Carbohydrate Research, 39 (1975) 33–38

THE USE OF POSITIVELY CHARGED LEAVING-GROUPS IN THE SYNTHESIS OF α-D-LINKED GLUCOSIDES. SYNTHESIS OF METHYL 2,3,4-TRI-*O*-BENZYL-6-*O*-(2,3,4,6-TETRA-*O*-BENZYL-α-D-GLUCOPYRANOSYL)-α-D-GLUCOPYRANOSIDE

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(Received July 15th, 1974; accepted August 7th, 1974)

ABSTRACT

Quaternary ammonium and triphenylphosphonium salts of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-D-glucopyranosyl bromide were readily prepared by reaction with tertiary amines and triphenylphosphine under anhydrous conditions. Methanolysis of these salts was studied to determine the conditions of solvent and temperature that would produce the highest yields of α-D-glucosides. The quaternary ammonium salts gave the highest yields with solvents of low dielectric constant and room temperature. The phosphonium salts gave moderate yields with diethyl ether at 50°. The synthesis of methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside by treatment of the quaternary ammonium salt of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was studied as a model for the synthesis of oligosaccharides. The anomeric composition of the disaccharide product could be easily determined from the optical rotation since the specific rotations of both the final product and of the gentiobioside analog are known. Under the best conditions, the yield of disaccharide was low (50%) and the reactions were not completely stereoselective.

INTRODUCTION

Recent reports from this laboratory have described the use of quaternary ammonium, phosphonium, and sulfonium salts of glycosyl derivatives in the synthesis of α-D-glycosides[1–3]. The C-1 salts were prepared from glycosyl bromide derivatives by the action of tertiary amines, trisubstituted phosphines, or disubstituted sulfides. The anomeric configuration of the salts was determined by optical rotation and n.m.r. data, and was predicted from the "reverse anomeric effect" described by Lemieux[4]. The alcoholysis of these onium salts gave, by inversion, predominantly pure α-D-glycosides with good yields in the presence of solvents of low dielectric constant. The rates of reaction were generally low, unless a large excess of the alcohol was used. The rates decreased as the reactive group of the alcohol became more hindered, in keeping with the SN2 character of the reaction.

Kronzer and Schuerch[3] have also reported the synthesis of α-D-galactosides starting from C-1 onium salts of D-galactosyl bromide, but both the low reactivity of these salts as intermediates and the hindered nature of the aglycon caused the synthesis of 3-*O*-α-D-galactopyranosyl-D-galactose to fail. We now report the methanolysis of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-β-D-glucopyranosyl onium salts performed in various solvents, in order to determine the optimum conditions for α-D-glucoside synthesis. We also report the synthesis of methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside starting from quaternary ammonium salts of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide.

RESULTS AND DISCUSSION

The quaternary ammonium and triphenylphosphonium salts of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide were prepared according to the method reported by West and Schuerch[2]. The salts were characterized by the insolubility in diethyl ether and by the n.m.r. spectra, which showed a doublet between δ 5.3 and 5.5 ($J_{1,2}$ 7.5 Hz) indicating a β-D anomer.

The onium salts were methanolyzed in a large excess of methanol (40:1) in admixture with a variety of solvents. As shown in Table I, the highest stereoselectivity

TABLE I

METHANOLYSIS OF 2,3,4-TRI-*O*-BENZYL-6-*O*-(*N*-PHENYLCARBAMOYL)-D-GLUCOPYRANOSYL ONIUM SALTS IN VARIOUS SOLVENTS[a]

Onium salt	*Solvent*	*Temp.* (°)	α *Anomer* (%)
Triethylammonium	diethyl ether	25	100
	dichloromethane	25	75
	tetrahydrofuran	25	80
	triethylamine–dichloromethane (5:3)	25	100
Triphenylphosphonium	diethyl ether	25	100
	dichloromethane	25	80
	tetrahydrofuran	50	75
	1,2-dimethoxyethane	50	75
4-Methylmorpholinium	4-methylmorpholine	25	100

[a]The ratio of alcohol to onium salt was 40:1, and 56.8 mmoles of onium salt were dissolved in 4.0 ml of solvent. The yields of methyl D-glucopyranosides were quantitative.

was observed in the presence of solvents of low dielectric constant, such as diethyl ether. The solvents of low dielectric constant have the disadvantage of dissolving the salts incompletely, and an excess of methanol was needed to make the system homogeneous. These solvents could not be used for the synthesis of oligosaccharides, since the monosaccharide derivatives are usually not used in excess and do not assist in dissolving the salts.

