Selective mono-acylation of 1,2- and 1,3-diols using (α,α-difluoralkyl)amines

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1. Introduction

Acylation of alcohols is a fundamental and important organic reaction; that has been frequently used for the protection of alcohols in both simple and complex molecules. Although many acylation methods are already known, a new and more efficient method is required.1 Recently, we reported the selective fluorination of alcohols using a new fluorination reagent, N,N-diethyl-α,α-difluoro-m-methylbenzylamine (DFMBA).2 In the reaction, a relatively high temperature was required (>100 °C), and at a lower temperature, a significant amount of an ester (2) derived from alcohol (1) and DFMBA was formed as a by-product. From these results, it can be presumed that the formation of adduct (4) in the reaction of 1 and DFMBA is fast, but the subsequent fluorination step is slow and 2 is formed by quenching 4 with water. Therefore, we applied α,α-difluoralkylamines for acylation of the alcohols by carrying out the reaction under mild conditions (Scheme 1).

Scheme 1. Reaction mechanism in the fluorination of alcohols with DFBA

2. Results and discussion

2.1. Benzoylation of alcohols with DFBA

As an acylation reagent, N,N-diethyl-α,α-difluorobenzylamine (DFBA)2d,3 was used instead of DFMBA because it reacts with alcohols to afford benzoyl esters. Initially, the reaction of DFBA with 1-decanol (1a) was examined (Table 1). When the reaction was carried out at 0 °C for 30 min using 1.1 eq of DFBA to 1a, decyl benzoate (2a) was obtained in 72% yield without the formation of decyl fluoride (3a). At 20 °C, the yield of 2a increased to 77%, but the formation of 3a (5%) was also observed. At 40 °C, a significant amount of 3a (22%) was formed. These results suggested that the fluorination of 1a proceeds at temperatures higher than 0 °C and can be prevented by carrying out the reaction at temperatures below 0 °C. Consequently, 2a could be obtained in 97 % yield without the formation of 3a by carrying out the reaction at 0 °C using 2 eq of DFBA. The benzoylation of 4-tert-butylphenol (1b) and cyclododecanol (1e) is slow, and a higher reaction temperature (20-40 °C) was required. However, the fluorination of these substrates is non-feasible or slower than that of 1a, and the corresponding benzoate (2b) or (2e) was obtained without the formation of the fluoride (3b) or (3e) under these conditions.

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Table 1  Benzylation of alcohols with DFBA

<table>
<thead>
<tr>
<th>R-OH</th>
<th>Temp.(°C)</th>
<th>DFBA / R-OH</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-decanol</td>
<td>0</td>
<td>1.1</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1.1</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>1.1</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2.0</td>
<td>97</td>
</tr>
<tr>
<td>4-tert-butylphenol</td>
<td>20</td>
<td>1.5</td>
<td>38 (43)</td>
</tr>
<tr>
<td></td>
<td>20a</td>
<td>2.0</td>
<td>73 (20)</td>
</tr>
<tr>
<td></td>
<td>40a</td>
<td>2.0</td>
<td>59 (22)</td>
</tr>
<tr>
<td>cyclohexanediol</td>
<td>0</td>
<td>1.1</td>
<td>46 (24)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>1.5</td>
<td>73 (11)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>2.0</td>
<td>94 (4)</td>
</tr>
</tbody>
</table>

*If otherwise not mentioned, the reaction was carried out in CH₂Cl₂ for 0.5 h.  
*Isolated yield based on 1 used.  In parentheses, recovered 1.  
*GC yield.  
*The reaction time is 1 h.  
*The reaction time is 3 h.

2.2. Mono-benzylation of diols

Selective mono-benzylation of diols is useful in organic synthesis, and many methods have been reported.¹ In the fluorination of 1,2- and 1,3-diols with DFMBA, selective mono-fluorination occurred through a cyclic intermediate and acylated fluorohydrins were obtained.² Therefore, we applied DFBA to the selective mono-benzylation of diols.² When prim-diols were used, the reaction was completed at 20 °C and the corresponding mono-benzyolated products were obtained in good yields (Entries 1-4 in Table 2). With cyclic diols, the reaction was carried out at 40 °C to afford mono-benzoates in good yields (Entries 8-10). The reaction of DFBA with diols is fast and is applicable to the mono-benzylation of less-reactive catechol and the sterically hindered pinacol (Entries 7 and 11). Even when 2 eq of DFBA to the diols was used, mono-benzoates were obtained selectively (Entries 6-11). Furthermore, from the isolated mono-benzoate (6j), the di-benzoate (7j) was obtained in good yield under the mono-benzylation conditions (Entry 12).

![Scheme 2](image)

Scheme 2. Reaction mechanism in mono-benzylation of diols with DFBA

Therefore, the selectivity observed in the mono-benzylation of diols with DFBA is not attributed to the steric hindrance generated in the second benzylation but to the reaction mechanism that includes a cyclic intermediate.⁸ As in the case of the fluorination reaction of diols with DFMBA, a cyclic amide acetal (8) must be initially formed in the reaction of dial 5 with DFBA.² The amide acetal 8 exists stably under the conditions and changes to mono-benzoate 6 upon the addition of water while excess DFBA is
decomposed to inert $N,N$-diethylbenzamide by the addition of water. Therefore, the benzylation of 6 to di-benzoate 7 scarcely occurred during the reaction, and 6 was obtained selectively (Scheme 2).

