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Review

Synthesis of polyfluoroalkyl containing thiopyran derivatives and their applications in fluoroorganic chemistry

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Dedicated to the memory of
Prof. M.O. LOZINSKY.

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ABSTRACT

An overview of syntheses and chemical properties of polyfluoroalkyl 2*H*- and 4*H*-thiopyrans, their hydrogenated (3,4- and 3,6-dihydrothiopyrans, and tetrahydrothiopyrans) and S-oxidized derivatives is presented. The first part is devoted to the synthetic methods starting from acyclic or cyclic precursors, and on multicomponent reactions. The second one deals with the chemical properties of thiopyran derivatives such as elimination reactions, [4+2] cycloadditions, sulfur or C=C double bond oxidations, and reactions with nucleophiles. The last part is focused on the biological evaluation of polyfluoroalkyl 2*H*-thiopyrans, especially as potential cardiotonic agents.

Contents

1. Introduction

Thiopyrans are 6-membered heterocyclic compounds which contain sulfur atom, bonded in a ring system with two double bonds and sp^3-hybridized carbon atom. Thiopyrans are classified as 2*H*-thiopyrans (**1**) or 4*H*-thiopyrans (**2**) depending on the position of the double bonds. Their hydrogenated derivatives are

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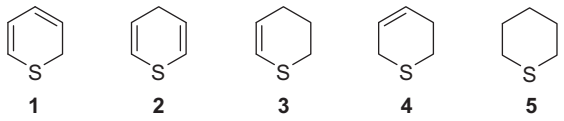


Fig. 1. Thiopyran derivatives outlined in this review.

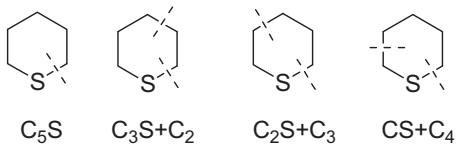


Fig. 2. Synthetic approaches to construction of thiopyran derivatives.

classified as 3,4-dihydro-2*H*-thiopyrans (**3**), 3,6-dihydro-2*H*-thiopyrans (**4**) and tetrahydrothiopyrans (**5**) (Fig. 1).

Syntheses and properties of 2*H*- and 4*H*-thiopyrans were described in several reviews [1–3]. In this paper, we describe an overview of syntheses and chemical properties of polyfluoroalkylthiopyrans, their hydrogenated and S-oxidized derivatives. Methods for the synthesis of polyfluoroalkyl substituted thiopyrans and their derivatives from acyclic and cyclic precursors will be given in Section 1. Chemical properties of polyfluoroalkyl thiopyran derivatives will be overviewed in Section 2 (eliminations, [4+2] cycloadditions, sulfur and C=C double bond oxidations, nucleophilic additions). Biological evaluation of fluoroalkyl substituted thiopyrans will be given in Section 3.

2. Syntheses and chemical properties of polyfluoroalkyl thiopyran derivatives

2.1. Methods of synthesis of polyfluoroalkyl substituted thiopyrans

Synthetic approaches to construction of six-membered heterocyclic framework (saturated or unsaturated) with sulfur atom, considered in this review, were divided into methods according to the number and type of atoms in reactants and classified as C_5S, C_3S+C_2, C_2S+C_3-cyclizations, and $CS+C_4$-cycloadditions (Fig. 2).

Syntheses of fluorine- and sulfur-containing substrates for construction of thiopyran cycles are also synthetic challenges, therefore attention will be also payed to the preparation of starting compounds.

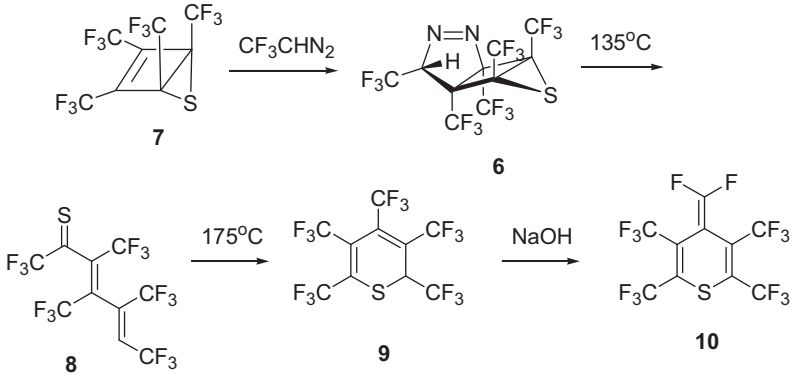
2.1.1. Syntheses from acyclic starting compounds

2.1.1.1. C_5S-cyclization. Thermolysis of tricyclic adduct **6** obtained from trifluorodiazoethane and tetrakis(trifluoromethyl) Dewar thiophene **7** gave the corresponding polyfluorinated thioketone **8**, which underwent electrocyclization to form 2,3,4,5,6-pentakis-(trifluoromethyl)-2*H*-thiopyran (**9**) upon further heating (no yield was reported) [4]. Structure assignments for **9** were facilitated by its rapid and clean transformation into dehydrofluorinated product **10** by treatment with aqueous NaOH (Scheme 1).

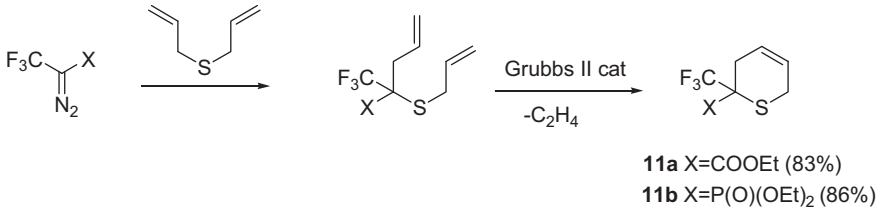
2-(Trifluoromethyl)-2-(ethoxycarbonyl)- and 2-(trifluoromethyl)-2-(O,O-diethylphosphonyl)-3,6-dihydro-2*H*-thiopyrans **11a**,**b** were obtained by alkene ring closing methathesis reaction in the presence of second generation Grubbs' catalyst [5] (Scheme 2).

2.1.1.2. C_3S+C_2-cyclization. This type of cyclization was based on cycloaddition reactions of sulfur-containing heterodiene (C_3S) with dienophiles (olefins or acetylenes, C_2).

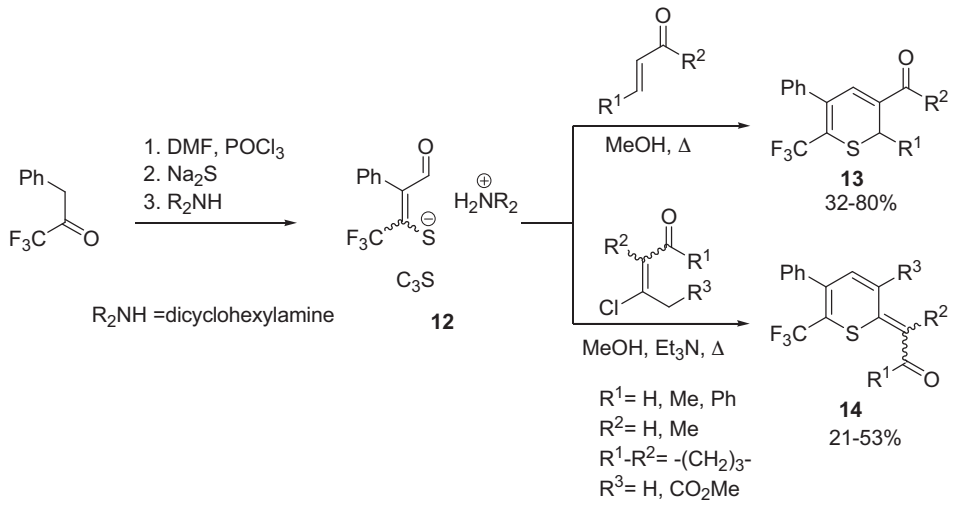
Dicyclohexylammonium salt of 2-phenyl-3-mercapto-4,4,4-trifluorocrotonic aldehyde (**12**) is a convenient precursor for the preparation of substituted trifluoromethyl containing 2*H*-thiopyran derivatives acting as C_3S-component [6]. It was shown that salt **12** reacted with acroleins or enones to form 3-acyl-5-phenyl-6-(trifluoromethyl)-2*H*-thiopyrans **13** whereas reactions with β-chlorovinylpropenes, activated with an electron-withdrawing group (COR^1), led to 2-(acylalkylidene)-5-phenyl-6-(trifluoromethyl)-2*H*-thiopyrans **14** (Scheme 3).



Scheme 1.



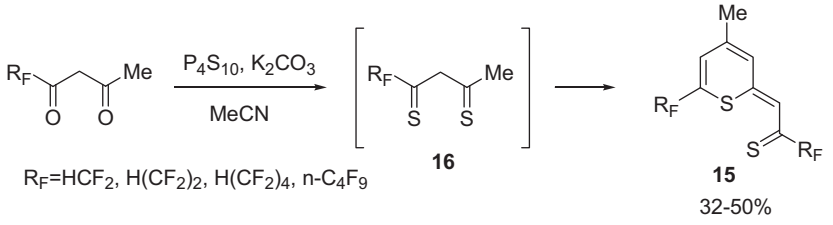
Scheme 2.



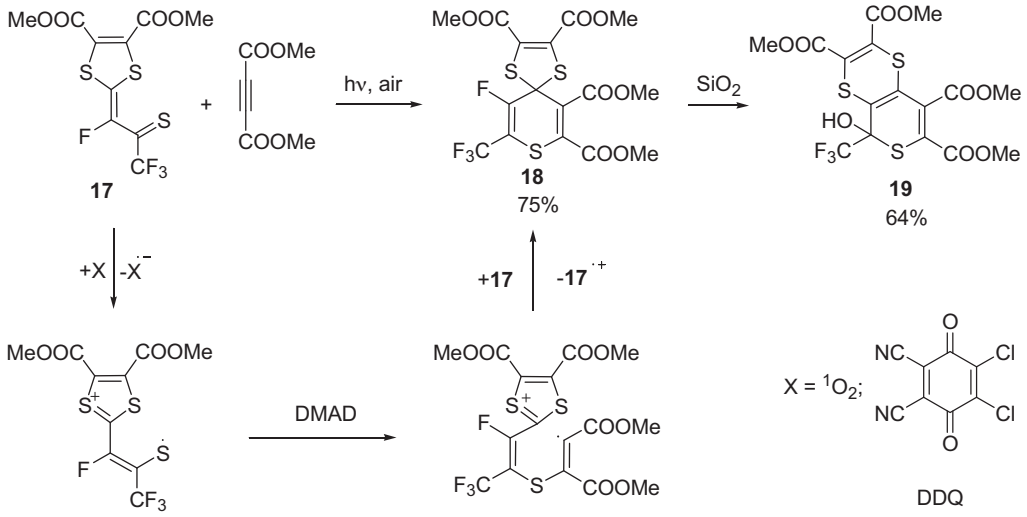
Scheme 3.

