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Note

Selective esterification of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside*

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Selective esterification of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside (**1**), a readily obtained compound[1], is of interest as it can afford intermediates for the synthesis of oligosaccharides and of 2- or 3-deoxyhexose derivatives that are transformable into deoxy dicarbonyl derivatives. Several methods have been reported for the selective benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, with a good yield of the 2-benzoate[2–5]. Methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside has been prepared in good yield by selective benzoylation of the parent diol with benzoyl chloride in pyridine at low temperature[6]. Tosylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with *p*-toluenesulfonyl chloride under phase-transfer conditions gave the 2-sulfonate exclusively[7], whereas tosylation in pyridine gave mainly[8] the 3-sulfonate. Selective benzoylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside[9], -α-D-altropyranoside[10], and -α-D-allopyranoside[10] has also been described. We now report preliminary observations on the selective esterification of compound **1**.

Benzoyl chloride, *p*-toluenesulfonyl chloride, acetyl chloride, and acetic anhydride were used as the esterification reagents. It was found that, when pyridine was used as the solvent for benzoylation, the 2-benzoate (**2**) was the major product, the ratio of which to the 3-benzoate (**3**) was 5:1, with ~15% of the diester **11** formed. An attempt to get good selectivity for 3-benzoylation by lowering the reaction temperature was unsuccessful, the ratios of compound **2** to **3** at −20, −45, and −55° being 4.8:1, 4.2:1, and 4:1, respectively. When benzoylation was conducted under phase-transfer conditions, the 2-benzoate was the major product at the early stages of the reaction. However, when the concentration of 2-benzoate became appreciable, the 3-benzoate and 2,3-dibenzoate began to be formed, and a mixture was obtained, with poor selectivity. The copper complex, which proved to

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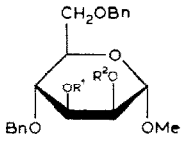

Bn = $PhCH_2$

Compound	R^1	R^2
1	H	H
2	H	Bz
3	Bz	H
4	H	Ts
5	Ts	H
6	H	Ac
7	Ac	H
8	Ts	Bz
9	Bz	Ts
10	Ac	Ac
11	Bz	Bz
12	Ts	Ts

be effective for selective 3-alkylation of compound **1** in oxolane[11], was not selective for esterification; a 3:2 ratio of 3-benzoate to 2-benzoate was obtained.

Tosylation of **1** with *p*-toluenesulfonyl chloride in pyridine afforded mainly the 3-tosylate derivative **5**, the ratio of which to the 2-tosylate **4** was 2.7:1, whereas tosylation under phase-transfer conditions gave the 2-tosylate almost exclusively.

Acetylation of **1** with acetyl chloride in pyridine gave 2-acetate (**6**) as the major and the 3-acetate (**7**) as the minor product, together with a little diacetate (**10**) and starting material, in the ratios of 3.3:1:0.2:0.7. However, acetylation with acetic anhydride in pyridine gave mainly the 3-acetate, together with the 2-mono- and 2,3-di-acetate, and starting material in the ratios of 6:1:3:1. This result is similar to that for the acetylation of 4,6-*O*-benzylidene-α-D-mannopyranoside with acetic anhydride in pyridine[12].

The regioselectivity of the esterification, and characterization of all of the

TABLE I

REGIOSELECTIVITY OF THE ESTERIFICATION OF METHYL 4,6-DI-*O*-BENZYL-α-D-MANNOPYRANOSIDE[a]

Solvent system	*Esterification reagent*	*Substituted products (wt %)*			
		Di-O-	2-O-	3-O-	*Unreacted starting material*
Pyridine	benzoyl chloride	16	70	14	—
	p-toluenesulfonyl chloride	—	21	57	22
	acetyl chloride	4	64	19	13
	acetic anhydride	27	9	55	9
Oxolane	benzoyl chloride (*via* copper complex)	—	36	54	10
CH_2Cl_2–5% NaOH	benzoyl chloride + $Bu_4N \cdot HSO_4$	28	34	38	—
	p-toluenesulfonyl chloride + Bu_4N HSO_4	—	90	6	4

[a]See Experimental section for details of the conditions used.

TABLE II

CHARACTERIZATION OF COMPOUNDS **2–12**

Compound	*Formula*	*Elemental analysis*				*M.p.* (°C)	*Optical rotation* (*in* $CHCl_3$)		*Chemical shifts* (δ)		*Coupling constants* (*Hz*)		
		Calc.		*Found*			$[\alpha]_D^{20}$ (degrees)	c	*H-2*	*H-3*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
		C	*H*	*C*	*H*								
2	$C_{28}H_{30}O_7$	70.29	6.28	70 08	6.21	74	−17.8	0.74	5.30		1.5	3	
3				70.20	6.25	78	+11.0	0.87		5.47		3	9
4	$C_{28}H_{32}O_8S$	63.64	6.06	63.72	6.05	syrup	+12.4	0.62	overlapped				
5				63.47	6.12	syrup	+42 6	0.77	overlapped				
6	$C_{23}H_{28}O_7$	66.35	6.73	66.18	6.80	syrup	+44.3	1.6	5.03		1.5	3	
7				66.12	6 68	syrup	+75.5	1.3		5.18		3	9
8	$C_{35}H_{36}O_9S$	66.46	5.70	66.58	5.62	93	+18.3	1.2	overlapped				
9				66.78	5.66	86	+5.3	1.4		5.32		3	9
10	$C_{25}H_{30}O_8$	65.50	6.55	65.38	6 60	syrup	+47.3	1.7	overlapped				
11	$C_{35}H_{34}O_8$	72.16	5.84	72.02	5 85	105	−73.5	0.87	overlapped				
12[a]	$C_{35}H_{38}O_{10}S_2$	61.58	5.57	61.47	5.61	amorphous	+36.0	1 2	overlapped				

