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Oxidation and chlorination reactions of perfluoroketene-N,S-acetals

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ABSTRACT

The paper presents the results of the investigation of oxidation and chlorination reactions of perfluoroketene-N,S-acetals. Oxidation reactions of perfluoroketene-N,S-acetals proved to be dependent on the nature of oxidizing agent and led to the formation of corresponding sulfone in the case of *m*-chloroperbenzoic acid or amides of α-H-perfluoroalkane carboxylic acids in the case of *tert*-butyl hydroperoxide or hydrogen peroxide. Reaction of 1-*tert*-butylsulfanyl-2,3,3,4,4,4-hexafluoro-1-[N-methyl,N-((S)-α-methylbenzyl)amino]-but-1-ene with sulfuryl chloride demonstrated the chlorination of perfluoroketene-N,S-acetals as a new approach in the synthesis of chiral α-chloro perfluoroalkane carboxylic acid amides.

1. Introduction

Perfluoroketene dithioacetals were shown to be a versatile synthons in the synthesis of fluorinated products, especially heterocycles [1]. The main disadvantage of this strategy consists in low availability and expensiveness of fluorinated aldehydes, which are used for the preparation of perfluoroketene dithioacetals [2]. That is why the search for cheaper reagents, offering a favorable alternative to perfluoroketene dithioacetals, is of current interest.

Recently, we have shown that perfluoroketene dithioacetal analogues, such as perfluoroketene-N,S-acetals **2**, can be easily obtained in good yields by the reaction of accessible polyfluoroalkanethioncarboxylic acid N,N-dialkylamides **1** with organolithium reagents [3] (Scheme 1).

The present paper deals with the investigation of perfluoroketene-N,S-acetals **2** chemical properties, as for a new type of fluorinated compounds, which have not been studied before. We focused our work on N,S-acetals containing S-*tert*-butyl group for its unique properties. Starting from classical aspects, such as steric hindrance and stability of the corresponding carbocation, the compounds bearing S-*tert*-butyl group are widely used in synthetic organic chemistry [4].

2. Results and discussion

The methodology based on the substitution of vinylic fluorine atom of perfluoroketene dithioacetals by potassium enolate of acetone is a valuable tool for the synthesis of fluorinated heterocycles [5]. We examined the possibility of the substitution of vinylic fluorine atom of perfluoroketene-N,S-acetals **4a**,**b** by this reagent (Scheme 2). However, we have found that N,S-acetals **4a**,**b** did not react with potassium enolate of acetone using the same conditions as for perfluoroketene dithioacetals (at 0 °C) [5] or under reflux in THF (Scheme 2).

The mobility of vinylic fluorine atom can be reinforced by the increase of electron-withdrawing property of the substituents at the carbon atoms of the C=C bond. In our case, this possibility appears by sulfur atom oxidation into powerful electron-withdrawing sulfonyl group.

For this purpose we have studied reactions of N,S-acetals **4a**,**b** with different oxidizers. To the best of our knowledge, oxidation reactions of fluorinated N,S-acetals were not described in the literature. In non-fluorinated series only one example of N,S-acetal oxidation has been reported so far [6]. Lead tetraacetate was used as oxidizing agent but this reaction proceeds without changes of sulfur oxidation state.

We have found that the nature of the oxidizer strongly influences the oxidation reaction of **4a**,**b**. Thus, vinylsulfone **5** was obtained as a mixture of two geometric isomers (the ratio is 3:1 according to ^{19}F NMR) by simple treatment of perfluoroketene-N,S-acetal **4a** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature (Scheme 3).

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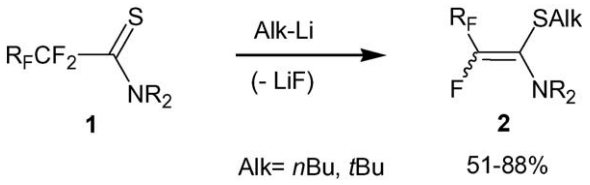
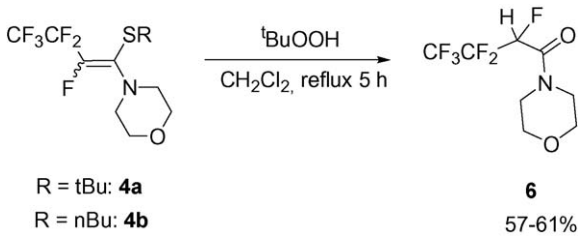


Scheme 1.



Scheme 4.

Unfortunately, sulfone **5** did not react with potassium ketone enolate, the starting material was recovered quantitatively. Probably, electron-donating influence of N,N-dialkylamino group prevents the nucleophilic attack on the sp^2 carbon atom bonded to fluorine.

The reactions of perfluoroketene-N,S-acetals with well-known and widely used oxidizers such as hydrogen peroxide and *tert*-butyl hydroperoxide led to the desulfurization products. Treatment of N,S-acetals **4a**,**b** with *tert*-butyl hydroperoxide (98%) in dichloromethane under reflux gave amide **6** in moderate yields (Scheme 4).

Reaction of N,S-acetal **4a** with hydrogen peroxide (30% aq.) proceeded less cleanly. Nevertheless, it also led to the formation of amide **6**, which was identified in the reaction mixture by means of ^{19}F NMR.

The mechanism of such transformations is not clear yet. It may be supposed that amide **6** results from the intermediately formed sulfone **5** under the action of *tert*-butyl hydroperoxide. But independent experiment has shown that sulfone **5** did not undergo transformations during several hours of reflux in dichloromethane in the presence of *tert*-butyl hydroperoxide.

We have found that sulfone **5** was transformed into amide **6** only under harder conditions: by the reaction with concentrated hydrochloric acid in boiling dioxane (Scheme 5).

In this case the first step of the reaction could be the protonation of nitrogen atom of **5** leading to intermediates **7** and **8**. It is known that protonation of enamine proceeds at the nitrogen atom with the following transfer of the proton to carbon [7,8]. Subsequent addition of water to intermediate **8** accompanied with elimination of *tert*-butylsulfinic acid from **9** gave amide **6**.

In opposite to sulfone **5**, treatment of perfluoroketene-N,S-acetal **4a** with concentrated hydrochloric acid in dioxane afforded α-hydroperfluoroalkylthioamide **10** (Scheme 6). This fact is in striking contrast with the results of the perfluoroketene-S,S-acetals acidic hydrolysis leading to the formation of thioesters **13** [2].

