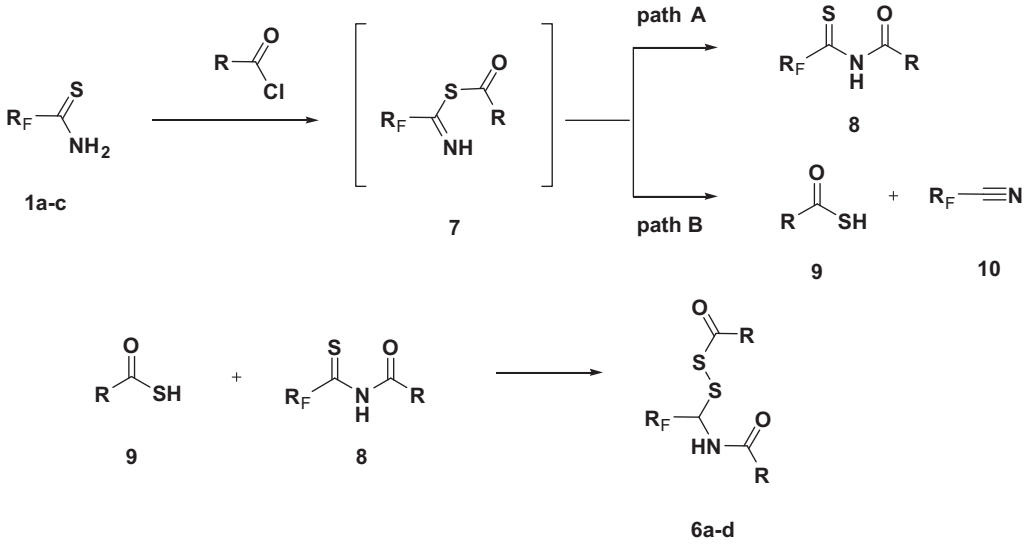
In contrast to the reactions of thioamides **1a–c** with 5-hydroperfluoropentanoyl chloride, heating a mixture of trifluorothioacetamide **1a** with benzoyl chloride at 100 °C for 13 h resulted in the formation of new fluorine-containing disulfide **6a** (Scheme 4). The reaction with benzoyl chloride was extended to other thioamides **1b,c** and proceeded in the same manner with cyclopropanoyl chloride giving compounds **6a–d** (Scheme 4).

NMR (^{19}F, ^{1}H, ^{13}C) and MS data of compounds **6a–d** are in good agreement with the proposed structures. In the ^{13}C NMR spectra of



$R_F = CF_3$	**1a**	$R_F = CF_3$	R = Ph	**6a** (50%)
$R_F = H(CF_2)_2$	**1b**	$R_F = H(CF_2)_2$	R = Ph	**6b** (34%)
$R_F = C_3F_7$	**1c**	$R_F = C_3F_7$	R = Ph	**6c** (77%)
		$R_F = C_3F_7$	R = *c*-Pr	**6d** (30%)

Scheme 4.

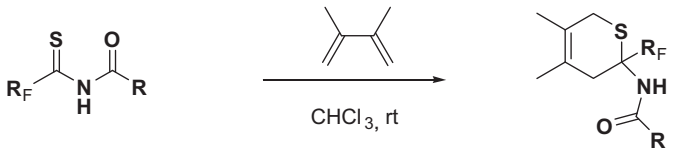


Scheme 5.

disulfides **6a–d** the signals observed in the ranges of 166.5–173.4 ppm and 189.5–197.7 ppm are characteristic of an amide and thioester function, correspondingly [12]. In the ^{19}F NMR spectra of **6b–d** fluorine atoms of the CF_2 group attached to the asymmetric carbon atom were identified as an AB-system.

We propose the following scheme for the formation of disulfides **6a–d** (Scheme 5). The initially formed *S*-acyl intermediates **7** can undergo transformations into two pathways. According to the pathway A, rearrangement of **7** gave *NH*-acyl thioamides **8**. It should be noted that the formation of *S*-acyl derivatives and their transformation into *N*-acyl compounds in the reactions of non-fluorinated thioamides with acyl chlorides was demonstrated by Walter and Saha [13]. Pathway B includes the elimination of nitriles and the formation of thiocarboxylic acid **9**. Such a reaction pathway was proposed by Goerdeler et al. for the reaction of benzamide with aromatic acid chlorides [3]. The thiophilic addition of thiocarboxylic acid **9** to *NH*-acyl thioamides **8** gives final disulfides **6a–d**.

