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Note

On the selectivity of stannylene-mediated alkylation and esterification of methyl 4,6-*O*-benzylidene α-D-glucopyranoside

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Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) is a widely used starting material for many carbohydrate-based organic syntheses. Selective protection of its free hydroxyl groups is usually desirable, and the use of the 2,3-*O*-dibutylstannylene derivative **2**, normally prepared using dibutyltin oxide, has received much attention for this purpose [1,2]. As part of an ongoing programme utilising carbohydrates as cyclitol precursors, we have studied the selectivity of stannylene-mediated alkylation and esterification of **1**.

A recent report [3] claimed that benzoylation, tosylation, and benzylation of **2** (obtained from **1** and dibutyltin dimethoxide) in toluene gave exclusively the 3-*O*-substituted product in each case. However, in our hands, these acylation and sulfonylation conditions gave exclusively the 2-*O*-substituted products, in 72 and 69% yields, respectively. These results are consistent with those of a previous report [4] which employed dioxane as solvent. The benzylation conditions were found to give a mixture of the 2-*O*-benzyl and 3-*O*-benzyl derivatives **3** and **4** in an approximate ratio of 2.7:1. This mixture of monosubstituted derivatives with **4** as the minor product is consistent with a previous report [5], where DMF was used as solvent, and with our own results in both this solvent and in refluxing acetonitrile (Table 1).

The only conditions we have found to give **4** as the major product involve treating **2** with benzyl bromide in DMF at room temperature in the presence of caesium fluoride [6], a method widely used in cyclitol chemistry [7]. This procedure gives **3** and **4** in an approx-

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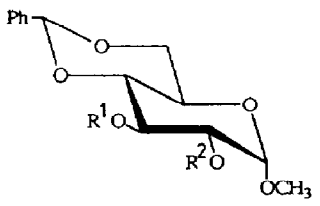

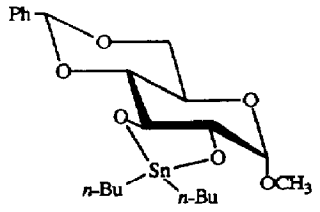

1 $R^1=R^2=H$
3 $R^1=H$; $R^2=Bn$
4 $R^1=Bn$; $R^2=H$
5 $R^1=H$; $R^2=Bz$
6 $R^1=H$; $R^2=Ts$
7 $R^1=H$; $R^2=All$
8 $R^1=All$; $R^2=H$
9 $R^1=H$; $R^2=PMB$
10 $R^1=PMB$; $R^2=H$

2

Bz = benzoyl
Ts = *p*-toluenesulfonyl
Bn = benzyl; All = allyl
PMB = *p*-methoxybenzyl

imate ratio of 1:2. Allyl bromide and *p*-methoxybenzyl chloride were also found to give 3-*O*-alkyl derivatives as major products under these conditions (Table 1).

We report here our data on the selectivity of stannylene-mediated alkylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) and also describe the novel 2- and 3-*p*-methoxybenzyl ethers of **1**.

1. Experimental

TLC was performed on Silica Gel 60F plates (Merck) with detection by UV light or methanolic phosphomolybdic acid. Flash-column chromatography was performed on silica

Table 1
Yields [a] of 2- and 3-*O*-alkylated methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

Alkylating reagent	Conditions	Product yield (%)	
		2-*O*-Alkylation	3-*O*-Alkylation
Benzyl bromide	*A*	41	15
	B	46	19
	C	49	13
	D	25	52
Allyl bromide	*B*	42	14
	D	19	40
p-Methoxybenzyl chloride	*C*	48	18
	D	17	25

[a] See Experimental section for conditions. Yields are based upon isolated products.

gel (SORBSIL C 60). The ^1H and ^{13}C NMR spectra (internal Me_4Si) were recorded on a Jeol JMN-GX270 or JMN-GX400 spectrometer. Mass spectra were recorded at the Mass Spectrometry Service, University of Bath. Microanalysis was carried out by the Microanalysis Service, University of Bath. Melting points (uncorrected) were determined using a Reichert–Jung Thermo Galen Kofler Block. Optical rotations at 589 nm were measured with an Optical Activity Ltd. Polarimeter Type AA-10.

