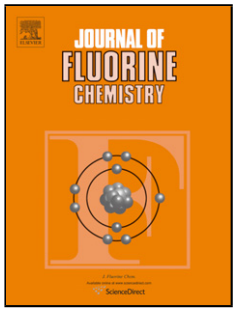

Title: Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective [3 + 2]-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones

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Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective (3+2)-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones

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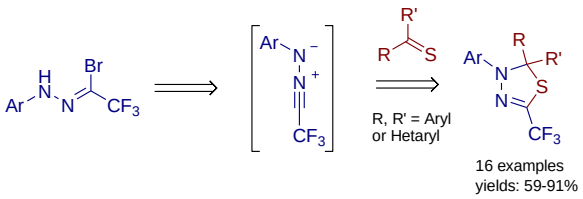
Graphical abstract:



Highlights

- First examples of 1,3,4-thiadiazole derivatives functionalized with the CF_3 group at the C(5) atom were prepared by (3+2)-cycloadditions of the *in situ* generated fluorinated nitrile imines onto selected thioketones. The reactions proceeded in high yields, in a fully regioselective manner, and with a remarkable tolerance to functional group present in the starting nitrile imine.

Abstract

A series of hydrazonoyl bromides prepared from readily available *N*-arylhydrazones of fluoral was used for the *in situ* generation of fluorinated nitrile imines. These 1,3-dipoles were efficiently trapped with aryl and hetaryl thioketones yielding fluoromethylated 2,3-dihydro-1,3,4-thiadiazoles. The (3+2)-cycloadditions occurred with complete regioselectivity yielding the respective products in high yields. Reactions proceeded with remarkable tolerance to functional groups, and the corresponding N^3-aryl derivatives bearing halogens, methoxy, benzoyloxy, methoxycarbonyl, and nitrile substituents at the *para* position of the phenyl ring were prepared as crystalline products. Spectroscopic data (^{13}C and ^{19}F NMR) of the obtained (3+2)-cycloadducts evidenced remarkable relationship between the shielding effect of the CF_3 group and the electronic properties of the *para*-substituents.

Keywords: nitrile imines, thioketones, (3+2)-cycloaddition, fluoroalkylated *N,S*-heterocycles, 1,3,4-thiadiazoles.

1. Introduction

The (3+2)-cycloaddition reactions (*Huisgen reactions*) are considered as the most powerful method, which can be applied for the synthesis of manifold of five-membered heterocycles [1]. In this context, nitrile imines are classified as an important group of propargyl-type of 1,3-dipoles widely applied for the preparation of various *N*-containing systems [2]. In synthetic procedures, they are typically generated *in situ* by treatment of hydrazonoyl halides with a base, and subsequently are trapped with an appropriate C=X (X = C, N, O, S, Se) or C≡X (X = C, N) dipolarophile to give heterocyclic products, such as pyrazoles, pyrazolines, 1,3,4-oxadiazoles, 1,2,3- or 1,2,4-triazoles, etc. [3]. Surprisingly, applications of nitrile imines for the preparation of CF_3-functionalized heterocycles *via* the (3+2)-cycloaddition approach has been only little explored. In a series of pioneer publications by Tanaka et al. the chemistry of prototypical trifluoroacetonitrile phenylimine has been studied in reactions with diverse ethylenes and acetylenes [4], as well as with imines [5], and carbonyl compounds [6]. However, the general protocol developed by this group have been applied for the synthesis of compounds of biological importance [7], and other materials with special properties [8], only to a limited extent.

On the other hand, thioketones were demonstrated to react as 'superdipolarophilic' agents in the (3+2)-cycloadditions with such 1,3-dipoles as diazoalkanes, thiocarbonyl *S*-methanides, and nitrones [9]. Some of cycloaliphatic [10] and aromatic [11] thioketones, *e.g.* thiobenzophenone (**1a**) and its derivatives, have also been applied as powerful dipolarophiles in the reactions with some *C*-aryl-*N*-aryl nitrile imines yielding 2,3-dihydro-1,3,4-thiadiazoles in a regioselective manner. Taking into account well documented biological significance of diverse 1,3,4-thiadiazoles [12], and also importance of fluorine for tuning of biological activity of organic molecules [13], in continuation of our ongoing studies aimed at the exploration of thioketones in organic synthesis [14], we paid some attention to hitherto unreported 1,3,4-thiadiazolines functionalized with the CF_3 group located at the C(5) atom. Thus, two diaryl thioketones, namely thiobenzophenone (**1a**) and 9*H*-fluorene-9-thione (**1b**), three symmetrical dihetaryl analogues **1c-e**, and also non-symmetrical phenyl/hetaryl representatives **1f-h**, depicted in Figure 1, were selected for the reaction with the title *C*-trifluoromethylated nitrile imines **2**, readily available by dehydrohalogenation of bromides **3** (Scheme 1) [4a]. In addition, thioketone **1i** functionalized with ferrocenyl moiety, was involved in the study.

2. Results and Discussion

The synthesis of bromides **3a-h**, used as precursors of nitrile imines **2** was performed according to general protocol elaborated for the preparation of trifluoroacetaldehyde arylhydrazones of type **4** and related compounds [15]. Subsequent radical bromination of the hydrazone moiety led to products **3** [16]. As shown in Scheme 2, *p*-substituted phenylhydrazines **5** were efficiently converted into the respective hydrazones **4** by the reaction with commercial fluoral hydrate. The reaction was carried out in a closed ampoule at 75 °C overnight, in the presence of molecular sieves 4Å, following the reported procedure [15b]. The desired products were isolated and identified as pure samples after single flash chromatography. Freshly prepared fluoral hydrazones **4** were subsequently brominated with *N*-bromosuccinimide, in DMF solution, and the desired bromides **3** were isolated in fair to good overall yields (45-80%). Due to the limited stability of hydrazone **4g**, both in solid state and in

solution, the lowest yield of 28% (after 2 steps) was obtained for the derivative **3g** bearing the *p*-methoxycarbonyl group.

The test experiment was carried out using bromide **3b** and thiobenzophenone (**1a**) selected as a model diaryl thioketone (Scheme 3). Typically, to a portion of **1a** (in THF) a solution of **3b** in dry THF/Et_3N mixture was added; after ca. 1h the characteristic blue color of the starting thioketone ceased indicating completion of the reaction. After analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, which showed only one set of signals attributed to a sole (3+2)-cycloaddition product, the subsequent flash column chromatography (FCC) afforded the pure product as a yellow solid. The signal (singlet) was found at 2.17 ppm, side by side with two broadened doublets, typical for the *p*-tolyl moiety, at 6.79, and 6.82 ($J \approx 8.8$ Hz each) ppm, respectively. Two additional sets of signals, found in aromatic region, clearly indicated the presence of two equivalent phenyl groups. The presence of two quartets registered in the ^{13}C NMR spectrum at 119.9 ($^1J_{C\text{-}F}$ = 270.8 Hz), and 130.3 ppm ($^2J_{C\text{-}F}$ = 40.5 Hz), respectively, supplemented by ^{19}F NMR data, confirmed the presence of the CF_3CH= unit. In addition, another diagnostic signal in the ^{13}C NMR spectrum , attributed to a quaternary carbon atom, was found at 94.7 ppm. The ESI-MS supplemented by the combustion analysis, confirmed the molecular formula as $C_{22}H_{17}F_3N_2S$. Based on these data, the structure of the isolated product was elucidated as the 5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole derivative **6a** (Scheme 3, Figure 2). Next, the reaction of thioketone **1b** with bromide **3b** was carried out in analogous manner, and the desired (3+2)-cycloadduct, i.e. spiro-derivative **6b** was formed as a sole product, isolated in high yield of 78% as a crystalline material.

