A convenient stereoselective synthesis of β-D-glucopyranosides

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The Koenigs-Knorr method plays a prominent role in the stereoselective synthesis of alkyl D-glucopyranosides via glycosidic linkage. Such an approach requires costly and toxic promoter salts of silver or mercury, which have additional separation problems. In a novel method a less toxic promoter salt like LiCO₃ is used for glycosidation of several fatty alcohols including an aromatic alcohol. LiCO₃ can be easily separated from the reaction mass and gives good yield.

Keywords: Koenigs-Knorr method, β-D-glucopyranosides, alkyl glucosides, LiCO₃

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There are many β-D-glucopyranosides possessing primary alcohols as an aglycone part in nature. The development of stereoselective methods for the formation of glycosidic linkages presents a considerable challenge to synthetic chemists. Although well developed chemical formation of glycosidic linkage involves several steps of selective protection, deprotection and coupling involving a metal catalyst. Glycosylation of simple alcohols with fully acetylated derivatives of common and inexpensive monosaccharide can be performed by Lewis acid promotion in a suitable solvent. Such glycosylation is normally carried out using expensive heavy metal catalysts, having separation problems, and gives only moderate yield (40-50%). This problem encountered during glycosylation has led to the search for the development of cost-effective and less toxic promoter based synthetic routes. Many authors have used the Koenigs-Knorr method to study biological and toxicological behaviour of alkyl glucosides. According to the Koenigs-Knorr method, D-glucose is converted to peracetylated glycosyl halide through treatment with hydrogen bromide or hydrogen chloride. This unstable reactive intermediate can be isolated in a high degree of purity and can be converted to the corresponding peracetylated alkylglucosides by the addition of the respective alcohols in the presence of silver or mercury salts. Such promoter leads to nucleophilic attack and gives the corresponding glycosylated sugar. Some of the advantages of Koenigs-Knorr method are: (i) it is a low temperature process, so degree of polymerization of glucose can be controlled; (ii) absence of any strong acid promoter and low temperature avoids charring of saccharides; (iii) final product has minimum colored impurity, so appearance and clarity are good. The main drawback is the use of costly and toxic promoters like silver and mercury, which involves additional separation efforts. With this in mind critical glycosylation of tetra-O-acetyl bromo-β-D-glucopyranosides with alcohols in the presence of LiCO₃ as a promoter was carried out.

Results and Discussion

The peracete of glucose is readily prepared as the β-anomer by standard procedure. When 1,2-trans sugar per-O-acetate (step-1, Scheme I) is dissolved as per standard procedure in acetic acid containing hydrobromic acid, 2,3,4,6-tetra-O-acetyl-α-glycosyl bromide is formed. Compound shows inversion of configuration, so instead of β-D-glycosyl halide, α-glycosyl halide is formed with high degree of purity. This unstable reactive intermediate product can be isolated in dichloromethane and converted to the corresponding peracetylated alkyl glucosides. Addition of the tetraacetyl bromoglucoside 3 to a solution of the acceptor substrate dissolved in
Step 1: Preparation of peracetyl glucosyl bromide.

2: 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranosides.
3: 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside.

Step II – Preparation of β-D-Glucopyranosides.

4: 2,3,4,6-tetra-O-acetyl-β-D-alkylglucopyranosides
5: β-D-alkylglucopyranosides
6: n-heptyl-β-D-glucosides
7: n-octyl-β-D-glucosides
8: n-nonyl-β-D-glucosides
9: n-decyl-β-D-glucosides
10: n-dodecyl-β-D-glucosides
11: n-meristyl-β-D-glucosides
12: 2-phenylethyl-β-D-glucosides

Scheme I – Stereoselective synthesis of β-D-glucopyranosides from D-glucose.
dichloromethane containing LiCO₃ was carried out over a period of 16-24 hr. The reaction can be easily monitored by TLC and terminated when the formation of the desired product is maximum. The results are summarized in Table I. The structure of all products was determined by either direct comparison with corresponding β-D-glucopyranosides or analysis of ¹H NMR data. Identification of the β-configuration of the anomeric center was easily achieved via analysis of the C-H/C-H coupling constant (d, J = 7.8 Hz) as shown in Table II. The physical data of β-D-glucopyranosides were identical with those of the reported β-D-glucopyranosides¹¹-¹⁴. Chemical yield of β-D-glucopyranosides varied between 40-67% depending on the alcohols used. In order to avoid the cleavage of the β-D-glucopyranosides, alcohols and peracetyl glucosylbromide were taken in dichloromethane in presence of molecular sieves. Compounds 1 and 2 were obtained in yield of 65-67%. Reaction time was 16-18 hr. Higher alcohols show similar good yield and reaction time. When 2-phenylethanol reacted with peracetyl bromoglucoside 3, it gave 45% yield.

