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Synthesis of 2-Aryl-2-trifluoromethyl-1,3-thiazolidin-4-ones and 2-Aryl-2-trifluoromethyltetrahydro-4*H*-1,3-thiazin-4-ones and Their Oxidation with Hydrogen Peroxide

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Abstract—Reactions of aryl trifluoromethyl ketone imines with 2-sulfanylacetic and 3-sulfanylpropanoic acids afforded 2-aryl-2-trifluoromethyl-1,3-thiazolidin-4-ones and 2-aryl-2-trifluoromethyltetrahydro-4*H*-1,3-thiazin-4-ones, respectively. Their subsequent oxidation with hydrogen peroxide gave the corresponding 2-aryl-2-trifluoromethyl-1,3-thiazolidin-4-one 1-oxides and 2-aryl-2-trifluoromethyltetrahydro-4*H*-1,3-thiazin-4-one 1-oxides and 1,1-dioxides.

Keywords: aryl trifluoromethyl ketone imines, 1,3-thiazolidin-4-ones, tetrahydro-4*H*-1,3-thiazin-4-ones, 2-sulfanylacetic acid, 2-sulfanylpropanoic acid, oxidation, hydrogen peroxide

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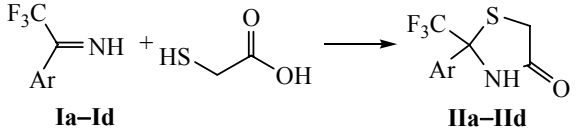
Hydrogenated 1,3-thiazole and 1,3-thiazine derivatives are quite promising compounds from the viewpoint of modern medicinal chemistry. This follows from advantages in the field of design of biologically active 1,3-thiazolidin-4-ones [1–3] and tetrahydro-1,3-thiazin-4-ones [4, 5] via targeted introduction of pharmacophoric fragments into base systems.

In recent time, trifluoromethyl groups possessing unique physicochemical and biological properties have been widely used as efficient pharmacophores [6–8]. The most convenient procedures for the synthesis of the majority of known trifluoromethyl-substituted 1,3-thiazolidin-4-ones and tetrahydro-1,3-thiazin-4-ones were based on reactions of highly electrophilic hexa(penta)fluoroacetone imines [9, 10] or trifluoromethylpyruvic acid esters [11, 12] with 2-sulfanylacetic and 3-sulfanylpropanoic acids, respectively. We previously developed a synthetic approach to 2-aryl-2-trifluoromethyl-1,3-thiazolidin-4-ones via condensation of 2-sulfanylacetic acid or its alkyl esters with 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates [13, 14]. However, the latter are difficultly accessible compounds, which somewhat restricts the preparative scope of the proposed approach. Therefore, in the present work we tried to develop a convenient procedure for the synthesis of the aforesaid S,N-heterocycles by reactions of 2-sulfanylacetic and 3-sulfanylpropanoic acids with aryl trifluoromethyl ketone imines that are less electrophilic [15] than Schiff bases derived from hexa(penta)fluoroacetone and trifluoromethylpyruvic acid esters.

Ketimines **Ia**–**Id** smoothly reacted with 2-sulfanylacetic acid in diethyl ether at room temperature to give 2-aryl-2-trifluoromethyl-1,3-thiazolidin-4-ones **IIa**–**IId** in 71–83% yield. The products were identical to those reported previously [13] (Scheme 1). 3-Sulfanylpropanoic acid failed to react with **Ib**–**Id** under analogous conditions. When the reaction was carried out in polar DMF, 3-sulfanylpropanoic acid added to the C=N bond of **Ib**–**Id** with formation of acyclic adducts **A** which displayed in the ^{19}F NMR spectra a signal at δ_F –74 ppm due to the CF_3 group [13]. The subsequent intramolecular cyclization of

Scheme 1.



Ia–Id **IIa–IId**

Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**).

adducts **A** into 2-aryl-2-trifluoromethyl-1,3-thiazin-4-ones **IIIa**–**IIIc** was achieved by treatment with thionyl chloride at –90°C, followed by raising the temperature to ambient (Scheme 2). However, the reaction selectivity was low, and the yield of target compounds **III** did not exceed 19–46%.

The cyclic structure of thiazines **IIIa**–**IIIc** was confirmed by the NMR data. Their ^{19}F NMR spectra characteristically contained a signal at δ_F –75 ppm due to the CF_3 group. The asymmetric C^2 atom gave rise to a quartet signal at δ_C 67 ppm (J_{CF} = 28.9 Hz) in the ^{13}C NMR spectra. Diastereotopic methylene protons resonated in the ^1H NMR spectra as multiplets at δ 2.66–2.91 (3H) and 3.23–3.34 ppm (1H).

