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<td>Author(s)</td>
<td>Fukuhara, Tadahito; Hara, Shoji</td>
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<tr>
<td>Citation</td>
<td>Synlett, 2009(2): 198-200</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2009-01-22</td>
</tr>
<tr>
<td>Doc URL</td>
<td><a href="http://hdl.handle.net/2115/42569">http://hdl.handle.net/2115/42569</a></td>
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<tr>
<td>Rights</td>
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<td>Type</td>
<td>article (author version)</td>
</tr>
<tr>
<td>File Information</td>
<td>hara-108.pdf</td>
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Desulfurizing Difluorination Reaction of Benzyl Sulfides Using IF$_5$

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Received: The date will be inserted once the manuscript is accepted.

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, particularly, α,α-difluorocarbonyl compounds which are widely used in various areas of bioorganic and medicinal chemistry. Several methods have been developed for the synthesis of α,α-difluorocarbonyl compounds, such as Pummerer-type fluorination of α-thiocarbonyl compounds, electrophilic fluorination of carbonyl compounds, deoxyfluorination of α-ketocarbonyl compounds, and building-block methods. 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.

Previously, we reported the novel polyfluorination reaction of aryl alkyl sulfides using IF$_5$ with concomitant migration of the arylthio group. 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](image)

The reaction of ethyl 2-methylthio-2-phenyl acetate 1a with IF$_5$ was examined (Table 1). The desulfurizing fluorination reaction of 1a proceeds at 0 °C–room temperature in hexane or CH$_2$Cl$_2$, 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

<table>
<thead>
<tr>
<th>Solvent</th>
<th>React. time</th>
<th>Temp. °C</th>
<th>Yield (%)$^b$</th>
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</thead>
<tbody>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>hexane</td>
<td>2</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>hexane</td>
<td>2</td>
<td>rt</td>
<td>73</td>
</tr>
<tr>
<td>THF</td>
<td>18</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>MeCN</td>
<td>18</td>
<td>rt</td>
<td>trace</td>
</tr>
</tbody>
</table>

$^a$ 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 and desulfurizing fluorination of the sulfide are well known, but the desulfurizing fluorination reaction is rare. Consequently, two fluorine atoms can be introduced into the benzyl position, substituting for one sulfur group and one hydrogen atom.

For the desulfurizing fluorination 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. 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 IF₅, desulfurizing difluorination reaction occurred to give (difluoromethyl)benzene 7 (Scheme 2).

\[
\begin{align*}
\text{COOBu} & \quad \text{MeS} \quad \text{IF₅ / hexane} \quad \text{rt 1h} \quad \text{COOBu} \\
4 & \quad 5 \\
\text{Ph} & \quad \text{SMe} \quad \text{IF₅ / CH₂Cl₂} \quad \text{rt 2h} \quad \text{Ph} \\
6 & \quad 7 \\
\end{align*}
\]

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).

\[
\begin{align*}
\text{Ar} & \quad \text{W} \quad \text{IF₅} \quad \text{slow} \quad \left[ \begin{array}{c}
\text{Ar} \quad \text{W} \quad \text{H} \\
\text{RS} \quad \text{Ar} \quad \text{W} \quad \text{H} \\
\end{array} \right] \\
1 & \quad \underset{\text{fast}}{\text{IF₅}} \\
\text{Ar} & \quad \text{W} \quad \text{F} \quad \text{IF₅} \\
3 & \quad \text{2} \\
\end{align*}
\]

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 IF₅-Et₃N-3HF which did not cause the desulfurizing reaction. When 1a was subjected to a reaction with IF₅-Et₃N-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, ¹⁹F NMR analysis of the crude mixture showed the formation of 3a (-140.19 ppm) and the absence of 2a (-104.5 ppm). From the crude 3a, 2a was obtained in 70% yield by the reaction with IF₅. 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).

\[
\begin{align*}
\text{Ph} & \quad \text{COOEt} \quad \text{MeS} \quad \text{IF₅-Et₃N-3HF} \quad 0 °C \quad 35 \min \\
1a & \quad 3a \\
\text{IF₅ / CH₂Cl₂} \quad \text{rt 2h} \quad \text{Ph} & \quad \text{COOEt} \\
3a & \quad 2a \\
\end{align*}
\]

Scheme 4
Table 2 Desulfurizing Difluorination of Various Benzyl Sulfides with IF$_5$$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>Solvent</th>
<th>React time (h)</th>
<th>Product</th>
<th>Yield(%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph–CH–COOEt MeS 1a</td>
<td>hexane</td>
<td>2</td>
<td>Ph–CF$_2$–COOEt 2a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Ph–CH–COMe MeS 1b</td>
<td>hexane</td>
<td>2</td>
<td>Ph–CF$_2$–COMe 2b</td>
<td>(81)</td>
</tr>
<tr>
<td>3</td>
<td>Ph–CH–CN MeS 1c</td>
<td>hexane</td>
<td>2</td>
<td>Ph–CF$_2$–CN 2c</td>
<td>(71)</td>
</tr>
<tr>
<td>4</td>
<td>Ph–CH–COPh MeS 1d</td>
<td>CH$_2$Cl$_2$</td>
<td>0.75</td>
<td>Ph–CF$_2$–COPh 2d</td>
<td>85</td>
</tr>
<tr>
<td>5c</td>
<td>Ph–CH–COPh p-ClC$_6$H$_4$S 1d'</td>
<td>CH$_2$Cl$_2$</td>
<td>1</td>
<td>2d</td>
<td>73</td>
</tr>
<tr>
<td>6d</td>
<td>CH–COOEt SMe 1e</td>
<td>CH$_2$Cl$_2$</td>
<td>0.5</td>
<td>2e</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Br–C$_6$H$_4$–CH–COOEt MeS 1f</td>
<td>hexane</td>
<td>5</td>
<td>Br–C$_6$H$_4$–CF$_2$–COOEt 2f</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>Ph–CH–CO–SEt PhS 1g</td>
<td>CH$_2$Cl$_2$</td>
<td>0.4</td>
<td>2g</td>
<td>76</td>
</tr>
<tr>
<td>9</td>
<td>Ph–CH–CONEt$_2$ PhS 1h</td>
<td>CH$_2$Cl$_2$</td>
<td>1</td>
<td>2h</td>
<td>78</td>
</tr>
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</table>