As other thiocarbonyl compounds containing polyfluoroalkyl groups [14], *NH*-acyl thioamides **4a–c, 2c** are active dienophiles



$R_F = CF_3$	$R = H(CF_2)_4$	**4a**	$R_F = CF_3$	$R = H(CF_2)_4$	**11a** (62%)
$R_F = H(CF_2)_2$	$R = H(CF_2)_4$	**4b**	$R_F = H(CF_2)_2$	$R = H(CF_2)_4$	**11b** (50%)
$R_F = C_3F_7$	$R = H(CF_2)_4$	**4c**	$R_F = C_3F_7$	$R = H(CF_2)_4$	**11c** (53%)
$R_F = C_3F_7$	$R = CH_3$	**2c**	$R_F = C_3F_7$	$R = CH_3$	**11d** (72%)

Scheme 6.

and readily react with 2,3-dimethylbutadiene to afford new thiopyran derivatives **11a–d** (Scheme 6).

In conclusion, we have shown that the outcome of the acylation reactions of primary polyfluoroalkanethiocarboxylic acid amides depends on the reaction conditions and the nature of acyl chloride. The reactions of polyfluoroalkanethioamides with benzoyl- and cyclopropanonyl chlorides in the absence of a base afforded novel fluorine-containing disulfide derivatives, while the use of 5-hydroperfluoropentanoyl chloride allowed obtaining *NH*-acyl thioamides. Preparation of *NH*-acetyl derivatives was achieved conducting the reaction in acetonitrile at −20 °C in the presence of pyridine. The obtained *NH*-acyl thioamides are more reactive in cycloaddition reactions with 2,3-dimethylbutadiene as compared with primary and *N*-alkyl(aryl) polyfluoroalkanethioamides which react under drastic conditions.

3. Experimental

The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian-VXR-300 instrument at 299.9, 75.4 and 282.2 MHz, respectively. Tetramethylsilane (^{1}H NMR: δ = 0.00 ppm), $CHCl_3$ (^{13}C NMR: δ = 77.16 ppm), C_6F_6 (^{19}F NMR: δ = −162.9 ppm) were used as internal standards for ^{1}H, ^{13}C and ^{19}F NMR spectra. MS data were obtained on ADSI MS, Agilent 1100\DAD\MSD VL G1965 instrument. UV–visible spectra were recorded on a SHIMADZU UV-3110 spectrophotometer.

The progress of all reactions was monitored by ^{19}F NMR spectroscopy. Silica gel Merck 60 (40–63 μm) was used for column chromatography. Elemental analysis was performed in Analytical Laboratory of the Institute of Organic chemistry, NAS of Ukraine.

3.1. General procedure for the reaction of polyfluoroalkanethioamides (1a–c) with acetyl chloride

A solution of acetyl chloride (21.0 mmol, 1.4 eqiuv.) in acetonitrile (10 mL) was added dropwise at −20 °C under argon atmosphere to a solution of the corresponding polyfluoroalkanethioamide (15.0 mmol, 1.0 eqiuv.) (**1a–c**) and pyridine (21.0 mmol, 1.4 eqiuv.) in acetonitrile (40 mL). The reaction mixture was stirred at −20 °C for 0.5 h and then for 16 h at room temperature. The solvent was evaporated *in vacuo* at room temperature and diethyl ether (50 mL) was added to the residue. In the case of the isolation of compound (**3**), the precipitate formed was filtered off, washed with water (10 mL) and dried. For the isolation of compounds (**2b,c**) the precipitate was filtered off and the filtrate was washed with water (3 × 10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* giving *NH*-acetyl derivatives (**2b,c**).

3.1.1. N,N′-[2,4-Bis(trifluoromethyl)-1,3-dithitane-2,4-diyl]diacetamide (3)

Yield: 35%. Colorless solid. Mixture of stereoisomers (the ratio is 85:15 according to ^{19}F NMR). ^{1}H NMR (DMSO-d_6, δ ppm): 1.96 (s, 3H, CH_3), 10.07 (bs, 1H, NH). ^{19}F NMR (DMSO-d_6, δ ppm): −78.7 (m, 3F, CF_3 major), −80.4 (m, 3F, CF_3 minor). ^{13}C NMR (DMSO-d_6, δ ppm): 22.4 (s, CH_3), 56.8 (q, $^{2}J_{C,F}$ = 36.8 Hz, CCF_3), 123.7 (q, $^{1}J_{C,F}$ = 284.2 Hz, CF_3), 169.9 (s, C=O). MS: *m/z* = 343 [M+1]. Anal. Calcd. for $C_8H_8F_6N_2O_2S_2$: C, 28.1; H, 2.4; N, 8.2; S, 18.7. Found: C, 28.1; H, 2.5; N, 8.1; S, 18.7.