Table 2 Mono-benzylation of diols with DFBA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp. (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO$_2$OH</td>
<td>20</td>
<td>HO$_2$OBz</td>
<td>84$^c$ (5)</td>
</tr>
<tr>
<td>2$^d$</td>
<td>HO$_2$OH</td>
<td>20</td>
<td>HO$_2$OBz</td>
<td>82$^c$ (4)</td>
</tr>
<tr>
<td>3</td>
<td>HO$_2$OH</td>
<td>20</td>
<td>HO$_2$OBz</td>
<td>94 (4)</td>
</tr>
<tr>
<td>4$^e$</td>
<td>HO$_2$OH</td>
<td>20</td>
<td>HO$_2$OBz</td>
<td>70$^c$ (12)</td>
</tr>
<tr>
<td>5</td>
<td>EtOOC$_2$OH</td>
<td>40</td>
<td>EtOOC$_2$OBz</td>
<td>71 (0)</td>
</tr>
<tr>
<td>6$^f$</td>
<td>HO$_2$OH</td>
<td>40</td>
<td>HO$_2$OBz</td>
<td>91 (0)</td>
</tr>
<tr>
<td>7$^g$</td>
<td>HO$_2$OH</td>
<td>20</td>
<td>HO$_2$OBz</td>
<td>86 (2)</td>
</tr>
<tr>
<td>8$^f$</td>
<td>HO$_2$OH</td>
<td>40</td>
<td>HO$_2$OBz</td>
<td>92 (3)</td>
</tr>
<tr>
<td>9$^f$</td>
<td>HO$_2$OH</td>
<td>40</td>
<td>HO$_2$OBz</td>
<td>87 (5)</td>
</tr>
<tr>
<td>10$^f$</td>
<td>HO$_2$OH</td>
<td>40</td>
<td>HO$_2$OBz</td>
<td>95 (0)</td>
</tr>
<tr>
<td>11$^f$</td>
<td>HO$_2$OH</td>
<td>40</td>
<td>HO$_2$OBz</td>
<td>89 (4)</td>
</tr>
<tr>
<td>12$^f$</td>
<td>6j</td>
<td>40</td>
<td>7j</td>
<td>99</td>
</tr>
</tbody>
</table>

$^a$ If otherwise not mentioned, the reaction was carried out in CH$_2$Cl$_2$ for 0.5 h using 1.1 eq. of DFBA to substrate. $^b$ Isolated yield based on substrate used. In parentheses, yield of dibenzoate obtained by GC. $^c$ H NMR yield. $^d$ The reaction time is 3 h. $^e$ The reaction time is 5 h. $^f$ 2 eq of DFBA to the substrate was used. $^g$ The reaction time is 1 h.
Generally, after the aqueous work-up, only mono-benzoate 6 was obtained and the presumed cyclic intermediate 8 could not be isolated. However, in the reaction of diethyl tartrate 5e with DFBA, the corresponding amide acetal 8e was isolated, and it changed to mono-benzoate 6e under acidic conditions (Scheme 3).

![Scheme 3. Isolation and reaction of cyclic amide acetal 8e](image)

Next, we examined the regioselectivity in the benzoylation of unsymmetrical diols. With 1,3-butanediol (5l) having prim- and sec-alcohol, regioselectivity was not observed, and 3-hydroxybutyl benzoate (6l) and 4-hydroxybut-2-yl benzoate (6l') were obtained as a 1:1 mixture. On the other hand, in the reaction with 4-methyl-2,4-pentandiol (5m) having sec- and tert-alcohol, the benzoylation selectively occurred at sec-alcohol to afford 4-hydroxy-4-methylbut-2-yl benzoate (6m) in 83% yield (Scheme 4).  

![Scheme 4. Benzoylation of unsymmetrical diols with DFBA](image)

The selective protection of one hydroxy group in sugars is important for their transformation to oligosaccharides. Therefore, we applied the present benzoylation reaction to sugars. When methyl 5-O-benzoyl-β-D-ribofuranose (9) was subjected to the reaction with DFBA, selective mono-benzoylation occurred to afford methyl 3,5-di-O-benzoyl-β-D-ribofuranose (10) and methyl 2,5-di-O-benzoyl-β-D-ribofuranose (11) in 34% and 38% yields, respectively. With methyl 4,6-O-benzylidene-β-D-glucopyranoside (12), methyl 3-benzoyl-4,6-O-benzylidene-β-D-glucopyranoside (13) was obtained in 54% yield with minor products of 2-benzoyl-4,6-O-benzylidene-β-D-glucopyranoside (14) (18%) and dibenzoate (15) (6%) (Scheme 5).
2.3. Acylation of diols with various $\alpha,\alpha$-difluoroalkylamines

As various difluoroalkylamines can be prepared from amides in two steps, the present mono-benzoylation reaction of diols can be extended to other acylation reactions. The selective mono-nicotinylolation, formylation, and pivaloylation as well as 3-methylbenzoylation of diols were achieved by using $N$-(difluoropyridin-3-yl)methyl)-$N,N$-diethyldiamine, $N$-(difluoromethyl)morpholine, $N$-(1,1-difluoro-2,2-dimethylpropyl)pyrrolidine, and DFBMA as shown in Table 3.
Table 3. Acylation of diols with various α,α-difluoroalkylamines