In the next step of the study hetaryl thioketones **1c-h** were reacted with nitrile imine **2b** generated *in situ* from **3b**. Again, the expected (3+2)-cycloadducts **6c-h** were formed in fully regioselective fashion (Figure 2), and isolated in high yields (72-91%).

In addition, the structure of compound **6g** derived from unsymmetrical phenyl/thien-2-yl thioketone (**1g**) was unambigously established by single-crystal X-ray analysis (Figure 3).

Compound **6g** crystallizes as a racemate in the centrosymmetric orthorhombic space group Pbca. In accordance with the spectroscopic data, bonds in the heterocyclic ring were formed regioselectively between the thiocarbonyl C-atom and the N-atom as well as the S- and the C-atom of the nitrile imine. The molecular structure is depicted in Figure 3. The 2,3-dihydro-1,3,4-thiadiazoles ring exhibits large differences in the C-S and C-N bond distances, respectively.

Finally, ferrocenyl/methyl thioketone (**1i**) was reacted with **2b** to afford the expected product **6i** in a moderate yield (59%). However, in that case small amount of non-identified side product was formed and the attempted preparation of the analytically pure sample was unsuccessful.

The influence of the *para*-substituent in the aryl ring, present in the nitrile imine molecule **2**, on reactivity was also tested. For that reason, a series of *N*-aryl nitrile imine precursors **3a**,**c-h**, bearing either electron-donating or electron-withdrawing groups X at the para position, were used in reactions with the model di(thien-2-yl) thioketone (**1d**) (Scheme 4). In all cases the expected 2,3-dihydro-1,3,4-thiadiazoles **6j-p** were isolated as crystalline materials in high yield, irrespectively of the type of substituent X (Table 1). Thus, not only halogens

(F, Cl) but also benzoyloxy, methoxycarbonyl, and nitrile functional groups are well tolerated and do not influence the course of the (3+2)-cycloaddition reactions.

The mechanism of the (3+2)-cycloaddition reactions leading to 1,3,4-thiadiazoles **6** deserves a brief comment. In our continuing studies on the (3+2)-cycloadditions with hetaryl thioketones, recently we reported a step-wise diradical mechanisms postulated for their reactions with diazomethanes [19] and thiocarbonyl *S*-methanides [14c,20]. A likely explanation of the observed deviation from the classical concerted pathway was the influence of the 'heavy atom effect' [21] resulting from the presence of sulfur or selenium in the heterocycle rings. The observed complete regioselectivity in the formation of cycloadducts **6** could also be explained by the 'diradical pathway' involving the initially formed, resonance stabilized, intermediate 1,5-diradicals **7** (Figure 4). These species are perfectly stabilized both at the 'benzhydrylic center' substituted with hetaryl rings as well as at the 'arylamino center'; the subsequent ring closure results in the complete regioselectivity of the studied reaction. However, for the presented reaction, a concerted (but non-synchronous) mechanism, initiated by the thiophilic approach of the positive termini of the dipole located at the *C*-CF_3, is also conceivable.

In extension of the study, the influence of substituents X on the spectroscopic properties of 1,3,4-thiadiazoles **6d**,**j-p** has been studied. Similarly to hydrazones **4** [15b], the registered ^{13}C and ^{19}F NMR spectra of **6** demonstrated, that the increase of electron-withdrawing character of substituent X led to growing shielding effect of the CF_3 group; at the same time, deshielding of the ^{13}C nuclei at C(5) was observed (Figure 5). Detailed analysis of chemical shifts evidenced that they correlate with the Hammett σ_p parameter of X [18], and the correlation fits to quadratic function. This correlation suggests, that, in the studied series of 5-trifluoromethyl-1,3,4-thiadiazoles, the C(5) atom is a part of the conjugated system in which the fluorine atoms of the CF_3 group display a shielding effect via the shift (hyperconjugation) of electron density along the σ-bonds.

3. Conclusions

The *in situ* generated *C*-trifluoromethyl, *N*-aryl nitrile imines **2**, formally derived from trifluoroacetonitrile, efficiently react with aryl, hetaryl, and ferrocenyl thioketones yielding trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles **6** with complete regioselectivity. A likely explanation of the reaction mechanism is a stepwise, diradical pathway with resonance stabilized 1,5-diradical intermediate **7**. The influence of the *p*-substituent located in the aryl ring on the chemical shift of the CF_3 group was also investigated. The presented protocol enable application of nitrile imine precursors, i.e. bromides **3** functionalized at the aryl ring with halogens, and also with Bz, COOMe, and CN functional groups as masked phenolic and carboxylic moieties, and nicely supplements other, already reported methods applied for the preparation of fluorinated 1,3,4-thiadiazole derivatives of biological importance [22].

4. Experimental Part

4.1. General supporting information

Solvents and chemicals were purchased and used as received without further purification. Aryl (**1a**,**b**) [23], hetaryl (**1d-h**) [24], and ferrocenyl (**1i**) [25] thioketones were prepared following the literature procedures based

on thionation of the corresponding ketones with Lawesson's reagent. Thioketone **1c** was prepared by the reaction of *N*-methylpyrrole with thiophosgene in the presence of triethylamine [26]. Trifluoroacetaldehyde hydrazones **4a**-**h** were prepared following the literature procedure by condensation of excess fluoral hydrate with the respective hydrazine hydrochloride in MeOH, in the presence of molecular sieves 4Å, at 75 °C (closed tube) [15b]. Products were purified by FCC or by standard chromatography column on silica gel (230–400 mesh, Merck or Fluka). Unless stated otherwise, yields refer to analytically pure samples. NMR spectra were recorded with 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 KBr pellets). MS were performed with a Varian 500-MS LC Ion Trap or with a Finnigan MAT-95 instruments. 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) or with a polarizing optical microscope (Opta-Tech) and are uncorrected. Single crystal X-ray data were collected with a Bruker D8 diffractometer (Mo Kα radiation, λ = 0.71073 Å) equipped with a Photon CMOS detector; the structure solution and refinement was performed by using SHELXS-97 [27] and SHELXL-2014 [28]. CCDC-1503892 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.

*4.2. General procedure (GP1) for the synthesis of bromides **3***

To a solution of trifluoracetaldehyde arylhydrazone **4** (2.0 mmol) in dry DMF (5 mL) was added solid NBS (392 mg, 2.2 mmol) and the resulting mixture was stirred at room temperature until the starting hydrazone was fully consumed (typically 1-3 hrs; TLC monitoring, petroleum ether/EtOAc 9:1). Then H_2O (15 mL) was added, and the mixture was extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with brine, then was dried over $MgSO_4$, and the solvents were removed in vacuo. Crude mixture was column chromatographed on silica (hexanes gradient hexanes/AcOEt 9:1) to give product **3** which was used for the next step without further purification.

