Journal of Fluorine Chemistry 131 (2010) 172–183

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Asymmetric induction in thia-Diels-Alder reactions of chiral polyfluoroalkylthionocarboxylates

Vadim M. Timoshenko [a,*], Sergiy A. Siry [a], Alexander B. Rozhenko [a,b], Yuriy G. Shermolovich [a]

[a] Institute of Organic Chemistry NAS of Ukraine, Murmanska str. 5, 02660 Kyiv, Ukraine
[b] University of Bielefeld, Universitätstr. 25, 33615 Bielefeld, Germany

ARTICLE INFO

Article history:
Received 22 July 2009
Received in revised form 16 November 2009
Accepted 18 November 2009
Available online 24 November 2009

Keywords:
Thioesters
Fluorine
Thia-Diels-Alder reaction
Dihydrothiopyrans
Asymmetric induction
DFT
Transition state

ABSTRACT

A series of chiral *S*- or *O*-alkyl thionoesters have been synthesized by treatment of trifluorothioacetyl- or 2,2,3,3-tetrafluorothiopropionyl chloride with corresponding thiols or alcohols. The thia-Diels-Alder reaction of the thionoesters with symmetrical 1,3-dienes proceeds with diastereoselectivity up to 60%. Structures of cycloaddition products and corresponding transition states have been studied at the DFT level of approximation. The experimentally observed diastereomeric excess has been referred to differences in activation energies of transition states, preceding formation of the diastereomeric cycloaducts.

1. Introduction

Synthetic methodologies based on the Diels-Alder reaction are widely employed in organic chemistry and have an enormous spectrum of application. Using heterodienes or heterodienophiles in the [4 + 2] cycloaddition reaction makes it possible to construct complex natural products or their analogues containing a six-membered heterocyclic framework [1]. Thiocarbonyl compounds are well known representatives of heterodienophiles which have found applications in total syntheses [2,3], for preparation of thioglycoside derivatives [4] and thiashikimic acid [5]. Electron-withdrawing groups in α-position to the thiocarbonyl group lower the LUMO energy of the heterodienophile and significantly facilitate the cycloaddition. Therefore, polyfluroalkyl thioaldehydes [6], thioketones [7], dithioesters [6–9] are excellent dienophiles and can be used for syntheses of diverse sulfur-containing heterocycles. For symmetrical dienes, at least one new stereogenic centre is generated by Diels-Alder reaction. Therefore, the application of a proper chiral dienophiles could influence the stereochemical outcome of the cycloaddition and can be used in the construction of optically active compounds.

Continuing our studies on applications of polyfluoroalkylthinocarboxylic acids derivatives in syntheses of new fluorine–sulfur-containing compounds, we were interested to study an asymmetric variant of the thia-Diels-Alder reaction of alkyl polyfluoro dithioesters with dienes. For this purpose suitable dithioesters bearing chiral groups were necessary. In this paper we describe a preparation of such chiral substrates, a study of their cycloaddition reactions and a comparison of the diastereoselectivity in these reactions. Additionally, *O*-alkyl polyfluorothionoates have been synthesized for comparison, dienophilic properties of which have not been described to date.

2. Results and discussion

Several synthetic methods are known for the preparation of perfluoroalkyldithiocarboxylates, developed in our laboratory [8–10] and by others groups [11–14]. In order to obtain a series of dithioesters involving a chiral group we have developed another, new and simple method which consists in nucleophilic displacement of chlorine in polyfluorothioalkanoyl chlorides **1** by sulfur in reactions with optically active mercaptanes. Trifluorothioacetyl chloride **1a** and 2,2,3,3-tetrafluorothiopropionyl chloride **1b** were prepared according to the known procedure [15] from corresponding benzyl 1,1-dichloropolyfluoroalkyl sulfides [16] (Fig. 1).

The following chiral thiols prepared according to the described procedure we have chosen as nucleophiles for reactions with chlorides **1**: (1*S*)-10-mercaptocamphor **2a** [17], (1*S*)-thioisoborneol **2b** [18], (1*S*)-thioborneol **2c** [19], (1*S*,2*S*,5*R*)-thioneomenthol **2d** [20] and racemic α-phenethylthiol **2e** [21].

* Corresponding author. Tel.: +380 44 499 4938; fax: +380 44 573 2643.
E-mail address: vadim@ioch.kiev.ua (V.M. Timoshenko).

0022-1139/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2009.11.011

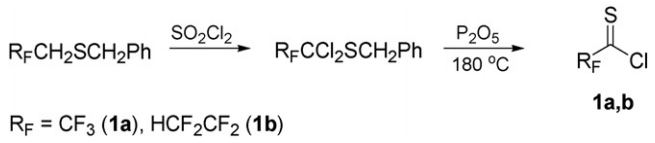
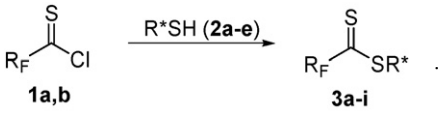


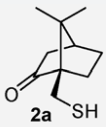
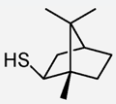
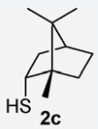
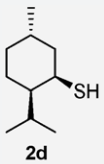
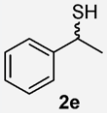
Fig. 1. Synthesis of polyfluorothioalkanoyl chlorides **1** [15,16].

Thiols **2** smoothly react with chlorides **1** in inert solvents at room temperature with evolution of hydrogen chloride yielding dithioesters **3** (Table 1). Progress of reactions was monitored by the ^{19}F NMR spectroscopy. Addition of bases (e.g., triethylamine, NaH) leads to a substantial contamination of reaction mixture, probably due to a thiophilic attack, typical for reactions of fluoroalkyl thiocarbonyl compounds with nucleophiles [22]. Dithioesters **3** have been easily purified by column chromatography and isolated in good yields as red liquids stable at storage.

We have tried to extend this synthetic protocol to reactions of chloride **1** with optically active alcohols for preparing chiral *O*-alkyl polyfluorothionocarboxylates (Method A, Table 2). In literature the preparation of *O*-methyl ester is described by treatment of **1b** with an excess of methanol [15]. We have found that chloride **1b** readily reacts under similar conditions with isopropanol as a model secondary alcohol to give the corresponding thionoester (**4a**) in 78% of yield. The reactions of chlorides **1a**,**b**

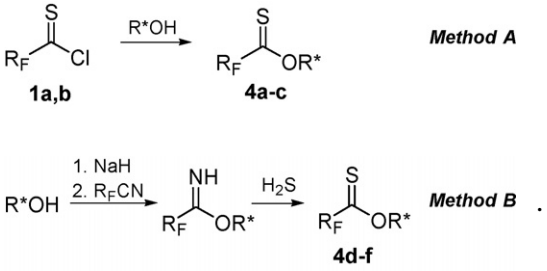
Table 1
Synthesis of dithioesters **3a**–**i**.

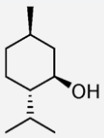
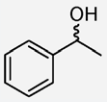


Ester	R_f	Mercaptane **2** (R*SH)	Reaction conditions[a]	Yield (%)
3a	CF_3	 **2a**	$CHCl_3$, 2 h	82
3b	$H(CF_2)_2$		$CHCl_3$, 7 days	75
3c	CF_3	 **2b**	$CHCl_3$, 2 h	80
3d	$H(CF_2)_2$		Hexane, 2 days	70
3e	CF_3	 **2c**	Hexane, 48 h	70
3f	CF_3	 **2d**	Hexane, 7 days	62
3g	$H(CF_2)_2$		Hexane, 10 days	60
3h	CF_3	 **2e**	Hexane–ether, 16 h	85
3i	$H(CF_2)_2$		Hexane–ether, 16 h	90

[a] Reactions proceeded at room temperature.

Table 2
Synthesis of thionoesters **4a**–**f**.



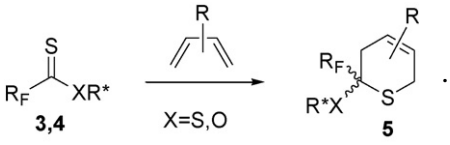
Ester	R_f	Alcohol (R*OH)	Reaction conditions	Yield (%)
4a	$H(CF_2)_2$		Method A, *i*-PrOH, 10 min	78
4b	CF_3		Method A, benzene, 4 days	50
4c	$H(CF_2)_2$		Method A, benzene, 4 days	40
4d	CF_3		Method B	73
4e	$H(CF_2)_2$		Method B	70
4f	$H(CF_2)_2$		Method B	22

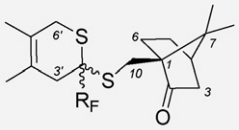
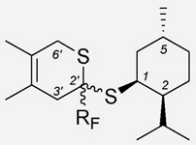
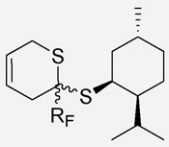
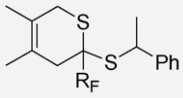
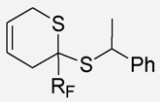
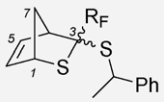
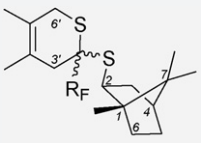
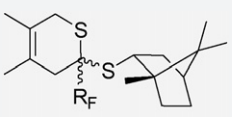
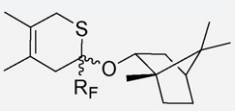
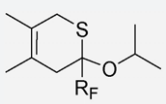
with (1*R*,2*S*,5*R*)-menthol have proceeded in benzene solution for 4 days, after purification by chromatography the target *O*-menthyl esters (**4b**,**c**) were isolated in 40–50% yields. But our efforts to carry out the reaction of (1*S*)-borneol with chloride **1b** were unsuccessful. At room temperature no reaction has been observed in benzene or chloroform after 1 week; heating the reaction mixture was accompanied by decomposition, what follows from ^{19}F NMR monitoring of the reaction. Attempts to replace borneol with the corresponding trimethylsilyl derivative were also unsuccessful: the reaction has not practically proceeded at room temperature and provided a very low yield of the target product at heating, probably, due to the numerous side processes. Our attempt to use a racemic 2-methylbenzyl alcohol has failed, too. Therefore we apply another approach to the synthesis of thionoesters, which consists in thiolysis of iminoesters. Similar strategy was developed for the preparation of perfluoroalkyl dithioesters [11] and trichlorothionoacetates [23]. Treatment of the corresponding alcohol with trifluoroacetonitrile or tetrafluoropropionitrile (obtained by dehydration of trifluoroacetamide or tetrafluoropropionamide with P_2O_5, respectively) afforded iminoesters. Thiolysis of the latter with gaseous hydrogen sulfide in presence of acetic acid has yielded *O*-alkyl thionoesters **4d**–**f** (Method B) (Table 2).

Esters **4a**–**e** are stable yellow liquids, compound **4f** decomposes slowly even at storage in freezer.

Similarly to others known fluoroalkyl *S*-alkyl(aryl)thiocarboxylates [7–10], dithioesters **3** readily react with symmetrical conjugated dienes, such as 1,3-butadiene, 2,3-dimethyl-1,3-butadiene (DMB) or cyclopentadiene giving corresponding [2 + 4]-cycloadducts **5a**–**m** (Table 3) as colourless or slightly yellow oils in good to excellent yields (75–98%). Depending on nature of the substrate and diene the cycloaddition can take a time

Table 3
Diels-Alder reactions of thionoesters **3**,**4**.



Entry	Compounds	R_f	Cycloadduct	Reaction conditions[a]	Total yield (%)	Diastereomeric excess (*de*), % [b]
1	**5a**	CF_3		24 h, 20 °C	80	12
2				6 days, −20 °C	83	14
3	**5b**	$H(CF_2)_2$		4 days, 20 °C	75	16
4	**5c**	CF_3		16 h, 20 °C	92	**56**
5				24 h, 20 °C[c]	94	56
6				6 days, −20 °C	94	**60**
7	**5d**	$H(CF_2)_2$		20 days, 20 °C	90	50
8	**5e**	CF_3		3 days, 20 °C[c]	90	56
9	**5f**	CF_3		1 h, 20 °C	95	22
10				16 h, −20 °C	94	34
11				1 min, 110 °C	90	16
12	**5g**	$H(CF_2)_2$		24 h, 20 °C	98	8
13	**5h**	CF_3		24 h, 20 °C[c]	98	32
14	**5i**	CF_3		0.5 min, 20 °C	90	38:5:52:5[d]
15	**5j**	$H(CF_2)_2$		5 min, 20 °C	85	39:3:2:56[d]
16	**5k**	CF_3		3 days, 20 °C	98	18
17				6 days, −20 °C	98	16
18	**5l**	$H(CF_2)_2$		5 days, 20 °C	85	20
19	**5m**	CF_3		2 days, 20 °C	90	10
20	**5n**	CF_3		5 h, 130 °C[e]	80	6
21	**5o**	$H(CF_2)_2$		5 h, 130 °C[e]	75	20
22	**5p**	$H(CF_2)_2$		5 h, 130 °C[e]	88	–

[a] In excess of diene if not mentioned other.
[b] Determined by HPLC analyses if not mentioned other.
[c] In benzene.
[d] Mixture of *endo*/*exo* diastereomers, ratio was determined by the ^{19}F NMR spectroscopy.
[e] In a pressure tube, benzene.

from minutes to several days. In all cases completion of the reaction could be easily detected by disappearance of the red colour of dithioester. For instance, the reaction of dithioester **3h** with the conformationally rigid and more reactive cyclopentadiene at room temperature has completed in a few minutes, whereas it has taken up to 24 h for the same reaction with butadiene; the rate of the reaction with DMB is intermediate (Table 3, entries 9, 13, 14). Another noteworthy observation is that trifluodithioacetates are generally more reactive than tetrafluorodithiopropionates. All dihydrothiopyrans **5a**–**h**,**k**,**l** are stable compounds, in contrast to cyclopentadiene-based cycloadducts **5i**,**j**. The red colour observed at heating the compounds **5i**,**j** above 40 °C indicates the retro-Diels-Alder process yielding the starting dithioester.

