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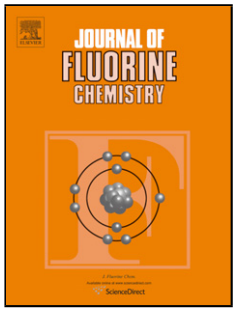

Title: Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: an access to fluorinated 1,3,4-thiadiazine derivatives via (3+3)-annulation

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Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: an access to fluorinated 1,3,4-thiadiazine derivatives via (3+3)-annulation

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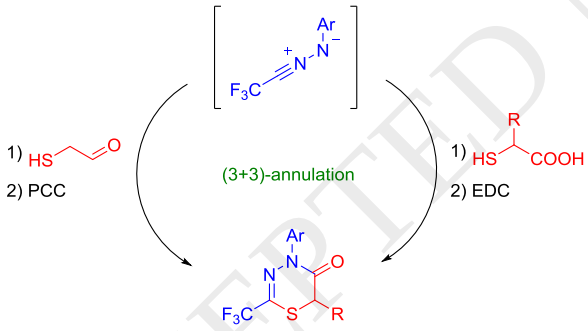
Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 70th birthday

Graphical abstract:



Graphical abstract

- nitrile imines derived from trifluoroacetonitrile can easily be trapped by bifunctional S-nucleophiles
- adducts obtained with mercaptoethanal undergo a spontaneous (3+3)-cyclisation to give 6-membered products

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- oxidation of 1,3,4-thiadiazin-5-ols with PCC leads to the expected 1,3,4-thiadiazin-5-one derivatives
- 1:1 adducts obtained with mercaptocarboxylic acids undergo cyclization only in the presence of EDC methiodide

Abstract

The *in situ* generated highly electrophilic nitrile imines derived from trifluoroacetonitrile are efficiently trapped by monomeric mercaptoacetaldehyde at room temperature in THF solution. The initially formed 1:1 adducts undergo spontaneous cyclization leading to 6-membered 5,6-dihydro-1,3,4-thiadiazin-5-ols bearing the CF_3 group at the C(2) atom in good yields. Subsequent oxidation of the latter products using $C_5H_5N{\cdot}HCl{\cdot}CrO_3$ (PCC) led smoothly to the expected 1,3,4-thiadiazin-5-ones as final products. Alternatively, analogous 2-trifluoromethylated heterocycles were obtained via trapping of the same nitrile imines with α-mercaptocarboxylic acids followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDC methiodide) induced cyclisation of the initially formed 1:1 adducts. In general, efficiency of the second approach was lower and depended on the type of substituent attached to phenyl ring in the starting 1,3-dipole.

Keywords: fluorinated nitrile imines, mercaptoacetaldehyde, α-mercaptocarboxylic acids, (3+3)-annulation, trifluoromethylated 1,3,4-thiadiazines.

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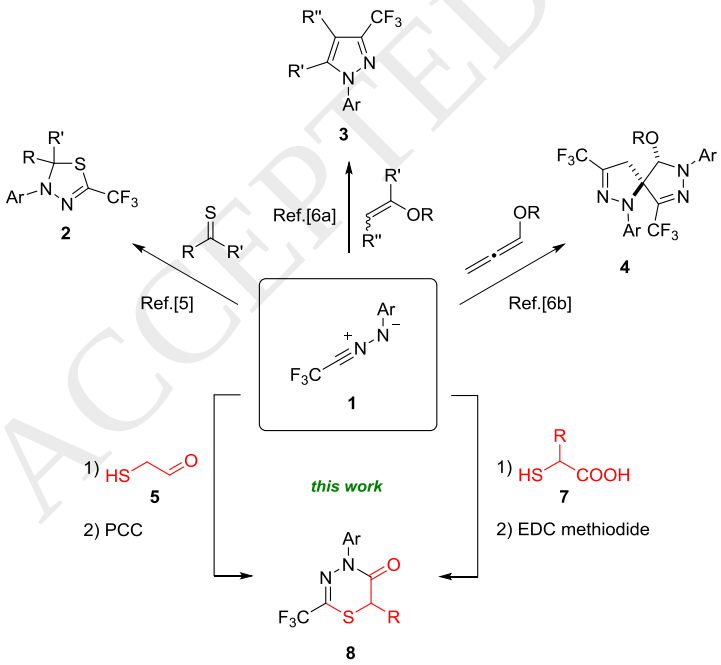
1. Introduction

According to Huisgen classification nitrile imines belong to the class of so-called propargyl-allenyl 1,3-dipoles [1]. Over decades they have been widely applied in the (3+2)-cycloaddition reactions leading to diverse nitrogen-containing five-membered heterocycles [2]. However, along with their tendency to react as 1,3-dipoles, they are also known as electrophilic reagents, and the reactions with O-, N-, and S-nucleophiles are reported [3]. In our continuing studies on (3+2)-cycloadditions with fluorinated nitrogen-centered 1,3-dipoles [4-6], much attention was paid to strongly electron-deficient nitrile imines **1** derived from trifluoroacetonitrile. For example, we found that they react easily not only with aromatic and aliphatic thioketones but also with monomeric thiochalcones yielding the 1,3,4-thiadiazole derivatives of type **2** in a fully regioselective manner [5]. In addition, they underwent cycloadditions with less reactive electron-rich C=C dipolarophiles such as vinyl ethers and alkoxyallenes leading to pyrazoles **3** and more complex spirobipyrazolines **4**, respectively [6]; the latter products being formed in a highly diastereoselective fashion via formal double (3+2)-cycloaddition (Scheme 1) [6b].

Mercaptoacetaldehyde (**5**), easily available from its stable dimer 1,4-dithiane-2,5-diol (**6**), is well known as a versatile building block for the preparation of the S-containing organic products [7], and its reactions with nitrile imines afforded 1,3,4-thiadiazine derivatives formed via spontaneous cyclisation of the initial 1:1 adducts [8].

The goal of the present work was to examine the course of the reactions between the in situ generated nitrile imines **1** and mercaptoacetaldehyde under mild conditions. In addition, similar reactions with other bifunctional substrates, e.g. α-mercaptocarboxylic acids **7** were also of interest. Both procedures were expected to open up an access to hitherto unknown trifluoromethylated 1,3,4-thiadiazin-6-ones **8** in a complementary approach (Scheme 1).



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Scheme 1. Reactions of fluorinated nitrile imines **1** with thiocarbonyls (thioketones and thiochalcones), vinyl ethers, and alkoxyallenes leading to (3+2)-cycloadducts **2-4**, and (3+3)-annulations of **1** with bifunctional substrates **5** and **7** described herein.