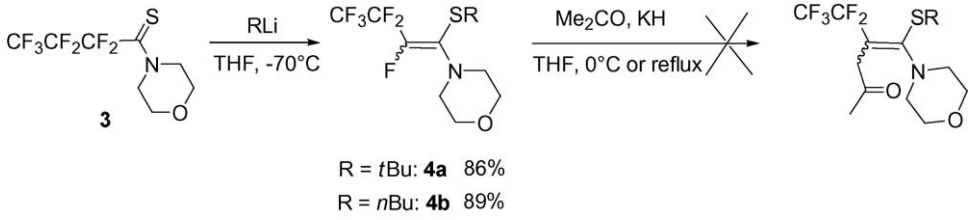
It should be noted that to the best of our knowledge there is only one example of non-fluorinated ketene-N,S-acetals acidic hydrolysis leading to the formation of corresponding thioesters [9].

The compound **6** contains asymmetric carbon atom and it was interesting to check the application of chiral induction concept in order to obtain optically active hexafluorobutyric acid derivatives. For this purpose, a chiral center should be presented in the starting molecule of N,S-acetal, which can influence the stereochemistry of the oxidation reaction with *tert*-butyl hydroperoxide. Thus, we have used chiral amine **14** [10] for the preparation of perfluoroketene-N,S-acetal **17** (Scheme 7).

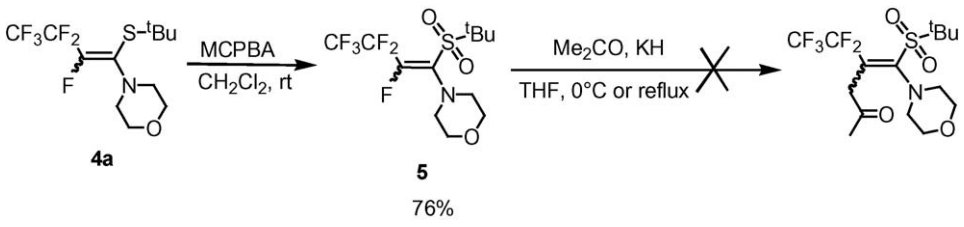
Reaction of **17** with *tert*-butyl hydroperoxide resulted in the formation of amide **18** which was obtained as a mixture of diastereomers (the ratio is 2:1 according to ^1H NMR, d.e. = 33%) in 43% yield after purification on silica gel (Scheme 8). Diastereomers of **18** were not separated by column chromatography.

In order to obtain optically active 2,3,3,4,4,4-hexafluorobutyric acid **20**, we carried out acidic hydrolysis of amide **18** using concentrated (98%) sulfuric acid (1 h at 100 °C). However, instead of the desired acid, we obtained amide **19** resulted from the cleavage of α-(methyl)benzyl group (Scheme 9). Obviously, this reaction proceeded in the same way as acid catalyzed debenzylation of amides [11]. At this stage we observed the complete racemization of the amide **19**.

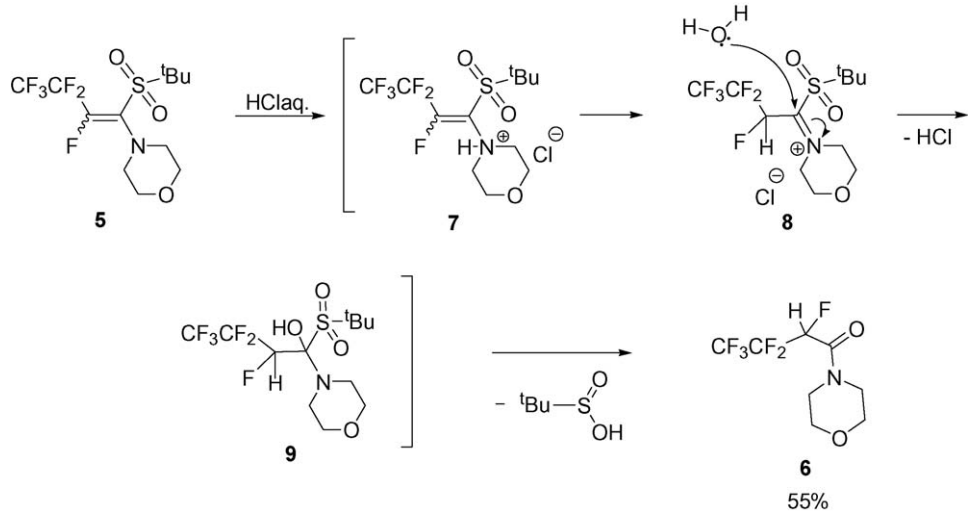
Another approach to the synthesis of chiral polyfluoroalkane carboxylic acid derivatives was based on our results of the perfluoroketene-N,S-acetals chlorination. We have found that treatment of N,S-acetal **4a** with sulfuryl chloride in dichloromethane led to the formation of α-chloroamide **24** in 36% yield (Scheme 10). The formation of compound **24** could be explained by



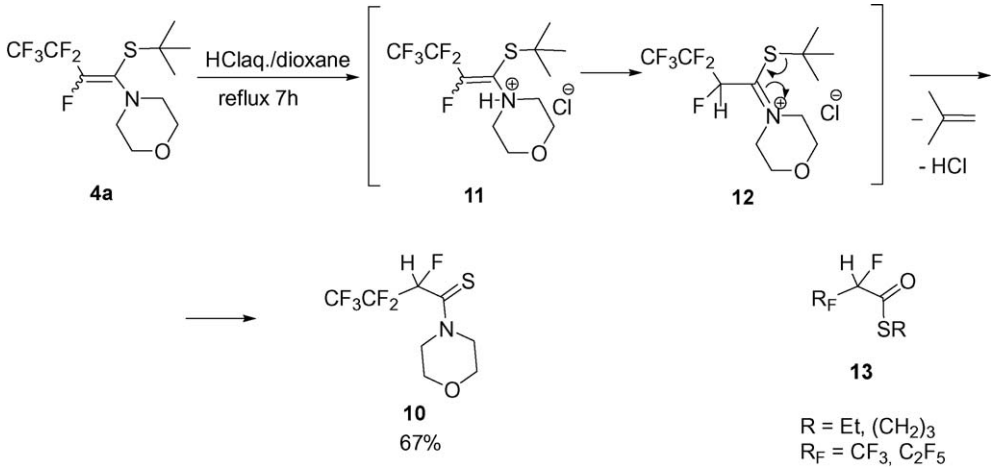
Scheme 2.



