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Tin-mediated equilibration of the benzoate esters of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

Martin W. Bredenkamp * and Hendrik S. C. Spies

Department of Chemistry, Stellenbosch University, Private Bag X1, Matieland, 7602 South Africa

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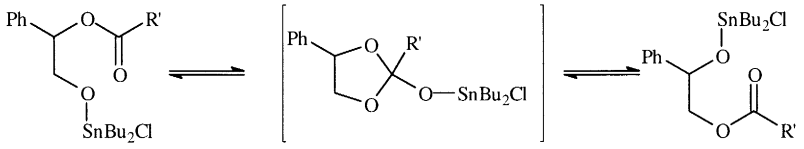
Abstract

The selective dibutyltin oxide-mediated benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside at position 2 is not a post-acylation phenomenon as is the case with the equivalent benzoylation of phenylethyleneglycol. ^{1}H NMR temperature studies have shown that such equilibration occurs only above 85°C in toluene-d_8 for the glucopyranoside.

Keywords: acylation; carbohydrates; NMR; tin compounds.

The selectivity in acylation of phenylethylene glycol mediated by dibutyltin oxide has been very elaborately shown[1] to occur when the resultant dibutylchlorostannyl group is removed by quenching. Prior to quenching, the chlorostannyl group, in an equilibration process, exchanges places with the acyl group via a proposed stannyl glycol *ortho* ester intermediate (Scheme 1). The equilibrium, which is completely functional at ambient temperature, favours the isomer **1** due to the greater steric demands of the dibutylchlorostannyl group relative to the acyl group. On quenching, the selectivity in favour of the ester of the secondary alcohol is further enhanced by the better accessibility the quenching agent has to the chlorostannyl group at the primary position.



(**1**) (**2**)

Scheme 1.

In the light of this process of equilibration, the selectivity of acylation in sugars raises a question. Dibutyltin oxide-mediated benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**), for example (Scheme 2), yields the 2-benzoate **6** on aqueous work up.[2] It would, however, be expected that

* Corresponding author. Fax: 27-21-808-3360; e-mail: mwb@maties.sun.ac.za (M. W. Bredenkamp)

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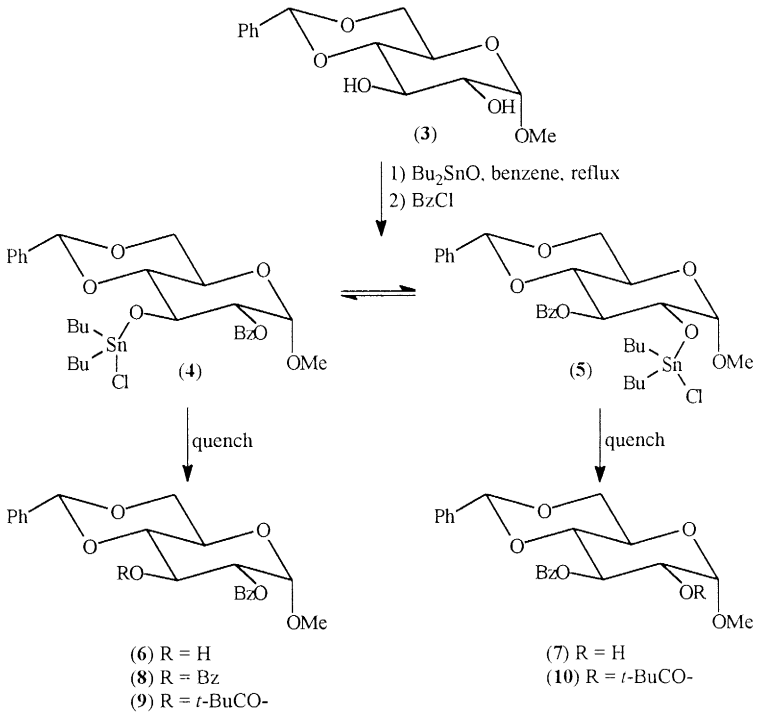
the 3-benzoate **7** should be the main product for three reasons: (i) the bulkier dibutylchlorostannyl group should be more stable at the 2-*O*-position (**5**) since the axiality of the anomeric position allows for more space at position *O*-2; (ii) the quenching agent should access the 2-*O*- (**5**) rather than the 3-*O*-stannyl group (**4**) better for steric reasons and (iii) the axial anomeric oxygen atom (**5**) should stabilise the 2-*O*-stannyl group by chelation, whereas chelation by the oxygen atom at position 4 (**4**) is less favourable because it is equatorial. This implies that: (i) there is no equilibration of the chlorostannyl intermediate at ambient temperature, after tin mediated-benzoylation has occurred, or (ii) equilibration favours the 3-chlorostannyl isomer **4** sufficiently to yield **6** on quenching, or (iii) quenching is very selective towards the 3-chlorostannyl isomer **4**. We herewith present our investigation into this anomaly.