2. Results and Discussion

A series of recent papers demonstrate that the title trifluoroacetonitrile imines **1** are readily available via base-mediated dehydrohalogenation of the respective hydrazonoyl bromides of type **9** [5-6], and the requisite precursors were prepared in a two-step protocol comprising condensation of fluoral hydrate with arylhydrazines [9] followed by bromination of the resulting hydrazones with NBS [5a]. In a test experiment the reaction of *N*'-tolyl bromide **9a** (X = CH_3) and 1,4-dithiane-2,5-diol (**6**, 0.55 equiv.) was carried out in dry THF at room temperature, in the presence of excess of Et_3N (5.0 equiv.) (Scheme 2). The reaction progress was monitored by TLC until the starting bromide **9a** was fully consumed (2 hrs). The resulting mixture was examined by ^{1}H NMR, and only one set of signals attributed to the sole intermolecular product could be found in this spectrum. Subsequent purification by flash column chromatography provided analytically pure material isolated as a fairly stable colourless solid (78% yield), and the structure of the expected 5,6-dihydro-1,3,4-thiadiazin-5-ol derivative **10a** was confirmed by spectroscopic methods. For example, in the ^{1}H NMR spectrum, the diagnostic absorptions of the diastereotopic protons at C(6) were found at 2.93 (dd, J = 1.7, 12.9 Hz) and 3.18 (dd, J = 3.4, 12.9 Hz) ppm. In addition, along with the characteristic pattern attributed to the *p*-tolyl group, the signals located at 3.06 (d, J = 10.7 Hz) and 5.64 (ddd, J = 1.7, 3.4, 10.7 Hz) ppm clearly evidenced the presence of the C(5)H(OH) group. In the ^{13}C NMR spectrum two diagnostic quartets found at 119.7 ($^1J_{C\text{-}F}$ = 273.0 Hz) and 120.7 ($^2J_{C\text{-}F}$ = 38.9 Hz) ppm, and a singlet located at –67.6 ppm in the ^{19}F NMR spectrum confirmed the presence of the CF_3-C= unit. Moreover, the (-)-ESI-MS spectrum showed the molecular peak of $[M–H]^-$ at m/z = 273.5, which corresponded to the formula $C_{11}H_{11}F_3N_2OS$.

In continuation of the study, a series of trifluoromethylated 5,6-dihydro-1,3,4-thiadiazinols of type **10** was prepared starting with differently substituted hydrazonoyl bromides **9**, including representatives functionalized with either strongly electron-donating (**9c**) or electron-withdrawing (**9f**,**g**) groups located at the *para* position of the phenyl ring. In all the studied cases, the expected heterocyclic products **10** were isolated in fine yields (64-92%), irrespective of the electronic properties of substituent X, although longer reaction times (up to 4hr) were noticed for the transformations of nitrile imines **1** functionalized with EWGs attached to the phenyl ring. The decrease in reaction rates can be explained by reduced nucleophilicity of NH group present in the initially formed S-adduct. For that reason, the subsequent spontaneous cyclisation is expected to be a limiting step. Notably, neither nitrile nor nitro and ester moieties interfered with the outcome of the developed (3+3)-annulation reaction.

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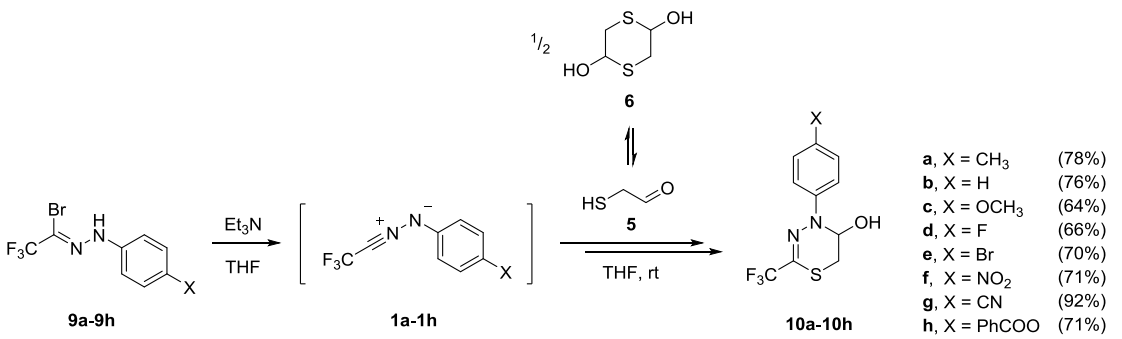
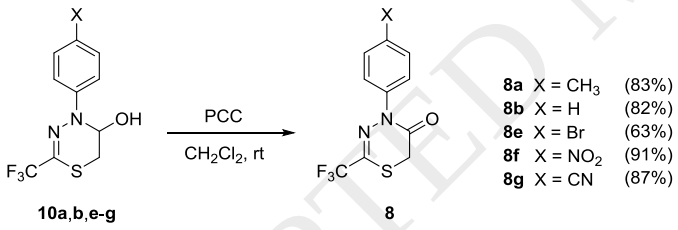


Scheme 2. Synthesis of 1,3,4-thiadiazin-5-ols **10a-10h** via (3+3)-annulation of mercaptoacetaldehyde (**5**) with the *in situ* generated trifluoroacetonitrile imines **1a-1h**.

The presence of the hemiaminal group in the newly synthesized 1,3,4-thiadiazine derivatives **10** offers several possibilities for further functionalization of the core heterocycle. Particularly, taking into account the well documented significance of the 1,3,4-thiadiazinone derivatives as biologically active compounds [10], we paid some attention to oxidation protocols. Thus, the behavior of the model N-tolyl substituted 1,3,4-thiadiazin-5-ol **10a** was briefly checked in reactions with selected mild oxidants. Unfortunately, neither treatment with activated MnO_2 nor with IBX under standard reaction conditions (CH_2Cl_2, 24 hr) provided the desired product. However, the use of excess of pyridinium chlorochromate (PCC, 1.5 equiv.) as an oxidizing agent in CH_2Cl_2 at room temperature, afforded after 2h the expected thiadiazinone derivative **8a**, which was isolated by flash column chromatography in high yield of 83% (Scheme 3). Analogous transformations were also performed starting with **10a**,**b**,**e-g** to give the expected 1,3,4-thiadiazin-5-one derivatives **8** in high yields of 63-91%.



