Review

Synthesis of Fluorinated and Fluoroalkylated Heterocycles Containing at Least One Sulfur Atom via Cycloaddition Reactions †

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† Dedicated to Professor Stanisław Leśniak on the occasion of his 70th birthday.

Abstract: Fluorinated heterocycles constitute an important group of organic compounds with a rapidly growing number of applications in such areas as medicinal chemistry, agrochemical production, polymer chemistry, as well as chemistry of advanced materials. In the latter case, fluorinated thiophenes are considered as a lead class of compounds with numerous spectacular applications. On the other hand, cycloaddition reactions offer a superior methodology for stereo-chemically controlled synthesis of heterocycles with a diverse ring size and a variable number of heteroatoms. A comprehensive review of methods based on cycloaddition reactions and applied for construction of fluorinated and/or fluoroalkylated S-heterocycles has not yet been published. For this reason, the main goal of the presented review was to fill the existing gap and to summarize the results published over last six decades. In this context, the [3+2]- and [4+2]-cycloadditions (Huisgen reactions, and Diels–Alder reactions, respectively) are of special importance. Some questions related to the discussed mechanisms of cycloaddition processes observed in reactions with electron deficient, fluorinated substrates (dipolarophiles and dienophiles), and electron-rich sulfur containing counter partners, are of fundamental importance for the development of interpretations of organic reaction mechanisms.

Keywords: fluorinated and fluoroalkylated organic compounds; sulfur heterocycles; organic synthesis; cycloaddition reactions; organic reaction mechanisms

1. Introduction

In recent decades, we have witnessed the growing importance of fluorinated organic compounds in practically all areas of organic synthesis, and the elaboration of new methods for the preparation of fluorinated heterocycles belongs to the challenging problems of current organic chemistry [1,2]. It is well known that one of the best methods for the construction of the non-aromatic, heterocyclic compounds are cycloaddition reactions, and those most frequently applied are [2+1]-, [2+2]-, [3+2]- and [4+2]-cycloadditions. Starting with properly designed components containing fluorine (thiocarbonyl compounds, carbones, 1,3-dipoles, dienes), the synthesis of a fluorinated S-heterocycle can be achieved via a cycloaddition step or by further transformation of the initially obtained cycloadduct. The presence of electron-withdrawing fluorooalkyl groups enhance the reactivity of both dipolarophiles and dienophiles. Similarly, fluorinated 1,3-dipoles display high reactivity towards electron-rich dipolarophiles and [3+2]-cycloadditions performed with thiocarbonyl dipolarophiles are of special importance for the construction of fluoroalkylated sulfur heterocycles. For materials chemistry, the development of methods for the synthesis and studies on the reactivity of fluorinated heterocycles are of great interest. In a
recent comprehensive review, the methods applied for syntheses of diverse heterocycles bearing fluorine atoms and/or fluoroalkylated substituents were summarized. However, sulfur-containing heterocycles are inadequately represented, mainly by fluorothiazole and fluorobenzothiazole derivatives [3]. The goal of the present work is an overview of the methods which are of practical importance for the preparation of fluorine-containing sulfur heterocycles upon exploration of cycloaddition reactions as basic tools for the construction of the heterocyclic core.

2. Three-Membered S-Heterocycles (Thiiranes)

The [2+1]-cycloaddition of difluorocarbene, generated by thermal decomposition of PhHgCF_3 (Seyfert’s reagent) in boiling benzene, with 2,2,4,4-tetramethyl-3-thioxocyclobutanone (1a) and its dithioxo analogue 1b gave the corresponding spirocyclic gem-difluorothiiranes 2a,b (Scheme 1) [4]. In the case of 1b, the formation of two isomeric 2:1-adducts, i.e., cis- and trans-3, in a ratio of 3:1 was also observed.

Scheme 1. Cycloaddition of difluorocarbene with cyclobutanethiones 1a,b to give thiiranes 2 and dithiirane 3.

Aromatic thioketones 1c,d react under the same conditions with: CF_2 yielding gem-difluoroethenes 4 via spontaneous desulfurization of the intermediate thiiranes 2c,d (Scheme 2) [4]. The mechanism of the desulfurization process is not known, but it is very likely that CF_2 can play an important role in this reaction.

Scheme 2. Difluorocarbene in [2+1]-cycloaddition with aromatic thioketones leading to gem-difluoroalkenes 4 via intermediate gem-difluorothiiranes 2.

The analogous desulfurization of an intermediate gem-difluorothiirane, generated from trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate and dithioesters, led to gem-difluorovinyl sulfides [5].

Heating of perfluoropropenoxide in the presence of difluorothiophosgene (thiocarbonyl fluoride) or trifluorothiaoacetyl fluoride in a closed reactor under pressure at 175 °C yielded the corresponding perfluorinated thiiranes 2e and 2f, respectively, in fair yields (Figure 1) [6]. The same method was applied for the preparation of chlorotrifluorothiirane (2g) [6,7].

In the case of trifluoromethyl dithiochloroformate, the thermal reaction with perfluoropropenoxide leads to the corresponding vinyl sulfide 4c, formed via spontaneous desulfurization of the intermediate thirane [8]. In all of these reactions, thermal decomposition of perfluoropropenoxide leads to difluorocarbene as the reactive intermediate.
A superior method for the preparation of fluorinated thiiranes is the 1,3-dipolar electrocyclization (1,3-DE) of transient, fluorinated thiocarbonyl S-methanides 7, generated from the corresponding 1,3,4-thiadiazolines 6 (Scheme 3, Table 1). The latter heterocycles are smoothly formed via [3+2]-cycloaddition of a thiocarbonyl compound as dipolarophile with diazomethane derivatives 5. The fluorine atom or a fluoroalkyl group may originate either from one or from both reaction partners.

