Tetrahedron 69 (2013) 1322–1336

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Hetero-Diels–Alder reactions of perfluoroalkyl thioamides with electron-rich 1,3-dienes: synthesis of new 2-aminosubstituted-3,6-dihydro-2*H*-thiopyrans and related compounds

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ARTICLE INFO

Article history:
Received 24 September 2012
Received in revised form 23 November 2012
Accepted 26 November 2012
Available online 5 December 2012

Dedicated to Professor Charles Portella (Université de Reims Champagne Ardenne, France) for his retirement

Keywords:
Fluorine
Sulfur
Heterocycle
2*H*-Thiopyran
1,3-Thiazolidin-4-one
Thioamide
Hetero-Diels–Alder reaction
Microwave

ABSTRACT

Hetero-Diels–Alder reactions of perfluoroalkyl thioamides with electron-rich 1,3-dienes such as 2,3-dimethylbutadiene, isoprene or penta-1,3-diene gave a simple and efficient access to new 2-aminosubstituted-3,6-dihydro-2*H*-thiopyrans. Three different procedures were used depending on the nature of the polyfluoroalkyl chains (R_F=CF_3, $(CF_2)_nCF_3$, $(CF_2)_4H$) and on the nitrogen substituents of the thioamides (R^1, R^2=H, *p*-Tol, morpholino, Ac). Moreover, cycloadditions of silyloxydienes (1- or 2-trimethylsilyloxy-1,3-butadiene and Danishefsky's diene) with *N*-acyl,*N*-tolyl trifluoromethylthioamides afforded in almost all cases the corresponding 3,6-dihydro-2*H*-thiopyrans or 3-oxo-tetrahydrothiopyrans. For non-symmetrical 1,3-dienes, the regio- and stereochemistry of the reactions were studied (especially using X-ray diffraction analysis) indicating a strong similarity with those reported for fluorinated thiocarboxyl derivatives. Finally, two silylated 3,6-dihydro-2*H*-thiopyrans underwent an unexpected base-induced ring contraction to give new 1,3-thiazolidin-4-ones.

1. Introduction

Thiocarbonyl derivatives are well known for their practical and synthetic applications in reactions with electrophiles or nucleophiles, cyclizations, and cycloadditions.[1] Certain derivatives bearing an electron-withdrawing group are especially useful in hetero-Diels–Alder reactions.[2] Among them, polyfluorinated thiocarbonyl and thiocarboxyl derivatives are efficient electron-poor dienophiles. Indeed, addition of perfluoroalkyl substituents to a thiocarbonyl group substantially raises its dienophilic character allowing reactions with electron-rich 1,3-dienes in order to synthesize fluorine-containing thiopyrans.[3] In this introduction, we will focus only on hetero-Diels–Alder reactions of polyfluorinated thiocarbonyl and thiocarboxyl derivatives, respectively.

The two main fluorinated thiocarbonyl derivatives are trifluorothioacetaldehyde and hexafluorothioketone. The first one is a very unstable compound, which spontaneously polymerizes even at low temperature, but, which is a very active heterodienophile.[4] It is worth noting that perfluoroalkyl analogs (C_4F_9, $(CF_2)_4H$)[5] are slightly more stable and efficient in hetero-Diels–Alder reactions. Hexafluorothioacetone or its stable dimeric form reacts with electron-rich 1,3-dienes such as substituted 1,3-butadienes, anthracene or furan.[6a–c] Other polyfluorinated thioketones were found to have similar properties.[6d]

Polyfluorinated thiocarboxyl derivatives belong to a large family of compounds: thioacyl halides (chloride or fluoride),[6b,7] thionoesters,[8] dithioesters,[9] and thioamides. All of those compounds (except the latter) behave as active heterodienophiles with electron-rich acyclic or cyclic 1,3-dienes giving fluorinated thiopyran derivatives.

Our interest in this field began in connection with the preparation of polyfluorodithioesters and their hetero-Diels–Alder reactions.[9] Although their syntheses required strong conditions or

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http://dx.doi.org/10.1016/j.tet.2012.11.086

expensive reagents, these dithioesters were stable compounds, easy handled, and very efficient heterodienophiles at room temperature affording good to excellent yields of cycloadducts. On the contrary, thioamides and polyfluorinated analogs were easily prepared by thionation of the corresponding amides[10] but there were only few examples of their [4+2] cycloaddition reactions with 1,3-dienes. On the one hand, *N*,*N*-disubstituted thioformamides[11] or cyano analogs[12] react with both electron-poor or electron-rich 1,3-dienes yielding variously substituted dihydrothiopyrans. On the other hand, only one example of a [4+2] cycloaddition of *N*-methyl-*N*-acetyltrifluorothioacetamide was described by H.G. Viehe et al.; this result was explained by the enhancement of the thioamide reactivity due to the introduction of the electron-withdrawing substituent on the nitrogen atom.[13]

The main question of our study was the following: is it possible to perform efficient [4+2] cycloaddition reactions of polyfluoroalkyl-containing thioamides **1** with electron-rich 1,3-dienes in order to obtain new 3,6-dihydro-2*H*-thiopyrans **2** (Scheme 1).

In a recent article, we reported the first examples of hetero-Diels–Alder reactions of perfluoroalkyl thioamides with 2,3-dimethylbutadiene under microwave heating, allowing high conversion and moderate yields of 3,6-dihydro-2*H*-thiopyrans.[14] Those cycloadditions seemed to be dependent on both the nature of the perfluoroalkyl chain and on the substituent attached to the nitrogen atom. In this paper, we present an expanded investigation of hetero-Diels–Alder reactions of trifluoromethyl- or polyfluoroalkylthioamides with various electron-rich 1,3-dienes (acyclic or cyclic, symmetrical or non-symmetrical), as well as the study of their regio- and stereoselectivity.

2. Results and discussion

Our first [4+2] cycloaddition reactions were performed with 2,3-dimethylbuta-1,3-diene (**3**) as a symmetrical model of alkyl-substituted 1,3-dienes in order to find the best conditions. Then, the optimized conditions were extended to symmetrical cyclic diene (cyclohexa-1,3-diene (**4**)) and non-symmetrical dienes such as isoprene (**5**) and penta-1,3-diene (**6**). Finally, the reactivity of silyloxy-1,3-dienes (1-(trimethylsilyloxy)butadiene (**7**) and Danishefsky's diene **8**) was studied.

2.1. Reactions with 2,3-dimethylbuta-1,3-diene (3) and cyclohexa-1,3-diene (4)

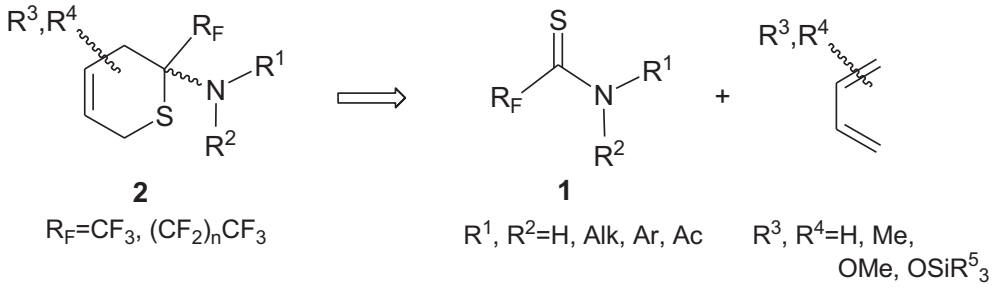
The use of microwave heating has been extensively described in the literature,[15] especially in heterocyclic chemistry[16] and cycloadditions.[17] Rate enhancement, higher yields, and easier handling of reaction mixtures are the main benefits usually mentioned for this technology.[18] Indeed, in our preliminary study,[14] we have shown that thioamides **9** reacted with an excess of 2,3-dimethylbuta-1,3-diene (**3**) in *N*-methylpyrrolidin-2-one (NMP) in a sealed tube under microwave heating at 85–180 °C, in the presence of Weflon™ (Scheme 2, Table 1: Method 1).

The choice of such conditions needs several comments: (a) the reaction was conducted stepwise, adding new portions of 2,3-dimethylbutadiene to the reaction mixture every 30 min in order to diminish diene polymerization. Diene was rapidly introduced via a syringe without opening the vial, avoiding release of chemicals into atmosphere. The overall reaction time was 3 h and the global quantity of 2,3-dimethylbutadiene reached 15–20 equiv; (b) NMP as solvent was justified by its efficiency to transform electromagnetic energy into thermal energy.[19] This polar aprotic solvent allows working up to 200 °C without troublesome vapor and high pressure in the tubes; (c) Weflon™ (Teflon™ filled with graphite) was used in order to better transfer heat to the reaction mixture, thus avoiding 'hot spots'.

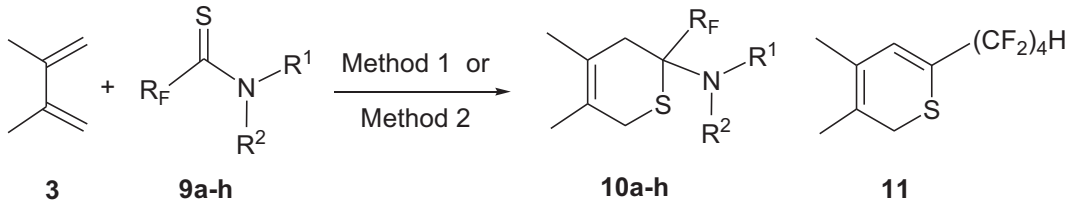
Using the optimized conditions (Method 1), [4+2] cycloadditions of primary (Table 1: entry 1), secondary (entries 2 and 3), and tertiary (entries 6–8) perfluoroalkyl thioamides **9a**–**c**,**f**–**h** with 2,3-dimethylbutadiene (**3**) afforded moderate to good yields (15–49%) of new 3,6-dihydro-2*H*-thiopyrans **10a**–**c**,**f**–**h** (Scheme 2), after purification by silica gel column chromatography. Nevertheless, conversions were not complete, reaching a maximum of 83%. In addition to cycloadducts **10**, polymerization products of diene and other minor non-identified fluorinated by-products appeared in the crude mixture. Moreover, the behavior of cycloadduct **10c** (Table 1: entry 3) bearing an octafluoroalkyl chain was slightly different than the others giving a spontaneous desamination reaction into 2*H*-thiopyran **11** during microwave heating of the reaction mixture (Scheme 2). This process was only observed with $(CF_2)_4H$ perfluoroalkyl chain; the CF_3-analog of **11** was not detected in the crude reaction mixture of thioamide **9b** and 2,3-dimethylbutadiene.

Although new cycloadducts **10a**–**c**,**f**–**h** were obtained in moderate to good yields (Scheme 2, Table 1), Method 1 suffered from several drawbacks namely, only partial conversion of starting thioamides, use of a large excess of diene **3** (15–20 equiv) and a few difficulties for scaling-up the reaction. Therefore, we looked for the possibility to enhance the dienophilic character of the perfluoroalkyl thioamides **9**.

Literature precedent has shown that the reactivity of thioamides can be improved by the addition of an electron-withdrawing substituent on the nitrogen atom. Indeed, α-cyano thioamides[12] react smoothly with 2,3-dimethylbutadiene in dichloromethane solution at room temperature; while *N*-acetyl thioformamide[20] behaves as an efficient dienophile with cyclohexa-1,3-diene or anthracene under titanium tetrachloride activation. These results were explained by the decrease in the electron-donating ability of the nitrogen lone pair. The same type of activation was already used in the fluorinated series regarding the unique example of [4+2] cycloaddition with *N*-methyl-*N*-acetyltrifluorothioacetamide with 2,3-dimethylbutadiene.[13] Therefore, these methods were combined to prepare and use *N*-acetyl and



Scheme 1.



Scheme 2. Reagents and conditions. Method 1: diene (15–20 equiv), NMP, μw 300 W, 85–180 °C, 3 h. Method 2: diene (1.5–2.0 equiv), CH_2Cl_2, rt, 4–24 h.

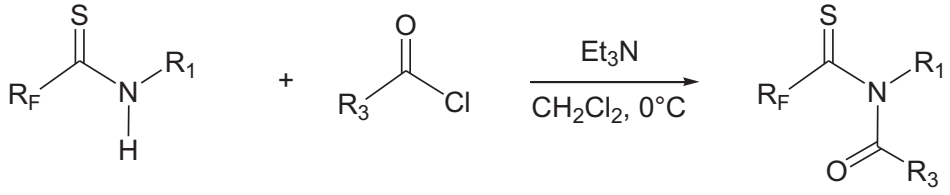
Table 1
Reactions of thioamides **9a**–**h** with 2,3-dimethylbutadiene (**3**)

Entry	Thioamide	R^1	R^2	R_F	Method[a]	*T* (°C)	Conv.[b] (%)	Cycloadduct[c] (%)
1	**9a**	H	H	CF_3	1	85	57	**10a**: 35
2	**9b**	H	*p*-Tol	CF_3	1	125	54	**10b**: 26
3	**9c**	H	*p*-Tol	$(CF_2)_4H$	1	145	50	**10c**: 15[d]
4	**9d**	Ac	*p*-Tol	CF_3	2[e]	25	100	**10d**: 78
5	**9e**	Ac	*p*-Tol	$(CF_2)_4H$	2[f]	25	100	**10e**: 69
6	**9f**	$(CH_2)_2O(CH_2)_2$		CF_3	1	180	83	**10f**: 45
7	**9g**	$(CH_2)_2O(CH_2)_2$		CF_3CF_2	1	180	70	**10g**: 49
8	**9h**	$(CH_2)_2O(CH_2)_2$		$CF_3(CF_2)_2$	1	180	50	**10h**: 28

[a] Method 1: diene (15–20 equiv), NMP, μw 300 W, 85–180 °C, 3 h. Method 2: diene (1.5–2.0 equiv), CH_2Cl_2, rt, 4–24 h.
[b] Conversion was based on ^{19}F NMR spectra of the reaction mixture.
[c] Isolated yields. All pure cycloadducts were obtained by purification by silica gel column chromatography.
[d] Desamination of **10c** into compound **11** took place during heating of the reaction mixture under microwave irradiation.
[e] Reaction time: 4 h.
[f] Reaction time: 24 h.

N-benzoyl polyfluoroalkylthioamides **9d**,**e**,**i**,**k**,**l**. The desired compounds were obtained in almost quantitative yields by usual acylation reactions from the corresponding thioamides **9b**,**c**,**j** in the presence of the appropriate acid chloride and triethylamine at 0 °C (Scheme 3). *N*-Acetyl derivatives **9d**,**e**,**k** are unstable compounds and were used immediately after isolation.

In order to compare the dienophilic character of thioamides **9b**–**e**, molecular orbital calculations were performed at the B3LYP/6-31G** level of theory. The geometries of compounds **9b**–**e** were first optimized and the energies of HOMO, LUMO, and their orbital coefficients were computed using the Gaussian 03[21] package of programs. The corresponding energy values and dihedral angles



9b: R_F=CF_3, R_1=*p*-Tol
9c: R_F=$H(CF_2)_4$, R_1=*p*-Tol
9j: R_F=CF_3, R_1=*n*-Pr

R_F=CF_3, R_1=*p*-Tol, R_3=Me, **9d** (95%)
R_F=$H(CF_2)_4$, R_1=*p*-Tol, R_3=Me, **9e** (97%)
R_F=CF_3, R_1=*p*-Tol, R_3=Ph, **9i** (95%)
R_F=CF_3, R_1=*n*-Pr, R_3=Me, **9k** (94%)
R_F=CF_3, R_1=*p*-Tol, R_3=Et, **9l** (95%)

Scheme 3.

