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Selective synthesis of fluorinated carbohydrates using \(N,N\)-diethyl-\(\alpha,\alpha\)-difluoro-(\(m\)-methylbenzyl)amine

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Abstract: Deoxyfluorination of a hydroxy group in carbohydrates was carried out using \(N,N\)-diethyl-\(\alpha,\alpha\)-difluoro-(\(m\)-methylbenzyl)amine. A primary hydroxy group in carbohydrates was effectively converted to the corresponding fluoride under micro-wave irradiation or at 100°C. Deoxyfluorination of hydroxy groups at the anomeric position proceeded at below room temperature, and glycosyl fluorides could be obtained in good yields. The reaction chemoselectively proceeded, and various protecting groups of carbohydrates can survive under the reaction conditions.

Fluorinated carbohydrates have recently received much attention because of their important role for the study of the enzyme-carbohydrate interactions as well as their interesting biological activities.\(^1\) We found that \(N,N\)-diethyl-\(\alpha,\alpha\)-difluoro-(\(m\)-methylbenzyl)amine (1)\(^2\) is a selective reagent for a fluorinated carbohydrate synthesis (eq. 1).

\[ \text{NEt}_2\text{F} \quad \text{1} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{OH} \quad \text{2} \quad \rightarrow \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{F} \quad \text{NEt}_2 \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{2} \quad \rightarrow \quad \text{3} \quad \text{4} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{NEt}_2 \quad \text{1} \quad \text{NEt}_2 \quad \text{2} \quad \rightarrow \quad \text{3} \quad \text{4} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{NEt}_2 \quad \text{1} \quad \text{NEt}_2 \]

The deoxyfluorination of 1,2;3,4-di-\(O\)-isopropylidene-\(\alpha\)-D-galactopyranose (2) by 1 slowly proceeded under the thermal conditions in a hydrocarbon solvent and only 20% of 2 was converted to 6-deoxy-6-fluoro-1,2;3,4-di-\(O\)-isopropylidene-\(\alpha\)-D-galactopyranose (3) at 150 °C in 72 h.\(^4\) On the other hand, the reaction proceeded more quickly under the micro-wave

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irradiation conditions and 3 was isolated in 70% yield in 20 min (Table 1). The reaction of methyl 2,3-O-isopropylidene-β-D-ribofuranose (4) with N,N-diethylaminosulfur trifluoride (DAST) was previously reported to cause migration of the methoxy group from 1- to 5-position, and an unexpected 5-O-methyl-2,3-O-isopropylidene-β-D-ribofuranosyl fluoride was obtained instead of the expected 5-deoxy-5-fluoro derivative (5). In the reaction of 4 with 1 under the micro-wave irradiation conditions, 5 could be obtained in 51% yield with the methoxy group migrated product (20% yield). Migration of the methoxy group could be prevented by carrying out the reaction in dioxane at 100 °C in the presence of KF to selectively give 5 in 67% yield. Similarly, an α-isomer (7) could be stereospecifically obtained in 63% yield from an α-ribose derivative (6). Under the same conditions, 1,2,3,4-tetra-O-acetyl-α-D-glucopyranose (8) could be converted to 1,2,3,4-tetra-O-acety-6-deoxy-6-fluoro-α-D-glucopyranose (9) in 68% yield. DFMBA 1 can be also used for the deoxyfluorination of nucleosides and 2’,3’-O-isopropylideneuridine (10) could be converted to 5’-deoxy-5’-fluoro derivative (11) in 55% yield without migration of the uracil ring under the micro-wave irradiation conditions.
Table 1. Deoxyfluorination of primary hydroxy group in sugars and a nucleoside using DFMBA\(^\text{a}\)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Condition</th>
<th>Product</th>
<th>Yield, (%)(^\text{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 2" /></td>
<td>MW 20 min heptane</td>
<td><img src="image" alt="Structure 3" /></td>
<td>70</td>
</tr>
<tr>
<td><img src="image" alt="Structure 4" /></td>
<td>100 °C 16 h dioxane</td>
<td><img src="image" alt="Structure 5" /></td>
<td>67(^\text{c,d})</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /></td>
<td>100 °C 24 h dioxane</td>
<td><img src="image" alt="Structure 7" /></td>
<td>63(^\text{c,d})</td>
</tr>
<tr>
<td><img src="image" alt="Structure 8" /></td>
<td>100 °C 6 h dioxane</td>
<td><img src="image" alt="Structure 9" /></td>
<td>68(^\text{c})</td>
</tr>
<tr>
<td><img src="image" alt="Structure 10" /></td>
<td>MW 10 min heptane</td>
<td><img src="image" alt="Structure 11" /></td>
<td>55</td>
</tr>
</tbody>
</table>

\(^{a}\) If otherwise not mentioned, 2 equiv of DFMBA to substrate was used. \(^{b}\) Isolated yield based on substrate used. \(^{c}\) 4 equiv of KF to substrate was added. \(^{d}\) 2.5 equiv of DFMBA to substrate used.

