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IF5–pyridine–HF: air- and moisture-stable fluorination reagent

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IF$_5$-pyridine-HF: air- and moisture-stable fluorination reagent

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ABSTRACT : IF$_5$-pyridine-HF, an air- and moisture-stable solid, can be used as a fluorination reagent for the introduction of fluorine atoms to the $\alpha$-position of the sulfur atom in sulfides. The desulfurizing-fluorination reactions of benzylic sulfides, thioacetals, and 2-(methylthio)-1,3-dithiane derivatives were also performed using this reagent.

Keywords: IF$_5$-pyridine-HF, air- and moisture-stable solid, fluorination reagent, desulfurizing-fluorination

1. Introduction

Organofluorine compounds are widely used, as medicines, pesticides, functional materials, and so on. They are generally prepared artificially by using fluorination reagents because organofluorine compounds are rare in nature. Therefore, the role of the fluorination reagent is important for making the desired organofluorine compounds, and many fluorination reagents have been produced and used. However, most of them are sensitive to air and moisture, and special skills and equipments are required for their use. Therefore, more stable fluorination reagents that can be used without such skills and equipments are desired. We previously reported fluorination reactions using IF$_5$ for the selective introduction of fluorine atoms to a substrate. However, IF$_5$ is also unstable in air and decomposes, generating HF. During our continuous study of fluorination reactions using IF$_5$, we found that upon mixing IF$_5$ with pyridine-HF (HF 50 mol% pyridine 50 mol%), an air-stable white solid was formed. Herein, we report the fluorination reactions using this stable fluorination reagent, IF$_5$-pyridine-HF.

2. Results and discussion

Initially, we compared the reactivity of IF$_5$-pyridine-HF with that of IF$_5$. In the reaction of IF$_5$ with ethyl 2-(arylthio)propionate 1, a poly-fluorination reaction took place with the migration of an arylthio group to give ethyl 3-(arylthio)-2,2,3-trifluoropropionate 2 selectively. On the other hand, when 1 was added to a suspension of IF$_5$-pyridine-HF in CH$_2$Cl$_2$, the color of the mixture changed to dark red, and
mono-fluorination occurred at the $\alpha$-position of the sulfur group, giving ethyl 2-(arylthio)-2-fluoropropionate 3. Under these conditions, 2 was not formed at all (Scheme 1).

![Chemical structure](image)

**Scheme 1.** Reactivity of IF$_5$-pyridine-HF in fluorination of sulfide 1

In the reaction of decyl 2-arylthioacetate 4 with two equivalents of IF$_5$-pyridine-HF, the mono-fluorinated product was obtained in 63% yield, with a 17% yield of the difluorinated product 5; it was difficult to obtain the mono-fluorinated product selectively. On the other hand, when four equivalents of IF$_5$-pyridine-HF were used, 5 was formed selectively in 54% yield, and the yield of the mono-fluorinated product was only 3%. From 2-(arylthio)cyclohexanone 6, the mono-fluorinated product 7 was obtained in 76% yield, as shown in Table 1.

| Table 1. Fluorination of $\alpha$-(arylthio)carbonyl compounds using IF$_5$-pyridine-HF$^a$ |
|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Substrate                        | IF$_5$-pyridine-HF/substrate      | Product                           | Yield %$^b$                      |
|                                  |                                  |                                  |                                  |
| ![Chemical structure](image)     | 4.0                               | ![Chemical structure](image)     | 54$^c$                           |
|                                  | ![Chemical structure](image)     | ![Chemical structure](image)     |                                  |
| ![Chemical structure](image)     | 2.0                               | ![Chemical structure](image)     | 76                               |

$^a$ The reaction was carried out in CH$_2$Cl$_2$ at room temperature for 24 h, Ar = p-Cl-C$_6$H$_4$.

$^b$ Isolation yield based on substrate.

$^c$ Mono-fluorinated product was also formed in 3% yield.
The desulfurizing-difluorination reaction of benzylic sulfide is one of the typical reactions of IF$_5$.\textsuperscript{4e} When 2-(arylthio)-1,2-diphenylethanone 8 was subjected to the reaction with IF$_5$ at 0 °C for 5 h, the desulfurizing-difluorination reaction took place to give 2,2-difluoro-1,2-diphenylethanone 9 exclusively. On the other hand, in the reaction of IF$_5$-pyridine-HF with 8 under the same conditions, the yield of 9 was only 5\% and formation of a new fluorine compound was observed. From chemical shift in $^{19}$F NMR spectra, the new compound was estimated to be mono-fluorinated compound 10\textsuperscript{6} and its yield was 63\%. In the desulfurizing-difluorination reaction of 8, 10 was formed initially as a precursor of 9.\textsuperscript{4e} Therefore, in the reaction of 8 with IF$_5$-pyridine-HF, the desulfurizing-difluorination was not yet completed under these conditions, and the reactivity of IF$_5$-pyridine-HF was found to be lower than that of IF$_5$ (Scheme 2).