$^a$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$_2$Cl$_2$ (0.975g, 1.5 mmol) in a Teflon$^{TM}$ 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$_2$S$_2$O$_3$ and dried over MgSO$_4$. Purification by column chromatography (silica gel / hexane-ether) gave 2a (144 mg) in 72% yield. liquid; IR (liquid film): 2987, 1763, 1267, 1104 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ –104.49 (s, 2F) (lit$^{1a}$ –103.9); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 13.82, 63.09, 113.36 (t, $^1J_{c-F} = 252.9$ Hz), 125.41 (t, $^2J_{c-F} = 6.7$ Hz, 2C), 128.61, 130.96 (t, $^3J_{c-F} = 1.9$ Hz, 2C), 132.81 (t, $^4J_{c-F} = 25.9$ Hz), 164.21 (t, $^5J_{c-F} = 35.5$ Hz); HRMS(EI) Calculated for C$_{10}$H$_{10}$F$_2$O$_2$: (M$^+$) 200.0649. Found: 200.0649.

2,2-Difluoro-1,2-diphenylethanone (2d): liquid; IR (liquid film): 1703, 1450, 1256, 1135 cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 7.43–7.61 (m, 8H), 8.02–8.04 (m, 2H); $^{19}$F NMR (376MHz, CDCl$_3$): $\delta$ –98.12 (s, 2F) {lit$^{11}$ –98.0 (s, 2F)}; $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 116.88 (t, $^1J_{c-F} = 253.9$ Hz), 125.59 (t, $^2J_{c-F} = 5.8$ Hz, 2C), 128.62 (2C), 128.81 (2C), 130.25 (t, $^4J_{c-F} = 2.9$ Hz, 2C), 130.91, 132.10, 133.08 (t, $^2J_{c-F} = 30.7$ Hz); HRMS(EI) Calculated for C$_{14}$H$_{10}$F$_2$O: (M$^+$) 232.0670. Found: 232.0683.
Ethyl bromophenyl-2,2-difluoroacetate (a mixture of o- and p-isomers; ratio: 1 : 4) (2f): liquid; IR (liquid film): 1767, 1267, 1105 cm⁻¹; ¹H NMR (400MHz, CDCl₃): 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); ¹⁹F NMR (376MHz, CDCl₃): δ -102.51 (s, 0.4 F), -104.73 (s, 1.6 F); ¹³C NMR (ortho) (100MHz, CDCl₃): δ 13.66, 63.28, 112.68 (t, J_CF = 253.0 Hz), 120.24 (t, J_CF = 4.8 Hz), 125.59 (t, J_CF = 1.9 Hz), 127.35, 127.58 (t, J_CF = 8.6 Hz), 132.11, 132.74 (t, J_CF = 24.0 Hz), 162.92 (t, J_CF = 34.5 Hz); ¹³C NMR (para) (100MHz, CDCl₃): δ 13.71, 63.23, 112.92 (t, J_CF = 252.6 Hz), 127.11 (t, J_CF = 5.8 Hz, 2C), 131.74 (t, J_CF = 26.8 Hz), 131.85 (2C), 133.93, 163.63 (t, J_CF = 35.5 Hz); HRMS(EI) Calculated for C₁₂H₁₂BrF₂O₂: (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; ¹H NMR (400MHz, CDCl₃): δ 6.84–6.99 (m, 2H), 7.45–7.61 (m, 5H), 7.79–7.85 (m, 1H); ¹⁹F NMR (376MHz, CDCl₃): δ -100.12 to -100.22 (m, 1F), -100.61 (d, J = 14.0 Hz, 2F), -102.62 to -102.75 (m, 1F); ¹³C NMR (100MHz, CDCl₃): δ 105.17 (t, J_CF = 25.9 Hz), 111.95 (dd, 2_J_CF = 22.0, 3_J_CF = 3.8 Hz), 116.10 (t, 4_J_CF = 253.9 Hz), 118.73 (dd, 2_J_CF = 12.5, 3_J_CF = 3.8 Hz), 125.78 (t, 5_J_CF = 6.5 Hz, 2C), 128.66, 130.98 (t, 4_J_CF = 1.9 Hz, 2C), 132.00 (t, 3_J_CF = 25.2 Hz), 132.96–133.16 (m), 162.24 (dd, J_CF = 264.4, 3_J_CF = 12.5 Hz), 166.15 (dd, 2_J_CF = 259.7, 3_J_CF = 12.5 Hz), 187.52 (td, 5_J_CF = 34.0, 4_J_CF = 2.9 Hz); HRMS(EI) Calculated for C₁₄H₁₄F₂O: (M⁺) 268.0511. Found: 268.0518.

Acknowledgment

We are grateful to Asahi Glass Co., Ltd. for their gift of IF₃.

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Desulfurizing Difluorination Reaction of Benzyl Sulfides Using IF$_5$

$$\text{Ar}_W \text{RS} \xrightarrow{\text{IF}_5} \text{Ar}_W \text{HF}_2$$

$W = \text{COOR}', \text{COR}', \text{CN}, \text{CONR}_2'$