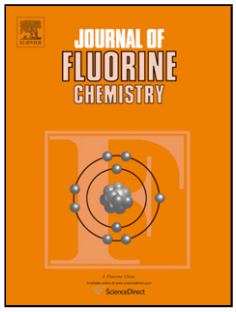

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Expected and unexpected results in reactions of fluorinated nitrile imines with (cyclo)aliphatic thioketones

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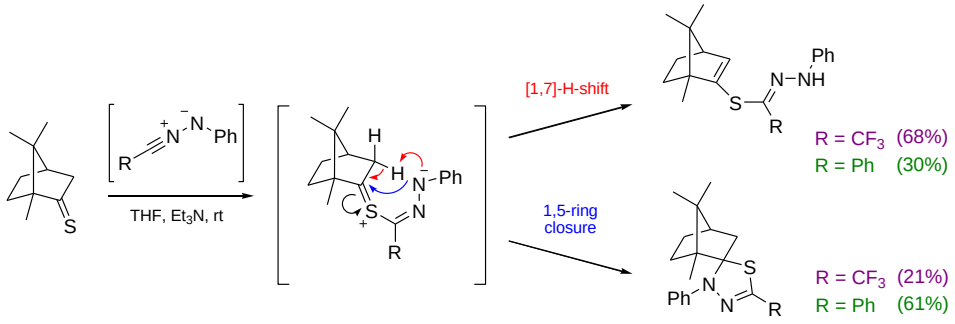
Graphical abstract:



Highlights

Cycloaliphatic thioketones undergo (3+2)-cycloaddition with fluorinated nitrile imines. 2,3-Dihydro-1,3,4-thiadiazoles were obtained in a fully regio- and diastereoselective manner. Unexpectedly, enolisable thiocamphor yielded the insertion product of the thioenol form as the major product.

Abstract

A series of (cyclo)aliphatic thioketones have been tested towards trifluoroacetonitrile imines, generated *in situ* via base-induced dehydrohalogenation of the respective hydrazonoyl bromides. Typically, non-enolisable thioketones yielded exclusively 3-triflurомethyl-2,3-dihydro-1,3,4-thiadiazoles as a result of completely regio-,

chemo-, and diastereoselective (3+2)-cycloaddition, depending on the starting material, while in the case of 2,2,4,4-tetramethylcyclobutane-1,3-dithione a competitive rearrangement followed by trapping of title 1,3-dipole by the C=S group of the initially formed dithioester was observed. Enolizable (1*R*)-thiocamphor also provided the expected (3+2)-cycloadducts along with the insertion products in ratio reflecting electronic properties of the nitrile imine. The latter results indicate remarkable electrophilic nature of the electron-deficient fluorinated nitrile imines, and implies possible step-wise mechanism of the studied reaction.

Keywords: fluorinated nitrile imines, thioketones, (3+2)-cycloaddition, fluoroalkylated heterocycles, trifluoromethylated 1,3,4-thiadiazoles.

1. Introduction

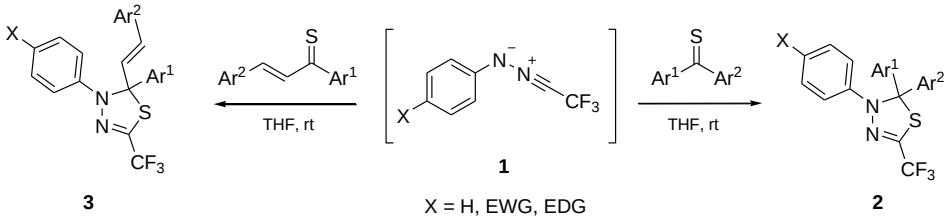
In spite of bad reputation attributed to thioketones as odorous and unstable sulfur analogs of ketones, recent three decades witnessed rapid development of synthetic methods based on new application of aryl, hetaryl, and non-enolisable aliphatic thiones [1,2]. Especially important are cycloaddition reactions as since many years thioketones are considered as *superdipolarophilic* [3] and *superdienophilic* [4] reagents. In recent three decades, both aromatic and cycloaliphatic thioketones were tested in reactions with diverse 1,3-dipoles, and 5-membered heterocycles such as 1,3-dithiolanes, 1,3-oxathiolanes, 1,3-thiazoles, 1,4,2-oxathiazoles, and 1,3,4-thiadiazoles were obtained as final products [1,3,5]. In addition, hetero-Diels-Alder reactions with aryl and hetaryl thioketones as heterodienophiles or heterodienes offer an excellent access to 6-membered thiopyran derivatives [6]. Moreover, in a recent publication we reported the first asymmetric version of a thia-Diels-Alder reaction [7]. Along with growing number of publications focused on synthetic exploration of thioketones, important observations related to mechanistic aspects of the cycloaddition reactions with thioketones were also discussed. Thus, reactions of hetaryl thioketones with diazomethane and thiocarbonyl *S*-methanides were shown to occur via stepwise mechanism with delocalized diradicals as key intermediates [8]. Similarly, [4+2]-cycloadditions of aryl and heteroaryl thioketones with electron-rich 2,4-hexadienes were evidenced to involve intermediate diradicals [9].

In general, (3+2)-cycloadditions of thioketones with diazomethane and its derivatives can be considered as an excellent method for the construction of 2,5-dihydro-1,3,4-thiadiazole skeleton (Figure 1) [10]. The cycloadducts obtained thereby are prepared either as target products or as precursors of the *in situ* generated reactive thiocarbonyl ylides (thiocarbonyl *S*-methanides), which are formed via thermal elimination of nitrogen ((3+2)-cycloreversion reactions). It is well known that such 1,3,4-thiadiazole derivatives obtained from diazomethane and aromatic thioketones are stable only at ca. −70 °C but analogous products derived from adamantanethione or other non-enolizable cycloaliphatic thioketones undergo decomposition only upon heating [10d]. On the other hand, derivatives of 2,3-dihydro-1,3,4-thiadiazoles are available via [3+2]-cycloaddition of thioketones with nitrile imines [11]. Thus, due to well documented significance of 1,3,4-thiadiazoles and their dihydro derivatives [12], (3+2)-cycloadditions with thioketones and appropriate 1,3-dipoles deserve attention as a straightforward method for their preparation.

2,5-dihydro-1,3,4-thiadiazole 2,3-dihydro-1,3,4-thiadiazole

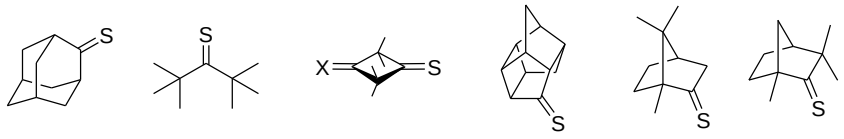
Figure 1. Structures of 1,3,4-thiadiazole derivatives available via (3+2)-cycloadditions with thioketones with diazoalkanes and nitrile imines, respectively.