[a]Compound **12** was synthesized by standard method[13].

new compounds by elemental analysis, optical rotation, and ^{1}H-n.m.r. spectroscopy are shown in Tables I and II, respectively.

EXPERIMENTAL

General methods. — Melting points were determined with a "Meltemp" apparatus and a 76-cm immersion thermometer. Optical rotations were determined with a Perkin–Elmer Model 241-MC polarimeter for solutions in a jacketed, 1-dm cell at 20°. Thin-layer chromatography (t.l.c.) was performed on silica gel, with detection by sulfuric acid solution in methanol (30%). Analytical l.c. was achieved by use of a pump (Model YSB-1, made in China), a stainless-steel column packed with silica gel (10 × 150 mm, made in China), a differential refractometer (LDC/Milton Roy Model 1107L, U.S.A.) and ethyl acetate–petroleum ether (b.p. 60–90°) as the eluant at a flow rate of 4.0 mL/min. ^{1}H-N.m.r. spectra were recorded with a Varian XL-100-15 spectrometer, with chloroform-*d* as the solvent and tetramethylsilane (Me_4Si) as the internal standard; chemical shifts are given in p.p.m.

For esterification with pyridine as the solvent, the esterification reagent (1.2 equiv.) was slowly added to a stirred solution of the carbohydrate ether **1** in anhydrous pyridine (2 mL), and the reaction, at room temperature for several hours or several days, was monitored by t.l.c., with 1:3 ethyl acetate–petroleum ether as the solvent. For benzoylation at low temperature, the conditions were as given in the literature[6]. Processing of the esterifications was performed according to standard methods. For esterification by phase-transfer, the esterification reagent (1.2 equiv.) was added to a stirred mixture of carbohydrate ether **1** in dichloromethane (5 mL) and 5% aqueous sodium hydroxide (1.12 mL, 2.1 equiv.) containing tetrabutylammonium hydrogensulfate (35 mg), and the reaction was conducted at room temperature and monitored by t.l.c. For benzoylation by the copper-complex method, compound **1** was treated with 2 equiv. of sodium hydride (80% in oil) in oxolane (12 mL), and anhydrous cupric chloride (1 mol. equiv.) was added to the stirred solution. Hydrogen evolution and formation of a green solution occurred. The green solution was boiled under reflux for 1 h with benzoyl chloride (1.05 equiv.), cooled to room temperature, and kept overnight for completion of the reaction. The mixture was now treated with ammonium hydroxide and water, repeatedly extracted with dichloromethane, and the extracts were combined, and evaporated to dryness. The amount of compound **1** used in all of the foregoing experiments was 250 mg.

After processing, the reaction mixtures were separated by analytical l.c., with 1:1 ethyl acetate–petroleum ether as the eluant. The fraction sequence in this l.c. was di-, 2- and then 3-esterified derivative, and starting material. For the benzoylation products, further chromatography was done of the first fraction obtained with the 1:1 eluant, with 1:3 eluant, in order to separate the dibenzoate from the 2-benzoate. The ^{1}H-n.m.r. spectra of compounds **2–12** had in common some general features, in that all of the compounds showed OCH_3 as a singlet in

the same region, the compounds containing benzoyl and tosyl groups had a broadened distribution of aromatic H signals, and the compounds containing tosyl and acetyl groups showed the CH_3 in the ester groups as a singlet in similar regions. Isomers 2- and 3-esterified by acetyl or benzoyl groups were readily distinguished by ^{1}H-n.m.r. spectroscopy. The former showed H-2 downfield as a pseudotriplet, because $J_{2e,3a}$ and $J_{1e,2e}$ are similar, whereas the latter showed H-3 downfield as an obvious quartet, because $J_{3a,4a}$ is much bigger than $J_{2e,3a}$. For tosylates, it was difficult to distinguish the 2- and the 3-esters as the H-2 or H-3 signal was overlapped by other proton signals. Therefore, 2- and 3-esters were characterized by benzoylation, to afford the 3-*O*-benzoyl-2-*O*-*p*-tolylsulfonyl- (**9**) and 2-*O*-benzoyl-3-*O*-*p*-tolylsulfonyl- (**8**) D-mannopyranoside derivatives, respectively. Compounds **8** and **9** were identical with the product prepared from tosylation of **2** and **3**, respectively. The ratios of different fractions were measured by the fraction weights obtained after separating by analytical l.c. and evaporating the eluant.

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