Effective Fluorination Reaction with Et₃N•3HF Under Microwave Irradiation

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**Effective Fluorination Reaction with Et$_3$N•3HF Under Microwave Irradiation**

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**Abstract:** Fluorination reaction of epoxides and alkyl mesylates can be effectively achieved by reaction with Et$_3$N•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 reagents could be avoided.

**Key words:** microwave irradiation, epoxides, fluorination, ring opening, Et$_3$N•3HF

Among HF reagents, Et$_3$N•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 Et$_3$N•3HF often require high temperature and long reaction time due to its low reactivity. For instance, the reaction of Et$_3$N•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 had not so far been well developed.$^4$

We wish to report here that the fluorination reaction using Et$_3$N•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 equivalents of Et$_3$N•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 microwave 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 Et$_3$N·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 Et$_3$N·3HF to 1 equivalent of substrate was necessary, while 10 equivalents of the reagent were used under the thermal conditions.

As Et$_3$N·3HF is close to neutral, the reaction can tolerate functional groups such as a double bond ($1d$) and an ester ($3b$) as shown in Table 1.

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. The $^1$H NMR (400MHz) and $^{19}$F NMR (376MHz) spectra were recorded in CDCl$_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, $\delta$, are referred to TMS ($^1$H) and CFCl$_3$ ($^{19}$F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. A commercially available GoldStar microwave oven (500W, 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 in the oven top and an 8 cm length of Teflon$^{\text{TM}}$ 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 reactor which is a Teflon$^{\text{TM}}$ PFA tube with a
diameter of 10 mm and a length of 8 cm sealed at one end. Et$_3$N·3HF was purchased from Aldrich Chemical Co. Epoxides 1a-d were purchased from Tokyo Kasei Co. (1c was a mixture of cis- and trans-isomer) and used without further purification. The epoxide 1e was prepared from dec-1-ene by the oxidation and the mesylates 3a, b were prepared from the corresponding alcohols.
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 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="1a" /></td>
<td>2</td>
<td><img src="image" alt="2a" /></td>
<td>61</td>
</tr>
<tr>
<td><img src="image" alt="1b" /></td>
<td>10</td>
<td><img src="image" alt="2b" /></td>
<td>60</td>
</tr>
<tr>
<td><img src="image" alt="1c" /></td>
<td>10</td>
<td><img src="image" alt="2c" /></td>
<td>76&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><img src="image" alt="1d" /></td>
<td>2</td>
<td><img src="image" alt="2d" /></td>
<td>71&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td><img src="image" alt="1e" /></td>
<td>2</td>
<td><img src="image" alt="2e" /></td>
<td>45</td>
</tr>
<tr>
<td><img src="image" alt="1f" /></td>
<td>2</td>
<td><img src="image" alt="2f" /></td>
<td>47</td>
</tr>
<tr>
<td>Ph-(CH₂)₃-OMs</td>
<td>2</td>
<td>Ph-(CH₂)₃-F</td>
<td>63&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>AcO-(CH₂)₆-OMs</td>
<td>1</td>
<td>AcO-(CH₂)₆-F</td>
<td>77&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a) If otherwise not mentioned, 0.6 equiv of Et₃N·3HF to substrate was used.
b) Isolated yields based on substrate used.
c) A mixture of two stereoisomers was used.
d) A mixture of two stereoisomers was obtained.
e) A mixture of two regioisomers was obtained.
f) 1.0 equiv of Et₃N·3HF was used.
g) 1.2 equiv of Et₃N·3HF was used.

Fluorination Reactions with Et₃N·3HF; trans-2-fluorocyclohexanol (2a); Typical Procedure
Cyclohexene oxide (98 mg, 1 mmol) and Et₃N·3HF (97 mg, 0.6 mmol) were introduced into a reactor consisting of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end. The open end of 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 X) and the combined ethereal layers were dried (MgSO₄). Purification by column chromatography (silica gel/hexane- Et₂O) gave 2a in 61% yield; mp 22-23 °C (lit.² 23-24 °C).

