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

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Abstract

Ring-opening fluorination reactions of epoxides using tetrabutylammonium bifluoride (TBABF)-KHF_2, or Et_3N-3HF under microwave irradiation were applied for the introduction of a fluorine atom into the carbohydrate molecules. When TBABF-KHF_2 was used as the fluorination reagent, a fluorine atom was introduced regioselectively and various functional groups can tolerate the conditions. When Et_3N-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)-KHF_2 shows good regioselectivity in ring-opening fluorination of terminal epoxides [9]. We also found that application of microwave

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irradiation to the ring-opening fluorination of epoxides using Et_3N-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.

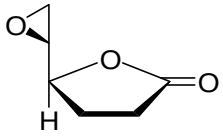
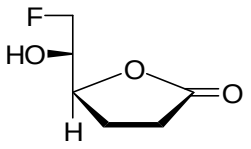
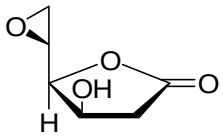
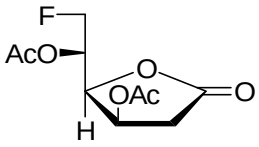
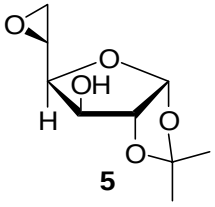
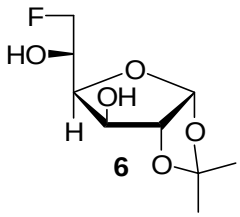
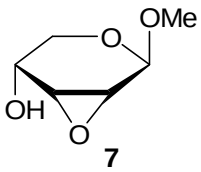
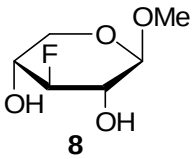
2. Results and Discussion

2.1. Fluorinated carbohydrates synthesis using TBABF-KHF_2 or Et_3N-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)-KHF_2 [7] or Et_3N-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-KHF_2 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 Et_3N-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 Et_3N-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 Et_3N-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-KHF_2 regioselectively proceeded at 70 °C in 48h to give **6** in 78% yield (Entry 4), while the reaction of **5** with Et_3N-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*-ribopyranoside (**7**) was previously carried out using TBATF-KHF_2 at 130 °C for 12h and methyl 3-deoxy-3-fluoro-β-*D*-xylopyranoside (**8**) was obtained in 70% yield with its regioisomer (6%) [14]. When TBABF-KHF_2 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 Et_3N-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-openin fluorination of epoxides

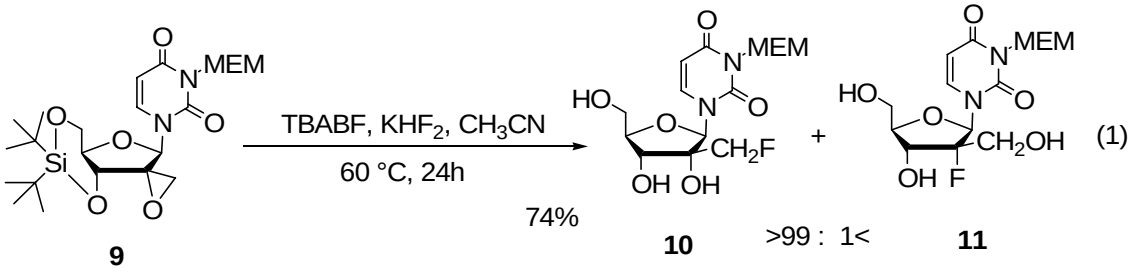
Entry	Substrate	Method	React. Cond.	Product	Yield, %[a]
1	 **1**	A	70 °C, 48h	 **2**	63 (>99)
2		B	140 °C, 10 min		80 (≥98)
3	 **3**	B	120 °C, 25 min	 **4**	67 (>99)
4	 **5**	A	70 °C, 48h[b]	 **6**	78 (>99)
5		B	120 °C, 45 min		74 (>99)
6	 **7**	A	120 °C, 5h[c]	 **8**	70 (>99)
7		B	150 °C, 30 min		55 (>99)

a. Isolation yield based on epoxide used. In parentheses, regioselectivity. Method A: If otherwise not mentioned, TBABF-KHF_2 was used without solvent. Method B: Et_3N-3HF was used without solvent under microwave irradiation. b. CH_3CN 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 KHF_2 at 130 °C for 8h [16]. However, the desired product **10** was

obtained only in 35% yield with many by-products including its regioisomer **11**. When the reaction was carried out using TBABF-KHF_2 in CH_3CN, **11** could be obtained in 74% yield without the formation of **11** (eq 1).



