Iodofluorination of alkenes using IF5-pyridine-HF

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Abstract: Iodofluorination of alkenes was performed by using IF5-pyridine-HF and a reductant such as KI or Sn powder. The addition of IF to the double bond proceeded with stereo- and regio-selectivity. In the reaction with internal alkenes, the trans-addition product was obtained selectively. With terminal alkenes, the addition took place regioselectively to give 1-iodo-2-fluoroalkanes.

Key words: fluorine, addition, stereoselective synthesis, halogenation, alkenes

Iodofluorination of alkenes is a convenient method for the synthesis of organofluorine compounds. Iodofluorination was originally performed by iodine monofluoride generated from I2 and F2 gas. As alternatives to the hazardous F2 gas and I2, reagents for F- and I+ sources have been used to generate “IF” species for the iodofluorination. However, some of the reagents for the F- source are still hazardous, while some reagents for I+ source are not readily available. Moreover, the reactivity of the IF species is dependent on the reagents used. Therefore, a more convenient and effective method for the iodofluorination reaction of alkenes is still desired. Recently, we reported a stable fluorinating reagent, IF5-pyridine-HF, and its application to fluorination reactions. During the course of our study on the new fluorination reaction using IF5-pyridine-HF, we found that this reagent can be employed in the iodofluorination of alkene via reduction with KI or Sn, to obtain the corresponding iodofluoroalkane (Equation 1).

![Equation 1 Iodofluorination of alkenes using IF5-pyridine-HF](image)

Table 1 Iodofluorination of 1a by IF5-pyridine-HF and a reductanta

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant</th>
<th>Yield %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I2</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>KI</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>NaI</td>
<td>78</td>
</tr>
</tbody>
</table>

aThe reaction was carried out at room temperature for 17 h using 1 eq. of IF5-pyridine-HF and reductant in CH2Cl2.
bIsolated yield based on 1a.

The use of KI was favorable for the reaction of 1a, and 2a was obtained in good yield (Entry 1 in Table 2). In contrast, when KI was used in the reaction of 1-dodecene, 2-fluoro-1-iodododecane was formed as the major product, but its regioisomer, 1-fluoro-2-iodododecane, was also formed (91:9 ratio). For the reaction of 1b, Sn powder was more suitable, and 2b was selectively formed in 82 % yield (Entry 2). The present iodofluorination reaction proceeded stereoselectively, and trans-1-fluoro-2-iodocyclohexane was selectively formed from cyclohexene (Entry 3). Furthermore, when trans-and cis-5-decenes were used, the corresponding 5S*, 6R*-5-fluoro-6-iododecane and (5R*, 6R*)-5-fluoro-6-iododecane were selectively formed (Entries 5 and 6). As the reaction proceeded under mild conditions, functional groups such as ester and free hydroxy group were tolerated (Entries 7, 8, 9, and 10). Furthermore, it was possible to distinguish between two double bonds of different reactivities. In the reaction of diene, where one double bond is less reactive than the other due to the electron-withdrawing substituent, the iodofluorination selectively took place at the more reactive double bond (Entry 9). Iodofluorination of electron-deficient alkenes is rare, and there are only a few reported examples. The present iodofluorination is applicable to wide variety of alkenes, including electron-deficient alkenes. When 4-methylpent-3-en-2-one was used in the reaction, the corresponding iodofluorination product was obtained regioselectively (Entry 10).

Although IF5-pyridine-HF is unreactive to alkenes, IF5 was used for the iodofluorination of alkenes after reduction to IF species. Therefore, in the present study, reductants such as I2, KI, and NaI were used to generate IF species from IF5-pyridine-HF. All the reductants used were found to be effective for the iodofluorination of cyclooctadecene, and 1-fluoro-2-iodocyclooctadecene was obtained in good yield (Table 1).
Table 2: Iodofluorination of alkenes using IF$_5$-pyridine-HF and a reductant

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Reductant</th>
<th>Product</th>
<th>Yield, %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Alkene 1a" /></td>
<td>KI</td>
<td><img src="image2" alt="Product 2a" /></td>
<td>78</td>
</tr>
<tr>
<td>2$^c$</td>
<td><img src="image3" alt="Alkene 1b" /></td>
<td>Sn</td>
<td><img src="image4" alt="Product 2b" /></td>
<td>82</td>
</tr>
<tr>
<td>3$^c$</td>
<td><img src="image5" alt="Alkene 1c" /></td>
<td>Sn</td>
<td><img src="image6" alt="Product 2c" /></td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Alkene 1d" /></td>
<td>KI</td>
<td><img src="image8" alt="Product 2d" /></td>
<td>(52)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Alkene 1e" /></td>
<td>KI</td>
<td><img src="image10" alt="Product 2e" /></td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Alkene 1f" /></td>
<td>KI</td>
<td><img src="image12" alt="Product 2f" /></td>
<td>58</td>
</tr>
<tr>
<td>7$^c$</td>
<td><img src="image13" alt="Alkene 1g" /></td>
<td>Sn</td>
<td><img src="image14" alt="Product 2g" /></td>
<td>77</td>
</tr>
<tr>
<td>8$^c$</td>
<td><img src="image15" alt="Alkene 1h" /></td>
<td>Sn</td>
<td><img src="image16" alt="Product 2h" /></td>
<td>(86)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17" alt="Alkene 1i" /></td>
<td>KI</td>
<td><img src="image18" alt="Product 2i" /></td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19" alt="Alkene 1j" /></td>
<td>KI</td>
<td><img src="image20" alt="Product 2j" /></td>
<td>(67)</td>
</tr>
</tbody>
</table>

