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METHANOLYSIS OF ACETYLATED SUGARS AND GLYCOSIDES IN THE PRESENCE OF TIN OXIDES AND ALKOXIDES*

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ABSTRACT

A simple, regioselective *O*-deacetylation procedure is described which involves ≤0.5 equiv. of Bu_3SnOMe or Bu_2SnO in methanol. Anomeric acetates are considerably more reactive than primary and secondary acetates, thereby enabling selective removal, to give ~70% of products with HO-1 unsubstituted. Prolonged reaction resulted in complete deacetylation. Secondary acetates were removed faster than primary acetates and the overall rates of reaction were influenced greatly by the anomeric substituent in the order of OAc ≫ OH > OMe. No acyl migration took place under the reaction conditions.

INTRODUCTION

In the presence of Bu_3SnOMe and $(Bu_3Sn)_2O$ in a variety of non-hydroxylic solvents, acetylated sugars selectively afforded the Bu_3SnO-1 derivatives which were readily hydrolysed to give products with HO-1 unsubstituted[1]. Total deprotection was easily effected by methanolyses catalysed by cyanide[2a,b] or magnesium oxide[3]. The use of Bu_2SnO for *N*- and *O*-deacetylation of an *N*-glycosyl derivative[4], transesterifications catalysed by organotin reagents[5], and selective deacetylation at the anomeric position *via* ammonolysis[6] have been described. We now report on the regioselective *O*-deacetylation of acetylated sugars and glycosides using ≤0.5 equiv. of Bu_3SnOMe or Bu_2SnO in methanol at 50°.

RESULTS AND DISCUSSION

Two series of compounds were examined, namely, *A*, derivatives having an anomeric acetate group (**1–4**, Table I) and *B*, methyl glycosides (**9–12**, Table II).

The reactions were monitored by 300-MHz ^{1}H-n.m.r. spectroscopy on solu-

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tions in CD_3OD*. In spite of the complexity of some of the mixtures, enough individual multiplets could be assigned to permit both identification and quantification of the compounds present at any time. The kinetic data served as the basis of Figs. 1–3 and Tables I and II. When possible, further identification of intermediates was carried out by t.l.c.

The anomeric substituent in the methyl glycosides was not affected under the reaction conditions. Although total *O*-deacetylation is of synthetic value, regioselective mono-deacetylation is impractical. In the absence of the tin reagent, the rate of methanolysis was negligible.

For compounds in series *A*, the effect of Bu_2SnO was greater than that of Bu_3SnOMe, as can be seen from the results in Fig. 1 and Table I. This higher reactivity may be attributed to the intermediacy of $Bu_2Sn(OMe)_2$[5], $(Bu_2MeOSn)_2$[7], or $Bu_2MeOSnOH$[8]. The existence of the last intermediate has been questioned[7,9]. The reactivities of the β-acetates (**1**β and **4**β) were higher than those of the corresponding α-acetates (**1**α and **4**α) and the differences were more pronounced in the presence of Bu_2SnO. Nevertheless, the rates of reactions of the α anomers were sufficiently fast to enable the selective removal of AcO-1 in the presence of a primary acetate, *e.g.*, **4**. At its maximum, the amount of 1-deprotected sugar (*i.e.*, **8**) constituted 70% of the mixture. The reaction[1] of α-acetates with Bu_3SnOMe in inert solvents resulted in considerably lower yields (30%), owing to concomitant loss of AcO-1 and AcO-6.

The ^{1}H-n.m.r. data of the compounds with HO-1 unsubstituted, some of which were isolated, indicated that they were α,β-mixtures, probably because of

