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Benzothiazol-2-yl(difluoro)methanesulfonic Acid: Synthesis and Reactions

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Abstract—The condensation of *o*-aminothiophenol with sulfodifluoroacetic acid led to the formation of benzothiazol-2-yl(difluoro)methanesulfonic acid whose aryldiazonium salts were converted by pyrolysis into aryl benzothiazol-2-yl(difluoro)methanesulfonates.

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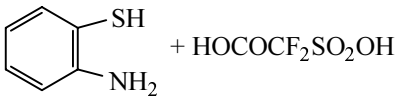
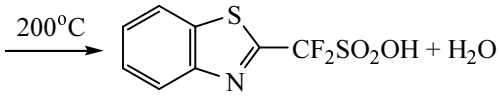
We formerly prepared benzothiazol-2-yl(difluoro)-methanesulfonyl fluoride, an analog of trifluoromethanesulfonyl fluoride containing a benzothiazolyl group instead of one fluorine atom. The preparation method consisted in reacting cyanodifluoromethanesulfonyl fluoride with 2-aminothiophenol to give the benzothiazol-2-yl(difluoro)-methanesulfonyl fluoride in a 32% yield [1]. The alkaline hydrolysis of the sulfonyl fluoride followed by acidifying resulted in the preparation of benzothiazol-2-yl(difluoro)-methanesulfonic acid in an overall yield not exceeding 22%.

The goal of the present study was a development of a preparative procedure for the synthesis of benzothiazol-2-yl(difluoro)methanesulfonic acid and investigation of its properties.

We found that in the condensation of the available sulfodifluoroacetic acid [2] with the 2-aminothiophenol (**I**) formed acid **II** in a 70% yield notwithstanding the relatively rigid reaction conditions.

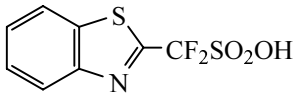


I

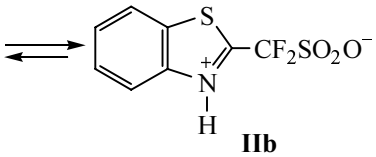


IIa

Sulfonic acid **IIa** is a high-melting colorless crystalline compound whereas its closest analog, the trifluoromethanesulfonic acid is a fluid. Apparently benzothiazol-2-yl(difluoro)methanesulfonic acid (**IIa**) exist in the form of an internal salt **IIb**.

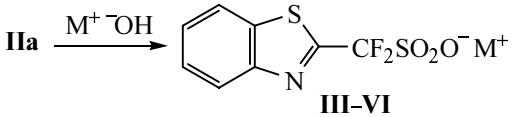


IIa



IIb

Sulfonic acid **IIa** formed with various cations salts soluble in water. In the synthesis of salts **III–VI** we used the alkali metals hydroxides, and the zinc salt **VII** was prepared form the zinc oxide.

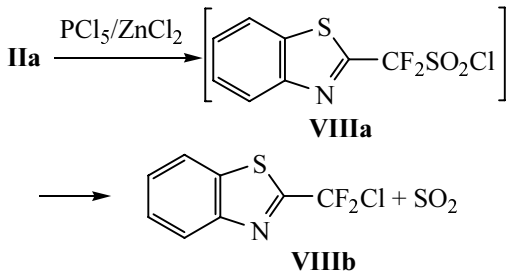


III–VI

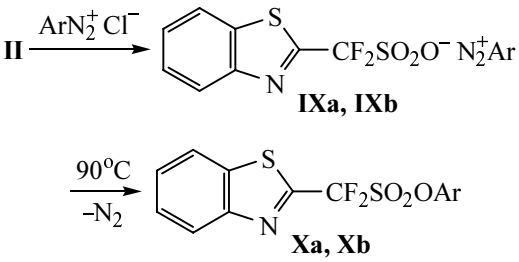
M = NH_4, Li, Na, K.

