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Note

Use of benzoyl chloride–tetrabutylammonium iodide–potassium carbonate–benzene in selective benzoylation of some 4,6-*O*-benzylidene-α-D-hexopyranosides*

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The selective esterification of monosaccharides has been the subject of many studies[2] because an acyl group offers the advantages of a good protecting group, namely, ease of attachment and ease of removal.

Many useful methods for selective esterification have been developed, and various reagents, showing different selectivities, have permitted protection of individual hydroxyl groups[2].

We have tried to develop methods of esterification that do not require stringent exclusion of water, but which show a useful degree of selectivity, and a good degree of conversion of starting alcohol into ester.

RESULTS AND DISCUSSION

The phase-transfer tosylation of methyl 4,6-*O*-benzylidene-glucopyranosides and α-D-mannopyranoside by Garegg *et al.*[3] not only achieved good efficiency but also showed selectivities different, in some instances, from those achieved by using different esterifying systems. These phase-transfer reactions show bias towards esterification at O-2. Thus the β-glucopyranoside gave nearly twice as much 2-sulfonate as 3-sulfonate, whereas the 3-ester predominates with other methods of esterification[2]. The α-mannopyranoside gave the 2-sulfonate exclusively by the phase-transfer method, whereas other esterifying methods give the 3-ester almost exclusively[2]. On the other hand, the α-glucopyranoside was transformed largely into the 2-ester by both the phase-transfer method and by other methods[2].

Unfortunately, the phase-transfer method for preparing methyl 2-*O*-benzoyl-

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4,6-*O*-benzylidene-α-D-glucopyranoside was not as successful as had been hoped because of the efficient isomerization of the 2-benzoate to the 3-benzoate during the reaction. The ester migration was no doubt due to interaction of the 2-benzoate with hydroxide ion[2] at the phase interface, as the rate of isomerization increased as the phases were more efficiently dispersed in each other.

An indication of the course of this reaction is given in Table I. Although the 2-benzoate was formed preferentially, production of the 3-benzoate by direct esterification of the 3-hydroxyl group and by ester migration from O-2 became appreciable after a significant concentration of the 2-benzoate had been achieved. In addition, the efficiency of the conversion of the diol into the 2-benzoate was quite low at the optimal time for termination of the reaction to provide the 2-ester.

This efficiency of ester migration was exploited by Szeja[4], who prepared methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-galactopyranoside (benzene–aqueous sodium hydroxide–tetrabutylammonium chloride–benzoyl chloride) in 78% yield, and observed that the addition of hexamethylphosphoric triamide to the medium promoted formation of the 3-benzoate, no doubt by effecting a greater efficiency of interphase dispersal and hence ester migration.

In an effort to curtail this ester migration, we decided to develop a system that would have the gross features of the phase-transfer process, namely, the esterification of a tetrabutylammonium alkoxide in a medium of low polarity, while avoiding an excess of strong base that would catalyze the ester-migration process.

We were unable to achieve complete reaction between methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and sodium hydride, in tetrahydrofuran, in the presence of tetrabutylammonium iodide. However, on stirring the suspended reagents with benzoyl chloride in tetrahydrofuran for ~20 h, methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside was obtained in 65% yield, with no appreciable (<5%) production of the isomeric 3-benzoate.

It was immediately recognized that sodium hydride was acting largely as an agent to remove the hydrogen chloride produced in the reaction, and so we reconstituted the reaction with crushed, anhydrous, potassium carbonate instead of sodium hydride. Again, almost exclusive formation of the 2-benzoate was observed.

TABLE I

PHASE-TRANSFER BENZOYLATION OF METHYL 4,6-*O*-BENZYLIDENE-α-D-GLUCOPYRANOSIDE

Time of reaction[a] *(min)*	*Yield (%) of combined monobenzoates isolated*	*Ratio of 2-benzoate to 3-benzoate*
10	54	11.6 : 1
60	68	7.7 : 1
120	73	5.6 : 1

[a]The rates of esterification and isomerization varied greatly with rapidity of stirring, and these results refer to one particular series of experiments

Significantly, the substitution of tetrabutylammonium hydrogensulfate for tetrabutylammonium iodide not only resulted in a much slower reaction but also led to total loss of selectivity.

