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A route to fluorocontaining *N*,*S*-heterocycles *via* octafluoro-2,3-epoxybutane

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Abstract

The reaction of octafluoro-2,3-epoxybutane **1** with 2-aminothiophenol gave three kinds of novel fluorocontaining *N*,*S*-heterocyclic compounds depending on the solvent nature: 2,3-bis(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-ol **2**, 2-trifluoromethyl-2-[1-(2-aminophenylthio)-2,2,2-trifluoroethyl]-1,3-benzothiazolidine **6** and 5a,11a-bis(trifluoromethyl)-5a,6,11a,12-tetrahydro-5,11-dithia-6,12-diazanaphthacene **5**. Use of the toluene, dioxane, tetrahydrofuran, acetonitrile and dimethoxyethane gave the unexpected dihydrobenzothiazine **2** (*RS*,*SR* > *RR*,*SS*) in good to moderate yields. In dimethylsulfoxide and *N*,*N*-dimethylacetamide, unusual cyclization occurred resulting in benzothiazolidine **6** (*RS*,*SR*/*RR*,*SS* ~ 1:1) in moderate yields. Formation of minor 1,1,1,3,4,4,4-heptafluoro-3-(2-aminophenylthio)-2,2-dihydroxybutane **4** which was converted into bis(benzothiazine) **5** was observed in all solvents tested with the exception of toluene and dioxane. The molecular structure of the *RS*,*SR*-diastereomer of dihydrobenzothiazine **2**, bis(benzothiazine) **5** and the *RS*,*SR*-diastereomer of benzothiazolidine **6** has been established by X-ray crystallography.

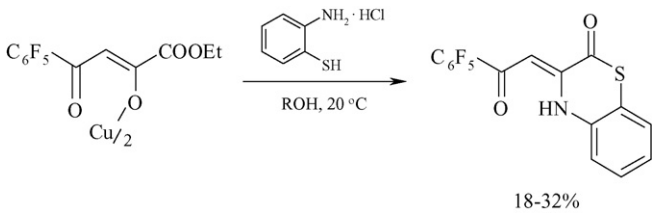
Keywords: Octafluoro-2,3-epoxybutane; 2-Aminothiophenol; 2,3-Bis(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-ol; 2-Trifluoromethyl-2-[1-(2-aminophenylthio)-2,2,2-trifluoroethyl]-1,3-benzothiazolidine; 1,1,1,3,4,4,4-Heptafluoro-2,2-dihydroxy-3-(2-aminophenylthio)butane; 5a,11a-Bis(trifluoromethyl)-5a,6,11a,12-tetrahydro-5,11-dithia-6,12-diazanaphthacene

1. Introduction

The intensive development at last years of the chemistry of *N*,*S*-heterocycles such as thiazines and thiazoles including fluorocontaining ones is connected with their high physiological activity [1–4]. Thiazine and thiazole skeleton belongs to such biologically active compounds as pesticides, fungicides, bactericides [5] and herbicides [6]. Some thiazine and thiazole derivatives can be useful as organic electroluminescent material [7].

The principal methods for preparation of perfluoroalkylcontaining thiazoles known from the literature are based on interaction of fluorinated precursors such as perfluoroolefins, their thiocyanate derivatives and fluorocontaining aldehydes with mono- and dinucleophilic reagents [8].

Although the building block approach has been also applied to the formation of perfluoroalkyl- and perfluoroarylcontaining thiazines relatively few examples of such syntheses have been published. Thus, the reaction of copper chelate of ethylpentafluorobenzoylpyruvate with 2-aminothiophenol hydrochloride gave 3,4-dihydro-3-pentafluorobenzoylmethyliden-2*H*-1,4-benzothiazin-2-one [9]:



18-32%

The interaction of 4-ethoxy-1,1,1-trifluoro-3-buten-2-one with 2-aminothiophenol led to 2-trifuoroacetyl-2*H*-1,4-benzothiazine, and with thioethanolamine hydrochloride—to 5,6-dihydro-2-trifluoroacetyl-4*H*-1,4-thiazine [10]:

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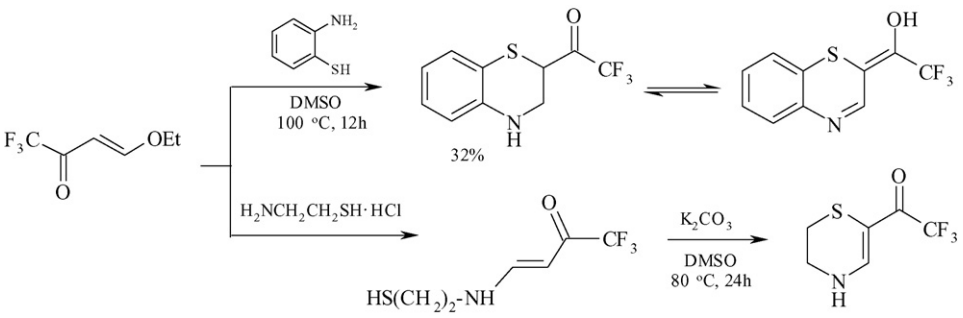


Terminal perfluoroolefin oxides have been found to be convenient precursors for synthesis both of thiazols and thiazines: the reaction of the former with thiourea yielded 2-aminothiazolines containing perfluoroalkyl substituents [11], and the reaction of hexafluoropropylene oxide with 2-aminothiophenol yielded benzothiazine with trifluoromethyl substituent [12] (Scheme 1).

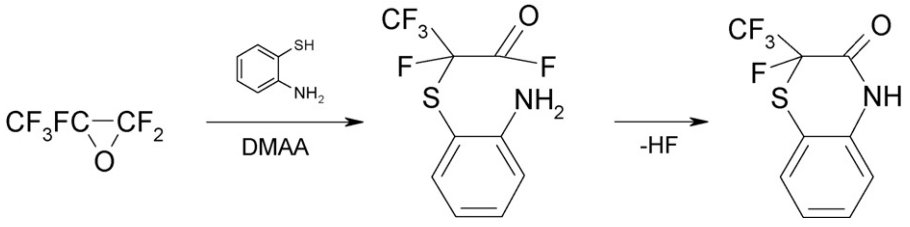
At the same time, we have shown previously that oxides of internal perfluoroolefins are excellent building blocks for synthesis of a large variety of 5,6-membered heterocycles such as diazines, quinaxolines, oxazines, benzoxazines and thiazolines [13–16]. Continuing our efforts directed towards synthesis of fluorocontaining heterocycles we report in the present paper on conversion of internal octafluoro-2,3-epoxybutane **1** (*cis*:*trans* ~ 10:90) [17] into new *N*,*S*-heterocycles: bis(trifluoromethyl)dihydrobenzothiazine **2**, bis(trifluoromethyl)bis(benzothiazine) **5** and trifluoromethylcontaining benzothiazolidine **6** using 2-aminothiophenol. To investigate the effect of a solvent on a direction of the reaction aprotic solvents possessing different polarity [18], such as toluene, dioxane, tetrahydrofuran, dimethoxyethane, acetonitrile, *N*,*N*-dimethylacetamide (DMAA) and dimethylsulfoxide (DMSO), have been tested.

2. Results and discussion

As it has been shown earlier, 2-aminothiophenol readily reacts with perfluoro-1,2-epoxypropane in *N*,*N*-dimethylacetamide to give 2-fluoro-2-trifluoromethyl-3,4-dihydro-2*H*-1,4-benzothiazin-3-one as a result of the initial attack of SH group of the dinucleophile at the central carbon atom [12] (Scheme 1).

We have found in contrast to that a similar reaction of oxirane **1** with 2-aminothiophenol in toluene and dioxane possessing low polarity, low ionizing and dissociating ability [18] both at deficiency and excess of the dinucleophile leads to an unexpected heterocyclic product, 2,3-bis(trifluoromethyl)-3,4-dihydro-2*H*-1,4-benzothiazin-2-ol **2** [2*R*3*R*,2*S*3*S*/2*R*3*S*, 2*S*3*R* ~ 2:98 (toluene); 2*R*3*R*,2*S*3*S*/2*R*3*S*,2*S*3*R* ~ 20:80 (dioxane)] (Scheme 2, path a; Table 1, runs 1 and 2).