Scheme 3. Oxidation of selected 5,6-dihydro-1,3,4-thiadiazin-5-ols **10** with PCC leading to 1,3,4-thiadiazin-5-ones **8**.

In extension of the study, we turned our attention to α-mercaptocarboxylic acids of type **7** as the alternative bifunctional HS-nucleophiles for the preparation of target fluorinated 1,3,4-thiadiazine derivatives [11]. As shown in Scheme 4, the test experiment was performed using model N-tolylhydrazonoyl bromide **9a** and thioglycolic acid (**7a**), in dry THF, in the presence of excess of Et_3N. The reaction progress was monitored by TLC, and after the nitrile imine precursor **9a** was fully consumed, the resulting mixture was acidified with diluted HCl followed by standard aqueous work-up. ^1H NMR spectrum of mother liquor showed the presence two diagnostic signals (singlets) located at 3.57 (2 H, CH_2) and 9.60 (1 H, NH) ppm along with the characteristic absorptions attributed to the *p*-tolyl group. That can serve as confirmation of the structure of acyclic adduct **11a** formed as the major component of the mixture. Following the general protocol for the synthesis of amides and other carboxylic acid derivatives [12], 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDC

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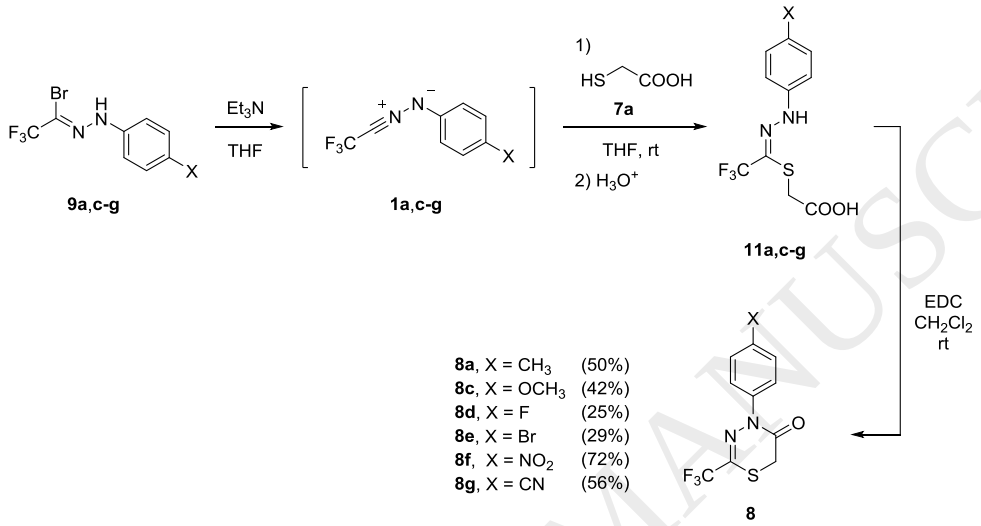
methiodide) was examined as the coupling reagent for the subsequent cyclisation step. As expected, treatment of crude **11a** with EDC methiodide under standard reaction conditions (dry THF, room temperature) provided after 16hr the desired 1,3,4-thiadiazin-5-one derivative **8a** in 27% yield (for 2 steps). Brief optimization of the final annulation step with respect *e.g.* to the type of the solvent, and stoichiometry of substrates indicated that running the reaction in dry CH_2Cl_2 in the presence of slight excess EDC methiodide leads to product **8a** in a satisfactory overall yield of 50%. Next, a series of nitrile imines **1c**-**1g** was tested in the reaction with thioglycolic acid (**7a**) under analogous reaction conditions to provide the expected formal (3+3)-annulation products **8c**-**8g** in moderate yields.



Scheme 4. Synthesis of 1,3,4-thiadiazin-5-ones **8** via two-step (3+3)-annulation of nitrile imines **1** and α-mercaptocarboxylic acid **7a**.

Finally, another three HS-nucleophiles functionalized with carboxylic groups, namely 2-mercaptopropionic acid (**7b**), mercaptosuccinic acid (**7c**), and 3-mercaptopropionic acid (**12**) were involved into the study, and their reactions with hydrazonoyl bromide **9f** (X = NO_2) provided solely the expected adducts of type **11** (Scheme 5). Subsequent treatment of compound **11h** with EDC methiodide afforded 6-methylated derivative **8h** in fair overall yield of 55%. In contrast, the attempted cyclisation of **11i** under analogous reaction conditions led mainly to decomposition products formed, very likely, via competitive rearrangement of the first formed adduct [13]. Expected 7-membered 1,3,4-thiadiazepine derivative could not be found in the crude reaction mixture. Similarly, the reaction of thiohydrazonate derivative **11j** with the same coupling agent provided a complex mixture of highly polar components, presumably the corresponding EDC-adducts of **11j**, along with unidentified decomposition products, although in this case, the formation of 6-membered product of type **8** in trace amounts only was observed.

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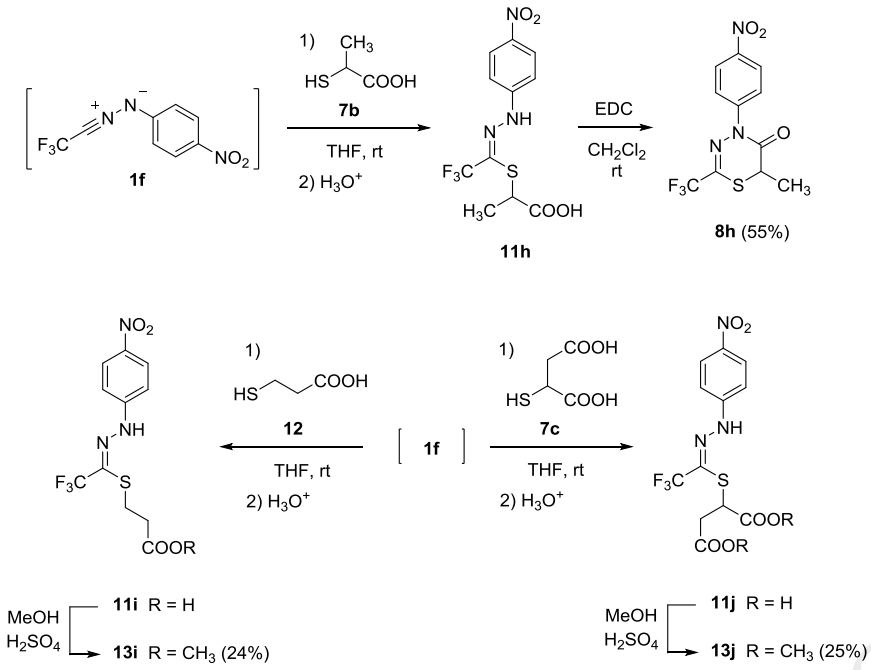

Scheme 5. Trapping of *in situ* generated nitrile imine **1f** with 2-mercaptopropionic acid (**7b**), mercaptosuccinic acid (**7c**), and 3-mercaptopropionic acid (**12**), and selected transformations of the initial adducts **11h**-**11j**.

