Tetrahedron Letters No. 52, pp 5051 - 5054. 0040-4039/79/1222-5051$02.00/0


# SYNTHESIS OF ARYL β-D-GLUCOPYRANOSIDES AND ARYL β-D-GLUCOPYRANOSIDURONIC ACIDS

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Summary: Tetra-O-benzyl-α-D-glucopyranosyl bromide in dichloromethane reacts stereospecifically with solutions of phenols in aqueous sodium or potassium hydroxide, in the presence of phase transfer catalysts, to give good yields of tetra-O-benzyl aryl-β-D-glucopyranosides which are converted into the corresponding aryl β-D-glucopyranosiduronic acids by sequential catalytic debenzylation and catalytic oxidation.

Many aromatic compounds are metabolised by animals to phenolic derivatives which then become conjugated with D-glucuronic acid prior to their excretion. To assist in the unequivocal identification and quantification (e.g. by radioassay procedures) of such conjugated metabolites it is therefore necessary to have readily available, a convenient synthesis of aryl β-D-glucopyranosiduronic acids. In this laboratory, except with simple phenols, attempts to form aryl β-D-glucopyranosiduronic acids by direct reaction of phenols with methyl (2,3,4-tri-O-acetyl-α-D-glucopyranosylbromide)uronate by any of the many variations described for Koenigs-Knorr procedures[1,2] were completely unsuccessful or gave low yields. Also for some complex aromatic derivatives (notably the hydroxy dibenz[b,f][1,4]oxazepin-11(10H)-ones[3] which are formed by mammalian metabolism of the sensory irritant dibenz[b,f][1,4]oxazepine), attempts to form aryl β-D-glucopyranosides were also unsuccessful with previously described procedures.[4,5,6] However, the synthetic method described below has been developed and gives moderate to good yields of aryl β-D-glucopyranosides without any requirement for stringent control of reaction conditions.

The method is to treat a solution of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosylbromide in dichloromethane with an aqueous solution of the phenol in sodium hydroxide in the presence of a phase transfer catalyst. The generalised procedure is:-

A mixture of the aglycon (2 - 3 mmol), freshly prepared 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosylbromide[7] (0.6 g, 1 mmol), water (8 - 10 ml), dichloromethane (8 - 10 ml), sodium (or potassium) hydroxide (20 - 25 mmol) and triethylbenzylammonium chloride (0.05 g) was stirred at room temperature for between 8 - 60 h, depending on the aglycon. The organic phase was separated, washed with water, dried ($MgSO_4$) and concentrated and the residue which usually crystallised was purified either by recrystallisation or by chromatography over silica in mixtures of ether and light petroleum. Yields are shown in Table 1. Where necessary, recovery of unreacted phenol was readily effected by acidification and extraction of the aqueous phase.

Under similar conditions attempts to react phenol with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosylbromide gave unacceptably low yields. Methyl (2,3,4-tri-O-acetyl-α-D-glucopyranosylbromide)uronate was essentially unsuccessful affording hydrolysis products, unchanged starting materials and probably disaccharide derivatives.

Table 1

| Aglycon | 2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosides | | | | β-D-glucopyranosides | | |
|---|---|---|---|---|---|---|---|
| | Yield | M.p.[a] | $\alpha_D$ ($CHCl_3$) (C= ca. 0.5) | Anomeric carbon $^{13}C$ shift | M.p.[b] | $\alpha_D$ (lit.) | Anomeric carbon $^{13}C$ shift |
| Phenol | 68 | 76 | -9.8 | 101.6 | 174 | -68.5 (-70.9) | 101.8 |
| 2-Cresol | 60 | 94 | -8.8 | 101.2 | 169 | -67.4 (-68.7) | 102.5 |
| 3-Chlorophenol | 53 | 67 | -16.9 | 101.4 | 176 | -79.8 (-79.6) | 102.2 |
| 4-Methoxyphenol | 54 | 78 | -2.4 | 102.6 | 174 | -64 | 102.6 |
| 4-Nitrophenol | 56 | 97-98 | -33.5 | 100.6 | - | - | - |
| 1-Naphthol | 57 | 130 | -54.9 | 101.3 | 170-171 | - | 101.3 |
| 4-Hydroxydibenz⌈b,f⌉⌈1,4⌉ oxazepin-11(10H)-one | 41 | 89-90 | -146.7 | 102.4 | 146 | -43.6 | 102.7 |
| 7-Hydroxydibenz⌈b,f⌉⌈1,4⌉ oxazepin-11(10H)-one | 44 | 135 | -15.7 | 101.9 | 216 | -65.3 | 102.5 |
| Morphine | 30 | Syrup | -51.5 | 102.4 | - | - | - |
| 8-Hydroxyquinoline | 36 | 99-100 | -46.9 | 102.5 | - | - | - |
| Thiophenol | 44 | 88 | -5.1 | 87.2 | 128-130 | -71.6 (-70.5) | 88.4 |

[a] Recrystallised from hexane or mixtures with benzene and ether.

[b] Recrystallised from hexane - ethanol mixtures.