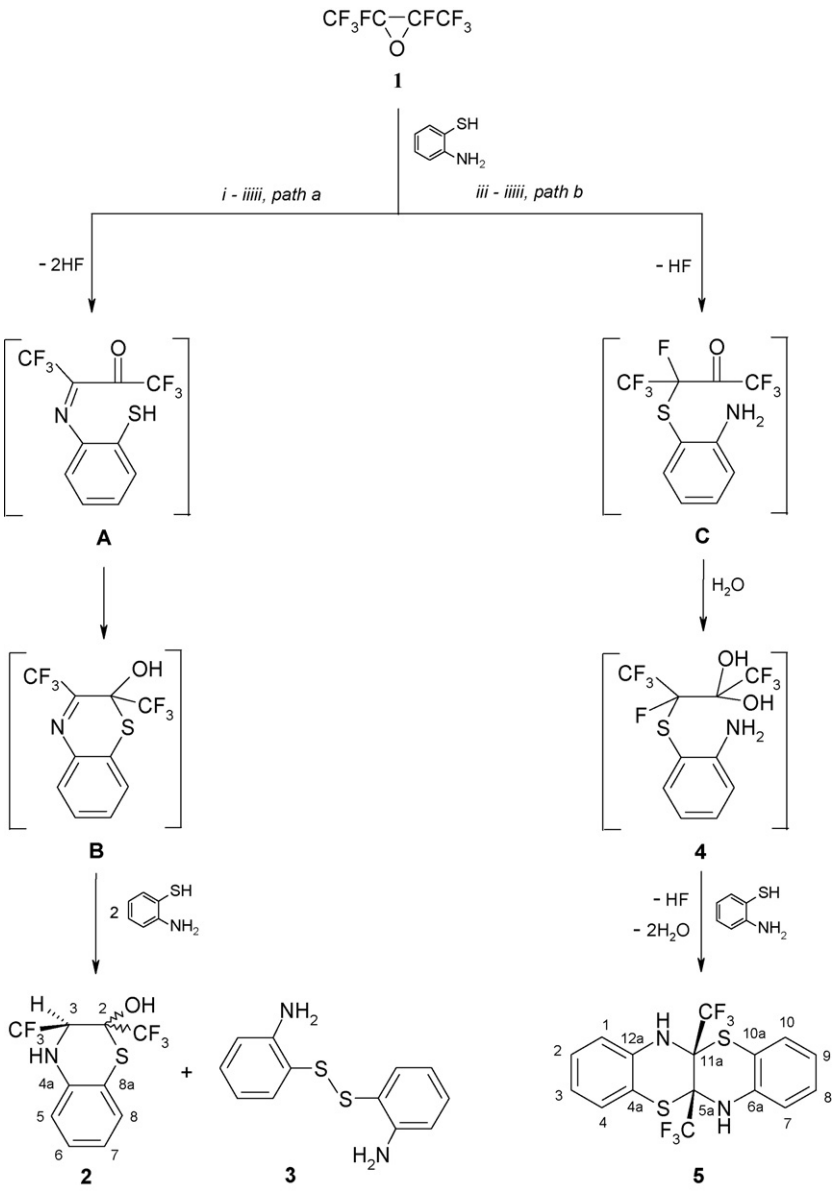
Probably, in this case the other type of interacting takes place: the first step of the reaction is the attack of amino group of the dinucleophile at one of the epoxide carbon atoms giving intermediate **A** and then 2,3-bis(trifluoromethyl)-2*H*-1,4-benzothiazin-2-ol **B**. As in the case of diazenecarboxamides containing N=N bond [19] the intermediate **B** is reduced to afford dihydrobenzothiazine **2** under the action of thiol function of 2-aminothiophenol. At the same time, the



Scheme 1.

Table 1
Effect of a solvent type on a product distribution

Run no.	Solvent	Composition and ratio of the reaction products (mol.%, from ^{19}F NMR)
1	Dioxane	**2** (*RR*,*SS*/*RS*,*SR* ~ 20:80)
2	Toluene	**2** (*RR*,*SS*/*RS*,*SR* ~ 2:98)
3	Tetrahydrofuran	**2** (*RR*,*SS*/*RS*,*SR* ~ 37:63), **4** ~ 72:28
4	Dimethoxyethane	**2** (*RR*,*SS*/*RS*,*SR* ~ 9:91), **4** ~ 57:43
5	Acetonitrile	**2** (*RR*,*SS*/*RS*,*SR* ~ 16:84), **4** ~ 74:26
6	Dimethylsulfoxide	**6** (*RS*,*SR*/*RR*,*SS* ~ 43:57), **4** ~ 75:25
7	*N*,*N*-Dimethylacetamide	**6** (*RS*,*SR*/*RR*,*SS* ~ 46:54), **4**, **2** (*RR*,*SS*/*RS*,*SR* ~ 29:71) ~ 74:22:4



Scheme 2. (i) Dioxane, 100 °C, 20 h; (ii) toluene, 100 °C, 25 h; (iii) tetrahydrofuran, 100 °C, 5 h; (iiii) dimethoxyethane, 100 °C, 9.5 h; (iiiii) acetonitrile, 100 °C, 5.5 h.

nucleophile is oxidized to give 2,2′-diaminodiphenyldisulfide **3**.

Such direction of the reaction can be explained by higher reactivity of NH_2 group of the nucleophile probably due to the absence of the charged *S*-nucleophile in toluene and dioxane.

The structure of (*RS*,*SR*)-diastereomer of benzothiazine **2** with *anti*-arrangement of groups CF_3 isolated in an individual form was determined by ^{19}F, ^{1}H, ^{13}C NMR, IR spectroscopy, GC–MS, elemental analysis and X-ray analysis.

In the ^{19}F NMR spectrum of compound (*RS*,*SR*)-**2** a doublet of quartets at −70.3 ppm was found for the CF_3CHNH group ($^{3}J_{F–H}$ 6.9, $^{5}J_{F–F}$ 4.3 Hz), and a quartet at −79.6 ppm was assigned to fluorine nuclei of the $CF_3(CS)OH$ group ($^{5}J_{F–F}$ 4.3 Hz). The molecule of the compound was determined to have *anti*-position of groups CF_3 by a weak coupling between the latter [14].

The additional sets of signals in the ^{19}F, ^{1}H and ^{13}C NMR spectra of the crude **2** were assigned to (*RR*,*SS*)-diastereomer of benzothiazine **2** with *syn*-arrangement of groups CF_3.

The structure of the molecule (*RS*,*SR*)-**2** determined by X-ray study is shown in Fig. 1. Crystals are formed by two independent molecules with H-bond between the hydroxy groups (O(1)H···O(1A) 2.082 Å, O(1)···O(1A) 2.816 Å, Fig. 2). It is noteworthy that H-bond is formed between the centers with opposite configurations (*RS* and *SR*, respectively) and crystal is heterochiral not only due to centrosymmetric space group *P*-1. Other interesting intermolecular contacts are N(1)H···F(3) 2.473 Å (N(1)···F(3) 3.118 Å) and F(3a)···F(6a) 2.855 Å. Measured C–CF_3 bonds at C(9) 1.538 Å and C(9A) 1.531 Å are longer then C–CF_3 at C(8) 1.525 Å and C(8a) 1.518 Å, probably, due to presence C(9)–S (C(9A)–S) and C(9)–O (C(9A)–O) bonds.