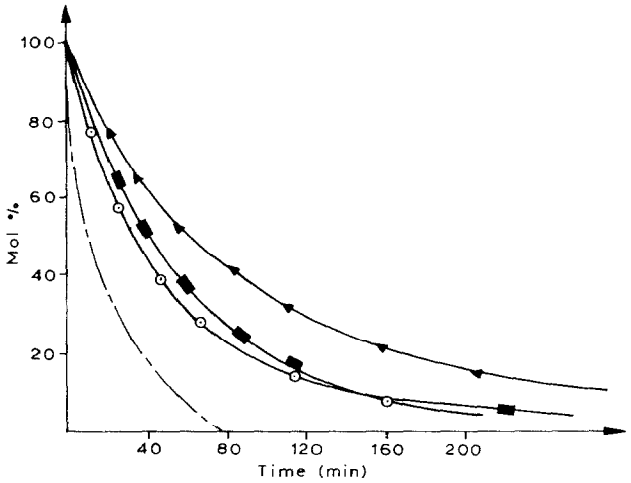


Fig. 1. Loss of AcO-1 from **1** as a function of catalyst and anomeric configuration: **1**α, —▲—, Bu_3SnOMe; —⊙—, Bu_2SnO; **1**β, —■—, Bu_3SnOMe; —·—, Bu_2SnO.

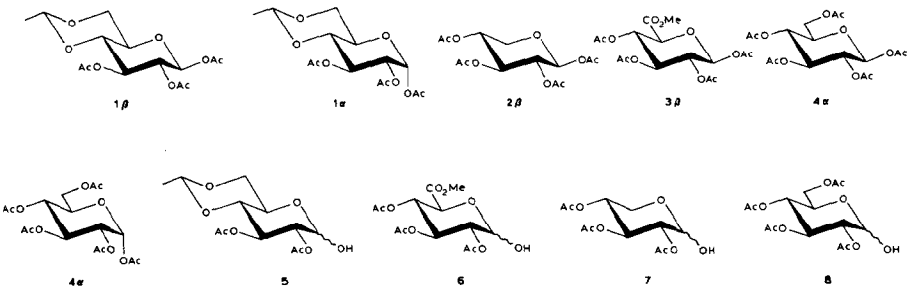
*The ^{1}H-n.m.r. data are reported in the Ph.D. Thesis of J. Herzig, Bar Ilan University, 1986, and are available on request.

TABLE I

REACTION CONDITIONS AND PRODUCTS FOR SERIES A IN CD_3OD AT 50°

Starting sugar	$t_{1/2}$ *(min)*	*Catalyst* Bu_3SnOMe *(I)* Bu_2SnO *(II)*	*Reaction time (h)*	*Percent in mixture*	*Products isolated (%)*	*α,β-Ratio*	
1β	40	I	3.5	75[a]	72	0.8:1	**5**
	9	II	0.75	80[a]	65	0.8:1	
1α	60	I	4.5	70[a]		0.8:1	
	28	II	1.75	55[a]		0.8:1	
2β		I	2	80[a]	72	3.1:1	**6**
		II	0.75	75[b]	58	3.2:1	
3β		II	0.75	80[b]			**7**
4β	24	I	2.5	[c]	70	2:1	**8**
		II	1	70[b]			
4α	29	I	3	70[a]			
		II	1	70[b]			

[a]Determined by n.m.r. spectroscopy, [b]Determined by t.l.c. [c]Not determined.