Scheme 3. [3+2]-Cycloadditions of thiocarbonyl compounds 1 with diazoalkanes 5 leading to thiiranes 2 via 2,5-dihydro-1,3,4-thiadiazoles 6.

| Products R1 | R2 | R3 | R4 | Yield (%) |
|-------------|----|----|----|-----------|
| 2h          | CF3| CF3| Ph | Ph        | 77.5 [9]   |
| 2i          | Ph | Ph | CF3| CO2Me    | 57 [10]    |
| 2j          | Cl | Cl | CF3| CF3      | 49 [11]    |
| 2k          | F  | Cl | CF3| CF3      | 60 [11]    |
| 2l          | CF3| H  |    |          | 81 [12]    |
| 2m          | CF3| H  |    |          | 79 [12]    |
| 2n          | CF3| H  |    |          | 75 [12]    |
| 2o          | CF3| H  |    |          | 71 [12]    |

Hexafluorothioacetonate (1e) is known as a highly reactive dipolarophile, which easily reacts with diphenyldiazomethane (5a) at a low temperature in pentane solution to yield 2,2-diphenyl-3,3-bis(trifluoromethyl)thiirane (2h) after the spontaneous elimination of N2 [9]. A similar reaction course with immediate evolution of N2 was observed in reactions of thiobenzophenone (1c) with methyl α-diazo-3,3,3-trifluoropropanoate (5b) [10] as well as thiophosgene or monofluorothiophosgene with 2-diazohexafluoropropane (5c) [11].
The sterically crowded cyclobutanethiones 1a,h react with 2,2,2-trifluorodiazoethane (5d) in CH\textsubscript{2}Cl\textsubscript{2} solution at room temperature, and after 24 h, the spirocyclic thiiranes 2l and 2m, respectively, were isolated in good yields [12]. However, in analogous reactions stopped just after de-coloration of the mixture (ca. 60 min), the corresponding [3+2]-cycloadducts 6a,b were obtained as relatively stable solids in good yields. In contrast to the cycloaliphatic thioketones 1a,h, thiobenzophenone (1c) reacted with 5d under the same conditions to give 3,3,3-trifluoro-1,1-diphenylpropene as the product of spontaneous desulfurization of the in situ-formed thiirane.

Only in the case of 2,2,5,5-tetrakis(trifluoromethyl)-1,3,4-thiadiazoline (6a), formed from 2-diazohexafluoropropane (5c) and hexafluorothioacetone (1e), was no evolution of N\textsubscript{2} observed, and this product could be distilled in vacuum without decomposition [13]. The presence of four CF\textsubscript{3} groups in 6a results in unusual stability, as in other cases 1,3,4-thiadiazolines are known to eliminate N\textsubscript{2} easily [14].

3. Four-Membered S-Heterocycles

3.1. Thietanes

Hexafluorothioacetone (1e), existing in an equilibrium with its dimer 8a, displays high reactivity in [2+2]-cycloadditions with both electron-rich and electron-deficient C=C bonds. Selected examples of these reactions are depicted in Scheme 4 [15–19]. The first reactions of that type were reported with vinyl ethers and thioethers, which yielded 4-substituted 2,2-bis(trifluoromethyl)thietanes 9a,b in a regioselective manner [15]. Analogous [2+2]-cycloadditions were performed with N-vinylformamide and N-vinylcarbazole, leading to products 9c and 9d, respectively [18].

![Scheme 4. [2+2]-Cycloadditions of hexafluorothioacetone (1e) leading to thietanes 9.](image-url)

In the case of gem-disubstituted ethylenes, the corresponding thietanes were obtained with both 1,1-bis(dimethoxy)- and 1,1-bis(methylsulfanyl)ethene as well as with the
electron-deficient 1,1-bis(trifluoromethyl)ethylene [17]. Whereas the disulfanyl derivative afforded the product 9f as a stable compound, the dimethoxy analogue gave the opposite regioisomer as the product of the kinetic control, which after three months at 25 °C converted completely to the thermodynamic product 9e. Unexpectedly, the electron-deficient 1,1-bis(trifluoromethyl)ethylene yielded the same type of regioisomer as observed in the case of electron-rich ethenes. The structures of the stable products 9g [17], 9e and 9f [20] were established by X-ray crystallography. In addition, styrene and the in situ-generated norbornadiene are captured by 1e yielding the corresponding thietane derivatives 9h and 9i, respectively [19,21].

The [2+2]-cycloadditions of alkenes and 1,3-dienes with the in situ-generated S,S-dioxide of 1e, i.e., bis(trifluoromethyl)sulfene (10), afforded thietane-S,S-dioxides of type 11 (Scheme 5). In all cases, these products were formed regio-selectively [22].

![Scheme 5. Synthesis of thietane-S,S-dioxides 11 via [2+2]-cycloaddition of bis(trifluoromethyl)sulfene (10) with alkenes.](image)

In the reactions with 1,3-dienes, such as 2,5-dimethylhexa-2,4-diene and (E,E)- and (E,Z)-hexa-2,4-dienes, [2+2]-cycloadditions also governed the formation of four-membered products 11f,g. In the two latter cases, mixtures of trans- and cis-isomers were formed. The (E,E)-diene yielded a 96:4 mixture of trans- and cis-11g, whereas the (E,Z)-diene gave the cis-isomer as the major component (18:82).

