Short Communication

β-Selectivity of Sterically Hindered Acyl Chlorides in the Acylation of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose

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1-O-Acyl sugars occur widespread in nature,¹ and as a result their synthesis is important. 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose (1) is the ideal starting material for the synthesis of 1-O-acetylglucoses (glycosyl esters can also be made directly from glucose³) and 1-O-acetylgluconic acids,² since it is readily available,³ and the benzyl groups can be removed in the presence of a glycosyl ester.

Several methods of controlling the stereoselectivity of the acylation of 1 have been reported using special techniques, such as using acyl fluorides in the presence of cesium fluoride,⁴ or by acylating the Li-salt, pseudo-urea derivative⁵ or trichloroacetimidate⁶ of 1. Straightforward pyridine-catalysed acylation of 1 generally gives mixtures containing mostly the α-isomer.⁵ In some cases, such as the p-nitrobenzoate, the pure α-ester has been obtained.⁷

Recently surprisingly high β-selectivity in the pyridine-4-dimethylaminopyridine (DMAP)-catalysed pivaloylation of 1 was discovered.⁸ Thus it was decided to investigate whether this selectivity might be more general.

First the ratio of α : β esters in the pyridine–DMAP catalysed-acylation of 1 with a number of different acid chlorides was studied (Scheme 1) to see whether the 2,2-dimethylpentanoic ester, the 2,4,6-trimethylbenzoic ester and the 2-methylpropanoic ester the β-anomer was crystallised in 86, 24 and 45% yield, respectively (see the Experimental), otherwise the mixture of anomeric esters was obtained as a syrup.

Compared with the acylation of 1 in pyridine without DMAP (Table 1) it was noted that addition of DMAP resulted in increased formation of the β-ester which was especially pronounced for pivaloyl chloride, though this sterically hindered acid chloride also showed β-selectivity in the pyridine-catalysed reaction.

This raised two questions: why does the addition of DMAP lower the α : β-ratio, and why do the sterically hindered acid chlorides form mostly β-ester? Since equatorial alcohols are acylated faster than axial,⁹ k₃ would be expected to be larger than k₂ (Scheme 2). The α : β ratio of the product depends on the first-order rate constants according to eqn. (1).

\[
a / \beta = k_3 (k_{-1} + k_1) / k_2 k_1. \tag{1}
\]

Thus if k₁ and k₋₁ were large (fast mutarotation) and k₂ and k₃ small (slow acylation) the reaction would lead predominantly to β-ester (α/β ~ k₂k₋₁/k₃k₁),

**Scheme 1.**

**Scheme 2.**

β-selectivity observed for the pivaloyl chloride might be general. As seen in Table 1 most of the acid chlorides gave mainly the α-anomer. Only the hindered acid chlorides pivaloyl chloride, 2,2-dimethylpentanoyl chloride and 2,4,6-trimethylbenzoyl chloride gave predominantly the β-ester, and the two first gave exclusively β. In case of the...
Table 1. The anomic ratio of esters obtained from the reaction of tetrabenzyloxyglucose (1) with RCOCl in CH₂Cl₂-pyridine 10 : 1.

<table>
<thead>
<tr>
<th>R</th>
<th>With 0.1% DMAP α : β</th>
<th>Without DMAP α : β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>6 : 1</td>
<td>10 : 1*</td>
</tr>
<tr>
<td>Et</td>
<td>3 : 1</td>
<td>10 : 1*</td>
</tr>
<tr>
<td>Pr</td>
<td>6 : 1</td>
<td>10 : 1*</td>
</tr>
<tr>
<td>i-Pr</td>
<td>3 : 1</td>
<td></td>
</tr>
<tr>
<td>t-Bu</td>
<td>0 : 1*</td>
<td>1 : 6</td>
</tr>
<tr>
<td>CH₂CH₂(CH₂)₂C</td>
<td>0 : 1</td>
<td></td>
</tr>
<tr>
<td>CHCl₂</td>
<td>6 : 1</td>
<td></td>
</tr>
<tr>
<td>Cl₂CH</td>
<td>15 : 1</td>
<td></td>
</tr>
<tr>
<td>CH₂CHBr</td>
<td>15 : 1</td>
<td></td>
</tr>
<tr>
<td>PhCH₂</td>
<td>1 : 1</td>
<td></td>
</tr>
<tr>
<td>(E)-CH₂CH = CH</td>
<td>7 : 1</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>3 : 1</td>
<td>6 : 1</td>
</tr>
<tr>
<td>2-CiC₅H₄</td>
<td>2 : 1</td>
<td></td>
</tr>
<tr>
<td>2,4,6-Me₃C₆H₃</td>
<td>1 : 3</td>
<td></td>
</tr>
</tbody>
</table>

