Carbohydrate Research, 34 (1974) 71–78

THE USE OF 2,3,4,6-TETRA-*O*-BENZYL-α-D-GLYCOPYRANOSYL IODIDES IN α-GLYCOSIDE SYNTHESIS

FRANK J. KRONZER AND CONRAD SCHUERCH

Department of Chemistry, State Univ. of New York College of Environmental Science and Forestry, Syracuse, New York 13210 (U. S. A.)

(Received November 21st, 1973; accepted in revised form, February 4th, 1974)

ABSTRACT

2,3,4,6-Tetra-*O*-benzyl-α-D-gluco- and -α-D-galactopyranosyl iodides react rapidly in acetonitrile and other solvents with limited excesses of methanol, ethanol, 2-propanol, and cyclohexanol in the presence of 2,6-lutidine. The products obtained from the lower alcohols, contain a high proportion of α glycoside. The highest ratios of α- to β-anomer are obtained at low concentrations of alcohol. The high rates, stereoselectivity, and lack of side-reactions observed suggest that the alcoholysis of glycosyl iodides should be tested as a route to oligosaccharide synthesis.

INTRODUCTION

In 1929, Helferich and Gootz[1] reported that 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl iodide was readily obtained by treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with sodium iodide in acetone. They also obtained benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside in low yield by treatment of the crystalline glucosyl iodide with an excess of benzyl alcohol. Since that time, glycosyl bromide and glycosyl chloride derivatives have been preferred as intermediates for glycoside synthesis, and their alcoholysis reactions have been studied quite extensively, but the reactions of glycosyl iodide derivatives have received little attention[2,3].

Glycosyl halides having nonparticipating blocking groups at C-2 are known to be more useful than ester derivatives for the preparation of α-linked glycosides[4–15]. However, the benzylated glycosyl chlorides react extremely slowly with alcohols, unless electrophilic metal salts are present. Some encouraging results have been obtained with benzylated glycosyl bromides[4,8], but the reactions are still quite slow in the absence of a large excess of the alcohol or electrophilic metal salt. Unfortunately, the stereoselectivity of the alcoholysis reactions is sensitive to the reaction conditions[5] and to the structures of the reactants[15]. For example, we obtained[5] the most favorable ratio of α- to β-anomers of methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide when the methanol concentration was minimal and no metal salts were added to increase the reaction rate (α to β = 93:7). However, the reaction was too slow to be practical.

We decided to study the benzylated glucosyl and galactosyl iodides because they

were expected to react faster than the bromides and, thus, might permit the use of the equimolar quantities of alcohol and halide that are desirable for oligosaccharide synthesis. Furthermore, it was expected that, at low alcohol concentrations, a high ratio of α- to β-glycosides would be obtained. The results reported herein on model methanolyses and ethanolyses of perbenzylated glycosyl iodides fulfill these expectations and suggest that glycosyl iodides having nonparticipating blocking groups may be useful for the synthesis of α-linked oligosaccharides.

RESULTS AND DISCUSSION

The fully benzylated glucopyranosyl and galactopyranosyl bromides are very sensitive to hydrolysis and somewhat unstable. We expected that the fully benzylated glycopyranosyl iodides would be even more reactive so we did not attempt to isolate them. Instead, we prepared the glycosyl iodides immediately before alcoholysis or *in situ*. 2,3,4,6-Tetra-*O*-benzyl-α-D-glycopyranosyl chlorides and bromides were prepared from the corresponding 2,3,4,6-tetra-*O*-benzyl-1-*O*-(*N*-phenylcarbamoyl)-β-D-glycopyranoses with hydrogen chloride or hydrogen bromide in dichloromethane solution[16,17] and isolated as syrups.