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>R₂NCF₂R'</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
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<td>5h</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>88 (0)⁰⁻c⁻d</td>
</tr>
<tr>
<td>5c</td>
<td><img src="image3.png" alt="Image" /> DFMA</td>
<td><img src="image4.png" alt="Image" /></td>
<td>92 (8)⁰⁻c⁻d</td>
</tr>
<tr>
<td>5i</td>
<td>DFMA</td>
<td><img src="image5.png" alt="Image" /></td>
<td>87 (4)⁰⁻c⁻d</td>
</tr>
<tr>
<td>5j</td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td>82 (4)</td>
</tr>
<tr>
<td>5m</td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
<td>89 (0)⁰⁻c⁻d</td>
</tr>
</tbody>
</table>

³ If otherwise not mentioned, the reaction was carried out in CH₂Cl₂ at 20 °C for 0.5 h using 1.1 eq. of difluoroalkylamine to substrate. ⁴ Isolated yield based on substrate used. In parentheses, yield of diacylated product. ⁵ 2 eq. of difluoroamine to substrate was used. ⁶ The reaction was carried out at 40 °C.

3. Conclusion

The selective mono-benzoylation of 1,2- or 1,3-diols was achieved by using N,N-diethyl-α,α-difluorobenzylamine (DFBA). The reaction was completed under mild conditions in a short reaction time, and prim-, sec-, and tert-diols and catechol could be converted to the corresponding mono-benzoates. It was shown that the reaction proceeded through a cyclic amide acetal. The selective mono-nicotinylation, formylation, and pivaloylation of diols were also performed by using the corresponding difluoroalkylamines.

4. Experimental

4.1. General

The IR spectra were recorded using a JASCO FT/IR-410. The ^1H NMR (400 MHz), and ^13C NMR (100 MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, were referred to TMS. The EI and ESI high-resolution mass spectra were measured on a JEOL JMS-T100GCV. DFMA was donated from Mitsubishi Gas Chemical Company, INC. DFBA, N-(difluoromethyl)morpholine, and N-(1,1-difluoro-2,2-dimethylpropyl)pyrrolidine were prepared according to the previously reported
N-(Difluoropyridin-3-yl)methyl)-N,N-diethylamine was prepared from N,N-diethyl nicotinamide according to the literature (bp 52-54 °C / 0.1 mmHg). They were stored in a Teflon bottle under N₂. The small scale reaction can be carried out using glassware, but use of Teflon wares is recommended.

4.2. Benzoylation of alcohols with DFBA

4.2.1. Decyl benzoate (2a)

To a CH₂Cl₂ solution (3 mL) of DFBA (199 mg, 1.0 mmol) was added at 0 °C under N₂ atmosphere 1a (79 mg, 0.5 mmol), and the mixture was stirred at 0 °C for 30 min. Then, the mixture was poured into sat. aq NaHCO₃ (20 mL) and extracted with diethyl ether (20 mL X 3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane:Et₂O = 10:1) gave 2a (127 mg) in 97% yield; IR (neat) 2925, 1721, 1274 cm⁻¹. ¹H NMR δ 8.06-8.04 (m, 2H), 7.56 (dd, J = 7.5, 7.5 Hz, 1H), 7.44 (dd, J = 7.5, 7.5 Hz, 2H), 4.32 (t, J = 6.7 Hz, 2H), 1.80-1.73 (m, 2H), 1.48-1.27 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H). ¹³C NMR δ 166.64, 132.73, 130.49, 129.49 (2C), 128.26 (2C), 65.10, 31.86, 29.50 (2C), 29.27, 29.26, 28.69, 26.02, 22.65, 14.09.

4.2.2. 4-tert-Butylphenyl benzoate (2b)

The reaction was carried out as in the case of 4.2.1, using DFBA (199 mg, 1.0 mmol) and 1b (75 mg, 0.5 mmol) at 20 °C for 3 h. Purification by column chromatography (silica gel/hexane:Et₂O = 10:1) gave 2b (93 mg) in 73% yield; white solid. mp 78 °C (lit. 80-82 °C). IR (KBr) 2963, 1734, 1264 cm⁻¹. ¹H NMR δ 8.20 (d, J = 6.9 Hz, 2H), 7.65-7.62 (m, 1H), 7.51 (dd, J = 7.6, 7.6 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.7 Hz, 2H), 1.34 (s, 9H). ¹³C NMR δ 165.34, 148.68, 148.56, 133.49, 130.15 (2C), 129.68, 128.52 (2C), 126.39 (2C), 120.98 (2C), 34.49, 31.42 (3C).

4.2.3. Cyclohexyl benzoate (2c)

The reaction was carried out as in the case of 4.2.1, using DFBA (199 mg, 1.0 mmol) and 1c (92 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:Et₂O = 10:1) gave 2c (135 mg) in 94% yield; white solid. mp 38-40 °C (KBr) 2935, 1713, 1276 cm⁻¹. ¹H NMR δ 8.24 (d, J = 8.0 Hz, 2H), 7.53 (dd, J = 7.6, 7.1 Hz, 1H), 7.42 (dd, J = 7.9, 7.4 Hz, 2H), 5.29-5.23 (m, 1H), 1.87-1.79 (m, 2H), 1.69-1.61 (m, 2H), 1.45-1.33 (m, 18H). ¹³C NMR δ 166.19, 132.60, 130.89, 129.45 (2C), 128.20 (2C), 72.85, 29.05(2C), 24.13(2C), 23.91, 23.28 (2C), 23.09 (2C), 20.82 (2C).