Two possible solutions to the problem of homogeneity were investigated. Firstly, such solvents that completely dissolve the salts as tetrahydrofuran, dichloromethane, and 1,2-dimethoxyethane were tried. Unfortunately, complete solubilization of the salts resulted in decreased stereoselectivity. Polar solvents are believed to cause an equilibrium between the onium salt and the corresponding glucosyl bromide[2]. Then, the alcohol can react with either of these species with a resultant loss of stereoselectivity. The problem can be eliminated by a mixed solvent system in which the nucleophile used to prepare the salt, *i.e.* triethylamine, is present in excess. Under these conditions, the reactions are completely homogeneous and stereoselective to give high yields of α-D-glucosides.

The second alternative solution was to use a nucleophile that can also dissolve the salt, and thus act as solvent. Most tertiary amines proved to be poor solvents for the salts, but 4-methylmorpholine was an exception. Not only did it dissolve both the ammonium salt and the alcohols, but it also gave completely stereoselective reactions.

The triphenylphosphonium salts gave about the same results as the quaternary ammonium salts, but the rates of reaction were generally lower. The reaction mixtures had to be heated (to 50°) to insure high yields of glucosides, even in the presence of a large excess of alcohol. No attempt was made to use the triphenylphosphonium salts in the synthesis of disaccharides.

After the conditions necessary for completely homogeneous and stereoselective reactions had been determined, the synthesis of a disaccharide was attempted. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was chosen as the alcohol reactant, since it has a primary hydroxyl group that would react relatively rapidly. It was treated with 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl ammonium salts to give the two disaccharides, methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α- and β-D-glucopyranosyl)-α-D-glucopyranoside, which have specific rotations of +59° and +17.4°, respectively, in chloroform. The relative amounts of α and β disaccharide formed could be calculated from the specific rotation ($[\alpha]_{obs}^{25}$) of the disaccharide fraction according to the equation: $\alpha(\%) = ([\alpha]_{obs}^{25} - 17.4°) \cdot (59° - 17.4°)^{-1} \cdot 100$. Table II shows the results of the reactions.

It was surprising that no reaction gave a completely stereoselective product. The best stereoselectivity was obtained in solvents of low dielectric constant, but the yields of disaccharide were low due to insolubility of the salt. The use of diethyl ether or triethylamine alone resulted in no coupling, again due to the insolubility of the salt.

The 4-methylmorpholinium salt proved to be very unreactive at room temperature, and when the reaction mixture was heated to 50°, the salt decomposed to form 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol. The structure of this by-product was confirmed by its reaction with bromine, the n.m.r. spectrum, and the agreement of the physical constants with a previous report[5]. 4-Methylmorpholine is thus able to abstract a proton from C-2. Attempts at increasing the reaction rate by the use of a bulkier amine, 4-ethylmorpholine, were unsuccessful.

An attempt at increasing the yield by the use of the sodium salt of the alcohol, prepared by treatment of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside with sodium

TABLE II

REACTION OF 2,3,4,6-TETRA-*O*-BENZYL-β-D-GLUCOPYRANOSYL ONIUM SALTS WITH METHYL 2,3,4-TRI-*O*-BENZYL-α-D-GLUCOPYRANOSIDE[a]

Onium salt	*Solvent*	*Time (h)*	*Temp. (°)*	*Yield (%)*	*α Anomer (%)*
Triethyl-ammonium	triethylamine–diethyl ether (2:1)	24	25	30	92
	triethylamine–acetone (2:1)	48	25	50	50
	1,2-dimethoxyethane	24	25		[b]
	triethylamine	96	50	trace	
	triethylamine–dichloromethane (5:3)	48	25	10	50
4-Methyl-morpholinium	4-methylmorpholine	48	25		
	4-methylmorpholine	48	50		[c]
	4-methylmorpholine	96	25	10	22
	diethyl ether	96	36	50	50
	4-ethylmorpholine	48	50		[c]

[a]The ratio of onium salt to alcohol was 1.2:1, and 56.8 mmoles of onium salt were dissolved in 4.0 ml of solvent. [b]The sodium salt of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was the alcohol; it gave a quantitative yield of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol. [c]Only a trace of the disaccharide was present; most of the product was 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol.

hydride in 1,2-dimethoxyethane, resulted in the quantitative yield of 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol by abstraction of the C-2 proton, followed by elimination of the 4-methylmorpholinyl residue at C-1 of the 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl-4-methylmorpholinium salt.