3.1.2. N-(2,2,3,3-Tetrafluoropropanethioyl)acetamide (2b)

Yield: 70%. Yellow-red crystals. mp 59–62 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.58 (s, 3H, CH_3), 6.37 (tt, $^{2}J_{H,F}$ = 53.1 Hz, $^{3}J_{H,F}$ = 5.4 Hz, 1H, HCF_2), 9.70 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −119.2 (m, 2F, CF_2), −139.4 (dm, $^{2}J_{F,H}$ = 53.1 Hz, 2F, HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 26.6 (s, CH_3), 109.4 (tt, $^{1}J_{C,F}$ = 252.4 Hz, $^{2}J_{C,F}$ = 32.9 Hz, HCF_2), 110.7 (tt, $^{1}J_{C,F}$ = 269.2 Hz, $^{2}J_{C,F}$ = 28.2 Hz, CF_2), 170.0 (s, C=O), 186.5 (t, $^{2}J_{C,F}$ = 23.5 Hz, C=S). MS: *m/z* = 202 [M−1]. Anal. Calcd. for $C_5H_5F_4NOS$: C, 29.6; H, 2.5; N, 6.9; S, 15.8. Found: C, 29.7; H, 2.6; N, 6.7; S, 15.9.

3.1.3. N-(2,2,3,3,4,4,4-Heptafluorobutanethioyl)acetamide (2c)

Yield: 65%. Pink solid. mp 70–72 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.59 (s, 3H, CH_3), 9.51 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −81.3 (m, 3F, CF_3), −112.4 (m, 2F, CF_2), −125.9 (m, 2F, CF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 26.5 (s, CH_3), 107.0–119.5 (m, $CF_3CF_2CF_2$), 170.3 (s, C=O), 181.8 (t, $^{2}J_{C,F}$ = 25.4 Hz, C=S). MS: *m/z* = 270 [M−1]. Anal. Calcd. for $C_6H_4F_7NOS$: C, 26.6; H, 1.5; N, 5.2; S, 11.8. Found: C, 26.8; H, 1.8; N, 5.2; S, 11.9.

3.2. General procedure for the reaction of polyfluoroalkanethioamides (1a–c) with 2,2,3,3,4,4,5,5-octafluoropentanoyl chloride

A mixture of polyfluoroalkanethioamide (**1a–c**) (10.0 mol, 1.0 equiv.) and 2,2,3,3,4,4,5,5-octafluoropentanoyl chloride (30.0 mol, 3.0 equiv.) was heated at 100 °C for 1 h. The crude product was purified by fractional distillation to give the corresponding *NH*-acyl derivative (**4a–c**).

3.2.1. 2,2,3,3,4,4,5,5-Octafluoro-N-(2,2,2-trifluoroethanethioyl)pentanamide (4a)

Yield: 84%. Deep red liquid. bp 68–70 °C (0.08 mmHg). ^{1}H NMR ($CDCl_3$, δ ppm): 6.11 (tt, $^{2}J_{H,F}$ = 51.8 Hz, $^{3}J_{H,F}$ = 5.1 Hz, 1H, HCF_2), 9.97 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −71.0 (m, 3F, CF_3), −121.1 (m, 2F, CF_2), −125.5 (m, 2F, CF_2), −130.6 (m, 2F, CF_2), −140.3 (dm, $^{2}J_{F,H}$ = 51.8 Hz, 2F, HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 104.0–114.0 (m, 4 × CF_2), 115.5 (q, $^{1}J_{C,F}$ = 279.4 Hz, CF_3), 155.3 (t, $^{2}J_{C,F}$ = 28.4 Hz, C=O), 179.1 (q, $^{2}J_{C,F}$ = 38.0 Hz, C=S). MS: *m/z* = 356 [M−1]. Anal. Calcd. for $C_7H_2F_{11}NOS$: C, 23.6; H, 0.6; N, 3.9; S, 9.0. Found: C, 23.6; H, 0.7; N, 3.7; S, 9.2.