Polyfluorinated β-dicarbonyl compounds were converted to (Z)-4-methyl-2-(polyfluorothioacylmethylene)-6-(polyfluoroalkyl) -2*H*-thiopyrans **15** under nucleophilic thionation conditions (phosphorus (V) sulfide and potassium carbonate) in moderate yields (Scheme 4). The authors [7] suggested the formation of β-dithiocarbonyl intermediate **16** which underwent the condensation giving final products **15**. Structure one of them (R_F = HCF_2CF_2) was established by single crystal X-ray diffraction.

The reaction of 2-(trifluorothioacetylfluoromethylene)-1,3-dithiol (**17**) with dimethyl acetylenedicarboxylate (DMAD) was reported to give substituted 4*H*-thiopyran **18** as the product of formal [4+2]-cycloaddition of heterodiene **17** and dienophile (Scheme 5). However, the authors [8] pointed that formation of 4*H*-thiopyran took place only in the presence of air and light or required the addition of dichlorodicyanoquinone (DDQ) to proceed in the dark. The mechanism involving ion-radical intermediates was proposed instead of concerted hetero-Diels–Alder reaction pathway. According to this suggestion, the electron-deficient DDQ or singlet oxygen acted as initiator abstracting the electron from the molecule of **17**. The radical cation was able to add to triple bond of DMAD giving the corresponding intermediate which afforded thiopyran **18** after cyclization and electron transfer from another



Scheme 4.



Scheme 5.

molecule of dithione **17**. The resulting product was readily transformed to 2*H*-thiopyran derivative **19** in the presence of water or silica gel when purification by silica gel chromatography was attempted.

2.1.1.3. C_2S+C_3-cyclization. 2*H*-Thiopyran derivatives were also prepared from C_2S sulfur containing reagents and α,β-unsaturated trifluoroketone (C_3 fragment). For example, 4-(trifluoromethyl)-2*H*-thiopyran **20** was obtained in moderate yield in the acid-catalysed reaction of ethyl benzylidenetrifluoroacetylacetate **21** with malonic acid thioanilide methyl ester [9] (Scheme 6).

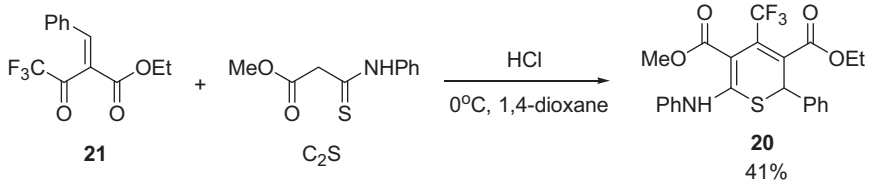
Compounds with two fused thiopyran rings **22** were reported to be formed upon the treatment of polyfluorinated acids thioamides **23** with allylmagnesium halides. The authors [10] proposed a reaction pathway involving a participation of perfluorothioketones formed from thioamides **23** and organomagnesium reagents. Thioketones were transformed into magnesium dienethiolate which upon oxidation gave thiyl radicals capable of head-to-tail dimerization affording the final products **22** as diastereomeric mixtures (Scheme 7).

2.1.1.4. $CS+C_4$-cycloaddition of thiocarbonyl compounds. Those synthetic methods include the reactions of [4+2]-cycloaddition of thiocarbonyl compounds and 1,3-dienes and present the most widely employed methodology to construct the six-membered heterocyclic framework. Progress of this approach is connected with a synthetical availability of the fluoroalkyl thiocarbonyl substrates, which syntheses will also be considered in this review.

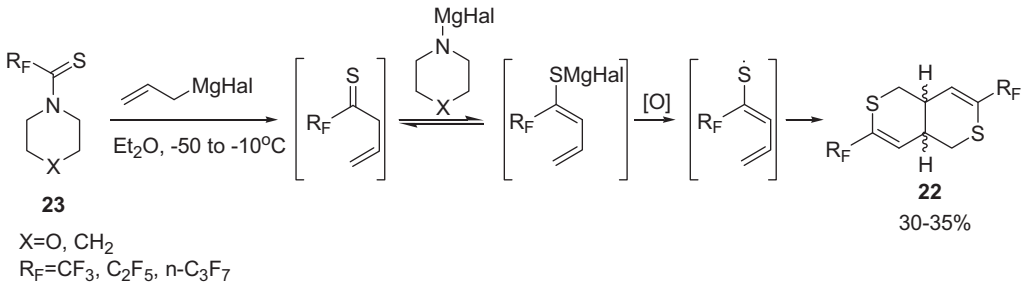
Known sulfur containing heterodienophiles are polyfluorinated thioaldehydes, thioketones, thioamides, dithioesters, and their S-oxidized derivatives such as sulfines and sulfenes. 3,6-Dihydro-2*H*-thiopyrans are the primary products of cycloaddition. In some cases, they are stable enough for isolation; sometimes, they readily undergo further transformations which will be further discussed in detail.

Trifluorothioacetaldehyde **24** is a highly reactive heterodienophile and, due to its strong tendency to polymerization proceeding even at −78 °C, thioaldehyde **24** is not convenient for synthetic applications. It was generated in situ by pyrolysis of 2-(trifluoromethyl)-1,3-dithiolane derivatives **25** [11] and trapped at low temperature with 1,3-dienes giving cycloadduct **26** (Scheme 8). Trifluorothioacetaldehyde **24** was also prepared from its anthracene cycloadduct **27** by heating. The latter is obtained by thionation of trifluoroacetaldehyde by means of phosphorus (V) sulfide in the presence of anthracene [12].

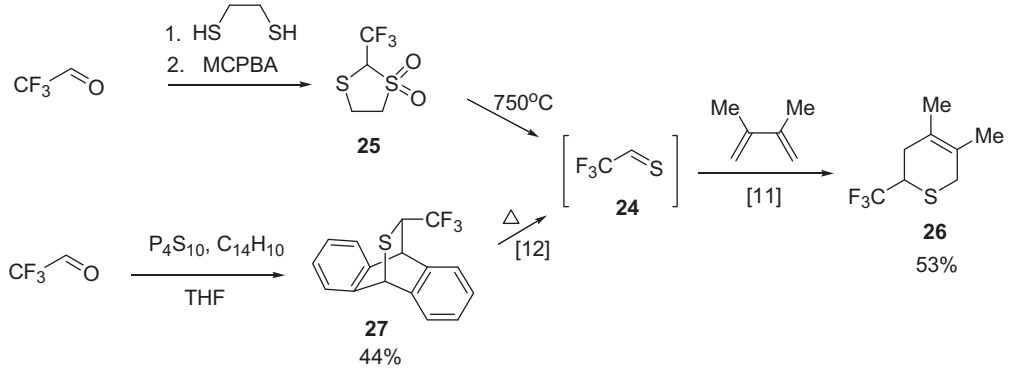
The thionation of higher homologs of polyfluorinated aldehydes with thionophosphates was also reported. When the reaction of **28** was carried out in the presence of 1,3-diene [13] or anthracene [14], cycloadducts **29** and **30** were formed, respectively (Scheme 9).



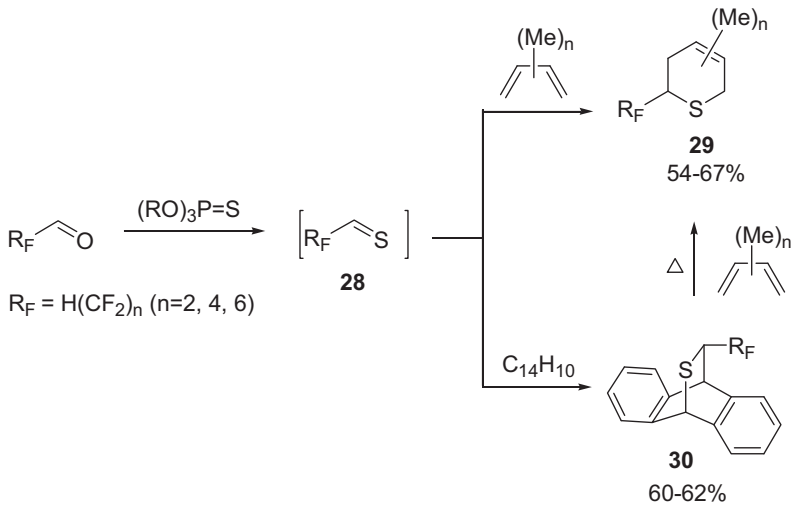
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

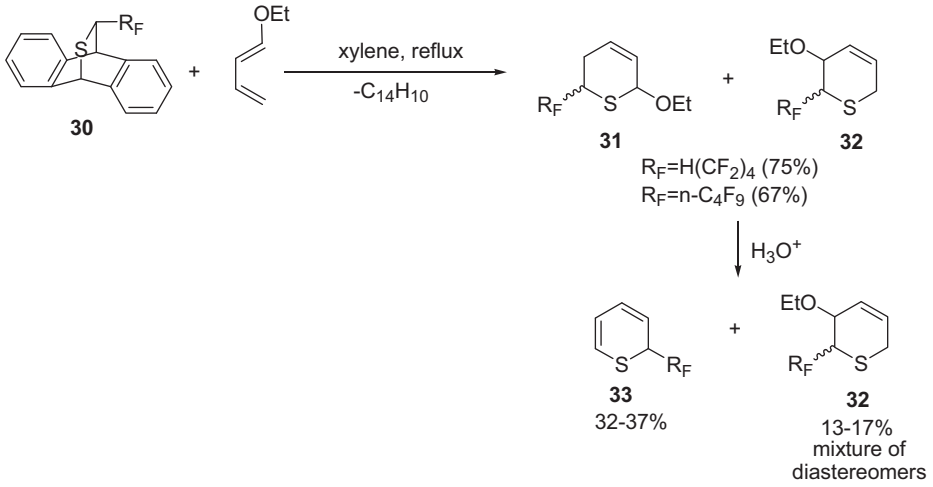
Although thioaldehydes with a long polyfluoroalkyl chain ($R_F = H(CF_2)_n$) exhibited low stability too, compounds **28** showed a lower tendency to polymerization than **24**.

Adducts **30** were used for generation of thioaldehydes at elevated temperature. The cycloaddition of such perfluorinated thioaldehydes with 1-ethoxy-(1*E*)-buta-1,3-diene was reported to proceed with low regioselectivity. Mixtures of 6-ethoxy-2-(polyfluoroalkyl)-3,6-dihydro-2*H*-thiopyrans **31** and 2-(polyfluoroalkyl)-3-ethoxy-3,6-dihydro-2*H*-thiopyrans **32** were obtained. The aqueous acidic treatment of the mixtures led to hydrolysis of cycloadducts **31** to 2-(polyfluoroalkyl)-2*H*-thiopyrans **33**, compounds **32** remaining unchanged. At the end of the sequence, compounds **32** and **33** were isolated both in moderate yields [15] (Scheme 10).