Scheme 2.

In order to obtain reference compounds, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**)[3] was treated with benzoyl chloride in pyridine yielding **6** and **7** and the 2,3-dibenzoate **8**.[4] The mixture was easily separated using flash chromatography. The ^{1}H and ^{13}C NMR chemical shifts are given in Tables 1 and 2, respectively. The benzoylchlorostannyl intermediate (**4** and/or **5**) was then prepared as in Scheme 2, the only difference being the exchange of the benzene for chloroform before benzoylation to best simulate the conditions used by Roelens[1] on phenylethyleneglycol. Both the ^{1}H and ^{13}C NMR of the intermediate reveal a species that is almost identical to compound **6**[5] without the OH signal and with satellites at the H-3 signal indicating ^{3}J-coupling to ^{119}Sn and ^{117}Sn. Two sets of butyl signals are also observed (Tables 1 and 2). The ^{1}H NMR spectrum well characterises the tin complex **4** without a trace of signals that may be assigned to the isomer **5**. As quenching agent the bulky pivaloyl chloride was used to enhance selectivity for the 2-*O*-position on the assumption of equilibration between **4** and **5**. The 2-*O*-benzoyl-3-pivaloate **9**[6] was formed without a trace of the 3-*O*-benzoyl-2-pivaloate **10**. This result was confirmed twice, firstly by the reversed order of acylation (PivCl then BzCl) by dibutyltin

oxide-mediation, yielding the isomer **10**.[6] Secondly, a good yield of the 3-benzoate **7** was obtained by dibutyltin oxide-mediated trimethylsilylation, followed by benzoylation and then desilylation.

Table 1
Selected ^{1}H NMR chemical shifts ($CDCl_3$) of derivatives of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[a]

Compd.	1	2	3	4	5	6ax	6eq	PhC**H**	Me	Other[b]
3[7]	4.689	3.545	3.877	3.424	3.754	3.683	4.244	5.480	3.386	
4	5.073	5.039	4.347	3.633	3.911	3.796	4.324	5.575	3.395	Bu_2Sn[c]
4-C_7D_8	5.010	5.103	4.259	3.306	3.825	3.520	4.114	5.301	3.061	Bu_2Sn[d]
5-C_7D_8	4.485	3.693	5.792	3.474	3.792	3.474	4.164	5.221	2.949	Bu_2Sn[d]
6	5.069	5.037	4.346	3.620	3.907	3.788	4.320	5.567	3.389	
7	4.842	3.816	5.590	3.747	3.938	3.786	4.328	5.519	3.470	
9	5.059	5.128	5.795	3.764	3.996	3.821	4.353	5.559	3.407	1.059[e]
10	4.981	5.020	5.901	3.820	4.023	3.820	4.338	5.527	3.434	1.058[e]

[a]Data (downfield from internal TMS at δ 0.0) were obtained in $CDCl_3$, and where indicated in toluene-d_8, with a Varian VXR 300 (300 MHz) at 25°C. [b]Aromatic signals are not shown. [c]δ 0.946 and 0.948 (Bu-4); 1.393 and 1.418 (Bu-3) and 1.717 – 1.881 (Bu-2 and -1). [d]0.925 and 0.997 (Bu-4); 1.387 and 1.497 (Bu-3) and 1.8 – 2.2 (Bu-2 and -1). [e]*t*-$BuCO_2$.

