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Facile synthesis of α,α-difluoroalkyl aryl thioethers and their oxidative desulfurization–fluorination to trifluorides

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ABSTRACT

Alkyl 2-arylthio-2,2-difluoroacetates are synthesized in 52–77% yield from alkyl 2-(arylthio)acetates via two succeeding fluoro-Pummerer rearrangements using the reagents combination of *N*-haloimides as electrophiles and excess Py·9HF as the fluoride source at room temperature. Subsequent treatment of the formed fluorinated thioethers with the same reagents at elevated temperature gave alkyl trifluoroacetates in almost quantitative yield under optimised conditions by oxidative desulfurization–fluorination.

1. Introduction

The introduction of fluorine atoms into biologically active substances is known to modify their pharmacological properties and their therapeutical potency. The particular properties of fluorine, such as high electronegativity, relatively small size, low polarisability of the C–F-bond and, in many cases, increased lipophilicity of fluorine containing organic molecules can have considerable impact on the behavior of such molecules in a biological environment [1,2]. Due to their specific properties organofluorine compounds hold huge promise as building blocks for the construction of biologically active compounds [3].

Especially, difluoromethylene compounds with their exceeding characteristics have attracted much interest in bioorganic and medicinal chemistry [4]. The CF_2/O transposition in difluoromethylenephosphonates as phosphonate mimics has a stabilizing effect and prevents hydrolytic decomposition [5]. Also α,α-difluorinated ketones and difluoromethylene groups adjacent to glycosidic and other acetal moieties do stabilize the molecules and are used as transition state mimics in biological systems [6].

Therefore, their synthesis came into the focus of organic chemists. In our previous work we reported a new oxidative desulfurization–difluorination method for alkyl aryl thioethers delivering geminal difluorides via a fluoro-Pummerer-like rearrangement and a subsequent oxidative desulfurization–fluorination reaction. Various terminal difluorinated compounds bearing additional reactive functionalities in ω-position were obtained in moderate to excellent yields (Scheme 1) [7].

However, also α,α-difluoroalkyl aryl thioethers belong to an interesting class of difluoromethylene compounds. They are very important as building blocks for the construction of complex difluorinated molecules and are expected to be good precursors to difluoromethyl radicals by homolytic cleavage of the S–CF_2 bond. Fuchigami and co-workers investigated the photoinduced S–CF_2 bond cleavage of various α,α-difluorinated sulfides in order to generate corresponding difluoromethyl radicals, which could be trapped with various unsaturated compounds [8a]. Lequeux et al. reported the homolytic cleavage of the S–CF_2 bond of sulfanyldifluoromethylphosphonate using AIBN/*n*-Bu_3SnH in the presence of various olefins to provide unsaturated difluoromethylphosphonate adducts [9]. Moreover, these authors and Eto et al. used α,α-difluoroalkyl aryl thioethers as building blocks for the synthesis of acrylthionucleosides [10] and 1,2,4-triazoles with a difluoro substituted sulfonylmethylene unit [11]. Furthermore, Yagupolskii and co-workers oxidized difluorinated sulfides to sulfoxides and converted them to aryl-(*N*-trifluoromethylsulfonylimino)thiodifluoroacetic acids in order to check their optical properties [12].

Several methods for the synthesis of α,α-difluorosulfides are already known in literature. In 1990 Fuchigami et al. synthesized ethyl 2,2-difluoro-2-(phenylthio)acetate by electrochemical fluorination of ethyl 2-fluoro-2-(phenylthio)acetate with $Et_3N·3HF$ as a fluoride source [13]. Seven years later the direct electrochemical α,α-difluorination of ethyl

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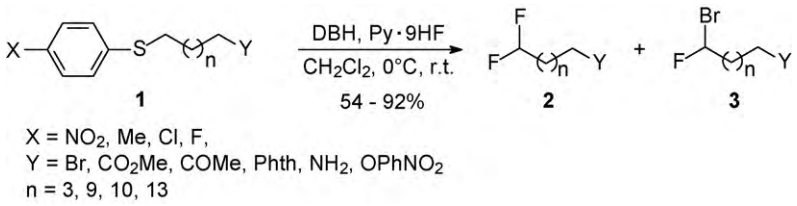


Scheme 1. Desulfurization–difluorination of alkyl aryl thioethers **1** with DBH/Py·9HF.

2-(phenylthio)acetate with $Et_4NF{\cdot}4HF$ was successful [8]. Moreover, 2,2-difluorinated building blocks were frequently used for the construction of ethyl 2-arylthio-2,2-difluoroacetates. By way of example, Yagupolskii et al. obtained ethyl 2,2-difluoro-2-(phenylthio)acetates by nucelophilic substitution of ethyl difluoroiodoacetate with thiophenols in the presence of a base [12b]. Also ethyl bromodifluoroacetate was successfully applied to synthesize the latter compound [14]. Furthermore, the $Na_2S_2O_4$ mediated addition of difluoroiodomethylsulfanyl benzene to alkenes and alkynes gave 2,2-difluoro-4-iodoalkyl aryl sulfides [15]. The synthesis of alkyl 2-arylthio-2,2-difluoroacetates is also possible from arylthioacetates with IF_5-$Et_3N{\cdot}3HF$ [16] or difluoroiodotoluene [17] and also from corresponding dichloro compounds by chloride–fluoride exchange with $Et_3N{\cdot}3HF$ and $ZnBr_2$ [18]. However, the mentioned reactions require special equipment for anodic fluorination or the use of IF_5-$Et_3N{\cdot}3HF$. For the other transformations α,α-dichlorinated starting materials or application of expensive building blocks are necessary.

In this paper we present a new method for the synthesis of alkyl 2-arylthio-2,2-difluoro-acetates, by direct introduction of two fluorine atoms into arylthioacetates in good yields and its transformation to trifluorides. The chemicals used in this work are inexpensive, easy to handle and do need the safety precautions for experiments with Py·9HF (Olah's reagent).

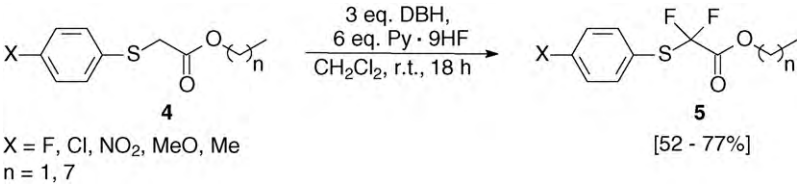
2. Results and discussion

Using the oxidative desulfurization–difluorination approach various aliphatic ω-substituted thioethers were converted to geminal difluorinated alkanes in good yields [7]. However, treatment of alkyl aryl thioethers with electron withdrawing substituents like fluorine, oxygen, carbonyl or carboxyl in β-position under the conditions of the desulfurization–difluorination approach did not lead exclusively to the geminal difluorides of type **2**. The reaction of arylthioacetates **4**, bearing a carboxyl function in α-position to the potential fluorinating position, led to corresponding 2,2-difluoro-2-arylthioacetates **5**. Thus, reacting alkyl 2-(arylthio)acetates (**4a**–**h**) with 2 equiv. of DBH and 6 equiv. of Olah's reagent the alkyl 2-arylthio-2,2-difluoroacetates (**5a**–**d**, **5f**–**h**) were obtained in good yields (Table 1). The reaction with the *p*-methoxy substituted thioether **4e**, however, did not proceed selectively. Though product **5e** was identified in the product mixture by ESI mass spectrometry and ^{19}F NMR spectroscopy, its separation from also formed bromoaryl compounds was not possible. However, pure compound **5e** was synthesized from ethyl 2-bromo-2,2-difluoroacetate by nucleophilic substitution with 4-methoxythiophenol [19].

Under the standard reaction conditions (3 equiv. of DBH, 6 equiv. of Olah's reagent, room temperature) [7], oxidation of sulfur in difluorides **5** occurred and, after aqueous work up, the corresponding 2,2-difluoroacetyl sulfoxide was found as a by-product in some cases. However, no alkyl trifluoroacetates were found.

