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Multi-step reactions of *N*-monosubstituted (polyfluoroalkane)thioamides with alkyllithium reagents

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Dedicated to the 100th anniversary of Prof. Ivan Ludvigovich Knunyants

Abstract

Reactions of *N*-alkyl- or *N*-aryl(perfluoroalkyl)thiocarboxamides with alkyl lithium reagents are described. Trifluorothioacetamides are converted into the corresponding lithium salts. Compounds bearing a long polyfluorinated chain terminated by a CHF_2 group and compounds containing an *N*-alkyl substituent with a proton adjacent to nitrogen react further *via* a multi-step reaction sequence involving HF elimination and then vinylic fluorine substitution and/or S_N' type fluorine substitution. These transformations led to unsaturated *N*-monosubstituted polyfluorinated thioamides.

Keywords: Thioamides; Organo-lithium reagents; Fluoride elimination; Fluorine substitution

1. Introduction

The presence of fluorine atoms significantly affects the reactivity of polyfluoroalkanethiocarboxylic acid derivatives. Reactions of perfluoro dithioesters with organometallic reagents give the corresponding dithioacetals through a two-step sequence ''thiophilic addition–β-elimination'' [1]. Furthermore, while organometallic reagents react with non-fluorinated thioamides exclusively at carbon [2], except for the enolizable substrates where deprotonation can occur [3], allylmagnesium reagents react with *N*,*N*-dialkyl(perfluoro)thioamides at carbon and alkyllithium reagents react *via* the above mentioned two-step domino reaction to give *N*,*S*-perfluoroketene acetals [4] (Scheme 1).

We have extended our investigation to *N*-monosubstituted polyfluorothioamides. The reactivity of these compounds proved to depend strongly on the nature of both the polyfluoroalkyl and *N*-alkyl group and to be different than *N*,*N*-disubstituted perfluorothioamides. We report in this paper the results of this investigation.

2. Results and discussion

Treatment of *N*-alkyl(aryl) trifluorothioacetamides **3a–c** with an excess of *tert*-butyl lithium gave only the corresponding lithium salts **4a–c**. Thioamides **3a–c** can then be recovered in practically quantitative yields after treatment of the reaction mixture with concentrated aqueous HCl (Scheme 2). Methylation of **4a** followed by an acidic hydrolysis of the intermediate imidate led to the *S*-methyl trifluoroethanethioate **5** with 85% yield. The structure of **5** was confirmed by comparison of experimental IR and NMR data with the ones described in the literature [5].

Treatment of *N*-*p*-tolyl- and *N*-*tert*-butyl thioamides **6**,**7** with an excess of *tert*-butyllithium led to the δ,ε-unsaturated derivatives **8**,**9** (Scheme 3). Formation of these compounds can be explained according to the reaction sequence depicted in Scheme 3. The successive nitrogen deprotonation and

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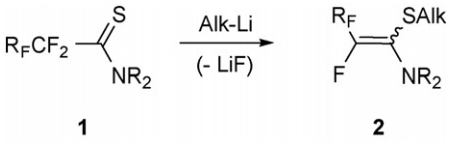


Scheme 1.

dehydrofluorination gives the unsaturated salt **10** which undergoes the substitution of a vinyl fluoride by the *tert*-butyl group [6]. Acid hydrolysis gave finally 2,2,3,3,4,5-hexafluoro-6,6-dimethyl(hept-4-ene)thioamides **8** and **9** in 73% and 56% yields, respectively. The *E*-configuration of the double bond was confirmed by the ^{19}F NMR spectrum ($^3J_{FF}$ = 126.0 and 133.0 Hz for compounds **8** and **9**, respectively) [7].

Interestingly, reactions of *tert*-butyllithium with pentafluoroethyl and heptafluoropropyl *N*-ethyl and *N*-propyl thioamides proceed in a more complicated way due to the presence of an α-proton on the *N*-substituent.

The reaction of *N*-propyl-pentafluoropropanethioamide **11** with *tert*-butyllithium led to the formation of the α,β-unsaturated thioamide **14** in good yield (69%) (Scheme 4). The formation of compound **14** could result from a step-by-step transformation of the originally formed lithium salt which begins by a 1,4-HF elimination leading to the aza diene **17**. A vinylogue S_N' type substitution of fluorine, then a vinyl fluorine substitution by the *tert*-butyl group yields the lithium salt **18** which is finally hydrolyzed into compound **14**.

The structure of **14** was determined by a single crystal X-ray diffraction (Fig. 1). The N(1) atom has trigonal-planar bond configuration (sum of the bond angles is 360° within the estimated errors limits). Due to the $n_{N(1)}$–$\pi_{C(1)=S(1)}$ conjugation, the N(1)–C(1) bond of 1.333(6) Å is significantly shortened in comparison with the standard value for the N(sp^3)–C(sp^3) single bonds of 1.43–1.45 Å [8,9], reflecting the

