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<td>Author(s)</td>
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<tr>
<td>Citation</td>
<td>Synthesis, 2003(8): 1157-1159</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2003-06</td>
</tr>
<tr>
<td>Type</td>
<td>article (author version)</td>
</tr>
<tr>
<td>File Information</td>
<td>micro-wave.pdf</td>
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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. 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. 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. However, the fluorination reaction using HF reagents under microwave irradiation had not so far been well developed.

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 $\text{Et}_3\text{N} \cdot 3\text{HF}$ 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 $\text{Et}_3\text{N} \cdot 3\text{HF}$ to 1 equivalent of substrate was necessary, while 10 equivalents of the reagent were used under the thermal conditions.

As $\text{Et}_3\text{N} \cdot 3\text{HF}$ 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 $^1\text{H}$ NMR (400MHz) and $^{19}\text{F}$ NMR (376MHz) spectra were recorded in CDCl$_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, $\delta$, are referred to TMS ($^1\text{H}$) and CFCl$_3$ ($^{19}\text{F}$), 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. 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. (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>
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<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&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10</td>
<td>2c</td>
<td>76&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>1d</td>
<td>2</td>
<td>2d</td>
<td>71&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td>1e</td>
<td>2</td>
<td>2e</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2f</td>
<td>47</td>
</tr>
<tr>
<td>Ph-(CH₂)₃-OMs</td>
<td>2</td>
<td>3a</td>
<td>63&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>AcO-(CH₂)₆-OMs</td>
<td>1</td>
<td>3b</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).

**trans-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).

**trans-2-Fluorocyclododecan-1-ol (trans-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