![Scheme 2](image)

**Scheme 2.** Reactivity of IF$_5$-pyridine-HF in desulfurizing-difluorination reaction of 8

Although the desulfurizing-difluorination reaction of 8 with IF$_5$-pyridine-HF was slow at 0 °C, the reaction was completed at room temperature in 5 h, and 9 was obtained in 88\% yield (Entry 1 in Table 2). Similarly, the reactions of various benzylic sulfides (11, 13, 15, and 17) with IF$_5$-pyridine-HF proceeded at room temperature or at 40 °C to give the corresponding desulfurizing-difluorination products (12, 14, 16, and 18) in good yields.

**Table 2.** Desulfurizing-difluorination of benzylic sulfides using IF$_5$-pyridine-HF\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Yield %\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>rt, 5 h</td>
<td>9</td>
<td>88</td>
</tr>
</tbody>
</table>
The conversion of carbonyl dithioacetal to *gem*-difluoride is commonly used to introduce fluorine atoms selectively at desired positions in the molecules; many fluorination reagents have been used for this conversion. Therefore, we applied IF$_5$-pyridine-HF to the reaction with the carbonyl dithioacetal. The reactions of various 1-naphthaldehyde dithioacetals with IF$_5$-pyridine-HF were examined. When the 1,3-dithiolane derivative was used, the desired *gem*-difluoride was obtained in 57% yield, and 1-naphthaldehyde was also formed in 10% yield (Entry 1 in Table 3). Similar results were obtained with the 1,3-dithiane derivative and bis(hexylthio)methane derivative (Entries 2 and 3). However, when the bis(phenylthio)methane derivative was used, the *gem*-difluoride was obtained in the highest yield of 74% (Entry 4).

Table 3. The Reaction of naphthaldehyde dithioacetals with IF$_5$-pyridine-HF$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt, 24 h</td>
<td>89$^c$</td>
<td><img src="image1" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td>rt, 5 h</td>
<td>79</td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td>40 °C, 24 h</td>
<td>98$^d$</td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td>40 °C, 24 h</td>
<td>(99)$^d$</td>
<td><img src="image4" alt="Image" /></td>
</tr>
</tbody>
</table>

$^a$ If otherwise not mentioned, the reaction was carried out in CH$_2$Cl$_2$ using 2 eq of IF$_5$-pyridine-HF.

$^b$ Isolation yield based on substrate, in parenthesis, $^{19}$F NMR yield.

$^c$ 1.5 eq of IF$_5$-pyridine-HF was used.

$^d$ 3 eq of IF$_5$-pyridine-HF was used.
From various bis(phenylthio)acetals of aromatic aldehydes and ketones, the corresponding gem-difluorides were obtained in good yields. A dithioacetal of an aliphatic ketone, such as adamantone, is also applicable to this reaction, and 2,2-difluoroadamantane 32 was obtained (Entry 7 in Table 4). However, in the reaction with the bis(phenylthio)acetal of acetophenone, which has protons at the $\alpha$-position of the carbonyl group, the desired gem-difluoride was not obtained, but a complex mixture was formed.

**Table 4.** The reaction of aldehyde and ketone dithioacetals with IF$_5$-pyridine-HF$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>75</td>
</tr>
</tbody>
</table>

$^a$ The reaction was carried out in CH$_2$Cl$_2$ using 2 eq of IF$_5$-pyridine-HF.  
$^b$ Isolation yield based on dithioacetal used.
The introduction of the trifluoromethyl group to an aromatic ring is an important reaction, and many methods for this have been reported.\textsuperscript{11} We planned to make a trifluoromethyl compound by the reaction of the 2-methylthio-1,3-dithiane derivative 34 with IF$_5$-pyridine-HF. The starting compound 34 was prepared from the 1,3-dithiane derivative 33 of an aromatic aldehyde by metatation with BuLi, followed by reaction with dimethyl disulfide.\textsuperscript{12} The reaction of the 2-(methylthio)-1,3-dithiane derivative of 1-naphthaldehyde 34a with IF$_5$-pyridine-HF was completed at room temperature in 12 h, and 1-trifluoromethylnaphthalene 35a was obtained in 78% yield.\textsuperscript{13} When an electron-donating group was attached to the aromatic ring (34e), the reaction with IF$_5$-pyridine-HF was fast and the reaction was completed in a shorter time. On the other hand, when an electron-withdrawing group was attached (34c), the reaction was slower and a higher temperature (40 °C) was required to obtain the trifluoromethyl product 35c, as shown in Table 5. The application of the present method to an aliphatic aldehyde was not successful and the corresponding trifluoromethyl derivative was not formed by the reaction of the 2-(methylthio)-1,3-dithiane derivative of the aliphatic aldehyde with IF$_5$-pyridine-HF.
Table 5. Conversion of aldehyde thioacetal to trifluoromethyl group

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield of 34, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reaction condition</th>
<th>Yield of 35, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure" /> 33a</td>
<td>87</td>
<td>rt, 12 h</td>
<td>78</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /> 33b</td>
<td>92</td>
<td>rt, 24 h</td>
<td>83</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /> 33c</td>
<td>61&lt;sup&gt;c&lt;/sup&gt;</td>
<td>40 C, 48 h</td>
<td>54</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /> 33d</td>
<td>61</td>
<td>rt, 24 h</td>
<td>62</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /> 33e</td>
<td>71</td>
<td>rt, 7 h</td>
<td>60</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield based on thioacetal 33.