Cycloadducts **5i**,**j** were obtained as mixtures of four stereoisomers – pair of *endo*/*exo* isomers and pair of diastereomers – with predominance of one type of selectivity (entries 14 and 15), but the NMR analysis of the mixtures did not allow to determine the stereochemistry of major and minor isomers.

In contrast to dithioesters **3**, thionoesters **4** are much less reactive toward dienes. *O*-Isopropyl ester **4a**, chosen as the model compound to establish and optimize the conditions for cycloaddition, did not react with excess of DMB at room temperature even for several weeks. Attempts to accelerate the reaction with addition of such catalysts as $Cu(OTf)_2$, $BF_3{\cdot}Et_2O$, $Ti(OPr\text{-}i)_4$, $ZnCl_2$ in different solvents have had no effect, too. The reaction has not proceed or led to the decomposition of the substrate. Cycloaddition has occurred only at elevated temperature in a pressure tube. Heating a mixture of **4a** with an excess of DMB in benzene at 130 °C for 5 h has provided adduct **5p** in 88% yield after purification with column chromatography (Table 3, entry 22). Similar conditions we have applied to other *O*-alkyl thionoesters synthesized. Holding the mixture of bornyl esters **4d**,**e** with DMB in benzene at 130 °C for 5 h has given dihydrothiopyrans **5n**,**o** in good yields (Table 3, entries 20 and 21). At the same time no desired cycloadduct has been obtained with 2-methylbenzyl derivative **4f**, due to low thermal stability of the starting ester. The thermal reactions of *O*-menthyl esters **4b**,**c** with DMB proceed with considerable tarring and yield complex mixtures of products containing only small amounts of the target cycloadducts.

All dihydrothiopyran derivatives **5**, as follows from NMR and GC/MS data, arise as mixtures of two diastereomers, but they cannot be separated with column chromatography. The observed diastereomeric excess (*de*) has not practically changed when reactions are carried out without solvent or in solution (benzene, chloroform) or/and at use of catalysts ($BF_3{\cdot}Et_2O$, $Cu(OTf)_2$, $Ti(OPr\text{-}i)_4$, $ZnCl_2$). Therefore, the variation of steric and electronic factors affects the cycloaddition diastereoselectivity.

The results summarized in Table 3 show that all the thionoesters **3**,**4** demonstrate some extent of asymmetric induction. From the data listed in Table 3 it is seen that for all types of thionoesters lengthening of the polyfluoroalkyl substituent from CF_3 to HCF_2CF_2 provides only modest differences in *de*. Changing the heteroatom nature at the dienophilic thiocarbonyl group does not affect significantly the diastereoselectivity of the cycloaddition: the similar low *de* values were found for *S*-bornyl and *O*-bornyl cycloadducts **5m** and **n** (entries 19 and 20). These observations make it possible to conclude that for stereochemical outcome of cycloaddition the nature of fluoroalkyl group and the heteroatom are of less importance. The comparable values of *de* have been observed for the camphoryl (**5a**), thioisobornyl (**5k**) and thiobornyl (**5m**) adducts (entries 1, 16 and 19), which is an evidence of the insignificant influence of a bulk substituent at the thiolic sulfur in this series. Somewhat better selectivity has been observed for *S*-phenylethyl cycloadduct **5f** (entry 9), but these changes are rather minor, too. The highest diastereoselectivity has been observed in reactions of *S*-neomenthyl dithioesters **3f**,**g** (entries 4–8) with dienes, yielding 2-polyfluoroalkyl-2-(*S*-neomenthyl)-3,6-dihydro-2*H*-thiopyrans **5c**–**e** as mixture of diastereomers in excellent total yields and 50–60% *de*.

As the thia-Diels-Alder cycloaddition can be reversible, the formed *de* should be controlled both kinetically and thermodynamically. In the latter case, a thermodynamically more stable adduct would prevail in the mixture. The kinetically controlled formation of the adducts can proceed via two structurally different transition states, which in turn differ by their free activation energies. This might provide a more rapid formation of one of the diastereomeric adducts, connected with the lower activation energy barrier, resulting in formation of an unequal mixture of diastereomeric adducts.

This aspect we have investigated in detail using quantum chemistry (DFT) calculations. The thia-Diels-Alder cycloaddition of thiocarbonyl compounds with butadiene was previously studied using Hartree–Fock, MP2, MP4 and DFT (B3LYP) levels of approximation [24]. Results obtained using B3LYP method and modest 6-31G* basis sets were comparable with those calculated at the more superior MP4 level of theory. According to these calculations, the reaction proceeded with concerted cleavage of the C=S π-bond and building two C–C and C–S σ-bonds. At the same time, for definite thiono-derivatives, e.g., thiono-analogues of Meldrum's acid, malonic acid and other α,α-dioxothiones, a stepwise mechanism was predicted via thiiranium zwitterionic intermediate [25].

We have studied the asymmetric induction theoretically using the DFT (B3LYP/6-31G**) level of approximation on example of the cycloaddition of DMB with dithioester **3f**. In order to find the conformations with the lowest total energies a variety of conformers have been analyzed. Thermodynamic characteristics (ΔE^1 and ΔG^1) for reaction (1), calculated for the most favoured conformations of starting material and products are collected in Table 4. Our calculations indicate the exothermic character of the reaction relative to *s-trans*-DMB, which is in line with the experimentally observed equilibrium shift towards adduct **5c**.

$$\textit{s-trans}\text{-DMB} + \mathbf{3f} \rightarrow \mathbf{5c} + \Delta E^1(\Delta G^1) \quad (1)$$

A significantly reduced exothermicity observed from ΔE^1 to ΔG^1 values is referred to the corresponding entropy contribution to the ΔG values by forming an adduct from two isolated molecules. The conformations of cycloadducts with the equatorial orientation of the sulfur-containing substituent in the neomenthyl moiety (NM) are approximately 1.7–1.8 kcal/mol less stable than those with the axial position of this substituent (**5cA**–**5cD**, Fig. 2).

The differences in total energies calculated for adducts **5cA**-(*R*) and **5cB**-(*S*) with the axial position of the CF_3 group in the thiopyran ring and **5cC**-(*R*) and **5cD**-(*S*) with CF_3 group in the equatorial position lie in the range of only about 0.4–0.5 kcal/mol (Table 4, $\Delta\Delta E$ to $\Delta\Delta G$ values). For the most favourable (*R*)- and (*S*)-adducts, **5cC** and **5cD**, the difference in $\Delta\Delta G$ values is only 0.35 kcal/mol (see Table 4). We have carried out geometry re-optimization for the most favourable structures **5cC** and **5cD** using the larger basis 6-311G** basis sets and additionally performed single-point energy calculations using the Dunning's cc-pVTZ basis sets (Table 5). In all cases a low influence of the asymmetric centre configuration (atom C-1 in NM) on the thermodynamic stability of the diastereomeric cycloadducts is obvious. Thus, it is not probably responsible for the experimentally observed diastereomeric excess.

More likely, the observed effect can be determined by transition state structures (TS), preceding formation of diastereomers **5c**. The product which corresponds to the transition state with lower activation energy, will arise in excess. The calculated equilibrium TS structures with *endo*- (**6A** and **6B**) and *exo*-orientation of the CF_3

Table 4
Total energy values (E), Zero Point Energy (ZPE) and Thermal Correction to Gibbs Free Energy (TCGFE) correction values, corrected energy magnitudes (E + ZPE and E + TCGFB), lowest vibration frequencies (ν), reaction energies (ΔE^1 and ΔG^1) and corresponding activation energies (ΔE^{TS} and ΔG^{TS}), and relative energies ($\Delta\Delta E$ and $\Delta\Delta G$) for different conformations of **5c** and transition states **6**.

Structure	Substituent position	R/S[a]	E (a.u.)	ZPE (a.u.)	E + ZPE (a.u.)	ν (cm^{-1})	ΔE (kcal/mol)	$\Delta\Delta E$ (kcal/mol)	TCGFB a.u.)	E + TCGFB (a.u.)	ΔG (kcal/mol)	$\Delta\Delta G$ (kcal/mol)
5cA	CF_3 *ax*	R	−1799.332099	0.443670	−1798.888429	16.9	−17.94[b]	0.23	0.388128	−1798.943971	−3.14[b]	0.16
5cB	CF3 *ax*	S	−1799.331945	0.443765	−1798.888180	18.1	−17.78[b]	0.39	0.388484	−1798.943461	−2.82[b]	0.48
5cC	CF_3 *eq*	R	−1799.332498	0.443700	−1798.888798	12.8	−18.17[b]	**0.00**	0.388278	−1798.944220	−3.30[b]	**0.00**
5cD	CF_3 *eq*	S	−1799.331624	0.443648	−1798.887976	12.8	−17.65[b]	0.52	0.387970	−1798.943654	−2.95[b]	0.35
6A	CF_3 *endo*	[R][c]	−1799.272996	0.439656	−1798.833397	−352.3	14.47[d]	**0.00**	0.382210	−1798.890786	27.30[d]	**0.00**
6B	CF_3 *endo*	[S][c]	−1799.272176	0.439599	−1798.832577	−315.6	14.99[d]	0.51	0.382768	−1798.889408	28.16[d]	0.86
6C	CF_3 *exo*	[R][c]	−1799.271881	0.439732	−1798.832149	−310.0	15.26[d]	0.78	0.383083	−1798.888798	28.54[d]	1.25
6D	CF_3 *exo*	[S][c]	−1799.270587	0.439565	−1798.831022	−264.9	15.96[d]	1.49	0.382747	−1798.887840	29.14[d]	1.85

[a] Configuration of the C-2′ asymmetric centre in thiopyran moiety.
[b] Reaction (1) energy (ΔE^1 or ΔG^1).
[c] Configuration resulting from the transition state.
[d] Activation energy (ΔE^{TS} and ΔG^{TS}) calculated for reaction (1).

group (**6C** and **6D**) are shown in Fig. 3. **6A** and **6B** indicate similar C–C and C–S distances whereas for **6C** and **6D** C–S distances have been found to be significantly shorter than C–C ranges. At first glance, this fact could predict the C–S bonded stable intermediate as a minimum at the potential energy surface. However, this is not a case and corresponding structures can be located neither directly nor scanning the corresponding intrinsic reaction coordinates. Thus, the concerted mechanism of the Diels-Alder cycloaddition, i.e. the formation of the C–C and C–S σ-bonds during the single cyclization process, has been postulated basing on the calculation data obtained.

