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A new one-pot synthesis of difluoro(organylsulfinyl)acetic acid esters

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Dedicated to Professor Tatlow on the occasion of his 80th birthday.

Abstract

A novel single-step method for the synthesis of esters of difluoro(organylsulfinyl)acetic acids, by reacting aromatic compounds with isopropyl chlorosulfinyldifluoroacetate, was developed. The feasibility of transforming the sulfoxide intermediates into corresponding sulfides and sulfones was demonstrated.

Keywords: Sulfoxides; Sulfones; Sulfinylation; Difluoro(organylsulfinyl)acetates

1. Introduction

Fluoroalkyl sulfoxides are much less known compared with the corresponding sulfides or sulfones. However some of them have already found wide application, for example, the insecticide Fipronyl [1]. Fluorinated sulfoxides can be obtained by oxidation of corresponding sulfides [2], by nucleophilic trifluoromethylation of sulfinyl halides and esters of sulfinic acids with CF_3SiMe_3 in the presence of fluoride ion [3], or by the direct introduction of the group –$S(O)CF_3$ into aromatic compounds by the action of sodium triflinate, trifluoromethanesulfonic acid and trifluoromethanesulfonic anhydride [4]. Optically active sulfoxides, with a fluorinated alkyl substituent in the α-position relative to the sulfinyl group, have been obtained for the first time by us [5] through separation of the diastereomeric salts of the corresponding arylsulfinyldifluoroacetic acids. Previously, we prepared arylsulfinyldifluoroacetic acids and their esters by oxidation of the corresponding sulfides [5], but sulfones were formed therewith as by-products.

2. Results and discussion

Now, we report a one-pot procedure for the synthesis of arylsulfinyldifluoroacetic acid esters from aromatic compounds and isopropyl chlorosulfinyldifluoroacetate (**1**); compound (**1**) is prepared from its sodium derivative described earlier [6] (Scheme 1).

The sulfinyl chloride (**1**) turned out to be a convenient reagent to introduce –$S(O)CF_2COOR$ groups into aromatic compounds in the presence of Friedel-Crafts catalysts. It was found that, the higher electron density in the ring of the aromatic substrate **2**, the less active catalyst should be used and in some cases the reaction proceeds in the absence of any catalyst (Table 1).

N,*N*-Dimethylaniline and *N*,*N*-diethylaniline react with **1**, exothermally and without a catalyst, to give sulfoxides **3a** and **3b**, respectively. The corresponding sulfinylated derivatives of *N*-methylindole and *N*-methylpyrrole were obtained in a similar way, without catalysts, but the second substrate gave a 4:1 mixture of 2- and 3-isomer.

Anisole does not give the desired product under the above conditions and its reaction with **1** was conducted in the presence of $AlCl_3$, $FeCl_3$, $SnCl_4$ or trifluoromethanesulfonic acid. Heavy tarring occurred with $AlCl_3$ even if the reaction was initiated at −7 °C (at a lower temperature no reaction was observed). Iron(III) chloride is also too active and the yield of the expected product **3e** is as low as 40%. Also the use of trifluoromethanesulfonic acid as the catalyst did not produce the desired result.

The optimum catalyst for the sulfinylation of anisole with **1** was found to be $SnCl_4$. The reaction when carried out at 0–20 °C afforded isopropyl 4-methoxyphenylsulfinyldifluoroacetate (**3e**) in 85% yield. Also in the sulfinylation of 1,3-dimethoxybenzene, $SnCl_4$ is the best catalyst.

In contrast to anisole and 1,3-dimethoxybenzene, unsubstituted benzene enters into the sulfinylation reaction only in

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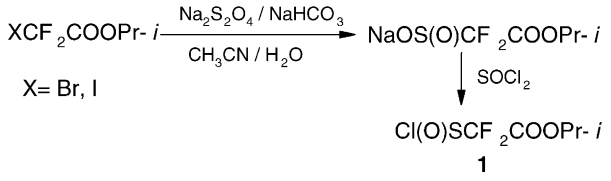


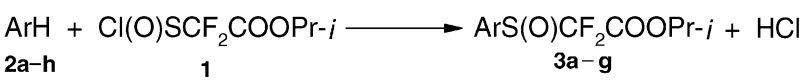
Scheme 1.