We attempted to synthesize acid **IIa** chloride to be used in preparation of the acid derivatives. However it turned out that neither sulfonic acid **IIa** nor its sodium salt **V** reacted with the phosphorus pentachloride. We also failed to obtain the corresponding sulfonyl chloride treating acid **IIa** with the phosphorus pentachloride in

the presence of zinc chloride. Instead of benzothiazol-2-yl(difluoro)methanesulfonyl chloride (**VIIIa**) we isolated 2-(difluorochloromethyl)benzothiazole (**VIIIb**) originating obviously from the decomposition of chloride **VIIIa** under the reaction conditions.



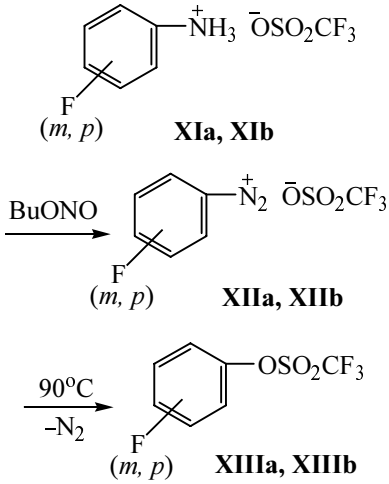
Benzothiazol-2-yl(difluoro)methanesulfonic acid (**IIa**) with water solutions of aryldiazonium chlorides gave rise to salts **IXa** and **IXb** which eliminated nitrogen on pyrolysis to give aryl esters **Xa** and **Xb**.



Ar = 3-FC_6H_4 (**a**), Ar = 4-FC_6H_4 (**b**).

The reaction of acid **IIa** with aryldiazonium chlorides followed by decomposition of the diazonium salts can be a convenient preparation method for aryl benzothiazol-2-yl(difluoro)methanesulfonates.

We tried to estimate the electronic character of the benzothiazol-2-yl(difluoro)methanesulfonyloxy group and to compare it with the closest analog, the trifluoromethanesulfonyloxy group. To this end we prepared *m*-fluoro- and *p*-fluorophenyl trifluoromethanesulfonates **XIIIa** and **XIIIb** by decomposition of the *m*-fluoro- and *p*-fluorophenyldiazonium trifluoromethanesulfonates **XIIa** and **XIIb**.



Chemical shifts δ_F were measured in the ^{19}F NMR spectra of benzothiazol-2-yl(difluoro)methanesulfonyloxy and trifluoromethanesulfonyloxy groups, and also of the fluorine atoms in the *m*-fluoro- and *p*-fluorophenyl esters of the corresponding sulfonic acids. These data were used in the calculation of the σ-constants of substituted difluoromethanesulfonyloxy groups containing as a substituent either fluorine atom or a benzothiazolyl moiety.

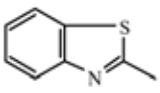
The calculation of the σ_I and σ_R constants was performed by formulas from [3], and the σ_m and σ_p constants, by formulas from [4] (see the table).

As seen from the table, the benzothiazol-2-yl(difluoro)-methanesulfonyloxy group is similar in the values of the σ_I and σ_R substituents to the trifluoromethanesulfonyloxy group, with a little less inductive effect than that of the latter. This result is in agreement with the smaller value of the σ_I of the benzothiazolyl moiety as compared with that of the fluorine atom (0.37 and 0.44 respectively [3]). Both benzothiazol-2-yl(difluoro)methanesulfonyloxy and trifluoromethanesulfonyloxy groups are π-donors. Therewith the values of σ_R constants of benzothiazol-2-yl-(difluoro)methanesulfonyloxy group and trifluoromethanesulfonyloxy group according to the calculations based on our experimental data equal –0.19 and –0.17 respectively. The close σ_I and σ_R values for trifluoromethanesulfonyloxy group were reported before [5].

EXPERIMENTAL

^1H and ^{19}F NMR spectra were registered on a spectrometer VXR-300 at operating frequency 299.9 and 282.2 MHz respectively, internal references TMS and CCl_3F, solvent DMSO-d_6 (compounds **II–VII**), $CDCl_3$ (compounds **VIIIb, Xa, Xb, XIIIa**, and **XIIIb**).

