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Synthesis of Cyclic Sulfonamides by Reaction of *N*-Sulfinyl-3-(trifluoromethyl)aniline with Norbornenes

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Abstract—*N*-Sulfinyl-3-(trifluoromethyl)aniline reacted with bicyclo[2.2.1]hept-2-ene and bicyclo[2.2.1]-hepta-2,5-diene to give the corresponding Diels–Alder adducts which were oxidized to 8-trifluoromethyl-2,3,4,4a,6,10b-hexahydro-5λ^6-1,4-methanodibenzo[*c*,*e*][1,2]thiazine-5,5(1*H*)-diones. The cycloaddition occurred predominantly with participation of the S=N–C^1=C^6 fragment of *N*-sulfinyl-3-(trifluoromethyl)aniline and exclusively at the *endo* side of bicyclo[2.2.1]heptenes.

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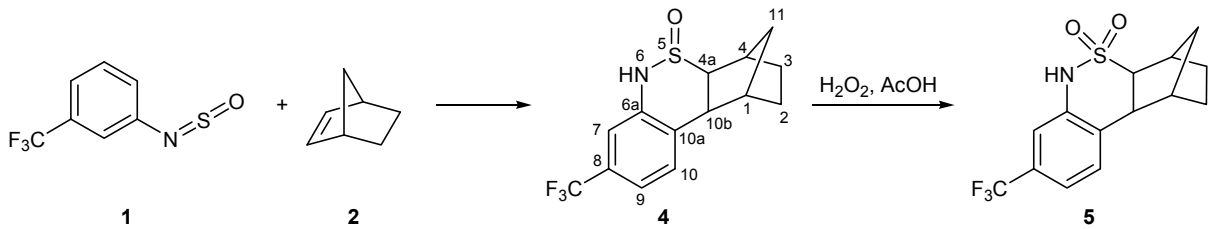
Among all known pharmacophoric groups, sulfonamido group has been studied most thoroughly, and sulfonamides occupy a leading position in pharmaceutics [1], whereas fluorinated medicines have been introduced into pharmacological practice relatively recently. However, by the beginning of the XXI century various fluorinated derivatives have firmly occupied their pharmaceutical niche. Fluoroaromatic and fluoroaliphatic molecular fragments in combination with other pharmacophoric moieties are often present in efficient drugs with a broad spectrum of action [2]. For example, trifluoromethyl group is present in the antitumor drugs sorafenib [3] and nilotinib [4], drugs acting on the central nervous system (aprepitant [5], ezogabine [6]) and urogenital system (dutasteride [7], silodosin [8]), and antidiabetic drug sitagliptin [9]. The anti-HIV drug tipranavir possesses both trifluoromethyl and sulfonamide functionalities [10].

We endeavored to synthesize sulfonamides possessing a trifluoromethyl group according to the protocol developed by us previously [11, 12], namely by hetero-Diels–Alder reaction of *N*-sulfinyl-3-(trifluoromethyl)-aniline (**1**) with bicyclo[2.2.1]heptenes, norbornene (**2**) and norbornadiene (**3**). In this reaction, *N*-sulfinyl-aniline acts as diene toward strained cycloolefins as dienophiles, and *meta* position of the CF_3 group with respect to the N=S=O group provides the possibility of formation in each case of structural isomers differing by the position of the trifluoromethyl group relative to the newly formed heterocyclic fragment.

