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Synthesis of *gem*-difluorides from aldehydes using DFMBA

Tsukasa Furuya, Tsuyoshi Fukuhara, Shoji Hara *

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

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Abstract

Synthesis of *gem*-difluorides from aldehydes was effectively achieved using DFMBA and Et_3N-3HF under microwave irradiation or conventional thermal heating. Both aromatic and aliphatic aldehydes could be converted to the corresponding *gem*-difluorides in good yields.

Keywords: Microwave-irradiation; Aldehyde; Fluorination; *gem*-Difluoride

1. Introduction

Introduction of a *gem*-difluoromethyl group into bioactive compounds can enhance or change their activity dramatically [1,2]. Therefore, much effort has been paid to develop a novel and efficient method to introduce the *gem*-difluoromethyl group into molecules [3–8]. Direct conversion of a carbonyl group to the *gem*-difluoride is the most straightforward method and diethylaminosulfur trifluoride (DAST) [9,10] and its modifications such as Deoxofluor™ [11–13] have been most frequently used for such purpose. However, they incur a problem of thermal stability and a novel method using more stable reagents has been desired [14–16]. Recently, α, α-difluoroamines were reported as a thermally stable fluorination reagent [17–20], and we reported that a hydroxyl group of sugars can be effectively converted to a fluoride by *N,N*-diethyl-α, α-difluoro-(*m*-methylbenzyl)amine (DFMBA) under microwave irradiation [19,20]. We report here an application of DFMBA for synthesis of the *gem*-difluoro compounds from the aldehydes.

2. Results and discussion

The reaction was carried out using a microwave oven for organic synthesis which can keep the temperature in the oven constant during the reaction by controlling the power. When *p-t*-butylbenzaldehyde (**1a**) was subjected to the reaction with DFMBA under microwave irradiation at 180 °C for 20 min, the expected *gem*-difluoro compound (**2a**) could be obtained in 61% yield but **1a** still remained in the reaction mixture (Entry 1 in Table 1). Additional use of Et_3N-3HF as a fluoride source was found to be effective to accelerate the reaction. By the addition of 0.2 equiv. of Et_3N-3HF, the yield of **2a** could be improved to 89% (Entry 2). The best result was obtained by using 1 equiv. of Et_3N-3HF and 2 equiv. of DFMBA to **1a**, and **2a** was obtained in 96% yield (Entry 3). When the reaction was carried out using 1.5 equiv. of DFMBA (Entry 4), at lower temperature (Entry 5), or for a shorter time (Entry 6), the yields of **2a** decreased. When the reaction mixture was heated by a conventional oil bath at 180 °C for 20 min, the yield of **2a** slightly decreased (Entry 7). However, in this reaction, the effect of microwave was not so clear as in the previous cases [19,20].

Under similar reaction conditions, various aromatic aldehydes (**1a–e**) and aliphatic aldehydes (**1f–j**) could be converted to the corresponding *gem*-difluoro compounds (**2a–j**) in high to good yields (Table 2).

Under the reaction conditions, the ester group (**1c**, **i**), alkoxy group (**1b**, **e**), hydroxyl group (**1d**), and double bond (**1g**, **h**, **j**) remained unchanged. The reaction of DFMBA with ketone is very slow under the reaction conditions. When a mixture of benzaldehyde and acetophenone was subjected to the reaction with DFMBA and Et_3N-3HF, the benzaldehyde

* Corresponding author. Tel.: +81 11 706 6556; fax: +81 11 706 6556.
E-mail address: hara@org-mc.eng.hokudai.ac.jp (S. Hara).

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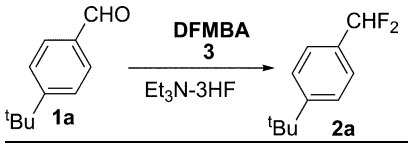
Table 1
gem-Difluorination of aldehydes using DFMBA[a]



Entry	Et_3N-3HF (equiv. to **1a**)	Temperature (°C)	Yield (%)[b]
1	0	180	61
2	0.2	180	89
3	1	180	96 (80)
4[c]	1	180	90
5	1	170	88
6[d]	1	180	91
7[e]	1	180	93

[a] If otherwise not mentioned, the reactions were carried out for 20 min under micowave irradiation using 2 equiv. of **3** to **1a**.
[b] ^{19}F NMR yield based on 1a. In parenthesis, isolated yield.
[c] 1.5 equiv. of **3** to **1a** was used.
[d] The microwave irradiation was carried out for 10 min.
[e] Oil bath heating was used instead of microwave irradiation.