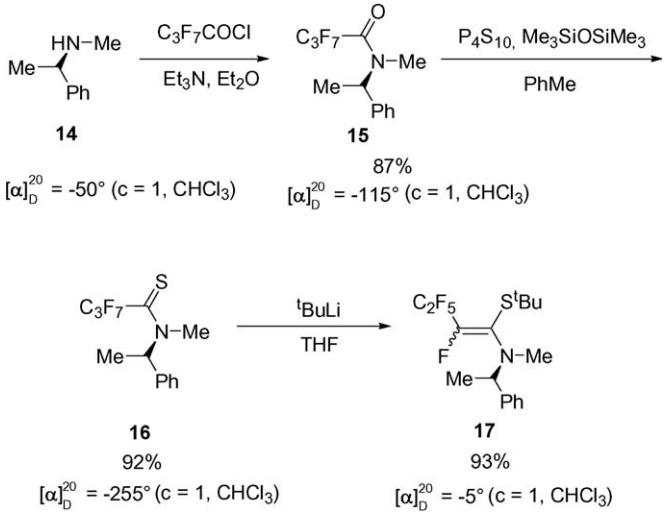
Scheme 3.



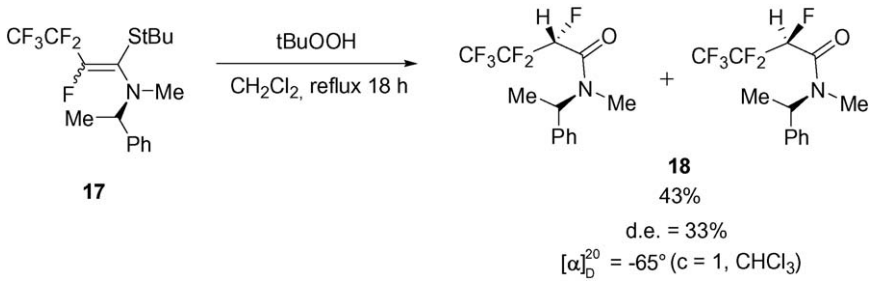
Scheme 5.



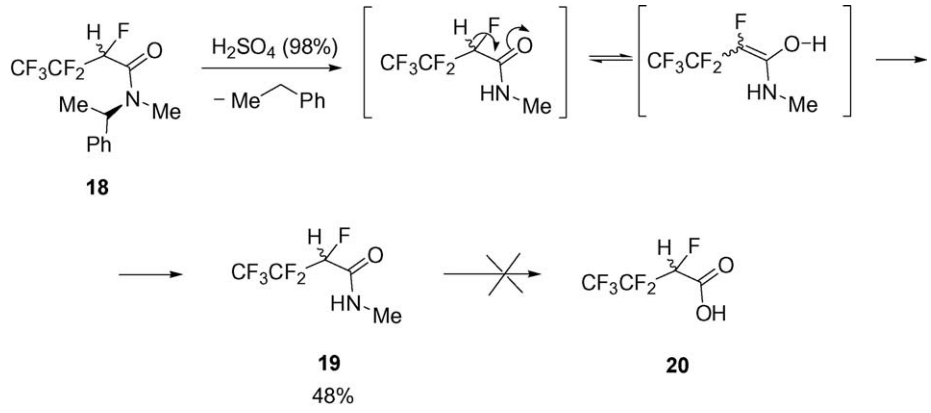
Scheme 6.



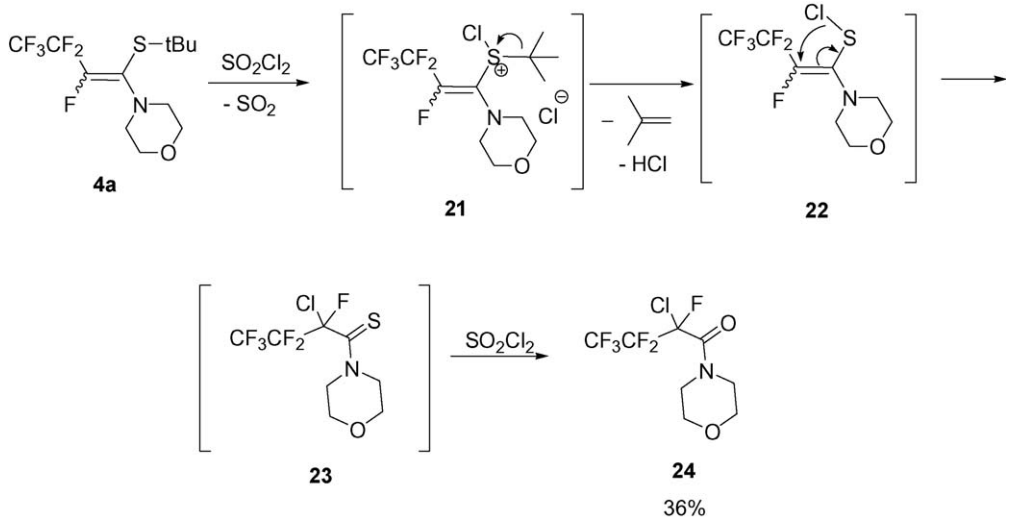
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

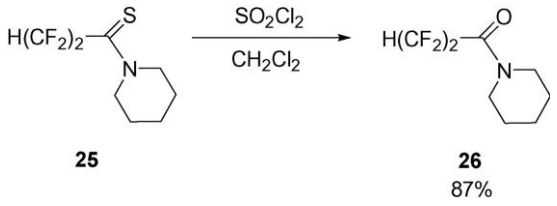
the initial attack of sulfuryl chloride on sulfur atom of N,S-acetal **4a** with the formation of S-chlorosulfonium ion **21** (Scheme 10). Then, fragmentation of **21** took place giving sulfenyl chloride **22**. This process was facilitated by the release of isobutylene.

In order to enforce our proposed mechanism, three published experimental results have to be taken into account. Firstly, it was reported that chlorination of 2-cyano-1,3,3,3-tetrafluoro-1-(*tert*-butylsulfanyl)propene proceeded in a similar way giving corresponding sulfenyl chloride which was a useful precursor of thiazole derivative [12].

Secondly, α-chloroamide **24** was obtained by 1,3-migration of chlorine atom from sulfur of **22** to C_β atom via intermediate **23** (Scheme 10). This chlorotropy phenomenon in the triad C–C–S was already described in the literature for perfluoro-2-methyl-2-pent-3-ensulfenylchloride [13].

Finally, thioamide **23** was oxidized with sulfuryl chloride to amide **24** (Scheme 10). Oxidative property of sulfuryl chloride was already exemplified by oxidation of sulfides to sulfoxides [14]. Nevertheless, to confirm our hypothesis, we performed quantitative oxidation of thioamide **25** to amide **26** using sulfuryl chloride in dichloromethane at room temperature (Scheme 11).

Reaction of perfluoroketene-N,S-acetal **17**, which contains one asymmetric center, with sulfuryl chloride did not lead to the formation of the diastereomers of amide **27**. From the reaction



Scheme 11.

mixture, the N-methylamide **28** was isolated in 32% yield (Scheme 12). 1-Chloro-1-phenylethane was detected by GC–MS in the crude mixture.