### 3.2. 1,3-Dithietanes

The perfluorinated thioketone 1e (hexafluoroacetone) and α,α,α-trifluorothioacetophenone (1i) easily undergo head-to-tail dimerization to give 1,3-dithietanes 8a and 8b, respectively (Scheme 6) [17,23]. In both cases, the thioketones are prepared from corresponding starting materials and dimerize spontaneously in the reaction mixture.

![Scheme 6. Formation of 1,3-dithietanes 8 by the head-to-tail [2+2]-cycloaddition (dimerization) of thiocarbonyl compounds.](image)
The analogous tendency for the [2+2]-cycloaddition leading to the 1,3-dithietane derivative 8c, formed as an 85:15 mixture of trans- and cis-isomer, was reported for N-acetyl trifluoroacetic thioamide (12) [24]. Some examples of the use of dithietane 8a in organic synthesis were recently described in a review [25].

The reaction of thioketones or alkenes with bis(trifluoromethyl)thioketene (13) results in the regioselective formation of 1,3-dithietanes 14 (Scheme 7) or thietanes, correspondingly [26].

Scheme 7. The regioselective [2+2]-cycloaddition of thioketone 1e with thioketene 13 leading to 1,3-dithietane 14.

4. Five-Membered S-Heterocycles
4.1. Thiolanes (Tetrahydrothiophenes)

The thiolane ring constitutes a core fragment in many compounds demonstrating diverse types of biological activities and they have found numerous therapeutic applications [27–29]. In spite of numerous commercial offers for their supply in large quantities, there are only a limited number of reports available on efficient laboratory synthesis of the 2- or 3-trifluoromethylated thiolanes. Obviously, in this situation the studies that are focused on the exploration of the cycloaddition methodology for the synthesis of this class of S-heterocycles remain the most relevant.

An attractive approach to the synthesis of fluoroalkylated thiolanes is the use of electron-rich, S-centered 1,3-dipols known as thiocarbonyl ylides (thiocarbonyl S-methanides) 15. They have to be generated in situ, preferably by thermal decomposition of corresponding 1,3,4-thiadiazolines. In the presence of a suitable dipolarophile, e.g., fluorinated α,β-unsaturated ketones 16, they easily undergo [3+2]-cycloaddition leading to five-membered S-heterocycles 17 (Scheme 8). If such dienophiles belong to the group of electron-deficient ethylenes, they are prone substrates for the [3+2]-cycloadditions with 15 [30].

Scheme 8. Reaction of thiocarbonyl S-methanides 15 with fluorinated α,β-unsaturated ketones 16 leading to thiolanes 17.

The new 4-trifluoromethyl thiolanes 18 containing an ester, sulfone, sulfonamide, sulfoximine or phosphonate moiety at C(3) were prepared by [3+2]-cycloaddition reactions of 3,3,3-trifluoropropene derivatives with the parent thiocarbonyl ylide 19 generated in situ from chloromethyl trimethylsilyl sulfide (Scheme 9) [31].
Scheme 9. Synthesis of 3-substituted 4-(trifluoromethyl)tetrahydrothiophenes (thiolanes) 18.

Recently, a new method for the synthesis of 2-trifluoromethyl thiolanes 21, based on the transformation of the unsaturated six-membered sulfoxide 20, was elaborated. The latter compound was prepared by the [4+2]-cycloaddition of the corresponding dithiocarboxylate with a suitable 1,3-diene. Taking into account the high total yield of isolated products, this ring contraction may be considered as a method of choice for the preparation of 2-trifluoromethyl thiolanes 21 (Scheme 10) [32].

Scheme 10. The two-step synthesis of diastereoisomeric 2-trifluoromethyl tetrahydrothiophenes (thiolanes) 21 via intermediate 3,4-dihydro-2H-thiopyran 1-oxide 20.

4.2. 1,3-Dithiolyanes

Middleton and Sharkey observed the formation of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithiolane (22) when hexafluorothioacetone was treated with diazomethane in pentane solution at −78 °C and subsequently the reaction mixture was rapidly distilled (Scheme 11) [9].

Apparently, 1,3,4-thiadiazoline 23, formed at a low temperature, is not a stable cycloadduct and spontaneously eliminated nitrogen to generate hexafluorothioacetone S-methanide (24), which was in situ-trapped by the starting thiketone yielding 22 in a regioselective manner; formation of the isomeric 2-CH2 derivative was not observed. Another, colorless minor product with the molecular formula C14H4F24S4 was also reported, but its structure could not be elucidated.
Scheme 11. Formation of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithiolane (22).

Some N,N-disubstituted thioamides containing polyfluoroalkyl substituents enter [3+2]-cycloaddition with the parent thiocarbonyl S-methanide (19) and new 4-polyfluoroalkyl-1,3-dithiolanes 25 were obtained in these reactions in good to high yields (Scheme 12, Equation (A)) [33].

Scheme 12. Formation of 1,3-dithiolanes 25, 26, 27 and 30 via [3+2]-cycloadditions of thiocarbonyl S-methanide (19) with a fluorinated thioamide (equation (A)) and of the fluorinated thiocarbonyl S-ethanide 29 with aromatic thioketones (equation (B)), respectively.

