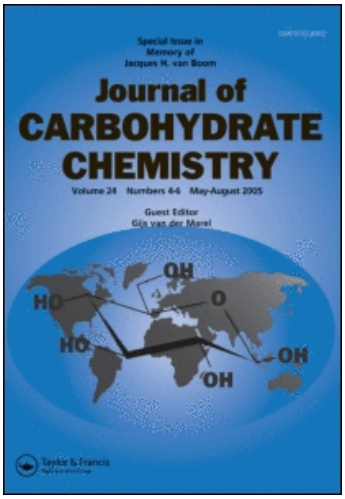


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

The Reaction of Methyl 2,4,6-Tri-0-benzoyl-3-0-benzyl-β-D-galactopyranoside with 1,1-Dichloromethyl Methyl Ether

Pavol Kováač[a]; Noel F. Whittaker[a]; Cornelis P. J. Glaudemans[a]
[a] NIADDK, National Institutes of Health, Bethesda, Maryland

To cite this Article Kováač, Pavol , Whittaker, Noel F. and Glaudemans, Cornelis P. J.(1985) 'The Reaction of Methyl 2,4,6-Tri-0-benzoyl-3-0-benzyl-β-D-galactopyranoside with 1,1-Dichloromethyl Methyl Ether', Journal of Carbohydrate Chemistry, 4: 2, 243 — 254
To link to this Article: DOI: 10.1080/07328308508058835
URL: http://dx.doi.org/10.1080/07328308508058835

J. CARBOHYDRATE CHEMISTRY, 4(2), 243-254 (1985)

THE REACTION OF METHYL 2,4,6-TRI-O-BENZOYL-3-O-BENZYL-β-D-GALACTOPYRANOSIDE WITH 1,1-DICHLOROMETHYL METHYL ETHER

Pavol Kováč, Noel F. Whittaker, and Cornelis P. J. Glaudemans
NIADDK, National Institutes of Health, Bldg. 4
Bethesda, Maryland 20205

Received December 19, 1984 - Final Form March 22, 1985

ABSTRACT

When methyl 2,4,6-tri-O-benzoyl-3-O-benzyl-β-D-galactopyranoside (1) is treated in purified chloroform at 55-60° with excess of dichloromethyl methyl ether in the presence of a catalytic amount of freshly fused zinc chloride for 1 h the corresponding α-glycosyl chloride 2 can be isolated by column chromatography in 75-80% yield. Compound 2 is an important intermediate in the synthesis of oligosaccharides containing a glycosyl-3-O-galactosyl sequence. Under the described reaction conditions the conversion 1 → 2 is accompanied by a slow anomerisation of 1 to give methyl 2,4,6-tri-O-benzoyl-3-O-benzyl-α-D-galactopyranoside. Prolonged treatment of 2 with the used excess of the reagent results in complete debenzylation of the substrate and the conversion of the putative 2,4,6-tri-O-benzoyl-α-D-galactopyranosyl chloride into the corresponding 3-O-formyl and 3-O-dichloromethyl derivatives.

Stepwise synthesis of (1→3)-β-D-galactooligosaccharides depends largely upon the availability of a 2-O-acylated D-galactosyl halide bearing a selectively removable protecting group at O-3. Compounds of this type are not readily available, their preparation requires a large number of steps and involves amorphous intermediates the isolation of which has to