Reactions of *N*-acetyl thioamides **9d**,**e** with 2,3-dimethylbutadiene (**3**) (1.5–2.0 equiv) at room temperature in dichloromethane solution (Table 1: Method 2: entries 4, 5) afforded the corresponding cycloadducts **10d**,**e** in good yields. In comparison to non *N*-acetylated thioamides **10b**,**c** (entries 2, 3), there was full conversion of starting material and significant yield improvement (from 26% to 78%, from 15% to 69%, respectively). Moreover, Method 2 had several advantages: the use of only a slight excess of diene (1.5–2.0 equiv), which greatly facilitated work-up and silica gel column chromatography; and a reaction at room temperature, which avoided partial desamination.

between the phenyl ring and the thioamide moiety are collected in Table 2. Diels–Alder reactions are under orbital control and since the 1,3-diene is electron-rich and the dienophiles electron-poor, the preceding reactions are under normal control: therefore, their reactivity was related to the energy gap between the HOMO of the diene and the LUMO of the dienophile: 'the lower the gap, the easier the reaction'. Therefore, the presence of the *N*-acetyl electron-withdrawing group increases the reactivity of **9d**,**e**. Moreover, whereas molecules **9b** and **9c** are quite planar (Figs. 1 and 2 and Table 2: entries 1 and 2), the introduction of an acetyl group into molecules **9d** and **9e** also forces the thioamide to be out

Table 2
HOMO, LUMO energy values and dihedral angles of thioamides **9b**–**e**

Entry	Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	Dihedral angle (°)
1	**9b**	−6.18	−1.94	0.41
2	**9c**	−6.18	−2.01	0.40
3	**9d**	−6.31	−2.45	68.19
4	**9e**	−6.36	−2.51	67.52

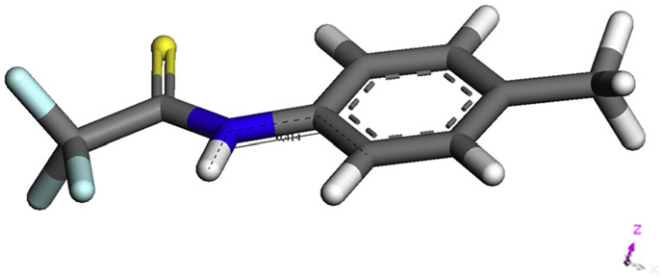


Fig. 1. Optimized geometry of compound **9b**.

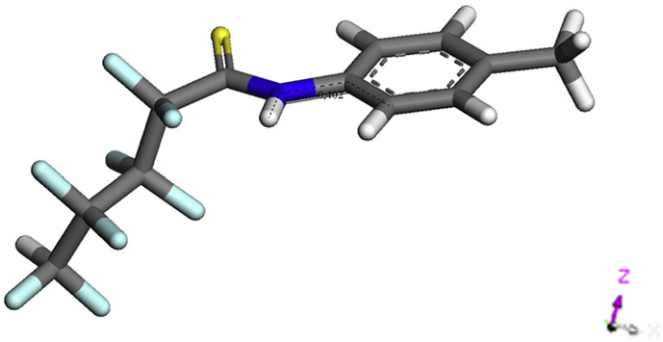


Fig. 2. Optimized geometry of compound **9c**.

of the plane of the phenyl ring (Figs. 3 and 4 and Table 2: entries 3 and 4). The corresponding lack of conjugation between the phenyl ring and the thioamide leads to a significant lowering of the LUMO energies, explaining probably the reactivity differences of molecules **9b**,**c** compared to the corresponding *N*-acetylated compounds **9d**,**e**.

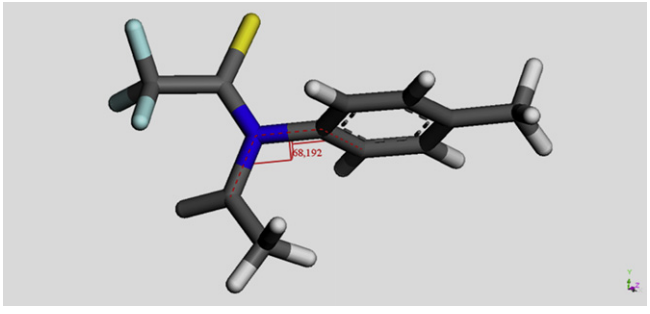


Fig. 3. Optimized geometry of compound **9d**.

The next step was to extend our methodology to symmetrical cyclic 1,3-diene choosing cyclohexa-1,3-diene (**4**) as a model. Applying Method 1, no conversion of the starting material was observed in reaction of thioamide **9b** or thiomorpholide **9f**. On the contrary, *N*-acetyl thioamide **9d** was successfully converted (Method 2, yield: 58%) into bicyclic compound **12** as a mixture of (0.3:1) *exo*/*endo* isomers (Scheme 4).

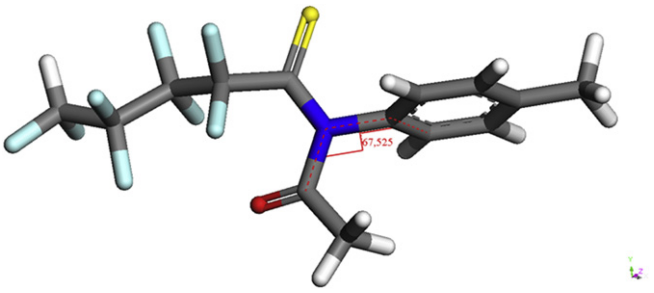


Fig. 4. Optimized geometry of compound **9e**.

There are few examples in the literature in which cyclohexa-1,3-diene reacts with non-symmetrical polyfluoroalkyl thiocarbonyl derivatives;[7,9d,22] and in most cases, the stereochemistry was not discussed in detail. The outcome of this reaction for non-fluorinated thioaldehydes has been more thoroughly studied, showing *endo* selectivity during cycloadduct formation.[23] In our case, we could also reasonably assume that major isomer had an *endo* configuration.

2.2. Reactions with isoprene (5) and penta-1,3-diene (6)

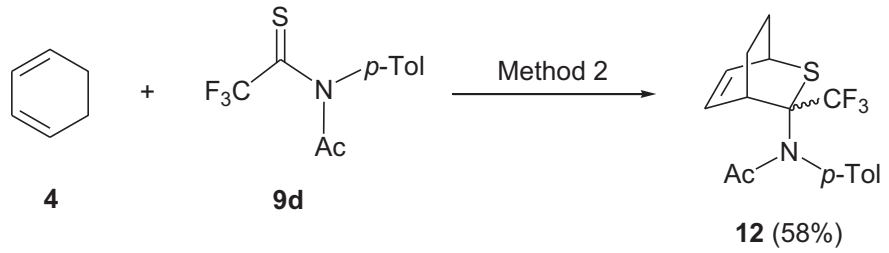
We then turned our attention on the study of regio- and stereochemistry of our [4+2] cycloaddition reactions using non-symmetrical alkyl-substituted 1,3-dienes. It has been shown in the literature that [4+2] cycloadditions of perfluoroalkyl thiocarbonyl derivatives with isoprene give a mixture of regioisomers in equal ratio[5a] or with a slight excess of one isomer.[9d] No reaction has been described however using penta-1,3-diene in the fluorinated series, but one could expect the formation of both regio- and stereoisomers. Indeed, thioacetaldehyde reacts with penta-1,3-diene affording a mixture (77:23) of two regioisomers.[23a]

*2.2.1. Reactions with isoprene (**5**).* In the presence of isoprene (**5**), thioamides **9** were expected to give a mixture of two regioisomers. When applying Methods 1 and 2, the same behavior described for the reactions with 2,3-dimethylbutadiene was observed. With thioamide **9f** (R^1, R^2=$(CH_2)_2O(CH_2)_2$), use of Method 1 led to a 19% yield of cycloadducts **13a**, **14a** as a mixture (52:48) of regioisomers (Scheme 5). Reactions with *N*-acetyl- and *N*-benzoyl thioamides **9d**, **9i** proceeded smoothly with isoprene at room temperature affording good yields (76% and 67%, respectively) of the corresponding cycloadducts **13b**,**c** and **14b**,**c** as non-separable mixtures of regioisomers. Reaction with *N*-benzoyl thioamide **9i** was very slow (almost total conversion after 60 d). It is worth noting that regioisomers **13b**,**c** were greatly favored (85:15 mixture). This regioselectivity, although better, was still the same as previously observed for difluorophosphono dithioesters (60:40 mixture of regioisomers)[9d] or for thiones derived from Meldrum's acid and malonates.[24]

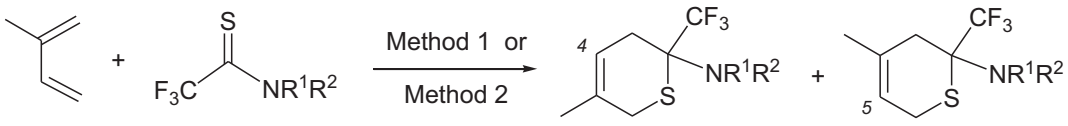
The major regioisomer **13b** was assigned to be the 5-methyl cycloadduct. Indeed, in ^{1}H NMR spectrum of the mixture, the vinylic proton was significantly shifted downfield ($\delta_{H\text{-}5}$=5.77 ppm) in minor isomer **14b**, compared with the major isomer **13b** ($\delta_{H\text{-}4}$=5.16 ppm). Moreover, the structure of the major regioisomer **13b** was confirmed by X-ray diffraction analysis (Fig. 5).

*2.2.2. Reactions with penta-1,3-diene (**6**).* Reactions with penta-1,3-diene (**6**) were more complicated as a mixture of two regioisomers was expected, each regioisomer being itself a mixture of diastereoisomers.

The first attempt with thioamide **9f** using Method 1 failed; no conversion of the starting material was observed even using a large



Scheme 4. Reagents and conditions. Method 2: diene (2.0 equiv), CH_2Cl_2, rt, 4 h: conv. 100%, mixture of (0.3:1) *exo*/*endo* isomers.



a) $R^1,R^2=(CH_2)_2O(CH_2)_2$: 19% (52:48)[a]

b) R^1=Ac, R^2=*p*-Tol: 76% (85:15)[b]

c) R^1=Bz, R^2=*p*-Tol: 67% (85:15)[b]

Scheme 5. Reagents and conditions. [a]Method 1: diene (20 equiv), NMP, μw 300 W, 180 °C, 3 h. [b]Method 2: diene (1.5 equiv), CH_2Cl_2, rt, 18 h to 60 d.

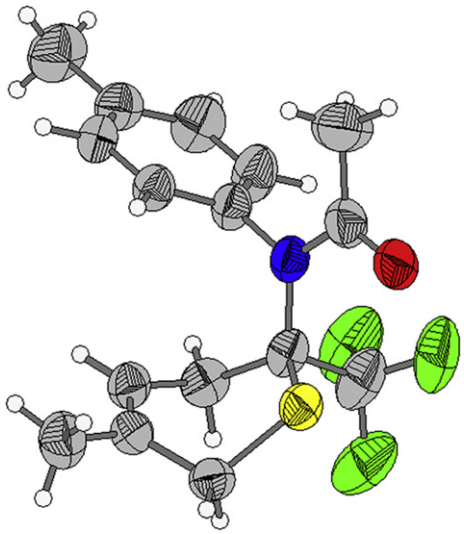
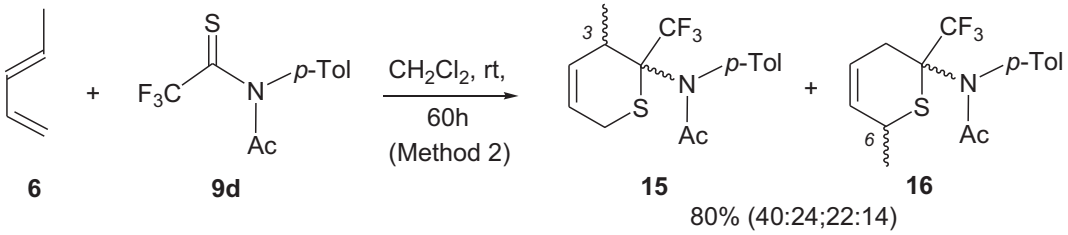


Fig. 5. ORTEP representation of compound **13b** (displacement ellipsoids with 50% of probability).

excess of diene and a long reaction time. On the contrary, reaction of compound **9d** with penta-1,3-diene in dichloromethane (Method 2) led to 80% yield of cycloadducts **15** and **16** as a complex mixture (40:24; 22:14) of regio- and diastereoisomers (Scheme 6). The ratio of isomers was determined from ^{19}F NMR spectra of the crude reaction mixture. All isomers were not fully separated by silica gel column chromatography but several enriched fractions were obtained allowing assignment of their structures by NMR. The structure of regioisomers was deduced from comparison of ^1H NMR signals of the protons attached to the methyl substituent. Thus, in 6-methyl isomers **16**, the cyclic methine protons were significantly shifted downfield ($\delta_{H\text{-}6}$=4.30, 3.79 ppm) compared with the 3-methyl isomers ($\delta_{H\text{-}3}$=3.43, 3.54 ppm), due to the sulfur atom attached on the same carbon. Moreover, multiplicity of the H-3 protons in the 3-methyl isomers (compound **15**) was complex due to an additional splitting because of the long-range $^4J_{H-F}$ coupling with fluorine atoms of CF_3-group. Cyclic methine proton (H-6) of other regioisomers **16** appeared as a doublet of quartet ($^3J_{H,H}$=6.8 Hz, $^3J_{H,H}$=6.6 Hz) due to the absence of $^5J_{H-F}$ coupling (too long distance between H-6 and fluorine atoms). It is also worth noting that the 3-methyl cycloadducts **15** were obtained as the major regioisomers, this observation being in good agreement with the literature.[24,25] Unfortunately, we were not able to determine the stereochemistry of cycloadducts **15** and **16**.



Scheme 6.

2.3. Reactions with 1-(trimethylsilyloxy)butadiene (7) and Danishefsky's dienes 8a,b

We then investigated the reaction of perfluoroalkyl thioamides **9** with silyloxy-1,3-dienes, especially 1-(trimethylsilyloxy)butadiene (**7**) and Danishefsky's dienes **8a**,**b** to have access to new fluorinated dihydro-2*H*-thiopyrans and 3-oxo-tetrahydrothiopyrans (which could be valuable precursors for the synthesis of thiopyranose derivatives). There are only a few examples of hetero-Diels–Alder reactions of silyloxy-1,3-dienes with polyfluorinated thiocarbonyl or thiocarboxyl derivatives. On the one hand, perfluorodithioesters and 1-trimethylsilyloxy-butadiene have been reported to proceed with low regio- and stereoselectivity to give a mixture of four dihydro-2*H*-thiopyrans.[9b] On the other hand, Danishefsky's diene reacts with perfluoroalkyl thioacetaldehyde (generated in situ from its corresponding anthracene cycloadduct)[26] or with phosphonodifluorodithioacetate[9d] affording a mixture of regioisomers, which were then converted by acid hydrolysis or TMSOTf treatment into dihydrothiopyranones.

*2.3.1. Reactions with 1-(trimethylsilyloxy)buta-1,3-diene (**7**).* Reactions of thioamides **9** with 1-(trimethylsilyloxy)buta-1,3-diene (**7**) were carried out under usual conditions (Scheme 7: Methods 1–3). The regio- and stereoselectivity depend on the substitution pattern of thioamides. *N*-Acetyl thioamide **9d** was transformed (100% conversion after 4 h) into a mixture of two regioisomers, each of them being obtained as a mixture of two diastereoisomers (Table 3: entry 1). The ratio (50:12; 24:14) of isomers was determined according to the ^{19}F NMR data of the reaction mixture. The separation of this mixture was very difficult; only cycloadduct **17a** was obtained as a single diastereoisomer after silica gel column chromatography. Unfortunately, it was not possible to determine its stereochemistry. When a dichloromethane solution of **17a** was kept at room temperature for several days, a spontaneous quantitative desilylation occurred leading to compound **18** (Fig. 6).