3.2.2. 2,2,3,3,4,4,5,5-Octafluoro-N-(2,2,3,3-tetrafluoropropanethioyl)pentanamide (4b)

Yield: 94%. Deep red liquid. bp 37–38 °C (0.08 mmHg). UV (hexane, nm): λ_{max} = 271. ^{1}H NMR ($CDCl_3$, δ ppm): 6.10 (tt, $^{2}J_{H,F}$ = 51.7 Hz, $^{3}J_{H,F}$ = 5.1 Hz, 1H, HCF_2), 6.27 (tt, $^{2}J_{H,F}$ = 53.0 Hz, $^{3}J_{H,F}$ = 5.1 Hz, 1H, HCF_2), 10.22 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −118.9 (m, 2F, CF_2), −122.1 (m, 2F, CF_2), −125.5 (m, 2F, CF_2), −130.1 (m, 2F, CF_2), −138.6 (m, 4F, 2 × HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 105.0–113.5 (m, 6 × CF_2), 155.2 (t, $^{2}J_{C,F}$ = 28.2 Hz, C=O), 183.9 (t, $^{2}J_{C,F}$ = 27.0 Hz, C=S). MS: *m/z* = 388 [M−1]. Anal. Calcd. for $C_8H_3F_{12}NOS$: C, 24.7; H, 0.8; N, 3.6; S, 8.2. Found: C, 24.7; H, 0.8; N, 3.6; S, 8.3.

3.2.3. 2,2,3,3,4,4,5,5-Octafluoro-N-(2,2,3,3,4,4,4-heptafluorobutanethioyl)-pentanamide (4c)

Yield: 95%. Deep red liquid. bp 40–42 °C (0.08 mmHg). ^{1}H NMR ($CDCl_3$, δ ppm): 6.09 (tt, $^{2}J_{H,F}$ = 51.9 Hz, $^{3}J_{H,F}$ = 5.1 Hz, 1H, HCF_2), 10.00 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −81.4 (t, $^{3}J_{F,F}$ = 13.0 Hz, 3F, CF_3), −113.2 (m, 2F, CF_2), −122.1 (m, 2F, CF_2), −125.5 (m, 2F, CF_2), −126.4 (m, 2F, CF_2), −130.0 (m, 2F, CF_2), −138.3 (dm, $^{2}J_{F,H}$ = 51.9 Hz, 2F, HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 105.0–115.0 (m, 6 × CF_2), 117.4 (q, $^{1}J_{C,F}$ = 288.1 Hz, CF_3), 155.1 (t, $^{2}J_{C,F}$ = 28.2 Hz, C=O), 178.4 (t, $^{2}J_{C,F}$ = 26.7 Hz, C=S). MS: *m/z* = 456 [M−1]. Anal. Calcd. for $C_9H_2F_{15}NOS$: C, 23.7; H, 0.4; N, 3.1; S, 7.0. Found: C, 23.8; H, 0.5; N, 2.9; S, 7.1.

3.3. Dimerization of 2,2,3,3,4,4,5,5-octafluoro-N-(2,2,2-trifluoro-ethanethioyl)pentanamide (4a)

2,2,3,3,4,4,5,5-Octafluoro-*N*-(2,2,2-trifluoro-ethanethioyl)pentanamide (**4a**) (0.50 g, 1.4 mmol) was heated at 100 °C for 40 h. The

crude product was recrystallized from hexane to give the compound (**5**).

*3.3.1. N,N′-[2,4-Bis(trifluoromethyl)-1,3-dithitane-2,4-diyl]bis(2,2,3,3,4,4,5,5-octafluoropentanamide) (**5**)*

Yield: 31%. Colorless solid. Mixture of stereoisomers (the ratio is 55:45 according to ^{19}F NMR). ^{1}H NMR (DMSO-d$_6$, δ ppm): 7.07 (tm, $^{2}J_{H,F}$ = 50.4 Hz, 2H, 2 × HCF_2), 11.96 (bs, 2H, 2 × NH). ^{19}F NMR (Et_2O, δ ppm): −80.9 (m, 3F, CF_3 major), −82.5 (m, 3F, CF_3 minor), −121.3 (m, 2F, CF_2), −126.1 (m, 2F, CF_2), −131.1 (m, 2F, CF_2), −140.3 (dm, $^{2}J_{F,H}$ = 50.4 Hz, 2F, HCF_2). ^{13}C NMR (DMSO-d$_6$, δ ppm): 55.5 (q, $^{2}J_{C,F}$ = 37.3 Hz, *C*CF_3), 105.5–113.0 (m, 4 × CF_2), 123.3 (q, $^{1}J_{C,F}$ = 283.3 Hz, CF_3), 156.8 (t, $^{2}J_{C,F}$ = 27.5 Hz, C=O major), 157.3 (t, $^{2}J_{C,F}$ = 27.5 Hz, C=O minor). MS: *m/z* = 356 [(M/2)−1]. Anal. Calcd. for $C_{14}H_4F_{22}N_2O_2S_2$: C, 23.5; H, 0.6; N, 3.9; S, 9.0. Found: C, 23.7; H, 0.5; N, 4.0; S, 9.2.

