Carbohydrate Research, 103 (1982) 165–169
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

Selective monobenzylation of methyl α-L-rhamnopyranoside and its 4-benzyl ether in the presence of tin(II) chloride

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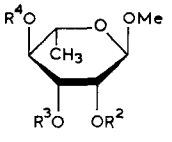
(Received April 6th, 1981; accepted for publication in revised form, August 12th, 1981)

The selective benzylation of saccharides yields specifically protected intermediates of synthetic utility[1–4] that would otherwise be available only after multistep procedures. Recent publications have described the preparation of some mono- and di-substituted benzyl ethers of methyl α-L-rhamnopyranoside by using different procedures[5–8]. The papers[7,8] witness an expanding application of organotin compounds, and especially of dibutyltin oxide, also in the methyl 6-deoxyhexopyranoside field. Wagner *et al.*[2] have shown and well documented with several examples that an equimolar amount of dibutyltin oxide forms with suitably disposed OH groups of a sugar moiety the corresponding, covalent dibutylstannylene derivative. The dibutylstannylene function serves, however, not as a protecting group, but rather as an activator for the hydroxyl groups of a sugar residue in subsequent alkylation reactions. An entirely different mechanism is involved in complexation of methyl 6-deoxyhexopyranosides with a catalytic amount of tin(II) chloride and resulting activation of the OH groups (see later). The potential of complexation with tin(II) chloride for regioselective synthesis is now emplified in the selective monobenzylation of methyl α-L-rhamnopyranoside (**1**) and its 4-benzyl ether (**2**) with benzyl bromide.

Treatment of **1** in dry ethyl acetate or acetonitrile, with an excess of benzyl



Bn = $PhCH_2$

	R^2	R^3	R^4
1	H	H	H
2	H	H	Bn
3	H	Bn	H
4	Bn	H	H
5	Bn	H	Bn
6	H	Bn	Bn

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TABLE I

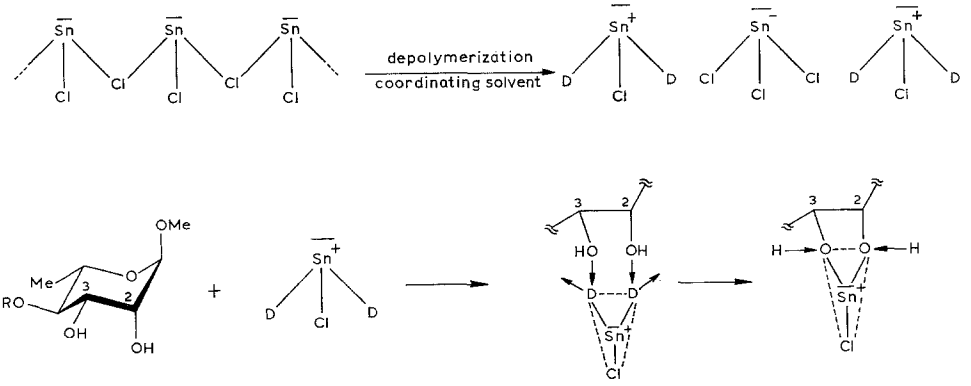
YIELDS (%) OF THE BENZYLATION PRODUCTS FROM **1** AND **2** AND THEIR DEPENDENCE ON THE EQUIVALENTS OF BENZYL BROMIDE AND THE SOLVENTS USED

Benzyl bromide (equiv.)	**1**						**2**			
	Acetonitrile			*Ethyl acetate*			*Acetonitrile*		*Ethyl acetate*	
	2	**3**	**4**	**2**	**3**	**4**	**5**	**6**	**5**	**6**
3	0.9	33.4	5.7	5.0	23.6	26.7	2.8	8.8	5.9	24.4
6	0.6	44.9	4.4	3.0	42.1	17.7	3.1	18.6	8.4	39.1
9	0.5	52.2	4.7	2.4	64.2	22.6	4.1	34.2	9.1	48.2

bromide in the presence of tin(II) chloride and triethylamine for 32 h at 110° yielded a syrup. Depending on the concentration of benzyl bromide and the solvent used, g.l.c. analysis showed very different isomer distributions of the corresponding benzyl ethers, in addition to unreacted **1** (Table I). Column chromatography on silica gel yielded crystalline methyl 3- and syrupy 2-*O*-benzyl-α-L-rhamnopyranosides (**3** and **4**), the latter being contaminated with **2** (0.5–5%, g.l.c.). Compound **4** was acetylated and purified on silica gel to give syrupy **4** in almost quantitative yield following deacetylation.