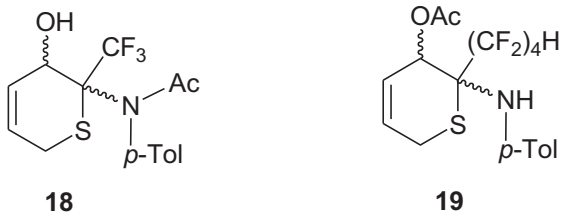


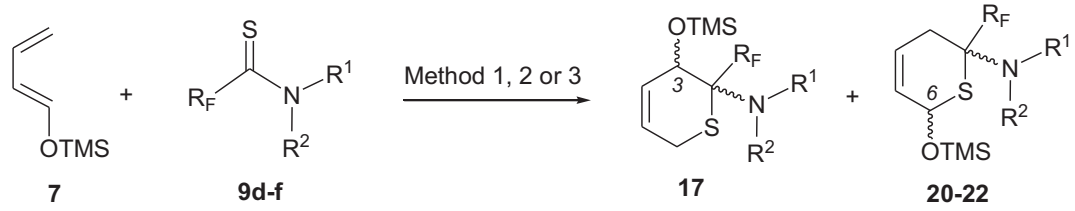
Fig. 6. By-products **18** and **19**.

of isomers). The behavior of the cycloadduct bearing an octofluorobutyl chain was different from compounds **17**. Indeed, during silica gel purification, a desilylation process followed by an N→O acetyl group migration[27] occurred giving compound **19** confirming indirectly the regiochemistry of cycloaddition reaction, when both hydroxy and amino groups have vicinal position (Fig. 6).

Regioisomers **20** and **21** (Table 3: entries 1 and 2) were characterized in the crude mixture but spontaneously decomposed during silica gel column chromatography. We assume that those regioisomers containing a hemithioaminal function are less stable to hydrolysis. A similar observation was also made in the reaction of trifluoromethyl or octofluorobutyl dithioesters with 1-(trimethylsilyloxy)buta-1,3-diene.[9b]

Finally, as previously observed for alkyl-substituted 1,3-dienes, thiomorpholide **9f** did not react under microwave irradiation (Table 2: entry 3). Nevertheless, regioisomers **22** (mixture (67:33) of non-separated diastereoisomers) were obtained in low 12% yield by simple heating of 1,3-diene **7** and compound **9f** (Table 3: entry 4, Method 3).

*2.3.2. Reaction with 2-(trimethylsilyloxy)buta-1,3-diene (**23**).* Reactions were then extended to 2-(trimethylsilyloxy)buta-1,3-diene. The reaction of thioamide **9d** with 1,3-diene (**23**) was regioselective and led,



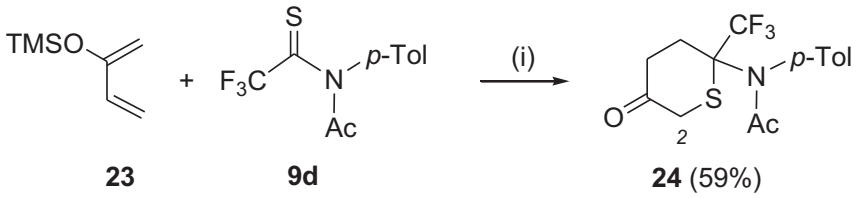
Scheme 7. Reagents and conditions. Method 1: diene (10 equiv), NMP, μw 300 W, 180 °C, 3 h. Method 2: diene (1.5 equiv), CH_2Cl_2, rt. Method 3: diene (10 equiv), neat, 150 °C, 3 h.

Table 3
Reaction of thioamides **9d**–**f** with 1-trimethylsilyloxy-buta-1,3-diene (**7**)

Entry	Thio-amide	R^1	R^2	R_F	Method[a]	Conv.[b] (%)	Compound **17**[c] (%)	Compounds **20**–**22**[c] (%)
1	**9d**	Ac	*p*-Tol	CF_3	2; 4 h	100[e]	**17**: 17	**20**[d]
2	**9e**	Ac	*p*-Tol	$(CF_2)_4H$	2; 24 h	100[f]	[g]	**21**[d]
3	**9f**	$(CH_2)_2O(CH_2)_2$		CF_3	1	~0	—	—
4	**9f**	$(CH_2)_2O(CH_2)_2$		CF_3	3	27	—	**22**: 12[h]

[a] Method 1: diene (10 equiv), NMP, μw 300 W, 180 °C, 3 h. Method 2: diene (1.5 equiv), CH_2Cl_2, rt. Method 3: diene (10 equiv), neat, 150 °C, 3 h.
[b] Conversion and ratio of isomers were based on ^{19}F NMR spectra of the reaction mixture.
[c] Isolated yields. All pure cycloadducts were obtained after purification by silica gel column chromatography as mixtures of diastereomers.
[d] Decomposition of cycloadducts **20**, **21** was observed during purification by silica gel chromatography.
[e] Ratio of isomers: 50:12; 24:14.
[f] Ratio of isomers was not determined.
[g] Cycloadduct was spontaneously transformed into *O*-acetylated derivative **19** (yield: 11%).
[h] Ratio of diastereoisomers: 67:33.

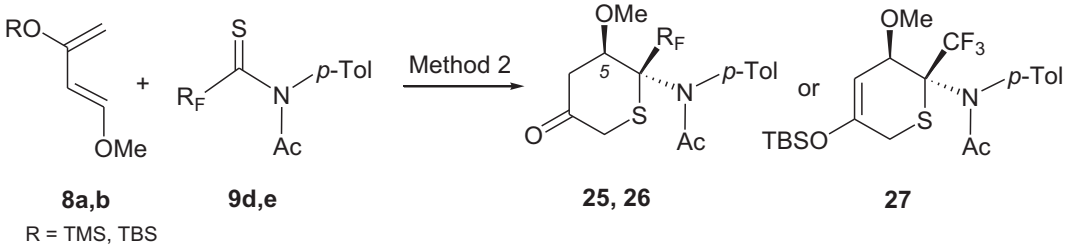
The reaction of the octafluorobutyl thioamide **9e** was more difficult (100% conversion after 24 h, Table 2: entry 2) and complex affording *O*-acetylated derivative **19** (11% isolated yield) and unstable cycloadducts **21** (it was not possible to determine the ratio after hydrolysis of silylated cyclodduct, to the formation of corresponding thiopyran-3-one **24** (Scheme 8). The other regioisomer was not detected in the ^{19}F NMR spectrum of the reaction mixture. Desilylation of the initially formed cycloadduct was performed by adding



Scheme 8. Reagents and conditions. (i) (1) Method 2: diene (1.0 equiv), CH_2Cl_2, rt, 15 h then (2) H^+, MeOH.

methanol containing a catalytic amount of HCl directly to the reaction mixture. Compound **24** was then isolated in 59% yield after silica gel column chromatography. The methylene protons of **24** appear as an AB-system ($\delta_{H\text{-}2}$=2.96 ppm, 3.61 ppm) without any additional splitting as could be expected for other regioisomer.

*2.3.3. Reactions with Danishefsky's dienes **8a**,**b**.* The reactions with Danishefsky's dienes **8a**,**b** were then investigated in order to study the regio- and stereochemistry of our cycloadditions. When CF_3–thioamide **9d** reacted in the presence of 1.0 equiv of diene **8a** in CH_2Cl_2 solution for 1 h (Scheme 9: Method 2, Table 4), only one peak of the CF_3-group was observed in the ^{19}F NMR spectrum of the reaction mixture, thus indicating that the reaction was totally regio- and stereoselective. The 3-oxo-tetrahydrothiopyran **25** was obtained in 60% yield as the unique diastereoisomer from spontaneous hydrolysis of the silyl enol ether intermediate during purification by silica gel column chromatography. Both the methoxy group (δ_{OMe}=3.28 ppm) and the methine proton ($\delta_{H\text{-}5}$=4.81 ppm) had characteristic chemical shifts showing them attached on the C-5 thiopyran ring.



Scheme 9. Reagents and conditions. Method 2: diene (1.0 equiv), CH_2Cl_2, rt, 1 h.

Table 4
Reactions of thioamides **9d**,**e** with Danishefsky's dienes **8a**,**b**

Entry	Diene (R)	Thioamide	R_F	Compounds **25**, **26**[a,b] (%)	Compound **27**[a,b] (%)
1	**8a** (TMS)	**9d**	CF_3	**25**: 60	—
2	**8a** (TMS)	**9e**	$(CF_2)_4H$	**26**: 62	—
3	**8b** (TBS)	**9d**	CF_3	—	**27**: 75

[a] Quantitative conversion based on ^{19}F NMR spectra of the reaction mixture.
[b] Isolated yields after purification by silica gel column chromatography.

The hetero-Diels–Alder reaction was then extended to octafluorobutyl thioamide **9e**. Similarly, 3-oxo-tetrahydrothiopyran **26** was obtained in 62% yield in a regio- and diastereoselective manner (Table 4: entry 2).

In order to isolate the cycloadduct as well as to determine its relative configuration, thioamide **9d** was treated under the same conditions with *tert*-butyldimethylsilyloxy-1,3-diene **8b** (Scheme 9). As expected, the corresponding *O*-TBS silyl enol ether **27** was more hydrolytically stable and was obtained in 75% yield, after silica gel column chromatography (Table 4: entry 3). The relative configuration of compound **27** was ascribed by X-ray diffraction analysis (Fig. 7) showing a cis relationship between the OMe and the CF_3-groups. The regioselectivity of these hetero-Diels–Alder reactions is in good agreement with those reported by E. Pfund et al. for phosphonodifluorodithioacetate,[9d] but is significantly different than what was observed for the reaction of perfluoroalkyl thioacetaldehyde.[26]

Then, the hetero-Diels–Alder reaction of Danishefsky's diene **8a** with thiomorpholide **9f** was performed. When a mixture of **8a** and **9f** was heated at 150 °C for 3 h (Method 3) directly followed by aqueous acidic hydrolysis and subsequent flash column chromatography (Scheme 10), cycloadducts **28** were obtained in low yield as a mixture of diastereoisomers (67:33, their stereochemistry was not determined), accompanied by γ-thiopyrone **29**. The latter was probably formed by spontaneous morpholine and methanol elimination starting from the corresponding cycloadducts **28**. It is worth noting that another synthesis of compound **29** has been recently described by decarboxylation of corresponding 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid.[28]

Firstly, only two peaks of the CF_3-groups related to the two diastereoisomers of compound **28** were observed in the ^{19}F NMR spectra of the crude reaction mixture. Moreover, ^1H NMR of major stereoisomer showed characteristic shifts for the thiopyran 'anomeric' MeO-group (δ_{OMe}=3.46 ppm) and the corresponding methine proton ($\delta_{H\text{-}6}$=4.92 ppm).

Secondly, the regioselective outcome of the reaction of thiomorpholide **9f** with Danishefsky's diene **8a** is the opposite of thioamides **9d**,**e** (Scheme 9, Table 4) but the same as with 1-(trimethylsilyloxy)buta-1,3-diene (**7**) (Table 3: entries 3 and 4). It clearly shows that on the one hand, the presence of only one electron-withdrawing substituent such as a polyfluoroalkyl group in carboxylic acid thioamides **9f**–**h**, is not enough to overcome the π-donating effect of the nitrogen atom; on the other hand, an additional acceptor substituent, particularly one acetyl or benzoyl group on thioamide nitrogen, is needed to reverse C=S bond polarization, thus making thioamides **9d**,**e** good dienophiles in non-catalyzed hetero-Diels–Alder reactions.

*2.3.4. Ring contraction to 1,3-thiazolidin-4-ones **31**.* As we have mentioned above (Scheme 9), desilylation of primary cycloadducts of type **27** using acid catalysis provided the expected deprotected

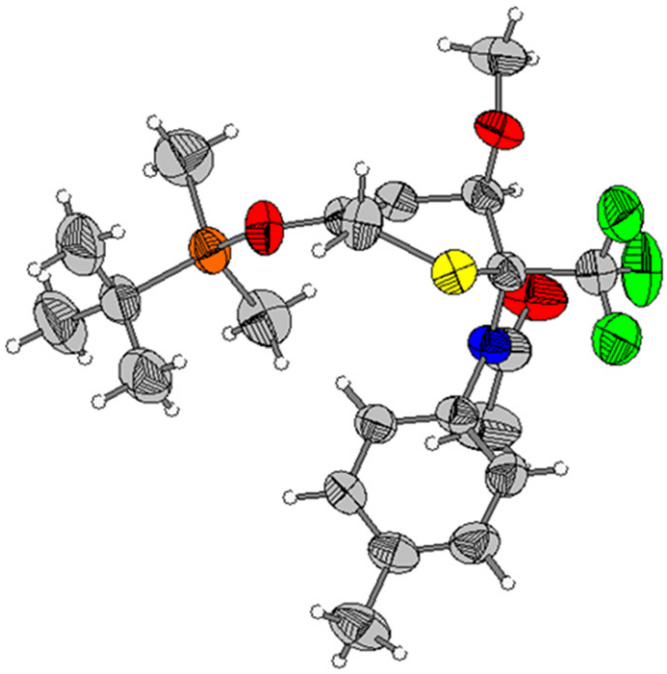


Fig. 7. ORTEP representation of compound **27** (displacement ellipsoids with 50% of probability).

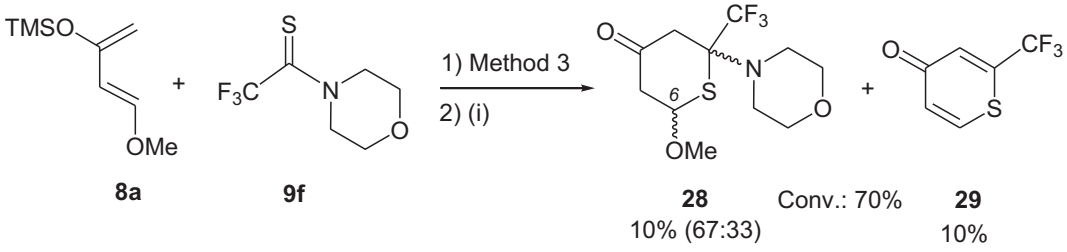
analysis was used to determine the structure and the relative configuration of thiazolidinone **31a** (Fig. 8).

Few other comments concerning the rearrangement have to be added:

(a) First, the primary silylated cycloadduct obtained from thioamide **9d** (Scheme 8) when treated with TBAF in CH_2Cl_2, produced only the derivative **24** without any rearrangement. Pure compound **24** did not also react with TBAF.

(b) Secondly, the influence of *N*-acyl substituent (R^2=H, Me) on the course of the rearrangement was also studied. The silylated cycloadduct **30c** was reacted with TBAF in CH_2Cl_2 in order to obtain the corresponding 5-methyl-substituted thiazolidinone. Unfortunately, it gave only desilylated product **32** (yield: 55%), without any rearrangement. Pure thiopyran-3-one **32** did not react with TBAF, CH_2Cl_2 or Cs_2CO_3, THF too.

