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Short communication

Synthesis and optical activity of aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids and their derivatives

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Abstract

Synthesis and ^{19}F NMR studies of a new type of optically active sulfur(IV) compounds—aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids and their derivatives are described.

Keywords: Synthesis; Aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids; Optical asymmetry; Trifluoromethyl group

1. Introduction

In our previous work we described preparation of a new type of optically active sulfur(IV) derivatives—organylsulfoxydifluoroacetic acids [1]. These compounds have a difluoromethylene group attached to the chiral center, and it was found that their optical purity could be easily controlled by monitoring of diastereotopic fluorine atoms by ^{19}F NMR spectroscopy.

Exchange of the oxygen atom with the more electron withdrawing $=NSO_2CF_3$ group commonly leads to the formation of derivatives with unusual properties [2–4]. Therefore, it was interesting to study the possibility of preparing the optically active nitrogen analogs of sulfoxides containing trifluoromethylsulfonylimino group instead of oxygen atom.

Earlier we described the synthesis of (*N*-trifluoromethylsulfonyl)aryltrifluoromethylsulfimides [5]. However, these compounds have chiral sulfur attached to the trifluoromethyl group with magnetically equivalent fluorine atoms. Therefore, our aim in this work was to synthesize aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids and their amides as model compounds for investigation of optical asymmetry of α-fluoroalkyl substituted sulfinylimino derivatives.

The starting compounds were ethyl esters of aryldifluoroacetic acids, which were converted to their corresponding sulfimides using the dichloroimide of trifluoromethanesulfonic acid as an imination reagent, as it was shown before on aryltrifluoromethyl sulfides [5].

However, all attempts to convert the ethyl esters to the corresponding acids without the destruction of $S{=}NSO_2CF_3$ bond by hydrolysis in acidic or basic conditions were unsuccessful.

Therefore, the synthesis of analogous *tert*-butyl esters was carried out. However, we were not able to synthesize such type of compounds by the reaction of thiophenols with *tert*-butyl ester of iododifluoroacetic acid as the later one appears to be hydrolytically and thermally unstable compound.

Arylthiodifluoroacetates (**1**) were synthesized by the reaction of acidic chloroanhydrides [1] and *tert*-butyl alcohol in the presence of Et_3N as a base (Scheme 1).

Compounds **1a–f** were reacted with *N*,*N*-dichloroimide of trifluoromethanesulfonic acid [6] at mild conditions (0–20 °C) with the formation of derivatives **2a–f** in high yields (Scheme 2). Esters **2a–f** given in NMR ^{19}F spectra signals of AB-system that belongs to difluoromethylene group with magnetically non-equivalent fluorine atoms.

Thermolyses of esters **2a–f** for 10–12 h at 85–97 °C gave acids **3a–f** in high yields (65–70%) (Scheme 3).

In order to investigate the optical asymmetry of synthesized sulfinylimines compounds **3c** and **e** were reacted with

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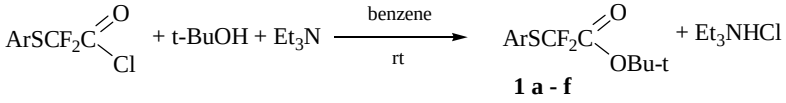
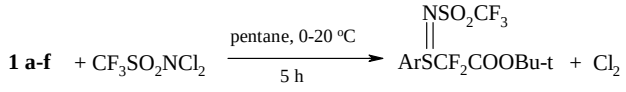


1 a - f

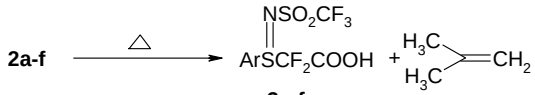
1a: Ar = Ph **1d**: Ar = 4-BrC_6H_4
1b: Ar = 4-FC_6H_4 **1e**: Ar = 4-$CH_3OC_6H_4$
1c: Ar = 4-ClC_6H_4 **1f**: Ar = 4-$O_2NC_6H_4$

Scheme 1. Synthesis of *tert*-butyl esters of arylthiodifluoroacetic acids.