4.3. Mono-Benzoylation of diols

4.3.1. 2-Hydroxyethyl benzoate (6a)

To a CH₂Cl₂ solution (3 mL) of DFBA (111 mg, 0.55 mmol) was added at room temperature under N₂ atmosphere 5a (31 mg, 0.5 mmol), and the mixture was stirred at 20 °C for 30 min. Then, the mixture was poured into sat. aq NaHCO₃ (20 mL) and extracted with diethyl ether (20 mL X 3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. The yield of 6a was determined by ¹H NMR using 1,4-dimethoxybenzene as an internal standard (80%) and the yield of dibenzoate was determined by GC (5%). Pure 6a was obtained by column chromatography (silica gel/hexane:EtOAc = 2:1); IR (neat) 3424, 2952, 1719, 1277 cm⁻¹. ¹H NMR δ 8.08-8.06 (m, 2H), 7.60-7.56 (m, 1H), 7.48-7.44 (m, 2H), 4.49-4.47 (m, 2H), 3.99-3.95 (m, 2H), 2.07 (t, J = 5.9 Hz, 1H). ¹³C NMR δ 166.93, 133.12, 129.73, 129.60 (2C), 128.33 (2C), 66.56, 61.17.

4.3.2. 3-Hydroxypropan-1-yl benzoate (6b)

The reaction was carried out as in the case of 4.3.1, using DFBA (110 mg, 0.55 mmol) and 5b (38 mg, 0.5 mmol) at 20 °C for 3 h. The yield of 6b (82%) was determined by ¹H NMR using 1,4-dimethoxybenzene as an internal standard. Pure 6b was obtained by column chromatography (silica gel/hexane:EtOAc = 2:1); IR (neat) 3416, 2960, 1718, 1277 cm⁻¹. ¹H NMR δ 8.04 (d, J = 7.3 Hz, 2H), 7.59-7.55 (m, 1H), 7.45 (dd, J = 7.7, 7.7 Hz, 2H), 4.50 (t, J = 6.2 Hz, 2H), 3.78 (dt, J = 6.0, 6.0 Hz,
2H), 2.05-1.99 (m, 2H), 1.93 (t, J = 5.6 Hz, 1H). 13C NMR δ 167.00, 133.04, 130.01, 129.57 (2C), 128.37 (2C), 61.73, 59.10, 31.84.

4.3.3. 3-Hydroxy-2,2-dimethylpropan-1-yl benzoate (6c)15

The reaction was carried out as in the case of 4.3.1. using DFBA (110 mg, 0.55 mmol) and 5e (52 mg, 0.5 mmol) at 20 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 3:1) gave 6c (98 mg) in 94% yield. IR (neat) 3438, 2963, 1720, 1274 cm\(^{-1}\). 1H NMR δ 8.04 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 7.4, 7.4 Hz, 1H), 7.45 (dd, J = 6.9, 6.9 Hz, 2H), 4.18 (s, 2H), 3.40 (s, 2H), 1.01 (s, 6H).

13C NMR δ 167.07, 133.08, 129.91, 129.55 (2C), 128.37 (2C), 69.68, 68.08, 36.64, 21.51 (2C).

4.3.4. [1-(Hydroxyethyl)cyclopropyl]methyl benzoate (6d)

The reaction was carried out as in the case of 4.3.1. using DFBA (110 mg, 0.55 mmol) and 5d (51 mg, 0.5 mmol) at 20 °C for 5 h. The yield of 6d (70%) was determined by 1H NMR using 1,4-dimethoxybenzene as an internal standard. Pure 6d was obtained by column chromatography (silica gel/hexane:EtOAc = 1:1). IR (neat) 3423, 2950, 1714, 1274 cm\(^{-1}\). 1H NMR δ 8.07-8.05 (m, 2H), 7.60-7.56 (m, 1H), 7.48-7.44 (m, 2H), 4.33 (s, 2H), 3.53 (d, J = 5.9 Hz, 2H), 2.16 (t, J = 6.1 Hz, 1H), 0.69-0.59 (m, 4H).

13C NMR δ 167.10, 133.06, 130.01, 129.62 (2C), 128.37 (2C), 68.65, 66.62, 22.56, 8.93 (2C). HRMS (ESI) calcd for C12H12O1Na (M+Na) 229.08352, found 229.08335.

4.3.5. (2S, 3S)-Diethyl 2-benzyloxy-3-hydroxybutyrate (6e)16

The reaction was carried out as in the case of 4.3.1 using DFBA (110 mg, 0.55 mmol) and 5e (103 mg, 0.5 mmol) at 40 °C for 30 min. After the reaction, THF (3 mL) and 1M HCl (3 mL) were added and the mixture was stirred at 20 °C overnight. Then, the mixture was poured into sat. aq NaHCO\(_3\) (20 mL) and extracted with diethyl ether (20 mL X 3). The combined organic layer was dried over MgSO\(_4\) and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane:EtOAc = 1:1) gave 6e (110 mg) in 71% yield; white solid. mp 51-53 °C (lit.16 56-59 °C). IR (KBr) 3428, 2982, 1763, 1748, 1718, 1265, 1225 cm\(^{-1}\). 1H NMR δ 8.05-8.03 (m, 2H), 7.59 (dd, J = 7.4, 7.4 Hz, 1H), 7.45 (dd, J = 7.8, 7.8 Hz, 2H), 5.66 (d, J = 2.2 Hz, 1H), 4.86 (dd, J = 7.5, 2.4 Hz, 1H), 4.33-4.21 (m, 4H), 3.26 (d, J = 7.3 Hz, 1H), 1.31 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H). 13C NMR δ 170.87, 166.49, 165.23, 133.63, 129.92 (2C), 128.70, 128.49 (2C), 73.43, 70.66, 62.65, 62.16, 14.06, 14.03.

