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

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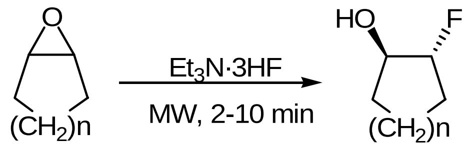
Abstract: Fluorination reaction of epoxides and alkyl mesylates can be effectively achieved by reaction with $Et_3N{\cdot}3HF$ under microwave irradiation. The reaction time could be greatly reduced compared to the reaction under thermal conditions. The reactions were completed in a few minutes and the use of large excess 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-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 had 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 equivalents 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 microwave as shown in Table 1.

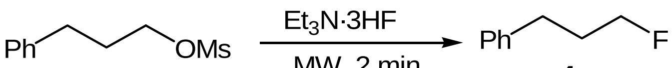


1a, n = 2
1b, n = 4

2a, n = 2
2b, n = 4

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



3a **4a**

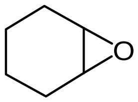
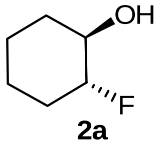
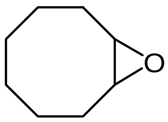
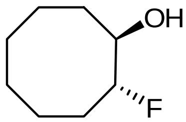
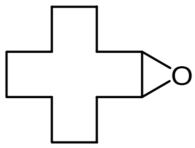
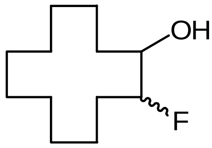
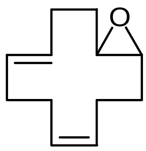
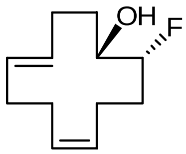
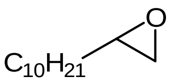
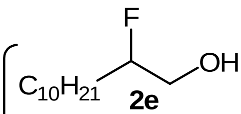
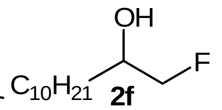
Equation 2

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. 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, δ , 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™ 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. $Et_3N\cdot 3HF$ 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 used without further purification. The epoxide **1e** was prepared from dec-1-ene by the oxidation[7] and the mesylates **3a**, **b** were prepared from the corresponding alcohols.[8]

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**	45
		 **2f**	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) If otherwise not mentioned, 0.6 equiv of $Et_3N{\cdot}3HF$ 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 $Et_3N{\cdot}3HF$ was used.
g) 1.2 equiv of $Et_3N{\cdot}3HF$ was used.

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

Cyclohexene oxide (98 mg, 1 mmol) and $Et_3N{\cdot}3HF$ (97 mg, 0.6 mmol) were introduced into a reactor consisting of a Teflon^{TM} 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_2O (3 X) and the combined ethereal layers were dried ($MgSO_4$). Purification by column chromatography (silica gel/hexane- Et_2O) 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, $CDCl_3$): 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).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -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, $CDCl_3$): 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).

^{19}F NMR (376 MHz, $CDCl_3$): 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}.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{19}F NMR (376 MHz, $CDCl_3$): 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}.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{19}F NMR (376 MHz, $CDCl_3$): 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}.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -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}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = -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, $CDCl_3$): δ = 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, $CDCl_3$): δ = -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, $CDCl_3$): δ = 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, $CDCl_3$): δ = -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, $CDCl_3$): δ = 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, $CDCl_3$): δ = -218.95 (tt, *J* = 47.3, 25.0 Hz, 1F).

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