A few polarimetric measurements gave an approximate idea of the relative reactivities of the tetra-*O*-benzyl-α-D-glycopyranosyl halides. In 2 h, at ambient temperature, a solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride in

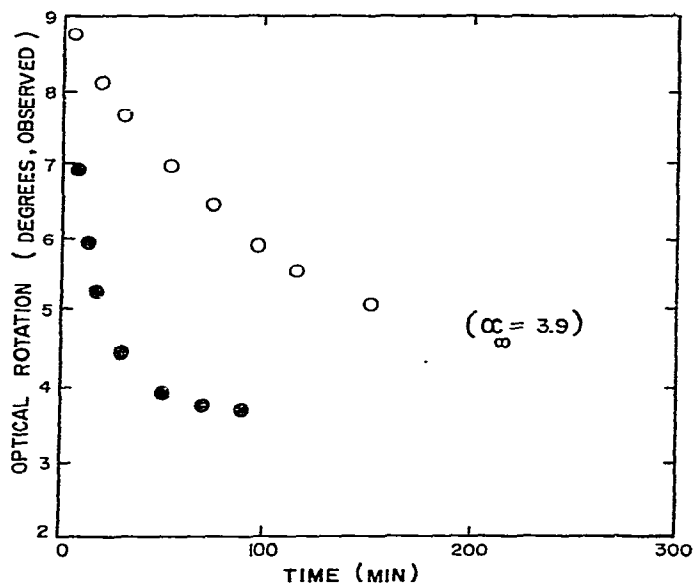

Fig. 1. Reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide and 2-propanol with and without sodium iodide (See Experimental for conditions): with sodium iodide ●, without sodium iodide ○.

acetonitrile and lutidine and 10 equiv. of methanol showed no change in optical rotation. However, when 5.4 equiv. of sodium iodide were added, the specific rotation increased by 10% in about 10 min and thereafter decreased rapidly. In a similar experiment, 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide reacted completely with 5 equiv. of 2-propanol within 8 h in the absence of sodium iodide, but reacted completely in 1.5 h in the presence of 1 equiv. of sodium iodide (Fig. 1).

Although tetra-*O*-benzyl-α-D-glycopyranosyl chlorides react much more slowly with sodium iodide than do the corresponding bromides, they are more convenient to use because they can be readily prepared and purified in larger quantities. They are also more stable and insensitive to hydrolysis. In any case, sodium iodide, the acid acceptor, and alcohol can be added to the chloride conveniently at the same time and the glycosyl iodide generated slowly *in situ*. We found that it was advisable to use more than 1 equiv. of sodium iodide to obtain satisfactory rates. Typically, 3.7 to 4.0 equiv. of sodium iodide in acetonitrile was sufficient to convert the glycosyl chlorides into iodides and to produce high yields of glycoside in 16 h. These conditions became our usual standard, although they were perhaps not optimal for obtaining high ratios of α- to β-anomers.

In preparative experiments with methanol, pure glycosides could be obtained only when an acid acceptor was present. In this role, diisopropylamine was unsatisfactory and led to byproducts, but the use of 2,6-lutidine was successful. Acetone and a few other solvents were shown to be generally less satisfactory than acetonitrile. Reactions carried out in acetonitrile in the presence of lutidine led to high yields of pure glycosides having a high proportion of α anomer (usually over 90%) when a limited excess of methanol was present (Table I). With a large excess of methanol, the reactions were less stereoselective, as had previously been observed with several benzylated α-D-glucopyranosyl bromides[5]. The relative amounts of α- and β-glycosides produced and the degree of conversion of chloride were readily estimated by n.m.r.

The preparation of glycosides of ethanol, 2-propanol, and cyclohexanol was also studied under the "standard" conditions (*in situ* generation of a glycosyl iodide from a chloride, 3.7 equiv. of sodium iodide and 2 equiv. of alcohol, in acetonitrile and lutidine; see Table II and Experimental.) In the absence of known samples of the pure anomeric glycosides, glycoside-forming reactions were also carried out with the corresponding glycosyl bromides and a large excess of alcohol in dichloromethane solution. Under the latter conditions, a mixture of anomers was probable. In every case, the glycosidic products from the reaction of an iodide and of a limited amount of alcohol had at least as high a positive specific rotation as that of the products obtained from the corresponding bromide. Usually, the specific rotation of the products obtained from the iodide was higher. N.m.r. spectra of the ethyl 2,3,4,6-tetra-*O*-benzyl-D-glycopyranosides gave more detailed structural information than did the optical rotations. The relative areas of groups of peaks in n.m.r. spectra of the products were consistent with those expected of ethyl glycosides. Furthermore, the methyl peaks of the ethyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides and the ethyl

