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Author(s)	Akiyama, Yuriko; Hiramatsu, Chiharu; Fukuhara, Tsuyoshi et al.
Citation	Journal of Fluorine Chemistry, 127(7), 920-923 https://doi.org/10.1016/j.jfluchem.2006.04.001
Issue Date	2006-07
Doc URL	https://hdl.handle.net/2115/14466
Type	journal article
File Information	jfluchem_127(7)_920-923.pdf



Selective introduction of a fluorine atom into carbohydrates and a nucleoside by ring-opening fluorination reaction of epoxides

Yuriko Akiyama, Chiharu Hiramatsu, Tsuyoshi Fukuhara, Shoji Hara*

Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

Abstract

Ring-opening fluorination reactions of epoxides using tetrabutylammonium bifluoride (TBABF)-KHF₂, or Et₃N-3HF under microwave irradiation were applied for the introduction of a fluorine atom into the carbohydrate molecules. When TBABF-KHF₂ was used as the fluorination reagent, a fluorine atom was introduced regioselectively and various functional groups can tolerate the conditions. When Et₃N-3HF was used under microwave irradiation, the reaction time could be remarkably shortened compared with the conventional oil-bath heating.

Keywords: Fluorinated carbohydrates; Ring-opening fluorination; Epoxides; Microwave

1. Introduction

Fluorinated carbohydrates have recently received much attention because of their important role in the study of enzyme-carbohydrate interactions as well as their interesting biological activities [1,2] and application for positron emission tomography [3]. The ring-opening fluorination reactions of epoxides have been used to introduce a fluorine atom into the carbohydrate molecules [4-6]. However, problems such as regioselectivity, formation of undesired by-products, and long reaction time remained unsolved [7,8]. Recently, we found that tetrabutylammonium bifluoride (TBABF)-KHF₂ shows good regioselectivity in ring-opening fluorination of terminal epoxides [9]. We also found that application of microwave

irradiation to the ring-opening fluorination of epoxides using Et₃N-3HF can remarkably shorten the reaction time [10]. We applied these methods to the fluorinated carbohydrate and nucleoside synthesis, and succeeded in improving the yield, selectivity, and/or shortening the reaction time.

2. Results and Discussion

2.1. Fluorinated carbohydrates synthesis using TBABF-KHF₂ or Et₃N-3HF under microwave irradiation

2,3,6-Trideoxy-6-fluoro-*D*-arabino-hexano-1,4-lactone (**2**) was previously prepared from an epoxide (**1**) by the ring-opening fluorination using tetrabutylammonium dihydrogen trifluoride (TBATF)-KHF₂ [7] or Et₃N-3HF [8] in 70% or 55% yield, respectively. However, long time was required to complete the reactions (at 75 °C for 39h or at 70 °C for 3 days, respectively). When TBABF-KHF₂ was used for the reaction with **1**, it failed to improve the result (Entry 1 in Table 1). On the other hand, under the microwave irradiation condition, the reaction of **1** with Et₃N-3HF was completed in 10 min and **2** was obtained in 80% yield (Entry 2). Not only could the reaction time be remarkably shortened but also the yield could be improved. Application of the microwave irradiation method was found to be effective to shorten the reaction time in the fluorination of 2-deoxy-5,6-epoxy-*D*-arabino-hexano-1,4-lactone (**3**) with Et₃N-3HF, and the fluorinated product was isolated as a diacetate (**4**) in 67% yield after the microwave irradiation for 25 min at 120 °C (Entry 3). The reaction of **3** with Et₃N-3HF was

previously carried out under conventional oil-bath heating and it took 3 days at 70 °C to obtain the fluorinated product in 65% yield [8]. A 6-fluoro-6-deoxy-*D*-glucofuranose derivative (**6**), which was previously prepared by nucleophilic substitution reaction from cyclic sulfonate of the diol [11,12], was directly prepared from an epoxide (**5**). The fluorination of **5** with TBABF-KHF₂ regioselectively proceeded at 70 °C in 48h to give **6** in 78% yield (Entry 4), while the reaction of **5** with Et₃N-3HF was completed in 45 min at 120 °C under microwave irradiation to give **6** in 74 % yield without formation of the regioisomer (Entry 5). In these reactions, the products could be obtained with higher regioselectivity than in the cases of simple terminal epoxides [9,10]. The high selectivity can be attributed to an oxygen atom located at the α -carbon of the epoxides [13].