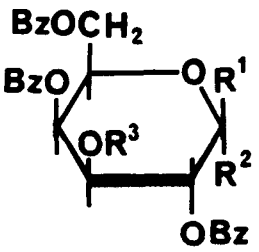
 0732-8303/85/0402-0243$3.50/0

be done by chromatography (e.g. ref. 1). We have recently described an efficient synthesis of the methyl β-glycoside of β-(1→3)-D-galactobiose.[2] One of the key intermediates in that synthesis was methyl 2,4,6-tri-O-benzoyl-3-O-benzyl-β-D-galactopyranoside (1), a crystalline compound obtained readily in two steps from the commercially available methyl β-D-galactopyranoside. It has been previously shown[3] that fully acylated carbohydrates or their glycosides can be conveniently converted into the corresponding glycosyl halides by treatment with dihalogenomethyl methyl ethers in the presence of a Lewis acid catalyst. However, reports on a successful cleavage with dihalogenomethyl methyl ethers of anomeric substituents in carbohydrates bearing alkyl ether groups are scarce. Among these are syntheses of glycosyl halides derived from 4-O-methyl-D-glucuronic acid[4] from the corresponding per-O-acyl derivatives and of methyl 1-chloro-1-deoxy and 1-bromo-1-deoxy-2,3,4-tri-O-methyl-α-D-galactopyranuronate[5] from the corresponding methyl α-glycoside. If a corresponding glycosyl halide could be obtained from 1 in good yield by cleavage with a dihalogenomethyl methyl ether it might open the possibility to efficiently synthesize building blocks for important oligosaccharides containing a glycosyl-(1→3)-D-galactosyl sequence.

Bock et al.[6] have observed that, unlike with dichloromethyl methyl ether, the fast formation of glycosyl bromides from fully acylated saccharides or methyl glycosides treated with dibromomethyl methyl ether is followed by a slow reaction in which the pyranosyl bromides are converted into bromodeoxypyranosyl bromides. The above observation and the importance of glycosyl chlorides in the silver triflate - catalyzed glycosylation reactions made dichloromethyl methyl ether the reagent of choice for the work described herein.

Treatment of compound 1 at 55-60° in chloroform with 1,1-dichloromethyl methyl ether in the presence of a catalytic

amount of zinc chloride resulted in its rapid conversion into a product moving much faster on TLC. When about 50% of the starting material was consumed (30 min) the formation of another product, moving marginally faster than the starting



	R^1	R^2	R^3
1	OMe	H	Bn
2	H	Cl	Bn
3	H	OMe	Bn
4	OAc	H	Bn
5	H	Cl	CHO
6	H	Cl	$CHCl_2$
7	OAc	H	CHO
8	H	Cl	H

material, could be noticed. When the reaction was terminated at this stage the products isolated by chromatography were identified by spectral and elemental analysis as 2 (faster, largely preponderating) and 3 (slower of the two products, formed by anomerization of 1 in the presence of a Lewis acid). In agreement with the structure 2 the EI mass spectrum showed a peak at m/z 565 ($[M - Cl]^+$). The CI mass spectrum showed a peak at m/z 618 ($[M + 18]^+$, all m/z values refer to the nominal mass, i.e. ^{35}Cl). The CI spectrum of the minor product isolated at this stage showed peaks at m/z 614 ($[M + 18]^+$), 597 ($[M + 1]^+$) and 565 ($[M+1 - MeOH]^+$), indicating that partial isomerization of the starting material had occurred.

Structure 3 was substantiated by elemental analysis and analysis of its ^{1}H- and ^{13}C NMR data.

The emergence of 3 in the reaction mixture suggested that by prolonging the reaction time this glycoside, in analogy with other α-glycosides,[3,5] would also be cleaved to give 2, the overall yield of which could thus be increased. This, however, proved to be only partially the case. After the reaction time of 60 min, when almost all 1 had reacted, 3 was still present and the formation of a new product, with a TLC mobility between those of 2 and 3, commenced. This notwithstanding, the reaction time of 60 min was found optimal for obtaining the highest yield of 2 which, under these conditions, could be isolated in 75-80% yield by column chromatography of the processed reaction mixture. When the reaction was continued beyond this point the amount of the new product increased (TLC), obviously at the expense of the desired glycosyl halide 2, and after a total reaction time of 8 h this new product, later shown to be 5, was the major reaction component. At this point TLC showed the absence of either 1 or 3 in the reaction mixture, the presence of 2 and 5, as well as small amount of a component less polar than 2, later shown to be 6. The amount of 6 in the mixture gradually increased and after 24 h the composition of the reaction mixture stablized, and remained unchanged during 2 more days. In this way the glycoside 1 treated for 24 h with 1,1- dichloromethyl methyl ether in chloroform at 55-60° in the presence of a catalytic amount of zinc chloride gave a 1:1 mixture of the glycosyl halides 5 and 6.

