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Note

The anomalous reactivity of the bis(dibutylstannylene) acetal of pentaerythritol: a case of triple activation

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Abstract

The only dibutyltin derivative of pentaerythritol which is observed by refluxing with dibutyltin oxide in methanol is a bis(dibutylstannylene) acetal. This is converted to the expected dibenzyl ether with benzyl bromide, in the presence of tetraethylammonium bromide in boiling toluene, but benzoylation at room temperature gives a tribenzoate. A mechanism is suggested to account for this triple activation.

Keywords: Pentaerythritol; Stannylenes; Triple activation

There is current interest in the utilization of partially protected pentaerythritol derivatives to prepare conjugates of organic compounds with various carrier molecules.[1] This led us to examine the course of derivatization by the stannylene method.[2] This approach allows a strictly regiospecific substitution at one of the oxygen atoms in a diol. In unprotected oligosaccharide glycosides the substitution is again regiospecific, despite the great number of potentially reactive oxygen atoms.[3] However, application of the method to pentaerythritol revealed unexpected anomalies.

Refluxing a mixture of pentaerythritol with two equivalents of dibutyltin oxide in methanol, followed by evaporation to dryness gave the bis(dibutylstannylene) acetal of pentaerythritol. From what is known about the relative instability of monomeric 2,2-dibutyl-1,3,2-dioxastannolane with respect to its oligomers,[4] this product is most probably a polymer. As expected, treatment with benzyl bromide in the presence of tetramethylammonium bromide in boiling toluene[5] afforded the ether **6** in 70% yield, identical with a specimen prepared by another route. This 'one-pot' preparation from pentaerythritol appears to be the most convenient access to ether **6**, as the described procedure involving benzylation of the benzylidene derivative requires three steps.[6] Although benzylation of stannylenes is normally possible in polar solvents at 100 °C without a catalyst, we have observed no reaction under these conditions in *N*,*N*-dimethylformamide solution.

By analogy, we expected that the benzoylation of the bis(dibutylstannylene) acetal at room temperature would yield a dibenzoate in an efficient way. In fact, the reaction of 1.7 mmol of benzoyl chloride with 1 mmol of stannylene gave a 3:1 mixture of the triben-

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zoate **1** (as the main constituent) with the expected dibenzoate **2** as a minor product. Practically all the benzoyl chloride was consumed, while 43% of the starting material had not reacted. Thus, it appears that the third benzoylation step was more rapid than the first ones. The same experiment with 3.4 or 6.9 mmol of benzoyl chloride gave only the tribenzoate **1**, which was obtained in 70% yield, without any di- or tetrabenzoate[7] **5**.

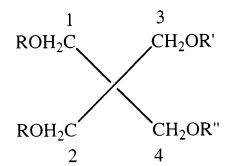
We must first dismiss the explanation of a common supplementary esterification by the reagent in great excess. Such a reaction would necessitate basic conditions, and be generally much slower at room temperature than the benzoylation of hydroxyl groups activated by conversion into dibutylstannylene acetals. However, in our case, the medium is neutral and the reaction is very fast, being complete in less than 5 min at room temperature. This is the characteristic reactivity of the stannylene acetals.

We suggest the following mechanism for this triple activation. In the likely[8] intermediate **7**, intramolecular coordination would give the stannoxane **8**, which may be reactive as such, or be converted to some kind of reactive stannoxane, for instance after disproportionation and elimination of dibutyldichlorotin. Apparently these intermediates do not form, or are not reactive under the conditions of benzylation (111 °C, ionic catalyst).

We can now reinvestigate the course of the stannylenation of pentaerythritol with the knowledge we have of its reactions. Although the formation of a monostannylene derivative appears likely as a first step, we have found no evidence for its existence. Refluxing equimolecular amounts of dibutyltin oxide and pentaerythritol gave a mixture which afforded only the tribenzoate **1** on benzoylation. This behavior contrasts with that of polyhydroxylated oligosaccharides, which are activated at only one site when treated with an equimolecular amount of dibutyltin oxide. We have shown elsewhere[5] that mixtures of stannylenes undergo a rapid intermolecular equilibration in favor of the most stable derivative.[9] Thus, our observation might be explained by the greater stability of the polymer.