Likewise, benzylation of **2** (ref. 9) gave a mixture of syrupy methyl 2,4- and 3,4-di-*O*-benzyl-α-L-rhamnopyranosides (**5** and **6**), the respective yields of which are given in Table I.

The aforementioned benzylations present a part of our detailed studies on regioselective alkylation of methyl 6-deoxyhexopyranosides as catalysed by tin(II) chloride. Anhydrous tin(II) chloride is depolymerized on dissolution, and may form



D = donor atom of the coordinating solvent, for instance, of acetonitrile

R = H or Bn

Scheme 1

complexes with various solvents. The stereochemistry of such complexes and the bond strength of the coordinated solvent molecules to a tin(II) atom vary in accordance with the solvent used[10,11]. If sufficiently labile complexes are created, two molecules of the solvent, coordinated to tin(II) in *cis*-disposition, may be displaced by suitably arranged OH groups of the sugar residue (Scheme 1)[12].

Thus, a system of two vicinal hydroxyl groups, sufficiently close to form a complex with the catalyst, is a prerequisite for the reaction. A similar observation has also been made by Chittenden[13].

In compound **1**, the complex is preferentially formed between HO-2 and HO-3, whereas complexation between HO-3 and HO-4 is of minor importance[12]. This is in accordance with our CNDO/2 quantum-chemical calculations[12] which showed the following decrease in electron density: HO-3 > HO-2 > HO-4. Moreover, the orientation of the hydroxyl groups is also an important factor, and the spatial disposition of the HO-2 and HO-3 groups apparently favours complex formation. Recent n.m.r. studies[14] have brought additional evidence in this field.

The foregoing results have primarily been applied in the regioselective synthesis of monobenzyl ethers of **1**. Accordingly, the choice of properties of solvent, namely, its weakness of bonding to the tin(II) atom and the stereochemistry of the coordination sphere of the intermediate complex[10,11], is of fundamental importance for this reaction. As benzylation did not proceed in dimethyl sulfoxide, *N*,*N*-dimethylformamide, 1,4-dioxane, oxolane, and 1,2-dimethoxyethane, this result might indicate that these solvents most probably do not fulfil the aforementioned criteria. On the other hand, when acetonitrile and ethyl acetate were used, fairly good yields of the monobenzyl ethers were obtained, especially in ethyl acetate (Table I).

Compound **2** was less readily converted into the corresponding dibenzyl ethers and the yield of **5** was especially meagre. Reactions in ethyl acetate yielded better results (Table I).

By varying the concentration of benzyl bromide, a different distribution of isomers was achieved. It is evident that increasing the amount of reagent gives higher yields and simultaneously favours the formation of 3- and 3,4-dibenzyl ethers. However, no benzylation took place when benzyl chloride was used instead of benzyl bromide.

The influence of concentration of tin(II) chloride upon the reaction was also investigated. Over a wide range of concentration (5–50 mmol.dm^{-3}), no substantial difference in the yields and isomer distribution was found. This result indicates a catalytic effect of tin(II) chloride in the benzylation reaction.

Among the bases examined as proton scavengers, triethylamine gave the best results. It appears that the base forms only very labile adducts with the catalyst under the experimental conditions used. This assumption is based on related studies of Hsu *et al.*[15], who investigated the formation of trimethylamine adduct with tin(II) halides.

As in most chemical reactions, longer reaction-times and elevated temperatures

increased the yields of benzylated products. Heating for 32 h at 110° gave optimal conversions.

Thus, the complexation of tin(II) chloride with **1** and **2** proved highly specific and permitted selective benzylation at the HO-2 and HO-3. Further examples of the regioselective enhancement of the nucleophility of hydroxyl groups in sugar residues by complexation with tin(II) chloride, and applications to various reactions, will be found in future publications.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage and are uncorrected. Optical rotations were measured for solutions in chloroform with a Perkin–Elmer Model 141 polarimeter. T.l.c. was performed on Silufol plates (Kavalier, Czechoslovakia) with *A* 5:2 chloroform–acetone, *B* 10:1 chloroform–ethyl acetate, and *C* 4:1 chloroform–ethyl acetate, and components were detected by charring after spraying with 20% aqueous ammonium sulfate. Dry-column chromatography was performed on Silikagel L (40–56 μm, Lachema n.p. Brno).

G.l.c. of trifluoroacetylated products of the benzylation reactions was performed with a Hewlett–Packard Model 5711 A chromatograph using a column (200 × 0.32 cm) of 3% of OV-225 on 80–100 mesh Chromosorb W AW-DMCS, over a programmed temperature-range of 100 (4 min) to 190° at 4°/min, and over 120 (4 min) to 210° at 4°/min for the less-volatile dibenzyl ethers.