*3.4. General procedure for the synthesis of disulfides (**6a–d**)*

A mixture of polyfluoroalkanethioamide (**1a–c**) (20.0 mmol, 1.0 eqiuv.) and the corresponding acyl chloride (40.00 mmol, 2.0 eqiuv.) was heated at 100 °C for 13–25 h. After the completion of the reaction, the excess of acyl chloride was removed *in vacuo* (0.08 mmHg). The crude product was purified by recrystallization from ethanol. *N*-[1-(benzoyldithio)-2,2,3,3-tetrafluoro-propyl]-benzamide (**6b**) was purified by column chromatography on silica gel (eluent:mixture (70:30) of ethyl acetate and hexane).

*3.4.1. N-[1-(Benzoyldithio)-2,2,2-trifluoroethyl]benzamide (**6a**)*

Yield: 50%. Colorless solid. mp 160–163 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 6.04 (dq, $^{3}J_{H,H}$ = 10.0 Hz, $^{3}J_{H,F}$ = 7.0 Hz, 1H, CH), 6.86 (d, $^{3}J_{H,H}$ = 10.0 Hz, 1H, NH), 7.43 (m, 4H, Ph), 7.52 (t, $^{3}J_{H,H}$ = 7.6 Hz, 1H, Ph), 7.62 (t, $^{3}J_{H,H}$ = 7.6 Hz, 1H, Ph), 7.75 (d, $^{3}J_{H,H}$ = 7.6 Hz, 2H, Ph), 7.83 (d, $^{3}J_{H,H}$ = 7.6 Hz, 2H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −73.8 (d, $^{3}J_{F,H}$ = 7.0 Hz, 3F, CF_3). ^{13}C NMR (DMSO-d$_6$, δ ppm): 59.0 (q, $^{2}J_{C,F}$ = 33.6 Hz, CH), 123.5 (q, $^{1}J_{C,F}$ = 278.6 Hz, CF_3), 127.4 (s, 2 × CH, Ph), 127.8 (s, 2 × CH, Ph), 128.2 (s, 2 × CH, Ph), 129.0 (s, 2 × CH, Ph), 130.8 (s, C_q, Ph), 132.5 (s, CH, Ph), 134.5 (s, C_q, Ph), 134.6 (s, CH, Ph), 166.8 (s, CONH), 187.0 (s, COS). MS: *m/z* = 372 [M+1]. Anal. Calcd. for $C_{16}H_{12}F_9NO_2S_2$: C, 51.7: H, 3.3; N, 3.8; S, 17.3. Found: C, 51.9; H, 3.3; N, 4.0; S, 17.4.

*3.4.2. N-[1-(Benzoyldithio)-2,2,3,3-tetrafluoropropyl]benzamide (**6b**)*

Yield: 34%. Colorless solid. mp 95–97 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 6.01 (dt, $^{3}J_{H,F}$ = 14.3 Hz, $^{3}J_{H,H}$ = 10.0 Hz, 1H, CH), 6.33 (tt, $^{2}J_{H,F}$ = 53.0 Hz, $^{3}J_{H,F}$ = 4.7 Hz, 1H, HCF_2), 6.84 (d, $^{3}J_{H,H}$ = 10.0 Hz, 1H, NH), 7.43 (m, 4H, Ph), 7.52 (t, $^{3}J_{H,H}$ = 7.2 Hz, 1H, Ph), 7.62 (t, $^{3}J_{H,H}$ = 7.2 Hz, 1H, Ph), 7.76 (d, $^{3}J_{H,H}$ = 7.2 Hz, 2H, Ph), 7.84 (d, $^{3}J_{H,H}$ = 7.2 Hz, 2H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −122.3 (dm, $^{2}J_{F,F}$ = 268.7 Hz, 1F, CF_AF$_B$), −124.1 (dm, $^{2}J_{F,F}$ = 268.7 Hz, 1F, CF$_A$F$_B$), −138.6 (dm, $^{2}J_{F,H}$ = 53.0 Hz, 2F, HCF_2). MS: *m/z* = 404 [M+1]. Anal. Calcd. for $C_{17}H_{13}F_4NO_2S_2$: C, 50.6; H, 3.3; N, 3.5; S, 15.9. Found: C, 50.9; H, 3.5; N, 3.8; S, 16.0.