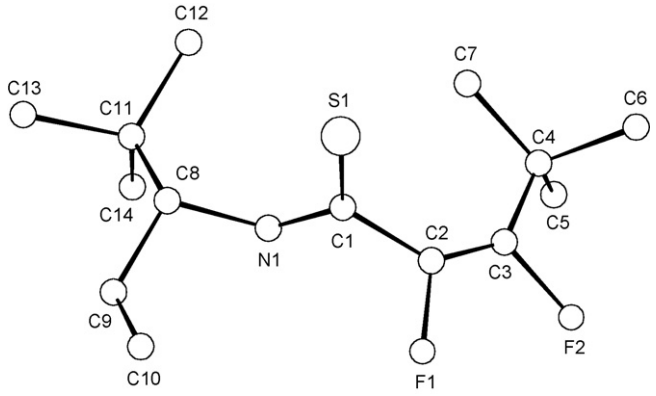


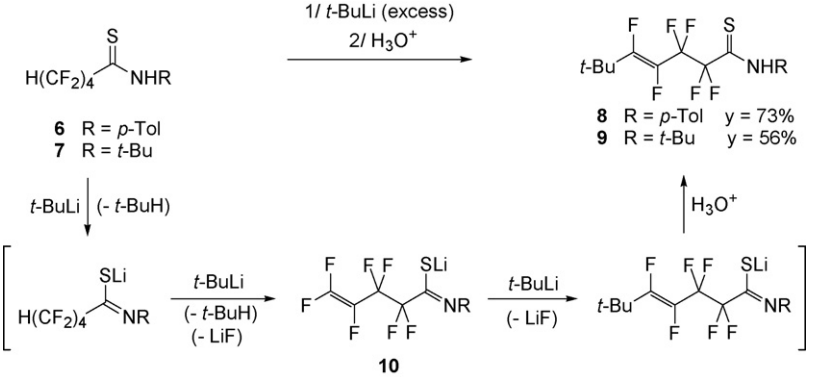
Fig. 1. A perspective view and labelling scheme for the molecule **14**. Selected bond lengths (Å) and angles (°): S(1)–C(2) 1.660(5), N(1)–C(1) 1.333(6), N(1)–C(8) 1.459(7), C(1)–C(2) 1.476(8), C(2)–C(3) 1.302(9), N(1)C(1)C(2) 113.6(4), C(1)N(1)C(8) 126.9(4).

significant charge delocalization over the S(1)=C(1)–N(1) bond chain. The *Z*-configuration of C^2=C^3 double bond is in agreement with ^{19}F NMR data ($^3J_{FF}$ = 7.0 Hz) [7].

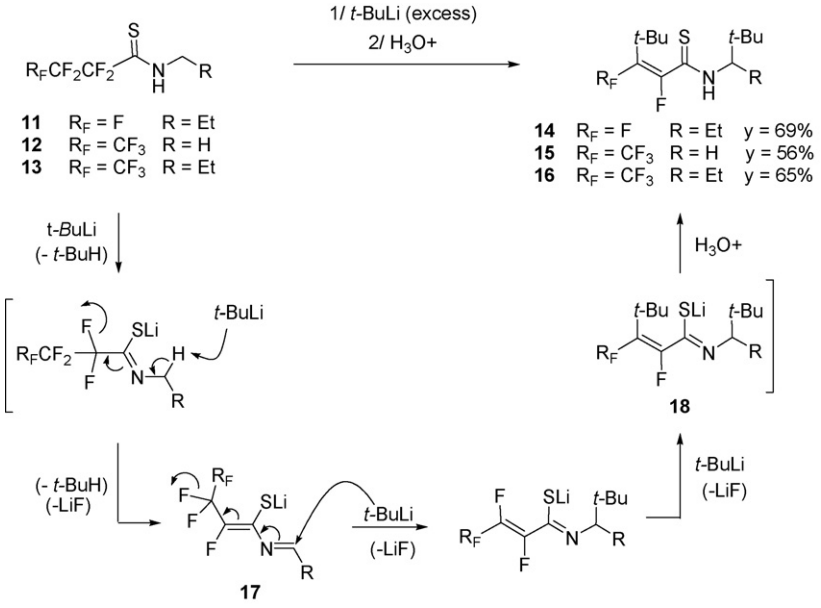
Formation of similar unsaturated α-F-β-CF_3-containing compounds **15**, **16** occurs when thioamides **12**, **13** are treated with excess of *t*-BuLi (Scheme 4). The *cis*-relation between CF_3 group and fluorine atom at C^2=C^3 double bond was ascribed according to ^{19}F NMR data ($^4J_{FF}$ = 30.0 Hz) [7]. Thioamide **12** reacts similarly with the stronger nucleophilic methyl lithium leading to thioamide **19**, even if **19** was isolated in only 30% yield from a complex mixture (Scheme 5).

It should be mentioned that the lithium salt **4a** derived from *N*-methyl-trifluorothioacetamide **3a** proved to be stable in the presence of an excess of *tert*-butyllithium (Scheme 2). This difference with higher homologues could be due to a less efficient withdrawing effect of the CF_3 group in comparison

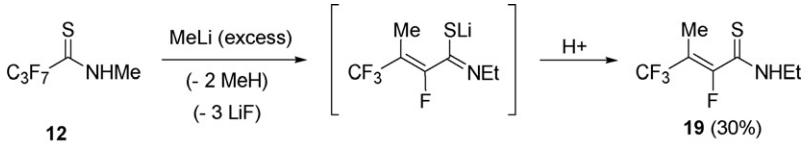
Scheme 2.



Scheme 3.