Compound **28** proved to be optically active in accordance with $[\alpha]_D^{20} = +2^\circ$ (c = 0.75, $CHCl_3$) measurements. A 50% enantiomeric excess was determined by means of ^{19}F NMR experiments using lanthanoid shift reagent, such as europium tris[3-(heptafluoropropylhydrohymethylene) (+)-camphorate], on the basis of relative intensity measurement of two parts of AB-system of CF_2 group signals of at −118.3 and −120.2 ppm ($^2J_{FAFB}$ = 276.4 Hz) of major enantiomer and at −117.9 and −124.4 ppm ($^2J_{FAFB}$ = 284.1 Hz) of minor one, respectively (see Section 3). This result let us propose that presence of chiral substituent in ketene-N,S-acetal **17** can induce the chiral induction during the chlorination reaction.

Compound **28** is the first example of optically active α-chloro perfluoroalkane acids derivatives. Obviously, in this case, compound **28** was not formed with a big enantiomeric excess. Further improvements are under investigation.

In conclusion, oxidation, chlorination and nucleophilic substitution reactions of perfluoroketene-N,S-acetals were investigated. Perfluoroketene-N,S-acetal **4a** and its sulfonyl derivative **5** did not react with nucleophiles such as ketone enolates, probably because of electron-donating properties of N,N-dialkylamino group. Oxidation reactions of perfluoroketene-N,S-acetals **4a**,**b** proved to be dependent on the nature of oxidizing agents and lead to the formation of corresponding sulfone in the case of MCPBA or α-H-perfluoroalkane carboxylic acid amides in the case of *tert*-butyl hydroperoxide or hydrogen peroxide. Chlorination of chiral N,S-acetal **17** with sulfuryl chloride demonstrated a new approach to the synthesis of chiral α-chloro perfluoroalkane carboxylic acid derivatives.

3. Experimental

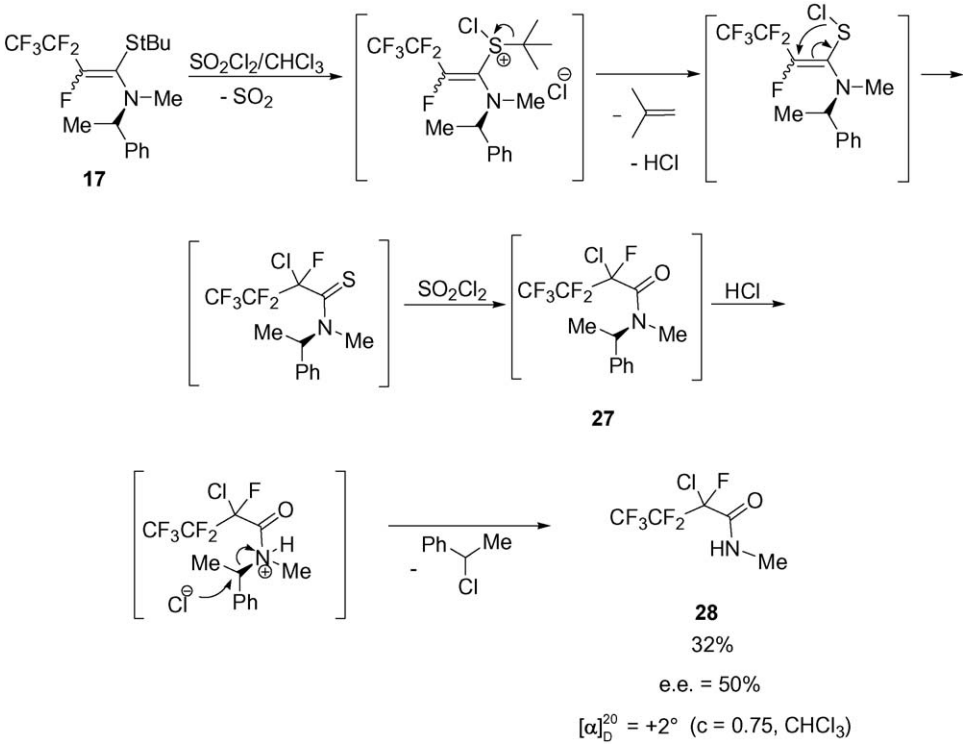
The ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian-VXR-300 instrument at 299.9, 75.4 and 282.2 MHz respectively. Chemical shifts are given in ppm referenced to signals of $CHCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm) for ^1H and ^{13}C NMR spectra and from C_6F_6 (δ_F = −162.9 ppm) as internal standard for ^{19}F NMR spectra. MS data was obtained on ADSI MS, Agilent 1100\DAD\MSD VL G1965 instrument.

Tetrahydrofuran (THF) was dried by distillation over sodium and benzophenone. 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. Preparation of thioamides (3, 16, 25)

The slightly modified method of thioamides synthesis described in Ref. [15] was used.

Phosphorus pentasulfide (11.11 g, 25.00 mmol, 0.6 eq.) was added to a suspension of amide (40.00 mmol, 1.0 eq.) in a solution of hexamethyldisiloxane (HMDSO) (12.99 g, 80.00 mmol, 2.0 eq.) in toluene (100 ml). The reaction mixture was stirred at 80 °C; the reaction was followed by ^{19}F NMR, monitoring the disappearance of starting amide peaks. The mixture was cooled to room



Scheme 12.

temperature. Solid material was filtered off and washed with 50 ml of diethyl ether. Solvents and excess of HMDSO were removed *in vacuo* (10–15 mm Hg) up to 1/2 of volume and residue was diluted with 50 ml of diethyl ether. Organic phase was successively washed with saturated aqueous $NaHCO_3$ solution (4× 50 ml), saturated aqueous NaCl solution (2× 100 ml) and water (2× 100 ml). Aqueous phase was additionally extracted with diethyl ether (2× 100 ml). Combined ethereal extracts were dried over Na_2SO_4 and solvents were removed *in vacuo*. The residue was distilled under reduced pressure.

N-morpholino-2,2,3,3,4,4,4-heptafluorobutanethioamide (**3**). Yield: 80%. Yellow liquid. bp 100–101 °C (10 mm Hg). ^{1}H NMR ($CDCl_3$, δ ppm): 3.7–4.4 (m, 8H, morpholino). ^{19}F NMR ($CDCl_3$, δ ppm): −81.1 (m, 3F, CF_3), −98.7 (m, 2F, CF_2CF_2CS), −124.0 (m, 2F, CF_2CS). Anal. Calcd. for $C_8H_8F_7NOS$: C, 32.1; H, 2.7; N, 4.7; S, 10.7. Found: C, 32.2; H, 2.8; N, 4.7; S, 10.8.