*3.4.3. N-[1-(Benzoyldithio)-2,2,3,3,4,4,4-heptafluorobutyl]benzamide (**6c**)*

Yield: 77%. Colorless solid. mp 100–103 °C. IR (KBr, cm^{-1}): 3300 (NH), 1666 (NHCOPh), 1553 (SCOPh). ^{1}H NMR ($CDCl_3$, δ ppm): 6.28 (ddd, $^{3}J_{H,F}$ = 14.8 Hz, $^{3}J_{H,H}$ = 10.4 Hz, $^{3}J_{H,F}$ = 5,2 Hz, 1H, CH), 6.85 (d, $^{3}J_{H,H}$ = 10.4 Hz, 1H, NH), 7.38 (m, 4H, Ph), 7.48 (t, $^{3}J_{H,H}$ = 7.6 Hz, 1H, Ph), 7.59 (t, $^{3}J_{H,H}$ = 7.6 Hz, 1H, Ph), 7.69 (d, $^{3}J_{H,H}$ = 7.6 Hz, 2H, Ph), 7.76 (d, $^{3}J_{H,H}$ = 7.6 Hz, 2H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −81.2 (m, 3F, CF_3), −113.0 (dm, $^{2}J_{F,F}$ = 293.3 Hz, 1F, CF_AF$_B$), −120.5 (dm, $^{2}J_{F,F}$ = 293.3 Hz, 1F, CF$_A$F$_B$), −125.8 (m, 2F, CF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 57.6 (dd, $^{2}J_{C,F}$ = 30.8 Hz, $^{2}J_{C,F}$ = 22.4 Hz, CH), 109.0–119.0 (m, $CF_3CF_2CF_2$), 127.4 (s, 2 × CH, Ph), 128.0 (s, 2 × CH, Ph), 128.8 (s, 2 × CH, Ph), 129.1 (s, 2 × CH, Ph), 132.1 (s, C_q, Ph,), 132.6 (s, CH, Ph), 134.81 (s, C_q, Ph), 134.83 (s, CH, Ph), 166.5 (s, CONH), 189.5 (s, COS). MS: *m/z* = 472 [M+1]. Anal. Calcd. for $C_{18}H_{12}F_7NO_2S_2$: C, 45.9; H, 2.6; N, 3.0; S, 13.6. Found: C, 46.1; H, 2.6; N, 3.2; S, 13.4.

*3.4.4. N-{1-[(Cyclopropylcarbonyl)dithio]-2,2,3,3,4,4,4-heptafluorobutyl}cyclo-propane-carboxamide (**6d**)*

Yield: 30%. Colorless solid. mp 105–108 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 0.84 (m, 2H, cyclopropyl), 1.04 (m, 2H, cyclopropyl), 1.14 (m, 2H, cyclopropyl), 1.29 (m, 2H, cyclopropyl), 1.34 (m, 2H, cyclopropyl), 2.22 (m, 2H, cyclopropyl), 5.97 (ddd, $^{3}J_{H,F}$ = 14.8 Hz, $^{3}J_{H,H}$ = 10.3 Hz, $^{3}J_{H,F}$ = 5.3 Hz, 1H, CH), 6.15 (d, $^{3}J_{H,H}$ = 10.3 Hz, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −81.9 (m, 3F, CF_3), −114.0 (dm, $^{2}J_{F,F}$ = 285.2 Hz, 1F, CF_AF$_B$), −121.5 (dm, $^{2}J_{F,F}$ = 285.2 Hz, 1F, CF$_A$F$_B$), −126.5 (m, 2F, CF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 8.3 (s, CH_2, cyclopropyl), 8.7 (s, CH_2, cyclopropyl), 12.7 (s, 2 × CH_2, cyclopropyl), 14.4 (s, CH, cyclopropyl), 21.1 (s, CH, cyclopropyl), 57.0 (dd, $^{2}J_{C,F}$ = 30.6 Hz, $^{2}J_{C,F}$ = 22.1 Hz, CH), 108.8–119.0 (m, $CF_3CF_2CF_2$), 173.4 (s, CONH), 197.7 (s, COS). MS: *m/z* = 400 [M+1]. Anal. Calcd. for $C_{12}H_{12}F_7NO_2S_2$: C, 36.1; H, 3.0; N, 3.5; S, 16.0. Found: C, 36.1; H, 3.2; N, 3.8; S, 16.3.

*3.5. General procedure for cycloaddition reaction of the compounds (**2c, 4a–c**)*

2,3-Dimethylbutadiene (2.0 mmol, 1.0 equiv.) was added to a solution of compound (**2c, 4a–c**) (2.0 mmol, 1.0 equiv.) in chloroform (10 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated *in vacuo* and the crude product was purified by chromatography on silica gel (eluent:mixture (70:30) of hexane and ethyl acetate) to afford thiopyran (**11a–d**).