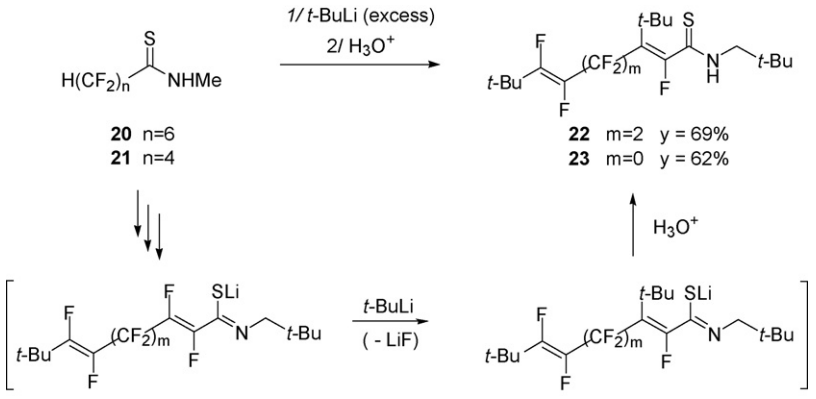
Scheme 4.



Scheme 5.

with longer perfluoroalkyl groups, hence to a less acidic NH-hydrogen. Another explanation may be the relative stability of the enethiolate resulting from the 1,4-HF elimination. Assuming that fluorinated enethiolates behave similarly to perfluorinated enolates [10], reaction of **4a** with *tert*-butyllithium would lead to a terminal enethiolate, less stable than the internal enethiolate derived from a longer R_F containing salt.

N-Methyl-*ω*-*H*-perfluoroheptane- and pentanethioamides **20**, **21** react with an excess of *t*-BuLi giving thioamides **22**, **23** in fair yields (Scheme 6). Decreasing the amount of *t*-BuLi led to the formation of an inseparable complex mixture of products. Thioamide **22** contains two double bonds separated by two difluoromethylenic groups. The presence of the vinylic fluorine atom in α-position was ascertained by NMR spectroscopy: the signal corresponding to the C=S group, which appears as a doublet at 191.1 ppm ($^2J_{CF}$ = 31.0 Hz) supports the =C(F)–C=S fragment structure. The *E*-geometry of C^6(F)=C^7(F) double bond was confirmed by a $^3J_{F,F(E)}$ value (131.0 Hz) similar to the one observed with compounds **8**, **9** described above. The *transoid* configuration of the C^2=C^3–C^4=C^5 fragment of compound **23** was ascertained by the $^2J_{(C^2\underline{F},C^5\underline{F})}$ value (12.0 Hz). A larger value would be expected for a *cisoid* configuration, owing to the spatial proximity of fluorine atoms [11]. Similarly, the value $^4J_{(C^2\underline{F},C^4\underline{F})}$ = 36.0 Hz is significant of the *Z*-configuration [7b].



Scheme 6.

3. Conclusion

The products of the reaction of various *N*-monosubstituted polyfluoroalkane thioamides with *t*-BuLi and MeLi strongly depend on the nature of the polyfluoroalkyl and *N*-alkyl moieties. In the case of trifluorothioacetamides and *N*-*tert*-butyl- or *N*-arylthioamides with long fluorinated chain, reaction stops at the lithium salt stage. On the other hand, reactions of *t*-BuLi or MeLi with *N*-alkylthioamides containing an α-proton on the *N*-alkyl substituent and a polyfluoroalkyl substituent larger than CF_3 gave *N*-monosubstituted α,β-unsaturated fluorinated thioamides *via* a multi-step sequence combining deprotonation and substitution steps.

The α,β-unsaturated fluorinated thioamides described here are among the first representatives of this family of products, which were so far reported in only one publication [12]. Further study of these new compounds is under progress.

4. Experimental

4.1. General

The ^1H, ^{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. Chemical shifts are given in ppm referenced to signals of the proton in $CHCl_3$ ($\delta_H = 7.26$, $\delta_C = 77.16$) for ^1H and ^{13}C NMR spectra and from C_6F_6 ($\delta_F = -162.9$ ppm) as internal standard for ^{19}F NMR spectra. MS data were obtained on ADSI MS, Agilent 1100\DAD\MSD VL G1965 instrument.

All reactions were performed under nitrogen atmosphere. Solvents (tetrahydrofuran and diethyl ether) were dried by distillation over sodium and benzophenone. The progress of all reactions was monitored by NMR ^{19}F 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.

Starting thioamides (**3**, **6**, **7**, **11**, **12**, **13**, **20**, **21**) were synthesized on general procedure by thionation of corresponding amides which were obtain according to the method described in [13].

4.2. Synthesis of (polyfluoralkane)thioamides. General procedure

Phosphorous pentasulfide (11.1 g, 25 mmol) was added to a suspension of corresponding amide (40 mmol) in mixture of hexamethyldisiloxane (80 mmol) and 100 mL of toluene. The reaction mixture was stirred at 80 °C, the time of the reaction was followed by ^{19}F NMR, monitoring the disappearance of starting amides peaks. The mixture was cooled to room temperature, solid material was filtered off and washed with 50 mL of diethyl ether. Solvents and excess of HMDSO were removed in vacuum (10–15 mmHg) up to 1/2 of volume and residue was diluted with 50 mL of diethyl ether. Organic solution was consecutively washed with saturated aqueous $NaHCO_3$ solution (4× 50 mL), saturated aqueous NaCl solution (2× 100 mL) and water (2× 100 mL). Water phase was additionally washed with diethyl ether (2× 100 mL). Combined ethereal extracts were dried over Na_2SO_4 and solvents were removed in vacuum. The residue was crystallized from hexane or distilled.