* Ref. 2.  Ref. 8.

while the reverse (slow mutarotation and fast acylation) would result in predominantly α-ester (α/β ~ k₂/k₁). The mutarotation of I was studied by the optical rotation by the method described by Swain and Brown, and found to be first order in the sugar concentration. The rate constant (k₁ + k₋₁) at 22°C in CH₂Cl₂-pyridine 10 : 1 (v/v), 0.1 % DMAP was 9.7 x 10⁻⁵ s⁻¹ corresponding to a half-life of 120 min, while the rate constant in CH₂Cl₂-pyridine 10 : 1 (v/v) was 3.2 x 10⁻⁵ s⁻¹ corresponding to a half-life of 360 min. The equilibrium contained 55% α-anomer corresponding to a equilibrium constant of K = 0.82. The larger k₁ and k₋₁ in the presence of DMAP explain the increased formation of β-ester, if k₂ and k₃ were increased to a lesser extent by DMAP. The β-selectivity of the hindered acid chlorides might be explained in a similar manner. The acylation of I was followed by NMR spectroscopy for six acyl chlorides. Since the concentration of I was much lower than the concentration of the reagents, the reaction could be expected to follow first-order kinetics in sugar concentration. With acetyl chloride, butyryl chloride, chloroacetyl and (E)-crotonyl chloride the reaction was almost instantaneous, with a pseudo-first-order rate constant k₂ = 5 x 10⁻⁵ s⁻¹. The reaction with pivaloyl chloride and mesityl chloride was much slower. The reaction with pivaloyl chloride was complete within 6 h and had a pseudo-first-order rate constant k₂ ~ 2 x 10⁻⁴ s⁻¹. The reaction with mesityl chloride was finished after 48 h and had a rate constant of 1.3 x 10⁻⁴ s⁻¹.

The first four acyl chlorides had k₂ and k₃ much larger than k₁ and k₋₁ resulting in the high α : β ratio. The last two, owing to steric hindrance, had k₂ smaller than k₁ and k₋₁, causing a low α : β-ratio. While pivaloyl chloride had k₂ ≤ 2 x 10⁻⁶ s⁻¹ the reaction of 2,4,6-trimethylbenzoyl chloride did not exhibit a large difference in k₂ and k₃ (k₂ ~ 2 x 10⁻⁶ and k₃ ~ 1.1 x 10⁻⁴). Therefore, even though low reactivity in an acid chloride results in β-selectivity this selectivity is not necessarily high, since the ratio k₂/k₃ varies considerably.

Experimental

The NMR spectra were recorded on either a Bruker AC-250 or a AH-90 instrument. Tetramethylsilane was used as an internal reference. Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer PE 241 instrument. Microanalyses were performed by Leo Microanalytical Laboratory. Concentrations were performed by rotary evaporation in vacuo at 40°C.

Acylation procedure. 2,3,4,6-Tetra-O-benzyl-α-d-glucose (I, 1.0 g, 1.85 mmol) was dissolved in dichloromethane (10 ml) and pyridine (1.0 ml, 0.98 g, 12.4 mmol), 4-dimethylaminopyridine (10 mg, 0.082 mmol) and the acyl chloride (7.4 mmol) were added in close succession in that order. The resulting solution was stirred for 24 h at 25°C. Dichloromethane (20 ml) was added, and the solution was washed with hydrochloric acid (1 M, 20 ml), aqueous NaHCO₃ solution (sat., 20 ml) and water (20 ml). Drying (MgSO₄) and concentration usually left an oily residue of the anomeric esters in 90-95% yield. The anomeric ratio was analysed by ¹H NMR spectroscopy.

