Effective Fluorination Reaction with Et₃N·3HF Under Microwave Irradiation

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Abstract: Fluorination reaction of epoxides and alkyl mesylates can be effectively achieved by reaction with Et₃N·3HF under microwave irradiation. The reaction time could be greatly reduced compared to the reaction under thermal conditions. The reactions were completed in a few minutes and the use of large excess of reagents could be avoided.

Key words: microwave irradiation, epoxides, fluorination, ring opening, Et₃N·3HF

Among HF reagents, Et₃N·3HF has been widely used as a fluorinating reagent because it is commercially available, is close to neutral, has a high boiling point, and can be used in glassware.¹ However, the fluorination reactions using Et₃N·3HF often require high temperature and long reaction time due to its low reactivity. For instance, the reaction of Et₃N·3HF with cyclohexene oxide (1a) was carried out at 115 °C for 3.5 hours to give trans-2-fluorocyclohexanol (2a) in 69% yield.² In the reaction with cyclooctene oxide (1b), it took 4 hours at 155 °C to obtain 2-fluorocyclooctanol (2b) in 54% yield. Recently, microwave irradiation has been used in many reactions to reduce the reaction time and to avoid the use of a large excess of reagents.³ However, the fluorination reaction using HF reagents under microwave irradiation has not so far been well developed.⁴ We wish to report here that the fluorination reaction using Et₃N·3HF is accelerated dramatically by microwave irradiation to provide fluorinated products in a short time.

Under the microwave irradiation conditions, the fluorination reaction of 1a and 1b was completed in 2 and 10 minutes, respectively, and only 0.6 equivalent of Et₃N·3HF to 1 equivalent of 1 was required to obtain the corresponding fluoroalcohols 2a and 2b in 61 and 60% yields, respectively (Equation 1). Various epoxides 1a–e could be converted to the corresponding fluoroalcohols 2a–f in 2–10 minutes under the irradiation of microwaves as shown in Table 1.

Nucleophilic substitution reaction of a fluoride with organic halides and mesylates is also a versatile method to obtain organofluorine compounds. However, the reaction of alkyl mesylate 3a with Et₃N·3HF is reported to be sluggish under thermal conditions and the corresponding fluoride 4a was formed in only 20% yield after 20 hours at 80 °C.⁵ On the other hand, under microwave irradiation, the fluorination was completed in 2 minutes and 4a was obtained in 63% yield (Equation 2). Moreover, under the microwave irradiation conditions, only 1.2 equivalents of Et₃N·3HF was necessary to 1 equivalent of the substrate, while 10 equivalents of the reagent were used under the thermal conditions.

Equation 1

Equation 2

The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were recorded using a Jasco FT/IR-410 spectrometer. The ¹H NMR (400 MHz) and ¹⁹F NMR (376 MHz) spectra were recorded in CDCl₃ on a Jeol JNM-A400II FT NMR and the chemical shifts are referred to TMS (¹H) and CFCl₃ (¹⁹F), respectively. The EI-HRMS were measured on a Jeol JMS-700TZ spectrometer.

A commercially available Gold Star microwave oven (500 W, MW-JIK96H5) was modified to accept a port for connecting a reactor to a reflux condenser located outside the oven.⁶ A hole of 10 mm diameter was drilled at the top of the oven and an 8 cm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reflux condenser located outside the oven. A hole of 10 mm diameter was drilled at the top of the oven and an 8 cm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reflux condenser located outside the oven. A hole of 10 mm diameter was drilled at the top of the oven and an 8 cm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reflux condenser located outside the oven. A hole of 10 mm diameter was drilled at the top of the oven and an 8 cm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reflux condenser located outside the oven.

Fluorination Reactions with Et₃N·3HF; trans-2-Fluorocyclohexan-1-ol (2a); Typical Procedure

Microwav e-Assisted Fluorination Reaction with Et₃N·3HF

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the reactor was connected to the port in the oven and the port was connected to a reflux condenser located outside the oven. Then, the reaction mixture was submitted to microwave irradiation for 2 min. After cooling, the reaction mixture was poured into aq NaHCO₃ soln. The product was extracted with Et₂O (3×) and the combined ethereal layers were dried (MgSO₄). Purification by column chromatography (silica gel, eluent: hexane–Et₂O) gave 2a in 61% yield; mp 22–23 °C (Lit.² mp 23–24 °C).

IR (film): 3377 cm⁻¹ (OH).

¹H NMR (400 MHz, CDCl₃): δ = 4.26 (ddt, J = 48.8, 8.5, 2.4 Hz, 1 H), 3.91–3.83 (m, 1 H), 2.44 (s, 1 H), 2.05–1.41 (m, 12 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −182.59 (d, J = 51.3 Hz, 1 F).