The regioisomeric 1,3-dithiolanes of type 26 and 27 were synthesized via a domino reaction initiated by thermal N2 extrusion from the CF3-substituted 1,3,4-thiadiazole 28, and the in situ-generated, reactive thiocarbonyl ylide 29 (X = CO) trapped thioketones 1k, l yielding mixtures of 26 and 27 in favor of the sterically less hindered 5-CF3 isomer 26 (Scheme 12, Equation (B)) [12,34].
The 2,2,2-trifluorodiazoethane easily reacts with cycloaliphatic and aromatic thioke-tones forming corresponding 1,3,4-thiadiazolines of type 28, which were subsequently used as precursors of fluorinated thiacarbonyl S-ethanides 29 [12]. For example, 2,2,4,4-tetramethyl-3-thioxocyclobutanone (1a) reacts with trifluorodiazoethane to form 1,3,4-thiadiazoline 28a, which, after elimination of N₂ at room temperature, serves as the source of 29 (X = CO). This intermediate is efficiently trapped with thiobenzophenone to give, in contrast to the corresponding S-methanide, the less hindered 1,3-dithiolane 30a as the sole cycloadduct (Scheme 12).

An unexpected formation of 1,3-dithiolanes 31 was observed upon treatment of perfluoropropene with elemental sulfur in the presence of vinyl O-alkyl ethers in DMF solution at 45–65 °C using CsF as a catalyst. Under the same conditions, dihydrofuran gave the bicyclic 1,3-dithiolane 32 in a 58% yield as a mixture of cis- and trans-isomer (Scheme 13) [17].

Scheme 13. Reaction of the in situ-generated hexafluoroacetoacetone (1e) with enol ethers yielding 1,3-dithiolanes 31 and 32.

4.3. 1,3-Dithioles

Replacement of the electron-rich vinyl ethers in the CsF-catalyzed sulfurization reactions of perfluoropropene by the electron-deficient dimethyl acetylenedicarboxylate (DMAD) led to the corresponding 1,3-dithiole 33 in a 70% yield (Scheme 14) [17].

Scheme 14. Efficient trapping of the postulated 3,3-bis(trifluoromethyl)dithiirane by dimethyl acetylenedicarboxylate (DMAD) leading to 1,3-dithiole derivative 33.

The formation of both 1,3-dithiolanes 31/32 and 1,3-dithiole 33 in the fluoride anion-catalyzed sulfurization of perfluoropropene was explained via [3+2]-cycloaddition of in situ-generated 3,3-bis(trifluoromethyl)dithiirane 34 onto the C=C and C≡C bond, respectively (Scheme 15). It is very likely that these cycloaddition reactions comprise the interception of an intermediate diradicaloid 35, generated by homolytic cleavage of the S–S bond of the congested dithiirane ring (Scheme 15) [17].
Scheme 15. Proposed mechanism of the fluoride anion-catalyzed sulfurization of perfluoropropene; participation of 3,3-bis(trifluoromethyl)dithiirane (34) in the formation of 1,3-dithiole 33.

4.4. 1,2-Dithiolanes

The 3,3-bis(trifluoromethyl)-5-alkoxy-1,2-dithiolanes 36 were prepared by the CsF-initiated reaction of 4-alkoxy-2,2-bis(trifluoromethyl)thiethanes 9a (see Section 3.1) with elemental sulfur in DMF solution (Scheme 16) [16,17].

Scheme 16. Preparation of fluoroalkylated 1,2-dithiolanes 36 starting with thietane 9a.

The fluoride anion is supposed to open the four-membered ring of the starting 9a yielding the thiolate anion as an intermediate, which subsequently reacts with another molecule of 9a. Ring closure of the postulated intermediate occurs with elimination of an olefinic side product and formation of the 1,2-dithiole derivative 36 in yields between 73 and 87% [17].

In a recent publication, an alternative mechanism for the formation of 1,2-dithiole derivatives via sulfurization of 2,3-diarylcylopentapenthiones 37 with elemental sulfur in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) was formulated to explain the role of the fluoride anion as an activator. This mechanism corresponds to a formal [2+3]-cycloaddition of elemental sulfur (as $\text{S}_2$) with the congested three-membered ring (Scheme 17) [35].
Scheme 17. Formation of 1,2-dithiole-3-thiones 38 by fluoride-catalyzed ring expansion (sulfurization) of cyclopropenethiones 37.

Similar reactions of 2,3-diarylcyclopropenethiones, without explanation of the crucial role of the fluoride anion, have also been published [36,37]. It has to be stressed that the fluoride anion-mediated sulfurization of 2,3-diarylcyclopropenethiones 37 should be considered as a useful method for the synthesis of 1,2-dithiole-3-thiones of type 38. The latter sulfur heterocycles are of importance as biologically active compounds, and in a recent review, the method of their synthesis as well as diverse transformations have been summarized [38].

4.5. 1,3-Oxathiolanes

Thiocarbonyl S-methanides 15, generated in situ by N2 elimination from 1,3,4-thiadiazolines (see Section 4.1), undergo regioselective [3+2]-cycloaddition with the activated carbonyl group of trifluoropyruvic methyl ester to give 1,3-oxathiolanes 39a in a good yield (Scheme 18) [10].
In contrast to the \( \alpha,\beta \)-unsaturated ketones 16 (Scheme 8), the isomeric trifluoromethyl ketones 16\(^{\prime}\) react with thiocarbonyl ylides 15 in a chemo- and regioselective manner via [3+2]-cycloaddition with the carbonyl group to yield 5-styryl-5-trifluoromethyl-1,3-oxathiolanes 39\(^{\prime}\) (Scheme 18) [30].