It is known that introduction of a sulfoxide or sulfonyl group into molecules organic compounds often endows them with biological activity [16, 17]. Particular attention was given to the synthesis of sulfoxides and sulfonyl derivatives from 1,3-thiazolidin-4-ones [18–22] and 1,3-thiazin-4-ones [23, 24], though only one 2-fluoroalkyl-substituted thiazolidine 1,1-dioxide has been reported [9].

Hydrogen peroxide plays a specific role in modern methodologies for environmentally safe transformation of sulfides into sulfoxides and sulfones [25–28]. It seemed reasonable to examine the behavior of 2-trifluoromethyl-substituted thiazolidin-4-ones **IIa**–**IId** and thiazin-4-ones **IIIa**–**IIIc** under the action of hydrogen peroxide. Monitoring of the reaction progress by ^{19}F NMR showed that the conversion of

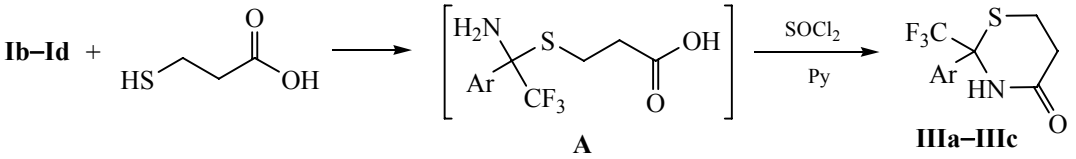
Fractions of diastereoisomers **IVa**–**IVd**, **Va**, and **Vb** according to the ^{19}F NMR data

Compound no.	Stereoisomer fraction, % (δ_F, ppm)	
	1*S*,*R*,2*S*,*R*	1*S*,*R*,2*R*,*S*
IVa	74 (–71.73)	26 (–70.20)
IVb	78 (–71.78)	22 (–70.25)
IVc	83 (–71.62)	17 (–70.22)
IVd	81 (–71.75)	19 (–70.28)
Va	44 (–72.27)	56 (–70.55)
Vb	47 (–72.52)	53 (–70.82)

IIa–**IId** into the corresponding sulfoxides in acetic acid at room temperature in the presence of 5 equiv of H_2O_2 was 73–78% in 48 h. The optimal conditions for the selective formation of sulfoxides **IVa**–**IVd** were temperature 50°C and reaction time 5 h (Scheme 3). Even when the reaction mixture was heated for 10 h uner reflux, no further oxidation to sulfones was observed. According to the ^{19}F, compound **IVa**–**IVd** were mixtures of two diastereoisomers whose ratio varied from 74 : 26 to 83 : 17 (see table).

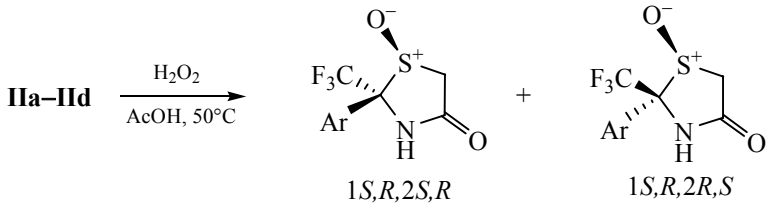
The major stereoisomer characteristically showed in the ^1H NMR spectrum two *AB* doublets from the diastereotopic methylene protons at δ 3.54–3.59 and 3.82–4.06 ppm (J = 16.8–17.4 Hz), while the corresponding signals of the minor stereoisomer were singlets in the region δ 3.47–3.50 ppm. The fluorine nuclei resonated in the ^{19}F NMR spectra of **IV** at δ_F –71.62 to –71.78 (major isomer) or –70.20 to –70.28 ppm (minor isomer). We succeeded in isolating the major

Scheme 2.

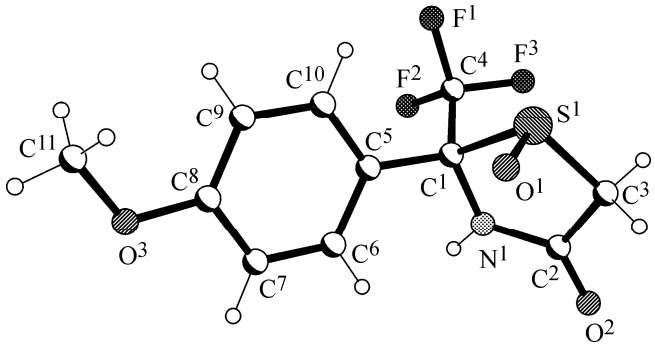


Ar = 4-FC_6H_4 (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**).