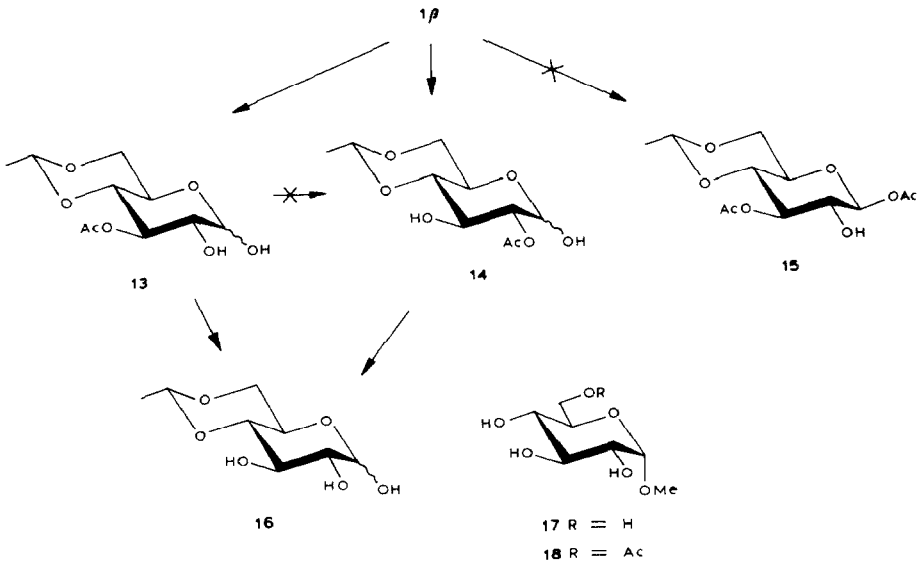


organotin-catalysed mutorotation. The addition of Bu_3SnOMe to a solution of **5α** in methanol caused instantaneous isomerisation.

The concentration of the products with HO-1 unsubstituted increased during 3–5 h, then decreased because of polydeacetylation (Fig. 2). After some 50–70 h, the major product was the *O*-deacetylated compound.

Because of the small number of acetyl groups, 1,2,3-tri-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranose (**1β**) was used for mechanistic studies. After the initial removal of AcO-1 (→**5**), preferential methanolysis of AcO-2 occurred, to give **13** (monitored by integration of the H-3 peak at 5.25 p.p.m.). The higher reactivity of AcO-2 may be attributed to its proximity to HO-1 which can readily assume a *cis* relationship. The polarising influence of a vicinal OH group on the rate of methanolysis has been discussed[2a]. The next intermediate detected was **14** (monitored by integration of the H-3 peak at 5.04 p.p.m.), which could have been formed from **5** or *via* acyl migration from **13**, but no evidence for acyl migration under conditions of neutral methanolysis was observed. If the rate of acyl methanolysis in **13** was lower than the rate of acyl migration **13**→**14**, then the

accumulation of **14** prior to the formation of **16** should have been observed. The fact that **16** began to appear only after 12 h, when both **13** and **14** were still present and accounted for ~40% of the reaction mixture, indicated that acyl transfer was slower than the rate of loss of AcO-3. Therefore, it is reasonable to assume that **14** was formed directly from **5**. Since all the n.m.r. signals could be accounted for and attributed to the compounds mentioned above, the presence of **15** was excluded, which implies that 2→1 acyl migration did not occur. For **9**, where AcO-3 and HO-2 are *trans*, acyl migration should be even slower. Acyl migrations have been observed under more basic conditions, such as in methanolysis in the presence of cyanide[2a] or MgO[3].



Primary acetates were less reactive than secondary acetates. Thus, the mixture of products formed from **4β** after 24 h consisted mainly of **8** and 3,4,6-tri-*O*-acetyl-α,β-D-glucopyranose, with no appreciable amounts of 2,3,4-tri-*O*-acetyl-α,β-D-glucopyranose. Similar observations were made with the methyl glycosides.

For the compounds in series *B* (methyl glycosides), the kinetics of total deacetylation were investigated in an attempt to assess the reactivity of the various acetyl groups. Reactions in CD_3OD could be followed readily by the appearance of the signal (2.02 p.p.m.) for $MeCOOCD_3$, in addition to the changes in the signals for H-1, H-3, and OMe. An instantaneous exchange of $Bu_3SnOMe \rightarrow Bu_3SnOCD_3$ took place upon dissolution of the former in CD_3OD.

Although, for **11α**, AcO-2 was removed initially, this was not so for **9β** and **12β**, which may be rationalised by the complexation of the tin atom with MeO-1 in the 1,2-*cis* derivative **11α**[7a] (**11α→19→20**). In β-glycosides, several secondary positions appear to be equally reactive. Primary acetates were less reactive than