N-methyl-N-((S)-α-methylbenzyl)-2,2,3,3,4,4,4-heptafluorobutanethioamide (**16**). Yield: 92%. Liquid. Mixture of rotamers (the ratio is 2/1 according to ^{19}F NMR). $[\alpha]_D^{20} = -255^\circ$ (c = 1, $CHCl_3$). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.62 (d, $^3J_{H,H}$ = 6.9 Hz, 3H, CH–*Me*), 2.98 (s, 3H, N–Me), 7.10 (q, $^3J_{H,H}$ = 6.9 Hz, 1H, CH–N), 7.2–7.4 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −81.3 (t, $^3J_{F,F}$ = 10.5 Hz, 3F, CF_3), −98.1 (dm, $^2J_{F,F}$ = 269.2 Hz, 1F, $CF_AF_BCF_2CS$), −101.1 (dm, $^2J_{F,F}$ = 269.2 Hz, 1F, $CF_AF_BCF_2CS$), −122.9 (m, 2F, CF_2CS). Selected data for minor isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.72 (d, $^3J_{H,H}$ = 6.9 Hz, 3H, CH–*Me*), 3.08 (s, 3H, N–Me), 5.78 (q, $^3J_{H,H}$ = 6.9 Hz, 1H, CH–N). ^{19}F NMR ($CDCl_3$, δ ppm): −80.9 (t, $^3J_{F,F}$ = 10.5 Hz, 3F, CF_3), −96.9 (dm, $^2J_{F,F}$ = 275.8 Hz, 1F, $CF_AF_BCF_2CS$), −98.9 (dm, $^2J_{F,F}$ = 275.8 Hz, 1F, $CF_AF_BCF_2CS$), −123.1 (m, 2F, CF_2CS). Anal. Calcd. for $C_{13}H_{12}F_7NS$: C, 45.0; H, 3.5; N, 4.0; S, 9.2. Found: C, 44.9; H, 3.6; N, 4.0; S, 9.3.

N-Piperidino-2,2,3,3-tetrafluoropropanethioamide (**25**). Yield: 83%. Yellow liquid. bp 114–116 °C (15 mm Hg). ^{1}H NMR ($CDCl_3$, δ ppm): 1.76 (m, 6H, piperidino), 3.95 (m, 2H, piperidino), 4.16 (m, 2H, piperidino), 6.80 (tt, $^2J_{H,F}$ = 53.4 Hz, $^3J_{H,F}$ = 5.6 Hz, 1H, HCF_2). ^{19}F NMR ($CDCl_3$, δ ppm): −114.6 (m, 2F, CF_2CS), −136.9 (dm, $^2J_{F,H}$ = 53.4 Hz, 2F, HCF_2). Anal. Calcd. for $C_8H_{11}F_4NS$: C, 41.9; H, 4.8; N, 6.1; S, 14.0. Found: C, 42.0; H, 4.9; N, 6.0; S, 14.1.

3.2. Preparation of amide (**15**)

To a solution of heptafluorobutyryl chloride (8.37 g, 36 mmol, 1 eq.) in diethyl ether (40 ml), a solution of (S)-N-methyl-1-phenylethylamine [10] (4.86 g, 36 mmol, 1 eq.) and triethylamine (3.64 g, 36 mmol, 1 eq.) in diethyl ether (40 ml) was added dropwise at −10 °C under argon atmosphere. Reaction mixture was then stirred at −5 °C for 1 h and 1 night at room temperature. The precipitate was filtered off and the filtrate was washed with water (2× 40 ml). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*, giving N-methyl-N-((S)-α-methylbenzyl)-2,2,3,3,4,4,4-heptafluorobutanamide.

N-methyl-N-((S)-α-methylbenzyl)-2,2,3,3,4,4,4-heptafluorobutanamide (**15**). Yield: 87%. Liquid. Mixture of rotamers (the ratio is 2/1 according to ^{19}F NMR). $[\alpha]_D^{20} = -115^\circ$ (c = 1, $CHCl_3$). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.56 (d, $^3J_{H,H}$ = 7.5 Hz, 3H, CH–*Me*), 2.80 (s, 3H, N–Me), 5.99 (q, $^3J_{H,H}$ = 7.5 Hz, 1H, CH–N), 7.2–7.4 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −80.8 (t, $^3J_{F,F}$ = 8.8 Hz, 3F, CF_3), −113.3 (m, 2F, CF_2), −126.3 (m, 2F, CF_2CO). Selected data for minor isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.66 (d, $^3J_{H,H}$ = 6.6 Hz, 3H, CH–*Me*), 2.69 (s, 3H, N–Me), 5.43 (q, $^3J_{H,H}$ = 6.6 Hz, 1H, CH–N). ^{19}F NMR ($CDCl_3$, δ ppm): −80.4 (t, $^3J_{F,F}$ = 8.7 Hz, 3F, CF_3), −115.5 (m, 2F, CF_2), −126.1 (m, 2F, CF_2CO). Anal. Calcd. for $C_{13}H_{12}F_7NO$: C, 47.1; H, 3.7; N, 4.2. Found: C, 47.0; H, 3.8; N, 4.2.

Preparation of starting amides for the synthesis of (**3**) and (**25**) was performed according to the method described in Ref. [16].

3.3. General procedure for the preparation of perfluoroketene-N,S-acetals (**4a,b** and **17**) [3]

t-BuLi (8.40 mmol, 1.2 eq., 1.7 M solution in pentane) or n-BuLi (8.40 mmol, 1.2 eq., 1.6 M solution in hexane) was added dropwise to a solution of corresponding thioamide (7.00 mmol, 1.0 eq.) in THF (20 ml) at −70 °C under argon atmosphere. The reaction mixture was stirred −70 °C for 0.5 h and allowed to warm to room temperature for 5 h. MeOH (2 ml) was added to the reaction mixture. Solvents were removed *in vacuo* at room temperature and petroleum ether (30 ml) was added to the residue. After filtration, the solvent was evaporated *in vacuo* to give the products (**4a**,**b** and **17**).

1-*tert*-Butylsulfanyl-2,3,3,4,4,4-hexafluoro-1-morpholino-but-1-ene (**4a**). Yield: 86%. Oil. Mixture of isomers (the ratio is 2/1 according to ^{19}F NMR). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.41 (s, 9H, t-Bu), 2.81 (m, 4H, 2× NCH_2), 3.70 (m, 4H, 2× OCH_2). ^{19}F NMR ($CDCl_3$, δ ppm): −84.1 (m, 3F, CF_3), −114.5 (m, 2F, CF_2), −124.3 (m, 1F, CF). Selected data for minor isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.36 (s, 9H, t-Bu). ^{19}F NMR ($CDCl_3$, δ ppm): −83.7 (m, 3F, CF_3), −110.1 (m, 2F, CF_2), −133.6 (m, 1F, CF). MS: m/z = 338 [M+1]. Anal. Calcd. for $C_{12}H_{17}F_6NOS$: C, 42.7; H, 5.1; N, 4.2; S, 9.5. Found: C, 42.6; H, 5.3; N, 4.3; S, 9.6.