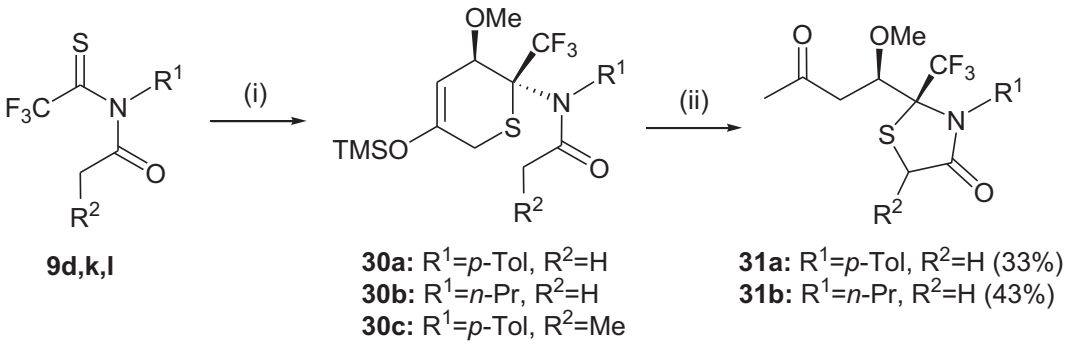
(c) Finally, we have screened the effect of other bases on desilylated 3-oxo cycloadducts. For example, the rearranged product **31a** was obtained from the desilylated 3-oxo thiopyran **25** using Cs_2CO_3 in THF (full conversion of starting material after 24 h at room temperature was monitored by ^{19}F NMR). Using *i*-Pr_2NH as a base, we have also detected (by ^{19}F NMR) the formation of rearranged product **31a**, but conversion was low (~20%). Moreover, the usage of stronger base such as *t*-BuOK or NaH in THF resulted only in decomposition of thiopyran ring.



Scheme 10. Reagents and conditions. Method 3: diene (2 equiv), neat, 150 °C, 3 h; (i): TFA or HCl, THF/H_2O.

thiopyrans **25** and **26**. But it was also noticed that treatment with TBAF for the same purpose resulted in the formation of a new product, which had a different chemical shift in the ^{19}F NMR spectrum. Careful optimization of the reaction parameters allowed us to find the correct conditions for the formation of this compound as the major product. Thus, addition of solid TBAF trihydrate to a dichloromethane solution of primary silylated cycloadducts **30a**,**b** led to the formation of the corresponding 1,3-thiazolidin-4-ones **31a**,**b** in moderate overall yields (Scheme 11). X-ray diffraction

There are few literature examples of base-induced ring contraction of 3,6-dihydro-2*H*-thiopyrans yielding thiolanes (in one case),[29a] or vinyl cyclopropanes and cyclopentenes bearing an exocyclic sulfide function.[29b,c] 2,2-Disubstituted 1,3-thiazolidin-4-ones with a CF_3-group being one of the substituents at the C-2 position are also known and are usually obtained in the reaction of thioglycolic acid or its esters with 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates[30a,b] or methyl 3,3,3-trifluoro-2-iminopropanoate.[30c]



Scheme 11. Reagents and conditions. (i): Method 2: diene **8a** (1 equiv), CH_2Cl_2, rt, 1 h; (ii): TBAF trihydrate, rt, 15 h.

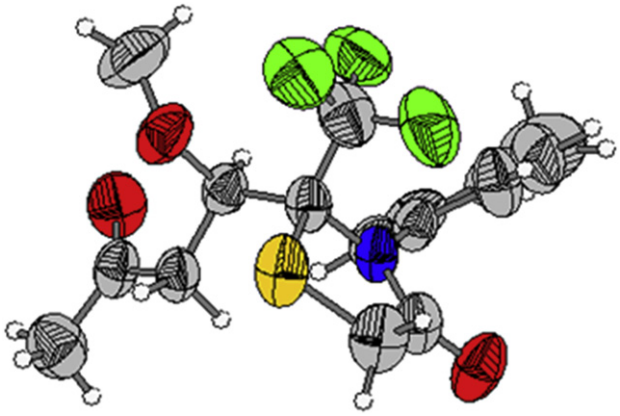


Fig. 8. ORTEP representation of compound **31a** (displacement ellipsoids with 50% of probability).

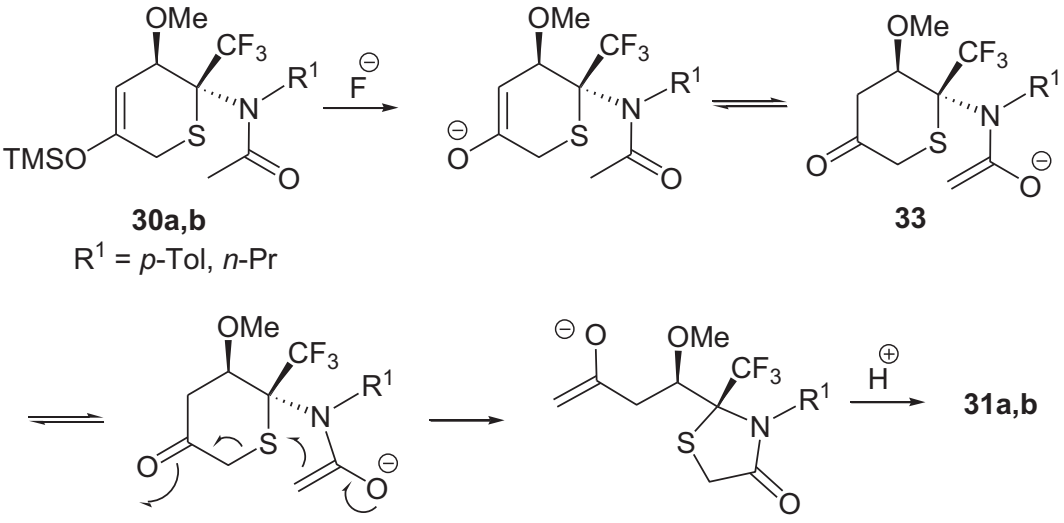
In our case we can propose the following mechanism for this ring contraction reaction (Scheme 12). Fluoride anion could attack the silyl enol ether of compounds **30** giving first a cyclic enolate, which could then lead to the *N*,*O*-acetal enolate **33** after a protonation–deprotonation equilibrium. Finally, the latter could then undergo a ring opening of 3,6-dihydro-2*H*-thiopyran—ring closure into the corresponding 1,3-thiazolidin-4-one **31** (Scheme 12).

isoprene (**5**), penta-1,3-diene (**6**), 1- and 2- trimethylsilyloxy-1,3-butadiene (**7** and **23**), and Danishefsky's dienes **8a**,**b**. The observed regioselectivity is almost the same as reported in the literature for fluorinated thiocarbonyl or thiocarboxyl derivatives. The structural assignment of compounds **13**, **17**, **20**–**22**, **24**–**27** was based on NMR data or X-ray diffraction analyses. Relative configuration was usually not determined except for cycloadducts **25**–**27**. It was also shown that cycloadducts **30** underwent base-induced ring contraction into new fluorinated 1,3-thiazolidin-4-ones **31**. Finally, it is worth noting that the prepared 3,6-dihydro-2*H*-thiopyrans could be valuable compounds as it was earlier demonstrated that some fluorine-containing dihydrothiopyran derivatives possess potential cardiotonic activity.[31]

4. Experimental

4.1. General methods

Reagents and solvents were generally the best quality commercial grade and used without further purification. Focused microwave irradiations were carried out in pressurized (0–20 bar) sealed vessels (0–20 bar, 10 mL tubes, sealed with a septum) with a CEM *Discover*™ focused microwave reactor (monomode system).[18a] Power input (0–400 W) was monitored by computer as infrared measurement and continuous feedback temperature



Scheme 12. Possible mechanism for the formation of thiazolidinones **31a**,**b**.

3. Conclusion

We have described an extended investigation of hetero-Diels–Alder reactions of trifluoromethyl- and polyfluoroalkylthioamides with various electron-rich 1,3-dienes. The microwave-assisted reactions (Method 1: 15–20 equiv of diene) of thioamides **9a**–**c**,**f**–**h** worked quite well with 2,3-dimethylbuta-1,3-diene affording moderate yields of cycloadducts **10a**–**c**,**f**–**h**. The nature of polyfluoroalkyl chains and substituents on the nitrogen atom of the thioamides had a significant influence on the yields of compounds **10**. On the contrary, *N*-acetyl-thioamides **9d**,**e** reacted smoothly at room temperature in the presence of a slight excess of diene (Method 2) with alkyl-substituted dienes as well as silyloxydienes leading to the corresponding cycloadducts in good yields. Study of regio- and stereoselectivity was also investigated using control. The experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located underneath the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a target temperature was selected together with a power. The target temperature was reached with a ramp of 2 min and the chosen microwave power stay constant to hold the mixture at this temperature. The time of the reaction did not include the ramp period. All reactions were followed by ^{19}F NMR of the crude mixture or by thin layer chromatography (TLC) on silica gel (Merck, Darmstadt, Germany) and revealed using UV light or ethanolic solution of phosphomolybdic acid. Purification of all cycloadducts was carried out using flash silica gel column chromatography (70–200 μm). The purity of synthetic products was established by NMR spectroscopic data, and MS analysis. MS: Thermo Finnigan,

LCQ Advantage Max, Electrospray Ionization, source heater T=220 °C, capillary voltage=33 V. High resolution mass spectra (HRMS) were recorded with a Q-TOF Micromass Instrument in the positive ESI (CV=30 V) mode. ^{1}H (300 MHz), ^{19}F (280 MHz), and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance DMX 300 instrument. All the experiments were recorded using $CDCl_3$ as solvent. TMS signal or the residual signal of deuterated solvent was taken as internal reference for ^{1}H and ^{13}C spectra and the $CFCl_3$ signal for ^{19}F spectra. Crystal structures of compounds **13b**, **27**, and **31a** were determined from single-crystal X-ray diffraction analysis on a Bruker© SMART APEX diffractometer (with Mo Kα1 radiation: 0.71073 Å). Data were deposited to the Cambridge Crystallographic Data Centre.

4.2. Typical procedure for the synthesis of *N*-acyl thioamides 9d,e,i,k (Scheme 3)

To a solution of thioamide **9b** (0.66 g, 3 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.46 g, 4.5 mmol). The reaction mixture was cooled in an ice-bath, then a solution of acetyl chloride (0.32 g, 4 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h then evaporated in vacuo. The residue was treated with dry Et_2O and filtered. Evaporation of the filtrate in vacuo provided *N*-acetyl thioamide **9d** (0.75 g, 95%) as a red oil.

*4.2.1. N-(2,2,2-Trifluoroethanethioyl)-N-(p-tolyl)acetamide (**9d**).* Mixture (70:30) of rotamers ($CDCl_3$). ^{19}F NMR ($CDCl_3$, δ ppm): −62.0 (s, CF_3, major), −72.0 (s, CF_3, minor). ^{1}H NMR ($CDCl_3$, δ ppm): 2.18 (s, 3H, MeCO, major), 2.30 (s, 3H, MeCO, minor), 2.36 (s, 3H, Me *p*-Tol, minor), 2.41 (s, 3H, Me *p*-Tol, major), 6.86 (d, $^3J_{H,H}$=8.0 Hz, 2H, CH_{Ar}, minor), 7.08 (d, $^3J_{H,H}$=8.0 Hz, 2H, CH_{Ar}, major), 7.18 (d, $^3J_{H,H}$=8.0 Hz, 2H, CH_{Ar}, minor), 7.30 (d, $^3J_{H,H}$=8.0 Hz, 2H, CH_{Ar}, major). GC/MS: m/z=219 [M^+−Ac].

*4.2.2. N-(2,2,3,3,4,4,5,5-Octafluoropentanethioyl)-N-(p-tolyl)acetamide (**9e**).* Yield: 97% (1.15 g). Mixture (85:15) of rotamers ($CDCl_3$). Red oil. Spectral data for the major rotamer is given. ^{19}F NMR ($CDCl_3$, δ ppm): −111.8 (m, CF_2), −123.3 (m, CF_2), −129.4 (m, CF_2), −137.8 (dm, $^2J_{F,H}$=52.0 Hz, HCF_2). ^{1}H NMR ($CDCl_3$, δ ppm): 2.23 (s, 3H, MeCO), 2.36 (s, 3H, Me *p*-Tol), 6.15 (tt, $^2J_{F,H}$=52.0, $^3J_{F,H}$=5.7 Hz, 1H, HCF_2), 6.86 (d, $^3J_{H,H}$=8.0 Hz, 2H, CH_{Ar}), 7.19 (d, $^3J_{H,H}$=8.0 Hz, 2H, CH_{Ar}).

*4.2.3. N-(2,2,2-Trifluoroethanethioyl)-N-(p-tolyl)benzamide (**9i**).* Yield: 95% (0.35 g). Mixture (75:25) of rotamers ($CDCl_3$). Yellow oil. ^{19}F NMR ($CDCl_3$, δ ppm): −62.0 (s, CF_3, minor), −71.4 (s, CF_3, major). ^{1}H NMR ($CDCl_3$, δ ppm): 2.32 (s, 3H, Me *p*-Tol, major), 2.35 (s, 3H, Me *p*-Tol, minor), 6.9–7.9 (m, 9H, CH_{Ar}).

*4.2.4. N-(2,2,2-Trifluoroethanethioyl)-N-(propyl)acetamide (**9k**).* Yield: 94% (0.45 g). Mixture (85:15) of rotamers ($CDCl_3$). Red oil. ^{19}F NMR ($CDCl_3$, δ ppm): −62.2 (s, CF_3, major), −72.6 (s, CF_3, minor). ^{1}H NMR of the major rotamer ($CDCl_3$, δ ppm): 0.96 (t, $^3J_{H,H}$=7.5 Hz, 3H, $CH_3CH_2CH_2$), 1.72 (m, 2H, $CH_3CH_2CH_2$), 2.45 (s, 3H, MeCO), 3.95 (m, 2H, NCH_2).

*4.2.5. N-(2,2,2-Trifluoroethanethioyl)-N-(p-tolyl)propionamide (**9l**).* Yield: 95% (1.2 g). Mixture (55:45) of rotamers ($CDCl_3$). Oil. ^{19}F NMR ($CDCl_3$, δ ppm): −61.9 (s, CF_3, major), −72.0 (s, CF_3, minor).

4.3. Typical procedure for the reactions of thioamides 9 with 1,3-dienes

4.3.1. Method 1. A stirring bar and one piece of Weflon® (Weflon® is Teflon® filled with graphite) were placed in a 10 mL pressure vessel. Thioamide **9g** (0.25 g, 1 mmol), *N*-methylpyrrolidin-2-one (NMP) (3 mL), and 2,3-dimethylbuta-1,3-diene (**3**) (0.56 mL, 5 mmol) were then added. The tube was sealed with a Teflon septum and heated in CEM Discover® microwave reactor (reaction parameters: standard mode, T=180 °C, μW power: 300 W, running time: 30 min). After one run, another portion of 1,3-diene **3** (0.28 mL, 2.5 mmol) was added with a syringe through the septum and reaction mixture was heated again under the same conditions. Addition of new portions of diene and heating were continued until ^{19}F NMR of reaction mixture showed maximum conversion (total heating time: 3 h, 1,3-diene: 15–20 equiv, see Table 1). The reaction mixture was then poured into water (50 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were washed with water (30 mL), dried over $MgSO_4$, evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: mixture petroleum ether (PE) and ethyl acetate, 9:1). Combined fractions containing **10g** were evaporated and redissolved in MeOH (5–10 mL) to precipitate impurities of polymerized diene. After filtration and solvent evaporation, pure compound **10g** (0.16 g, 49%) was obtained as a colorless oil (Scheme 2, Table 1: entry 7).

4.3.2. Method 2. 2,3-Dimethylbuta-1,3-diene (0.17 mL, 1.5 mmol) was added to a solution of thioamide **9d** (0.20 g, 0.75 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 4 h until disappearance of the red color of the starting thioamide, then evaporated in vacuo. The residue was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate, 4:1) affording the desired product **10d** (0.20 g, 78%) (Scheme 2, Table 1: entry 4).