Scheme 3.



Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**).



Structure of the molecule of (1*SR*,2*SR*)-2-(4-methoxyphenyl)-2-(trifluoromethyl)-1,3-thiazolidin-4-one 1-oxide (**IVd**) according to the X-ray diffraction data (methylene chloride solvate molecule is not shown); principal geometric parameters: S^1–O^1 1.472(3), S^1–C^1 1.923(3), S^1–C^3 1.793(3), C^1–N^1 1.434(4), C^2–N^1 1.339(4), C^2–C^3 1.510(5), C^2–O^2 1.219(4), C^1–C^4 1.531(5), C^1–C^5 1.506(5) Å; $C^3S^1C^1$ 90.17 (15), $N^1C^1S^1$ 104.5(2), $C^2N^1C^1$ 120.4(3), $N^1C^2C^3$ 111.9(3), $C^2C^3S^1$ 109.7(2), $O^1S^1C^1$ 105.89(16), $O^1S^1C^3$ 107.75(17), $O^2C^2N^1$ 124.8(3), $O^2C^2C^3$ 123.3(3)°.

stereoisomer by fractional crystallization from benzene–hexane (1 : 1).

The structure of **IVd** was also proved by X-ray analysis (see figure). Compound **IVd** crystallized from methylene chloride as 1 : 1 solvate. The S^1–C^1 bond in molecule **IVd** is appreciably longer than S^1–C^3 [1.923(3) and 1.793(3) Å, respectively], presumably due to the presence of a strong electron-withdrawing CF_3 group induces a considerable shift of electron density. The C^1–N^1 bond length is typical of a single C–N bond, whereas the N^1–C^2 bond is appreciably shortened and may be regarded as delocalized C–N bond due to conjugation of the lone electron pair on the N^1 atom and carbonyl π-bond. On the basis of the X-ray diffraction data for **IVd**, the major stereoisomers of **IVa**–**IVd** were assigned 1*SR*,2*SR* configuration.

Thiazin-4-ones **IIIb** and **IIIc** reacted with 3.5 equiv of hydrogen peroxide at temperature (48 h) with selective formation of sulfoxides **Va** and **Vb** as mixtures of two diastereoisomers at ratios of 56 : 44 (**Va**) and 53 : 47 (**Vb**) (according to the ^{19}F NMR data). Pure diastereoisomers were isolated from the reaction mixtures by fractional crystallization from propan-2-ol. Treatment of **IIIa**–**IIIc** with 5 equiv of hydrogen peroxide for 4 days resulted in complete oxidation of the sulfur atom and formation of 43–54% of 2-aryl-2-trifluoromethyltetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxides **VIa**–**VIc** (Scheme 4). Raising the temperature to 50–60°C led to sharply reduced yield of **VI** because of decomposition of the thiazine ring.

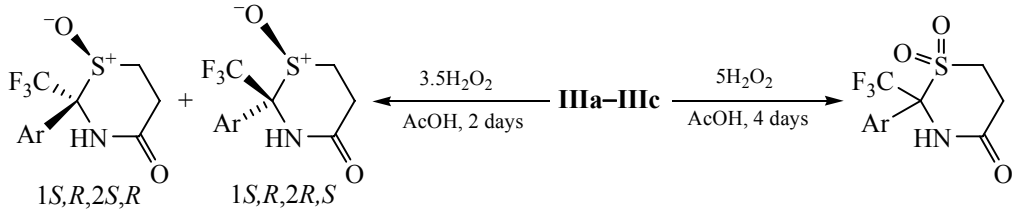
Thus, noncatalytic hydrogen peroxide oxidation of relatively strained 2-trifluoromethylthiazolidin-4-ones give the corresponding sulfoxides with no further oxidation, whereas more flexible 2-trifluoromethyltetrahydro-4*H*-1,3-thiazin-4-ones can be converted into both sulfoxide and sulfonyl derivatives.

