

Free Radical Brominative Ring Opening of 1,2-*O*-Benzylidene Pyranoses: A Route to Glycosylating Agents

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Bromination of fully protected 1,2-*O*-benzylidenated pyranoses with bromotrichloromethane and u.v. light or *N*-bromosuccinimide gives 2-*O*-benzoyl glycosyl bromides in good yields, which may be converted *in situ* to glycosides and disaccharides.

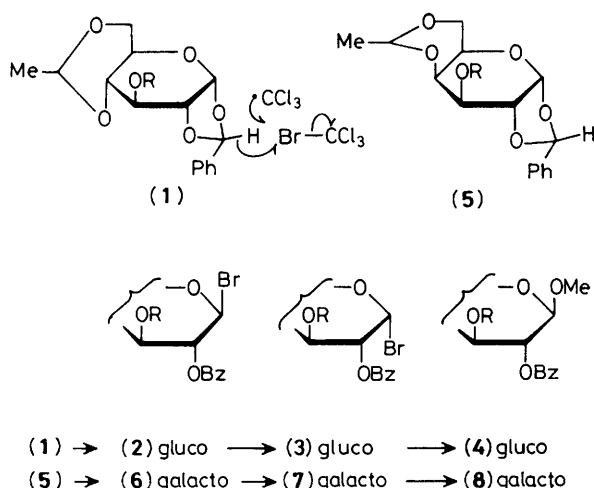
Free radical bromination is a well established way of preparing vicinal bromo-deoxy-sugar benzoates¹ from 2,3-, 3,4-, and 4,6-*O*-benzylidene glycopyranoses but to our knowledge it has never been applied to 1,2-*O*-benzylidenated sugar derivatives. The reaction is usually brought about by heating a solution of the sugar derivative in carbon tetrachloride containing *N*-bromosuccinimide (NBS) under reflux,² but we have recently shown that u.v. irradiation of similar solutions containing bromotrichloromethane (BTM) in place of NBS is equally efficient.^{3,4}

We now report that 1,2-*O*-benzylidene glycopyranose derivatives⁵ are readily converted, in high yield, into the corresponding 2-*O*-benzoylglycopyranosyl bromides when they are photobrominated with bromotrichloromethane (BTM) in carbon tetrachloride solution or treated under the standard NBS conditions. We found the photoreaction to be cleaner and faster, and the glycosyl bromides formed may be used *in situ*, although their isolation is simple since the reactants and by-products in the photoreaction are volatile.

In a typical example, a solution of 3-*O*-acetyl-1,2-*O*-benz-

Table 1. Selected n.m.r. data for the anomeric centres for glycosyl bromides and methyl glycosides. Ac = acetyl, Bz = benzoyl, Ts = tosyl.

R	(2)			Glucose derivative (3)			(4)		
	δ	^1H $J_{1,2}/\text{Hz}$	$^{13}\text{C}(\text{C}-1,1')$ δ	δ	^1H $J_{1,2}/\text{Hz}$	$^{13}\text{C}(\text{C}-1,1')$ δ	δ	^1H $J_{1,2}/\text{Hz}$	$^{13}\text{C}(\text{C}-1,1')$ δ
Ac	5.72 (d)	8.0	79.3, 80.1 ^a	6.71 (d)	4.0	87.8, 87.9 ^a	4.59 (d)	8.0	102.7, ^a 102.5
Bz							4.66 (d)	8.5	102.7 ^a
Bu ^t CO							4.56 (d)	8.0	102.7 ^a
Ts	6.30 (d)	8.0		7.20 (d)	4.0		4.54 (d)	8.0	
Bu ^t Me ₂ Si				6.59 (d)	4.0		4.48 (d)	7.9	
Glc(Ac) ₄	5.90 (d)	7.0	79.7, 99.7	6.66 (d)	4.0	88.0, 100.3	4.50 (d)	8.0	102.1, 100.1
	4.78 (d)	7.8 (1',2')		4.81 (d)	7.8 (1',2')				102.5, ^a 100.5 ^a
Gal(Ac) ₄	5.98 (d)	7.5		6.62 (d)	4.0	88.1, 101.1	4.66 (d)	8.0	
				4.32 (d)	8.0 (1',2')		4.32 (d)	8.0 (1',2')	
R	(6)			Galactose derivative (7)			(8)		
	δ	^1H $J_{1,2}/\text{Hz}$	$^{13}\text{C}(\text{C}-1,1')$ δ	δ	^1H $J_{1,2}/\text{Hz}$	$^{13}\text{C}(\text{C}-1,1')$ δ	δ	^1H $J_{1,2}/\text{Hz}$	$^{13}\text{C}(\text{C}-1,1')$ δ
Ac	5.54 (d)	8.0		6.97 (d)	3.2	90.2, 91.4 ^a	4.54 (d)	6.5	102.1
Bz				6.95 (d)	3.2	90.2	4.62 (d)	8.0	102.1
Bu ^t CO				6.73 ^a (d)	3.5	91.4 ^a	4.55 (d)	8.0	101.9