TABLE I

METHANOLYSIS OF 2,3,4,6-TETRA-*O*-BENZYL-α-D-GALACTOPYRANOSYL IODIDE AND 2,3,4,6-TETRA-*O*-BENZYL-α-D-GLUCOPYRANOSYL IODIDE

Solvent	*Acid acceptor*	*Molar ratio of methanol to galactosyl halide*	*Ratio of α- to β-anomer*
Tetra-*O*-benzyl-α-D-galactopyranosyl iodide:			
Acetone	none	3	[a–d]
Acetone	diisopropylamine	3	[a–c,e]
Acetone	2,6-lutidine	2	90:10[a–c]
Acetonitrile	none	2	91:9[d]
Acetonitrile	diisopropylamine	2	89:11[e]
Acetonitrile	2,6-lutidine	2	88:12
Acetonitrile	2,6-lutidine	2	90:10[f]
Acetonitrile	2,6-lutidine	40	71:29
Dichloromethane	2,6-lutidine	2	86:14[d,g]
Ethyl ether	2,6-lutidine	2	90:10[g]
Benzene	2,6-lutidine	2	71:29[g]
Tetra-*O*-benzyl-α-D-glucopyranosyl iodide:			
Acetone	2,6-lutidine	2	95:5[a–c]
Acetonitrile	none	3	95:5[d]
Acetonitrile	diisopropylamine	2	94:6[e]
Acetonitrile	2,6-lutidine	2	92:8
Acetonitrile	2,6-lutidine	40	75:25
Acetonitrile	2,6-lutidine	2	96:4[f]
Dichloromethane	2,6-lutidine	2	95:5[g]

[a]Low yield of glycoside obtained. [b]Impurity peaks near δ 1.4. [c]Impurity peak near δ 3.25. [d]Impurity peak near δ 4.3. [e]Impurity peaks near δ 1.2. [f]Glycosyl iodide generated *in situ* from glycosyl chloride and excess sodium iodide. [g]Glycosyl iodide generated in acetonitrile from glycosyl bromide and sodium iodide.

TABLE II

OPTICAL ROTATIONS OF 2,3,4,6-TETRA-*O*-BENZYL-D-GLYCOPYRANOSIDES PREPARED BY TWO METHODS

Sugar	*Alcohol*	*Method*[a]	*Optical rotation*[b]
D-Glucose	Ethanol	A	+21
D-Glucose	Ethanol	B	+16
D-Glucose	2-Propanol	A	+28
D-Glucose	2-Propanol	B	+28
D-Glucose	Cyclohexanol	A	+42
D-Galactose	Ethanol	A	+17
D-Galactose	Ethanol	B	+13
D-Galactose	2-Propanol	A	+28
D-Galactose	2-Propanol	B	+27
D-Galactose	Cyclohexanol	A	+38

[a]A: Prepared in acetonitrile from 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl chloride and sodium iodide with 2 equiv. of alcohol. B: Prepared in dichloromethane from 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl bromide and a large excess of alcohol. [b]In degrees, $[\alpha]_D^{25}$ (*c* 1.5–2.0, chloroform).