In recent publications we demonstrated that aryl and hetaryl thioketones [13] as well as structurally similar thiochalcones [14] are superior trapping reagents for the *in situ* generated nitrile imines of type **1** derived from trifluoroacetonitrile, and these (3+2)-cyloadditions opens a convenient access to trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles **2** and **3**, which in all cases were formed in a regio- and chemoselective manner (Scheme 1).



Scheme 1. Chemo- and regioselective (3+2)-cycloadditions of fluorinated nitrile imines **1** with (het)aryl thioketones and thiochalcones leading to 2,3-dihydro-1,3,4-thiadiazoles **2** and **3**, respectively.

Prompted by earlier results we decided to examine (3+2)-cycloadditon reactions of fluorinated nitrile imines **1** with selected (cyclo)aliphatic thioketones **4a**-**4g** (Figure 2). The latter are known as relatively stable compounds which can be prepared in the lab using standard methods and subsequently applied in cycloaddition experiments without special precautions. It is worth of mentioning, that thiocamphor (**4g**) belongs to the class of the enolizable thioketones but in contrast to other representatives of that type (e.g. thioacetone or thioacetophenone) does not undergo decomposition under standard conditions and can be used as a reactive C=S dipolarophile [15]. In contrast to diverse aryl and hetaryl thioketones, which have extensively been studied in the (3+2)-cycloaddition reactions with nitrile imines [11], cycloaliphatic analogs **4** have only occasionally been tested as dipolarophiles in reactions of that type [16].



4a **4b** **4c** X = O, **4d** X = S *rac*-**4e** (1*R*)-**4f** (1*R*)-**4g**

Figure 2. Thioketones **4a**-**4g** selected for the study in the (3+2)-cycloadditions with fluorinated nitrile imines **1**.

As demonstrated in earlier studies, fluorinated nitrile imines **1** are attractive 1,3-dipoles which can efficiently be explored in the synthesis of trifluoromethylated 5-membered nitrogen heterocycles. They can be generated *in situ* by treatment of hydrazonoyl halides with triethylamine in the presence of suitable dipolarophile [17]. After the first publications by Tanaka et al. who described their reactions initially with ethylenic and

acetylenic dipolarophiles [17,18], and later on with some imines [19], we reported on their explorations in reactions with aryl and hetaryl thioketones [13] as well as thiochalcones acting as C=S dipolarophiles, exclusively. In continuation of our study, the aim of the present work was examination of the scope and limitations in reactions of fluorinated nitrile imines **1** with less reactive, sterically crowded thioketones; hence, one aliphatic **4b** and six cycloaliphatic i. e. **4a**,**4c**-**g** thioketones including bifunctional dithione **4d** and three chiral representatives **4e**-**g** were selected for the study (Figure 2).

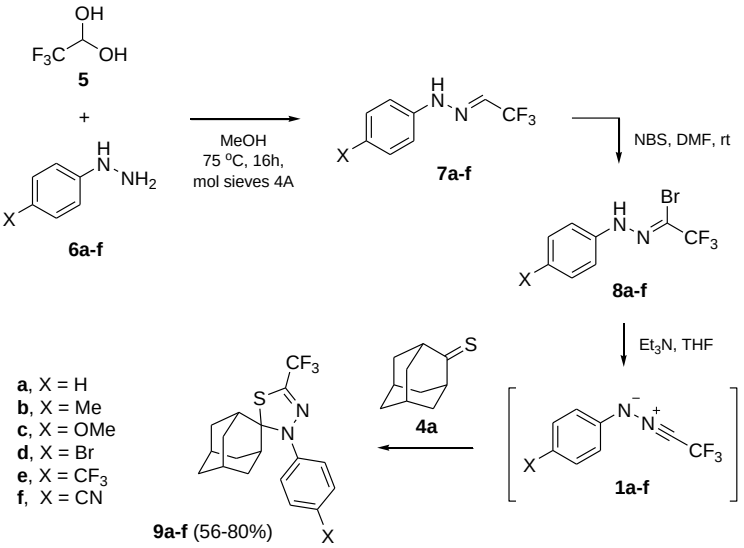
2. Results and Discussion

As shown in Scheme 2, readily available hydrazonoyl bromides of type **5** were used as suitable precursors of nitrile imines **1**. The starting compounds were prepared in a two-step procedure from fluoral hydrate (**5**) and arylhydrazones **6**. Thus, condensation of **5** and **6** was carried out according to general protocol elaborated for trifluoroacetaldehyde arylhydrazones and related compounds [20], and led after 16 hrs heating at 75 °C in methanolic solution, in the presence of freshly activated molecular sieves 4Å, to a series of arylhydrazones **7**. The expected products **7a**-**7f** were subsequently converted into the respective hydrazonoyl bromides of type **8** via chemoselective radical bromination of the CH=N group using NBS, in dry DMF solution [13,21]. The desired bromides **8a**-**8f** were obtained as spectroscopically pure samples after single flash chromatographic purification, and were isolated in high overall yield of 50-70%.

The first, test experiments were carried out using adamantanethione (**4a**) and bromide **8a** used as precursor of nitrile imine **1a** (Scheme 2). Typically, the reaction was performed in dry THF, at room temperature, in the presence of Et_3N as a base, using a slight excess of bromide **8a** (1.1 equiv.). The reaction progress was monitored by TLC until the starting thioketone **4a** was fully consumed; in most cases reaction times of 3-4 hours were required for the completion. As expected, the ^{1}H NMR spectrum registered for the crude reaction mixture showed only one set of the signals attributed to a sole (3+2)-cycloadduct; the subsequent flash CC purification provided pure product isolated as a pale yellow solid, in 62% yield. Two sets of signals found in aromatic region of the ^{1}H NMR spectrum clearly indicated the presence of the Ph group. On the other hand, two characteristic quartets found in the ^{13}C NMR spectrum at 119.8 ($^1J_{C\text{-}F}$ = 272.9 Hz) and 144.1 ppm ($^2J_{C\text{-}F}$ = 37.9 Hz) as well as singlet at –65.1 ppm present in the ^{19}F NMR spectrum evidenced the presence of the CF_3-C= unit. In addition, in the ^{13}C NMR spectrum another C_{sp3} signal attributed to the spiro-C atom was found in the expected, diagnostic region (δ = 97.5 ppm). Similar signals with comparable chemical shifts were observed for a previously described series of 5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazoles **2** [13], and therefore the structure of the isolated product was elucidated as the expected (3+2)-cycloadduct **9a**. Moreover, its structure was further confirmed by the high resolution (ESI-TOF) MS spectrum in which the molecular peak of $[M+H]^+$ found at *m/z* = 353.13 corresponded to the expected molecular formula $C_{18}H_{20}F_3N_2S$.