We noted that the reagents (quite possibly the benzoyl iodide produced in the mixture) also reacted with tetrahydrofuran to produce an appreciable amount of iodine. This side reaction, with the observation that non-polar media promoted the selectivity of the acylation process, led us to choose benzene as the solvent for the reaction.

Whether the benzoylating agent was benzoyl iodide or benzoyl chloride was not absolutely clear. Benzoyl cyanide has been produced in an analogous reaction of benzoyl chloride and tetrabutylammonium cyanide[5]. Benzoyl iodide has been produced by the reaction of benzoyl chloride with hydrogen iodide[6]. This reactivity of benzoyl chloride with "halide" nucleophiles led us to assume the presence of benzoyl iodide in the mixture. However, the odor of benzoyl chloride was detectable in the reaction mixture up until the esterification process ceased (after ~55 h), thus indicating that an equilibrium had been established between benzoyl chloride plus iodide ion and benzoyl iodide plus chloride ion.

The cleavage of ethers by acyl iodides[7] is well known, and so our observation of reaction between the reagent and tetrahydrofuran supports the presence of benzoyl iodide in the reaction mixture. Benzoyl iodide has been shown to form polar, acylium-like ion-pairs in the presence of electrophiles in non-polar solvents[8]. This

TABLE II

ACYLATION OF METHYL 4,6-*O*-BENZYLIDENE-α-D-HEXOPYRANOSIDE BY THE ACYL CHLORIDE–TETRABUTYLAMMONIUM IODIDE METHOD

Acyl chloride[a]	*Parent sugar*	*Time of reaction*[b] *(h)*	*Solvent*[c]	*Yield (%) of combined monoesters isolated*	*Ratio of 2-ester to 3-ester*
Benzoyl chloride	α-glucoside	18	benzene	54.2	9.5:1
		53	benzene	81.3	7.7:1
		74	benzene	60.8[d]	0.71.1
p-Nitrobenzoyl chloride	α-glucoside	24	benzene	24.4	0.71:1
		24	CH_2Cl_2	28.1	0.42:1
		48	CH_2Cl_2	51.0	0.42:1
Benzoyl chloride	α-alloside	24	CH_2Cl_2	49.8	2 7:1
		72	CH_2Cl_2	66.7	1:1
		36	THF	48.7	1:1
p-Nitrobenzoyl chloride	α-alloside	48	CH_2Cl_2	31.9	0 42.1
Benzoyl chloride	α-galactoside	48	benzene	50 3	0.50:1
		73	benzene	40.6[d]	0.28:1

[a]Exactly one molar equivalent of acyl chloride was used. [b]These times were not chosen merely to represent useful reaction, but to highlight features of the reactions. [c]Solutions or suspensions (1%) of the sugars were used. [d]Some hydrolysis of the monoester at the surface of the K_2CO_3 must have occurred.

type of ion pair should be a very reactive acylating agent. Acyl iodides are also known to be much more reactive than acyl chlorides[9].

We therefore assumed that benzoyl iodide was the acylating agent, the concentration of benzoyl iodide being maintained in the reaction by the aforementioned equilibrium.

An interesting feature of esterifications with benzoyl chloride–tetrabutylammonium iodide is that the reactions were selective only when the mixtures had a pale-yellow color. Occasionally, for reasons not yet clear, a mixture would either not develop the yellow color, or the yellow color would vanish before significant reaction had occurred. These reactions always provided equal amounts of 2- and 3-esters. Table II shows the progress of acylations performed with acyl chloride–tetrabutylammonium iodide–potassium carbonate and various solvents.