1-n-Butylsulfanyl-2,3,3,4,4,4-hexafluoro-1-morpholino-but-1-ene (**4b**). Yield: 89%. Oil. Mixture of isomers (the ratio is 6/1 according to ^{19}F NMR). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 0.92 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.50 (m, 4H, $CH_3CH_2CH_2$), 2.83 (t, $^3J_{H,H}$ = 7.2 Hz, 2H, CH_2–S), 2.89 (m, 4H, 2× NCH_2), 3.69 (m, 4H, 2× OCH_2). ^{19}F NMR ($CDCl_3$, δ ppm): δ −84.5 (m, 3F, CF_3), −115.1 (m, 2F, CF_2), −135.4 (m, 1F, CF). Selected data for minor isomer: ^{19}F NMR ($CDCl_3$, δ ppm): −84.7 (m, 3F, CF_3), −110.9 (m, 2F, CF_2), −139.3 (m, 1F, CF). MS: m/z = 338 [M+1]. Anal. Calcd. for $C_{12}H_{17}F_6NOS$: C, 42.7; H, 5.1; N, 4.2; S, 9.5. Found: C, 42.6; H, 5.3; N, 4.1; S, 9.6.

1-*tert*-Butylsulfanyl-2,3,3,4,4,4-hexafluoro-1-[N-methyl,N-((S)-α-methylbenzyl)amino]-but-1-ene (**17**). Yield: 93%. Oil. Mixture of isomers (the ratio is 2.5/1 according to ^{19}F NMR). $[\alpha]_D^{20} = -5^\circ$ (c = 1, $CHCl_3$). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.33 (d, $^3J_{H,H}$ = 6.7 Hz, 3H, CH–*Me*), 1.45 (s, 9H, t-Bu), 2.39 (s, 3H, N–Me), 4.29 (q, $^3J_{H,H}$ = 6.7 Hz, 1H, *CH*–Me), 7.2-7.4 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −83.9 (m, 3F, CF_3), −113.9 (dd, $^2J_{F,F}$ = 284.4 Hz, $^3J_{F,F}$ = 8.9 Hz, 1F, CF_AF_B), −115.2 (dd, $^2J_{F,F}$ = 284.4 Hz, $^3J_{F,F}$ = 8.9 Hz, 1F, CF_AF_B), −127.9 (m, 1F, CF). Selected data for minor isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.38 (s, 9H, t-Bu), 1.55 (d, $^3J_{H,H}$ = 7.2 Hz, 3H, CH–*Me*), 2.68 (s, 3H, N–Me), 5.20 (q, $^3J_{H,H}$ = 7.2 Hz, 1H, *CH*–Me). ^{19}F NMR ($CDCl_3$, δ ppm): −84.4 (m, 3F, CF_3), −109.7 (d, $^2J_{F,F}$ = 274.8 Hz, 1F, CF_AF_B), −122.6 (d, $^2J_{F,F}$ = 274.8 Hz, 1F, CF_AF_B), −130.6 (m, 1F, CF). MS: m/z = 385 [M+1]. Anal. Calcd. for $C_{17}H_{21}F_6NS$: C, 53.0; H, 5.5; N, 3.6; S, 8.3. Found: C, 52.9; H, 5.7; N, 3.7; S, 8.5.

3.4. Oxidation reaction of perfluoroketene-N,S-acetal (**4a**) with MCPBA

To a solution of perfluoroketene-N,S-acetal (**4a**) (2.36 g, 7.00 mmol, 1.0 eq.) in dichloromethane (25 ml), a solution of MCPBA (3.62 g, 21.00 mmol, 3.0 eq.) in dichloromethane (10 ml) was added at room temperature. The mixture was stirred for 4 h at this temperature. The precipitate of *m*-chlorobenzoic acid was filtered off and a half of filtrate was evaporated *in vacuo*. After cooling at 4 °C for 4 h, the new precipitate was again filtered and the filtrate was evaporated *in vacuo*. Finally, the product (**5**) was crystallized from hexane as colorless solid. Analytical sample was obtained after recrystallization from hexane.

1-*tert*-Butylsulfonyl-2,3,3,4,4,4-hexafluoro-1-morpholino-but-1-ene (**5**). Yield: 76%. Solid. mp 78 °C. Mixture of isomers (the ratio is 3/1 according to ^{19}F NMR). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.43 (s, 9H, t-Bu), 2.78 (m, 2H, CH_2 morpholino), 3.5–3.9 (m,

6H, morpholino). ^{19}F NMR ($CDCl_3$, δ ppm): −84.2 (m, 3F, CF_3), −111.8 (m, 1F, CF), −117.3 (m, 2F, CF_2). ^{13}C NMR ($CDCl_3$, δ ppm): 23.9 (s, $(CH_3)_3C$), 51.8 (s, CH_2–N), 63.5 (s, CH_2–O), 66.5 (s, $(CH_3)_3C$–SO_2), 109.3 (m, CF_2), 116.6 (m, CF_3), 136.8 (dm, $^2J_{C,F}$ = 20.1 Hz, *C*=CF), 151.5 (dt, $^1J_{C,F}$ = 285.2 Hz, $^2J_{C,F}$ = 25.5 Hz, CF=). Selected data for minor isomer: ^{19}F NMR ($CDCl_3$, δ ppm): −110.9 (m, 1F, CF), −120.8 (m, 2F, CF_2). MS: *m*/*z* = 370 [M+1]. Anal. Calcd. for $C_{12}H_{17}F_6NO_3S$: C, 39.0; H, 4.6; N, 3.8; S, 8.7. Found: C, 38.9; H, 4.8; N, 4.0; S, 8.8.

3.5. Hydrolysis reaction of perfluoroketene-N,S-acetal (4a)

To a solution of perfluoroketene-N,S-acetal (**4a**) (1.01 g, 3.00 mmol, 1.0 eq.) in dioxane (10 ml) a few drops of concentrated hydrochloric acid was added. The reaction mixture was refluxed for 7 h, and then solvent was evaporated *in vacuo*. The residue was dissolved in chloroform (15 ml) and washed with water (2× 10 ml). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Thioamide (**10**) was obtained as pure compound.