$^a$If otherwise not mentioned, the reaction was carried out at room temperature for 17 h using 1 eq. of IF$_5$-pyridine-HF and KI as a reductant in CH$_2$Cl$_2$.

$^b$Isolated yield based on alkene used. In parentheses, $^{19}$F NMR yield.

$^c$3 eq. of IF$_5$-pyridine-HF and 2 eq of Sn powder were used.

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. Sn powder of ~45 µm and 99.5 % purity was used. IF$_5$ in a cylinder was supplied by Daikin industries, Ltd.
Anhydrous HF in a cycler was purchased from Stella Chemifa Corporation. IF₅-pyridine-HF was prepared from IF₅ and pyridine-HF by the previously reported method. Glassware can be used for the reaction, but use of Teflon™ or polyethylene ware is recommended.

**General Procedure of Iodofluorination of Alkenes Using KI as a Reductant**

To a CH₂Cl₂ solution (3 mL) of an alkene (0.5 mmol) and IF₅-pyridine-HF (161 mg, 0.5 mmol) was added at 0 °C Sn powder (119 mg, 1.0 mmol), and the mixture was stirred at 0 °C for 30 min and at room temperature for 17 h. Then, the solid part was removed by filtration through a celite, and the filtrate was poured into water (20 mL). The product was isolated by column chromatography (silica gel/hexane) in 78% yield as a colorless liquid.

**Trans-1-Fluoro-2-iododicyclocyclohexane (2c)**

The reaction was performed using Sn powder as the reductant, and 2c was isolated by column chromatography (silica gel/hexane) in 54% yield as a colorless liquid.

**1-Fluoro-2-iodododecane (2a)**

The reaction was performed using KI as the reductant, and 2a was isolated by column chromatography (silica gel/hexane) in 78% yield as a colorless liquid.

IR (neat): 2957, 1466 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.53-4.36 (dm, J = 49.4 Hz, 1H), 3.35-3.27 (m, 2H), 1.77-1.69 (m, 2H), 1.44-1.27 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H).

19F NMR (376 MHz, CDCl₃): δ = −171.40 to −171.76 (m, 1F).

13C NMR (100 MHz, CDCl₃): δ = 97.4 (d, 1JC-F = 177.4 Hz), 34.9 (d, 1JC-F = 21.0 Hz), 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 24.8 (d, 3JC-F = 4.7 Hz), 22.9, 14.2, 7.26 (d, 2JC-F = 24.8 Hz).

**1-Fluoro-2-iodo-1-phenylethane (2d)**

The reaction was performed using KI as the reductant, and the yield of 2d was determined to be 52% by 19F NMR using fluorobenzene as an internal standard, and pure 2d was isolated by column chromatography (silica gel/hexane).

IR (neat): 3033, 1454, 960, 699 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.44-7.34 (m, 5H), 5.55 (d, J = 47.6, 7.6, 5.6 Hz, 1H), 3.54-3.43 (m, 2H); 19F NMR (376 MHz): δ = −166.7 to −166.9 (m, 1F).

13C NMR (100 MHz, CDCl₃): δ = 138.0 (d, 1JC-F = 19.4 Hz), 129.4, 129.3 (2C), 125.9 (d, 1JC-F = 6.6 Hz, 2C), 93.6 (d, 1JC-F = 180.3 Hz), 7.7 (d, 2JC-F = 28.6 Hz).

**2-Fluoro-1-iodododecane (2b)**

The reaction was performed using Sn powder as the reductant, and 2b was isolated by column chromatography (silica gel/hexane) in 82% yield as a white solid.

Mp. 27-31°C.

IR (KBr): 2923, 1465, 884 cm⁻¹.
1.99-1.28 (m, 12H), 0.93 (t, J = 7.2 Hz, 6H). The reaction was performed using KI as the reductant, and 2f was isolated by column chromatography (silica gel/hexane) as a white colorless liquid.

Methyl 2-Fluoro-1-iodoundecanoate (2g)

The reaction was performed using Sn powder as the reductant, and 2g was isolated by column chromatography (silica gel/hexane-ether) in 82 % yield as a white solid.

Mp. 35-39 °C.

IR (KBr): 2957, 1465 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.52-4.36 (dm, J = 4.85 Hz, 1H), 3.67 (s, 3H), 3.37-3.24 (m, 2H), 2.32 (t, J = 7.4 Hz, 2H), 1.78-1.61 (m, 4H), 1.46-1.30 (m, 10H).