4.3.6. (2R, 3R)-3-Hydroxybutan-2-yl benzoate (6f)17

The reaction was carried out as in the case of 4.3.1. using DFBA (199 mg, 1.0 mmol) and 5f (45 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 6f (88 mg) in 89% yield; IR (neat) 3443, 2980, 1714, 1276 cm\(^{-1}\). 1H NMR δ 8.07-8.05 (m, 2H), 7.60-7.56 (m, 1H), 7.46 (dd, J = 8.0, 8.0 Hz, 2H), 5.07-5.00 (m, 1H), 3.95-3.89 (m, 1H), 2.00 (brs, 1H), 1.36 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 6.3 Hz, 3H). 13C NMR δ 166.23, 133.04, 130.21, 129.56 (2C), 128.37 (2C), 75.42, 70.10, 19.00, 16.21.

4.3.7. 3-Hydroxy-2,3-dimethylbutan-2-yl benzoate (6g)18

The reaction was carried out as in the case of 4.3.1. using DFBA (199 mg, 1.0 mmol) and 5g (59 mg, 0.5 mmol) at 20 °C for 1 h. IR (neat) 3439, 2988, 1714, 1287 cm\(^{-1}\). 1H NMR δ 7.99 (d, J = 7.0 Hz, 2H), 7.55 (dd, J = 7.3, 7.3 Hz, 1H), 7.44 (dd, J = 7.8, 7.8 Hz, 2H), 3.78 (s, 1H), 1.64 (s, 6H), 1.31 (s, 6H). 13C NMR δ 166.48, 132.84, 131.15, 129.40 (2C), 128.28 (2C), 89.89, 74.73, 25.13(2C), 21.78 (2C).

4.3.8. cis-2-Hydroxyhexahexyl benzoate (6h)19

The reaction was carried out as in the case of 4.3.1. using DFBA (199 mg, 1.0 mmol) and 5h (58 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 6h (101 mg) in 92% yield; IR (neat) 3469, 2939, 1716, 1279 cm\(^{-1}\). 1H NMR δ 8.06 (d, J = 7.0 Hz, 2H), 7.58 (dd, J = 7.3, 7.3 Hz, 1H), 7.46 (dd, J = 7.9, 7.9 Hz, 2H), 5.24-5.21 (m, 1H), 3.97 (brs, 1H), 2.06-1.38 (m, 8H). 13C NMR δ 166.23, 133.06, 130.37, 129.60 (2C), 128.41 (2C), 74.61, 69.64, 30.40, 27.37, 21.81, 21.52.
4.3.9. cis-2-Hydroxycyclopentyl benzoate (6i)\(^{19}\)

The reaction was carried out as in the case of 4.3.1. using DFBA (199 mg, 1.0 mmol) and SI (51 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 6i (90 mg) in 87% yield; IR (neat) 3468, 2970, 1715, 1278 cm\(^{-1}\). \(^1\)H NMR δ 8.05 (d, J = 7.1 Hz, 2H), 7.58 (dd, J = 7.8, 7.8 Hz, 1H), 7.45 (dd, J = 7.7, 7.7 Hz, 2H), 5.26-5.22 (m, 1H), 4.34-4.30 (m, 1H), 2.17-1.60 (m, 6H). \(^13\)C NMR δ 166.39, 133.04, 130.07, 129.57 (2C), 128.34 (2C), 77.36, 73.30, 30.78, 28.12, 19.41.

4.3.10. cis-2-Hydroxycyclodecyl benzoate (6j)

The reaction was carried out as in the case of 4.3.1. using DFBA (199 mg, 1.0 mmol) and 5j (100 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 6j (144 mg) in 95% yield; white solid, mp 111 °C (lit.\(^{20}\) 112.5-113.5 °C), IR (KBr) 3523, 2926, 1700, 1276 cm\(^{-1}\). \(^1\)H NMR δ 8.07-8.05 (m, 2H), 7.59-7.55 (m, 1H), 7.45 (dd, J = 7.8, 7.4 Hz, 2H), 5.32 (t, J = 6.0 Hz, 1H), 4.00 (d, J = 5.2 Hz, 1H), 1.88-1.36 (m, 20H). \(^13\)C NMR δ 166.70, 133.02, 130.25, 129.61 (2C), 128.36 (2C), 71.46, 71.42, 28.89-21.31 (10C).

4.3.11. 2-Hydroxyphenyl benzoate (6k)

The reaction was carried out as in the case of 4.3.1. using DFBA (199 mg, 1.0 mmol) and 5k (55 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 3:1) gave 6k (95 mg) in 89% yield; white solid: mp 130 °C (lit.\(^{21}\) 130°C), IR (KBr) 3411, 1715, 1273 cm\(^{-1}\). \(^1\)H NMR δ 8.24-8.22 (m, 2H), 7.68 (dd, J = 7.5, 7.5 Hz, 1H), 7.54 (dd, J = 7.7, 7.7 Hz, 2H), 7.22-7.17 (m, 2H), 7.09-7.07 (m, 1H), 7.01-6.97 (m, 1H), 5.43 (s, 1H). \(^13\)C NMR δ 165.07, 147.25, 138.77, 134.04, 130.38 (2C), 128.73, 128.71 (2C), 127.18, 122.50, 121.12, 118.06.