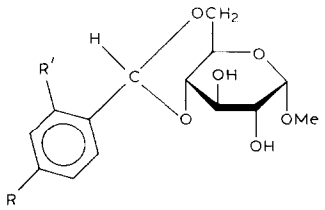
A number of significant features of the reactions are immediately recognizable. First, the lower the polarity of the solvent used, the greater was the selectivity of the reaction. Second, ester migration was still a feature of the reaction and was most pronounced when the esterifying agent had all been consumed. Thus, after 55 h, all of the benzoyl chloride had been used in the esterification of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, and during the time-span of 53–74 h, the ratio of 2-ester to 3-ester had changed from 7.7:1, to 0.72:1. No diesters were detected in these reactions.

It was obvious that some of the esterifying agent was reacting with the traces of water present in the mixture (no special effort had been made to keep the system scrupulously dry), thus limiting the net conversion of sugar into monoester, but we chose to explore the characteristics of the reactions by using exactly one molar equivalent of the esterifying agent per mol of the sugar. In this way, the relative efficiencies of the competing reactions could be recognized, these being: (*a*) formation of monoester, (*b*) formation of diester, (*c*) ester migration throughout the course of the reaction and after the acylating agent had been exhausted, and (*d*) the decomposition of the acylating agent by traces of water. There is no doubt that, for an efficient preparative reaction, the quantity of esterifying agent used should be increased to ~1.2 mol per mol of sugar.

The selectivity observed in the formation of the *p*-nitrobenzoates seemed to be opposite from that observed in the formation of the benzoates. Whereas *p*-nitrobenzoylation was significantly slower than benzoylation, the ease of migration of the *p*-nitrobenzoyl group is known to be significantly greater than that of the benzoyl group[2]. It was very likely that initial *p*-nitrobenzoylation could have occurred preferentially at O-2, even though the data indicated otherwise, because the 3-ester can be generated by both direct esterification of the 3-hydroxyl group and by the relatively rapid migration of the *p*-nitrobenzoyl group from O-2 to O-3 (ref. 2).

The nature of the solvent seems to be crucial to the success of these selective esterification reactions. Polar solvents not only facilitate acyl migration, but also deemphasize the relative nucleophilicities of the free hydroxyl groups and hence promote non-selective reactions.

The disadvantages in using very non-polar solvents lie primarily in the low solubilities of sugar derivatives and some reagents in these media. There is now available to carbohydrate chemists an array of protected sugars freely soluble in such non-polar solvents as benzene. These derivatives, such as compounds **1** and **2**, may



1 R = H, R' = $OCH_2CH{=}CHPh$

2 R = OCH_2Ph, R' = H

be made in high yield by acetal exchange[10]. The use of glycosides having larger, hydrophobic aglycons would also increase the solubilities of the sugar derivatives in non-polar sovents, while not affecting the ease of manipulation of the sugar to any marked extent.

The observation that the "softer" the leaving group of the acylating agent the more selective the reagent is in esterification reactions[1] is supported by success in the use of benzoyl cyanide[2] and benzoyl iodide. Other species remain to be explored.

EXPERIMENTAL

Esterification. — A typical esterification with benzoyl chloride–tetrabutylammonium iodide and potassium carbonate in benzene was as follows.

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (0.2433 g, 0.863 mmol), tetrabutylammonium iodide (0.3260 g, 0.883 mmol), and potassium carbonate (0.5986 g, 4.38 mmol) were suspended in benzene (20 mL) and stirred for 0.5 h at room temperature. Benzoyl chloride (0.1 mL, 0.861 mmol) was then added and the mixture was stirred for 53 h at room temperature. The potassium carbonate was filtered off by using a sintered No. 3 Büchner funnel, the organic solution washed with brine (2 × 40 mL), dried over sodium sulfate and evaporated to a solid (0.3661 g). Purification of the components of the mixture by preparative t.l.c. provided* methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (0.2397 g), methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (0.0310 g), and methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (0.0459 g).

*All of the esters were isolated and characterized by i.r., u.v., and n.m.r. spectroscopy, specific rotation, and analytical data. No new compounds were produced.

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