<sup>b</sup> Isolated yield based on thioorthoformate 34. 3 eq of IF<sub>5</sub>-pyridine-HF to 34 was used.

<sup>c</sup> LDA was used as a base instead of BuLi.

3. Conclusion

IF<sub>5</sub>-pyridine-HF, prepared by mixing IF<sub>5</sub> with pyridine-HF, is an air- and moisture-stable white solid. Although its reactivity is lower than that of IF<sub>5</sub>, it can be used safely for fluorination reactions such as the introduction of one or two fluorine atoms to the α-position of the sulfur atom in sulfides, and the
introduction of two or three fluorine atoms by the desulfurizing-fluorination reaction of benzylic sulfides, thioacets, and 2-(methylthio)-1,3-dithiane derivatives.

4. Experimental section

General Methods. The melting points were measured with a Yanagimoto micro melting-point apparatus. The IR spectra were recorded using a JASCO FT/IR-410. The $^1$H NMR (400 MHz) spectra, $^{19}$F NMR (376 MHz) spectra, and $^{13}$C NMR (100 MHz) were recorded in CDCl$_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, $\delta$, is referred to TMS ($^1$H, $^{13}$C) and CFCl$_3$ ($^{19}$F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. IF$_5$ in a cylinder was supplied by Asahi Glass Co., Ltd. Although IF$_5$-pyridine-HF can be handled in air without special care, IF$_5$ is hygroscopic and decomposes in air. Therefore, when IF$_5$-pyridine-HF is prepared, IF$_5$ should be handled in bench hood with rubber gloved hands. The reaction using IF$_5$-pyridine-HF was performed in a Teflon™ FEP centrifuge tube with a tight screw cap or a reactor made of polyethylene. Silicate glassware is slightly damaged by it.

Preparation of pyridine-HF (HF 50 mol% pyridine 50 mol%). Pyridine-HF was prepared by the addition of freshly distilled pyridine to an equimolar amount of anhydrous HF at 0 °C. As it is highly exothermal, slow and careful addition of pyridine is required. More conveniently, it can be prepared by dilution of commercial pyridine-HF (HF 70w% pyridine 30w%) with calculated amount of pyridine at 0 °C. It is also exothermal but milder.

Preparation of IF$_5$-pyridine-HF. From a cylinder, IF$_5$ (30g, 135 mmol) was transferred through a Teflon™ tube into a 500mL round bottomed flask made of Teflon™ PFA under an N$_2$ atmosphere. The flask was cooled with ice bath and CCl$_4$ (135 mL) was introduced. Then, pyridine-HF (13.38 g, 135 mmol) was dropwisely added at 0 °C. A white solid appeared immediately and the resulting mixture was stirred at 0 °C for 30 min and at room temperature for 2 h. The solid was separated by filtration using filter funnel made of polyethylene and filter paper made of Teflon™, washed with CCl$_4$ (150 mL X 2). The remained solvent was removed under vacuum to give 41 g of a white solid (95% yield), which can be handled in air and kept in a Teflon™ bottle. IF$_5$-pyridine-HF decompose gradually above 100 °C, and it is soluble in DMF, slightly soluble in CH$_3$CN, and insoluble in hexane; $^1$H NMR (400MHz, CD$_3$CN) $\delta$ 8.75-8.72 (m, 2H), 8.60-8.55 (m, 1H), 8.60-8.55 (m, 2H). $^{19}$F NMR (376MHz, CD$_3$CN) $\delta$ -149.17 (s).

4.1. Fluorination of sulfide with IF$_5$-pyridine-HF

4.1.1. Ethyl 2-[(4-chlorophenyl)thio]-2-fluoropropanoate (3)

To a CH$_2$Cl$_2$ solution (2 mL) of ethyl 2-[(4-chlorophenyl)thio]propanoate (1) (122 mg, 0.5 mmol) was added at room temperature IF$_5$-pyridine-HF (370 mg, 1.15 mmol), and the
mixture was stirred at room temperature for 24 h. The resulting dark red solution was poured into water (20 mL) and extracted with CH₂Cl₂ (20 mL X 3). The combined organic layer was washed with aq NaHCO₃ and aq Na₂S₂O₃, and dried over MgSO₄. After concentration under reduced pressure, 3 was isolated in 89% yield by column chromatography (silica gel/hexane-ether); IR (neat) 2985, 1754 (C=O), 1476, 1279, 1127 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.10-3.98 (m, 2H), 1.90 (d, J = 18.3 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz) δ 167.7 (d, JF-C = 30.6 Hz), 136.9 (2C), 136.3, 129.1 (2C), 127.5, 101.6 (d, JF-C = 233.7 Hz), 62.2, 24.2 (d, JF-C = 24.8 Hz), 13.8; HRMS (EI) calcd for C₁₁H₁₂ClFO₂S 262.02306, found 262.02227.

