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 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 had 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 equivalents 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 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 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. 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 to 1 equivalent of substrate was necessary, while 10 equivalents of the reagent were used under the thermal conditions.

As Et₃N·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 ¹H NMR (400MHz) and ¹⁹F NMR (376MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, Δ, are referred to TMS (¹H) and CFCl₃ (¹⁹F), 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. A hole of 10 mm diameter was drilled in the oven top 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 reactor which is a Teflon™ 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. (1e 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.8
### Table 1  Fluorination Using Et$_3$N·3HF Under Microwave Irradiation$^a$

<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 OH</td>
<td>61</td>
</tr>
<tr>
<td>1b</td>
<td>10</td>
<td>2b OH</td>
<td>60</td>
</tr>
<tr>
<td>1c$^c$</td>
<td>10</td>
<td>2c OH</td>
<td>76$^d$</td>
</tr>
<tr>
<td>1d</td>
<td>2</td>
<td>2d OH</td>
<td>71$^{e,f}$</td>
</tr>
<tr>
<td>1e</td>
<td>2</td>
<td>2e OH</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2f OH</td>
<td>47</td>
</tr>
<tr>
<td>Ph-(CH$_2$)$_3$OMs</td>
<td>2</td>
<td>Ph-(CH$_2$)$_3$F</td>
<td>63$^g$</td>
</tr>
<tr>
<td>3a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AcO-(CH$_2$)$_6$OMs</td>
<td>1</td>
<td>AcO-(CH$_2$)$_6$F</td>
<td>77$^g$</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ If otherwise not mentioned, 0.6 equiv of Et$_3$N·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 used.
$^f$ A mixture of two regioisomers was obtained.
$^g$ 1.0 equiv of Et$_3$N·3HF was used.

Fluorination Reactions with Et$_3$N·3HF; *trans*-2-fluorocyclohexanol (2a); Typical Procedure
Cyclohexene oxide (98 mg, 1 mmol) and Et$_3$N·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 NaHCO$_3$ soln. The product was extracted with Et$_2$O (3 X) and the combined ethereal layers were dried (MgSO$_4$). Purification by column chromatography (silica gel/hexane-Et$_2$O) gave 2a in 61% yield; mp 22-23 °C (lit.$^2$ 23-24 °C).

IR (film) 3377 (-OH) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 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).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -182.59 (d, $J$ = 51.3 Hz, 1F).

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

Yield: 60%; oil$^2$

IR (film) 3410 (-OH) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 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).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -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$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.55 (dm, $J$ = 49.3 Hz, 1H), 3.92-3.86 (m, 1H), 2.49 (s, 1H), 1.91-1.34 (m, 20H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -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$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 4.71(dm, $J$ = 48.1 Hz, 1H), 3.97-3.89 (m, 1H), 1.90 (s, 1H), 1.80-1.18 (m, 20H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -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$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 5.55-5.23 (m, 4H), 4.81-4.58 (m, 1H), 4.02-3.91 (m, 1H), 2.32-1.43 (m, 13H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -185.88 (brs, 0.6F), -192.68 (brs, 0.4F).

HRMS(EI) Calcd for C$_{12}$H$_{19}$FO (M$^+$) 198.1420. Found 198.1436.

**2-Fluorododecan-1-ol (2e)**

Yield: 45%, oil.$^{10}$

IR (film) 3301 (-OH) cm$^{-1}$.
1H 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$^{-1}$.

1H 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$^{-1}$.

1H 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$^{-1}$.

1H 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

(1)  

(2)  

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(8)  