4.6. 1,3,4-Thiadiazole Derivatives

A new and accessible method for the synthesis of 2-amino-3-phenyl-2-polyfluoroalkyl-2,3-dihydro-1,3,4-thiadiazolines 40 containing various functional groups at C(5) via [3+2]-cycloaddition reactions of polyfluoroalkane thioamides 41 with fluorinated nitrile imines 42\(a\) was recently described (Scheme 19, equation above) [39,40]. Regioselective [3+2]-cycloaddition of 1,3-dipoles 42\(b\) with aryl, hetaryl and ferrocenyl thioketones [41,42] as well as with 2,3-diphenylcyclopropenethione [43] lead to the formation of a new type of fluoroalkylated 2,3-dihydro-1,3,4-thiadiazoles 43 and 44, respectively.

Scheme 19. Synthesis of highly functionalized, 2-trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles 40 and 43–45 via [3+2]-cycloaddition of nitrile imines 42\(a,b\) with diverse thiocarbonyl compounds.

Analogously, fluorinated nitrile imines 42\(b\) react with monomeric aryl/hetaryl substituted thiocarbones yielding 2-styryl-substituted 1,3,4-thiazolidines 45 in a chemo- and regioselective manner (Scheme 19, equation below) [44].
Remarkably, cycloadditions of non-fluorinated nitrile imines with thiocarbanones have not been studied to the date. However, chalcones were reported to react with non-fluorinated nitrile imines upon selective involvement of the C=C bond in [3+2]-cycloaddition reactions leading to pyrazole derivatives [45,46].

An interesting and rather unexpected observation was made in the course of studying the [3+2]-cycloaddition of thiocarbonyl ylide 46 to 1,2-bis(trifluoromethyl)ethylene 1,2-dicarbonitrile. Along with the expected five-membered product, i.e., the thiolane 47, formation of a seven-membered thiazepine derivative 48, with a ketenimine fragment incorporated into the heterocyclic ring, occurred predominantly (ratio 87:22) (Scheme 20) [47]. Its reaction with methanol gave the spirocyclic thiazepine derivative 49 as a mixture of two diastereoisomers.

Scheme 20. Synthesis of the first fluorinated derivative of a 1,3-thiazepine 48 via non-concerted, stepwise cycloaddition of the sterically crowded thiocarbonyl S-methanide 46 with electron deficient 1,2-bis(trifluoromethyl)ethylene 1,2-dicarbonitrile.

Other sterically crowded thiocarbonyl S-methanides that were derived, e.g., from 2,2,6,6-tetramethylcyclohexanethione, reacted with electron deficient, fluorinated ethylenes analogously, yielding seven-membered products. Some of them were isolated as crystalline materials and their structures, as well as that of some products of their further conversions, were unambiguously confirmed by X-ray measurements [48,49]. The formation of these unusual N,S-heterocycles was explained by the non-concertedness of the expected cycloaddition process and formation of stabilized zwitterionic intermediates of type 50, which competitively can undergo either 1,5- or 1,7-cyclization yielding the five-membered thiolane 47 or the seven-membered 1,3-thiazepine 48, respectively. The unusual stability of the heterocumulene (ketenimine) unit –N=C=C– was rationalized by ‘the magic effect’ of the trifluoromethyl group located at the neighboring C-atom [50]. Some chemical properties of 48 will be described in Section 6.

4.7. 1,4,2-Oxathiazoles

The 3-trifluoro- or difluoromethylated 1,4,2-oxathiazoles 51 can be efficiently prepared via the regioselective [3+2]-cycloaddition of fluorinated nitrile oxides 52 with thioketones 1 (Scheme 21) [51]. The nitrile oxides 52 are generated in situ by treatment of hydroximoyl bromides 53, which are obtained conveniently in two steps from the corresponding aldehyde derivatives 54, with triethylamine [52].
Scheme 21. Preparation of tri- and difluoromethyl-substituted 1,4,2-oxathiazoles 51 via [3+2]-cycloaddition of di- and trifluoroacetonitrile N-oxides (52) with thioketones 1.

5. Six-Membered S-Heterocycles
5.1. Thiopyran Derivatives

Synthetic methodologies based on the hetero-Diels–Alder reaction are widely employed in organic chemistry. 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. Thiocarbonyl compounds are well-known representatives of heterodienophiles which, for example, found applications for the preparation of thioglycoside derivatives [53] or thiashikimic acid [54]. Electron-withdrawing groups in \( \alpha \)-position to the thiocarbonyl group lower the LUMO energy of the heterodienophile and facilitate the cycloaddition. Therefore, the polyfluoroalkyl thiocarbonyl compounds are excellent dienophiles and can be used for the preparation of diverse sulfur-containing heterocycles.

So far, the [4+2]-cycloaddition reactions of polyfluoroalkyl thiocarbonyl compounds with 1,3-dienes remain the main method for the synthesis of fluorine-containing derivatives of thiopyrans. Fluorinated thioaldehydes, thioketones, esters, amides, and halides of polyfluoroalkyl thionocarboxylic acids are used as thiocarbonyl compounds.

The extremely reactive polyfluoroalkane-derived thioaldehydes were synthesized, and their existence was proved by spectroscopic methods and their Diels–Alder reactions [55–57]. The trifluorothioacetaldehyde (55a) as well as the thioketones CF$_3$C(S)R (R = Me, Ph) could be obtained in good yields by flash vacuum pyrolysis of 1,3-dithiolane-1,1-dioxides (Scheme 22, equation shown above) [23,55]. The thioaldehydes 55b,c with longer perfluoroalkane chains were prepared by the reactions of the corresponding aldehydes with trimethylthiophosphates [56]. Various Diels–Alder products 56–60 were prepared by the reactions of these thioaldehydes as well as of polyfluoroalkyl-substituted sulfines 61 (Scheme 22, equation shown below), and the stereochemical considerations were presented in the published articles [23,57,58].
Scheme 22. Synthesis of fluoroalkylated thiopyran derivatives 56–59 and thiopyran 1-oxides 60 via thia-Diels–Alder reactions of fluorinated thioaldehydes 55 and sulfines 61, respectively.