The LiCO₃ promoted reaction involving glycosidic bond formation is thought to be mechanistically similar to the Koenigs-Knorr method for formation of glycosides⁵. Lithium as the active site of LiCO₃ leads nucleophilic attack on carbon-1 leading to nucleophilic substitution. Carboxylate ion, which acts as a general base, abstracts a proton from the alcohol. Nucleophilic alcohol presumably attacks at the β-side to exclusively afford β-D-glucopyranosides as the main product.

**Conclusion**

LiCO₃ promoted glycosidation of alcohols 1-7 gives stereoselectively β-D-glucopyranosides 6-12 in moderate yield respectively. The advantages include low cost of the promoter, operation at rt, comparative good yield and selectivity for final product. The stricter enforcement of legislation on the release of waste and restrictions on the use of toxic substances are being used as measures to control environmental pollution¹⁵. This made the present method using LiCO₃ environment friendly and highly suitable for industrial applications.

**Experimental Section**

Melting points were determined using capillary method and are uncorrected. Specific rotations were recorded on a manual polarimeter. Infrared spectra were recorded on Buck Scientific Inc. Model 500 spectrophotometer. ¹H NMR were recorded on Hitachi Inc. NMR spectrometer and operated at 300 MHz. Thin layer chromatography (TLC): Silica gel G for TLC (LR Grade) was used. TLC analysis did not entail any particular sample preparation. 10 mL of an ethanolic solution (0.5-1%) was applied to the TLC plate in the form of 1 cm lines with solutions of alkyl glucoside calibration substances. The TLC plate was then placed in a TLC chamber and the chromatograms were developed [Mobile phase Methanol (9):Water (1)]. When the solvent front moved 8 cm from its starting position, the plate was removed from the chamber, dried and the spots were detected by spraying a solution containing 0.5 g thymol in 5% sulfuric acid in ethanol. Non-carbohydrate compounds were detected by using 1% anisaldehyde dissolved in 2% sulfuric acid in glacial acetic acid. The plate was heated to 105°C until the glucosides became visible as red spots. Identification was based on the colour of the spots and on the distance traveled by the spots from the baseline by comparison with those of the same plate. The pentaacetyl glucose (Rf value – 0.78) moved farthest followed by the alkyl mono glucosides

<table>
<thead>
<tr>
<th>Compd</th>
<th>ROH (1 eq.)</th>
<th>glu-OR G (%)</th>
<th>Yield* Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃(CH₂)₆-OH</td>
<td>glu-O-(CH₂)₆-CH₃</td>
<td>6(65) 16</td>
</tr>
<tr>
<td>2</td>
<td>CH₃(CH₂)₇-OH</td>
<td>glu-O-(CH₂)₇-CH₃</td>
<td>7(67) 18</td>
</tr>
<tr>
<td>3</td>
<td>CH₃(CH₂)₈-OH</td>
<td>glu-O-(CH₂)₈-CH₃</td>
<td>8(65) 20</td>
</tr>
<tr>
<td>4</td>
<td>CH₃(CH₂)₉-OH</td>
<td>glu-O-(CH₂)₉-CH₃</td>
<td>9(64) 21</td>
</tr>
<tr>
<td>5</td>
<td>CH₃(CH₂)₁₁-OH</td>
<td>glu-O-(CH₂)₁₁-CH₃</td>
<td>10(66) 22</td>
</tr>
<tr>
<td>6</td>
<td>CH₃(CH₂)₁₃-OH</td>
<td>glu-O-(CH₂)₁₃-CH₃</td>
<td>11(67) 24</td>
</tr>
<tr>
<td>7</td>
<td>Ph(CH₂)₂-OH</td>
<td>glu-O-(CH₂)₂-Ph</td>
<td>12(45) 20</td>
</tr>
</tbody>
</table>

*Isolated yield after purification.
(Rt value = 0.71), di-(Rf value = 0.66) and oligo glycosides (Rt value = 0.61) respectively.