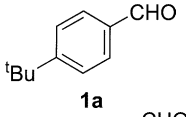
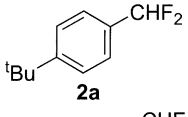
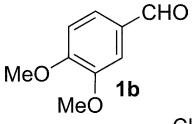
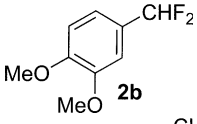
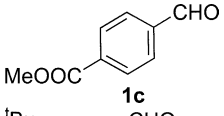
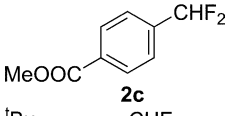
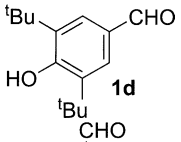
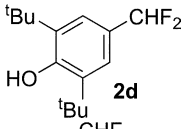
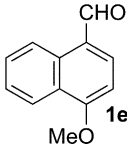
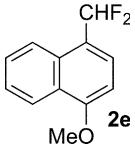
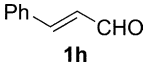
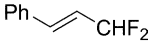
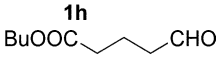
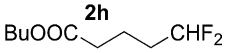
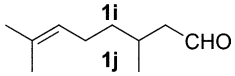
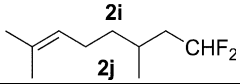
was selectively converted to difluoromethylbenzene and most of the acetophenone remained unchanged. Therefore, in the reaction with 4-formylbenzophenone (**4**), which has both ketone and aldehyde groups in the molecule, the aldehyde group was selectively converted to the *gem*-difluoride and 4-difluoromethylbenzophenone (**5**) could be obtained in 92% yield (Scheme 1). Under the reaction conditions, the conversion of the ketone part to the *gem*-difluoride was observed by $^{19}FNMR$ only in low yield (<3%).

3. Experimental

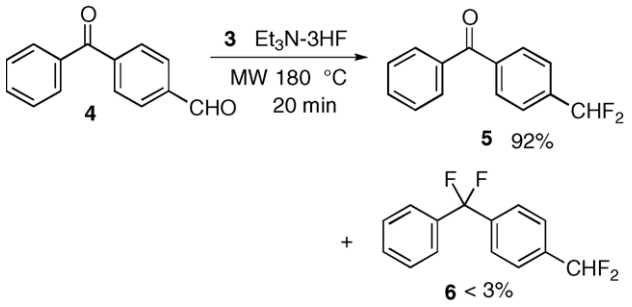
3.1. General methods

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 (270 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-EX270 FT NMR and the chemical shift, δ, is referred

Table 2
Reaction of aldehydes with DFMBA[a]

Aldehyde	Reaction conditions	Product	Yield (%)[b]
 **1a**	180 °C, 20 min	 **2a**	80
 **1b**	180 °C, 20 min	 **2b**	88
 **1c**	180 °C, 20 min	 **2c**	85
 **1d**	150 °C, 30 min	 **2d**	61
 **1e**	180 °C, 20 min	 **2e**	84
$C_{10}H_{21}-CHO$ **1f**	180 °C, 20 min	$C_{10}H_{21}-CHF_2$ **2f**	75
$CH_2=CH(CH_2)_8-CHO$ **1g**	180 °C, 20 min	$CH_2=CH(CH_2)_8-CHF_2$ **2g**	71
 **1h**	180 °C, 20 min	 **2h**	77
 **1i**	170 °C, 20 min	 **2i**	60
 **1j**	180 °C, 20 min	 **2j**	(70)

[a] Reactions were carried out using 2 equiv. of DFMBA and 1 equiv. of Et_3N-3HF to **1**.
[b] Isolated yield based on substrate used and in parenthesis, $^{19}FNMR$ yield.



Scheme 1.

to TMS. ^{19}F NMR (376 MHz) spectra and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to $CFCl_3$ (^{19}F) and TMS (^{13}C), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. Microwave irradiation was carried out using an IDX microwave oven for organic synthesis (0–300 W, IMCR-25003) having temperature control. Et_3N-3HF was purchased from Aldrich Chemical Co. and distilled before use. Aldehydes (**1a–h**, **j**) were purchased from Tokyo Kasei Co. Butyl 5-oxopentanoate (**1i**) was prepared by PCC oxidation of butyl 5-hydroxypentanoate obtained by transesterification of δ-valerolactone. 4-Formylbenzophenone (**4**) was prepared by the oxidation of 4-(bromomethyl)acetophenone [21].