N-morpholino-2,3,3,4,4,4-hexafluorobutanethioamide (**10**). Yield: 67%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 3.7–4.0, 4.2–4.4 (m, 8H, morpholino), 6.24 (ddd, $^2J_{H,F}$ = 47.8 Hz, $^3J_{H,F}$ = 20.7 Hz, $^3J_{H,F}$ = 4.7 Hz, 1H, CHF). ^{19}F NMR ($CDCl_3$, δ ppm): −83.6 (dd, $^3J_{F,FA}$ = 12.4 Hz, $^3J_{F,FB}$ = 1.5 Hz, 3F, CF_3), −119.3 (dm, $^2J_{F,F}$ = 280.0 Hz, 1F, CF_AF_B), −127.8 (dm, $^2J_{F,F}$ = 280.0 Hz, 1F, CF_AF_B), −180.0 (dm, $^2J_{H,F}$ = 47.8 Hz, 1F, CHF). MS: *m*/*z* = 282 [M+1]. Anal. Calcd. for $C_8H_9F_6NOS$: C, 34.2; H, 3.2; N, 5.0; S, 11.4. Found: C, 34.1; H, 3.4; N, 5.0; S, 11.5.

3.6. Hydrolysis reaction of sulfone (5)

To a solution of sulfone (**5**) (1.11 g, 3.00 mmol, 1.0 eq.) in dioxane (10 ml) few drops of concentrated hydrochloric acid were added. The reaction mixture was refluxed for 7 h. Then solvent was evaporated *in vacuo*, the residue was dissolved in chloroform (15 ml) and washed with water (2× 10 ml). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent:mixture (90:10) of petroleum ether and ethyl acetate) to give the amide (**6**).

N-morpholino-2,3,3,4,4,4-hexafluorobutaneamide (**6**). Yield: 55%. Oil. ^{1}H NMR ($CDCl_3$, δ ppm): 5.54 (ddd, $^2J_{H,F}$ = 46.5 Hz, $^3J_{H,F}$ = 18.6 Hz, $^3J_{H,F}$ = 4.8 Hz, 1H, CHF), 3.6–3.8 (m, 8H, morpholino). ^{19}F NMR ($CDCl_3$, δ ppm): −83.5 (dd, $^3J_{F,FA}$ = 10.5 Hz, $^3J_{F,FB}$ = 1.5 Hz, 3F, CF_3), −123.7 (dm, $^2J_{F,F}$ = 283.9 Hz, 1F, CF_AF_B), −128.5 (dm, $^2J_{F,F}$ = 283.9 Hz, 1F, CF_AF_B), −200.3 (dm, $^2J_{H,F}$ = 46.5 Hz, 1F, CHF). MS: *m*/*z* = 266 [M+1]. Anal. Calcd. for $C_8H_9F_6NO_2$: C, 36.2; H, 3.4; N, 5.3. Found: C, 36.4; H, 3.5; N, 5.3.

3.7. General procedure for the oxidation reaction of perfluoroketene-N,S-acetals (4a,b and 17) with tert-butyl hydroperoxide

The mixture of perfluoroketene-N,S-acetal (**4a**,**b** or **17**) (0.80 mmol, 1.0 eq.) and *tert*-butyl hydroperoxide (1.60 mmol, 2.0 eq.) in dichloromethane (10 ml) was refluxed for 5 h. After the completion of the reaction (checked by ^{19}F NMR of the crude mixture), the solvent was evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent:mixture (90:10) of petroleum ether and ethyl acetate) to give the corresponding amide (**6** or **18**).

N-morpholino-2,3,3,4,4,4-hexafluorobutaneamide (**6**). Yield: 57% (obtained from **4a**). Yield: 61% (obtained from **4b**).

N-methyl,N-((S)-α-methylbenzyl)-2,3,3,4,4,4-hexafluorobutaneamide (**18**). General procedure was used but the reaction mixture was refluxed for 18 h after addition of 3.0 eq. of *tert*-butyl hydroperoxide. Yield: 43%. Oil. Diastereomeric ratio: ∼2/1 (according to ^{1}H NMR data). $[\alpha]_D^{20} = -65^\circ$ (*c* = 1, $CHCl_3$). Major isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.56 (d, $^3J_{H,H}$ = 7.2 Hz, 3H, CH–*Me*), 2.72 (s, 3H, N–Me), 5.58 (ddd, $^2J_{H,F}$ = 47.6 Hz, $^3J_{H,F}$ = 17.7 Hz, $^3J_{H,F}$ = 4.4 Hz, 1H, CHF), 6.05 (q, $^3J_{H,H}$ = 7.2 Hz, 1H, *CH*–Me), 7.3–7.4 (m, 5H, Ph). ^{19}F NMR ($CDCl_3$, δ ppm): −83.8 (dd, $^3J_{F,FA}$ = 10.2 Hz, $^3J_{F,FB}$ = 1.5 Hz, 3F, CF_3), −123.3 (dm, $^2J_{F,F}$ = 287.6 Hz, 1F, CF_AF_B), −128.6 (dm, $^2J_{F,F}$ = 287.6 Hz, 1F, CF_AF_B), −201.1 (dm, $^2J_{H,F}$ = 47.6 Hz, 1F, CHF). Selected data for minor isomer: ^{1}H NMR ($CDCl_3$, δ ppm): 1.54 (d, $^3J_{H,H}$ = 7.2 Hz, 3H, CH–*Me*), 6.00 (q, $^3J_{H,H}$ = 7.2 Hz, 1H, *CH*–Me). ^{19}F NMR ($CDCl_3$, δ ppm): −83.7 (m, 3F, CF_3), −200.5 (dm, $^2J_{H,F}$ = 47.6 Hz, 1F, CHF). MS: *m*/*z* = 314 [M+1]. Anal. Calcd. for $C_{13}H_{13}F_6NO$: C, 49.9; H, 4.2; N, 4.5. Found: C, 49.8; H, 4.3; N, 4.4.

3.8. Reaction of α-hydroamide (18) with concentrated sulfuric acid

Amide (**18**) (0.78 g, 2.50 mmol, 1 eq.) was dissolved in concentrated (98%) sulfuric acid (5 ml) and the reaction mixture was heated at 100 °C for 1 h. After cooling, it was poured into a mixture of ice and water (10 ml), and then extracted with ether (3× 15 ml). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Amide (**19**) was purified by sublimation *in vacuo* (0.07 mm Hg) at 120 °C.