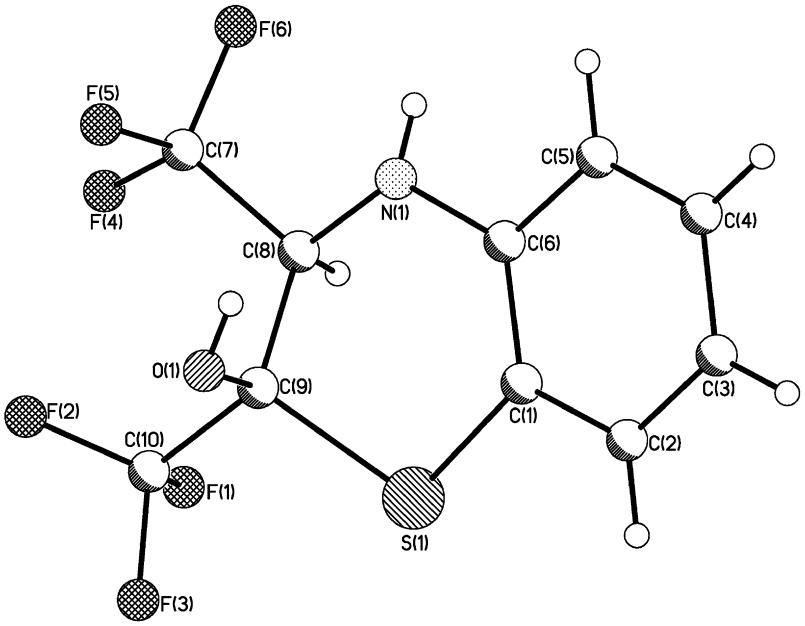


Fig. 1. The molecular structure of (*RS*,*SR*)-isomer of compound (**2**).

A similar reaction of oxirane **1** with 2-aminothiophenol in tetrahydrofuran having polarity, ionizing and dissociating ability, close to that of dioxane [18], also promoted the preferable formation of benzothiazine **2** (72%, *RR*,*SS*/*RS*,*SR* ~ 37:63). But in this case ~28% of the starting oxirane **1** reacted with 2-aminothiophenol affording the ring opening product, 1,1,1,3,4,4,4-heptafluoro-2,2-dihydroxy-3-(2-aminophenylthio)butane **4**, which probably was formed from 1,1,1,3,4,4,4-heptafluoro-3-(2-aminophenylthio)butane-2-one **C** after adding of water into the reaction mixture (Scheme 2, path b; Table 1, run 3). Formation of compound **4** can be explained by the initial attack of SH group of the reagent. This is probably due to rather high basicity of the solvent [18] which promotes some activation of thiol function.

The structure of compound **4** has been determined using GC–MS, NMR ^{1}H and ^{19}F by comparing with model compounds: 2,2-dihydroxyoctafluorobutane and 2,2-dihydroxydodecafluorohexane [16]. Attempts to obtain diol **4** in individual form were not successful: removal of the remaining solvent and 2-aminothiophenol from the crude product led to decomposition of compound **4** and formation of complex product mixtures.

Use of acetonitrile, the aprotic solvent with rather a high polarity but low ionizing and dissociating power [18] also gave a mixture of products **2**, **4** with predominant formation of

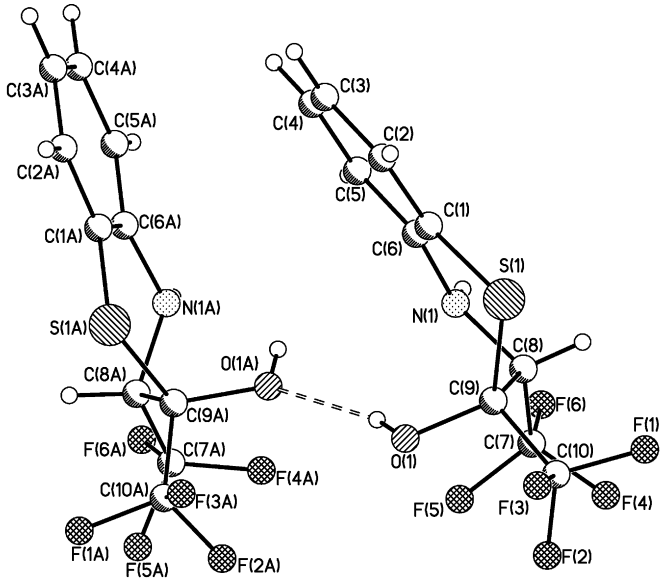


Fig. 2. The general view of the two independent isomers (*RS* and *SR*) of compound (**2**) in unit cell.

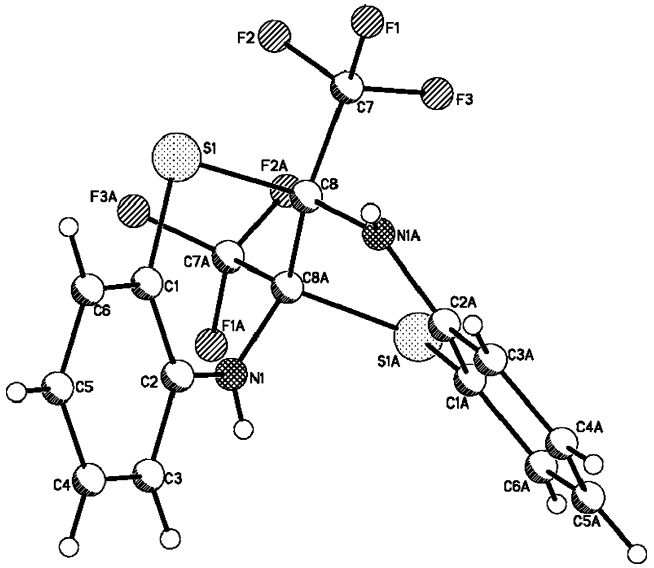


Fig. 3. 5a,11a-Bis(trifluoromethyl)-5a,6,11a,12-tetrahydro-5,11-dithia-6,12-diazanaphthacene (**5**) from X-ray data.

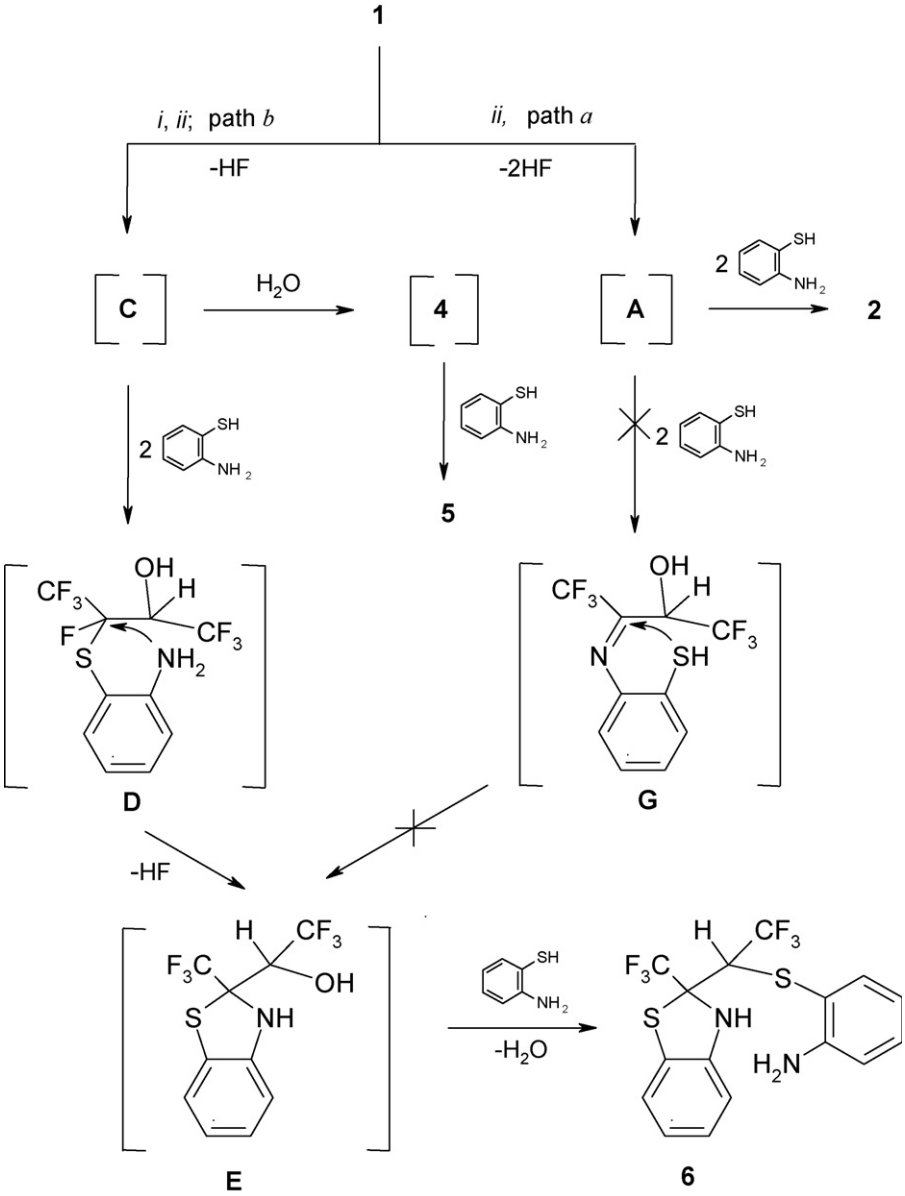
compound **2** (74%, *RR*,*SS*/*RS*,*SR* ∼ 16:84) (Scheme 2; Table 1, run 5).