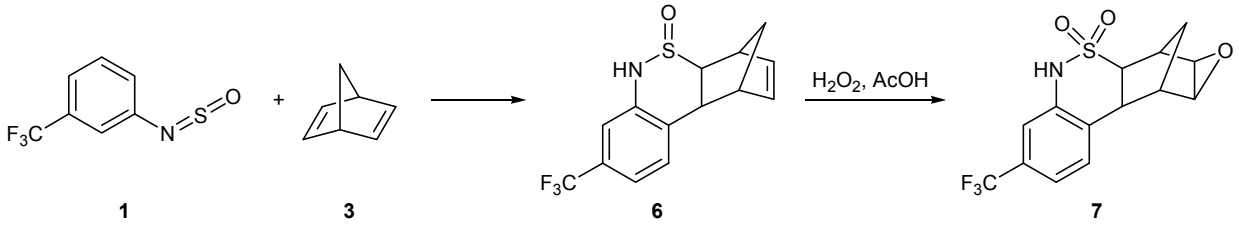
The reactions were carried out by heating the reactants at a diene-to-dienophile ratio of 1:1.5 without a solvent in a sealed ampule on a boiling water bath for 8–10 h, and the yields exceeded 80%. In the reaction of *N*-sulfinylaniline **1** with norbornene (**2**) (Scheme 1) we isolated a crystalline product which characteristi-

Scheme 1.



1 **2** **4** **5**

Scheme 2.



cally displayed in the IR spectrum absorption bands due to stretching vibrations of S=O (1055 cm^{-1}), C–F (1121, 1172, 1327 cm^{-1}), and N–H bonds (3142 cm^{-1}). Its ^1H NMR spectrum contained signals at δ 9.12 and 9.22 (NH), 7.0–7.5 (H_{arom}), and 1.0–3.5 ppm (bicyclic fragment). The ^{19}F NMR spectrum showed signals at δ_F –61.5 and –57.5 ppm. These findings, in combination with the elemental analysis data, indicated formation of a 1:1 adduct, and the ^1H NMR spectral pattern in the aromatic region (one-proton singlet and two one-proton *AB* doublets) proved the position of the trifluoromethyl group on C^8. Figure 1 shows the structure of 8-trifluoromethyl-2,3,4,4a,6,10b-hexahydro-5λ^4-1,4-methanodibenzo[*c*,*e*][1,2]thiazin-5(1*H*)-one (**4**) determined by X-ray analysis. It is seen that diene **1** approached the dienophile **2** molecule at the *endo* side.

The oxidation of adduct **4** with hydrogen peroxide in acetic acid at room temperature (24 h) afforded compound **5** whose IR spectrum displayed absorption bands at 1144, 1334 cm^{-1} (SO_2), 1121, 1317 cm^{-1} (CF_3), and 3172 cm^{-1} (N–H). The ^1H and ^{19}F NMR spectra of **5** were analogous to the spectra of **4** with the difference that some signals were displaced downfield, the largest downfield shift being observed for the NH proton signal (Δδ = 1.0 ppm).

The reaction of **1** with norbornadiene (**3**) under similar conditions gave adduct **6** (Scheme 2). It showed in the IR spectrum absorption bands typical of stretching vibrations of S=O (1057 cm^{-1}), CF_3 (1126, 1171, 1332 cm^{-1}), and N–H bonds (3180 cm^{-1}). The ^1H and ^{19}F NMR spectra of **6** resembled those of **4**, but the ^1H NMR spectrum of the former lacked signals assignable to the CH_2CH_2 fragment (multiplet at δ 1.45–1.65 ppm in the spectrum of **4**); instead, a multiplet signal was observed at δ 6.30–6.40 ppm due to olefinic protons.

Adduct **6** was oxidized with hydrogen peroxide in acetic acid at room temperature (24 h). The IR spectrum of the product (compound **7**) contained absorption bands corresponding to SO_2 (1141, 1325 cm^{-1}), CF_3 (1175, 1330 cm^{-1}), and N–H stretching modes (3201 cm^{-1}). The ^1H and ^{19}F NMR spectra of **7** were similar to the spectra of **6**, but some proton signals of **7** were located in a weaker field; the largest downfield shift was observed for the NH signal (Δδ = 1.0 ppm). Furthermore, the ^1H NMR spectrum of **7** lacked olefinic proton signals, but signals from two oxirane protons appeared in the region δ 3.40–3.50 ppm (^3J = 3.0–3.2 Hz).

The proposed structure of adduct **7** was confirmed by X-ray analysis (Fig. 2). Both Diels–Alder reaction and subsequent epoxidation were characterized by *endo* selectivity.