^a Measured in C₆D₆, all others measured in CDCl₃.**Scheme 1**

ylidene-4,6-*O*-ethylidene- α -D-glucopyranose† (1, R = Ac) (1 g) in carbon tetrachloride (65 ml) containing BTM (2.3 ml) was irradiated‡ for 30 min, after which analysis by t.l.c. and/or ^1H n.m.r. spectroscopy§ showed the reaction to be complete. The ^1H and ^{13}C n.m.r. spectra of the crude photolysate indicated that (1, R = Ac) had undergone quantitative conversion to the β -bromide (2, R = Ac). Evaporation of the solvent at this stage gave a gum which yielded, from ether/light petroleum, crystals of the unstable β -bromide (2, R = Ac),⁶ [α]_D -60° (CHCl₃). If, however, the irradiated solution containing the β -bromide was left in the dark for 4 days [or for *ca.* 1 h in the presence of tetra-*n*-butylammonium bromide

(0.8 mol.equiv.)] then the α -bromide (3, R = Ac) was formed in quantitative yield as ascertained by the ^1H and ^{13}C n.m.r. spectra of the crude reaction mixture. Evaporation of the solvent and crystallisation from ether/light petroleum gave the α -bromide (3, R = Ac), [α]_D $+226^\circ$ (CHCl₃) (m.p. 141–143 °C). Alternatively, the solution of the anomerized photolysate could be added directly to methanol containing silver carbonate or mercury(II) cyanide which gave methyl 3-*O*-acetyl-2-*O*-benzoyl-4,6-*O*-ethylidene- β -D-glucopyranoside (4, R = Ac) (760 mg), [α]_D 4.2° (CHCl₃), (m.p. 99–101 °C), in 70% yield from (1, R = Ac) after column chromatography.

The bromination is highly selective towards the benzylidene group, shown by the 4,6-*O*-ethylidene residue remaining unchanged, and functional groups such as benzoates, pivaloates, tosylates, *t*-butyldimethylsilyl and suitably acetylated glycosyl residues are compatible with the reaction conditions, shown by seven compounds (1, R = Ac, Bz, Bu^tCO, Ts, Bu^tMe₂Si, GlcAc₄, or GalAc₄) all undergoing similar transformations, see Table 1.¶

The initial stage of the reaction is assumed to be free radical (Scheme 1) followed by subsequent heterolytic ring opening by bromide ions, analogous to the mechanism involved when NBS brings about similar transformations,² although not to a single product as appears to be the case in most of the photoreactions. With NBS and, for example, the acetyl or benzoyl derivatives (1, R = Ac or Bz) the β -bromides (2, R = Ac or Bz) were contaminated with *ca.* 10% of their α -anomer (3, R = Ac or Bz) and *ca.* 10% of an uncharacterised product. However, with the tosyl derivative (1, R = Ts), the crude product from the thermal bromination was much less clean than that produced photochemically.

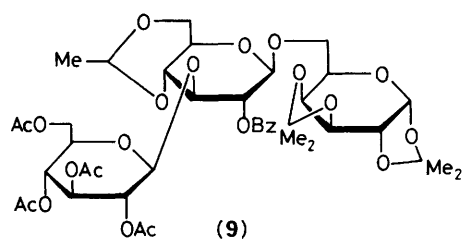
The three galactose isomers (5, R = Ac, Bz, or Bu^tCO) also reacted in a similar fashion although usually the ^1H n.m.r. spectra of their irradiated solutions revealed only the presence of the α -galactosyl bromides (7), see Table 1. However the β -galactosyl bromide (6, R = Ac) was seen as the only material present in the photolysates of the 3-*O*-acetyl deriva-

† The *R* or *S*-compound or an *RS*-mixture may be used: we have shown that isomerization at the benzylidene acetal carbon occurs early in the photoreaction.

‡ Irradiation was carried out in a 15 mm diameter quartz tube situated 3 cm from a 450 medium pressure mercury lamp.

§ Measured directly on the photolysate.

¶ GlcAc₄ is 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl and GalAc₄ is the galactosyl isomer.



tive (**5**, R = Ac) that had been irradiated at -10°C . Therefore it appears that these β -galactosyl bromides anomerize faster than their glucose analogues, in keeping with the higher reactivity of the former bromides.⁷

Thus 1,2-*O*-benzylidene acetals are potentially useful derivatives of sugars used in the block synthesis of oligosaccharides,⁸ since they may be used partially to protect the sugar to be glycosylated and by subsequent activation transform the oligomer chain, to which the sugar has been attached, into a glycosylating agent. This approach is exemplified by the synthesis of trisaccharide (**9**).

The disaccharide (**1**, R = GlcAc₄) (80 mg) was sequentially photolysed and anomerized as described earlier. The solvent was evaporated from the α -bromide (**3**, R = GlcAc₄) then 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (26 mg), mercury(II) cyanide (30 mg) in chloroform (2 ml), and nitromethane (1 ml) were added directly. After 48 h, usual

work up followed by chromatography gave the pure trisaccharide (**9**) (80 mg) (79%).||

Received, 8th October 1987; Com. 1469

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|| Data for (**9**): $[\alpha]_{\text{D}} -8^{\circ}$ (CHCl_3), ^1H n.m.r. δ 5.37 (d, H-1, J 5.0 Hz), 4.74 (d, H-1', J 7.5 Hz), 4.72 (d, H-1'', J 7.8 Hz), 1.67, 1.92, 1.98, 2.08 (4s, Ac), 1.18, 1.14, 1.26, 1.40 (4s, Me₂C), 1.34 (d, MeCH, J 5.3 Hz). ^{13}C n.m.r. δ 96.2, 101.2, 100.0 (C-1, C-1', C-1'' respectively), also discrete signals for the other 39 carbon atoms.