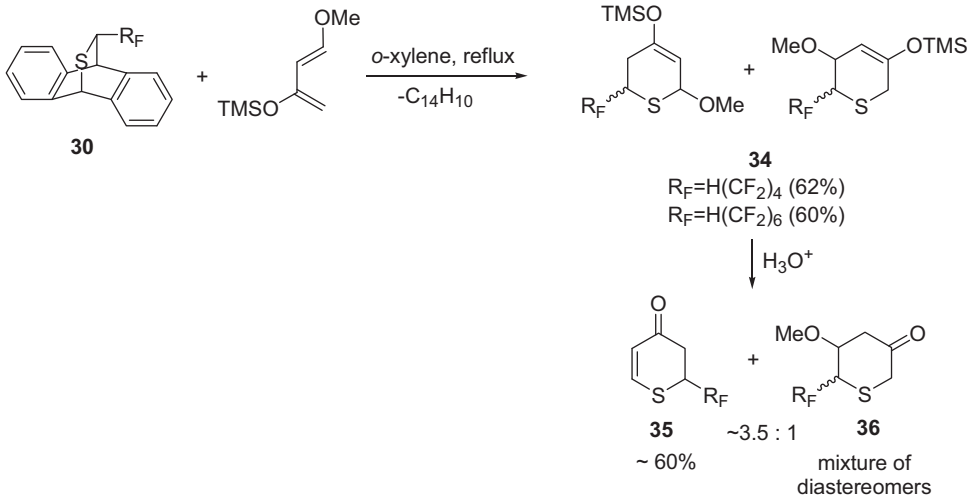
Similar reactions with (1*E*)-1-methoxy-3-(trimethylsilyloxy)-buta-1,3-diene (Danishevsky's diene) were also investigated. The results showed that the introduction of two electron-donating substituents into the diene did not change noticeably the regioselectivity of the cycloaddition. Cycloadducts **34** were directly hydrolysed into mixtures of 2-(polyfluoroalkyl)-3,4-dihydrothiopyran-4-ones **35** and 5-methoxy-6-(polyfluoroalkyl)-tetrahydrothiopyran-3-ones **36** (Scheme 11). The composition of the mixtures of **35** and **36** allowed to establish the regioselectivity of the cycloaddition; only 3,4-dihydrothiopyranones **35** were isolated in a pure state [16].

Polyfluorothioketones are also active dienophiles. Among them, hexafluorothioacetone (HFTA) (**37**) was the most studied representative of this class of compounds; its chemistry was recently reviewed [17]. Hexafluorothioacetone **37** was prepared in 60% yield by the addition of *bis*-(perfluoroisopropyl)-mercury to refluxing sulfur [18]. Being a very reactive heterodienophile, HFTA reacted with 1,3-dienes such as butadiene and 2,3-dimethylbuta-1,3-diene, at −78 °C, forming the corresponding cycloadduts **38** and **39**. 2-Chlorobuta-1,3-diene and 1-methoxybuta-1,3-diene reacted with compound **37** leading to the formation of regioisomeric mixtures of compounds **40** and **41** (Scheme 12) [18,19].

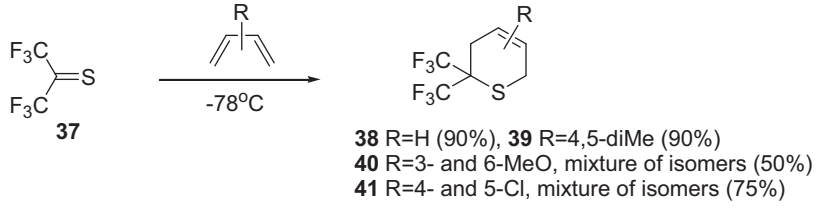
HFTA is not convenient for practical applications because of its gaseous state (bp +8 °C) and its tendency to dimerization resulting in 2,2,4,4-tetrakis-(trifluoromethyl)-1,2-dithiethane (**42**). The dimerization of hexafluorothioacetone (**37**) in the presence of inorganic fluoride is a reversible process but dimer **42** prevails at normal conditions. The addition of 2,3-dimethylbuta-1,3-diene to the former mixture shifts the equilibrium to thioketone **37** which readily forms corresponding cycloadduct **39** [20] (Scheme 13). Thus, hexafluorothioacetone dimer (**42**) can be used as synthetical equivalent of unstable monomeric form **37**.



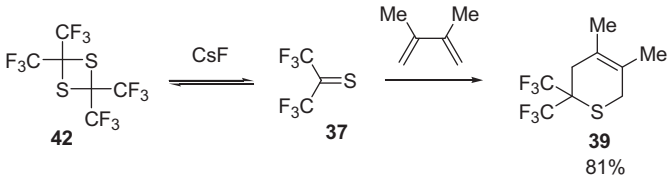
Scheme 10.



Scheme 11.



Scheme 12.



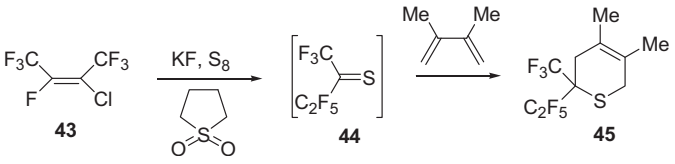
Scheme 13.

Other polyfluorinated thioketones were found to have similar properties. Octafluorobutan-2-thione dimer was formed in the reaction of 1,1,1,2,4,4,4-heptafluoro-3-chlorobut-2-ene (**43**) with sulfur and potassium fluoride [21], monomeric thioketone **44** being considered as the reaction intermediate. The appearance of thioketone during the reaction was established by its trapping with 2,3-dimethylbuta-1,3-diene giving the adduct **45** (no yield was reported) [22] (Scheme 14).

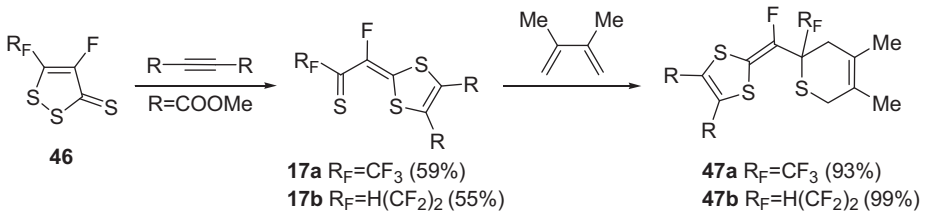
Polyfluorothioketones can also be obtained by the pyrolysis of 2-polyfluoroalkyl-2-alkyl (or 2-aryl)-1,3-dithiolane-1,1-dioxides [11] or by the thionation of corresponding ketones in the presence of anthracene (again, thioketones were generated from their corresponding cycloadducts at elevated temperature) [12].

α,β-Unsaturated polyfluorinated thioketones **17a**,**b** were reported to be formed in the reactions of 4-fluoro-5-(polyfluoroalkyl)-1,2-dithiol-3-thiones **46** with dimethyl acetylenedicarboxylate as electron-deficient alkyne [23]. These thioketones were stable enough for their isolation and characterization. They gave easily stable cycloadducts **47a**,**b** upon treatment with 2,3-dimethylbuta-1,3-diene (Scheme 15).

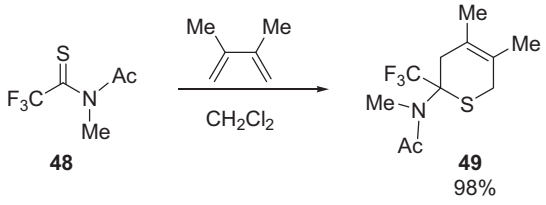
Polyfluorinated thioamides are relatively poor heterodienophiles due to the electron-donating influence of amide nitrogen atom. The introduction of an electron-withdrawing substituent to nitrogen atom was reported to enhance the reactivity of thioamides towards 1,3-dienes. For example, N-acetylated derivative of N-methyltrifluorothioacetamide **48** reacted with



Scheme 14.



Scheme 15.



Scheme 16.

2,3-dimethylbuta-1,3-diene under mild conditions giving substituted 3,6-dihydro-2*H*-thiopyran derivative **49** [24] (Scheme 16).

Cycloadditions of fluorinated thioamides **50** without electron-withdrawing substituent at the nitrogen atom, were achieved by microwave activation of the reaction mixture in the presence of Weflon™ composite (Teflon™ filled with graphite) [25] (Scheme 17).

The low isolated yield of **51d** was caused by the elimination of *p*-tolylamine from cycloadduct with the formation of 3,4-dimethyl-6-(4-*H*-perfluorobutyl)-2*H*-thiopyran (**52**) [25]. The addition of triflic acid accelerated the elimination of amine from compound **51d** while other cycloadducts **51a–c**,**e** formed the corresponding stable ammonium salts (Scheme 18).

Thioacyl fluorides were reported to be less reactive than hexafluorothioacetone. Nevertheless trifluorothioacyl fluoride (**53**), prepared by thermal reactions of perfluoroethyl mercurials with sulfur [18], reacted even at −78 °C with butadiene to give the corresponding 3,6-dihydro-2*H*-thiopyran **54**, but it underwent slow hydrogen fluoride elimination providing 6-(trifluoromethyl)-2*H*-thiopyran (**55**) in 56% yield (Scheme 19) [19].

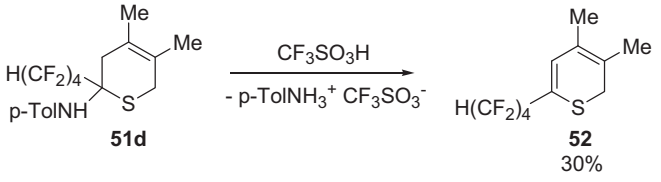
Recently, a method for the preparation of polyfluorinated thioacyl chlorides **56** consisting in heating of readily available benzyl 1,1-dichloropolyfluoroalkyl sulfides **57** with phosphorus (V) oxide, was published [26]. This method is very attractive due to the exclusion of working with volatile and toxic compounds which were the drawbacks for earlier preparations of thioacyl fluorides [18]. Reactions of thiocarbonyl chlorides **56** with 1,3-dienes proceeded rapidly at 0 °C. The stability of the cycloadducts **58** was dependant on the length of the polyfluoroalkyl chain. Trifluorothioacetyl chloride (**56a**) afforded a relatively stable adduct **58a** which was isolated. Thiocarbonyl chlorides with longer polyfluoroalkyl chains **56b**,**c** gave 6-polyfluoroalkyl 2*H*-thiopyrans **59a–c**, HCl elimination from the initially formed cycloadducts **58b–d** proceeded spontaneously during distillation. It is worth noting that the first example of the synthesis of compound **59b** was reported by Sizov et al. [26]. Dehydrochlorination of **58a** into thiopyran **55** was achieved by heating a DMF solution of **58a** at 100 °C for 2 h [27] (Scheme 20).