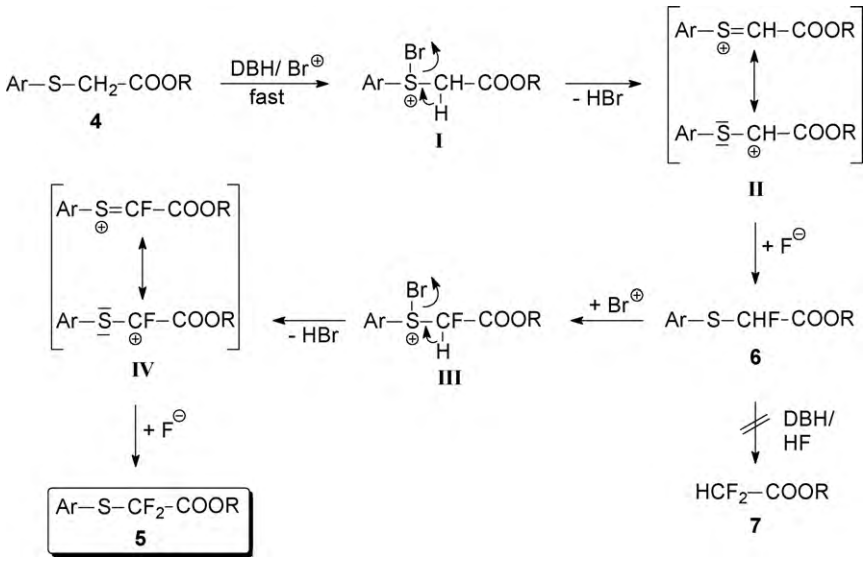
The suggested mechanism of formation of the alkyl 2-arylthio-2,2-difluoroacetates **5** involves two fluoro-Pummerer-like rearrangements (Scheme 2). Compounds **6**, the products of the first rearrangement, were not found in the product mixture. Also difluoroacetates **7**, the products of oxidative desulfurization–difluorination [7] of **6**, were not identified. Obviously, due to the additional strong electron withdrawing effect of the carbonyl group, the elimination of the arylthio group does not occur. Instead, compounds **6** are attacked by the electrophile again and subsequent HBr elimination from **III** with formation of **IV** is faster than the formation of **7** by oxidative desulfurization–fluorination. Finally, fluoride is added to the carbenium ion **IV** forming the thioethers **5** (Scheme 2).

Table 1
Synthesis of alkyl 2-arylthio-2,2-difluoroacetates.



Entry	Compound	X	*n*	Yield (%)
1	**5a**	NO_2	1	77
2	**5b**	Cl	1	72
3	**5c**	F	1	65
4	**5d**	Me	1	71
5	**5e**	OMe	1	60[a]
6	**5f**	NO_2	7	25[b]
7	**5g**	Cl	7	67
8	**5h**	Me	7	52

[a] Synthesized by nucleophilic substitution of ethyl 2-bromo-2,2-difluoroacetate with 4-methoxythiophenol according to Ref. [19].
[b] Low yield because of decomposition during column chromatography on silica gel.

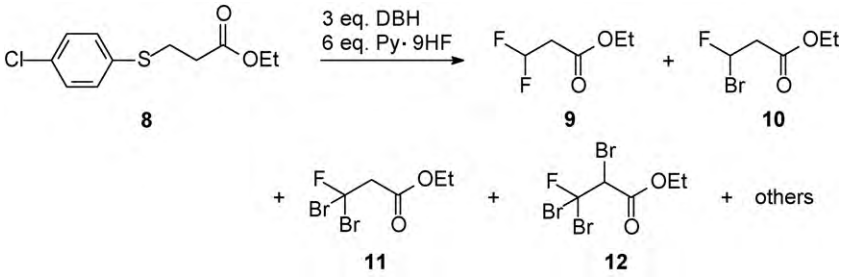


Scheme 2. Plausible mechanism of formation of the alkyl 2-arylthio-2,2-difluoro-acetates **5**.

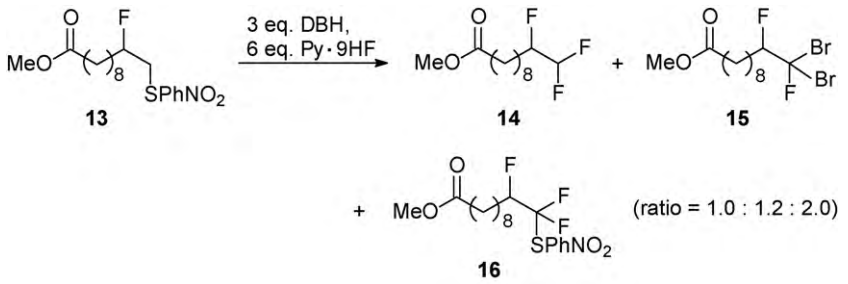
The conversion of ethyl 3-(arylthio)propionate (**8**), with a CH_2-group between the reaction centre and the ester group, with 3 equiv. of *N*,*N*-dibromo-5,5-dimethylhydantoine (DBH) and 6 equiv. of Olah's reagent did not lead to ethyl 3-arylthio-3,3-difluoropropionate. The main product of this reaction was ethyl 3,3-difluoropropionate (**9**, 35%, ^{19}F NMR). Additionally, ethyl 3-bromo-3-fluoropropionate (**10**, 2%), ethyl 3,3-dibromo-3-fluoropropionate (**11**, 17%) and ethyl 2,3,3-tribromo-3-fluoropropionate (**12**, 2%) were found by ^{19}F NMR spectroscopy besides other not identified products (Scheme 3). This result shows that the electron withdrawing effect of an ester group in β-position to the reaction centre is not sufficient to prevent the desulfurization step, but decelerated the reaction rate and directed the reaction towards oxidative desulfurization–difluorination and desulfurization–polybromination.

In order to find out whether a fluorine substituent in β-position to the potential fluorination position is influencing the fluoro-Pummerer rearrangement, we prepared methyl 10-fluoro-11-(4-nitrophenylthio)undecanoate (**13**) according to our earlier protocol of arylsulfenyl fluorination of olefins [20]. The reaction of this thioether with DBH and Olah's reagent under standard conditions gave a mixture of the trifluoride **14**, the dibromodifluoride **15** and the trifluorinated thioether **16** in a ratio of 1:1.2:2 (Scheme 4).

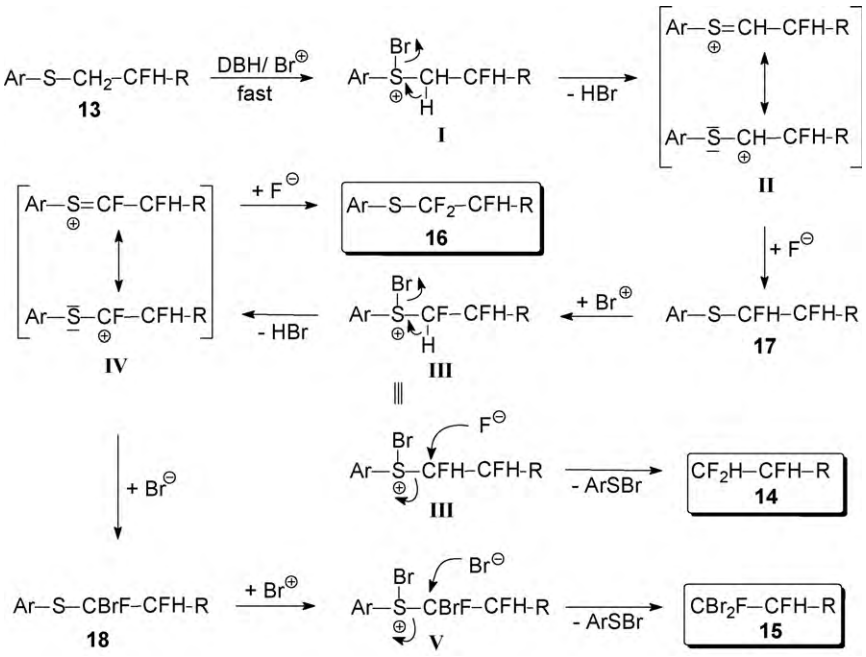
Longer reaction time or bigger amounts of DBH did not lead to higher yields or to a complete conversion of the thioether **13** to the geminal difluoride **14**, but rather to the formation of polybrominated and polyfluorinated substances and partial decomposition. After 3 days of reaction time, decomposition was complete and 1-bromo-4-nitrobenzene was identified as the main product. Due to the electron withdrawing effect of the fluorine atom in β-position, the electron density at sulfur is reduced in comparison to the non-fluorinated compound. So the attack of the bromonium ion and particularly the HBr elimination from **I** to form the carbenium ion **II**, which is destabilized by the β-fluoro substituent, is slowed



Scheme 3. Oxidative desulfurization–difluorination of ethyl 3-(arylthio)propionate (**8**).