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance DRX-500 spectrometer at 500.13 and 127.75 MHz, respectively, from solutions in $CDCl_3$ (**II**–**V**) or DMSO-d_6 (**VI**) using tetramethylsilane as internal reference. The ^{19}F NMR spectra were obtained on a Varian Gemini instrument at 188.14 MHz using trichlorofluoromethane as reference. The mass spectra were obtained on an Agilent 1100/DAD/HSD/VLG119562 instrument.

The X-ray diffraction data for compound **IVd** were acquired on a Bruker Smart Apex II diffractometer (MoK_α radiation, graphite monochromator, θ_{max} = 26.34°, spherical segment $-7 \le h \le 11$, $-10 \le k \le 11$, $-12 \le l \le 12$) from a 0.33×0.19×0.14-mm single crystal at room temperature. Triclinic crystal system, space group *P*-1; $C_{12}H_{12}Cl_2F_3NO_3S$, *M* 378.19; unit

Scheme 4.



Ar = 4-MeC_6H_4 (**Va**), 4-$MeOC_6H_4$ (**Vb**), 4-FC_6H_4 (**VIa**), 4-MeC_6H_4 (**VIb**), 4-$MeOC_6H_4$ (**VIc**).

cell parameters: a = 9.2506(14), b = 9.5460(12), c = 10.2802(13) Å; α = 77.251(7), β = 74.218(7), γ = 65.095(7)°; V = 786.47(18) Å^3; Z = 2; d_{calc} = 1.597 g/cm^3; μ = 0.586 mm^{-1}; F(000) = 384. Total of 9813 reflection intensities were measured, 3114 of which were independent (averaging R-factor 0.0370). A correction for absorption was applied by the multiscan technique using SADABS (T_{min}/T_{max} = 0.8301/0.9224). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using Bruker SHELXTL software [29]. All hydrogen atoms (except for N^{1}H) were refined according to the riding model, and the position of N^{1}H was refined in isotropic approximation. All 3114 independent reflections, includ-ing 2116 reflections with $I > 2\sigma(I)$ were involved in the refinement (204 variables, 10.4 reflections per variable). The final divergence factors were $R_1(F)$ = 0.0594, $wR_2(F^2)$ = 0.1506 for reflections with $I > 2\sigma(I)$ and $R_1(F)$ = 0.0890, $wR_2(F^2)$ = 0.1694 (goodness of fit 1.059) for all independent reflections; residual electron density from the Fourier difference map after the last iteration – 0.78 and –0.65 e/Å^3.

General procedure for the synthesis of compounds IIa–IId. A solution of 1.84 g (0.02 mol) of 2-sulfanylacetic acid in 40 mL of anhydrous diethyl ether was added under stirring at room temperature to a solution of 0.02 mol of ketimine **Ia**–**Id** in 40 mL of anhydrous diethyl ether, and the mixture was stirred for 10 h at room temperature. The solvent was evaporated, and the residue was recrystallized from benzene–hexane. The physicochemical constants of compounds **IIa**, **IIc**, and **IId** coincided with those given in [12]. Yield 83 (**IIa**), 71 (**IIc**), 77% (**IId**).

2-(4-Fluorophenyl)-2-(trifluoromethyl)-1,3-thiazolidin-4-one (IIb). Yield 75%, mp 152–153°C (from hexane–benzene, 4:1). IR spectrum, ν, cm^{-1}: 1705 (C=O), 3385 (N–H). ^{1}H NMR spectrum, δ, ppm: 3.66 d (1H, CH$_2$, J = 15.6 Hz), 7.11 t (2H, H$_{arom}$, J = 8.8 Hz), 7.49–7.54 m (2H, H$_{arom}$), 9.10 s (1H, NH). ^{13}C NMR spec-trum, δ_C, ppm: 32.87 (C^5), 69.29 q (C^2, $^2J_{CF}$ = 31.4 Hz), 115.44 d (C$_{arom}$, $^2J_{CF}$ = 35.2 Hz), 125.34 q (CF$_3$, $^1J_{CF}$ = 284.1 Hz), 126.70 d (C$_{arom}$, $^3J_{CF}$ = 11.3 Hz), 131.69 (C$_{arom}$), 162.36 d (C$_{arom}$, $^1J_{CF}$ = 247.6 Hz), 173.71 (C^4). ^{19}F NMR spectrum, δ_F, ppm: –78.31 (CF$_3$), –112.43 (C$_6$H$_4$F). Mass spectrum: m/z 266 [M + 1]$^+$. Found, %: C 45.52; H 2.51; F 28.78. $C_{10}H_7F_4NOS$. Calculated, %: C 45.25; H 2.66; F 28.65. M 265.23.