In continuation of the study, the same thioketone **4a** was briefly checked towards selected nitrile imines **1b**-**1f** functionalized with either electron-donating or electron-withdrawing groups located at the *para* position of the aryl ring. In all cases, the expected 1,3,4-thiadiazole derivatives **9b**-**9f** were isolated as sole (3+2)-cycloadducts in fair yields (56-80%), irrespectively to the electronic nature of the *para*-substituent. However, in the case of bromides **8e** and **8f** bearing strongly electron-withdrawing groups (CF_3 and CN, respectively), longer

reaction times (up to 6 hrs) were needed to complete the conversion of these substrates into the respective products **9e** and **9f**.



Scheme 2. Two-step synthesis of hydrazonoyl bromides **8**, generation of nitrile imines **1a-1f** via base-induced dehydrobromination of **8**, and their trapping with adamantanethione (**4a**) leading to 2,3-dihydro-1,3,4-thiadiazoles **9a-9f**.

Following the general protocol developed for the synthesis of 2,3-dihydro-1,3,4-thiadiazoles **9**, a series of thioketones **4b**, **4c**, **4e** and **4g** was examined in the reaction with the model nitrile imine **1a** yielding expected (3+2)-cycloadducts **10**-**13** (Figure 3). The smooth formation of **10** (69% yield, reaction time 1 hr) derived from bulky di(*tert*-butyl)thioketone (**4b**) deserves a brief comment, as this extremely crowded thioketone was shown to react only with highly reactive, small 1,3-dipoles such as diazomethane [22]. The observed result is consistent with our more recent finding, that thioketone **4b** is a suitable reaction partner also for more sterically demanding D-glyceraldehyde-derived *N*-benzyl nitrone, however, in that case remarkably longer reaction time was necessary to complete the reaction [2c]. Treatment of 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4c**) with **1a** also provided single product **11** in excellent yield (>98%), as a result of a fully chemoselective (3+2)-cycloaddition of nitrile imine molecule onto the C=S bond. The ^{1}H NMR of the crude reaction mixture confirmed complete conversion of the starting thione after 2 hrs; however, analytically pure material **11** was isolated in 48% yield only, due to partial decomposition of the product during purification on silica.

As the first chiral model we selected 'cage thioketone' *rac*-**4e**, which was reacted with nitrile imine **1a** in a typical manner. As expected, the corresponding 1,3,4-thiadiazole *rac*-**12** was formed solely via the exclusive *exo*-face attack of **1a** onto the C=S group. The observed result is in full accordance to other reports on both nucleophilic additions and (3+2)-cycloadditions with Cookson's 'birdcage' thioketone **4e** and related compounds [2a,23]. Similarly, excellent facial stereoselectivity was observed in the reaction of enantiomerically pure tiofenchone ((1*R*)-**4g**), which captured **1a** from the *endo*-face only. Standard flash chromatography enabled isolation of this single diastereomer **13** in moderate yield of 56%.

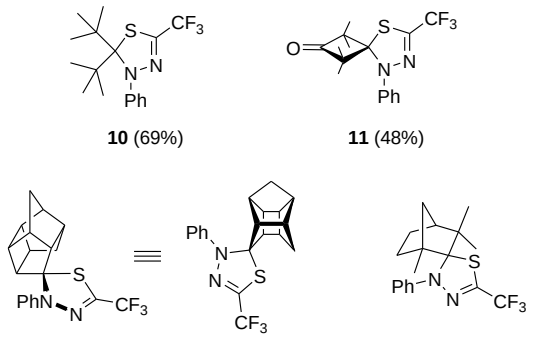
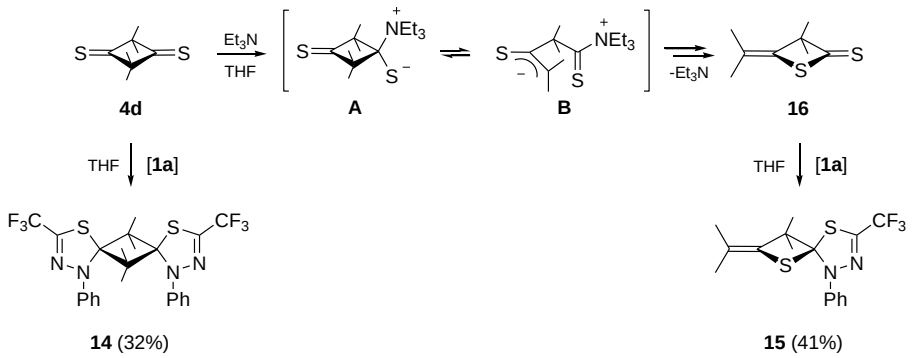


Figure 3. Achiral and chiral 2,3-dihydro-1,3,4-thiadiazoles **10**-**13** obtained from nitrile imine **1a** and corresponding thioketones **4**.

In contrast to 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4c**) the reaction with dithione **4d** performed in the presence of 2.2 equivalents of hydrazonoyl bromide **8a** and excess Et_3N led to a mixture of two products in a ratio of *ca*. 2:3 (**14**:**15**) (Scheme 3). The reaction mixture was separated chromatographically, and two fractions were obtained in fair yields of 32 and 41%, respectively. The ^{1}H NMR spectrum of the less polar fraction revealed the presence of four signals (singlets) located at 1.32, 1.50, 1.68 and 1.74 ppm attributed to four non-equivalent Me groups. In the ^{13}C NMR spectrum, along with characteristic signal of the =*C*-CF_3 found at 131.6 (q, $^2J_{C\text{-}F}$ = 40.8 Hz) ppm, two another signals of the C_{sp2} atoms were found at 120.6 and 129.7 ppm, respectively, indicating the presence of the C=CMe_2 unit. The low-field shift of the latter C_{sp2} suggested that it belongs to the thietanethione skeleton. It is known that dithione **4d** undergoes ring rearrangement induced by a strong base such us sodium methanolate or fluoride anion [24], and isomerizes via intermediates **A** and **B** yielding dithiolactone **16**. Apparently, also in the presence of Et_3N, in the THF solution, dithione **4d** undergoes a competitive isomerisation to **16**, which is subsequently trapped with **1a** yielding the (3+2)-cycloadduct **15** as the major product.



Scheme 3. Two competitive (3+2)-cycloaddition reactions observed in the case of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**4d**).

Remarkably, the starting dithione **4d** undergoes (3+2)-cycloaddition with **1a** onto both C=S bonds to afford the *cis*-configured bis-cycloadduct **14** as the single stereoisomer. The structure of the isolated product **14** was unambigously confirmed by X-ray diffraction analysis (Figure 4). It is worth mentioning that in contrast to the presented reaction with nitrile imine **1a**, the (3+2)-cycloaddition of **4d** with diazomethane led to a 1:3 mixture of *cis*- and *trans*-configured bis-cycloadducts, respectively [25]. The observed result points out that the

subsequent formation of the second 1,3,4-thiadiazole ring in **14** occurs with preferred *syn* orientation of both heterocyclic rings.