Scheme 4. Oxidative desulfurization–difluorination and geminal difluorination of methyl 10-fluoro-11-(4-nitrophenylthio)undecanoate (**13**).



Scheme 5. Suggested mechanism of products formation from methyl 10-fluoro-11-(4-nitrophenylthio)undecanoate (**13**).

down (Scheme 5). The carbenium ion **II** is reacting with fluoride to the vicinal difluoride **17**. This compound was not found among the products, but reacted in a second fluoro-Pummerer rearrangement via **III** either to the carbenium/sulfonium ion **IV**, which is attacked by fluoride to form **16**. Alternatively, the sulfonium ion **III** can also be attacked directly by a fluoride ion to form the difluoride **14** by desulfurization. By addition of a bromide to **IV**, subsequent attack of a bromonium ion at sulfur of **18** (not identified among the products) and elimination of the arylthio group by the attack of a second bromide at **V**, the dibromodifluoride **15** is formed (Scheme 5).

The electronic nature of the intermediate **III** is obviously decisive for the reaction pathway after the first fluoro-Pummerer rearrangement occurred. The ability of an α-fluorine to stabilize a positive charge and the electron withdrawing effect of the β-fluorine substituent on the other hand cause the higher acidity of the proton at the α-C-atom. Therefore, the probability of deprotonation of **III** rises over thioether elimination compared to the situation of compounds without the electron withdrawing effect of a β-fluorine substituent.

A valuable amplification of the alkyl 2-arylthio-2,2-difluoroacetates **5** seemed to be their adoption in a oxidative desulfurization–fluorination to form the corresponding trifluorides. In this way a difluoro alkyl aryl thioether would be converted into a CF_3 group in the last reaction step of a given reaction sequence. Hence, this method might be appropriate for ^{18}F-labelling of medicinally relevant ligands for the positron-emission-tomography (PET).

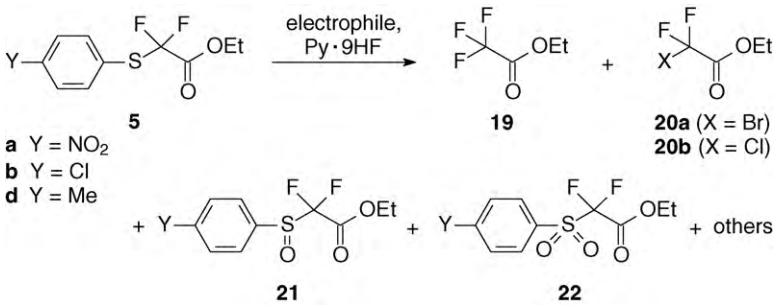
Examples for a fluorodesulfurization of α,α-difluorinated molecules are already known in literature. Methyl arenedithiocarboxylates are readily converted into Ar–CF_3 by treatment with DBH as the electrophile and *n*-$Bu_4N^+H_2F_3^-$ as a fluorinating reagent. Replacing DBH by *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) led to difluorom(methylthio)methyl substituted aromatic compounds. These difluorinated products, Ar–CF_2SMe, were shown to be suitable as precursors for the synthesis of trifluoro compounds. By a further oxidative desulfurization–fluorination step with DBH and *n*-$Bu_4N^+H_2F_3^-$ these compounds were converted to the corresponding trifluorides. However, only trifluoromethyl substituted aromatics have been synthesized by this method so far [21].

Another motivation for the substitution of an arylthio group by fluoride was given by the work of Gomèz et al. They managed to transform unprotected thioglycosides to glycosyl fluorides using the combination of NIS/Olah's reagent or *N*-chlorosuccinimide (NCS)/$Et_3N{\cdot}3HF$. Unfortunately, for this oxidative desulfurization fluorination a large excess of Olah's reagent (20–40 equiv.) or triethylamine trishydrofluoride (40–120 equiv.) was needed [22]. Nevertheless, this reaction was interesting for future syntheses, because of the presence of electron withdrawing groups next to the reaction centre. Due to the influence of electron withdrawing groups the elimination of the arylthio group – as already shown above for compounds **4** and **13** – is disfavored under our standard conditions.

Based on the results of Kuroboshi and Hiyama [21] and Gomèz and co-workers [22] we tried to substitute the arylthio group of different *para*-substituted α,α-difluoroalkyl aryl thioethers by fluoride. Instead of *n*-$Bu_4N^+H_2F_3^-$ our standard conditions for the oxidative desulfurization–difluorination (3 equiv. of DBH, 6 equiv. of Py·9HF) were used. The reactions were carried out in a 0.1 mmol scale. Due to the high volatility of the products the solvent was not removed after aqueous workup, but the organic layer was directly investigated by ^{19}F NMR spectroscopy.

For initial experiments we have chosen ethyl 2,2-difluoro-2-(4-nitrophenylthio)acetate (**5a**) as a model compound, because in earlier studied desulfurization–difluorination reactions the *p*-nitro-substituent at the arylthio group accelerated the reaction rate [7]. However, under standard conditions no conversion to the trifluoride was observed by ^{19}F NMR spectroscopy after 20 h of reaction time at room temperature (Table 2, entry 1). Also the use of NIS as an electrophile and 20 or 40 equiv. of Olah's reagent, according to the results of Gomèz et al., did not lead to any reaction (entries 2 and 3). In the reaction with DBH, enhancement of the amount of fluorinating reagent to 20 equiv. led to little conversion of **5a** to trifluoride **19** and bromofluoride **20a** (entry 4). Finally, heating of the reaction mixture to 40 °C resulted in complete conversion to trifluoride **19** in 18 h (entry 5). Shortening of the reaction time up to 6.5 h at 40 °C was possible (entry 6), but decreasing the amount of Olah's reagent to 10 and 5 equiv. led to lower conversion (entries 7–9). Due to decomposition of the fluorinating reagent, heating of the reaction mixture above 50 °C is not possible.

Table 2
Oxidative desulfurization–fluorination of ethyl 2-arylthio-2,2-difluoroacetates **5**.



Entry	Elektrophile (equiv.)	Py·9HF (equiv.)	Y	Temperature (°C)/time (h)	Products (^{19}F NMR)					
					5	**19**	**20**	**21**	**22**	Others
1	DBH (3.0)	6.0	NO_2	30 min, 0 °C; 20 h, RT	50	–		50	–	–
2	NIS (1.2)	20.0	NO_2	30 min, −10 °C; 20 h, RT	100	–	–	–	–	–
3	NIS (1.2)	40.0	NO_2	30 min, 0 °C; 18 h, RT	100	–	–	–	–	–
4	DBH (3.0)	20.0	NO_2	30 min, 0 °C; 18 h, RT	65	12	23	–	–	–
5	DBH (3.0)	20.0	NO_2	30 min, 0 °C; 18 h, 40 °C	–	100	–	–	–	–
6	DBH (3.0)	20.0	NO_2	6.5 h, 40 °C	3	88	9	–	–	–
7	DBH (3.0)	10.0	NO_2	20 h, 45 °C	12	76	12	–	–	–
8	DBH (3.0)	10.0	NO_2	7 h, 45 °C	33	43	24	–	–	–
9	DBH (3.0)	5.0	NO_2	20 h, 45 °C	38	55	7	–	–	–
10	NCS (3.0)	1.1	NO_2	1 h, 45 °C	90	–	–	10	–	–
11	DBH (3.0)	10.0	Cl	7 h, 45 °C	–	61	39	–	–	–
12	DBH (3.0)	10.0	Cl	3 h, 45 °C	–	68	32	–	–	–
13	DBH (3.0)	5.0	Cl	6 h, 45 °C	6	37	37	20	–	–
14	NCS (3.0)	1.1	Cl	1 h, 45 °C	45	15	–	19	21	–
15	DBH (3.0)	10.0	Me	7 h, 45 °C	–	66	8	–	–	26[a]
16	DBH (3.0)	10.0	Me	3 h, 45 °C	22	37	6	–	–	35[a]
17	DBH (3.0)	5.0	Me	6 h, 45 °C	66	19	8	–	–	7[a]
18	DBH (3.0)	1.1	Me	1 h, 45 °C	48	2	–	18	–	32[a]
19	NCS (3.0)	1.1	Me	1 h, 45 °C	–	50	–	–	50	–
20	NCS (3.0)	1.1	Me	18 h, 45 °C		75			25	

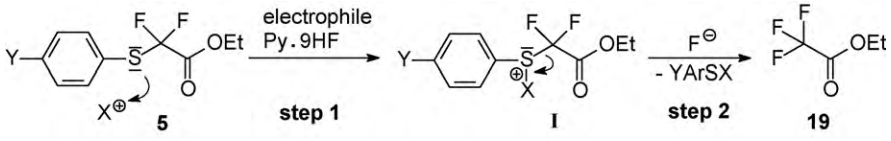
[a] Substances from starting material.