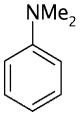
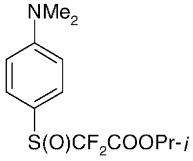
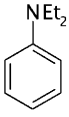
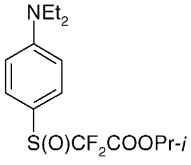
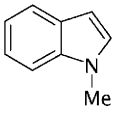
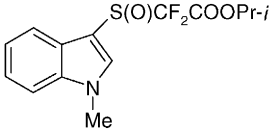
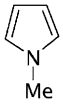
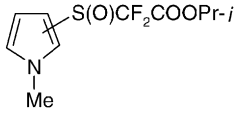
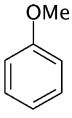
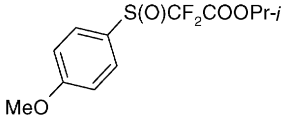
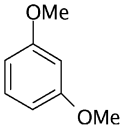
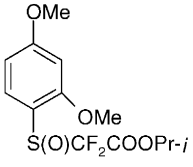
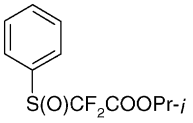
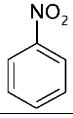
the presence of $FeCl_3$ and the substrate is transformed into isopropyl phenylsulfinyldifluoroacetate (**3g**) in 65% yield (Table 1).

Toluene, in the presence of different catalysts, gives a difficult-to-separate mixture of products. Chlorobenzene and nitrobenzene do not react with **1** even in the presence of $AlCl_3$.

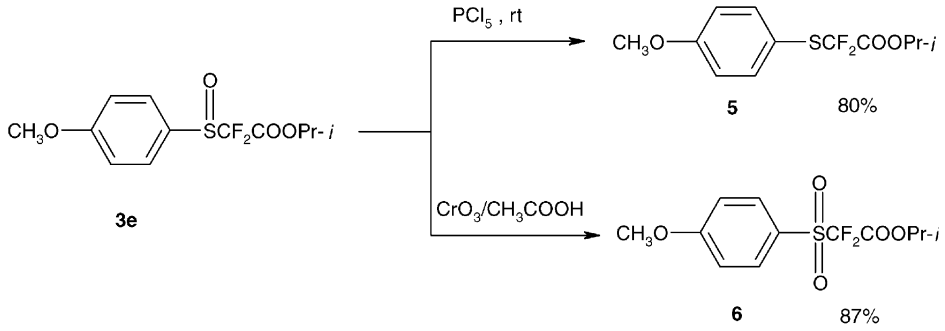
Esters **3a–g** were hydrolyzed with alkali into corresponding arylsulfinyldifluoroacetic acids (**4a–g**) (Table 2).

Table 1
Preparation of arylsulfinyldifluoroacetates



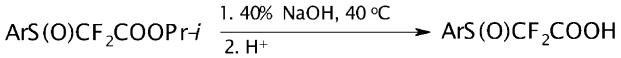
Entry	Arene (**2**)	Time (h)	Product (**3**)	Isolated yield (%)		
				No catalyst	$FeCl_3$	$SnCl_4$
a		3		90		
b		3		85		
c		4		80		
d		3		78[a]		
e		2			40	85
f		1.5				80
g		2.5			65	
h		24	No reaction			

[a] A 4:1 mixture of 2- and 3-isomer.



Scheme 2.

Table 2
Preparation of arylsulfinyldifluoroacetic acids



3a–g 4a–g

Product (**4**)	R	Melting point (°C)	Yield of **4** (%)
4a	4-$Me_2NC_6H_4$	170–171[a]	75
4b	4-$Et_2NC_6H_4$	179–180[a]	70
4c	1-Methyl-3-indolyl	180–181[a]	72
4d	1-Methyl-2-pyrrolyl	178–179[a]	81
4e	4-$MeOC_6H_4$	135–136[b]	80
4f	2,4-$(MeO)_2C_6H_3$	162–163[b]	84
4g	Ph	75–76[c]	78

[a] Crystallized from benzene-ethyl acetate.
[b] Crystallized from benzene.
[c] Crystallized from benzene-hexane.

Fluorine atoms in compounds **1**, **3a–g** and **4a–g** are diastereotopic, owing to the close proximity to the chiral sulfur center [5], and magnetically nonequivalent in ^{19}F NMR spectra.

Using **3e** as an example, the feasibility was demonstrated of transforming the sulfoxides into the corresponding sulfides and sulfones (Scheme 2). Sulfoxide **3e** was converted into sulfide **5** by the reaction with PCl_5, previously used for reduction of aryl trifluoromethyl sulfoxides into aryl trifluoromethyl sulfides [7]. The oxidation of **3e** into sulfone **6** was performed with CrO_3 in glacial acetic acid.

