



Title	Effective Fluorination Reaction with Et ₃ N•3HF Under Microwave Irradiation
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Effective Fluorination Reaction with Et₃N·3HF Under Microwave Irradiation

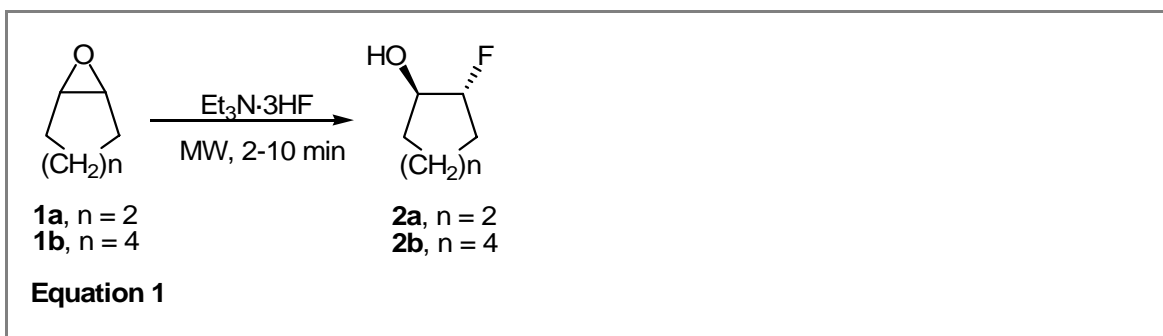
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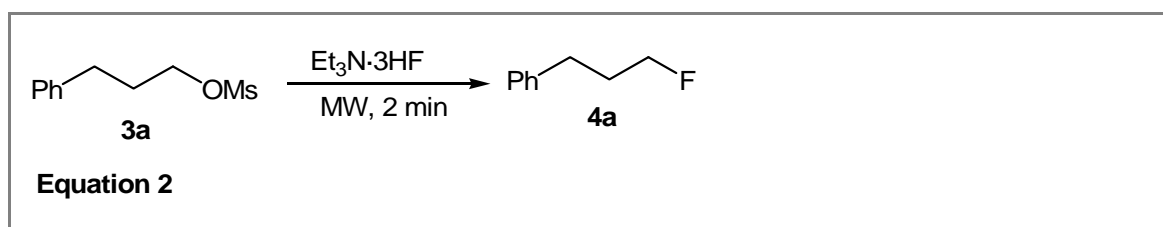
Abstract: Fluorination reaction of epoxides and alkyl mesylates can be effectively achieved by reaction with Et₃N·3HF under microwave irradiation. The reaction time could be greatly reduced compared to the reaction under thermal conditions. The reactions were completed in a few minutes and the use of 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 $\text{Et}_3\text{N}\cdot 3\text{HF}$ 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.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 $\text{Et}_3\text{N}\cdot 3\text{HF}$ to 1 equivalent of substrate was necessary, while 10 equivalents of the reagent were used under the thermal conditions.



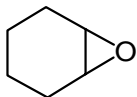
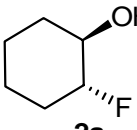
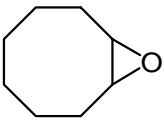
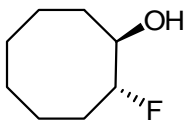
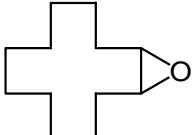
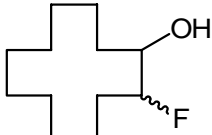
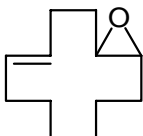
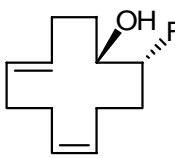
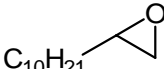
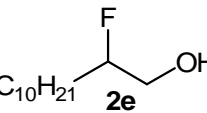
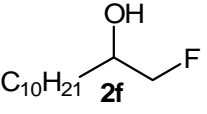
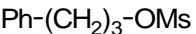

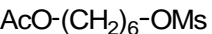

As $\text{Et}_3\text{N}\cdot 3\text{HF}$ is close to neutral, the reaction can tolerate functional groups such as a double bond (**1d**) and an ester (**3b**) as shown in Table 1.

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 ^1H 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 (^1H) 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 TeflonTM 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 TeflonTM PFA tube with a

diameter of 10 mm and a length of 8 cm sealed at one end. $\text{Et}_3\text{N}\cdot 3\text{HF}$ 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 oxidation⁷ and the mesylates **3a, b** were prepared from the corresponding alcohols.⁸

Table 1 Fluorination Using Et₃N·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	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">  2e </div> <div style="margin-right: 10px;">  2f </div> </div>	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">45</div> <div style="margin-right: 10px;">47</div> </div>
 3a	2	 4a	63 ^g
 3b	1	 4b	77 ^g

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 TeflonTM 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.

^1H 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} .

^1H 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} .

^1H 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} .

^1H 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).

References

- (1) (a) McClinton, M. A. *Aldrichchimica Acta* **1995**, 28, 31.
(b) Haufe, G. J. *Prakt. Chem.*, **1996**, 338, 99.
- (2) Wölker, D.; Haufe, G. J. *Org. Chem.* **2002**, 67, 3015.
- (3) Loupy, A. “*Microwaves in Organic Synthesis*” Wiley-VCH, Weinheim, **2002**, and references are cited therein.
- (4) For the fluorination reaction using HF reagent under microwave-irradiation, see: Coe, P.; Waring, T.; Mercier, C. WO 97/41083 A1, **1997**; *Chem. Abstr.* **1998**, 128, 13127.
- (5) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.*, **1990**, 31, 6527.
- (6) Michael, D.; Mingos, P.; Baghurst, D. R. *Chem. Soc. Rev.*, **1991**, 20, 1.
- (7) Paquette, L. A.; Barrett, J. H. *Org. Synth. Col. Vol. 5*; Wiley; New York, **1973**, 467.
- (8) Photis, J. M.; Paquette, L. A. *Org. Synth. Col. Vol. 6*, Wiley; New York, **1988**, 482.

- (9) Michael, D.; Schlosser, M.; *Tetrahedron*, **2000**, 56, 4253.
- (10) (a) Tamura, M.; Shibakami, M.; Arimura, T.; Kurosawa, S.; Sekiya, A. *J. Fluorine Chem.*, **1995**, 70, 1.
(b) Tamura, M.; Shibakami, M.; Sekiya, A. *J. Fluorine Chem.*, **1997**, 85, 147.
(c) Landini, D.; Penso, M. *Tetrahedron Lett.*, **1990**, 31, 7209.
- (11) (a) Patrick, T. B.; Johri, K. K.; White, D. H. *J. Org. Chem.*, **1983**, 48, 4158.
(b) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. *J. Fluorine Chem.*, **2001**, 109, 25.
- (12) Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron*, **2001**, 57, 3315.