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Synthesis and optical activity of difluoro(organylsulfinyl)acetic acids and their esters

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Abstract—Representatives of a new type of optically active sulfur(IV) compound, arylsulfinyldifluoroacetic acids, have been prepared.

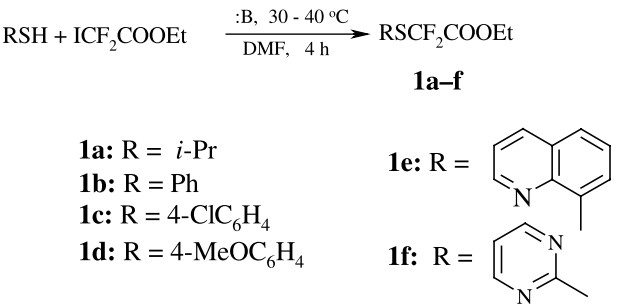
Optically active sulfoxides comprise an important group of chiral organosulfur compounds. They are used in asymmetric synthesis and in stereochemical research as model compounds.[1]

Fluorine-containing, optically active, sulfoxides with a perfluoroalkyl group immediately bonded to the sulfur atom are unknown. Meanwhile the synthesis of such compounds is of great interest. The presence of a difluoromethylene group at the chiral sulfur atom may allow one to monitor the optical activity and purity of the compounds by the NMR spectroscopy. The alkyl or aryl trifluoromethyl sulfoxides that we have synthesized earlier,[2] are unsuitable for verifying this suggestion as the fluorine atoms of the trifluoromethyl groups are equivalent and give only one singlet signal in ^{19}F NMR spectra. The spectra of sulfoxides with a difluoromethylene unit, $RS(O)CF_2R'$, should be more informative in this respect. Their fluorine atoms are magnetically non-equivalent and this can be used to check the stereochemical nature of the molecules by ^{19}F NMR spectroscopy.

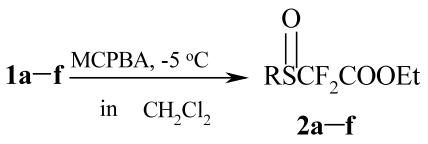
In order to reveal the supposed optical asymmetry in the fluorine-containing sulfoxides, we decided to synthesize the previously unknown arylsulfinylacetic acids $RS(O)CF_2COOH$.

At first we prepared the starting arylthiodifluoroacetates by heating the corresponding sodium arenethiolates with phenyl or sodium chlorodifluoroacetates. The use of methyl chlorodifluoroacetate in this reaction led to alkylation products of the arenethiolates, i.e. to methylthioarenes.[3] Burton obtained ethyl difluoro(phenylthio)acetate **1b** by reacting ethyl bromodifluoroacetate with sodium benzenethiolate in dimethylformamide.[4] We have found that ethyl difluoroiodoacetate, like perfluoroalkyl iodides,[5] reacts under mild conditions with alkane-, arene- or heteroarenethiolates in dimethylformamide, in the presence of base to give the corresponding sulfides **1** (Scheme 1).[6a]

Attempts to oxidize sulfide **1c** with chlorine in the presence of $SbCl_5$, as described in Ref. 2c, were not



Scheme 1. Reaction of thiolates with ethyl difluoroiodoacetate.



Scheme 2. Ethyl difluoro(organylsulfinyl)acetates **2**.

Keywords: synthesis; optically active sulfoxides; difluoro(organylsulfinyl)acetic acids.

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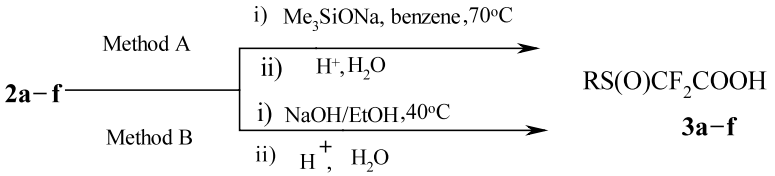


Scheme 3. Preparation of difluoro(organylsulfinyl)acetic acids **3**.