EXPERIMENTAL

The elemental analyses were obtained on a EuroEA 3000 CHNS analyzer. The IR spectra were recorded in KBr on a Bruker Vertex 70 spectrometer with Fourier transform. The ^1H and ^{19}F NMR spectra were measured on a Bruker Avance 400 spectrometer at 400.0 and 376.5 MHz, respectively. The ^1H chemical shifts were determined relative to the residual proton signal of the deuterated solvent (DMSO-d_6). The melting points were measured with an Electrothermal Digital Mel-Temp 3.0 melting point apparatus.

The X-ray analyses of single crystals of **4** and **7** were performed on a Bruker SMART Apex II diffractometer (graphite monochromator, λMoK_α 0.71073 Å)

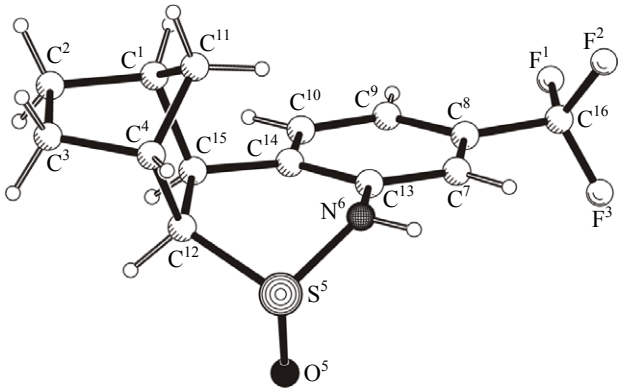


Fig. 1. Structure of the molecule of 8-trifluoromethyl-2,3,4,4a,6,10b-hexahydro-5λ^4-1,4-methanodibenzo[*c*,*e*][1,2]-thiazin-5(1*H*)-one (**4**) according to the X-ray diffraction data.

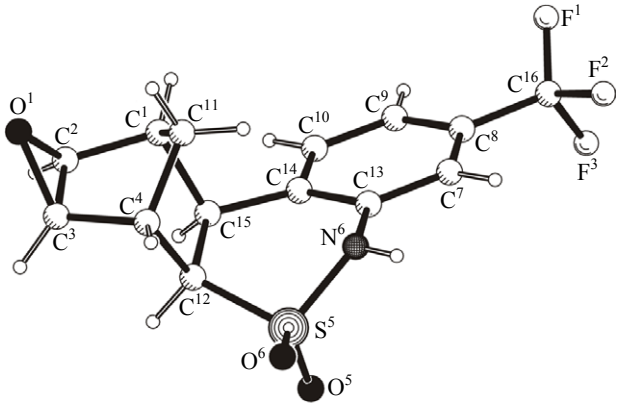


Fig. 2. Structure of the molecule of 8-trifluoromethyl-2,3,4,4a,6,10b-hexahydro-5λ^6-2,3-epoxy-1,4-methanodibenzo[*c*,*e*][1,2]thiazine-5,5(1*H*)-dione (**7**) according to the X-ray diffraction data.

at 293 K. Corrections for absorption were applied empirically using SADABS [13]. The structures were solved by the direct method using SHELXS [14]. The positions of non-hydrogen atoms were refined first in isotropic and then in anisotropic approximation usng SHELXL-97 [14]. Both structures showed disordering of fluorine atoms in the trifluoromethyl group by two positions with approximately equal populations. Hydrogen atoms attached to carbons were placed into calculated positions which were refined according to the riding model. The position of the NH hydrogen atom in both structures was determined from the difference Fourier maps and was refined in isotropic approximation. All calculations were performed with the aid of WinGX [15] and APEX2 [16]. The X-ray diffraction data for compounds **4** and **7** were deposited to the Cambridge Crystallographic Data Centre.