The fluorination of an internal epoxide in methyl 2,3-anhydro- β -*D*-ribofuranoside (**7**) was previously carried out using TBATF-KHF₂ at 130 °C for 12h and methyl 3-deoxy-3-fluoro- β -*D*-xylofuranoside (**8**) was obtained in 70% yield with its regioisomer (6%) [14]. When TBABF-KHF₂ was used, the reaction with **7** proceeded at 120 °C in 5h to selectively provide **8** in 70% yield (Entry 6). The reaction of **7** with Et₃N-3HF was completed in 30 min under the microwave irradiation and **8** was obtained in 55 % yield (Entry 7). In both cases, formation of the regioisomer was not observed.

Table 1
Fluorination of carbohydrates by ring-open fluorination of epoxides

Entry	Substrate	Method	React. Cond.	Product	Yield, % ^a
1		A	70 °C, 48h		63 (>99)
2		B	140 °C, 10 min		80 (≥98)
3		B	120 °C, 25 min		67 (>99)
4		A	70 °C, 48h ^b		78 (>99)
5		B	120 °C, 45 min		74 (>99)
6		A	120 °C, 5h ^c		70 (>99)
7		B	150 °C, 30 min		55 (>99)

a. Isolation yield based on epoxide used. In parentheses, regioselectivity. Method A: If otherwise not mentioned, TBABF-KHF₂ was used without solvent. Method B: Et₃N-3HF was used without solvent under microwave irradiation. b. CH₃CN was used as solvent. c. Heptane was used as solvent.

2.2. Application for the fluorinated nucleoside derivative synthesis

Synthesis of nucleoside derivatives having fluorine atoms at the sugar part is of great interest because such analogs having important bioactivities such as antiviral and anticancer activities were found [15]. 2'-C-β-Fluoromethyluridine derivative (**10**) was recently prepared from the corresponding 2'-α-spiroepoxyuridine derivative (**9**) by the reaction with KHF₂ at 130 °C for 8h [16]. However, the desired product **10** was

3.2. Preparation of TBABF

To a 1 M THF solution of TBAF (30 ml, 30 mmol) in a glass flask was added 46% aq HF (1.3 g, 30 mmol), and the volatile part was removed by an evaporator. Complete removal of water gave pure TBABF as a highly viscous liquid which is difficult to handle. Therefore, we recommend removing the water completely just before use. ^1H NMR (CD_2Cl_2 , $-80\text{ }^\circ\text{C}$) $\delta = 16.23$ (t, $J_{\text{HF}} = 122.9$ Hz, $^1\text{HF}_2$) [lit. [20] 16.12 (t, $J_{\text{HF}} = 122.7$ Hz)], ^{19}F NMR (CD_2Cl_2 , $-80\text{ }^\circ\text{C}$) $\delta = -151.5$ (d, $J_{\text{HF}} = 123.0$ Hz, $^1\text{HF}_2$) [lit. [20] $\delta = -147.5$ (d, $J_{\text{HF}} = 123.3$ Hz)]

3.3. Fluorinated carbohydrates synthesis

3.3.1. 2,3,6-Trideoxy-6-fluoro-D-arabino-hexano-1,4-lactone (**2**) [7,8]

Method A: A mixture of crude TBABF (423 mg, 1.5 mmol) and KHF_2 (12 mg, 0.15 mmol) in a glass flask was kept at $100\text{ }^\circ\text{C}$ / 0.55 mmHg for 15 min to remove water completely. After cooling to room temperature, **1** (64 mg, 0.5 mmol) and CH_3CN (1 ml) were added, and the mixture was stirred at $70\text{ }^\circ\text{C}$ for 48h. After cooling to room temperature, water (2 ml) and ether (2 ml) were added. The separated aqueous layer was extracted with ether three times, and the combined organic phase was dried over MgSO_4 and concentrated under reduced pressure. Purification by column chromatography (silica gel/ $\text{AcOEt-CH}_2\text{Cl}_2$) gave **2** (47 mg, 0.32 mmol) in 63% yield.

