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Note

Selective benzoylation and tosylation of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside*

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In our previous work, selective esterification of methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside (**1**) was described[1]. Under phase-transfer conditions, introduced by Garegg et al.[2] tosylation of **1** with *p*-toluenesulfonyl chloride gave the 2-sulfonate exclusively. However, highly selective 2-benzoylation was rather difficult and benzoylation of **1** with benzoyl chloride in pyridine gave [1] the 2- and 3-benzoate in the ratio of 5:1. It has been reported[3] that benzoylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**2**) with benzoyl chloride by the phase-transfer method affords the 2-benzoate fairly selectively (2- and 3-benzoates in the ratio of 4.7:1) in the presence of sodium iodide or perchlorate as a migration-retarding reagent. On the other hand, selective 3-benzoylation and exclusive 3-benzylation of **1** have been achieved by the copper-complex method[4]. Regioselective substitution of hydroxyl groups *via* organotin derivatives has also been described[5–13]. High regioselectivity for 3-alkylation was achieved through *O*-stannylene derivatives of compound **2**, whereas, benzoylation of **2** gave the 2-benzoate as the major product[6–8,12]. The molecular structure of crystalline methyl 4,6-*O*-benzylidene-2,3-*O*-(dibutylstannyiene)-α-D-mannopyranoside was determined[13]. We now describe some new observations on regioselective acylation of **1** by various kinds of methods that afforded 2- and 3-selective acylation, respectively with satisfactory results.

Because, in our previous research[1], benzoylation of **1** under phase-transfer conditions in dichloromethane or benzene with benzoyl chloride, in the presence of sodium iodide as the migration-retarding reagent, did not give satisfactory results, the migration-retarding reagents were changed to sodium acetate and benzenesulfonate, whereupon, more-selective 2-benzoylation than that reported[1] was observed, the ratio of 2- to 3-benzoate being 6.4:1, but the migration-retarding reagents

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were not effective for benzoylation with benzoic anhydride under the same conditions.

When **1** was benzoylated with benzoyl chloride in a mixture of benzene and aqueous sodium hydroxide (5%, saturated with sodium benzenesulfonate), in the presence of Me$_2$SO instead of a phase-transfer catalyst, the 2-benzoate was obtained in the ratio of 8.7:1 over the 3-benzoate. Without sodium benzenesulfonate, selectivity for the 2-benzoate decreased. Unexpectedly, sodium acetate had little influence on the migration under these conditions. Tosylation by this method afforded, almost exclusively, the 2-tosylate. The influence of the concentration of Me$_2$SO upon the ratio of the products was also investigated. Me$_2$SO (0.1 mL) in benzene (5 mL) afforded a moderate reaction rate with high selectivity. Increase of Me$_2$SO accelerated the reaction, but made separation of the products difficult. If the proportion of Me$_2$SO used was too small, the reaction proceeded rather slowly,

TABLE I

REGIOSELECTIVITY OF 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-*	*Starting material*
Benzene–BnEt$_3$NBr–5% NaOH(CH$_3$CO$_2$Na, or C$_6$H$_5$SO$_3$Na)	benzoyl chloride	4	83	13	trace
	benzoic anhydride	2	52	37	10
Benzene–BnEt$_3$NBr–5%NaOH	benzoyl chloride	6	59	35	trace
	benzoic ahydride	4	50	33	13
	tosyl chloride	trace	90	6	4
Benzene-Me$_2$SO-5%NaOH (C$_6$H$_5$SO$_3$Na)	benzoyl chloride (2.5h)[b]	1	51	4	44
	(8 h)	2	70	8	20
Benzene-Me$_2$SO-5% NaOH	benzoyl chloride (2.5 h)	1	52	5	42
	(8 h)	3	40	18	39
	tosyl chloride	1	78	3	18
Oxolane (by copper complex)	benzoyl chloride	2	13	85	trace
	tosyl chloride	trace	5	77	18
	(1.5 equiv.)	5	7	70	18
(by Bu$_2$SnO, method A)	benzoyl chloride	2	9	67	22
	benzoic anhydride	trace	14	43	43
	tosyl chloride (Bu$_4$NBr)	3	10	74	13
(by Bu$_2$SnO, method B)	benzoyl chloride	trace	41	59	trace
	benzoic anhydride	1	42	48	9
	tosyl chloride (Bu$_4$NBr)	trace	18	82	trace
Pyridine	benzoic anhydride	trace	12	34	53

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

although the ratio of 2- to 3-benzoate was high.