*4.2.1. N-(4-methoxyphenyl)-trifluoroacetohydrazonoyl bromide (**3a**)*

Reaction time 1h; 523 mg (88%); orange oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.80 (s, 3 H, OMe), 6.88 (d_{br}, $J \approx 9.0$ Hz, 2 H), 7.09 (d_{br}, $J \approx 9.0$ Hz, 2 H), 7.94 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 55.6 (q, OMe), 102.7 (q, $^2J_{C\text{-}F}$ = 43.7 Hz), 114.9, 115.5 (2 d, 4 CH), 119.3 (q, $^1J_{C\text{-}F}$ = 270.9 Hz, CF_3), 135.3, 155.8 (2 s, 2 *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –66.6 (s, CF_3) ppm; IR (film): ν = 3316 (N-H), 3009–2841 (=C-H, C-H), 1592, 1518, 1233, 1175-1109 (CF_3) cm^{-1}; EI-HRMS: *m/z* $[M]^+$ calcd for $C_9H_8BrF_3N_2O$: 295.9772; found: 295.9782.

*4.2.2. N-(p-Tolyl)-trifluoroacetohydrazonoyl bromide (**3b**)*

Reaction time 1h; 534 mg (95%); orange solid, mp 33-34 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.31 (s, 3 H, Me), 7.04 (d_{br}, $J \approx 8.3$ Hz, 2 H), 7.13 (d_{br}, $J \approx 8.3$ Hz, 2 H), 7.98 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151

MHz): δ = 20.7 (q, Me), 103.2 (q, $^{2}J_{C\text{-}F}$ = 43.6 Hz), 114.2 (d, 2 CH), 118.4 (q, $^{1}J_{C\text{-}F}$ = 270.9 Hz, CF_3), 130.0 (d, 2 CH), 133.0, 139.2 (2 s, 2 *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –66.7 (s, CF_3) ppm; IR (KBr): ν = 3306 (N-H), 3028–2866 (=C-H, C-H), 1609, 1527, 1238, 1180-1070 (CF_3) cm^{-1}; ESI-MS (*m*/*z*): 319 (100, $[M+K]^+$); elemental analysis calcd (%) for (280.0): C 38.46, H 2.87, N 9.97; found: C 38.56, H 2.96, N 9.75.

*4.2.3. N-Phenyl-trifluoroacetohydrazonoyl bromide (**3c**)*

Reaction time 1h; 358 mg (67%); yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.03-7.07, 7.14-7.17, 7.32-7.36 (3 m, 1 H, 2 H, 2 H, Ph), 8.04 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 103.9 (q, $^{2}J_{C\text{-}F}$ = 43.8 Hz), 114.2 (d, 2 CH), 118.4 (q, $^{1}J_{C\text{-}F}$ = 271.3 Hz, CF_3), 123.0, 129.5 (2 d, 3 CH), 141.4 (s, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –66.8 (s, CF_3) ppm; IR (film): ν = 3316 (N-H), 3091–2923 (=C-H), 1591, 1511, 1239, 1195-1100 (CF_3) cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_8H_6BrF_3N_2$: 265.9667; found: 265.9668.

*4.2.4. N-(p-Fluorophenyl)-trifluoroacetohydrazonoyl bromide (**3d**)*

Reaction time 2h; 348 mg (61%); yellow solid, mp 43-44 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.01-7.05 (m, 2 H), 7.09-7.13 (m, 2 H), 7.99 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 104.0 (q, $^{2}J_{C\text{-}F}$ = 43.8 Hz), 115.5 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz, 2 CH), 116.2 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz, 2 CH), 118.3 (q, $^{1}J_{C\text{-}F}$ = 271.4 Hz, CF_3), 137.7 (d, $^{4}J_{C\text{-}F}$ = 2.6 Hz, *i*-C), 158.9 (d, $^{1}J_{C\text{-}F}$ = 241.6 Hz, *i*-CF) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –66.8 (s, CF_3), –121.1 (m, Ar-F) ppm; IR (KBr): ν = 3319 (N-H), 2983–2854 (=C-H), 1606, 1516, 1242, 1206, 1170-1090 (CF_3) cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_8H_5BrF_4N_2$: 283.9572; found: 283.9577.

*4.2.5. N-(p-Benzoyloxyphenyl)-trifluoroacetohydrazonoyl bromide (**3e**)*

Reaction time 2h; 612 mg (79%); orange solid, mp 94-95 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.20 (s_{br}, 4 H), 7.50-7.54, 7.63-7.66 (2 m, 2 H, 1 H), 8.09 (s_{br}, 1 H, NH), 8.19-8.22 (m, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 104.2 (q, $^{2}J_{C\text{-}F}$ = 43.8 Hz), 115.0 (d, 2 CH), 118.3 (q, $^{1}J_{C\text{-}F}$ = 271.4 Hz, CF_3), 122.8, 128.6 (2 d, 4 CH), 129.5 (s, *i*-C), 130.2 (d, 2 CH), 133.6 (d, CH), 139.3, 146.4 (2 s, 2 *i*-C), 165.3 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –66.8 (s, CF_3) ppm; IR (KBr): ν = 3291 (N-H), 3095–2920 (=C-H), 1723 (C=O), 1600 (C=C), 1518, 1277, 1239, 1201, 1180-1100 (CF_3), 1085, 1065 cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{10}BrF_3N_2O_2$: 385.9878; found: 385.9880.

*4.2.6. N-(p-Chlorophenyl)-trifluoroacetohydrazonoyl bromide (**3f**)*

Reaction time 1h; 555 mg (92%); red oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.09 (d_{br}, $J \approx$ 8.8 Hz, 2 H), 7.29 (d_{br}, $J \approx$ 8.8 Hz, 2 H), 8.02 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 104.8 (q, $^{2}J_{C\text{-}F}$ = 43.8 Hz), 115.4 (d, 2 CH), 118.3 (q, $^{1}J_{C\text{-}F}$ = 271.7 Hz, CF_3), 128.0 (s, *i*-C), 129.6 (d, 2 CH), 140.1 (s, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –66.9 (s, CF_3) ppm; IR (film): ν = 3322 (N-H), 3034–2863 (=C-H), 1603, 1505, 1245, 1170-1095 (CF_3) cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_8H_5BrClF_3N_2$: 299.9277; found: 299.9281.

*4.2.7. N-(p-Methoxycarbonylphenyl)-trifluoroacetohydrazonoyl bromide (**3g**)*

Reaction time 2h; crude product was purified by CC (SiO_2, petroleum ether/dichloromethane 1:1) to give **3g** (253 mg, 39%) as a colorless solid, mp 147-148 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.90 (s, 3 H, Me), 7.18

(d_{br}, $J \approx 8.8$ Hz, 2 H), 8.01 (d_{br}, $J \approx 8.8$ Hz, 2 H), 8.25 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): $\delta = 51.9$ (q, Me), 106.2 (q, $^2J_{C\text{-}F} = 43.9$ Hz), 113.6 (d, 2 CH), 118.2 (q, $^1J_{C\text{-}F} = 272.0$ Hz, CF_3), 124.6 (s, *i*-C), 131.9 (d, 2 CH), 145.0 (s, *i*-C), 166.5 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -67.3$ (s, CF_3) ppm; IR (film): $\nu =$ 3318 (N-H), 3011–2847 (=C-H), 1692 (C=O), 1603, 1296, 1245, 1185-1080 (CF_3) cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{10}H_8BrF_3N_2O_2$: 323.9721; found: 323.9725.