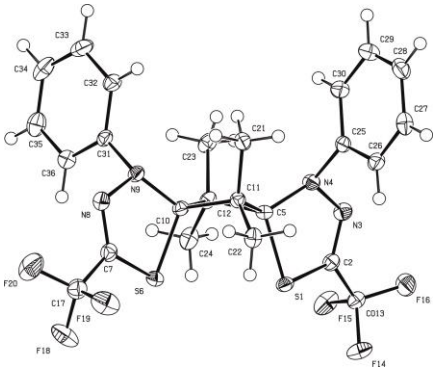
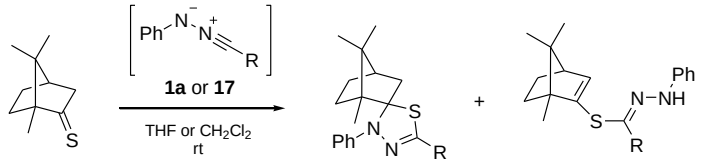


Figure 4. A view of the molecular structure of **14**. Displacement ellipsoids are drawn at the 50% probability level.

Reaction of *C*,*N*-diaryl nitrile imines with (–)-thiocamphor ((1*R*)-**4f**) have recently been studied, and the diastereoselective formation of (3+2)-cycloadducts of type **18** as single products was reported [16b,c]. The structure of two 1,3,4-thiadiazole derivatives of that type was unambigously confirmed by the X-ray diffraction analysis [16c]. In our case, however, fluorinated nitrile imine **1a** was reacted with (1*R*)-**4f** yielding unexpectedly a mixture of two products which were separated by flash chromatography. Whereas the more polar fraction forming a minor product was identified as the expected 1,3,4-thiadiazole **18a** (21%), the structure of the less polar compound (major fraction) was elucidated as carbothiohydrazonate **19a** (68%). In the ^{1}H NMR of **19a** diagnostic signal located at 5.62 ppm (d, J = 3.4 Hz) was attributed to the ethylenic proton =CH. In the same spectrum, a broad, H/D-exchangeable singlet of the PhNH group was also observed. In the ^{13}C NMR spectrum of this compound two characteristic signals attributed to C_{sp2} atoms, found at 131.8 and 134.0 ppm, clearly confirmed the presence of the enthiol-ether (C=C-S) unit (for comparison with a similar structure of the Me-sulfide, see Ref. [26]).

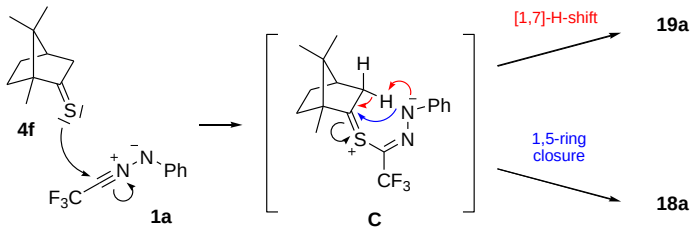


18a, R = CF_3 (21%) **19a**, R = CF_3 (68%)
18b, R = Ph (61%) **19b**, R = Ph (30%)

Scheme 4. Comparison of the reaction outcomes of (–)-thiocamphor ((1*R*)-**1f**) with fluorinated and non-fluorinated nitrile imines **1a** and **17**, respectively.

The formation of the products of type **19** has not been reported for the reaction of thiocamphor and *C*,*N*-diaryl nitrile imines [16]. Therefore, the reaction of the well known nitrile imine **17** with **4f** was carefully examined, and the ^{1}H NMR analysis of crude reaction mixture confirmed the presence of the already reported (3+2)-cycloadduct **18b** along with compound **19b** (Scheme 4). However, in that case the ratio of both intermolecular products was 64:36 in favor of the 1,3,4-thiadiazole derivative **18b**, isolated in high 61% yield.

Based on this result we conclude, that the fluorinated nitrile imine **1a** prefers the formation of acyclic derivative **19a**, which formally corresponds to the insertion product of thioenolate form of **4f** into **1a**. The influence of the solvent and the base used was briefly examined, using variable amounts of Et_3N (from 1 to 5 equiv.) and changing the solvent to dichloromethane. Irrespective of the applied reaction conditions, in all cases the formation of the same ~3:7 mixture of **18a**:**19a** was observed. The enhanced amount of the insertion product **19a** formed in the reaction with fluorinated nitrile imine **1a** deserves a comment. It seems likely, that the presence of electron-withdrawing CF_3 group enhances electrophilic character of the 1,3-dipole **1a**, and favors its interaction with the nucleophilic sulfur atom. This interaction results in increasing CH-acidity of the neighboring CH_2 group, and enables departure of proton. The formation of the **18**/**19** mixture suggests that the reaction of thiocamphor **4f** with nitrile imines **1** may occur via an intermediate zwitterion **C** in which the 1,5-ring closure competes with the proton transfer (Scheme 5). Attempted trapping of the postulated intermediate **C** with MeOH added to the reaction mixture was unsuccessful. On the other hand, an insertion reaction of the enethiol form of thiocamphor, presumably existing in a very low concentration with its thione form in THF solution, can't be excluded. However, in the ^1H NMR spectrum (600 MHz, $CDCl_3$) of a mixture of thiocamphor and excess Et_3N, the respective enethiol form of **4f** could not be detected.



Scheme 5. Postulated step-wise reaction of thiocamphor (1*R*)-**4f** with fluorinated nitrile imine **1a** leading to a formal (3+2)-cycloadduct **18a** and the isomeric insertion product **19a**.

3. Conclusions

The presented study showed, that cycloaliphatic thioketones **4** in analogy to hetaryl representatives are suitable trapping agents for the *in situ* generated *C*-trifluoromethylated nitrile imines **1** yielding, in most cases, *spiro*-2,3-dihydro-1,3,4-thiadiazoles functionalized with the CF_3 group. Depending on the substitution pattern of the starting thioketone, the reactions proceeded in a regio-, chemo- and diastereoselective manner to afford the expected (3+2)-cycloadducts in high yields. Unexpectedly, in contrast to classical *C,N*-diaryl nitrile imines, the reaction of fluorinated analogue **1a** with enolizable thiocamphor provided carbothiohydrazonate derivative **19a** as a major product formed, very likely, via competitive stepwise, zwitterionic pathway. Taking into account the importance of 1,3,4-thiadiazole derivatives [12,27], and in general, rapidly growing interest in fluorinated heterocycles [28], presented approach can be of interest in the context of practical applications in medicinal, materials, and agro-chemistry. In addition, presented systems in which an electron rich heterodipolarophile (thioketone) reacts with an electron deficient 1,3-dipole (fluorinated nitrile imine) is of interest for the development of the discussion on the cycloaddition mechanisms, which can follow a step-wise, zwitterionic pathway [5a,29].