successful. Sulfoxide **2c** was obtained by this procedure in a low 35% yield. The major product of the reaction was 4-chlorobenzenesulfonyl chloride, even on oxidation at 0°C with a stoichiometric amount of chlorine gas. We managed to prepare sulfoxides **2a–f** in high yields by oxidation of sulfides **1a–f** with *meta*-chloroperbenzoic acid (MCPBA) in dichloromethane (Scheme 2).[6b] Ethyl arylthiodifluoroacetates are oxidized under these conditions more easily than the corresponding aryl trifluoromethyl sulfides. Thus, phenyl trifluoromethyl sulfide was oxidized to the sulfoxide with MCPBA at 0°C. Sulfide **1b** is transformed into sulfoxide **2b** at −5°C while at 0°C the major product is the corresponding sulfone.

Esters **2a–f** were saponified, with sodium trimethylsilanolate in benzene (method A) or with ethanolic sodium hydroxide (method B), into the corresponding sodium difluoro(organylsulfinyl)acetates and converted further into free acids **3a–f** by acidification (Scheme 3).[6c]

In order to compare the spectroscopic data, the known compound, ethyl 4-chlorophenylsulfonyldifluoroacetate **4c** and the corresponding acid **5c** were prepared (Scheme 4).[3a,4]

4-$ClC_6H_4SO_2CF_2COOEt$ **4c** 4-$ClC_6H_4SO_2CF_2COOH$ **5c**

Scheme 4.

The ^{19}F NMR spectra of sulfides **1a–f** and sulfones **4c**, **5c** show singlets due to the magnetically equivalent fluorine atoms of the difluoromethylene groups, whereas the spectra of sulfoxides **2a–f** and **3a–f** present an AB pattern due to the diastereotopic nature of their fluorine atoms.

The analysis of the ^{19}F NMR spectra makes it possible to control the oxidation of sulfides **1** and the purity of the products. As the oxidation proceeds, the singlet signal of the CF_2 group in the starting sulfides **1** at −79 to −85 ppm disappears, giving rise to an AB pattern at −108 to −112 ppm corresponding to the sulfoxide. The sulfones display a singlet between −109 and −110 ppm.

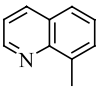
To obtain optically active sulfoxides from acids **3b–e**, we prepared their salts **6b–e** with (*R*)-(+)-α-methylbenzylamine (Scheme 5).[6d]

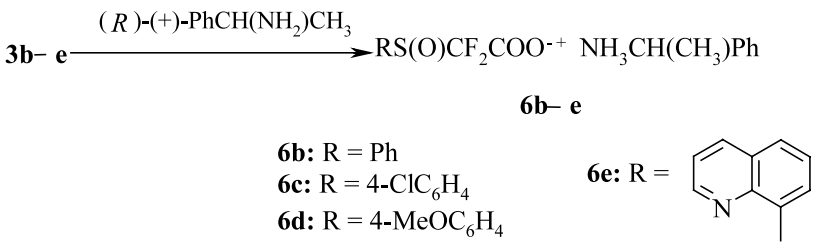
Salts **6** were formed as viscous oils in nearly quantitative yields. They possess two chiral centers and are a mixture of two diastereomers in the ratio of 1:1, as determined from their ^{19}F NMR spectra which display two AB patterns.

Salt **6c** was separated into two individual crystalline diastereomers **7c** and **8c** by fractional crystallization from anhydrous benzene and benzene/hexane. The ^{19}F NMR spectra of the diastereomers correspond to particular AB patterns in the spectrum of the starting salt **6c**.

Salt **6d** was separated by crystallization into pure oily diastereomer (−,+)-**8d** and crystalline substance (+,+)-**7d** (optical purity of about 60% ee). Salts **6** and their diastereomers are characterized in Table 1.[6d]

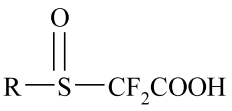
Table 1. Characterization of salts **6–8** $RS(O)CF_2COO^-$ $^+NH_3CH(CH_3)Ph$

Entry	Salt	R	Mp (°C)
1	**6b**	Ph	Oil
2	**6c**	4-ClC_6H_4	Oil
3	**6d**	4-$MeOC_6H_4$	Oil
4	**6e**		Oil
5	**7c**	4-ClC_6H_4	135–136
6	**7d**	4-$MeOC_6H_4$	126–128
7	**8c**	4-ClC_6H_4	129–130
8	**8d**	4-$MeOC_6H_4$	Oil



Scheme 5. Preparation of amine salts **6**.