The aryl tetra-O-benzyl-β-D-glucopyranosides were smoothly converted into the corresponding aryl β-D-glucopyranosides by hydrogenolysis over palladium on charcoal. Isolated yields were in excess of 70%. [This procedure is unsuitable where the aglycon, e.g. morphine, is unsaturated and easily hydrogenated].

Examples of the aryl β-D-glucopyranosides that have been prepared by the phase transfer procedure are given in Table 1 where yields for the tetra-O-benzyl derivatives and m.ps, $[\alpha]_D$'s and C-1 $^{13}C$ n.m.r. chemical shifts for both the tetra-O-benzyl and the debenzylated materials are listed. For the tetra-O-benzyl derivatives the anomeric $^1H$ signals were masked by the benzylic protons in the $^1H$ n.m.r. Thus the anomeric purity of the tetra-O-benzyl derivatives was determined principally on the $^{13}C$ data. The C-1 $^{13}C$ signal for β-D-glucopyranosides are at 100 - 102 ppm approximately, whereas the corresponding α-D-glucopyranosides have C-1 $^{13}C$ signals at ca. 95 ppm. The anomeric purity of the debenzylated materials was confirmed by $^1H$ n.m.r. where in methanol solution only H-1 doublets characteristic of β-D-glucopyranosides were observed.

Attempts to convert aryl β-D-glucopyranosides to aryl β-D-glucopyranosiduronic acids by an experimental procedure as equally undemanding as for the synthesis of the aryl β-D-glucopyranosides has not been completely successful in that only low to moderate yields were obtained. The method which employs the catalytic oxidation procedure of Heyns and uses phenyldiazomethane to convert the uronic acid to its benzyl ester to assist in its isolation and purification prior to hydrogenolysis is as follows:-

The aryl β-D-glucopyranoside (0.5 - 1.0 g) was taken up in water (30 - 50 ml) at 85 - 90°. Freshly prepared platinum black (0.25 - 0.5 g) was added, the pH adjusted to 8 - 10 with 0.5N sodium bicarbonate solution and oxygen passed through the mixture. The pH and temperature were maintained at these levels and the oxidation continued until t.l.c. (chloroform - methanol, 9:1) showed an absence of starting material. The catalyst was removed by centrifugation. The resulting brown solution was treated with an excess of Amberlite 1R-120 ($H^+$ form). The resin was filtered off and the filtrate evaporated to dryness. The residue was taken up in methanol (5 - 10 ml) and treated with excess ethereal phenyldiazomethane.[11] The excess phenyldiazomethane was discharged with acetic acid, the solution concentrated and the residue chromatographed over silica with chloroform - methanol (95:5) to afford the benzyl ester of the uronic acid.

The procedure was illustrated by the oxidation of phenyl, 4-methoxyphenyl and 2-tolyl-α-D-glucopyranosides which were converted to the corresponding uronic acid benzyl esters in yields of 39, 17 and 30% respectively. Hydrogenolysis (Pd/C in ethanol solution) gave the free uronic acid in ca. 90% yield.

The high stereoselectivity of the phase transfer promoted reactions of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide with phenols to afford β-D-glucopyranosides as the only isolated products may be contrasted with other reports[8,9] of glycosidation of α-D-glucopyranosyl halides protected by benzyl and other non-participating substituents, where glycoside formation gives preponderantly and sometimes exclusively α-D-glucopyranosides. Such procedures, which are under homogeneous conditions, have been suggested[8] as convenient methods for α-D-glucopyranoside synthesis. Indeed, under homogeneous conditions 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl-bromide is sufficiently reactive to react with simple phenols in benzene in the absence of acid acceptors to give a preponderance of aryl α-D-glucopyranosides. However under these conditions the more complex phenols were very unreactive, in cases due to their sparing solubility.

The success of the phase transfer approach for promoting reactions between many phenols and

2,3,4,6-tetra-O-benzyl-α-D-glucopyranosylbromide and the failure of the approach under essentially the same conditions to produce aryl glycosides even with simple phenols from 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosylbromide and methyl (2,3,4-tri-O-acetyl-α-D-glucopyranosylbromide)uronate implies that the procedure requires fully etherified glucopyranosyl derivatives or at least glucopyranosyl derivatives with non-participating groups[10] at C-2 and perhaps C-6. This implication and the mechanistic consequences remains to be investigated as does some of the possible reasons for the stereospecificity of the β-D-glucopyranoside formation in the presence but not in the absence of phase transfer conditions.

Preliminary experiments to determine whether other phase transfer catalysts than triethylbenzylammonium chloride could be used advantageously in aryl glycoside formation were carried out using 2-cresol as the phenol. The results in Table 2 showed no obvious differences between catalysts.

Table 2

Effect of Phase Transfer Catalyst on the Yield of Glucopyranoside from 2-Cresol and Tetrabenzyl-α-D-glucopyranosyl bromide

| Catalyst | Yield |
|---|---|
| Triethylbenzylammonium chloride | 60 |
| Tetrabutyl ammonium hydrogen sulphate | 57 |
| Cetyl trimethylammonium bromide | 44 |
| Adogen | 62 |

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**(Received in UK 8 October 1979)**