The total energies calculated for **6C** and **6D**, where sterically more demanding *S*-neomenthyl moiety is *exo*-oriented, are higher than those found for **6A** and **6B**, with *endo*-position of this substituent. Thus, only the former transition state structures play a role in the course of reaction. In turn, **6B**, preceding the (*S*)-adduct,

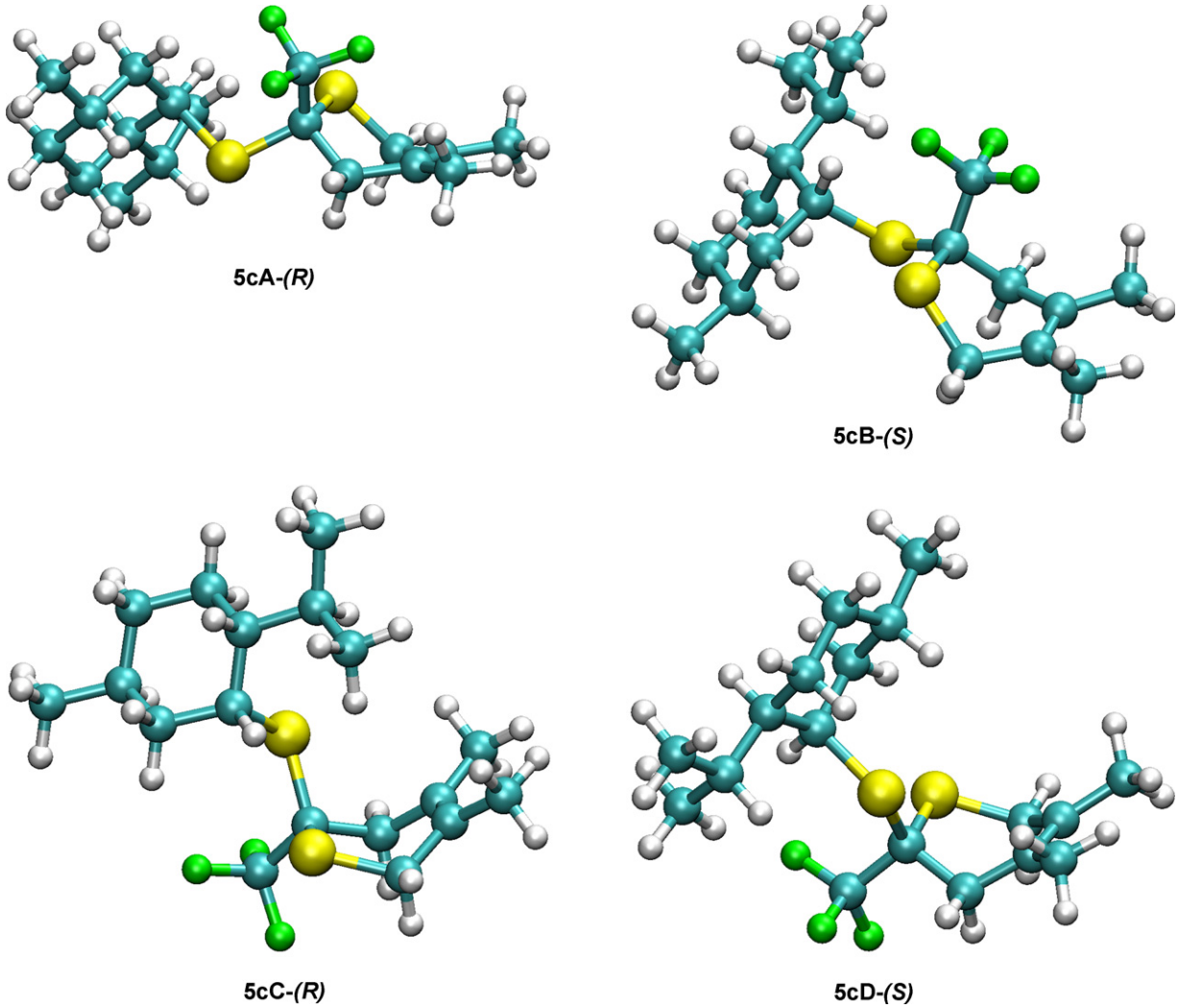


Fig. 2. Calculated (B3LYP/6-31G**) equilibrium Diels-Alder adducts with equatorial (**5cA** and **5cB**) and axial equatorial (**5cC** and **5cD**) position of the CF_3 group corresponding to the lowest total energies. (*R*) and (*S*) correspond to the configuration at the C-2′ asymmetric centre of thiopyran moiety.

Table 5
Total energy values (E), Zero Point Energy (ZPE) correction values, corrected energy magnitudes (E+ZPE), lowest vibration frequencies (ν), reaction (1) energies (ΔE^1), and corresponding activation energies (ΔE^{TS} and ΔG^{TS}), and relative energies ($\Delta\Delta E$) for different conformations of **5c** and transition states **6**.

Structure	B3LYP/6-311G**				B3LYP/cc-pVTZ//B3LYP/6-311G**			
	E (a.u.)	E+ZPE (a.u.)	ν (cm^{-1})	ΔE (kcal/mol)	$\Delta\Delta E$ (kcal/mol)	E (a.u.)	ΔE^a (kcal/mol)	$\Delta\Delta E^a$ (kcal/mol)
5cA	−1799.618442	−1799.177587	5.8	−14.55[b]	0.52	−1799.728190	−14.02[b]	0.77
5cB	−1799.618185	−1799.177194	15.2	−14.30[b]	0.76	−1799.727415	−13.54[b]	1.25
5cC	−1799.619499	−1799.178411	17.4	−15.06[b]	**0.00**	−1799.729414	−14.79[b]	**0.00**
5cD	−1799.618795	−1799.177849	11.8	−14.71[b]	**0.35**	−1799.728528	−14.24[b]	**0.56**
6A	−1799.562230	−1799.125392	−319.5	16.32[c]	**0.00**	−1799.672901	18.22[c]	**0.00**
6B	−1799.560903	−1799.124222	−350.8	17.06[c]	**0.73**	−1799.671658	19.00[c]	**0.78**
6C	−1799.560742	−1799.123830	−315.2	17.30[c]	0.98	−1799.671535	19.08[c]	0.86
6D	−1799.559543	−1799.122859	−273.4	17.91[c]	1.59	−1799.670061	20.01[c]	1.78

[a] Calculated using uncorrected E values.
[b] Reaction (1) energy (ΔE^1).
[c] Activation energy (ΔE^{TS}) for reaction (1).

possesses the higher activation energy values, ΔE^{TS} and ΔG^{TS}, than those for **6A** ($\Delta\Delta E$ = 0.51 kcal/mol; $\Delta\Delta G$ = 0.86 kcal/mol). Re-optimization of the structures using larger (6-311G**) basis sets yields similar ΔE^{TS} and $\Delta\Delta E$ values (Table 5). Probably, the difference found in the activation energies can cause preferable formation of the (*R*)-adduct which in turn determines the experimentally observed diastereomeric excess. In general, the authors want to emphasize that the calculated activation energy values (ΔE^{TS} and ΔG^{TS}) as those should be taken up with care, due to the rather low level of approximation used for calculations. But the constant contributions of inaccuracies of the B3LYP method and restricted basis sets may be partially cancelled out going to the

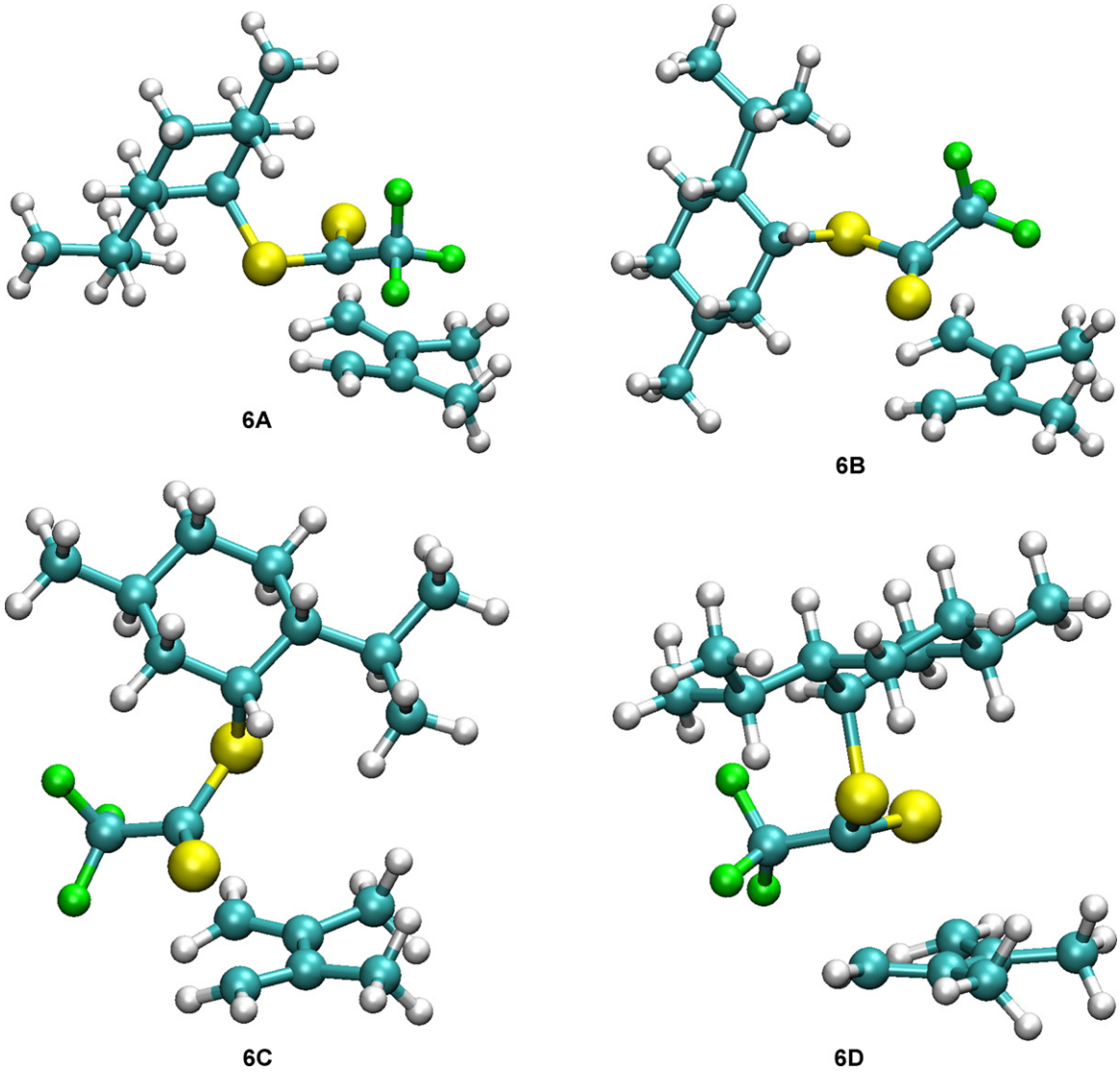


Fig. 3. Calculated (B3LYP/6-31G**) transition state structures for the Diels-Alder cycloaddition with *exo*-(**6A** and **6B**) and *endo*-position of the CF_3 group (**6C** and **6D**) corresponding to the lowest total energies. The C–C and C–S distances (Å) connected with the intrinsic reaction coordinate (in parentheses distances calculated at the B3LYP/6-311G** level of theory): **6A** 2.384, 2.412 (2.408, 2.345); **6B** 2.323, 2.428 (2.353, 2.362); **6C** 2.435, 2.366 (2.433, 2.340); **6D** 2.506, 2.360 (2.498, 2.330).

relative energies ($\Delta\Delta E$ and $\Delta\Delta G$ values), which are of importance for the discussion of the experimental results.

In order to support this statement we have carried out the reaction of dithioesters **3a**, **3c**, **3f** and **3h** with DMB at low temperature, and **3h** with DMB in boiling toluene. In the former case, reaction times have significantly increased. It should be also noted that *de* has not changed for compounds **3a** and **3c** (entries 2 and 17, Table 3) whereas it has been slightly improved for esters **3f** and **3h** (entries 6 and 10). On the other hand, the *de* value in case of **3h** clearly decreases with rising temperature (entries 9–11). These experimental observations are in accordance with the kinetically controlled cycloaddition resulting in the formation of diastereomeric excess for the adducts.

3. Conclusion

In summary, we have shown that the nucleophilic substitution at the thiocarbonyl group in polyfluorothioalkanoyl chlorides is a versatile method for the preparation of the *S*- and *O*-thionocarboxylates. This methodology has allowed us to synthesize a series of thionoesters with various optically active substituents which can serve as chiral auxiliaries in asymmetric syntheses. We have observed the first example of asymmetric induction in the thia-Diels-Alder cycloaddition involving polyfluoroalkylthionocarboxylates which have provided 2-fluoroalkyl-2-alkylsulfanyl-3,6-dihydro-2*H*-thiopyrans in low to modest *de* (6–60%). The influence of nature of the diene and dienophile and reaction conditions on the asymmetric induction of cycloaddition have been examined. It has been found that electronic factors have a minimal effect on a stereoselectivity of the cycloaddition. Quantum chemistry (DFT) calculations indicate that the differences in activations energies are larger than the relative energies of the cyclic adducts at all used levels of theory. This makes it possible to suggest that the stereoselectivity found for the formation of thiopyranes is kinetically driven: the observed *de* is referred to the slightly different activation free energies inherent to the corresponding transition states. This conclusion is in line with the experimentally found dependence of *de* on temperature.