*4.2.8. N-(p-Cyanophenyl)-trifluoroacetohydrazonoyl bromide (**3h**)*

Reaction time 3h; crude product was purified by CC (SiO_2, petroleum ether/dichloromethane 1:1) to give **3h** (455 mg, 78%) as a pale yellow solid, mp 155-156 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 7.23$ (d_{br}, $J \approx 8.8$ Hz, 2 H), 7.62 (d_{br}, $J \approx 8.8$ Hz, 2 H), 8.23 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): $\delta = 106.1$ (s, CN), 107.6 (q, $^2J_{C\text{-}F} = 44.0$ Hz), 114.5 (d, 2 CH), 118.1 (q, $^1J_{C\text{-}F} = 272.3$ Hz, CF_3), 118.8 (s, *i*-C), 133.9 (d, 2 CH), 144.8 (s, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -67.3$ (s, CF_3) ppm; IR (KBr): $\nu = 3221$ (N-H), 3170–2984 (=C-H), 2230 (C≡N), 1603, 1521, 1340, 1242, 1182-1103 (CF_3) cm^{-1}; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_9H_5BrF_3N_3$: 290.9619; found: 290.9618.

*4.3. General procedure (GP2) for the synthesis of 5-trifluromethyl-2,3-dihydro-1,3,4-thiadiazoles **6a-p***

A mixture of the respective bromide **3** (1.0 mmol) and Et_3N (2.5 mL) in dry THF (4 mL) was added dropwise to a solution of thioketone **1** (1.0 mmol) in THF (3 mL) and the resulting mixture was stirred and room temperature until the color of the starting thioketone faded (typically 30 min to 3 hrs). The precipitate triethylamine hydrochloride was filtered off, and the solvents were removed under reduced pressure. The resulting mixture was purified by chromatography column (SiO_2, 95:5 petroleum ether/dichloromethane 95:5 gradient 6:4), and the product **6** was recrystallized from petroleum ether.

*4.3.1. 2,2-Diphenyl-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6a**)*

Reaction time 40 min; 295 mg (74%); yellow crystals, mp 97-98 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 2.17$ (s, 3 H, Me), 6.79 (d_{br}, $J \approx 8.8$ Hz, 2 H, Tol), 6.82 (d_{br}, $J \approx 8.8$ Hz, 2 H, Tol), 7.31-7.38, 7.58-7.62 (2 m, 6 H, 4 H, 2 Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): $\delta = 20.5$ (q, Me), 94.7 (s, C-2), 119.0 (d, 2 CH, Tol), 119.9 (q, $^1J_{C\text{-}F} =$ 270.8 Hz, CF_3), 128.2, 128.7 (2 d, 6 CH, Ph), 128.8 (d, 2 CH, Tol), 128.9 (d, 4 CH, Ph), 130.3 (q, $^2J_{C\text{-}F} = 40.5$ Hz, C-4), 132.4, 139.7 (2 s, 2 *i*-C, Tol), 139.8 (s, 2 *i*-C, Ph) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): $\delta = -63.47$ (s, CF_3) ppm; IR (KBr): $\nu =$ 3085–2850 (=C-H, C-H), 1510, 1270, 1190, 1140-1090, 1050-1005 (CF_3) cm^{-1}; ESI-MS (*m*/*z*): 421 (100, $[M+Na]^+$), 399 (27, [M+H]+); elemental analysis calcd (%) for $C_{22}H_{17}F_3N_2S$ (398.1): C 66.32, H 4.30, N 7.03, S 8.05; found: C 66.44, H 4.25, N 7.13, S 7.99.

*4.3.2. Spiro[(3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole)-2,9'-(9'H-fluorene)] (**6b**)*

Reaction time 30 min; 308 mg (78%); yellow crystals, mp 128-129 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta =$ 2.01 (s, 3 H, Me), 6.48 (d_{br}, $J \approx 8.5$ Hz, 2 H, Tol), 6.65 (d_{br}, $J \approx 8.5$ Hz, 2 H, Tol), 7.25 (td, $J \approx 1.1$, 7.6 Hz, 2 H), 7.34 (td, $J \approx 1.1$, 7.6 Hz, 2 H), 7.56 (d, $J \approx 7.6$ Hz, 2 H), 7.66 (d, $J \approx 7.6$ Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): $\delta = 20.5$ (q, Me), 89.8 (s, spiro-C), 117.8 (d, 2 CH, Tol), 119.8 (q, $^1J_{C\text{-}F} = 270.7$ Hz, CF_3), 120.4, 125.8, 129.0 (3 d, 2 CH each), 129.1 (d, 2 CH, Tol), 130.5 (d, 2 CH), 130.5 (q, $^2J_{C\text{-}F} = 40.7$ Hz, C-4), 132.7, 138.2,

139.3, 145.2 (4 s, 6 *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.35 (s, CF_3) ppm; IR (KBr): ν = 3090–2860 (=C-H, C-H), 1505, 1268, 1182, 1190-1130 (CF_3), 1017 cm^{-1}; ESI-MS (*m*/*z*): 419 (72, $[M+Na]^+$), 397 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{22}H_{15}F_3N_2S$ (396.1): C 66.65, H 3.81, N 7.07, S 8.09; found: C 66.63, H 3.97, N 7.17, S 8.04.

*4.3.3. 2,2-Di(1-methylpyrrol-2-yl)-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6c**)*

Reaction time 35 min; 327 mg (81%); pale orange crystals, mp 108-110 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.22 (s, 3 H, Me), 3.66 (s, 6 H, 2 NMe), 6.06 (dd, *J* = 2.7, 3.8 Hz, 2 H, Pyr), 6.11 (dd, *J* = 1.9, 3.8 Hz, 2 H, Pyr), 6.70 (pseudo-t, *J* ≈ 2.3 Hz, 2 H, Pyr), 6.89 (d, *J* = 8.6 Hz, 2 H, Tol), 6.95 (d, *J* = 8.6 Hz, 2 H, Tol) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.5 (q, Me), 36.1 (q, 2 NMe), 86.2 (s, C-2), 107.1, 113.3 (2 d, 4 CH, Pyr), 117.5 (d, 2 CH, Tol), 120.0 (q, $^1J_{C\text{-}F}$ = 271.0 Hz, CF_3), 126.6, 127.9 (d, s, 2 CH, 2 *i*-C, Pyr), 129.0 (d, 2 CH, Tol), 130.8 (q, $^2J_{C\text{-}F}$ = 40.4 Hz, C-4), 132.1, 139.7 (2 s, 2 *i*-C, Tol) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.49 (s, CF_3) ppm; IR (KBr): ν = 3098–2873 (=C-H, C-H), 1559, 1511, 1268, 1192, 1165-1120 (CF_3), 1013 cm^{-1}; ESI-MS (*m*/*z*): 427 (27, $[M+Na]^+$), 405 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{20}H_{19}F_3N_4S$ (404.1): C 59.39, H 4.74, N 13.85, S 7.93; found: C 59.23, H 4.98, N 13.76, S 7.99.

*4.3.4. 2,2-Di(thien-2-yl)-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6d**)*

Reaction time 30 min; 333 mg (81%); orange crystals, mp 82-83 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.24 (s, 3 H, Me), 6.91 (s_{br}, 4 H, Tol), 6.94 (dd, *J* = 3.7, 5.1 Hz, 2 H, Th), 7.09 (dd, *J* = 1.3, 3.7 Hz, 2 H, Th), 7.42 (dd, *J* = 1.3, 5.1 Hz, 2 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.7 (q, Me), 89.6 (s, C-2), 119.7 (q, $^1J_{C\text{-}F}$ = 271.2 Hz, CF_3), 121.5 (d, 2 CH, Tol), 126.9, 128.5, 128.9 (3 d, 6 CH, Th), 129.1 (d, 2 CH, Tol), 130.8 (q, $^2J_{C\text{-}F}$ = 40.7 Hz, C-4), 134.6, 139.2 (2 s, 2 *i*-C, Tol), 144.5 (s, 2 *i*-C, Th) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.57 (s, CF_3) ppm; IR (KBr): ν = 3120–2930 (=C-H, C-H), 1565, 1509, 1274, 1160-1103 (CF_3), 1027 cm^{-1}; EI-MS (*m*/*z*): 410 (100, $[M]^+$); elemental analysis calcd (%) for $C_{18}H_{13}F_3N_2S_3$ (410.0): C 52.67, H 3.19, N 6.82, S 23.43; found: C 52.56, H 3.33, N 6.75, S 23.44.