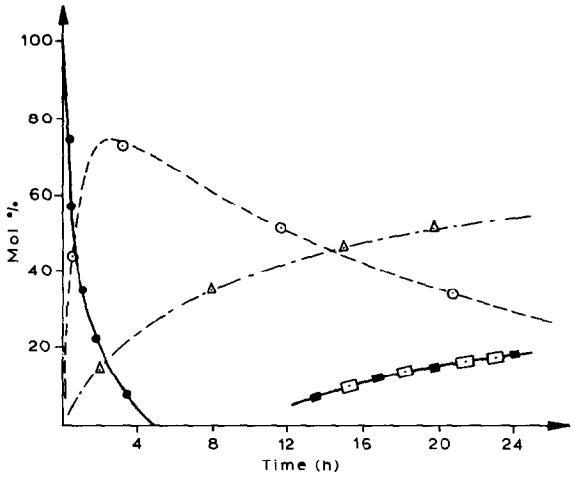
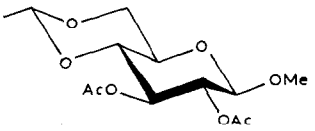
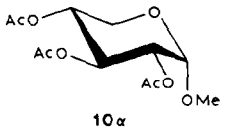


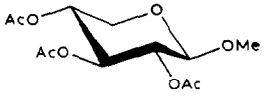
Fig. 2. Bu_3SnOMe-catalysed methanolysis of **1β**: —●—, **1β**; —⊙—, **5**; —△—, **13** + **14**; —□—, **16**.



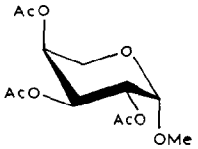
9β



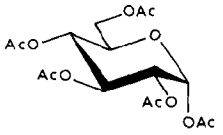
10α



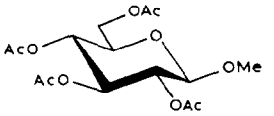
10β



11α



12α



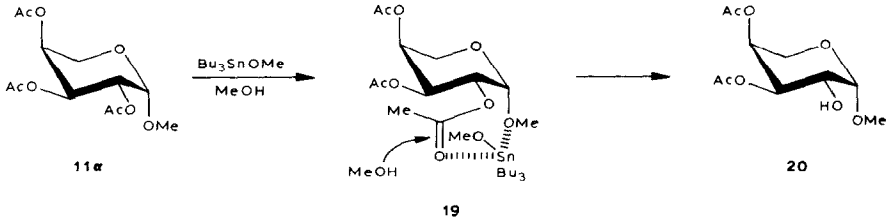
12β

TABLE II

RATES OF DEACETYLATION IN SERIES B

Compound	$t_{1/2}$	*Compound*	$t_{1/2}$
9β	>24	**11α**	13.5
10α	7	**12α**	8.5
10β	12.5	**12β**	14

secondary, and, after 70 h, AcO-6 intermediates, such as **18**[10] (monitored by integration of the signal for OMe at 3.41 p.p.m.), were the major ones along with the fully *O*-deacetylated products (*e.g.*, **17**, Fig. 3). This phenomenon, which is not due to acyl migration, may reflect an interaction of the tin reagents and the acetate groups. The higher reactivity of secondary acetates is rather surprising, since the Bu_3SnOMe-catalysed methanolysis of ethyl acetate was considerably faster than that of isopropyl acetate (50% *vs.* 5% conversion after 20 h at 50°). The $t_{1/2}$ values of the compounds of series *B* are listed in Table II.



The methanolyses described above afford a general route for the total deacetylation of sugar acetates, and for the selective removal of AcO-1. For this reaction, these solvolyses are also useful in assessing the reactivities of the various acetyl groups. Deacetylation at the anomeric position is much faster (average $t_{1/2}$ of 40 and 18.5 min for Bu_3SnOMe or Bu_2SnO, respectively) as compared to total deacetylation in series *B* (average $t_{1/2}$ 11.5 h). The methanolyses may be rationalised in terms of either the formation of reactive sugar–OSn intermediates or as resulting from enhanced electrophilicity of the carbonyl carbon by polarisation[11].