1,2,3,4,6-penta-O-acetyl-β-D-glucopyranosides 2

A mixture of 1 (27 mmoles), acetic anhydride (12.4 mL) and sodium acetate (3.2 mmoles) was taken in a round bottom flask and heated to 93°C for 2 hr. After the reaction, the reaction mixture was poured into cold water, cooled for 30 min at 10°C and gradually warmed to 30°C. The mass was filtered through celite and washed with methanol to afford peracetylated glucose 2. Yield 85%; m.p.132°C, Lit.16 m.p.112-14°C; [α]D25 67% (c=0.51, CH3OH); IR(KBr): 3412, 2928, 2831, 1075, 1030 cm -1. Anal. Found C, 59.1; H, 9.87. Calcd for C, 59.2; H, 9.20.Calcd for C, 55.7; H, 9.28%.

2,3,4,6-tetra-O-acetyl-α-D-glucosyl bromide 3

A mixture of 2 (7.78 mmoles), glacial acetic acid (6.3 mL) and hydrobromic acid (3.87 mL, 49% in acetic acid) was stirred in a round bottom flask for 2 hr at 30°C. After completion of reaction the mixture was poured into ice water (50 mL), and extracted with dichloromethane (3×50 mL). The combined dichloromethane layer was washed swiftly with chilled water (2×50 mL), 5% brine solution (2×50 mL) and then finally chilled water (2×50 mL), dried over CaCl2 and then concentrated to afford 3 (6.72 mmoles, 90%). Observed m.p. 87-89°C, reported m.p. 88°C.

n-Heptyl-β-D-glucopyranosides 6

A mixture of 3 (6.72 mmoles), n-heptanol (6.72 mmoles) and LiCO3 (8.12 mmoles) in dichloromethane was stirred in a round bottom flask for 16 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (toluene/ethyl acetate=15:5) to afford 2,3,4,6-tetra acetyl-n-heptyl-β-D-glucopyranosides (1.63 g, 70%) as a colorless solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (4.1 mmoles) with methanol and sodium methoxide at rt for 24 hr to get β-D-glucopyranosides 6 (0.75 g, 65%), m.p. 73-75°C; [α]D25 32° (c=0.51, CH3OH); IR(KBr): 3378, 2930, 2864, 1079, 1037 cm -1. Anal. Found C, 55.00; H, 9.20.Calcd for C, 55.7; H, 9.28%.

n-Octyl-β-D-glucopyranosides 7

A mixture of 3 (6.72 mmoles), n-octanol (6.72 mmoles) and LiCO3 (8.20 mmoles) in dichloromethane was stirred in a round bottom flask for 18 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (toluene/ethyl acetate=15:5) to afford 2,3,4,6-tetra acetyl-n-octyl-β-D-glucopyranosides (1.91 g, 4.6 mmoles) as a colour-less solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (0.91 mmoles) with methanol and sodium methoxide at rt for 24 hr to get β-D-glu-copyranosides 7 (0.91 g, 67%). m.p. 61.5-2.5°C; [α]D25 33.8° (c=0.58, H2O); IR(KBr): 3412, 2928, 2831, 1075, 1030 cm -1. Anal. Found C, 57.50; H, 9.60. Calcd. for C, 57.53; H, 9.58%.

n-Nonyl-β-D-glucopyranosides 8

A mixture of 3 (6.72 mmoles), n-nonylnol (6.72 mmoles) and LiCO3 (8.20 mmoles) in dichloromethane was stirred in a round bottom flask for 20 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (toluene/ethyl acetate=15:5) to afford 2,3,4,6-tetra acetyl-n-nonyl- β-D-glucopyranosides (2.10 g, 5.4 mmoles) as a colourless solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (5.4 mmoles) with methanol and sodium methoxide at rt for 24 hr to get β-D-glucopyranosides 8 (1.03 g, 68%). IR(KBr): 3412, 2928, 2831, 1075, 1030 cm -1. Anal. Found C, 59.1; H, 9.87. Calcd for C, 59.2; H, 9.86%.