σ-Constants of substituted difluoromethanesulfonyloxy groups RCF_2SO_2O

R	δ_F^m	δ_F^p	σ_I	σ_R	σ_m	σ_p
	4.12	0.0	0.74 + 0.03	–0.19 + 0.01	0.59	0.48
F	4.93	0.83	0.88 + 0.04	–0.17 + 0.01	0.74	0.64

Commercial *o*-aminothiophenol (**I**) was used, sulfodifluoroacetic acid was synthesized by procedure [2].

Benzothiazol-2-yl(difluoro)methanesulfonic acid (IIa). A mixture of 1.25 g (10 mmol) of *o*-aminothiophenol (**I**) and 1.93 g (11 mmol) of sulfodifluoroacetic acid was within 1 h gradually heated to 200°C under reduced pressure (20 mm Hg), and the heating at this temperature was continued for 3 h more. On cooling activated carbon and 10 ml of acetonitrile was added to the reaction mixture. The mixture was boiled, then filtered, and the mother liquor was evaporated. Yield 1.86 g (70%), colorless crystals, mp 255–257°C. ^{1}H NMR spectrum, δ, ppm: 7.58 m ($2H_{arom}$), 8.13 d ($1H_{arom}$, *J* 8.1 Hz), 8.19 d ($1H_{arom}$, *J* 7.6 Hz). ^{19}F NMR spectrum, δ, ppm: –99.1 s. Found, %: C 36.09; H 1.79; N 5.21; S 24.26. $C_8H_5F_2NO_3S_2$. Calculated, %: C 36.22; H 1.90; N 5.28; S 24.17.

Ammonium benzothiazol-2-yl(difluoro)methanesulfonate (III). In 8 ml of 25% aqueous ammonia was dissolved 2.65 g (10 mmol) of acid **IIa**, the solution was evaporated on a water bath, the residue was ground and dried in a vacuum (20 mm Hg) at 100°C. Yield quantitative, t.decomp. 282°C. ^{1}H NMR spectrum, δ, ppm: 7.58 m ($2H_{arom}$), 8.16 d ($1H_{arom}$, *J* 8.5 Hz), 8.20 d ($1H_{arom}$, *J* 7.5 Hz). ^{19}F NMR spectrum, δ, ppm: –97.8 s. Found, %: C 34.22; H 2.84; N 9.86; S 22.84. $C_8H_8F_2N_2O_3S_2$. Calculated, %: C 34.04; H 2.86; N 9.92; S 22.72.

Lithium, sodium, and potassium salts were obtained similarly from the corresponding hydroxides in quantitative yields.

Lithium benzothiazol-2-yl(difluoro)methanesulfonate (IV). T.decomp. 244°C. ^{1}H NMR spectrum, δ, ppm: 7.58 m ($2H_{arom}$), 8.14 d ($1H_{arom}$, *J* 8.1 Hz), 8.20 d ($1H_{arom}$, *J* 7.7 Hz). ^{19}F NMR spectrum, δ, ppm: –97.8 s. Found, %: C 35.31; H 1.53; N 5.21; S 23.73. $C_8H_4F_2LiNO_3S_2$. Calculated, %: C 35.43; H 1.49; N 5.16; S 23.65.

Sodium benzothiazol-2-yl(difluoro)methanesulfonate (V). T.decomp. 259°C. ^{1}H NMR spectrum, δ, ppm: 7.58 m ($2H_{arom}$), 8.14 d ($1H_{arom}$, *J* 7.7 Hz), 8.20 d ($1H_{arom}$, *J* 7.2 Hz). ^{19}F NMR spectrum, δ, ppm: –97.7 s. Found, %: C 33.60; H 1.35; N 4.78; S 22.24. $C_8H_4F_2NNaO_3S_2$. Calculated, %: C 33.45; H 1.40; N 4.87; S 22.32.