It seems clear that these onium salts of glycosyl bromides cannot be used as intermediates in the synthesis of oligosaccharides, since the rates of reaction are much too low. The salts can be used to synthesize pure α-D-glycosides when the alcohol is reactive and present in large excess.

EXPERIMENTAL

General. — N.m.r. spectra were determined with a Varian A-60-A spectrometer on solutions in chloroform-*d* and with tetramethylsilane as internal standard. Optical rotations were determined with a Perkin–Elmer model 141 polarimeter equipped with a jacketed 1-dm cell kept at 25°.

Materials. — Diethyl ether, tetrahydrofuran, and 1,2-dimethoxyethane were dried with sodium wire, and distilled before use. Dichloromethane, triethylamine, and 4-methyl- and 4-ethyl-morpholine were dried with calcium hydride, and then distilled. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide was prepared by the method of Ishikawa and Fletcher[6]. 2,3,4-Tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide was prepared by the method of Kronzer and Schuerch[3].

Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was prepared by the method of Eby and Schuerch[7].

Preparation and methanolysis of onium salts of 2,3,4-tri-O-benzyl-6-O-(N-phenylcarbamoyl)-α-D-glucopyranosyl bromide. — A solution of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide (250 mg) in diethyl ether (3.0 ml) was introduced into a high-vacuum-reaction vessel under a stream of dry nitrogen. The vessel was stoppered and the solvent distilled off under vacuum. Triethylamine or 4-methylmorpholine (4.0 ml) was distilled into the vessel, and the mixture was kept overnight. The triphenylphosphonium salt was synthesized by adding the solution of the glucosyl bromide in diethyl ether to a weighed amount of triphenylphosphine (1.2 equiv.) in the reaction vessel. This mixture was also kept overnight. The solvent used to prepare the salt was distilled off, and the solvent for the methanolysis reaction was distilled into this vessel. Methanol (1.0 ml) was added to the mixture under a stream of dry nitrogen, and the vessel was stoppered. The solution was stirred, and then kept overnight. The vessel was opened, the contents poured into water (30 ml), and the product extracted with dichloromethane. The organic phase was washed with water, dilute acetic acid if an amine was used as the solvent, and a sodium chloride solution, dried over magnesium sulfate, and evaporated to a syrup. The syrups were analyzed by proton n.m.r. spectroscopy to determine the amounts of α- and β-D-glucoside formed, according to the procedure of Frechet and Schuerch[8]. The yields of methyl D-glucopyranosides were quantitive. The results of the methanolysis reactions are shown in Table I.

Preparation of methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside. — A solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (250 mg) in diethyl ether (3 ml) was introduced into a high-vacuum-reaction vessel under a stream of nitrogen. The ether was distilled off under vacuum. Triethylamine and 4-methyl- or 4-ethyl-morpholine (4.0 ml) was distilled into the vessel, and the solution was stirred and kept overnight. The amine was distilled off, and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (180 mg, 1 equiv.) was added. The solvent used for the reaction was distilled into the vessel, and the contents were mixed and kept either at room temperature or 50° for 24–96 h. The reaction vessel was opened, the contents poured into water (30 ml), and the product extracted with dichloromethane. The organic phase was washed with water, dried (magnesium sulfate), and evaporated to a syrup. The syrup was examined by t.l.c. (silica gel, 9:1 benzene–ether) to determine if any disaccharide was present. The disaccharide, if present, was isolated after column chromatography on silicic acid and elution with dichloromethane. The disaccharide fraction was evaporated to a syrup and weighed to determine the yield. The amounts of α and β anomers present were determined from the optical rotation of the syrup. The results are shown in Table II.

ACKNOWLEDGMENT

This work was completed with financial support from the National Science Foundation (grant GP-28373).

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