2,3,4,6-tetra-*O*-benzyl-D-galactopyranosides appeared as simple triplets with a J $\approx$ 7 Hz in the samples prepared by the glycosyl chloride–sodium iodide procedure. In contrast, two sets of triplets were observed in the spectra of samples prepared from the tetra-*O*-benzyl-α-D-glycopyranosyl bromides and excess ethanol (Table II). However, the peaks were located too closely to allow any quantitative interpretation of anomeric ratios. Since the optical rotations of the ethyl glycosides prepared by the tetra-*O*-benzyl-α-D-glycopyranosyl chloride–sodium iodide method are positive and higher than those of the glycosides prepared by reaction of the bromides with an excess of ethanol, the former method gives predominantly α-D-glycoside. The 2-propyl D-glucopyranosides and galactopyranosides prepared by the two methods had nearly identical n.m.r. spectra and optical rotations, indicating that both methods gave about the same mixture of α- and β-anomers. In all the samples, the n.m.r. spectra of the methyl groups were two doublets of nearly equal intensity, indicating that the methyl groups in the 2-propyl aglycon were probably forced into nonequivalent positions. The alternative explanation that a 1:1 mixture of α and β anomers was obtained appears improbable, especially since small shoulders, which probably represent small amounts of the β anomer were visible on the two peaks. The n.m.r. spectra of the cyclohexyl glucopyranosides and galactopyranosides were uninformative, since they contained, in the alkyl proton region, only very broad peaks due to slow conformational changes in the cyclohexyl aglycon.

2,3,4,6-Tetra-*O*-benzyl-α-D-glycopyranosyl iodides thus appear to be very similar to 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl bromides in their reactions with alcohols. However they have important advantages. Firstly, they react so much faster than bromides or chlorides that it is quite feasible to allow them to react with limited excesses of the alcohol without the use of heavy metal salts as catalysts. Thus, a very substantial source of side reactions is removed and better yields can generally be expected. Furthermore, the faster rate also permits conditions to be chosen which favor high ratios of α to β anomers (*i.e.*, low alcohol concentrations), and the product mixture is thus more satisfactory for isolation of the α anomer. In addition, there are very clear indications in this and previous work[8,18,19] that, under identical conditions, the three halides will usually yield various ratios of α to β-anomers, in the order I > Br > Cl. These ratios probably reflect differences in the rates of anomerization of the halides prior to glycoside formation.

More information is needed about variations in the rates and stereoselectivity of glycoside formation as a function of alcohol structure, and as a function of the structure of blocking groups on the glycosyl halide, (*cf.* the work of Ishikawa and Fletcher[8] and others[5,18].) This work reemphasizes the significant control possible on the glycoside-forming reaction by a judicious choice of the leaving group.

EXPERIMENTAL

General. — Optical rotations were determined with a Perkin–Elmer model 141 polarimeter equipped with a 1-dm cell fitted with a water jacket for circulating water

from a constant temperature bath at 25°. N.m.r. spectra were recorded with a Varian A-60 analytical spectrophotometer on solutions in chloroform-*d* and with tetramethylsilane as the internal standard.

Solvents, acid acceptors, and alcohols were dried thoroughly and distilled into the high-vacuum reaction vessel or transferred with a syringe. Acetone was dried over molecular sieves. Methanol was distilled from a solution of sodium methoxide. All the other solvents, acid acceptors, and alcohols were dried over calcium hydride.

Polarimetric study of glycoside synthesis. — 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride (40 mg) was dissolved in dry acetonitrile (1 ml) containing methanol (23 mg, 10 equiv.) and lutidine (10 mg). The solution was placed into a 1-dm polarimeter tube. The optical rotation of the solution remained constant for a period of 2 h. When sodium iodide (58 mg, 5.4 equiv.) was added and dissolved with shaking, a precipitate of sodium chloride began to form after a few minutes. Although the optical rotation was difficult to follow because of the precipitate, it increased by 10% after 10 min, and then it began to decrease rapidly. These changes were apparently due to the conversion of the glucopyranosyl chloride into the glucopyranosyl iodide and subsequent methanolysis of the iodide.

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl bromide (60 mg) was dissolved in acetonitrile (1.0 ml) containing 2-propanol (30 mg, 5 equiv.). The solution was placed into a 1-dm tube and the optical rotation as a function of time was recorded. The reaction was complete after 8 h. A similar reaction mixture, containing the same amounts of the other reactants and 1 equiv. (15 mg) of sodium iodide, gave immediately a precipitate of sodium bromide, and the reaction was complete after 1.5 h (Fig. 1).