4. Experimental

4.1. General

^{19}F NMR spectra (188.14 MHz) were recorded on a Varian Gemini-200 spectrometer with C_6F_6 ($\delta_F = -162.9$ ppm relative to $CFCl_3$) as internal standard. ^{1}H NMR (299.94 MHz) spectra were obtained on a Varian VXR-300 spectrometer, ^{13}C NMR, APT, COSY, HETCOR spectra were obtained on a Bruker Avance 400 spectrometer (100.62 MHz for ^{13}C and 400.13 MHz for ^{1}H) in $CDCl_3$ solutions with Me_4Si as internal standard. Silica gel Merck 60 (40–63 μm) was used for chromatography. Thin-layer chromatography using precoated plastic plates (Polygram® Sil G/UV254) were visualised by UV light or by an I_2 vapour. Diastereomeric ratio of cycloadducts **5** was determined by HPLC analysis on the Agilent 1100 instrument (UV, detection wavelength: 215 nm) on Zorbax Eclipse XDB-C18 column (4.6 mm × 250 mm, 5 μm) using MeCN–H_2O or MeOH–H_2O as mobile phases (1 ml/min) at 25 °C. MS data were obtained on the Hewlett-Packard 5890\5972 apparatus (GC/MS) at 70 eV in the electron impact mode.

4.2. Synthesis of dithioesters 3 (Table 1). Common procedure

A solution of corresponding thiole (10 mmol) in inert solvent (10 ml) was treated with excess chloride **1** (11 mmol) at room temperature. The reaction was monitored by ^{19}F NMR spectroscopy. After the reaction time indicated in Table 1, the solvent was removed under reduced pressure and crude dithioester was purified by silica gel column chromatography. The less polar red fraction was collected. Yields of dithioesters **3a–i** are given in Table 1.

4.2.1. [(1S)-7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methyl trifluoroethanedithioate (3a)

Red liquid, R_f 0.65 (CCl_4:EtOAc, 10:1). ^{19}F NMR ($CDCl_3$): δ −66.14 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.94 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.38–1.47 (1H, m), 1.54–1.63 (1H, m), 1.81–1.90 (1H, m), 1.94 (1H, d, J = 19.0 Hz, *endo*-H-3), 1.97–2.10 (1H, m), 2.18 (1H, t, J = 4.2 Hz, H-4), 2.44 (1H, dm, J = 19.0 Hz, *exo*-H-3), 3.33 (1H, d, J = 13.8 Hz, H-10), 3.53 (1H, d, J = 13.8 Hz, H-10). GC/MS (m/e): 296 (M^+, 25%). Anal. Calcd for $C_{12}H_{15}F_3OS_2$: C, 48.63; H, 5.10; S, 21.64. Found: C, 48.09; H, 5.12; S, 21.42.

4.2.2. [(1S)-7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methyl 2,2,3,3-tetrafluoropropanedithioate (3b)

Red liquid, R_f 0.70 (CCl_4:EtOAc, 10:1). ^{19}F NMR ($CDCl_3$): δ −112.33 (AB, J = 264.0 Hz, CF_2), −138.48 (2F, dm, J = 52.8 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 0.97 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.38–1.46 (1H, m), 1.53–1.62 (1H, m), 1.81–1.91 (1H, m), 1.94 (1H, d, J = 19.0 Hz, *endo*-H-3), 1.97–2.10 (1H, m), 2.17 (1H, t, J = 4.2 Hz), 2.44 (1H, dt, J = 18.6 Hz, *exo*-H-3), 3.33 (1H, d, J = 13.8 Hz, H-10), 3.53 (1H, d, J = 13.8 Hz, H-10), 6.31 (1H, tt, J = 52.8, 5.3 Hz, HCF_2). ^{13}C NMR ($CDCl_3$): δ 19.76 (CH_3), 20.13 (CH_3), 26.73 (CH_2), 26.84 (CH_2), 32.92 (t, J = 2.1 Hz, C-10), 42.93 (C-3), 43.61 (C-4), 48.36 (C-7), 60.65 (C-1), 109.89 (tt, J = 254.0, 33.0 Hz, HCF_2), 112.93 (tt, J = 259.0, 27.0 Hz, CF_2), 216.30 (C=O), 218.24 (t, J = 24.0 Hz, C=S). GC/MS (m/e): 328 (M^+, 22%). Anal. Calcd for $C_{13}H_{16}F_4OS_2$: C, 47.55; H, 4.91; S, 19.53. Found: C, 47.57; H, 5.16; S, 19.39.

4.2.3. (1S)-Exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl trifluoroethanedithioate (3c)

Red liquid, R_f 0.70 (hexane). ^{19}F NMR ($CDCl_3$): δ −65.68 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.99–1.34 (3H, m), 1.47–1.83 (3H, m), 2.03 (1H, m), 4.12 (1H, dd, J = 9.0, 5.2 Hz, *endo*-H-2). GC/MS (m/e): 282 (M^+, 29%). Anal. Calcd for $C_{12}H_{17}F_3S_2$: C, 51.04; H, 6.07; S, 22.71. Found: C, 51.10; H, 6.09; S, 22.56.

4.2.4. (1S)-Exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 2,2,3,3-tetrafluoropropanedithioate (3d)

Red liquid, R_f 0.75 (hexane). ^{19}F NMR ($CDCl_3$): δ −111.76 (AB, J = 259.6 Hz, CF_2), −138.66 (2F, dm, J = 53.7 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 0.88 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.99–1.34 (2H, m), 1.47–1.83 (3H, m), 2.07 (1H, m), 4.16 (1H, dd, J = 9.3, 5.0 Hz, *endo*-H-2), 6.31 (1H, tt, J = 53.7, 5.7 Hz, HCF_2). GC/MS (m/e): 314 (M^+, 28%). Anal. Calcd for $C_{13}H_{18}F_4S_2$: C, 49.66; H, 5.77; S, 20.40. Found: C, 49.69; H, 5.78; S, 20.21.

4.2.5. (1S)-Endo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl trifluoroethanedithioate (3e)

Red liquid, R_f 0.70 (hexane). ^{19}F NMR ($CDCl_3$): δ −66.05 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.91 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.12 (1H, dd, J = 13.9, 4.4 Hz, *endo*-H-3), 1.19–1.32 (1H, m, H-5), 1.47–1.72 (3H, m, H-5,6), 1.73–1.91 (2H, m, H-4,6), 2.66 (1H, ddd, J = 13.9, 11.0, 4.0 Hz, *exo*-H-3), 4.09 (1H, dt, J = 11.0, 4.0 Hz, *exo*-H-2). GC/MS (m/e): 282 (M^+, 32%). Anal. Calcd for $C_{12}H_{17}F_3S_2$: C, 51.04; H, 6.07; S, 22.71. Found: C, 51.09; H, 6.09; S, 22.50.

4.2.6. (1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl trifluoroethanedithioate (3f)

Red liquid, R_f 0.75 (hexane). ^{19}F NMR ($CDCl_3$): δ −66.15 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.69 (3H, d, J = 6.6 Hz, CH_3), 0.89 (3H, d, J = 6.3 Hz, CH_3), 0.93 (3H, d, J = 6.9 Hz, CH_3), 1.00–1.46 (6H, m),

1.61–2.03 (3H, m), 4.48 (1H, m, CH–S). GC/MS (*m*/*e*): 284 (M^+, 19%). Anal. Calcd for $C_{12}H_{19}F_3S_2$: C, 50.68; H, 6.73; S, 22.55. Found: C, 50.72; H, 6.77; S, 22.38.

*4.2.7. (1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2,2,3,3-tetrafluoropropanedithioate (**3g**)*

Red liquid, R_f 0.80 (hexane). ^{19}F NMR ($CDCl_3$): δ −109.93 (1F, AB, J = 261.0 Hz, CF_2), −113.93 (1F, AB, J = 261.0 Hz, CF_2), −138.67 (2F, dm, J = 53.1 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 0.68 (3H, d, J = 6.9 Hz, CH_3), 0.89 (3H, d, J = 6.6 Hz, CH_3), 0.93 (3H, d, J = 6.3 Hz, CH_3), 1.00–1.15 (2H, m), 1.25–1.59 (4H, m), 1.83 (1H, dm, J = 15 Hz), 1.89–2.03 (2H, m), 4.51 (1H, m, CH–S), 6.31 (1H, tt, J = 53.1, 4.5 Hz, HCF_2). GC/MS (*m*/*e*): 316 (M^+, 18%). Anal. Calcd for $C_{13}H_{20}F_4S_2$: C, 49.35; H, 6.37; S, 20.27. Found: C, 49.39; H, 6.40; S, 20.02.

*4.2.8. 1-Phenylethyl trifluoroethanedithioate (**3h**)*

Red liquid, R_f 0.35 (hexane). ^{19}F NMR ($CDCl_3$): δ −66.19 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 1.76 (3H, d, J = 7.2 Hz, CH_3), 5.03 (1H, q, J = 7.2 Hz, CH–S), 7.29–7.37 (5H, m, C_6H_5). GC/MS (*m*/*e*): 250 (M^+, 23%). Anal. Calcd for $C_{10}H_9F_3S_2$: C, 47.98; H, 3.62; S, 25.62. Found: C, 48.00; H, 3.64; S, 25.40.

*4.2.9. 1-Phenylethyl 2,2,3,3-tetrafluoropropanedithioate (**3i**)*

Red liquid, R_f 0.40 (hexane). ^{19}F NMR ($CDCl_3$): δ −112.40 (2F, m, CF_2), −138.60 (2F, dm, J = 53.1 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 1.76 (3H, d, J = 7.2 Hz, CH_3), 5.05 (1H, q, J = 7.2 Hz, CH–S), 6.27 (1H, tt, J = 53.1, 5.1 Hz, HCF_2), 7.29–7.36 (5H, m, C_6H_5). GC/MS (*m*/*e*): 282 (M^+, 18%). Anal. Calcd for $C_{11}H_{10}F_4S_2$: C, 46.80; H, 3.57; S, 22.72. Found: C, 46.81; H, 3.57; S, 22.60.

*4.3. Synthesis of thionoesters **4** (Table 2)*

*4.3.1. Method A. From chlorides **1a**,**b***

Common procedure as for synthesis of dithioesters was employed. Reaction conditions are displayed in Table 2. Purification by distillation (for **4a**) or with column chromatography (for **4b**,**c**).

*4.3.1.1. O-Isopropyl 2,2,3,3-tetrafluoropropanethioate (**4a**).* Yellow liquid, bp 130–131 °C. ^{19}F NMR ($CDCl_3$): δ −117.35 (2F, dt, J = 8.5, 5.0 Hz, CF_2), −138.05 (2F, dt, J = 53.0, 8.5 Hz, CF_2H). ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, d, J = 6.2 Hz, CH_3), 5.69 (1H, septet, J = 6.2 Hz, CH), 6.14 (1H, tt, J = 53.0, 5.0 Hz, HCF_2). ^{13}C NMR ($CDCl_3$): δ 20.75 (CH_3), 78.38 (CH–O), 109.34 (tt, J = 258.0, 28.2 Hz, CF_2), 109.54 (tt, J = 252.0, 35.7 Hz, HCF_2), 199.82 (t, J = 28.0 Hz, C=S). GC/MS (*m*/*e*): 204 (M^+, 10%). Anal. Calcd for $C_6H_8F_4OS$: C, 35.29; H, 3.95; S, 15.70. Found: C, 35.30; H, 3.98; S, 15.50.

*4.3.1.2. O-[(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl]-trifluoroethanethioate (**4b**).* Yellow liquid, R_f 0.55 (hexane). ^{19}F NMR ($CDCl_3$): δ −72.62 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.77 (3H, d, J = 6.9 Hz, CH_3), 0.92 (3H, d, J = 7.2 Hz, CH_3), 0.95 (3H, d, J = 6.9 Hz, CH_3), 1.00–1.22 (3H, m), 1.42–1.64 (1H, m), 1.65–1.95 (4H, m), 2.17 (1H, dm, J = 11.7 Hz), 5.37 (1H, m, CH-O). GC/MS (*m*/*e*): 268 (M^+, 15%). Anal. Calcd for $C_{12}H_{19}F_3OS$: C, 53.71; H, 7.14; S, 11.95. Found: C, 53.78; H, 7.18; S, 11.70.

*4.3.1.3. O-[(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl]-2,2,3,3-tetrafluoropropanethioate (**4c**).* Yellow liquid, R_f 0.65 (hexane). ^{19}F NMR ($CDCl_3$): δ −116.58 (2F, AB, J = 266.0 Hz, CF_2), −137.38 (2F, dm, J = 53.2 Hz, CF_2H). ^{1}H NMR ($CDCl_3$): δ 0.75 (3H, d, J = 6.9 Hz, CH_3), 0.92 (3H, d, J = 7.1 Hz, CH_3), 0.95 (3H, d, J = 6.9 Hz, CH_3), 0.99–1.21 (3H, m), 1.45–1.62 (1H, m), 1.64–1.91 (4H, m), 2.16 (1H, dm, J = 9.6 Hz), 5.42 (1H, m, CH-O), 6.14 (1H, tt, J = 53.2, 5.0 Hz, HCF_2). GC/MS (*m*/*e*): 300 (M^+, 17%). Anal. Calcd for $C_{13}H_{20}F_4OS$: C, 51.98; H, 6.71; S, 10.68. Found: C, 52.01; H, 6.73; S, 10.49.