19F NMR (376 MHz, CDCl₃): δ = -171.4 to -171.8 (m, 1F).

13C NMR (100 MHz, CDCl₃): δ = 71.4 (d, J_C-F = 177.3 Hz), 51.6, 34.8 (d, J_C-F = 21.0 Hz), 34.2, 29.3, 29.2 (2C), 29.1, 25.0, 24.7 (d, J_C-F = 3.8 Hz), 7.2 (d, J_C-F = 24.8 Hz).

11-Fluoro-10-iodoundecan-1-ol (2h)

The reaction was performed using Sn powder as the reductant, and the yield of 2h was determined to be 86 % by 19F NMR using fluorobenzene as an internal standard. Pure 2h was isolated by column chromatography (silica gel/hexane-ether) as a white solid.

Mp. 48-50 °C.

IR (KBr): 3304 (-OH), 2924, 1736 (C=O), 1437, 1173 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.54-4.37 (dm, J = 4.80 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 3.37-3.24 (m, 2H), 1.79-1.30 (m, 16H).

19F NMR (376 MHz, CDCl₃): δ = -170.9 to -171.2 (m, 1F). (lit: -171.2 to -171.6 (m, 1F)).

13C NMR (100 MHz, CDCl₃): δ = 92.3 (d, J_C-F = 177.4 Hz), 63.1, 34.9 (d, J_C-F = 21.0 Hz), 32.8, 29.5, 29.4 (2C), 29.3, 25.8, 24.8 (d, J_C-F = 4.8 Hz), 7.22 (d, J_C-F = 25.7 Hz).

(5R*, 6R*)-5-Fluoro-6-iododecane (2f)

The reaction was performed using Sn powder as the reductant, and 2f was isolated by column chromatography (silica gel/hexane-ether) in 87 % yield as a colorless solid.

IR (neat): 2957, 1465 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.14-3.99 (m, 2H), 1.99-1.28 (m, 12H), 0.93 (t, J = 7.2 Hz, 6H).

19F NMR (376 MHz, CDCl₃): δ = -171.4 to -171.8 (m, 1F).

13C NMR (100 MHz, CDCl₃): δ = 71.4 (d, J_C-F = 177.3 Hz), 51.6, 34.8 (d, J_C-F = 21.0 Hz), 34.2, 29.3, 29.2 (2C), 29.1, 25.0, 24.7 (d, J_C-F = 3.8 Hz), 7.2 (d, J_C-F = 24.8 Hz).

(2j)-Ethyl 7-fluoro-6-iodo-3,7-dimethyloct-2-enoate

The reaction was performed using Sn powder as the reductant, and 2j was isolated by column chromatography (silica gel/hexane-ether) in 67 % yield as a colorless solid.

IR (neat): 2983, 1715 (C=O), 1650, 1147 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 5.73 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.98-3.92 (m, 1H), 2.53-2.46 (m, 1H), 2.26-2.16 (m, 1H), 2.16 (s, 3H), 2.04-1.93 (m, 1H), 1.90-1.79 (m, 1H), 1.60 (d, J = 15.2 Hz, 3H), 1.55 (d, J = 15.2 Hz, 3H), 1.28 (t, J = 14.4 Hz, 3H).

19F NMR (376 MHz, CDCl₃): δ = -133.6 (brs, 1F).

13C NMR (100 MHz, CDCl₃): δ = 166.9, 157.8, 117.1, 96.4 (d, J_C-F = 173.6 Hz), 59.9, 42.7 (d, J_C-F = 24.8 Hz), 41.1, 32.6 (d, J_C-F = 3.8 Hz), 27.6 (d, J_C-F = 24.8 Hz), 23.7 (d, J_C-F = 24.8 Hz), 19.0, 14.6.

HRMS (EI) Caled for C₁₂H₂₀O₂FI 365.03842, found 365.03894.

4-Fluoro-3-iodo-4-methylpentan-2-one (2j)

The reaction was performed using KI as the reductant, and the yield of 2j was determined to be 67 % by 19F NMR using fluorobenzene as an internal standard and pure 2j was isolated by column chromatography (silica gel/hexane-ether) as a colorless liquid.

IR (neat): 2987, 1705 (C=O), 1538 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.64 (d, J = 14.8 Hz, 1H), 2.64 (s, 3H), 1.64 (d, J = 12.0 Hz, 3H), 1.59 (d, J = 10.8 Hz, 3H).

19F NMR (376 MHz, CDCl₃): δ = -130.8 (brs, 1F).

13C NMR (100 MHz, CDCl₃): δ = 201.5, 93.9 (d, J_C-F = 177.3 Hz), 41.0 (d, J_C-F = 23.9 Hz), 28.2 (d, J_C-F = 3.8 Hz), 25.8 (d, J_C-F = 22.9 Hz), 25.7 (d, J_C-F = 23.8 Hz).

HRMS (EI) Caled for C₁₂H₁₀OFI 243.97604, found 243.97507.

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References