3.2. Preparation of DFMBA

DFMBA was prepared by a modification of reported procedure [22]. To a CH_2Cl_2 (50 ml) solution of *N,N*-diethyl-*m*-methylbenzamide (13.8 g, 72 mmol), was added at 0 °C a CH_2Cl_2 (20 ml) solution of oxalic chloride (9.9 g, 78 mmol). After the addition, the mixture was stirred at 40 °C for 2 h. Then the mixture was cooled to 0 °C again, and Et_3N-3HF (8.7 g, 53 mmol) and Et_3N (10.1 g 100 mmol) were added successively. The mixture was stirred at room temperature for 2 h and a generated precipitate was removed by filtration. The precipitate was washed with CH_2Cl_2 (100 ml) and the combined filtrate was concentrated under reduced pressure. A hexane (100 ml) was added to the residue and the generated solid was removed by filtration again. The solid was washed with a hexane (50 ml) and the filtrate was concentrated under reduced pressure. The distillation of the residue gave DFMBA (12.6 g, 59 mmol) in 82% yield (bp 81–83 °C/4 mmHg). Glassware can be used. All operations should be carried out under minimum contact to moisture.

3.2.1. Synthesis of p-difluoromethyl-t-butylbenzene (2a) [23]

p-t-Butylbenzaldehyde (162 mg, 1 mmol), DFMBA (426 mg, 2 mmol), and Et_3N-3HF (161 mg, 1 mmol) were introduced into a reactor 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 a reflux condenser. Then, the reaction mixture was submitted for 20 min to microwave-irradiation and during the irradiation, the temperature was kept at 180 °C. After cooling, the reaction mixture was poured into an aqueous $NaHCO_3$ 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/hexane-ether) gave **2a** in 80% yield. IR: (neat) ν 2966, 1622, 1379, 1076, 1027 cm^{-1}. ^{1}H NMR δ 1.33 (s, 9H), 6.63 (t, J = 56.6 Hz, 1H), 7.42–7.50 (m, 4H). ^{19}F NMR δ −110.48 (d, J = 56.8 Hz, 2F) [23]. ^{13}C NMR δ 31.19 (3C, –C(<u>C</u>H$_3$)$_3$), 34.84(–<u>C</u>(CH$_3$)$_3$), 114.89 (t, J = 236.5 Hz, –CHF_2), 125.29 (t, J = 5.8 Hz, C-1), 125.60 (2C, C-3, C-5), 131.50 (t, J = 22.3 Hz, 2C, C-2, C-6), 153.98 (C-4).

3.2.2. 1-Difluoromethyl-3,4-dimethoxybenzene (2b) [13]

IR: (neat) ν 2964, 2942, 2841, 1612, 1523, 1268, 1025 cm^{-1}. ^{1}H NMR δ 3.91 (s, 3H), 3.92 (s, 3H), 6.60 (t, J = 56.4 Hz, 1H), 6.89–7.07(m, 3H). ^{19}F NMR δ −108.70 (d, J = 56.8 Hz, 2F) [13]. ^{13}C NMR δ 55.83 (–OCH_3), 55.85 (–OCH_3), 107.87 (t, J = 9.9 Hz, C-1), 110.54 (C-5), 114.83 (t, J = 236.1 Hz, –CHF_2), 118.65 (t, J = 14.0 Hz, C-6), 126.79 (t, J = 22.7 Hz, C-2), 149.12 (C-3 or C-4), 150.78 (C-3 or C-4).

3.2.3. Methyl p-difluoromethylbenzoate (2c)

White solid. mp 36.5–37 °C. IR: (KBr) ν 2964, 1723, 1281, 1014 cm^{-1}. ^{1}H NMR δ 3.95 (s, 3H), 6.69 (t, J = 56.0 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 8.13 (d, J = 8.1 Hz, 2H). ^{19}F NMR δ −112.85 (d, J = 56.2 Hz, 2F). ^{13}C NMR δ 52.38 (–OCH_3), 113.97 (t, J = 238.6 Hz, –CHF_2), 125.62 (t, J = 5.8 Hz, 2C, C-2, C-6), 129.93 (2C, C-3, C-5), 132.27 (C-4), 138.42 (t, J = 57.5 Hz, C-1), 166.24 (C=O). HRMS (EI): calc. for $C_9H_8O_2F_2$: 186.0492; found: 186.0493.