4.1.2. Decyl 2-[(4-chlorophenyl)thio]-2,2-difluoroacetate (5)

IR (neat) 2926, 2855, 1767, 1293, 1113 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 4.21 (t, J = 6.7 Hz, 2H), 1.65-1.62 (m, 2H), 1.29-1.27 (m, 14H), 0.89 (t, J = 6.7 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ −82.57 (s, 2F); ¹³C NMR (100 MHz) δ 161.5 (t, JF-C = 32.2 Hz), 137.8 (2C), 137.3, 129.5 (2C), 123.2 (t, JF-C = 2.8 Hz), 119.7 (t, JF-C = 288.0 Hz), 67.8, 31.9, 29.5, 29.4, 29.3, 29.1, 28.1, 25.5, 22.7, 14.1; HRMS (EI) calcd for C₁₈H₂₅ClF₂O₂S 378.1232, found 378.1230.

4.1.3. 2-[(4-Chlorophenyl)thio]-2-fluorocyclohexanone (7)

White solid; mp 54.5–55.5 °C. IR (KBr) 2950, 1729, 1477 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.42 (m, 2H), 7.33-7.29 (m, 2H), 2.91-2.82 (m, 1H), 2.50-2.34 (m, 2H), 2.25-1.90 (m, 4H), 1.77-1.65 (m, 1H); ¹⁹F NMR (376 MHz, CDCl₃) δ −128.13 (d, J = 12.4 Hz, 1F); ¹³C NMR (100 MHz) δ 200.3 (d, JF-C = 20.0 Hz), 136.1 (2C), 129.4 (3C), 126.4 (d, JF-C = 1.9 Hz), 105.2 (d, JF-C = 238.6 Hz), 38.9, 38.7 (d, JF-C = 20.1 Hz), 26.7, 23.1 (d, JF-C = 6.7 Hz); HRMS (EI) calcd for C₁₂H₁₂ClFOS 258.0281, found 258.0281.

4.2. Desulfurizing difluorination of a benzylic sulfide with IF₅-pyridine-HF

4.2.1. 2,2-Difluoro-1,2-diphenylethanone (9)

To a CH₂Cl₂ solution (2 mL) of the 2-[(4-chlorophenyl)thio]-1,2-diphenylethanone (8) (169 mg, 0.5 mmol) was added at room temperature IF₅-pyridine-HF (322 mg, 1 mmol). The mixture was stirred at room temperature for 5 h. The resulting dark red solution was poured into water (20 mL) and extracted with CH₂Cl₂ (20 mL X 3). The combined organic layer was washed with aq NaHCO₃ and aq Na₂S₂O₃, and dried over MgSO₄. After concentration under reduced pressure, 9 was isolated in 88% yield by column chromatography (silica gel/hexane-CH₂Cl₂); IR (neat) 1703 (C=O), 1450, 1256, 1135 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.61 (m, 8H), 8.02–8.04 (m, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ −98.12 (s, 2F) \{lit: −98.44 (s, 2F)\}; ¹³C NMR (100 MHz, CDCl₃) δ 116.88 (t, J_C-F = 253.9 Hz), 125.59 (t, J_C-F = 5.8 Hz,
When the reaction was carried out at 0 °C for 5 h, two singlet peaks appeared at -98 ppm for 9 and at -128 ppm for 10 in 19F NMR. Their yields were determined to be 5% (9) and 63% (10) by using fluorobenzene as an internal standard. During the isolation by silica gel column chromatography, 10 was decomposed and its isolation was failed.

4.2.2. Butyl 2,2-difluoro-2-phenylacetate (12)

IR (neat) 2963, 1764 (C=O), 1265, 1105 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.60 (m, 2H), 7.49-7.45 (m, 3H), 4.24 (t, J = 6.6 Hz, 2H), 1.68-1.60 (m, 2H), 1.37-1.28 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz) δ 164.3 (t, 2J₉-C = 35.7 Hz), 132.8 (t, 2J₉-C = 25.8 Hz), 130.9, 128.6 (2C), 125.4 (t, 3J₉-C = 6.2 Hz, 2C), 113.4 (t, 1J₉-C = 251.9 Hz), 66.8, 30.2, 18.9, 13.5; HRMS (EI) calcd for C₁₂H₁₄F₂O₂: (M⁺) 228.09619, found 228.09563.

