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The synthesis of chiral 1,2,4-benzothiadiazine derivatives

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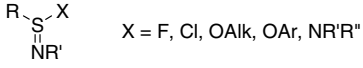
Abstract—Novel enantiomerically pure benzothiadiazines were prepared using the commercially available enantiopure (1*R*,2*S*,5*R*)-(−)-menthol and 1,7-dichloro-3-trifluoromethyl-1λ^4-benzo[1,2,4]thiadiazine.

1. Introduction

Chiral compounds of sulfur are of great importance for chemical[1] and biological processes.[2] Sulfonium salts, sulfoxides and sulfoximines are the basic classes of compounds with a chiral sulfur atom, which are studied the most intensively.[3]

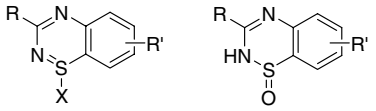
As for chiral iminoderivatives of tetravalent sulfur, sulfylimines are the most studied among them.[4] Data regarding chiral derivatives of sulfinimidic acids **1** are rare in the literature, although studies of this type of compounds have played an essential part in determination of the stereochemistry of nucleophilic substitution at a sulfur atom.[5]



1

Previous investigations of 1,2,4-benzothiazines **2** and **3**,[6] which can be considered as derivatives of cyclic sulfinimidic acids, have shown that some of them possess a high biological activity.[7]

Compounds **2** and **3** contain an asymmetric sulfur atom. In the present work we investigated the possibility of preparing optically active cyclic of sulfinimidic acids derivatives with the aim of determining their stereochemical stability, and the stereochemistry of reactions of nucleophilic substitution at the sulfur atom, followed by a study of the biological activity of the individual enantiomers.

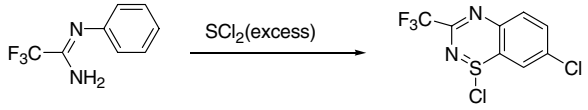


2 **3**

X = OR", NR_2"'

2. Results and discussion

We used 1,7-dichloro-3-trifluoromethyl-1λ^4-benzo[1,2,4]-thiadiazine **4**, which we had obtained earlier by the reaction of *N*-phenylamidine with sulfur dichloride.[8]



4

Compound **4** reacts with (1*R*,2*S*,5*R*)-(−)-menthol to form a diastereomeric mixture in the ratio 1.8:1. This ratio was determined by comparison of the CF_3 group fluorine nucleus signals integral intensities in the NMR ^{19}F spectrum of the reaction mixture. These signals differ by 0.2 ppm (see Section 4), which makes the diastereomer ratio determination quite valid.

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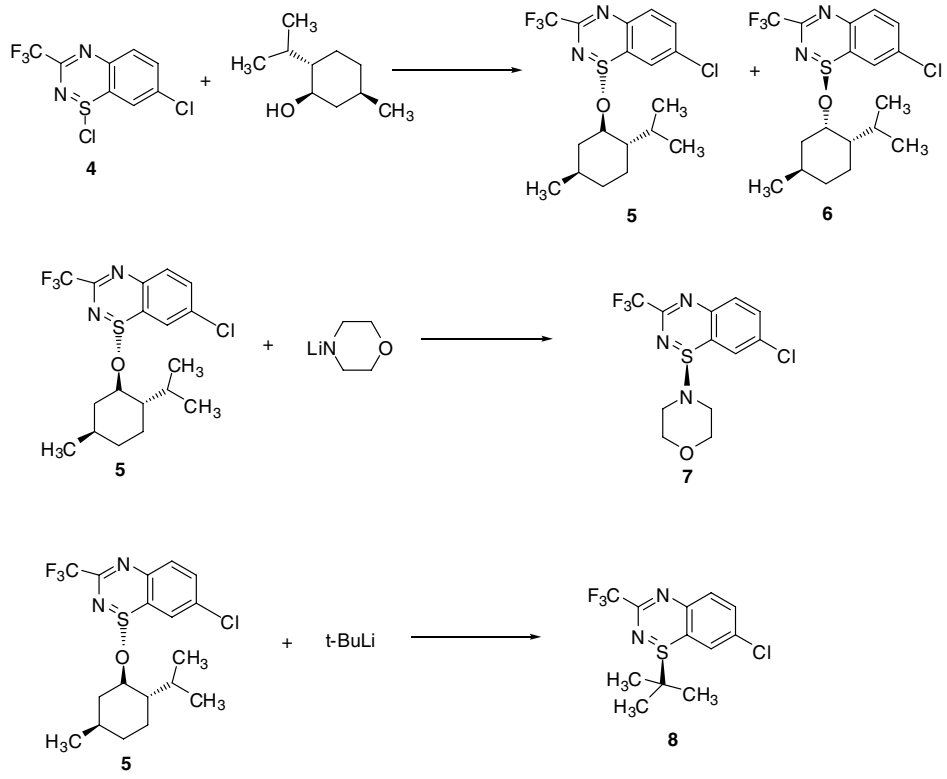


Diastereomer **5**, formed in a larger amount was isolated in an individual state using chromatography on silica gel with a yield of 20%. The structure of this compound and the absolute configuration of this sulfur atom in this structure has been determined by the single crystal X-ray diffraction (Fig. 1).