In order to test an alternative base-induced cyclisation approach [3d,11b], the first formed carboxylic acids **11i** and **11j** were converted into their methyl esters **13i** and **13j** in overall 24% and 25% yield, respectively (Scheme 5). Unfortunately, attempted activation of the NH group in compounds **13** with K_2CO_3, LiOH, MeONa, LDA, and NaH gave no satisfactory result, and either starting materials were recovered or decomposition products were formed depending on the reaction conditions. Apparently, limited stability of **13** in the presence of hydroxide and alkoxide reflect remarkably electrophilic character of esters **13**, enhanced by the presence of the strongly electron-withdrawing CF_3 group, and the observed decomposition is presumably initiated by nucleophilic attack onto the C atom of the thiohydrazonate group. Also, attempted cyclisation of **13i** and **13j** by heating either in solution (refluxing EtOH or toluene) or neat (120 °C) was in vain.

3. Conclusions

The presented study showed, that *in situ* generated electron-deficient fluorinated nitrile imines **1** can be smoothly trapped by bifunctional HS-nucleophiles, and in the case of mercaptoacetaldehyde (**5**) spontaneous cyclisation of the initial adducts leads to 1,3,4-thiadiazin-5-ols **10** as formal (3+3)-annulation products. The latter compounds could be easily oxidized to 1,3,4-thidiazin-5-ones of type **8** by treatment with PCC. In contrast, the analogous S-adducts derived from α-mercaptocarboxylic acids **7** cyclized to a desired fluorinated 1,3,4-thidiazin-5-one **8** only upon treatment with the appropriate carbodiimide used as a coupling agent (EDC methiodide). The presented complementary approaches leading to a novel fluorinated 1,3,4-thiadiazines **10** and **8** nicely supplement protocols for the preparation of 1,3,4-thiadiazinones described in the literature [14], and other synthetic methods

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towards fluoroalkylated N-heterocycles of practical applications [15]. In addition, the presented study emphasizes the importance of nitrile imines as useful, versatile building blocks for the efficient preparation of not only 5-membered heterocycles by (3+2)-cycloadditions with appropriate dipolarophiles but also larger, 6-membered ring products formed via two-step (3+3)-annulation approach using bifunctional nucleophiles.

4. Experimental Part

4.1. General information

Solvents and reagents were purchased (Sigma-Aldrich, Acros) and used as received without further purification. THF was dried over sodium–benzophenone and freshly distilled before usage. Dichloromethane was dried over CaH_2 prior to use. 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 column chromatography on silica gel (230–400 mesh). Reported yields refer to analytically pure samples. NMR spectra were measured on a Bruker AVIII 600 MHz (^{1}H NMR [600 MHz]; ^{13}C NMR [151 MHz]; ^{19}F NMR [565 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 [$CDCl_3$]) or to $CFCl_3$ (δ = 0.00 ppm) used as an external standard in ^{19}F NMR measurements. For detailed peak assignments in ^{13}C NMR 2D spectra were taken (COSY, HMQC, HMBC). IR spectra were measured with a FTIR NEXUS spectrometer (as thin film or KBr pellets). MS (ESI) were performed with a Varian 500-MS LC Ion Trap. 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. Hydrazonoyl bromides **9a-9h** were obtained by treatment of the corresponding arylhydrazones with N-bromosuccinimide (NBS), in dry DMF, following the literature protocol [5a]. The latter trifluoroacetaldehyde hydrazones 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 our earlier report [9].

*4.2. Synthesis of 1,3,4-thiadiazin-5-ones **8***

Method A: To a solution of 5,6-dihydro-1,3,4-thiadiazin-5-ol **10** (1.0 mmol) in dichloromethane (10 mL) was added PCC (323 mg, 1.5 mmol) and the resulting mixture was stirred at room temperature until the starting **10** was fully consumed (TLC monitoring, 2-10 h). The mixture was filtered through a short pad of Celite, and the solvent was removed under reduced pressure. The crude product **8** was purified by flash column chromatography (SiO_2, CH_2Cl_2).

Method B: To a solution of hydrazonoyl bromide **9** (1.0 mmol) and α-mercaptocarboxylic acid **7** (1.1 mmol) in dry THF (10 mL) was added dropwise Et_3N (2 mmol, 0.3 mL), and the resulting mixture was stirred at room temperature overnight. Then, reaction was acidified with aq. HCl (5%) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (10 mL), solid EDC methiodide was added (171 mg, 1.1 mmol) and the resulting mixture was stirred at room temperature overnight. The precipitate was filtered off, the solvents were

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removed in vacuo, and the residue was purified by column chromatography (CC) to give 1,3,4-thiadiazin-5-one derivatives **8**.

*4.2.1. 4-(p-Tolyl)-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8a**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), *Method A*: 227 mg (83%), *Method B*: 137 mg (50%), colourless solid, mp 45–47 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.38 (s, 3 H, CH_3), 3.64 (s, 2 H, 6-H_2), 7.24, 7.30 (2 d_{br}, $J \approx$ 8.4 Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 21.1 (q, CH_3), 26.4 (t, C-6), 119.2 (q, $^1J_{C\text{-}F}$ = 275.0 Hz, CF_3), 125.1, 129.5 (2 d, 4 CH), 135.9 (q, $^2J_{C\text{-}F}$ = 39.5 Hz, C-2), 137.7, 138.1 (2 s), 156.6 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.1 (s, CF_3) ppm; IR (KBr): *v* 1694 (C=O), 1514, 1327, 1304, 1213, 1196, 1141, 1123, 1014 cm^{-1}; ESI-MS (*m/z*): 297.1 (100, $[M+Na]^+$), 275.1 (28, $[M+H]^+$); elemental analysis calcd (%) for $C_{11}H_9F_3N_2OS$ (274.3): C 48.17, H 3.31, N 10.21, S 11.69; found: C 48.21, H 3.44, N 10.21, S 11.66.