2 a-f

Scheme 2. Preparation of *tert*-butyl esters of aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids (**2**).



3a-f

Scheme 3. Preparation of aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids (**3**).

(*R*)(+)-α-methylbenzylamine; the corresponding salts as a mixture of diastereomers were prepared. In the NMR ^{19}F spectra of diastereomeric salts, the signals of difluoromethylene groups are observed as a single AB-system, that does not permit to use this salts for isomers separation. Therefore, the synthesis of the (*R*)(+)-α-methylbenzylamide of aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acid (**5**) by the imination reaction of the amide (**4**) was carried out; the amide (**4**) was prepared by the reaction of chloroanhydrides 4-chlorophenylthiodifluoroacetic acid and (*R*)(+)-α-methylbenzylamine (Scheme 4).

The NMR ^{19}F investigations of amide (**5**) showed the formation of two diastereomers in a 1:1 proportion and which were presented on the spectra as two AB-systems with J^1(FF) coupling constants of 198 and 201 Hz, respectively.

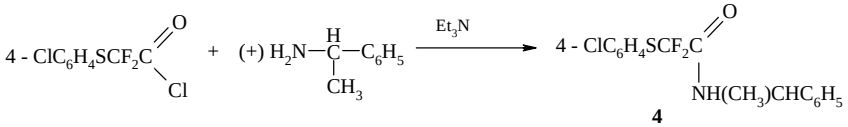
The diastereomers were separated by column chromatography using hexane–*iso*-propanol mixture as an eluent giving two individual compounds (**6**) and (**7**) with 98% purity (monitored by ^{19}F NMR spectroscopy).

In the current paper, the synthesis of aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids and their derivatives are described. It was shown that fluorine atoms of difluoromethylene groups in these compounds are magnetically non-equivalent and are presented as AB-system in NMR ^{19}F spectra. The new type of optically active sulfur(IV) derivatives—*N*-trifluoromethylsulfonylimides with fluorinated group attached to α-position to the chiral center are described.

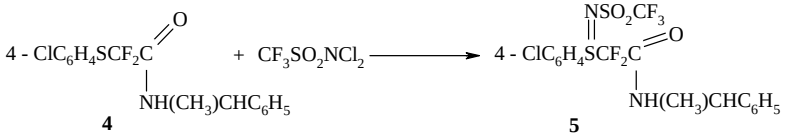
2. General procedures

2.1. Preparation of tert-butyl esters of arylthiodifluoroacetic acids (1)

Forty millimoles of thionyl chloride was added to 20 mmol of the corresponding arylthiodifluoroacetic acid at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred at 60 °C till gas evolution had ceased. All volatile compounds were removed in vacuum, and the residue was dissolved in dry benzene. To this residue, 20 mmol of Et_3N and 40 mmol of dry *tert*-butanol were added at 10 °C. The reaction mixture was stirred for additional 12 h. The volatile compounds were evaporated away, and the residue was washed with water, extracted with dichloromethane, and dried over $MgSO_4$. Solvent was evaporated, and the crude product purified by column



4



4 **5**

Scheme 4. Preparation of (*R*)(+)-α-methylbenzylamide of aryl(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acid (**5**).

chromatography using hexane–benzene mixture as an eluent; mp (°C): **1a** (oil), **1b** (oil), **1c** (oil), **1d** (oil), **1e** (oil), **1f** (46).

*2.1.1. (**1a**) $C_6H_5SCF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.42 (s, 9H), 6.25–6.47 (m, 5H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −79.80 (s, 2F).

*2.1.2. (**1b**) 4-$FC_6H_4SCF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.36 (s, 9H), 6.92–7.54 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −80.5 (s, 2F), −104.73 (s, 1F).

*2.1.3. (**1c**) 4-$ClC_6H_4SCF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.49 (s, 9H), 7.58–7.82 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −80.12 (s, 2F).

*2.1.4. (**1d**) 4-$BrC_6H_4SCF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.51 (s, 9H), 7.71–7.85 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −81.1 (s, 2F).

*2.1.5. (**1e**) 4-CH_3O $C_6H_4SCF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.54 (s, 9H), 2.98 (s, 3H), 7.56–7.67 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −81.2 (s, 2F).