^{13}C-N.m.r. spectra were recorded at ambient temperature with a Jeol FX-60 instrument in chloroform-*d* solutions, with tetramethylsilane as the internal standard. The following f.t. techniques were used: noise and off-resonance decouplings with repetition time of 1 s, pulse-width 4 μs (45° flip angle), and 2500 Hz sweep-width (8K real data points). An average number of accumulations was 3000 for noise and 8000 for off-resonance decouplings.

Anhydrous tin(II) chloride was obtained by dehydrating reagent-grade stannous chloride dihydrate, $SnCl_2 \cdot 2\ H_2O$, with acetic anhydride and was stored under anhydrous conditions.

Anal. Calc. for $SnCl_2$: Sn, 62.6; Cl, 37.4. Found: Sn, 62.3; Cl, 37.2.

Selective benzylations. — *A. Methyl* α-L-*rhamnopyranoside* (**1**). In a representative experiment, to a solution of **1** (2 g, 11.2 mmol) in dry ethyl acetate or acetonitrile (100 mL) containing tin(II) chloride (190 mg, 1 mmol), and excess of benzyl bromide (4–11.9 mL, 33.6–100.8 mmol, see Table I) and triethylamine (2.3 mL, 16.6 mmol) were added. The mixture was kept in a sealed tube overnight at room temperature and then heated for 32 h at 110°. The cooled solution was filtered to remove triethylamine hydrobromide and the filtrate was evaporated and partitioned between chloroform and water. The organic phase was concentrated to low volume and the two major products (R_F 0.5 and 0.4, t.l.c., solvent *A*) were isolated by chromatography on a column (3.2 × 40 cm) of silica gel with solvent *A*.

The faster-moving component was **3**, m.p. 82–84°, $[\alpha]_D^{22}$ −37.5° (*c* 0.84);

lit.[8] m.p. 80°, $[\alpha]_D$ −26.1° (chloroform); ^{13}C-n.m.r.: δ 137.4–128.0 (Ph), 100.4 (C-1), 67.7 (C-2), 79.8 (C-3), 71.5 (C-4), 67.7 (C-5), 71.7 (CH_2 of Bn), 54.8 (OMe), and 17.7 (Me).

Anal. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51; OMe, 11.57. Found: C, 62.64; H, 7.49; OMe 11.66.

The slower-moving component was syrupy **4** contaminated, depending on the conditions used, by various proportions of **2** (0.5–5%, g.l.c.). Acetic anhydride and pyridine (1:1, v/v) were added and, after heating for 1 h at 100°, the mixture was evaporated. Water and methanol were evaporated several times from residue and the product was then chromatographed on a column (2.2 × 40 cm) of silica gel using *B* as eluant. Eluted first was peracetylated **4** (R_F 0.7, t.l.c., solvent *B*), which on conventional treatment with 0.2M sodium methoxide in methanol gave an almost quantitative yield of syrupy **4**, $[\alpha]_D^{22}$ +8.6° (*c* 1.6); ^{13}C-n.m.r.: δ 137.5–127.9 (Ph), 98.0 (C-1), 78.2 (C-2), 73.0 (C-3), 73.8 (C-4), 67.7 (C-5), 73.0 (CH_2 of Bn), 54.8 (OMe), and 17.5 (Me).

B. Methyl 4-O-benzyl-α-L-rhamnopyranoside (**2**). — The title compound[9], m.p. 105–107°, $[\alpha]_D^{22}$ −66.8° (*c* 1.2), gave the following ^{13}C-n.m.r. data: δ 138.3–127.9 (Ph), 100.4 (C-1), 71.0 (C-2), 71.4 (C-3), 81.6 (C-4), 67.0 (C-5), 74.9 (CH_2 of Bn), 54.8 (OMe), and 18.1 (Me).

Benzylation of **2** with benzyl bromide in the presence of catalyst, following the procedure described in *A* afforded two major products (R_F 0.6 and 0.4, t.l.c., solvent *C*), in addition to unreacted **2**. These were separated on a column of silica gel with solvent *C*. The faster-moving product was syrupy **5**, $[\alpha]_D^{22}$ −16.1°; lit.[5] −15.4° (chloroform).

Eluted next was syrupy **6**, $[\alpha]_D^{22}$ −49.8°; lit.[5] −46.4° (chloroform). The ^{13}C-n.m.r. spectra of both compounds were in agreement with the data reported[5].

The yields of **3**, **4**, **5**, and **6** isolated from the reactions were comparable with those determined by g.l.c. analysis (Table I).

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