Changing the *p*-substituent at the phenyl ring from nitro to chloride, which is less electron withdrawing, the reaction occurred also with lower amount of Olah's reagent and less reaction time. With 3 equiv. of DBH and 10 equiv. of Py·9HF complete conversion was obtained in 3 h at 45 °C with a good ratio of 68:32 (trifluoride/bromodifluoride) (Table 2, entry 12). With 5 equivalents of Olah's reagent almost complete conversion of **5b** was observed after 6 h at 45 °C, but besides **19** and **20a** the sulfoxide **21b** (20%) was detected (entry 13). The formation of the sulfoxide **21b** after aqueous workup proves that a bromosulfonium ion of type **I** (see Scheme 6) was already formed from **5b**, but the next reaction step towards **19** is slow. The formation of sulfoxides by reaction of thioethers with halogens in the presence of water is already known [23]. Changing the electrophile NCS prevented the formation of the chlorodifluoride **20b**, but did not lead to better results concerning the trifluoride **19** (entry 14).

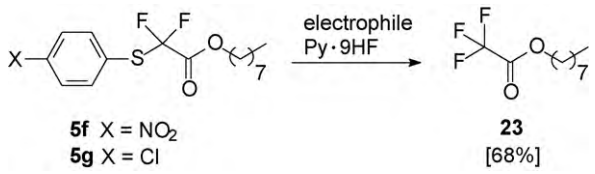
Using ethyl 2,2-difluoro-2-(4-methylphenylthio)acetate **5d** with a *p*-methyl substituent on the phenyl ring, the first step of the reaction, the attack of the electrophile on sulfur should proceed faster because of the electron donating properties of the methyl group, while the second reaction step, the elimination of the arylthio group should be slower compared to the reaction with *p*-chloro and *p*-nitro compounds.

The experiments proved that the thioether **5d** needed longer reaction time for conversion, compared to the chlorophenyl thioether **5b** and showed lower conversion using DBH as the electrophile (Table 2, entries 15–18). However, changing the electrophile from DBH to NCS did not only prevent the formation of compound **20b** but also led to much better conversion towards the trifluoride **19**. The only by-product found in the product mixture was the sulfone **22d** formed by oxidation of the sulfur with NCS and hydrolysis as principally known in literature [23]. After 1 h at 45 °C a 1:1 mixture of trifluoride **19** and sulfone **22d** was formed (entry 19). Elongation of the reaction time to 18 h did not show complete conversion to the trifluoride, 25% of sulfone **22d** were still found in the product mixture showing that the desulfurization/fluorination step is very slow due to the stabilization of the intermediary sulfonium ion by the tolyl group (entry 20).

The described experiments reveal that the oxidative desulfurization–fluorination of ethyl 2-arylthio-2,2-difluoroacetates **5** is significantly depending on the electronic properties of the substituent at the phenyl ring. For the relative rate two controlling



Scheme 6. Formation of the trifluoride **19** by oxidative desulfurization–fluorination of **5**.



Scheme 7. Synthesis of octyl trifluoroacetate (**23**).

steps are important. The first step is the attack of the bromonium ion at the sulfur, the second step is the addition of a fluoride with elimination of the arylthio group (Scheme 6).

The nitro group impedes the electrophilic attack at sulfur by −I and −M-effects, while it accelerates the attack of fluoride at the α-position with elimination of the arylthio group. The *p*-chloro substituent with a weaker −I- and a +M-effect in contrast to the nitro group accelerates the attack of the electrophile, but slows down the desulfurization/fluorination step. This explains the occurrence of the sulfoxide after hydrolytic workup. By the positive inductive effect of the methyl substituent at the phenyl ring the electrophilic attack is further facilitated, but the elimination of the arylthio group is even slower.

Moreover, the experiments prove the reaction to be also dependent on the electrophile and the reaction time. The use of DBH led to better results with thioethers **5a** (Table 2, entries 4–9) and **5b** (Table 2, entries 11–13), while NCS favored the formation of **19** from the *p*-methyl substituted thioether **5d** (Table 2, entries 19 and 20). Carrying out the reaction with NCS and 1.1 equivalents of Olah's reagent over 1 h at 45 °C, the *p*-methyl substituted compound **5d** showed the best conversion to the trifluoride **19** (50%) and the sulfone **22d** (50%) (Table 2, entry 19), while the product mixture of the *p*-chloro compound **5b** still possessed 45% (Table 2, entry 14) and the *p*-nitro compound **5a** even 90% (Table 2, entry 10) of the respective starting material.

The first reaction step, the attack of the electrophile on sulfur is most fast in the case of the *p*-methyl substituted compound **5d**. Therefore, in short reaction time more of the starting material is already converted to the carbenium/sulfonium ion **I** (Scheme 6) and the possibility of further reaction by attack of fluoride and elimination of the arylthio group is given. However, due to the electron donating effect of the methyl group at the phenyl ring the second reaction step is disfavored and the formed carbenium/sulfonium ion **I** is reacting very slowly. Therefore, the sulfone **22** is formed during the aqueous work up. For a complete conversion of the formed carbenium/sulfonium ion **I** to the trifluoride **19** even longer reaction time is needed (Table 2, entry 20).

For the complete analytical characterization higher boiling compounds are necessary. Therefore alkyl 2-arylthio-2,2-difluoroacetates with a longer alkyl chain were synthesized and adopted to the oxidative desulfurization–fluorination reaction (Scheme 7). Octyl 2,2-difluoro-2-(4-nitrophenylthio)acetate (**5f**) and octyl 2-(4-chlorophenylthio)-2,2-difluoro-acetate (**5g**) were converted successfully to their corresponding trifluorides **23** with 3 equiv. of DBH and 20 equiv. of Olah's reagent in dry CH_2Cl_2 at 45 °C over night. After column chromatography the trifluoride **23** was isolated in 68% yield. No bromodifluoride, sulfoxide or sulfone were detected.

3. Conclusion

Application of the new oxidative desulfurization–difluorination method to alkyl aryl thioethers with electron withdrawing substituents like fluorine, oxygen, carbonyl or carboxyl did not lead to the geminal difluorinated compounds exclusively. While the reaction with an electrophile (DBH or NCS) and Py·9HF (Olah's reagent) of alkyl aryl thioethers with a fluorine or an ester group in β-position to the potential desulfurization/fluorination position led to a mixture of fluorinated and brominated compounds, arylthio acetates **4** bearing a carboxyl function in α-position are converted to 2-arylthio-2,2-difluoroacetates **5**. This reaction proceeds via two succeeding fluoro-Pummerer-like rearrangements. Due to the strong electron withdrawing effect of the carbonyl group the elimination of the arylthio group is disfavoured and dehydrobromination and subsequent fluorination leads to arylthio-difluoroacetates.

By treatment of the 2-arylthio-2,2-difluoroacetates **45** with an electrophile, a large excess of Py·9HF and heating to 45 °C, the corresponding trifluorides **19** were obtained. When NCS was used as an electrophile, the formation of the chlorodifluoride **20b** was avoided. Depending on the substituent of the arylthio group, the reaction was also possible with lower amounts of fluorinating reagent and in a shorter reaction time.