3. Conclusion

Simple and convenient methods were developed for the synthesis of arylsulfinyldifluoroacetic acids and their esters and for transformation of the latter into corresponding sulfides and sulfones.

4. Experimental

4.1. General

Boiling and melting points are uncorrected. ^1H NMR: Varian VXR-300 (300 MHz) (TSM as internal standard). ^{19}F NMR: Varian VXR-300 (288 MHz) ($CFCl_3$ as internal standard).

4.2. Preparation isopropyl chlorosulfinyldifluoroacetate (*1*)

Sodium salt of isopropyl difluoro(sulfino)acetate (4 g, 17.8 mmol) was added in small portions to thionyl chloride (5 ml) at 0 °C. The mixture was stirred, until the evolution of gas ceased, allowed to warm up to RT and the stirring was continued for a further 6 h. The mixture was filtered, the unreacted $SOCl_2$ was distilled off and the residue was purified by distillation to give 3.1 g (65%) **1**.

The bp is 85–87 °C (18 Torr); ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, $J = 6$ Hz, 6H), 5.3 (spt, 1H). ^{19}F NMR (282 MHz, $CDCl_3/CCl_3F$): $\delta = -106.4$ (d, $J = 223$ Hz, 1F), -111.0 (d, $J = 223$ Hz, 1F).

4.3. Typical experimental procedure for the reaction of (*1*) to give *3a–d*

To a stirred solution of *N*,*N*-dimethylaniline (2.83 g, 23.4 mmol) in CH_2Cl_2 (10 ml) cooled to 0 °C was added agent **1** (1.1 g, 5.4 mmol). The mixture was warmed to RT in 30 min and stirred at this temperature for a further 2 h. The solvent was removed by distillation and the residue was extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (benzene:hexane 2:1) to give **3a** as white crystals.

4.3.1. 4-$(Me)_2NC_6H_4S(O)CF_2COOPr$-i (*3a*)

Melting point 81–82 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (d, $J = 6$ Hz, 6H), 3.04 (s, 6H), 5.06 (spt, 1H), 7.14 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3/CCl_3F$): $\delta = -111.2$(d, $J = 224$ Hz, 1F), -112.3 (d, $J = 224$ Hz, 1F). Anal. calcd. for $C_{13}H_{17}F_2NO_3S$: C, 51.13; H, 5.61; N, 4.58; S, 10.50. Found: C, 51.24; H, 5.73; N, 4.61; S, 10.48.

4.3.2. 4-$(Et)_2NC_6H_4S(O)CF_2COOPr$-i (*3b*)

White crystals, mp 63–64 °C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$–1.29 (m, 12H), 3.39 (q, 4H), 5.05 (spt, 1H), 7.12 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$/

CCl_3F): $\delta = -111.3$ (d, $J = 226$ Hz, 1F), -112.4 (d, $J = 226$ Hz, 1F). Anal. calcd. for $C_{15}H_{21}F_2NO_3S$: C, 54.03; H, 6.35; N, 4.20; S, 9.62. Found: C, 53.62; H, 6.15; N, 4.41; S, 9.74.

*4.3.3. 1-Methyl-3-indolyl S(O)CF_2COOPr-i (**3c**)*

White crystals, mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.70$ (d, $J = 6.2$ Hz, 6H), 3.45 (s, 3H), 4.58 (spt, 1H), 6.87–7.52 (m, 5H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -109.8$ (d, $J = 222$ Hz, 1F), -111.3 (d, $J = 222$ Hz, 1F). Anal. calcd. for $C_{14}H_{15}F_2NO_3S$: C, 53.49; H, 4.49; N, 4.45; S, 10.20. Found: C, 53.50; H, 4.70; N, 4.41; S, 9.98.

*4.3.4. 1-Methyl-2-pyrrolyl S(O)CF_2COOPr-i (**3d**)*

Oil; ^{1}H NMR (300 MHz, $(CD_3)_2CO$): $\delta = 1.30$ (m, 6H); 3.80, 3.94 (s, 3H); 5.00 (m, 1H), 6.29–7.21 (m, 3H). ^{19}F NMR (282 MHz, $(CD_3)_2CO$/CCl_3F): 2-isomer, $\delta = -106.7$ (d, $J = 220$ Hz, 1F), -110.8 (d, $J = 220$ Hz, 1F); 3-isomer, $\delta = -109.6$ (d, $J = 223$ Hz, 1F), -115.2 (d, $J = 223$ Hz, 1F). Anal. calcd. for $C_{10}H_{13}F_2NO_3S$: C, 45.27; H, 4.94; N, 5.28; S, 12.08. Found: C, 45.32; H, 4.92; N, 5.32; S, 12.30.