IR (film) 3377 (-OH) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.26 (dm, J = 51.3 Hz, 1H), 3.59-3.68 (m, 1H), 2.45 (brs, 1H), 2.13-1.99 (m, 2H), 1.77-1.69 (m, 2H), 1.51-1.20 (m, 4H).

19F NMR (376 MHz, CDCl₃): δ = -182.59 (d, J = 51.3 Hz, 1F).

trnas-2-Fluorocyclooctan-1-ol (2b)

Yield: 60%; oil²
IR (film) 3410 (-OH) cm⁻¹.

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

19F NMR (376 MHz, CDCl₃): δ = -172.03 - 172.24 (m, 1F).

trnas-2-Fluorocyclododecan-1-ol (trnas-2c)

Yield: 76% (cis/trans mixture); mp 65.5-67 °C (lit.⁹ 64-65 °C).
IR (KBr) 3337 (-OH) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.55 (dm, J = 49.3 Hz, 1H), 3.92-3.86 (m, 1H), 2.49 (s, 1H), 1.91-1.34 (m, 20H).

19F NMR (376 MHz, CDCl₃): δ = -193.93 - 194.24 (m, 1F).

cis-2-Fluorocyclododecan-1-ol (cis-2c)

Yield: 76% (cis/trans mixture); mp 87-88 °C (lit.⁹ 84-86 °C).
IR (KBr) 3390 (-OH) cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.71(dm, J = 48.1 Hz, 1H), 3.97-3.89 (m, 1H), 1.90 (s, 1H), 1.80-1.18 (m, 20H).

19F NMR (376 MHz, CDCl₃): δ = -191.15 (brs, 1F).

12-Fluorocyclododeca-4,8-dien-1-ol (2d) (a mixture of two regioisomers)

Yield: 71%; oil.
IR (film) 3375 (-OH) cm⁻¹.

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

19F NMR (376 MHz, CDCl₃): δ = -185.88 (brs, 0.6F), -192.68 (brs, 0.4F).
HRMS(EI) Calcd for C₁₂H₁₉FO (M⁺) 198.1420.  Found 198.1436.

2-Fluorododecan-1-ol (2e)

Yield: 45%, oil.¹⁰
IR (film) 3301 (-OH) cm⁻¹.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.58 (dm, $J$ = 50.3 Hz, 1H), 3.78-3.61 (m, 2H), 1.82 (s, 1H), 1.76-1.26 (m, 12H), 0.88 (t, $J$ = 6.8 Hz, 3H).
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -190.07- -190.45 (m, 1F).

1-Fluorododecan-2-ol (2f)
Yield: 47%; oil.$^{10}$
IR (film) 3376 (-OH) cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.50-4.20 (m, 2H), 3.94-3.82 (m, 1H), 1.99 (s, 1H), 1.46-1.26 (m, 12H), 0.88 (t, $J$ = 6.6 Hz, 3H).
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -288.85 (dt, $J$ = 47.6, 17.7 Hz, 1F).

1-Fluoro-3-phenylpropane (4a)
Yield: 63%; oil.$^3,11$
IR (film) 2963 cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.49-7.11 (m, 5H), 4.46 (dt, $J$ = 47.1, 6.1 Hz, 2H), 2.75 (t, $J$ = 7.8 Hz, 2H), 2.08-1.95 (m, 2H).
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -220.62 (tt, $J$ = 47.1, 25.0 Hz, 1F) (lit.$^3$ –220.2).

1-Acetoxy-6-fluorohexane (4b)
Yield: 77%; oil.$^{12}$
IR (film) 1740 (C=O) cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.45 (dt, $J$ = 47.3, 6.1 Hz, 2H), 4.07 (t, $J$ = 6.6 Hz, 2H), 2.05 (s, 3H), 1.77-1.62 (m, 4H), 1.49-1.37 (m, 4H).
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -218.95 (tt, $J$ = 47.3, 25.0 Hz, 1F).

References