2,3,4,6-Tetra-O-benzyl-1-O-(2,2-dimethylpentanoyl)-β-d-glucopyranoside (2a). From 1 (5.0 g) and 2,2-dimethylpentanoyl chloride was obtained an oily residue (8.86 g). Ether–pentane gave crystalline 2a (5.14 g, 85%, m.p. 65–68°C). Recrystallisation gave m.p. 72.0–72.5°C, [α]°D + 19.7° (c 1.0, CHCl₃); ¹H NMR (CDCl₃): δ 0.8 (t, 3 H, J = 7.5 Hz, H-5'), 1.2 (s, 6 H, 2 Me), 1.3 (m, 2 H, H-4'), 1.5 (m, 2 H, H-3'), 3.5–3.8 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6a), 4.5 (m, 3 H, Bn), 4.8 (m, 5 H, Bn), 5.6 (d, 1 H, J₁₂ = 8.0 Hz, H-1), 7.1–7.4 (m, 20 H, Bn). ¹C NMR: δ 14.4 (C-5'), 17.9 (C-4'), 24.6, 250 (2 Me), 42.2 (C-2'), 42.8 (C-3'), 67.9 (C-6), 73.3, 74.7, 74.8, 75.5 (2 C), 77.2, 80.7, 84.7 (C-2, C-3, C-4, C-5, 4 Bn), 94.1 (C-1), 127.4–128.2 (Bn), 137.9–138.3 (Bn), 176.4 (C = O). NMR of the mother liquor material revealed no α-anomer present. Anal. C₄₅H₃₆O₁₄: C, H.

2,3,4,6-Tetra-O-benzyl-1-O-(2-methylpropanoyl)-β-d-glucopyranoside (2b). From 1 (5.0 g) and 2-methylpropanoyl chloride (6.25 ml, 6.36 g) an oily residue was obtained. Crystallisation from ether–pentane gave pure 2b (1.33 g, 24%, m.p. 87–89°C). Recrystallisation from ether–pentane gave m.p. 87–88°C, [α]°D + 16.6° (c 1, CHCl₃). ¹H NMR (CDCl₃): δ 1.15 (d, 3 H, J = 7 Hz, Me), 1.2 (d, 3 H, J = 7 Hz, Me), 2.6 (septet, 1 H, CH), 3.5–3.8 (m, 6 H, C-2, C-3, C-4, C-5, C-6, C-6a), 4.6 (m, 3 H, Bn), 4.8 (m, 5 H, Bn), 5.6 (d, 1 H, J₁₂ = 7.5 Hz, H-1), 7.1–7.4 (m, 20 H, Bn).
$^{13}$C NMR: $\delta$ 18.5, 18.7 (2 Me), 33.8 (CH), 67.8 (C-6), 73.3, 74.8 (2C), 75.4, 75.5, 77.1, 80.8, 84.7 (C-2, C-3, C-4, C-5, 4 Bn), 94.0 (C-1), 127.5–128.3 (Bn), 137.7–137.9 (Bn), 175.3 (C = O). The mother liquor contained the α : β ester in a ratio of 9 : 1. Anal. C$_{38}$H$_{42}$O$_7$; C, H.

2,3,4,6-Tetra-O-benzyl-1-O-(2,4,6-trimethylbenzoyl)-β-D-glucopyranose (2e). From 1 (2.5 g) and 2,4,6-trimethylbenzoyl chloride using an extended reaction time of 72 h, a residue (4.41 g) was obtained. Addition of ether–pentane gave crystalline 2e (1.84 g, 58%, m.p. 109–114°C). Recrystallisation from EtOH gave 1.44 g (45%) of a product with m.p. 125–127°C, $[\alpha]_D^{20} + 5.2^\circ$ (c 2.2, CDCl$_3$). (Lit. 11 m.p. 129.5–131.5°C, $[\alpha]_D^{20} + 8$ (c 2.4, CHCl$_3$). Lit. 12 m.p. 131.0–131.5 $[\alpha]_D^{20} + 1.6$ (c 1.0, CH$_2$Cl$_2$). $^{13}$C NMR (CDCl$_3$): $\delta$ 20.0 (2 Me), 21.6 (Me), 68.6 (C-6), 73.9, 75.3, 75.4, 75.1, 76.3, 77.8, 81.1, 85.3 (C-2, C-3, C-4, C-5, 4 Bn), 94.9 (C-1), 128.0–128.7 (Bn + Ar), 130.5, 135.7 (Ar), 138.3–138.7 (Bn), 140.0 (Ar), 169.1 (COO).

References


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