4.2.3. N,N-Diethyl-2,2-difluoro-2-phenylacetamide (14)

IR (neat) 2979, 1669 (C=O), 1452, 1364, 1251, 1178, 775, 700, 642 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 7.0 Hz, 2H), 7.44-7.49 (m, 3H), 3.42 (q, J = 7.0 Hz, 2H), 3.25 (q, J = 7.2 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.0 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -104.65 (s, 2F); ¹³C NMR (100 MHz) δ 162.7 (t, 2JC-F = 29.7 Hz), 133.9 (t, 2JC-F = 23.6 Hz), 130.7 (t, 4JC-F = 1.9 Hz, 2C), 128.7, 125.1 (t, 3JC-F = 5.8 Hz, 2C), 115.5 (t, 1JC-F = 251.5 Hz), 42.0 (t, 4JC-F = 3.8 Hz), 41.4, 13.7, 12.2; HRMS (EI) calcd for C₁₂H₁₅F₂NO: 227.1122, found 227.1128.

4.2.4. 1-(Perfluoroethyl)naphthalene (16)

IR (neat) 3059, 1133 cm⁻¹; ¹H NMR δ 7.52-7.62 (m, 3H), 7.83 (d, J = 7.3 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 8.04 (J = 8.2 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H); ¹⁹F NMR δ -83.97 (s, 3F), -108.90 (s, 2F) (lit. -84.86 (s, 3F), -111.07 (s, 2F)); ¹³C NMR δ 134.1, 133.3, 129.9, 129.0, 127.6, 127.4 (t, 2JC-F = 9.5 Hz), 126.4, 124.7-124.8 (m), 124.3, 124.2 (t, 2JC-F = 21.7 Hz), 119.7 (tq, 2JC-F = 39.3 Hz, 1JC-F = 287.0 Hz), 115.3 (tq, 1JC-F = 255.3 Hz, 2JC-F = 39.4 Hz).

4.2.5. 1,4-Dimethyl-2-(perfluoroethyl)benzene (18)

IR (neat) 2931, 1207, 1187 cm⁻¹; ¹H NMR δ 7.14-7.31 (m, 3H), 2.43 (t, J = 3.0 Hz, 3H), 2.36 (s, 3H); ¹⁹F NMR δ -85.24 (s, 3F), -111.07 (s, 2F) (lit. -84.86 (s, 3F), -111.04 (s, 2F)); ¹³C NMR δ 135.8, 134.7 (t, 2JC-F = 2.2 Hz), 132.5, 132.4, 128.5 (t, 2JC-F = 8.6 Hz), 126.6 (t, 2JC-F = 21.7 Hz), 119.7 (tq, 2JC-F = 40.1 Hz, 1JC-F = 286.1), 115.0 (tq, 1JC-F = 254.2 Hz, 2JC-F = 38.2 Hz), 20.7, 19.7-19.8 (m).

4.3. Desulfurizing-fluorination of dithioacetal with IF₅-pyridine-HF
4.3.1. 1-(Difluoromethyl)naphthalene (20)

To a CH$_2$Cl$_2$ solution (1.0 mL) of naphthaldehyde diphenyl dithioacetal (19) (179 mg, 0.5 mmol) was added at room temperature IF$_3$-pyridine-HF (321 mg, 1 mmol) and the mixture was stirred at room temperature for 24h. The resulting dark red solution was poured into water (20 mL) and extracted with ether (20 mL X 3). The combined organic layer was washed with aq NaHCO$_3$ and aq Na$_2$S$_2$O$_3$, and dried over MgSO$_4$. After concentration under reduced pressure, 20 was isolated by column chromatography (silica gel/hexane-CH$_2$Cl$_2$) in 74% yield; IR (neat) 1514, 1349, 1242 cm$^{-1}$; $^1$H NMR $\delta$ 8.19-7.49 (m, 7H), 7.14 (t, $J$ = 55.8 Hz, 1H); $^{19}$F NMR $\delta$ -111.48 (d, $J$ = 56.0 Hz, 2F) (lit.$^{16}$ -111.1); $^{13}$C NMR $\delta$ 133.7, 131.5, 129.7, 129.5 (t, $^2J_{C-F}$ = 21.1 Hz), 128.7, 127.1, 126.4, 124.8 (t, $^3J_{C-F}$ = 8.6 Hz), 124.6, 123.5, 115.4 (t, $^1J_{C-F}$ = 239.5 Hz).

4.3.2. 4-(Difluoromethyl)-1,1'-biphenyl (22)

White solid. mp 71-72 °C (lit.$^{17}$ 77.0-77.5 °C); IR (KBr) 1414, 1380, 1226, 1077, 1024, 767 cm$^{-1}$; $^1$H NMR $\delta$ 7.69-7.39 (m, 9H), 6.70 (t, $J$ = 56.5 Hz, 1H); $^{19}$F NMR $\delta$ -110.98 (d, $J$ = 57.3 Hz, 2F); $^{13}$C NMR $\delta$ 143.7 (t, $^5J_{C-F}$ = 1.9 Hz), 140.2, 133.2 (t, $^2J_{C-F}$ = 22.1 Hz), 128.9 (2C), 127.9, 127.4 (2C), 127.2 (2C), 126.0 (t, $^3J_{C-F}$ = 6.2 Hz, 2C), 114.7 (t, $^1J_{C-F}$ = 238.5 Hz).