DFMBA 1 is also applicable for the selective synthesis of glucosyl fluorids.\(^{11}\) Deoxyfluorination reaction of hydroxy groups at the anomeric position in various carbohydrates with 1 proceeded at below room temperature and the corresponding glycosyl fluorides could be obtained in good yields (Table 2). Most of the protecting groups of the carbohydrates such as acetonide (12), benzyl ether (14), acetate (16), and
silyl ether (18) can tolerate the reaction conditions. Moreover, hydroxy groups at other than the anomeric position were not converted to fluoride by 1 at below room temperature. For instance, 2,3-O-isopropylidene-D-ribofuranose (20) reacted with 2.4 eq of 1 at 0 °C to give 2,3-O-isopropylidene-5-O-m-methylbenzoyl-D-ribofuranosyl fluoride (21) in 70% yield. Under the reaction conditions, only the hydroxy group at the anomeric position was selectively deoxyfluorinated and the hydroxy group at the 5-position was only acylated. Furthermore, D-xylose (22), having four free hydroxy groups, can be directly converted to 2,3,4-tri-O-m-methylbenzoyl-D-xylopyranosyl fluoride (23) in 60% yield by the reaction with 8 equiv of 1.
Table 2. Deoxyfluorination of anomeric hydroxy group in sugars using DFMBAa

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Product</th>
<th>Yield, (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Sugar 12" /></td>
<td><img src="image" alt="Product 13" /></td>
<td>90c</td>
</tr>
<tr>
<td><img src="image" alt="Sugar 14" /></td>
<td><img src="image" alt="Product 15" /></td>
<td>85</td>
</tr>
<tr>
<td><img src="image" alt="Sugar 16" /></td>
<td><img src="image" alt="Product 17" /></td>
<td>80</td>
</tr>
<tr>
<td><img src="image" alt="Sugar 18" /></td>
<td><img src="image" alt="Product 19" /></td>
<td>80d</td>
</tr>
<tr>
<td><img src="image" alt="Sugar 20" /></td>
<td><img src="image" alt="Product 21" /></td>
<td>70d,e</td>
</tr>
<tr>
<td><img src="image" alt="Sugar 22" /></td>
<td><img src="image" alt="Product 23" /></td>
<td>60c,f,g</td>
</tr>
</tbody>
</table>

a) If otherwise not mentioned, the reaction was carried out in CH2Cl2 at room temperature for 1 h with 1.2 equiv of DFMBA. b) Isolated yield based on sugar used. c) The reaction was carried out without any solvent. d) The reaction was carried out at 0 °C. e) 2.4 equiv of DFMBA to sugar was used. f) 8 equiv of DFMBA to sugar was used. g) The reaction was carried out for 12 h.

Acknowledgment

We are grateful to Mitsubishi Gas Chemical Company Inc. for their donation of DFMBA and its ARC data.
References and Notes


2. Previously, *N,N*-dimethyl-α,α-difluorobenzylamine was used for the deoxyfluorination of simple alcohols and carboxylic acids.³


4. DF MBA is a thermally stable fluorinating regent and its exothermic starting point (ARC) is 180.0 °C.⁵


7. Into a reactor consisting of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, were introduced heptane (1 ml), ¹ (213 mg, 1 mmol), and ² (130 mg, 0.5 mmol). The open end of the reactor was connected to a port in a domestic microwave oven and the port was connected to a reflux condenser located outside the oven.⁸ Then, the reaction mixture was submitted to micro-wave irradiation for 20 min. During the irradiation, the reaction mixture was refluxed vigorously. After the reaction, the reaction mixture was poured into aq NaHCO₃ and extracted with ether three times. The combined ethereal layers were dried over MgSO₄ and extracted with ether three times. The combined ethereal layers were dried over MgSO₄ and extracted with ether three times. The combined ethereal layers were dried over MgSO₄ and extracted with ether three times. Purification by column chromatography (silica gel/hexane-Et₂O) gave ³ in 70% yield. IR (neat) 2990, 1184, 1256, 1213, 1072 cm⁻¹; ¹HNMR (400 MHz, CDCl₃) δ 1.34 (s, 6H), 1.45 (s, 3H), 1.55 (s, 3H), 4.07 - 4.10 (m, 1H), 4.27 (dd, J = 2.0, 8.1 Hz, 1H), 4.35 (dd, J = 2.4, 5.1 Hz, 1H), 4.48-4.65 (3H, m), 5.56 (d, J = 4.9 Hz, 1H); ¹⁹FNMR (376 MHz, CDCl₃) δ –231.73 (dt, J = 14.0, 47.6 Hz, 1F); ¹³CNMR (100 MHz, CDCl₃) δ 24.39, 24.88, 25.90, 26.00, 66.60 (d, J = 22.3 Hz), 770.39, 70.47, 70.55, 82.04 (d, J = 167.9 Hz), 96.15, 108.78, 109.63; HRMS calcd for C₁₂H₁₉O₅F 262.1216, found 262.1215.


10. As for a review of fluorinated nucleosides, see: Pankiewicz, K. W. *Carbohydr.*
Res. 2000, 327, 87-105.