4. Experimental Part

4.1. General information

All solvents were purchased and used as received without further purification. THF was dried over sodium–benzophenone and freshly distilled before usage. If not stated otherwise, reactions were carried out under argon in flame-dried flasks with addition of the reactants by using syringes; subsequent manipulations were conducted in air. Products were purified by standard chromatography column on silica gel (230–400 mesh, Merck or Fluka). NMR spectra were measured on a Bruker AVIII 600 MHz (^{1}H NMR [600MHz]; ^{13}C NMR [151 MHz]) or with a Varian Gemini 2000BB 200 MHz (^{19}F NMR [188 MHz]) instruments. Chemical shifts are reported relative to solvent residual peaks (^{1}H NMR: δ = 7.26 ppm [$CDCl_3$]; ^{13}C NMR: δ = 77.0 ppm [$CDCl_3$]). For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC). IR spectra were measured with a FTIR NEXUS spectrometer (as thin film or KBr pellets). MS were performed with a Varian 500-MS LC Ion Trap (ESI) or with a Waters MaldiSYNAPT G2-S HDMS (ESI-TOF-HRMS). Elemental analyses were obtained with a Vario EL III (Elementar Analysensysteme GmbH) instrument. Melting points were determined in capillaries with a MEL-TEMP II apparatus (Aldrich), and are uncorrected. Optical rotations were measured with an Anton-Paar MCP 500 at the temperatures indicated. Single crystal X-ray data were collected with a Rigaku Oxford Diffraction XtaLAB Synergy, Pilatus 300K diffractometer (Cu Kα radiation, λ = 1.54178 Å, PhotonJet (Cu) X-ray Source with mirror); the structure solution and refinement was performed by using SHELXS-97 [30] and SHELXL-2014 [31]. CCDC-1547224 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Starting materials: Adamantanethione (**4a**) [32], 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**4c**) [3a], 2,2,4,4-tetramethylcyclobutane-l,3-dithione (**4d**) [3a], and pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-thione (*rac*-**4e**) [33], were obtained by thionation of the corresponding ketones with P_4S_{10}, in pyridine. For the synthesis of di(*tert*-butyl)thioketone (**4b**) a protocol involving reaction of di(*tert*-butyl)ketimines lithium salt with CS_2 was applied [34], while thiofenchone ((*R*)-**4g**) was prepared from the corresponding ketone in methanolic solution by passing through mixed streams of H_2S and HCl gas, in the presence of trimethyl orthoformate [35]. (1*R*)-(–)-Thiocamphor ((*R*)-**4f**) is commercially available (TCI). Trifluoroacetaldehyde arylhydrazones **7** were prepared by heating methanolic solutions of the appropriate hydrazine and excess fluoral hydrate in a closed ampoule at 75 °C overnight, in the presence of molecular sieves 4Å according to literature protocol [20b]. Hydrazonoyl bromides **8** were obtained by treatment of the corresponding arylhydrazones **7** with NBS in dry DMF as described in an earlier report [13].

4.2. General procedure for the reaction of thioketones 4a-4g with nitrile imines

To a mixture of the respective hydrazonoyl halide (1.1 equiv. for each C=S group) and thioketone **4** (1.0 mmol) in dry THF (5 mL) was added dropwise Et_3N (0.8 mL) and the resulting mixture was stirred at room temperature until the starting thioketone was fully consumed (TLC monitoring, petroleum ether/CH_2Cl_2 4:1, visualization: *p*-anisaldehyde stain; typically up to 4 hrs for nitrile imines **1**, and 16 hrs for nitrile imine **17**). The precipitate triethylamine salt was filtered off, and the solvents were removed under reduced pressure. The resulting mixture was purified by flash chromatography column (FCC) on SiO_2 (deactivated with 2% Et_3N in

petroleum ether) using petroleum ether/dichloromethane mixtures as an eluent, and the isolated products were analyzed by spectroscopic methods.

*4.2.1. Spiro[adamantane-2,2'-(3'-phenyl-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole)] (**9a**):*

Reaction time 2h; FCC (SiO_2, petroleum ether/CH_2Cl_2 4:1), pale yellow solid, 218 mg (62%); mp 76–77 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.52, 1.71, 1.83, 2.07–2.09, 2.36 (5 m, 2H, 2H, 4H, 4H, 2H, Ad), 7.33-7.39, 7.51–7.53 (2 m, 3H, 2H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.4, 32.9, 37.5, 37.8, 38.1 (Ad), 97.5 (s, spiro-C), 119.8 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 128.7, 129.0, 130.2, 142.8 (3 d, s, Ph), 144.1 (q, $^2J_{C\text{-}F}$ = 37.9 Hz, C-5) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.1 (s, CF_3) ppm; IR (KBr): ν 2937–2854, 1596, 1331, 1194, 1149, 1137, 1024, 1008, 964, 774, 701 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{20}F_3N_2S$: 353.1299; found: 353.1292.

*4.2.2. Spiro{adamantane-2,2'-[3'-(p-tolyl)-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole]} (**9b**):*

Reaction time 2h; FCC (SiO_2, petroleum ether/CH_2Cl_2 85:15), colorless solid, 293 mg (80%); mp 70–71 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.52, 1.71, 1.83, 2.08–2.10, 2.34 (5 m, 2H, 2H, 4H, 4H, 2H, Ad), 2.36 (s, 3H, Me), 7.16-7.17, 7.39–7.41 (2 m, 2H, 2H, Tol) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.2 (q, Me), 26.4, 33.0, 37.7, 37.8, 38.1 (Ad), 97.6 (s, spiro-C), 119.8 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 129.6, 129.9, 138.6, 140.1 (2 d, 2 s, Tol), 144.0 (q, $^2J_{C\text{-}F}$ = 37.7 Hz, C-5) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.1 (s, CF_3) ppm; IR (KBr): ν 2961–2906, 1507, 1452, 1334, 1216, 1132, 1024, 1010, 961, 825 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{22}F_3N_2S$: 367.1456; found: 367.1449.