4.2.1. *N*-Methyl-2,2,2-trifluorothioacetamide (**3a**)

As described in [14].

4.2.2. *N*-tert-Butyl-2,2,2-trifluorothioacetamide (**3b**)

Yield 61%, yellow liquid, bp 55–57 °C (10 mmHg). ^1H NMR ($CDCl_3$): δ, 1.57 (9H, s, *t*-Bu), 7.59 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −71.2 (3F, s, CF_3). Anal. calculated for $C_6H_{10}F_3NS$: C, 38.91; H, 5.44; N, 7.56; S, 17.31. Found: C, 38.88; H, 5.47; N, 7.58; S, 17.29.

4.2.3. *N*-(4-Methylphenyl)-2,2,2-trifluorothioacetamide (**3c**)

Yield 78%, yellow needles, mp 54–55 °C (from hexane). ^1H NMR ($CDCl_3$): δ, 2.06 (3H, s, CH_3), 6.92–7.32 (4H, m, aromatic), 8.91 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −70.6 (3F, d, CF_3, $^4J_{FH} = 11$ Hz). Anal. calculated for $C_9H_8F_3NS$: C, 49.31; H, 3.68; N, 6.39; S, 14.63. Found: C, 49.21; H, 3.71; N, 6.43; S, 14.69.

4.2.4. *N*-(4-Methylphenyl)-2,2,3,3,4,4,5,5-octafluoropentanethioamide (**6**)

Yield 92%, orange liquid, bp 92–97 °C (0.035 mmHg). ^1H NMR ($CDCl_3$): δ, 2.38 (3H, br, CH_3), 6.16 (1H, tt, HCF_2, $^2J_{HF} = 52$ Hz, $^3J_{HF} = 5$ Hz), 7.26–7.58 (4H, m, H aromatic), 9.28 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −138.2 (2F, dm, CHF_2, $^2J_{FH} = 52$ Hz), −130.2, −123.4, −111.6 (6F, m, 3× CF_2). Anal. calculated for $C_{12}H_{19}F_8NS$: C, 41.03; H, 2.58; N, 3.99; S, 9.13. Found: C, 41.05; H, 2.59; N, 3.95; S, 9.16.

4.2.5. *N*-tert-Butyl-2,2,3,3,4,4,5,5-octafluoropentanethioamide (**7**)

Yield 90%, orange liquid, bp 38–42 °C (0.01 mmHg). ^1H NMR ($CDCl_3$): δ, 1.57 (9H, s, *t*-Bu), 6.17 (1H, tt, HCF_2, $^2J_{HF} = 52$ Hz, $^3J_{HF} = 6$ Hz), 7.55 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −138.3 (2F, dm, CHF_2, $^2J_{FH} = 52$ Hz), −130.4, −123.6, −111.4 (6F, m, 3× CF_2). Anal. calculated for $C_9H_{11}F_8NS$: C, 34.07; H, 3.49; N, 4.42; S, 10.11. Found: C, 34.05; H, 3.51; N, 4.39; S, 10.08.

4.2.6. 2,2,3,3,3-Pentafluoro-*N*-propyl-propanethioamide (**11**)

Yield 73%, yellow liquid, bp 110–114 °C (0.75 mmHg). ^1H NMR ($CDCl_3$): δ, 0.98 (3H, t, CH_3, $^3J_{HH} = 7$ Hz), 1.78 (2H, m, CH_2CH_3), 3.66 (2H, m, CH_2NH), 8.01 (1H, br, NH), ^{19}F NMR ($CDCl_3$): δ, −114.9 (2F, m, CF_2), −82.3 (3F, m, CF_3). Anal. calculated for $C_6H_8F_5NS$: C, 32.58; H, 3.65; N, 6.33; S, 14.50. Found: C, 32.61; H, 3.68; N, 6.34; S, 14.48.

4.2.7. *N*-Methyl-2,2,3,3,4,4,4-heptafluorothiobutyramide (**12**)

Yield 80%, yellow liquid, bp 72–74 °C (0.035 mmHg). ^1H NMR ($CDCl_3$): δ, 3.27 (3H, d, CH_3, $^3J_{HH} = 5$ Hz), 8.11 (1H, br,

NH). ^{19}F NMR ($CDCl_3$): δ, −124.2 (2F, m, CF_2CS), −110.3 (2F, m, CF_2CF_2CS), −80.1 (3F, m, CF_3). Anal. calculated for $C_5H_4F_7NS$: C, 24.70; H, 1.66; N, 5.76; S, 13.19. Found: C, 24.79; H, 1.69; N, 5.76; S, 13.19.

4.2.8. N-Propyl-2,2,3,3,4,4,4-heptafluorothiobutyramide (**13**)

Yield 82%, yellow liquid, bp 78–82 °C (0.035 mmHg). ^{1}H NMR ($CDCl_3$): δ, 1.01 (3H, t, CH_3, $^3J_{HH}$ = 7 Hz), 1.70 (2H, m, CH_2CH_3), 3.61 (2H, m, $NHCH_2$), 7.81 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −125.7 (2F, m, CF_2CS), −112.4 (2F, m, CF_2CF_2CS), −81.2 (3F, m, CF_3). Anal. calculated for $C_7H_8F_7NS$: C, 31.00; H, 2.97; N, 5.16; S, 11.82. Found: C, 30.91; H, 3.00; N, 5.12; S, 11.81.