4.3.12. cis-1,2-Dibenzoylexcyclodecane (7j)

The reaction was carried out as in the case of 4.3.6. using DFBA (199 mg, 1.0 mmol) and 6j (152 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 5:1) gave 7j (205 mg) in 99% yield; IR (neat) 2935, 1715, 1259 cm\(^{-1}\). \(^1\)H NMR δ 8.01 (d, J = 7.7 Hz, 4H), 7.55 (dd, J = 7.6, 7.3 Hz, 2H), 7.42 (dd, J = 7.7, 7.6 Hz, 4H), 5.50 (t, J = 6.3 Hz, 2H), 2.01-1.83 (m, 4H), 1.59-1.25 (m, 16H). \(^13\)C NMR δ 166.11 (2C), 132.86 (2C), 130.37 (2C), 129.60 (4C), 128.29 (4C), 73.62, 73.44, 26.18-21.45 (10C). HRMS (ESI) calcd for C\(_{25}\)H\(_{30}\)O\(_2\)Na (M\(^{+}\)+Na) 431.21928, found 431.22011.

4.3.13. (4S, 5S)-Diethyl 2-(diethylamino)-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (8e)

To a CH\(_2\)Cl\(_2\) solution (3 mL) of DFBA (199 mg, 1.0 mmol) was added at 20 °C under N\(_2\) atmosphere 5e (206 mg, 1.0 mmol), and the mixture was stirred for 10 min. Then, the mixture was poured into sat. aq NaHCO\(_3\) (20 mL) and extracted with diethyl ether (20 mL X 3). The combined organic layer was dried over MgSO\(_4\) and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane:Et\(_2\)O = 2:1) gave 8e (112 mg) in 31% yield. To a THF solution (3 mL) of 8e (112 mg, 0.31 mmol) was added 1 M aq HCl (3 mL) and the mixture was stirred at 20 °C overnight. The mixture was poured into sat. aq NaHCO\(_3\) (20 mL) and extracted with diethyl ether (20 mL X 3). The combined organic layer was dried over MgSO\(_4\) and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane:EtOAc = 1:1) gave 6e (54 mg) in 88% yield. 8e: IR (neat) 2981, 1748, 1117 cm\(^{-1}\). \(^1\)H NMR δ 7.63-7.60 (m, 2H), 7.34-7.32 (m, 3H), 4.73 (d, J = 6.2 Hz, 1H), 4.59 (d, J = 6.2 Hz, 1H), 4.28 (q, J = 7.0 Hz, 2H), 4.08-3.91 (m, 2H), 2.77 (q, J = 7.1 Hz, 4H), 1.31 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H), 0.99 (t, J = Hz, 6H). \(^13\)C NMR δ 169.26, 169.02, 139.02, 128.67, 127.71 (2C), 127.55 (2C), 124.48, 75.91, 75.13, 61.74, 61.49, 40.28 (2C), 14.08, 13.99 (2C), 13.90. HRMS (EI) calcd for C\(_{19}\)H\(_{23}\)O\(_2\)N found 366.19111, found 366.19214.

4.3.14. 3-Hydroxybutyl benzoate (6l)\(^{22}\) and 4-hydroxybut-2-yl benzoate (6l')\(^{22}\)

The reaction was carried out as in the case of 4.3.6 using DFBA (149 mg, 0.75 mmol) and 5l (45 mg, 0.5 mmol) at 0 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 1:1) gave a mixture of 6l and 6l' (77 mg) in 79% yield ( inseparable). From 1H NMR spectra, 6l and 6l' were found to be formed in 1:1 ratio; \(^1\)H NMR δ 8.06-8.03 (m, 2H), 7.59-7.55 (m, 1H), 7.47-7.43 (m, 2H),...
5.43-5.34 (m, 0.5H, 6′), 4.64-4.58 (m, 0.5H, 6), 4.41-4.36 (m, 0.5H, 6I), 3.98-3.97 (m, 0.5H, 6I), 3.70-3.66 (m, 1H, 6I′), 2.53 (brs, 0.5H), 2.14 (brs, 1H), 1.99-1.80 (m, 2H), 1.38 (t, J = 0.7Hz, 1.5H, 6I′), 1.25 (t, J = 0.8 Hz, 1.5H, 6I).

4.3.15. 4-Hydroxy-4-methylpentan-2-yl benzoate (6m)²³

The reaction was carried out as in the case of 4.3.1, using DFBA (199 mg, 1.0 mmol) and SI (59 mg, 0.5 mmol) at 20 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 6m (92 mg) in 83% yield. IR (neat) 3480, 2975, 1714, 1281 cm⁻¹. ¹H NMR δ 8.06-8.02 (m, 2H), 7.59-7.39 (m, 3H), 5.48-5.37 (m, 1H), 2.07 (dd, J = 14.8, 8.7 Hz, 1H), 1.77 (dd, J = 14.9, 3.3 Hz, 1H), 1.39 (d, J = 6.3 Hz, 3H), 1.28 (s, 3H), 1.26 (s, 3H). ¹³C NMR δ 166.17, 132.94, 130.44, 129.46 (2C), 128.37 (2C), 70.00, 69.36, 49.02, 29.91, 29.68, 21.76.

