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Note

The selective benzoylation of methyl 4,6-*O*-benzylidene-α-D-glycopyranosides

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Phase-transfer catalysis is a versatile preparative method[1], and several applications in the synthesis of esters have been reported[2-5]. Phase-transfer catalysis was reported to be unsatisfactory for the selective benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) and to be limited to acyl groups that are resistant to base-catalysed migration and deacylation[6].

It has now been found that the reaction of **1** with 1 mol of benzoyl chloride under phase-transfer conditions (dichloromethane, aqueous 40% sodium hydroxide, tetrabutylammonium chloride) in the presence of sodium iodide or perchlorate gave the 2-benzoate as a major product. In the absence of these salts, an equimolar mixture of 2- and 3-benzoates was formed (see Experimental). Likewise, when methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**2**) was treated with 1 mol of benzoyl chloride under phase-transfer conditions, a ~1:1 equilibrium mixture of the 2- and 3-benzoates was formed; a good yield of the 2-benzoate was obtained if the acylation was performed in the presence of sodium iodide or perchlorate.

When a solution of the quaternary ammonium salt and the 2-benzoate of **1** or **2** in dichloromethane was stirred with aqueous 40% sodium hydroxide saturated with sodium iodide or sodium perchlorate, the rate of benzoyl migration was greatly retarded. Anion-partitioning selectivity accounts for the inability of quaternary salts to catalyse displacement reactions[7]. Also, there is a correlation between the rate constant of phase-transfer-catalysed reactions and the ability of the catalyst to extract the anion into the organic phase. In the presence of lipophilic anions, the fraction of ammonium salt that is paired with hydroxide ions markedly decreases and, in consequence, acyl rearrangements are retarded. Thus, the rate of isomerisation of the 2-benzoate of **1** catalysed by tetrabutylammonium hydroxide is markedly decreased in the presence of sodium iodide. The inhibition of phase-transfer-catalysed reactions by preferentially extractable, poorly hydrated anions has been reported[8,9] and our results indicate a similar inhibition of an intramolecular rearrangement.

The composition of the product did not depend on the "softness" of the inorganic ions present in the reaction mixture, and benzoyl iodide was not formed

TABLE I

PRODUCTS OF BENZOYLATION OF METHYL 4,6-*O*-BENZYLIDENE-α-D-GLYCOPYRANOSIDES UNDER MODIFIED CONDITIONS OF PHASE-TRANSFER CATALYSIS

Configuration of glycoside	*Product*	*Yield (%)*	*M.p. (degrees)*	$[\alpha]_D^{20}$ *(degrees)*	*Ref.*
gluco	2-Benzoate	72[a], 62[b]	170–171	+112.5	11
	3-Benzoate	4[a]	219–220	+34	11
	2,3-Dibenzoate	4[a]	153	+93	11
manno	2-Benzoate	52[a]	Amorphous	−44	12
	3-Benzoate	11[a]	132	−36	12
altro	2-Benzoate	91[b]	137–138	−5	12
allo	2-Benzoate	89[b]	114–115	−76	13

[a]After chromatography. [b]After crystallisation of the reaction mixture.

(g.l.c.) in the presence of sodium iodide. Thus, in contrast to recently reported results[6], benzoyl chloride is the acylating agent, and inorganic ions only influence the rate of isomerisation of benzoates.

Benzoylation of methyl 4,6-*O*-benzylidene-α-D-altro- and -allo-pyranoside under the modified conditions of phase-transfer catalysis gave the 2-benzoates in yields of 91% and 89%, respectively, and t.l.c. revealed only minor amounts of the 3-benzoates.

The above results show that HO-2 in methyl 4,6-*O*-benzylidene-α-D-glycopyranosides is more reactive then HO-3 towards benzoyl chloride under conditions of phase-transfer catalysis, which accords with the observation that the overall rate of esterification depends on the acidity of the hydroxyl group and that steric factors are relatively unimportant[2,3,10].

The data in Table I show that the yields of 2-benzoates obtained under the modified conditions of phase-transfer catalysis are good and compare favourably with those obtained by other methods.

EXPERIMENTAL

Silica Gel G (Merck) was used for t.l.c., together with benzene–ethyl acetate (2:1) and detection by charring with sulphuric acid. Column chromatography was performed on Silica Gel 60 (Merck) with benzene–ether (9:1) for elution of dibenzoates, and benzene–ether (7:1) for starting compounds. G.l.c. was performed with a Willy Giede 18.3 gas chromatograph, using a column (3 m × 4 mm) of 25% of SE-30 on Chromosorb W HMDS (60–80 mesh) at 120°, a flame-ionisation detector, and argon at 50 mL/min as carrier gas. Retention times: benzoyl chloride, 200 s; benzoyl iodide, 540 s. Melting points are uncorrected. Rotations were measured on a Zeiss-Polamat A polarimeter for solutions in chloroform.

Benzoylation of methyl 4,6-O-benzylidene-D-glycopyranosides. Equimolar quantities of sugar and acid chloride (10 mmol) in dichloromethane (25 mL) were stirred with tetrabutylammonium chloride (1 mmol) and aqueous 40% sodium hydroxide (2 mL) saturated with sodium iodide or perchlorate. Each reaction was monitored by t.l.c. and was complete in 5–10 min. The reaction mixture was neutralised with sulphuric acid (1:10), and the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated. The products were subjected to chromatography. For the *gluco*, *altro*, and *allo* compounds, a pure product was obtained by crystallisation of the final residue from ethyl acetate–hexane.

Isomerisation of the monobenzoates. — A solution of the monobenzoate (0.12 g) and tetrabutylammonium chloride (0.01 mmol) in dichloromethane (5 mL) was stirred for 10 min with 0.2 mL of (*a*) aqueous 40% sodium hydroxide; (*b*) aqueous 10% tetrabutylammonium hydroxide; (*c*), (*a*) saturated with sodium perchlorate or sodium iodide; and (*d*), (*b*) saturated with sodium iodide. Each mixture was neutralised with sulphuric acid, and the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated. The residue was subjected to chromatography. Appropriate fractions were concentrated and homogeneous products were obtained. Under conditions (*a*) and (*b*), the 2- and 3-benzoates of methyl 4,6-*O*-benzylidene-α-D-gluco- (**1**) and -manno-pyranoside (**2**) gave approximately equimolar mixtures of monobenzoates. Under conditions (*c*), the 2-benzoates of **1** and **2** were unaffected; under conditions (*d*), the 2-benzoate of **1** was unaffected

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