In order to achieve high selectivity for 3-acylation, two methods were employed: the copper-complex method[4] and the dibutylstannylene oxide method[6,12]. In our previous work[1], selective benzoylation of **1** by the copper- complex method was not effective, but when benzoyl chloride was added to the copper complex of **1** at ambient instead of the boiling temperature[1], fairly selective 3-benzoylation was observed, the ratio of 3- to 2-benzoate being 6.5:1. Application of the method to tosylation of **1** with *p*-toluenesulfonyul chloride also gave the 3-tosylate in the ratio of 3- to 2-tosylate of 15:1.

The dibutyltin oxide method was also used for 3-acylation of **1**. Different results were observed when benzoylation of the *O*-stannylene derivative of **1**, prepared by a reported method[6], was conducted in polar and nonpolar solvents, respectively. In benzoylation with benzoyl chloride and benzoic anhydride in the polar solvent oxolane, the ratios of the 3- to 2-benzoate were 7.4:1 and 3:1, respectively. When the reactions were conducted in benzene, the ratios of 3- to 2-benzoate were 1.4:1 and 1.1:1, respectively. By tosylation of **1** with *p*-toluenesulfonyl chloride with the same polar and nonpolar solvents in the presence of tetrabutylammonium bromide, the corresponding 3- and 2-tosylates were obtained in the ratio of 7.4:1 and 4.6:1, respectively. The addition of tetrabutylammonium bromide was necessary, as otherwise the reaction proceeded rather slowly. These results suggest that the reaction selectivity is dependent on the coordination state of the stannylene derivative, in agreement with the results obtained by Holzapfel *et al.*[12,13].

The results are given in Table I.

EXPERIMENTAL

General methods. — 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 (4.6 × 250 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 2.0 mL/min.

The amount of compound **1** used in all experiments was 0.5 mmol (1 equiv.).

For esterification by the phase-transfer technique, the esterification reagent (1.2 equiv.) was added to a stirred mixture of the diol **1** in benzene (5 mL) and 5% aqueous sodium hydroxide (0.8 mL, 2.1 equiv. saturated with sodium acetate or benzenesulfonate, or not) containing benzyltriethylammonium bromide (25 mg). The reaction was conducted at room temperature, and monitored by t.l.c. Working up the reaction was conducted according to a reported procedure[2].

For acylation by the Me_2SO method, that acylating reagent (1.2 equiv.) was added to a stirred mixture of **1** in benzene (5 mL) and 5% aqueous sodium hydroxide (0.8 mL, 2.1 equiv. saturated with sodium benzenesulfonate or not) at ambient temperature in the presence of Me_2SO (0.1 mL). The reaction was monitored by t.l.c. Processing of the reaction was the same as that used for the reaction by that phase-transfer method[2].

For acylation by the copper-complex method, **1** was treated with 2 equiv. of sodium hydride in oxolane (6 mL), and anhydrous cupric chloride (1.1 mol. equiv.) was then added to the stirred solution. After hydrogen evolution had ceased, the acylating reagent (1.2 equiv.) was added to the green solution at room temperature. The mixture was kept overnight for the completion of the reaction, treated with ammonium hydroxide and water, and repeatedly extracted with dichloromethane. The extracts were combined, dried (sodium sulfate), and evaporated to dryness.

For esterification by the dibutyltin oxide method, the diol **1** and dibutyltin oxide (1.2 mol. equiv.) were suspended in methanol (10 mL), the mixture was boiled under reflux until the suspension became a clear solution, and this was cooled and evaporated. Acylation reagent (1.2 equiv.) was added to the solution of the *O*-stannylene complex of compound **1** in oxolane (5 mL, method A) or benzene (5 mL, method B). For tosylation by this method, the reaction was conducted in the presence of tetrabutylammonium bromide (25 mg). The reactions were monitored by t.l.c. and a reported work-up procedure was employed after esterification[6].

For benzoylation in pyridine, the reaction was conducted according to the reported method[1].

After processing, the reaction mixtures were separated by analytical l.c. according to a reported method[1].

The ratios of the fractions were determined by measurement of the peak areas in comparision with those of external standards.

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