Polyfluorinated dithioesters are also active heterodienophiles and react with 1,3-dienes affording corresponding 2-(polyfluoroalkyl)-2-sulfanyl-3,6-dihydro-2*H*-thiopyrans. The reactivity of dithioesters was demonstrated in the pioneering work by Middleton [18] who recognized their high dienophilic properties. Dithioesters **60a–c** were obtained from reactions of thioacyl fluorides with mercaptans (Scheme 21).

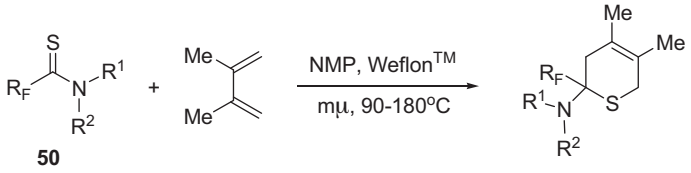
But the first examples of polyfluoroalkyldithiocarboxylates were reported by Brown and Pater [28]. Their method leading to fluorinated dithioesters **60a**,**d**,**e** consisted in the addition of thiols to fluorinated nitriles **61** followed by treatment of resulting thioimidates with hydrogen chloride and subsequent reaction with hydrogen sulfide (Scheme 22).

Similar method for the preparation of fluorinated dithioesters **60** from thioimidate salts was reported by Viehe and co-workers [24]. The salts were obtained by the S-alkylation of N,N-dialkylthioacetamide **50** or by the chlorination of **50** followed by the addition of thiol. Subsequent treatment of thioimidate salts with hydrogen sulfide afforded dithioesters **60** (Scheme 23).

Convenient approach to S-alkyl perfluoroalkyl (or perfluorophenyl)-dithiocarboxylates **60** consisted in the addition of carbon

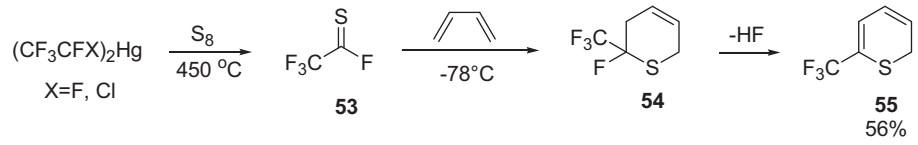


Scheme 18.

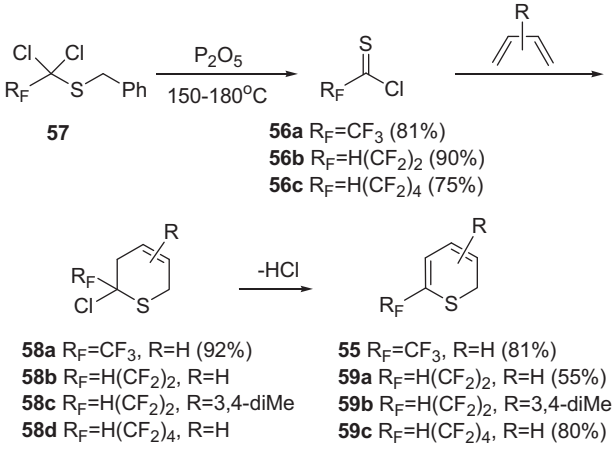


51a R_F=CF_3, R^1,R^2=$(CH_2)_2O(CH_2)_2$ (43%)
51b R_F=n-C_4F_9, R^1,R^2=$(CH_2)_2O(CH_2)_2$ (28%)
51c R_F=CF_3, R^1=H, R^2=p-Tol (26%)
51d R_F=$H(CF_2)_4$, R^1=H, R^2=p-Tol (15%)
51e R_F=CF_3, R^1=R^2=H (35%)

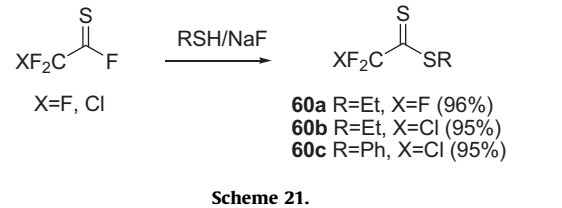
Scheme 17.



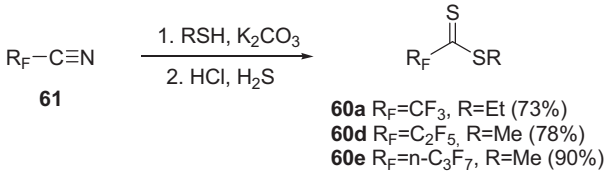
Scheme 19.



Scheme 20.



Scheme 21.



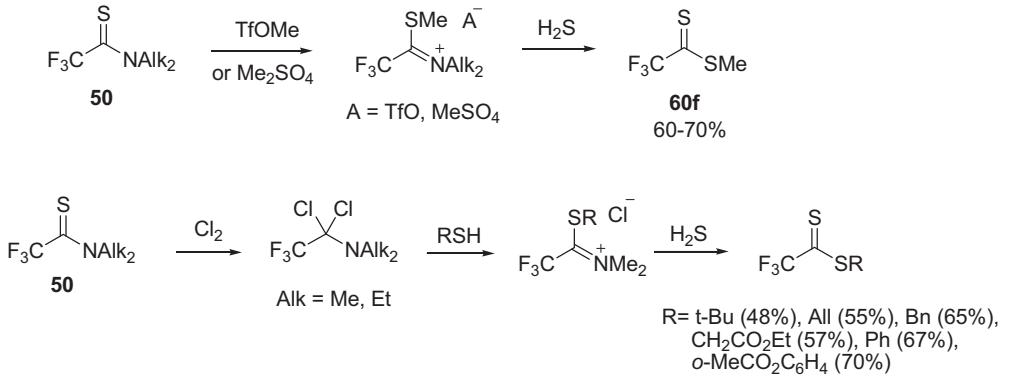
Scheme 22.

disulfide to the carbanion, generated upon treatment of polyfluoroalkyl (or perfluorophenyl) trimethylsilanes **61** with tetramethylammonium fluoride, followed by the alkylation reaction of the resulting dithiocarboxylate anions [29] (Scheme 24).

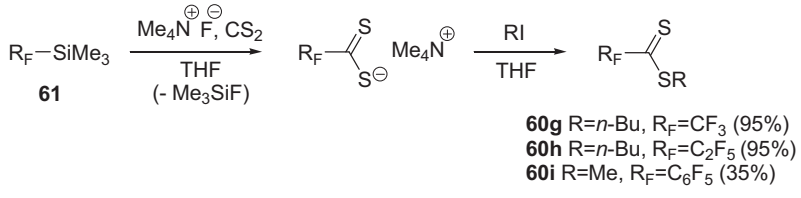
Another approach to perfluoroalkyldithioesters consisted in replacing of two chlorine atoms in alkyl-(1,1-dichloropolyfluoroalkyl) sulfides **62a** [30,31] or 1,1-dichloro-3,3-difluoro-1-(propylsulfanyl)-propan-2-one **62b** [32] by sulfur atom using cadmium or zinc sulfide reagents. Dithioesters **60**, obtained by this method, readily gave substituted 3,6-dihydro-2*H*-thiopyrans **63** in the presence of 2,3-dimethylbuta-1,3-diene (Scheme 25).

This methodology of chlorine replacement cannot be applied to the preparation of aryl dithiocarboxylates. Nevertheless, they were obtained in good yields starting from 1,1-dichloropolyfluoroalkanesulfenyl chlorides **64** and thiols in the presence of zinc chloride [33]. Starting from dithioesters **60**, the authors have prepared several 3,6-dihydro-2*H*-thiopyran derivatives **63** in high yields (Scheme 26).

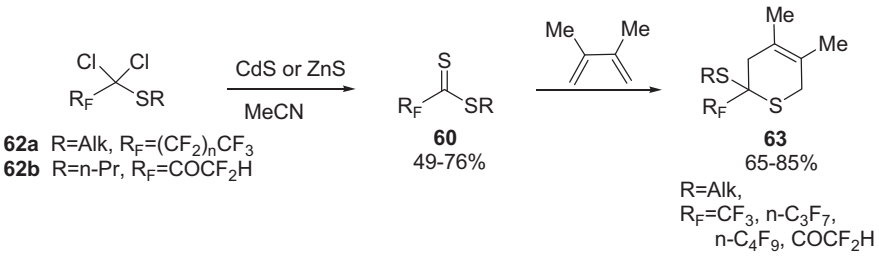
An asymmetric variant of thia-Diels–Alder reaction of alkyl polyfluoro dithioesters with 1,3-dienes was also studied based on dithioesters bearing chiral group. A series of chiral *S*- or *O*-alkyl thionoesters **65** as chiral heterodienophiles were synthesized by



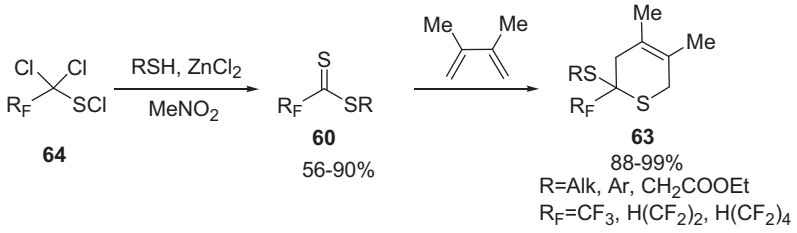
Scheme 23.



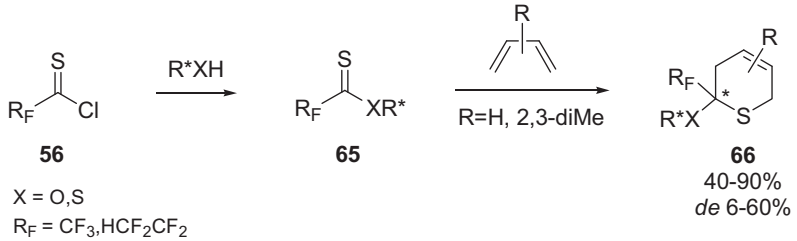
Scheme 24.



Scheme 25.



Scheme 26.



Scheme 27.

