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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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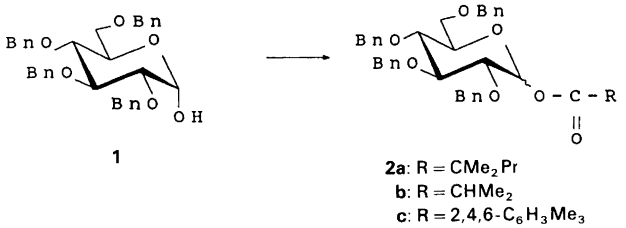
1-*O*-Acyl sugars occur widespread in nature,[1] and as a result their synthesis is important. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (**1**) is the ideal starting material for the synthesis of 1-*O*-acylglucoses (glycosyl esters can also be made directly from glucose[1]) and 1-*O*-acylglucuronic 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 stereochemistry 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 derivative[6] or trichloroacetimidate[7] of **1**. Straightforward pyridine-catalysed acylation of **1** generally gives mixtures containing mostly the α-isomer.[8] In some cases, such as the *p*-nitrobenzoate, the pure α-ester has been obtained.[3] Recently surprisingly high β-selectivity in the pyridine–4-dimethylaminopyridine (DMAP)-catalysed pivaloylation of **1** was discovered.[2] 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



Scheme 1.

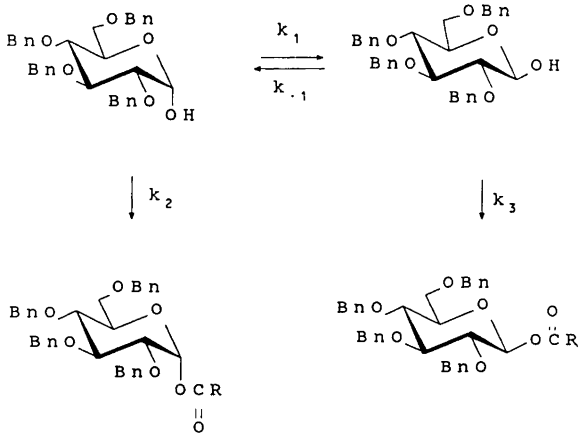
β-selectivity observed for the pivaloyl chloride might be general. As seen in Table 1 most of the acid chlorides gave mainly the α-anomer. Only the hindered acid chlorides pivaloyl chloride, 2,2-dimethylpentanoyl chloride and 2,4,6-trimethylbenzoyl chloride gave predominantly the β-ester, and the first two gave exclusively β. In case of 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] k_3 would be expected to be larger than k_2 (Scheme 2). The α : β ratio of the product depends on the first-order rate constants according to eqn. (1).

$$\alpha/\beta = k_2(k_{-1} + k_3)/k_1 k_3. \quad (1)$$

Thus if k_1 and k_{-1} were large (fast mutarotation) and k_2 and k_3 small (slow acylation) the reaction would lead predominantly to β-ester ($\alpha/\beta \sim k_2 k_{-1}/k_3 k_1$),



Scheme 2.

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Table 1. The anomeric ratio of esters obtained from the reaction of tetrabenzylglucose (**1**) with RCOCl in CH_2Cl_2–pyridine 10 : 1.

R	With 0.1 % DMAP α : β	Without DMAP α : β
Me	6 : 1	10 : 1[b]
Et	3 : 1	
Pr	6 : 1	10 : 1[b]
i-Pr	3 : 1	
t-Bu	0 : 1[a]	1 : 6
$CH_3CH_2CH_2(CH_3)_2C$	0 : 1	
$ClCH_2$	6 : 1	
Cl_2CH	15 : 1	
CH_3CHBr	15 : 1	
$PhCH_2$	1 : 1	
(*E*)-$CH_3CH=CH$	7 : 1	
Ph	3 : 1	6 : 1
2-ClC_6H_4	2 : 1	
2,4,6-$Me_3C_6H_3$	1 : 3	

[a] Ref. 2. [b] Ref. 8.

while the reverse (slow mutarotation and fast acylation) would result in predominantly α-ester ($\alpha/\beta \sim k_2/k_1$). The mutarotion of **1** was studied by the optical rotation by the method described by Swain and Brown,[10] and found to be first order in the sugar concentration. The rate constant ($k_1 + k_{-1}$) at 22°C in CH_2Cl_2–pyridine 10 : 1 (v/v), 0.1 % DMAP was 9.7×10^{-5} s^{-1} corresponding to a half-life of 120 min, while the rate constant in CH_2Cl_2–pyridine 10 : 1 (v/v) was 3.2×10^{-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 k_1 and k_{-1} in the presence of DMAP explain the increased formation of β-ester, if k_2 and k_3 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 **1** was followed by NMR spectroscopy for six acyl chlorides. Since the concentration of **1** 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 konstant $k_2 \geqslant 5 \times 10^{-3}$ s^{-1}. The reaction with pivaloyl chloride and mesitoyl chloride was much slower. The reaction with pivaloyl chloride was complete within 6 h and had a pseudo-first-order rate constant $k_3 \sim 2 \times 10^{-4}$ s^{-1}. The reaction with mesitoyl chloride was finished after 48 h and had a rate constant of 1.3×10^{-5} s^{-1}.

The first four acyl chlorides had k_2 and k_3 much larger than k_1 and k_{-1} resulting in the high α : β ratio. The last two, owing to steric hindrance, had k_2 smaller than k_1 and k_{-1} causing a low α : β-ratio. While pivaloyl chloride had $k_2 \leqslant 2 \times 10^{-6}$ s^{-1} the reaction of 2,4,6-trimethylbenzoyl chloride did not exhibit a large difference in k_2 and k_3 ($k_2 \sim 2 \times 10^{-6}$ and $k_3 \sim 1.1 \times 10^{-5}$). Therefore, even though low reactivity in an acid chloride results in β-selectivity this selectivity is not necessarily high, since the ratio k_2/k_3 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[3] (**1**, 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 $NaHCO_3$ solution (sat., 20 ml) and water (20 ml). Drying ($MgSO_4$) and concentration usually left an oily residue of the anomeric esters in 90–95% yield. The anomeric ratio was analysed by ^{1}H NMR spectroscopy.

*2,3,4,6-Tetra-*O*-benzyl-1-*O*-(2,2-dimethylpentanoyl)-β-D-glucopyranose* (**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, $[\alpha]_D^{20} + 19.7°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 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, $J_{12} = 8.0$ Hz, H-1), 7.1–7.4 (m, 20 H, Bn). ^{13}C NMR: δ 14.4 (C-5′), 17.9 (C-4′), 24.6, 25.0 (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. $C_{41}H_{48}O_7$: C, H.

*2,3,4,6-Tetra-*O*-benzyl-1-*O*-(2-methylpropanoyl)-β-D-glucopyranose* (**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, $[\alpha]_D^{20} + 16.6$ (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 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, $J_{12} = 7.5$ Hz, H-1), 7.1–7.4 (m, 20 H, Bn).

^{13}C NMR: δ 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 (**2c**). 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 **2c** (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, $[\alpha]_D^{20} + 5.2°$ (*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_2Cl_2). ^{13}C NMR ($CDCl_3$): δ 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).

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