*2.1.6. (**1f**) 4-O_2N $C_6H_4SCF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.48 (s, 9H), 7.78–8.23 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −80.92 (s, 2F).

*2.2. Preparation of tert-butyl esters of aryl(N-trifluoromethylsulfonyl)thiodifluoroacetic acids (**2**)*

To the solution of 5 mmol of *tert*-butyl ester of arylthiodifluoroacetic acid (**1**) 5.5 mmol of $CF_3SO_2NCl_2$ was added at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred till gas evolution had ceased. After 3–4 h, the oily residue solidifies. The crude product was filtered off, washed with pentane (5 ml), H_2O (2 × 10 ml), and, finally, dried over potassium hydroxide. Yield: 95–98%. All the *tert*-butyl esters are solids, slowly decomposing at 60–90 °C with the formation of acids (**3**).

*2.2.1. (**2a**) $C_6H_5S(NSO_2CF_3)CF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.45 (c, 9H), 7.23–7.45 (m, 5H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −76.9 (s, 3F), −94.1 (d, 2F, J_{FF} = 208 Hz), −103.6 (d, 2F, J_{FF} = 208 Hz). Analytically calculated for $C_{13}H_{14}F_5NO_4S_2$: C, 38.32; H, 3.44; S, 15.72. Found: C, 38.44; H, 3.45; S, 15.76.

*2.2.2. (**2b**) 4-$FC_6H_4S(NSO_2CF_3)CF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.48 (s, 9H), 7.37–7.92 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −79.4 (s, 3F), −102.45 (s, 1F), −98.9 (d, 2F, J_{FF} = 199 Hz), −99.9 (d, 2F, J_{FF} = 199 Hz). Analytically calculated for $C1_3H_{13}F_6NO_4S_2$: C, 36.71; H, 3.06; S, 15.06. Found: C, 36.44; H, 2.89; S, 14.96.

*2.2.3. (**2c**) 4-$ClC_6H_4S(NSO_2CF_3)CF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.60 (s, 9H), 7.66–7.85 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.4 (s, 3F), −96.4 (d, 2F, J_{FF} = 207 Hz), −103.4 (d, 2F, J_{FF} = 207 Hz). Analytically calculated for $C_{13}H_{13}ClF_5NO_4S_2$: C, 35.34; H 2.97; S 14.51. Found: C, 35.20; H, 3.04; S, 14.54.

*2.2.4. (**2d**) 4-$BrC_6H_4S(NSO_2CF_3)CF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.62 (s, 9H), 7.73–7.85 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −77.7 (s, 3F), −97.1 (d, 2F, J_{FF} = 206 Hz), −102.7 (d, 2F, J_{FF} = 206 Hz). Analytically calculated for $C_{13}H_{13}BrF_5NO_4S_2$: C, 32.11; H, 2.89; S, 13.19. Found: C, 32.25; H, 2.90; S, 13.16.

*2.2.5. (**2e**) 4-CH_3O $C_6H_4S(NSO_2CF_3)CF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.61 (s, 9H), 3.2 (s, 3H), 7.70–7.79 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.1 (s, 3F), −94.2 (d, 2F, J_{FF} = 210 Hz), −102.4 (d, 2F, J_{FF} = 210 Hz). Analytically calculated for $C_{14}H_{16}F_5NO_4S_2$: C, 38.44; H, 3.69; S, 14.66. Found: C, 38.72; H, 3.77; S, 14.65.

*2.2.6. (**2f**) 4-O_2N $C_6H_4S(NSO_2CF_3)CF_2COOBu$-t*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.60 (s, 9H), 8.12–8.52 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.3 (s, 3F), −95.4 (d, 2F, J_{FF} = 203 Hz), −101.3 (d, 2F, J_{FF} = 203 Hz). Analytically calculated for $C_{13}H_{13}F_5N_2O_6S_2$: C, 34.51; H, 2.89; S, 14.17. Found: C, 34.43; H, 2.90; S, 14.40.