4.3.2. Method B. From iminoesters. General procedure

*4.3.2.1. O-[(1S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl]-trifluoroethanethioate (**4d**).* NaH (10 mg, 60% in mineral oil, 0.25 mmol) was added in one portion under argon to a solution of (1*S*)-borneol (3.08 g, 20 mmol) in anhydrous THF (8 ml). The resulting suspension was stirred at r.t. for 5 min to completion of hydrogen evolution and then cooled down to 0 °C. The gaseous CF_3CN, generated at heating of trifluoroacetamide (2.5 g, 22 mmol) with P_2O_5 (3.2 g, 22 mmol), was passed into mixture and it was allowed to stirr at r.t. for 8 h. A mixture was acidified with 0.02 ml of AcOH and evaporated to give in a residue a heavy oil of iminoester which was analysed by ^{1}H NMR spectroscopy and used in the next step without purification. The crude iminoester was dissolved in mixture of THF (5 ml) and AcOH (5 ml) at stirring and dry H_2S was passed through solution at −5 to 0 °C to complete absorbtion. The reaction mixture was allowed to stir at r.t. for 10 h, volatile products were removed in vacuum (10–15 mmHg) and the residue was submitted to column chromatography over silica gel with hexane as eluent to give 3.84 g (73%) of thionoester **4d**. Yellow liquid, R_f 0.65. ^{19}F NMR ($CDCl_3$): δ −72.31 (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.91 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.02 (1H, dd, J = 14.0, 3.4 Hz, *endo*-H-3), 1.23–1.31 (1H, m, H-5), 1.39–1.48 (1H, m, H-6), 1.78–1.86 (2H, m, H-5,6), 1.98–2.05 (1H, m, H-4), 2.49 (1H, ddd, J = 14.0, 9.9, 3.0 Hz, *exo*-H-3), 5.36 (1H, dt, J = 9.9, 3.0 Hz, *exo*-H-2). GC/MS (*m*/*e*): 266 (M^+, 29%). Anal. Calcd for $C_{12}H_{17}F_3OS$: C, 54.12; H, 6.43; S, 12.04. Found: C, 54.14; H, 6.47; S, 11.89.

*4.3.2.2. O-[(1S)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl]-2,2,3,3-tetrafluoropropanethioate (**4e**).* According to procedure described for **4d**, from 3.08 g (20 mmol) of (1*S*)-borneol the thionoester **4e** (4.30 g, 70%) was obtained as yellow liquid, R_f 0.55 (hexane). ^{19}F NMR ($CDCl_3$): δ −116.99 (2F, m, CF_2), −137.62 (2F, dm, J = 53.1 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.94 (3H, s, CH_3), 1.03 (1H, dd, J = 14.0, 3.4 Hz, *endo*-H-3), 1.06–1.31 (1H, m, H-5), 1.39–1.50 (1H, m, H-6), 1.77–1.86 (2H, m, H-5,6), 1.94–2.03 (1H, m, H-4), 2.44–2.55 (1H, ddd, J = 14.0, 9.5, 4.0 Hz, *exo*-H-3), 5.39 (1H, dt, J = 9.5, 2.8 Hz, *exo*-H-2), 6.13 (1H, tt, J = 53.1, 4.8 Hz, HCF_2). ^{13}C NMR ($CDCl_3$): δ 13.52, 19.00, 19.68 (CH_3), 27.59 (C-5), 27.87 (C-6), 36.19 (C-3), 44.95 (C-4), 48.17 (C-7), 49.65 (C-1), 90.97 (C-2), 109.56 (tt, J = 255.0, 27.6 Hz, CF_2), 109.66 (tt, J = 251.0, 35.5 Hz, HCF_2), 200.53 (t, J = 28.0 Hz, C=S). GC/MS (*m*/*e*): 298 (M^+, 28%). Anal. Calcd for $C_{13}H_{18}F_4OS$: C, 52.34; H, 6.08; S, 10.75. Found: C, 52.38; H, 6.10; S, 10.50.

*4.3.2.3. O-(1-Phenylethyl) 2,2,3,3-tetrafluoropropanethioate (**4f**).* It was obtained according to procedure described for **4d**. Yellow liquid, R_f 0.40 (hexane). ^{19}F NMR ($CDCl_3$): δ −117.14 (2F, m, CF_2), −137.83 (2F, dm, J = 53.1 Hz, CF_2H). ^{1}H NMR ($CDCl_3$): δ 1.73 (3H, d, J = 6.8 Hz, CH_3), 6.14 (1H, tt, J = 53.1, 4.8 Hz, HCF_2), 6.49 (1H, q, J = 6.8 Hz, CH–O), 7.28–7.44 (5H, m, C_6H_5). GC/MS (*m*/*e*): 266 (M^+, 30%). Anal. Calcd for $C_{11}H_{10}F_4OS$: C, 49.62; H, 3.79; S, 12.04. Found: C, 49.68; H, 3.83; S, 11.89.

*4.4. Cycloadducts **5a**–**m** (Table 3). Common procedure*

Dithioester **3a**–**i** (1 mmol) and excess (2 mmol) of DMB or cyclopentadiene (for cycloadducts **5i**,**j**) were allowed to react at the temperature and for the time indicated in Table 3 until red colour of the reaction mixture disappeared. For cycloadducts **5e**,**h** the dithioester (1 mmol) was added to a solution of 1,3-butadiene (0.16 g, 3 mmol) in 5 ml of benzene and the reaction flask was sealed. After reaction was finished volatile products were removed in vacuum (0.03–0.05 mmHg) and the crude cycloadduct was analysed by HPLC and NMR spectroscopy to determine the isomers ratio. Additional purification was performed in case of need with column chromatography over silica gel.

*4.4.1. (1S)-1-({[4,5-Dimethyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran-2-yl]thio}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**5a**)*

Colourless solid, yield 80%. R_f 0.60–0.65 (CCl_4:EtOAc, 10:1), mp 40–48 °C, mixture of isomers in the ratio 44:56 from HPLC, solvent MeCN:H_2O (85:15), t_r 15.8 (minor) and 16.4 (major) min. ^{19}F NMR ($CDCl_3$) (here and further in the text the signals of major isomer are marked with asterisk): δ −73.81 (s, CF_3), −79.19 (s, CF_3). ^1H NMR ($CDCl_3$): δ 0.90* (s, CH_3), 0.93 (s, CH_3), 1.04* (s, CH_3), 1.06 (s, CH_3), 1.34–1.41 (m, 1H of both isomers), 1.52–1.64 (m, 1H of both isomers), 1.69 (s, CH_3), 1.70* (s, CH_3), 1.76 (s, CH_3), 1.78* (s, CH_3), 1.86 (d, J = 18.5 Hz *endo*-H-3), 1.87* (d, J = 18.5 Hz, *endo*-H-3), 1.93–2.04 (m, CH_2 of both isomers), 2.07 (m, H-4 of both isomers), 2.18* (d, J = 17.7 Hz, H-3′), 2.23 (d, J = 17.7 Hz, H-3′), 2.34* (m, *exo*-H-3), 2.40 (m, *exo*-H-3), 2.73 (d, J = 12.5 Hz, H-10 of both isomers), 2.78–2.91 (m, H-3′,6′ of both isomers), 2.99 (d, J = 12.5 Hz, H-10), 3.06* (d, J = 12.5 Hz, H-10), 3.37 (d, J = 16.1 Hz, H-6′), 3.51* (d, J = 16.1 Hz, H-6′). ^{13}C NMR ($CDCl_3$): δ 19.23, 19.30, 19.98, 20.05, 20.07, 20.08, 20.20, 20.44 (CH_3 of both isomers), 26.11, 26.90, 26.96, 27.58 (C-5,6 of both isomers), 27.86* (q, J = 2.0 Hz, C-6′), 28.34 (q, J = 2.0 Hz, C-6′), 29.66* (s, C-3′), 29.67 (s, C-3′), 37.29 (q, J = 1.5 Hz, C-10), 37.41* (C-10), 43.15* (C-3), 43.19 (C-3), 43.38* (C-4), 43.75 (C-4), 48.08* (C-7), 48.09 (C-7), 59.41* (q, J = 27.2 Hz, C-2′), 59.22 (q, J = 27.1 Hz, C-2′), 60.43* (C-1), 60.97 (C-1), 122.77, 123.05, 123.52, 123.85 (C-4′,5′ of both isomers), 126.85 (q, J = 281.0 Hz, CF_3), 126.93* (q, J = 281.0 Hz, CF_3), 217.07 (C=O), 217.18* (C=O). GC/MS (*m*/*e*): 378 (M^+, 2%), 195 (M^+–$C_{10}H_{15}OS$, 21%), 194 (M^+–$C_{10}H_{16}OS$, 68%), 193 ($C_8H_9F_3S^+$, 20%), 179 (100%). Anal. Calcd for $C_{18}H_{25}F_3OS_2$: C, 57.12; H, 6.66; S, 16.94. Found: C, 57.15; H, 6.70; S, 16.75.

*4.4.2. (1S)-1-({[4,5-Dimethyl-2-(1,1,2,2-tetrafluoroethyl)-3,6-dihydro-2H-thiopyran-2-yl]thio}methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**5b**)*

Colourless oil, yield 75%. R_f 0.60–0.65 (CCl_4:EtOAc, 10:1), mixture of isomers in the ratio 42:58 from HPLC, solvent MeCN:H_2O (85:15), t_r 23.2 (minor) and 25.6 (major) min. ^{19}F NMR ($CDCl_3$): δ −115.73 (1F, AB, J = 266.0 Hz, CF_2), −117.16* (1F, AB, J = 263.0 Hz, CF_2), −120.41* (1F, AB, J = 263.0 Hz, CF_2), −121.26 (1F, AB, J = 266.0 Hz, CF_2), −133.54 (2F, ddm, J = 300.0, 53.3 Hz, HCF_2 of both isomers), −136.21* (1F, ddm, J = 300.0, 53.3 Hz, HCF_2), −137.37 (1F, ddm, J = 300.5, 53.3 Hz, HCF_2). ^1H NMR ($CDCl_3$): δ 0.91, 0.92, 1.03, 1.04 (s, $C(CH_3)_2$ of both isomers), 1.36–1.43 (m, 1H of both isomers), 1.50–1.65 (m, 1H of both isomers), 1.69 (s, CH_3 of both isomers), 1.76 (s, CH_3), 1.77* (s, CH_3), 1.85 (d, J = 18.3 Hz *endo*-H-3), 1.87* (d, J = 18.3 Hz, *endo*-H-3), 1.93–2.03 (m, CH_2 of both isomers), 2.07 (H-4 of both isomers), 2.17* (d, J = 18.1 Hz, H-3′), 2.20 (d, J = 19.1 Hz, H-3′), 2.38 (dm, J = 18.3 Hz, *exo*-H-3 of both isomers), 2.68 (d, J = 12.7 Hz, H-10), 2.75–2.87 (m, H-3′,6′,10 of both isomers), 3.01* (d, J = 12.7 Hz, H-10), 3.34* (d, J = 15.9 Hz, H-6′), 3.48 (d, J = 16.3 Hz, H-6′), 6.52* (tdd, J = 53.3, 8.4, 3.5 Hz, HCF_2), 6.64 (tdd, J = 53.3, 9.9, 2.0 Hz, HCF_2). ^{13}C NMR ($CDCl_3$): δ 19.25, 19.30, 19.80, 20.09, 20.17, 20.18, 20.28, 20.29 (CH_3 of both isomers), 26.76, 26.92, 26.96, 27.36 (C-5 + C-6 of both isomers), 27.97* (dd, J = 4.0, 1.4 Hz, C-6′), 28.17 (d, J = 4.0 Hz, C-6′), 29.08 (C-10), 29.28* (C-10), 36.88* (dt, J = 3.0, 2.0 Hz C-3′), 37.00 (dt, J = 3.0, 2.5 Hz, C-3′), 43.15, 43.16 (C-3 of both isomers), 43.48* (C-4), 43.58 (C-4), 48.07 (C-7), 48.25* (C-7), 59.50* (t, J = 22.0 Hz, C-2′), 59.94 (t, J = 22.0 Hz, C-2′), 60.42* (C-1), 60.63 (C-1), 109.58 (tm, J = 252.0 Hz, HCF_2 of both isomers), 120.48 (tm, J = 260.0 Hz, CF_2 of both isomers), 122.51, 122.93, 123.66, 124.03 (C-4′,5′ of both isomers), 216.91* (C=O), 217.03 (C=O). GC/MS (*m*/*e*): 410 (M^+, 2%). Anal. Calcd for $C_{19}H_{26}F_4OS_2$: C, 55.59; H, 6.38; S, 15.62. Found: C, 55.62; H, 6.40; S, 15.50.