The structures of 5 and 6 agree with the following spectral and chemical evidence: The ^{1}H NMR spectra of both substances in question showed the absence of benzylic protons and the presence of low field doublets (Table 1) characteristic of glycosyl halides. The signals in the aromatic region

TABLE 1

^{1}H NMR Data (in $CDCl_3$) For 1 - 7 At 220 MHz

Compound	Chemical shifts[a]										Coupling constants (Hz)						
	H-1	H-2	H-3	H-4	H-5	H-6	H-6'	CH	OMe	COMe	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1[b]	4.54d	5.54dd	3.82dd	5.92dd	4.10td	4.63dd	4.44dd		3.52s		8.0	10.0	3.4	1.0	6.3	6.5	11.3
2[c]	6,58d	5.64dd	4.31dd	6.06d	4.75t	4.46dd	4.57dd				4.0	10.0	3.5	1.0	6.5	6.5	11.0
3[d]	5.23d	5.48dd	4.22dd	5.98d	4.57		4.36m		3.38s		3.5	10.0	3.5	1.0	e	e	e
4[f]	5.87d	5.66dd	3.46dd	5.98d	4.23t	4.57dd	4.41dd			2.05	8.0	10.0	3.0	1.0	6.5	5.0	11.0
5	6.65d	5.73dd	5.98dd	6.04dd	4.88dt	4.42dd	4.61dd	7.95s			4.0	10.5	3.5	1.0	6.0	6.5	11.0
6	6.59d	5.74dd	5.27dd	6.27d	4.85t	4.45dd	4.55dd	7.18s			4.0	10.0	3.5	1.0	6.0	6.5	12.0
7	6.01d	5.78dd	5.53dd	5.92d	4.40t	4.60dd	4.37dd	7.88s		2.08	8.0	10.0	3.5	1.0	e	7.5	10.0

[a]Peak multiplicities: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; m, multiplet; [b]benzylic protons appear as doublets at δ 4.71 and 4.51, ^{2}J 12.7 Hz; [c]benzylic protons appear as doublets at δ 4.80 and 4.61, ^{2}J 12.0 Hz; [d]benzylic protons appear as doublets at δ 4.77 and 4.59, ^{2}J 12 Hz; [e] not determined due to overlapping of signals; [f]benzyl protons appear as doublets at δ 4.68 and 4.88, ^{2}J 12 Hz.

integrated in each case to 16 protons. One of these appeared as a singlet due to the loss of the benzylic substitution and a gain of an isolated CH group attached to a strongly electron withdrawing grouping. The chemical shift of the singlet (Table 1) suggested strongly[7] that 5 was a formate. This agreed with the observation that compared to the ^{1}H NMR spectrum of 2 showing the four-line pattern for H-3 upfield (Table 1), the H-3 in the spectrum of 5 appeared downfield, indicating that this proton is proximal to an electron withdrawing, likely an acyl, group. The CI spectrum of 5 showed both $[M+1]^+$ and $[M + 18]^+$ ion peaks. Exact mass measurement of the highest m/z fragment, 503 ($[M - Cl]^+$), fits a molecular formula $C_{28}H_{23}O_9$. The presence of a formyl group at O-3 in 5 is confirmed also by ^{13}C NMR spectroscopy. Compared to the spectrum of 2, the spectrum of 5 contained an additional, higher field carbonyl signal which appeared as a doublet when the spectrum was taken in the "off resonance" mode. In the ^{13}C NMR spectrum of 6 the signal of the dichloromethyl substituent appeared at 96.8 ppm. In agreement with the structure 6 the position of the signal of H-3 in its ^{1}H NMR spectrum is between those of H-3 in the spectra of 2 and 5. The CI mass spectrum of 6 shows a three-chlorine isotope pattern at nominal mass m/z 610 ($[M + 18]^+$). The EI mass spectrum of 6 showed a two-chlorine isotope pattern at a nominal mass 557 ($[M - Cl]^+$), and accurate mass measurement for this fragment suggested the elemental composition to be $C_{28}H_{23}Cl_2O_8$.