4.2.9. N-Methyl-2,2,3,3,4,4,5,5,6,6,7,7-dodecafluoroheptanethioamide (**20**)

Yield 82%, yellow needles, mp 36–38 °C (from hexane), bp 70–72 °C (0.07 mmHg). ^{1}H NMR ($CDCl_3$): δ, 3.26 (3H, d, CH_3, $^3J_{HH}$ = 5Hz), 6.05 (1H, tt, HCF_2, $^2J_{HF}$ = 52 Hz, $^3J_{HF}$ = 5 Hz), 8.05 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −138.2 (2F, dm, CHF_2, $^2J_{FH}$ = 52 Hz), −130.8, −124.6, −123.4, −121.2, −111.0 (10F, m, 5× CF_2). Anal. calculated for $C_8H_5F_{12}NS$: C, 25.61; H, 1.34; N, 3.73; S, 8.55. Found: C, 25.60; H, 1.36; N, 3.71; S, 8.54.

4.2.10. N-Methyl-2,2,3,3,4,4,5,5-octafluoropentanethioamide (**21**)

Yield 84%, light-yellow liquid, bp 49–50 °C (0.06 mmHg). ^{1}H NMR ($CDCl_3$): δ, 3.26 (3H, d, CH_3, $^3J_{HH}$ = 5 Hz), 6.14 (1H, tt, HCF_2, $^2J_{HF}$ = 52 Hz, $^3J_{HF}$ = 6 Hz), 8.04 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −138.0 (2F, dm, CHF_2, $^2J_{FH}$ = 52 Hz), −130.0, −123.2, −111.8 (6F, m, 3 × CF_2). Anal. calculated for $C_6H_5F_8NS$: C, 26.19; H, 1.83; N, 5.09; S, 11.65. Found: C, 26.17; H, 1.85; N, 5.07; S, 11.64.

4.3. S-Methyl trifluoroethanethioate (**5**)

tert-Butyllithium (3.7 mL of 1.7 M solution in pentane, 3 mmol) was added at −70 °C under a nitrogen atmosphere to a stirred solution of thioamide **3a** (0.14 g, 1 mmol) in THF (40 mL). The mixture was stirred for 30 min at −70 °C, and was slowly warmed to room temperature for 3 h. The MeI (0.28 g, 2 mmol) was added to the reaction mixture at room temperature and reaction mixture was stirred at this temperature for 4 h. The solution obtained was acidified by 2 mL of 20% aqueous HCl and diluted with diethyl ether (3 mL). Organic layer was separated, the water layer was extracted with diethyl ether (2× 5 mL). The combined ethereal solution was washed with water (2× 5 mL), dried over Na_2SO_4 and solvent was removed at atmospheric pressure. The compound **5** was obtained as light-red liquid. Yield 1.2 g (85%), bp 71 °C. ^{1}H NMR ($CDCl_3$): δ, 2.50 (s, CH_3). ^{19}F NMR ($CDCl_3$): δ, −76.5 (s, CF_3). IR (film): 1707 cm^{-1} (C=O) [5].

4.4. Reactions of thioamides with tert-butyllithium. General procedure

To a stirred solution of 1 mmol of thioamide (**3a–c**, **6**, **7**, **11**, **12**, **13**, **20**, or **21**) in THF (50 mL) was added a solution of *tert*-butyllithium (1.7 M in pentane) at −78 °C under a nitrogen atmosphere (3 mmol for **3a–c**, 6 mmol for **6**; 6 mmol for **7**; 6 mmol for **11**; 8 mmol for **12**; 8 mmol for **13**; 25 mmol for **20**; 9 mmol for **21**) for 30 min (for **3a–c**, **6**, **7**, **12**, **13**) or for 1.5 h (for **11**, **20** and **21**). Reaction mixture was stirred at −78 °C for 30 min and slowly warmed to room temperature for 3 h. Methanol (3 mL) and 20% aqueous solution of HCl (5–10 mL) was added to the reaction mixture until pH ≈4 and diluted with diethyl ether (30 mL). Organic layer was separated and washed with water (2× 50 mL). The aqueous layer was extracted with ether (2× 50 mL). Ethereal extract was dried over Na_2SO_4 and solvent was removed under reduced pressure (10–20 mmHg) at 30–35 °C. The crude oil was purified by column chromatography on silica gel.