Aromatic thioketones, such as thiofluorenone (1k) and thiobenzophenone (1c) and its derivatives, were demonstrated to react with cyclopentadiene and other cyclic and acyclic 1,3-dienes at room temperature yielding the expected bicyclic thiopyrans 62 (Scheme 23). The kinetic measurements demonstrated ‘superdienophilic’ reactivity for both thioketones and structurally similar selones [59]. Remarkably, polyhalogenated cyclopentadienes bearing chlorine and fluorine substituents definitely reacted slower and the studied [4+2]-cycloadditions could be performed at room temperature only with the ‘superdipolarophilic’ thiofluorenone (1k). Its reaction with 1,2,3,4-tetrachloro-5,5-difluorocyclopentadiene leading to thiopyran derivative 63 is depicted in (Scheme 23) [60].

A simple procedure for the preparation of new Diels–Alder adducts of different polyfluorinated thioketones 64 was elaborated recently (Scheme 24) [61,62]. The corresponding adducts of type 65 (e.g., 65a–f) have been prepared in a 30–78% yield by the reaction of perfluorinated olefins, sulfur and 1,3-dienes in the presence of CsF acting as a catalyst.
Scheme 23. Reactions of aromatic thioketones 1c and 1k with cyclopentadiene and its 1,2,3,4-tetrachloro-5,5-difluoro derivative, respectively.

Scheme 24. Simple procedure for the synthesis of thia-Diels–Alder cycloadducts 65 of polyfluorinated thioketones 64.
The regiochemistry of the Diels–Alder reaction of open-chain 1,3-dienes with hexafluoroacetone, generated in situ by thermal, CsF-catalyzed decomposition of its dimer 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane (8a), was studied recently and the results were discussed in detail [63].

The pioneering works of W. Middleton described the first examples of the Diels–Alder reactions of trifluoroacetyl fluoride [64] and perfluorinated thioketones [65] with 1,3-dienes. These reactions were studied in more detail much later. The cycloaddition of the chloride and fluoride of polyfluoroalkane thiocarboxylic acids with 1,3-dienes proceeded rapidly at 0 °C. The stability of the cycloadducts formed depended on the length of the polyfluoroalkyl chain. Trifluoroacetyl chloride afforded a relatively stable adduct 66, which was isolated and characterized spectroscopically (Scheme 25). Chlorides with longer chains gave directly 2H-thiopyrans 67 after the evaporation of the reaction mixture. Dehydrochlorination of the CF$_3$-substituted thiopyran was achieved only after heating at 100 °C [66]. The thiopyrans obtained turned out to be convenient starting compounds for the 2H-thiopyrans 67 preparation of the first 2-polyfluoroalkyl-substituted thiopyrylium salts, which in turn can efficiently be used for the synthesis of fluorinated thiopyranosides and nucleosides [66].

![Scheme 25](image)

Scheme 25. Synthesis of fluorinated 2H-thiopyrans 67 and their aromatization to thiopyrylium salts 68.

Another interesting synthetic application of fluorinated thiopyran derivatives 66 consists in the formation of 2-polyfluoroalkylthiophenes 69/70 via the sulfur-assisted ring contraction of 4,5-dibromo-2-chloro-2-(tri- or difluoromethyl)tetrahydrothiopyrans 71 (Scheme 26) [67].

![Scheme 26](image)

Scheme 26. Sulfur-assisted ring contraction of 4,5-dibromo-2-chloro-2-(perfluoroalkyl)tetrahydrothiopyrans 71 leading to fluoroalkylated thiophenes 69.
Over the past two decades, the factors affecting the reactions of polyfluoroalkane thiocarboxylic acid esters with 1,3-dienes of various structures have been studied in detail and diverse synthetic applications of the obtained derivatives of dihydrothiopyrans have been considered [32,68–70]. As a result of these reactions, at least one new stereogenic center was generated by the Diels–Alder addition. Therefore, the application of a proper chiral thionoester could influence the stereochemical outcome of the cycloaddition and could be used in the construction of optically active compounds.

The preparation of a series of thionoesters 72 with various optically active substituents, which can serve as chiral auxiliaries in asymmetric syntheses, allowed the observation of the first examples of asymmetric induction in the thia-Diels–Alder cycloaddition involving polyfluoroalkane thionocarboxylates, which provided 2-fluoroalkyl-2-alkylsulfanyl-3,6-dihydro-2H-thiopyrans 73 in good yields but a low to modest de of 6–60% (Scheme 27, Table 2) [70].

The influence of the nature of the diene and dienophile and the reaction conditions on the asymmetric induction of the cycloaddition have been examined. It has been found that electronic factors have a minimal effect on the stereoselectivity of the cycloaddition. Quantum chemistry (DFT) calculations indicate that the differences in the activation energies are larger than the relative energies of the cyclic adducts. This result allows the conclusion that the stereoselectivity of the formation of thiopyrans 73 is kinetically driven: the observed de refers to different free-activation energies inherent to the corresponding transition states.