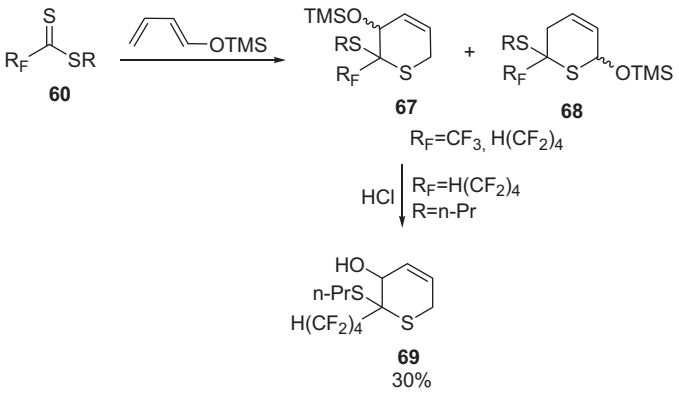
treatment of thioacylchlorides **56** with optically pure thiols or alcohols [34] (Scheme 27). Influence of the nature of the diene and dienophile and reaction conditions on the asymmetric induction were examined: it was shown that cycloaddition of thionoesters **65** with symmetrical dienes proceeded with a diastereoselectivity up to 60% affording 3,6-dihydro-2*H*-thiopyrans **66**.

Quantum chemistry (DFT) calculations of cycloaddition products and the corresponding transition states allowed to conclude that stereoselectivity found for the formation of thiopyrans, was kinetically driven: the diastereomeric excess (*de*) was referred to differences in activation energies of transition states, preceding formation of the diastereomeric cycloadducts.

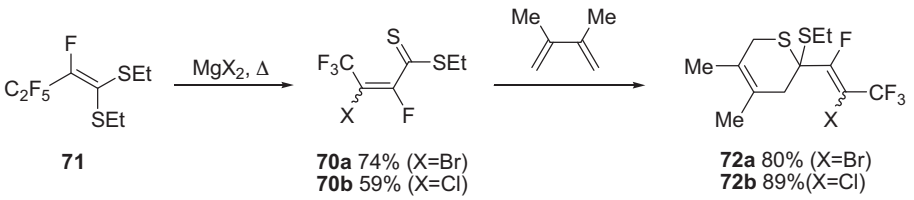
[4+2]-Cycloadditions of fluorinated dithioesters **60** and 1-(trimethylsilyloxy)-buta-1,3-diene were reported to proceed with low regio- and stereoselectivity giving the mixture of four possible isomers **67** and **68** [30]. In one case, the isolation of major desilylated cycloadduct **69** was achieved via acid hydrolysis and subsequent purification (Scheme 28).

Fluorinated dithiocrotonic acid esters **70a**,**b** were prepared from fluorinated ketenedithioacetal **71** by thermal reactions with magnesium halides (Scheme 29). α,β-Unsaturated dithioesters **70a**,**b** were reactive heterodienophiles giving corresponding cycloadducts **72a**,**b** with 2,3-dimethylbuta-1,3-diene [35].

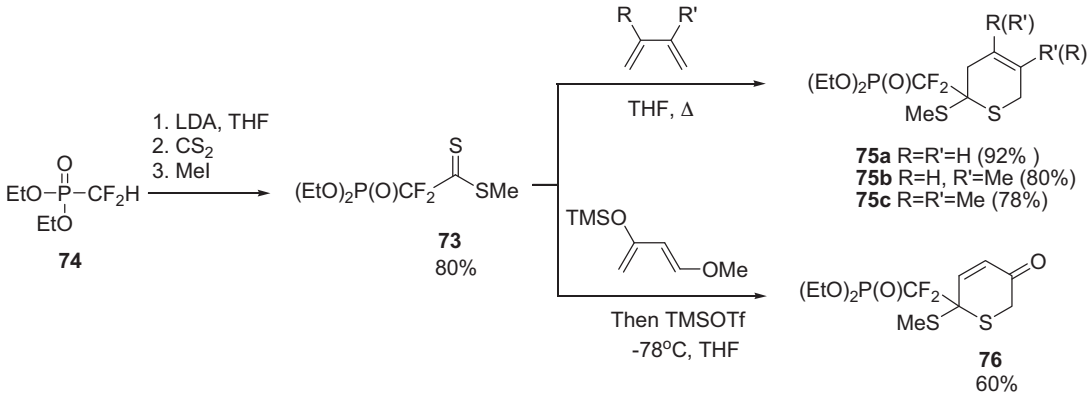
Dithioester **73** derived from diethyl (difluoromethyl)phosphonate (**74**), behaved also as C=S heterodienophile. The features of its reactions with 1,3-dienes including the stereoselectivity of the cycloaddition with cyclopentadiene and the regioselectivity of the reaction of Danishevsky's diene were studied in detail [36]. In contrast to perfluorinated dithioesters **60**, compound **73** reacted with dienes under thermal conditions. Heating of **73** in sealed tube at 50 °C with butadiene or refluxing in THF with 2,3-dimethyl-1,3-butadiene, isoprene or Danishevsky's diene provided 3,6-dihydro-2*H*-thiopyrans **75a**–**c**. Cycloadditions with nonsymmetrical dienes were not regioselective: in the case of isoprene, a (6:4) mixture of two regioisomers **75b** was obtained with 5-Me substituted derivative as the major compound. Reaction with Danishevsky's diene gave, after treatment of the crude reaction mixture with TMSOTf and purification, the enone **76** in 60% yield (Scheme 30).



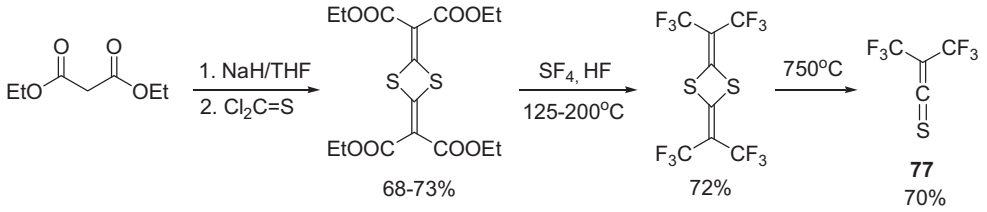
Scheme 28.



Scheme 29.



Scheme 30.



Scheme 31.

Bis(trifluoromethyl)ketene (**77**) is one of the few representatives of stable thioketenes. It was prepared from its cyclic dimer (called 2,4-bis(hexafluoroisopropylidene)-1,3-dithietane) which was synthesized starting from malonic ester [37] (Scheme 31).

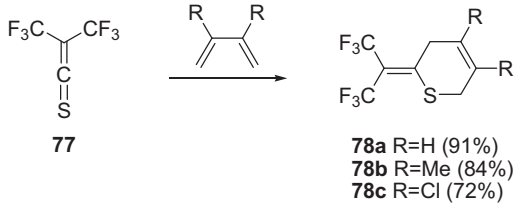
Bis(trifluoromethyl)ketene (**77**) reacted with different 1,3-dienes such as buta-1,3-dienes, anthracene and cyclopentadienyl derivatives, affording stable cycloadducts [37,38]. For example, reactions of compound **77** with symetrical buta-1,3-dienes provided 2-(hexafluoroisopropylidene)-3,6-dihydro-2*H*-thiopyrans (**78a–c**) (Scheme 32).

Sulfines or thiocarbonyl-S-oxides belong to particular group of thiocarbonyl compounds. Indeed, sulfines bearing a polyfluoroalkyl group are capable of [4+2]cycloaddition reactions with conjugated dienes resulting in the formation of 2-polyfluoroalkyl-3,6-dihydro-2*H*-thiopyran-S-oxides.

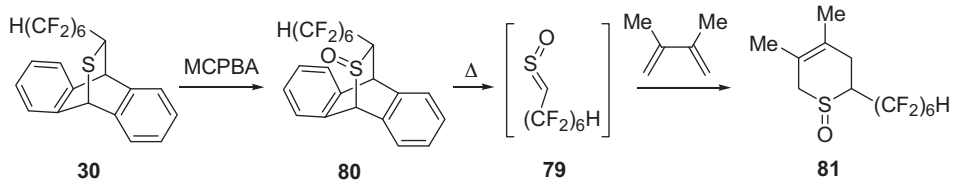
Fluorinated thioaldehyde-S-oxide (polyfluoroalkylsulfine) **79** was generated from its corresponding anthracene adduct **80** which was itself prepared by the oxidation (MCPBA) of thioaldehyde adduct **30** [14]. Sulfine **79** was unstable and decomposed in 1 h at 20 °C but was characterized by NMR measurements. Moreover, 4,5-dimethyl-2-(6-*H*-perfluorohexyl)-3,6-dihydro-2*H*-thiopyran (**81**) was obtained by the treatment of sulfine **79** with 2,3-dimethylbuta-1,3-diene; no yield of **81** was reported in the paper (Scheme 33).

Similarly trifluoromethyl sulfines and thioketone-S-oxides reacted as dienophiles in hetero-Diels–Alder reactions. Indeed, bis(trifluoromethyl)sulfine (**82**) was obtained by thermolysis its anthracene adduct **83** in 91% yield [39]. Compound **82** was stable at the normal conditions and reacted with 2,3-dimethylbuta-1,3-diene giving the corresponding cycloadducts **84** [40] (Scheme 34).

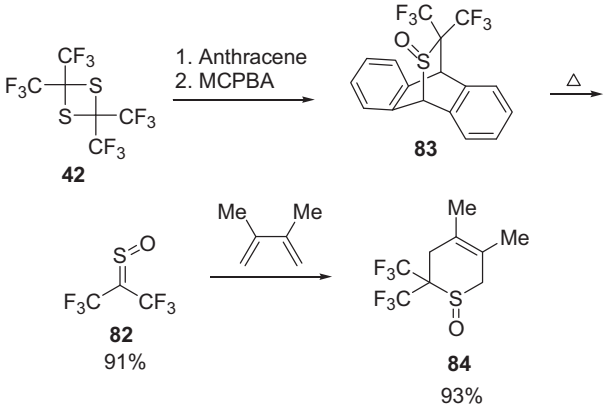
The hydrolysis of 1,1-dichloro-2,2,2-trifluoroethanesulfenyl chloride (**85**) resulted in the formation of the chloro(trifluoromethyl)sulfine (**86**) in low 26% yield; but when the reaction was carried out in the presence of anthracene, the corresponding cycloadduct **87** was easily formed (Scheme 35). The heating of the latter in vacuum afforded pure sulfine **86** in 67% yield after two steps. Chlorine atom of **86** was readily replaced by sulfanyl group by reaction with benzylmercaptan in the presence of base. Both sulfine **86** and S-oxide of dithioester **88** were active hetero-dienophiles and reacted with aliphatic 1,3-diene in mild conditions



Scheme 32.



Scheme 33.



Scheme 34.

affording the corresponding 3,6-dihydro-2*H*-thiopyran-S-oxide derivatives **89**, **90** (Scheme 35) [41].