General procedure for the synthesis of compounds IIIa–IIIc. A solution of 1.27 g (0.012 mol) of 3-sulfanylpropanoic acid in 5 mL of DMF was added under stirring to a solution of 0.01 mol of ketimine **Ib**–**Id** in 10 mL of anhydrous DMF, cooled to 0°C. The mixture was allowed to warm up to room temperature and stirred for 10 h, and 2 mL (0.025 mol) of pyridine was added. The mixture was placed in a propan-2-ol bath cooled to the freezing point (ca. –90°C), 0.91 mL (0.0125 mol) of thionyl chloride was added, and the mixture was kept for 10 h at room temperature and evaporated at 40–50°C under reduced pressure (water-jet pump). The residue was dissolved in 50 mL of methylene chloride, the solution was neutralized with a solution of sodium hydrogen carbonate, and the organic phase was separated, washed with water (2×10 mL), dried over anhydrous sodium sulfate, and evaporated. The oily residue was ground with 5 mL of diethyl ether, and the precipitate was filtered off and dried in air.

2-(4-Fluorophenyl)-2-(trifluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-one (IIIa). Yield 27%, mp 138–139°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3210 (N–H). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 2.66–2.90 m (3H, CH$_2$), 3.24–3.32 m (1H, CH$_2$), 7.09–7.14 m (2H, CH), 7.49 s (1H, NH), 7.61–7.65 m (2H, CH). ^{13}C NMR spectrum, δ_C, ppm: 23.68 (C^6), 32.63 (C^5), 67.42 q (C^2, $^2J_{CF}$ = 28.9 Hz), 115.58 d (C$_{arom}$, $^2J_{CF}$ = 21.4 Hz), 125.25 q (CF$_3$, $^1J_{CF}$ = 286.6 Hz), 129.15 d (C$_{arom}$, $^3J_{CF}$ = 7.5 Hz), 132.46 d (C$_{arom}$, $^4J_{CF}$ = 2.5 Hz), 162.42 d (C$_{arom}$, $^1J_{CF}$ = 247.6 Hz), 170.17 (C^4). ^{19}F NMR spectrum (CDCl$_3$), δ_F, ppm: –75.03 (CF$_3$), –112.31 (C$_6$H$_4$F). Mass spectrum: m/z 280 [M + 1]$^+$. Found, %: C 47.56; H 3.13; F 27.02. $C_{11}H_9F_4NOS$. Calculated, %: C 47.31; H 3.25; F 27.21. M 279.25.

2-(4-Methylphenyl)-2-(trifluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-one (IIIb). Yield 46%, mp 145–147°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3190 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH$_3$), 2.66–2.91 m (3H, CH$_2$), 3.24–3.34 m (1H, CH$_2$), 6.89 s (1H, NH), 7.23 d (2H, H$_{arom}$, J = 8.1 Hz), 7.49 d (2H, H$_{arom}$, J = 8.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.60 (CH$_3$), 23.66 (C^6), 32.66 (C^5), 67.58 q (C^2, $^2J_{CF}$ = 28.9 Hz), 125.43 q (CF$_3$, $^1J_{CF}$ = 286.6 Hz); 126.51, 129.19, 133.20, 138.95 (C$_{arom}$); 170.24 (C^4). ^{19}F NMR spectrum: δ_F –74.99 ppm. Mass spectrum: m/z 276 [M + 1]$^+$. Found, %: C 52.59; H 4.57; F 20.93. $C_{12}H_{12}F_3NOS$. Calculated, %: C 52.36; H 4.39; F 20.70. M 275.29.

2-(4-Methoxyphenyl)-2-(trifluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-one (IIIc). Yield 19%, mp 151–153°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3200 (N–H). ^{1}H NMR spectrum, δ, ppm: 2.66–2.91 m (3H, CH$_2$), 3.23–

3.32 m (1H, CH_2), 3.82 s (3H, CH_3), 6.93 d (2H, H_{arom}, J = 9.0 Hz), 6.99 s (1H, NH), 7.54 d (2H, H_{arom}, J = 9.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.64 (C^6), 32.66 (C^5), 55,35 (CH_3), 67.50 q (C^2, $^2J_{CF}$ = 28.9 Hz), 113.95 (C_{arom}), 125.40 q (CF_3, $^1J_{CF}$ = 286.6 Hz), 127.86 (C_{arom}), 128.13 (C_{arom}), 159.80 (C_{arom}), 170.21 (C^4). ^{19}F NMR spectrum ($CDCl_3$): δ_F –75.10 ppm. Mass spectrum: *m*/*z* 292 $[M + 1]^+$. Found, %: C 49.23; H 4.06; F 19.39. $C_{12}H_{12}F_3NO_2S$. Calculated, %: C 49.48; H 4.15; F 19.57. *M* 291.29.

