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Desulfurizing Difluorination Reaction of Benzyl Sulfides Using IF_5

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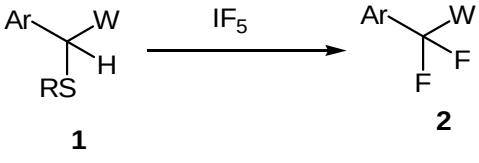
Abstract: A desulfurizing difluorination reaction of benzyl sulfides having a functional group such as an ester, a ketone, a nitrile, or an amide was performed by a reaction with IF_5. Consequently, *gem*-difluoro compounds could be obtained selectively.

Key words: fluorination, desulfurization, hypervalent iodine, oxidation, sulfide

Organofluorine compounds often exhibit unique biological activities,[1] particularly, α,α-difluorocarbonyl compounds which are widely used in various areas of bioorganic and medicinal chemistry.[2] Several methods have been developed for the synthesis of α,α-difluorocarbonyl compounds, such as Pummerer-type fluorination of α-thiocarbonyl compounds,[3] electrophilic fluorination of carbonyl compounds,[2b,4] deoxyfluorination of α-ketocarbonyl compounds,[5] and building-block methods.[6] Pummerer-type difluorination of α-thiocarbonyl compounds proceeds under mild conditions. However, the removal of the thio group from the products is difficult. The deoxyfluorination reaction of α-ketocarbonyl compounds with (diethylamino)sulfur trifluoride (DAST) or Deoxofluor has been frequently used for the synthesis of α,α-difluorocarbonyl compounds. However, when this method is applied to the reaction with α-diketones for the synthesis of α,α-difluoroketones, it is difficult to distinguish the two carbonyl groups in the substrate, and undesired side reactions can occur, such as the polyfluorination reaction.[5c,d]

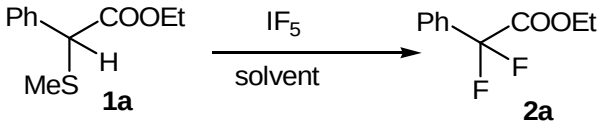
Previously, we reported the novel polyfluorination reaction of aryl alkyl sulfides using IF_5 with concomitant migration of the arylthio group.[7] During the study of fluorination of the sulfides using IF_5, we found that in the reaction of benzyl sulfides **1** with IF_5, a Pummerer-type fluorination and a desulfurizing fluorination reaction occur successively to give *gem*-difluoro compounds **2** selectively (Scheme 1).



Scheme 1

The reaction of ethyl 2-methylthio-2-phenyl acetate **1a** with IF_5 was examined (Table 1). The desulfurizing difluorination reaction of **1a** proceeds at 0 °C–room temperature in hexane or CH_2Cl_2, and ethyl 2,2-difluoro-2-phenylacetate **2a** was obtained selectively. On the other hand, the reaction is slower in polar solvents, such as DMF or THF, and even after 18 h, **1a** remained unchanged.

Table 1 Solvent Effect in a Desulfurizing Difluorination Reaction[a]



Solvent	React. time	Temp. °C	Yield (%)[b]
CH_2Cl_2	2	0	66
hexane	2	0	61
hexane	2	rt	73
THF	18	rt	0
MeCN	18	rt	trace

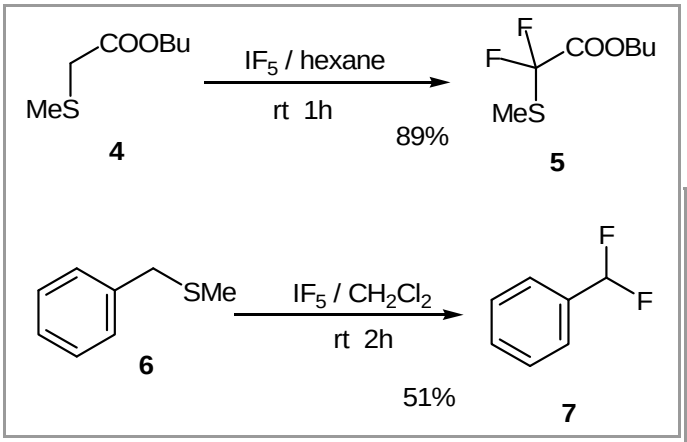
[a] 1.5 eq of IF_5 to **1a** was used. [b]Isolated yield based on **1a**

The present desulfurizing difluorination reaction is applicable to various benzyl sulfides (Table 2). The desulfurization reaction occurs not only in alkyl sulfides (Entries 1-4 and 6-8) but also in aryl sulfides (Entries 5 and 9). As aryl substituents, 1-naphthyl (Entry 6) and bromophenyl group (Entry 7) as well as phenyl group are effective in inducing the desulfurizing difluorination reaction. From the substrates with a functional group such as an ester (Entries 1, 6, and 7), ketone (Entries 2, 4, 5, and 8), nitrile (Entry 3), and amide (Entry 9), the corresponding *gem*-difluoro compounds (**2a-h)** could be obtained in good yields.