Methanolysis experiments. — High-vacuum techniques were used in these experiments. A solution of 2,3,4,6-tetra-*O*-benzyl-α-D-gluco- or α-D-galactopyranosyl bromide (220 mg) in 1 ml of dry ethyl ether was evaporated to a syrup that was dried for several hours *in vacuo* in a high-vacuum reaction vessel. Dry sodium iodide (218 mg, 4 equiv.) was added and dry acetonitrile (2 ml) was distilled into the reaction vessel. After the mixture had been stirred magnetically for approximately 10 min, the precipitation of sodium bromide was complete and methanol (23 mg, 2 equiv.) was distilled into the vessel from a calibrated capillary tube. The mixture was stirred over night and then poured into water (~100 ml). The aqueous mixture was extracted with carbon tetrachloride, and the carbon tetrachloride solution was dried over sodium sulfate, decolorized by passing it through a small silica gel column, and evaporated to a syrup that was dried for several hours *in vacuo*, and then dissolved in chloroform-*d* for n.m.r. analysis.

Methanolysis experiments in solvents other than acetone and acetonitrile required a slightly different procedure, since the sodium iodide was insoluble. 2,3,4,6-Tetra-*O*-benzyl-α-D-glycopyranosyl iodide was prepared in acetonitrile as previously described, acetonitrile was distilled off, and the new solvent and methanol were distilled into the reaction vessel. In other experiments, the relative amounts of 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl bromide, methanol, and sodium iodide

were varied. It was found that no more than 1 equiv. of sodium iodide was needed. When acid acceptors were used, they were distilled into the reaction vessel or added with a syringe.

Four equivalents of sodium iodide was used for the methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl chlorides in the presence of sodium iodide. Since the initial reaction between the glycosyl chloride and sodium iodide was slow, methanol was added with the solvent and acid acceptor. The remainder of the procedure was identical to that just described. When only 1 equiv. of sodium iodide was used, the reaction product contained unreacted 2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranosyl chloride.

The ratios of α- to β-glycosides produced in the methanolysis experiments were determined from the relative areas of the methoxyl proton peaks. These were located at δ 3.35 and δ 3.52 for the α- and β-anomers of methyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside, respectively, and δ 3.37 and 3.57 for the α- and β-anomers of methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside, respectively. These assignments were confirmed by comparison of these spectra to spectra of model compounds. The accuracy of the determinations of the α to β-glycoside ratio is limited to about ±5% because the β-methoxyl peaks are superimposed on multiplets from a portion of the sugar-ring, proton spectra.

When acetone was used as solvent, the n.m.r. spectra of the products contained a doublet near δ 1.48 and sharp singlets near δ 3.25 and 4.3. A singlet near δ 4.3 was present when an acid acceptor was not used and was probably due to benzyl alcohol or benzyl iodide resulting from cleavage of benzyl groups by hydrogen iodide. Use of diisopropylamine as an acid acceptor gave impurities showing peaks near δ 1.38. These could have been due to an amine salt or a glycosylamine. Use of acetonitrile as the solvent and 2,6-lutidine as the acid acceptor gave essentially pure glycosides. Although small amounts of impurities which could not be detected readily by n.m.r., may have been present, the yields have been nearly quantitative.