*4.4.3. 2-{[(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl]thio}-4,5-dimethyl-2-trifluoromethyl-3,6-dihydro-2H-thiopyran (**5c**)*

Colourless oil, yield 92%. R_f 0.65–0.70 (CCl_4), mixture of isomers in the ratio 22:78 from HPLC, solvent MeCN:H_2O (92:8), t_r 26.4 (minor) and 28.6 (major) min. ^{19}F NMR ($CDCl_3$): δ −73.51 (s, CF_3), −73.62* (s, CF_3). ^1H NMR ($CDCl_3$): δ 0.83–1.02 (d, $3CH_3$ of both isomers), 1.04–1.29 (m, 4H of both isomers), 1.55–2.17 (m, 4H of both isomers), 1.75 (s, CH_3 of both isomers), 1.78 (s, CH_3 of both isomers), 2.38 (d, J = 16.6 Hz, H-3′ of both isomers), 2.70* (d, J = 16.6 Hz, H-3′), 2.76 (d, J = 16.6 Hz, H-3′), 3.02 (d, J = 15.8 Hz, H-6′), 3.06* (d, J = 15.8 Hz, H-6′), 3.26* (d, J = 15.8 Hz, H-6′), 3.33 (d, J = 15.8 Hz, H-6′), 3.48* (m, H-1), 3.54 (m, H-1). GC/MS (*m*/*e*): 366 (M^+, 2%), 194 (M^+–$C_{10}H_{20}S$, 89%), 179 (60%), 138 ($C_{10}H_{18}^+$, 40%). Anal. Calcd for $C_{18}H_{29}F_3S_2$: C, 58.98; H, 7.97; S, 17.50. Found: C, 56.01; H, 7.99; S, 17.32.

*4.4.4. 2-{[(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl]thio}-4,5-dimethyl-2-(1,1,2,2-tetrafluoroethyl)-3,6-dihydro-2H-thiopyran (**5d**)*

Colourless oil, yield 90%. R_f 0.72–0.78 (CCl_4), mixture of isomers in the ratio 25:75 from HPLC, solvent MeCN:H_2O (92:8), t_r 19.8 (minor) and 21.6 (major) min. ^{19}F NMR ($CDCl_3$): δ −109.35 (1F, AB, J = 259.0 Hz, CF_2), −113.51 (1F, AB, J = 259.0 Hz, CF_2), −117.45* (1F, AB, J = 263.0 Hz, CF_2), −120.41* (1F, AB, J = 263.0 Hz, CF_2), −131.70–136.87 (2AB of both isomers, J = 299.0, 54.3 Hz, HCF_2). ^1H NMR ($CDCl_3$): δ 0.84–0.96 (d, $3CH_3$ of both isomers), 0.98–1.23 (m, 4H of both isomers), 1.58–2.09 (m, 4H of both isomers), 1.75 (s, CH_3 of both isomers), 1.77 (s, CH_3 of both isomers), 2.35 (d, J = 17.0 Hz, H-3′ of both isomers), 2.80* (d, J = 17.0 Hz, H-3′), 2.83 (d, J = 17.2 Hz, H-3′), 2.98 (d, J = 15.5 Hz, H-6′), 3.01* (d, J = 15.5 Hz, H-6′), 3.33 (d, J = 15.5 Hz, H-6′), 3.34* (d, J = 15.5 Hz, H-6′), 3.41 (m, H-1), 3.47* (m, H-1), 6.53 (tt, J = 52.6, 5.9 Hz, HCF_2), 6.57* (tt, J = 52.6, 5.9 Hz, HCF_2). GC/MS (*m*/*e*): 398 (M^+, 2%), 227 (M^+–$C_{10}H_{19}S$, 100%), 226 (M^+–$C_{10}H_{20}S$, 81%), 211 (64%). Anal. Calcd for $C_{19}H_{30}F_4S_2$: C, 57.26; H, 7.59; S, 16.09. Found: C, 57.29; H, 7.61; S, 15.98.

*4.4.5. 2-{[(1S,2S,5R)-2-Isopropyl-5-methylcyclohexyl]thio}-2-trifluoromethyl-3,6-dihydro-2H-thiopyran (**5e**)*

Colourless oil, yield 90%, mixture of isomers in the ratio 22:78 from HPLC, solvent MeCN:H_2O (85:15), t_r 28.0 (minor) and 29.3 (major) min. ^{19}F NMR ($CDCl_3$): δ −73.40* (s, CF_3), −73.50 (s, CF_3). ^1H NMR ($CDCl_3$): δ 0.86–0.92 (d, $2CH_3$ of both isomers), 0.98–1.00 (d, CH_3 of both isomers), 1.12–1.38 (m, 4H of both isomers), 1.65–2.17 (m, 4H of both isomers), 2.49 (dm, J = 16.5 Hz, H-3′ of both isomers), 2.83 (dm, J = 16.5 Hz, H-3′ of both isomers), 3.17 (m, H-6′ of both isomers), 3.47 (m, H-1,H-6′ of both isomers), 5.77, 5.93 (m, H-5′,6′ of both isomers). GC/MS (*m*/*e*): 338 (M^+, 2%), 167 (M^+–$C_{10}H_{19}S$, 63%), 138 ($C_{10}H_{18}^+$, 10%). Anal. Calcd for $C_{19}H_{28}F_4S_2$: C, 56.77; H, 7.44; S, 18.95. Found: C, 56.80; H, 7.48; S, 18.70.

*4.4.6. 4,5-Dimethyl-2-[(1-phenylethyl)thio]-2-trifluoromethyl-3,6-dihydro-2H-thiopyran (**5f**)*

Colourless oil, yield 95%, mixture of isomers in the ratio 39:61 from HPLC, solvent MeCN:H_2O (75:25), t_r 20.1 (minor) and 21.1 (major) min. ^{19}F NMR ($CDCl_3$): δ −74.09 (s, CF_3), −74.58* (s, CF_3). ^1H NMR ($CDCl_3$): δ 1.32 (s, CH_3), 1.58 (d, J = 7.1 Hz, $\underline{CH_3}$–CH), 1.64* (br, $2CH_3$–C=), 1.66* (d, J = 7.1 Hz, $\underline{CH_3}$–CH), 1.72 (s, CH_3), 2.12 (d, J = 17.8 Hz, H-3′), 2.14* (d, J = 17.8 Hz, H-3′), 2.58–2.98 (m, H-3′ of both isomers + 3H-6′), 3.46 (1H, d, J = 16.0 Hz, H-6′), 4.28 (q, J = 7.1 Hz, CH–Me), 4.32* (q, J = 7.6 Hz, $\underline{CH}$–CH_3), 7.27 (m, C_6H_5 of both isomers). ^{13}C NMR ($CDCl_3$): δ 19.12 (s, CH_3), 19.18* (s, CH_3), 19.55 (s, CH_3), 20.03* (s, CH_3), 24.69* (s, CH_3), 25.51 (s, CH_3), 29.99* (s, C-6′), 30.39 (s, C-6′), 36.68 (q, J = 1.5 Hz, C-3′), 37.60* (q, J = 1.5 Hz, C-3′), 45.44* (q, J = 1.0 Hz, CHS), 45.60 (q, J = 1.0 Hz, CHS), 59.23 (q, J = 28.0 Hz, C-2′), 60.66* (q, J = 27.0 Hz, C-2′), 122.65, 122.98, 123.45, 124.19 (C-4′,5′ of both isomers), 126.57* (q,

J = 281.0 Hz, CF_3), 126.69 (q, J = 283.0 Hz, CF_3), 126.95, 127.00, 127.02, 127.10, 128.52, 128.65 (CH–Ar of both isomers), 144.66 (C–Ar), 145.71* (C–Ar). GC/MS (m/e): 332 (M^+, 2%), 227 (M^+–C_8H_9, 14%), 194 (M^+–$C_8H_{10}S$, 89%), 105 ($C_8H_9^+$, 100%). Anal. Calcd for $C_{16}H_{19}F_3S_2$: C, 57.81; H, 5.76; S, 19.29. Found: C, 57.82; H, 5.77; S, 19.25.

4.4.7. 4,5-Dimethyl-2-[(1-phenylethyl)thio]-2-(1,1,2,2-tetrafluoroethyl)-3,6-dihydro-2H-thiopyran (5g)

Colourless oil, yield 98%, mixture of isomers in the ratio 46:54 from HPLC, solvent MeCN:H_2O (85:15), t_r 8.5 (minor) and 9.3 (major) min. ^{19}F NMR ($CDCl_3$): δ −117.30* (1F, AB, J = 266.0 Hz, CF_2), −119.68 (1F, AB, J = 266.0 Hz, CF_2), −121.10 (1F of both isomers, AB, J = 266.0 Hz), −133.46 (1F, AB d, J = 299.0, 53.1 Hz, HCF_2), −134.50* (1F, AB d, J = 299.0, 53.1 Hz, HCF_2), −135.78* (1F, AB d, J = 299.0, 53.1 Hz, HCF_2), −136.38 (1F, AB d, J = 299.0, 53.1 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, CH_3), 1.57* (d, J = 7.2 Hz, CH_3CH), 1.63 (d, J = 7.2 Hz, CH_3CH), 1.64 (s br, CH_3 of both isomers), 1.72* (s, CH_3), 2.09* (1H, AB, J = 18.0 Hz, H-3′), 2.15 (1H, AB, J = 19.0 Hz, H-3′), 2.60–2.94 (m, H-3′ of both isomers + 3H-6′), 3.49 (1H, AB, J = 16.2 Hz, H-6′), 4.24 (2 q, J = 7.2 Hz, CH–CH_3 of both isomers), 6.14* (1H, tdd, J = 53.1, 7.6, 4.4 Hz, HCF_2), 6.47 (1H, tdd, J = 53.1, 7.2, 4.5 Hz, HCF_2), 7.26 (m, C_6H_5 of both isomers). GC/MS (m/e): 364 (M^+, 2%), 259 (M^+–C_8H_9, 10%), 226 (M^+–$C_8H_{10}S$), 211 (100%), 105 ($C_8H_9^+$, 85%). Anal. Calcd for $C_{17}H_{20}F_4S_2$: C, 56.02; H, 5.53; S, 17.60. Found: C, 56.05; H, 5.56; S, 17.50.

4.4.8. 2-[(1-Phenylethyl)thio]-2-trifluoromethyl-3,6-dihydro-2H-thiopyran (5h)

Pale-yellow oil, yield 98%, mixture of isomers in the ratio 34:66 from HPLC, solvent MeCN:H_2O (75:25), t_r 24.6 (minor) and 26.2 (major) min. ^{19}F NMR ($CDCl_3$): δ −74.15 (s, CF_3), −74.94* (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 1.62 (d, J = 7.2 Hz, CH_3), 1.67* (d, J = 7.2 Hz, CH_3), 2.29 (m, H-3′ of both isomers), 2.64–2.91 (m, H-3′ of both isomer +2H-6′ of major isomer), 3.10 (dm, J = 16.6 Hz, H-6′), 3.51 (dm, J = 16.6 Hz, H-6′), 4.32 (q, J = 7.2 Hz, CH–CH_3), 4.34* (q, J = 7.2 Hz, CH–CH_3), 5.47 (m, H-4), 5.67* (m, H-4), 5.80 (m, H-4 of both isomer), 7.28 (m, C_6H_5 of both isomers). GC/MS (m/e): 304 (M^+, 2%). Anal. Calcd for $C_{14}H_{15}F_3S_2$: C, 55.24; H, 4.97; S, 21.07. Found: C, 55.26; H, 4.99; S, 20.90.

4.4.9. 3-[(1-Phenylethyl)thio]-3-trifluoromethyl-2-thiabicyclo[2.2.1]hept-5-ene (5i)

Pale-yellow oil, yield 90%. R_f 0.40–0.45 (hexane:CH_2Cl_2, 5:1), mixture of four isomers. Data for two main isomers are given. ^{19}F NMR ($CDCl_3$): δ −63.95 (s, CF_3), −65.71* (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 1.58 (d, J = 7.1 Hz, CH_3), 1.68 (d, J = 9.5 Hz, 1H-7), 1.71* (d, J = 7.1 Hz, CH_3), 1.83* (d, J = 9.5 Hz, 1H-7), 2.36 (d, J = 9.5 Hz, 1H-7), 2.37* (d, J = 9.5 Hz, 1H-7), 3.03 (m, H-4), 3.52* (m, H-4), 4.13 (m, H-1), 4.19* (m, H-1), 4.39 (q, J = 7.1 Hz, CH–CH_3), 4.47* (q, J = 7.1 Hz, CH–CH_3), 5.77 (m, H-6), 5.94* (m, H-6), 6.42 (dd, J = 5.3, 2.8 Hz, H-5), 6.52* (dd, J = 5.0, 2.8 Hz, H-5), 7.21–7.41 (m, H–Ar of both isomers). GC/MS (m/e): 250 (M^+–C_5H_6, 2%), 105 ($C_8H_9^+$, 100%). Anal. Calcd for $C_{15}H_{15}F_3S_2$: C, 56.94; H, 4.78; S, 20.27. Found: C, 56.99; H, 4.82; S, 20.01.