4.4.1. (2Z)-N-(1-Ethyl-2,2-dimethylpropyl)-2,3-difluoro-4,4-dimethyl-pent-2-enethioamide (**14**)

Yield 0.21 g (68%), pale-yellow crystals, eluent petroleum ether-Et_2O 20:1, mp 70 °C (from petroleum ether). ^{1}H NMR ($CDCl_3$): δ, 0.96 (3H, t, CH_3CH_2, $^3J_{HH}$ = 7 Hz), 0.98 (9H, s, *t*–Bu–CH), 1.30 (9H, d, *t*–Bu–CF, $^4J_{HF}$ = 2 Hz), 1.36 (1H, m, CH_AH_B–CH_3, overlapped with *t*–Bu–CF), 1.86 (1H, ddt, CH_AH_B–CH_3, J_{AB} = 15 Hz, $^3J_{HH}$ = 3 Hz, $^3J_{HH}$ = 7 Hz), 4.53 (1H, dt, CH, $^3J_{HH}$ = 3 Hz, $^3J_{HH}$ = 10 Hz), 7.20 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −129.3 (1F, d, CF–C=S, $^3J_{FF(Z)}$ = 7 Hz), −130.1 (1F, dm, CF–*t*–Bu, $^3J_{FF(Z)}$ = 7 Hz, $^4J_{FH}$ = 2 Hz). ^{13}C NMR ($CDCl_3$): δ, 11.3 (s, CH_3CH_2), 23.7 (s, CH_3CH_2), 26.7 (s, $(CH_3)_3$C–CH), 27.5 (s, $(CH_3)_3$C–CF), 34.2 (s, $(CH_3)_3$C–CH), 35.9 (s, $(CH_3)_3$C–CH), 65.0 (s, $(CH_3)_3$C–CF), 143.6 (dd, $(CH_3)_3$C–CF, J_{CF} = 248 Hz, $^2J_{CF}$ = 25 Hz), 155.4 (dd, CF–C=S, J_{CF} = 259 Hz, $^2J_{CF}$ = 15 Hz), 189.1 (d, C=S, $^2J_{CF}$ = 20 Hz). MS, *m/z* (rel. int.): 300.2 $[M + Na]^+$ (100%), 278.2 $[M + H]^+$ (55%). Anal. calculated for $C_{14}H_{25}F_2NS$: C, 60.61; H, 9.08; N, 5.05; S, 11.56. Found: C, 60.64; H, 9.06; N, 5.08; S, 11.55.

4.4.2. (4E)-2,2,3,3,4,5-Hexafluoro-6,6-dimethyl-N-(4-methylphenyl)hept-4-enethioamide (**8**)

Yield 0.27 g (73%), oil, eluent hexane-ethyl acetate 4:1. ^{1}H NMR ($CDCl_3$): δ, 1.23 (9H, t, *t*–Bu, $^4J_{HF}$ = 2 Hz), 2.35 (3H, s, CH_3–C_6H_4), 7.20–7.58 (4H, m, aromatic), 9.53 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −113.4 (2F, m, CF_2–C=S), −117.5 (2F, dm, CF_2CF_2, $^3J_{FF}$ = 37 Hz), −142.5 (1F, dt, C^4F, $^3J_{FF}$ = 37 Hz, $^3J_{FF(E)}$ = 126 Hz), −165.4 (1F, d, C^5F, $^3J_{FF(E)}$ = 126 Hz). MS, *m/z* (rel. int.): 368.0 $[M–H]^+$ (18%). Anal. calculated for $C_{16}H_{17}F_6NS$: C, 52.03; H, 4.64; N, 3.79; S, 8.68. Found: C, 52.04; H, 4.66; N, 3.81; S, 8.66.

4.4.3. (4E)-N-(tert-Butyl)-2,2,3,3,4,5-hexafluoro-6,6-dimethyl-hept-4-enethioamide (**9**)

Yield 0.18 g (56%), oil, eluent hexane-ethyl acetate 4:1, purity about 90% according to ^{19}F and ^{1}H NMR data. ^{1}H NMR

($CDCl_3$): δ, 1.24 (9H, t, *t–Bu*–C^5F, $^4J_{HF}$ = 2 Hz), 1.56 (9H, s, *t–Bu*–NH), 7.57 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −112.9 (2F, m, CF_2–C=S), −117.1 (2F, dm, CF_2CF_2, $^3J_{FF}$ = 28 Hz), −142.3 (1F, dt, C^4F, $^3J_{FF}$ = 28 Hz, $^3J_{FF(E)}$ = 133 Hz), −165.7 (1F, d, C^5F, $^3J_{FF(E)}$ = 133 Hz). MS, *m/z* (rel. int.): 335.1 $[M–H]^+$ (74%). Anal. calculated for $C_{13}H_{19}F_6NS$: C, 46.56; H, 5.71; N, 4.18; S, 9.56. Found: C, 46.53; H, 5.74; N, 4.15; S, 9.58.

*4.4.4. (2Z)-N-(2,2-Dimethylpropyl)-2-fluoro-4,4-dimethyl-3-(trifluoromethyl)pent-2-enethio-amide (**15**)*

Yield 0.17 g (56%), eluent hexane-ethyl acetate 4:1, yellow crystals, mp 99–101 °C (from hexane). ^1H NMR ($CDCl_3$): δ, 1.04 (9H, s, *t–Bu*–CH_2), 1.31 (9H, s, *t*–Bu–C^3), 3.51 (2H, dd, CH_2, $^2J_{HH}$ = 6 Hz, $^3J_{HH}$ = 2 Hz), 7.46 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −54.9 (3F, d, CF_3, $^4J_{FF}$ = 31 Hz), −82.3 (1F, q, C^2F, $^4J_{FF}$ = 31 Hz). ^{13}C NMR ($CDCl_3$): δ, 190.2 (d, C=S, $^2J_{CF}$ = 29 Hz), 156.0 (dq, C^2F, J_{CF} = 270 Hz, $^3J_{CF}$ = 4 Hz), 124.3 (qd, CF_3, J_{CF} = 279 Hz, $^3J_{CF}$ = 2 Hz), 117.6 (qd, C^3, $^2J_{CF}$ = 4 Hz, $^2J_{CF}$ = 26 Hz), 57.0 (s, $NHCH_2$), 33.2 (s, $(CH_3)_3C$–C^3), 32.0 (s, $(CH_3)_3C$–CH_2), 29.8 (s, $(CH_3)_3C$–C^3), 27.7 (s, $(CH_3)_3C$–CH_2). MS, *m/z* (rel. int.): 300.2 $[M + H]^+$ (20%). Anal. calculated for $C_{13}H_{21}F_4NS$: C, 52.16; H, 7.07; N, 4.68; S, 10.71. Found: C, 52.18; H, 7.05; N, 4.65; S, 10.73.