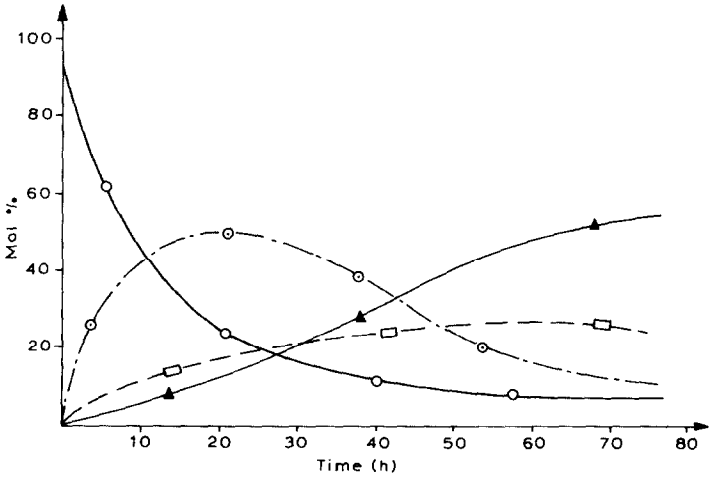


Fig. 3. Bu_3SnOMe-catalysed methanolysis of **12α**: —○—, **12α**; —▲—, **17**; —□—, **18**; —⊙—, unidentified intermediates.

EXPERIMENTAL

General. — ^{1}H-N.m.r. spectra were recorded with a Bruker AM-300 spectrometer for solutions in CD_3OD (internal Me_4Si). G.l.c. was effected with a Varian 3700 chromatograph, on a 0.1% SP 1000 column at 65°. All reactions were carried out in AR MeOH under anhydrous conditions in flame-dried glass apparatus. Reactions were monitored by t.l.c. on silica gel (Merck, 5554), using ethyl acetate–hexane (1:1) for HO-1 products and $CHCl_3$–MeOH (9:1) for total *O*-deacetylations and detection by charring with sulfuric acid. Flash column chromatography was carried out on silica gel (Merck, 9385) using the same solvents. Compounds **2β**, **4α**, and **4β** were commercial products, and **1α**, **1β**, **3β**, **5**, **9β**, **10α**, **10β**, **11α**, **12α**, and **12β** were prepared according to literature procedures.

Deacetylation. (*a*) *General procedure.* To a solution of the acetylated compound (1–10 mmol) in MeOH (2–20 mL) was added the tin reagent (0.5–5 mmol), and the resulting mixture (solutions for Bu_3SnOMe and suspensions for Bu_2SnO) was stirred at 55° (2–3 h for mono-deacetylation, 70 h for polydeacetylation). The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

(*b*) *1,2,3,4,6-Penta-*O*-acetyl-β-*D*-glucopyranose* (**4β**). To a suspension of **4β** (3.9 g, 10 mmol) in methanol (20 mL), under nitrogen at 55°, was added Bu_3SnOMe (1.6 g, 5 mmol). The clear solution, which was obtained within a few minutes, was kept for 2.5 h at 55°. The methanol was flash evaporated and the residue was purified by flash chromatography (ethyl acetate–hexane, 1:1), to give a 2:1 α,β-mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**8**; 2.45 g, 70%). ^{1}H-N.m.r. data (CD_3OD): α epimer, δ 5.47 (dd, *J* 10.0 and 9.5 Hz, H-3), 5.31 (d, *J* 3.6 Hz, H-1), 5.00 (t, *J* 9.6 Hz, H-4), 4.79 (dd, *J* 10.0 and 3.5 Hz, H-2), 4.30–4.05 (m, H-5,6,6), 2.045, 2.04, 2.015 and 1.985 (4 s, each 3 H, 4 Ac); β epimer, δ 5.24 (t, *J* 9.5 Hz, H-3), 5.01 (dd, *J* 9.8 and 9.2 Hz, H-4), 4.82 (m, H-1), 4.79 (m, H-2), 4.30–4.05 (m, H-6,6), 3.85 (ddd, *J* 10.0, 5.0 and 2.5 Hz, H-5*a*), 2.025, 2.01, and 1.965 (3 s, 3, 6, and 3 H, 4 Ac).

Ethyl and isopropyl acetates. — A solution of the ester (1 mmol) and Bu_3SnOMe (159 mg, 0.5 mmol) in MeOH (1.5 mL) was stirred for 24 h at 50°. Samples (0.5 mL) taken at intervals were analysed by g.l.c.

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