*3.5.1. N-[4,5-Dimethyl-2-(trifluoromethyl)-3,6-dihydro-2H-thiopyran-2-yl]-2,2,3,3,4,4,5,5-octafluoropentanamide (**11a**)*

Yield: 62%. Colorless oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.74 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.70 (d, $^{2}J_{H,H}$ = 16.4 Hz, 1H, CH_AH$_B$), 3.14 (d, $^{2}J_{H,H}$ = 16.6 Hz, 1H, SCH_AH$_B$), 3.34 (d, $^{2}J_{H,H}$ = 16.4 Hz, 1H, CH$_A$$H_B$), 3.57 (d, $^{2}J_{H,H}$ = 16.6 Hz, 1H, SCH$_A$$H_B$), 6.10 (tt, $^{2}J_{H,F}$ = 51.8 Hz, $^{3}J_{H,F}$ = 5.4 Hz, 1H, HCF_2), 6.32 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −79.3 (m, 3F, CF_3), −120.7 (dm, $^{2}J_{F,F}$ = 273.6 Hz, 1F, CF_AF$_B$), −122.3 (dm, $^{2}J_{F,F}$ = 273.6 Hz, 1F, CF$_A$F$_B$), −126.9 (m, 2F, CF_2), −130.5 (dm, $^{2}J_{F,F}$ = 288.8 Hz, 1F, CF_AF$_B$), −132.3 (dm, $^{2}J_{F,F}$ = 288.8 Hz, 1F, CF$_A$F$_B$), −139.1 (dm, $^{2}J_{F,H}$ = 51.8 Hz, 2F, HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 18.7 (s, CH_3), 19.7 (s, CH_3), 30.1 (s, SCH_2), 33.3 (s, CH_2), 67.5 (q, $^{2}J_{C,F}$ = 23.0 Hz, *C*CF_3), 105.1–119.4 (m, CF_3, 4 × CF_2), 123.3 (s, C_q), 124.7 (s, C_q), 156.7 (t, $^{2}J_{C,F}$ = 26.4 Hz, C=O). MS: *m/z* = 438 [M−1]. Anal. Calcd. for $C_{13}H_{12}F_{11}NOS$: C, 35.5; H, 2.8; N, 3.2; S, 7.3. Found: C, 35.6; H, 2.8; N, 3.3; S, 7.5.

*3.5.2. N-[4,5-Dimethyl-2-(1,1,2,2-tetrafluoroethyl)-3,6-dihydro-2H-thiopyran-2-yl]-2,2,3,3,4,4,5,5-octafluoropentanamide (**11b**)*

Yield: 50%. Yellow oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.73 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.73 (d, $^{2}J_{H,H}$ = 16.4 Hz, 1H, CH_AH$_B$), 3.13 (d, $^{2}J_{H,H}$ = 16.6 Hz, 1H, SCH_AH$_B$), 3.36 (d, $^{2}J_{H,H}$ = 16.4 Hz, 1H, CH$_A$$H_B$), 3.51 (d, $^{2}J_{H,H}$ = 16.6 Hz, 1H, SCH$_A$$H_B$), 6.10 (tm, $^{2}J_{H,F}$ = 52.1 Hz, 2H, 2 × HCF_2), 6.40 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −120.1 (dm, $^{2}J_{F,F}$ = 275.4 Hz, 1F, CF_AF$_B$), −121.8 (dm, $^{2}J_{F,F}$ = 275.4 Hz, 1F, CF$_A$F$_B$), −123.4 (dm, $^{2}J_{F,F}$ = 273.5 Hz, 1F, CF_AF$_B$), −125.0 (dm, $^{2}J_{F,F}$ = 273.5 Hz, 1F, CF$_A$F$_B$), −126.4 (m, 2F, CF_2), −130.0 (dm, $^{2}J_{F,F}$ = 290.2 Hz, 1F, CF_AF$_B$), −131.9 (dm, $^{2}J_{F,F}$ = 290.2 Hz, 1F, CF$_A$F$_B$), −134.9 (m, 2F, CF_2), −138.7 (dm, $^{2}J_{F,H}$ = 52.1 Hz, 2F, HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 18.7 (s, CH_3), 19.8 (s, CH_3), 30.1 (s, SCH_2), 33.3 (s, CH_2), 67.1 (t, $^{2}J_{C,F}$ = 24.6 Hz, *C*CF_2), 105.2 −118.0 (m, 6 × CF_2), 130.1 (s, C_q), 131.8 (s, C_q), 156.8 (t, $^{2}J_{C,F}$ = 26.6 Hz, C=O). MS: *m/z* = 470

[M−1]. Anal. Calcd. for $C_{14}H_{13}F_{12}NOS$: C, 35.7; H, 2.8; N, 3.0; S, 6.8. Found: C, 35.6; H, 2.8; N, 2.8; S, 7.0.