*2.3. Preparation of aryl(N-trifluoromethylsulfonyl)-thiodifluoroacetic acids (**3**)*

Ten millimoles of the corresponding *tert*-butyl ester (**2**) was stirred for 10 h at 85–97 °C. At room temperature 5 ml of H_2O was added. The water phase was extracted with dichloromethane (2 × 5 ml). The organic fractions were combined and washed with 5 ml of water. The combined water fractions were evaporated in vacuum and the residue washed with dry benzene (2 × 5 ml). Yields of the acids (**3**): 55–70%; mp (°C): **3a**, 120–121; **3b**, 127–128; **3c**, 130–132; **3d**, 134–135; **3e**, 79–80; **3f**, 154–155.

*2.3.1. (**3a**) $C_6H_5S(NSO_2CF_3)CF_2COOH$*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 1.45 (s, 9H), 6.23–6.45 (m, 5H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −76.9 (s, 3F), −94.1 (d, 2F, J_{FF} = 207 Hz), −103.6 (d, 2F, J_{FF} = 207 Hz); IR: ν_{as} (SO_2) = 1350, ν_s (SO_2) = 1020, ν (S=N) = 1450, ν_{as} (C=O) = 1780, ν_{as} (OH) = 1230, ν (CF_3) = 1225. Analytically calculated for $C_9H_6F_5NO_4S_2$: C, 30.77; H, 1.71; S, 18.23. Found: C, 30.79; H, 2.20; S, 18.23.

*2.3.2. (**3b**) 4-$FC_6H_4S(NSO_2CF_3)CF_2COOH$*

NMR ^{1}H ($CDCl_3/CCl_3F$) δ: 7.39–7.95 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −79.4 (s, 3F), −98.9 (d, 2F, J_{FF} = 208 Hz), −104.7 (d, 2F, J_{FF} = 208 Hz), −100.7

(s, 1F). Analytically calculated for $C_{19}H_5F_6NO_4S_2$:C, 29.27; H, 1.36; S, 17.34. Found: C, 29.30; H, 1.42; 17.54.

*2.3.3. (**3c**) 4-$ClC_6H_4S(NSO_2CF_3)CF_2COOH$*

NMR ^{1}H ($CDCl_3$/CCl_3F) δ: 8.36–8.64 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.3 (s, 3F), −96.4 (d, 2F, J_{FF} = 209 Hz), −104.2 (d, 2F, J_{FF} = 209 Hz). Analytically calculated for $C_9H_5ClF_5NO_4S_2$: C, 28.02; H 1.30; S 16.60. Found: C, 28.25; H, 1.27; S, 16.51.

*2.3.4. (**3d**) 4-$BrC_6H_4S(NSO_2CF_3)CF_2COOH$*

NMR ^{1}H ($CDCl_3$/CCl_3F) δ: 8.11 (s, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.03 (s, 3F), −98.97 (d, 2F, J_{FF} = 221 Hz), −101.88 (d, 2F, J_{FF} = 221 Hz). Analytically calculated for $C_9H_5BrF_5NO_4S_2$: C, 25.12; H, 1.16; S, 14.88. Found: C, 24.94; H, 1.13; S, 14.91.

*2.3.5. (**3e**) 4-CH_3O $C_6H_4S(NSO_2CF_3)CF_2COOH$*

NMR ^{1}H ($CDCl_3$/CCl_3F) δ: 3.4 (s, 3H), 8.14–8.21 (m, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.0 (s, 3F), −98.2 (d, 2F, J_{FF} = 212 Hz), −104.2 (d, 2F, J_{FF} = 212 Hz); IR: ν_{as} (SO_2) = 1350, ν_s (SO_2) = 1020, ν (S=N) = 1490, ν_{as} (C=O) = 1740, ν_{as} (OH) = 1190, ν (CF_3) = 1140. Analytically calculated for $C_{10}H_8F_5NO_4S_2$: C, 31.50; H, 2.10; S, 16.80. Found: C, 31.72; H, 2.27; S, 16.65.