Much less is known about the reactions of derivatives of polyfluoroalkane thionocarboxylic acid such as the O-esters and amides. However, even the available data allow a conclusion to be drawn about the significant effect of the nature of the heteroatom in the AlkF-C(S)XR (X = S,O,N) on the rate of the cycloaddition reaction. Thus, in the case of dithioethers 72a–d, the reaction with 2,3-dimethylbuta-1,3-diene proceeds at room temperature, while a similar reaction with the ester 72e requires vigorous heating [70].
Table 2. Fluoroalkylated 2,4-dihydrothiopyrans 73 prepared via thia-Diels–Alder cycloadditions of perfluoroalkane thionoesters.

| RF     | Cycloadduct 73 | Reaction Conditions (Excess of Diene) | Yield (%) | Diastereomeric Excess (de) (%) |
|--------|----------------|--------------------------------------|-----------|-------------------------------|
| a CF₃  | H(CF₂)₂        | −20 °C–20 °C 1–4 days                | 75–83     | 14–16                         |
| b CF₃  | H(CF₂)₂        | −20 °C–20 °C 1–6 days                | 90–94     | 50–60                         |
| c CF₃  |                | 20 °C 3 days                         | 90        | 56                            |
| d CF₃  | H(CF₂)₂        | −20 °C–20 °C 3–6 days                | 85–98     | 16–20                         |
| e CF₃  | H(CF₂)₂        | 130 °C 5 h                           | 75–80     | 6–20                          |

Alkylamides of polyfluoroalkane thiocarboxylic acids 74a–d do not react with 1,3-dienes even after many hours of heating in a sealed ampoule. A successful reaction to give 3,6-dihydro-2H-thiopyrans 75a–d was ensured only by microwave activation in N-methylpyrrolidone (NMP) solution [71] or using an N-acylated thioamide derivative 76 (Scheme 28) [69]. The positive results observed in the last cases, leading to products 77, was explained by the electron-withdrawing influence of the amide substituent on the thio-carbonyl group.

Scheme 28. Thia-Diels–Alder cycloaddition of perfluoroalkane thiocarboxylic acid amides yielding fluoroalkylated 2,4-dihydrothiopyrans 75 and 77.
The high activity of hexafluorothioacetone in cycloaddition reactions with 1,3-dienes is explained by the influence of the electron-withdrawing trifluoromethyl groups. In the case of thioacid derivatives, the opposite effect is observed. The electronegativity of the nitrogen and oxygen atoms is significantly higher than that of sulfur, but the rates of cycloaddition reactions are lower. Perhaps the reason for this unexpected effect may be the interaction of the sulfur-carbon multiple bond orbitals with the orbitals of oxygen or nitrogen heteroatoms, which is not so significant in the case of the sulfur atom due to the larger size of the latter.

5.2. 1,4-Dithiines, 1,4-Dithianes and 1,2,4,5-Tetrathianes

Syntheses of fluorine-containing derivatives of 1,4-dithiane by cycloaddition reactions are only known in two examples. In an early work, it was suggested that the formation of 1,4-dithiane 78 and 2,3-dihydro-1,4-thiines 79 as the result of the reaction of bis(trifluoromethyl)dithietane 80 to acetylenes and olefins occurs according to the Diels–Alder reaction of the intermediate bisthiocarbonyl compound 81, which is formed via a preliminary cleavage of the sulfur–sulfur bond of 80 (Scheme 29) [72].

![Scheme 29](image)

The 2,3-bis(benzylthio)-2,3-bis(octafluoropentyl)-1,4-dithiane 82 was obtained by dimerization of thiocarbonyl S-methanide 83 generated in the reaction of dithioester 84 with diazomethane (Scheme 30) [73]. The characteristic structural feature of this compound is the cis-configuration of the fluoroalkyl substituents in the six-membered ring.

![Scheme 30](image)

The thermal reaction of bis(trifluoromethyl)sulfine (85) with thiophosgene at 110 °C leads to 3,3,6,6-tetrakis(trifluoromethyl)-1,2,4,5-tetrathiane (86) as a minor product (3%) resulting from the thermal decomposition of the initially formed sulfenylchloride 87, which in this case was isolated as the major product (Scheme 31) [74].
Scheme 31. Formation of the first perfluoroalkylated derivatives of 1,2,4,5-tetrathianes 86 and 89.

The decomposition of 2-diazohexafluoropropane (88) in carbon disulfide at 150–175 °C produced the tetrathiane 89 in trace amounts, presumably formed via the addition of bis(trifluoromethyl)carbene to carbon disulfide and the subsequent dimerization of the adduct (Scheme 31) [26].

5.3. 6H-1,3,4-Thiadiazines

Substituted thiobenzophenones 1c,1-o were reacted with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (90), and in contrast to other dienes studied by Sauer et al., these reactions had to be performed in boiling toluene at 100 °C. Under these conditions, thiofluorenone (1k) underwent decomposition and for this reason it could not be used in the studied hetero-Diels–Alder reactions with 90. The initially formed [4+2]-cycloadducts 91 with thiobenzophenones could not be isolated and the target products, 6H-1,3,4-thiadiazines 92, were formed in situ after the spontaneous extrusion of nitrogen (Scheme 32) [60].

Scheme 32. Synthesis of 6H-1,3,4-thiadiazines 92 from aromatic thioketones and bis(trifluoromethyl)tetrazine 90.
A similar course of hetero-Diels–Alder reaction was observed when 1,2,4,5-tetrazine 90 was treated with alkyl thioformates in boiling toluene. The desired 6H-1,3,4-thiadiazines 93 were obtained as stable compounds and could be distilled yielding analytically pure materials (Scheme 33) [75]. In contrast, under the same conditions, the reaction of 90 with thioformamides led to 4-aminopyrazoles 94a as the sole products in ca. 20% yield. The initially formed [4+2]-cycloadducts, 6H-1,3,4-thiadiazines 93b, underwent an unexpected ring contraction to give the bicyclic thirane 95a, followed by elimination of sulfur. The final products were identified as pharmacologically interesting 3,5-trifluoromethyl-4-aminopyrazoles 94a (Scheme 33) [75].