*4.2.2. 4-Phenyl-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8b**)*

CC (SiO_2, CH_2Cl_2), *Method A*: 213 mg (82%), colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.65 (s, 2 H, 6-H_2), 7.34-7.37, 7.43-7.46 (2 m, 1 H, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.4 (t, C-6), 119.1 (q, $^1J_{C\text{-}F}$ = 275.2 Hz, CF_3), 125.1, 128.0, 128.9 (3 d, 5 CH), 136.2 (q, $^2J_{C\text{-}F}$ = 39.5 Hz, C-2), 140.0 (s), 156.6 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –68.1 (s, CF_3) ppm; IR (KBr): *v* 2930, 1690 (C=O), 1597, 1494, 1327, 1198, 1124, 1016, 691 cm^{-1}; ESI-MS (*m/z*): 261.2 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{10}H_7F_3N_2OS$ (260.2): C 46.15, H 2.71, N 10.76, S 12.32; found C 46.41, H 2.87, N 10.88, S 12.21.

*4.2.3. 4-(4-Methoxyphenyl)-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8c**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:1 gradient CH_2Cl_2), *Method B*: 122 mg (42%), colourless solid, mp 85–86 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.63 (s, 2 H, 6-H_2), 3.83 (s, 3 H, OCH_3), 6.95, 7.33 (2 d_{br}, $J \approx$ 9.1 Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.4 (t, C-6), 55.5 (q, OCH_3), 114.2 (d, 2 CH), 119.2 (q, $^1J_{C\text{-}F}$ = 275.1 Hz, CF_3), 126.6 (d, 2 CH), 133.1 (s), 135.8 (q, $^2J_{C\text{-}F}$ = 39.3 Hz, C-2), 156.6 (s, C=O), 159.2 (s, *C*OMe) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.1 (s, CF_3) ppm; IR (KBr): *v* 1704 (C=O), 1513, 1333, 1254, 1193, 1143, 1020, 1009 cm^{-1}; ESI-MS (*m/z*): 313.1 (100, $[M+Na]^+$), 291.1 (89, $[M+H]^+$); elemental analysis calcd (%) for $C_{11}H_9F_3N_2O_2S$ (290.3): C 45.52, H 3.13, N 9.65, S 11.05; found: C 45.55, H 3.17, N 9.62, S 11.04.

*4.2.4. 4-(4-Fluorophenyl)-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8d**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 2:3), *Method B*: 69 mg (25%), thick colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.64 (s, 2 H, 6-H_2), 7.10-7.14, 7.40-7.43 (2 m, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.3 (t, C-6), 115.8 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, 2 CH), 119.1 (q, $^1J_{C\text{-}F}$ = 275.2 Hz, CF_3), 127.0 (d, $^3J_{C\text{-}F}$ = 8.7 Hz, 2 CH), 136.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, *i*-C), 136.5 (q, $^2J_{C\text{-}F}$ = 39.5 Hz, C-2), 156.7 (s, C=O), 161.8 (d, $^1J_{C\text{-}F}$ = 248.2 Hz, *i*-C) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.1 (s, CF_3), –113.2 (m, Ar-F) ppm; IR (KBr): *v* 1697 (C=O), 1508, 1331, 1238, 1199, 1124, 1020 cm^{-1}; ESI-MS (*m/z*): 279.2 (100, $[M+H]^+$); elemental analysis (%) for $C_{10}H_6F_4N_2OS$ (278.2): C 43.17, H 2.17, N 10.07, S 11.52; found: C 43.13, H 2.24, N 10.01, S 11.51.

*4.2.5. 4-(4-Bromophenyl)-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8e**)*

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CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), *Method A*: 213 mg (63%), *Method B*: 98 mg (29%), colourless solid, mp 54–56 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.64 (s, 2 H, 6-H_2), 7.35, 7.56 (2 d_{br}, $J \approx 8.8$ Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.4 (t, C-6), 119.1 (q, $^1J_{C\text{-}F}$ = 275.3 Hz, CF_3), 121.6 (s), 126.5, 132.0 (2 d, 4 CH), 136.8 (q, $^2J_{C\text{-}F}$ = 39.5 Hz, C-2), 139.0 (s), 156.6 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.1 (s, CF_3) ppm; IR (KBr): ν 1698 (C=O), 1489, 1329, 1200, 1147, 1130, 1011 cm^{-1}; ESI-MS (*m*/*z*): 341.0 (97, [M{^{81}Br}+Na]$^+$), 339.0 (100, [M{^{79}Br}+H]$^+$); elemental analysis calcd (%) for $C_{10}H_6BrF_3N_2OS$ (339.1): C 35.42, H 1.78, N 8.26, S 9.45; found: C 35.42, H 1.69, N 8.30, S 9.58.

*4.2.6. 4-(4-Nitrophenyl)-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8f**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:3), *Method A*: 279 mg (91%), *Method B*: 220 mg (72%), colourless solid, mp 98–100 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.70 (s, 2 H, 6-H_2), 7.75, 8.29 (2 d_{br}, $J \approx 9.2$ Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.6 (t, C-6), 119.0 (q, $^1J_{C\text{-}F}$ = 275.6 Hz, CF_3), 124.2, 124.7 (2 d, 4 CH), 138.4 (q, $^2J_{C\text{-}F}$ = 39.8 Hz, C-2), 144.8, 146.3 (2 s), 156.8 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.2 (s, CF_3) ppm; IR (KBr): ν 1701 (C=O), 1516, 1354, 1333, 1314, 1297, 1200, 1146, 1128 cm^{-1}; ESI-MS (*m*/*z*): 306.1 (100, [M+H]$^+$); elemental analysis calcd (%) for $C_{10}H_6F_3N_3O_3S$ (305.2): C 39.35, H 1.98, N 13.77, S 10.50; found: C 39.32, H 2.03, N 13.63, S 10.43.

*4.2.7. 4-(5-Oxo-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-4-yl)benzonitrile (**8g**)*

CC (SiO_2, petroleum ether/EtOAc 4:1), *Method A*: 248 mg (87%), *Method B*: 160 mg (56%), pale yellow solid, mp 111–112 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.68 (s, 2 H, 6-H_2), 7.67, 7.72 (2 d_{br}, $J \approx 8.1$ Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 26.5 (t, C-6), 111.1, 118.0 (2 s), 118.9 (q, $^1J_{C\text{-}F}$ = 275.6 Hz, CF_3), 124.8, 132.7 (2 d, 4 CH), 138.1 (q, $^2J_{C\text{-}F}$ = 39.8 Hz, C-2), 143.4 (s), 156.7 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.2 (s, CF_3) ppm; IR (KBr): ν 2229 (C≡N), 1707 (C=O), 1604, 1332, 1303, 1182, 1146, 1134, 1107 cm^{-1}; ESI-MS (*m*/*z*): 308.0 (100, [M+Na]$^+$), 286.1 (32, [M+H]$^+$); elemental analysis calcd (%) for $C_{11}H_6F_3N_3OS$ (285.2): C 46.32, H 2.12, N 14.73, S 11.24; found: C 46.42, H 2.15, N 14.68, S 11.11.

