Effective Fluorination Reaction with $Et_3N{\cdot}3HF$ Under Microwave Irradiation

Tomotake Inagaki, Tsuyoshi Fukuhara, Shoji Hara*

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
Fax +81(11)7066556; E-mail: hara@org-mc.eng.hokudai.ac.jp

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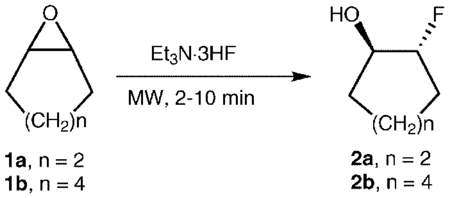
Abstract: Fluorination reaction of epoxides and alkyl mesylates can be effectively achieved by reaction with $Et_3N{\cdot}3HF$ under microwave irradiation. The reaction time could be greatly reduced compared to the reaction under thermal conditions. The reactions were completed in a few minutes and the use of large excess of reagents could be avoided.

Key words: microwave irradiation, epoxides, fluorination, ring opening, $Et_3N{\cdot}3HF$

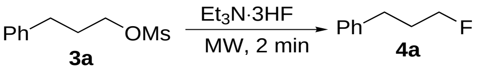
Among HF reagents, $Et_3N{\cdot}3HF$ has been widely used as a fluorinating reagent because it is commercially available, is close to neutral, has a high boiling point, and can be used in glassware.[1] However, the fluorination reactions using $Et_3N{\cdot}3HF$ often require high temperature and long reaction time due to its low reactivity. For instance, the reaction of $Et_3N{\cdot}3HF$ 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 $Et_3N{\cdot}3HF$ 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 $Et_3N{\cdot}3HF$ 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.



Equation 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 $Et_3N{\cdot}3HF$ 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 $Et_3N{\cdot}3HF$ was necessary to 1 equivalent of the substrate, while 10 equivalents of the reagent were used under the thermal conditions.



Equation 2

As $Et_3N{\cdot}3HF$ 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 spectrometer. The ^1H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ on a Jeol JNM-A400II FT NMR and the chemical shifts are referred to TMS (^1H) and $CFCl_3$ (^{19}F), 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 reactor which is a Teflon™ PFA tube with a diameter of 10 cm and a length of 8 cm sealed at one end. $Et_3N{\cdot}3HF$ 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 were used without further purification. The epoxide **1e** was prepared from dec-1-ene by oxidation[7] and the mesylates **3a**,**b** were prepared from the corresponding alcohols.[8]

Fluorination Reactions with $Et_3N{\cdot}3HF$; *trans*-2-Fluorocyclohexan-1-ol (2a); Typical Procedure

Cyclohexene oxide (**1a**; 98 mg, 1 mmol) and $Et_3N{\cdot}3HF$ (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

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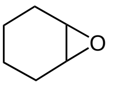
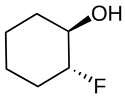
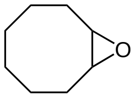
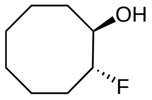
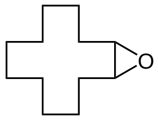
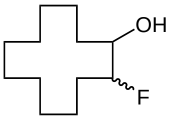
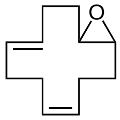
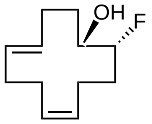
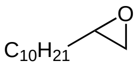
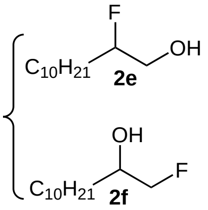
Table 1 Fluorination Using $Et_3N{\cdot}3HF$ Under Microwave Irradiation[a]

Substrate	React. Time (min)	Product	Yield (%)[b]
 **1a**	2	 **2a**	61
 **1b**	10	 **2b**	60
 **1c**[c]	10	 **2c**	76[d]
 **1d**	2	 **2d**	71[e,f]
 **1e**	2	 **2e** **2f**	45 47
$Ph-(CH_2)_3-OMs$ **3a**	2	$Ph-(CH_2)_3-F$ **4a**	63[g]
$AcO-(CH_2)_6-OMs$ **3b**	1	$AcO-(CH_2)_6-F$ **4b**	77[g]

[a] Unless otherwise mentioned, 0.6 equiv of $Et_3N{\cdot}3HF$ to 1 equiv of 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 $Et_3N{\cdot}3HF$ was used.

[g] 1.2 equiv of $Et_3N{\cdot}3HF$ was used.

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_2O (3 ×) and the combined ethereal layers were dried ($MgSO_4$). Purification by column chromatography (silica gel, eluent: hexane–Et_2O) 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, $CDCl_3$): $\delta = 4.26$ (dm, $J = 51.3$ Hz, 1 H), 3.59–3.68 (m, 1 H), 2.45 (br s, 1 H), 2.13–1.99 (m, 2 H), 1.77–1.69 (m, 2 H), 1.51–1.20 (m, 4 H).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -182.59$ (d, $J = 51.3$ Hz, 1 F).

trans-2-Fluorocyclooctan-1-ol (2b)
Yield: 60%; oil.[2]

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

^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.52$ (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).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -172.03$ to -172.24 (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, $CDCl_3$): $\delta = 4.55$ (dm, $J = 49.3$ Hz, 1 H), 3.92–3.86 (m, 1 H), 2.49 (s, 1 H), 1.91–1.34 (m, 20 H).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -193.93$ to -194.24 (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, $CDCl_3$): $\delta = 4.71$(dm, $J = 48.1$ Hz, 1 H), 3.97–3.89 (m, 1 H), 1.90 (s, 1 H), 1.80–1.18 (m, 20 H).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -191.15$ (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, $CDCl_3$): $\delta = 5.55$–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).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -185.88$ (br s, 0.6 F), -192.68 (br s, 0.4 F).

HRMS (EI): *m*/*z* 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 cm^{-1} (OH).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.58$ (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).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -190.07$ to -190.45 (m, 1 F).

1-Fluorododecan-2-ol (2f)
Yield: 47%; oil.[10]

IR (film): 3376 cm^{-1} (OH).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.50$–4.20 (m, 2 H), 3.94–3.82 (m, 1 H), 1.99 (s, 1 H), 1.46–1.26 (m, 12 H), 0.88 (t, $J = 6.6$ Hz, 3 H).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -228.85$ (dt, $J = 47.6, 17.7$ Hz, 1 F).

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, 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).

^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -220.62$ (tt, $J = 47.1, 25.0$ Hz, 1 F) (Lit.[3] $\delta = -220.2$).

1-Acetoxy-6-fluorohexane (4b)
Yield: 77%; oil.[12]

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

^1H 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).

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