Compound **4**. Triclinic crystal system, space group *P*-1; $C_{14}H_{14}F_3NOS$; unit cell parameters (20°C): a = 11.160(2), b = 12.291(2), c = 22.217(4) Å; α = 86.290(3), β = 76.229(3), γ = 70.234(2)°; V = 2785.0(9) Å^3; Z = 8; d_{calc} = 1.437 g/cm^3; μ_{Mo} = 2.61 cm^{-1}. Intensities of 21492 reflections were measured, including 6021 reflections with $I \geq 2\sigma(I)$. Final divergence factors: R = 0.0613 [reflections with $I \geq 2\sigma(I)$], R_w = 0.1348 (all reflections). CCDC entry no. 1413122.

Compound **7**. Monoclinic crystal system, space group $P2_1/n$; $C_{14}H_{12}F_3NO_3S$; unit cell parameters (20°C): a = 11.20(1), b = 8.52(1), c = 14.61(2) Å; β = 91.714(15)°; V = 1394(3) Å^3; Z = 4; d_{calc} = 1.579 g× cm^{-3}; μ_{Mo} = 2.79 cm^{-1}. Intensities of 7982 reflections were measured, including 2122 reflections with $I \geq 2\sigma(I)$. Final divergence factors: R = 0.0474 [reflections with $I \geq 2\sigma(I)$], R_w = 0.1166 (all reflections). CCDC entry no. 1413121.

***N*-Sulfinyl-3-(trifluoromethyl)aniline (1)** was synthesized by reaction of 3-(trifluoromethyl)aniline with an equimolar amount of thionyl chloride in boiling benzene according to [12]. The product was distilled under reduced pressure, bp 105–107°C (12 mm).

8-Trifluoromethyl-2,3,4,4a,6,10b-hexahydro-5λ^4-1,4-methanodibenzo[*c*,*e*][1,2]thiazin-5(1*H*)-one (4). A mixture of 10.4 g (0.05 mol) of compound **1** and 7.1 g (0.075 mol) of norbornene (**2**) was heated in a sealed ampule on a water bath (95–100°C) for 10 h. After cooling, the mixture solidified and was treated with petroleum ether, and the precipitate was filtered off on a Büchner funnel, washed with cold petroleum ether, and recrystallized from ethanol. Yield 86%, mp 176–177°C. IR spectrum, ν, cm^{-1}: 3142 s (NH); 1121 v.s, 1172 s, 1327 s (CF_3); 1055 s (S=O). ^{1}H NMR spectrum, δ, ppm: 1.02 d (1H, 11-H, $^2J_{HH}$ = 10.0 Hz), 1.40–1.55 m (4H, 2-H, 3-H), 1.60 d (1H, 11-H, $^2J_{HH}$ = 10.0 Hz), 2.20 s and 2.42 s (1H each, 1-H, 4-H), 3.10 d and 3.35 d (1H each, 4a-H, 10b-H, $^3J_{HH}$ = 8.6 Hz), 7.13 s (1H, 7-H), 7.28 d (1H, 9-H, $^3J_{HH}$ = 8.0 Hz), 7.43 d (1H, 10-H), 9.20 s (1H, NH). ^{19}F NMR spectrum: δ_F –61.24 ppm, s (CF_3). Found, %: C 55.78; H 4.68; N 4.70; S 10.75. $C_{14}H_{14}F_3NOS$. Calculated, %: C 55.81; H 4.65; N 4.65; S 10.63.