*4.4. Typical experimental procedure for the reaction of (**1**) to give **3e–g***

To anisole (1 ml) was added agent **1** (1.1 g, 5.4 mmol) at 0 °C followed by $SnCl_4$ (1.3 g, 5 mmol). The temperature was raised to RT and the mixture was stirred until the evolution of gas ceased. After completion of the reaction, the mixture was poured onto crushed ice and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), concentrated and the residue was purified by chromatography (benzene:hexane 4:1) to give **3e** as an oily substance.

*4.4.1. 4-$MeOC_6H_4$S(O)CF_2COOPr-i (**3e**)*

Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (d, $J = 5.8$ Hz, 6H), 3.40 (s, 3H), 4.87 (spt, 1H), 7.25 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -110.7$(d, $J = 226$ Hz, 1F), -112.8 (d, $J = 226$ Hz, 1F). Anal. calcd. for $C_{12}H_{14}F_2O_4S$: C, 49.31; H, 4.83; S, 10.97. Found: C, 49.27; H, 4.65; S, 10.78.

*4.4.2. 2,4-$(MeO)_2C_6H_3$S(O)CF_2COOPr-i (**3f**)*

White crystals, mp 56–57 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (d, $J = 6$ Hz, 6H), 3.73 (s, 3H), 3.85 (s, 3H), 5.07 (spt, 1H), 6.46 (d, $^4J = 2$ Hz, 1H), 6.68 (dd, $^3J = 9$ Hz, $^4J = 2$ Hz, 1H), 7.71 (d, $^3J = 9$ Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -109.02$ (d, $J = 217$ Hz, 1F), -110.01 (d, $J = 217$ Hz, 1F). Anal. calcd. for $C_{13}H_{16}F_2O_5S$: C, 49.44; H, 5.00; S, 9.95. Found: C, 49.84; H, 5.00; S, 9.85.

*4.4.3. PhS(O)CF_2COOPr-i (**3g**)*

Oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (d, $J = 6.1$ Hz, 6H), 4.12 (spt, 1H), 7.28–7.92 (m, 5H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -110.1$ (d, $J = 227$ Hz, 1F), -112.3 (d, $J = 227$ Hz, 1F). Anal. calcd. for $C_{11}H_{12}F_2O_3S$: C, 50.37; H, 4.61; S, 12.22. Found: C, 50.10; H, 4.43; S, 11.98.

The reaction mixture containing **3e** turned red, whereas in the case of **3f** it was violet apparently due to protonation of the sulfoxide oxygen atom. This suggestion was confirmed by formation of the same color on bubbling hydrogen chloride through a solution of **3e** in CH_2Cl_2.

*4.5. Typical procedure for preparation of acids **4a–g***

To a 40% aqueous solution of NaOH (5 ml) was added ester **3a** (0.9 g, 3 mmol) and the mixture was stirred at 40 °C until complete dissolution then it was cooled and filtered. The filtrate was acidified to pH 5 and extracted with CH_2Cl_2. The extract was washed with a saturated solution of NaCl and concentrated to leave **4a** which was purified by crystallization from benzene-ethyl acetate (Table 2). Compounds **4e** and **4g** show no depression of mixed mp with authentic samples of the compounds obtained by another method [5].

*4.5.1. 4-$(Me)_2NC_6H_4$S(O)CF_2COOH (**4a**)*

Yellow crystals; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.01$ (s, 6H), 7.17 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -111.2$ (d, $J = 224$ Hz, 1F), -112.3 (d, $J = 224$ Hz, 1F). Anal. calcd. for $C_{10}H_{11}F_2NO_3S$: C, 45.63; H, 4.18; N, 5.32; S, 12.20. Found: C, 45.56; H, 4.40; N, 5.23; S, 11.93.

*4.5.2. 4-$(Et)_2NC_6H_4$S(O)CF_2COOH (**4b**)*

Yellow crystals; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.21$ (t, 6H), 3.5 (q, 4H), 7.14 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -109.8$ (d, $J = 228$ Hz, 1F), -113.2 (d, $J = 228$ Hz, 1F). Anal. calcd. for $C_{12}H_{15}F_2NO_3S$: C, 49.47; H, 5.19; N, 4.80; S, 11.01. Found: C, 49.51; H, 5.30; N, 4.82; S, 10.95.