Table 2
Selected ^{13}C NMR chemical shifts ($CDCl_3$) of derivatives of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[a]

Compd.	1	2	3	4	5	6	PhCH	Me	BzCO	Other[b]
3[7]	99.1	72.4	71.1	80.9	62.3	68.8	101.5	55.3		
4	97.82	74.12	68.82	81.55	62.10	68.95	102.09	55.53	166.26	Bu_2Sn[c]
4-C_7D_8	98.35	74.59	69.02	81.96	62.65	69.23	102.04	55.01	166.15	Bu_2Sn[d]
5-C_7D_8	100.79	72.41	73.44	79.35	63.25	69.06	101.72	55.13	166.15	Bu_2Sn[d]
6	97.80	74.12	68.87	81.50	62.07	68.94	102.08	55.53	166.24	
7	100.29	72.06	73.08	78.91	62.85	69.01	101.54	55.67	166.68	
9	97.95	72.40	68.53	79.42	62.52	68.94	101.30	55.48	165.95	^{t}BuCO[e]
10	97.88	71.53	69.47	79.37	62.58	68.93	101.59	55.63	165.38	^{t}BuCO[f]

[a]Data (δ downfield from internal TMS at δ 0.0) were obtained in $CDCl_3$, and where indicated in toluene-d_8, with a Varian VXR 300 (75 MHz) at 25°C. [b]Aromatic signals are not shown. [c]δ 13.55 and 13.60 (Bu-4); 26.47, 26.61, 27.13 and 27.31 (Bu-3 and -2) and 32.28 and 32.89 (Bu-1). [d]δ 13.75 and 13.87 (Bu-4); 26.87, 27.12, 27.73 and 27.81 (Bu-3 and -2) and 32.51 and 33.29 (Bu-1). [e]δ 26.95 (q), 38.76 (s), 177.24 (CO). [f]δ 26.78 (q), 38.69 (s), 178.08 (CO).

At this stage, no evidence for an equilibration process had been obtained. Yet the possibility of its existence at ambient temperature had not been disproved. If the 2-*O*-chlorostannyl-3-*O*-benzoyl intermediate **5** could be prepared along an alternate route and an equilibrium existed that greatly favoured the isomeric intermediate **4**, then the latter should be observed as the only compound by ^{1}H NMR as before. Such an alternate preparation could be obtained by treating the 3-benzoate **7** with 0.5 mol equivalents of bis(dibutylchlorotin) oxide in refluxing toluene. Before this reaction was tried, it was first performed on the isomeric 2-benzoate **6** as a control reaction. Surprisingly this yielded a 1:1 mixture of **4** and **5**, respectively, as observed by ^{1}H and ^{13}C NMR. The equilibrating role of this process was confirmed by similar results with 1 and 2 mol equiv. of $(Bu_2ClSn)_2O$ on **6** and 1 mol equiv. on **7**.

Quite clearly the equilibrating role that $(Bu_2ClSn)_2O$ plays implies that the stannylene species involved is not the same as that derived from Bu_2SnO/BzCl, or alternately, temperature plays a role. The reflux temperature of toluene (111°C) was used to incorporate the chlorostannyl species into **6** and **7** which already contained benzoyl esters, whereas ambient temperature was not exceeded after the addition of benzoyl chloride to the Bu_2SnO complex of **3**. An NMR temperature study was thus conducted on a fresh sample of **4** generated by complexing Bu_2SnO onto **3** in refluxing toluene followed by the addition of

BzCl at ambient temperature. The toluene was removed and a sample dissolved in toluene-d_8 in an NMR tube. As before the sample consisted of a tin complex of the 2-benzoate **4**. This did not change at even 85°C for 35 min in the NMR probe. The tube was then heated at 108°C for 75 min in an oil bath, during which time isomerisation occurred furnishing a 2:1 mixture of the 2-benzoate **4** relative to the 3-benzoate **5**. This isomer mixture changed to 1:1 after 16 h of heating. Some debenzoylation also occurred.

Post-acylation equilibration is clearly not an ambient temperature process for the dibutyltin oxide-mediated benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**) as is the case with phenylethylene glycol.[1] It is likely that other sugar derivatives, due to the rigidity of the ring structures, will also experience post-acylation equilibration only at elevated temperatures. We are now investigating sugar *cis*-diols and also sugar tri- and tetrols in this respect.

Acknowledgements

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