*4.2.8. 6-Methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-4H-1,3,4-thiadiazin-5(6H)-one (**8h**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 1:4), *Method B*: 175 mg (55%), light orange solid, mp 69–71 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.62 (d, J = 7.1 Hz, 3 H, CH_3), 3.81 (q, J = 7.1 Hz, 1 H, 6-H), 7.73, 8.29 (2 d_{br}, $J \approx$ 9.2 Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 15.9 (q, CH_3), 34.3 (d, C-6), 119.1 (q, $^1J_{C\text{-}F}$ = 275.3 Hz, CF_3), 124.2, 124.7 (2 d, 4 CH), 137.5 (q, $^2J_{C\text{-}F}$ = 39.8 Hz, C-2), 145.2, 146.2 (2 s), 160.6 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –68.4 (s, CF_3) ppm; IR (KBr): ν 1708 (C=O), 1602, 1516, 1353, 1329, 1115 cm^{-1}; ESI-MS (*m*/*z*): 342.0 (100, [M+Na]$^+$); elemental analysis calcd (%) for $C_{11}H_8F_3N_3O_3S$ (319.3): C 41.38, H 2.53, N 13.16, S 10.04; found: C 41.56, H 2.73, N 13.29, S 10.10.

*4.3. Synthesis of 1,3,4-thiadiazin-5-ols **10**; general procedure*

To a solution of the respective hydrazonoyl bromide **9** (1.0 mmol) and 1,4-dithiane-2,5-diol (**6**, 84 mg, 0.55 mmol) in dry THF (10 mL) was added dropwise Et_3N (0.7 mL) and the resulting mixture was stirred at ambient temperature until the starting bromide was fully consumed (TLC monitoring). The precipitate

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triethylammonium salt was filtered off, and the solvents were removed in vacuo. The resulting material was purified by column chromatography (CC) to afford 1,3,4-thiadiazin-5-ols **10**.

*4.3.1. 4-(p-Tolyl)-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-ol (**10a**):*

Reaction time 2h; CC (SiO_2, CH_2Cl_2), 215 mg (78%), colourless solid, mp 83–84 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.33 (s, 3 H, Me), 2.93 (dd, J = 1.7, 12.9 Hz, 1 H, 6-H), 3.06 (d, J = 10.7 Hz, 1 H, OH), 3.18 (dd, J = 3.4, 12.9 Hz, 1 H, 6-H), 5.64 (ddd, J = 1.7, 3.4, 10.7 Hz, 1 H, 5-H), 7.16, 7.29 (2 d, J = 8.4 Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 20.6 (q, Me), 28.5 (t, C-6), 71.1 (d, C-5), 116.6 (d, 2 CH), 119.7 (q, $^1J_{C\text{-}F}$ = 273.0 Hz, CF_3), 120.7 (q, $^2J_{C\text{-}F}$ = 38.9 Hz, C-2), 129.7 (d, 2 CH), 133.2, 143.0 (2 s) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –67.6 (s, CF_3) ppm; IR (KBr): ν 3416 (OH), 1578, 1511, 1331, 1263, 1188, 1137, 999, 813 cm^{-1}; (-)-ESI-MS (*m/z*): 275.3 (100, $[M-H]^-$); elemental analysis calcd (%) for $C_{11}H_{11}F_3N_2OS$ (276.3): C 47.82, H 4.01, N 10.14, S 11.60; found: C 47.80, H 4.15, N 10.47, S 11.56.

*4.3.2. 4-Phenyl-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-ol (**10b**):*

Reaction time 2h; CC (petroleum ether/CH_2Cl_2 1:1 gradient CH_2Cl_2), 199 mg (76%), colourless solid, mp 45–47 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.92 (dd, J = 1.7, 12.9 Hz, 1 H, 6-H), 3.16 (dd, J = 3.4, 12.9 Hz, 1 H, 6-H), 3.21 (d, J = 10.4 Hz, 1 H, OH), 5.66 (ddd, J = 1.7, 3.4, 10.4 Hz, 1 H, 5-H), 7.10-7.13, 7.35-7.42 (2 m, 1 H, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 28.5 (t, C-6), 70.8 (d, C-5), 116.4 (d, 2 CH), 119.6 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CF_3), 121.6 (q, $^2J_{C\text{-}F}$ = 38.9 Hz, C-2), 123.5 (d, CH), 129.2 (d, 2 CH), 145.0 (s) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –67.7 (s, CF_3) ppm; IR (KBr): ν 3408 (OH), 2359, 1599, 1493, 1327, 1263, 1190, 1134, 1014, 758 cm^{-1}; ESI-MS (*m/z*): 263.1 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{10}H_9F_3N_2OS$ (262.3): C 45.80, H 3.46, N 10.68, S 12.22; found: C 45.71, H 3.52, N 10.64, S 12.07.

*4.3.3. 4-(4-Methoxyphenyl)-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-ol (**10c**):*

Reaction time 2h; CC (SiO_2, petroleum ether/CH_2Cl_2 1:1 gradient CH_2Cl_2), 187 mg (64%), red oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.91 (dd, J = 1.7, 12.8 Hz, 1 H, 6-H), 3.14 (dd, J = 3.4, 12.8 Hz, 1 H, 6-H), 3.26 (s_{br}, 1 H, OH), 3.78 (s, 3 H, OMe), 5.55 (dd_{br}, $J \approx$ 1.7, 3.4 Hz, 1 H, 5-H), 6.86-6.89, 7.28-7.31 (2 m, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 28.4 (t, C-6), 55.5 (q, OMe), 71.4 (d, C-5), 114.4, 118.5 (2 d, 2 CH each), 119.7 (q, $^1J_{C\text{-}F}$ = 272.9 Hz, CF_3), 120.5 (q, $^2J_{C\text{-}F}$ = 38.7 Hz, C-2), 139.3, 156.2 (2 s) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –67.6 (s, CF_3) ppm; IR (film): ν 3463 (OH), 2973, 1593, 1575, 1515, 1324, 1247, 1143, 1014, 822 cm^{-1}; ESI-MS (*m/z*): 293.1 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{11}H_{11}F_3N_2O_2S$ (292.3): C 45.20, H 3.79, N 9.58, S 10.97; found: C 45.35, H 3.97, N 9.67, S 10.80.