*4.2.3. Spiro{adamantane-2,2'-[3'-(4''-methoxyphenyl)-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole]} (**9c**)*

Reaction time 4h; FCC (SiO_2, petroleum ether/CH_2Cl_2 7:3), pale yellow oil, 244 mg (64%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.44, 1.71, 1.83, 2.08-2.10, 2.31 (5 m, 2H, 2H, 4H, 4H, 2H, Ad), 3.81 (s, 3H, OMe), 6.86–6.88, 7.42–7.45 (2 m, 2H, 2H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.4, 33.0, 37.7, 37.9, 38.1 (Ad), 55.4 (q, OMe), 97.6 (s, spiro-C), 114.0 (d, C_6H_4), 119.8 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 131.2 (d, C_6H_4), 135.2 (s, C_6H_4), 144.0 (q, $^2J_{C\text{-}F}$ = 37.8 Hz, C-5), 159.5 (s, C_6H_4) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.1 (s, CF_3) ppm; IR (film): ν 3004–2858, 1605, 1508, 1454, 1333, 1248, 1186, 1144, 1024, 837 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{21}F_3N_2OSNa$: 405.1224; found: 405.1219.

*4.2.4. Spiro{adamantane-2,2'-[3'-(4''-bromophenyl)-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole]} (**9d**)*

Reaction time 2h; FCC (SiO_2, petroleum ether/CH_2Cl_2 7:3), pale yellow solid, 289 mg (67%); mp 93–95 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.53, 1.72, 1.79-1.88, 2.04-2.07, 2.32 (5 m, 2 H, 2 H, 4 H, 4 H, 2 H, Ad), 7.39-7.41, 7.49-7.51 (2 m, 2 H, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 26.2, 26.5, 33.0, 37.5, 37.7, 38.0 (Ad), 97.4 (s, spiro-C), 119.6 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CF_3), 122.5, 131.7, 132.2, 141.8 (s, 2 d, s, C_6H_4), 145.1 (q, $^2J_{C\text{-}F}$ = 38.1 Hz, C-5) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –65.1 (s, CF_3) ppm; IR (KBr): 3054-2858, 1557, 1483, 1331, 1189, 1146, 1027, 965, 838 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{19}BrF_3N_2S$: 431.0404; found: 431.0387.

*4.2.5. Spiro{adamantane-2,2'-[3'-(4''-trifluoromethylphenyl)-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole]} (**9e**)*

Reaction time 6h; FCC (SiO_2, petroleum ether/ CH_2Cl_2 7:3), pale yellow oil, 239 mg (57%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.54, 1.72, 1.79, 1.90, 2.04–2.07, 2.37 (6 m, 2H, 2H, 1H, 3H, 4H, 2H, Ad), 7.65 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.1, 26.6, 33.0, 37.5, 37.7, 38.0 (Ad), 97.5 (s, spiro-C), 119.6 (q, $^1J_{C\text{-}F}$ = 273.2 Hz, CF_3), 123.8 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, CF_3), 126.2 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, C_6H_4), 130.4 (d, C_6H_4), 130.7 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, *i*-C, C_6H_4), 145.3 (q, $^2J_{C\text{-}F}$ = 38.2 Hz, C-5), 146.2 (s, *i*-C, C_6H_4) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.2, –63.2 (2 s, 2 CF_3) ppm; IR (film): ν 2916–2860, 1614, 1562, 1454, 1409, 1321, 1277–1020, 848 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{19}F_6N_2S$: 421.1173; found: 421.1161.

*4.2.6. Spiro{adamantane-2,2'-[3'-(4''-cyanophenyl)-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole]} (**9f**)*

Reaction time 6h; FCC (SiO_2, petroleum ether/CH_2Cl_2 1:1), colorless solid, 211 mg (56%); mp 107–108 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.53–1.59, 1.72, 1.78, 1.90–2.06, 2.37 (5 m, 2H, 2H, 1H, 7H, 2H, Ad), 7.62–7.63, 7.67–7.69 (2 m, 2H, 2H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.0, 26.5, 33.0, 37.47, 37.54, 37.8 (Ad), 97.6 (s, spiro-C), 112.2 (s, CN), 118.0 (s, *i*-C, C_6H_4), 119.5 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CF_3), 130.7, 133.0 (2 d, C_6H_4), 145.4 (q, $^2J_{C\text{-}F}$ = 38.4 Hz, C-5), 147.2 (s, *i*-C, C_6H_4) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.2 (s, CF_3) ppm; IR (KBr): ν 2934–2917, 2230, 1603, 1500, 1337, 1200, 1133, 1022, 847 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{19}F_3N_3S$: 378.1252; found: 378.1237.

*4.2.7. 2,2-Bis-(tert-butyl)-3-phenyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**10**)*

Reaction time 1h; FCC (SiO_2, petroleum ether/CH_2Cl_2 4:1), light orange oil, 237 mg (69 %). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.31 (s, 18H, 2-^{t}Bu), 7.18–7.20, 7.31–7.33, 7.56–7.57 (3 m, 1H, 2H, 2H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 30.2, 46.2 (q, s, 2-^{t}Bu), 113.1 (s, spiro-C), 120.2 (q, $^1J_{C\text{-}F}$ = 270.1 Hz, CF_3) 125.9, 126.1 (2 d, 3$CH_{arom.}$), 126.8 (q, $^2J_{C\text{-}F}$ = 39.6 Hz, C-5), 128.5 (d, 2$CH_{arom.}$), 145.9 (s, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –63.5 (s, CF_3) ppm; IR (film): ν 3431–2932, 1584, 1494, 1362, 1244, 1180, 1125, 1106, 1026, 714 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{24}F_3N_2S$: 345.1612; found: 345.1605.

*4.2.8. 5-Phenyl-1,1,3,3-tetramethyl-7-trifluoromethyl-8-thia-5,6-diazaspiro[3,4]oct-6-en-2-one (**11**):*

Reaction time 2h; FCC (SiO_2, petroleum ether/CH_2Cl_2 4:1), light orange oil, 164 mg (48%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.23, 1.39 (2 s_{br}, 6H each, 4Me), 7.25–7.28, 7.33–7.36, 7.38–7.40 (3 m, 1H, 2H, 2H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 22.2, 25.0 (2 q, 4Me), 67.9 (s, 2 *i*-C, 2*C*Me_2), 95.2 (s, spiro-C), 119.5 (q, $^1J_{C\text{-}F}$ = 272.4 Hz, CF_3), 125.5, 127.2, 129.3 (3 d, Ph), 140.1 (q, $^2J_{C\text{-}F}$ = 39.3 Hz, C-5), 143.9 (s, $C_{arom.}$), 217.3 (C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –66.8 (s, CF_3) ppm; IR (film): ν 3088–2872, 1788 (C=O), 1491, 1195, 1144, 1026 cm^{-1}; ESI-MS (*m*/*z*): 343.1 (100, $[M+H]^+$), 327.1 (54).