Methyl 2-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside (**5**).—A mixture of **1** (5.0 g, 17.7 mmol) and dibutyltin dimethoxide (4.1 mL, 19.5 mmol) was heated under reflux in dry toluene (300 mL) for 1 h under Dean–Stark conditions. The solution was cooled to 0°C under N_2 and triethylamine (0.1 mL, 0.9 mmol) was added. Benzoyl chloride (2.3 mL, 19.5 mmol) was added dropwise and the solution was stirred at room temperature for 1 h, when TLC indicated a single product corresponding to the 2-*O*-benzoyl derivative (R_f 0.74 in 2:3 hexane–EtOAc) [cf. 3-*O*-benzoyl derivative had R_f 0.43 in same solvent system]. The solution was stirred with MeOH (5 mL) for 5 min and the solvents were evaporated in vacuo. The residue was dissolved in diethyl ether (300 mL) and the solution was stirred with satd aq $NaHCO_3$ (100 mL) for 30 min. The resulting suspension was filtered through Celite and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by flash chromatography (7:3 hexane–EtOAc) to give exclusively the title compound **5** (4.9 g, 72%); mp 170–172°C (EtOH) [lit. [8] 169–170°C]; $[\alpha]_D$ +108.5° (*c* 1.2, $CHCl_3$) [lit. [8] 108°].

Methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside (**6**).—Compound **1** (500 mg, 1.8 mmol) was stannylated as above and cooled to 0°C. Triethylamine (0.01 mL, 0.1 mmol) and tosyl chloride (355 mg, 1.8 mmol) were added and the solution was stirred at room temperature for 16 h. The solvent was evaporated in vacuo and the residue was subjected to flash chromatography (7:3 hexane–EtOAc) to give exclusively the title compound **6** (533 mg, 69%); R_f 0.63 in 2:3 hexane–EtOAc; mp 152–154°C (EtOH) [lit. [9] 153–154°C]; $[\alpha]_D$ +60.0° (*c* 0.8, $CHCl_3$) [lit. [9] +64.2°].

Methyl 2-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**3**) *and methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside* (**4**).—(*A*) Compound **1** (4.9 g, 17.4 mmol) was stannylated as above and the mixture was cooled to room temperature. Tetrabutylammonium iodide (9.7 g, 26.1 mmol) and benzyl bromide (2.3 mL, 19.1 mmol) were added and the mixture was stirred at 50°C under N_2 for 48 h. The mixture was purified as for **5**. Flash chromatography (7:3 hexane–EtOAc) gave **3** (2.6 g, 41%) R_f 0.50 in 2:3 hexane–EtOAc; mp 128–130°C (EtOAc–hexane) [lit. [10] 129.5°C]; $[\alpha]_D$ +35.4° (*c* 5.0, $CHCl_3$) [lit. [10] +35°].

Further elution gave **4** (1.0 g, 15%); R_f 0.31 in 2:3 hexane–EtOAc; mp 184–187°C (EtOH) [lit. [10] 185°C]; $[\alpha]_D$ +77.8° (*c* 5.0, $CHCl_3$) [lit. [10] +84°].

(*B*) A mixture of **1** (10.4 g, 37.0 mmol) and dibutyltin oxide (10.1 g, 40.7 mmol) in toluene (300 mL) was heated under reflux for 3 h under Dean–Stark conditions. The solution was cooled and concentrated in vacuo. To the white residue thus obtained was added dry DMF (30 mL) and benzyl bromide (6.4 mL, 53.8 mmol). This mixture was stirred at 100°C for 3 h, then cooled. Purification and flash chromatography as above gave **3** (6.3 g, 46%) and **4** (2.7 g, 19%).

(*C*) A mixture of **1** (9.7 g, 34.2 mmol), dibutyltin oxide (9.1 g, 36 mmol), tetrabutylammonium iodide (12.7 g, 34.2 mmol), benzyl bromide (4.5 mL, 37.7 mmol), and

MeCN (400 mL) was heated under reflux for 16 h via a Soxhlet thimble containing 4A molecular sieves. The solution was cooled and concentrated in vacuo. Purification and flash chromatography as above gave **3** (6.2 g, 49%) and **4** (1.6 g, 13%).

(*D*) Compound **1** (11.3 g, 39.9 mmol) was stannylated as in method *B*. To the concentrated residue were added CsF (15.2 g, 99.8 mmol, dried in vacuo over P_2O_5 at 60°C for 24 h), dry DMF (40 mL), and benzyl bromide (5.2 mL, 43.9 mmol). This suspension was stirred at room temperature under N_2 for 16 h. Purification and flash chromatography as above gave **3** (3.7 g, 25%) and **4** (7.7 g, 52%).