N-methyl-2,3,3,4,4,4-hexafluorobutaneamide (**19**). Yield: 48%. Solid. mp 64 °C. ^{1}H NMR ($CDCl_3$, δ ppm): 2.94 (s, 3H, NH–*Me*), 5.23 (ddd, $^2J_{H,F}$ = 46.1 Hz, $^3J_{H,F}$ = 16.8 Hz, $^3J_{H,F}$ = 4.8 Hz, 1H, CHF), 7.02 (brs, 1H, NH). ^{19}F NMR ($CDCl_3$, δ ppm): −82.9 (dd, $^3J_{F,FA}$ = 12.0 Hz, $^3J_{F,FB}$ = 1.5 Hz 3F, CF_3), −122.9 (dm, $^2J_{F,F}$ = 284.3 Hz, 1F, CF_AF_B), −127.7 (dm, $^2J_{F,F}$ = 284.3 Hz, 1F, CF_AF_B), −205.8 (dm, $^2J_{H,F}$ = 46.1 Hz, 1F, CHF). MS: *m*/*z* = 210 [M+1]. Anal. Calcd. for $C_5H_5F_6NO$: C, 28.7; H, 2.4; N, 6.7. Found: C, 28.8; H, 2.5; N, 6.6.

3.9. General procedure for the chlorination reaction of perfluoroketene-N,S-acetals (4a, 17) with sulfuryl chloride

Mixture of perfluoroketene-N,S-acetal (**4a** or **17**) (2.50 mmol, 1.0 eq.) and sulfuryl chloride (5.00 mmol, 2.0 eq.) in dichloromethane (10 ml) (for **4a**) or in chloroform (10 ml) (for **17**) was stirred 16 h at room temperature (for **4a**) or was heated at 50 °C for 30 min (for **17**). After the completion of the reaction (checked by ^{19}F NMR of the crude mixture), the solvent was evaporated *in vacuo* and the crude product was purified by fractional distillation to give the desired amide (**24** or **28**).

N-morpholino-2-chloro-2,3,3,4,4,4-hexafluorobutaneamide (**24**). Yield: 36%. Liquid. bp 65 °C/ 0.07 mm Hg. ^{1}H NMR ($CDCl_3$, δ ppm): 3.6–4.0 (m, 8H, morpholino). ^{19}F NMR ($CDCl_3$, δ ppm): −77.6 (dd, $^3J_{F,FA}$ = 11.3 Hz, $^3J_{F,FB}$ = 1.5 Hz, 3F, CF_3), −116.9 (dm, $^2J_{F,F}$ = 276.6 Hz, 1F, CF_AF_B), −127.7 (dm, $^2J_{F,F}$ = 276.6 Hz, 1F, CF_AF_B), −126.9 (m, 1F, CFCl). ^{13}C NMR ($CDCl_3$, 50 °C, δ ppm): 43.7 (s, NCH_2), 66.7 (s, OCH_2), 101.9 (dt, $^1J_{C,F}$ = 272.8 Hz, $^2J_{C,F}$ = 27.3 Hz, CFCl), 109.8 (m, CF_2), 118.6 (qt, $^1J_{C,F}$ = 288.1 Hz, $^2J_{C,F}$ = 34.7 Hz, CF_3), 158.7 (d, $^2J_{C,F}$ = 21.5 Hz, CO). MS: *m*/*z* = 302 [M+1], 300 [M+1]. Anal. Calcd. for $C_8H_8ClF_6NO_2$: C, 32.1; H, 2.7; Cl, 11.8; N, 4.7. Found: C, 32.0; H, 2.8; Cl, 12.0; N, 4.5.

N-methyl-2-chloro-2,3,3,4,4,4-hexafluorobutaneamide (**28**). Yield: 32%. Liquid. bp 120 °C. $[\alpha]_D^{20} = +2^\circ$ (*c* = 0.75, $CHCl_3$), e.e. = 50%. ^{1}H NMR ($CDCl_3$, δ ppm): 3.46 (s, 3H, NH–*Me*). ^{19}F NMR ($CDCl_3$, δ ppm): −79.3 (dd, $^3J_{F,FA}$ = 14.5 Hz, $^3J_{F,FB}$ = 1.5 Hz, 3F, CF_3), −118.3 (dm, $^2J_{F,F}$ = 274.7 Hz, 1F, CF_AF_B), −120.2 (dm, $^2J_{F,F}$ = 274.7 Hz, 1F, CF_AF_B), −121.0 (m, 1F, CFCl). Selected ^{19}F NMR spectrum data of the mixture of compound **28** with europium tris[3-(heptafluoropropylhydrohymethylene) (+)-camphorate]. Major enantiomer:

−118.3 (dm, $^2J_{F,F}$ = 276.4 Hz, 1F, CF_AF_B), −120.2 (dm, $^2J_{F,F}$ = 276.4 Hz, 1F, CF_AF_B). Minor enantiomer: −117.9 (dm, $^2J_{F,F}$ = 284.1 Hz, 1F, CF_AF_B), −124.4 (dm, $^2J_{F,F}$ = 284.1 Hz, 1F, CF_AF_B).

^{13}C NMR ($CDCl_3$, δ ppm): 29.6 (s, NH–*Me*), 102.2 (dt, $^1J_{C,F}$ = 260.2 Hz, $^2J_{C,F}$ = 27.7 Hz, CFCl), 109.5 (m, CF_2), 117.9 (qt, $^1J_{C,F}$ = 286.9 Hz, $^2J_{C,F}$ = 34.4 Hz, CF_3), 161.4 (d, $^2J_{C,F}$ = 21.5 Hz, CO). MS: m/z = 246 [M+1], 244 [M+1]. Anal. Calcd. for $C_5H_4ClF_6NO$: C, 24.7; H, 1.7; Cl, 14.6; N, 5.8. Found C, 24.5; H, 1.8; Cl, 14.7; N 5.9.

3.10. Reaction of thioamide (25) with sulfuryl chloride

Mixture of thioamide (**25**) (2.30 g, 10.00 mmol, 1.0 eq.) and sulfuryl chloride (2.70 g, 20.00 mmol, 2.0 eq.) in dichloromethane (50 ml) was stirred 16 h at room temperature. After the completion of the reaction (checked by ^{19}F NMR of the crude mixture), the solvent was evaporated *in vacuo* and the crude product was purified by fractional distillation to give amide (**26**).

N-piperidino-2,2,3,3-tetrafluoropropanamide (**26**). Yield: 87%. Yellow liquid. bp 33–34 °C (0.05 mm Hg). ^1H NMR ($CDCl_3$, δ ppm): 1.68 (m, 6H, piperidino), 3.60 (m, 4H, piperidino), 6.29 (tt, $^2J_{H,F}$ = 52.2 Hz, $^3J_{H,F}$ = 6.0 Hz, 1H, HCF_2). ^{19}F NMR ($CDCl_3$, δ ppm): −119.9 (m, 2F, CF_2CS), −136.9 (dm, $^2J_{F,H}$ = 52.2 Hz, 2F, HCF_2). Anal. Calcd. for $C_8H_{11}F_4NO$: C, 45.1; H, 5.2; N, 6.6. Found: C, 45.0; H, 5.3; N, 6.6.

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