*4.2.9. (±)-Spiro{pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,8}]undecane-8,2'-(3'-phenyl-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole} (rac-**12**):*

Reaction time 3h; FCC (SiO_2, petroleum ether/CH_2Cl_2 4:1), colorless solid, 148 mg (66%); mp 96–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.17 (d_{br}, $J \approx 10.5$ Hz, 1H), 1.19–1.24 (m, 1H), 1.58 (d_{br}, $J \approx 10.5$ Hz, 1H), 1.96 (s_{br}, 1 H), 2.24–2.27 (m, 2H), 2.39–2.41 (m, 2H), 2.51–2.54 (m, 1H), 2.69–2.70 (m, 1H), 2.73–2.80 (m, 1H), 2.89–2.93 (m, 1H), 7.22–7.32 (m, 5H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 28.5, 33.6, 35.6, 41.0, 42.3, 42.8, 44.5, 45.9, 46.9, 52.8 (2 t, 8 d, cage), 94.7 (s, spiro-C), 119.9 (q, $^1J_{C\text{-}F}$ = 271.7 Hz, CF_3), 126.8, 127.0, 128.7 (3 d, Ph), 143.4 (s, *i*-C) ppm, the signal of the *C*-CF_3 was not found; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –64.5 (s, CF_3) ppm; IR (KBr): ν 3023–2870, 1596, 1491, 1363, 1267, 1183, 1140, 1022, 960, 774, 711, 695 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{18}F_3N_2S$: 363.1143; found: 363.1128.

4.2.10. (1R,2R,4S)-Spiro{1,3,3-trimethylbicyclo[2.2.1]heptane-2,2'-(3'-phenyl-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole)} ***(13)***

Reaction time 5h; FCC (SiO_2, petroleum ether/CH_2Cl_2 9:1), colorless oil, 198 mg (56%). $[\alpha]_D^{20}$ +195.6 (*c* 0.31, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.95 (m, 3H, Me), 1.23–1.25 (m, 4H), 1.36-1.42 (m, 4H), 1.53–1.64 (m, 3H), 1.75 (s, 1H), 2.42 (s_{br}, 1H), 7.18, 7.28–7.31, 7.47–7.49 (3 m, 1H, 2H, 2H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 19.3 (q, Me), 23.8 (t, $2CH_2$), 28.2 (q, Me), 29.9 (q, Me), 40.4 (t, CH_2), 49.0 (d, CH), 53.6 (s, 2 *i*-C), 110.4 (s, spiro-C), 120.1 (q, $^1J_{C\text{-}F}$ = 270.8 Hz, CF_3), 125.4, 126.0, 128.2 (2 d_{br}, d, Ph), 145.9 (s, *i*-C, Ph) ppm, the signal of the =*C*-CF_3 was not found due to low intensity; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –64.4 (s, CF_3) ppm; IR (film): ν 2966, 2875, 1593, 1491, 1462, 1360, 1240, 1190, 1132, 1099, 1026, 985, 748, 696 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{21}F_3N_2SNa$: 377.1275; found: 377.1262.

4.3. Reaction of dithione ***4d*** *with nitrile imine* ***1a***

Following the general procedure, the reaction of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**4d**, 1.0 mmol) with hydrazonoyl bromide **8a** (2.2 equiv.) provided after 3h at room temperature a mixture containing **14** and **15** in a 2:3 ratio. Purification by flash column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) provided pure **15** (148 mg, 41%, first eluted) and **14** (174 mg, 32%, second eluted).

4.3.1. cis-6,6,12,12-Tetramethyl-1,8-diphenyl-3,10-bis(trifluoromethyl)-4,11-dithia-1,2,8,9-tetraazadispio[4.1.4.1]dodeca-2,9-diene ***(14)****:*

Colourless solid, mp 177–178 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.09, 1.28 (2 s_{br}, 6H each, 4Me), 7.40 (s_{br}, 10H, 2Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 23.6, 27.1 (2 q, 2Me each), 58.4 (s, 2 *i*-C, 2 *C*-Me_2), 96.5 (s, 2 spiro-C), 119.5 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, 2 CF_3), 129.2, 129.4, 129.5 (3 d, 2Ph), 143.3 (q, $^2J_{C\text{-}F}$ = 38.4 Hz, 2 =*C*–CF_3), 143.5 (s, 2 *i*-C, 2Ph) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.3 (s, $2CF_3$) ppm; IR (KBr): ν 3097–2959, 1557, 1490, 1385, 1336, 1198, 1044, 894, 770, 696 cm^{-1}; HRMS (ESI-TOF): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{23}F_6N_4S_2$: 545.1268; found: 545.1262; elemental analysis calcd (%) for $C_{24}H_{22}F_6N_4S_2$ (544.1): C 52.93, H 4.07, N 10.29, S 11.78; found: C 52.97, H 4.27, N 10.41, S 11.83.

Suitable crystals of **14** for an X-ray crystal structure determination were obtained from petroleum ether/CH_2Cl_2 mixture by slow evaporation of the solvents.

4.3.2. 3,3-Dimethyl-2-isopropylidene-5-phenyl-7-trifluoromethyl-1,8-dithia-5,6-diazaspiro[3.4]oct-6-ene ***(15)****:*

Light orange oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.32 (s_{br}, 3H, Me), 1.50 (s, 3H, Me), 1.68 (s_{br}, 3H, Me), 1.74 (s, 3H, Me), 7.15–7.18, 7.31–7.34, 7.68–7.70 (3 m, 1H, 2H, 2H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 19.7, 21.7, 23.0, 29.8 (4 q, 4Me), 67.1 (s, *i*-C, *C*Me$_2$), 101.4 (s, spiro-C), 119.6 (q, $^1J_{C\text{-}F}$ = 271.1 Hz, CF_3), 120.6 (s, =*C*Me$_2$), 122.6, 124.9, 128.4 (3 d, Ph), 129.7 (s, *C*=CMe$_2$), 131.6 (q, $^2J_{C\text{-}F}$ = 40.8 Hz, C-5), 142.8 (s, *i*-C, Ph) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –63.6 (s, CF_3) ppm; IR (film): ν 2970, 2934, 2859, 1493, 1363, 1257, 1194, 1138, 1028 cm^{-1}; HRMS (ESI-TOF): *m*/*z* [M+H]$^+$ calcd for $C_{16}H_{18}F_3N_2S_2$: 359.0863; found: 359.0861.

*4.4. Reaction of thiocamphor ((1R)-**4f**) with nitrile imine **1a***

According to general protocol, the reaction of thioketone (1*R*)-**4f** (1.0 mmol) with hydrazonoyl bromide **8a** (1.1 equiv.) yielded after 2h at room temperature a mixture of (3+2)-cycloadduct **18a** and product **19a** in a 29:71 ratio, respectively. Chromatography purification (SiO_2, petroleum ether/CH_2Cl_2 4:1) provided pure **19a** (241 mg, 68%, first eluted) and **18a** (74 mg, 21%, second eluted).