When treated with silver acetate, glycosyl halides 2 and 5 gave the expected β-acetates 4 and 7, respectively, which were fully characterized and their structures confirmed by the analysis of their NMR spectral data. The reaction of 2 was much faster than that of 5 (see Experimental) reflecting the effect of a benzyl group upon the reactivity of glycosyl

halides, even when this group is distant from the anomeric center. Compound 6 was not fully characterized since, due to its extreme sensitivity towards moisture, it could not be obtained pure. It decomposed partially during TLC to give 5, and during column chromatography to even more polar products. The conversion 6 → 5 on TLC plates should not be surprising since as a dichloromethyl ether 6 is expected to react readily with water.

When a sample of 6 that contained (TLC) 5-10% of 5 was reacted with silver acetate its slow conversion to 5 at the initial stage of the reaction could be observed, and the acetate 7 was isolated eventually as the major reaction product.

The reaction of 1 studied under the conditions described here can be summarized as follows: In a rapid reaction, the glycoside 1 is converted to the corresponding glycosyl halide 2. The reaction is accompanied by a very slow anomerization of 1 to give 3. Prolonged contact of 2 with the reaction system containing hydrogen chloride, methyl formate, zinc chloride and an excess of the dichloromethyl methyl ether reagent eventually leads to complete debenzylation of 2, to form (presumably) 8, and subsequent conversion of the latter to the halides 5 and 6.

The formation of an O-formate and a dichloromethyl ether on treatment of a carbohydrate derivative with dichloromethyl methyl ether is not without a precedent. Bognar et al.[8] cleaved 1,6-anhydro-2,3,4-tri-O-acetyl-β-D-glucopyranose with 1,1-dichloromethyl methyl ether and observed the conversion of the initially formed 2,3,4-tri-O-acetyl-α-D-glucopyranosyl chloride into the corresponding 6-O-formyl and 6-O-dichloromethyl derivative. The chemical properties described[8] for the latter derivatives compare well with those observed here for 5 and 6. The known ability of dihalogenomethyl methyl ethers to

cleave alkyl ethers[3] together with a possibility of subsequent transformation of the formed alcohols[8] may have discouraged the wide use of these reagents to make glycosyl halides from carbohydrates bearing alkyl ether groups. Although the likelihood of the aforementioned conversions should not be disregarded when alkylated sugar derivatives are treated under similar conditions, as we have shown[4,5] and demonstrate now, cleavage of glycosides and acetates of sugars bearing an alkyl group to form the corresponding glycosyl halides can be conveniently performed under controlled conditions.

EXPERIMENTAL

Melting points were determined with a Buchi melting point apparatus. Optical rotations were measured using a Perkin-Elmer automatic polarimeter Model 241 MC. Preparative chromatography was performed by gradient elution form slurry-packed columns od Silica Gel 60 (Merck, Cat. No. 9385 or 15111). Thin-layer chromatography (TLC) on glass slides coated with Silica Gel G (Analtech) was performed with A, carbon tetrachloride-ethyl acetate 15:1; and B, carbon tetrachloride-acetone 4:1. Detection was by charring with 5% (v/v) sulfuric acid in ethanol and by UV light.

Ammonia CI mass spectra were recorded with a Finnigan 1015D spectrometer at source pressure and temperature of 133 Pa and 100°; respectively. EI mass spectra were taken at 70 eV, with a V. G. micromass 7070F instrument at an ion source temperature of 210°.