Synthesis of glycosides from higher alcohols. — 2,3,4,6-Tetra-*O*-benzyl-α-D-gluco- or α-D-galactopyranosyl chloride (200 mg), sodium iodide (200 mg, 3.7 equiv.), 2,6-lutidine (0.1 ml), dry acetonitrile (2.0 ml), and alcohol (2 equiv.) were stirred in a high-vacuum reaction vessel for about 2 h, and then kept at room temperature. Reaction with the primary alcohols was allowed to take place for 16 h and reaction with the secondary alcohols for 48 h, but these reaction times are quite arbitrary and perhaps much less time could have been allowed. The mixture was poured into water, the water was extracted with carbon tetrachloride, and the carbon tetrachloride solution was dried over sodium sulfate, decolorized by passing it through a small silica gel column, and evaporated to a syrup. This was dried for several hours *in vacuo* and 30–40 mg was weighed into a 2-ml volumetric flask for optical rotation determination (*c* 1.5–2, chloroform). Specific rotations were calculated on the basis of the weight of the product. The remainder of the syrup was dissolved in chloroform-*d* for n.m.r. analysis.

*Glycoside synthesis from 2,3,4,6-tetra-*O*-benzyl-α-D-gluco- and -α-D-galacto-*

pyranosyl bromides with excess alcohol. — 2,3,4,6-Tetra-*O*-benzyl-α-D-glycopyranosyl bromide (200 mg) was dissolved in alcohol (5 ml) and dichloromethane (5 ml), and the mixture was kept overnight. It was evaporated to a syrup which was dissolved in carbon tetrachloride. The solution was dried over sodium sulfate, decolorized by passing it through a small silica gel column, and evaporated to a syrup that was dried for several hours *in vacuo*. An aliquot (30–40 mg) was withdrawn for determination of the optical rotation (*c* 1.5–2, chloroform), and the remainder of the syrup was dissolved in chloroform-*d* for n.m.r. analysis.

ACKNOWLEDGMENT

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

REFERENCES

1 B. HELFERICH AND R. GOOTZ, *Ber.*, 62 (1929) 2791.
2 R. K. NESS, H. G. FLETCHER, JR., AND C. S. HUDSON, *J. Amer. Chem. Soc.*, 72 (1950) 2200.
3 H. J. JENNINGS, *Can. J. Chem.*, 49 (1971) 1355.
4 P. W. AUSTIN, F. E. HARDY, J. G. BUCHANAN, AND J. BADDILEY, *J. Chem. Soc.*, (1965) 1419.
5 F. J. KRONZER AND C. SCHUERCH, *Carbohyd. Res.*, 27 (1973) 379.
6 M. L. WOLFROM, A. O. PITTET, AND I. C. GILLAM, *Proc. Nat. Acad. Sci. U.S.*, 47 (1961) 700.
7 M. L. WOLFROM, A. THOMPSON, AND D. R. LINEBACK, *J. Org. Chem.*, 28 (1963) 860.
8 T. ISHIKAWA AND H. G. FLETCHER, JR., *J. Org. Chem.*, 34 (1969) 563.
9 H. M. FLOWERS, *Carbohyd. Res.*, 18 (1971) 211.
10 M. DEJTER-JUSZYNSKI AND H. M. FLOWERS, *Carbohyd. Res.*, 18 (1971) 219.
11 A. KLEMER, E. BUHE, AND R. KUTZ, *Ann.*, 739 (1970) 185.
12 P. J. PFÄFFLI, S. H. HIXSON, AND L. ANDERSON, *Carbohyd. Res.*, 23 (1972) 195.
13 H.J. JENNINGS, *Chem. Commun.*, (1967) 772.
14 H. HASEGAWA, N. KURIHARA, D. NISHIMURA, AND M. NAKAJIMA, *Agr. Biol. Chem.*, 32 (1968) 1130.
15 J. M. FRÉCHET AND C. SCHUERCH, *J. Amer. Chem. Soc.*, 93 (1971) 492.
16 F. J. KRONZER AND C. SCHUERCH, *Carbohyd. Res.*, 27 (1973) 379; 33 (1974) 273.
17 R. EBY AND C. SCHUERCH, *Carbohyd. Res.* 34 (1974) 79.
18 J. M. FRÉCHET AND C. SCHUERCH, *J. Amer. Chem. Soc.*, 94 (1972) 604.
19 A. J. RHIND-TUTT AND C. A. VERNON, *J. Chem. Soc.*, (1960) 4637.