A Convenient Synthesis of α-D-Glucopyranosides

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An improved preparation of alkyl α-D-glucopyranosides involves the reaction of tetra-*O*-benzyl-D-glucose with *p*-toluenesulfonyl chloride and an alcohol under phase-transfer conditions.

Several methods have been reported for preparation of α-D-glucopyranosides, using glycosyl compounds with non-participating groups at C-2.[1] In the Koenigs-Knorr method,[2] and later reported efficient variations[3] thereof, the first step is the activation of the anomeric center by formation of a glycosyl halide. One way of improving the α-glycoside synthesis is the generation of a better leaving group. The reaction of halides with silver salts of strong acids like the *p*-toluenesulfonate[4] (tosylate) or the trifluoromethanesulfonate[5] (triflate) salts allows the generation and *in situ* use of glycosyl derivatives so that the reaction proceeds much faster. The reaction of a glucose derivative containing a free anomeric hydroxy group with trifluoromethanesulfonic anhydride, methanesulfonic anhydride, and 2,4,6-trimethylpyridine[6] or with 4-nitrobenzenesulfonyl chloride, silver triflate, and triethylamine[7-10] affords an intermediate sulfonate; if an alcohol is then introduced, glycoside synthesis is effected in an overall one-pot reaction. In reported glycoside synthese, it is important to carfully exclude moisture. We have found that the preparation of 1-*O*-sulfonates can be effected by treatment of the respective alcohols with sulfonyl halides under phase-transfer conditions,[11] and we have observed that diols on treatment with sulfonyl chlorides under phase-transfer conditions undergo esterification followed by intramolecular nucleophilic displacement to give oxiranes.[12] We now report the application of this method to the synthesis of glycosides **4** via intermolecular nucleophilic substitution of the intermediate glucosyl 1-*O*-sulfonates **3**.

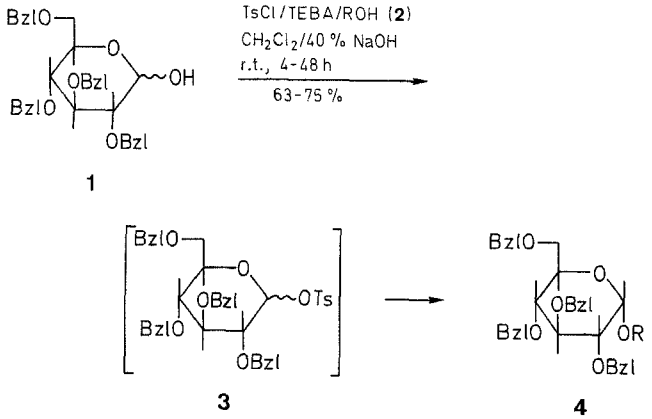
Thus, treatment of the 2,3,4,6-*O*-protected pyranoside **1** with tosyl chloride under phase-transfer conditions gives glucosyl tosylates **3**. The alcoholysis of **3** probably proceeds via ion-pair intermediates which undergo rapid anomerization

α-D-Glp$^+$ + Ts$^-$ ⇄ β-D-Glp$^+$ + Ts$^-$

as has already been postulated.[4] It has been shown that β-glucosyl derivatives with electronegative leaving groups at C-1 are more reactive in the glucosidation reaction than the corresponding α-anomers;[1] thus, under the proposed conditions greater preference for β-glucosidation is observed.

The initially formed reactive tosylate **3** can react with the added alcohol **2** or the pyranose **1** itself, forming glucoside **4** or trehalose, respectively. To avoid the latter side reaction, the alcohol **2** is used in excess.

The procedure described constitutes a convenient method for the preparation of α-D-glucosides derived from primary, secondary, or tertiary alcohols. The availability of the starting material, the simplicity of the operation, and the high stereoselectivity of the reaction are among distinct advantages of the described route to alkyl α-D-glucopyranosides. A related synthesis of *S*-glycosyl thiocarbonates is described in the following communication.[15]



4	R	4	R	4	R
a	CH_3	**c**	*c*-C_6H_{11}	**e**	cholesteryl
b	$C_6H_5CH_2$	**d**	*t*-C_4H_9		

Alkyl α-D-Glucopyranosides 4; General Procedure:

A solution of tetra-*O*-benzyl-D-glucopyranose (**1**; 0.54 g, 1.0 mmol), tosyl chloride (0.21 g, 1.1 mmol), TEBA (0.07 g, 0.3 mmol), and the alcohol **2** (4.0 mmol) in CH_2Cl_2 (10 mL) is stirred with 40% aqueous NaOH (5 mL) at room temperature. The reaction is monitored by TLC (Kieselgel 60 G, Merck; benzene/EtOAc, 8: 1, disappearance of **1**). When the reaction is complete the organic layer is separated, washed with H_2O (3 × 10 mL), and dried ($MgSO_4$). The solvent is evaporated and the crude product **4** is chromatographed on a column (20 × 2 cm, 25 g silica gel 0.063–0.2 mm) using benzene/Et_2O 40:1 as eluent.

Benzyl Tetra-O-benzyl-α-D-glucopyranoside (**4b**); yield: 75%.

$C_{41}H_{41}O_6$ (629.8) calc. C 78.20 H 6.56 found 78.35 6.51

^{1}H-NMR ($CDCl_3$): δ = 3.59–4.09 (m, 15 H); 5.11 (d, 1 H, *J* = 3.5 Hz, H-1); 7.25 (br s, 25 H_{arom}).

Table. Alkyl α-D-Glucopyranosides **3** Prepared

Product[a,b]	Reaction Time (h)	Yield[c] (%)	Ratio[d] α/β	mp (°C)[e] found	mp (°C)[e] reported	$[\alpha]_D^{20}$ found	$[\alpha]_D^{20}$ reported
3a	4	63	75/25	syrup	syrup[8]	+29	+28[8]
3b[f]	12	75	90/10	syrup		+40	
3c	24	71	90/10	syrup	syrup[8]	+52	+45[8]
3d	48	65	95/5	syrup	syrup[13]	+45	+39[13]
3e	24	68	95/5	137–138 (EtOH/EtOAc)	137.5–138.5[6]	+46	+47[6]

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.18.
[b] All products gave NMR data in agreement with Lit. data.
[c] Yield of isolated product **3** based on **1**.
[d] Ratio α/β estimated by integration of the ^{1}H-NMR spectra of crude **3a**, or by TLC of crude **3b–e**.
[e] Uncorrected; measured with a Boethius apparatus.
[f] IR and NMR spectra identical with those of the benzylation product of benzyl α-D-glucopyranoside.[14]

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