*3.5.3. 2,2,3,3,4,4,5,5-Octafluoro-N-[2-(heptafluoropropyl)-4,5-dimethyl-3,6-dihydro-2H-thiopyran-2-yl]pentanamide (**11c**)*

Yield: 50%. Brown oil. ^{1}H NMR ($CDCl_3$, δ ppm): 1.74 (s, 6H, 2 × CH_3), 2.78 (d, $^2J_{H,H}$ = 16.5 Hz, 1H, CH_AH_B), 3.15 (d, $^2J_{H,H}$ = 16.8 Hz, 1H, SCH_AH_B), 3.34 (d, $^2J_{H,H}$ = 16.5 Hz, 1H, CH_AH_B), 3.69 (d, $^2J_{H,H}$ = 16.8 Hz, 1H, SCH_AH_B), 6.10 (tt, $^2J_{H,F}$ = 51.8 Hz, $^3J_{H,F}$ = 5.4 Hz, 1H, HCF_2), 6.33 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −82.1 (m, 3F, CF_3), −115.5 (dm, $^2J_{F,F}$ = 279.1 Hz, 1F, CF_AF_B), −117.2 (dm, $^2J_{F,F}$ = 279.1 Hz, 1F, CF_AF_B), −119.9 (dm, $^2J_{F,F}$ = 275.9 Hz, 1F, CF_AF_B), −121.6 (dm, $^2J_{F,F}$ = 275.9 Hz, 1F, CF_AF_B), −124.0 (m, 2F, CF_2), −126.4 (m, 2F, CF_2), −130.0 (dm, $^2J_{F,F}$ = 289.3 Hz, 1F, CF_AF_B), −131.9 (dm, $^2J_{F,F}$ = 289.3 Hz, 1F, CF_AF_B), −138.7 (dm, $^2J_{F,H}$ = 51.8 Hz, 2F, HCF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 18.7 (s, CH_3), 19.8 (s, CH_3), 30.1 (s, SCH_2), 33.1 (s, CH_2), 67.8 (t, $^2J_{C,F}$ = 25.4 Hz, CCF_2), 105.0–120.0 (m, CF_3, 6 × CF_2), 122.6 (s, C_q), 124.7 (s, C_q), 156.4 (t, $^2J_{C,F}$ = 26.0 Hz, C=O). MS: *m/z* = 538 [M−1]. Anal. Calcd. for $C_{15}H_{12}F_{15}NOS$: C, 33.4; H, 2.2; N, 2.6; S, 6.0. Found: C, 33.5; H, 2.3; N, 2.6; S, 6.2.

*3.5.4. N-[(2-Heptafluoropropyl)-4,5-dimethyl-3,6-dihydro-2H-thiopyran-2-yl]-acetamide (**11d**)*

Yield: 72%. Colorless solid. mp 120–122 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 1.75 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.98 (s, 3H, CH_3CO) 2.63 (d, $^2J_{H,H}$ = 16.1 Hz, 1H, CH_AH_B), 3.09 (d, $^2J_{H,H}$ = 16.4 Hz, 1H, SCH_AH_B), 3.31 (d, $^2J_{H,H}$ = 16.1 Hz, 1H, CH_AH_B), 3.81 (d, $^2J_{H,H}$ = 16.4 Hz, 1H, SCH_AH_B), 5.52 (bs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −82.1 (m, 3F, CF_3), −114.6 (dm, $^2J_{F,F}$ = 276.6 Hz, 1F, CF_AF_B), −116.4 (dm, $^2J_{F,F}$ = 276.6 Hz, 1F, CF_AF_B), −123.0 (dm, $^2J_{F,F}$ = 287.1 Hz, 1F, CF_AF_B), −125.3 (dm, $^2J_{F,F}$ = 287.1 Hz, 1F, CF_AF_B). ^{13}C NMR ($CDCl_3$, δ ppm): 18.8 (s, CH_3), 19.8 (s, CH_3), 24.4 (s, CH_3CO), 30.4 (s, SCH_2), 33.5 (s, CH_2), 67.7 (t, $^2J_{C,F}$ = 25.1 Hz, CCF_2), 107.0–120.0 (m, $CF_3CF_2CF_2$), 123.1 (s, C_q), 125.6 (s, C_q), 169.5 (s, C=O). MS: *m/z* = 354 [M+1]. Anal. Calcd. for $C_{12}H_{14}F_7NOS$: C, 40.8; H, 4.0; N, 4.0; S, 9.1. Found: C, 40.9; H, 4.1; N, 3.9; S, 9.1.

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