Table 2. Characterization of optically active acids **9** and **10**



9, 10

Entry	Acid	R	Mp (°C)	Specific rotation $[\alpha]_D^{20}$ (c 0.01, EtOH)
1	**9c**	4-ClC_6H_4	147–148	+142.5
2	**9d**	4-$MeOC_6H_4$	133–134	+78.5
3	**10c**	4-ClC_6H_4	145–146	−136.2 (ee ~ 95%)
4	**10d**	4-$MeOC_6H_4$	134–135	−55.2 (ee ~ 60%)

The diastereomeric salts **7c**,**d** and **8c**,**d** were transformed, by acidification, into the corresponding free acids **9** and **10** (Table 2),[6e] which are the first representatives of optically active sulfoxides with a fluoroalkylene group at the sulfur atom. Therefore, to prove the optical purity of sulfoxides **9**,**10** we obtained the L-menthyl esters of the appropriate acids by reacting them with L-menthol in the presence of DCC.[6f] The ^{19}F NMR spectra of **9c**-L-menthyl ester showed only two doublets, at δ (ppm/CF_3Cl): −101.7 (d, 2F, J = 220 Hz); −105.1 (d, 2F, J = 220 Hz), whereas the spectrum of **10c**-L-menthyl ester presented not only signals of the major diastereomer at δ (ppm/CF_3Cl): −107.7 (d, 2F, J = 220 Hz); −112.5 (d, 2F, J = 220 Hz), but also minor ones (~3%).

In summary we have demonstrated a method for the synthesis of previously unknown difluoro(organylsulfinyl)acetic acids and their esters. The fluorine atoms of the difluoromethylene group bonded to the optically active sulfur atom are magnetically non-equivalent. Optically active sulfoxides with a fluorinated alkyl substituent in the α-position with respect to the sulfinyl group have been obtained for the first time through separation of the diastereomeric salts of the corresponding arylsulfinyldifluoroacetic acids with (*R*)-(+)-α-methylbenzylamine.