4. Experimental

4.1. General methods

Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). For HPLC, a Merck-Hitachi system D-7000 with a pump L-7150 and a refractometer Shodex RI-72 were used. GC analyses were performed with HP-1 column (30 m, 0.32 mm diameter, film 0.25 μm) from Hewlett-Packard. NMR spectra were recorded on a Bruker ARX300 and a Bruker DPX300 (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz; ^{19}F NMR, 282 MHz), Bruker AMX 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) and Varian Inova (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) spectrometers. TMS (^{1}H), $CDCl_3$ (^{13}C) and $CFCl_3$ (^{19}F) were used as internal standards. Mass spectra were recorded on Thermo-Finningan MAT8200 (EI, 70 eV), Waters-Micromass GCT (GCToF, EI), and Waters-Micromass Quatromicro GC (GC/CI and EI, 70 eV) instruments. All air and moisture-sensitive reactions were performed under argon atmosphere. Solvents were purified and dried where necessary by literature methods. The reactions with Olah's reagent were performed in Teflon™ flasks. The alkyl aryl thioethers were prepared from the corresponding thiophenols and alkyl halides under basic conditions [19].

4.2. Synthesis of α,α-difluoro alkyl aryl thioethers 5

4.2.1. General procedure

Olah's reagent (0.69 mL, 3 mmol, 6 equiv.) was added to a solution of the corresponding thioether (0.5 mmol) in dry CH_2Cl_2 (10 mL) in a Teflon™ flask via a polypropylene/polyethylene syringe. DBH (1.0 mmol, 2 equiv.) was added and the mixture was stirred for 17 h at room temperature. Then ice-water was added and the reaction mixture was neutralized with concentrated NH_3. The phases were separated and the aqueous layer was extracted with Et_2O (3× 20 mL). The combined organic phases were washed with 0.1 N aq. HCl (2× 20 mL) and 5% aqueous $NaHCO_3$ (2× 20 mL) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the products were purified by column chromatography.

*4.2.1.1. Ethyl 2,2-difluoro-2-(4-nitrophenylthio)acetate (**5a**).* The reaction was carried out in a 0.5 mmol scale with ethyl 2-(4-nitrophenylthio)acetate (**4a**) in 17 h at room temperature. After column chromatography (silica gel, pentane/diethyl ether, 95:5) **5a** was isolated as a yellow crystalline compound. Yield: 107 mg (77%). Mp.: 51 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (t, 3H, CH_3, $^3J_{H,H}$ = 7.2 Hz), 4.34 (q, 2H, CH_2, $^3J_{H,H}$ = 7.2 Hz), 7.81 (d, 2H, CH, $^3J_{H,H}$ = 8.9 Hz), 8.25 (d, 2H, CH, $^3J_{H,H}$ = 8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (q), 64.1 (t), 119.5 (st, $^1J_{C,F}$ = 289.7 Hz), 124.1 (d), 133.3 (st, $^3J_{C,F}$ = 2.3 Hz), 136.5 (d), 148.9 (s), 160.9 (st,

$^{2}J_{C,F}$ = 31.8 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.0 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 277 (100) [M^+], 204 (79) [$C_7H_4F_2NO_2S^+$], 188 (24) [$C_7H_4F_2NOS^+$], 158 (40) [$C_7H_4F_2S^+$], 155 (24) [$C_6H_4NO_2S^+$], 123 (15) [$C_4H_5F_2O_2^+$], 45 (15) [$C_2H_4O^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{10}H_9F_2NO_4SNa^+$: 300.0113; found: 300.0113. Anal. calcd. for $C_{10}H_9F_2NO_4S$: C, 43.32; H, 3.27; N, 5.05. Found: C, 42.89; H, 3.05; N, 4.89.

*4.2.1.2. Ethyl 2-(4-chlorophenylthio)-2,2-difluoroacetate (**5b**) [8,24].* The reaction was carried out in a 4.55 mmol scale with ethyl 2-(4-chlorophenylthio)acetate (**4b**) in 17 h at room temperature. After column chromatography (silica gel, pentane/diethylether 98:2) **5b** was isolated as a colorless oil. Yield: 871 mg (72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.2 Hz), 4.29 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.1 Hz), 7.38 (d, 2H, CH, $^{3}J_{H,H}$ = 8.7 Hz), 7.55 (d, 2H, CH, $^{3}J_{H,H}$ = 8.5 Hz).^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (q), 63.7 (t), 119.7 (st, $^{1}J_{C,F}$ = 287.9 Hz), 123.1 (st, $^{3}J_{C,F}$ = 2.6 Hz), 129.5 (d), 137.4 (s), 137.9 (d), 161.4 (st, $^{2}J_{C,F}$ = 32.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −82.6 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 266 (60) [M^+], 193 (100) [$C_7H_4F_2ClS^+$], 143 (28) [$C_6H_4ClS^+$], 108 (36) [$C_6H_4S^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{10}H_9ClF_2O_2SNa^+$: 288.9878; found: 288.9875. Anal. calcd. for $C_{10}H_9ClF_2O_2S$: C, 45.04; H, 3.40. Found: C, 44.69; H, 3.32.

*4.2.1.3. Ethyl 2,2-difluoro-2-(4-fluorophenylthio)acetate (**5c**) [12b].* The reaction was carried out in a 3.0 mmol scale with ethyl 2-(4-fluorophenylthio)acetate (**4d**) in 17 h at room temperature. After column chromatography (silica gel, pentane/diethyl ether, 99:1) the product **5c** was isolated as a colorless oil. Yield: 484 mg (65%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.1 Hz), 4.28 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.2 Hz), 7.10 (m, 2H, CH), 7.61 (m, 2H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (q), 63.6 (t), 116.5 (dd, $^{3}J_{C,F}$ = 22.2 Hz), 119.7 (std, $^{1}J_{C,F}$ = 287.5 Hz, $^{6}J_{C,F}$ = 1.9 Hz), 120.0 (sm), 138.9 (dd, $^{3}J_{C,F}$ = 9.0 Hz), 161.5 (st, $^{2}J_{C,F}$ = 32.3 Hz), 164.4 (sd, $^{2}J_{C,F}$ = 252.1 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −83.0 (s, 2F), −109.6 (m, 1F). MS (EI-GC-inlet): *m/z* (%) 250 (73) [M^+], 177 (100) [$C_7H_4F_3S^+$], 157 (6) [$C_7H_3F_2S^+$], 127 (42) [$C_6H_4FS^+$], 108 (3) [$C_6H_4S^+$], 95 (33) [$C_6H_4F^+$], 83 (55) [$C_4H_3O_2^+$]. HRMS (ESI): [M+Na^+] calcd for $C_{10}H_9F_3O_2SNa^+$: 273.0168; found: 273.0174.

*4.2.1.4. Ethyl 2,2-difluoro-2-(4-methylphenylthio)acetate (**5d**) [11].* The reaction was carried out in a 3.0 mmol scale with ethyl 2-(4-methylphenylthio)acetate (**4d**) in 3 days at room temperature or as an alternative 22 h at 45 °C. However, heating to 45 °C causes the formation of ring brominated thioethers as by-products. After column chromatography (silica gel, pentane/diethyl ether, 97:3) **5d** was isolated as a colorless oil. Yield: 87 mg (71%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.2 Hz), 2.38 (s, 3H, CH_3), 4.26 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.2 Hz), 7.20 (d, 2H, CH, $^{3}J_{H,H}$ = 7.9 Hz), 7.49 (d, 2H, CH, $^{3}J_{H,H}$ = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (q), 21.3 (q), 63.5 (t), 120.0 (st, $^{1}J_{C,F}$ = 286.9 Hz), 121.1 (st, $^{3}J_{C,F}$ = 2.7 Hz), 130.0 (d), 136.7 (d), 141.1 (s), 161.7 (st, $^{2}J_{C,F}$ = 32.4 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −83.1 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 246 (100) [M^+], 173 (89) [$C_8H_7F_2S^+$], 153 (17) [$C_8H_6FS^+$], 123 (29) [$C_7H_7S^+$], 91 (33) [$C_7H_7^+$], 45 (21) [$C_2H_4O^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{11}H_{12}F_2O_2SNa^+$: 269.0418; found: 269.0418.

*4.2.1.5. Ethyl 2,2-difluoro-2-(4-methoxyphenylthio)acetate (**5e**) [8,24].* According to the method described by Dong et al. [19] ethyl 2-bromo-2,2-difluoroacetate and methoxythiophenol were converted to ethyl 2,2-difluoro-2-(4-methylphenylthio)acetate (**5e**) in a 1 mmol scale. After column chromatography (silica gel, pentane/diethyl ether, 40:1) a colorless oil was isolated (156 mg, 60%).