*4.5.3. 1-Methyl-3-indolyl S(O)CF_2COOH (**4c**)*

Yellow crystals; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.51$ (s, 3H), 6.78–7.30 (m, 5H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -110.1$ (d, $J = 225$ Hz, 1F), -112.3 (d, $J = 225$ Hz, 1F). Anal. calcd. for $C_{11}H_9F_2NO_3S$: C, 48.52; H, 2.96; N, 5.14; S, 11.77. Found: C, 48.34; H, 3.20; N, 5.35; S, 12.06.

*4.5.4. 1-Methyl-2-pyrrolyl S(O)CF_2COOH (**4d**)*

Yellow crystals; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.74$ (s, 3H), 6.31–7.04 (m, 3H). ^{19}F NMR (282 MHz, $CDCl_3$/CCl_3F): $\delta = -105.6$ (d, $J = 225$ Hz, 1F), -110.5 (d, $J = 225$ Hz, 1F). Anal. calcd. for $C_7H_7F_2NO_3S$: C, 37.67; H, 3.16; N, 6.28; S, 14.36. Found: C, 37.52; H, 2.98; N, 6.20; S, 14.30.

*4.5.5. 4-$MeOC_6H_4$S(O)CF_2COOH (**4e**)*

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.56$ (s, 3H), 7.92 (A_2B_2m, 4H), 10.70 (br, s, 1H). ^{19}F NMR (282 MHz,

$CDCl_3/CCl_3F$): $\delta = -110.7$(d, $J = 226$ Hz, 1F), -112.8 (d, $J = 226$ Hz, 1F).

*4.5.6. 2,4-$(MeO)_2C_6H_3S(O)CF_2COOH$i (**4f**)*

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.18$ (s, 3H), 4.22 (s, 3H), 7.09 (s, 1H), 7.20 (d, ^3J=3 Hz, 1H), 7.93 (d, $^3J = 3$ Hz, 1H), 11.02 (br, s, 1H). ^{19}F NMR (282 MHz, $CDCl_3/CCl_3F$): $\delta = -109.02$ (d, $J = 217$ Hz, 1F), -110.01 (d, $J = 217$ Hz, 1F). Anal. calcd. for $C_{10}H_{10}F_2O_5S$: C, 42.85; H, 3.60; S, 11.44. Found: C, 42.80; H, 3.51; S, 11.32.

*4.5.7. $PhS(O)CF_2COOH$ (**4g**)*

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.46$–7.97 (m, 5H), 10.87 (br, s, 1H). ^{19}F NMR (282 MHz, $CDCl_3/CCl_3F$): $\delta = -110.1$ (d, $J = 225$ Hz, 1F), -112.3 (d, $J = 225$ Hz, 1F).

*4.6. Preparation of sulfide (**5**)*

To sulfoxide **3e** (1.5 g, 5 mmol) was added PCl_5 (1.12 g, 5.4 mmol), the mixture was stirred at RT, until the evolution of gas ceased, and extracted with CH_2Cl_2. The extract was washed with a 10% aqueous solution of soda and with water, dried ($MgSO_4$), and concentrated to give **5** as an oil; ^{1}H NMR (300 MHz, $CDCl_3$): 1.31 (d, $J = 6.3$ Hz, 6H), 3.21 (s, 3H), 4.02 (spt, 1H), 7.24 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): -79.2 (s, 2F). Anal. calcd. for $C_{12}H_{14}F_2O_3S$: C, 49.20; H, 4.78; S, 10.87. Found: C, 49.31; H, 4.73; S, 10.78.

*4.7. Preparation of sulfone (**6**)*

To a solution of **3e** (0.9 g, 3 mmol) in glacial acetic acid (7 ml) was added CrO_3 (1 g, 10 mmol). The mixture was heated at 60 °C for 3 h, poured into water, and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$), and concentrated to leave sulfone **6** as crystals, mp 87 °C (from benzene). ^{1}H NMR (300 MHz, $CDCl_3$): 1.27 (d, $J = 5.8$ Hz, 6H), 3.24 (s, 3H), 4.30 (spt, 1H), 7.18 (A_2B_2m, 4H). ^{19}F NMR (282 MHz, $CDCl_3/CFCl_3$): -110.7 (s, 2F). Anal. calcd. for $C_{12}H_{14}F_2O_5S$: C, 46.70; H, 4.54; S, 10.40. Found: C, 46.83; H, 4.65; S, 10.40.

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