^{13}C NMR and ^{1}H NMR spectra were taken for solutions in $CDCl_3$ (internal standard, Me_4Si) with a Varian FX 100 and Varian HR 220 spectrometers, respectively.

Chloroform was washed with concentrated sulfuric acid (twice) and water, dried with phosphorus pentaoxide, and distilled. 1,1-Dichloromethyl methyl ether (DCMME) was

purchased from Aldrich Chemical Co., and used as supplied. Solution in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 40°/2 kPa.

2,4,6-Tri-O-benzoyl-3-O-benzyl-α-D-galactopyranosyl chloride (2) and methyl 2,3,6- tri-O-benzoyl-3-O-benzyl-α-D-galactopyranoside (3).

A mixture of 1 (1 g), DCMME (3 mL) and freshly fused zinc chloride (∿10 mg) in chloroform (3 mL) was stirred at 55-60° with the exclusion of atmospheric moisture for 30 min. The mixture was concentrated and the two products (R_f 0.35 and 0.2, solvent A, c.f. 0.1 for the starting material) were isolated by chromatography. The material eluted first was 2 (0.43 g), $[\alpha]_D$ +175° (c 0.86, chloroform). ^{13}C NMR data: δ 165.9, 165.6 (1C, 2C, 3xCOPh), 92.2 (C-1), 72.6 (C-3), 71.6 (CH_2, benzylic), 70.3, 70.1 (C-2, C-5), 67.3 (C-4), 62.3 (C-6).

Anal. Calcd for $C_{34}H_{29}ClO_8$: C, 67.94; H, 4.86. Found: C, 67.94; H, 5.15.

Eluted next was 3 (60 mg, 6%), $[\alpha]_D$ +149.4° (c 0.7 chloroform). ^{13}C NMR data: δ 92.2 (C-1), 72.6 (C-3), 71.6 (CH_2, benzylic), 70.3, 70.1 (C-2, C-5), 67.3 (C-4), 62.3 (C-6), 55.4 (Me).

Anal. Calcd for $C_{35}H_{32}O_9$: C, 70.45; H, 5.40. Found: C, 70.39; H, 5.66.

Eluted last was unchanged (TLC, ^{13}C NMR) starting material.

With prolonged reaction time (1 h), the glycosyl halide 2 was isolated in 75-80% yield.

2,4,6-Tri-O-benzoyl-3-O-formyl (5) and 3-O-dichloromethyl-α-D-galactopyranosyl chloride (6). - A solution of 1 (5 g) in chloroform (15 mL) was treated with DCMME (15 mL) and freshly fused zinc chloride (∿ 50 mg) as described above. After 24 h TLC (solvent A showed the absence of either 1, 2 or 3 and the

presence of two components only, in an ∿1:1 ratio (R_f 0.4 and 0.25). The composition of the reaction mixture had not changed after a further 2 d. After processing, chromatography gave first 6 (0.8 g, 16%) which contained 10% of the slower moving component (TLC). ^{13}C NMR data: δ165.9, 165.5, 165.2 (3xCOPh), 96.8 (doublet in an off-resonance spectrum, $CHCl_2$), 91.8 (C-1), 72.0 (C-3), 70.3 (C-5), 68.8, 68.3 (C-2, C-4), 62.1 (C-6).

Eluted next was the glycosyl halide 5 (3.1 g, 62%), $[\alpha]_D$ +154.7° (c 0.95, chloroform). ^{13}C NMR data: δ 165.5, 165.4 (1C, 2C, 3xCOPh), 159.5 (doublet in the off resonance spectrum, COH), 91.4 (C-1), 70.0 (C-5), 68.6 (C-3), 68.0 (C-2), 66.8 (C-4), 61.7 (C-6).

Anal. Calcd for $C_{28}H_{23}ClO_9$: C, 62.40; H, 4.30. Found: C, 62.78; H, 4.61.