Dimethoxyethane having a low polarity, low ionizing and dissociating power [18] led to formation of compounds **2**, **4** approximately in equal percentage (**2/4** ∼ 57:43). Increase of the compound **4** yield in this case is probably conditioned by cation complexing properties of the solvent [18] promoting thiolate anion formation (Scheme 2; Table 1, run 4).

Note, the intermediate **C** (Scheme 2) did not afford the intramolecular cyclization product during the reactions, possibly, due to solvation of NH_2 and C=O groups. But in all cases crude products obtained containing compound **4** and 2-aminothiophenol (probably as adduct, from ^{1}H NMR) gave 5a,11a-bis(trifluoromethyl)-5a,6,11a,12-tetrahydro-5,11-dithia-6,12-diazanaphthacene **5** on standing for several weeks. In ^{19}F spectra of the crude products signals of compound **4** were disappeared and the signal at −70.9 ppm of compound **5** was appeared. The structure of compound **5** has been proved by IR, ^{1}H, ^{19}F, ^{13}C NMR spectroscopy, elemental analysis and X-ray analysis.

The structure of the molecule **5** determined by X-ray study is shown in Fig. 3. Crystals of the compound are tetragonal, space group $I4_1$. The structure has *cis*-orientation of CF_3-groups. Bond lengths and angles are typical for this class of compounds.

In polar dimethylsulfoxide and *N*,*N*-dimethylacetamide, unusual cyclization occurred resulting in formation of 2-trifluoromethyl-2-[1-(2-aminophenylthio)-2,2,2-trifluoroethyl]-1,3-benzothiazolidine **6**. Thus, treating oxirane **1** with 2-aminothiophenol in dimethylsulfoxide yielded mainly compound **6** as a mixture of diastereomers (*RS*,*SR*/*RR*,*SS* ∼ 43:57, ∼75%) and diol **4** (∼25%) (Table 1, run 6). When the reaction was carried out in *N*,*N*-dimethylacetamide benzothiazolidine **6**



Scheme 3. (i) 2-Aminothiophenol, dimethylsulfoxide, 100 °C, 1 h; (ii) 2-aminothiophenol, *N*,*N*-dimethylacetamide, 100 °C, 3.5 h.

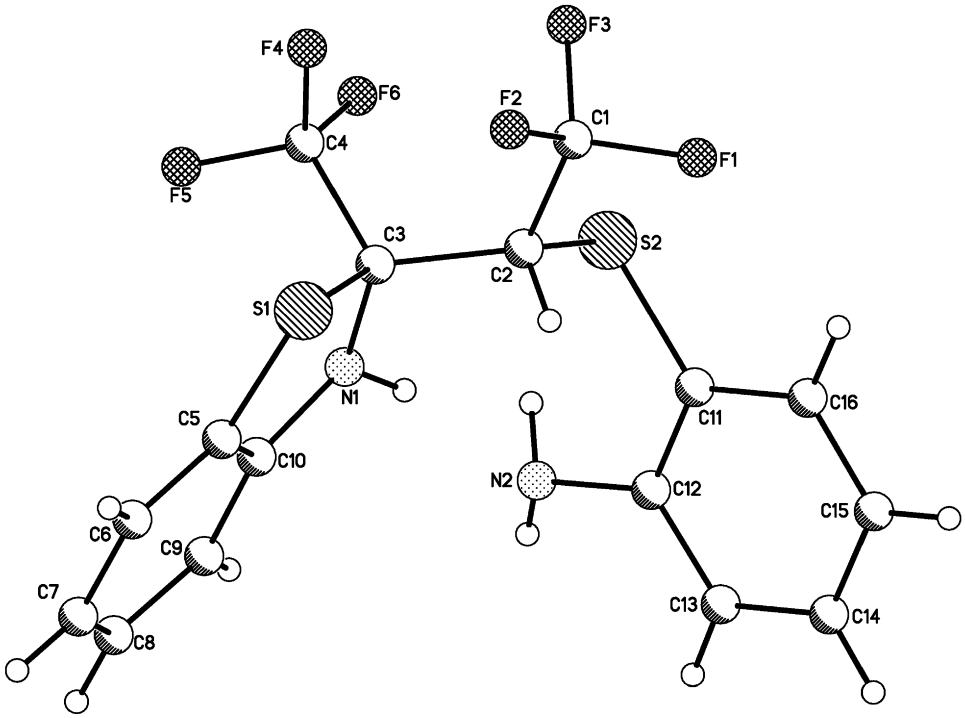


Fig. 4. The molecular structure of (*RS*,*SR*)-isomer of compound (**6**).

(*RS*,*SR*/*RR*,*SS* ~ 46:54, ~74%), diol **4** (~22%) and benzothiazine **2** (*RR*,*SS*/*RS*,*SR* ~ 29:71, ~4%) were obtained (Table 1, run 7).

The scheme of the reactions can be rationalized as shown in Scheme 3.

As in the case of the reaction between hexafluoro-1,2-epoxypropane and 2-aminothiophenol [12] (Scheme 1), the polar solvents apparently promote the formation of the reactive thiolate anion which attacks the epoxide carbon atom **1** with subsequent ring opening and formation of intermediate **C** (Scheme 3, path b). After that 2-aminothiophenol reduces the carbonyl group of the latter resulting in 1,1,1,3,4,4,4-heptafluoro-3-(2-aminophenylthio)buthan-2-ol **D**. The attack of NH_2 group at the C-3 atom of intermediate **D** with elimination of HF gives benzothiazolidine **E**. The further nucleophilic substitution of OH group in intermediate **E** by SH function of 2-aminothiophenol with elimination of H_2O leads to product **6**. At the same time, intermediate **C** can add a molecule of H_2O to yield *hem*-diol **4**. Note, the reaction can proceed *via* the initial attack of NH_2 group of 2-aminothiophenol and intermediates **A** and **G** (Scheme 3, path a). But the preferable formation of compound **4** in a similar reaction carried out in *N*,*N*-dimethylacetamide–water (exp.) confirms the first path of the reaction (Scheme 3, path b).

The structure of (*RS*,*SR*)-diastereomer **6** isolated in individual form by recrystallization of stereoisomer mixture was determined by IR, ^{19}F, ^{1}H, ^{13}C NMR spectroscopy, GC–MS and elemental analysis.