3. Experimental

3.1. General Experimental Procedures

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shifts, δ, are referred to TMS (^{1}H and ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Microwave irradiation was carried out using an IDX microwave oven for organic synthesis (0-300 W, IMCR-25003) equipped with a temperature control system. Compounds **1** [17], **3** [17], **5** [18], **7** [19], and **9** [16] were prepared according to literatures. KHF_2 and 46 % aq HF were purchased from Wako Pure Chemical Industries. Ltd. Et_3N-3HF and TBAF (1 M solution in THF) were purchased from Aldrich.

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. ^{1}H NMR (CD_2Cl_2, -80 ºC) δ = 16.23 (t, J_{HF} = 122.9 Hz, $^{-}HF_2$) [lit. [20] 16.12 (t, J_{HF} = 122.7 Hz)], ^{19}F NMR (CD_2Cl_2, -80 ºC) δ = -151.5 (d, J_{HF} = 123.0 Hz, $^{-}HF_2$) [lit. [20] δ = -147.5 (d, J_{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 ºC / 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 ºC 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/AcOEt-CH_2Cl_2) gave **2** (47 mg, 0.32 mmol) in 63% yield.
Method B: To a reactor of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end**, 1** (64 mg, 0.5 mmol) and Et_3N-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 $NaHCO_3$ solution. The product was extracted with ether three times and the combined ethereal layers were dried over $MgSO_4$. Purification by column chromatography (silica gel/AcOEt-CH_2Cl_2) 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). ^{13}C 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. ^{19}F 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 Et_3N-3HF (97 mg, 0.6 mmol) at 120 ºC for 25 min as in the case of **1**. After the reaction, the mixture was poured into an aq $NaHCO_3$ solution, extracted with ether three times, and dried over $MgSO_4$. After concentration, Ac_2O (1 ml) and 60% $HClO_4$ (0.03 ml) were added and the mixture was stirred at room temperature overnight. The mixture was poured into an aq $NaHCO_3$ solution, extracted with ether three times, and dried over $MgSO_4$. After concentration, **4** (82 mg, 0.33 mmol) was isolated by column chromatography (silica gel/AcOEt-CH_2Cl_2) 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). ^{13}C

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 $C_9H_{11}O_6$ (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 ºC 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 ºC 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}. ^{1}H 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, $J_{C\text{-}F}$ = 19.0 Hz), 75.13, 78.46 (d, $J_{C\text{-}F}$ = 5.8 Hz), 84.68 (d, $J_{C\text{-}F}$ = 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 ºC 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 Et_3N-3HF (803 mg, 5 mmol) at 150 ºC for 30 min as in the case of **1**, and **8** (46 mg, 0.28 mmol) was isolated by column chromatography (silica gel/AcOEt-CH_2Cl_2) in 55% yield. White solid: mp 102-104 ºC (lit. [14] 104-105 ºC). IR (KBr) 3312, 2924, 1384, 1065, 1028 cm^{-1}. ^1H NMR δ = 2.35 (d, *J* = 3.7Hz, 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). ^{13}C 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). ^{19}F 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 KHF_2 (45 mg, 0.15 mmol), **9** (55 mg, 0.11 mmol) and CH_3CN (2 ml) were added, and the mixture was stirred at 60 ºC 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 $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/AcOEt-CH_2Cl_2) gave **10** (27 mg, 0.083 mmol) in 74% yield. Viscous liquid: IR (neat) 3428, 2926, 1714, 1660, 1461, 1075 cm^{-1}. ^1H NMR (CD_3OD) 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 δ = 58.86, 59.81, 67.67, 69.45, 70.93, 71.58, 78.85 (d, $J_{C\text{-}F}$ = 18.2 Hz), 81.57 (d, $J_{C\text{-}F}$ = 175.3 Hz), 82.07, 90.51, 101.51, 140.08, 151.57, 163.06. ^{19}F NMR (CD_3OD) δ = –225.90 (t, J = 46.1 Hz, 1F).

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