*4.3.5. 2,2-Di(selenophen-2-yl)-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6e**)*

Reaction time 45 min; 459 mg (91%); pale brown crystals, mp 94-96 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.25 (s, 3 H, Me), 6.93 (d_{br}, *J* ≈ 8.5 Hz, 2 H, Tol), 7.00 (d_{br}, *J* ≈ 8.5 Hz, 2 H, Tol), 7.17 (dd, *J* = 3.8, 5.7 Hz, 2 H, Sel), 7.25 (dd, *J* = 1.2, 3.8 Hz, 2 H, Sel), 8.12 (dd, *J* = 1.2, 5.7 Hz, 2 H, Sel) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.8 (q, Me), 93.5 (s, C-2), 119.6 (q, $^1J_{C\text{-}F}$ = 271.2 Hz, CF_3), 122.3, 129.0 (2 d, 4 CH, Tol), 129.4 (d, 2 CH, Sel), 130.8 (q, $^2J_{C\text{-}F}$ = 40.8 Hz, C-4), 131.3, 134.7 (2 d, 4 CH, Sel), 134.8, 139.2 (2 s, 2 *i*-C, Tol), 151.5 (s, 2 *i*-C, Sel) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.52 (s, CF_3) ppm; IR (KBr): ν = 3113–2857 (=C-H, C-H), 1565, 1511, 1268, 1170-1141 (CF_3), 1027 cm^{-1}; ESI-MS (*m*/*z*): 507 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{18}H_{13}F_3N_2SSe_2$ (505.9): C 42.87, H 2.60, N 5.56, S 6.36; found: C 42.99, H 2.84, N 5.60, S 6.57.

*4.3.6. 2-(Fur-2-yl)-2-phenyl-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6f**)*

Reaction time 35 min; 280 mg (72%); pale yellow crystals, mp 117-118 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.22 (s, 3 H, Me), 6.35 (dd, *J* = 1.8, 3.4 Hz, 1 H, Fur), 6.51 (dd, *J* = 0.8, 3.4 Hz, 1 H, Fur), 6.90 (d, *J* = 9.2 Hz, 2

H, Tol), 6.91 (d, J = 9.2 Hz, 2 H, Tol), 7.37-7.44 (m, 3 H, Ph), 7.45 (dd, J = 0.8, 1.8 Hz, 1 H, Fur), 7.59-7.61 (m, 2 H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.5 (q, Me), 88.7 (s, C-2), 110.7, 113.6 (2 d, 2 CH, Fur), 118.4 (d, 2 CH, Tol), 119.8 (q, $^1J_{C\text{-}F}$ = 271.1 Hz, CF_3), 127.4, 128.7 (2 d, 4 CH, Ph), 128.9 (d, 2 CH, Tol), 129.0 (d, CH, Ph), 130.0 (q, $^2J_{C\text{-}F}$ = 40.7 Hz, C-4), 132.5, 139.5, 139.7 (3 s, 3 *i*-C, Tol, Ph), 144.2, 150.2 (d, s, CH, *i*-C, Fur) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.48 (s, CF_3) ppm; IR (KBr): ν = 3139–2917 (=C-H, C-H), 1562, 1508, 1264, 1168-1095 (CF_3) cm^{-1}; ESI-MS (*m*/*z*): 389 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{20}H_{15}F_3N_2OS$ (388.1): C 61.85, H 3.89, N 7.21, S 8.26; found: C 61.88, H 4.07, N 7.18, S 8.03.

*4.3.7. 2-Phenyl-2-(thien-2-yl)-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6g**)*

Reaction time 30 min; 291 mg (72%); pale yellow crystals, mp 117-118 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.21 (s, 3 H, Me), 6.87 (m_c, 4 H, Tol), 6.88 (dd, J = 3.7, 5.2 Hz, 1 H, Th), 6.97 (dd, J = 1.3, 3.7 Hz, 1 H, Th), 7.35 (dd, J = 1.3, 5.2 Hz, 1 H, Th), 7.37-7.43, 7.65-7.68 (2 m, 3 H, 2 H, Ph) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.6 (q, Me), 91.7 (s, C-2), 119.7 (d, 2 CH, Tol), 119.8 (q, $^1J_{C\text{-}F}$ = 271.0 Hz, CF_3), 126.6 (d, CH, Th), 127.6, 128.5 (2 d, 4 CH, Ph), 128.6 (d, CH, Th), 128.9 (d, 2 CH, Tol), 129.0 (d, CH, Ph), 130.1 (q, $^2J_{C\text{-}F}$ = 40.7 Hz, C-4), 130.3 (d, CH, Th), 133.3 139.5 (2 s, 2 *i*-C, Tol), 140.8 (s, *i*-C, Ph), 144.0 (s, *i*-C, Th) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.52 (s, CF_3) ppm; IR (KBr): ν = 3102–2863 (=C-H, C-H), 1563, 1508, 1271, 1155-1100 (CF_3) cm^{-1}; ESI-MS (*m*/*z*): 427 (41, $[M+Na]^+$), 405 (100, $[M]^+$); elemental analysis calcd (%) for $C_{20}H_{15}F_3N_2S_2$ (404.1): C 59.39, H 3.74, N 6.93, S 15.86; found: C 59.35, H 3.76, N 6.88, S 15.78. Suitable crystals for an X-ray crystal structure determination were obtained from petroleum ether solution by slow evaporation of the solvent.

*4.3.8. 2-Phenyl-2-(selenophen-2-yl)-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6h**)*

Reaction time 45 min; 362 mg (80%); pale yellow crystals, mp 132-134 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.22 (s, 3 H, Me), 6.90 (m_c, 4 H, Tol), 7.11-7.14 (m, 2 H, Sel), 7.37-7.42, 7.66-7.69 (2 m, 3 H, 2 H, Ph), 8.07 (dd, J = 2.2, 4.7 Hz, 1 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.6 (q, Me), 93.7 (s, C-2), 119.8 (q, $^1J_{C\text{-}F}$ = 271.0 Hz, CF_3), 119.9 (d, 2 CH, Tol), 127.7, 128.5 (2 d, 4 CH, Ph), 128.9 (d, 2 CH, Tol), 129.0 (d, CH, Sel), 129.1 (d, CH, Ph), 130.0 (q, $^2J_{C\text{-}F}$ = 40.7 Hz, C-4), 132.4 (d, CH, Sel), 133.4 (s, *i*-C, Tol), 134.8 (d, CH, Sel), 139.4 (s, *i*-C, Tol), 140.8 (s, *i*-C, Ph), 151.0 (s, *i*-C, Sel) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.49 (s, CF_3) ppm; IR (KBr): ν = 3091–2851 (=C-H, C-H), 1562, 1508, 1277, 1165-1115 (CF_3) cm^{-1}; ESI-MS (*m*/*z*): 453 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{20}H_{15}F_3N_2SSe$ (452.0): C 53.22, H 3.35, N 6.21, S 7.10; found: C 52.99, H 3.34, N 6.25, S 7.12.

