Phase-Transfer Catalyzed Synthesis of Acetylated Aryl β-D-Glucopyranosides and Aryl β-D-Galactopyranosides

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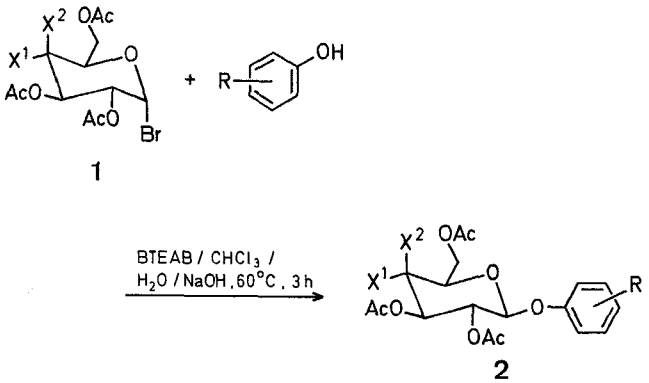
The synthesis of aryl glycosides has historically attracted interest because these compounds are widespread in nature and hence are frequently the final target of a total synthesis and because of their utility in the elucidation and assay of enzyme activity, particularly, glycosidases. In spite of this interest, no general method for the synthesis of aryl glycosides exists which possesses the desirable characteristics of good yields, high stereospecificity, and reproducibility[1-4]. Recently, several reports on the application of phase-transfer catalysis to the synthesis of aryl glycosides have appeared. In the first procedure[5], resin-bound phenoxides are employed in the condensation with 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromides to produce the desired nitrophenyl β-D-galactopyranosides and β-D-glucopyranosides. Despite the good yields obtained, the generality of this method has not been explored. Initial preparation of the resin-bound phenoxide is required and this limits the ease and scale-up of this method. The second procedure[6] involves the phase-transfer catalyzed condensation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide with the appropriate aryl aglycon in a two-phase dichloromethane/aqueous alkaline system containing a phase-transfer catalyst. The failure of acetylated glucosyl halides to react similarly lead to the conclusion that the phase-transfer method requires a fully etherified glucopyranosyl derivative, or at least one with non-participating groups at C-2 and C-6, to be successful. These results are in direct contrast to our own findings on the application of phase-transfer catalysis to glycosylation.

Acetylated aryl β-D-glucopyranosides **(2h–m)** and aryl β-D-galactopyranosides **(2a–g)** can be synthesized efficiently from their respective 2,3,4,6-tetra-*O*-acetyl-α-D-glycosyl bromides **(1)** by condensation with the appropriate sodium phenoxide in a chloroform/water two-phase system employing benzyltriethylammonium bromide as catalyst.



X^1 = OAc, X^2 = H (glucose)
X^1 = H, X^2 = OAc (galactose)
BTEAB = $C_6H_5-CH_2-\overset{\oplus}{N}(C_2H_5)_3Br^{\ominus}$

The product is isolated by simple aqueous work up and purification is achieved, without recourse to chromatography, by crystallization from ethanol. The yields obtained range from moderate (glucose series) to good (galactose series) (see Table).

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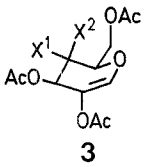
Table. Aryl 2,3,4,6-Tetra-*O*-acetyl-β-D-glycopyranosides (**2**)

2	Parent sugar	R in Aglycon	Yield[a] [%]	m.p. [°C]		$[\alpha]_D^{22}$ (*c* 2, $CHCl_3$)		Reference
				found	reported	found	reported	
a	galactose	4-NO_2	70	143–145°	145–146°	−10°	−11°	5
b		3-NO_2	73	105–106°	110–112°	− 8°	− 9°	5
c		4-OCH_3	56	98–100°	102–103°	+ 2.7°	+ 2.9°	2
d		4-Br	62	98–100°	102–103°	+ 4.8°	+ 4.4°	11
e		3-Br	70	89–91°	90–91°	+ 1.2°	+ 1.2°	2
f		4-CH_3	51	98–100°	99–100°	+ 3.9°	+ 4.2°	11
g		H	64	120–122°	123–124°	−27.6°	−26.4°	8
h	glucose	2-NO_2	68	158–159°	161–162°	+41.5°	+42.0°	5
i		4-NO_2	58	172–174°	174–175°	−39.3°	−37.0°	5
j		4-Cl	34	118–120°	124°	−20.8°	−20.5°	3
k		H	30	118–120°	124–125°	−21.7°	−22°	8
l		4-C_6H_5	38	151–153°	155°	−13.2°	−12.3°	3
m		4-Br	36	125–126°	133°	−18.4°	−19.2°	9