Scheme 33. [4+2]-Cycloadditions of 1,2,4,5-tetrazine 90 with alkyl thioformates and thioformamides leading to bis-trifluoromethylated 1,3,4-thiadiazines 93a and pyrazoles 94a, respectively.

In an analogous manner, 6H-1,3,4-thiadiazine 93c, formed via [4+2]-cycloaddition/N₂-elimination mechanism from in situ-generated thiobenzaldehyde and bis(trifluoromethyl)tetrazine 90, was converted into 4-phenyl-3,5-bis(trifluoromethyl)pyrazole 94b (Scheme 34) [75].

Scheme 34. Formation of pyrazole 94b via the unstable 6H-1,3,4-thiadiazine 93c in the hetero-Diels–Alder reaction of 90 with in situ-generated thiobenzaldehyde.

6. Seven-Membered, Sulfur-Containing Heterocycles

Information on the syntheses of sulfur- and fluorine-containing seven-membered heterocycles via a stepwise [4+3]-cycloaddition reaction is fragmentary. The first example of such a reaction, leading to a trifluoromethylated, seven-membered N,S-heterocycle, was discussed in Section 4.6 (Scheme 20).

The ketenimine fragment in the heterocycle 48 easily reacts with nucleophiles, yielding new types of 1,3-thiazepine derivatives 49, 96 and 97 [76]. In addition, it enters [2+2]-cycloaddition reactions with vinyl ethers and the [3+2]-cycloaddition with diazomethane to give fused heterocycles 98/99 and 100/101, respectively (Scheme 35) [77]. In the latter
cases, the reaction proceeds non-chemoselectively via the addition of CH₂N₂ onto the C=C and C=N double bond to give the primary, non-isolable cycloadducts 102 and 103, which in situ eliminate N₂ and HF, respectively, to give the final products.

Scheme 35. Synthesis of new 5,6-bis(trifluoromethyl)-2,3,6,7-tetrahydro-1,3-thiazepine derivatives via reactions of seven-membered ketenimines 48 with nucleophiles or 1,3-dipoles.

A surprising dimerization of the ketenimine 48b occurred in acetonitrile at room temperature in the presence of KF as a catalyst. The formation of two diastereoisomers of product 104 in a ratio of 1:1 was explained by the fluoride ion-initiated reaction mechanism via intermediate 105 (Scheme 36) [78].

Scheme 36. Base-catalyzed dimerization of the seven-membered, cyclic ketenimine 48b initiated by fluoride anion-assisted, heterocyclic ring-opening.
The assumption of the likely \([4+3]\)-cycloaddition reaction of intermediately formed thioketone \(S\)-sulfide (thiosulfine) 106 with elemental sulfur \(S_8\) has been suggested by the authors of [79] while studying the reaction of hexafluoroacetone hydrazone (107) with disulfur dichloride. The expected bis(trifluoromethyl)hexathiacycloheptane (108) was only isolated in a 3% yield (Scheme 37).

\[
\text{Scheme 37. Formation of the hexathiacycloheptane 108 via an assumed \([4+3]\)-cycloaddition.}
\]

7. Conclusions and Outlook

The biological utility of fluorinated organic compounds [80], including sulfur heterocycles, e.g., thiolanes [32,81] and benzothiazoles [82], is demonstrated by recently published reviews and original works. Without a doubt, fluorinated and fluoroalkylated thio-phenes are the most prominent \(S\)-heterocycles, widely applied in diverse areas of materials chemistry [83–86]. On the other hand, some fluorinated \(S\)-heterocycles, e.g., \(S\)-(trifluoromethyl)dibenzothiophenium salts (so-called “Umemoto reagents”), are of great importance for the current organic synthesis as fluorinating/fluoroalkylating reagents [87]. In general, fluorine-containing \(S\)-heterocycles have rarely been prepared by the direct fluorination/fluoroalkylation of the parent systems and one of the important issues is the regioselectivity of these processes, which complicates the preparation of pure products. For all these reasons, the exploration of highly selective cycloaddition reactions, based on thiocarbonyl dipolarophiles or dienophiles, known as superdipolarophiles [88] and superdienophiles [60], respectively, offers a perfect methodology for the solution of this problem. Thiocarbonyl compounds are also perfect trapping reagents for carbenes in \([2+1]\)-cycloadditions leading to fluorinated thiiranes or their desulfurized derivatives [4]. Remarkably, difluorocarbene reacts with the \(C=S\) bond via carbophilic attack, and in these reactions, it resembles the nucleophilic dimethoxycarbene [89] and not the electrophilic dichloro- or dibromocarbene [90].

The present review is aimed at presenting for the first time the synthetic potential of diverse cycloaddition reactions in practical applications for the selective preparation of fluorinated and fluoroalkylated \(S\)-heterocycles from three-membered thiiranes to seven-membered \(N,S\)-rings. In addition, the review should be considered as a supplement to the two, recently published reviews on the \([4+2]\)-cycloadditions performed with fluorinated dienes or dienophiles leading, via multi-step mechanisms, to aromatic/heteroaromatic six-membered carbo- and heterocyclic products [91], as well as on the thia-Diels–Alder reactions based on the exploration of sulfur-containing reagents [92].

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