4.3.3. Methyl 4-(difluoromethyl)benzoate (24)

White solid. mp 38 °C (lit.$^{18}$ 36.5-37.0 °C); IR (KBr) 1724 (C=O), 1442, 1281 cm$^{-1}$; $^1$H NMR $\delta$ 8.13 (d, $J$ = 8.0 Hz, 2H), 7.59 (d, $J$ = 8.1 Hz, 2H), 6.70 (t, $J$ = 56.7 Hz, 1H), 3.95 (s, 3H); $^{19}$F NMR $\delta$ -112.86 (d, $J$ = 57.9 Hz, 2F); $^{13}$C NMR $\delta$ 166.2, 138.4 (t, $^2J_{C-F}$ = 22.5 Hz), 132.3 (t, $^4J_{C-F}$ = 1.9 Hz), 129.9 (2C), 125.6 (t, $^3J_{C-F}$ = 6.3 Hz, 2C), 114.0 (t, $^1J_{C-F}$ = 240.9 Hz), 52.3.

4.3.4. 4-(Difluoromethyl)benzyl acetate (26)

IR (neat) 2961, 1743 (C=O), 1380, 1227 cm$^{-1}$; $^1$H NMR $\delta$ 7.51 (d, $J$ = 8.2 Hz, 2H), 7.44 (d, $J$ = 8.1 Hz, 2H), 6.65 (t, $J$ = 57.0 Hz, 1H), 5.14 (s, 2H), 5.12 (s, 3H); $^{19}$F NMR $\delta$ -111.35 (d, $J$ = 56.0 Hz, 2F); $^{13}$C NMR $\delta$ 170.7, 138.7 (t, $^5J_{C-F}$ = 1.9 Hz), 134.2 (t, $^2J_{C-F}$ = 22.8 Hz), 128.2 (2C), 125.8 (t, $^3J_{C-F}$ = 6.2 Hz, 2C), 114.4 (t, $^1J_{C-F}$ = 240.0 Hz), 65.5, 20.8; HRMS (EI) calcd for C$_{10}$H$_{10}$F$_2$O$_2$ 200.06489, found 200.06395.

4.3.5. Difluorodiphenylmethane (28)

IR (neat) 1453, 1274, 1223 cm$^{-1}$; $^1$H NMR $\delta$ 7.51-7.41 (m, 10H); $^{19}$F NMR $\delta$ -89.43 (s, 2F) (lit.$^{10f}$ -89); $^{13}$C NMR $\delta$ 137.6 (t, $^2J_{C-F}$ = 28.3 Hz, 2C), 129.8 (t, $^3J_{C-F}$ = 1.9 Hz, 4C), 128.4 (2C), 125.8 (4C), 120.7 (t, $^1J_{C-F}$ = 243.0 Hz).

4.3.6. 9,9-Difluoro-9H-fluorene (30)
White solid. mp 46-48 °C (lit. 47-48 °C). IR (KBr) 1918, 1454, 1261 cm⁻¹; ¹H NMR δ 7.62 (d, J = 7.0 Hz, 2H), 7.56 (d, J = 7.3 Hz, 2H), 7.45 (dd, J = 7.5, 7.5 Hz, 2H), 7.33 (dd, J = 7.6, 7.6 Hz, 2H); ¹⁹F NMR δ -112.12 (s, 2F); ¹³C NMR δ 139.4 (t, J_C-F = 5.3 Hz, 2C), 137.9 (t, J_C-F = 25.1 Hz, 2C), 132.0 (2C), 128.7 (2C), 123.7 (2C), 123.2 (t, J_C-F = 24.4 Hz, 2C).

4.3.7. 2,2-Difluoroadamantane (32)

White solid. mp 102-103 °C (lit. 104-105 °C); IR (KBr) 2938, 2917, 1389, 1121 cm⁻¹; ¹H NMR δ 2.18 (brs, 2H), 1.97 (brs, 2H), 1.94 (brs, 2H), 1.86 (brs, 2H), 1.78-1.72 (m, 6H); ¹⁹F NMR δ -100.41 (s, 2F); ¹³C NMR δ 125.5 (t, J_C-F = 248.2 Hz), 36.6 (2C), 35.8 (t, J_C-F = 4.0 Hz, 2C), 34.0 (t, J_C-F = 4.0 Hz, 2C), 26.4.