Additional sets of signals in ^{1}H, ^{13}C, ^{19}F spectra of crude product **6** were assigned to (*RR*,*SS*)-isomer **6**. GC–MS specter of the latter was practically identical to that of (*RS*,*SR*)-**6**.

To obtain more precise information about the thiazolidine **6** structure the X-ray investigation of monocrystal **6** prepared by fractional crystallization has been carried out. It has been found *RS*,*SR*-configuration of the molecules. Due to centrosymmetric space group $P2_1/n$ crystals are formed by both (*RS*)- and (*SR*)-enantiomers. Conformation of the molecules in crystals is stabilized by strong intramolecular H-bond between benzothiazolidine NH and nitrogen of amino group (N(1)H···N(2) 2.236 Å, N(1)···N(2) 3.099 Å). Also strong intermolecular contacts N(2)H···F(5a) 2.523 Å (N(2)···F(5a) 3.171 Å) and N(2)H···C(9a) 2.677 Å (N(2)···C(9a) 3.486 Å) are presented to form ''dimeric'' packing of molecules in crystals. The structure of the molecule *RS*,*SR*-**6** determined by X-ray study is shown in Fig. 4.

3. Conclusion

In conclusion, we have reported the approach towards synthesis of novel 5-, 6-membered trifluoromethylcontaining *N*,*S*-heterocyclic compounds – dihydrobenzothiazine **2**, thiazolidine **6** and bis(benzothiazine) **5** – through the reaction of octafluoro-2,3-epoxybutane **1** with 2-aminothiophenol.

Use of toluene, dioxane, tetrahydrofuran, acetonitrile and dimethoxyethane gives the unexpected product, dihydrobenzothiazine **2** (*RS*,*SR* > *RR*,*SS*), in good to moderate yields. This is likely due to the initial attack of the amino group of the dinucleophile and subsequent reduction of the intermediate bezothiazine.

A similar reaction in dimethylsulfoxide and *N*,*N*-dimethylacetamide affords benzothiazolidine **6** (*RS*,*SR*/*RR*,*SS* ~ 1:1) probably as a result of the initial attack of thiol function of 2-aminothiophenol, in moderate yields.

Formation of minor 1,1,1,3,4,4,4-heptafluoro-3-(2-aminophenylthio)-2,2-dihydroxybutane **4** with subsequent its conversion into bis(benzothiazine) **5** is observed in all solvents studied excluding toluene and dioxane.

Compounds prepared in this work are of interest as biologically active substances and new convenient precursors for synthesis of complex heterocyclic systems.

4. Experimental

^{1}H, ^{13}C (^{1}H decoupled), ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400, 100 and 376 MHz, respectively. Chemical shifts are reported in ppm (δ) from internal $(CH_3)_4Si$ for hydrogen and carbon and internal CCl_3F for fluorine ($CDCl_3$). Mass spectra were obtained on a Fisions GC–MS instrument with detector MD 800, quartz capillary column HP-5, 25 m × 0.25 mm, thickness of a stationary phase film 0.25 μm, the carrier-gas—helium, ionization energy 70 eV. Infrared spectra were obtained on a Perkin Elmer Spectrum One FT-IR spectrometer in Nujol. The $\nu_{max.}$ are reported in cm^{-1}. Elemental analyses were carried out on a Perkin Elmer PE 2400 elemental analyzer. Thin-layer chromatography (TLC) was performed on Silufol UV-254 plates, column chromatography—on silica gel 0.35–0.070 mm (220–440 mesh). Melting points were measured in open capillaries and are reported uncorrected. Oxirane (**1**) was prepared according to a reported procedure [17].

4.1. Crystallographic data for structure for (RS,SR)-2,3-bis(trifluoromethyl)-3,4-dihydro-2H-1,4-benzothiazine-2-ol (2)

$C_{10}H_7F_6NOS$ crystal at 295(2) K is triclinic, space group P-1 a = 7.675(3) Å, b = 9.786(4) Å, c = 16.036(9) Å, α = 83.03(4)°, β = 84.93(4)°, γ = 76.00(3)°, V = 1157.8(9) Å^3, Z = 4, M = 303.23, d_{calc} = 1.740 g/cm^3, μ(Mo Kα) = 0.350 mm^{-1}, F(0 0 0) = 608. Intensities of 18,769 reflections were measured with "Xcalibur 3" CCD diffractometer, λ(Mo Kα) = 0.71073 Å, ω-scans with 1.0° steps in ω and 10 c per frame exposure, θ range for data collection 2.26–31.69°, and 7103 (R(int) = 0.0411) independent reflections were used in further refinement. The structure was solved by direct methods and refined by full-matrix least-squares technique against on F^2 in anisotropic–isotropic approximation. Hydrogen atoms were located from Fourier synthesis and refined in riding model. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0392, $wR2$ = 0.0381. R indices (all data) $R1$ = 0.1413, $wR2$ = 0.0413, Goodness-of-fit on F^2 1.000, largest diff. peak and hole 0.242 and −0.343 einstein Å^{-3}, completeness to θ = 26.00° 99.7%. All calculations were performed using SHELXTL [20].

4.2. Crystallographic data for structure 5a,11a-bis(trifluoromethyl)-5a,6,11a,12-tetrahydro-5,11-dithia-6,12-diaza-naphthacene (5).

$C_{16}H_{10}F_6N_2S_2$ crystal at 295(2) K is tetragonal, space group $I4_1$ $a = b$ = 11.6434(5) Å, c = 12.1925(11) Å, $\alpha = \beta = \gamma$ = 90.00°, V = 1652.92(18) Å^3, Z = 4, M = 303.23, d_{calc} = 1.641 g/cm^3, μ(Mo Kα) = 0.388 mm^{-1}, F(0 0 0) = 824. Intensities of 2728 reflections were measured with "Xcalibur 3" CCD diffractometer, λ(Mo Kα) = 0.71073 Å, ω-scans with 0.5° steps in ω and 10 c per frame exposure, θ range for data collection 3.50–26.36°, and 1600 (R(int) = 0.0136) independent reflections were used in further refinement. Absorption correction was not performed. The structure was solved by direct methods and refined by full-matrix least-squares technique against on F^2 in anisotropic approximation. Hydrogen atoms were located from Fourier synthesis and refined in riding model. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0258, $wR2$ = 0.0656. R indices (all data) $R1$ = 0.0305, $wR2$ = 0.0677. Goodness-of-fit on F^2 1.001, largest diff. peak and hole 0.125 and −0.135 einstein Å^{-3}, completeness to θ = 26.36° 98.8%. All calculations were performed using SHELXTL [20].

4.3. Crystallographic data for (RS,SR)-(2-trifluoromethyl-2-[1-(2-aminophenylthio)-2,2,2-trifluoroethyl]-1,3-benzothiazolidine) (6)

$C_{16}H_{12}F_6N_2S_2$ crystal at 295(2) K is monoclinic, space group $P2_1/n$ a = 9.1184(5) Å, b = 17.9086(4) Å, c = 10.6367(7) Å, α = 90°, β = 94.332(5)°, γ = 90°, V = 1731.99(15) Å^3, Z = 4, M = 410.40, d_{calc} = 1.574 g/cm^3, μ(Mo Kα) = 0.370 mm^{-1}, F(0 0 0) = 832. Intensities of 20,479 reflections were measured with "Xcalibur 3" CCD diffractometer, λ(Mo Kα) = 0.71073 Å, ω-scans with 1.0° steps in ω and 10 c per frame exposure, θ range for data collection 2.84–31.68°, and 5329 (R(int) = 0.0411) independent reflections were used in further refinement. The structure was solved by direct methods and refined by full-matrix least-squares technique against on F^2 in anisotropic–isotropic approximation. Hydrogen atoms were located from Fourier synthesis and refined in riding model. Final R indices [$I > 2\sigma(I)$] $R1$ = 0.0368, $wR2$ = 0.0676. R indices (all data) $R1$ = 0.1035, $wR2$ = 0.0731, Goodness-of-fit on F^2 1.001, largest diff. peak and hole 0.213 and −0.163 einstein Å^{-3}, completeness to θ = 26.00° 99.2%. All calculations were performed using SHELXTL on IBM PC AT [20].