*4.3.9. 2-Ferrocenyl-2-methyl-3-p-tolyl-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6i**)*

Reaction time 45 min; 261 mg (59%); orange crystals, mp 105-106 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.90 (s, 3 H, Me), 2.24 (s, 3 H, Me), 4.10 (s_{br}, 1 H, Fc), 4.20 (s, 5 H, Fc), 4.22 (s_{br}, 1 H, Fc), 4.45 (s_{br}, 1 H, Fc), 4.93 (s_{br}, 1 H, Fc), 6.71 (d_{br}, $J \approx$ 8.3 Hz, 2 H, Tol), 6.91 (d_{br}, $J \approx$ 8.3 Hz, 2 H, Tol) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 20.8, 25.3 (2 q, 2 Me), 68.5, 69.3 (2 d, 2 CH, Fc), 69.5 (d, 6 CH, Fc), 70.4 (d, CH, Fc), 87.8 (s, *i*-C, Fc), 91.5 (s, C-2), 120.0 (q, $^1J_{C\text{-}F}$ = 270.5 Hz, CF_3), 123.0, 128.9 (2 d, 4 CH, Tol), 130.5 (q, $^2J_{C\text{-}F}$ = 40.1 Hz, C-4), 134.9, 138.9 (2 s, 2 *i*-C, Tol) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –64.06 (s, CF_3) ppm; IR (KBr): ν = 3120–

2860 (=C-H, C-H), 1565, 1510, 1270, 1185, 1150-1070 (CF_3), 1030 cm^{-1}; EI-MS (*m*/*z*): 444 (100, $[M]^+$), 244 (58); elemental analysis calcd (%) for $C_{21}H_{19}F_3FeN_2S$ (444.1): C 56.77, H 4.31, N 6.31, S 7.22; found: C 56.51, H 4.37, N 6.28, S 7.13.

*4.3.10. 3-p-Methoxyphenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6j**)*

Reaction time 75 min; 307 mg (72%); pale orange crystals, mp 72-74 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.72 (s, 3 H, OMe), 6.63 (d_{br}, $J \approx 9.1$ Hz, 2 H, Tol), 6.91 (d_{br}, $J \approx 9.1$ Hz, 2 H, Tol), 6.93 (dd, J = 3.7, 5.1 Hz, 2 H, Th), 7.00 (dd, J = 1.3, 3.7 Hz, 2 H, Th), 7.42 (dd, J = 1.3, 5.1 Hz, 2 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 55.3 (q, OMe), 90.2 (s, C-2), 113.5 (d, 2 H), 119.6 (q, $^1J_{C\text{-}F}$ = 271.3 Hz, CF_3), 124.4 (d, 2 H), 127.0, 128.6, 129.1 (3 d, 6 CH, Th), 130.9 (q, $^2J_{C\text{-}F}$ = 40.6 Hz, C-4), 134.8 (s, *i*-C), 144.6 (s, 2 *i*-C, Th), 157.5 (s, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.59 (s, CF_3) ppm; IR (KBr): ν = 3120–2840 (=C-H, C-H), 1510, 1350, 1245, 1145, 1080-1025 (CF_3) cm^{-1}; ESI-MS (*m*/*z*): 449 (13, $[M+Na]^+$), 427 ($[M+H]^+$); elemental analysis calcd (%) for $C_{18}H_{13}F_3N_2OS_3$ (426.0): C 50.69, H 3.07, N 6.57, S 22.55; found: C 50.62, H 3.25, N 6.52, S 22.48.

*4.3.11. 3-Phenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6k**)*

Reaction time 45 min; 269 mg (68%); light green crystals, mp 82-83 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.94 (dd, J = 3.7, 5.1 Hz, 2 H, Th), 6.99-7.04, 7.09-7.11 (2 m, 3 H, 2 H, Ph), 7.11 (dd, J = 1.3, 3.7 Hz, 2 H, Th), 7.42 (dd, J = 1.3, 5.1 Hz, 2 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 89.5 (s, C-2), 119.6 (q, $^1J_{C\text{-}F}$ = 271.3 Hz, CF_3), 121.2, 124.7 (2 d, 2 CH, CH, Ph), 126.9, 128.4, 128.6 (3 d, 6 CH, Th), 129.1 (d, 2 CH, Ph), 131.4 (q, $^2J_{C\text{-}F}$ = 40.9 Hz, C-4), 141.7 (s, *i*-C), 144.5 (s, 2 *i*-C, Th) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.63 (s, CF_3) ppm; IR (KBr): ν = 3123–2993 (=C-H), 1575, 1492, 1271, 1160-1125 (CF_3) cm^{-1}; EI-MS (*m*/*z*): 396 (100, $[M]^+$); elemental analysis calcd (%) for $C_{17}H_{11}F_3N_2S_3$ (396.0): C 51.50, H 2.80, N 7.07, S 24.26; found: C 51.24, H 2.86, N 6.98, S 24.17.

*4.3.12. 3-p-Fluorophenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6l**)*

Reaction time 3 h; 327 mg (79%); creamy crystals, mp 51-52 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.78-6.82 (m, 2 H), 6.95 (dd, J = 3.7, 5.1 Hz, 2 H, Th), 6.94-7.00 (m, 2 H), 7.06 (dd, J = 1.3, 3.7 Hz, 1 H, Th), 7.44 (dd, J = 1.3, 5.1 Hz, 2 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 89.9 (s, C-2), 115.1 (d, $^2J_{C\text{-}F}$ = 22.6 Hz, 2 CH), 119.5 (q, $^1J_{C\text{-}F}$ = 271.5 Hz, CF_3), 123.8 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, 2 CH), 127.1, 128.8, 129.2 (3 d, 6 CH, Th), 132.0 (q, $^2J_{C\text{-}F}$ = 40.7 Hz, C-4), 137.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, *i*-C), 144.2 (s, 2 *i*-C, Th), 160.3 (d, $^1J_{C\text{-}F}$ = 245.1 Hz, *i*-CF) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.68 (s, CF_3), –117.49 (m, Ar-F) ppm; IR (KBr): ν = 3110–2995 (=C-H), 1586, 1502, 1349, 1195-1115 (CF_3), 1021 cm^{-1}; ESI-MS (*m*/*z*): 415 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{17}H_{10}F_4N_2S_3$ (414.0): C 49.26, H 2.43, N 6.76, S 23.21; found: C 49.23, H 2.55, N 6.77, S 23.18.