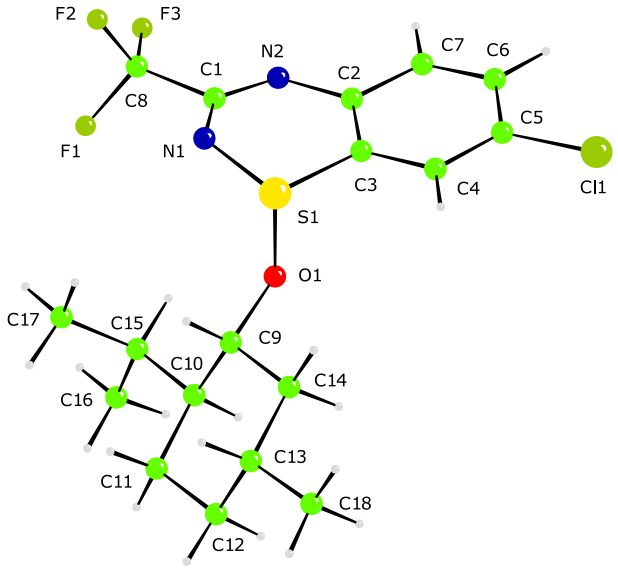


Figure 1. Perspective view and labeling scheme for the molecule (*S*)-(−)-7-chloro-1((1*R*,2*S*,5*R*)-(−)-2-isopropyl-5-methyl-cyclohexyloxy)-3-trifluoromethyl-1λ⁴-benzo[1,2,4]-thiadiazine **5**. Selected bond lengths (Å) and angles (°): S(1)–N(3) 1.671(2), S(1)–N(1) 1.614(2), S(1)–C(3) 1.753(2), N(1)–C(1) 1.352(6), N(2)–C(1) 1.294(6), N(2)–C(2) 1.395(6), C(2)–C(3) 1.395(6); N(1)S(1)N(3) 111.2(1), N(1)S(1)C(3) 103.3(1), N(3)S(1)C(3) 100.9(1).

Ester **5** is configurationally stable for 1 month at room temperature. Disappearance of its optical activity is observed only after boiling in chloroform for 5 min.

The stereochemical stability of compound **5** is sufficient for obtaining new optically active derivatives of 1,2,4-benzothiadiazines by nucleophilic substitution reactions. So, Li-morpholide reaction on **5** at −10 °C results in the formation of the optically active morpholide of sulfinimidic acid **7**.

The results of the specific angle of rotation of the plane-polarized light determination for raw product show that the data for crude product **7** obtained from the reaction mixture by evaporation of the solvent and for that purified by crystallization from hexane are very close. $\{[\alpha]_D^{20} = +1165$ and $+1188$ (0.5, $CHCl_3$), respectively$\}$. This allows us to conclude that the reaction proceeds enantioselectively without the formation of any important quantities of the racemic product or other enantiomer.

The structure of compound **7** determined by single crystal X-ray diffraction (Fig. 2) shows unequivocally that nucleophilic substitution at the sulfur atom in ester **5** passes with the configuration inversion of Ref. 9 (regarding the inversion mechanism of nucleophilic substitution at sulfur atom). In both molecules **5** and **7** the S(1)N(1)N(2)C(1–7) central system is not exactly planar (deviations from the least-square plane exceed 0.26 Å); the S(1) atom has pyramidal bond configuration (sum of the bond angles 310.3° and 315.4°, respectively).

Compound **7** as well as **5** are configurationally stable at room temperature, but are easily (5 min) racemized at boiling in benzene or chloroform.