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary no. CCDC 642383–642385. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

4.4. The reaction of oxirane (1) with 2-aminothiophenol

4.4.1. Procedure 1

A mixture of oxirane **1** (4.8 g, 22.4 mmol), 2-aminothiophenol (2.8 g, 22.4 mmol) and dioxane (10 ml) was heated in a sealed tube in a boiling water bath, with intermittent shaking. After cooling (−70 °C), the tube was opened and the residual oxirane condensed into a cooled trap (−70 °C). Then a solid of 2-aminothiophenol hydrofluoride was filtered off. The filtrate was poured into ice water (200 ml), and the resultant precipitate was collected by filtration and dried at room temperature. The

solid obtained (3.4 g) containing benzothiazine **2** (*RR*,*SS*/*RS*,*SR* ~ 20:80) and disulfide **3** [from ^{19}F, ^{1}H NMR and TLC (eluent: $CHCl_3$–MeOH, 10:0.5; R_F **2** = 0.36; R_F **3** = 0.74)] (Table 1, run 1) was extracted with hot hexane. The hexane extract was dried under $MgSO_4$ and evaporated. The solid residue (mainly the compound **2** with remaining disulfide **3**) was separated by a column chromatography (SiO_2, eluent: $CHCl_3$–MeOH, 10:0.5) to give 1.0 g (44.2%) of the benzothiazine **2** (*RR*,*SS*/*RS*,*SR* ~ 5:1). After that compound **2** was recrystallized from hexane, then—from a mixture hexane–benzene (10:0.5) to give colorless crystals of compound *RS*,*SR*-(**2**), 0.75 g (33%). Recrystallization of crude compound **3** from a mixture hexane–$CHCl_3$ (10:1) afforded yellow crystals of disulfide **3**.

*4.4.1.1. (RS,SR)-2,3-Bis(trifluoromethyl)-3,4-dihydro-2H-1,4-benzothiazine-2-ol (**2**).* mp 71–73 °C. IR: ν 1570 (C=C), 2640, 2710, 3320, 3360, 3410 (NH, OH). ^{1}H NMR: δ 3.56 (1H, s, OH), 4.28 (1H, qd, $^{3}J_{HF}$ 6.9, $^{3}J_{HH}$ 3.0 Hz, CF_3**CH**NH,), 4.45 (1H, br.s, NH), 6.76 (1H, dd, *J* 7.4, 1.1 Hz, H-5), 6.86 (1H, ddd, *J* 8.1, 7.1, 1.1 Hz, H-7), 7.04–7.08 (2H, m, H-6, H-8). ^{13}C NMR (DMSO-d_6): δ 52.9 (q, $^{2}J_{CF}$ 27.9 Hz, C-3), 76.2 (q, $^{2}J_{CF}$ 30.0 Hz, C-2), 114.4 (s, C-8a), 115.6 (s, C-5), 118.4 (s, C-7), 123.9 (q, $^{1}J_{CF}$ 287.4 Hz, CF_3), 124.4 (q, $^{1}J_{CF}$ 287.0 Hz, CF_3), 125.4 (s), 125.8 (s) (C-6, C-8), 137.5 (s, C-4a). ^{19}F NMR: δ −79.6 (3F, q, $^{5}J_{FF}$ 4.3 Hz, CF_3-C^2), −70.3 (3F, dq, $^{3}J_{HF}$ 6.9, $^{5}J_{FF}$ 4.3 Hz, CF_3-C^3). GC–MS, *m*/*z* (rel. int.): 304 $[M+1]^+$ (7.7), 303 $[M]^+$ (88.1), 234 $[M-CF_3]^+$ (18.4), 216 $[M-CF_3-H_2O]^+$ (10.4), 207 $[M+1-CF_3-CO]^+$ (8.5), 206 $[M-CF_3-CO]^+$ (100), 204 $[M-CF_3H-COH]^+$ (8.4), 184 $[M-C_2F_5]^+$ (11.0), 174 $[M-CF_3CSO]^+$ (10.4), 166 (13.2), 165 $[M-2CF_3]^+$ (14.3), 150 (14.2), 146 $[M-2CF_3-H_2O-H]^+$ (15.1), 142 $[M-C_6H_4NH_2-CF_3]^+$ $]^+$ (8.9), 137 (9.6), 136 $[M-2CF_3-CO-H]^+$ (84.3), 109 (27.0), 108 $[C_6H_4S]^+$ (7.9), 104 $[C_6H_4NHCH]^+$ (16.4), 96 $[CF_3CNH]^+$ (10.5), 93 $[C_6H_5NH_2]^+$ (8.8), 77 $[C_6H_5]^+$ (10.1), 69 $[CF_3]^+$ (29.7). Anal. Calcd for $C_{10}H_7F_6NSO$: C, 39.6; H, 2.3; F, 37.6; N, 4.6; S, 10.6. Found: C, 39.6; H, 2.3; F, 37.7; N, 4.3; S, 10.2.

*4.4.1.2. (RR,SS)-2,3-Bis(trifluoromethyl)-3,4-dihydro-2H-benzothiazin-2-ol (**2**).* ^{1}H NMR: δ 3.44 (1H, s, OH), 4.17 (1H, dq, $^{3}J_{HF}$ $^{3}J_{HH}$ 6.8 Hz, CF_3**CH**NH), 4.65 (1H, br.s, NH), 6.78 (1H, m, H-5), 6.88 (1H, m, H-7), 7.04–7.08 (2H, m, H-6, H-8). ^{13}C NMR (DMSO-d_6): δ 56.8 (q, $^{2}J_{CF}$ 30.3 Hz, C-3), 76.4 (q, $^{2}J_{CF}$ 31.5 Hz, C-2), 114.9 (s, C-8a), 115.7 (s, C-5), 118.2 (s, C-7), 123.0 (q, $^{1}J_{CF}$ 283.1 Hz, CF_3), 123.7 (q, $^{1}J_{CF}$ 279.5 Hz, CF_3), 126.4 (s), 127.6 (s) (C-6, C-8), 138.3 (s, C-4a). ^{19}F NMR: δ: −76.5 (3F, q, $^{5}J_{FF}$ 9.6 Hz, CF_3-C^2), −72.2 (3F, qd, $^{5}J_{FF}$ 9.6, $^{3}J_{FH}$ 6.9 Hz, CF_3-C^3).

*4.4.1.3. 2,2′-Diaminodiphenyldisulfide (**3**).* mp 90–91 °C (lit. mp 91.5–92.5 °C [21]). IR: ν 1555, 1570, 1600, 1610 (C=C, NH), 3165, 3190, 3285, 3365 (NH). ^{1}H NMR: δ 4.28 (4H, br.s, $2NH_2$), 6.58 (2H, m, 2CH), 6.71 (2H, m, 2CH), 7.15 (4H, m, 4CH). Anal. Calcd for $C_{12}H_{12}N_2S_2$: C, 58.1; H, 4.8; N, 11.3; S, 25.8. Found: C, 58.2; H, 4.8; N, 11.2; S, 26.0.

4.4.2. Procedure 2

In a similar manner, oxirane **1** (2.9 g, 13.4 mmol) was treated with 2-aminothiophenol (1.7 g, 13.6 mmol) in toluene (20 ml). After cooling (−70 °C), the tube was opened and the residual oxirane condensed into a cooled trap (−70 °C). The precipitate of 2-aminothiophenol hydrofluoride was filtered off, and the filtrate was evaporated to give yellow solid (1.6 g) containing benzothiazine **2** (*RR*,*SS*/*RS*,*SR* ~ 2:98) and disulfide **3** (from ^{19}F, ^{1}H NMR, Table 1, run 2). The solid was extracted with hot hexane, and the extract was evaporated. The obtained crystals (compound **2** with residual disulfide **3**) was purified by a column chromatography (SiO_2, eluent: $CHCl_3$–MeOH, 10:0.5) to yield 0.6 g (43.8%) of *RS*,*SR*-isomer of benzothiazine **2**.