4.3.3. Method 3. Thioamide **9f** (0.20 g, 1 mmol) and 1-(trimethylsilyloxy)buta-1,3-diene (**7**) (1.8 mL, 10 mmol) were heated at 150 °C in a 10 mL pressure vessel sealed with Teflon septum with stirring in an oil bath for 3 h. Then, after evaporation of volatiles, the reaction mixture was purified by silica gel column chromatography (eluent: mixture petroleum ether and ethyl acetate, 9:1) affording the desired product **22** (40 mg, 12%) as a mixture (67:33) of diastereoisomers (Scheme 7, Table 3: entry 4).

4.4. Reactions of thioamides 9a–h with 2,3-dimethylbuta-1,3-diene (3) (Scheme 2, Table 1)

*4.4.1. (4,5-Dimethyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl)amine (**10a**).* Method 1. Yield: 35% (0.15 g). Oil. ^{19}F NMR ($CDCl_3$, δ ppm): −81.3 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.64 (s, 3H, Me), 1.67 (s, 3H, Me), 2.01 (br s, 2H, NH_2), 2.20 (d, $^2J_{H,H}$=16.5 Hz, 1H, CH_AH_B), 2.67 (d, $^2J_{H,H}$=16.5 Hz, 1H, CH_AH_B), 3.07 (d, $^2J_{H,H}$=16.8 Hz, 1H, SCH_AH_B), 3.35 (d, $^2J_{H,H}$=16.8 Hz, 1H, SCH_AH_B). ^{13}C NMR ($CDCl_3$, δ ppm): 19.1 (s, CH_3), 20.4 (s, CH_3), 29.8 (s, SCH_2), 38.6 (s, CH_2), 63.7 (q, $^2J_{C,F}$=28.5 Hz, CCF_3), 123.5 (s, C_q), 124.1 (s, C_q), 126.1 (q, $^1J_{C,F}$=282.7 Hz, CF_3). GC/MS: m/z=211 [M^+]. Anal. Calcd for $C_8H_{12}F_3NS$: C, 45.48; H, 5.73; N, 6.63; S, 15.18. Found: C, 45.37; H, 5.84; N, 6.51; S, 15.22.

*4.4.2. (4,5-Dimethyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl)(p-tolyl) amine (**10b**).* Method 1. Yield: 26% (0.16 g). Oil. ^{19}F NMR ($CDCl_3$, δ ppm): −77.1 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.70 (s, 3H, Me), 1.74 (s, 3H, Me), 2.27 (s, 3H, Me tolyl), 2.40 (d, $^2J_{H,H}$=17.6 Hz, 1H, CH_AH_B), 2.79 (d, $^2J_{H,H}$=18.0 Hz, 1H, SCH_AH_B), 2.85 (d, $^2J_{H,H}$=17.6 Hz, 1H, CH_AH_B), 3.16 (d, $^2J_{H,H}$=18.0 Hz, 1H, SCH_AH_B), 6.93 (d, $^3J_{H,H}$=8.1 Hz, 2H, tolyl), 7.01 (d, $^3J_{H,H}$=8.1 Hz, 2H, tolyl). ^{13}C NMR ($CDCl_3$, δ ppm): 19.1 (s, CH_3), 20.2 (s, CH_3), 20.7 (s, CH_3), 30.1 (s, SCH_2), 38.4 (s, CH_2), 66.7 (q, $^2J_{C,F}$=28.5 Hz, CCF_3), 120.2 (s, 2×CHAr), 123.0 (s, C_q), 124.3 (s, C_q), 125.9 (q, $^1J_{C,F}$=286.4 Hz, CF_3), 129.2 (s, 2×CHAr), 131.1 (s, C_q Ar), 140.7 (s, C_q Ar). GC/MS: m/z=301 [M^+].

Anal. Calcd for $C_{15}H_{18}F_3NS$: C, 59.78; H, 6.02; N, 4.65; S, 10.64. Found: C, 59.92; H, 6.15; N, 4.60; S, 10.68.

*4.4.3. [4,5-Dimethyl-2-(1,1,2,2,3,3,4,4-octafluorobutyl)-3,6-dihydro-2H-thiopyran-2-yl]-(p-tolyl)amine (**10c**).* Method 1. Yield: 15% (0.13 g). Oil. ^{19}F NMR ($CDCl_3$, δ ppm): −110.5 (dm, $^2J_{F,F}$=280.2 Hz, 1F, CF_AF_B), −112.4 (dm, $^2J_{F,F}$=280.2 Hz, 1F, CF_AF_B), −120.5 (dm, $^2J_{F,F}$=291.5 Hz, 1F, CF_AF_B), −122.6 (dm, $^2J_{F,F}$=291.5 Hz, 1F, CF_AF_B), −130.8 (m, 2F, CF_2), −138.0 (dm, $^2J_{F,H}$=52.2 Hz, 2F, HCF_2). ^{1}H NMR ($CDCl_3$, δ ppm): 1.71 (s, 3H, Me), 1.76 (s, 3H, Me), 2.27 (s, 3H, Me tolyl), 2.51 (d, $^2J_{H,H}$=17.1 Hz, 1H, CH_AH_B), 2.81 (d, $^2J_{H,H}$=16.2 Hz, 1H, SCH_AH_B), 2.93 (d, $^2J_{H,H}$=17.1 Hz, 1H, CH_AH_B), 3.02 (d, $^2J_{H,H}$=16.2 Hz, 1H, SCH_AH_B), 6.02 (tt, $^2J_{H,F}$=52.2 Hz, $^3J_{H,F}$=5.4 Hz, 1H, HCF_2), 6.92 (d, $^3J_{H,H}$=8.4 Hz, 2H, tolyl), 7.00 (d, $^3J_{H,H}$=8.4 Hz, 2H, tolyl). MS (ESI^+): *m*/*z*=472 [M+K]. Spontaneous desamination of **10c** into compound **11**[14] took place during heating under microwave irradiation.

*4.4.4. N-(4,5-Dimethyl-2-(trifluoromethyl)-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)-acetamide (**10d**).* Method 2. Yield: 78% (0.20 g). Oil. R_f=0.55 (PE/EtOAc, 4:1). ^{19}F NMR ($CDCl_3$, δ ppm): −71.7 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.40 (s, 3H, =CCH_3), 1.72 (s, 3H, *Me*CO), 1.77 (s, 3H, =CCH_3), 2.39 (s, 3H, Me *p*-Tol), 2.40 (d, $^2J_{H,H}$=15.4 Hz, 1H, CH_2), 2.64 (d, $^2J_{H,H}$=15.4 Hz, 1H, CH_2), 3.01 (s, 2H, CH_2S), 7.0–7.2 (m, 4H, *p*-Tol). ^{13}C NMR ($CDCl_3$, δ ppm): 18.6 (s, CH_3), 19.3 (s, CH_3), 21.2 (s, CH_3 *p*-Tol), 26.2 (s, CH_3CO), 32.4 (s, CH_2S), 38.0 (q, $^3J_{C,F}$=1.7 Hz, CH_2), 73.9 (q, $^2J_{C,F}$=28.2 Hz, C_q), 125.6 (s, C_q), 126.2 (q, $^1J_{C,F}$=288.0 Hz, CF_3), 129.1 (s, C_q), 129.9, 130.0, 130.6, 131.1 (s, CH *p*-Tol), 138.4 (s, C_q, C_{Ar}–Me), 139.1 (s, C_q, C_{Ar}–N), 171.6 (s, C=O). GC/MS: *m*/*z*=300 [M^+–Ac], 179, 150, 107. FTIR (film, cm^{-1}): 3351, 2923, 1687, 1510, 1368, 1295, 1171. HRMS (ESI^+): calcd for $C_{17}H_{20}F_3NOSNa$ *m*/*z* 366.1115, found 366.1123.

*4.4.5. N-(4,5-Dimethyl-2-(1,1,2,2,3,3,4,4-octafluorobutyl)-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)acetamide (**10e**).* Method 2. Yield: 69% (0.25 g). Oil. R_f=0.55 (PE/EtOAc, 4:1). ^{19}F NMR ($CDCl_3$, δ ppm): −102.3 (1F, CF_2, *AB*, $^2J_{F,F}$=278.0 Hz), −105.9 (1F, CF_2, *AB*, $^2J_{F,F}$=278.0 Hz), −121.2, −121.4 (2F, 2×m, CF_2), −130.1, −130.4 (2F, 2×m, CF_2), −137.4, −137.5 (2F, 2×dm, HCF_2, $^2J_{F,H}$=52.0 Hz). ^{1}H NMR ($CDCl_3$, δ ppm): 1.36 (s, 3H, =CCH_3), 1.69 (s, 3H, *Me*CO), 1.78 (s, 3H, =CCH_3), 2.38 (s, 3H, Me *p*-Tol), 2.47 (d, $^2J_{H,H}$=15.3 Hz, 1H, CH_2), 2.88 (d, $^2J_{H,H}$=14.7 Hz, 1H, CH_2S), 3.08 (m, 2H, CH_2+CH_2S), 6.08 (tt, $^2J_{H,F}$=52.0 Hz, $^3J_{H,F}$=5.7 Hz, 1H, HCF_2), 7.0–7.2 (m, 4H, *p*-Tol). ^{13}C NMR ($CDCl_3$, δ ppm): 18.7 (s, CH_3), 19.2 (s, CH_3), 21.2 (s, CH_3 *p*-Tol), 26.7 (s, CH_3CO), 32.3 (s, CH_2S), 37.1 (t, $^3J_{CF}$=3.3 Hz, CH_2), 77.8 (m, C_q, CCF_2, overlapping with $CDCl_3$), 107.9 (tt, $^1J_{C,F}$=254.0, $^2J_{C,F}$=30.1 Hz, HCF_2), 104–121 (m, $CF_2CF_2CF_2$), 126.3, 129.2 (s, C_q), 129.8, 129.9, 131.0, 131.1 (s, CH_{Ar}), 139.0 (s, C_q, C_{Ar}Me), 139.2 (s, C_q, C_{Ar}N), 172.5 (s, C=O). FTIR (film, cm^{-1}): 3422, 2926, 1689, 1510, 1368, 1292, 1171, 732. HRMS (ESI^+): calcd for $C_{20}H_{21}F_8NOSK$ *m*/*z* 514.0853, found 514.0846.

*4.4.6. 4-(4,5-Dimethyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl)morpholine (**10f**).* Method 1. Yield: 45% (0.13 mg). Oil. R_f=0.37 (PE/EtOAc, 9:1). ^{19}F NMR ($CDCl_3$, δ ppm): −71.3 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.71 (s, 3H, Me), 1.75 (s, 3H, Me), 2.44 (d, $^2J_{H,H}$=17.5 Hz, 1H, CH_AH_B), 2.69 (m, 2H, NCH_2), 2.79 (d, $^2J_{H,H}$=16.4 Hz, 1H, SCH_AH_B), 2.83 (d, $^2J_{H,H}$=17.5 Hz, 1H, CH_AH_B), 3.13 (m, 2H, NCH_2), 3.23 (d, $^2J_{H,H}$=16.4 Hz, 1H, SCH_AH_B), 3.59 (m, 4H, $O(CH_2)_2$). ^{13}C NMR ($CDCl_3$, δ ppm): 18.9 (s, CH_3), 20.0 (s, CH_3), 30.4 (s, CH_2S), 35.2 (q, $^3J_{C,F}$=1.1 Hz, CH_2), 47.2 (s, CH_2N), 68.1 (s, CH_2O), 71.0 (q, $^2J_{C,F}$=24.9 Hz, CCF_3), 122.5 (s, C_q), 123.9 (s, C_q), 126.6 (q, $^1J_{C,F}$=293.1 Hz, CF_3). GC/MS: *m*/*z*=281 [M^+]. HRMS (ESI^+): calcd for $C_{12}H_{18}F_3KNOS$ *m*/*z* 320.0698, found 320.0692.

*4.4.7. 4-(4,5-Dimethyl-2-(pentafluoroethyl)-3,6-dihydro-2H-thiopyran-2-yl)morpholine (**10g**).* Method 1. Yield: 49% (0.16 mg). R_f=0.35 (PE/EtOAc, 9:1). ^{19}F NMR ($CDCl_3$, δ ppm): −78.5 (3F, m, CF_3), −109.8 (1F, CF_2, *AB*, $^2J_{F,F}$=276.1 Hz), −114.3 (1F, CF_2, *AB*, $^2J_{F,F}$=276.1 Hz). ^{1}H NMR ($CDCl_3$, δ ppm): 1.72 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.42 (d, $^2J_{H,H}$=17.4 Hz, 1H, CH_2), 2.6–3.0 (m, 6H), 3.25 (d, $^2J_{H,H}$=16.7 Hz, 1H, CH_2S), 3.59 (m, 4H, CH_2O). ^{13}C NMR ($CDCl_3$, δ ppm): 19.1 (s, CH_3), 20.0 (s, CH_3), 31.0 (s, CH_2S), 36.0 (m, CH_2), 48.1 (dd, $^4J_{C,F}$=$^4J_{C,F}$=3.7 Hz, CH_2N), 67.8 (s, CH_2O), 74.1 (dd, $^2J_{C,F}$=$^2J_{C,F}$=21.7 Hz, C_q, CCF_2), 116.4 (ddq, $^1J_{C,F}$=$^1J_{C,F}$=266.4 Hz, $^2J_{CF}$=34.6 Hz, CF_2), 119.5 (qdd, $^1J_{C,F}$=288.5, $^2J_{C,F}$=$^2J_{C,F}$=37.5 Hz, CF_3), 123.7 (s, C_q), 124.8 (s, C_q). GC/MS: *m*/*z*=331 [M^+], 298, 249, 229, 212, 179, 130, 86. FTIR (film, cm^{-1}): 3436, 2857, 1641, 1455, 1325, 1213, 1122, 729. HRMS (ESI^+): calcd for $C_{13}H_{19}F_5NOS$ *m*/*z* 332.1108, found 332.1114.

*4.4.8. (2-Heptafluoropropyl-4,5-dimethyl-3,6-dihydro-2H-thiopyran-2-yl)morpholine (**10h**).* Method 1. Yield: 28% (0.21 g). Oil. ^{19}F NMR ($CDCl_3$, δ ppm): −81.4 (m, 3F, CF_3), −109.9 (dm, $^2J_{F,F}$=285.0 Hz, 1F, $CF_AF_BCF_3$), −110.5 (dm, $^2J_{F,F}$=285.0 Hz, 1F, $CF_AF_BCF_3$), −121.1 (dm, $^2J_{F,F}$=287.7 Hz, 1F, CF_AF_B), −125.4 (dm, $^2J_{F,F}$=287.7 Hz, 1F, CF_AF_B). ^{1}H NMR ($CDCl_3$, δ ppm): 1.73 (s, 3H, Me), 1.75 (s, 3H, Me), 2.49 (d, $^2J_{H,H}$=17.1 Hz, 1H, CH_AH_B), 2.7–3.0 (m, 6H, $N(CH_2)_2$+CH_AH_B+-SCH_AH_B), 3.25 (d, $^2J_{H,H}$=17.0 Hz, 1H, SCH_AH_B), 3.61 (m, 4H, $O(CH_2)_2$). GC/MS: *m*/*z*=381 [M^+]. HRMS (ESI^+): calcd for $C_{14}H_{18}F_7KNOS$ *m*/*z* 420.0634, found 420.0641.