*4.4.5. (2Z)-N-(1-Ethyl-2,2-dimethylpropyl)-2-fluoro-4,4-dimethyl-3-(trifluoromethyl)pent-2-ene-thioamide (**16**)*

Yield 0.2 g (65%), eluent hexane-ethyl acetate 4:1, yellow crystals, mp 118–120 °C (from hexane). ^1H NMR ($CDCl_3$): δ, 0.97 (3H, t, CH_3CH_2, $^3J_{HH}$ = 7 Hz), 0.99 (9H, s, *t*–Bu–CH), 1.36 (9H, s, *t*–Bu–C^3), 1.37 (1H, m, CH_AH_B–CH_3, overlapped with *t*–Bu–C^3), 1.87 (1H, ddt, CH_AH_B–CH_3, J_{AB} = 15 Hz, $^3J_{HH}$ = 10 Hz, $^3J_{HH}$ = 7 Hz), 4.53 (1H, dt, CH–NH, $^3J_{HH}$ = 10 Hz, $^3J_{HH}$ = 3 Hz), 7.14 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −56.0 (3F, d, CF_3, $^4J_{FF}$ = 30 Hz), −82.7 (1F, q, C^2F, $^4J_{FF}$ = 30 Hz). MS, *m/z* (rel. int.): 328.4 $[M + H]^+$ (37%). Anal. calculated for $C_{15}H_{25}F_4NS$: C, 55.02; H, 7.70; N, 4.28; S, 9.79. Found: C, 55.08; H, 7.74; N, 4.25; S, 9.77.

*4.4.6. (2Z,6E)-3-tert-Butyl-N-(2,2-dimethylpropyl)-2,4,4,5,5,6,7-heptafluoro-8,8-dimethylnona-2,6-dienethioamide (**22**)*

Yield 0.32 g (69%), white needles, eluent hexane–ethyl acetate 4:1, mp 117–122 °C (from petroleum ether). ^1H NMR ($CDCl_3$): δ, 1.03 (9H, s, *t–Bu*–CH_2), 1.26 (9H, t, *t–Bu*–CF, $^4J_{HF}$ = 2 Hz), 1.33 (9H, s, *t–Bu*–C^3), 3.51 (2H, dd, CH_2NH, $^2J_{HH}$ = 6 Hz, $^3J_{HH}$ = 2 Hz), 7.32 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −76.1 (1F, quintet, C^2F, $^4J_{FF}$ = 27 Hz), −99.8 (2F, d, C^4F_2, $^4J_{FF}$ = 27 Hz), −113.3 (2F, dt, C^5F_2, $^3J_{FF}$ = 28 Hz, $^4J_{FF}$ = 12 Hz), −144.7 (1F, dt, C^6F, $^3J_{FF}$ = 28 Hz, $^3J_{FF(E)}$ = 131 Hz), −168.3 (1F, dd, C^7F, $^3J_{FF(E)}$ = 131 Hz, $^4J_{FF}$ = 12 Hz). ^{13}C NMR ($CDCl_3$): δ, 26.9 (s, $(CH_3)_3C$–CH_2), 27.5 (s, $(CH_3)_3C$–C^3), 30.5 (s, $(CH_3)_3C$–C^7), 31.8 (s, $(CH_3)_3C$–CH_2), 34.3 (s, $(CH_3)_3C$–C^3), 35.6 (d, $(CH_3)_3C$–C^7, $^2J_{CF}$ = 17 Hz), 56.6 (s, CH_2), 115.1 (tm, C^5F_2, J_{CF} = 266 Hz), 117.1 (dt, C^3, $^2J_{CF}$ = 20 Hz, $^2J_{CF}$ = 25 Hz), 118 (tm, C^4F_2, J_{CF} = 264 Hz), 138.9 (dt, C^6F, J_{CF} = 272 Hz, $^2J_{CF}$ = 27 Hz), 156.2 (dt, C^2F, J_{CF} = 268 Hz, $^3J_{CF}$ = 7 Hz), 161.8 (dd, C^7F, J_{CF} = 259 Hz, $^2J_{CF}$ = 39 Hz), 191.1 (d, C=S, $^2J_{CF}$ = 31 Hz). MS, *m/z* (rel. int.): 450.0 $[M + H]^+$ (52%). Anal. calculated for $C_{20}H_{30}F_7NS$: C, 53.44; H, 6.73; N, 3.12; S, 7.13. Found: C, 53.43; H, 6.75; N, 3.14; S, 7.10.