Both the Pummerer-type fluorination[3,8] and desulfurizing fluorination[8,9] of the sulfide are well known, but the desulfurizing difluorination reaction is rare.[10] Consequently, two fluorine atoms can be introduced into the benzyl position, substituting for one sulfur group and one hydrogen atom.

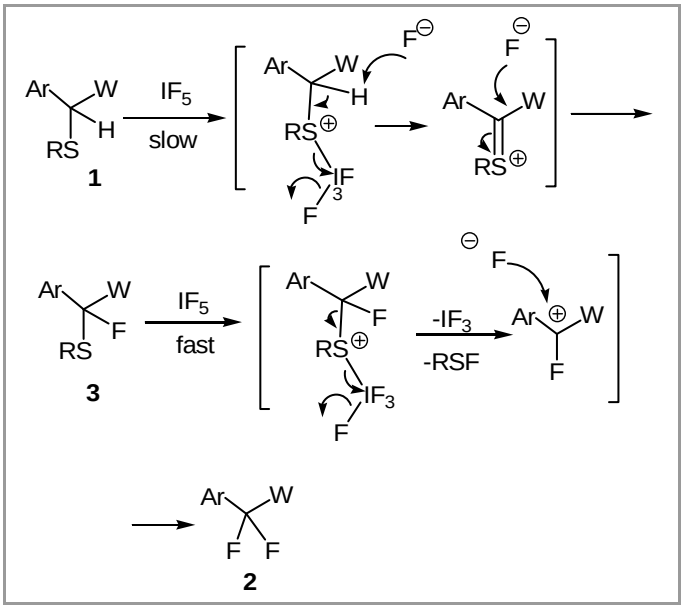
For the desulfurizing difluorination reaction, the presence of an aryl group is critical. When butyl 2-methylthioacetate **4** was subjected to reaction with IF_5, the Pummerer-type difluorination reaction occurs without desulfurization to give butyl α,α-difluoro-α-(methylthio)acetate **5** selectively. The aryl group must be stabilizing a carbocation generated by the elimination of the sulfur group and accelerating the desulfurizing fluorination step.[10] On the other hand, the presence of an electron-withdrawing group is not critical. When methyl benzyl sulfide **6** was used for the reaction

with IF_5, desulfurizing difluorination reaction occured to give (difluoromethyl)benzene **7** (Scheme 2).



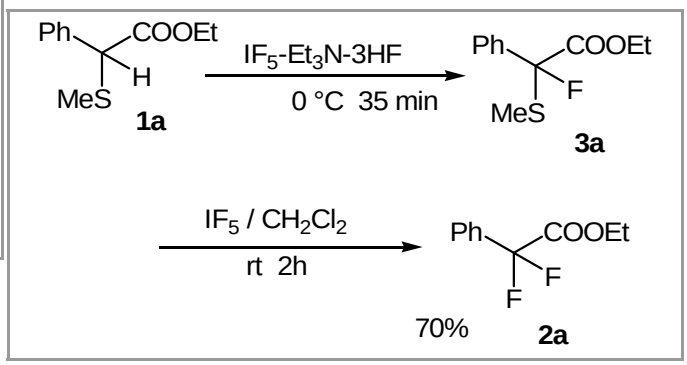
Scheme 2

The reaction possibly proceeds as follows: (1) a fluorine atom is introduced at the α-position of the sulfur group via the Pummerer-type fluorination reaction to give a mono-fluoro sulfide **3**. (2) Desulfurizing fluorination occurs to give a difluoro compound **2**. We tried to find the mono-fluorinated sulfide **3** in the reaction mixture, but failed. The second step, the desulfurizing-fluorination step, must be rapid under the conditions and it is difficult to find **3** (Scheme 3).



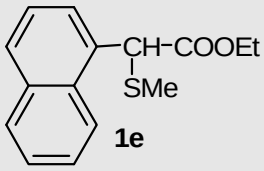
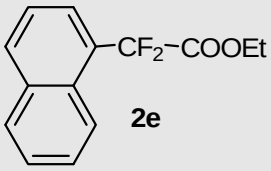
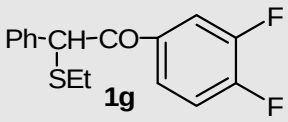
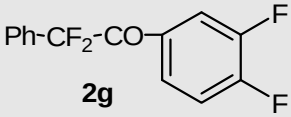
Scheme 3