Bis(trifluoromethyl)sulfene (**91**) was also a reactive heterodienophile, but in contrast to the corresponding sulfine, it was very unstable. In situ generation of this sulfene by the treatment of 1,1,1,3,3,3-hexafluoropropane-2-sulfonyl fluoride tris(dimethylamino)sulfonium salt (**92**) with silicon tetrafluoride in the presence of 2,3-dimethylbuta-1,3-diene was reported to give 2,2-bis(trifluoromethyl)-3,6-dihydro-2*H*-thiopyran-S,S-dioxide (**93**) as a cycloadduct in 41% yield [42] (Scheme 36).

2.1.2. Syntheses from cyclic precursors

There are very few examples related to the use of thiopyran derivatives as cyclic precursors. Unsubstituted tetrahydrothiopyran (**94**) was reported to react with hexafluoropropene in the presence of di-*tert*-butyl peroxide in a radical pathway affording 2-(1,1,2,3,3,3-hexafluoropropyl)tetrahydrothiopyran (**95**) in 56% yield [43] (Scheme 37).

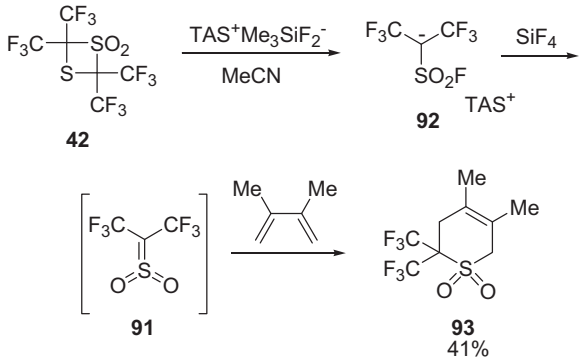
2.1.3. Syntheses from trifluoromethyl α,β-unsaturated ketones

4-(Trifluoromethyl)-4-hydroxytetrahydrothiopyrans **96** were obtained in the reaction of alkenyl trifluoromethyl ketones **97** with ammonium hydrosulfide [44] (Scheme 38). Reactions formally proceeded as the Michael addition of hydrosulfide anion **98** to the double bonds of the second molecule of enones with subsequent aldol condensations. The reaction of unsaturated ketone **97** with R^1 = H, R^2 = Ph was stereospecific; only one isomer among the eight possible ones was formed.

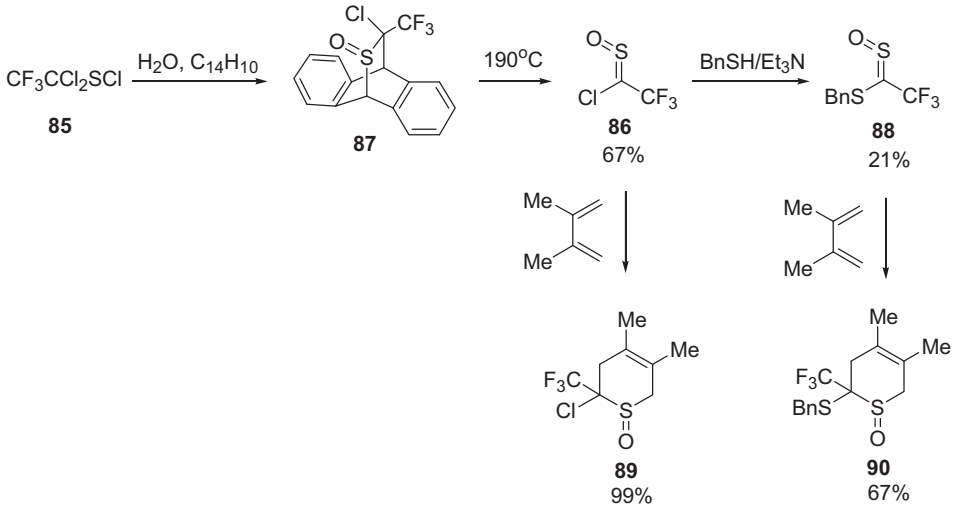
2.2. Chemical properties of polyfluoroalkyl thiopyran derivatives

2.2.1. Transformations 3,6-dihydro-2H-thiopyrans and tetrahydrothiopyrans into 2H-thiopyrans

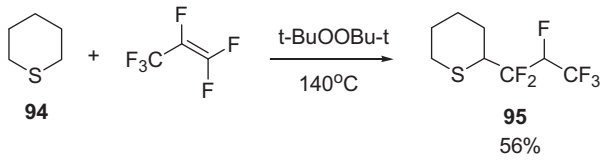
3,6-Dihydro-2*H*-thiopyrans are the initial products of the hetero-Diels–Alder reactions of thiocarbonyl compounds with 1,3-dienes. As it was mentioned above (Scheme 20), cycloadducts coming from thioacylhalides and dienes underwent spontaneous



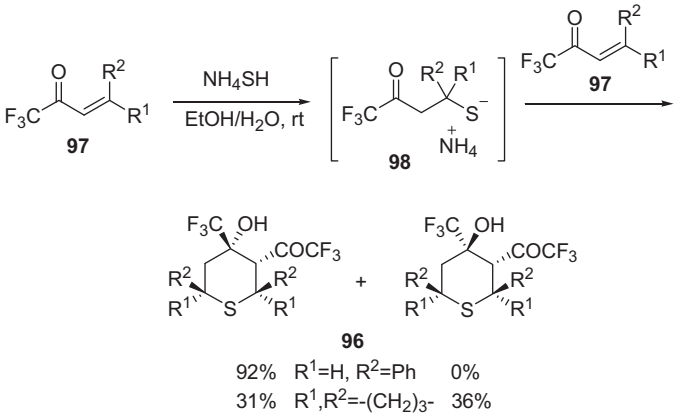
Scheme 36.



Scheme 35.



Scheme 37.

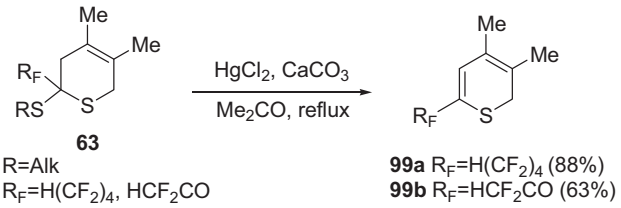


Scheme 38.

loss of hydrogen halide leading to the formation of 2*H*-thiopyrans [19,26]. The cycloadducts of thioacylhalides and cyclopentadiene, cyclohexa-1,3-diene or anthracene cannot eliminate hydrogen halide due to the too high strain energy of the products coming when the double bond is at the bridgehead atom (Bredt's rule) [45].

The adducts **63** obtained from acyclic dienes and dithioesters (Schemes 25 and 26) are fairly stable but they can eliminate thiol in special conditions. Thus, heating of these adducts in the presence of mercury (II) chloride and calcium carbonate, in acetone afforded 2*H*-thiopyrans **99a**,**b** [32,46] (Scheme 39).

The C=C double bond of polyfluoro sulfur-containing cycloadducts may also react with bromine to give the corresponding dihalogenated intermediates which are efficient precursors for the synthesis of 2*H*-thiopyrans upon elimination reactions. Indeed, 2,2-bis(trifluoromethyl)-3,6-dihydro-2*H*-thiopyran (**38**) formed the product **100** resulting from the addition of bromine to C=C double bond. The treatment of **100** with alcoholic solution of alkali led to dehydrobromination reaction



Scheme 39.

affording 2,2-bis(trifluoromethyl)-2*H*-thiopyran (**101**) and small amounts of 4-bromo-2,2-bis(trifluoromethyl)-3,4-dihydro-2*H*-thiopyran (**102**) [19] (Scheme 40).

2.2.2. Thiopyrans as dienes in [4+2] cycloadditions

As it was reported by Middleton [19], 2H-thiopyran **101** possessed properties of 1,3-diene. It reacted with hexafluorothioacetone forming an adduct as well as underwent the slow self-dimerization at storage, but structures of products were not established.

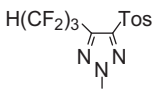
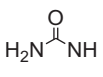
2.2.3. Oxidation of polyfluoroalkyl thiopyran derivatives

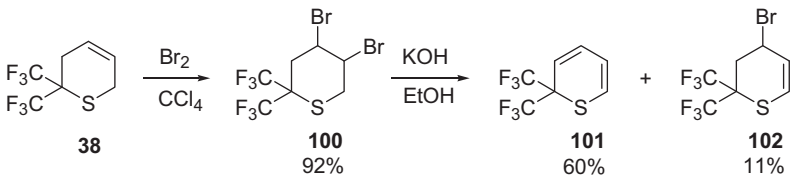
2.2.3.1. Oxidation to thiopyrylium salts. Oxidative aromatization of 2*H*-thiopyrans was well-known methodology for preparation of thiopyrylium salts [47]. In fluorinated series two synthetic approaches to thiopyrylium salts were described [27]. 6-Polyfluoroalkyl-2*H*-thiopyrans **55** was reacted with sulfuryl chloride followed by treatment of the resulting intermediates with perchloric acid to give salts **103a**,**b**. Another approach consisted in reactions of thiopyrans **55** with trityl tetrafluoroborate. Thiopyrylium tetrafluoroborates **103c**,**d** are more convenient in handling: they are stable, more soluble in organic solvents, and less dangerous in contrast to perchlorates **103a**,**b** which were found to be explosive at evaluated temperature and to have a low solubility (Scheme 41).

Thiopyrylium salt **103c** was highly electrophilic compound and easily reacted with *O*-, *N*-, *S*- and *C*-nucleophiles to give 2-substituted or a mixture of 2- and 4-substituted thiopyran derivatives**104** and **105** [27] (Schemes 42 and 43, Table 1).

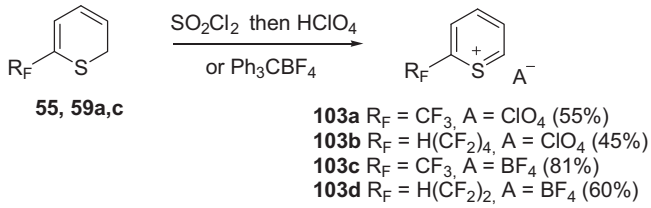
Alcohols, urea and sodium azide formed solely 2-substituted 2*H*-thiopyrans **104**, whereas imidazoles, sodium thiolacetate, nitromethane and K-salt of substituted 1,2,3-triazole gave mixtures of 2*H*- and 4*H*-thiopyrans **104** and **105**. Reaction of **103c** with potassium cyanide gave an unseparable mixture of thiopyrans **106a–c** [27] (Scheme 43).

Table 1
Preparation of thiopyran derivatives **104** and **105** from thiopyrylium salt **103c**.