*2.3.6. (**3f**) 4-O_2N $C_6H_4S(NSO_2CF_3)CF_2COOH$*

NMR ^{1}H ($CDCl_3$/CCl_3F) δ: 8.12–8.52 (s, 4H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.5 (s, 3F), −94.9 (d, 2F, J_{FF} = 205 Hz), −100.7 (d, 2F, J_{FF} = 205 Hz). IR: ν_{as} (NO_2) = 1660, ν_s (NO_2) = 1420, ν_s (SO_2) = 1050, ν_{as} (C=O) = 1770, ν_{as} (OH) = 1250, ν (CF_3) = 1225. Analytically calculated for $C_9H_5F_5N_2O_6S_2$: C, 27.27; H, 1.26; S, 16.16. Found: C, 27.30; H, 1.29; S, 16.40.

*2.4. Preparation of aryl(N-trifluoromethylsulfonyl)-thiodifluoroacetic acid amide (**4**)*

Hundred millimoles of thionyl chloride was added to 50 mmol of 4-chlorophenylthiodifluoroacetic acid at room temperature. The reaction mixture was heated for 3 h at 60 °C (till gas evolution had ceased). All volatile compounds were removed under vacuum, and the residue was dissolved in benzene (10 ml). To residue in benzene 50 mmol of (*R*)(+)-α-methylbenzylamine and 50 mmol of Et_3N were added. The reaction mixture was stirred for additional 12 h. The precipitate was filtered off and washed with dry benzene (5 ml). The solvent was evaporated, and the crude product was crystallized from benzene–hexane mixture. Yield of (**4**): 87%; mp (°C): 135–136. NMR ^{1}H ($CDCl_3$) δ (ppm/CCl_3F): 1.40 (d, 3H), 4.98 (m, 1H), 6.2 (s, 2H), 7.11–7.58 (m, 9H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −83.2 (s, 2F). Analytically calculated for $C_{16}H_{14}ClF_2NOS$: C, 56.30; H, 4.10; N, 4.11. Found: C, 56.41; H, 4.20; N, 3.95.

*2.5. Reaction of amide (**4**) with N,N-dichloroamide of trifluoromethanesulfonic acid*

The method of preparation is analogous to (**2**). The oily product was obtained as a mixture of two diastereomers. The NMR ^{1}H ($CDCl_3$/CCl_3F) δ: NMR ^{1}H ($CDCl_3$) δ (ppm/CCl_3F): 1.54 (d, 3H), 4.24 (m, 1H), 6.45 (s, 1H), 7.41–7.68 (m, 9H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.5 (s, 3F), −99.1 (d, 2F, J_{FF} = 198 Hz), −104.1 (d, 2F, J_{FF} = 198 Hz); −78.6 (s, 3F), −99.2 (d, 2F, J_{FF} = 201 Hz), −102.2 (d, 2F, J_{FF} = 201 Hz).

*2.6. Separation of sulfinimino derivative (**5**) into the individual diastereomers*

The corresponding diastereomers were separated by column chromatography using hexane–*iso*-propanol (2%) mixture as an eluent and taking fractions of 3 ml; mp (°C): **6**, 94–96; **7**, 106–107. $[\alpha]_D^{18}$ (*c* 0.002, $CHCl_3$): **6**, +163; **7**, −94. **6**, NMR ^{1}H ($CDCl_3$) δ (ppm/CCl_3F): 1.53 (d, 3H), 4.21 (m, 1H), 6.44 (s, 1H), 7.41–7.68 (m, 9H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.5 (s, 3F), −99.1 (d, 2F, J_{FF} = 198 Hz), −104.1 (d, 2F, J_{FF} = 198 Hz); **7**, NMR ^{1}H ($CDCl_3$) δ (ppm/CCl_3F): 1.55 (d, 3H), 4.26 (m, 1H), 6.43 (s, 1H), 7.41–7.68 (m, 9H); NMR ^{19}F ($CDCl_3$) δ (ppm/CCl_3F): −78.6 (s, 3F), −99.2 (d, 2F, J_{FF} = 201 Hz), −102.2 (d, 2F, J_{FF} = 201 Hz). Analytically calculated for $C_{17}H_{14}ClF_5N_2O_3S_2$: C, 41.80; H, 2.87; N, 5.74. Found: C, 41.96; H, 2.97; N, 5.86.

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