4.4.3. Procedure 3

The reaction of oxirane **1** (4.8 g, 22.4 mmol) with 2-aminothiophenol (2.8 g, 22.4 mmol) in 14 ml of THF gave yellow solid product (2.5 g) containing benzothiazine **2**, hem-diol **4**, disulfide **3** and residual 2-aminothiophenol [from ^{19}F, ^{1}H NMR and TLC (eluent: $CHCl_3$–MeOH, 10:0.5; R_F **2** = 0.36; R_F **3** = 0.74)] (Table 1, run 3). The crude product was allowed to stand at room temperature over 3 weeks. The product obtained consisted of compounds **2**, **3** and **5** [from ^{19}F, ^{1}H NMR and TLC (eluent: $CHCl_3$–hexane, 1:2; R_F **2** = 0.28; R_F **3** = 0.18; R_F **5** = 0.95)] was worked up as in Procedure 1. Column chromatography (SiO_2, eluent: $CHCl_3$–hexane, 1:2) gave 0.7 g (31%) of compound (**2**, *RR*,*SS*/*RS*,*SR* ~ 7:11) and 0.1 g (2.2%) of compound **5** as colorless crystals.

*4.4.3.1. 5a,11a-Bis(trifluoromethyl)-5a,6,11a,12-tetrahydro-5,11-dithia-6,12-diaza-naphthacene (**5**).* mp 180 °C. IR: ν 1494, 1592 (NH, C=C), 2750, 3377, 3400 (NH). ^{1}H NMR: δ 4.38 (2H, s, 2NH), 6.44 (2H, d, 2CH), 6.81–6.85 (2H, m, 2CH), 6.95–6.99 (2H, m, 2CH), 7.04 (2H, d, 2CH). ^{13}C NMR: δ 67.4 (q, $^{2}J_{CF}$ 27.0 Hz, C-5a, C-11a), 122.5 (q, $^{1}J_{CF}$ 287.7 Hz, 2 CF_3), 113.2 (s, C-4a, C-10a), 116.0 (s, C-1, C-7), 121.1 (s, C-3, C-9), 127.2 (s), 127.6 (s) (C-2, C-4, C-8, C-10), 137.0 (s, C-6a, C-12a). ^{19}F NMR: δ −70.9 ($2CF_3$). GC–MS, *m*/*z* (rel. int.): 408 $[M]^+$ (10.5), 285 $[M-C_6H_4(S)NH]^+$ (6.5), 204 $[M-CF_3CSC_6H_4NH]^+$ (100), 184 $[M-CF_3CSC_6H_4NH-HF]^+$ (48), 136 (23), 102 (14), 69 $[CF_3]^+$ (12.5). Anal. Calcd for $C_{16}H_{10}F_6N_2S_2$: C, 47.1; H, 2.5; F, 27.9; N, 6.9; S, 15.7. Found: C, 46.9; H, 2.5; F, 27.9; N, 6.9; S, 15.7.

4.4.4. Procedure 4

The reaction of oxirane **1** (5.0 g, 23.1 mmol) with 2-aminothiophenol (2.9 g, 23.2 mmol) in 10 ml of dimethoxyethane gave yellow solid product (2.7 g) containing benzothiazine **2**, hem-diol **4**, disulfide **3** and remaining 2-aminothiophenol (Table 1, run 4). The crude product was allowed to stand at room temperature over 3 weeks and then worked up as in Procedure 3. Column chromatography (SiO_2, eluent: $CHCl_3$–hexane, 1:2) gave 0.35 g (15%) of compound **2** (*RR*,*SS*/*RS*,*SR* ~ 1:9) and 0.2 g (4.2%) of compound **5**.

4.4.5. Procedure 5

The reaction of oxirane **1** (6.0 g, 27.7 mmol) with 2-aminothiophenol (3.5 g, 28 mmol) in 10 ml of acetonitrile gave yellow solid product (3.3 g) containing benzothiazine **2**, hem-diol **4**, disulfide **3** and remaining 2-aminothiophenol (Table 1, run 5). The crude product was allowed to stand at room temperature over 3 weeks and then worked up as in Procedure 3. Column chromatography (SiO_2, eluent: $CHCl_3$–hexane, 1:2) gave 0.7 g (24.7%) of compound **2** (*RR*,*SS*/*RS*,*SR* ∼ 3:17) and 0.1 g (2.2%) of compound **5**.

4.4.6. Procedure 6

In a similar manner, oxirane **1** (3.3 g, 15.28 mmol) was treated with 2-aminothiophenol (1.9 g, 15.20 mmol) in 5 ml of DMAA for 3.5 h. After cooling (−70 °C), the tube was opened and the residual oxirane condensed into a cooled trap (−70 °C). Then the reaction mixture was poured into ice water (200 ml), and the lower organic layer was separated, twice washed with water and dried (∼40 °C). The resinous residue obtained (2.7 g) consisted of benzothiazolidine **6** (*RS*,*SR*/*RR*,*SS* ∼ 46:54), diol **4**, benzothiazine **2** (*RR*,*SS*/*RS*,*SR* ∼ 29:71) and disulfide **3** (from IR, ^{19}F, ^{1}H NMR and GC–MS) (Table 1, run 7). The residue was reprecipitated from chloroform by hexane to give yellow crystals of disulfide **3** which were filtered off. The filtrate obtained was evaporated, and the residue containing thiazolidine **6** as a major product was purified by column chromatography (eluent: hexane–$CHCl_3$, 1:1; R_F **6**$_{RS,SR}$ = 0.90, R_F **6**$_{RR,SS}$ = 0.85) to give 0.8 g (51%) of the compound **6** (*RS*,*SR*/*RR*,*SS* ∼ 7:3). Fractional recrystallization from hexane–benzene yielded 0.2 g (13%) of compound **6** (*RS*,*SR*/*RR*,*SS* = 2:3, mp 80–125 °C), 0.15 g (10%) of compound **6** (*RS*,*SR*/*RR*,*SS* = 4:1, mp 77–82 °C) and 0.15 g (10%) of compound *RS*,*SR*-**6** as colorless crystals.

*4.4.6.1. (RS,SR)-(2-Trifluoromethyl-2-[1-(2-aminophenylthio)-2,2,2-trifluoroethyl]-1,3-benzothiazolidine) (**6**).* mp 82–83 °C. IR: ν 1582, 1614 (C=C, NH_2), 3226 (br), 3344, 3389, 3438 (NH, NH_2). ^{1}H NMR: δ 4.09 (1H, q, $^{3}J_{HF}$ 8.8 Hz, CF_3**CH**-S), 4.32 (2H, br.s, NH_2), 5.78 (1H, br.s, NH), 6.62 (1H, d, *J* 7.7 Hz, CH ar), 6.74 (2H, m, 2CH ar), 6.95 (1H, td, *J* 7.7, 1.2 Hz, CH ar), 6.98 (1H, dd, *J* 7.6, 1.0 Hz, CH ar). 7.17 (1H, ddd, *J* 8.2, 7.3, 1.7 Hz, CH ar), 7.46 (1H, dd, *J* 7.9, 1.4 Hz, CH ar). ^{13}C NMR: δ 62.2 (q, $^{2}J_{CF}$ 27.4 Hz, C-2), 78.2 (q, $^{2}J_{CF}$ 31.4 Hz, C-3), 124.2 (q, $^{1}J_{CF}$ 285.6 Hz, CF_3), 124.6 (q, $^{1}J_{CF}$ 280.7 Hz, CF_3), 109.1 (s), 116.1 (s), 116.2 (s), 120.1 (s), 120.7 (s), 121.0 (s), 123.0 (s), 126.2 (s), 131.5 (s), 136.6 (s), 143.5 (s), 148.1 (s) (carbon atoms of aromatic cycles). ^{19}F NMR: δ −77.8 (3F, q, $^{5}J_{FF}$ 8.1 Hz, CF_3-C^2), −65.2 (3F, dq, $^{3}J_{HF}$ $^{5}J_{FF}$ 8.2 Hz, CF_3-C^3). GC–MS, *m*/*z* (rel. int.): 217 [$M - C_6H_4S(NH)_2 - CF_3$]$^+$ (7.1), 207 (14.2), 206 [$C_6H_4(NH_2)(S)CHCF_3$]$^+$ (6.7), 204 [$CF_3C(S)(NH)C_6H_4$]$^+$ (100), 184 (27.9), 136 [$C_6H_4(NH_2)SC$]$^+$ (5.8), 109 (6.5), 108 [C_6H_4S]$^+$ (8.4), 102 (7.2), 97 (9.0), 93 (7.1), 80 (45.4), 69 [CF_3]$^+$ (11.4). Anal. Calcd for $C_{16}H_{12}F_6N_2S_2$: C, 46.8; H, 2.9; F, 27.8; N, 6.8; S, 15.6. Found: C, 46.7; H, 2.8; F, 27.5; N, 6.9; S, 15.8.