*4.4.7. (2Z,4E)-3-tert-Butyl-N-(2,2-dimethylpropyl)-2,4,5-trifluoro-6,6-dimethyl-hepta-2,4-diene-thioamide (**23**)*

Yield 0.21 g (62%), white crystals, mp 33–35 °C (from hexane). ^1H NMR ($CDCl_3$): δ, 1.03 (9H, s, *t–Bu*–CH_2), 1.18 (9H, t, *t–Bu*–CF, $^4J_{HF}$ = 2 Hz), 1.33 (9H, d, *t–Bu*–C^3, $^5J_{HF}$ = 1 Hz), 3.12 (1H, dd, CH_AH_B–NH, J_{AB} = 14 Hz, $^3J_{HH}$ = 4 Hz), 3.65 (1H, dd, CH_AH_B–NH, J_{AB} = 14 Hz, $^3J_{HH}$ = 7 Hz), 6.94 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −109.7 (1F, dd, C^2F, $^4J_{FF}$ = 36 Hz, $^5J_{FF}$ = 12 Hz), −139.5 (1F, dd, C^5F, $^3J_{FF(E)}$ = 137 Hz, $^5J_{FF}$ = 12 Hz), −151.5 (1F, dd, C^4F, $^3J_{FF(E)}$ = 137 Hz, $^4J_{FF}$ = 36 Hz). MS, *m/z* (rel. int.): 350.5 $[M + H]^+$ (22%). Anal. calculated for $C_{18}H_{30}F_3NS$: C, 61.86; H, 8.65; N, 4.01; S, 9.17. Found: C, 61.88; H, 8.67; N, 3.99; S, 9.15.

*4.5. Reaction of thioamide (**12**) with methyllithium*

Methyllithium (6.2 mL of 1.6 M solution in ether, 10 mmol) was added at −90 °C under a nitrogen atmosphere to a stirred solution of thioamide **12** (0.4 g, 1.65 mmol) in diethyl ether (10 mL). The mixture was stirred for 90 min at −90 °C, and was slowly warmed to room temperature and stirred for 5 h. The solution was acidified by trifluoroacetic acid (≈1 mL) until pH ≈ 4 and solvents were removed in vacuum (10–15 mmHg). Compound **19** was obtained as oil by the extraction from the residue with warm hexane (2× 10 mL).

*4.5.1. (2Z)-N-Ethyl-2,4,4,4-tetrafluoro-3-methylbut-2-enethioamide (**19**)*

Yield 0.09 g (30%), oil, ^1H NMR ($CDCl_3$): δ, 1.39 (3H, t, CH_3CH_2, $^3J_{HH}$ = 7 Hz), 2.21 (3H, d, CH_3C^3=), 3.47 (2H, q, CH_3CH_2, $^3J_{HH}$ = 7 Hz), 7.34 (1H, br, NH). ^{19}F NMR ($CDCl_3$): δ, −63.4 (3F, d, CF_3, $^4J_{FF}$ = 23 Hz), −103.7 (1F, q, C^2F, $^4J_{FF}$ = 23 Hz). MS, *m/z* (rel. int.): 215.0 $[M + H]^+$ (45%). Anal. calculated for $C_7H_9F_4NS$: C, 39.07; H, 4.22; N, 6.51; S, 14.90. Found: C, 39.09; H, 4.25; N, 6.48; S, 14.87.

*4.6. X-ray structure determination for (**14**)*

4.6.1. Crystal data

$C_{14}H_{25}F_2N_1S_1$, M 277.41, triclinic, a = 11.692(4), b = 12.855(4), c = 17.726(5) Å, α = 79.87(2), β = 83.88(3), γ = 79.45(2)°, V = 2570.7(14) Å^3, Z = 6 d_c = 1.07 g cm^{-3}, space group $P\bar{1}(N2)$, μ = 17.3 cm^{-1}, $F(0\,0\,0)$ = 900, crystal size ca. 0.25 mm × 0.56 mm × 0.66 mm.

4.6.2. Data collection

All crystallographic measurements were performed at room temperature on a CAD4 Enraf–Nonius diffractometer operating in the ω–2θ scan mode (the scanning rate ratio $\omega/2\theta$ = 1.2). Intensity data were collected with θ_{max} = 65° ($0 \le h \le 13$, $-14 \le k \le 14$, $-19 \le l \le 19$) using Cu Kα radiation

($\lambda = 1.54178$ Å). During the data collection the crystal has decomposed, decay correction was applied. Intensities of 8915 reflections (8446 unique reflections, $R_{int} = 0.024$) were measured. Data were corrected for Lorenz and polarization effects and an empirical absorption correction based on azimuthal scan data [15] was applied.

4.6.3. Structure solution and refinement

The structure was solved by direct methods and refined by full-matrix least-square technique in the anisotropic approximation for non-hydrogen atoms using CRYSTALS program package [16]. In the refinement 3542 reflections with $I \geq 4(I)$ were used. Over 70% of the hydrogen atoms were located in the difference Fourier maps. Remaining hydrogen atoms were placed in calculated positions. All hydrogen atoms were included in the final refinement with the fixed positional and thermal parameters. Convergence was obtained at $R = 0.086$ and $R_w = 0.098$, GOF = 1.019 (487 parameters; observed/variable ratio 7.2; the largest positive and negative peaks in the final difference map are 0.43 and -0.43 e/Å^3). Chebushev weighting scheme [17] with parameters 2.81, 2.05, and 1.92 was used. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 625104. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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