Table 1 Fluorination Using Et₃N·3HF Under Microwave Irradiation

<table>
<thead>
<tr>
<th>Substrate</th>
<th>React. Time (min)</th>
<th>Product</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2</td>
<td>2a</td>
<td>61</td>
</tr>
<tr>
<td>1b</td>
<td>10</td>
<td>2b</td>
<td>60</td>
</tr>
<tr>
<td>1c</td>
<td>10</td>
<td>2c</td>
<td>76²</td>
</tr>
<tr>
<td>1d</td>
<td>2</td>
<td>2d</td>
<td>71³</td>
</tr>
<tr>
<td>C₁₀H₂₁O</td>
<td>2</td>
<td>2e</td>
<td>45</td>
</tr>
<tr>
<td>Ph-(CH₂)₃-OMs</td>
<td>1</td>
<td>2f</td>
<td>47</td>
</tr>
<tr>
<td>AcO-(CH₂)₆-OMs</td>
<td>1</td>
<td>3a</td>
<td>63⁴</td>
</tr>
<tr>
<td>AcO-(CH₂)₆-OMs</td>
<td>1</td>
<td>4a</td>
<td>77⁴</td>
</tr>
</tbody>
</table>

a Unless otherwise mentioned, 0.6 equiv of Et₃N·3HF to 1 equiv of substrate was used.

b Isolated yields based on substrate used.

² A mixture of two stereoisomers was used.

³ A mixture of two stereoisomers was obtained.

⁴ A mixture of two regioisomers was obtained.

⁵ 1.0 equiv of Et₃N·3HF was used.

⁶ 1.2 equiv of Et₃N·3HF was used.

trans-2-Fluorocyclooctan-1-ol (2b)
Yield: 60%; oil.²
IR (film): 3410 cm⁻¹ (OH).

¹H NMR (400 MHz, CDCl₃): δ = 4.52 (ddt, J = 48.8, 8.5, 2.4 Hz, 1 H), 3.91–3.83 (m, 1 H), 2.44 (s, 1 H), 2.05–1.41 (m, 12 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −172.03 to −194.24 (m, 1 F).

trans-2-Fluorocyclododecan-1-ol (trans-2c)
Yield: 76% (cis/trans mixture); mp 65.5–67 °C (Lit.⁹ mp 64–65 °C).

IR (KBr): 3337 cm⁻¹ (OH).

¹H NMR (400 MHz, CDCl₃): δ = 4.55 (dm, J = 49.3 Hz, 1 H), 3.92–3.89 (m, 1 H), 2.49 (s, 1 H), 1.91–1.34 (m, 20 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −172.03 to −172.24 (m, 1 F).

cis-2-Fluorocyclododecan-1-ol (cis-2c)
Yield: 76% (cis/trans mixture); mp 87–88 °C (Lit.⁹ mp 84–86 °C).

IR (KBr): 3390 cm⁻¹ (OH).

¹H NMR (400 MHz, CDCl₃): δ = 4.71 (dm, J = 49.3 Hz, 1 H), 3.97–3.89 (m, 1 H), 1.90 (s, 1 H), 1.80–1.18 (m, 20 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −191.15 (br s, 1 F).

12-Fluorocyclododeca-4,8-dien-1-ol (2d) (a mixture of two regioisomers)
Yield: 71%; oil.

IR (film): 3375 cm⁻¹ (OH).

¹H NMR (400 MHz, CDCl₃): δ = 5.55–5.23 (m, 4 H), 4.81–4.58 (m, 1 H), 4.02–3.91 (m, 1 H), 2.32–1.43 (m, 13 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −185.88 (br s, 0.6 F), −192.68 (br s, 0.4 F).


2-Fluorododecan-1-ol (2e)
Yield: 45%; oil.¹⁰
IR (film): 3301 cm⁻¹ (OH).

¹H NMR (400 MHz, CDCl₃): δ = 4.58 (dm, J = 50.3 Hz, 1 H), 3.78–3.61 (m, 2 H), 1.82 (s, 1 H), 1.76–1.26 (m, 12 H), 0.88 (t, J = 6.8 Hz, 3 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −190.07 to −190.45 (m, 1 F).

1-Fluoro-3-phenylpropane (4a)
Yield: 63%; oil.¹¹
IR (film): 2963 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.49–7.11 (m, 5 H), 4.46 (dt, J = 47.1, 6.1 Hz, 2 H), 2.75 (t, J = 7.8 Hz, 2 H), 2.08–1.95 (m, 2 H).

¹十九F NMR (376 MHz, CDCl₃): δ = −220.62 (dt, J = 47.1, 25.0 Hz, 1 F) (Lit.³ δ = −220.2).
**1-Acetoxy-6-fluorohexane (4b)**

Yield: 77%; oil. \(^{12}\)

IR (film): 1740 cm\(^{-1}\) (C=O).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.45\) (dt, \(J = 47.3, 6.1\) Hz, 2 H), 4.07 (t, \(J = 6.6\) Hz, 2 H), 2.05 (s, 3 H), 1.77–1.62 (m, 4 H), 1.49–1.37 (m, 4 H).

\(^19\)F NMR (376 MHz, CDCl\(_3\)): \(\delta = -218.95\) (tt, \(J = 47.3, 25.0\) Hz, 1 F).

**References**