Table 1
^{1}H NMR spectra of pentaerythritol derivatives **1**–**6**

	Protons				
	1, 2	3	4	OH	Others
1	4.60	4.60	3.70	2.85	
2	4.49	3.73	3.73	3.04	
3	4.50	4.34	3.70	2.04 (Ac)	2.07
4	4.85	4.06 (d), 4.36 (d)		4.50	
	4.31	*J* 12 Hz			(PhC*H*)
5	4.70	4.70	4.70		
6	3.65	3.58	3.58	2.69	



1 R = R' = Bz, R" = OH

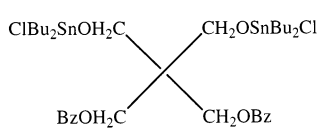
2 R = Bz, R' = R" = OH

3 R = Bz, R' = Ac, R" = OH

4 R = Bz, R', R" = CHPh

5 R = R' = R" = Bz

6 R = Bn, R' = R" = OH



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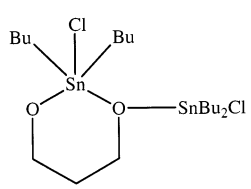

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1. Experimental

General.—Samples were examined on Silica Gel TLC plates (E. Merck), with 1:1 petroleum ether–EtOAc as eluent, unless otherwise stated, and inspected under UV light at 254 nm. Preparative chromatographic separations were achieved with open columns filled with silica gel (40 mL per gram of mixture). ^{1}H NMR spectra (250 MHz) were recorded in chloroform-*d* in the presence of Me_4Si and chemical shifts are reported in Table 1. Aromatic protons are not tabulated, the signals for all derivatives appear at 7.40–7.60 and 8.02 ppm.

Preparation of the dibutyltin derivative of pentaerythritol.—A mixture of pentaerythritol (1.36 g, 10 mmol) and dibutyltin oxide (5.0 g,

20 mmol) was refluxed in methanol for a few hours. The solvent was removed by evaporation and the glassy residue was dried first by keeping for 1 day at 40 °C under diminished pressure, and then by coevaporation with toluene. The product was stored in a dessicator (P_2O_5) but did not appear to be hygroscopic.

2,2-Bis(benzyloxymethyl)-1,3-propanediol (**6**).—A suspension of the above stannylene derivative (0.6 g, 1 mmol) in toluene (10 mL) in the presence of BnBr (0.5 mL, 4 mmol) and tetraethylammonium bromide (135 mg) was heated at reflux for 4 h, cooled to rt and stirred with water (20 mL). Evaporation of the organic phase gave a residue from which was separated by chromatography (EtOAc) the crystalline dibenzyl ether **6** (211 mg, 70%), mp 67–70 °C, raised to 73 °C by one crystallization from petroleum ether, R_f 0.35. This was identical with a sample prepared according to Ref. 6.

3 - O - Benzoyl - 2,2 - bis(benzoyloxymethyl)-1,3-propanediol (**1**).—Benzoyl chloride (0.8 mL, 6.9 mmol) was added to a suspension of the above stannylene derivative (0.6 g, 1 mmol) in toluene (5 mL). After 10 min at rt, water (10 mL) was added to the clear solution, and the mixture was stirred vigorously for 4 h, while the medium was kept neutral by the addition of a sodium hydrogencarbonate solution. The organic layer was separated, and the solvent was removed by evaporation. Chromatography of the residue (706 mg), with 8:1, 4:1, 2:1, and 1:1 petroleum ether–EtOAc mixtures as eluent, separated the tribenzoate **1** as a glass (318 mg, 70%), R_f 0.35 (2:1 petroleum ether–EtOAc). Anal. Calcd for $C_{26}H_{24}O_7$: C, 69.64; H, 5.35. Found: C, 69.45; H, 5.57.

A similar experiment conducted with 3.4 mmol of BzCl per mmol of stannylene gave the same tribenzoate as the only product which could be detected on a TLC plate.

2,2-Bis(benzoyloxymethyl)-1,3-propanediol (**2**).—To a suspension of the above stannylene derivative (1.2 g, 2 mmol) in dry toluene (10 mL), BzCl (0.40 mL, 3.4 mmol) was added, and the mixture was stirred for 5 min at rt. Dissolution was then complete. Processing of the mixture and chromatography conducted as above, separated first the tribenzoate (373 mg, 0.83 mmol), R_f 0.5. Extraction of the column with EtOAc; followed by chromatography (1:1 petroleum ether–EtOAc) gave the crystalline dibenzoate **2** (108 mg, 0.31 mmol), mp 75 °C, R_f 0.30, identical to a sample prepared as described below.

Preparation of dibenzoate **2** *from benzylidene-pentaerythritol.*—Benzoylation of benzylidene–pentaerythritol (0.6 g, 2.68 mmol) with BzCl (0.75 mL) in pyridine (3 mL) gave, after the usual working up, the dibenzoate **4** (891 mg, 77%), mp 122 °C (MeOH). A solution of this compound (2.43 g, 5.6 mmol) in AcOH (25 mL) and water (15 mL) was kept at 90 °C for 3 h. After evaporation of the solvents, chromatography of the residue (1:1 petroleum ether–EtOAc) first gave the acetate **3** (615 mg) and then the crystalline dibenzoate **2** (731 mg, 38%), mp 75 °C. This compound could not be crystallized from common solvents. Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.28; H, 5.81; Found: C, 66.44; H, 6.01.

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