8-Trifluoromethyl-1,2,3,4,4a,6,10b-hexahydro-5λ^6-1,4-methanodibenzo[*c*,*e*][1,2]thiazine-5,5(1*H*)-dione (5). Compound **4**, 3.0 g (0.01 mol), was dissolved by stirring in a minimal amount of warm (50°C) glacial acetic acid. After complete dissolution, the heating was turned off, and 15 mL of 30% hydrogen peroxide was added. The mixture was kept for 24 h and diluted with water, and the precipitate was separated by decanting and recrystallized from ethanol. Yield 65%, mp 162–163°C. IR spectrum, ν, cm^{-1}: 3172 s (NH); 1144 s, 1334 s (SO_2); 1121 s, 1317 s (CF_3). ^{1}H NMR spectrum, δ, ppm: 1.17 d (1H, 11-H, $^2J_{HH}$ = 10.3 Hz), 1.45–1.62 m (4H, 2-H, 3-H), 1.78 d (1H, 11-H, $^2J_{HH}$ = 10.3 Hz), 2.34 s and 2.72 s (1H each, 1-H, 4-H), 3.33 s and 3.57 s (1H each, 4a-H, 10b-H), 7.08 s (1H, 7-H), 7.37 d (1H, 9-H, $^3J_{HH}$ = 8.0 Hz), 7.52 d (1H, 10-H, $^3J_{HH}$ = 8.0 Hz), 10.25 s (1H, NH). ^{19}F NMR spectrum: δ_F –56.55 ppm, s (CF_3). Found, %: C 52.92; H 4.38; N 4.46; S 10.18. $C_{14}H_{14}F_3NO_2S$. Calculated, %: C 53.00; H 4.42; N 4.42; S 10.09.

8-Trifluoromethyl-4,4a,6,10b-tetrahydro-5λ^4-1,4-methanodibenzo[*c*,*e*][1,2]thiazin-5(1*H*)-one (6) was synthesized as described above for compound **4**. Yield

82%, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3180 s (NH); 1126 v.s, 1171 s, 1332 v.s (CF_3); 1057 s (S=O). ^1H NMR spectrum, δ, ppm: 1.15 d and 1.77 d (1H each, 11-H, $^2J_{HH}$ = 8.9 Hz), 2.82 s (1H, 1-H or 4-H), 2.87 d (1H, 4a-H or 10b-H, $^3J_{HH}$ = 8.7 Hz), 3.12 s (1H, 4-H or 1-H), 3.18 d (1H, 10b-H or 4a-H, $^3J_{HH}$ = 8.7 Hz), 6.30–6.40 m (2H, 2-H, 3-H), 7.18 s (1H, 7-H), 7.33 d (1H, 9-H, $^3J_{HH}$ = 7.8 Hz), 7.52 d (1H, 10-H, $^3J_{HH}$ = 7.8 Hz), 9.35 s (1H, NH). ^{19}F NMR spectrum: δ_F –61.20 ppm, s (CF_3). Found, %: C 56.23; H 3.98; N 4.60; S 10. 66. $C_{14}H_{12}F_3NOS$. Calculated, %: C 56.18; H 4.01; N 4.68; S 10.70.

8-Trifluoromethyl-2,3,4,4a,6,10b-hexahydro-5λ^6-2,3-epoxy-1,4-methanodibenzo[*c*,*e*][1,2]thiazine-5,5(1*H*)-dione (7) was synthesized as described above for compound **5**. Yield 60%, mp 199–201°C. IR spectrum, ν, cm^{-1}: 3201 s (NH); 1175 s, 1330 s (CF_3); 1141 s, 1325 s (SO_2). ^1H NMR spectrum, δ, ppm: 1.12 d and 1.38 d (1H each, 11-H, $^2J_{HH}$ = 10.7 Hz), 2.62 s and 3.00 s (1H each, 1-H, 4-H), 3.43 d and 3.47 d (1H each, 2-H, 3-H, $^3J_{HH}$ = 3.2 Hz), 3.61 d and 3.68 d (1H each, 4a-H, 10b-H, $^3J_{HH}$ = 9.2 Hz), 7.13 s (1H, 7-H), 7.42 d (1H, 9-H, $^3J_{HH}$ = 8.0 Hz), 7.57 d (1H, 10-H, $^3J_{HH}$ = 8.0 Hz), 10.40 s (1H, NH). ^{19}F NMR spectrum: δ_F –61.35 ppm, s (CF_3). Found, %: C 50.66; H 3.67; N 4.30; S 9.72. $C_{14}H_{12}F_3NO_3S$. Calculated, %: C 50.76; H 3.63; N 4.23; S 9.67.

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