4.4. Methylthiolation of 1,3-dithiane derivatives

4.4.1. 2-(Methylthio)-2-(naphthalen-1-yl)-1,3-dithiane (34a)

To a THF solution (6 mL) of 2-(naphthalene-1-yl)-1,3-dithiane (33a) (246 mg, 1 mmol) was added at -30 °C a 1.6 M hexane solution of BuLi (0.63 mL, 1 mmol), and the mixture was stirred at 0 °C for 1.5h. Then, dimethyl disulfide (188 mg, 2 mmol) was added and the mixture was stirred at 0 °C for 2 h and at room temperature over night. The reaction mixture was poured into water (20 mL) and extracted with ether (20 mL X 3). The combined organic layer was dried over MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (silica gel/ hexane-ether) gave 34a in 87% yield; White solid, mp 104-105 °C; IR (KBr) 2912, 783 cm⁻¹; ¹H NMR δ 9.49 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 7.3 Hz, 1H), 7.84 (dd, J = 7.5, 7.4 Hz, 2H), 7.54-7.42 (m, 3H), 3.58 (dd, J = 11.7, 11.6, 2.6 Hz, 2H), 2.81 (dd, J = 14.4, 5.1, 3.2 Hz, 2H), 2.25-2.17 (m, 1H), 2.11-2.00 (m, 1H), 1.94 (s, 3H); ¹³C NMR δ 135.1, 134.4, 130.4, 130.3, 128.8, 128.4, 127.4, 125.5, 124.4, 124.1, 64.4, 29.0 (2C), 24.5, 16.2; HRMS (EI) calcd for C₁₅H₁₆S₃, 292.0414, found 292.0408.

4.4.2. 2-[(1,1'-Biphenyl)-4-yl]-2-(methylthio)-1,3-dithiane (34b)

White solid. mp 93-94 °C; IR (KBr) 2903, 1481, 1401, 1272 cm⁻¹; ¹H NMR δ 8.05-7.99 (m, 4H), 3.92 (s, 3H), 3.41-3.34 (m, 2H), 2.77-2.72 (m, 2H), 2.17-2.13 (m, 1H), 2.03-1.92 (m, 1H), 2.02 (s, 3H); ¹³C NMR δ 141.0, 140.3, 139.8, 128.7(2C), 128.2(2C), 127.4, 127.1(2C), 127.0(2C), 63.7, 28.8(2C), 24.3, 16.3; HRMS (EI) calcd for C₁₇H₁₈S₃, 318.0571, found 318.0570.

4.4.3. Methyl 4-[2-(methylthio)-1,3-dithian-2-yl]benzoate (34c)

White solid. mp 51-52 °C; IR (KBr) 2910, 1719 (C=O), 1283, 1114 cm⁻¹; ¹H NMR δ 8.05-7.99 (m, 4H), 3.92 (s, 3H), 3.41-3.34 (m, 2H), 2.77-2.72 (m, 2H), 2.17-2.10 (m, 1H), 1.97 (s, 3H), 1.94-1.87 (m, 1H); ¹³C NMR δ 166.4, 145.8, 129.8, 129.6 (2C), 127.8 (2C), 63.4, 52.1, 28.7 (2C), 24.1, 16.1; HRMS (EI) (M⁺-SMe) calcd for C₁₃H₁₃O₂S₂, 253.03570, found 253.03503.
4.4.4. 2-(4-Isobutylphenyl)-2-(methylthio)-1,3-dithiane (34d)

IR (neat) 2952, 2912, 1410 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 7.81 (d, \(J = 8.3\) Hz, 2H), 7.15 (d, \(J = 8.3\) Hz, 2H), 3.43-3.36 (m, 2H), 2.77-2.71 (m, 2H), 2.47 (d, \(J = 7.1\) Hz, 2H), 2.17-2.11 (m, 1H), 1.96 (s, 3H), 1.94-1.83 (m, 2H), 0.90 (d, \(J = 6.7\) Hz, 6H); \(^13\)C NMR 141.9, 138.0, 129.1 (2C), 127.3 (2C), 63.7, 44.9, 30.0, 28.7 (2C), 24.4, 22.3 (2C), 16.2; HRMS (EI) (M\(^+-\)-SMe) calcd for C\(_{14}\)H\(_{19}\)O\(_2\)S\(_2\), 251.09282, found 251.09223.

4.4.5. 5-[2-(Methylthio)-1,3-dithian-2-yl]benzo[d][1,3]dioxole (34e)

White solid. mp 73-74 °C; IR (KBr) 2899, 1484, 1254, 1034 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 7.49 (d, \(J = 1.7\) Hz, 1H), 7.45 (dd, \(J = 1.8, 8.2\) Hz, 1H), 6.78 (d, \(J = 8.3\) Hz, 1H), 5.98 (s, 2H), 3.36 (dd, \(J = 11.4, 11.6\) Hz, 2H), 2.77-2.71 (m, 2H), 2.16-2.10 (m, 1H), 1.99 (s, 3H), 1.95-1.86 (m, 1H); 13C NMR \(\delta\) 147.7, 147.4, 134.6, 121.6, 108.5, 107.3, 101.3, 63.6, 28.9 (2C), 24.2, 16.2; HRMS (EI) (M\(^+-\)-Me) calcd for C\(_{11}\)H\(_{11}\)O\(_2\)S\(_3\), 270.9911, found 270.9917.