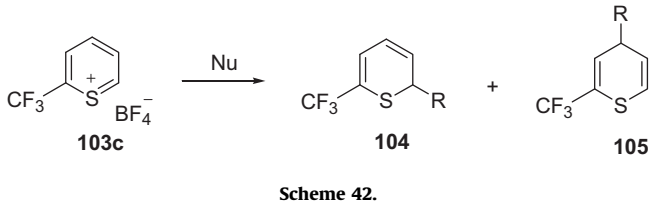
R	MeO	*i*-PrO					N_3		CH_2NO_2
Ratio of **104**:**105**	1:0	1:0	5:1	3:1	1:1.5	1:0	1:0	3:1	1:2
Yield, %	61	90	98	95	70	33	90	65	88



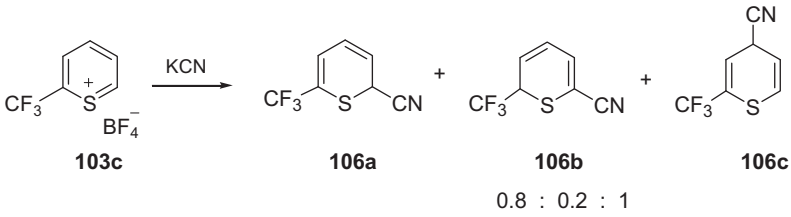
Scheme 40.



Scheme 41.

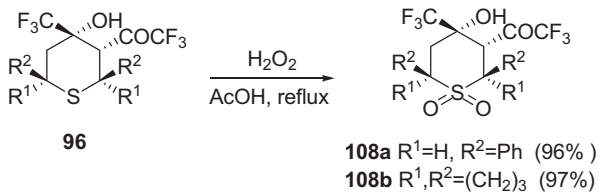


Scheme 42.



Scheme 43.

Scheme 44.



Scheme 45.

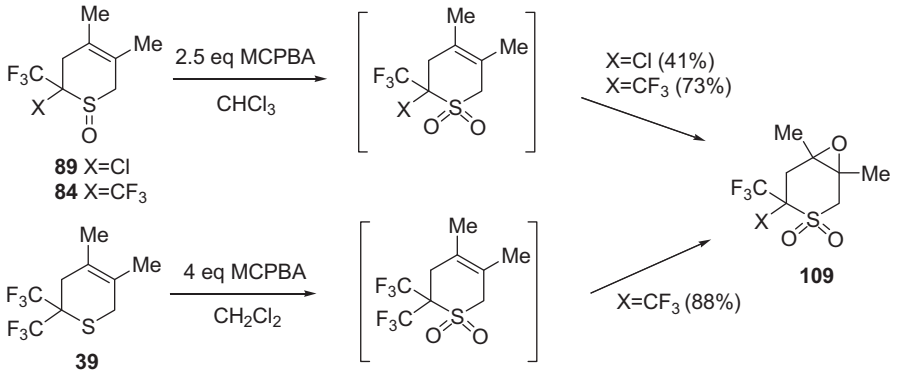
2.2.3.2. Oxidation of cyclic sulfur. Sulfur atom in thiopyran derivatives can be successively oxidized to sulfoxides and/or sulfones. Several examples of the oxidation of 3,6-dihydro-2*H*-thiopyran derivatives having fluorinated substituents were described in literature.

Treatment of 3,6-dihydro-2*H*-thiopyran **29** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at 20 °C afforded S-oxide **107**; its yield was not reported [14] (Scheme 44).

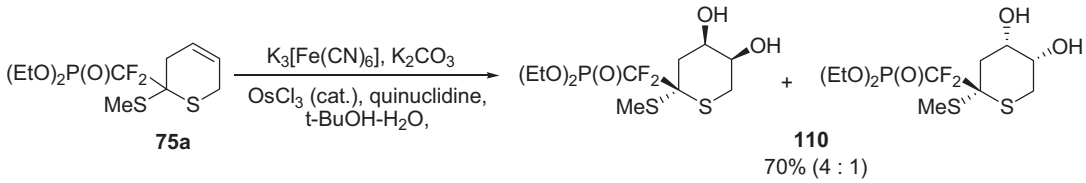
Tetrahydrothiopyrans **96** which were described by Sanin et al. [44], were readily oxidized to corresponding sulfones **108a**,**b** by the treatment with hydrogen peroxide in acetic acid (Scheme 45).

3,6-Dihydro-2*H*-thiopyran-S-oxides **84**, **89** obtained from sulfines and 1,3-dienes (Schemes 34 and 35) can be oxidized to S,S-dioxides; however, C=C double bond also undergoes the oxidation (Scheme 46). For example, overoxidation to **109** was typical for 4,5-dimethyl-3,6-dihydro-2*H*-thiopyran-S-oxides **84**, **89** due to the electron-donating effect of two methyl groups on the C=C double bond [40,41] (Scheme 46). The oxidation of hexafluorothioacetone cycloadduct **39** proceeded also with oxidation of sulfur atom together with epoxidation of C=C double bond [48].

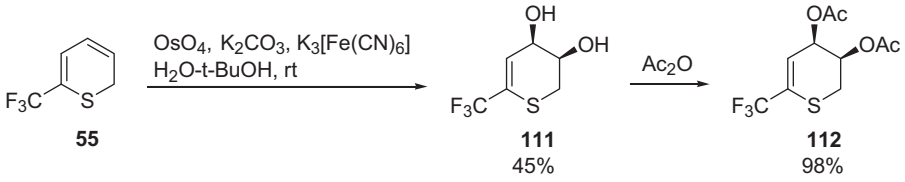
2.2.3.3. Selective oxidation of the double bonds. The oxidation of the C=C double bond in the presence of sulfide moeity is rather problematic because of the easiness of sulfur oxidation by the action of most common oxidizers. Osmium tetraoxide is probably the sole oxidizer which affords the selective dihydroxylation reaction without the oxidation of sulfur atom. Osmium tetraoxide is toxic and expensive reagent, but it can be used in catalytic amounts with potassium hexacyanoferrate (III) as cooxidant in aqueous *tert*-butanol solution in the presence of potassium carbonate. OsO_4 can be also replaced by non-volatile osmium (III) chloride. Using this approach, cycloadduct **75a** of methyl (diethoxyphosphoryl)difluorodithioacetate and butadiene was transformed into the mixture of diastereomeric diols



Scheme 46.



Scheme 47.



Scheme 48.

110 (Scheme 47). The major component was formed by the attack of the molecule from the less hindered side being opposite to methylsulfanyl group [36].

Applying the similar oxidizing system, 6-(trifluoromethyl)-2*H*-thiopyran (**55**) was dihydroxylated to 3,4-*cis*-dihydroxy-6-(trifluoromethyl)-3,4-dihydro-2*H*-thiopyran (**111**) [49] (Scheme 48). The remaining double bond was inert to further oxidation on extending the reaction time or using an excess of oxidiser. Taking into account that OsO_4 is an electrophilic reagent, the reaction outcome was explained by the electron-withdrawing effect of the trifluoromethyl group which prevented attack on the C5–C6 double bond. Diol **111** which appeared as a stable crystalline compound, was converted into diacetate **112** by protection of the two hydroxy groups.

Another approach was described for obtaining the *trans*-diol analogue of **111**. 2*H*-Thiopyran **55** was regioselectively bromohydroxylated by reaction with *N*-bromosuccinimide (NBS) in a mixture of 1,2-dimethoxyethane (DME) and water. Treatment of *trans*-bromohydrin **113** with an excess of potassium hydroxide gave *trans*-diol **114** in 45% yield. A two-step reaction proceeded also through oxirane intermediate **115**, which was isolated by careful treatment of bromohydrine with KOH. *Trans*-diol **114** was acetylated to provide the protected derivative **116** [49] (Scheme 49).

Diacetates **112** and **116** were used to obtain trifluoromethyl-containing thiopyranoside derivatives. Initially, sulfur atom was oxidized with MCPBA giving thiopyrane-S-oxides **117** and **118**, which then reacted with acetic anhydride and boron trifluoride diethyl ether complex by an additive Pummerer pathway giving tetraacetyl derivatives of trifluoromethyl-containing thiopyranoses **119** and **120** [49] (Scheme 50). The diastereomeric mixtures of tetraacetates **119** and **120** were not separated; their stereochemistry was established based on NMR data.

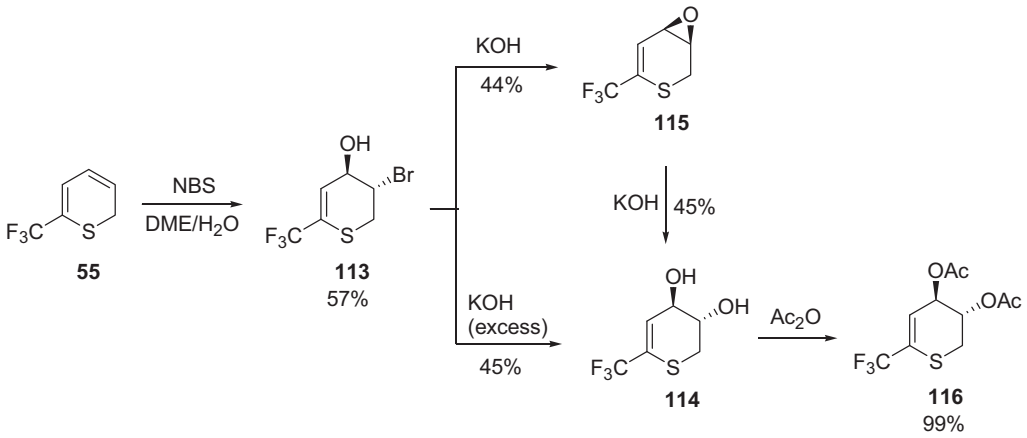
2.2.4. Reactions of polyfluroalkyl substituted 3,6-dihydro-2H-thiopyrans with nucleophiles

The cycloadduct **39** obtained from hexafluorothioacetone and 2,3-dimethylbuta-1,3-diene underwent unusual transformations induced by the action of organomagnesium reagent. The attack of nucleophilic reagent on sulfur atom (thiophilic addition) with subsequent ring opening led to the formation of unstable fluorinated carbanion which easily eliminated fluoride anion affording 2-substituted pentafluoropropene **121** in moderate yield [48] (Scheme 51).