4.3.16. Methyl 3,5-di-O-benzyol-β-D-ribofuranoside (10) and methyl 2,5-di-O-benzoyl-β-D-ribofuranoside (11)

The reaction was carried out as in the case of 4.3.6 using 2.0 eq of DFBA (199 mg, 1.0 mmol) at 40 °C for 30 min. The yields of 10 (34%) and 11 (38%) were determined by ¹H NMR using 1,4-dimethoxybenzene as an internal standard, respectively. Pure 10 and 11 were obtained by column chromatography (silica gel/CHCl₃:acetone = 20:1). ¹³C NMR (neat) 3489, 2936, 1724, 1273 cm⁻¹. ¹H NMR δ 8.04 (d, J = 7.9 Hz, 4H), 7.60 (dd, J = 7.6, 7.4 Hz, 1H), 7.54 (dd, J = 7.5, 7.4 Hz, 1H), 7.45 (dd, J = 7.8, 7.8 Hz, 2H), 7.38 (dd, J = 7.8, 7.7 Hz, 2H), 5.54 (dd, J = 6.3, 4.8 Hz, 1H), 4.98 (s, 1H), 4.67-4.46 (m, 4H), 3.38 (s, 3H). ¹³C NMR δ 166.25, 165.71, 133.62, 133.09, 129.78 (2C), 129.71, 129.68 (2C), 128.91, 128.52 (2C), 128.32 (2C), 108.48, 78.35, 74.71, 74.30, 64.95, 55.26. ¹³C NMR δ 166.48, 166.10, 133.53, 133.11, 129.81 (2C), 129.75, 129.68 (2C), 129.08, 128.46 (2C), 128.34 (2C), 105.94, 80.78, 77.09, 71.11, 64.56, 55.14.

4.3.17. Methyl 3-benzoyl-4,6-O-benzylidene-β-D-glucopyranoside (13) and methyl 2-benzoyl-4,6-O-benzylidene-β-D-glucopyranoside (14)

The reaction was carried out as in the case of 4.3.6 using DFBA (120 mg, 0.6 mmol) and 12 (141 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 13 (104 mg) in 54% yield and 14 (35 mg) in 18% yield, and 15 (15 mg) in 6% yield, respectively. ¹³C NMR δ 8.10-8.08 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.46-7.41 (m, 4H), 7.32-7.30 (m, 3H), 5.55 (brs, 1H), 5.48 (t, J = 9.4 Hz, 1H), 4.47 (d, J = 7.5 Hz, 1H), 4.42 (dd, J = 8.5, 4.9 Hz, 1H), 3.87-3.80 (m, 2H), 3.75-3.70 (m, 1H), 3.64-3.58 (m, 1H), 3.63 (s, 3H), 2.73 (d, J = 3 Hz, 1H). ¹³C NMR δ 166.63, 136.78, 133.27, 129.92 (2C), 129.55, 129.00, 128.34 (2C), 128.17 (2C), 126.04 (2C), 104.57, 101.41, 78.55, 74.36, 73.60, 68.63, 66.45, 57.68. ¹³C NMR δ 8.09 (d, J = 7.1 Hz, 2H), 7.61-7.38 (m, 8H), 5.60 (s, 1H), 5.19 (dd, J = 9.0, 8.0 Hz, 1H), 4.62 (d, J = 7.8 Hz, 1H), 4.42 (dd, J = 10.4, 3.2 Hz, 1H), 4.07 (dt, J = 3.2, 9.1 Hz, 1H), 3.86 (t, J = 10.2 Hz, 1H), 3.58-3.54 (m, 1H), 3.52 (s, 3H), 2.63 (d, J = 3.3 Hz, 1H). ¹³C NMR δ 165.91, 136.84, 133.32, 129.94 (2C), 129.56, 129.33, 128.40 (2C), 128.36 (2C), 126.25 (2C), 102.37, 101.91, 80.90, 74.66, 72.42, 68.61, 66.16, 57.26. ¹³C NMR δ 7.97-7.94 (m, 4H), 7.54-7.31 (m, 10H), 5.79 (t, J = 9.5 Hz, 1H), 5.56 (s, 1H), 5.47 (dd, J = 8.0, 9.6 Hz, 1H), 4.71 (d, J = 7.8 Hz, 1H), 4.45 (dd, J = 4.9, 10.4 Hz, 1H), 3.96-3.88 (m, 2H), 3.74-3.68 (m, 1H), 3.54 (s, 3H).

4.3.18. cis -2-Hydroxyxycyclohexyl nicotinate (16)

The reaction was carried out as in the case of 4.3.1, using N-(difluoro(pyridin-3-yl)methyl)-N,N-diethyiamine (200 mg, 1.0 mmol) and 5h (58 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 16 (97 mg) in 88% yield; IR (neat) 3393, 2939, 1720, 1288 cm⁻¹. ¹H NMR δ 9.24 (s, 1H), 8.78 (d, J = 4.7 Hz, 1H), 8.31 (dd, J = 8.0, 3.2 Hz, 1H), 7.40 (dd, J = 7.8, 4.9 Hz, 1H), 5.28-5.26 (m, 1H), 4.01 (s, 1H), 2.21-1.41 (m, 8H). ¹³C NMR δ 164.78, 153.14, 150.61, 137.16, 126.38, 123.30, 75.21, 69.25, 30.35, 27.36, 21.61, 21.57. HRMS (ESI) calcld for C₁₂H₁₅O₃NNa (M⁺+Na) 244.09441; found 244.09473.
4.3.19. 3-Hydroxy-2,2-dimethylpropan-1-yl-3-methylbenzoate (17a)