4.5. Reaction of thioamide 9d with cyclohexa-1,3-diene (4) (Scheme 4)

*4.5.1. N-(p-Tolyl)-N-(3-(trifluoromethyl)-2-thiabicyclo[2.2.2]oct-5-en-3-yl)acetamide (**12**).* Reaction (Method 2) of thioamide **9d** (0.20 g, 0.75 mmol) with cyclohexa-1,3-diene (**4**) (0.15 mL, 1.5 mmol) gave compound **12** as a mixture (1:0.3) of *endo*/*exo* isomers (0.15 g, yield: 58%). Oil. R_f=0.52 (PE/EtOAc, 4:1). GC/MS: *m*/*z*=341 [M^+], 220, 193, 165. FTIR (film, cm^{-1}): 3436, 2945, 1683, 1511, 1366, 1312, 1278, 1174, 722. HRMS (ESI^+): calcd for $C_{17}H_{19}F_3NOS$ *m*/*z* 342.1139, found 342.1132. *Major endo isomer **12a***: ^{19}F NMR ($CDCl_3$, δ ppm): −68.6 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.5–2.2 (m, 4H, 2×CH_2), 1.80 (s, 3H, *Me*CO), 2.39 (s, 3H, Me *p*-Tol), 3.48 (m, 1H, CH), 5.24 (m, 1H, CH), 6.34 (ddd, $^3J_{H,H}$=8.7 Hz, $^3J_{H,H}$=7.5 Hz, $^4J_{H,H}$=1.2 Hz, 1H, =CH), 6.61 (dd, $^3J_{H,H}$=8.7 Hz, $^3J_{H,H}$=5.8 Hz, 1H, =CH), 7.1–7.3 (m, 4H, *p*-Tol). ^{13}C NMR ($CDCl_3$, δ ppm): 19.3 (s, CH_2), 21.2 (s, CH_3 *p*-Tol), 27.6 (s, CH_2), 27.8 (s, CH_3CO), 32.1 (s, CH), 36.7 (s, CH), 83.8 (q, $^2J_{C,F}$=27.2 Hz, C_q, CCF_3), 125.9 (q, $^1J_{C,F}$=287.6 Hz, CF_3), 128.8 (q, $^4J_{CF}$=3.2 Hz, =CH), 129.3, 130.1, 132.0, 133.4 (s, CH_{Ar}), 136.0 (q, $^5J_{CF}$=1.7 Hz, =CH), 138.5 (s, C_q, C_{Ar}Me), 141.9 (s, C_q, C_{Ar}N), 172.8 (s, C=O). *Minor exo isomer **12b***: ^{19}F NMR ($CDCl_3$, δ ppm): −67.8 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.5–2.2 (m, 4H, 2×CH_2), 1.80 (s, 3H, *Me*CO), 2.41 (s, 3H, Me *p*-Tol), 2.93 (m, 1H, CH), 3.50 (m, 1H, CH), 5.92 (dd, $^3J_{H,H}$=8.7, $^3J_{H,H}$=7.5 Hz, 1H, =CH), 6.68 (dd, $^3J_{H,H}$=8.7 Hz, $^3J_{H,H}$=5.8 Hz, 1H, =CH), 7.1–7.4 (m, 4H, *p*-Tol). ^{13}C NMR ($CDCl_3$, δ ppm): 18.0 (s, CH_2), 21.2 (s, CH_3 *p*-Tol), 25.3 (s, CH_3CO), 29.5 (s, CH_2), 34.7 (s, CH), 37.7 (s, CH), 78.4 (q, $^2J_{C,F}$=25.7 Hz, C_q, CCF_3), 120–127 (CF_3 not visible), 126.9 (s, CH_{Ar}), 129.7 (q, $^4J_{C,F}$=3.5 Hz, =CH), 129.8, 130.4, 130.7 (s, CH_{Ar}), 137.9 (s, C_q, C_{Ar}Me), 138.4 (q, $^5J_{C,F}$=1.0 Hz, =CH), 138.6 (s, C_q, C_{Ar}N), 173.3 (s, C=O).

4.6. Reactions of thioamides 9d,f,i with isoprene (5) (Scheme 5)

*4.6.1. 4-(5- or 4-Methyl-2-(trifluoromethyl)-3,6-dihydro-2H-thiopyran-2-yl)morpholine (**13a**) or (**14a**).* Compounds **13a** and **14a** were obtained (Method 1) as a mixture (52:48) of regioisomers from thioamide **9f** (0.20 g, 1 mmol) and isoprene (**5**) (2.5 mL, 25 mmol). They were not separated by silica gel column chromatography (eluent: mixture petroleum ether and ethyl acetate, 9:1); analyses were done on the mixture. Yield: 19% (50 mg). Oil. R_f=0.38 (PE/EtOAc, 9:1). ^{19}F NMR ($CDCl_3$, δ ppm): −71.1 (s, CF_3), −71.2 (s, CF_3). ^{1}H NMR ($CDCl_3$, δ ppm): 1.74 (s, 3H, CH_3), 1.77 (s, 3H, CH_3),

2.4–3.4 (m, 16H, CH_2N+CH_2+CH_2S), 3.5–3.6 (m, 8H, CH_2O), 5.39 (m, 1H, HC=), 5.63 (m, 1H, =CH). ^{13}C NMR ($CDCl_3$, δ ppm): 23.6, 24.3 (s, CH_3), 25.5 (s, CH_2), 29.1 (s, CH_2), 29.5 (s, CH_2), 33.7 (s, CH_2), 47.2, 47.3 (s, CH_2N), 68.2, 68.3 (s, CH_2O), 70.1, 70.7 (q, $^2J_{C,F}$=25.1 Hz, C_q, CCF_3), 117.3, 117.9 (s, =CH), 126.7, 126.9 (q, $^1J_{C,F}$=293.5 Hz, CF_3), 130.6, 131.6 (s, C_q, CMe). MS (ESI^+): m/z=268 [M^+], 234. FTIR (film, cm^{-1}): 3402, 2852, 1684, 1646, 1451, 1260, 1147, 935, 727. HRMS (ESI^+): calcd for $C_{11}H_{17}F_3NOS$ m/z 268.0983, found 268.0988.

*4.6.2. N-(5- and 4-Methyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)-acetamides (**13b**) and (**14b**).* Compounds **13b** and **14b** were obtained (Method 2) as a mixture (85:15) of regioisomers from thioamide **9d** (0.55 g, 2.1 mmol) and isoprene (**5**) (0.30 mL, 2.9 mmol). They were not separated by silica gel column chromatography (eluent: PE/EtOAc, 4:1). Yield: 76% (0.52 g). R_f=0.55 (PE/EtOAc, 4:1). On standing the major isomer **13b** was spontaneously crystallized out from the mixture. *Major isomer (5-methyl)* ***13b***: Colorless crystals. Mp=63–64 °C (from hexane). ^{19}F NMR ($CDCl_3$, δ ppm): −72.5 (s). ^1H NMR ($CDCl_3$, δ ppm): 1.71 (s, 3H, *Me*CO), 1.87 (s, 3H, =CCH_3), 2.28 (dm, $^2J_{H,H}$=15.4 Hz, 1H, CH_AH_B), 2.41 (s, 3H, Me *p*-Tol), 2.63 (dd, $^2J_{H,H}$=15.4 Hz, $^3J_{H,H}$=6.6 Hz, 1H, CH_AH_B), 2.80 (d, $^2J_{H,H}$=14.7 Hz, 1H, SCH_AH_B), 3.14 (d, $^2J_{H,H}$=14.7 Hz, 1H, SCH_AH_B), 5.16 (br s, 1H, =CH), 7.06–7.24 (m, 4H, *p*-Tol). ^{13}C NMR ($CDCl_3$, δ ppm): 21.0 (s, CH_3), 22.2 (s, CH_3), 25.8 (s, CH_3), 30.7 (q, $^3J_{C,F}$=2.0 Hz, CH_2), 31.3 (s, SCH_2), 74.2 (q, $^2J_{C,F}$=28.1 Hz, CCF_3), 119.5 (s, *CH*=CCH_3), 126.2 (q, $^1J_{C,F}$=287.6 Hz, CF_3), 129.6, 129.7, 130.2, 130.8 (s, CH Ar), 138.6, 138.8, 139.2 (3×s, 2×C_q Ar+C_q Het), 171.3 (s, C=O). MS (ESI^+): m/z=352 [M+Na^+], 330 [M^+]. X-ray crystal structure determination of **13b**. $C_{16}H_{18}F_3NOS$, M=329.37, monoclinic, $P2_1/c$ (Nr 14), a=14.304(1)Å, b=8.2377(6)Å, c=15.921(1) Å, β=118.432(5)°, V=1649.7(2)Å^3, Z=4, d_{calcd}=1.326. A total of 12,633 reflections were collected at room temperature using a three-circle goniometer of a Bruker SMART APEX diffractometer equipped with a CCD area detector and Mo Kα radiation (λ=0.71069 Å). The structure was solved by direct methods with SHELXS-97[32] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97[33] available with the WinGX[34] package. The hydrogen atoms were located by Fourier-difference synthesis and fixed geometrically according to their environment with a common isotropic temperature factor. The final cycle of full matrix least square refinement on F^2 was based on 3362 observed reflections and 203 variable parameters and converged with unweighted and weighted agreement factors of $R1$=0.0454, $wR2$=0.1224 for 2876 reflections with $I>2\sigma I$ and $R1$=0.0520, $wR2$=0.1282 for all data. The data have been deposited to the Cambridge Crystallographic Data Centre (Nr CCDC 811996). ORTEP representation of compound **13b** is given in Fig. 5. *Selected data for minor isomer (4-methyl)* ***14b***: Oil. ^{19}F NMR ($CDCl_3$, δ ppm): −71.2 (s). ^1H NMR ($CDCl_3$, δ ppm): 5.77 (br s, 1H, =CH).

*4.6.3. N-(5- and 4-Methyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)-benzamides (**13c**) and (**14c**).* Compounds **13c** and **14c** were obtained (Method 2) as a mixture of regioisomers (85:15) from thioamide **9i** (0.16 g, 0.5 mmol) and isoprene (**5**) (0.1 mL, 1 mmol). They were not separated by silica gel column chromatography (eluent: PE/EtOAc, 9:1); analyses were done on the mixture. Yield: 67% (0.13 g). Oil. R_f=0.25 (PE/EtOAc, 9:1). *Major isomer (5-methyl)* ***13c***: ^{19}F NMR ($CDCl_3$, δ ppm): −72.5 (s). ^1H NMR ($CDCl_3$, δ ppm): 1.82 (s, 3H, =CCH_3), 2.25 (s, 3H, Me *p*-Tol), 2.41 (dm, $^2J_{H,H}$=15.4 Hz, 1H, CH_AH_B), 2.82 (d, $^2J_{H,H}$=14.6 Hz, 1H, SCH_AH_B), 2.95 (dd, $^2J_{H,H}$=15.4 Hz, $^3J_{H,H}$=6.8 Hz, 1H, CH_AH_B), 3.17 (d, $^2J_{H,H}$=14.7 Hz, 1H, SCH_AH_B), 4.95 (br s, 1H, =CH), 6.96–7.20 (m, 9H, *p*-Tol+Ph). ^{13}C NMR ($CDCl_3$, δ ppm): 21.0 (s, CH_3), 22.3 (s, CH_3), 31.2 (q, $^3J_{C,F}$=2.2 Hz, CH_2), 31.5 (s, SCH_2), 75.2 (q, $^2J_{C,F}$=28.0 Hz, CCF_3), 119.6 (s, *CH*=CCH_3), 126.4 (q, $^1J_{C,F}$=287.1 Hz, CF_3), 127.5, 127.7, 128.9, 129.0 (4×s, $CH_{p\text{-}Tol}$+CH_{Ph}), 137.5, 138.0, 138.3, 138.7 (4×s, $C_{q\ p\text{-}Tol}$+C_{qPh}+C_{qHet}), 172.1 (s, C=O). HRMS (ESI^+): calcd for $C_{21}H_{20}F_3NONaS$ m/z 414.1115, found 414.1124. *Selected data for minor isomer (4-methyl)* ***14c***: ^{19}F NMR ($CDCl_3$, δ ppm): −71.8 (s). ^1H NMR ($CDCl_3$, δ ppm): 5.81 (br s, 1H, =CH).

4.7. Reactions of thioamide 9d with penta-1,3-diene (6) (Scheme 6)

*4.7.1. N-(3- and 6-Methyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)-acetamides (**15**) and (**16**).* Compounds **15** and **16** were obtained (Method 2) as a mixture of two regioisomers (each regioisomer being a mixture of two diastereoisomers) (40:24; 22:14) from thioamide **9d** (0.55 g, 2.1 mmol) and penta-1,3-diene (**6**) (0.3 mL, 2.9 mmol). Isomers were not fully separated by silica gel column chromatography (eluent: PE/EtOAc, 6:1); but several enriched fractions with certain isomers were obtained allowing structural assignment of regioisomers by NMR. Yield: 80% (0.26 g). GC/MS (m/z)=329 [M^+]. HRMS (ESI^+): calcd for $C_{16}H_{18}F_3NONaS$ m/z 352.0959, found 352.0963. *3-Methyl regioisomer: major diastereoisomer* ***15a***: Colorless solid. Mp=123–125 °C (from hexane). R_f=0.42 (PE/EtOAc, 6:1). ^{19}F NMR ($CDCl_3$, δ ppm): −72.9 (s). ^1H NMR ($CDCl_3$, δ ppm): 1.36 (d, $^3J_{H,H}$=7.2 Hz, 3H, CH_3), 1.71 (s, 3H, MeCO), 2.27 (dm, $^2J_{H,H}$=15.5 Hz, 1H, CH_AH_B), 2.41 (s, 3H, Me *p*-Tol), 2.67 (dd, $^2J_{H,H}$=15.5 Hz, $^3J_{H,H}$=6.8 Hz, 1H, CH_AH_B), 3.43 (m, 1H, CHMe), 5.45 (m, 1H, =CH), 6.08 (dt, $^3J_{H,H}$=9.0 Hz, $^3J_{H,H}$=3.0 Hz, 1H, =CH), 7.07–7.30 (m, 4H, *p*-Tol). *Selected data for minor diastereoisomer* ***15b***: R_f=0.24 (PE/EtOAc, 6:1). ^{19}F NMR ($CDCl_3$, δ ppm): −70.6 (s). ^1H NMR ($CDCl_3$, δ ppm): 3.54 (m, 1H, CHMe). *6-Methyl regioisomer: major diastereoisomer* ***16a***: R_f=0.48 (PE/EtOAc, 6:1). ^{19}F NMR ($CDCl_3$, δ ppm): −67.7 (s). ^1H NMR ($CDCl_3$, δ ppm): 1.36 (d, $^3J_{H,H}$=6.6 Hz, 3H, CH_3), 1.74 (s, 3H, MeCO), 2.41 (s, 3H, Me *p*-Tol), 2.94 (dm, $^2J_{H,H}$=17.1 Hz, 1H, CH_AH_B), 3.43 (d, $^2J_{H,H}$=17.1 Hz, 1H, CH_AH_B), 4.30 (dq, $^3J_{H,H}$=6.8 Hz, $^3J_{H,H}$=6.6 Hz, 1H, CHMe), 5.69 (dm, $^3J_{H,H}$=10.5 Hz, 1H, =CH), 5.83 (dd, $^3J_{H,H}$=10.5, $^3J_{H,H}$=6.8 Hz, 1H, =CH), 7.1–7.3 (m, 4H, *p*-Tol). *Selected data for minor diastereoisomer* ***16b***: R_f=0.30 (PE/EtOAc, 6:1). ^{19}F NMR ($CDCl_3$, δ ppm): −63.7 (s). ^1H NMR ($CDCl_3$, δ ppm): 3.79 (m, 1H, CHMe).