General procedure for the synthesis of sulfoxides IVa–IVd. Thiazolidine **IIa**–**IId**, 0.002 mol, was dissolved in 20 mL of glacial acetic acid, 0.68 mL (0.01 mol) of 30% hydrogen peroxide was added, and the mixture was stirred for 5 h at 50°C and evaporated under reduced pressure. The residue was treated with 20 mL of water, and the precipitate was filtered off, dried in air, and recrystallized twice from benzene–hexane (1 : 1). Compound **IVd** was additionally recrystallized from methylene chloride.

(1*SR*,2*SR*)-2-Phenyl-2-(trifluoromethyl)-1,3-thiazolidin-4-one 1-oxide (IVa). Yield 60%, mp 131–132°C. IR spectrum, ν, cm^{-1}: 1715 (C=O), 3305 (N–H). ^1H NMR spectrum, δ, ppm: 3.56 d and 4.02 d (1H each, CH_2, J = 16.8 Hz), 7.49–7.62 m (5H, H_{arom}), 8.55 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 54.49 (CH_2), 83.84 q (C^2, $^2J_{CF}$ = 28.91 Hz), 123.41 q (CF_3, $^1J_{CF}$ = 284.10 Hz); 125.45, 127.94, 128.90, 130.73 (C_{arom}); 172.00 (C=O). ^{19}F NMR spectrum: δ_F –71.75 ppm. Mass spectrum: *m*/*z* 264 $[M + 1]^+$. Found, %: C 45.42; H 2.94; F 21.50. $C_{10}H_8F_3NO_2S$. Calculated, %: C 45.63; H 3.06; F 21.65. *M* 263.24.

(1*SR*,*2SR*)-2-(4-Fluorophenyl)-2-(trifluoromethyl)-1,3-thiazolidin-4-one 1-oxide (IVb). Yield 63%, mp 147–148°C. IR spectrum, ν, cm^{-1}: 1710 (C=O), 3310 (NH). ^1H NMR spectrum, δ, ppm: 3.59 d and 4.06 d (1H each, CH_2, J = 17.4 Hz), 7.20–7.27 m (2H, H_{arom}), 7.58–7.62 m (2H, H_{arom}) 8.54 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 54.77 (CH_2), 83.24 q (C^2, $^2J_{CF}$ = 28.90 Hz), 116.25 d (C_{arom}, $^2J_{CF}$ = 21.37 Hz), 122.19 (C_{arom}), 123.59 q (CF_3, $^1J_{CF}$ = 284.10 Hz), 130.18 d (C_{arom}, $^3J_{CF}$ = 8.80 Hz), 163.78 d (C_{arom}, $^3J_{CF}$ = 25.14 Hz), 171.87 (C=O). ^{19}F NMR spectrum, δ_F, ppm: –71.67 (CF_3), –109.74 (FC_6H_4). Mass spectrum: *m*/*z* 282 $[M + 1]^+$. Found, %: C 42.95; H 2.35; F 26.79. $C_{10}H_7F_4NO_2S$. Calculated, %: C 42.71; H 2.51; F 27.02. *M* 281.23.

(1*SR*,2*SR*)-2-(4-Methylphenyl)-2-(trifluoromethyl)-1,3-thiazolidin-4-one 1-oxide (IVc). Yield 57%, mp 137–138°C. IR spectrum, ν, cm^{-1}: 1715 (C=O), 3330 (NH). ^1H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 3.56 d and 4.02 d (1H each, CH_2, J = 17.1 Hz), 7.32 d (2H, H_{arom}, J = 8.1 Hz), 7.47 d (2H, H_{arom}, J = 8.1 Hz) 8.41 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.87 (CH_3), 54.57 (CH_2), 83.81 q (C^2, $^2J_{CF}$ = 28.90 Hz), 123.36 q (CF_3, $^1J_{CF}$ = 256.45 Hz); 122.08, 127.74, 130.00, 140.99 (C_{arom}); 172.02 (C=O). ^{19}F NMR spectrum: δ_F –71.66 ppm. Mass spectrum: *m*/*z* 278 $[M + 1]^+$. Found, %: C 47.72; H 3.55; F 20.73. $C_{11}H_{10}F_3NO_2S$. Calculated, %: C 47.65; H 3.64; F 20.56. *M* 277.27.