Using the difluorination conditions the thioether **4e** could be converted to the difluoro alkyl aryl thioether, but the isolation was only possible in low yields because of the formation of many by-products. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.2 Hz), 3.82 (s, 3H, CH_3), 4.26 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.2 Hz), 6.91 (d, 2H, CH, $^{3}J_{H,H}$ = 8.9 Hz), 7.53 (d, 2H, CH, $^{3}J_{H,H}$ = 8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8 (q), 55.4 (q), 63.5 (t), 115.0 (d), 115.1 (st, $^{3}J_{C,F}$ = 2.7 Hz), 120.0 (st, $^{1}J_{C,F}$ = 286.6 Hz), 138.5 (d), 161.7 (s), 161.8 (st, $^{2}J_{C,F}$ = 32.6 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −83.7 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 262 (42) [M^+], 189 (4) [$C_8H_7F_2OS^+$], 139 (100) [$C_7H_7OS^+$], 124 (8) [$C_6H_4OS^+$], 45 (2) [$C_2H_4O^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{11}H_{12}F_2O_2SNa^+$: 285.0367; found: 285.0358. Anal. calcd. for $C_{11}H_{12}F_2O_3S$: C, 50.37; H, 4.61. Found: C, 50.63; H, 4.74.

*4.2.1.6. Octyl 2,2-difluoro-2-(4-nitrophenylthio)acetate (**5f**).* The reaction was carried out in a 2.0 mmol scale with octyl 2-(4-nitrophenylthio)acetate (**4f**) in 17 h at room temperature. After column chromatography (silica gel, pentane/diethyl ether, 95:5) the product **5f** was isolated as a yellow oil. Yield: 180 mg (25%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, 14-CH_3, $^{3}J_{H,H}$ = 6.7 Hz), 1.20–1.40 (m, 10H, CH_2), 1.62 (m, 2H, CH_2), 4.27 (t, 2H, CH_2, $^{3}J_{H,H}$ = 6.7 Hz), 7.80 (d, 2H, CH, $^{3}J_{H,H}$ = 8.9 Hz), 8.25 (d, 2H, CH, $^{3}J_{H,H}$ = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q), 22.6 (t), 25.5 (t), 25.7 (t), 28.2 (t), 29.1 (t), 31.7 (t), 68.1 (t), 119.5 (st, $^{1}J_{C,F}$ = 289.6 Hz,), 124.0 (d), 133.4 (st, $^{3}J_{C,F}$ = 2.3 Hz), 136.4 (d), 148.9 (s), 161.0 (st, $^{2}J_{C,F}$ = 31.8 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −80.8 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 361 (17) [M^+], 344 (2) [M^+−OH], 331 (3) [M^+−NO], 249 (16) [$C_8H_5F_2NO_4S^+$], 204 (18) [$C_7H_4F_2NO_2S^+$], 157 (16) [$C_9H_{17}O_2^+$], 71 (69) [$C_5H_{11}^+$], 57 (100) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. HRMS (ESI): [M+Na^+] calcd for $C_{16}H_{21}F_2NO_4SNa^+$: 384.1052; found: 384.1104.

*4.2.1.7. Octyl 2-(4-chlorophenylthio)-2,2-difluoroacetate (**5g**).* The reaction was carried out in a 2.0 mmol scale with octyl 2-(4-chlorophenylthio)acetate (**4g**) in 17 h at room temperature. After column chromatography (silica gel, pentane/diethyl ether, 95:5) **5g** was isolated as a colorless oil. Yield: 466 mg (67%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, CH_3, $^{3}J_{H,H}$ = 6.7 Hz), 1.20–1.40 (m, 10H, CH_2), 1.62 (m, 2H, CH_2), 4.21 (t, 2H, CH_2, $^{3}J_{H,H}$ = 6.7 Hz), 7.38 (d, 2H, CH, $^{3}J_{H,H}$ = 8.7 Hz), 7.55 (d, 2H, CH, $^{3}J_{H,H}$ = 8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q), 22.6 (t), 25.6 (t), 28.2 (t), 29.0 (t), 29.1 (t), 31.7 (t), 66.8 (t), 119.7 (st, $^{1}J_{C,F}$ = 289.7 Hz), 123.2 (st, $^{3}J_{C,F}$ = 2.7 Hz), 129.6 (d), 137.4 (s), 137.9 (d), 161.5 (st, $^{2}J_{C,F}$ = 32.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −82.4 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 350 (50) [M^+], 238 (38) [$C_8H_5ClF_2O_2S^+$], 193 (38) [$C_7H_4ClF_2S^+$], 43 (16) [$C_6H_4ClS^+$], 108 (25) [$C_6H_4S^+$], 122 (75) [$C_3H_3O_2^+$], 57 (100) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{16}H_{21}F_2ClO_2SNa^+$: 373.0811; found: 373.0834. Anal. calcd. for $C_{16}H_{21}ClF_2O_2S$: C, 54.77; H, 6.03. Found: C, 54.06; H, 6.02.

*4.2.1.8. Octyl 2,2-difluoro-2-(4-methylphenylthio)acetate (**5h**).* The reaction was carried out in a 2.0 mmol scale with octyl 2-(4-methylphenylthio)acetate (**4h**) in 3 days at room temperature. After column chromatography (silica gel, pentane/diethyl ether, 200:1) **5h** was isolated as a colorless oil. Yield: 369 mg (52%). As by-products ringbrominated thioethers were detected, which could not be separated completely from the wished product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, CH_3, $^{3}J_{H,H}$ = 6.7 Hz), 1.24–1.37 (m, 10H, 13-CH_2), 1.56–1.69 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 4.19 (t, 2H, CH_2, $^{3}J_{H,H}$ = 6.7 Hz), 7.19 (d, 2H, CH, $^{3}J_{H,H}$ = 7.9 Hz), 7.49 (d, 2H, CH, $^{3}J_{H,H}$ = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (q), 22.6 (t), 25.5 (t), 28.1 (t), 29.0 (t), 31.7 (t), 67.5 (t), 120.0 (st, $^{1}J_{C,F}$ = 286.9 Hz), 121.1 (st, $^{3}J_{C,F}$ = 2.6 Hz), 130.0 (d), 136.6 (d), 141.0 (s), 162.3 (st, $^{2}J_{C,F}$ = 32.6 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −83.0 (s, 2F). MS (EI-GC-inlet): *m/z* (%) 330 (100) [M^+], 218 (79) [$C_9H_8F_2O_2S^+$], 173 (46) [$C_8H_7F_2S^+$], 123 (50) [$C_7H_7S^+$], 91 (21) [$C_7H_7^+$], 71 (21) [$C_3H_3O_2^+$], 57 (29) [$C_4H_9^+$], 43 (25) [$C_3H_7^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{17}H_{24}F_2O_2SNa^+$: 353.1357; found: 353.1357.

4.3. Oxidative desulfurization–fluorination of ethyl 3-(4-chlorophenylthio)propionate (8)

The reaction was carried out in a 0.5 mmol scale with ethyl 3-(4-chlorophenylthio)propionate (**8**), 3 equiv. (1.5 mmol) of DBH and 6 equiv. (3.0 mmol) of Olah's reagent in 17 h at room temperature. As the main product ethyl 3,3-difluoropropionate was formed. After column chromatography fractions enriched in compounds **9**, **10**, **11** or **12**, respectively, were separated and used for NMR spectroscopy. Due to the high volatility of the products and small scale of the reaction no yields could be defined.

4.3.1. Ethyl 3,3-difluoropropionate (9) [25]

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.15 Hz), 2.91 (dt, 2H, CH_2, $^{3}J_{H,F}$ = 15.5 Hz, $^{3}J_{H,H}$ = 4.9 Hz), 4.12 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.1 Hz), 6.18 (tt, 1H, CH, $^{2}J_{H,F}$ = 55.6 Hz, $^{3}J_{H,F}$ = 5.0 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −117.0 (dt, 2F, $^{2}J_{H,F}$ = 55.6 Hz, $^{3}J_{H,F}$ = 15.5 Hz). MS (EI-GC-inlet): *m*/*z* (%) 138 (13) [M^+], 123 (5) [$C_4H_5F_2O_2^+$], 111 (66) [$C_3H_5F_2O_2^+$], 93 (100) [$C_3H_3F_2O^+$], 73 (44) [$C_3H_5O_2^+$], 65 (59) [$C_2H_3F_2^+$], 51 (31) [CHF_2^+], 45 (56) [$C_2H_5O^+$].