4.4.10. 3-[(1-Phenylethyl)thio]-3-(1,1,2,2-tetrafluoroethyl)-2-thiabicyclo[2.2.1]hept-5-ene (5j)

Pale-yellow oil, yield 85%. R_f 0.40–0.45 (hexane:CH_2Cl_2, 5:1), mixture of four isomers. Data for two main isomers are given. ^{19}F NMR ($CDCl_3$): δ −105.56 (1F, AB, J = 263.0 Hz, CF_2), −106.23* (1F, AB, J = 263.0 Hz, CF_2), −114.46* (1F, AB, J = 263.0 Hz, CF_2), −116.09 (1F, AB, J = 263.0 Hz, CF_2), −136.41 (1F, d AB, J = 299.5, 53.4 Hz, HCF_2), −137.28* (2F, dm, J = 53.4 Hz, HCF_2), −139.04 (1F, d AB, J = 299.5, 53.4 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 1.56–1.65 (m, 1H-7 of both isomers), 1.63* (d, J = 7.1 Hz, CH_3), 1.70 (d, J = 7.1 Hz, CH_3), 2.38 (d, J = 8.1 Hz, 1H-7), 2.40* (d, J = 9.0 Hz, 1H-7), 3.24* (m, H-4), 3.54 (m, H-4), 4.16 (m, H-1 of both isomers), 4.34* (q, J = 7.1 Hz, CH–CH_3), 4.46 (q, J = 7.1 Hz, CH–CH_3), 5.84* (m, H-6), 5.94 (m, H-6), 6.33* (tdd, J = 53.4, 6.5, 5.1 Hz, HCF_2), 6.47 (tdd, J = 53.4, 8.1, 3.0 Hz, HCF_2), 6.45 (m, H-5 of both isomers), 7.21–7.36 (m, H–Ar of both isomers). ^{13}C NMR ($CDCl_3$): δ 24.59* (CH_3), 24.62 (CH_3), 47.60* (t, J = 2.3 Hz, C-1), 47.65 (C-1), 51.65* (C-7), 52.07 (C-7), 54.05* (t, J = 1.5 Hz, C-4), 54.90 (C-4), 55.05* (C–Me), 55.43 (t, J = 2.0 Hz, C–Me), 72.51* (dd, J = 21.3, 18.0 Hz, C-3), 73.14 (t, J = 19.0 Hz, C-3), 109.60 (tt, J = 252.0, 32.5 Hz, HCF_2), 109.72* (tt, J = 253.0, 33.0 Hz, HCF_2), 114.5–121.0 (m, CF_2 of both isomers), 126.94, 127.19, 127.33, 127.37. 128.75, 128.76 (CH–Ar of both isomers), 132.09 (C-6), 132.23* (C-6), 138.99* (t, J = 2.5 Hz, C-5), 139.19 (t, J = 2.0 Hz, C-5), 144.10 (C–Ar), 144.83* (C–Ar). GC/MS (m/e): 282 (M^+–C_5H_6, 4%), 105 ($C_8H_9^+$, 100%). Anal. Calcd for $C_{16}H_{16}F_4S_2$: C, 55.15; H, 4.63; S, 18.41. Found: C, 55.18; H, 4.68; S, 18.25.

4.4.11. 4,5-Dimethyl-2-trifluoromethyl-2-{[(1S)-exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]thio}-3,6-dihydro-2H-thiopyran (5k)

Pale-yellow oil, yield 98%, mixture of isomers in the ratio 41:59 from HPLC, solvent MeOH:H_2O (87:13), t_r 36.0 (major) and 37.6 (minor) min. ^{19}F NMR ($CDCl_3$): δ −74.08 (s, CF_3), −74.34* (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.82 (s, CH_3 of both isomers), 0.84* (s, CH_3), 0.90* (s, CH_3), 0.97 (s, CH_3), 0.99 (s, CH_3), 1.11–1.43 (m, CH_2 of both isomers), 1.61–1.77 (m, CH_2 + 2CH_3 of both isomers), 1.93–1.99 (m, CH_2 of both isomers), 2.15–2.24 (m, H-3′ of both isomers), 2.73–2.90 (m, H-3′ + H-6′ of both isomers), 3.00–3.05 (m, 2H-6′ of both isomers), 3.33 (dd, J = 15.2, 14.8, H-2 of both isomers). GC/MS (m/e): 364 (M^+, 2%), 194 (M^+–$C_{10}H_{18}S$, 100%), 179 (80%), 137 ($C_{10}H_{17}^+$, 81%). Anal. Calcd for $C_{18}H_{27}F_3S_2$: C, 59.31; H, 7.47; S, 17.59. Found: C, 59.35; H, 7.49; S, 17.36.

4.4.12. 4,5-Dimethyl-2-(1,1,2,2-tetrafluoroethyl)-2-{[(1S)-exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]thio}-3,6-dihydro-2H-thiopyran (5l)

Colourless oil, yield 85%. R_f 0.33 (hexane), mixture of isomers in the ratio 40:60 from HPLC, solvent MeOH:H_2O (87:13), t_r 27.0 (major) and 28.2 (minor) min. ^{19}F NMR ($CDCl_3$): δ −118.67* (1F, AB, J = 263.5 Hz, CF_2), −119.82 (1F, AB, J = 259.0 Hz, CF_2), −121.49 (2F, AB of both isomers), −132.47 (1F, ddm, J = 297.0, 54.0 Hz, HCF_2), −133.42* (1F, ddm, J = 297.0, 54.0 Hz, HCF_2), −136.69* (1F, ddm, J = 297.0, 54.0 Hz, HCF_2), −137.55 (1F, ddm, J = 297.0, 54.0 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 0.82* (s, CH_3), 0.84 (s, CH_3), 0.88* (s, CH_3), 0.90 (s, CH_3), 0.94 (s, CH_3), 0.95* (s, CH_3), 1.09–1.37 (m, CH_2 of both isomers), 1.62–1.76 (m, CH_2 of both isomers), 1.70 (s, CH_3 of both isomers), 1.76 (s, CH_3 of both isomers), 1.93–2.02 (m, CH_2 of both isomers), 2.12 (1H, d, J = 17.7 Hz, H-3′), 2.18* (1H, d, J = 17.7 Hz, H-3′), 2.78–2.87 (m, H-3′ + H-6′ of both isomers), 2.99–3.04 (m, H-2 of both isomers), 3.32* (1H, d, J = 14.7 Hz, H-6′), 3.37 (1H, d, J = 14.7 Hz, H-6′), 6.52* (1H, tdd, J = 54.0, 8.4, 3.5 Hz, HCF_2), 6.57 (1H, tdd, J = 54.0, 8.3, 3.4 Hz, HCF_2). ^{13}C NMR ($CDCl_3$): δ 14.37 (CH_3), 14.75* (CH_3), 19.20* (CH_3), 19.32 (CH_3), 19.74 (CH_3), 19.86* (CH_3), 20.31 (CH_3), 20.40* (CH_3), 20.98 (CH_3), 21.00* (CH_3), 27.45 (C-5), 27.51* (C-5), 29.24* (C-6′), 29.42 (C-6′), 36.86 (m, C-6′ of both isomers), 38.45 (C-6), 38.69* (C-6), 42.88* (m, C-3′), 44.15 (C-3′), 46.21* (C-4), 46.32 (C-4), 47.38* (C-7), 47.39 (C-7), 50.54 (C-1), 50.59* (C-1), 52.95* (q, J = 1.0 Hz, C-2), 53.19 (q, J = 1.5 Hz, C-2), 60.49* (t, J = 22.0 Hz, C-2′), 60.61 (t, J = 21.0 Hz, C-2′), 109.43 (tdd, J = 253.0, 32.0, 30.2, Hz, HCF_2), 109.62* (tdd, J = 253.0, 33.0, 30.0 Hz, HCF_2), 117.13* (tm, J = 261.0 Hz, CF_2), 117.16 (tm, J = 261.0 Hz, CF_2), 122.51, 122.57, 123.71, 124.13 (C-4′,5′ of both isomers). GC/MS (m/e): 396 (M^+, 2%), 227 (M^+–$C_{10}H_{17}S$, 73%), 226 (M^+–$C_{10}H_{18}S$, 100%), 137 ($C_{10}H_{17}^+$, 60%). Anal. Calcd for $C_{19}H_{28}F_4S_2$: C, 57.55; H, 7.12; S, 16.17. Found: C, 57.56; H, 7.13; S, 16.02.

*4.4.13. 4,5-Dimethyl-2-trifluoromethyl-2-{[(1S)-endo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]thio}-3,6-dihydro-2H-thiopyran (**5m**)*

Pale-yellow oil, yield 96%, mixture of isomers in the ratio 45:55 from HPLC, solvent MeCN:H_2O (95:5), t_r 24.3 (minor) and 25.3 (major) min. ^{19}F NMR ($CDCl_3$): δ −74.31* (s, CF_3), −74.42* (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.87, 0.88, 0.89, 0.91, 0.92, 0.94 (s, CH_3 of both isomers), 1.22–1.44 (m, *endo*-H-3 + H-5 of both isomers), 1.54–1.74 (m, H-4,5,6 of both isomers), 1.70 (s, CH_3 of both isomers), 1.76* (s, CH_3), 1.78 (s, CH_3), 2.20* (AB, J = 17.5 Hz, H-3′), 2.24 (AB, J = 17.5 Hz, H-3′), 2.43 (m, *exo*-H-3 of both isomers), 2.68–2.98 (m, H-6,3′,6′ of both isomers), 3.17 (dm, J = 10.9 Hz, *exo*-H-2), 3.24* (dm, J = 10.5 Hz, *exo*-H-2), 3.36* (AB, J = 16.2 Hz, H-6′), 3.40 (AB, J = 16.2 Hz, H-6′). GC/MS (*m*/*e*): 364 (M^+, 2%), 194 (M^+–$C_{10}H_{18}S$, 100%), 179 (62%). Anal. Calcd for $C_{18}H_{27}F_3S_2$: C, 59.31; H, 7.47; S, 17.59. Found: C, 59.32; H, 7.48; S, 17.42.

*4.5. Cycloadducts **5n–p** (Table 3). Common procedure*

A solution of thionoester **4a**,**d**,**e** (1 mmol) and DMB (0.33 g, 4 mmol) in dry benzene (2 ml) was heated in a pressure tube at 125–130 °C for 5 h. After cooling the solvent and excess of DMB were removed under reduced pressure. NMR spectra of crude mixture were recorded to establish the ratio of isomers before purification of cycloadducts over silica gel column chromatography with hexane as eluent.

*4.5.1. 4,5-Dimethyl-2-trifluoromethyl-2-{[(1S)-endo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}-3,6-dihydro-2H-thiopyran (**5n**)*

Pale-yellow oil, yield 80%. R_f 0.30–0.40 (hexane), mixture of isomers in the ratio 47:53 from HPLC, solvent MeCN:H_2O (92:8), t_r 19.3 (minor) and 21.2 (major) min. ^{19}F NMR ($CDCl_3$): δ −77.19 (s, CF_3), −78.21* (s, CF_3). ^{1}H NMR ($CDCl_3$): δ 0.72* (s, CH_3), 0.81 (s, CH_3), 0.82 (s, 2CH_3 of both isomers), 1.05–1.26 (m, *endo*-H-3 + H-5 of both isomers), 1.54–1.71 (m, H-4,5,6 of both isomers), 1.79 (s, 2CH_3 of both isomers), 1.85–1.98 (m, H-6 of both isomers), 2.04–2.19 (m, *exo*-H-3 of both isomers), 2.38 (AB, J = 14.7 Hz, H-3′), 2.41* (AB, J = 14.7 Hz, H-3′), 2.52 (AB, J = 14.7 Hz, H-3′), 2.53* (AB, J = 14.7 Hz, H-3′), 3.08 (AB, J = 14.1 Hz, H-6′ of both isomers), 3.10* (AB, J = 14.1 Hz, H-6′ of both isomers), 4.09 (dm, J = 9.1 Hz, *exo*-H-2), 4.13* (dm, J = 9.4 Hz, *exo*-H-2). ^{13}C NMR ($CDCl_3$): δ 13.31 (CH_3), 13.42* (CH_3), 18.67* (CH_3), 18.76 (CH_3), 18.98* (CH_3), 19.04 (CH_3), 19.81 (CH_3), 19.90* (CH_3), 20.67 (CH_3 of both isomers), 26.84 (CH_2), 26.87* (CH_2), 28.25* (CH_2), 28.31 (CH_2), 30.99* (CH_2), 31.52 (CH_2), 36.81* (q, CH_2, J = 1.5 Hz), 38.92 (q, CH_2, J = 1.5 Hz), 39.21 (q, CH_2, J = 1.2 Hz), 39.25* (CH_2), 45.14* (C-4), 45.16 (C-4), 47.21* (C-7), 47.34 (C-7), 49.61 (C-1), 49.70* (C-7), 80.46* (C-2), 81.48 (C-2), 90.66 (q, J = 27.0 Hz, C-2′), 90.93* (q, J = 27.0 Hz, C-2′), 125.26* (q, J = 287.0 Hz, CF_3), 126.78 (q, J = 287.0 Hz, CF_3), 126.37, 126.82, 127.27, 127.41 (C-4′,5′ of both isomers). GC/MS (*m*/*e*): 348 (M^+, 2%), 195 (M^+–$C_{10}H_{17}O$, 22%), 153 ($C_{10}H_{17}O^+$, 48%). Anal. Calcd for $C_{18}H_{27}F_3OS$: C, 62.04; H, 7.81; S, 9.20. Found: C, 62.06; H, 7.83; S, 8.98.