*4.3.4. 4-(4-Fluorophenyl)-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-ol (**10d**):*

Reaction time 3h; CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 185 mg (66%), yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.96 (dd, J = 1.7, 12.9 Hz, 1 H, 6-H), 3.08 (s_{br}, 1 H, OH), 3.20 (dd, J = 3.4, 12.9 Hz, 1 H, 6-H), 5.61 (dd_{br}, $J \approx$ 1.7, 3.4 Hz, 1 H, 5-H), 7.03-7.07, 7.34-7.37 (2 m, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 28.7 (t, C-6), 71.4 (d, C-5), 115.8 (d, $^2J_{C\text{-}F}$ = 22.7 Hz, 2 CH), 118.3 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 CH), 119.6 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CF_3), 121.5 (q, $^2J_{C\text{-}F}$ = 39.0 Hz, C-2), 141.6 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, *i*-C), 159.4 (d, $^1J_{C\text{-}F}$ = 242.9 Hz, *i*-C) ppm; ^{19}F NMR

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($CDCl_3$, 565 MHz): δ −67.7 (s, CF_3), −120.0 (m, Ar-F) ppm; IR (film): *v* 3421 (OH), 2362, 1508, 1331, 1267, 1230, 1190, 1134, 1014, 831 cm^{-1}; ESI-MS (*m/z*): 281.0 (37, $[M+H]^+$), 280 (100, M^+), 263 (28). elemental analysis calcd (%) for $C_{10}H_8F_4N_2OS$ (280.2): C 42.86, H 2.88, N 10.00, S 11.44; found: C 43.03, H 2.96, N 10.21, S 11.52.

*4.3.5. 4-(4-Bromophenyl)-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-ol (**10e**):*

Reaction time 3h; CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 239 mg (70%), colourless solid, mp 74–75 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.96 (dd, *J* = 1.7, 12.9 Hz, 1 H, 6-H), 3.05 (d_{br}, *J* ≈ 11.1 Hz, 1 H, OH), 3.22 (dd, *J* = 3.4, 12.9 Hz, 1 H, 6-H), 5.63 (ddd_{br}, *J* ≈ 1.7, 3.4, 11.1 Hz, 1 H, 5-H), 7.27-7.30, 7.44-7.47 (2 m, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 28.7 (t, C-6), 70.9 (d, C-5), 116.4 (s, CBr), 117.9 (d, 2 CH), 119.5 (q, $^1J_{C\text{-}F}$ = 273.8 Hz, CF_3), 122.3 (q, $^2J_{C\text{-}F}$ = 39.0 Hz, C-2), 132.1 (d, 2 CH), 144.1 (s) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –67.8 (s, CF_3) ppm; IR (KBr): *v* 3493 (OH), 2924, 2853, 1571, 1493, 1329, 1264, 1139, 1116, 1014, 824 cm^{-1}; (-)-ESI-MS (*m/z*): 339.3 (100, $[M\{^{79}Br\}-H]^-$), 341.3 (94, $[M\{^{81}Br\}-H]^-$); elemental analysis calcd (%) for $C_{10}H_8BrF_3N_2OS$ (341.1): C 35.21, H 2.36, N 8.21, S 9.40; found: C 35.37, H 2.54, N 8.48, S 9.60.

*4.3.6. 4-(4-Nitrophenyl)-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-5-ol (**10f**):*

Reaction time 3h; CC (SiO_2, petroleum ether/CH_2Cl_2 1:1), 218 mg (71%), brown solid, mp 135–136 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.08 (dd, *J* = 1.7, 13.1 Hz, 1 H, 6-H), 3.09 (d, *J* = 11.3 Hz, 1 H, OH), 3.32 (dd, *J* = 3.4, 13.1 Hz, 1 H, 6-H), 5.79 (ddd, *J* = 1.7, 3.4, 11.3 Hz, 1 H, 5-H), 7.52, 8.24 (2 d, *J* = 9.3 Hz, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 29.2 (t, C-6), 70.7 (d, C-5), 115.3 (d, 2 CH), 119.2 (q, $^1J_{C\text{-}F}$ = 274.0 Hz, CF_3), 125.4 (d, 2 CH), 126.0 (q, $^2J_{C\text{-}F}$ = 39.4 Hz, C-2), 143.2, 149.3 (2 s) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –68.1 (s, CF_3) ppm; IR (KBr): *v* 3428 (OH), 1591 (NO_2), 1511, 1431, 1343, 1311, 1260, 1195, 1140, 1113, 1014, 823 cm^{-1}; ESI-MS (*m/z*): 308.1 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{10}H_8F_3N_3O_3S$ (307.2): C 39.09, H 2.62, N 13.68, S 10.43; found: C 39.21, H 2.85, N 13.69, S 10.41.

*4.3.7. 4-(5-Hydroxy-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-4-yl)benzonitrile (**10g**):*

Reaction time 3h; CC (SiO_2, petroleum ether/AcOEt 1:1), 264 mg (92%), colourless solid, mp 155–156 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.04 (dd, *J* = 1.7, 13.1 Hz, 1 H, 6-H), 3.15 (s_{br}, 1 H, OH), 3.29 (dd, *J* = 3.4, 13.1 Hz, 1 H, 6-H), 5.74 (m_c, 1 H, 5-H), 7.47-7.52, 7.61-7.66 (2 m, 2 H each) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 29.0 (t, C-6), 70.6 (d, C-5), 106.2 (s, CN), 115.9 (d, 2 CH), 118.9 (s), 119.3 (q, $^1J_{C\text{-}F}$ = 273.9 Hz, CF_3), 125.2 (q, $^2J_{C\text{-}F}$ = 39.3 Hz, C-2), 133.5 (d, 2 CH), 147.8 (s) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –68.1 (s, CF_3) ppm; IR (KBr): ν = 3371 (OH), 2234 (CN), 1605, 1506, 1340, 1265, 1122, 1068, 1008, 829 cm^{-1}; (-)-ESI-MS (*m/z*): 286.0 (100, $[M-H]^-$); elemental analysis calcd (%) for $C_{11}H_8F_3N_3OS$ (287.3): C 45.99, H 2.81, N 14.63, S 11.16; found: C 46.15, H 3.04, N 14.67, S 11.30.