In order to confirm the reaction mechanism, mono-fluorinated intermediate **3a** was prepared by the other method. Previously, we reported the oxidative fluorination of the sulfides using IF_5-Et_3N-3HF which did not cause the desulfurizing reaction.[3c] When **1a** was subjected to a reaction with IF_5-Et_3N-3HF at 0 °C for 35 min, the consumption of **1a** and formation of a new product could be confirmed by GC. After work up, ^{19}F NMR analysis of the crude mixture showed the formation of **3a** (-140.19 ppm)[10a] and the absence of **2a** (-104.5 ppm). From the crude **3a**, **2a** was obtained in 70% yield by the reaction with IF_5. This result supports the view that the present desulfurizing difluorination reaction proceeds through the intermediate **3**, which was formed by the Pummerer-type fluorination reaction of **1** (Scheme 4).



Scheme 4

Table 2 Desulfurizing Difluorination of Various Benzyl Sulfides with IF_5[a]

Entry	1	Solvent	React time (h)	Product	Yield(%)[b]
1	Ph–CH(MeS)–COOEt **1a**	hexane	2	Ph-CF_2–COOEt **2a**	73
2	Ph-CH(MeS)–COMe **1b**	hexane	2	Ph-CF_2–COMe **2b**	(81)
3	Ph-CH(MeS)-CN **1c**	hexane	2	Ph-CF_2–CN **2c**	(71)
4	Ph–CH(MeS)–COPh **1d**	CH_2Cl_2	0.75	Ph–CF_2–COPh **2d**	85
5[c]	Ph-CH(*p*-ClC_6H_4S)-COPh **1d'**	CH_2Cl_2	1	**2d**	73
6[d]	 **1e**	CH_2Cl_2	0.5	 **2e**	70
7	Br-C_6H_4-CH(MeS)-COOEt **1f** *o*:*p* = 1:4	hexane	5	Br-C_6H_4-CF_2-COOEt **2f** *o*:*p* = 1:4	74
8	 **1g**	CH_2Cl_2	0.4	 **2g**	76
9	Ph–CH(PhS)–$CONEt_2$ **1h**	CH_2Cl_2	1	Ph-CF_2–$CONEt_2$ **2h**	78

[a]If otherwise not mentioned, the reaction was carried out at room temperature using 1.5 eq of IF_5. [b]Isolated yields based on substrate used. In paretheses, NMR yields. [c]The reaction was carried out at 0 °C. [d]The reaction was carried out at -20 °C.

Synthesis of ethyl 2,2-difluoro-2-phenylacetate (2a): To a IF_5-5CH_2Cl_2 (0.975g, 1.5 mmol) in a Teflon™ PFA bottle, a hexane solution (4 mL) of ethyl 2-methylthio-2-phenylacetate (**1a**) (210 mg, 1.0 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 2 h. Then, the mixture was poured into aqueous $NaHCO_3$ and extracted with ether three times. The combined organic phase was washed with aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. Purification by column chlomatography (silica gel / hexane-ether) gave **2a** (144 mg) in 72% yield. liquid; IR (liquid film): 2987, 1763, 1267, 1104 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 7.44–7.52 (m, 3H), 7.61 (d, *J* = 7.3 Hz, 2H); ^{19}F NMR (376MHz, $CDCl_3$): δ –104.49 (s, 2F) (lit[5a] –103.9); ^{13}C NMR (100MHz, $CDCl_3$): δ 13.82, 63.09, 113.36 (t, $^1J_{c\text{-}F}$ = 252.9 Hz), 125.41 (t, $^3J_{c\text{-}F}$ = 6.7 Hz, 2C), 128.61, 130.96 (t, $^4J_{c\text{-}F}$ = 1.9 Hz, 2C), 132.81 (t, $^2J_{c\text{-}F}$ = 25.9 Hz), 164.21 (t, $^2J_{c\text{-}F}$ = 35.5 Hz); HRMS(EI) Calculated for $C_{10}H_{10}F_2O_2$: (M^+) 200.0649. Found: 200.0645.

2,2-Difluoro-1,2-diphenylethanone (2d): liquid; IR (liquid film): 1703, 1450, 1256, 1135 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.43–7.61 (m, 8H), 8.02–8.04 (m, 2H); ^{19}F NMR (376MHz, $CDCl_3$): δ –98.12 (s, 2F) {lit[11] –98.0 (s, 2F)}; ^{13}C NMR (100MHz, $CDCl_3$): δ 116.88 (t, $^1J_{c\text{-}F}$ = 253.9 Hz), 125.59 (t, $^3J_{c\text{-}F}$ = 5.8 Hz, 2C), 128.62 (2C), 128.81 (2C), 130.25 (t, $^4J_{c\text{-}F}$ = 2.9 Hz, 2C), 130.91, 132.10, 133.08 (t, $^2J_{c\text{-}F}$ = 24.9 Hz), 134.20, 188.94 (t, $^2J_{c\text{-}F}$ = 30.7 Hz); HRMS(EI) Calculated for $C_{14}H_{10}F_2O$: (M^+) 232.0700. Found: 232.0683.