Elution of the column with acetone gave polar material (1.6 g), TLC of which suggested that partial decomposition of 5 and/or 6 occurred during preparative chromatography.

1-O-Acetyl-2,4,6-tri-O-benzoyl-3-O-benzyl-β-D-galacto-pyranose (4). A mixture of 2 (1 g), silver acetate (0.35 g) and drierite (1 g) in acetonitrile (5 mL) was stirred at room temperature until TLC (solvent A) showed that the reaction was complete (∿24 h). The mixture was diluted with carbon tetrachloride, filtered, concentrated, and the residue was chromatographed to give 4 (0.87 g, 77.8%, amorphous solid), $[\alpha]_D$ +108° (c 1.2, chloroform). ^{13}C NMR data: δ 169.1 ($COCH_3$), 166.0, 165.7, 165.1 (3 x COPh), 92.3 (C-1), 76.2 (C-3), 72.4 (C-5), 71.1 (CH_2, benzylic), 70.0 (C-2), 66.4 (C-4), 62.4 (C-6).

Anal. Calcd for $C_{36}H_{32}O_{10}$: C, 69.22; H, 5.16. Found: C, 68.94; H, 5.11.

1-O-Acetyl-2,4,6-tri-O-benzoyl-3-O-formyl-β-D-galacto-pyranoside (7). a) Compound 5 (1 g) was treated as described

above for the preparation of 4. After 3 d TLC showed that some unreacted starting material was still present. A fresh portion of silver acetate (0.2 g) was added and after further 2 d, when the reaction was complete, the mixture was processed, and the crude product was chromatographed to give 7 (0.78 g, 7%), mp 155-156° (from ethanol), $[\alpha]_D$ +67.8° (c 0.64, chloroform). ^{13}C NMR data: δ168.9 ($COCH_3$), 165.9, 165.5, 165.0 (3 x COPh), 159.6 (doublet in the off-resonance spectrum, COH), 92.3 (C-1), 72.3 (C-5), 70.3 (C-3), 68.5 (C-2), 67.6 (C-4), 61.8 (C-6).

Anal. Calcd for $C_{30}H_{26}O_{11}$: C, 64.05; H, 4.65. Found: C, 63.77; H, 4.95.

b) The glycosyl halide 6 (1 g), containing ∿5-10% of 5 (TLC) was treated as described in a). Monitoring by TLC (solvent A) showed that during the first 24 h the main reaction was the conversion 6→5. After 3 d, when some unreacted 5 was still present, more silver acetate (0.2 g) was added ans stirring was continued for 2 more d. After processing, chromatography of crude product yielded 7 (0.75 g, 71.8%), identical with the above described substance.

ACKNOWLEDGMENT

The authors are grateful to H. C. Yeh for recording the ^{13}C NMR spectra.

REFERENCES

1. M. A. Nashed, M. S. Chowdhary, and L. Anderson, Carbohydr. Res., 102, 99, (1982) .

2. P. Kováč, R. B. Taylor, and C. P. J. Glaudemans, Carbohydr. Res., in press.

3. H. Gross, I. Farkas, and R. Bognár, Z. Chem., 18, 201, (1978) and papers cited therein.

4. P. Kováč and R. Palovčík, Carbohydr. Res., 56, 399, (1977).

5. P. Kováč, I. Farkas, V. Mihálov, R. Palovčík, and R. Bognár, J. Carbohydr. Nucl. Nucl., 3, 57, (1976).

6. K. Bock, C. Pedersen, and P. Rasmussen, J. C. S. Perkin I., 1456, (1973).

7. High Resolution N.M.R. Spectra Catalog, Vols. 1 and 2, Varian Associates, Palo Alto, California, 1962/1963, Spectra Nos. 9 and 415.

8. R. Bognár, I. Farkas, M. Menyhárt, H. Gross, and H. Paulsen, Carbohydr. Res., 6, 404, (1968).