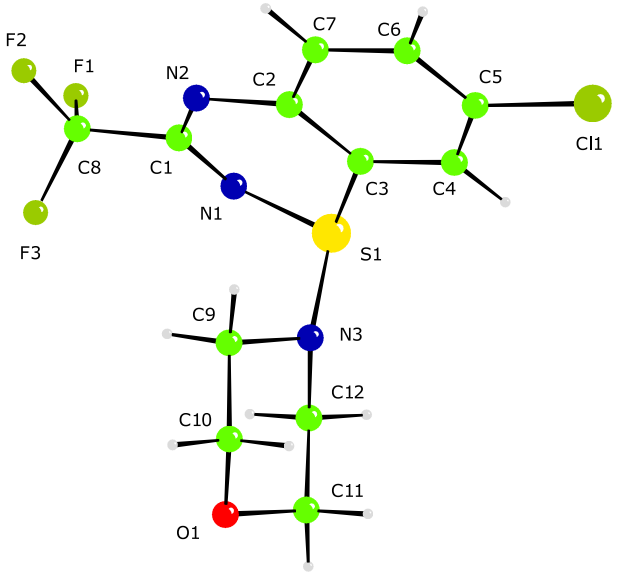
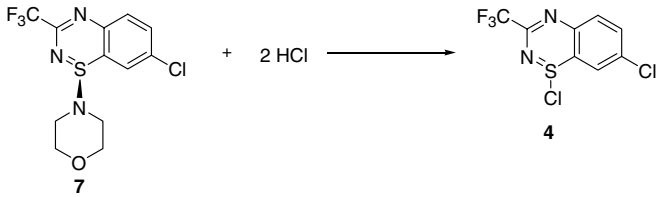


Figure 2. Perspective view and labeling scheme for the molecule (*S*)-(+)-7-chloro-1-morpholin-4-yl-3-trifluoromethyl-1λ^4-benzo[1,2,4]thiadiazine **7**. Selected bond lengths (Å) and angles (°): S(1)–O(1) 1.627(3), S(1)–N(1) 1.581(4), S(1)–C(3) 1.751(4), N(1)–C(1) 1.346(3), N(2)–C(1) 1.301(3), N(2)–C(2) 1.387(3), C(2)–C(3) 1.394(3); N(1)S(1)N(1) 108.5(2), O(1)S(1)C(3) 97.6(2), N(1)S(1)C(3) 104.2(2).

As the same time, optically active cyclic sulfilimine **8** obtained from ester **5** and *tert*-butyllithium is stereochemically stable under analogous conditions. As in the previous case, nucleophilic substitution of the alcohol residue changes the sign of the specific rotation in comparison with the starting compound **5**.

Thus, reactions of ester **5** with nucleophilic reagents can be considered a method for the preparation of optically active 1,2,4-benzothiadiazine derivatives.

We tried to explore the possibility of using the reactions with electrophilic reagents to obtain chiral 1,2,4-benzothiadiazines. In particular, it seemed interesting to verify the possibility of obtaining optically active cyclic sulfinimidic acid chloride. With this aim in mind, we investigated the reaction of optically active morpholide **7** with dry gaseous hydrogen chloride. However, this reaction leads to the formation of racemic acid chloride **4** only.



3. Conclusion

We have developed a highly efficient enantioselective synthesis of enantiomerically pure 1,2,4-benzothiadiazine derivatives. This method can be used for the synthesis of novel biologically active compounds.

4. Experimental

4.1. General

All solvents were purified according to the reported procedures. Reactions were carried out under an atmosphere of dry argon. ^{1}H NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ containing tetramethylsilane and C_6F_6 as internal standards on a Varian VXR-300 spectrometer operating at 300 MHz. All chemical shifts are given in parts per million. Optical rotations were measured on a Perkin–Elmer Polarimeter 341.Thin layer chromatography was performed using POLYGRAM® SIL G/UV$_{254}$ with benzene as eluent. Column chromatography was carried out using Merck type 60 silica gel (0.040–0.063 mm).

4.2. (*S*)-(−)-7-Chloro-1[(1*R*,2*S*,5*R*)-(−)-2-isopropyl-5-methyl-cyclohexyloxy]-3-trifluoromethyl-1λ^4-benzo[1,2,4]thiadiazine 5