*4.3.13. 3-p-Benzoyloxyphenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6m**)*

Reaction time 1.5 h; 418 mg (81%); creamy crystals, mp 97-98 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.97 (dd, J = 3.7, 5.1 Hz, 2 H, Th), 6.99 (d_{br}, $J \approx 9.0$ Hz, 2 H), 7.09 (d_{br}, $J \approx 9.0$ Hz, 2 H), 7.14 (dd, J = 1.2, 3.7 Hz, 2 H, Th), 7.45 (dd, J = 1.2, 5.1 Hz, 2 H, Th), 7.48-7.51, 7.61-7.64, 8.15-8.17 (3 m, 2 H, 1 H, 2 H, Bz) ppm; ^{13}C

NMR ($CDCl_3$, 151 MHz): δ = 89.7 (s, C-2), 119.6 (q, $^1J_{C\text{-}F}$ = 271.6 Hz, CF_3), 121.5, 122.3 (2 d, 4 CH), 127.1 (d, 2 CH, Th), 128.5 (d, 2 CH, Bz), 128.8, 129.2 (2 d, 4 CH, Th), 129.5 (s, *i*-C), 130.1 (d, 2 CH, Bz), 131.8 (q, $^2J_{C\text{-}F}$ = 40.9 Hz, C-4), 133.6 (d, CH, Bz), 139.4 (s, *i*-C), 144.1 (s, 2 *i*-C, Th), 147.9 (s, i-C), 164.9 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.65 (s, CF_3) ppm; IR (KBr): ν = 3117–3022 (=C-H), 1736 (C=O), 1496, 1252, 1204, 1170-1141 (CF_3), 1021 cm^{-1}; ESI-MS (*m*/*z*): 555 (40, $[M+K]^+$), 539 (43, $[M+Na]^+$), 517 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{24}H_{15}F_3N_2O_2S_3$ (516.0): C 55.80, H 2.93, N 5.42, S 18.62; found: C 55.88, H 3.00, N 5.43, S 18.74.

*4.3.14. 3-p-Chlorophenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6n**)*

Reaction time 2 h; 315 mg (73%); yellow crystals, mp 68-70 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.96 (dd, *J* = 3.7, 5.2 Hz, 2 H, Th), 6.96 (d_{br}, *J* ≈ 9.0 Hz, 2 H), 7.06 (d_{br}, *J* ≈ 9.0 Hz, 2 H), 7.12 (dd, *J* = 1.2, 3.7 Hz, 2 H, Th), 7.44 (dd, *J* = 1.2, 5.2 Hz, 2 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 89.3 (s, C-2), 119.5 (q, $^1J_{C\text{-}F}$ = 271.5 Hz, CF_3), 122.1 (d, 2 CH), 127.1 (d, 2 CH, Th), 128.4 (d, 2 CH), 128.9, 129.2 (2 d, 4 CH, Th), 129.9 (s, *i*-C), 132.2 (q, $^2J_{C\text{-}F}$ = 41.0 Hz, C-4), 140.3 (s, *i*-C), 144.0 (s, 2 *i*-C, Th) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.69 (s, CF_3) ppm; IR (KBr): ν = 3107–3041 (=C-H), 1568, 1492, 1271, 1188, 1155-1100 (CF_3), 1087, 1024 cm^{-1}; ESI-MS (*m*/*z*): 431 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{17}H_{10}ClF_3N_2S_3$ (430.0): C 47.38, H 2.34, N 6.50, S 22.32; found: C 47.44, H 2.50, N 6.38, S 22.46.

*4.3.15. 3-p-Methoxycarbonylphenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6o**)*

Reaction time 5 h; 331 mg (73%); light brown crystals, mp 97-98 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.84 (s, 3 H, OMe), 6.97 (dd, *J* = 3.7, 5.1 Hz, 2 H, Th), 7.10 (d_{br}, *J* ≈ 8.9 Hz, 2 H), 7.23 (dd, *J* = 1.2, 3.7 Hz, 2 H, Th), 7.43 (dd, *J* = 1.2, 5.1 Hz, 2 H, Th), 7.78 (d_{br}, *J* ≈ 8.9 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 51.9 (q, OMe), 88.5 (s, C-2), 118.4 (d, 2 CH), 119.4 (q, $^1J_{C\text{-}F}$ = 271.7 Hz, CF_3), 124.9 (s, *i*-C), 127.1, 128.9, 129.2 (3 d, 6 CH, Th), 130.1 (d, 2 CH), 132.9 (q, $^2J_{C\text{-}F}$ = 41.1 Hz, C-4), 143.8 (s, 2 *i*-C, Th), 145.5 (s, *i*-C), 166.5 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.83 (s, CF_3) ppm; IR (KBr): ν = 3098–2851 (=C-H), 1708 (C=O), 1606, 1283, 1258, 1192, 1179, 1150-1090 (CF_3), 1030 cm^{-1}; EI-MS (*m*/*z*): 454 (73, $[M]^+$), 210 (78), 192 (100); EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{13}F_3N_2O_2S_3$: 454.0091; found: 454.0082.

*4.3.16. 3-p-Cyanophenyl-2,2-di(thien-2-yl)-5-trifluoromethyl-2,3-dihydro-1,3,4-thiadiazole (**6p**)*

Reaction time 5.5 h; 312 mg (74%); red-orange crystals, mp 140-141 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.99 (dd, *J* = 3.7, 5.2 Hz, 2 H, Th), 7.15 (d_{br}, *J* ≈ 8.9 Hz, 2 H), 7.26 (dd, *J* = 1.2, 3.7 Hz, 2 H, Th), 7.38 (d_{br}, *J* ≈ 8.9 Hz, 2 H), 7.46 (dd, *J* = 1.2, 5.2 Hz, 2 H, Th) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 88.3 (s, C-2), 106.2 (s, CN), 118.4 (d, 2 CH), 118.6 (s, *i*-C), 119.3 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, CF_3), 127.2, 129.1, 129.2 (3 d, 6 CH, Th), 132.6 (d, 2 CH), 134.0 (q, $^2J_{C\text{-}F}$ = 41.3 Hz, C-4), 143.4 (s, 2 *i*-C, Th), 145.3 (s, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ = –63.81 (s, CF_3) ppm; IR (KBr): ν = 3135–2980 (=C-H), 2220 (C≡N), 1600, 1503, 1261, 1150-1090 (CF_3), 1024 cm^{-1}; EI-MS (*m*/*z*): 421 (77, $[M]^+$), 210 (100); elemental analysis calcd (%) for $C_{18}H_{10}F_3N_3S_3$ (421.0): C 51.29, H 2.39, N 9.97, S 22.82; found: C 51.29, H 2.36, N 9.90, S 22.94.

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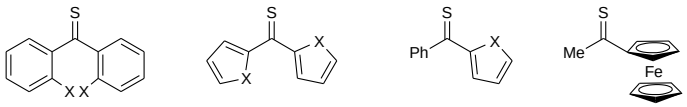


1a X = H
1b X = —

1c X = NMe
1d X = S
1e X = Se

1f X = O
1g X = S
1h X = Se

1i

Fig. 1. Thioketones **1a-i** selected for the study on (3+2)-cycloadditions with fluorinated nitrile imines **2**.

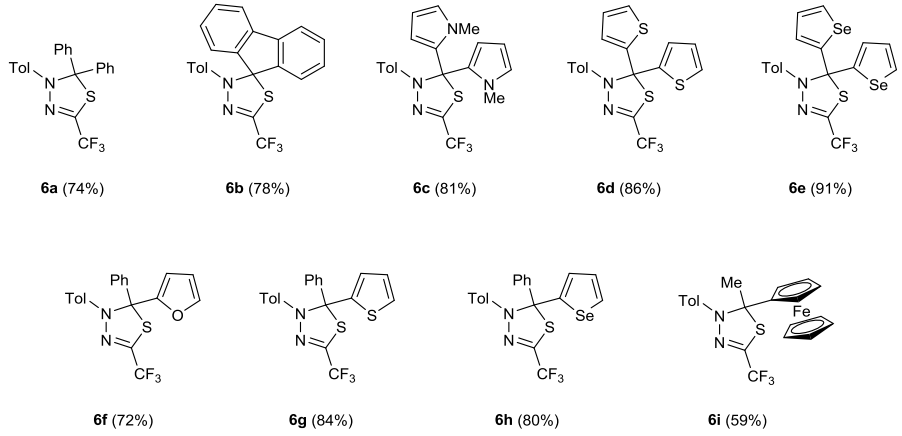


Fig. 2. Aryl, hetaryl, and ferrocenyl 2,3-dihydro-1,3,4-thiadiazoles **6a-i**.