4.8. Reactions of thioamides 9d–f with 1-trimethylsilyloxy-buta-1,3-diene (7) (Scheme 7, Table 3)

*4.8.1. N-(2-(Trifluoromethyl)-3- and 6-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)acetamide (**17**) and (**20**).* Compounds **17** and **20** were obtained (Method 2) as a mixture of two regioisomers (each regioisomer being itself a mixture of two diastereoisomers (crude mixture: 50:12; 24:14)) from thioamide **9d** (0.2 g, 0.75 mmol) and 1-trimethylsilyloxy-buta-1,3-diene (**7**) (0.26 mL, 1.5 mmol). The single diastereoisomer **17a** was obtained as the major product after silica gel column chromatography (eluent: PE/EtOAc, 4:1). Regioisomers **20a**,**b** were characterized in the crude mixture but spontaneously decomposed during silica gel purification. *3-Trimethylsilyloxy regioisomer: major diastereoisomer* **17a**: Yield: 17% (50 mg). Yellow solid. Mp=72–75 °C. R_f=0.55 (PE/EtOAc, 4:1). ^{19}F NMR ($CDCl_3$, δ ppm): −62.5 (s). ^1H NMR ($CDCl_3$, δ ppm): 0.14 (s, 9H, $SiMe_3$), 1.71 (s, 3H, MeCO), 2.39 (s, 3H, *Me* *p*-Tol), 2.83 (ddd, $^2J_{H,H}$=16.5 Hz, $^3J_{H,H}$=3.6 Hz, $^4J_{H,H}$=1.2 Hz, 1H, CH_2), 3.17 (ddd, $^2J_{H,H}$=16.5 Hz, $^3J_{H,H}$=3.6 Hz, $^4J_{H,H}$=1.2 Hz, 1H, CH_2), 5.87 (d, $^3J_{H,H}$=5.1 Hz, 1H, *CH*OTMS), 5.98 (dd, $^3J_{H,H}$=10.2 Hz, $^3J_{H,H}$=5.4 Hz, 1H, =CH), 6.06 (dt, $^3J_{H,H}$=10.2 Hz, $^3J_{H,H}$=3.9 Hz, 1H, =CH), 7.0–7.3 (m, 4H, CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): 0.4 (s, $SiMe_3$), 21.3 (s, *Me* *p*-Tol), 26.4 (s, CH_2), 27.1 (s, *Me*CO), 63.5 (s, *CH*OTMS), 77.9 (q, $^2J_{C,F}$=25.5 Hz, C_q), 125.0 (q, $^1J_{C,F}$=289.2 Hz, CF_3), 126.3 (s, =CH), 129.3, 129.5, 130.1, 130.4 (s, CH_{Ar}), 131.0 (q, $^4J_{C,F}$=1.8 Hz, =CH), 138.8 (s, C_q, C_{Ar}Me), 139.3 (s, C_q, C_{Ar}N), 172.6 (s, C=O). MS (ESI^+): m/z=404 [M+H]$^+$, 332, 314. FTIR (film, cm^{-1}): 3412, 2959, 1674, 1511, 1368, 1253, 1182, 887. HRMS (ESI^+): calcd for $C_{18}H_{24}F_3NO_2SSiNa$ m/z 426.1147, found 426.1138.

Selected data for minor diastereoisomer **17b**: ^{19}F NMR ($CDCl_3$, δ ppm): −67.3 (s). *6-Trimethylsilyloxy regioisomer*: *selected data for major diastereoisomer* **20a**: ^{19}F NMR ($CDCl_3$, δ ppm): −71.6 (s). *Selected data for minor diastereoisomer* **20b**: ^{19}F NMR ($CDCl_3$, δ ppm): −72.3 (s).

When a dichloromethane solution of **17a** was kept at room temperature for several days, a spontaneous quantitative desilylation occurred leading to compound **18** (Fig. 6). Colorless solid. Mp=130–131 °C. ^{19}F NMR ($CDCl_3$, δ ppm): −66.1 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.83 (s, 3H, MeCO), 2.42 (s, 3H, *Me p*-Tol), 2.84 (dd, $^2J_{H,H}$=17.3 Hz, $^3J_{H,H}$=3.6 Hz, 1H, CH_2), 3.34 (d, $^2J_{H,H}$=17.3 Hz, 1H, CH_2), 4.97 (br s, 1H, *CH*OH), 5.86–6.04 (m, 2H, CH=CH), 7.11 (d, $^3J_{H,H}$=8.1 Hz, 1H, CH_{Ar}), 7.18 (d, $^3J_{H,H}$=8.1 Hz, 1H, CH_{Ar}), 7.26 (d, $^3J_{H,H}$=8.1 Hz, 2H, CH_{Ar}). HRMS (ESI$^+$): calcd for $C_{15}H_{16}F_3NO_2NaS$ *m*/*z* 354.0752, found 354.0761.

*4.8.2. N-(2-(1,1,2,2,3,3,4,4-Octafluorobutyl)-3- and 6-(trimethylsilyloxy)-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)acetamide (**19**) and (**21**).* Cycloadducts **19** and **21** were obtained (Method 2) as a complex mixture of two regioisomers (each regioisomer being a mixture of two diastereoisomers whose ratio was not possible to determine in the crude mixture) from thioamide **9e** (0.4 g, 1 mmol) and 1-trimethylsilyloxy-buta-1,3-diene (**7**) (0.35 mL, 2 mmol). After silica gel column chromatography (eluent: PE/EtOAc, 4:1), the single diastereoisomer **19** was obtained as the result of a desilylation and an acetyl group migration. Regioisomers **21a**,**b** were characterized in the crude mixture but spontaneously decomposed during silica gel purification. *Compound* **19**: Yield: 11% (50 mg). Mp=60–62 °C. R_f=0.55 (PE/EtOAc, 4:1). ^{19}F NMR ($CDCl_3$, δ ppm): −108.0 (1F, CF_2, *AB*, $^2J_{F,F}$=289 Hz), −109.4 (1F, CF_2, *AB*, $^2J_{F,F}$=289 Hz), −122.6, −122.9 (2F, 2×m, CF_2), −130.2, −130.3 (2F, 2×m, CF_2), −137.5 (2F, dm, HCF_2, $^2J_{F,H}$=52.1 Hz). ^{1}H NMR ($CDCl_3$, δ ppm): 2.16 (s, 3H, MeCO), 2.28 (s, 3H, Me *p*-Tol), 2.84 (ddd, $^2J_{H,H}$=17.8 Hz, $^3J_{H,H}$=5.3 Hz, $^4J_{H,H}$=1.2 Hz, 1H, CH_2), 3.02 (ddd, $^2J_{H,H}$=17.9 Hz, $^3J_{H,H}$=5.2 Hz, $^4J_{H,H}$=2.6 Hz, 1H, CH_2), 4.31 (br s, 1H, NH), 5.47 (d, $^3J_{H,H}$=5.5 Hz, 1H, *CH*OAc), 5.98 (tt, $^2J_{H,F}$=52.1 Hz, $^3J_{H,F}$=5.7 Hz, 1H, HCF_2), 5.98–6.04 (m, 1H, HC=), 6.13 (m, 1H, =CH), 7.02 (d, $^3J_{H,H}$=8.0 Hz, 2H, 2×CH_{Ar}), 7.13 (d, $^3J_{H,H}$=8.0 Hz, 2H, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): 20.6 (s, *Me*CO), 21.0 (s, CH_3 *p*-Tol), 25.3 (s, CH_2), 68.7 (t, $^2J_{C,F}$=24.9 Hz, C_q, CCF_2), 70.5 (s, *CH*OAc), 107.8 (tt, $^1J_{C,F}$=254.2 Hz, $^2J_{C,F}$=30.0 Hz, HCF_2), 105–120 (m, $CF_2CF_2CF_2$), 117.9 (s, =CH), 125.8 (s, =CH), 127.7 (s, C_q, C_{Ar}Me), 129.4, 130.1 (s, CH_{Ar}), 140.8 (s, C_q, C_{Ar}N), 169.2 (s, C=O). GC/MS : m/z=403 [M^+−OAc]. FTIR (film, cm^{-1}): 3423, 2925, 1755, 1686, 1517, 1372, 1224, 1174, 1129. HRMS (ESI$^+$): calcd for $C_{18}H_{17}F_8NO_2SNa$ *m*/*z* 486.0750, found 486.0764.

*4.8.3. 4-(2-(Trifluoromethyl)-6-trimethylsiloxy-3,6-dihydro-2H-thiopyran-2-yl)morpholine (**22**).* Compounds **22a**,**b** were obtained (Method 3) as a mixture (67:33) of diastereomers from thioamide **9f** (0.2 g, 1.0 mmol) and 1-trimethylsilyloxy-buta-1,3-diene (**7**) (1.8 mL, 10 mmol). They were not separated by silica gel column chromatography (eluent: PE/EtOAc, 9:1); analyses were done on the mixture. Yield: 12% (40 mg). Oil. R_f=0.31 (PE/EtOAc, 9:1). ^{19}F NMR ($CDCl_3$, δ ppm): −71.2 (s, CF_3, major), −71.4 (s, CF_3, minor). ^{1}H NMR ($CDCl_3$, δ ppm): 0.2 (s, 18H, 2×$SiMe_3$), 2.5–3.2 (m, 12H, CH_2N+CH_2), 3.6 (m, 8H, CH_2O), 5.35 (br s, 1H, *CH*OTMS, major), 5.60 (br s, 1H, *CH*OTMS, minor), 5.7–5.8 (m, 2H, =CH), 5.8–5.9 (m, 2H, =CH). FTIR (film, cm^{-1}): 3402, 2855, 1723, 1614, 1453, 1288, 1119, 844, 726. HRMS (ESI$^+$): calcd for $C_{13}H_{23}F_3NO_2SSi$ *m*/*z* 342.1171, found 342.1174.

4.9. Reaction of thioamide 9d with 2-trimethylsilyloxy-buta-1,3-diene (23) (Scheme 8)

*4.9.1. N-(6-Trifluoromethyl-3-oxo-tetrahydrothiopyran-6-yl)-N-(p-tolyl)-acetamide (**24**).* 2-(Trimethylsilyloxy)buta-1,3-diene (**23**) (0.22 mL, 1.2 mmol) was added to a solution of thioamide **9d** (0.31 g, 1.2 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 15 h. ^{19}F NMR spectra of the reaction mixture showed full conversion of **9d** into primary silylated cycloadduct (δ_F=−72.2 ppm). HCl (1 mL of 0.5%) in MeOH solution was then added to the resulting mixture and it was stirred at room temperature for 6 h (^{19}F NMR of the reaction mixture showed full conversion of silylated cycloadduct into thiopyranone **24**). The solvent was then evaporated in vacuo and the residue was purified by silica gel column chromatography (eluent: mixture petroleum ether and ethyl acetate, 2:1) yielding compound **24** (0.24 g, 59%). Mp=115–117 °C. R_f=0.6 (PE/EtOAc, 2:1). ^{19}F NMR ($CDCl_3$, δ ppm): −75.0 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.78 (s, 3H, MeCO), 2.12–2.23 (m, 2H, CH_2), 2.32–2.41 (m, 1H, CH_2), 2.42 (s, 3H, Me *p*-Tol), 2.63–2.74 (m, 1H, CH_2), 2.96 (d, $^2J_{H,H}$=15.5 Hz, 1H, SCH_AH_B), 3.61 (d, $^2J_{H,H}$=15.5 Hz, 1H, SCH_AH_B), 7.18–7.28 (m, 4H, CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): 21.0 (s, *Me p*-Tol), 25.5 (s, *Me*CO), 26.6 (s, CH_2), 33.6 (s, CH_2), 37.8 (s, CH_2), 69.6 (q, $^2J_{C,F}$=29.6 Hz, C_q), 126.3 (q, $^1J_{C,F}$=287.6 Hz, CF_3), 130.0, 130.1, 130.3, 130.5 (4×s, 4×CH_{Ar}), 137.2 (s, C_q, C_{Ar}Me), 139.9 (s, C_q, C_{Ar}N), 172.3 (s, *CO*Me), 203.9 (s, C=O_{cyclic}). HRMS (ESI$^+$): calcd for $C_{15}H_{16}F_3NO_2SNa$ *m*/*z* 354.0752, found 354.0750.

4.10. Typical procedure for reactions of thioamides 9d,e with Danishefsky's dienes 8a,b (Scheme 9, Table 4)

Compound **25** (0.46 g, yield: 60%) was obtained (Method 2) as only one diastereoisomer from thioamide **9d** (0.55 g, 2.1 mmol) and Danishefsky's diene **8a** (0.4 mL, 2.1 mmol), after desilylation under neutral conditions and silica gel column chromatography (eluent: PE/EtOAc, 2:1).

*4.10.1. N-(5-Methoxy-6-trifluoromethyl-3-oxo-tetrahydrothiopyran-6-yl)-N-(p-tolyl)-acetamide (**25**).* Solid. Mp=146–147 °C. R_f=0.4 (PE/EtOAc, 2:1). ^{19}F NMR ($CDCl_3$, δ ppm): −66.3 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 1.76 (s, 3H, MeCO), 2.42 (s, 3H, Me *p*-Tol), 2.70 (dd, $^2J_{H,H}$=17.4 Hz, $^3J_{H,H}$=4.9 Hz, 1H, CH_AH_B), 2.93 (d, $^2J_{H,H}$=15.6 Hz, 1H, SCH_AH_B), 2.97 (dd, $^2J_{H,H}$=17.4 Hz, $^3J_{H,H}$=1.7 Hz, 1H, CH_AH_B), 3.28 (s, 3H, CH_3O), 3.74 (d, $^2J_{H,H}$=15.6 Hz, 1H, SCH_AH_B), 4.81 (dd, $^3J_{H,H}$=4.9 Hz, $^3J_{H,H}$=1.7 Hz, 1H, *CH*OMe), 7.12–7.28 (m, 4H, CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): 21.0 (s, *Me p*-Tol), 26.1 (s, *Me*CO), 37.7 (s, CH_2), 39.1 (s, CH_2), 58.0 (s, CH_3O), 74.2 (q, $^2J_{C,F}$=28.0 Hz, C_q), 77.5 (s, *CH*OMe), 125.4 (q, $^1J_{C,F}$=289.3 Hz, CF_3), 129.9, 130.2, 130.3, 130.4 (4×s, 4×CH_{Ar}), 137.8 (s, C_q, C_{Ar}Me), 139.7 (s, C_q, C_{Ar}N), 172.5 (s, *CO*Me), 202.0 (s, C=O_{cyclic}). HRMS (ESI$^+$): calcd for $C_{16}H_{18}F_3NO_3SNa$ *m*/*z* 384.0857, found 384.0847.