The reaction was carried out as in the case of 4.3.6 using DFMB (213 mg, 1.0 mmol) and 5e (51 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 3:1) gave 17a (96 mg) in 87% yield; IR (neat) 3447, 2962, 1719, 1279 cm⁻¹. ¹H NMR δ 7.85-7.83 (m, 2H), 7.40-7.32 (m, 2H), 4.18 (s, 2H), 3.38 (d, J = 5.2 Hz, 2H), 2.41 (s, 2H), 2.32 (brs, 1H), 1.02 (s, 6H). ¹³C NMR δ 167.26, 138.16, 133.84, 130.08, 129.83, 128.25, 126.69, 69.60, 68.07, 36.69, 21.51 (2C), 21.21. HRMS (ESI) calced for C₁₃H₁₀O₃Na (M⁺+Na) 245.11482, found 245.11487.

4.3.20. cis-2-Hydroxycyclopentyl 3-methylbenzoate (17b)

The reaction was carried out as in the case of 4.3.6 using DFMB (213 mg, 1.0 mmol) and 5i (51 mg, 0.5 mmol) at 40 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 3:1) gave 17b (97 mg) in 87% yield; IR (neat) 3470, 2968, 1714, 1280 cm⁻¹. ¹H NMR δ 7.86-7.84 (m, 2H), 7.40-7.32 (m, 2H), 5.25-5.21 (m, 1H), 4.33-4.29 (m, 1H), 2.41 (s, 3H), 2.13-1.62 (m, 6H). ¹³C NMR δ 166.57, 138.18, 133.85, 130.08, 129.97, 128.26, 126.72, 77.30, 73.33, 30.83, 28.13, 21.24, 19.45. HRMS (ESI) calced for C₁₃H₁⁰O₃Na (M⁺+Na) 243.09917, found 243.09905.

4.3.21. cis-2-Hydroxycyclooctyl formate (18)

The reaction was carried out as in the case of 4.3.1. using N-(difluoromethyl)morpholine (75 mg, 0.55 mmol) and 5j (100 mg, 0.5 mmol) at 20 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 2:1) gave 18 (93 mg) in 82% yield; IR (neat) 3379, 2947, 1727, 1200 cm⁻¹. ¹H NMR δ 8.14 (s, 1H), 5.21 (t, J = 6.1 Hz, 1H), 3.90-3.88 (m, 1H), 1.79-1.35 (m, 20H). ¹³C NMR δ 161.11, 75.51, 71.48, 29.02, 24.65, 24.51, 24.41, 23.65, 23.52, 21.78, 21.74 (2C), 21.15. HRMS (ESI) calced for C₁₂H₂₀O₃Na (M⁺+Na) 251.16177, found 251.16185.

4.3.22. (4-Hydroxy-4-methylpent-2-yl) pivalate (19) and (4-hydroxy-2-methylpent-2-yl) pivalate (20)

The reaction was carried out as in the case of 4.3.6. using N-((1-difluoro-2,2-dimethylpropyl)pyrrolidine (177 mg, 1.0 mmol) and 5m (59 mg, 0.5 mmol) at 20 °C for 30 min. Purification by column chromatography (silica gel/hexane:EtOAc = 3:1) gave 19 (72 mg) in 71% yield and 20 (36 mg) in 18% yield, respectively. 19: IR (neat) 3446, 2974, 1725, 1169 cm⁻¹. ¹H NMR δ 5.17-5.10 (m, 1H), 2.22 (brs, 1H), 1.90 (dd, J = 14.9, 9.0 Hz, 1H), 1.66 (dd, J = 14.9, 3.1 Hz, 1H), 1.25-1.22 (m, 6H), 1.19 (s, 9H). ¹³C NMR δ 178.11, 69.91, 68.56, 48.75, 38.55, 29.70, 29.52, 26.97 (3C), 21.46. HRMS (ESI) calced for C₁₅H₂₇O₄Na 225.14612, found 225.14613. 20: IR (neat) 3446, 2972, 1724, 1136 cm⁻¹. ¹H NMR δ 4.12-4.09 (m, 1H), 2.20 (brs, 1H), 1.96 (dd, J = 14.9, 9.2 Hz, 1H), 1.75 (dd, J = 14.8, 2.2 Hz, 1H), 1.53 (d, J = Hz, 3H), 1.23-1.19 (m, 6H), 1.17 (s, 9H). ¹³C NMR δ 177.69, 82.28, 64.76, 50.05, 39.25, 27.14 (3C), 26.84, 25.64, 24.56. HRMS (ESI) calced for C₁₄H₂₂O₄Na (M⁺+Na) 225.14612, found 225.14614.

Acknowledgment

We are grateful to Mitsubishi Gas Chemical Company, INC. for their donation of DFMB.

References and notes


5. *N,N*-Dimethylbenzamide diethylacetal was previously used as benzoylation of diols. However it is not suitable for a benzoylation reagent because it is unstable and difficult to store for a long time.


8. In the reaction of *N,N*-dimethylbenzamide dimethylacetal with diols, the cyclic amide acetals were isolated and they changed to mono-benzoylated products by acid treatment.

9. From NMR spectra of the crude mixture, formation of 4-fluoro-4-methylbut-2-yl benzoate and 4-methyl-4-buten-2-yl benzoate was observed (<3%).