4.3.2. Ethyl 3-bromo-3-fluoropropionate (10)

^{19}F NMR ($CDCl_3$, 282 MHz): δ −134.8 (m, 1F). MS (EI-GC-inlet): *m*/*z* (%) 200/198 (2/2) [M^+], 171/169 (4/4) [$C_3H_3BrFO_2^+$], 170/168 (23/22), 151/153 (98/100) [$C_3H_3BrFO^+$], 125/123 (16/16) [$C_2H_2BrF^+$], 117 (26) [$C_5H_6FO_2^+$], 89 (15) [$C_4H_9O_2^+$], 72 (14) [$C_3H_4O_2^+$], 45 (44) [$C_2H_5O^+$].

4.3.3. Ethyl 3,3-dibromo-3-fluoropropionate (11) [26,27]

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.2 Hz), 3.81 (d, 2H, CH_2, $^{3}J_{H,F}$ = 15.9 Hz), 4.26 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0 (q), 56.5 (td, $^{2}J_{C,F}$ = 20.4 Hz), 61.8 (t), 86.6 (qd, $^{1}J_{C,F}$ = 320.5 Hz), 165.3 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −48.7 (t, 1F, $^{3}J_{H,F}$ = 15.9 Hz). MS (EI-GC-inlet): *m*/*z* (%) 280/278/276 (<0.1/<0.1/<0.1) [M^+], 265/263/261 (21/41/24) [$C_4H_4Br_2F^+$], 251/249/247 (13/26/19), 235/233/231 (14/30/16) [$C_3H_2Br_2F^+$], 207/205/203 (12/20/12) [$C_2H_2Br_2F^+$], 171/169 (57/57), 151 (24), 126/124 (19/20) [$C_2H_2BrF^+$], 89 (100) [$C_4H_9O_2^+$], 73 (26) [$C_3H_5O_2^+$], 45 (76) [$C_2H_4O^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_5H_7Br_2FO_2Na^+$: 302.8648/300.8669/298.8689; found: 302.8643/300.88659/298.8681.

4.3.4. Ethyl 2,3,3-tribromo-3-fluoropropionate (12)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, 3H, CH_3, $^{3}J_{H,H}$ = 7.2 Hz), 4.20 (q, 2H, CH_2, $^{3}J_{H,H}$ = 7.2 Hz), 5.68 (d, 1H, CHBr, $^{3}J_{H,F}$ = 27.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (q), 61.1 (td, $^{2}J_{C,F}$ = 9.5 Hz), 61.8 (t), 105.7 (qd, $^{1}J_{C,F}$ = 320.5 Hz), 165.3 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −45.7 (d, 1F, $^{3}J_{H,F}$ = 27.2 Hz).

4.4. Oxidative desulfurization–difluorination of methyl 10-fluoro-11-(4-nitrophenylthio)undecanoate (13)

According to the general procedure methyl 10-fluoro-11-(4-nitrophenylthio)undecanoate (**13**, 0.5 mmol) was treated with 3 equiv. of DBH and 6 equiv. of Olah's reagent for 17 h at room temperature. Three products were obtained: methyl 10,11,11-trifluoroundecanoate (**14**), methyl 11,11-dibromo-10,10-difluoroundecanoate (**15**) und methyl 10,11,11-trifluoro-11-(4-nitrophenylthio)undecanoate (**16**) in a ratio: 1:1.2:2 (^{19}F NMR).

4.4.1. Methyl 10,11,11-trifluoroundecanoate (14)

The product was identified from a mixture (17:83) of methyl 10,11,11-trifluoroundecanoate (**14**) and **13**. No yield could be determined. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27–1.39 (m, 10H, CH_2), 1.41–1.65 (m, 2H, CH_2), 1.82–2.12 (m, 2H, CH_2), 2.30 (t, 2H, CH_2, $^{3}J_{H,H}$ = 7.5 Hz), 3.47 (m, 1H, CH), 3.67 (s, 3H, CH_3), 5.77 (tdd, 1H, CH, $^{2}J_{H,F}$ = 55.0 Hz, $^{3}J_{H,F}$ = 5.8 Hz, $^{3}J_{H,H}$ = 4.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.2 (td, $^{3}J_{C,F}$ = 3.0 Hz), 24.9 (t), 28.1 (tdt, $^{2}J_{C,F}$ = 20.4 Hz, $^{3}J_{C,F}$ = 3.0 Hz), 29.0, 29.1, 29.2 (t), 34.0 (t), 51.4 (q), 90.3 (dddd, $^{1}J_{C,F}$ = 175.8 Hz, $^{2}J_{C,F}$ = 26.9 Hz, $^{2}J_{C,F}$ = 25.8 Hz), 113.7 (dtd, $^{1}J_{C,F}$ = 244.6 Hz, $^{2}J_{C,F}$ = 31.7 Hz), 174.3 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −129.9 (dddd, 1F, $^{2}J_{F,F}$ = 296.1 Hz, $^{3}J_{F,F}$ = 12.0 Hz, $^{2}J_{H,F}$ = 55.0 Hz, $^{3}J_{H,F}$ = 9.9 Hz), (AB-spectra); −132.9 (m, 1F, $^{2}J_{F,F}$ = 296.2 Hz, $^{3}J_{F,F}$ = 13.5 Hz, $^{2}J_{H,F}$ = 55.0 Hz, $^{3}J_{H,F}$ = 10.2 Hz, $^{4}J_{H,F}$ = 1.7 Hz), (AB-spectra); −201.9 (m, 1F, $^{3}J_{F,F}$ = 13.4 Hz, $^{3}J_{F,F}$ = 12.1 Hz). MS (EI-GC-inlet): *m*/*z* (%) 254 (0.1) [M^+], 223 (6) [M^+−CH_3O], 143 (2) [$C_8H_{15}O_2^+$], 101 (4) [$C_5H_9O_2^+$], 87 (36) [$C_4H_7O_2^+$], 74 (100) [$C_3H_6O_2^+$], 59 (9) [$C_2H_3O_2^+$], 55 (11) [$C_4H_7^+$], 43 (11) [$C_3H_7^+$], 41 (11) [$C_3H_5^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{12}H_{21}F_3O_2Na^+$: 277.1390; found: 277.1390.

4.4.2. Methyl 11,11-dibromo-10,11-difluoroundecanoate (15)

After column chromatography (silica gel, pentane/diethyl ether, 90:3) **15** was isolated as a colorless oil. Yield: 60 mg (31%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27–1.39 (m, 10H, CH_2), 1.41–1.65 (m, 2H, CH_2), 1.82–2.12 (m, 2H, CH_2), 2.30 (t, 2H, CH_2, $^{3}J_{H,H}$ = 7.5 Hz), 3.67 (s, 3H, CH_3), 4.60 (tdd, 1H, CH, $^{2}J_{H,F}$ = 47.4 Hz, $^{3}J_{H,F}$ = 9.2 Hz, $^{3}J_{H,H}$ = 2.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.7 (td, $^{3}J_{C,F}$ = 2.0 Hz), 24.9 (t), 29.0, 29.1, (t), 34.0 (t), 30.5 (td, $^{2}J_{C,F}$ = 20.6 Hz), 51.4 (q), 96.7 (sdd, $^{1}J_{C,F}$ = 321.1 Hz, $^{2}J_{C,F}$ = 27.4 Hz), 97.2 (ddd, $^{1}J_{C,F}$ = 192.7 Hz, $^{2}J_{C,F}$ = 22.9 Hz), 174.2 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −63.4 (dd, 1F, $^{3}J_{F,F}$ = 27.0 Hz, $^{3}J_{H,F}$ = 8.8 Hz); −174.9 (dddd, 1F, $^{2}J_{H,F}$ = 47.3 Hz, $^{3}J_{H,F}$ = 38.4 Hz, $^{3}J_{F,F}$ = 27.0 Hz, $^{4}J_{H,F}$ = 15.5 Hz). MS (EI-GC-inlet): *m*/*z* (%) 396/394/392 (<0.1/<0.1/<0.1) [M^+], 365/363/361 (14/24/14) [M^+−CH_3O], 315/313 (14/14) [M^+−Br], 295/293 (3/3) [M^+−Br−HF], 168 (44) [$C_7H_6NO_2S^+$], 101 (3) [$C_5H_9O_2^+$], 87 (14) [$C_4H_7O_2^+$], 74 (100) [$C_3H_6O_2^+$], 59 (10) [$C_2H_3O_2^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{12}H_{20}Br_2F_2O_2Na^+$: 418.9655/416.9675/414.9696; found: 418.9660/416.9675/414.9698.