Method B: To a reactor of a TeflonTM PFA tube with a diameter of 10 mm sealed at one end, **1** (64 mg, 0.5 mmol) and $\text{Et}_3\text{N-3HF}$ (97 mg, 0.6 mmol) were introduced. The

open end of the reactor was connected to a reflux condenser. Then, the reactor part was submitted to microwave-irradiation for 10 min and during the irradiation, the temperature was kept at 140 °C. After cooling, the reaction mixture was poured into an aq NaHCO₃ solution. The product was extracted with ether three times and the combined ethereal layers were dried over MgSO₄. Purification by column chromatography (silica gel/AcOEt-CH₂Cl₂) gave **2** (59 mg, 0.4 mmol) in 80 % yield. Viscous liquid: IR (neat) 3429, 2963, 1774, 1192 cm⁻¹. ¹H NMR δ = 2.29-2.36 (m, 3H), 2.52-2.67 (m, 2H), 4.00-4.10 (dm, *J* = 19.4 Hz, 1H), 4.45-4.64 (m, 3H). ¹³C NMR δ = 22.50, 28.20, 70.55 (d, *J*_{C-F} = 19.0 Hz), 79.17 (d, *J*_{C-F} = 5.8 Hz), 83.31 (d, *J*_{C-F} = 169.5 Hz), 177.56. ¹⁹F NMR δ = -235.27(dt, *J* = 19.4, 47.0 Hz, 1F).

3.3.2. 2,6-Dideoxy-3,5-di-*O*-acetyl-6-fluoro-*D*-arabino-hexano-1,4-lactone (**4**)

Method B: The fluorination reaction of **3** (72 mg, 0.5 mmol) was carried out using Et₃N-3HF (97 mg, 0.6 mmol) at 120 °C for 25 min as in the case of **1**. After the reaction, the mixture was poured into an aq NaHCO₃ solution, extracted with ether three times, and dried over MgSO₄. After concentration, Ac₂O (1 ml) and 60% HClO₄ (0.03 ml) were added and the mixture was stirred at room temperature overnight. The mixture was poured into an aq NaHCO₃ solution, extracted with ether three times, and dried over MgSO₄. After concentration, **4** (82 mg, 0.33 mmol) was isolated by column chromatography (silica gel/AcOEt-CH₂Cl₂) in 66% yield. White solid: mp 88 °C. IR (KBr) 2969, 1783, 1740, 1254, 1041 cm⁻¹. ¹H NMR δ = 2.06 (s, 3H), 2.09 (s, 3H), 2.62 (d, *J* = 18.3 Hz, 1H), 2.92 (dd, *J* = 18.3, 5.5 Hz, 1H), 4.60-4.79 (m, 3H), 5.27 (ddt, *J* = 27.4, 9.8, 2.4 Hz, 1H), 5.66 (dd, *J* = 5.5, 3.7 Hz, 1H). ¹³C

NMR δ = 20.68, 20.70, 36.62, 68.05 (d, J = 18.2 Hz), 68.47, 77.13, 81.65 (d, J = 175.3 Hz), 169.50 (2C), 172.68. ^{19}F NMR δ = -236.80 (dt, J = 24.0, 47.0 Hz). HRMS (EI): Calcd for $\text{C}_9\text{H}_{11}\text{O}_6$ (M^+ - CH_2F): 215.0555, Found: 215.0543.

3.3.3. 6-Deoxy-6-fluoro-1,2-O-isopropylidene- α -D-glucofuranose (**6**) [11,21]

Method A: The fluorination reaction of **5** (101 mg, 0.5 mmol) was carried out using TBABF (423 mg, 1.5 mmol), KHF_2 (12 mg, 0.15 mmol) and CH_3CN (1 ml) at 70 °C for 48h as in the case of **1**, and **6** (86 mg, 0.39 mmol) was isolated by column chromatography (silica gel/AcOEt-hexane) in 78% yield.

Method B: The fluorination reaction of **5** (101 mg, 0.5 mmol) was carried out using Et_3N -3HF (805 mg, 5 mmol) at 120 °C for 45 min as in the case of **1**, and **6** (82 mg, 0.37 mmol) was isolated by column chromatography (silica gel/EtOAc-hexane) in 74% yield. Viscous liquid: IR (neat) 3434, 2989, 1377, 1073, 1011 cm^{-1} . ^1H NMR δ = 1.32 (s, 3H), 1.49 (s, 3H), 3.76 (brs, 2H), 4.09-4.21 (m, 2H), 4.37 (s, 1H), 4.54 (d, J = 3.4 Hz, 1H), 4.60-4.75 (m, 2H), 5.95 (d, J = 3.4 Hz, 1H). ^{13}C NMR δ = 26.04, 26.63, 68.87 (d, $J_{\text{C-F}}$ = 19.0 Hz), 75.13, 78.46 (d, $J_{\text{C-F}}$ = 5.8 Hz), 84.68 (d, $J_{\text{C-F}}$ = 169.5 Hz), 84.93, 104.82, 111.92. ^{19}F NMR δ = -233.94 (dt, J = 23.2, 47.6 Hz, 1F).