*Methyl 2-*O*-allyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**7**) *and methyl 3-*O*-allyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**8**).—Analogous treatments of the stannylene **2** with allyl bromide gave **7**, R_f 0.63 in EtOAc; mp 118.5–120°C (EtOAc–hexane) [lit. [11] 115–116°C]; $[\alpha]_D$ +70.0° (*c* 1.5, $CHCl_3$) [lit. [11] +75.8°]; and **8**, R_f 0.53 in EtOAc; mp 155°C [lit. [11] 154–155°C]; $[\alpha]_D$ +100.7° (*c* 1.5, $CHCl_3$) [lit. [11] +104°].

*Methyl 4,6-*O*-benzylidene-2-*O*-p-methoxybenzyl-α-*D*-glucopyranoside* (**9**) *and methyl 4,6-*O*-benzylidene-3-*O*-p-methoxybenzyl-α-*D*-glucopyranoside* (**10**).—Analogous treatments of the stannylene **2** with *p*-methoxybenzyl chloride gave **9** and **10**. Compound **9**: R_f 0.44 in 2:3 hexane–EtOAc; mp 102°C (EtOH); $[\alpha]_D$ +38.6° (*c* 1.4, Me_2CO); ^1H NMR ($CDCl_3$, 270 MHz): δ 2.75 (d, 1 H, *J* 2.2 Hz, exch., D_2O, OH), 3.35 (s, 3 H, OCH_3), 3.40–3.50 (m, 2 H, H-2 and H-4), 3.64–3.84 (m, 5 H, H-5, H-6*ax*, ArOCH_3), 4.12 (td, 1 H, *J* 2.2 and 9.3 Hz, simplifies to t on D_2O exch. H-3), 4.25 (dd, 1 H, *J* 4.4 and 9.7 Hz, H-6*eq*), 4.55 (d, 1 H, *J* 3.5 Hz, H-1), 4.62 and 4.69 (ABq, 2 H, J_{AB} 11.9 Hz, ArCH_2O), 5.50 (s, 1 H, H-7), 6.88 (d, 2 H, *J* 8.6 Hz, H-3 and H-5 of *p*-methoxybenzyl ring), 7.24–7.50 (m, 7 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ 55.14 (OCH_3), 55.22 (OCH_3), 61.90 (CH), 68.84 (C-6), 69.91 (CH), 72.82 (ArCH_2O), 79.06, 81.14 (CH), 98.57 (C-1), 101.81 (C-7), 113.83 (C-3 and C-5 of *p*-methoxybenzyl ring), 126.83, 128.83, 129.03, 129.64 (aromatic CH), 129.87 (C_q–C-7), 137.02 (C_q–CH_2O), 159.39 (C_q–OCH_3); FAB^+ mass spectrum: *m/z* 403 [$(M+1)^+$, 5%]; Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.6; H, 6.52%. Found: C, 65.8; H, 6.56%.

Compound **10**: R_f 0.25 in 2:3 hexane–EtOAc; mp 174–175.5°C (EtOH); $[\alpha]_D$ +45.8° (*c* 1.2, Me_2CO); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.42 (d, 1 H, *J* 7.3 Hz, exch, D_2O, OH), 3.43 (s, 3 H, OCH_3), 3.59–3.94 (m, 8 H, H-2, H-3, H-4, H-5, H-6*ax*, ArOCH_3), 4.28 (dd, 1 H, *J* 4.4 and 9.9 Hz, H-6*eq*), 4.71 (d, 1 H, J_{AB} 11.0 Hz, Ar$CHHO$), 4.77 (d, 1 H, *J* 4.0 Hz, H-1), 4.87 (d, 1 H, J_{AB} 11.0 Hz, Ar$CHHO$), 5.56 (s, 1 H, H-7), 6.84 (d, 2 H, *J* 8.5 Hz, H-3 and H-5 of *p*-methoxybenzyl ring), 7.24–7.51 (m, 7 H, aromatic CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.23 (OCH_3), 55.36 (OCH_3), 62.58 (CH), 69.00 (C-6), 72.31 (CH), 74.47 (ArCH_2O), 78.38, 81.95 (CH), 99.89 (C-1), 101.26 (C-7), 113.79 (C-3 and C-5 of *p*-methoxybenzyl ring), 126.02, 128.24, 128.95, 129.70 (aromatic CH), 130.54 (C_q–C-7), 137.38 (C_q–CH_2O), 159.25 (C_q–OCH_3); FAB^+ mass spectrum: *m/z* 403 [$(M+1)^+$, 5%]. Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.6; H, 6.52%. Found: C, 65.6; H, 6.53%.

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