Potassium benzothiazol-2-yl(difluoro)methanesulfonate (VI). T.decomp. 246°C. ^{1}H NMR spectrum, δ, ppm: 7.58 m ($2H_{arom}$), 8.14 d ($1H_{arom}$, *J* 7.0 Hz), 8.19 d ($1H_{arom}$, *J* 6.9 Hz). ^{19}F NMR spectrum, δ, ppm: –97.7 s. Found, %: C 31.81; H 1.41; N 4.67; S 21.06. $C_8H_4F_2KNO_3S_2$. Calculated, %: C 31.68; H 1.33; N 4.62; S 21.14.

Zinc benzothiazol-2-yl(difluoro)methanesulfonate (VII). Into a solution of 3 g (11.3 mmol) of acid **II** in 20 ml of water was added 1.5 g (18.5 mmol) of zinc oxide, and the suspension was stirred for 2 h at room temperature. Excess of the zinc oxide was filtered off, the filtrate was evaporated on a water bath, and the crystalline mass obtained was ground and dried in a vacuum (20 mm Hg) at 100°C. Yield 3.0 g (92%), t.decomp. 355°C. ^{1}H NMR spectrum, δ, ppm: 7.58 m ($2H_{arom}$), 8.11 d ($1H_{arom}$, *J* 7.9 Hz), 8.15 d ($1H_{arom}$, *J* 7.5 Hz). ^{19}F NMR spectrum, δ, ppm: –101.0 s. Found, %: C 32.45; H 1.33; N 4.73; S 21.71. $C_{16}H_8F_4N_2O_6S_4Zn$. Calculated, %: C 32.36; H 1.36; N 4.72; S 21.60.

2-(Difluorochloromethyl)benzothiazole (VIIIa). A mixture of 3.13 g (10.9 mmol) of sodium salt **V**, 6.9 g (33.2 mmol) of a fine powder of PCl_5, and 2.0 g of $ZnCl_2$ was heated for 2 h at 180°C. The volatile products were distilled off in a vacuum (20 mm Hg), 15 ml of dichloromethane were added to the residue, the mixture was filtered, and the filtrate was washed with 8 ml of ice water. The organic layer was separated and dried over $CaCl_2$, the solvent was removed. Yield 1.34 g (56%), colorless oily substance. ^{1}H NMR spectrum, δ, ppm: 7.57 m ($2H_{arom}$), 7.96 d ($1H_{arom}$, *J* 7.9 Hz), 8.19 d ($1H_{arom}$, *J* 7.5 Hz). ^{19}F NMR spectrum, δ, ppm: –47.95 s (publ.: –47.5 ppm [6]). Found, %: C 43.66; H 1.71; Cl 16.31; N 6.45; S 14.51. $C_8H_4ClF_2NS$. Calculated, %: C 43.75; H 1.84; Cl 16.14; N 6.38; S 14.60.

Aryldiazonium benzothiazol-2-yl(difluoro)methanesulfonates IXa and IXb. To a solution of aryldiazonium chloride prepared from 4.7 mmol of arylamine in 4 ml of 10% hydrochloric acid and 4.7 mmol of sodium nitrite was added 2.6 mmol of a solution of sulfonic acid **II** in 8 ml of water at 0–5°C, and the mixture was stirred for 15–20 min with a glass rod; the separated solidified precipitate was isolated and washed with ice water (2×1 ml) and dried in a vacuum desiccator for 24 h over phosphorus pentoxide with intermittent grinding.

3-Fluorophenyldiazonium benzothiazol-2-yl(difluoro)methanesulfonate (IXa). Yield 86%, t.decomp. 95°C. Found, %: C 43.31; H 2.00; N 10.93; S 16.43. $C_{14}H_8F_3N_3O_3S_2$. Calculated, %: C 43.41; H 2.08; N 10.85; S 16.56.

4-Fluorophenyldiazonium benzothiazol-2-yl(difluoro)methanesulfonate (IXb). Yield 64%, t.decomp. 96°C. Found, %: C 43.60; H 2.04; N 10.97; S 16.47. $C_{14}H_8F_3N_3O_3S_2$. Calculated, %: C 43.41; H 2.08; N 10.85; S 16.56.