3.2.4. 2,6-Di-t-butyl-4-difluoromethylphenol (2d)

White solid. mp 78.5–79 °C. IR: (KBr) ν 3634, 2955, 1442, 1372, 1077, 1005 cm^{-1}. ^{1}H NMR δ 1.45 (s, 18H), 5.46 (s, 1H), 6.57 (t, J = 57.2 Hz, 1H), 7.31 (s, 2H). ^{19}F NMR δ −107.68 (d, J = 56.8 Hz, 2F). ^{13}C NMR δ 30.08 (6C, –C(<u>C</u>H$_3$)$_3$), 34.38 (2C, –<u>C</u>(CH$_3$)$_3$), 115.77 (t, J = 236.7 Hz, –CHF_2), 122.55 (t, J = 5.8 Hz, 2C, C-2, C-6), 125.24 (t, J = 22.2 Hz, C-1), 136.19 (C-4),155.81 (2C, C-3, C-5). HRMS (EI): calc. for $C_{15}H_{22}OF_2$: 256.1639; found: 256.1637.

3.2.5. 1-Difluoromethyl-4-methoxynaphthalene (2e)

IR: (neat) ν 2970, 1586, 1229, 1011 cm^{-1}. ^{1}H NMR δ 4.03 (s, 3H), 6.78 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 55.3 Hz, 1H), 7.51–7.63 (m, 3H), 8.11–8.15 (m, 1H), 8.32–8.35 (m, 1H). ^{19}F NMR δ −109.65 (d, J = 55.5 Hz, 2F). ^{13}C NMR δ 55.64 (–OCH_3), 102.14 (2C, C_{Ar}), 115.98 (t, J = 235.7 Hz,

–CHF_2), 121.84 (t, J = 21.0Hz, C-1), 122.69 (C_{Ar}), 123.37 (C_{Ar}), 125.70 (C_{Ar}), 125.88 (t, J = 8.7 Hz, C_{Ar}), 127.60 (C_{Ar}), 130.72 (C_{Ar}), 157.68 (C-4). HRMS (EI): calc. for $C_{12}H_{10}OF_2$: 208.0700; found: 208.0697.

3.2.6. 1,1-Difluoroundecane (**2f**) [24]

IR: (neat) ν 2926, 1467, 1403, 1118 cm^{-1}. ^1H NMR δ 0.88 (t, J = 6.7 Hz, 3H), 1.18–1.50 (m, 16H), 1.71-1.92 (m, 2H), 5.79 (tt, J = 57.2, J = 4.6 Hz, 1H). ^{19}F NMR δ −116.31 (dt, J = 57.4, J = 17.1 Hz, 2F) [24]. ^{13}C NMR δ 14.09 (C-11), 22.12 (t, J = 5.4 Hz, C-3), 22.68, 29.06, 29.31, 29.37, 29.45, 29.55, 31.98, 34.09 (t, J = 20.6 Hz, C-2), 117.50 (t, J = 231.1 Hz, $-CHF_2$).

3.2.7. 1,1-Difluoro-10-undecene (**2g**)

IR: (neat) ν 2928, 2856, 1641, 1402, 1123 cm^{-1}. ^1H NMR δ 1.18–1.47 (m, 12H), 1.71–1.92 (m, 2H), 2.00–2.06 (m, 2H), 4.90–5.03 (m, 2H), 5.79 (tt, J = 57.1, J = 4.7 Hz, 1H), 5.74–5.89 (m, 1H). ^{19}F NMR δ −116.32 (dt, J = 57.37, J = 17.09 Hz, 2F). ^{13}C NMR δ 22.08 (t, J = 5.4 Hz, C-3), 28.86, 29.02 (2C), 29.24, 29.28, 33.76, 34.05 (t, J = 20.5 Hz, C-2), 114.15 (C-11), 117.49 (t, J = 237.4 Hz, –CHF_2), 139.15 (C-10). HRMS (EI): calc. for $C_{11}H_{20}F_2$: 190.1533; found: 190.1540.

3.2.8. 3,3-Difluoro-1-phenyl-1-propene (**2h**) [25]

IR: (neat) ν 3030, 1658, 1388, 1139, 1015 cm^{-1}. ^1H NMR δ 6.18–6.33 (m, 1H), 6.25 (dt, J = 5.4, J = 56.0 Hz, 1H), 6.84–6.92 (m, 1H), 7.31–7.46 (m, 5H). ^{19}F NMR δ −110.18 to −110.36 (m, 2F) [25]. ^{13}C NMR δ 115.37 (t, J = 232.5 Hz, –CHF_2), 120.95 (t, J = 23.5 Hz, C-2), 127.22 (2C, C_{Ar}), 128.80 (C_{Ar}), 129.39 (2C, C_{Ar}), 134.40 (C_{Ar}), 137.09 (t, J = 12.4 Hz, C-3).