*4.5.2. 4,5-Dimethyl-2-(1,1,2,2-tetrafluoroethyl)-2-{[(1S)-endo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]oxy}-3,6-dihydro-2H-thiopyran (**5o**)*

Pale-yellow oil, yield 75%. R_f 0.35–0.45 (hexane), mixture of isomers in the ratio 40:60 from HPLC, solvent MeCN:H_2O (92:8), t_r 12.2 (minor) and 13.3 (major) min. ^{19}F NMR ($CDCl_3$): δ −121.86 (1F, AB, J = 263.5, 8.0 Hz, CF_2), −122.14* (1F, AB, J = 266.5, 8.0 Hz, CF_2), −126.77* (1F, AB, J = 266.5, 8.0 Hz, CF_2), −127.01 (1F, AB, J = 256.0, 8.0 Hz, CF_2), −136.05* (d AB, J = 295.0, 53.3 Hz, HCF_2), −136.24 (d AB, J = 296.3, 53.3 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 0.79* (s, CH_3), 0.81 (s, CH_3), 0.82 (s, CH_3), 0.83* (s, CH_3), 0.84 (s, CH_3 of both isomers), 0.90–1.06 (m, *endo*-H-3 + H-5 of both isomers), 1.12–1.28 (m, H-5,6 of both isomers), 1.52–1.83 (m, H-4,6 of both isomers), 1.78 (s, 2CH_3 of both isomers), 2.06–2.23 (m, *exo*-H-3 of both isomers), 2.37–2.62 (m, H-3′ of both isomers), 2.99–3.21 (m, H-6′ of both isomers), 4.03* (dm, J = 9.3 Hz, *exo*-H-2), 4.21 (dm, J = 9.6 Hz, *exo*-H-2), 6.15 (td, J = 53.3, 4.5 Hz, HCF_2), 6.18* (td, J = 53.3, 4.3 Hz, HCF_2). ^{13}C NMR ($CDCl_3$): δ 13.59 (CH_3), 13.73* (CH_3), 18.67 (CH_3), 18.70* (CH_3), 18.93* (CH_3), 19.03 (CH_3), 19.78 (CH_3), 19.83* (CH_3), 20.20* (CH_3), 20.24 (CH_3), 27.09* (CH_2), 27.16 (CH_2), 28.25 (CH_2 of both isomers), 31.80* (CH_2), 32.32 (CH_2), 37.88* (m, CH_2), 38.09 (m, CH_2), 38.64* (CH_2), 39.05 (CH_2), 45.05* (C-4), 45.23 (C-4), 47.24* (C-7), 47.32 (C-7), 49.44* (C-1), 49.64 (C-1), 79.41 (C-2), 80.64* (C-2), 92.34* (t, J = 7.6 Hz, C-2′), 93.35 (dd, J = 22.5, 24.0 Hz, C-2′), 109.76 (tt, J = 252.5, 32.0 Hz, HCF_2), 109.79* (tt, J = 252.0, 31.0 Hz, HCF_2), 113.0–118.7 (tm, CF_2 of both isomers), 126.89, 127.09, 127.55, 127.56 (C-4′,5′ of both isomers). GC/MS (*m*/*e*): 380 (M^+, 2%), 227 (M^+–$C_{10}H_{17}O$, 36%), 153 ($C_{10}H_{17}O^+$, 66%). Anal. Calcd for $C_{19}H_{28}F_4OS$: C, 59.98; H, 7.42; S, 8.43. Found: C, 60.01; H, 7.43; S, 8.21.

*4.5.3. 2-Isopropoxy-4,5-dimethyl-2-(1,1,2,2-tetrafluoroethyl)-3,6-dihydro-2H-thiopyran (**5p**)*

Pale-yellow oil, yield 88%. R_f 0.5 (hexane). ^{19}F NMR ($CDCl_3$): δ −122.18 (1F, AB, dd, J = 267.1, 10.5 Hz, CF_2), −127.27 (1F, AB, ddd, J = 267.1, 20.3, 8.3 Hz, CF_2), −135.16 (1F, AB, ddd, J = 299.0, 53.5, 12.0 Hz, HCF_2), −137.66 (1F, AB, ddt, J = 299.0, 53.5, 11.0 Hz, HCF_2). ^{1}H NMR ($CDCl_3$): δ 1.13 (6H, d, J = 6.2 Hz, CH_3), 1.78 (3H, s, CH_3), 1.80 (3H, s, CH_3), 2.49 (2H, m, H-3), 3.09 (2H, m, H-6), 4.17 (1H, septet, J = 6.2 Hz, CH-O), 6.14 (tdd, J = 53.5, 8.1, 4.0 Hz, HCF_2). GC/MS (*m*/*e*): 286 (M^+, 2%). Anal. Calcd for $C_{12}H_{18}F_4OS$: C, 50.34; H, 6.34; S, 11.20. Found: C, 50.36; H, 6.36; S, 11.05.

4.6. Details of calculations

All the structures were fully optimized with the GAUSSIAN-03 set of programs [26] using the DFT (B3LYP [27,28]) level of approximation and 6-31G** basis sets [29–32]. The energy values were corrected adding the Zero Point Energy (ZPE) correction values or on the Thermal Correction to Gibbs Free Energy (TCGFE) correction values. Differences between corrected energy values yielded ΔE and ΔG magnitudes, respectively. All the transition states were located using an effective procedure published recently [33]. First the geometry was optimized with an only frozen C–S reaction coordinate fixed to 2.45 Å. Thereafter the geometry was fully optimized as a transition state structure, calculating force constants by the first optimization cycle. The most favoured structures were re-optimized using the larger 6-311G** standard basis sets. As default within the GAUSSIAN packet the mentioned basis sets are defined as the proper 6-311G Pople basis sets [34] for hydrogen and the second period atoms (C, F) and the (12s,9p) McLean-Chandler basis set [35] for sulfur, expanded with the appropriate polarization functions. All stationary points were characterized by the vibration frequencies, derived calculating the first and second derivatives analytically (zero and one imaginary frequency for the local minima and transition states, respectively). Additionally, structures **5A**–**D** and **6A**–**D** optimized at the B3LYP/6-311G** level of theory were used for the energy single-point calculations using more accurate cc-pVTZ Dunning's basis sets [36]. The optimized structures were pictured using the VMD program [37].

Acknowledgements

We greatly thank Enamine Ltd. (Kyiv) for performing GC/MS measurements and HPLC studies. We are also very grateful to Professor Dr. W.W. Schoeller and Professor Dr. U. Manthe, University of Bielefeld (Germany) for the access to the computer cluster and GAUSSIAN-03 set of program.

References

[1] D.L. Boger, S.M. Weinreb, in: H.H. Wasserman (Ed.), Hetero Diels-Alder Methodology in Organic Synthesis, vol. 47, Academic Press, San Diego, 1987.
[2] E. Vedejs, R.J. Galante, P.G. Goekjian, J. Am. Chem. Soc. 120 (1998) 3613–3622.
[3] S. Perreault, C. Spino, Org. Lett. 8 (2006) 4385–4388.
[4] D.M. Vyas, G.W. Hay, Can. J. Chem. 53 (1975) 1362–1366.
[5] D. Adam, A.A. Freer, N.W. Isaacs, G.W. Kirby, A. Littlejohn, M.S. Rahman, J. Chem. Soc., Perkin Trans. 1 10 (1992) 1261–1264.
[6] Yu.G. Shermolovich, Y.I. Slusarenko, L.N. Markovski, Zhurn. Org. Khim. (Russ.) 24 (1988) 1931–1934.
[7] W.J. Middleton, J. Org. Chem. 30 (1965) 1390–1394.
[8] Yu.G. Shermolovich, Y.I. Slusarenko, V.M. Timoshenko, A.B. Rozhenko, L.N. Markovski, J. Fluorine Chem. 55 (1991) 329–333.
[9] C. Portella, Yu.G. Shermolovich, O. Tschenn, Bull. Soc. Chim. Fr. 134 (1997) 697–702.
[10] V.M. Timoshenko, A.V. Tkachenko, Yu.G. Shermolovich, J. Fluorine Chem. 126 (2005) 361–364.
[11] H.C. Brown, R. Pater, J. Org. Chem. 27 (1962) 2858–2863.
[12] W.J. Middleton, E.G. Howard, W.H. Sharkey, J. Org. Chem. 30 (1965) 1375–1384.
[13] F. Laduron, C. Nyns, Z. Janousek, H.G. Viehe, J. Prakt. Chem. 339 (1997) 697–707.
[14] L.A. Babadzhanova, N.V. Kirij, Yu.L. Yagupolskii, J. Fluorine Chem. 125 (2004) 1095–1098.
[15] A.Yu. Sizov, A.N. Kovregin, R.N. Serdyuk, M.V. Vorob'ev, V.A. Porosyatnikov, A.A. Tsvetkov, D.O. Korneev, A.F. Ermolov, Russ. Chem. Bull. 55 (2006) 1156–1163.
[16] Yu. Shermolovich, V. Timoshenko, J. Fluorine Chem. 114 (2002) 157–161.
[17] A. Gayet, C. Bolea, P.G. Andersson, Org. Biomol. Chem. 2 (2004) 1887–1893.
[18] J.H. Zaidi, F. Naeem, K.M. Khan, R. Iqbal, Zia-Ullah, Synth. Commun. 34 (2004) 2641–2653.
[19] J. Haraszti, J. Prakt. Chem. 149 (1937) 301–310.
[20] J.M. Blanco, O. Caamafio, F. Fernandez, Tetrahedron 51 (1995) 935–940.
[21] R.M. Kellogg, J.W. Nieuwenhuijzen, K. Pouwer, T.R. Vries, Q.B. Broxterman, R.F.P. Grimbergen, B. Kaptein, R.M.L. Crois, E. de Wever, K. Zwaagstra, A.C. van der Laan, Synthesis (2003) 1626–1638.
[22] F. Grellepois, V.M. Timoshenko, Yu.G. Shermolovich, C. Portella, Org. Lett. 8 (2006) 4323–4326 (reference cited therein).
[23] R.G. Petrova, T.D. Churkina, R.G. Gasanov, B.V. Lokshin, R.Kh. Freidlina, Russ. Chem. Bull. 36 (1987) 323–326.
[24] V. Barone, R. Arnaud, P.Y. Chavant, Y. Vallée, J. Org. Chem. 61 (1996) 5121–5129.
[25] S. Perreault, M. Poirier, P. Léveillé, O. René, P. Joly, Y. Dory, C. Spino, J. Org. Chem. 73 (2008) 7457–7466.
[26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. itao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision B. 03, Gaussian, Pittsburgh, 2003.
[27] A.D. Becke, J. Chem. Phys. 98 (1993) 5648–5652.
[28] C. Lee, W. Yang, R.G. Parr, Phys. Rev. (B) 37 (1988) 785–789.
[29] R. Ditchfield, W.J. Hehre, J.A. Pople, J. Chem. Phys. 54 (1971) 724–728.
[30] W.J. Hehre, R. Ditchfield, J.A. Pople, J. Chem. Phys. 56 (1972) 2257–2261.
[31] P.C. Hariharan, J.A. Pople, Mol. Phys. 27 (1974) 209–214.
[32] P.C. Hariharan, J.A. Pople, Theor. Chim. Acta 28 (1973) 213–222.
[33] V.V. Pirozhenko, A.B. Rozhenko, A.P. Avdeenko, S.A. Konovalova, A.A. Santalova, Magn. Reson. Chem. 46 (2008) 811–817.
[34] M.J. Frisch, J.A. Pople, J.S. Binkley, J. Chem. Phys. 80 (1984) 3265–3269.
[35] A.D. McLean, G.S. Chandler, J. Chem. Phys. 72 (1980) 5639–5648.
[36] R.A. Kendall, T.H. Dunning Jr., R.J. Harrison, J. Chem. Phys. 96 (1992) 6796–6806.
[37] VMD for WIN-32, Version 1.8.2 (December, 4, 2003): W. Humphrey, A. Dalke, K. Schulten, J. Mol. Graphics, 14 (1996) 33–38.