*4.4.1. (1R,2R,4R)-Spiro[camphane-2,2'-(3'-phenyl-5'-trifluoromethyl-2',3'-dihydro-1',3',4'-thiadiazole)] (**18a**)*

Light orange oil; $[\alpha]_D^{20}$ +80.2 (*c* 0.06, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.93, 1.03 (2 s, 3H, 6H, 3Me), 1.07–1.13 (m, 1H), 1.51–1.56 (m, 1H), 1.70–1.75 (m, 2H), 1.85–1.87 (m, 1H), 2.26–2.28 (m, 1H), 2.49–2.58 (m, 1H), 7.31–7.40 (m, 5H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 11.5, 20.7, 20.8 (3 q, 3Me), 26.4, 28.2, 40.1 (3 t), 45.2 (d), 49.2, 58.4 (2 s), 96.7 (s, spiro-C) 119.7 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, CF_3), 128.1, 128.3, 129.1 (3 d, Ph), 143.1 (s, Ph) ppm, the signal of the =*C*-CF_3 was not found due to low intensity; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –65.2 (s, CF_3) ppm; IR (film): ν 3092–2889, 1570, 1491, 1392, 1190, 1140, 1022 cm^{-1}; HRMS (ESI-TOF): *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{22}F_3N_2S$: 355.1456; found: 355.1447.

*4.4.2. (1'R,4'R)-1',7',7'-Trimethylbicyclo[2.2.1]hept-2'-en-2'-yl 2,2,2-trifluoro-N'-phenylethanehydrazonothioate (**19a**):*

Light orange oil; $[\alpha]_D^{20}$ +29.7 (*c* 0.31, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.81, 0.86 (2 s, 3H each, 2Me), 1.01 (ddd, *J* = 3.6, 9.2, 12.3 Hz, 1H), 1.11 (s, 3H, Me), 1.19 (ddd, *J* = 3.7, 9.2, 12.4 Hz, 1H), 1.65 (ddd, *J* = 3.6, 8.6, 12.4 Hz, 1H), 1.90 (ddt, *J* ≈ 3.7, 8.6, 12.3 Hz, 1H), 2.37 (t_{br}, *J* ≈ 3.6 Hz, 1H), 5.62 (d, *J* = 3.4 Hz, 1H), 7.01–7.03, 7.12–7.13, 7.30–7.33 (3 m, 1H, 2H, 2H, Ph) 8.57 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 11.2, 19.4, 19.6 (3 q, 3Me), 26.0, 31.7 (2 t), 52.4 (d), 56.8, 56.9 (2 s, 2 *i*-C), 114.1 (d, Ph), 118.6 (q, $^2J_{C\text{-}F}$ = 38.3 Hz, C-5), 121.1 (q, $^1J_{C\text{-}F}$ = 271.9 Hz, CF_3), 122.8, 129.5 (2 d, Ph), 131.8 (d, =CH), 134.0 (s, =C-S), 141.9 (s, Ph) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –67.0 (s, CF_3) ppm; IR (film): ν 3089–2873, 1604, 1544, 1506, 1333, 1298, 1244, 1163, 1126, 987, 752 cm^{-1}; HRMS (ESI-TOF): *m*/*z* [M+H]$^+$ calcd for $C_{18}H_{22}F_3N_2S$: 355.1456; found: 355.1443.

*4.5. Reaction of thiocamphor ((1R)-**4f**) with nitrile imine **17***

Following the general method, the reaction of thioketone (1*R*)-**4f** (1.0 mmol) with *N*-phenylbenzohydrazonoyl chloride [36] (1.1 equiv.) used as precursor of nitrile imine **17** afforded after 16h at room temperature a mixture of cycloadduct **18b** and insertion product **19b** in ~64:36 ratio, respectively.

Purification of crude reaction mixture by flash column chromatography (SiO_2, petroleum ether/CH_2Cl_2 4:1) yielded analytically pure **19b** (109 mg, 30%, first eluted) and **18b** (221 mg, 61%, second eluted).

4.5.1. (1R,2R,4R)-Spiro[camphane-2,2'-(3',5'-diphenyl-2',3'-dihydro-1',3',4'-thiadiazole)] [16c] ***(18b)***

Colorless oil; $[\alpha]_D^{20}$ +674.8 (*c* 0.06, $CHCl_3$), +687.6 (*c* 0.44, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.96, 1.06, 1.13 (3 s, 3H each, 3Me), 1.32–1.24 (m, 1H), 1.57 (ddd, *J* = 4.4, 12.0, 13.2 Hz, 1H), 1.68 (t_{br}, *J* ≈ 4.5 Hz, 1H), 1.74–1.79 (m, 1H), 1.78 (d, *J* = 15.4 Hz, 1H), 2.22 (ddd, *J* = 3.2, 4.5, 15.4 Hz, 1H), 2.82 (ddd, *J* = 4.4, 9.6, 13.8 Hz, 1H), 7.24–7.27, 7.31–7.37, 7.40–7.42, 7.82–7.84 (4 m, 1H, 4H, 3H, 2H, 2 Ph) ppm; ESI-MS (*m*/*z*): 363.1 (100, $[M+H]^+$).

*4.5.2. (1'R,4'R)-1',7',7'-Trimethylbicyclo[2.2.1]hept-2'-en-2'-yl N'-phenylbenzohydrazonothioate (**19b**)*

Colorless oil; $[\alpha]_D^{20}$ +76.7 (*c* 0.37, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82, 0.84 (2 s, 3H each, 2Me), 0.98 (ddd, *J* = 3.6, 9.2, 12.3 Hz, 1H), 1.17 (s, 3H, Me), 1.24 (ddd, *J* = 3.7, 9.2, 12.4 Hz, 1H), 1.67 (ddd, *J* = 3.6, 8.7, 12.4 Hz, 1H), 1.90 (ddt, *J* ≈ 3.7, 8.7, 12.3 Hz, 1H), 2.35 (t_{br}, *J* ≈ 3.5 Hz, 1H), 5.69 (d, *J* = 3.4 Hz, 1H), 6.98–7.02, 7.24–7.27, 7.36–7.40, 7.43–7.46, 8.01–8.03 (5 m, 1H, 2H, 3H, 2H, 2H, 2Ph) 8.74 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 11.4, 19.3, 19.7 (3 q, 3Me), 25.9, 31.7 (2 t), 52.3 (d), 56.5, 57.1 (2 s, 2 *i*-C), 113.3, 120.8, 126.9, 128.1, 128.2, 129.3 (6 d, 2Ph), 131.3 (s, *i*-C), 132.4 (d, =CH), 136.6, 137.8, 143.8 (3 s, 3 *i*-C) ppm; ESI-MS (*m*/*z*): 363.2 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{23}H_{26}N_2S$ (362.2): C 76.20, H 7.23, N 7.73, S 8.84; found: C 76.24, H 7.20, N 7.68, S 8.78.

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