The solution of 1,7-dichloro-3-trifluoromethyl-1λ^4-benzo[1,2,4]thiadiazine **4** (2.87 g, 0.01 mol) in diethyl ether (30 ml) was added to the stirred solution of (1*R*,2*S*,5*R*)-(−)-menthol (1.56 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in diethyl ether (20 ml) at 0–5 °C. The reaction mixture was stirred at room temperature for 4 h. Triethylamine salt was filtered and the filtrate was evaporated in vacuum 10–20 mm. Hg at 20–25 °C. Hexane was added to the solid residue, solution obtained was filtered and evaporated in vacuum 10–20 mm. Hg at 20–25 °C to 1/3 of volume and cooled at 15 °C. The colorless crystal mixture of diastereomers **5**,**6** was filtered. Yield 3.25 g, 80%, mp 105–109 °C; ^{1}H NMR; δ: 0.52 (d, 3H, CH_3, $J = 7.0$)*, 0.77 (d, 3H, $(CH_3)_2CH$, $J = 7.0$ Hz)*, 0.86 (d, 3H, CH_3, $J = 6.6$ Hz), 0.88 (d, 3H, $(CH_3)_2CH$, $J = 6.6$ Hz), 0.89 (d, 3H, $(CH_3)_2CH$, $J = 6.6$ Hz), 0.95 (d, 3H, $(CH_3)_2CH$, $J = 7.0$ Hz)*, 3.93, 4.23 (m, 1H), 7.51 (d, 1H, $J = 1.7$ Hz), 7.55* (d, 1H, $J = 2.0$ Hz), 7.64–7.73 (m, 2H); ^{19}F NMR; δ: −73.6*, −73.4 (s, CF_3). (*—diastereomer **5**).

The diastereomer **5** was obtained as a colorless crystalline compound in an individual state by separation of the diastereomeric mixture using column chromatography (eluent—benzene). Yield 0.65 g, 20%. Mp 118–119 °C, $[\alpha]_D^{20} = -857.5$ (*c* 0.9, $CHCl_3$); ^{1}H NMR; δ: 0.52 (d, 3H, CH_3, $J = 7.0$ Hz), 0.77 (d, 3H, $(CH_3)_2CH$, $J = 7.0$ Hz), 0.95 (d, 3H, $(CH_3)_2CH$, $J = 7.0$ Hz), 0.80–0.98 (m, 2H), 1.09–1.16 (m, 2H), 1.42 (m, 2H), 1.59–1.7 (m, 3H), 2.23 (m, 1H), 3.93 (dt, 1H, $J = 4.5$, 11.0 Hz), 7.55 (d, 1H, $J = 2.0$ Hz), 7.66 (d, 1H, $J = 8.5$ Hz), 7.70 (dd, 1H, $J = 2.0$, 9.0 Hz); ^{19}F NMR; δ: −73.6 (s, CF_3). Anal. Calcd for $C_{18}H_{22}ClF_3N_2OS$: C, 55.13; H, 5.45; N, 6.88; S, 7.88. Found: C, 55.05; H, 5.38; N, 6.78; S, 7.68.

4.3. (*S*)-(+)-7-Chloro-1-morpholin-4-yl-3-trifluoromethyl-1λ^4-benzo[1,2,4]thiadiazine 7

The solution of *N*-lithium morpholide prepared from morpholine (0.52 g, 0.006 mol) and butyl lithium (4.1 ml, 1.6 M solution in hexane) in diethyl ether (10 ml) was added to the stirred solution (1.22 g, 0.003 mol) of compound **5** in diethyl ether (20 ml) at −10 °C. The reaction mixture was

stirred for 30 min at the above temperature and 12 h at room temperature, methanol (2 ml) with water (5 ml) was added and the organic layer was separated, washed with water (2×10 ml), dried over Na_2SO_4, and evaporated to dryness in vacuum 10–20 mm Hg at 20–25 °C. Hexane (5 ml) was added to the residue and the colorless crystal compound was filtered. Yield 0.99 g, 80%, mp 147–148 °C; $[\alpha]_D^{20} = +1224$ (*c* 0.4, $CHCl_3$); ^{1}H NMR; δ: 2.78–2.99 (m, 4H, CH_2NCH_2), 3.60–3.64 (m, 4H, CH_2OCH_2), 7.43 (d, 1H, $J = 2.3$ Hz), 7.48 (d, 1H, $J = 8.9$ Hz), 7.62 (dd, 1H, $J = 2.3$, 9.0 Hz); ^{19}F NMR; δ: −73.2 (s, CF_3). Anal. Calcd for $C_{12}H_{11}ClF_3N_3OS$: C, 42.67; H, 3.28; N, 12.44; S, 9.49. Found: C, 42.36; H, 3.21; N, 12.35; S, 9.45.