4.4.3. Methyl 10,11,11-trifluoro-11-(4-nitrophenylthio)undecanoate (16)

After column chromatography (silica gel, pentane/diethylether 90:3) the product **16** was isolated as a yellow, waxy substance. Yield: 150 mg (37%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29–1.48 (m, 10H, CH_2), 1.57–1.82 (m, 4H, CH_2), 2.31 (t, 2H, CH_2, $^{3}J_{H,H}$ = 7.5 Hz), 3.67 (s, 3H, CH_3), 4.63 (dm, 1H, CH, $^{2}J_{H,F}$ = 47.3 Hz), 7.80 (d, CH, $^{3}J_{H,H}$ = 8.8 Hz), 8.24 (d, CH, $^{3}J_{H,H}$ = 8.9 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 24.6 (t), 24.8 (t), 28.6, 28.8, 28.9, 29.0, (t), 34.0 (t), 51.4 (q), 92.4 (ddt, $^{1}J_{C,F}$ = 185.1 Hz, $^{2}J_{C,F}$ = 29.3 Hz), 123.9 (d), 127.1 (m, $^{1}J_{C,F}$ = 284.9 Hz, $^{2}J_{C,F}$ = 27.1 Hz), 134.0 (s), 136.2 (d), 148.6 (s), 174.2 (s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −80.9 (ddd, 1F, $^{1}J_{F,F}$ = 214.8 Hz, $^{2}J_{F,F}$ = 18.4 Hz, $^{3}J_{H,F}$ = 6.9 Hz), (AB-spectra); −85.8 (ddd, 1F, $^{1}J_{F,F}$ = 214.7 Hz, $^{2}J_{F,F}$ = 16.9 Hz, $^{3}J_{H,F}$ = 10.3 Hz), (AB-spectra); −191.9 (m, 1F, $^{3}J_{F,F}$ = 17.6 Hz). MS (EI-GC-inlet): *m*/*z* (%): 407 (8) [M^+], 390 (5) [M^+−OH], 376 (6) [M^+−CH_3O], 370 (1) [M^+−OH-HF], 334 (1) [$C_{15}H_{19}F_3NO_2S^+$], 292 (1) [$C_{12}H_{13}F_3NO_2S^+$], 278 (1) [$C_{11}H_{11}F_3NO_2S^+$], 155 (28) [$C_6H_5NO_2S^+$], 59 (68) [$C_2H_3O_2^+$], 55 (100) [$C_4H_7^+$], 43 (52) [$C_3H_7^+$], 41 (76) [$C_3H_5^+$]. HRMS (ESI): [M+Na^+] calcd. for $C_{18}H_{24}F_3NO_4SNa^+$: 430.1270; found: 430.1278.

4.5. Oxidative desulfurization–fluorination of alkyl 2-arylthio-2,2-difluoroacetates

4.5.1. General procedure

The reaction was carried out in a 20 mL-Teflon™ screwed vessel. To a solution of electrophile (DBH, NIS, NCS) in absolute CH_2Cl_2 (2 mL) Olah's reagent was added via a polypropylene/polyethylene syringe. The reaction mixture was cooled to 0 °C before the ethyl 2-arylthio-2,2-difluoroacetate, dissolved in abs. CH_2Cl_2 (1 mL), was added. The vessel was screwed tightly and reaction was stirred at the temperature and time given in Table 2.

Then the reaction mixture was neutralized with aqueous $NaHCO_3$ (first 5%, then saturated solution), transferred into an extraction funnel and washed with 10% aqueous $Na_2S_2O_3$ (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and directly used for ^{19}F NMR measurements. For the corresponding amounts of electrophile and Olah's reagent as well as for the reaction conditions see Table 2.

Due to the low scale reaction and low concentration of the products in the solvent mixture, the products were only identified by ^{19}F NMR measurements.

*4.5.1.1. Ethyl 2,2,2-trifluoroacetate (**19**) [28].* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −75.6 (s, 3F).

*4.5.1.2. Ethyl 2-bromo-2,2-difluoroacetate (**20a**) [29].* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −61.3 (s, 2F).

*4.5.1.3. Ethyl 2-chloro-2,2-difluoroacetate (**20b**) [30].* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −61.3 (s, 2F).

*4.5.1.4. Ethyl 2,2-difluoro-2-(4-nitrophenylsulfinyl)acetate (**21a**).* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −107.5 (d, 1F, $^2J_{F,F}$ = 229.4 Hz); −110.6 (d, 1F, $^2J_{F,F}$ = 230.0 Hz) (AB-spectra).

*4.5.1.5. Ethyl 2,2-difluoro-2-(4-chlorophenylsulfinyl)acetate (**21b**) [12b].* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −109.3 (d, 1F, $^2J_{F,F}$ = 227.8 Hz); −111.7 (d, 1F, $^2J_{F,F}$ = 227.8 Hz) (AB-spectra).

*4.5.1.6. Ethyl 2,2-difluoro-2-(4-methylphenylsulfinyl)acetate (**21d**).* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −110.6 (d, 1F, $^2J_{F,F}$ = 226.8 Hz); −111.8 (d, 1F, $^2J_{F,F}$ = 226.8 Hz) (AB-spectra).

*4.5.1.7. Ethyl 2,2-difluoro-2-(4-chlorophenylsulfonyl)acetate (**22b**) [12b].* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −108.0 (s, 2F).

*4.5.1.8. Ethyl-2,2-difluoro-2-(4-methylphenylsulfonyl)acetate (**22d**).* ^{19}F NMR ($CDCl_3$, 282 MHz): δ −108.5 (s, 2F).

*4.5.2. Octyl 2,2,2-trifluoroacetate (**23**) [31]*

A solution of DBH (88 mg, 0.3 mmol, 3 equiv.) and Olah's reagent (0.46 mL, 2.0 mmol, 20 equiv.) in abs. CH_2Cl_2 (2 mL) was cooled to 0 °C. After the addition of octyl 2,2-difluoro-2-(4-chlorophenylthio)acetate (**5f**, 35 mg, 0.1 mmol), dissolved in abs. CH_2Cl_2 (1 mL), the reaction was stirred for 30 min at 0 °C and at 40 °C over night. Then the reaction mixture was neutralized with aqueous $NaHCO_3$ (first 5%, then saturated solution), transferred into an extraction funnel and washed with 10% aqueous $Na_2S_2O_3$ (10 mL). The phases were separated and the organic layer was dried over anhydrous $MgSO_4$. After concentration under reduced pressure, and column chromatography (silica gel, pentane) the product **23** was obtained as a colorless liquid. Yield: 20 mg (68%). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (t, 3H, CH_3, $^3J_{H,H}$ = 6.9 Hz), 1.24–1.39 (m, CH_2), 1.56–1.81 (m, 4H, CH_2), 4.35 (t, 2H, CH_2, $^3J_{H,H}$ = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 13.5 (q), 22.2 (t), 25.1 (t), 27.6 (t), 28.7, 28.6 (t), 31.9 (t), 68.1 (t), 114.21 (qq, $^1J_{C,F}$ = 285.6 Hz), 157.07 (sq, $^2J_{C,F}$ = 41.7 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −75.6 (s, 3F). MS (EI-GC-inlet): *m/z* (%) 226 (<0.1) [M^+], 157 (3) [$C_9H_{17}O_2^+$], 127 (1) [$C_3H_2F_3O_2^+$], 112 (4) [$C_2F_3O_2^+$], 99 (5) [$C_7H_{15}^+$], 97 (7) [$C_2F_3O^+$], 83 (53) [$C_6H_{11}^+$], 84 (45) [$C_6H_{12}^+$], 70 (66) [$C_5H_{10}^+$], 69 (100) [CF_3^+], 55 (72) [$C_4H_9^+$], 43 (46) [$C_3H_7^+$], 41 (65) [$C_3H_5^+$].

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