*4.10.2. N-(5-Methoxy-6-(1,1,2,2,3,3,4,4-octafluorobutyl)-3-oxo-tetrahydrothiopyran-6-yl)-N-(p-tolyl)acetamide (**26**).* Yield: 62% (0.30 g). Oil. R_f=0.4 (PE/EtOAc, 3:1). ^{19}F NMR ($CDCl_3$, δ ppm): −98.0 (1F, CF_2, *AB*, $^2J_{F,F}$=278.0 Hz), −103.2 (1F, CF_2, *AB*, $^2J_{F,F}$=278.0 Hz), −120.2 (1F, CF_2, *AB*, $^2J_{F,F}$=295.1 Hz), −121.9 (1F, CF_2, *AB*, $^2J_{F,F}$=295.1 Hz), −129.7 (2F, m, CF_2), −137.0 (1F, dm, HCF_2, $^2J_{F,H}$=51.2 Hz), −137.6 (1F, dm, HCF_2, $^2J_{F,H}$=51.2 Hz). ^{1}H NMR ($CDCl_3$, δ ppm): 1.76 (s, 3H, MeCO), 2.40 (s, 3H, Me *p*-Tol), 2.92 (m, 1H, CH_2), 2.94 (s, 2H, CH_2), 3.43 (m, 1H, CH_2), 3.45 (s, 3H, OMe), 5.59 (br s, 1H, *CH*OMe), 6.09 (tt, $^2J_{H,F}$=51.2 Hz, $^3J_{H,F}$=5.6 Hz, 1H, HCF_2), 7.18–7.34 (m, 4H, CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): 21.3 (s, CH_3 *p*-Tol), 27.3 (s, *Me*CO), 37.5 (s, CH_2), 40.0 (s, CH_2), 57.7 (s, OCH_3), 75.0 (s, *CH*OMe), 78.7 (m, C_q), 129.7, 129.8, 130.3, 130.7 (4×s, 4×CH_{Ar}), 139.1 (s, C_q, C_{Ar}Me), 140.5 (s, C_q, C_{Ar}N), 173.4 (s, *CO*Me), 202.0 (s, CO_{cyclic}). GC/MS: *m*/*z*=493 [M^+], 350, 318, 250, 149, 100. FTIR (film, cm^{-1}): 3430, 2932, 1725, 1689, 1509, 1369, 1294. HRMS (ESI$^+$): calcd for $C_{19}H_{20}F_8NO_3S$ *m*/*z* 494.1036, found 494.1033.

4.10.3. N-(3-Methoxy-2-trifluoromethyl-5-(tert-butyldimethylsilyloxy)-3,6-dihydro-2H-thiopyran-2-yl)-N-(p-tolyl)acetamide

(**27**). Yield: 75% (0.67 g). Colorless crystal. Mp=116–118 °C. R_f=0.4 (PE/EtOAc, 9:1). ^{19}F NMR ($CDCl_3$, δ ppm): −62.9 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 0.21 (s, 3H, $SiCH_3$), 0.25 (s, 3H, $SiCH_3$), 0.96 (s, 9H, SiBu-*t*), 1.71 (s, 3H, MeCO), 2.40 (s, 3H, Me *p*-Tol), 2.56 (d, $^2J_{H,H}$=15.6 Hz, 1H, SCH_AH_B), 3.11 (dd, $^2J_{H,H}$=15.6 Hz, $^4J_{H,H}$=1.2 Hz, 1H, SCH_AH_B), 3.29 (s, 3H, CH_3O), 5.18 (dd, $^3J_{H,H}$=6.4 Hz, $^4J_{H,H}$=1.2 Hz, 1H, C=*CH*), 5.45 (d, $^3J_{H,H}$=6.4 Hz, 1H, *CH*OMe), 7.00 (d, $^3J_{H,H}$=8.1 Hz, 1H, CH_{Ar}), 7.14 (d, $^3J_{H,H}$=8.1 Hz, 1H, CH_{Ar}), 7.21 (d, $^3J_{H,H}$=8.1 Hz, 2H, 2×CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): −4.8 (s, $SiCH_3$), −4.4 (s, $SiCH_3$), 18.0 (s, C_q *t*-Bu), 21.2 (s, *Me p*-Tol), 25.5 (s, CH_3 *t*-Bu), 26.9 (s, *Me*CO), 28.8 (s, CH_2), 56.3 (s, CH_3O), 73.9 (s, *CH*OMe), 76.4 (q, $^2J_{C,F}$=27.5 Hz, C_q), 101.9 (s, *CH*=C), 125.0 (q, $^1J_{C,F}$=289.8 Hz, CF_3), 129.3, 129.5, 130.0, 130.8 (4×s, 4×CH_{Ar}), 138.8 (s, C_q, C_{Ar}Me), 139.3 (s, C_q, C_{Ar}N), 151.2 (s, C_q, =*C*OTBS), 172.1 (s, C=O). HRMS (ESI$^+$): calcd for $C_{22}H_{32}F_3NO_3SSiNa$ *m*/*z* 498.1722, found 498.1718. X-ray crystal structure determination of **27**. $C_{22}H_{32}F_3NO_3SSi$, *M*=475.64, triclinic, *P*-1 (Nr 2), *a*=11.314(1)Å, *b*=11.538(1)Å, *c*=12.048(2)Å, α=109.675(2)°, β=111.281(2)°, γ=104.073(2)°, *V*=1254.6(3)Å^3, *Z*=2, d_{calcd}=1.259. A total of 10,105 reflections were collected at room temperature using a three-circle goniometer of a Bruker SMART APEX diffractometer equipped with a CCD area detector and Mo Kα radiation (λ=0.71069 Å). The structure was solved by direct methods with SHELXS-97[32] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97[33] available with the WinGX[34] package. The hydrogen atoms were located by Fourier-difference synthesis and fixed geometrically according to their environment with a common isotropic temperature factor. The final cycle of full matrix least square refinement on F^2 was based on 5071 observed reflections and 288 variable parameters and converged with unweighted and weighted agreement factors of *R*1=0.0491, *wR*2=0.1343 for 4049 reflections with $I>2\sigma I$ and *R*1=0.0605, *wR*2=0.1433 for all data. The data have been deposited to the Cambridge Crystallographic Data Centre (Nr CCDC820012). ORTEP representation of compound **27** is given in Fig. 7.

4.11. Typical procedure for reaction of thioamide 9f with Danishefsky's diene 8a (Scheme 10)

Thioamide **9f** (0.25 g, 1.25 mmol) and Danishefsky's diene **8a** (0.55 mL, 2.5 mmol) were heated at 150 °C in a 10 mL pressure vessel sealed with Teflon septum with stirring in an oil bath for 5 h (Method 3). After evaporation of the volatiles, the residue was dissolved in THF (15 mL) and 1.5 mL of TFA or HCl (large excess) was added. The reaction mixture was stirred at room temperature for 20 h, and evaporated in vacuo. ^{19}F NMR spectra of the crude mixture revealed significant conversion of starting compound **9f** into cycloadducts but the latter were mainly decomposed during purification by silica gel column chromatography (eluent: mixture petroleum ether and ethyl acetate, 3:1) affording a mixture of compound **28** (40 mg, yield: 10%, mixture (67:33) of diastereoisomers) and the product **29** (40 mg, yield: 10%).

*4.11.1. 6-Methoxy-2-morpholino-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-4(3H)-one (**28**).* Oil. R_f=0.32 (PE/EtOAc, 3:1). Only analyses of major diastereoisomer are given. ^{19}F NMR ($CDCl_3$, δ ppm): −70.4 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 2.8–2.9 (m, 4H, 2×CH_2N), 2.87 (d, $^2J_{H,H}$=15.0 Hz, 1H, $CH_AH_BC_q$), 2.9 (m, 2H, CH_2CO), 3.27 (dd, $^2J_{H,H}$=15.0 Hz, $^4J_{H,H}$=1.2 Hz, 1H, $CH_AH_BC_q$), 3.46 (s, 3H, OCH_3), 3.70 (m, 4H, 2×CH_2O), 4.92 (dd, $^3J_{H,H}$=$^3J_{H,H}$=3.6 Hz, 1H, *CH*OMe). GC/MS: *m*/*z*=299 [M$^+$].

*4.11.2. 2-Trifluoromethyl-4H-thiopyran-4-one (**29**).*[28] Oil. R_f=0.25 (PE/EtOAc, 3:1). ^{19}F NMR ($CDCl_3$, δ ppm): −64.2 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 7.12 (d, $^3J_{H,H}$=10.3 Hz, 1H, CH), 7.35 (s, 1H, CH), 7.81 (d, $^3J_{H,H}$=10.3 Hz, 1H, CH). GC/MS: *m*/*z*=180 [M$^+$], 152, 133.

4.12. Typical procedure for the rearrangement of cycloadducts 30 into 1,3-thiazolidin-4-ones 31 (Scheme 11)

Danishefsky's diene **8a** (0.45 mL, 2.3 mmol) was added to a solution of thioamide **9d** (0.6 g, 2.3 mmol) in 10 mL of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 24 h. ^{19}F NMR spectra of the reaction mixture showed full conversion of **9d** into cycloadduct **30a** (δ_F=−62.9 ppm). Then, solid TBAF·3H$_2$O (1.45 g, 4.6 mmol) was added to the solution, which was stirred at room temperature for 15 h (^{19}F NMR of the reaction mixture showed full conversion of cycloadduct **30a** into thiazolidinone **31a**). Solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (eluent: mixture petroleum ether and ethyl acetate, 2:1) affording **31a** (0.27 g, 33%).

*4.12.1. 2-(1-Methoxy-3-oxobutyl)-3-(p-tolyl)-2-(trifluoromethyl) thiazolidin-4-one (**31a**).* Solid. Mp=146–147 °C. R_f=0.3 (PE/EtOAc, 2:1). ^{19}F NMR ($CDCl_3$, δ ppm): −69.6 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 2.31 (s, 3H, MeCO), 2.39 (s, 3H, Me *p*-Tol), 2.98 (d, $^2J_{H,H}$=18.1 Hz, 1H, CH_AH_B), 3.21 (dd, $^2J_{H,H}$=18.1 Hz, $^3J_{H,H}$=8.3 Hz, 1H, CH_AH_B), 3.31 (s, 3H, CH_3O), 3.65 (d, $^2J_{H,H}$=15.8 Hz, 1H, SCH_AH_B), 3.87 (d, $^2J_{H,H}$=15.8 Hz, 1H, SCH_AH_B), 4.48 (m, 1H, *CH*OMe), 6.95 (d, $^3J_{H,H}$=8.1 Hz, 2H, CH_{Ar}), 7.25 (d, $^3J_{H,H}$=8.1 Hz, 2H, CH_{Ar}). ^{13}C NMR ($CDCl_3$, δ ppm): 21.3 (s, *Me p*-Tol), 31.0 (s, SCH_2), 31.3 (s, *Me*CO), 46.6 (s, CH_2), 60.0 (s, CH_3O), 76.6 (q, $^2J_{C,F}$=28 Hz, C_q), 76.6 (s, *CH*OMe), 125.2 (q, $^1J_{C,F}$=287.0 Hz, CF_3), 128.8 (s, 2×CH_{Ar}), 130.5 (s, 2×CH_{Ar}), 132.9 (s, C_q, C_{Ar}Me), 139.9 (s, C_q, C_{Ar}N), 172.9 (s, C=O cyclic), 205.6 (s, C=O). HRMS (ESI$^+$): calcd for $C_{16}H_{18}F_3NO_3SNa$ *m*/*z* 384.0857, found 384.0862. X-ray crystal structure determination of **31a**. $C_{16}H_{18}F_3NO_3S$, *M*=361.37, triclinic, *P*-1 (Nr 2), *a*=7.929(1)Å, *b*=10.355(1)Å, *c*=11.316(1)Å, α=90.714(2)°, β=98.565(2)°, γ=106.499(2)°, V=879.4(1)Å^3, *Z*=2, d_{calcd}=1.365. A total of 7005 reflections were collected at room temperature using a three-circle goniometer of a Bruker SMART APEX diffractometer equipped with a CCD area detector and Mo Kα radiation (λ=0.71069 Å). The structure was solved by direct methods with SHELXS-97[32] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97.[33] The hydrogen atoms were located by Fourier-difference synthesis and fixed geometrically according to their environment with a common isotropic temperature factor. The final cycle of full matrix least square refinement on F^2 was based on 3518 observed reflections and 220 variable parameters and converged with unweighted and weighted agreement factors of *R*1=0.0525, *wR*2=0.1419 for 2714 reflections with $I>2\sigma I$ and *R*1=0.0665, *wR*2=0.1537 for all data. The data have been deposited to the Cambridge Crystallographic Data Centre (Nr CCDC816987). ORTEP representation of compound **31a** is given in Fig. 8.

*4.12.2. 2-(1-Methoxy-3-oxobutyl)-3-propyl-2-(trifluoromethyl)thiazolidin-4-one (**31b**).* Yield: 43% (0.28 g). Colorless crystals. Mp=88–90 °C. R_f=0.35 (PE/EtOAc, 2:1). ^{19}F NMR ($CDCl_3$, δ ppm): −72.4 (s). ^{1}H NMR ($CDCl_3$, δ ppm): 0.87 (t, $^3J_{H,H}$=7.5 Hz, 3H, $CH_3CH_2CH_2$), 1.49–1.69 (m, 2H, $CH_3CH_2CH_2$), 2.23 (s, 3H, MeCO), 2.45 (dd, $^2J_{H,H}$=18.0 Hz, $^3J_{H,H}$=1.7 Hz, 1H, CH_AH_B), 2.95 (m, 1H, NCH_AH_B), 3.01 (dd, $^2J_{H,H}$=18.0 Hz, $^3J_{H,H}$=8.0 Hz, 1H, CH_AH_B), 3.22 (m, 1H, NCH_AH_B), 3.40 (s, 3H, CH_3O), 3.43 (d, $^2J_{H,H}$=15.5 Hz, 1H, SCH_AH_B), 3.65 (d, $^2J_{H,H}$=15.8 Hz, 1H, SCH_AH_B), 4.64 (dd, 1H, $^3J_{H,H}$=8.0 Hz, $^3J_{H,H}$=1.7 Hz, *CH*OMe). ^{13}C NMR ($CDCl_3$, δ ppm): 11.4 (s, $CH_3CH_2CH_2$), 20.0 (s, $CH_3CH_2CH_2$), 30.8 (s, SCH_2), 31.1 (s, *Me*CO), 45.5 (s, NCH_2), 46.6 (s, CH_2), 59.9 (s, CH_3O), 75.6 (q, $^2J_{C,F}$=28.5 Hz, C_q), 75.8 (s, *CH*OMe), 125.5 (q, $^1J_{C,F}$=286.5 Hz, CF_3), 172.3 (s, C=O

cyclic), 205.6 (s, C=O). HRMS (ESI^+): calcd for $C_{12}H_{18}F_3NO_3SNa$ m/z 336.0857, found 336.0860.

*4.12.3. N-(5-Methoxy-6-trifluoromethyl-3-oxo-tetrahydrothiopyran-6-yl)-N-(p-tolyl)-propionamide (**32**).* Yield: 55% (0.19 g). Solid. R_f=0.5 (PE/EtOAc, 2:1). ^{19}F NMR ($CDCl_3$, δ ppm): −69.6 (s). ^1H NMR ($CDCl_3$, δ ppm): 1.14 (t, $^3J_{H,H}$=7.3 Hz, 3H, CH_3CH_2CO), 2.38 (s, 3H, *p*-Tol), 2.58 (q, $^3J_{H,H}$=7.3 Hz, 2H, CH_3CH_2CO), 2.91 (d, $^2J_{H,H}$=17.7 Hz, 1H, CH_AH_B), 3.18 (dd, $^2J_{H,H}$=17.7 Hz, $^3J_{H,H}$=8.7 Hz, 1H, CH_AH_B), 3.29 (s, 3H, CH_3O), 3.65 (d, $^2J_{H,H}$=15.7 Hz, 1H, SCH_AH_B), 3.86 (d, $^2J_{H,H}$=15.7 Hz, 1H, SCH_AH_B), 4.50 (d, $^3J_{H,H}$=8.7 Hz, 1H, *CH*OMe), 6.97 (d, $^3J_{H,H}$=8.1 Hz, 2H, CH_{Ar}), 7.25 (d, $^3J_{H,H}$=8.1 Hz, 2H, CH_{Ar}).

Acknowledgements

The authors thank Ambassade de France at Kiev (Institut de Coopération Franco-Ukrainienne) for financial support (O.S.K.), Pr. G. Dupas for theoretical calculations, Pr. Y.G. Shermolovich and T. Besson for interesting discussion, Dr. D. Harakat for HRMS analyses and Dr. K. Plé for English polishing. We also thank the Centre de Ressources Informatiques de Haute-Normandie (CRIHAN) for software optimization and technical support.

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