***O*-Aryl benzothiazol-2-yl(difluoro)methanesulfonates Xa and Xb**. Into a test tube placed into an oil bath heated to 130–135°C was charged by small portions dry finely ground aryldiazonium sulfonate **IXa** or **IXb**. The heating continued for 1 h, then the test tube was cooled, and the reaction product was extracted with hot hexane (30 ml), the extract was washed with 5% NaOH solution, the organic layer was dried with anhydrous $MgSO_4$, filtered, evaporated to 3 ml volume. The separated crystals were filtered off.

***m*-Fluorophenyl benzothiazol-2-yl(difluoro)-methanesulfonate (Xa).** Yield 61%, t.decomp. 78°C. ^{1}H NMR spectrum, δ, ppm: 7.10–7.14 m (3H), 7.42–7.44 m (1H), 7.56 m ($2H_{arom}$), 8.00 d ($1H_{arom}$, *J* 7.6 Hz), 8.20 d ($1H_{arom}$, *J* 7.8 Hz). ^{19}F NMR spectrum, δ, ppm: –94.21 s (2F), –109.46 s (1F). Found, %: C 44.83; H 2.20; N 3.77; S 17.12. $C_{14}H_8F_3NO_3S_2$. Calculated, %: C 46.75; H 2.23; N 3.90; S 17.81.

***p*-Fluorophenyl benzothiazol-2-yl(difluoro) methanesulfonate (Xb).** Yield 53%, mp 57–59°C. ^{1}H NMR spectrum, δ, ppm: 7.13–7.17 m (2H), 7.23–7.29 m (2H), 7.56 m ($2H_{arom}$), 7.96 d ($1H_{arom}$, *J* 7.6 Hz), 8.21 d ($1H_{arom}$, *J* 7.8 Hz). ^{19}F NMR spectrum, δ, ppm: –94.27 s (2F), –113.76 s (1F). Found, %: C 46.66; H 2.27; N 3.86; S 17.95. $C_{14}H_8F_3NO_3S_2$. Calculated, %: C 46.75; H 2.23; N 3.90; S 17.81.

Aryldiazonium trifluoromethanesulfonates XIIa and XIIb. In 5 ml of glacial acetic acid was dissolved 3 mmol of arylammonium trifluoromethanesulfonates **XIa** or **XIb** prepared from equimolar amounts of arylamine and trifluoromethanesulfonic acid, and 3 mmol of butyl nitrite was added. The reaction mixture was left overnight, the solution was evaporated, to the residue was added 8 ml of a mixture dichloromethane–pentane, 1:3, the separated crystals were filtered off and dried in a vacuum.

***m*-Fluorophenyldiazonium trifluoromethanesulfonate (XIIa).** Yield 76%, t.decomp. 109–110°C. Found, %: C 34.36; H 1.7; S 13.05. $C_7H_4F_4O_3S$. Calculated, %: C 34.43; H 1.6; S 13.11.

***p*-Fluorophenyldiazonium trifluoromethanesulfonate (XIIb).** Yield 71%, t.decomp. 95–96°C. Found, %: C 34.40; H 1.7; S 13.0. $C_7H_4F_4O_3S$. Calculated, %: C 34.43; H 1.6; S 13.11.

***O*-Aryl trifluoromethanesulfonates XIIIa and XIIIb**. Into a test tube placed into an oil bath heated to 110–120°C was charged by small portions finely ground aryldiazonium trifluoromethanesulfonate **XIIa** or **XIIb**. The heating continued for 1 h, then the test tube was cooled, and the reaction product was extracted with hot hexane (30 ml), the extract was washed with 5% NaOH solution, the organic layer was dried with anhydrous $MgSO_4$, filtered, evaporated to 3 ml volume. The separated crystals were filtered off. The physical constants of compounds **XIIIa** and **XIIIb** coincided with the published data [7].

***m*-Fluorophenyl trifluoromethanesulfonate (XIIIa)**. Yield 72%. ^{19}F NMR spectrum, δ, ppm: –73.20 s (3F), –108.65 s (1F).

***p*-Fluorophenyl trifluoromethanesulfonate (XIIIb)**. Yield 76%. ^{19}F NMR spectrum, δ, ppm: –73.20 s (3F), –112.79 s (1F).

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