n-Decyl-β-D-glucopyranosides 9

A mixture of 3 (6.7 mmole), n-decanol (6.72 mmoles) and LiCO3 (8.30 mmoles) in dichlorom-
thane was stirred in a round bottom flask for 20 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (toluene/ethyl acetate=15:5) to afford 2,3,4,6-tetra acetyl-\(\beta\)-d-glucopyranosides (2.05 g, 4.7 mmoles) as a colourless solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (4.7 mmoles) with methanol and sodium methoxide at rt for 24 hr to get \(\beta\)-d-glucopyranosides 9 (0.951 g, 64%). m.p.135.6°C; \([\alpha]_{D}^{25} = 27.8^o\) (H_2O); IR(KBr): 3386, 2925, 2829, 1080, 1036 cm\(^{-1}\). Anal. Found C, 70.57; H, 10.12%. Calcd. for C, 70.58; H, 10.15.

\(n\)-Dodecyl-\(\beta\)-d-glucopyranosides 10

A mixture of 3 (6.72 mmoles), \(n\)-dodecanol (6.72 mmoles) and LiCO_3 (8.30 mmoles) in dichloromethane was stirred in a round bottom flask for 22 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (toluene/ethyl acetate=15:5) to afford 2,3,4,6-tetra acetyl-\(n\)-dodecyl-\(\beta\)-d-glucopyranosides (2.22 g, 5.5 mmoles) as a colourless solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (2.22 g, 5.5 mmoles) with methanol and sodium methoxide at rt for 24 hr to get \(\beta\)-d-glucopyranosides 10 (1.08 g, 66%). m.p.144-45°C; \([\alpha]_{D}^{25} = -22.7^o\) (H_2O); IR(KBr): 3390, 2935, 2825, 1085, 1040 cm\(^{-1}\). Anal. Found C, 65.83; H, 10.35. Calcd for C, 65.85; H, 10.36%.

\(n\)-Meristyl-\(\beta\)-d-glucopyranosides 11

A mixture of 3 (6.72 mmoles), \(n\)-meristyl alcohol (6.72 mmoles) and LiCO_3 (8.30 mmoles) in dichloromethane was stirred in a round bottom flask for 24 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (toluene/ethyl acetate=15:5) to afford 2,3,4,6-tetraacetyl-\(n\)-meristyl-\(\beta\)-d-glucopyranosides (2.22 g, 4.8 mmoles) as a colourless solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (4.8 mmoles) with methanol and sodium methoxide at rt for 24 hr to get \(\beta\)-d-glucopyranosides 11 (1.1 g, 67%). IR(KBr): 3412, 2928, 2831, 1075, 1030 cm\(^{-1}\). Anal. Found C, 70.57; H, 13.50. Calcd for C, 70.58; H, 13.52%.

2-Phenylethyl-\(\beta\)-d-glucopyranosides 12

A mixture of 3 (6.72 mmoles), phenylethanol (6.72 mmoles) and LiCO_3 (8.30 mmoles) in dichloromethane was stirred in a round bottom flask for 18 hr at 30°C. After the reaction was over, the mixture was filtered through celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (CHCl_3/CH_3OH=10:5) to afford 2,3,4,6-tetraacetyl-2-phenylethyl-\(\beta\)-d-glucopyranosides (1.35 g, 3.4 mmoles) as a colourless solid. Deacetylation (step-2, Scheme I) of peracetylated glucosides was done by treatment of purified sample (3.4 mmoles) with methanol and sodium methoxide at rt for 24 hr to get \(\beta\)-d-glucopyranosides 12 (0.44 g, 45%). m.p. 38.5°C; \([\alpha]_{D}^{25} = 35.3^o\) (c=0.58, CH_3OH); IR(KBr): 3368, 2924, 1674, 1083, 1058, 1036 cm\(^{-1}\). Anal. Found C, 59.10; H, 7.04. Calcd for C, 59.15; H, 7.04%.

References
5 Koenigs W & Knorr E, Chem Ber, 34, 1901, 957.