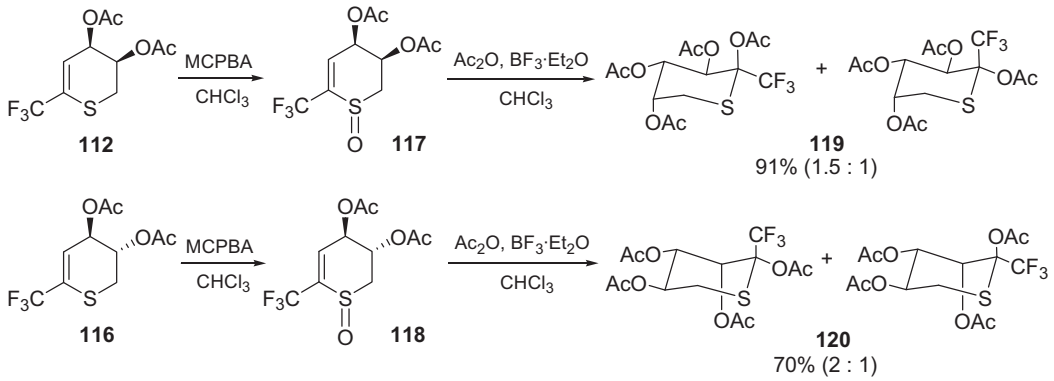
3. Biological evaluation of polyfluoroalkyl thiopyran derivatives

Among the subjects of this survey, there are one compound which possessed useful biological activity. Cycloadduct **122** of dithioester and 2,3-dimethylbuta-1,3-diene was claimed as potential cardiotonic drug [50] (Fig. 3).

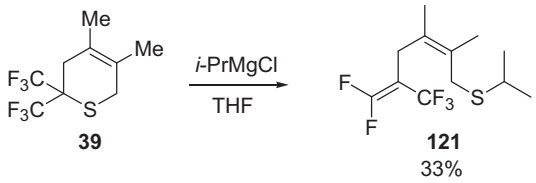
Compound **122** appeared to be an active positive inotropic agent. The cardiostimulating action of this compound on the left



Scheme 49.



Scheme 50.



Scheme 51.

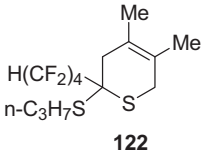


Fig. 3. Structure of fluorinated thiopyran with inotropic properties.

atrium of guinea pig appeared to be 10 times higher then the potency of commercial Amrinon. The toxicity of dihydrothiopyran **122** was shown to be much more lower than in the case of Amrinon. The high level of activity and low toxicity make this compound a potent drug.

4. Conclusions

The results summarized in the present review evidence that polyfluoroalkyl thiopyran derivatives (2*H*- and 4*H*-thiopyrans, 3,4- and 3,6-dihydrothiopyrans, and tetrahydrothiopyrans) form an interesting class of sulfur-containing heterocycles. Their main syntheses are based on building blocks strategy involving cyclization or cycloaddition reactions. The latter are the most developed approach using polyfluorinated reagents such as thioaldehydes, thioketones, thioamides, thioacyl halides, dithioesters, and thiocarbonyl-S-oxides. The resulting cycloadducts (3,6-dihydro-2*H*-thiopyrans especially) were then transformed into corresponding 2*H*-thiopyrans by elimination reactions, or were submitted to oxidations of sulfur atom, to dihydroxylations or related reactions of C=C double bond, or to oxidative aromatizations. Finally, the high positive inotrope activity and the low toxicity of the 2-octafluorobutyl-2-(*n*-propylsulfanyl)-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran emphasize on their interesting potential cardiotonic activity.

References

[1] J. Kuthan, Adv. Heterocycl. Chem. 59 (1994) 179–244.
[2] Kuthan, Adv. Heterocycl. Chem. 34 (1983) 145–303.
[3] M. Weissenfels, M. Pulst, D. Greif, Sulfur Rep. 15 (1993) 161–233.
[4] E.D. Laganis, D.M. Lemal, J. Am. Chem. Soc. 102 (1980) 6634–6636.
[5] D.V. Vorobyeva, A.K. Mailyan, A.S. Peregudov, N.M. Karimova, T.P. Vasilyeva, I.S. Bushmarinov, C. Bruneau, P.H. Dixneuf, S.N. Osipov, Tetrahedron 67 (2011) 3524–3532.
[6] G.M. Alvernhe, D. Greif, A.J. Laurent, M. Pulst, M. Weissenfels, J. Fluorine Chem. 70 (1995) 121–125.
[7] (a) K.I. Pashkevich, V.I. Saloutin, M.B. Bobrov, D.S. Yufit, Yu.T. Struchkov, Zhurn. Org. Khim. (Russ.) 24 (1988) 2397–2402;
(b) K.I. Pashkevich, M.B. Bobrov, V.I. Saloutin, Sulfur Lett. 14 (1992) 195–198.
[8] V.M. Timoshenko, J.-P. Bouillon, A.N. Chernega, Yu.G. Shermolovich, C. Portella, Eur. J. Org. Chem. (2003) 2471–2474.
[9] B.L. Finkelstein, M.R. Sethuraman, J. Heterocycl. Chem. 37 (2000) 1583–1586.
[10] F. Grellepois, V.M. Timoshenko, E.B. Rusanov, Yu.G. Shermolovich, C. Portella, J. Fluorine Chem. 131 (2010) 937–941.
[11] B. Schuler, W. Sundermeyer, Chem. Ber. 123 (1990) 177–184.
[12] J. Hasserodt, H. Pritzkow, W. Sundermeyer, Liebigs Ann. (1995) 95–104.
[13] Yu.G. Shermolovich, E.I. Slusarenko, L.N. Markovski, Zhurn. Org. Khim. (Russ.) 24 (1988) 1931–1934.
[14] L.N. Markovski, E.I. Slusarenko, Yu.G. Shermolovich, Zhurn. Org. Khim. (Russ.) 26 (1990) 912–914.
[15] L.N. Markovski, P.P. Kornuta, Yu.G. Shermolovich, Zhurn. Org. Khim. (Russ.) 35 (1999) 1172–1174.
[16] Yu.G. Shermolovich, P.P. Kornuta, E.I. Slusarenko, L.N. Markovski, Zhurn. Org. Khim. (Russ.) 33 (1997) 97–101.
[17] V.A. Petrov, in: A.A. Gakh, K.L. Kirk (Eds.), Fluorinated Heterocycles, ACS Symp. Series 1003, American Chemical Society, Washington, DC, USA, 2009, pp. 105–133 (Chapter 6).
[18] W.J. Middleton, E.G. Howard, W.H. Sharkey, J. Am. Chem. Soc. 83 (1961) 2589–2590.
[19] W.J. Middleton, J. Org. Chem. 30 (1965) 1390–1394.
[20] (a) T. Kitazume, T. Otaka, R. Takei, N. Ishikawa, Bull. Chem. Soc. Jpn. 49 (1976) 2491–2494;
(b) S.A. Postovoi, I.M. Vol'pin, N.I. Delyagina, M.V. Galakhov, Yu.V. Zeifman, L.S. German, Russ. Chem. Bull. 38 (1989) 1261–1264;
(c) V.A. Petrov, W. Marshall, J. Fluorine Chem. 128 (2007) 729–735.
[21] D.C. England, J. Org. Chem. 46 (1981) 153–157.
[22] D.J. Burton, Y. Inouye, Chem. Lett. 11 (1982) 201–204.
[23] V.M. Timoshenko, J.-P. Bouillon, Yu.G. Shermolovich, C. Portella, Tetrahedron Lett. 43 (2002) 5809–5812.
[24] F. Laduron, C. Nyns, Z. Janousek, H.G. Viehe, J. Prakt. Chem. 339 (1997) 697–707.
[25] S.S. Mikhailichenko, J.-P. Bouillon, T. Besson, Yu.G. Shermolovich, Tetrahedron Lett. 51 (2010) 990–993.
[26] 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) 1200–1208.
[27] S.A. Siry, V.M. Timoshenko, Tetrahedron Lett. 51 (2010) 6406–6409.
[28] H.C. Brown, R. Pater, J. Org. Chem. 27 (1962) 2858–2863.
[29] L.A. Babadzhanova, N.V. Kirij, Yu.L. Yagupolskii, J. Fluorine Chem. 125 (2004) 1095–1098.
[30] C. Portella, Yu.G. Shermolovich, O. Tschenn, Bull. Soc. Chim. Fr. 134 (1997) 697–702.
[31] Yu.G. Shermolovich, E.I. Slusarenko, V.M. Timoshenko, A.B. Rozhenko, L.N. Markovski, J. Fluorine Chem. 55 (1991) 329–333.
[32] Yu.G. Shermolovich, V.M. Timoshenko, V.V. Listvan, L.N. Markovsky, Mendeleev Commun. 8 (1998) 245–246.
[33] V.M. Timoshenko, A.V. Tkachenko, Yu.G. Shermolovich, J. Fluorine Chem. 126 (2005) 361–364.
[34] V.M. Timoshenko, S.A. Siry, A.B. Rozhenko, Yu.G. Shermolovich, J. Fluorine Chem. 131 (2010) 172–183.
[35] J.-P. Bouillon, Yu.G. Shermolovich, C. Portella, Tetrahedron Lett. 42 (2001) 2133–2135.
[36] E. Pfund, T. Lequeux, M. Vazeux, S. Masson, Tetrahedron Lett. 43 (2002) 2033–2036.
[37] M. Raash, J. Org. Chem. 35 (1970) 3470–3483.
[38] M. Raash, J. Org. Chem. 43 (1978) 2500–2508.

[39] A. Elsäßer, W. Sundermeyer, Chem. Ber. 118 (1985) 4553–4560.
[40] M. Schwab, W. Sundermeyer, Chem. Ber. 119 (1986) 2458–2465.
[41] H. Fritz, W. Sundermeyer, Chem. Ber. 122 (1989) 1757–1763.
[42] B.E. Smart, W.J. Middleton, J. Am. Chem. Soc. 109 (1987) 4982–4992.
[43] J. Chen, R.L. Kirchmeier, J.M. Shreeve, Inorg. Chem. 35 (1996) 6676–6681.
[44] A.V. Sanin, V.G. Nenajdenko, V.S. Kuz'min, E.S. Balenkova, J. Org. Chem. 61 (1996) 1986–1989.
[45] (a) J. Bredt, H. Thouet, J. Schtiitz, Liebigs Ann. 437 (1924) 1–13;
(b) K. Shea, Tetrahedron 36 (1980) 1683–1715.
[46] V.M. Timoshenko, PhD Thesis, Institute of Organic Chemistry of NAS of Ukraine, Kyiv, 1994.
[47] G. Doddi, G. Ercolani, Adv. Heterocycl. Chem. 60 (1994) 65–195.
[48] V.A. Petrov, S. Lustig, W. Marshall, J. Fluorine Chem. 128 (2007) 1227–1234.
[49] S.A. Siry, V.M. Timoshenko, Tetrahedron Lett. 52 (2011) 6260–6262.
[50] (a) L.N. Markovsky, Yu.G. Shermolovich, E.I. Slusarenko, V.M. Timoshenko, JP 06100555 (1994); Chem. Abs. 121:108523;
(b) L.N. Markovsky, Yu.G. Shermolovich, E.I. Slusarenko, V.M. Timoshenko, RU 2054426 (1996); Chem. Abs. 126:74746.