Ethyl bromophenyl-2,2-difluoroacetate (a mixture of *o*- and *p*-isomers, ratio; *o:p* = 1 : 4) (2f): liquid; IR (liquid film): 1767, 1267, 1105 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.3 Hz, 2.4 H), 1.33 (t, *J* = 7.4 Hz, 0.6 H), 4.30 (q, *J* = 7.2 Hz, 1.6 H), 4.36 (q, *J* = 7.2 Hz, 0.4 H), 7.34–7.75 (m, 0.8 H), 7.48 (d, *J* = 8.4 Hz, 1.6 H), 7.60 (d, *J* = 8.5 Hz, 1.6 H); ^{19}F NMR (376MHz, $CDCl_3$): δ –102.51 (s, 0.4 F), –104.73 (s, 1.6 F); ^{13}C NMR (ortho) (100MHz, $CDCl_3$): δ 13.66, 63.28, 112.68 (t, $^{1}J_{c\text{-}F}$ = 253.0 Hz), 120.24 (t, $^{3}J_{c\text{-}F}$ = 4.8 Hz), 125.59 (t, $^{4}J_{c\text{-}F}$ = 1.9 Hz), 127.35, 127.58 (t, $^{3}J_{c\text{-}F}$ = 8.6 Hz), 132.11, 132.74 (t, $^{2}J_{c\text{-}F}$ = 24.0 Hz), 162.92 (t, $^{2}J_{c\text{-}F}$ = 34.5 Hz); ^{13}C NMR (para) (100MHz, $CDCl_3$): δ 13.71, 63.23, 112.92 (t, $^{1}J_{c\text{-}F}$ = 252.6 Hz), 127.11 (t, $^{3}J_{c\text{-}F}$ = 5.8 Hz, 2C), 131.74 (t, $^{2}J_{c\text{-}F}$ = 26.8 Hz), 131.85 (2C), 133.93, 163.63 (t, $^{2}J_{c\text{-}F}$ = 35.5 Hz); HRMS(EI) Calculated for $C_{10}H_9BrF_2O_2$: (M^+) 277.9754. Found: 277.9757.

1-(3,4-Difluorophenyl)-2,2-difluoro-2-phenylethanone (2g): liquid; IR (liquid film): 1713, 1612, 1263 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 6.84–6.99 (m, 2H), 7.45–7.61 (m, 5H), 7.79–7.85 (m, 1H); ^{19}F NMR (376MHz, $CDCl_3$): δ –100.12 to –100.22 (m, 1F), –100.61 (d, *J* = 14.0 Hz, 2F), –102.62 to –102.75 (m, 1F); ^{13}C NMR (100MHz, $CDCl_3$): δ 105.17 (t, $^{2}J_{c\text{-}F}$ = 25.9 Hz), 111.95 (dd, $^{2}J_{c\text{-}F}$ = 22.0, $^{3}J_{c\text{-}F}$ = 3.8 Hz), 116.10 (t, $^{1}J_{c\text{-}F}$ = 253.9 Hz), 118.73 (dd, $^{2}J_{c\text{-}F}$ = 12.5, $^{3}J_{c\text{-}F}$ = 3.8 Hz), 125.78 (t, $^{3}J_{c\text{-}F}$ = 6.5 Hz, 2C), 128.66, 130.98 (t, $^{4}J_{c\text{-}F}$ = 1.9 Hz, 2C), 132.00 (t, $^{2}J_{c\text{-}F}$ = 25.2 Hz), 132.96–133.16 (m), 162.24 (dd, $^{1}J_{c\text{-}F}$ = 264.4, $^{2}J_{c\text{-}F}$ = 12.5 Hz), 166.15 (dd, $^{1}J_{c\text{-}F}$ = 259.7, $^{2}J_{c\text{-}F}$ = 12.5 Hz), 187.52 (td, $^{2}J_{c\text{-}F}$ = 34.0, $^{4}J_{c\text{-}F}$ = 2.9 Hz); HRMS(EI) Calculated for $C_{14}H_8F_4O$: (M^+) 268.0511. Found: 268.0518.

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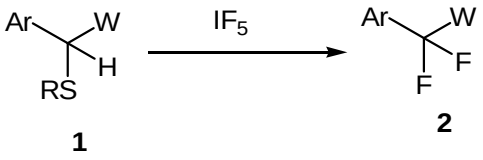

1 **2**

W = COOR', COR', CN, $CONR'_2$