(1*SR*,2*SR*)-2-(4-Methoxyphenyl)-2-(trifluoromethyl)-1,3-thiazolidin-4-one 1-oxide (IVd). Yield 66%, mp 154–156°C. IR spectrum, ν, cm^{-1}: 1715 (C=O), 3325 (NH). ^1H NMR spectrum, δ, ppm: 3.54 d (1H, CH_2, J = 17.2 Hz), 3.82 s (3H, CH_3O), 3.99 d (1H, CH_2, J = 17.2 Hz), 7.00 d (2H, H_{arom}, J = 8.8 Hz), 7.49 d (2H, H_{arom}, J = 8.8 Hz) 8.15 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 54.49 (CH_2), 55.01 (OCH_3), 83.65 q (C^2, $^2J_{CF}$ = 28.90 Hz); 114.28, 116.60, 129.39, 161.12 (C_{arom}); 123.50 q (CF_3, $^1J_{CF}$ = 285.36 Hz), 171.83 (C=O). ^{19}F NMR spectrum: δ_F –71.78 ppm. Mass spectrum: *m*/*z* 294.0 $[M + 1]^+$. Found, %: C 45.29; H 3.36; F 19.26. $C_{11}H_{10}F_3NO_3S$. Calculated, %: C 45.05; H 3.44; F 19.43. M 293.27.

General procedure for the synthesis of compounds Va and Vb. Thiazine **IVb** or **IVc**, 0.002 mol, was dissolved in 10 mL of glacial acetic acid, 0.4 mL of 30% hydrogen peroxide was added, and the mixture was kept for 48 h at room temperature and evaporated under reduced pressure. The residue was ground with water, and the precipitate was filtered off, washed with water, dried in air, and recrystallized twice from propan-2-ol.

(1*SR*,2*SR*)-2-(4-Methylphenyl)-2-(trifluoromethyl)-tetrahydro-4*H*-1,3-thiazin-4-one 1-oxide (Va). Yield 27%, mp 173–175°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 3200 (NH). ^1H NMR spectrum, δ, ppm: 2.39–2.56 m (5H, CH_2, CH_3), 2.92–3.00 m and 3.15–3.28 m (1H each, CH_2), 7.31 d (2H, H_{arom}, J = 8.1 Hz), 7.40 d (2H, H_{arom}, J = 8.1 Hz), 7.53 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.71 (CH_3), 21.69 (C^5), 38.09 (C^6), 80.08 q (C^2, $^2J_{CF}$ = 26.4 Hz), 123.58 q (CF_3, $^1J_{CF}$ = 285.4 Hz); 126.43, 129.28, 130.35, 140.33 (C_{arom}); 168.70 (C^4). ^{19}F NMR spectrum ($CDCl_3$): δ_F –72.25 ppm. Mass spectrum: *m*/*z* 292 $[M + 1]^+$. Found, %: C 49.57; H 4.29; F 19.34. $C_{12}H_{12}F_3NO_2S$. Calculated, %: C 49.48; H 4.15; F 19.57. *M* 291.29.

(1*SR*,2*SR*)-2-(4-Methoxyphenyl)-2-(trifluoromethyl)-

tetrahydro-4*H*-1,3-thiazin-4-one 1-oxide (Vb). Yield 25%, mp 167–169°C. IR spectrum, ν, cm^{-1}: 1685 (C=O), 3210 (NH). ^1H NMR spectrum, δ, ppm: 2.44–2.58 m (2H, CH_2), 2.93–3.01 m and 3.17–3.29 m (1H each, CH_2), 3.84 s (3H, CH_3), 7.00 d (2H, H_{arom}, J = 9.3 Hz), 7.23 s (1H, NH), 7.44 (2H, H_{arom}, J = 9.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.67 (C^5), 38.02 (C^6), 55.45 (OCH_3), 79.82 q (C^2, $^2J_{CF}$ = 26.4 Hz), 115.14 (C_{arom}), 123.60 q (CF_3, $^1J_{CF}$ = 287.9 Hz); 123.77, 128.06, 160.60 (C_{arom}); 168.70 (C^4). ^{19}F NMR spectrum ($CDCl_3$): δ_F –72.56 ppm. Mass spectrum: *m*/*z* 308 $[M + 1]^+$. Found, %: C 47.17; H 3.81; F 18.80. $C_{12}H_{12}F_3NO_3S$. Calculated, %: C 46.90; H 3.94; F 18.55. *M* 307.29.