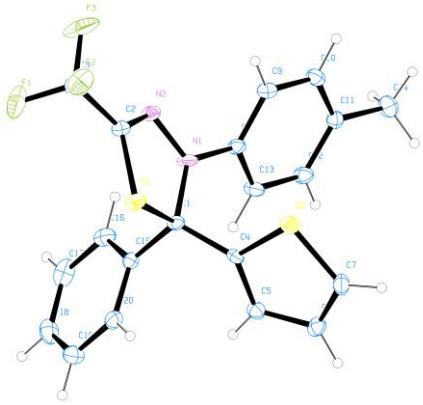


Fig. 3. Molecular structure (ORTEP [17]) of compound **6g**. Displacement ellipsoids are drawn at the 50% probability level, Selected bond lengths and angles. C1-S1 1.877(2), C2-S1 1.753(2), C2-N2 1.280(2), N1-N2 1.358(2), C1-N1 1.485(2) Å, C1-S1-C2 87.74(9), C4-S2-C7 91.87(9) °.

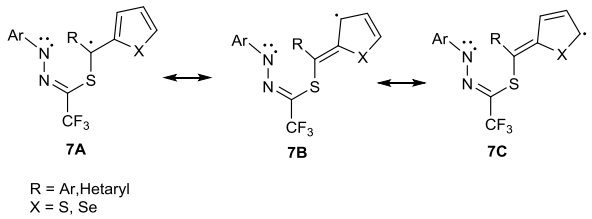


Fig. 4. Resonance stabilized diradical intermediates **7**.

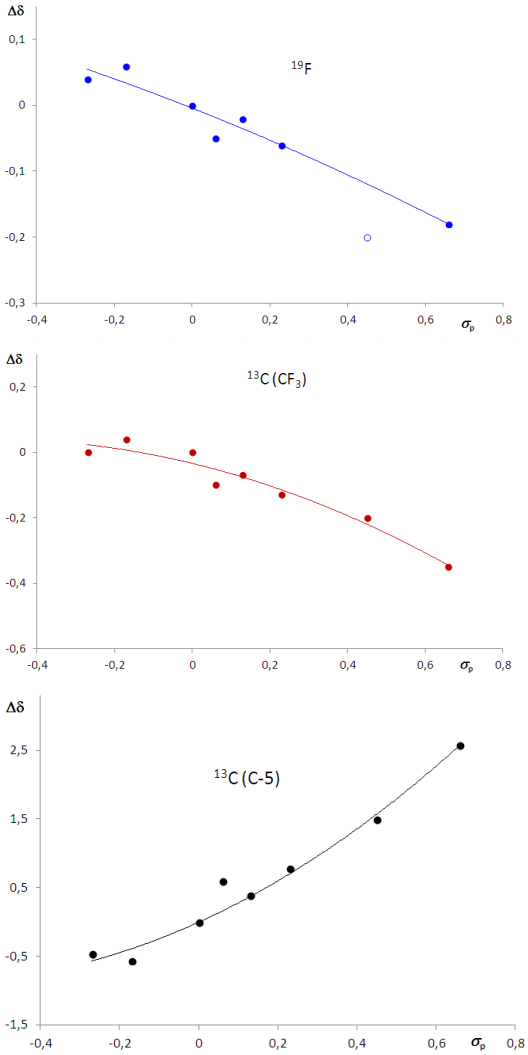
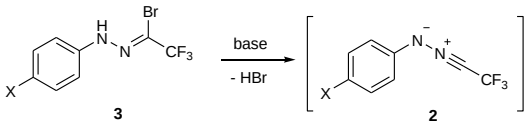
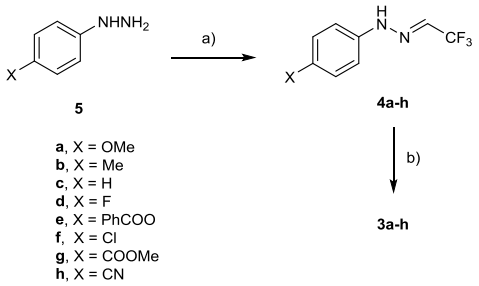


Fig. 5. Correlation of the difference ^{13}C, and ^{19}F NMR chemical shifts ($\Delta\delta=\delta_X-\delta_H$) for series of 2,2-di(thien-2-yl)-1,3,4-thiadiazoles **6d**,**j**-**p**; best fitting line without the open-circle datapoint.

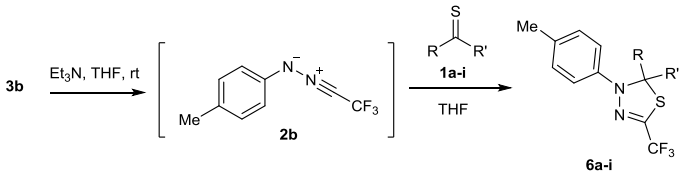


3 2

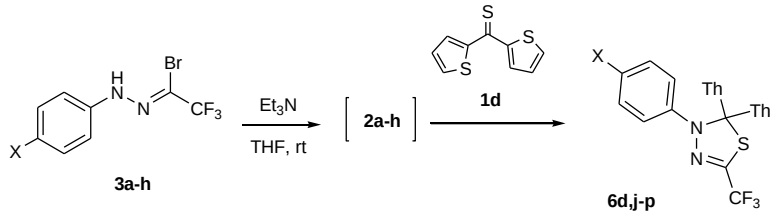
Scheme 1. Generation of nitrile imines **2** via dehydrohalogenation of trifluoroacetohydrazonoyl bromides **3**.



Scheme 2. Synthesis of trifluoroacetohydrazonoyl bromides **3a-h**. *Reagents and conditions*: a) $CF_3CH(OH)_2$; mol sieves 4Å, MeOH, closed ampoule, 75 °C, 16h; b) NBS, DMF, rt, 1-3h.



Scheme 3. Synthesis of 3-(*p*-tolyl)-5-trifluoromethyl-1,3,4-thiadiazoles **6a-i**.



Scheme 4. Synthesis of 2,2-di(thien-2-yl)-1,3,4-thiadiazoles **6d**,**j-p**.

Table 1. 3-Aryl-1,3,4-thiadiazoles **6d**,**j-p**.[a]

Entry	X	Reaction time	Product (yield)[b]	σ_p[c]
1	OMe	75 min	**6j** (72%)	–0.27
2	Me	30 min	**6d** (86%)	–0.17
3	H	45 min	**6k** (68%)	0.00
4	F	3 h	**6l** (79%)	0.06
5	PhCOO	1.5 h	**6m** (81%)	0.13
6	Cl	2 h	**6n** (73%)	0.23
7	COOMe	5 h	**6o** (73%)	0.45
8	CN	5.5 h	**6p** (74%)	0.66

[a]*Reagents and conditions*: bromides **3a-h** (1.0 equiv.), thioketone **1d** (1.0 equiv.), THF/Et_3N, rt, 0.5-3 hrs.
[b]Yield of isolated purified material, obtained as shown in Scheme 3.
[c]Ref. [18]