3.2.9. Butyl 5,5-difluoropentanoate (**2i**)

IR: (neat) ν 2963, 1736, 1175 cm^{-1}. ^1H NMR δ 0.94 (t, J = 7.3 Hz, 3H), 1.31–1.45 (m, 2H), 2.38 (t, J = 7.6 Hz, 2H), 1.56–1.67 (m, 2H), 1.74–1.99 (m, 4H), 4.09 (t, J = 6.6 Hz, 2H), 5.83 (tt, J = 56.8, J = 4.2 Hz, 1H). ^{19}F NMR δ −116.67 (dt, J = 56.8, J = 17.1 Hz, 2F). ^{13}C NMR δ 13.65 (–CH_3), 17.55 (t, J = 5.8 Hz, C-3), 19.09, 30.60, 33.05 (C-2), 33.35 (t, J = 10.3 Hz, C-4), 64.40 (–OCH_2–), 116.89 (t, J = 237.8 Hz, –CHF_2), 172.89 (C=O). HRMS (EI): calc. for $C_9H_{16}O_2F_2$: 194.1119; found: 194.1119.

3.2.10. 8,8-Difluoro-2,6-dimethyl-2-octene (**2j**)

IR: (neat) ν 2966, 2924, 1439, 1402, 1121, 1039 cm^{-1}. ^1H NMR δ 0.97 (d, J = 6.5 Hz, 3H), 1.17–1.44 (m, 2H), 1.60 (s, 3H), 1.55–2.04 (m, 5 H), 1.69 (s, 3H), 5.05–5.11 (m, 1H), 5.86 (tt, J = 57.0, J = 4.2 Hz, 1H). ^{19}F NMR δ −115.25 to −114.98 (m, 2F). ^{13}C NMR δ 17.63, 19.53, 25.16, 25.70, 27.47 (t, J = 5.4 Hz, C-6), 36.98 (C-4), 40.87 (t, J = 19.8 Hz, C-7), 117.12 (t, J = 237.0 Hz, –CHF_2), 124.05 (C-3), 131.73 (C-2). HRMS (EI): calc. for $C_{10}H_{18}F_2$: 176.1376; found: 176.1375.

3.3. The reaction of DFMBA and Et_3N-3HF with a mixture of benzaldehyde and acetophenone

Benzaldehyde (106 mg, 1 mmol), acetophenone (182 mg, 1 mmol), DFMBA (426 mg, 2 mmol), and Et_3N-3HF (161 mg, 1 mmol) were introduced into a reactor of a Teflon™ PFA tube and submitted to microwave-irradiation at 180° C for 20 min. After cooling, the reaction mixture was poured into an aqueous $NaHCO_3$ solution and extracted with ether. Fluorobenzene (96 mg, 1 mmol) was added as an internal standard, and difluoromethylbenzene was found to be formed in 82% yield with 2% yield of 1,1-difluoroethylbenzene from ^{19}F NMR. Difluoromethylbenzene: ^{19}F NMR δ −110.5 (d, J = 56.0 Hz) [9], 1,1-difluoroethylbenzene: ^{19}F NMRδ −87.6 (q, J = 18.2 Hz) [26].

3.4. 4-Difluoromethylbenzophenone (**5**)

White solid. mp 70–71 °C. IR: (KBr) ν 2924, 1651, 1284 cm^{-1}. ^1H NMR δ 6.73 (t, J = 56.1 Hz, 1H), 7.49–7.53 (m, 2H), 7.61–7.65 (m, 3H), 7.80–7.82 (m, 2H), 7.88 (d, J = 8.6 Hz, 2H). ^{19}F NMR δ −112.68 (d, J = 56.0 Hz, 2F). ^{13}C NMR δ 114.02 (t, J = 238.6 Hz, –CHF_2), 125.57 (t, J = 5.8 Hz, 2C, C-3, C-5), 128.44 (2C), 130.07 (2C), 130.22 (2C), 132.87, 137.00, 137.77 (t, J = 22.2 Hz, C-4), 139.69, 195.90 (C=O). HRMS (EI): calc. for $C_{14}H_{10}F_2$: 232.0700; found: 232.0693.

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