[a] All reactions were carried out on a 24 mmol scale.

In addition to the desired aryl-glycoside arising from displacement of the bromide at C-1, T.L.C. analysis of the crude reaction mixture indicates that β-elimination to form **3** and hydrolysis to form **4** have also occurred in both the *gluco*- and the *galacto*-series.



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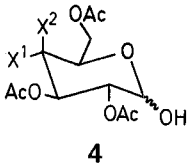
a X^1 = OAc, X^2 = H
b X^1 = H, X^2 = OAc



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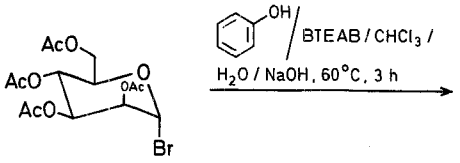
In general, the β-elimination is a more common side reaction in the *gluco*- than the *galacto* series. This is consistent with the work reported in Ref.[7] which investigated the condensation of hexopyranosyl bromides (D-*allo*, D-*gluco*, D-*gulo*, and D-*galacto*) with sodium 4-nitrophenoxide in dimethylformamide to determine the relative tendency for displacement at C-1 to form the 4-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-hexopyranoside versus β-elimination to give the 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-hex-1-enitol[7]. The tendency for the formation of tetra-*O*-acetyl-1,5-anhydro-D-hex-1-enitols decreased in the order D-*allo* > D-*gulo* > D-*gluco* > D-*galacto* whereas the preference for the formation of 4-nitrophenyl tetra-*O*-acetyl-β-D-hexopyranosides was in the reverse order (D-*allo* < D-*gulo* < D-*gluco* < D-*galacto*).

The hydrolysis side reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromides (**1**) is again more pronounced in the *gluco*-series than in the *galacto*-series. Attempts to minimize the hydrolysis reaction, by using alumina impregnated with sodium hydroxide and eliminating the aqueous phase as recently reported[13] were unsuccessful; similar yields of desired product were obtained by this procedure.

Phase-transfer catalyzed reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**5**) with phenoxide takes a different course. Anchimeric participation of the acetate at C-2 leads to the corresponding orthoester **6** in low yield. In addition, hydrolysis of **5** gives 2,3,4,6-tetra-*O*-acetyl-D-mannopyranose (**7**).

Spectral analysis of **6** provided convincing proof for the assigned structure. ^{1}H-N.M.R. analysis revealed the signal of the orthoester methyl group at $\delta = 1.85$ ppm. The stereochemistry of the orthoester methyl group has been tentatively assigned to the sterically less encumbered *endo* isomer. ^{13}C-N.M.R. analysis showed a signal of C-1 of the orthoester moiety at $\delta = 24.48$ ppm.



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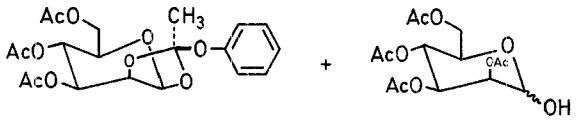

6 **7**

In summary, phase-transfer catalyzed glycosidation of acetylated α-D-glycosyl bromides provides for facile, stereospecific, synthesis of aryl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides and aryl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosides.