3.3.4. Methyl 3-deoxy-3-fluoro- β -D-xylopyranoside (**8**) [14]

Method A: The fluorination reaction of **7** (73 mg, 0.5 mmol) was carried out using TBABF (423 mg, 1.5 mmol), KHF_2 (12 mg, 0.15 mmol), and heptane (1 ml) as solvent at 120 °C for 5h as in the case of **1**, and **8** (61 mg, 0.37 mmol) was isolated by column chromatography (silica gel/AcOEt- CH_2Cl_2) in 70% yield.

Method B: The fluorination reaction of **7** (101 mg, 0.5 mmol) was carried out using Et₃N-3HF (803 mg, 5 mmol) at 150 °C for 30 min as in the case of **1**, and **8** (46 mg, 0.28 mmol) was isolated by column chromatography (silica gel/AcOEt-CH₂Cl₂) in 55% yield. White solid: mp 102-104 °C (lit. [14] 104-105 °C). IR (KBr) 3312, 2924, 1384, 1065, 1028 cm⁻¹. ¹H NMR δ = 2.35 (d, *J* = 3.7 Hz, 1H), 2.53 (d, *J* = 2.7 Hz, 1H), 3.30 (dd, *J* = 9.8, 11.7 Hz, 1H), 3.55 (s, 3H), 3.57-3.65 (m, 1H), 3.89-4.00 (m, 1H), 4.03-4.09 (m, 1H), 4.22 (d, *J* = 6.8 Hz, 1H), 4.39 (ddd, *J* = 8.1, 8.1, 52.0 Hz, 1H). ¹³C NMR δ = 57.24, 63.72 (d, *J*_{C-F} = 8.3 Hz), 68.39 (d, *J*_{C-F} = 19.0 Hz), 71.64 (d, *J*_{C-F} = 18.2 Hz), 95.42 (d, *J*_{C-F} = 181.9 Hz), 103.52 (d, *J*_{C-F} = 10.8 Hz). ¹⁹F NMR δ = -205.36 (ddt, *J* = 51.9, 5.5, 12.8 Hz, 1F).

3.4. Application for the fluorinated nucleoside derivative synthesis

3.4.1. 3-*N*-Methoxyethoxymethyl-2'-*C*-β-fluoromethyluridine (**10**) [15]

Method A: After complete removal of water from a mixture of the crude TBABF (423 mg, 1.5 mmol) and KHF₂ (45 mg, 0.15 mmol), **9** (55 mg, 0.11 mmol) and CH₃CN (2 ml) were added, and the mixture was stirred at 60 °C for 24h. After cooling to room temperature, water (2 ml) and ether (2 ml) were added. The separated aqueous layer was extracted with ether three times, and the combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel/AcOEt-CH₂Cl₂) gave **10** (27 mg, 0.083 mmol) in 74% yield. Viscous liquid: IR (neat) 3428, 2926, 1714, 1660, 1461, 1075 cm⁻¹. ¹H NMR (CD₃OD) δ = 3.32 (s, 3H), 3.30-3.35 (m, 1H), 3.48-3.51 (m, 2H), 3.72-3.74 (m, 2H),

3.80-3.83 (m, 1H), 3.97-4.03 (m, 2H), 4.25-4.28 (m, 2H), 4.30 (dd, $J = 10.0, 45.6$ Hz, 1H), 4.47 (dd, $J = 10.0, 48.1$ Hz, 1H), 5.41 (s, 2H), 5.70 (d, $J = 8.2$ Hz, 1H), 6.04 (s, 1H), 8.18 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR $\delta = 58.86, 59.81, 67.67, 69.45, 70.93, 71.58, 78.85$ (d, $J_{\text{C-F}} = 18.2$ Hz), 81.57 (d, $J_{\text{C-F}} = 175.3$ Hz), $82.07, 90.51, 101.51, 140.08, 151.57, 163.06$. ^{19}F NMR (CD_3OD) $\delta = -225.90$ (t, $J = 46.1$ Hz, 1F).

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