*4.3.8. 4-(5-Hydroxy-2-(trifluoromethyl)-5,6-dihydro-4H-1,3,4-thiadiazin-4-yl)phenyl benzoate (**10h**):*

Reaction time 4h; CC (SiO_2, CH_2Cl_2/AcOEt 95:5), 271 mg (71%), colourless solid, mp 131–133 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.97 (dd, *J* = 1.6, 12.8 Hz, 1 H, 6-H), 3.10 (d, *J* = 11.0 Hz, 1 H, OH), 3.23 (dd, *J* = 3.5, 12.8 Hz, 1 H, 6-H), 5.68 (ddd, *J* = 1.6, 3.5, 11.0 Hz, 1 H, 5-H), 7.19-7.23, 7.44-7.48, 7.49-7.54, 7.62-7.66, 8.19-8.22 (5 m, 3 × 2 H, 1 H, 2 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 28.7 (t, C-6), 71.3 (d, C-5), 117.5 (d, 2

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CH), 119.6 (q, $^{1}J_{C\text{-}F}$ = 273.1 Hz, CF_3), 121.8 (q, $^{2}J_{C\text{-}F}$ = 39.0 Hz, C-2), 122.4, 128.6 (2 d, 2 CH each), 129.4 (s), 130.2 (d, 2 CH), 133.6 (d, CH), 143.0, 147.0 (2 s), 165.4 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 565 MHz): δ –67.7 (s, CF_3) ppm; IR (KBr): *v* 3416 (OH), 2829, 1702 (C=O), 1452, 1504, 1320, 1265, 1126, 1008, 710 cm^{-1}; ESI-MS (*m/z*): 405.1 (100, $[M+Na]^+$), 383.1 (7, $[M+H]^+$); elemental analysis calcd (%) for $C_{17}H_{13}F_3N_2O_3S$ (382.4): C 53.40, H 3.43, N 7.33, S 8.38; found: C 53.45, H 3.56, N 7.42, S 8.38.

*4.4. Synthesis of thiohydrazonates **13i** and **13j***

To a solution of hydrazonoyl bromide **9f** (312 mg, 1.0 mmol) and 3-mercaptopropionic acid (**12**, 117 mg, 1.1 mmol) or mercaptosuccinic acid (**7c**, 165 mg, 1.1 mmol) in dry THF (10 mL) was added dropwise excess Et_3N (2 mmol, 0.3 mL) at room temperature, and the stirring was continued overnight. The resulting mixture was acidified with aq. HCl (5%), then extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4. After the solvents were removed under reduced pressure, the crude carboxylic acid **11i** or **11j** was dissolved in dry MeOH (10 mL), two drops of conc. H_2SO_4 were added, and the solution was refluxed overnight. The mixture was cooled to room temperature, quenched with $NaHCO_3$ (5%, 10 mL) and extracted with Et_2O (3 × 15 mL). Combined organics were dried (Na_2SO_4), filtered, the solvents were removed in vacuo, and the crude product **13i** or **13j** was purified by chromatography column.

*4.4.1. Methyl 3-((2,2,2-trifluoro-1-(2-(4-nitrophenyl)hydrazono)ethyl)sulfanyl)propanoate (**13i**)*

CC (SiO_2, petroleum ether/CH_2Cl_2 gradient CH_2Cl_2), 86 mg (24%), pale orange solid, mp 87–89 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.68 (t, *J* = 6.1 Hz, 2 H, CH_2), 3.08 (t, *J* = 6.1 Hz, 2 H, S-CH_2), 3.82 (s, 3 H, OMe), 7.39, 8.23 (2 d_{br}, *J* ≈ 9.1 Hz, 2 H each), 10.12 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 27.4, 33.1 (2 t, -CH_2CH_2-), 52.5 (q, OMe), 114.0 (d, 2 arom. CH), 120.8 (q, $^{1}J_{C\text{-}F}$ = 272.5 Hz, CF_3), 124.7 (q, $^{2}J_{C\text{-}F}$ = 38.6 Hz, *C*-CF_3), 125.8 (d, 2 arom. CH), 142.6, 147.5 (2 s), 172.8 (s, C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –66.4 (s, CF_3) ppm; ESI-MS (*m/z*): 374 (23, $[M+Na]^+$), 352.3 (100, $[M+H]^+$); elemental analysis calcd (%) for $C_{12}H_{12}F_3N_3O_4S$ (351.3): C 41.03, H 3.44, N 11.96, S 9.13; found: C 41.19, H 3.51, N 11.87, S 9.31.

*4.4.2. Dimethyl 2-((2,2,2-trifluoro-1-(2-(4-nitrophenyl)hydrazono)ethyl)sulfanyl)succinate (**13j**)*

CC (SiO_2, CH_2Cl_2), 102 mg (25%), pale yellow solid, mp 113–114 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.91 (dd, *J* = 9.9, 18.3 Hz, 1 H, -CH_2-), 3.06 (dd, *J* = 4.3, 18.3 Hz, 1 H, -CH_2-), 3.77, 3.84 (2 s, 2 × 3 H, 2 OMe), 4.00 (dd, *J* = 4.3, 9.9 Hz, 1 H, S-CH), 7.43, 8.24 (2 d_{br}, *J* ≈ 9.1 Hz, 2 H each), 10.48 (s_{br}, 1 H, NH) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz): δ 35.1 (t, -CH_2-), 42.3 (d, S-CH), 52.8, 53.2 (2 q, 2 OMe), 114.2 (d, 2 arom. CH), 120.5 (q, $^{1}J_{C\text{-}F}$ = 272.6 Hz, CF_3), 122.4 (q, $^{2}J_{C\text{-}F}$ = 39.0 Hz, *C*-CF_3), 125.8 (d, 2 arom. CH), 142.9, 147.4 (2 s), 170.8, 171.8 (2 s, 2 C=O) ppm; ^{19}F NMR ($CDCl_3$, 188 MHz): δ –66.4 (s, CF_3) ppm; IR (KBr): *v* 3210 (N-H), 1737 (C=O), 1719 (C=O), 1603, 1552, 1339, 1252, 1148, 1125, 1108, 988 cm^{-1}; ESI-MS (*m/z*): 432.0 (100, $[M+Na]^+$); elemental analysis calcd (%) for $C_{14}H_{14}F_3N_3O_6S$ (409.3): C 41.08, H 3.45, N 10.27, S 7.83; found: C 41.30, H 3.40, N 10.46, S 7.73.

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