Melting points were determined on a Laboratory Devices Mel-temp apparatus and are uncorrected. ^{1}H- and ^{13}C-N.M.R. spectra were recorded on Varian T-60 and JEOLCO FX-100 spectrometers, respectively. Optical rotations were recorded on a Perkin-Elmer 241 MC Polarimeter. Microanalysis were performed by the Atlantic Microlab Inc. Acetylated glucosyl- and galactosyl bromides were obtained from Sigma Chem. Co., St. Louis, MO.

Phenyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glycopyranosides (2g, k); Typical Procedure:

A solution of the appropriate 2,3,4,6-tetra-*O*-acetyl-α-D-bromohexose (**1**; 10 g, 24 mmol) in chloroform (100 ml) is stirred vigorously (overhead mechanical stirrer) at reflux (60°C) with a solution of phenol (4.58 g, 48 mmol) and benzyltriethylammonium bromide (5.53 g, 20 mmol) in aqueous 1.25 normal sodium hydroxide (50 ml, 62 mmol). After 3 h, the mixture is cooled and diluted with water (100 ml). The two phases are then separated and the organic layer washed with 1.25 normal sodium hydroxide (2 × 50 ml). The organic layer is dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude product is purified by crystallization from ethanol.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-phenoxy)ethylidene-α-D-mannopyranose (6):

This compound is synthesized from freshly prepared 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide[12] (**5**; 10 g, 24 mmol) and phenol (4.58 g, 48 mmol) using the same procedure as above. The product is recrystallized from ethanol; yield: 1.55 g (16%); colorless crystals, m.p. 178–180°C; $[\alpha]_D^{22}$: −1.5° (*c* 1, chloroform).

$C_{20}H_{24}O_{10}$	calc.	C 56.60	H 5.70
(424.4)	found	56.67	5.75

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 1.85$ (s, 3H); 2.03 (s, 3H); 2.04 (s, 3H); 2.10 (s, 3H); 3.46–3.86 (m, 1H); 4.06–4.3 (m, 3H); 4.9–5.5 (m, 3H); 7.0–7.5 ppm (m, 1H).

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 170.07$, 169.42, 129.14, 124.70, 124.32 [$H_3C—C(O—)_3$]; 122.88, 97.26, 75.91, 71.52, 70.14, 65.49, 62.45, 24.48 [$H_3C—C(O—)_3$]; 20.68 ppm.

Chromatography of the mother liguors affords compound **7** which is formed as a side product by hydrolysis of **5**; yield: 1.8 g (23%); m.p. 81–84°C; $[\alpha]_D^{22}$: +23.9° (*c* 1.5, chloroform) (Ref.[12], $[\alpha]_D^{22}$ of pure α-isomer: +23.1°).

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1 M. A. Jermyn, *Aust. J. Chem.* **8,** 403 (1955).

2 C. K. DeBruyne, J. Wouters-Leysen, *Carbohydr. Res.* **18,** 124 (1971).

3 T. D. Audichya, T. R. Ingle, J. L. Bose, *Indian J. Chem.* **9,** 315 (1971).

4 G. Grynkiewicz, *Pol. J. Chem.* **53,** 1571 (1979).

5 T. Iversen, R. Johansson, *Synthesis* **1979,** 823.

6 K. Brewster, J. M. Harrison, T. D. Inch, *Tetrahedron Lett.* **1979,** 5051.

7 R. H. Shah, O. P. Bahl, *Carbohydr. Res.* **74,** 105 (1979).

8 B. Helferich, E. Schmitz-Millebrecht, *Ber. Dtsch. Chem. Ges.* **66,** 378 (1933).

9 K. W. Rosemund, E. Güssow, *Arch. Pharm. (Weinheim)* **287,** 38 (1954).

10 Y. Tsuzuki, K. Tanaka, *Bull. Chem. Soc. Jpn.* **40,** 1208 (1967).

11 Z. Csuros, G. Deak, M. Haraszthy-Papp, *Acta Chim. Acad. Sci. Hung.* **42,** 263 (1964); *C. A.* **62,** 7848 (1965).

12 W. A. Bonner, *J. Am. Chem. Soc.* **80,** 3372 (1958).

13 B. Czech, S. Quici, S. L. Regen, *Synthesis* **1980,** 113.

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