4.5. The desulfurizing-fluorination reaction of 2-(methylthio)-1,3-dithiane derivatives with IF\(_5\)-pyridine-HF

4.5.1. 1-(Trifluoromethyl)naphthalene (35a)

To a CH\(_2\)Cl\(_2\) solution (2 mL) of 34a (146 mg, 0.5 mmol) was added at room temperature IF\(_5\)-pyridine-HF (482 mg, 1.5 mmol), and the mixture was stirred at room temperature for 12h. The mixture was poured into water (20 mL) and extracted with CH\(_2\)Cl\(_2\) (20 mL X 3). The combined organic layer was washed with aq NaHCO\(_3\) and aq Na\(_2\)S\(_2\)O\(_3\), and dried over MgSO\(_4\). After concentration under reduced pressure, 35a was isolated by column chromatography (silica gel, Hexane-CH\(_2\)Cl\(_2\)) in 78% yield; IR (neat) 3060, 1515, 1316, 1119 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 8.19 (d, \(J = 8.5\) Hz, 1H), 8.03 (d, \(J = 8.3\) Hz, 1H), 7.93 (d, \(J = 8.0\) Hz, 1H), 7.87 (d, \(J = 7.3\) Hz, 1H), 7.65-7.49 (m, 3H); \(^19\)F NMR \(\delta\) -60.39 (s, 3F) (lit. \(-59.72\) (s, 3F)); 13C NMR \(\delta\) 133.8, 132.7, 128.9, 128.7, 127.6, 126.6, 126.0 (q, \(^2J_{C-F} = 30.5\) Hz), 124.7 (q, \(^3J_{C-F} = 5.7\) Hz), 124.6 (q, \(^1J_{C-F} = 273.4\) Hz), 124.2 (q, \(^3J_{C-F} = 2.6\) Hz), 124.1.

4.5.2. 4-(Trifluoromethyl)-1,1'-biphenyl (35b)

White solid. mp 68-69 °C (lit. 69-70 °C); IR (KBr) 1614, 1334, 1116 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 7.68 (s, 5H), 7.58-7.38 (m, 4H); \(^19\)F NMR \(\delta\) -63.83 (s, 3F); \(^13\)C NMR \(\delta\) 144.7, 139.7, 129.3 (q, \(^2J_{C-F} = 32.6\) Hz), 129.0 (2C), 128.2, 127.4 (2C), 127.2 (2C), 125.7 (q, \(^3J_{C-F} = 3.8\) Hz, 2C), 124.3 (q, \(^1J_{C-F} = 271.8\) Hz).

4.5.3. Methyl 4-(trifluoromethyl)benzoate (35c)

IR (neat) 2957, 1731 (C=O), 1328, 1282, 1131 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 8.16 (d, \(J = 8.0\) Hz, 2H), 7.71 (d, \(J = 8.1\) Hz, 2H), 3.96 (s, 3H); \(^19\)F NMR \(\delta\) -63.73 (s, 3F) (lit. \(-62.9\) (s, 3F)); \(^13\)C NMR \(\delta\) 165.8, 134.4 (q, \(^2J_{C-F} = 32.9\) Hz), 133.3, 129.9 (2C), 125.4 (q, \(^3J_{C-F} = 3.6\) Hz, 2C), 123.6 (q, \(^1J_{C-F} = 272.8\) Hz), 52.5.

4.5.4. 1-Isobutyl-4-(trifluoromethyl)benzene (35d)
IR (neat) 2960, 1327, 1124 cm$^{-1}$; $^1$H NMR $\delta$ 7.52 (d, $J = 8.9$ Hz, 2H), 7.25 (d, $J = 8.9$ Hz, 2H), 2.53 (d, $J = 7.2$ Hz, 2H), 1.92-1.85 (m, 1H), 0.91 (d, $J = 6.5$ Hz, 6H); $^{19}$F NMR $\delta$ -62.87 (s, 3F); $^{13}$C NMR $\delta$ 145.8, 129.3 (2C), 128.0 (q, $^2J_{C,F} = 32.2$ Hz), 125.0 (q, $^3J_{C,F} = 3.7$ Hz, 2C), 124.4 (q, $^1J_{C,F} = 271.8$ Hz), 45.2, 30.1, 22.2 (2C); HRMS (EI) calcd for C$_{11}$H$_{13}$F$_3$ 202.09693, found 202.09653.

Acknowledgments

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References and notes


6. Previously, IF₅-Et₃N-3HF was reported as a stable, non-hazardous, and easy to handle reagent⁴a,⁷. However, IF₅-Et₃N-3HF is less stable than IF₅-pyridine-HF, and decomposes in air under emitting HF.


8. IF₅-pyridine-HF is soluble in polar solvent such as acetonitrile and DMF, and poorly soluble in CH₂Cl₂ and hexane. However, in the polar solvents, the fluorination reaction of 1 did not proceed.

9. Structure of 10 was estimated from the chemical sift of that of a previously reported similar compound, see: Brigaud, T.; Laurent, E. Tetrahedron Lett. 1990, 31, 2287.


11. For the recent reviews of aromatic trifluoromethylation, see: (a) Tomashenko, O. A.; Grushin, V. V. Chem. Rev. 2011, 111, 4475. (b) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. Tetrahedron, 2011, 67, 2161.