General procedure for the synthesis of compounds VIa–VIc. Thiazine **IVa–IVc**, 0.002 mol, was dissolved in 10 mL of glacial acetic acid, 1 mL of 30% hydrogen peroxide was added, and the mixture was kept for 4 days at room temperature and evaporated under reduced pressure. The residue was ground with water, and the precipitate was filtered off, washed with water (2×10 mL), and dried in air.

2-(4-Fluorophenyl)-2-(trifluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxide (VIa). Yield 54%, mp 187–188°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3190 (N–H). ^1H NMR spectrum, δ, ppm: 3.00 t (2H, CH_2, J = 6.6 Hz), 3.80 t (2H, CH_2, J = 6.6 Hz), 7.42 t (2H, H_{arom}, J = 8.7 Hz), 7.73 d.d (2H, H_{arom}, J = 5.1, 7.8 Hz), 9.73 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.42 (C^5), 44.63 (C^6), 78.65 q (C^2, $^2J_{CF}$ = 27.6 Hz), 115.80 d (C_{arom}, $^2J_{CF}$ = 22.6 Hz), 122.85 q (CF_3, $^1J_{CF}$ = 287.9 Hz), 123.15 (C_{arom}), 131.06 d (C_{arom}, $^3J_{CF}$ = 8.8 Hz), 163.52 d (C_{arom}, $^1J_{CF}$ = 248.9 Hz), 167.62 (C^4). ^{19}F NMR spectrum, δ_F, ppm: –67.58 (CF_3), –110.55 (FC_6H_4), Mass spectrum: *m*/*z* 312 $[M + 1]^+$. Found, %: C 42.70; H 3.05; F 24.66. $C_{12}H_{12}F_3NO_3S$. Calculated, %: C 42.45; H 2.91; F 24.42. *M* 311.26 .

2-(4-Methylphenyl)-2-(trifluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxide (VIb). Yield 50%, mp 196–198°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3215 (N–H). ^1H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 2.98 t (2H, CH_2, J = 6.6 Hz), 3.75 t (2H, CH_2, J = 6.6 Hz), 7.46 d (2H, H_{arom}, J = 8.4 Hz), 7.56 d (2H, H_{arom}, J = 8.4 Hz), 9.65 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.71 (CH_3), 30.44 (C^5), 44.57 (C^6), 78.92 q (C^2, $^2J_{CF}$ = 27.6 Hz), 122.96 q (CF_3, $^1J_{CF}$ = 287.9 Hz), 124.03 (C_{arom}), 128.32 (C_{arom}), 129.29 (C_{arom}), 140.68 (C_{arom}), 167.68 (C^4). ^{19}F NMR spectrum: δ_F –67.51 ppm. Mass spectrum: *m*/*z* 308 $[M + 1]^+$. Found, %: C 46.62; H 4.07; F 18.46. $C_{12}H_{12}F_3NO_3S$. Calculated, %: C 46.90; H 3.94; F 18.55. *M* 307.29.

2-(4-Methoxyphenyl)-2-(trifluoromethyl)tetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxide (VIc). Yield 43%, mp 189–191°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 3210 (N–H). ^1H NMR spectrum, δ, ppm: 2.98 t (2H, CH_2, J = 6.3 Hz), 3.74 t (2H, CH_2, J = 6.3 Hz), 3.81 s (3H, CH_3), 7.10 d (2H, H_{arom}, J = 8.7 Hz), 7.59 d (2H, H_{arom}, J = 8.7 Hz), 9.63 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 30.44 (C^5), 44.47 (C^6), 55,45 (CH_3), 88.76 q (C^2, $^2J_{CF}$ = 27.6 Hz), 114.11 (C_{arom}), 118.40 (C_{arom}), 122.99 q (CF_3, $^1J_{CF}$ = 287.9 Hz), 130.01 (C_{arom}), 161.00 (C_{arom}), 167.70 (C^4). ^{19}F NMR spectrum: δ_F –67.63 ppm. Mass spectrum: *m*/*z* 324 $[M + 1]^+$. Found, %: C 44.33; H 3.79; F 17.53. $C_{12}H_{12}F_3NO_4S$. Calculated, %: C 44.58; H 3.74; F 17.63. *M* 323.29.

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