4.4. (*S*)-(+)-1-*tert*-Butyl-7-chloro-3-trifluoromethyl-1λ^4-benzo[1,2,4]thiadiazine 8

The solution of *tert*-butyllithium (2.7 ml, 1.7 M in pentane) was added to the stirred solution (0.81 g, 0.002 mol) of compound **5** in diethyl ether (20 ml) at −70 °C. The mixture was stirred 40 min at the above temperature and 24 h at room temperature, methanol (2 ml) with water (5 ml) was added and the organic layer was separated, washed with water (2×10 ml), dried over Na_2SO_4, and evaporated to dryness in vacuum 10–20 mm Hg at 20–25 °C. Hexane (3 ml) was added to the residue and the yellow solid compound was filtered. Yield 0.53 g, 70%, mp 98 °C; $[\alpha]_D^{20} = +1014$ (*c* 0.37, $CHCl_3$); ^{1}H NMR; δ: 1.27 (s, 9H), 7.11 (d, 1H, $J = 2.0$ Hz), 7.29 (d, 1H, $J = 8.6$ Hz), 7.52 (dd, 1H, $J = 2.0$, 9.0 Hz); ^{19}F NMR; δ: −71.1 (s, CF_3). Anal. Calcd for $C_{12}H_{12}ClF_3N_2S$: C, 46.68; H, 3.92; N, 9.07; S, 10.38. Found: C, 46.82; H, 3.88; N, 8.99; S, 10.38.

4.5. 1,7-Dichloro-3-trifluoromethyl-1λ^4-benzo[1,2,3]thiadiazine 4

Dry gaseous hydrogen chloride (0.24 g, 0.0065 mol) was passed slowly through a stirred solution of (*S*)-(+)-7-chloro-1-morpholin-4-yl-3-trifluoromethyl-1λ^4-benzo[1,2,4]-thiadiazine **7** (1 g, 0,003 mol) in benzene (10 ml) at 20 °C. The reaction mixture was stirred for 1 h at this temperature, the hydrochloride salt was filtered, and the filtrate was evaporated in vacuum 10–20 mm Hg at 20–25 °C. The yield of racemic 1,7-dichloro-3-trifluoromethyl-1λ^4-benzo[1,2,3]thiadiazine was 0.76 g, 90%. Mp of this com-

Table 1. Crystal data and structure refinement parameters for the compounds **5** and **7**

	5	**7**
Empirical formula	$C_{18}H_{22}ClF_3N_2OS$	$C_{12}H_{11}ClF_3N_3OS$
Cell parameters		
a (Å)	9.677(2)	8.6098(3)
b (Å)	11.730(3)	8.6098(3)
c (Å)	17.960(3)	33.083(3)
α (°)	90	90
β (°)	90	90
γ (°)	90	120
V (Å^3)	2038.6	2123.9
Z	4	6
D_{calc} (g cm^{-3})	1.33	1.58
Crystal system	Orthorhombic	Trigonal
Space group	$P2_12_12_1$	$P3_221$
μ (cm^{-1})	3.25	4.52
F(000)	848	1032
Crystal size (mm)	$0.37 \times 0.43 \times 0.50$	$0.12 \times 0.20 \times 0.35$
Diffractometer	Enraf Nonius CAD4	Bruker Smart ApexII
Radiation type	Mo Kα	Mo Kα
Index ranges	$0 \geqslant h \geqslant 11$ $0 \geqslant k \geqslant 14$ $0 \geqslant l \geqslant 21$ (and corresponding Friedel pairs)	$-12 \geqslant h \geqslant 12$ $-10 \geqslant k \geqslant 11$ $-50 \geqslant l \geqslant 35$
θ_{max} (°)	25.5	32.6
No. of reflections		
Collected	4378	13,060
Independent	3584	4487
In refinement	2033	2906
R_{merge}	0.023	0.034
Cutoff	$I \geqslant 3\sigma(I)$	$I \geqslant 3\sigma(I)$
No. of refined parameters	263	191
Final R indices		
R_1(F)	0.049	0.041
R_w(F)	0.052	0.046
GOF	1.131	1.078
Flack parameter	0.07(12)	0.09(7)
Weighting coefficients:	1.20, 0.79, 0.94	1.33, 1.30, 0.96
Largest peak/hole (e cm^{-3})	−0.30/0.36	−0.45/0.51

pound (83 °C) and NMR ^{1}H, ^{19}F spectra are in accordance with the literature data.[8]

4.6. X-ray crystal structure determination of compounds 5 and 7

Crystal data, data collection, and processing parameters are given in Table 1. All crystallographic measurements were performed at 18 °C. All data were corrected for Lorentz and polarization effects; empirical absorption correction based on azimuthal scan data[10] was applied for **5**, absorption correction using the SADABS procedure[11] was applied for **7**. Both structures were solved by direct methods. All atoms were refined on F_{obs} by full-matrix least-squares technique in the anisotropic approximation. Chebushev weighting scheme[12] was used. All structural calculations were carried out using CRYSTALS program package.[13] The Flack test[14] was applied for the absolute configuration determination.

The full crystallographic data sets (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 629242 for **7** and CCDC 629504 for **5.** Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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