*4.4.6.2. (RR,SS)-(2-Trifluoromethyl-2-[1-(2-aminophenylthio)-2,2,2-trifluoroethyl]-1,3-benzothiazolidine) (**6**).* ^{1}H NMR: 3.80 (2H, br.s, NH_2): δ 4.00 (1H, q, $^{3}J_{HF}$ 8.2 Hz, CF_3**CH**-S), 5.10 (1H, br.s, NH), 6.65 (1H, dd, *J* 7.9, 0.6 Hz, CH ar), 6.75 (2H, m, 2CH ar), 6.82 (1H, td, *J* 7.6, 1.0 Hz, CH ar), 7.00 (1H, td, *J* 7.7, 1.1 Hz, CH ar), 7.09 (1H, dd, *J* 7.6, 1.1 Hz, CH ar), 7.20 (1H, ddd, *J* 8.0, 7.3, 1.4 Hz, CH ar), 7.56 (1H, dd, *J* 7.7, 1.2 Hz). ^{13}C NMR: δ 60.8 (q, $^{2}J_{CF}$ 27.7 Hz, C-2), 80.6 (q, $^{2}J_{CF}$ 31.7 Hz, C-3), 124.2 (q, $^{1}J_{CF}$ 285.7 Hz, CF_3), 124.8 (q, $^{1}J_{CF}$ 281.0 Hz, CF_3), 109.6 (s), 115.3 (s), 115.9 (s), 119.3 (s), 121.1 (s), 123.4 (s), 126.3 (s), 131.7 (s), 137.2 (s), 145.1 (s), 148.6 (s) (carbon atoms of aromatic cycles). ^{19}F NMR: δ −78.6 (3F, q, $^{5}J_{FF}$ 9.8 Hz, CF_3-C^2), −64.9 (3F, dq, $^{3}J_{HF}$ 8.7, $^{5}J_{FF}$ 9.8 Hz, CF_3-C^3). GC–MS, *m*/*z* (rel. int.): 217 [$M - C_6H_4S(NH)_2 - CF_3$]$^+$ (7.1), 207 (14.2), 206 [$C_6H_4(NH_2)(S)CHCF_3$]$^+$ (6.7), 204 [$CF_3C(S)(NH)C_6H_4$]$^+$ (100), 184 (27.9), 136 [$C_6H_4(NH_2)SC$]$^+$ (5.8), 109 (6.5), 108 [C_6H_4S]$^+$ (8.4), 102 (7.2), 97 (9.0), 93 (7.1), 80 (45.4), 69 [CF_3]$^+$ (11.4). Anal. Calcd for $C_{16}H_{12}F_6N_2S_2$: C, 46.8; H, 2.9; F, 27.8; N, 6.8; S, 15.6. Found: C, 46.7; H, 2.8; F, 27.5; N, 6.9; S, 15.8.

*4.4.6.3. 1,1,1,3,4,4,4-Heptafluoro-2,2-dihydroxy-3-(2-aminophenylthio)butane (**4**).* IR: ν 1586 (C=C), 1610 (NH), 3070, 3180, 3390 br., 3480 (NH, OH). ^{1}H NMR: δ 3.8 (4H, br.s, NH_2, 2OH), 6.6 (1H, m, CH), 6.7 (1H, m, CH), 7.2 (2H, m, 2CH) (aromatic protons). ^{19}F NMR: δ −140.4 (1F, qq, $^{3}J_{FF}$ $^{4}J_{FF}$ 11.2 Hz, CF_3**CF**), −78.4 (3F, dq, $^{4}J_{FF}$ 11.2, $^{5}J_{FF}$ 9.5 Hz, **CF$_3$**C(OH)$_2$), −72.8 (3F, dq, $^{3}J_{FF}$ 11.2, $^{5}J_{FF}$ 9.5 Hz, **CF$_3$**CFS). GC–MS, *m*/*z* (rel. int.): 322 [M − OH]$^+$ (8.2), 321 [$M - H_2O$]$^+$ (89.8), 252 [$M - H_2O - CF_3$]$^+$ (38.7), 235 [M − OH − H_2O − CF_3]$^+$ (10.5), 234 (11.0), 233 (7.2), 232 [$M - H_2O$ − HF − CF_3]$^+$ (54.7), 205 (9.4), 204 [$M - H_2O$ − HF − CF_3CO]$^+$ CF_3CO]$^+$ (100), 189 (6.1), 188 (40.2), 185 (9.0), 184 (61.7), 172 (14.5), 168 (5.5), 162 (8.6), 154 [$C_6H_4(NH)SCF$]$^+$ (14.7), 151 (5.5), 150 (12.9), 135 [$C_6H_4(NH)SC$]$^+$ (6.7), 124 [$C_6H_4(S)NH_2$]$^+$ (8.9), 123 (6.8), 122 (7.7), 120 [C_6H_4SC]$^+$ (27.3), 109 (12.4), 108 [C_6H_4S]$^+$ (8.3), 102 (7.2), 96 (19.0), 95 (9.6), 93 (6.3), 92 [$C_6H_4NH_2$]$^+$ (22.7), 91 (7.7), 80 (6.7), 77 [C_6H_5]$^+$ (14.7), 70 (7.6), 69 [CF_3]$^+$ (40.4).

4.4.7. Procedure 7

The reaction of oxirane **1** (6.4 g, 29.6 mmol) with 2-aminothiophenol (3.7 g, 29.6 mmol) in 10 ml of DMSO gave yellow solid product (3.7 g) containing thiazolidine **6** (*RS*,*SR*/*RR*,*SS* ∼ 43:57), hem-diol **4**, disulfide **3** and remaining 2-aminothiophenol (Table 1, run 6). The crude product was allowed to stand at room temperature over 3 weeks and then worked up as in Procedure 6. Column chromatography (SiO_2, eluent: $CHCl_3$–hexane, 1:2) gave 1.2 g (40%) of compound **6** (*RR*,*SS*/*RS*,*SR* ∼ 7:11) and 0.1 g (1.7%) of compound **5**.

4.4.8. Procedure 8

In a similar manner, oxirane **1** (5.2 g, 24.07 mmol) was treated with 2-aminothiophenol (3.0 g, 24 mmol) in 5 ml of DMAA + H_2O (∼98:2) at 70–75 °C for 1.5 h. Then the reaction mixture was poured into ice water (200 ml), and the lower organic layer was separated, washed with water once more and dried (∼40 °C). The resinous residue obtained (7.0 g) consisted of diol **4**, benzothiazine **2** (*RR*,*SS*/*RS*,*SR* ∼ 1:2) at a ratio ∼4:1,

2-aminothiophenol and small amounts of unidentified products (from IR, ^{19}F, ^{1}H NMR and GC–MS).

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