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6. **General procedures**. (a) *Preparation of sulfides **1***: A solution of ethyl difluoroiodoacetate (0.075 mol) in DMF (5 mL) and triethylamine (0.05 mol) were added to a solution of the appropriate thiol (0.05 mol) in DMF (7 mL) under a flow of argon, at 3–5°C. The mixture was treated as indicated in Scheme 1, poured onto ice, and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuum. Sulfides **1** were isolated by distillation or crystallization (for **1e**). Bp (torr)/mp (°C): **1a** 35 (0.1), **1b** 56 (0.01), **1c** 82 (0.01), **1d** 75 (0.01), **1e** 56, **1f** 86 (0.01). ^{19}F NMR ($CDCl_3$) δ (ppm/CF_3Cl): **1a** −81.3 (s, 2F), **1b** −79.9 (s, 2F), **1c** −82.9 (s, 2F), **1d** −81.9 (s, 2F), **1e** −82.7 (s, 2F), **1f** −85.3 (s, 2F).
(b) *Preparation of sulfoxides **2***: To a cooled solution of sulfide **1** (5 mmol) in anhydrous CH_2Cl_2 (7 mL) was added MCPBA (10 mmol, in a 50% concentration basis). The reaction conditions are presented in Scheme 2. The reaction mixture was filtered while cold. The filtrate was washed with a cold saturated solution of $NaHCO_3$ (4×5 mL), water and dried ($MgSO_4$). After removal of the solvent, the product was purified by silica gel chromatography or crystallization. Mp (°C): **2a** oil, **2b** oil, **2c** 20, **2d** 26, **2e** 53, **2f** 43. ^{19}F NMR ($CDCl_3$) δ (ppm/CF_3Cl): **2a** −106.4 (d, 2F, J = 234 Hz), −111.5 (d, 2F, J = 234 Hz); **2b** −110.3 (d, 2F, J = 227 Hz), −111.8 (d, 2F, J = 227 Hz); **2c** −110.6 (d, 2F, J = 228 Hz), −112.3 (d, 2F, J = 228 Hz); **2d** −111.4 (d, 2F, J = 229 Hz), −113.5 (d, 2F, J = 229 Hz); **2e** −105.6 (d, 2F, J = 209 Hz), −111.2 (d, 2F, J = 209 Hz); **2f** −104.5 (d, 2F, J = 224 Hz), −110.2 (d, 2F, J = 224 Hz).
(c) *Preparation of difluoro(organylsulfinyl)acetic acids **3**. Method A:* To a solution of ethyl difluoro(organylsulfinyl)acetate **2** (5 mmol) in anhydrous benzene (7 mL) was added Me_3SiONa (5 mmol) and the mixture was heated at 70°C for 2.5 h. After being cooled, the reaction mixture was filtered, the solid residue was dissolved in a minimum amount of water and acidified to pH 4–5. The product was taken up in CH_2Cl_2 (3×5 mL). The extract was washed with a small amount of ice-cold water, dried ($MgSO_4$), and concentrated. The title acids were purified by crystallization. *Method B:* Ester **2** (5 mmol) was added to the calculated amount of 40% ethanolic NaOH and the mixture was heated at 40°C for 4 h. Ethanol was removed by vacuum distillation, the residue was dissolved in a small amount of water and the resulting solution was acidified to pH 4–5. The product was isolated as in Method A. Mp (°C): **3a** oil, **3b** 77–78, **3c** 132–134, **3d** 147(dec), **3e** 150–152, **3f** 160(dec). ^{19}F NMR ($CDCl_3$) δ (ppm/CF_3Cl): **3a** −103.6

(d, 2F, $J=237$ Hz), −112.8 (d, 2F, $J=237$ Hz); **3b** −104.8 (d, 2F, $J=228$ Hz), −111.7 (d, 2F, $J=228$ Hz); **3c** −104.4 (d, 2F, $J=226$ Hz), −112.5 (d, 2F, $J=226$ Hz); **3d** −105.4 (d, 2F, $J=227$ Hz); −112.3 (d, 2F, $J=227$ Hz); **3e** −104.7 (d, 2F, $J=212$ Hz), −112.9 (d, 2F, $J=212$ Hz); **3f** −103.5 (d, 2F, $J=232$ Hz), −111.4 (d, 2F, $J=232$ Hz).

(d) *Preparation of salts **6–8**:* To a solution of the appropriate acid **3** (5 mmol) in anhydrous diethyl ether (5 mL) was added (*R*)-(+)-α-methylbenzylamine (5 mmol) dissolved in the same solvent (3 mL). The mixture was allowed to stand for 4 h, after which time the supernatant liquid layer was carefully decanted. The oily residue was washed with a small amount of anhydrous diethyl ether and dried under oil pump vacuum. The dried residue was mixed with anhydrous benzene (3 mL) and set aside for 48 h to crystallize. The precipitated fine crystals of one diastereomer were filtered off and the second diastereomer was precipitated from the filtrate with anhydrous hexane.

(e) *Typical procedure for the preparation of acids **9** and **10**:* A solution of salt **8c** (5 mmol) in a minimum amount of water was acidified with concentrated HCl to pH 4–5, and the product was extracted with diethyl ether (3×5 mL). The extract was washed with a small amount of ice-cold water, dried ($MgSO_4$), and evaporated to give pure acid **9c**.

(f) A mixture of **9c** or **10c**, L-menthol and DCC in pyridine in the presence of *p*-toluenesulfonic acid was stirred for 24 h, filtered and acetic acid added. After stirring for a further 12 h, the mixture was filtered, extracted with CH_2Cl_2, dried and evaporated to afford the corresponding ester. Mp (°C) for L-menthyl ester of acid **9c** = 108, for L-menthyl ester of acid **10c** = 76.